Assessment of Spondyloarthritis international Society (ASAS) classification criteria for axial spondyloarthritis and the implications of using these criteria for drug approval
Disclaimer Statement

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought this discussion regarding the impact of the ASAS classification criteria on drug development to this Advisory Committee in order to gain the Committee’s insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.
Clinical briefing document

1. Introduction

The purpose of this Arthritis Advisory Committee (AAC) meeting is to discuss the Assessment of Spondyloarthritis international Society (ASAS) classification criteria for axial spondyloarthritis (SpA) and the implications of using these criteria for drug approval by the FDA. A public discussion of this topic at an advisory committee meeting will assist the FDA in its assessment of whether to expand the currently utilized drug treatment from patients with ankylosing spondylitis (AS) to include other patients with inflammatory low back pain. This clinical briefing document will provide background on AS and axial SpA, the current framework for drug development in AS, and possible concerns related to expansion of the indication to axial SpA. During this AAC meeting, a specific development program will not be discussed. Instead, this AAC meeting will focus on publicly available scientific information.

2. Background

2.1. Overview of axial spondyloarthritis

SpA refers to a group of inflammatory diseases that share overlapping features, yet are heterogeneous in terms of clinical manifestations and disease severity. In general, patients are classified by whether they have predominantly axial involvement (axial SpA) or predominantly peripheral involvement (peripheral SpA). Given the heterogeneity of SpA, various classification criteria have been proposed. This Arthritis Advisory Committee meeting will focus on axial SpA.

Axial SpA encompasses a spectrum of disease severity that spans from self-limited inflammation to bony destruction of the spine. Ankylosing spondylitis (AS) is a well-characterized, chronic and progressive form of axial SpA. The majority of research performed over the last two decades has used the modified New York Criteria to identify patients with AS (Table 1). In addition, these criteria were used in clinical trials performed to support product registration for AS in the United States. The AS criteria are anchored by radiographic changes.

Table 1: Modified New York criteria for ankylosing spondylitis

<table>
<thead>
<tr>
<th>Clinical Criteria</th>
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</thead>
<tbody>
<tr>
<td>• Low Back pain and stiffness for longer than 3 months, which improve with exercise, but are not relieved by rest</td>
</tr>
<tr>
<td>• Restriction of motion of the lumbar spine in both the sagittal and frontal planes</td>
</tr>
<tr>
<td>• Restriction of chest expansion relative to normal values correlated for age and sex</td>
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<table>
<thead>
<tr>
<th>Radiologic criterion</th>
</tr>
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<tbody>
<tr>
<td>• Sacroiliitis grade ≥2 bilaterally, or grade 3-4 unilaterally</td>
</tr>
</tbody>
</table>

Definitive ankylosing spondylitis is present if the radiologic criterion is associated with at least one clinical criterion.

2.2 Development and potential limitations of ASAS criteria for axial SpA

The modified New York criteria have potential limitations in clinical practice as they are designed to identify patients with established AS and do not identify all patients in the larger...
spectrum of inflammatory back pain. Although the long-term benefit of early treatment in AS, with respect to disease progression, remains unclear, the Assessment of Spondyloarthritis International Society (ASAS) developed criteria for axial SpA with the goal of identifying more patients in the spectrum of inflammatory back pain, including patients with early AS. By design, these criteria were meant to be inclusive, as not to miss patients with the potential for developing progressive disease. As a result, the ASAS criteria identify a heterogeneous group of patients as described below.

The ASAS criteria for axial SpA require patients to have back pain for at least three months and age of onset less than 45 years (Figure 1). Subsequently either sacroiliitis on radiographs or magnetic resonance imaging (MRI) in addition to at least one typical SpA gesture or the presence of HLA-B27 in addition to at least two typical SpA features needs to be present.

