European Medicines Agency

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON PSORIATIC ARTHRITIS

Table 1: Organisations that commented on the draft Guideline as released for consultation

Add name followed by link to individual received comment (upon publication by Web Services)

	Name of Organisation or individual	Country
1	EFPIA	
2	Dr Kurt de Vlam, Prof R Westhovens, Dept Rheumatology, University Hospital Leuven	

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 16
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

GENERAL COMMENTS - OVERVIEW
SPECIFIC COMMENTS ON TEXT

INTRODUCTION		
Section, paragraph	**Comments and proposed change (if applicable)**	**Outcome**
Paragraph 3, last sentence	*"Axial forms might be settled in every point of this spectrum."* May be clearer as: *"Axial forms* ***may also range from mild to severe and disabling."***	Accepted
Paragraph 5, first sentence	*"Skin involvement may vary from mild to a severe disease, which activity is commonly not mirrored by arthritis activity"* We suggest the following rewording: *"Skin involvement may vary from mild to a severe disease* ***and skin activity is not*** *necessarily mirrored by arthritis activity"*	Accepted

1. PATIENTS CHARACTERISTICS AND SELECTION OF PATIENTS		
Section, paragraph	**Comment and proposed change (if applicable)**	**Outcome**
Paragraph 2, last sentence	*"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."* We suggest the addition of 'serologic' as indicated and suggest a change to wording to be clearer. *"There are no **serologic** tests to confirm the diagnosis, but X-rays can **aid** diagnosis and show the extent and location of joint damage".*	Accepted
Paragraph 4, last sentence	*"Around 5% have exclusively spinal involvement; while between 20-50% have involvement of both the spine and peripheral joints, being peripheral the predominant pattern."* We suggest the following to be clearer: "*Around 5% have exclusively spinal involvement; while between 20-50% have involvement of both the spine and peripheral joints, **usually with more prominent peripheral joint clinical features."***	Accepted
Paragraph 5, first sentence	"*The oligoarticular peripheral PsA is, in almost all cases, locally treated."* We consider that this statement is not necessarily accurate. Oligoarticular peripheral PsA may be treated systemically, especially if major weight bearing joints are affected or local therapy is for other reasons not an option.	It is agreed that in some cases mono/oligo arhritis may be resistant and systemic treatment is then considered, but inclusion in trials may not be appropriate as ACR changes will be less relevant. Almost is changed into most
Paragraph 6	*"Therefore, three clinical features of PsA are commonly found and will be covered in this guidance:"* We suggest use of **'pattern'** rather than 'features' to be consistent within the document. *"Therefore, three clinical **patterns** of PsA are commonly found and will be covered by this guidance"* **1.** *"A pure peripheral polyarticular joint PsA disease similar to rheumatoid arthritis".* If polyarticular PsA is truly similar to RA, then why is independent dose ranging required in section 3.1. We would appreciate consideration of this.	Accepted

1. PATIENTS CHARACTERISTICS AND SELECTION OF PATIENTS		
Section, paragraph	**Comment and proposed change (if applicable)**	**Outcome**
Paragraph 5 of page 4/10	This paragraph reads as follows: *"Patients between 16 and 18 years and those whose symptoms started prior to this should be not excluded from clinical trials".* It is not clear what "this" refers to in this sentence. We believe that the decision to include of patients between 16 and 18 years of age should be made on case by case basis contingent upon several factors such as quantity of kinetic and safety data available, etc and therefore it may be prudent to qualify the statement made in the guideline.	Before the age of 16, patients will be diagnosed of juvenile arthritis while diagnosis of PsA may be done in patients older than 16. The intention is to encourage the inclusion of patients between 16-18 unless there is medical reason to not doing so (not because of the legal age) "*Patients between 16 and 18 years should be not excluded from clinical trials".*
Paragraph 6 of page 4/10, last sentence and paragraph 7	*"Patients should have an active psoriatic arthritis as measured by the number of swollen and tender/painful joints (ACR joint count)."* *…* *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 the same way as severity of disease activity is given a minimal value for inclusion, the ACR joint count should be quantified for inclusion: e.g., Patients should have an active psoriatic arthritis as measured by a number of swollen and tender/painful joints (ACR joint count) > 3. It would be helpful to clarify the expectations regarding the use of the BASDAI. We interpret this section to mean that the BASDAI is required to assess disease activity for all clinical forms/manifestations of PsA, whether or not the psoriatic arthritis presentation is predominantly in the peripheral joints (e.g. rheumatoid arthritis-like presentation) or in the axial skeleton (e.g. spondylitis presentation).	*There is no need to establish as per guidance a minimum number of affected joints.* *Sentence about BASDAI activity has been moved to the previous paragraph.*

