30 June 2015

Submission of comments on 'Concept paper on clinical investigation of medicinal products for the treatment of Axial Spondyloarthritis’ - EMA/CHMP/80184/2015

Comments from:

| Name of organisation or individual |
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*Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.*

*When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).*

1. General comments

| Stakeholder number  *(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)  *(To be completed by the Agency)* |
| --- | --- | --- |
|  | We very much appreciate the EMA/RIWPs efforts in updating the AS guideline and it is agreed that clinical practice has evolved since publication of the 2009 CHMP “Guideline on Clinical Investigation of Medicinal Products for the Treatment of Ankylosing Spondylitis.” Acknowledgement that patients with axial spondyloarthritis (axSpA) who do not fulfil the modified New York (mNY) criteria of ankylosing spondylitis (AS) can present with disease activity and functional impairment similar to those observed in patients with AS is an important advancement in patient care and warrants appropriate consideration in the revised CHMP guideline.  We consider that the following key topics should be addressed in the future guideline and more details are provided in the specific comments section:   1. **Classification of axSpA**   It is appropriate to consider non-radiographic axial SpA (nr-axSpA) and AS (radiographic axSpA) as part of a common disease spectrum (axSpA), rather than as 2 distinct entities, and clinical investigation guidelines should reflect this situation in terms of potential clinical trial designs, whilst allowing flexibility in development approaches.  Based on considerations of selectively identifying patients fulfilling the ASAS classification criteria who have an inflammatory pathophysiology, recent nr-axSpA regulatory approvals in the EU have indicated patients with severe active nr-axSpA with objective signs of inflammation by elevated CRP and/or MRI. The revised guideline could acknowledge the potential for evolution of classification guidelines and/or identification of other prognostic biomarkers that may have utility in clinical practice and hence patient selection. The revised guideline should also provide clinical development guidance for a broad population in terms of disease severity.   1. **Epidemiology of axSpA**   As this EMA guideline is for clinical investigation for the whole spectrum of axial SpA, including nr-axSpA and AS, it would be appropriate to include prevalence data for axial SpA and also address the evolution towards a gender equilibrium in the prevalence of axSpA given improved diagnosis over the years.   1. **Treatment goals in terms of prevention of disease progression**   Treatment in an early phase of the axSpA disease has the potential to slow or inhibit osteodestructive and osteoproliferative changes characteristic of AS, which are likely irreversible in established AS and which may contribute to disability. However, to date, unlike rheumatoid arthritis and psoriatic arthritis, recent treatment advances (eg TNF inhibitors) have not demonstrated robust efficacy in randomised controlled clinical trials in terms of inhibition of structural damage (which in axSpA consists of both osteodestructive and osteoprofilerative changes). As such, existing treatment options in patients with an inadequate response to NSAIDs focus on improvement of signs and symptoms and improvement of physical function. This should be considered in the revised guideline in terms of required endpoint selection for confirmatory clinical trials i.e. efficacy in terms of signs and symptoms and/or improvements of physical functions are appropriate treatment goals, whilst prevention of structural progression remains an aspirational outcome, which, if demonstrated, should be allowed in the label but should not be a condition for approval.   1. **Prognosis should be defined more broadly**   Currently the factors mentioned that influence prognosis are only those associated with radiographic progression. Prognosis can pertain to either radiographic progression and/or progression of symptoms, disability, and survival and this should be reflected in the guideline.   1. **Extra-articular manifestations represent important treatment goals**   Given the prevalence of well-known extra-articular manifestations such as uveitis, inflammatory bowel disease and psoriasis, which have consequences for the therapeutic choices, the future guideline should provide optionality to seek a claim in the prevention of such manifestations. However, this should not be a mandatory requirement for registration. Documentation of history and new occurrences/flares of these manifestations should be recorded.   