Figure 1: ASAS classification criteria for axial spondyloarthritis

ASAS classification criteria for axial SpA

(in patients with back pain > 3 months and age at onset < 45 years)

Sacroiliitis on imaging* 
plus
≥ 1 SpA feature** 

or

HLA-B27 
plus
≥ 2 other SpA features**

** SpA features:
- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Crohn’s disease/ulcerative colitis
- Good response to NSAIDs
- Family history for SpA
- HLA-B27
- Elevated CRP

* Sacroiliitis on imaging:
- Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA
- or
- Definite radiographic sacroiliitis according to mod. New York criteria


One of the concerns is that patients with less specific clinical features would be classified as having axial SpA, yet could have mechanical back pain, rather than inflammatory back pain. Previous literature has also emphasized the potential of these criteria to increase the “heterogeneity of the resulting disease group and reducing the utility of these criteria for both clinical and research applications.” Whether the inclusive nature of these criteria poses a similar hurdle to drug development will be an important issue for the committee’s consideration.

2.3 Considerations regarding nomenclature
Definitions of terms used in this document are provided in Table 2. In this document, the term nonradiographic axial SpA (nr-axSpA) refers to patients who were diagnosed according to the ASAS criteria and do not meet modified New York criteria on x-rays for AS. Given the relatively recent introduction of the ASAS criteria, some previous research has classified patients
with nr-axSpA according to other criteria, such as European Spondyloarthropathy Study Group (ESSG) or Amor criteria. Throughout the remainder of this document, differences in classification criteria are highlighted only if they may significantly impact the interpretation of the data.

We acknowledge the debate within the AS research community regarding whether the term AS should be replaced with axial SpA. Some authors have argued that the term AS should be retained because axial SpA cases have far greater clinical heterogeneity than AS and have broader range of etiologies. While the ASAS criteria encompass patients with both AS and nr-axSpA, research and treatment guidelines frequently separate these patients into subgroups given differences in the patient populations (Section 2.4). For example, recent treatment guidelines for the use of anti-TNF agents in patients with axial SpA retained both the modified New York criteria as well as the ASAS axial SpA criteria in the recommendations for diagnosis.

Table 2: Definitions and terms used in this briefing document

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition of this term as used in this document</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial spondyloarthritis (axial SpA)</td>
<td>Patients fulfilling the ASAS criteria for axial spondyloarthritis.</td>
</tr>
<tr>
<td>Ankylosing spondylitis (AS)</td>
<td>Patients fulfilling the modified New York criteria for AS. Thus, patients with pelvis x-ray changes consistent with AS.</td>
</tr>
<tr>
<td>Non-radiographic axial spondyloarthritis (nr-axSpA)</td>
<td>Patients fulfilling the ASAS criteria for axial spondyloarthritis, but without pelvis x-ray changes consistent with AS. Of note, these patients may have MRI changes suggestive of sacroiliitis.</td>
</tr>
</tbody>
</table>

2.4 Differences between AS and nr-axSpA

Patient populations

Data suggest that the entities nr-axSpA and AS might describe different patient populations. From a drug development perspective, it is important to understand whether these disease entities are similar or different in order to more precisely define the risk/benefit profile for a product. While a subset of patients with nr-axSpA may have early AS, it is currently unknown what proportion of patients with nr-axSpA will progress to AS.

Although AS and nr-axSpA have overlapping features, there are also many differences between them. First, a number of studies suggest that AS and nr-axSpA differ in their gender ratios. A consecutive case series found that 31.8% of patients with nr-axSpA were male compared to 76.8% of patients with AS. Similar, findings were noted in the German Spondyloarthritis Inception Cohort (GESPIC). Additional anticipated demographic differences have been demonstrated, including younger age and shorter disease duration for patients with nr-axSpA compared to patients with AS.

In addition to demographic differences, studies have demonstrated genetic differences between AS and nr-axSpA. Published studies that have enrolled patients with nr-axSpA have demonstrated a lower proportion of patients with HLA-B27 than what has been historically seen in studies in AS.

