European Medicines Agency

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON ANKYLOSING SPONDYLITIS (CPMP/EWP/4891/03)

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

	Name of Organisation or individual	Country
1	EFPIA	
2	EULAR/ASAS	

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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW		
SPECIFIC COMMENTS ON TEXT		
1 INTRODUCTION		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
Paragraph 4 p. 3/13	We suggest the following addition: *"There are no solid prognostic parameters besides early radiographic progression, **but male sex, early age of onset, and early development of clinical hip involvement are associated with aggressive disease."***	*Accepted*
4 . PATIENTS CHARACTERISTICS AND SELECTION OF PATIENTS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Paragraph 2 Last line p. 4/13	Please change "*sacroiliac changes*" into "***sacroiliitis"***	*Accepted*
Paragraph 3 p.5/13	ASAS recommends the use of the axial SpA criteria which include MRI to define sacroiliitis and which also include all patients fulfilling the modified New York criteria. Depending on the indication for treatment, also criteria for peripheral SpA and/or for the entire group of SpA can be applied. Thus, MRI of the SI joints has become an important new additional tool for classifying/diagnosing SpA patients, especially those presenting with predominantly axial symptoms.	*It is deemed too premature to firmly consider the proposal to include patients not fulfilling the New York classification criteria but it is acknowledge that this might change in the future. Some references to these early stage forms of axial SpA have been included in the guideline. Some clarifications have been included to introduce these changes in the state of the art.*
Last paragraph p. 5/13	***"****The consideration of a patient as non-responder to NSAIDs requires documentation of the lack of response with appropriate doses and treatment durations."* It is difficult to standardise how sponsors and investigators are to document prior treatment with NSAIDs due to different doses, dosing regimens, and the lack of comparability among the many-marketed NSAID products. Therefore, the Guideline should acknowledge that sponsors are most likely to be able to document prior treatment with Drug A for Duration B and that a patient did not reach Criteria C for improvement.	*Not implemented. There are different generally accepted criteria to define a patient as insufficient responder to NSAIDs that should be followed* (e.g. *Consensus statement for the use of anti TNF in AS. Ann Rheum Dis 2006;65;316-320;m . BSR 2004: Failure of conventional treatment with two or more NSAIDs, each taken sequentially at maximum tolerated/recommended dosage for 4 weeks).*

Last paragraph. p. 5/13	A requirement of active disease for 3 months to test products in patients not controlled with NSAIDs is a tough requirement to fulfil in clinical practice. Especially with the availability of TNF-blockers on the market it will be very difficult and probably not ethical to withhold this treatment to fulfil this requirement to participate in a trial.	*Not accepted. NSAIDs have demonstrated to be very effective in treating sign and symptoms of AS. Contrary to antiTNF, these drugs have also demonstrated to prevent structural damage. Therefore, the ethical concern to delay the start of antiTNF therapy and make a try with NSAIDs is not supported any longer. Further, the requirement does not imply that patients should stay for 3 months with specific NSAIDs if there is not response. In fact, different NSAIDs can be tested sequentially during this period before concluding on the lack of response. It has been demonstrated that a patient can respond differentially to different NSAIDs and that lack of response to one NSAID does not necessarily translate into lack of response to other NSAIDs.* *Ref. Clinical and MRI findings in ankylosing spondylitis patients eligible for anti-TNF therapy. Response to short-term etoricoxib therapy. Jarrett SJ et al. University of Leeds, United Kingdom. Ann Rheum Dis. 2008 Oct 24*
Paragraph 8 p. 5/13	***"****The absence of HLA-B27 should not be an exclusion criterion."* This sentence should be reworded to eliminate the double negative so that it reads, ***"Patients who are HLA-B27 negative should not be routinely excluded from study participation; such patients may be included."*** Routine exclusion of HLA-B27 negative patients would result in the elimination of approximately 10-20% of AS patients who might otherwise benefit from intervention.	*Accepted: "Patients who are HLA-B27 negative should not be routinely excluded from study participation"*
Paragraph 8 p. 5/13	*"Patients between 16 and 18 years and those whose symptoms started prior to <u>this</u> should be not excluded from clinical trials."* Please clarify what "this" refers to in this sentence. The inclusion of patients between 16 and 18 years old should be handled on a case-by-case basis, contingent upon whether the compound to be studied is a new entity, the quantity of PK and safety data available, and whether a favourable benefit/risk ratio has been determined for adults	*Age of diagnosis of AS is > 16 years. So, we encourage the inclusion of these patients in clinical trials.* *This sentence now reads as follow: "Patient between 16 and 18 years should be not excluded from clinical trials".*
5. METHODS TO ASSESS EFFICACY		
Line no. + para no.	**Comment and Rationale**	**Outcome**
5.2 Other domains and instruments to be assessed	***"****Although levels of C reactive protein (CRP) or the erythrocyte sedimentation rate (ESR) may be related to the activity of the disease and its prognosis, there are no data to support them as useful surrogate variables to assess efficacy in AS."*	***Not implemented.*** *The inclusion of CRP in the ASAS score is not supported since biochemical parameters are quite sensitive to antiTNF therapies. So, it might well happen that an observed benefit in symptoms/physical function by means of the proposed criteria (ASAS 5/6) would mainly rely in this*

