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Guideline on the clinical investigation of medicinal products for the treatment of Axial Spondyloarthritis

Draft

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This guideline replaces Guideline on clinical investigations of medicinal products in the treatment of Ankylosing Spondylitis (EMA/CPMP/EWP/4891/03).

Comments should be provided using this template. The completed comments form should be sent to RIWPsecretariat@ema.europa.eu

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Guideline on the Clinical Investigation of Medicinal Products for the Treatment of Axial Spondyloarthritis

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Executive summary

This document is a revision of the Guideline on clinical investigation of medicinal products for the treatment of ankylosing spondylitis (CPMP/EWP/4891/03) which came into effect in May 2009. It should be considered as general guidance on the development of medicinal products for the treatment of axial spondyloarthritis and should be read in conjunction with other European and ICH guidelines which may apply to this disease area and patient population.

The current revision has taken into account that clinical practice has evolved since publication of the previous guideline and acknowledges that patients with axial spondyloarthritis (axial SpA) 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. These patients, captured under the term non-radiographic axial SpA, are considered in this revised CHMP guideline. The new guideline also reviews relevant treatment goals, new outcome measures for the treatment as well as the design of confirmatory trials in the light of the currently available treatment options.

The guideline will not include aspects of SpA in children since this has been addressed in the Guideline on Clinical Investigation of Medicinal Products for the Treatment of Juvenile Idiopathic Arthritis.

1. Introduction (background)

The concept of spondyloarthritis (SpA) comprises a group of diseases which share common clinical and genetic features, and includes ankylosing spondylitis (AS), psoriatic arthritis (PsA), arthritis/spondylitis with inflammatory bowel disease (IBD), reactive arthritis, as well as undifferentiated SpA. All of these can present with a predominantly peripheral or axial arthritis. The most common genetic feature is the presence of HLA-B27 antigen.

Ankylosing spondylitis is the most representative subtype of axial SpA and is diagnosed according to the mNY criteria, which requires the presence of radiographic sacroiliitis. It is now well established that patients with axial SpA who do not yet meet radiographic criteria for sacroiliitis according to the mNY criteria experience a significant burden of disease that is comparable to patients with well-defined AS. Given the diagnostic delay of 8-10 years in AS, 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. The new group is captured under the term “non-radiographic axial SpA” and can be identified by the presence of clinical features of axial SpA combined with either “imaging” evidence (active sacroiliitis seen on the MRI scan) or HLA-B27 positivity (“clinical arm”). These criteria seek for an earlier recognition of relevant axial SpA patients compared to the previously used mNY criteria for AS.

Axial SpA defines chronic inflammatory disease that involves primarily the sacroiliac joints and the axial skeleton. It is a largely genetically determined disease which has a strong association with the HLA-B27. Although prevalence data specifically for non-radiographic-axial SpA are limited for European cohorts, existing data suggest that the prevalence of axial SpA (including AS and non-radiographic forms) is estimated to be 0.3-0.8%. The prevalence of AS is estimated around 0.1 % - 0.5 % of the European population. While AS is more common in males (male to female ratio is estimated to be 2-3:1), women are slightly more often affected compared to men in the non-radiographic-axial SpA stage. Axial SpA tends to be more severe in men, in whom the spine is more frequently involved.

Clinical manifestations of axial SpA usually begin in late adolescence or early adulthood (mean age of onset 26 years) and onset after age 45 is rare. Clinical manifestations include lower back pain with predominant nocturnal pain, morning stiffness and impaired physical function. Also chest pain, pain and swelling of peripheral joints and extra-articular tenderness may occur as well as several

extraskeletal manifestations such as anterior uveitis, psoriasis, and inflammatory bowel disease. Cardiac conduction defects and aortic valve disease or renal disease, mainly in the form of secondary renal amyloidosis, may also be associated.

Axial SpA is a chronic disease that causes a substantial amount of pain and disability. Functional limitations relate to inflammation in the early phases of disease but also increase with duration of disease due to new bone formation. Although most patients are able to maintain functional capacity, there are also some patients with progressing disease who rapidly develop ankylosis at a young age. There are no solid prognostic parameters besides early radiographic progression, but male sex, MRI inflammation in sacroiliac joints and spine, increased CRP, and hip involvement early in the disease course have been associated with poor prognosis.