While some previous research has concluded that patients with AS and nr-axSpA have similar levels of disease activity, limited conclusions can be drawn. One previous research study compared measures of disease activity parameters in patients with nr-axSpA and AS. While not statistically significant, the proportion of AS patients with higher disease activity was larger for
eight measures, including global pain, back pain, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), patient’s global assessment, physician’s global assessment, Bath Ankylosing Spondylitis Functional Index (BASFI), Short Form-36 healthy survey mental component summary (SF-36 MCS), and ankylosing spondylitis quality of life questionnaire (ASQoL) compared to the proportion of nr-axSpA patients. Further, there were statistically significant differences between the proportion of AS and nr-axSpA patients with markers of disease activity that included objective markers of disease activity or composite endpoints that included objective markers, such as C-reactive protein (CRP) and Ankylosing Spondylitis Disease Activity Score (ASDAS). Similar findings were noted in the GESPIC study. However, both studies suggest that patients with nr-axSpA can have significant pain and functional limitation secondary to their illness.

Natural history
The disease course of axial SpA is thought to be highly variable and the long-term prognosis of patients with nr-axSpA is unknown. In contrast, while there is a spectrum of AS disease severity, the disease course of AS is often characterized by ongoing axial inflammation and radiographic progression associated with restricted mobility of the spine and decreased function.

The natural history of nr-axSpA has not yet been reliably established and it clearly varies more between cases than does the natural history of AS. To our knowledge, there are no longitudinal studies that have been published on the progression of this patient population using the ASAS classification criteria. Longitudinal studies have been performed using other classification criteria for axial SpA. For example, data from the GESPIC cohort, utilizing the ESSG criteria, suggest that progression from nr-axSpA to AS occurs in only a small percentage of patients. Of 95 patients with nr-axSpA at baseline, only 11.6% of patients developed AS over 2 years.

Further, a consecutive case series of 44 patients with nr-axSpA according to the ASAS classification criteria demonstrated that 61% of patients had symptom duration greater than 5 years, but by definition, none had radiographic changes. While it is known that radiographic changes in AS can be slow, it appears that a subset of patients with nr-axSpA might not develop structural changes. Further, previous literature suggests that up to half of patients with undifferentiated SpA have a self-limited illness with spontaneous remission after five years.

Thus, while some patients with nr-axSpA may have early AS, others appear to have a different disease course that may spontaneously remit or continue to have symptoms without clear structural progression. Defining the natural history of nr-axSpA is important to understanding the risk/benefit evaluation of a proposed treatment.

Treatment
In addition to nonpharmacological treatment, such as exercise and patient education, nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line therapy for patients with AS. For patients with AS who continue to have active disease despite NSAID treatment, tumor necrosis factor (TNF)-inhibitors (adalimumab, etanercept, infliximab, and golimumab) are approved therapies.

Even though the natural history of nr-axSpA is unknown, the observation that patients with nr-axSpA can have significant pain and functional limitations secondary to their illness has led investigators to treat patients with nr-axSpA with TNF-inhibitors. None of the TNF-inhibitors are approved in the United States to treat nr-axSpA. Thus, TNF-inhibitors are used off-label for patients with nr-axSpA. While some published data suggest efficacy of TNF-inhibitors in nr-axSpA, others have noted that response rates to therapy are lower in nr-axSpA than in AS. Important topics for this meeting will be whether the risk/benefit profile of treating patients with
nr-axSpA is different than the risk/benefit of treating patients with AS and whether nr-axSpA represents a clearly defined patient population that can be studied, and if so, how to study treatment options for nr-axSpA.

There are data to suggest that patients with AS and nr-axSpA have similar levels of disease activity. However, given the concerns regarding the unclear nature of the disease progression as patients with axial SpA may enter spontaneous remission, it is unknown if similar disease activity is an adequate reason to treat patients with the same classes of medications. Recently, the ASAS society published recommendations regarding when to initiate anti-TNF agents in patients with axial SpA. While axial SpA encompasses patients with both AS and nr-axSpA, the guidelines separated patients into those subgroups to be clearer. The guidelines do not recommend treating all patients with axial SpA according to the ASAS criteria with anti-TNF agents. Rather, the guidelines suggest treating patients with active disease for at least four weeks, with a BASDAI of at least 4 and “positive expert opinion.” Expert opinion is noted to be a doctor, usually a rheumatologist. The guidelines instruct that the expert should consider clinical features (history and examination) as well as either serum acute phase reactant levels and imaging results, such as radiographs demonstrating rapid progression or MRI scans indicating inflammation. Thus, the ASAS recommendations on when to start an anti-TNF inhibitor require a certain level of disease activity in a subset of patients with nr-axSpA.