1. PATIENTS CHARACTERISTICS AND SELECTION OF PATIENTS		
Section, paragraph	**Comment and proposed change (if applicable)**	**Outcome**
Last paragraph of page 4/10, first sentence **DMARD non-responders** (Last paragraph of page 4/10, last sentence)	*"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."* We suggest the change as indicated below because if the treatment is adequate then why would the disease be persistent? Reference should also be made to the *intensity* of the damage/disability as some patients with the *"arthritis mutilans"*-type of PsA are usually included in PsA trials: *"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* ***or progressing joint damage/disability (arthritis mutilans****) despite a~~n~~ normally adequate treatment*." *"….The lack of response (to DMARDs)should be well documented according to generally accepted criteria (e.g. standard dosage, 6 months treatment….)"* The requirement of at least 6 months of DMARD treatment (to address claim in patients "not responsive to DMARDs") prior to enrolling to the study with a new drug seems excessive. There is already data from infliximab, etanercept and adalimumab indicating that new biologic treatments slow progression of structural damage in PsA over as short time as 6 months. Requiring that the patients have at least 6 months of DMARDs to call them "DMARD non responders" may put some of the patients into a risk of irreversible radiographic progression.	Accepted Several clinical practice guidelines recommend 6 months DMARD therapy (2 months at full doses) before switching to anti TNF. However, it is agreed that it is not to the NfG to fix that limit and it is deleted maintaining the reference to "generally accepted criteria".

2. METHOD TO ASSESS EFFICACY		
Section, paragraph	**Comments and proposed change (if applicable)**	**Outcome**
First sentence	*"In recent years, efforts have been done in order to define…"* We suggest the following re-wording: *"In recent years, efforts have been made ~~in order~~ to define…*	Accepted

2. METHOD TO ASSESS EFFICACY		
Section, paragraph	**Comments and proposed change (if applicable)**	**Outcome**
2.1 Main domains to be assessed in PsA and instruments to be used in each domain	• *"Assessment of PsA disease activity is commonly made by the American College of Rheumatology joint count…..Dactylitis, whenever present, should be counted as one active joint"* Since dactylitis typically involves the distal interphalangeal, proximal interphalangeal and metacarpophalangeal (or metatarsophalangeal) joints of a digit, in addition to flexor and or extensor tendons, we wonder why would it only be counted as a single joint?	This is considered a well-established routine the usually accepted way to consider dactylitis. Not modified
Measure of function and disability	• **"***Measures of activity developed for AS.... Might be used to assess the effect on PsA axial activity"* We do not consider that the Bath Ankylosing Spondylitis Functional Index (BASFI) is a measure of disease activity. We do not believe that the draft guideline gives guidance on how to assess disability to get a prevention of disability claim This section only discusses the assessment of physical function using the HAQ in clinical trials).	Agreed. Reference to BASFI deleted
Measure of Structural Joint Damage **PARS score (Psoriasis Arthritis Ratingen score)**	First paragraph of page 6/10: **"***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."* This phenomenon is not a common outcome of erosive disease. Could there be a more common outcome given as an example? The last sentence of the second paragraph of page 6/10: *"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."* Should read *"All joints are scored separately for destruction (on a 0–5 scale) and proliferation (on a 0–4 scale), which can be summ**ed*** ~~*up*~~ *to give the total score or measured separately."*	Accepted
2.2 Other domains and instruments to	"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*	The idea is to assess the effect of the therapy on skin lesions in case they are present in order to gather information on the possible improvement

