European Medicines Agency
Evaluation of Medicines for Human Use

London, 23 June 2005
CPMP/EWP/438/04

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF PSORIATIC ARTHRITIS

DISCUSSION IN THE EFFICACY WORKING PARTY	April 2004 – April 2005
TRANSMISSION TO CHMP	June 2005
RELEASE FOR CONSULTATION	June 2005
DEADLINE FOR COMMENTS	December 2005

Note:

Any comments to this Guideline should be sent to the EMEA EWP Secretariat by e-mail: line.jensen@emea.eu.int or by fax: +44 20 74 18 86 13 by the end of December 2005.

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This Guideline is intended to provide guidance for the evaluation of new medicinal products in the treatment of psoriatic arthritis. This Guideline should be read in conjunction with Directive 2001/83/EC as amended and all other pertinent elements outlined in current and future EU and ICH guidelines and regulations, especially those on:

- Dose-Response Information to Support Drug Registration (ICH E4),
- Statistical Principles for Clinical Trials (ICH E9),
- Choice of Control Group in Clinical Trials (ICH E10)**,**
- The Extent of Population Exposure to Assess Clinical Safety for Drugs (ICH E1A),
- PtC on clinical investigation of medicinal products for treatment of psoriasis
- PtC on clinical investigation of medicinal products other than NSAIDs for treatment of rheumatoid arthritis.
- Ongoing draft on clinical investigation of medicinal products for treatment of ankylosing spondylitis.

This Guideline is intended to assist applicants during the development of psoriatic arthritis products. It is only guidance; any deviation from guidelines should be explained and discussed in the Clinical Overview.

INTRODUCTION

Psoriatic arthritis (PsA) is an inflammatory arthropathy associated with psoriasis, which is classified within the group of the spondyloarthritis. Psoriasis affects 1-3% of the population, with approximately a third of patients developing PsA. The estimated prevalence of PsA ranges between 0.1% and 1%. Psoriatic arthritis can develop at any time, but for most people it appears between the ages of 30 and 50, and it affects men and women equally.

With the exception of the distal interphalangeal joints (hands and feet), there are no predictable joints for involvement in PsA and the signs of inflammation are often non symmetrical and more difficult to detect compared with Rheumatoid Arthritis (RA). Spondyloarthopathy is often present. Some typical features of PsA are dactylitis and nail psoriasis. Extra-cutaneous and extra-articular manifestations are uncommon but may include conjunctivitis, uveitis, aortic insufficiency and pulmonary fibrosis.

Psoriatic arthritis may start slowly with mild symptoms, or develop quickly. Flares and remissions usually characterise the course of PsA. Left untreated, patients with PsA can have persistent inflammation, progressive joint damage, several physical limitations and disability. For most patients, skin manifestations predate the arthritis. Prognosis of PsA may range widely from a mild monoarthritic form with good prognosis to an erosive and destructive polyarticular form, comparable with that in patients with RA. Axial forms might be settled in every point of this spectrum.

Treatment includes physical therapy, patient education as well as medication. Mild PsA is generally treated with NSAIDs. When only few joints are involved, local injections of steroids might be effective. For extensive or severe PsA systemic conventional therapies such as methotrexate and sulfasalazin are standard therapies. Other products such as cyclosporine, antimalaric drugs and gold salts are also used, although there are limited data. Recently, drugs such as leflunomide and TNF-alpha antagonists have been added to the therapeutic armamentarium.

Skin involvement may vary from mild to a severe disease, which activity is commonly not mirrored by arthritis activity. Topical medications for mild forms including corticosteroid creams, ultraviolet irradiation and vitamin D cream are commonly used. More severe disease requires ultraviolet A

irradiation plus psoralens, cyclosporine and methotrexate. Several new biological treatments have been recently approved for the treatment of resistant patients.

Some of the available drugs intended to treat arthritis might have an effect, positive or negative, on skin lesions. In this sense, antimalaric drugs and systemic corticosteroids should be avoided because they can cause dermatitis or exacerbate psoriasis when they are discontinued. By contrast, treatments such as methotrexate and TNF-alpha antagonist are useful for both the skin lesions and the joint inflammation of psoriatic arthritis.