3. Regulatory considerations

The purpose of this AAC meeting is to discuss the implications of the ASAS classification criteria for drug approval. The foundation of the drug approval process is demonstration of efficacy and safety of the proposed product within the intended patient population and how the balance of efficacy and safety translates into a favorable risk/benefit assessment. Important contextual considerations related to the intended patient population are the severity and natural history of the disease if it is not treated. This section will review the foundation of drug approval, the current framework for drug approvals for AS, and possible concerns related to expansion of the indication to axial SpA.

3.1 Overview of drug approval

The Code of Federal Regulations (CFR) state that FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling. At this AAC meeting, we will focus on efficacy and safety considerations for drug approval.

To support approval, a product must demonstrate “substantial evidence consisting of adequate and well-controlled investigations…that the drug product will have the effect it purports or is represented to have under conditions of use prescribed, recommended, or suggested in the proposed labeling” (21 CFR 314.125(b)(5)). There are two important aspects of this requirement. First, the efficacy in the population being described in labeling must be convincingly demonstrated. Second, the evidence is from well-controlled investigations, which is intentionally plural, indicating that independent substantiation of efficacy results is generally required.

While conclusions of efficacy based on two persuasive studies are more secure than conclusions based on a single study, there are situations in which the FDA will rely upon evidence of effectiveness from a single study. Reliance on a single study is generally limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a
second trial would be practically or ethically impossible. In certain cases, effectiveness of an approved drug product for a new indication may be adequately demonstrated by a single study of a new use, with independent substantiation from study data in related uses\textsuperscript{17}.  

In addition, to support approval, the product must be shown to be safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling. For products intended for long-term treatment of non-life-threatening conditions, the International Conference on Harmonization (ICH) E1A standards have generally recommended that 1,500 patients be exposed to the investigational product, with 300 to 600 exposed for 6 months and 100 exposed for 1 year. For rheumatology-related immunosuppressive or immunomodulatory products, FDA has historically requested larger long-term safety databases to assess for uncommon serious adverse events with longer latency, such as malignancy.

The efficacy and safety evaluation forms the basis of the risk-benefit profile for a drug. This risk-benefit profile is considered in the context of the disease. Clinical judgment helps guide which risks are acceptable for a given benefit within the context of a certain patient population. Issues that are considered include whether patients have other therapeutic alternatives, the expected clinical benefit of the drug, and the severity and natural history of the disease.

3.2 General framework of drug development in AS
Since 1998, four drugs have been approved for the treatment the indication of “treatment of signs and symptoms of active AS”: infliximab, etanercept, adalimumab, and golimumab. All of the drugs are TNF-inhibitors (Table 3). At the time of approval, all of the drugs were either previously or concurrently approved for the treatment of rheumatoid arthritis.

Study Population
The study population for the trials used to support each of the approved products was adult patients with AS. Three of the four product labels note that study patients were required to fulfill the modified New York criteria for AS. All of the studies were performed in patients with active disease, which was defined in a variety of ways. In general, patients were required to have evidence of significant pain and disease activity. In the product labels, half of the studies included the requirement that patients needed to have failed other therapies commonly used to treat AS, such as NSAIDs. As the drugs were studied in a subset of the general AS population, the restricted population of patients with “active” disease is reflected in the indication.

Duration/Exposure
The primary efficacy and safety data for each of the products approved for AS are derived from one randomized, placebo-controlled, double-blind study of 24 weeks duration. The adalimumab prescribing information describes an open label extension of 28 weeks duration after the placebo-controlled study.