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be assessed	*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."* According to **§2.2. Other domains and instruments to be assessed**, active psoriasis is not mandatory for entry into a PsA study. This might lead to the situation that a study fails to show improvement in skin lesions due to lack of severity of skin lesions in the patient population. It is clearly stated in **§2.5. Skin Lesions** that "the impact of any treatment aimed for PsA should include a skin assessment." Would in this case marketing authorisation be granted although only an improvement of joints was demonstrated? <u>Enthesitis</u> For clarification we suggest: MASES (Maastricht Ankylosing Spondylitis Enthesis Score). There are other abbreviations/acronyms in the text that are not defined. It may be helpful to do so. <u>Quality of Life</u> We would appreciate more clarification in this section on how the effects of arthritis and psoriasis on QoL can be reliably differentiated.	or worsening on what will be a frequent concomitant condition. This is considered a relevant and useful information for physicians who manage patients with PsA and not intended to extend the indication. The sentence has been reworded to make it clearer. Accepted
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"* We suggest to reword as follows: *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* ***should be used*** *as efficacy endpoints,*	Reworded to "acceptable end points"

2. METHOD TO ASSESS EFFICACY		
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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)"* We suggest to reword as follows: *"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)* ***response criteria"*** ***"****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.* *…* *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."* It should be clearly stated that this assessment of **disease activity** only refers to the joints according to the definition of disease activity given in **§2.1. Main domains to be assessed in PsA and instruments to be used in each domain** (page 5/10). Furthermore, **disease activity** has been defined in this §2.1. as involving both peripheral and axial joints, although efficacy should be demonstrated separately for axial and peripheral involvement as stated in the second paragraph page 4/10 (but there are secondary end points specific to the axial involvement). Therefore, we suggest to replace *"disease activity*" by "*disease activity* ***at the joint level (peripheral and axial)****"*	Accepted

2. METHOD TO ASSESS EFFICACY		
Section, paragraph	**Comments and proposed change (if applicable)**	**Outcome**
	PsARC definition PsARC was defined differently in the sulfasalazine paper quoted by CHMP than presented in the draft guidelines. According to this paper (Clegg et all, Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis. Arthritis &Rheumatism 1996;Vol 39;no12:2013-20) treatment response in PsA was defined as: *"improvement in at least 2 out of 4 measures (patient self assessment, physician assessment, joint pain/tenderness score, joint swelling score) one of which must be joint pain/tenderness score or joint swelling score and no worsening in any of the 4 measures"* improvement in patient self-assessment and physician assessment were defined as "*improvement=decrease by 1 category on Likert scale"* and "*worsening=increase by 1 category on Likert scale"* joint pain/tenderness and joint swelling improvement were defined as "*decrease by =>30% in score and worsening by increase by =>30% in score."* Joint score does not equal joint count. Joint score represents joints scored for severity of pain or swelling on a scale from 0 to 3 and joint count represents number of painful or swollen joints. In summary the guidelines use the modified version of PsARC, which has not consistently being used in clinical trials in PsA (CHMP guidelines page 7). **Modified ACR joint count** The draft Guideline recommends counting dactylitis as one active joint. This may be problematic for ACR 20, 50, 70 analyses, when we have to demonstrate improvement counting separately joints constituting ACR 66/68 set. *"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."* We suggest that a small worsening may be acceptable in some parameters if other parameters are improved. In the draft *Guideline on Clinical Investigation of Medicinal Products for the Treatment of Juvenile Idiopathic Arthritis,*	Agreed

2. METHOD TO ASSESS EFFICACY		
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	CPMP/EWP/422/04, a worsening in one of the criteria is allowed. We suggest something similar to the above guideline be added or: *"One of the criteria improved has to be tenderness joint count (TJC) or swollen joint counts (SJC) and any worsening in any of the criteria should be* ***justified"***	It is not justified to modify the variable and accepting efficacy in case of worsening of any of the capital and related symptoms.
2.4 Secondary end points	The second sentence of 2.4. 2 reads as follows: "*Features unique to PsA such as dactylitis and enthesitis might also be assessed."* These features are shared by reactive arthritis/Reiter's syndrome and a few less common spondyloarthritides, i.e., they are not unique to psoriatic arthritis. We suggest to modify the sentence as follows::" *Features* ~~***unique to PsA***~~ *such as dactylitis and enthesitis might also be assessed".*	Accepted

3. STRATEGY AND DESIGN OF CLINICAL TRIALS		
Section, paragraph	**Comments and proposed change (if applicable)**	**Outcome**
3.1 Early Studies in Man	First sentence *"...specific dose response studies should be performed in patients with PsA."* We believe that where it may be true for some compounds that dose responses differ between RA and PsA, this has generally not been the case. We consider that the requirement for independent dose response testing is burdensome.	It is agreed that in some cases it will be acceptable to base the dose choice on previous dose response studies in other related indications. Sentence is reworded to :"Specific dose response studies may be performed or extrapolation of previous dose finding should be justified for patients with PsA"