1. **Guidance on requirements for withdrawal/discontinuation studies**   Randomized withdrawal studies that address the possibility of discontinuing treatment after sufficient improvement have not been required for approval of compounds for the treatment of AS. As such, this should also not be a prerequisite for approval of a new medicinal product for axial SpA.   1. **Evidence required for approval of novel mechanisms of action**   An investigational product, for which there is little to no precedence for a related indication, may require more data versus an established product where the possibility may exist to extrapolate from pre-existing data.  The guideline should provide guidance where 2 randomised controlled trials are required versus a single well designed randomised controlled trial. For instance, for a product approved in a related indication (eg PsA, RA), where there is therefore supporting safety data, a single well-controlled study with compelling data may suffice. |  |

1. Specific comments on text

| Line number(s) of the relevant text  *(e.g. Lines 20-23)* | Stakeholder number  *(To be completed by the Agency)* | Comment and rationale; proposed changes  *(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome  *(To be completed by the Agency)* |
| --- | --- | --- | --- |
| Line 4-5 |  | Comment: It is not clear from this document if the current AS guideline from 2009 will be wholly rewritten taking into account the broader definition of axial SpA, with and without definite radiographic sacroiliitis or will nr-axSpA be added as an addition to the existing AS text from 2009.  Proposed change: Change “Guideline on Clinical Investigation Medical Products for the Treatment of Ankylosing Spondylitis” to the Treatment of Axial Spondyloarhritis as a new guideline vs updating the current text to include nr-axSpA. |  |
| Line 34 |  | Comment: The ASAS criteria for axial SpA do not define a newly identified group of patients but rather broaden the scope compared to the modified New York (mNY) criteria for AS to include patients who in clinical practice have the same signs and symptoms as AS patients but simply don’t have the radiographic changes required by the mNY criteria. Such patients were often diagnosed as having “undifferentiated spondyloarthritis (uSpA)”. Similar to other rheumatic diseases such as undifferentiated arthritis or undifferentiated connective tissue disease, rheumatologists prefer to now better and more precisely characterize patients.  Proposed change (if any): we would propose to modify the text to state: “In 2009 ASAS (Assessment in SpondyloArthritis International Society) proposed criteria defining the entity of axial spondyloarthritis (axial SpA) which includes a broader set of patients than the 1984 mNY criteria for AS.” |  |
| Line 36 |  | Comment: The term used in the concept paper “without radiological findings” could suggest that nr-axSpA must not show changes even on MRI. This is incorrect.  Proposed change (if any): Change “without radiological findings” to “without radiological findings fulfilling the mNY criteria ” |  |
| Line 37 |  | Comment: As defined by the scientific community, the official term is “non-radiographic axial spondyloarthritis” and the respective abbreviation is “nr-axSpA” (and not “non-radiological axial spondyloarthritis (nr-AxSpa)” as currently stated).  Proposed change (if any): change to “non-radiographic axial spondyloarthritis (nr-axSpA)” |  |
| Line 38 |  | Comment: the guideline currently describes a prevalence of 0.1%-0.2% for AS in Western Europe.  According to published literature the AS prevalence in Northern Europe is around 0.12-0.15% (Haglund et al. Ann Rheum Dis 2011;70(6):943–8.; Geirsson et al. Clin Exp Rheumatol 2010;28(3):333–40; Kaipiainen-Seppanen O et al. J Rheumatol 1997;24(3):496–9) with the exception of Norway where the AS prevalence is higher with a prevalence of 1.1-1.4% (Gran T. et al. Ann Rheum Dis 1985;44;359-67).  In representative Western European countries the AS prevalence is 0.31% in France (Costantino et al. Ann Rheum Dis. 2015 Apr;74(4):689-93.) and 0.55% in Germany (Braun J et al. Arthritis Rheum 2005;52:4049-50).  In addition, the following prevalence data have been published for some Southern European countries: around 0.1% for Greece (Kassimos et al. Clin Rheumatol. 2014 Sep;33(9):1303-6.) and 0.37% in Italy (De Angelis R, Scand J Rheumatol [Research Support, Non-US Gov't].  2007;36(1):14–21.).  Proposed change (if any): change AS prevalence to at least up to 0.5% for Western Europe. |  |