The demonstration of efficacy on the different patterns of arthritis with an acceptable safety profile will be the main requirement for an approval of any new treatment for psoriatic arthritis. However, the clinical development should provide the relevant information that will allow physicians to select the best treatment option taking into account patient's characteristics within the available treatments. Therefore, the assessment of the possible impact (beneficial or deleterious) on skin lesions will be mandatory.

1. PATIENTS CHARACTERISTICS AND SELECTION OF PATIENTS

Psoriatic arthritis is a form of the spondyloarthritis (SpA), which classifies patients with related diseases on the basis of the 1991 proposal of the European Spondyloarthropathy Study Group (ESSG). The other clinical entities included are ankylosing spondylitis (the most common and severe form), reactive arthritis, inflammatory bowel disease-related arthritis and undifferentiated spondyloarthritides.

Several efforts have been made in order to establish classification and diagnostic criteria for PsA. Despite so, there are no generally accepted validated case definitions of PsA and at present, the diagnosis is based on clinical judgement. Specific patterns of joint inflammation together with the absence of rheumatoid factor (91-94%) and the presence of psoriasis skin lesions serve clinicians to diagnose PsA. There are no tests to confirm the diagnosis, but X-rays can be helpful to diagnosis and to show the extent and location of joint damage.

In clinical trials, clinically apparent psoriasis (skin or nails), present or documented history, should be a mandatory criterion to diagnose PsA

Several clinical patterns of arthritis have been identified in patients with PsA, although most of them overlapped. Currently, there is a substantial agreement in accepting two main patterns of arthritis in PsA, i.e. a peripheral joint disease, which can further have a polyarticular or a pauciarticular form of arthritis, and an axial disease. Approximately 95% of patients with PsA have involvement of the peripheral joints, of which the majority have a polyarticular form and some have an oligoarticular form of arthritis. Around 5% have exclusively spinal involvement; while between 20-50% have involvement of both the spine and peripheral joints, being peripheral the predominant pattern.

The oligoarticular peripheral PsA is, in almost all cases, locally treated and thus, this form will not be further discussed since locally applied therapies are not under the scope of this guidance.

Therefore, three clinical features of PsA are commonly found and will be covered by this guidance:

1. A pure peripheral polyarticular joint PsA disease, similar to rheumatoid arthritis
2. A predominant peripheral polyarticular joint disease with coexistent axial disease,
3. Patients with pure axial disease, quite similar to ankylosing spondilitis.

The polyarticular peripheral pattern of PsA shares several features with rheumatoid arthritis, which makes distinction between both rather difficult. In this clinical setting, the seronegativity for rheumatoid factor could help, however, due to its low predictability further clinical features should be considered in order to differentiate seronegative RA with coincidental psoriasis from patients with a peripheral PsA disease. Therefore, patients who displayed other characteristic signs of RA (i.e. nodules, extra-articular involvement, anticitrullinated protein antibodies) should be excluded and specific clinical features of PsA should be carefully recorded. In this sense, involved joints in PsA are usually less tender and swollen than in RA. Inflammation tends to be less symmetric in its distribution. Dactylitis and distal interphalangeal (DIP) joint involvement are common in PsA but are usually absent or uncommon in RA.

Psoriatic Spondylitis might be in a limited number of cases indistinguishable from ankylosing spondylitis. However, in most cases, axial involvement is a common secondary feature of a predominant peripheral PsA. It may present as sacroiliitis, which may be asymmetrical and asymptomatic, or spondylitis, which may occur without sacroiliitis and may affect any level of the spine in "skip" fashion. In this clinical setting, spondylitis tends to be less severe than that of AS, mobility is not commonly impaired and evolution to ankylosis is fairly uncommon. The anarchic presence of asymmetrical syndesmophytes is characteristic. Diagnosis on symptoms alone is insufficient due to the frequent asymptomatic involvement of the spine and sacroiliac joints in association with psoriasis. Therefore, X-ray and some cases, MRI and/or CT imaging might help to complete diagnosis. The presence of spinal involvement should be carefully addressed when selecting patients to participate in clinical trials.

The polyarticular peripheral pattern, with or without concomitant axial disease, constitutes the predominant pattern and so, this will be the target population in PsA clinical trials. However, since there is some evidence that the different clinical pattern of arthritis (axial or peripheral) in PsA responds in a different manner to therapy, efficacy should be demonstrated separately.

Demonstration of efficacy in the pure axial disease should follow the ankylosing spondylitis guidance.