According to clinical guidelines, physical therapy and non-steroidal anti-inflammatory drugs (NSAIDs) comprise the first line treatment in axial SpA. Physical therapy has a positive effect on stiffness and on spinal mobility and even on pain. NSAIDs are used to control pain with good response in up to 50-70% of axial SpA patients. It has been shown that NSAIDs given on continuous basis may provide benefit in terms of radiographic progression. So, due to their high symptomatic efficacy and possible disease-modifying properties, NSAIDs are considered the treatment of choice for the majority of patients with axial SpA and if tolerated, these are usually maintained as background therapy in patients with insufficient response.

Intra-articular corticosteroids may be used for sacroiliac or peripheral joint inflammation whereas systemic corticosteroids in general are of little benefit. Traditional non-biological disease modifying antirheumatic drugs are of limited value with the exception of sulfasalazine, which is used and have shown some effect on peripheral disease and extraarticular manifestations, but with no evidence of effect in severe disease or in patients with substantial spinal involvement. In contrast, the treatment with biological DMARDs is recommended for patients with persistent high disease activity despite conventional treatment with NSAIDs and physiotherapy.

2. Scope

Guidance is provided on the clinical development and evaluation of medicinal products for the systemic treatment of axial SpA, including both ankylosing spondylitis and non-radiographic axial SpA forms.

3. Legal basis and relevant guidelines

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

- Dose Response Information to Support Drug Registration (ICH E4)
- Note for Guidance on Population Exposure: The Extent of Population Exposure to assess Clinical Safety (ICH E1)
- Note for Guidance on Studies in Support of Special Populations: Geriatrics (ICH Topic E 7) and the Questions and Answers - EMEA/CHMP/ICH/604661/2009;
- Guideline on Statistical Principles for Clinical Trials (CPMP/ICH/363/96)
- Guideline on the Choice of control group in clinical trials (CPMP/ICH/364/96)
- Points to Consider on Multiplicity Issues in Clinical Trials (CPMP/EWP/908/99)

- Points to consider on Adjustment for Baseline covariates (CPMP/EWP/2863/99)
- Guideline on Missing Data in Confirmatory Clinical Trials (CPMP/EWP/1776/99 Rev.1)
- Guideline on the investigation of drug interactions (CPMP/EWP/560/95. Rev. 1)
- Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis (EMA/CHMP/239770/2014 Rev.2)

4. Patient selection

Both AS and non-radiographic-axial SpA represent the spectrum of axial SpA, as opposed to a disease continuum, with the presence or absence of radiographic sacroiliitis as the only differentiating clinical feature. In fact, a significant proportion of patients with non-radiographic-axial SpA will not progress to AS despite having been diagnosed for several years. Therefore, medicinal products intended for the treatment of axial SpA should provide efficacy and safety data in both, patients with AS and patients with non-radiographic axial SpA disease. Patients to be included in clinical trials should be selected according to generally accepted classification criteria. Both groups of patients can be studied in the same study provided that these are represented in adequate numbers that will permit sub-group analysis and also evaluation of consistency with the overall results of the study.

Ankylosing Spondylitis (AS)

The 1984 modified New York classification criteria are accepted criteria to diagnose AS with a high degree of specificity. Using these criteria the diagnosis relies strongly on the existence of changes in the sacroiliac joints exceeding grade 2 unilateral. The inter and intra-observer variability in the interpretation of radiographs is a known problem which may affect the specificity of the classification criteria, particularly regarding Grade 2 or Grade 3 abnormalities. This should be addressed in the planning of the study in order to accurately document the existence of a grade II degree in sacroiliac changes.

Non-radiographic axial SpA

The 2009 ASAS criteria defines a new group captured under the term “non-radiographic axial SpA” and can be identified by the presence of clinical features of axial SpA combined with either active sacroilitis seen on the MRI scan (“imaging” evidence) or HLA-B27 positivity (“clinical arm”). These criteria have been validated and accepted for the selection of patients in clinical trials. The main drawback of the ASAS criteria for selecting patients with non-radiographic-axial SpA is the high false positive rate when applying these criteria in settings with a low prevalence of axial SpA. Additional restrictions for inclusion such as the presence of objective signs of inflammation at baseline based on biomarkers may be implemented, i.e. MRI inflammatory findings by central reading and/or a positive (centrally determined) CRP that cannot be explained by other reasons than axial SpA. Other potentially prognostic biomarkers that may have utility for patient selection should be investigated.