| Additional information proposed for line 38 |  | Comment: As this EMA guideline is for clinical investigation for the whole spectrum of axial SpA, including nr-axSpA and AS, it would be appropriate to include prevalence data for axial SpA. There are at least 2 published studies providing prevalence data on nr-axSpA (2 in the US and 2 in Europe):   * The French GAZEL cohort provided an overall prevalence estimate of SpA of 0.43%, of which 75% were patients who fulfilled the ASAS axial SpA criteria. Therefore, the prevalence of axial SpA is approximately 0.32% in this French population. (Costantino F, et al. Ann Rheum Dis 2015;74:689–693) * In a Norwegian study, the total prevalence of undiagnosed axial SpA was estimated to be 0.13%. The background prevalence of AS in this region was 0.4%, which combined with undiagnosed axial SpA gives a total prevalence of axial SpA in this population of 0.53% (an increase of ~20%). Bakland et al. *Arthritis Care Res. (Hoboken)* 65, 448–453 (2013)).   Proposed change: Although prevalence data specifically for nr-axSpA are limited for European cohorts, existing data suggest that the prevalence of axial SpA (includes AS and nr-axSpA) is estimated to be 0.3-0.5%. |  |
| Line 39 |  | Comment: it is stated that AS is more prevalent in males, however as patient diagnosis has improved over the years the male to female ratio has become approximately equal in nr-axSpA which affects the overall gender distribution in the whole axSpA population (Feldtkeller et al., Curr Opin  Rheumatol 2000, 12:239–247).  Proposed change: Update male to female ratio for axSpA |  |
| Lines 42-43 |  | Comment: “maybe” is underestimating the burden of disease in terms of extraarticular manifestations in axSpA. According to published literature, AS patients can have extraarticular manifestations which adds to their overall disease burden in about 25% for uveitis, up to about 10% for psoriasis and up to about 7% for inflammatory bowel disease (Stolwijk C, et al. Ann Rheum Dis 2015;74:65–73; Vander Cruyssen B. et al. Ann Rheum Dis 2007;66:1072-7).  Proposed change : “Further, peripheral joints as well as extra-articular tissues such as entheses, the anterior uvea, skin (psoriasis), gut (inflammatory bowel disease) **are** involved in up to 26% (uveitis), 9% (psoriasis) and 7% (IBD) in patients with axSpA.”  Alternatively, please change the word “maybe” to “may be” as the statement is still correct as each patient may not necessarily have involvement of all of these anatomical structures.  The following should be added after the last sentence on Line 84: “The future guideline should discuss the importance of extra-articular manifestations (in addition to signs and symptoms of axSpA) which should allow for specific optional claims to be made in Section 5.1 of the SmPC (ie not a requirement for registration). However, given the current lack of consensus on outcome measures, these will need to be justified by the applicant.” |  |
| Lines 46-47 |  | Comment: Based on the statements around early disease and nr-axSpA, it could be inferred that the agency considers nr-axSpA to represent early disease. We would like to clarify that, historically, patients with axSpA were only identified when there was evidence of  sufficient structural damage of the SI joints on the radiographs (radiographic sacroiliitis, as determined by the mNY criteria), and such patients were diagnosed as having AS. Advances in the knowledge of axSpA has led to the understanding that some patients who have the clinical manifestations typical of this disease may not have evidence of radiographic sacroiliitis at presentation, and such  patients are now diagnosed as having non-radiographic axSpA (nr-axSpA). Therefore, both AS and nr-axSpA represent the spectrum of axSpA, as opposed to a disease continuum, with the presence or absence of radiographic sacroiliitis as the only differentiating clinical feature. This is further supported by data from several axSpA cohorts where a proportion of patients with nr-axSpA have not “progressed” to AS despite having been diagnosed for several years.  Proposed change (if any): No change proposed, however, the above important concept of axSpA being a disease spectrum should be considered when developing the guideline since this concept has been misunderstood in the past. |  |
| Lines 46-47 |  | Comment: It is stated that functional limitations in early disease are related to inflammation and that persistent disease results in new bone formation. There is currently no evidence to support that new bone formation occurs in all axial SpA patients and patients with nr-axSpA may have disease for greater than 10 years without development of x-ray damage.  Proposed change (if any):  Functional limitations in the early phases of disease relate to inflammation but ~~may increase~~ with persistent disease may also result~~ing~~ ~~in~~ from new bone formation.  It is requested to add a separate statement pertaining to radiographic progression which discusses progression in the SI joints and progression in the spine. |  |