Acute phase reactants	We agree that CRP or ESR should not be used alone to assess the efficacy in AS. Rather, CRP or ESR in conjunction with other AS-specific endpoints (like ASAS and BASDAI) adds to the assessment of a product's effectiveness in treating AS. The use of ESR or CRP is advocated by the ASAS Working Group to be included in the ASAS 5/6 criteria to give a more complete assessment of efficacy.	*parameters with no changes in the other components, which are considered more relevant from a clinical point of view.*
	Throughout the document the Visual Analogue Scale (VAS) is proposed. ASAS agrees that the VAS can be used, however, we have a preference for use of the Numerical Rating Scale (NRS).	*The proposal seems reasonable.* *Some changes are proposed for the draft guideline*
5.1. Main domains to be assessed	The following spinal mobility measures are included in the ASAS core set: occiput-to-wall, cervical rotation, lateral spinal flexion (or BASMI), modified Schober, and chest expansion. If the BASMI is used, either the BASMI10 or the BASMI linear should be used.	*The proposal is acceptable.* *Some changes are proposed for the draft guideline*
5.3 Main efficacy end points	Sub-section 2.3 contains two headers to differentiate between products that prevent structural damage (chronic improvement) and products intended to improve symptoms/function (acute improvement). However, the text is confusing as it mixes these concepts, particularly in Section 2.3.1 where it mentions the ASAS 40 and ASAS 5/6 under the symptoms/physical function header (acute improvement) but describes them as providing evidence of disease modification (chronic improvement). We suggest that this section clearly differentiate between the two claims. The second bullet in 2.3.1 suggests that *"Pain assessment (is) represented by the average of total and nocturnal pain scores…."* Pain assessment in ASAS 20 need not be an average of the 2 scores. It can be just 1 of them. Finally, none of the endpoints seem to be validated for novel therapies (non-NSAID like) and we feel are all highly speculative. We suggest that there should therefore be more flexibility towards taking endpoints which showed meaningful change in Phase II studies and allowing their use in Phase III. Section 3.1 should also make reference to this	*Not implemented.* *ASAS, whatever 20, 40 or 5/6, is a measure of changes in symptoms and physical function. A higher magnitude of change, as demonstrated by antiTNF, does not necessarily mean that they also prevent structural damage.* *Accepted. Both total and noctural pain provide relevant information and so it is considered that is better to analyse both scores. The wording will read: "Pain assessment represented by either total or nocturnal pain scores, both measured on a VAS scale with extremes labelled "no pain" and "most severe pain."* *Not accepted. Endpoints for phase III trials should be defined a priori and be selected considering what is relevant for the patient and not simply to confirm what has been seen in phase II trials, whatever its clinical relevance.*

5.4.4.Other secondary endpoints	The ASAS70 are not proposed by ASAS and the description of the content of these criteria is not clear	***Accepted.***
5.3.2 Additional claim to prevent structural damage	We suggest that for prevention of structural damage MRI should be considered as a possibility. Plain radiographs of the axial skeleton as a imaging modality has not been as well established as with peripheral joints.	*At present MRI is not accepted as a surrogate for structural damage, as it rather relates to inflammation.*
5.4.3 Global patient assessment	Text appears to be missing under this header.	*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.*

6. STRATEGY AND DESIGN OF CLINICAL TRIALS

Line no. + para no.	Comment and Rationale	Outcome
6.2 Therapeutic Confirmatory Studies		
Medicinal Products with a claim of improvement of symptoms and physical function P9/13	Second sentence of first paragraph reading: *"Therefore, new products belonging to therapeutic classes other than NSAIDs are expected to be combined with this standard therapy…"* it is not clear what "standard therapy" refers to in this sentence. We also suggest to add "***or who have intolerance, adverse reactions, or toxicity due to chronic NSAID use."*** after *"…in patients with insufficient control of their symptoms"*. Not every patient can take 3 months or more of NSAIDs at required doses. It is not clear what the recommendation should be in case of unacceptable risks associated with the use of NSAIDs either - For example, renal insufficiency, congestive heart failure, liver failure, difficult-to-control hypertension, peptic ulcer disease - aspirin allergy	*Not implemented. This may lead to inclusion of mainly NSAID refractory patients.*
p. 10/13	Second paragraph under "study design" reading: "*Products belonging to new therapeutic classes may need also comparison against anti TNF treatments in order to properly assess the benefit risk ratio of the new*	*A three-arm trial is recommended. The choice of comparators will depend on the patient population.*