Regardless of the finally included population, i.e. AS or non-radiographic axial SpA, patient’s characteristics should be well documented: demographics, duration of the disease, previous and concomitant therapies, concomitant diseases including those specific diseases related to axial SpA such as anterior uveitis, psoriasis, inflammatory bowel disease or cardiac disease (conduction, valve problems). All specific diagnostic actions taken by physicians before including patients (e.g. screening for latent tuberculosis) should be described in the selection criteria of the protocol.

In addition, there are some characteristics that may be considered in order to identify subpopulations where the benefit risk ratio of the new product might be different. These characteristics are the

severity and extent of the disease, the disease activity, the spinal and peripheral joint involvement and the lack of response to previous treatments.

Patients should be well characterised with respect to previous treatments received for axial SpA. Possible target patient groups that can be included in clinical trials are patients naive to or previously treated with biological treatment alternatives. The consideration of a patient as non-responder to NSAIDs (naive to biological alternatives) or to one or more biological medicinal products (i.e. biological insufficient responders) requires documentation of the lack of response with appropriate doses and treatment durations. Special attention should be paid to other patient characteristics that might be relevant depending on the mode of action of the product. In this sense, the levels of serologic markers of inflammation such as C reactive protein (CRP) or the erythrocyte sedimentation rate (ESR), the presence of inflammatory findings by MRI, among other scan be considered.

The absence of HLA-B27 should not be an exclusion criterion.

Disease activity at the moment of the enrolment in the trials should be distinguished from the level of damage and functional disability reached by the patients due to the evolution of the disease until that moment. Activity of disease should be assessed by means of validated scales and considering several aspects of the disease such as pain or stiffness. The use of composite simple scales such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) or the Ankylosing Spondylitis Disease Activity Score (ASDAS) is considered appropriate and may be complemented with the measurement of individual symptoms (e.g. pain) or global patient assessments of the disease with visual analogue scales.

Prior to inclusion patients should be required to have a certain degree of disease activity in order to show a sufficient treatment response (e.g. ASDAS $\geq$1.3 or BASDAI >4 and nocturnal/spinal pain as measured by visual analogue scale (VAS) > 4 cm at baseline). A minimum duration of active disease should be established before entering into the trial. A minimum duration of 3 months of active disease would be needed when assessing products to be used in patients not controlled with NSAIDs or biological medicinal products, unless therapy had to be withdrawn due to intolerance, toxicity or contraindications.

In addition to the disease activity at a given time, the severity of the disease is determined by other characteristics such as the level of irreversible structural damage, the involvement of peripheral joints and other organs, the concomitant diseases and the unresponsiveness to previous treatments.

Concomitant medication for axial SpA should be discontinued or remain on a stable dose for a sufficient period of time, depending on the drug, before randomization.

Subgroup analyses accounting for known prognostic factors (some of which will be stratification factors in the randomisation) should be predefined in the study protocol, according to the recommendations made in the relevant guidelines. The selection of the most relevant subgroups should be made on a case by case basis. It is expected that consistent effects in the relevant subgroups are shown to provide clear evidence of efficacy in the requested study population.

It is recommended that stratified randomisation is used to reduce the risk of imbalances in important prognostic factors such as prior use of biological medicinal products and/or the degree of activity. Depending on the mechanism of action of the medicinal products, other relevant factors might be considered.

5. Assessment of efficacy

5.1. Efficacy criteria / Treatment goals

From a regulatory point of view, the following goals of a therapy can be distinguished:

1) improvement of symptoms and signs such as pain and stiffness or enthesopathy,

2) improvement of physical function,

3) slowing or prevention of structural damage,

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

Medicinal products intended to improve symptoms/physical function

Improvement of sign and symptoms and improvement/maintenance of physical function are key relevant endpoints in all axial SpA patient groups. Different domains may be assessed separately or using composite indexes that bring together the assessment of several domains. The use of a composite measure is an appropriate way to assess the efficacy of a product. For this purpose only validated composite endpoints are acceptable as primary or secondary 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 response criteria are adequately justified, chosen before the study is started and thresholds are predefined.

Primary endpoints

The ASAS Response Criteria (ASAS 20, ASAS 40) have been extensively used in clinical trials. These are defined as an improvement of at least 20% or 40%, respectively, and an absolute improvement of at least 10 or 20 units, respectively, on a 0-100mm scale in at least 3 of the following domains: patient global assessment, pain, function, and morning stiffness with no worsening of the remaining domain

Although the percentage of patients reaching an ASAS 20 response has been accepted as primary endpoint for a number of products, a higher magnitude of the clinical response can be expected for biological medicinal products or products from a new therapeutic class. Thus, the ASAS 40 response criteria would the preferred primary endpoint. This index has been already used in several trials and may be considered an appropriate primary efficacy end point to assess major clinical response.