| Lines 47-49 |  | The concept paper acknowledges the concept of axSpA as constituting both AS and nr-axSpA subpopulations. Although AS and nr-axSpA have overlapping clinical features and in essence constitutes features of a common disease spectrum, the future guideline should reflect this situation in terms of potential clinical trial designs (e.g. stratification in a single axSpA study), whilst allowing flexibility in development approaches to support a global development plan that is suitable to meet requirements of global regulatory agencies.  Proposed change (if any): “The future guideline will clarify requirements for clinical development in support of an axSpA indication, whilst allowing flexibility for global development plans to meet global regulatory requirements.” This statement should be reflected in Line 85 after, “The GL will discuss how the new ASAS criteria will apply to the inclusion and characterization of patient populations for inclusion in trials for regulatory purposes.” |  |
| Lines 50-53 |  | Comment: This section on prognosis should be revised to clarify that prognosis can pertain to either radiographic progression and/or progression of symptoms, disability, and survival. Currently the factors mentioned are only those associated with radiographic progression.  Additionally, literature supports some difference in predictors of radiographic progression in the SI joints vs. the spine. The variables mentioned such as male sex, smoking, increased CRP are predictors for radiographic progression in the spine. In addition, existing syndesmophytes are also predictors for spinal progression as typically measured by the modified modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) (Poddubnyy D. et al. Arthritis Rheum 2012;64:1388- 1398; Van Tubergen A. et al. Ann Rheum Dis 2012;71:518–523; Baraliakos X. et al. J Rheumatol 2009;36;997-1002).  Predictors for radiographic progresssion in the sacroiliac joints (progression from nr-axSpA to AS) include elevated CRP, positive HLA-B27 and evidence of active inflammation on MRI in the SI-joints (sacroiliitis) (Poddubnyy et al. Ann Rheum Dis 2011;70:1369–1374; Bennett A.N. et al. Arthritis Rheum 2008;58:3413-3418).  Proposed change: Revise content to described prognosis as it pertains to radiographic progression, progression of symptoms, disability, and survival, or limit the section header to prognosis in terms of radiographic progression. |  |
| Line 57 |  | Comment: There are no data to support the statement that NSAIDs may cause deleterious effects on radiographic progression.  Proposed change: remove reference to deleterious effects of NSAIDs on radiographic progression. |  |
| 62-63 |  | Comment:  Minor typographical revision.  Proposed change (if any):  In recent ~~several~~ years, several studies of treatment with TNFi in AS, defined according to the mNY criteria, have been published. |  |
| Line 61-62 |  | Comment: The Concept Paper should acknowledge that there are patients who inadequately respond to or are intolerant of TNF-inhibitor agents as well  Proposed change (if any): |  |
| Lines 68-76 |  | Comment: It is important to use appropriate classification criteria for recruitment of target population (Axial SpA) in the clinical studies.  Proposed change (if any): Guideline should clarify the appropriate classification criteria to be used for recruitment of patients for example the ASAS criteria for axial SpA and modified New York criteria for AS. |  |
| Lines 68-92 |  | Please clarify the number of studies, minimum number of patients and study duration required for approval of a new drug in axial SpA as a primary indication.  Proposed change (if any): Add the following on Line 84: “The guideline will also consider the number of studies, study duration, and minimum number of patients required for approval of a product in the treatment of axSpA; taking into consideration the existing knowledge for the product (eg approved related indications).” |  |
| Lines 69 |  | Comment: Recommended wording change for clarity  Proposed change (if any): Change “for the treatment” to “to guide treatment” |  |
| Line 69-70 |  | Comment: the abbreviation for Ankylosing Spondylitis Disease Activity Score is “ASDAS”. It should be specified what is meant by “AS 20/40”: it should be “ASAS20/40” (20% and 40% improvement according to the Assessment of SpondyloArthritis international Society criteria ”  Proposed change: introduce “ASDAS” abbreviation; correct “AS 20/40” to “ASAS 20/40” |  |