The total size of the studies ranged from 277 to 356 patients and several of the programs included additional information from other smaller studies in AS patients.
Table 3: Data described in labels of products approved for ankylosing spondylitis after 1998

<table>
<thead>
<tr>
<th></th>
<th>Infliximab</th>
<th>Etanercept</th>
<th>Adalimumab</th>
<th>Golimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of approval of AS indication</td>
<td>12/17/04</td>
<td>7/24/03</td>
<td>8/28/06</td>
<td>4/24/09</td>
</tr>
<tr>
<td>Study design</td>
<td>R, DB, PC</td>
<td>R, DB, PC</td>
<td>R, DB, PC</td>
<td>R, DB, PC</td>
</tr>
<tr>
<td>Duration of studies (weeks)</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>OLE?</td>
<td>No</td>
<td>No</td>
<td>Yes, 28 (weeks)</td>
<td>No</td>
</tr>
<tr>
<td>Number of AS studies described in label</td>
<td>2 (1 small study in 70 AS patients)</td>
<td>3 (minimal details about 2 other studies: 40 patients and 84 patients)</td>
<td>2 (second R, DB, PC, study in 82 AS patients)</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>279 (78 placebo, 201 infliximab)</td>
<td>277 (139 placebo, 138 etanercept)</td>
<td>315 (107 placebo, 208 adalimumab)</td>
<td>356 (78 placebo, 138 golimumab 50mg, 140 golimumab 100mg)</td>
</tr>
<tr>
<td>Modified NY criteria?</td>
<td>Yes</td>
<td>Yes</td>
<td>Not mentioned</td>
<td>Yes</td>
</tr>
<tr>
<td>Patient population</td>
<td>Inadequate response to glucocorticoids, NSAIDS, analgesics, methotrexate or sulfasalazine</td>
<td>Inadequate response to NSAIDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active AS</td>
<td>BASDAI score &gt;4 and spinal pain &gt;4</td>
<td>Average morning stiffness duration and intensity ≥30 on a 100 unit VAS and 2 of the following 3 parameters: 1) patient global assessment, 2) average of nocturnal and total back pain, and 3) average score on the BASFI</td>
<td>BASDAI ≥4 cm, total back pain ≥40mm, and morning stiffness ≥1 hour</td>
<td>BASDAI ≥4 and total back pain VAS ≥4</td>
</tr>
<tr>
<td>Endpoints in label</td>
<td>ASAS 20/50/70, ASAS components, low level of disease activity, CRP, spinal mobility, SF-36 PCS, SF-36 MCS</td>
<td>ASAS 20/50/70, ASAS components, CRP, spine mobility measures</td>
<td>ASAS 20 response, ASAS components, BASDAI BASMI, CRP, ASQoL score, SF-36 PCS</td>
<td>ASAS 20/40, ASAS components</td>
</tr>
</tbody>
</table>

Abbreviations: R=randomized, D=double blind, PC=placebo controlled; OLE=open label extension; ASAS=Assessment in Ankylosing Spondylitis; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI=Bath Ankylosing Spondylitis Metrology Index; CRP=C-reactive protein; ASQoL=Ankylosing spondylitis Quality of Life Questionnaire score; SF-36 PCS=Short Form-36 Physical Component Summary score; SF-36 MCS=short form-36 mental component score; VAS=visual analogue scale

Source: Prescribing information for infliximab, etanercept, adalimumab, golimumab (accessed May 20, 2013)

Primary efficacy endpoints
The primary efficacy endpoints assessed in AS programs focused on validated measures of improvement in the signs and symptoms of AS. As radiographic disease progression in AS is slow, clinical AS programs have focused on improvement in signs and symptoms of AS, rather than changes in radiographic disease progression. Thus, most of the endpoints evaluated to support drug approval in AS involve patient reported outcomes related to pain and functional status, rather than radiographic markers of disease progression. These endpoints included Assessment in Ankylosing Spondylitis (ASAS) responses, Bath AS Functional Index (BASFI), and Bath AS Disease Activity Index (BASDAI).

An ASAS response is a composite, patient-reported outcome endpoint. The components of this endpoint include: patient’s global assessment, total back pain, function assessed using the BASFI, and inflammation assessed using the BASDAI.