Other validated and accepted methods to assess disease activity and physical function include the Ankylosing Spondylitis Disease Activity Score (ASDAS). Changes ≥1.1 units representing clinically important improvement and changes ≥2.0 units major improvement.

As more effective therapies become available for axial SpA, disease remission is increasingly regarded as an appropriate therapeutic goal. Complete remission in axial SpA has not formally been defined yet and may not be a realistic goal. Partial remission or low disease activity, based on generally accepted criteria, i.e. ASDAS ID, ASDAS <1.3, BASDAI<30, are more realistic while still relevant goals and have been used in clinical trials in axial SpA.

Secondary endpoints

Spinal mobility

The ASAS composite does not include the assessment of the spine mobility, which is a relevant efficacy parameter in axial SpA. Thus, if the ASAS index is chosen as primary endpoint, it should be supplemented with the assessment of spinal mobility as a key secondary endpoint.

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

BASDAI is a composite index that includes the assessment by the patients of their symptoms of pain, discomfort, stiffness and fatigue. It is a widely used measure of disease activity and its changes with treatment should be assessed. The percentage of patients with clinical response as measured by an improvement of at least a 50% from the baseline score in BASDAI is considered useful to judge the clinical benefit of a treatment.

Other secondary end points may be the individual components of the ASAS instrument as well as individual assessments of the main domains of the disease. Additional endpoints may be the ASAS 20, 50 or70 or the ASAS 5/6 as well as the peripheral tender joints and swollen joint count (change and percent change from baseline)if not selected as primary endpoints.

Quality of life endpoints may also be considered as secondary endpoints.

Acute phase reactants

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 axial SpA but can provide useful supportive information on the treatment effects.

Peripheral joints and entheses

Depending on the degree of peripheral joint involvement the assessment of peripheral joints may be of value in measuring efficacy of products to treat axial SpA.

Exploratory endpoints

Extra-articular manifestations

Given the prevalence of well-known extra-articular manifestations such as uveitis, inflammatory bowel disease and psoriasis, documentation of history and new occurrences/flares of these manifestations should be recorded.

Additional goal in the prevention of structural damage

To date, recent treatment advances have not demonstrated robust efficacy in randomised controlled clinical trials in terms of inhibition of structural damage (either osteodestructive or osteoproliferative changes). Thus, prevention of structural damage is considered a relevant endpoint to be assessed but not a requirement for approval. However, the relationship between inflammation and new bone formation in axial SpA remains unclear. This may be explained by the persistence of radiologic progression in patients who appear to otherwise respond well to treatment based on symptom control and quality of life. Therefore, it is highly encouraged to systematically monitor structural changes even in studies aimed to study the effect on symptoms and physical function.

5.2. Methods to assess efficacy criteria

Pain

Pain is adequately measured by means of patient self-answered VAS. Patient should be asked for both specific pain at night as well as overall pain due to Axial SpA. The question should refer to a recent past period (e.g. the past week or the past 48 hours).

Additional measures of pain may be provided by three out of the six items of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) that ask for pain and discomfort during the last week. The

three items assess 1) overall pain in neck, back or hip; 2) overall level of pain/swelling in joints other than neck, back or hip and 3)overall discomfort from any areas tender to touch or pressure. Pain can also be assessed by 2 out of the 6 items of the Ankylosing Spondylitis Disease Activity Score (ASDAS), which assess back pain and peripheral pain/swelling.

Physical function

There are several acceptable instruments to measure physical function and its changes in patients suffering from axial SpA. The most widely known instruments are two patient administered questionnaires: the Bath Ankylosing Spondylitis Functional Index (BASFI) and the Dougados Functional Index (DFI).The BASFI consists of 10 questions regarding ability to perform specific tasks as measured by visual analogue scales (VAS) whereas the DFI addresses similar aspects in 20 questions that should be answered by means of a three or five categories Likert scale. It appears that the BASFI is more sensitive to changes and easier to use than the DFI. To date, the DFI is hardly ever used and no longer recommended for clinical practice or research.