| Lines 71-74 |  | Comment:  Recent treatment advances (eg TNF inhibitors) have not demonstrated robust efficacy in randomised controlled clinical trials in terms of inhibition of structural damage (which in axSpA consists of both osteodestructive and osteoprofilerative changes). Existing treatment options in patients with an inadequate response to NSAIDs focus on improvement of signs and symptoms and improvement of physical function. As such, currently available treatment options should not lead to a change of emphasis of treatment goal. Whilst prevention of structural progression remains an aspirational outcome, this should not be the primary focus of confirmatory clinical trial designs i.e efficacy in terms of signs and symptoms and/or improvements of physical functions are appropriate treatment goals. As such, prevention of structural progression should not be a mandatory requirement for approval but the guideline should provide provisions on approaches to obtain a label claim for inhibition of structural progression cognizant of ethical and feasibility considerations with an outcome measure which generally has slower progression than observed in RA and PsA  Proposed change (if any):  The currently available treatment options may have implications for the choice of study population, the goals of treatment~~, either symptomatic or prevention of disease progression (i.e., bone damage)~~ and for the choice of endpoints, the choice of comparator study duration and time points for evaluation, as well as for the need for adequate discontinuation criteria. |  |
| Lines 71-74 |  | Comment: When considering the choice of inclusion criteria for nr-axSpA patients in a clinical study for the purpose of registration, it may be beneficial to have the x-ray grading according to the mNY criteria (1984) and MRI inflammation scoring performed by a trained central reader or a trained local reader to minimize the risk of inclusion of patients with mechanical back pain or with radiographic AS (FDA Division Briefing Document for Arthritis Committee Meeting (2013). |  |
| Lines 72-73 |  | Comment: The future guideline should, in addition to the ‘hard clinical endpoints’ such as ASDAS and ASAS20/40, also consider treatment goals related to important patient-related features such as health-related quality of life, physical function, pain, work productivity and fatigue (Smolen JS, Braun J, Dougados M, et al. Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force, Ann Rheum Dis, 2013)  Proposed change (if any): No specific change proposed to the concept paper, but points above should be considered in the draft guideline. |  |
| Line 74 |  | Randomized withdrawal studies that address the possibility of discontinuing treatment after sufficient improvement have not been required for approval of compounds for the treatment of AS. As such, this should also not be a prerequisite for approval of a new medicinal product for axial SpA. |  |
| Lines 77-80 |  | Comment:  The ASAS criteria for axial SpA do not create a significantly less well-defined disease state for those patients with nr-axSpA as compared to AS. While the mNY criteria do have a higher specificity, this is at the expense of a low sensitivity as these criteria are weighted heavily on permanent x-ray damage in the SI joints and do not take into consideration that patients with no current SI joint damage or a minimal amount of radiographic damage are excluded from classification and additionally do not consider the majority of clinical features used in practice to make a diagnosis. Nr-axSpA patients were considered to have axial SpA (though often called by other names such as undifferentiated SpA or pre-radiographic axial SpA) prior to the development of the ASAS classification criteria and in fact the criteria include the factors which a physician considers when making a diagnosis of axial SpA. As such, the external validity of study results is increased, not decreased by inclusion of all patients with axial SpA who are currently being seen in rheumatology practices.  Furthermore, inflammatory back pain (IBP) is only a symptom and by itself does not equal to a diagnosis of any specific disease (Van den Berg et al. Ann Rheum Dis. 2013 Oct;72(10):1646-53.). The sensitivity and specificity for IBP in the diagnosis of axial SpA are about 75% each (Ann Rheum Dis. 2006 Sep;65(9):1251-2. Arthritis Rheum. 2005 Apr;52(4):1000-8).  The ASAS classification criteria on axial SpA are classification and not diagnostic criteria (Braun et al. J Rheumatol. 2015 Jan;42(1):31-8.). As such, patients should first be diagnosed with axial SpA (AS or nr-axSpA) by rheumatologists (Ann Rheum Dis. 2013 Oct;72(10):1646-53.) prior to application of the ASAS classification criteria for inclusion in a clinical trial. As such, the ASAS classification criteria increase homogeneity of the study population.  Earlier diagnosis of all disease is a goal as this can facilitate appropriate and timely treatment to address current signs and symptoms and to prevent unnecessary investigations, loss of function, and, in some cases, may have the potential to prevent long-term damage/progression. While attempts for earlier diagnosis can lead to “less well defined disease” and increase the risk for an incorrect diagnosis this is not specific to axial SpA. For example, the introduction of the 2010 ACR / EULAR criteria for Rheumatoid Arthritis bear the same issue of “less well defined disease”. The 2010 ACR/EULAR criteria result in a pooled sensitivity of 82% and specificity of 61% across 17 studies. As compared to the classification criteria for RA, the ASAS axial SpA classification criteria have similar reported sensitivity of 82.9% and superior specificity of 84.4%. (Rudwaleit et al. 2009;68:777-783)  Proposed change: Delete the phrase “less well defined disease” and delete or revise the statements that follow – “This will likely result in less external validity of the study results. Misspecification with mechanical non-inflammatory back pain may occur” |  |