**Table 4: Outcome measures in AS**

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Definition</th>
<th>Range</th>
</tr>
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</table>
| ASAS (Assessment in Ankylosing Spondylitis) 20 response† | A patient is classified as having an ASAS20 response if both of the following is achieved:  
  - An improvement of 20% and an absolute improvement of ≥1 unit (on a scale of 0 to 10) from Baseline in ≥3 of the following 4 domains:  
    - Patient’s global assessment (VAS 0 to 100)  
    - Pain: assessed by total back pain (VAS 0 to 100)  
    - Function: assessed using the BASFI  
    - Inflammation: assessed using the last two stiffness assessments in the BASDAI  
  - Absence of deterioration from baseline (where deterioration is defined as a net worsening of >1 unit [on a scale of 0 to 10]) in the potential remaining domain | Yes or No       |
| Bath AS Functional Index (BASFI)                | A functional instrument (a higher score indicates worse function) based on the patient’s assessment of his/her ability to perform 10 selected activities during the past week using a visual analogue scale ranging from easy to impossible. The BASFI is the mean of these 10 questions. | 0 to 10        |
| Bath AS Disease Activity Index (BASDAI)         | A summary of 6 self-assessments (i.e., fatigue, spinal pain, joint pain, enthesitis, overall level of morning stiffness, and duration of morning stiffness). The first 4 scales are weighted by 0.2 and the last two are weighted by 0.1. The mean of the last two scales provide an assessment of stiffness that is used in the ASAS. | 0 (none) to 10 (very severe) |
| Bath AS Metrology Index (BASMI)                | Comprises the sum of 5 measures of hip and spine mobility [i.e. tragus-to-wall, lumbar flexion (Schober test), cervical rotation, lumbar side flexion, and intermalleolar distance] that are each categorized as 0 (mild), 1 (moderate), or 2 (severe) | 0 to 10 (lower score indicates better function) |

Abbreviations: VAS=visual analogue scale  
†ASAS40 and 70 response criteria are defined similarly, but with 40 and 70% improvement in the mentioned domains, respectively.
Risk/Benefit in AS
The ability to determine the risk/benefit of a potential drug product for a given indication is predicated on an understanding of the risks inherent in the underlying disease being targeted, and balancing these risks with both the risks and benefits of the proposed treatment. While there is a spectrum of AS disease severity, the disease course of AS is often characterized by ongoing axial inflammation and radiographic progression associated with restricted mobility of the spine and decreased function. A previous study found that less than 1% of AS patients enter remission and the risk of progression for patients with active disease is high. Thus, the risk/benefit evaluation of a product proposed for the treatment of AS occurs within the context of our knowledge that this is a chronic, progressive, and severe disease.

3.3. Development of ASAS classification criteria and potential impact on drug development
In recent years, there have been efforts made to facilitate and standardize making an earlier diagnosis of axial SpA and, subsequently, to treat patients earlier in the disease course. Previous criteria, such as the ESSG criteria and the Amor criteria were developed before MRI was available and classified patients as having spondyloarthropathy, rather than specifically classifying axial or peripheral disease. The ASAS group developed separate classification criteria for axial and peripheral SpA. The classification for axial SpA identified patients without radiographic sacroiliitis. Subsequently, drug efficacy studies have been performed and treatment recommendations have been released based on these classification criteria. The goal of this AAC meeting is to discuss the potential impact of using these classification criteria to define an indication for drug development.

Expanded population
While the exact prevalence of axial SpA is not known, use of the ASAS classification criteria for axial SpA rather than the historically used classification criteria for AS would markedly expand the population eligible for a given treatment, as shown in Figure 2. Currently, drugs have been approved for the more limited indication of AS (gray circle). These patients meet modified New York criteria for AS. Use of the ASAS classification criteria could potentially expand the indication to include all patients with axial SpA (solid and lined gray circles).
Concerns about the potential axial SpA indication as defined by the ASAS classification criteria

In addition to encompassing a broader population, because the ASAS criteria for axial SpA were developed relatively recently, there are limited data available on the natural history of axial SpA when defined by these criteria. This is further complicated by the likelihood that the broader population described by the ASAS criteria likely includes subgroups of patients that may have markedly different disease courses and prognoses—from patients who could have mechanical back pain (e.g., meeting ASAS criteria of HLA-B27 positive, family history of SpA and response to NSAIDs), to inflammatory back pain that is self-limited, to pre-radiographic AS that would be expected to be chronic and progressive. Each of these subgroups may have a different risk-benefit profile, which would make defining the overall risk-benefit profile for the axial SpA indication difficult.