3. STRATEGY AND DESIGN OF CLINICAL TRIALS		
Section, paragraph	**Comments and proposed change (if applicable)**	**Outcome**
3.2 Therapeutic Confirmatory Studies **page 9 paragraph 1**	Only SSZ has some minor effect on morning stiffness in PSA. Methotrexate has never been studied in an appropriate way in PSA. The add-on strategy will only evaluate the combination therapy and not the medicinal product itself because additive or synergistic effects cannot be excluded. So a true benefit/risk assessment of the product itself is not possible in this setting. Moreover there are no ethical issues about a short-term course of placebo in these patients. In general an "add on" trial should be avoided. Certainly when not all patients are taking a second drug.. In the latter case in reality 4 treatment groups are compared but study design and power calculation was designed for 2 treatment groups. A two arm study where patients receive either the new agent or an active comparator is subject to a number of limitations: using methotrexate as an active comparator seems logical since it is common daily practice but there are no validated data about efficacy of methotrexate in PsA to date Using TNF blockade as a active comparator and claiming superiority at short term makes it almost impossible for new drugs to be evaluated, especially chemical compounds.	MTX, as it happens frequently with old products has limited evidences. However, it is considered a standard therapy and it is a well accepted comparator product. In spite of the mentioned limitations, add- on therapy may well be a possible treatment to assess in patients with insufficient response to conventional DMARDs. In this situation patients may be candidates to add-on treatment to standard therapy or to be changed to a new biological therapy. In both situations, a three-arm study with non-inferiority hypothesis may be desirable. Alternatively, two-arm studies vs. standard therapy (e.g. approved biological therapies added to conventional DMARDs or not) might be acceptable.
Study Duration Second paragraph, second and third sentence	*Comparison to the available treatment options for these patients (e.g. anti-TNF) 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."* A three-arm trial versus anti-TNF treatments will dramatically complicate the conduct of such comparative trials for new therapeutic class products: blinding, potential long-term safety issues, exclusion of patients who could not be treated with TNF inhibitors because of underlying disease, but who could benefit of a new therapeutic agent with less safety concerns... Furthermore, it will significantly increase the number of patients to be included in the trial and the costs of these trials. We also believe that three arm studies should not require explicit comparisons between the new agent and the active comparator.	A three-arm trial is the preferred design but, in case it is not feasible due to patients or product characteristics, comparison may be obtained from two arm designs.

3. STRATEGY AND DESIGN OF CLINICAL TRIALS		
Section, paragraph	**Comments and proposed change (if applicable)**	**Outcome**
	We feel that the requirement to monitor structural changes for one year for a symptom-modifying drug is burdensome and we respectfully request that further consideration is given to this requirement. The draft guideline does not provide clear guidance on how much data is required to get an improvement of symptoms and physical function claim. The second sentence of this paragraph states that *'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 damages should be monitored for at least 1 year'.* From that statement, it is assumed that 24 weeks would be sufficient to get an improvement of symptoms and physical function claim. It is not clear why the guideline suggests that it is necessary to show that a symptom modifying drug is still working after one year. Dougado's data show that 6-week data is predictive of efficacy after a year (in ankylosing spondylitis), that the dropout rate from placebo treatment arms makes a placebo-controlled trial difficult to interpret, and it is known that patients stop taking symptom modifying medications if they do not work. Similarly the need for long-term x-ray data is not clear. In most instances, the ankylosing arthritis and Psoriatic Arthritis indications will be follow-on indications to osteoarthritis (OA) and rheumatoid arthritis and there will be data on 6-month efficacy and radiological progression in OA per the OA guidance. The need for same data in <u>each additional indication</u> may act as a disincentive to study additional patient populations, to the detriment of those patients. The last sentence of this paragraph also states that" in addition, the adequate duration of treatment should be addressed and data after stopping therapy should be provided". It would be helpful to clarify what types of data are expected to be collected	Accepted, requirement of one year monitoring has been deleted The demonstration of the maintenance of the effect over time is highly relevant. This guideline does not state a specific study design to demonstrate so, therefore, considerations given with regard to the dropout rate from placebo groups, etc., do not preclude the need for such data. Data after stopping treatment are relevant for example to assess rebound phenomenon