Demographic characteristics of patients, duration of the disease (both psoriasis and arthritis), previous and concomitant therapy as well as concomitant diseases should be well documented. In addition, some characteristics that may allow to identify subpopulations where the benefit risk ratio of the new product might be different, such as the severity and extent of the disease (both psoriasis and arthritis), the type of psoriasis, the disease activity (both psoriasis and arthritis), the spinal and peripheral joint involvement should be documented. Relevant identified subpopulations should be limited, justified and defined a priori in the study protocol. Statistical analysis should be adequate (see PtC concerning multiplicity in Clinical Trials).

Patients between 16 and 18 years and those whose symptoms started prior to this should be not excluded from clinical trials

Disease activity at the enrolment in the trials should be distinguished of the level of damage and functional disability reached by the patients due to the evolution of the disease. Activity of disease should be assessed by means of validated scales and considering several aspects of the disease such as pain and/or swelling. Patients should have an active psoriatic arthritis as measured by the number of swollen and tender/painful joints (ACR joint count).

In addition to the documentation of the axial involvement, the activity at this level should be assessed by means of the use of composite simple scales such as the 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.

Biologic measures of inflammation (i.e. erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)) should be recorded since a high ESR at presentation has been associated with progression of joint disease. Activity of the skin lesions, when present, should also be assessed using available validated tools for psoriasis.

For including patients a moderate to severe disease activity should be required in order to show a sufficient treatment response (e.g. BASDAI >4 or pain as measured by VAS >4).

In addition to the disease activity at a given time, the severity of the disease is determined by other characteristics such as persistency of disease activity despite an adequate treatment. A minimum duration of active disease should be established before entering into the trial. A duration of 4 weeks is sufficient to introduce products like NSAIDs, however, a minimum duration of 3 months of active disease would be needed when assessing products to be used in patients not controlled with NSAIDs (DMARDs). To support a therapeutic indication in patients with lack of response to previous DMARDs treatments (e.g. methotrexate or sulfasalazin) the appropriate target population should be included in clinical trials. The lack of response should be well documented according to generally accepted criteria (e.g. standard dosage, 6 months treatment,...) either in the clinical trial or in the patient medical records.

2. METHOD TO ASSESS EFFICACY

In recent years, efforts have been done in order to define the different core domains to assess efficacy of products for PsA as well as to develop and validate methods to assess changes in those domains. Many of the tools used to measure these domains have been borrowed from rheumatoid arthritis or ankylosing spondylitis and, although increasing data relate to PsA specifically, there are some instruments (i.e. the functional disability and enthesitis instruments as well as radiologic scoring methods) that require further validation.

Different domains may be assessed separately or using composite indices that bring together the assessment of several domains. From a regulatory point of view, we distinguish the following claims of a therapy:

1) Improvement of symptoms and signs of peripheral arthritis.
2) Improvement of physical function.
3) Improvement of symptoms and physical function related to axial disease.
4) Slowing or prevention of structural damage
5) Prevention of disability.

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

Disease activity in PsA

- Peripheral joint disease activity.

Assessment of PsA disease activity in the joints is commonly made by the American College of Rheumatology (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 RA, increased joint counts to cover distal interphalangeal 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 and the 66/68-joint graded assessment of tenderness/swelling). Dactylitis, whenever present, should be counted as one active joint. Although developed for the assessment of patients with RA, the appropriately modified ACR joint count has been demonstrated to be a reliable measure of activity in PsA.

- Axial inflammation.

Morning stiffness, spinal and nocturnal pain have been used as a measure of axial inflammation in the limited number of clinical trials that included PsA patients with concomitant axial pattern disease. Measures of activity developed for AS (e.g. the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Bath Ankylosing Spondylitis Functional Index (BASFI)) might be used to assess the effect on PsA axial activity.

Measure of function and disability

The assessment of physical function by self-reported questionnaire is the most extended and preferable approach. Two validated questionnaires for measuring physical function in RA and AS have been used in clinical trials of PsA: the Health Assessment Questionnaire (HAQ) and a modification for spondyloarthropathies (HAQ-S), respectively. Further, a modification of the HAQ for psoriasis (HAQ-SK) is also available. However, no specific measure of physical function valid to assess the variety of activities affected in the different patterns of PsA is currently available. Meantime, it seems reasonable to continue using the HAQ in clinical trials, especially in those trials that focus on patients with a predominant peripheral PsA disease.