Spinal stiffness

Spinal morning stiffness that improves with movement is a relevant symptom related to inflammation in axial SpA. The BASDAI index provides a good assessment of stiffness through the combination of two of its questions. One item measures the intensity of morning stiffness by means of a 100 mm VAS and the last item asks for the duration of stiffness from time of awakening. Both questions are referred to the situation during the previous week. The ASDAS scale also includes one item to assess duration of morning stiffness.

Patient global assessment

Patient subjective perception is an important complementary variable that may be measured by means of a visual analogue scale, asking the patients to inform on his/her global status during a recent past period (for example last week).

Spinal Mobility

Spinal mobility is of great importance in axial SpA and constitutes the most organ specific domain. Although it may be difficult to detect changes in spinal mobility on the short term and often more reflecting disease severity over time than ongoing inflammation, spinal mobility is considered an important measure to assess efficacy.

Several instruments have been developed and a combination of them may be used in clinical trials.

Chest expansion, modified Schober test, lateral spinal flexion and occiput to wall distance are amongst the most known methods to measure spinal mobility, however with substantially varying performance and reliability.

The Bath Ankylosing Spondylitis Metrology Index (BASMI) is a combined measure of spinal mobility and hip function that has been used in several clinical trials and is also an acceptable method. However, this index does not include all the well-established measures previously mentioned and therefore, if the BASMI index is used, it is recommended to add some of the other relevant single measures (e.g. chest expansion).

Structural damage

The assessment of structural damage and progression is mainly based on radiography. Osteodestructive and osteoproliferative changes are detectable and acute and chronic changes need to be differentiated. Structural damage may be detected by conventional radiographs, by MRI/T1 weighted sequences and by DEXA or quantitative CT measurements.

There are several radiological scores and recently, based on consensus, the modified SASSS has been chosen as the preferred validated and sensitive method to assess radiological changes. However, in order to assess the relevance of any changes, imaging methods should be supported by a demonstration of an effect on the clinical consequences of the slowing or prevention of the structural damage (i.e. an effect on spinal mobility).

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

Although not fully validated to assess changes over time, MRI of spine and sacroiliac joints can be used to assess signs and sequels of inflammation on imaging; it is particularly useful in the pre-radiographic stage. The role of MRI to assess changes in structural damage over time remains to be established.

Peripheral joints and entheses

Efficacy in peripheral joints may be measured as the count of the swollen or tender joints based on the 44 joint count without grading or weighting. The value in measuring efficacy in peripheral joints depends on the degree of involvement.

The assessment of affected entheses is time consuming if it is done in an extensive manner (e.g. Mander enthesis index based on 66 entheses). On the opposite end, the simple question included in the BASDAI about “discomfort because areas tender to touch or pressure” may not be sensitive enough to capture changes in enthesis inflammation status. Several indices have been developed in order to provide a feasible method to assess enthesopathy. The MASES index based on 13 entheses may be an acceptable instrument but also other instruments if validated and reliable might be appropriate.

Quality of life (QoL)

It may be assessed either using some specific scales (e.g. ASQoL) or general instruments (e.g. SF-36, FACIT-Fatigue, EQ-5D, or WPAI-GH).The use of accepted multidimensional scales assessing QoL may provide complementary information to the efficacy demonstrated by the main variables. These multidimensional scales are preferred over specific physical QoL scales that are closely related to the improvement of symptoms and physical function.

6. Study design

6.1. Pharmacology studies

6.1.1. Pharmacokinetics

The pharmacokinetic properties of the medicinal product should be thoroughly investigated in accordance with relevant guidelines regarding interactions, special populations and specific quality aspects (locally applied drugs, proteins and monoclonal antibodies).

6.1.2. Pharmacodynamics

The pharmacodynamic properties of the medicinal product should be investigated following existing guidelines. The mechanism of action should be investigated and discussed in relation to other relevant drugs that are available

6.1.3. Interactions

Interaction studies should be performed in accordance with the existing guidelines. Efficacy and safety implications of concomitant drugs likely to be co-administered in clinical practice (e.g. NSAIDs, conventional DMARDs) should be evaluated.

6.2. Therapeutic studies

6.2.1. Exploratory and dose finding studies

Specific dose response studies should be performed in patients with axial SpA. There are several antecedents of different response to medicinal products in patients with AS compared to the same product in other rheumatic diseases (i.e. rheumatoid arthritis) or other AS-related non-articular disorders (i.e. inflammatory intestinal disease). 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 axial SpA in order to find the posology regimen with the most favourable benefit-risk balance in this particular disease.