| Lines 78-80 |  | Comment: What distinguishes between inflammatory and non-inflammatory back pain requires clear explanation in the guideline  Proposed change (if any): Provide clarity on the exclusion of non-inflammatory back pain in the study population i.e. by an accepted/published clinical definition of IBP. |  |
| Line 80/81 |  | Comment:  It is not correct that validating imaging scores for nr-axSpA is a challenge. The Spondyloarthritis Research Consortium of Canada (SPARCC) MRI scores for the sacroiliac (SI) joints (0–72) and the spine (0–108) have been successfully used in at least 2 phase 3 trials of anti-TNF that included patients with nr-axSpA (adalimumab: EMEA/H/C/000481; and certolizumab: EMEA/H/C/001037). The scoring system discriminated between active treatment versus placebo with improvements in the score significantly greater with active treatment. Also, through further improvements in imaging techniques, more sensitive measures and scoring systems may emerge in the future and the guideline should allow flexibility for using such imaging scores once appropriately validated.  Proposed change (if any): delete or modify sentence. Allow flexibility in the use of validated imaging scores. |  |
| Line 82/83 |  | Comment: Clinical trials include patients who are candidates for new therapies due to sufficiently active disease that require further intervention rather than the severity of the disease historically; conversely pts with historical severe disease may not have current disease activity . As such, prescribing information would also reflect the need for active disease that could benefit from the therapy. In clinical practice, physicians make benefit-risk decisions when prescribing new therapies and are in the best position to make the right recommendation for individual patients.  Proposed change (if any): Please delete or revise this sentence. |  |
| Line 85 and 91/92 |  | Comment: We welcome that the new guideline touches on newer outcome measures including the Ankylosing Spondylitis Disease Activity Score (ASDAS), but more guidance and specific information on which of the ASDAS outcome measures could be used would be helpful. |  |
| 90-92 |  | Comment:  Minor typographical revision since the clause lacks a verb.  The RIWP recommends ~~that an~~ development of an updated guideline on the clinical investigation of medicinal products for the treatment of axial spondyloarthritis, addressing issues on adequate patient populations and outcome measures for clinical trials. |  |
| Lines 94-95 |  | Comment: We believe a typo was made in the date of release of the draft guideline since as per the RIWP work plan 2015, the draft guideline is scheduled to be released in 4Q2015. |  |
| 97-98 |  | Comment:  Minor typographical revision.  The RIWP will nominate a rapporteur within the group but will ~~relay~~ rely on the competence of the entire group as well as consulting other WPs or Committees as well as external experts. |  |
| Additional information proposed |  | Comment : There is no current regulatory guidance on how inhibition of radiographic progression in the sacroiliac joints and/or spine should be assessed. For the SI joints the mNY criteria provide the only available scoring system. For the spine the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) is the current standard. Additionally, guidance on the acceptability of imaging modalities for determining progression other than conventional x-ray is requested, such as MRI and computed tomography.  Proposed change: add guidance on the preferred measures of radiographic progression, acceptability of alternative imaging methods, and information on duration and recommended control group for trials for a structural inhibition claim in patients with nr-axSpA and/or AS. |  |
| Additional information proposed |  | Comment: role of STIR MRI of SI-joints and spine.  MRI of the SI-joints and spine are very well established in clinical practice as well as in clinical trials. Next to measuring CRP, MRI offers the opportunity to quantitatively and reliably characterize the inflammatory burden of a patient with axSpA in the SI-joints and spine.  Proposed change: add MRI of SI-joints and spine to list of outcome measures to assess disease activity and treatment effect. |  |

Please add more rows if needed.