Measure of Structural Joint Damage

The assessment of structural damage and progression in PsA can be assessed with conventional radiographs. 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.

Several scoring methods for the assessment of structural damage in peripheral joints in PsA have been proposed. All these are based on existing scoring systems for RA and have been adapted for use in PsA (i.e. the modified Steinbrocker scoring method, a modified Sharp score, the Sharp–Van der Heijde modified scoring method). However, due to the different and unpredictable pattern of joint damage in PsA, it remains to be determined which joints should be scored to get a valid measurement of joint damage. A specific radiographic method is the Psoriatic Arthritis Ratingen Score (PARS). It includes 40 joints of the hands and feet. All joints are scored separately for destruction (on a 0–5 scale) and proliferation (on a 0–4 scale), which can be sum up to give the total score or measured separately.

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.

MRI and ultrasounds, although not yet validated, might be useful in the evaluation of enthesopathy (a prominent feature of PsA) as well as in the assessment of sacroiliitis.

In summary, several radiological scores are available and it is considered that further evaluation of the various methods is needed. At present, the clinical relevance of the observed differences is unclear. Therefore, choice of the method, joints and features to be assessed as well as the clinically relevant differences should be predefined and justified.

2.2. Other domains and instruments to be assessed

- Skin disease activity

Although active psoriasis should not be a mandatory requirement for entry into clinical trials for PsA, the effect of any new therapy for PsA on skin lesions should be assessed separately from that on active arthritis. Different validated scoring methods to assess skin or nail lesions are available. Selection should consider the form of psoriasis (commonly plaque psoriasis), the body surface area involved, and the presence of nail lesions.

- Enthesitis

Several indices have been developed in order to provide a feasible method to assess enthesopathy. The Mander Index is not considered the most suitable for clinical trials. The MASES index is used in AS but requires further validation in PsA. At present, either the MASES index or other instruments if validated and reliable may be used.

- Biological measures of inflammation

Levels of C reactive protein (CRP) or the erythrocyte sedimentation rate (ESR) may be related to the activity of the disease. A high ESR at presentation has been associated with progression of joint disease and early mortality in PsA. However, the ESR is elevated in only half of the patients and there are no data to support them as useful surrogate variables to assess efficacy in PsA.

- Quality of Life

It may be assessed either using some specific scales (e.g. PsAQoL) or generic instruments (e.g. SF-36) Both have been tested in PsA and were found to be reliable, valid and responsive to change. 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 quality of life should be assessed independently.

- Global assessment

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

2.3. Main efficacy end points

The use of a composite measure based on previous domain assessment is an acceptable way to assess efficacy of a medicinal product. Only validated composite endpoints are considered valid as efficacy endpoints, provided that consistency is shown between different measures of the composite as well as with other single efficacy measures. It is very important that responder criteria are adequately justified, chosen before the study is started, and thresholds predefined.

The main efficacy endpoint will depend on the type of product and the intended therapeutic claim.

2.3.1. Medicinal products intended to improve symptoms/physical function

Two main responder criteria have been used in clinical trials for PsA: the Psoriatic Arthritis Response Criteria (PsARC) and the American College of Rheumatology (ACR).

The ACR20/50/70 response criteria were developed for RA. The ACR20 criteria required 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 activity, d) disability index of the HAQ and, e) acute-phase reactant. Analyses of ACR50 and ACR70 included the same criteria as ACR20, with the use of a higher percentage improvement (50% and 70%) instead of 20%. ACR20 response criteria have been used as the primary, or secondary, endpoint in most clinical trials in PsA. It has to be determined the magnitude of the response required to demonstrate a clinically meaningful effect in PsA. It seems reasonable to select ACR20 as the primary endpoint and to measure ACR50/70 as secondary information. As a general rule, the expected benefit/risk ratio of the new therapy might determine such decision.

The PsARC method was specifically developed for PsA and used in a large study of sulfasalazin in PsA. It has been assessed in most clinical trials in PsA up to now and it is considered an acceptable primary endpoint. PsARC response was defined as improvement in at least two of the following four criteria: a) ≥20% improvement in Physician Global assessment of disease activity, b) ≥20% improvement in Patient Global Assessment of Disease Activity, c) ≥30% improvement in tender joint count and d) ≥30% improvement in swollen joint count. One of the criteria improved has to be tenderness joint count (TJC) or swollen joint counts (SJC) and no worsening in any of the criteria should be observed.