The FDA recognizes that some patients without radiographic changes consistent with AS have inflammatory back pain that causes significant symptoms and decreased quality of life. Thus, it may be reasonable to expand the traditional AS indication with the goal of preventing joint damage. However, given the limited information regarding the natural history of inflammatory back pain as defined by the ASAS criteria, it is unclear what the possible framework is to support drug development in axial SpA.

Concerns regarding misclassification of “inflammatory back pain”

In considering the use of the ASAS classification criteria to potentially expand the number of patients with inflammatory back pain who are treated, it is important to consider the potential for misclassification with these criteria. Back pain is a common clinical problem, particularly in primary care. About one fourth of United States adults report low back pain in the past 3 months and back pain is the second most common
symptom-related reason for clinician visits in the United States\textsuperscript{22}. In contrast to the well described epidemiology of back pain, relatively little is known regarding the epidemiology of axial SpA. While the prevalence of axial SpA is unclear, it is clear that only a small percentage of patients with back pain have axial SpA. Further, recent data indicated low to moderate agreement in the classification of individual patients when using the ASAS criteria and rheumatology experts. The study indicated that 21\% of the patients were misdiagnosed in clinical practice\textsuperscript{23}. Misdiagnosis would be a major concern, as the risk-benefit profile of immunosuppressive or immunomodulatory therapies would likely not be favorable for non-inflammatory back pain.

4. Conclusions
Historically, treatments have been developed for definitively diagnosed AS, and were expected to be used indefinitely, given the chronic, progressive nature of AS. However, patients with less definitive inflammatory back pain may also suffer significant symptoms, functional disability, and work lost. The ASAS axial SpA criteria were developed to capture these patients in a more inclusive way in clinical practice; but the difficulty with trying to capture this group as a potential indication for drug approval is the possibility of differing risk-benefit profiles and differing natural histories that may require differing regulatory approaches. The FDA recognizes that inflammation can be present in the sacroiliac joints despite the absence of sacroiliitis on radiographs. However, we are concerned that the ASAS axial SpA criteria are overly broad and likely encompass a heterogeneous patient population. Thus FDA requests the committee’s input on whether a broader axial spondyloarthritis indication is a reasonable target indication for drug development; and if so, how best to approach clinical development programs for a broader indication, and what measures should be undertaken to ensure the risk-benefit profile remains favorable for the indicated population.

Reference List


Draft Topics for Discussion

1. Given the limitations of the data available on the natural history of the subgroups of patients with axial spondyloarthritis as defined by the ASAS criteria, discuss whether additional data are needed before implementing axial spondyloarthritis as an indication for clinical development programs.
   
   a) If so, describe your rationale and what data would be needed
   
   b) If not, describe your rationale for concluding no additional data are needed.

2. Discuss the pros and cons of using the ASAS classification criteria to define a population of patients with axial spondyloarthritis, as the basis of a new indication for product labels.
   
   a) Include discussion of the subgroups of axial spondyloarthritis patients captured by the ASAS criteria (e.g. ankylosing spondylitis and nonradiographic axial spondyloarthritis), differences in disease progression and the impact of this heterogeneity on risk/benefit assessment.
   
   b) Discuss whether certain parameters, such as elevated inflammatory markers or MRI evidence of inflammation, should be utilized to better define a subgroup of axial spondyloarthritis patients as the basis for a broadened indication.

3. Discuss the types of efficacy data, including the number of trials, the length of trials, and the endpoints evaluated, that would be needed to support the broader indication of axial spondyloarthritis as defined by the ASAS criteria.
   
   a) Include whether the type of efficacy data is different if the product already has established efficacy in AS.
   
   b) Discuss whether longer trials in patients with nr-axSpA are needed to assess how groups respond over time and to better inform the risk/benefit profile.

4. Discuss the types of safety data that would be needed to support the indication of axial spondyloarthritis.