	product. A three-arm trial is recommended." A three-arm trial versus anti TNF treatments is somewhat arbitrary and will dramatically complicate the conduct of such comparative trials for new therapeutic class products, which are not "injectable". Blinding, potential long-term safety issues and other factors of the study may be very difficult under these circumstances, and such a comparator may or may not be appropriate depending on the index drug. Furthermore, it will significantly increase the number of patients to be included in the trial and the costs of these trials. As with rheumatoid arthritis, not all patients warrant treatment with an anti-TNF and there is no consensus regarding the characteristics that define the appropriate recipient. Furthermore there is no conclusion regarding indications for reductions and cessation of therapy. We suggest that two-year placebo controlled trials are not practical and non interpretable either (differential drop out rate will make an assessment of efficacy impossible). Randomised withdrawal designs should be considered for demonstrating durability of effect. We question whether an active comparator is needed and whether this translates into a higher standard to demonstrate efficacy of a new product than is currently required. In addition, the durability of effect can be a function of a number of variables, such as the half-life and/or the amount of tissue penetration (among other factors). For example, Humira has a half-life of ~14 days and is likely to have a longer duration of effect after withdrawal compared to Enbrel (half-life is 4.25 days), but this is may not be the case for a small molecule with a shorter half life. In addition, the extent of tissue penetration can vary even among drugs with the same half-life and this can affect durability of effect. Therefore, we recommend that the last sentence in this comment state, "Randomised withdrawal designs <u>against placebo</u> should be considered for demonstrating durability of effect."	*Accepted. The new wording recommends randomised withdrawal trials against placebo for demonstrating durability of effect and to collect data after stopping therapy.*

Main end points and study duration	*"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."* Recently, Enbrel has been approved with a demonstration of the effect for a 6 month period. Therefore, we suggest replacing **"e.g. 1 year"** by: ***"6 months to 1 year"***. *"In addition, the adequate duration of treatment should be addressed and data after stopping therapy should be provided."* Please clarify what types of data are being referred to in this section. Also consider that once a subject discontinues study medication and completes participation in a study, the sponsor cannot dictate how subjects are managed. Subjects may receive interventions that have the potential to alter the course of disease (e.g. efficacy) and cause adverse events (e.g. safety), thereby confounding the analysis during the post-study period. It is unclear what benefit would derive from the collection of such uncontrolled data.	*Not accepted. The assessment of the maintenance of the effect requires at least 1 year.*
<u>Medicinal Products with a claim of slowing or prevention of structural damage</u>	*"From a therapeutic point of view, patients with mild disease activity may probably…"* We suggest that 'may probably' would be better expressed as *'might'* and thus the sentence would read as follows: *"From a therapeutic point of view, patients with mild disease activity* ***might…"*** *"Patients with severe disease activity cannot be maintained in a placebo-controlled trial for a long period…"* However the net effect is that you would need to compare subjects who have been on therapy for about 2 years, but were randomised to active treatment after 3 to 9 (12?) months of placebo period. This is a problem because very few experts would allow the placebo period to last for more than 6 months. For many, 3 months is enough. So if you then have active treatment starting no later than 3-6 months into trial, everybody will be on treatment for at least 18-24 months for the structural damage data. It is then highly unlikely you can compare treatment groups against each other in the trial--they will all have had fairly similar an and prolonged active drug treatment	*Accepted* *Slightly modified the previous text: "Differences between groups may be sustained at the end of the 2 years period reflecting the difference in the start of treatment".*
Paragraph 5, 1st sentence p. 10/13	*"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."*	*Accepted*

	We suggest to replace by: *Slowing of radiographic progression may itself not constitute a definite patient benefit and it is **not accepted as a surrogate** for long term clinical benefit.*	
7. CLINICAL SAFETY EVALUATION		
Line no. + para no.	**Comment and Rationale**	**Outcome**
7.1 Specific adverse events to be monitored	*"In addition to those that may be related to the pharmacological actions of the product …. it is necessary to give some reassurance on the lack of deleterious effect on the affected joints.…may provide reasonable information"* It is unclear what the last 2 lines mean. It seems to overemphasize the joints. It is also unlikely with current, preferred, mSASSS methodology, that structural change over 1 year will yield reasonable information, safety or efficacy.	*Accepted*