These criteria discriminate well between effective treatment and placebo. However, those criteria focus on peripheral polyarticular form of PsA and thus, many of the proposed core outcomes such as spondylitis and features unique to PsA such as dactylitis and enthesitis are not incorporated in those criteria. An international effort for developing a complete outcome for PsA that combines response criteria for peripheral arthritis and the other mentioned assessment is currently under way. Until such composite criteria became available, those relevant features lacking in the primary composite endpoint should be assessed separately as a secondary endpoint.

In summary, in most cases, a peripheral polyarticular form will be predominant and so, one of the above mentioned composite response criteria for peripheral arthritis should be used as the primary endpoint. Axial involvement should be assessed as an important secondary endpoint and efficacy on both peripheral and axial arthritis should be separately demonstrated in order to gain a broad indication in PsA. In the rare cases where a predominant axial involvement exists, the guidance as established in the AS Points to Consider should be followed.

2.3.2. Additional claim to prevent structural damage

Several radiological scoring systems are available and it is considered that further evaluation of the various methods is needed. At present, choice of the method should be justified and a priori definition of joints and features to be assessed as well as the minimum relevant change should be established. It is recommended to assess reliability and validity of the chosen method in the specific trial, at least in a subset of patients included in the trial.

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.

2.4. Secondary end points

2.4.1. Axial involvement

Morning stiffness, spinal and nocturnal pain as well as physical function should be measured as secondary end-points in clinical trials in PsA. The ASAS Response Criteria has been used to measure efficacy on the symptoms of AS and could be considered a valid composite measure of efficacy in axial arthritis in PsA. The ASAS response criteria (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 ASAS 40 included the same criteria as ASAS20, with the use of a higher percentage improvement (40%) instead of 20%.

2.4.2. Other secondary endpoints may be the individual components of the composite instruments, other composite criteria not assessed as primary endpoints, as well as individual assessments of the main domains of the disease. Features unique to PsA such as dactylitis and enthesitis might also be assessed. Additional endpoints may be the different percentages of improvement for each composite endpoint not included as primary outcome.

2.5. Skin lesions

From the patient's perspective PsA and psoriasis are 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 recommendations given by the CHMP "Guidance on clinical investigation of medicinal products indicated in the treatment of psoriasis" should be followed. However, when selecting within the available methods it should be beard in mind that assessment instruments designed for psoriasis trials may not be appropriate for PSA trials, since participants are selected for musculoskeletal disease and may have minimal skin disease.

3. STRATEGY AND DESIGN OF CLINICAL TRIALS

3.1 Early Studies in Man

Specific dose response studies should be performed in patients with PsA. There is not certainty that PsA and other arthropathic diseases such as rheumatoid arthritis or ankylosing spondylitis respond in a similar way to the same dosage. Therefore, dose guidance provided by previous studies in other related disorders is of limited value. An appropriate dose finding should be performed in patients with PsA in order to find the posology regimen with the most favourable benefit-risk ratio in this particular disease.

Whenever appropriate depending on the mechanism of action, efforts should be done to find different doses or intervals according to the respective patient characteristics (i.e. severity, inflammation) as well as to define the need for weight adjustment.

The target population may be constituted by PsA patients candidates to DMARDs (i.e. non-responder to NSAIDs) or by candidates to new and biological therapies both as monotherapy (i.e. non-responder to DMARDs) or as an added therapy to conventional systemic treatment (i.e. insufficient response to DMARDs). The choice of the population will depend mainly on the characteristics of the products (i.e. mechanism of action, expected safety profile,).

Placebo controlled parallel group studies are recommended. Several reasons support that placebo use is ethically acceptable in short-term studies (i.e. 12-24 weeks)..

The PsACR and the ACR 20 composite indices are appropriate measures for the exploratory trials and short duration trials (e.g. 12-24 weeks) may be sufficient.