Whenever appropriate and depending on the mechanism of action, efforts should be made to find different doses or intervals according to the respective patient characteristics (i.e. severity, inflammation).

Extrapolation of dose finding from other spondyloarthritis related entities may be possible.

Placebo controlled parallel group studies are recommended. The ASAS 20 composite index is an appropriate measure for the exploratory trials and short duration trials (e.g. 12-24 weeks) may be enough to demonstrate efficacy on symptoms of the disease.

6.2.2. Confirmatory studies

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

Design elements

Conventional treatment of axial SpA consists of NSAID combined with physical therapy, which are enough to control pain in most patients as well as to improve physical function. Therefore, new products belonging to therapeutic classes other than NSAIDs are expected to be tested in patients non-responder (or intolerant) to NSAIDs (naive to biological alternatives) or to one or more biological medicinal products (e.g. biological insufficient responders). Patients with insufficient control of their symptoms on NSAIDs, who are regularly taking them as part of their axial SpA therapy, can continue these treatments provided that they are on a stable dose before randomization.

There are no particular requirements for other background medications as their use is expected to be limited in axial SpA.

Biological naive patients

Studies should have a randomized, double blind, parallel group design. Efficacy of products claiming improvement in symptoms and disease activity or function are generally established by means of placebo controlled trials that may well be add-on trials where all patients receive physical therapy and NSAIDs.

Products belonging to new therapeutic classes may need also comparison against an accepted active comparator (e.g. anti TNF treatments) for the target population, in order to properly assess the benefit risk balance of the new product. A three-arm trial is recommended, particularly when biological naive patients are to be studied.

The concomitant standard therapy should be carefully documented and its impact on results analyzed based on a pre-established plan. Also the previous use and response to standard therapy should be documented.

Biological insufficient responders

Studies should have a randomized, double blind, parallel group design. Efficacy of products claiming improvement in symptoms and disease activity or function can be established by means of placebo controlled, randomized, double blind, parallel group and add-on trials, where patients receive concomitant standard therapy. Alternatively, an active controlled trial where patients are randomized to switch to another biological treatment (e.g. another TNFi) or the new medicinal product could be a possible design.

Patient selection / target population

Medicinal products intended for the treatment of axial SpA should provide efficacy and safety data in both, patients with AS and patients with non-radiographic SpA disease, otherwise appropriate restrictions in the indication will be applied. These patients could be studied in the same trial provided these are predefined subgroups with sufficient representation to permit analysis and evaluation of consistency with the overall results of the study.

Depending on the intended target population, biological naïve patients and/or patients previously treated with insufficient response to biologicals can be studied. In principle, these should be studied in separate clinical trials unless scientifically justified. If included in the same study, appropriate stratification should be pre-planned.

Patients with a sufficient degree of disease activity should be included in order to have a sensitive population to assess the effect on disease activity.

Choice of endpoints

Medicinal Products for the treatment of axial SpA are expected to improve symptoms and physical function. The primary end point depends on the expected extent of response induced by the product. For products other than NSAIDs (e.g. TNF inhibitors, other biological-DMARDs), responder rate of patients with an ASAS 40 at 12 or 24 weeks is an appropriate end point. Other endpoints like the ASDAS score and/or low disease activity may also be accepted. It is expected that a concomitant improvement in spinal mobility is also demonstrated.

Axial SpA 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.

Despite an adequate control of symptoms there may be residual structural inflammation. Therefore, monitoring of structural changes in the long term is encouraged.

In addition, the adequate duration of treatment should be addressed and data after stopping therapy as well as retreatment should be documented, i.e. at post-approval.

Slowing or prevention of structural damage

Confirmatory trials to demonstrate an effect on prevention of structural damage and subsequent function, spinal mobility and disability should be parallel group controlled trials of long duration (e.g. at least 2 years).Trials should be ideally double blind placebo controlled trials. However, it is acknowledged that such a long duration of a placebo controlled trial may not be acceptable due to ethical concerns.

From a therapeutic point of view, patients with mild disease activity may be enrolled in such a long trial as an add-on trial over standard therapy with NSAIDs, physical therapy or corticosteroids if needed. However, depending on the type of product (i.e. frequent/painful parenteral administrations) such a long placebo controlled trial may also have feasibility problems. On the other hand, this population may not be suitable to demonstrate prevention of structural damage due to their slight progression.

Patients with severe disease activity cannot be maintained in a placebo-controlled trial for a long period because of the availability of effective therapies other than NSAIDs (i.e. biological DMARDs). Therefore, unless an add-on therapy over biologicals was the aim of the therapy, alternative designs should be explored. A possible alternative may be a trial with a randomized delay of starting of the active treatment. Differences between groups may be sustained at the end of the 2 or 3 years period reflecting the difference in the start of treatment.

Slowing of radiographic progression may itself not constitute a definite patient benefit and it is currently not an accepted surrogate for long term clinical benefit. Although there is indirect evidence that, by favorably modifying the natural history of axial SpA in terms of structural changes, long-term clinical benefit will occur in a large proportion of patients, it would be expected that an applicant will provide additional evidence to support this surrogacy.

7. Safety aspects

7.1. Specific effects

Prior to licensing the safety database should be sufficient to characterise the safety profile of the medicinal product. A sufficiently robust and extensive safety database is required in order to balance benefits and risks. The analyses of safety data should particularly focus on specific adverse effects related to the mode of action or risks known for the specific substance class (e.g. for TNF-alpha blocker and other biological medicinal products: increased infectious risk, malignancies, and infusion reactions). Some of these specific adverse effects might occur after drug discontinuation and should be evaluated and documented for an appropriate period post study.

With drug substances severely affecting important physiologic organ functions, the early detection of the comprehensive adverse reaction profile for any newly introduced drug substance and especially any newly introduced therapeutic class presents a considerable challenge. Therefore it is clearly required that the general principles to achieve this are applied and efficiently introduced to the development of any new drug product to treat axial SpA. In addition, clinical trials may evaluate immune system function, e.g. serum immunoglobulins and lymphocyte subsets, as well as assessing immunogenicity for biologicals in order to better characterize the long-term safety consequences of any adverse findings.

To assess clinical safety and identify relevant adverse reactions an observation period of not less than 12 months is required. Taking into consideration the chronicity of the disease, and the need for long term treatment, longer periods may be more appropriate.

7.2. Long-term effects

The safety database to be submitted for assessing a new product should be sufficiently large taking into consideration the mechanism of action, safety profile and co-morbidities of the patients. When axial SpA is an additional indication for an already approved product, safety data obtained in trials in other indications can be considered as supportive, provided that the dosage regimen is the same, concomitant medication and population is expected to behave similarly (e.g. rheumatoid arthritis or psoriatic arthritis).

Considering the need for confirmatory trials for efficacy as well as the rest of studies specific in Axial SpA, it is possible that efficacy trials may provide also controlled safety data

Axial SpA is a prevalent chronic disease and treatments will need to be approved for long term treatment. Thus, safety assessment should be consistent with standard CHMP requirements for safety data on long-term treatments and reintroduction after stopping treatment. Detailed RMP's will need to be drawn up tailored to the likely risks and knowledge of the product.

8. Studies in special populations

8.1.1. Studies in elderly patients

Efficacy in older patients

Separate efficacy studies are not necessary in the elderly provided there is adequate representation of elderly patients in trials. Available data should be reported separately for patients aged 65-74, 75-85 and 85 and older.

Safety in older patients

The elderly merit particular attention with regard to safety, see Note for Guidance on Studies in Support of Special Populations: Geriatrics (ICH Topic E 7). Available data should be reported separately for patients aged 65-74, 75-85 and 85 and older.

8.1.2. Studies in paediatric patients

The requirements for the demonstration of efficacy and safety in the paediatric population are established in the EU JIA Guideline.

9. Definitions / abbreviations

Axial SpA: a broader term that covers both patients non-radiographic Axial SpA and patients with AS.

Non-radiographic Axial SpA: axial spondyloarthritis, which requires clinical features in combination with presence of imaging findings of sacroiliits by MRI, and/or HLA B27.

AS: ankylosing spondylitis, a subset of axial spondyloarthritis which requires the presence of radiographic sacroiliitis.

mNY criteria: modified New York Criteria for axial spondyloarthritis, includes clinical criteria (low back pain (≥3 months, improved by exercise and not relieved by rest), limitation of lumbar spine in sagittal and frontal planes, limitation of chest expansion (relative to normal values corrected for age and sex) plus radiological criteria (bilateral grade 2-4 sacroiliitis or unilateral 3-4 sacroiliitis). Fulfilment of the mNY criteria requires the presence of one of the radiological findings AND any clinical criteria.

10. References

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