3.2 Therapeutic Confirmatory Studies

Medicinal Products with a claim of improvement of symptoms and physical function:

Conventional treatment of PsA depends on the severity of the arthritis. Standard therapy in mild forms of PsA consists in NSAIDs and can be maintained in all treatment arms, providing therefore a standard treatment to the placebo arm. In more severe forms with polyarticular arthritis, conventional systemic therapies such as methotrexate or sulfasalazin constitute the standard therapy. In these cases, non-responsive patients may be candidates to new and biological therapies or patients may receive placebo or the investigational therapy added to that stable regimen.. Therefore, the benefit/risk assessment of any new product should take into account its possible place in therapeutics.

Study design

Studies should have a randomised, double blind, parallel group design. The appropriate design for those products intended to be used in patients non-responsive to NSAIDs is either a three-arm study where patients receive either the new agent or another established comparator (e.g. methotrexate) or placebo, or a two-arm study comparing the new agent to the established active comparator, seeking to show that the test product is superior.

Efficacy of products claiming improvement in patients non-responsive to conventional DMARDs may be established by means of a placebo controlled add-on trial where all patients receive established standard therapy (e.g.. methotrexate,). Comparison to the available treatment options for these patients (e.g. antiTNF) may be necessary for an appropriate benefit/risk assessment, particularly if the product belongs to a new therapeutic class. An active comparator trial or preferably, a three-arm trial may be useful for this purpose.

Alternatively, active comparator trials in which the new medicinal product is compared to an acceptable treatment option in these patients (e.g. approved biological therapies), with superiority (2-arm) or non-inferiority (3-arm with placebo as internal comparator) hypothesis, may be undertaken.

The concomitant standard therapy should be 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.

Study duration

PsA is a chronic disease and therefore, symptomatic treatment is expected to be maintained on the long term. Therefore, although efficacy may be demonstrated in 12-24 weeks trial, maintenance of the effect in longer trials (e.g. 1 year) should be demonstrated. To establish that a symptom-modifying drug does not have deleterious effects, structural changes should be monitored for at least one year. In addition, the adequate duration of treatment should be addressed and data after stopping therapy should be provided.

Medicinal Products with an additional claim of slowing or prevention of structural damage

Confirmatory trials to demonstrate an effect on prevention of structural damage should be parallel group controlled trials of long duration. The observation period needed is not less than two years, showing sustained effects for the effects after the first year.

Trials should be ideally double blind placebo controlled trials. However, it is acknowledged that such a long duration of a placebo-controlled trial may raise feasibility and ethical concerns.

A suitable design would be a placebo-controlled trial with an add-on design over standard therapy with NSAIDs or methotrexate. Patients with severe disease activity cannot be maintained in a placebo-controlled trial for a long period. Alternative designs may be a superiority trial vs. an active comparator (e.g. methotrexate) or a trial in which 2 years treatment with a new therapy shows superiority over another arm with a delayed start of treatment.

Slowing of radiographic progression may itself not constitute a definite patient benefit and it is a still not accepted surrogate for long term clinical benefit. Although there is indirect evidence that, by favourably modifying the natural history of PsA in terms of structural changes, long-term clinical

benefit will occur, it would be expected that an applicant would provide additional evidence to support this surrogacy. It is recommended that a clinical efficacy co-primary end point is added to the radiological score primary end point.

4. CLINICAL SAFETY EVALUATION

4.1 Specific adverse events to be monitored

In addition to those that may be related to the pharmacological actions of the product (infections, malignancies,..) it is necessary to give some reassurance on the lack of deleterious effect on the affected joints as well as on skin lesions. Monitoring of structural changes during at least one year may provide reasonable information

4.2 Extent of population exposure to assess clinical safety

Complete safety database should be submitted for assessing a new product. When PsA is an additional indication for an already approved product, safety data obtained in trials in other indications can be considered, provided that the dosage regimen is the same and population is expected to behave similarly (e.g. rheumatoid arthritis or ankylosing spondylitis).Considering the need for confirmatory trials for efficacy as well as the rest of studies specific in PsA, it is possible that efficacy trials may provide also controlled safety data.

4.3 Long term safety

The need for specific long term trials to demonstrate efficacy and the effect on structural changes will provide an adequate safety data base, likely to go beyond the minimum requirement of the CHMP/ICH guidance requesting 300-600 patients treated for 6 months or 100 patients treated for 12 months. Although this may depend on the characteristics of the product, in general, safety data from periods longer than one year are recommended

4.4. Development of antibodies

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