

FDA Arthritis Advisory Committee Meeting July 22, 2013: Introductory Remarks

Axial Spondyloarthritis: Regulatory Considerations on its use as an Indication for Drug Development

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Axial Spondyloarthritis (AxSpA)

- Historically, an umbrella term to capture the range of spondyloarthritides that affect the axial skeleton
 - Could include early through established Ankylosing Spondylitis (AS)
 - Also could include reactive arthritis, inflammatory bowel-disease related spondyloarthritis, or “undifferentiated” spondyloarthritis

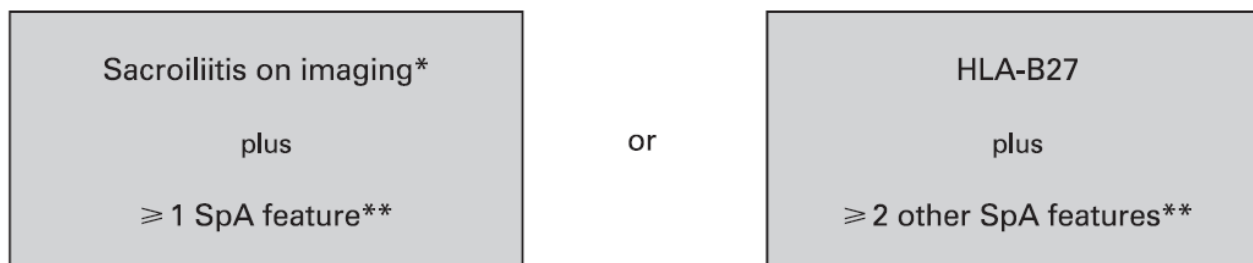
Ankylosing Spondylitis (AS)

- Definitively diagnosed AS has precedent as an indication for drug approval
 - TNF inhibitors since 2003
 - Corticosteroid labels long before that
 - Modern clinical trials utilized modified New York criteria (radiographic sacroiliitis) to identify patients for inclusion
- Recognizing that patients can have debilitating symptoms long before radiographic changes are apparent, early treatment of such patients may be clinically justifiable, if these patients can be reliably identified

ASAS classification criteria for AxSpA

ASAS classification criteria for axial SpA

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



** 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

Sensitivity 82.9%, specificity 84.4%; n = 649 patients with chronic back pain and age at onset $<$ 45 years. Imaging arm (sacroiliitis) alone has a sensitivity of 66.2% and a specificity of 97.3%.

** Note: Elevated CRP is considered a SpA feature in the context of chronic back pain

Potential limitations of AxSpA as identified by ASAS criteria

- More inclusive than modified New York criteria for AS
 - Increased heterogeneity of resulting population
- Unclear natural history
 - Potentially transitory nature of the diagnosis
- Potential for misclassification

Regulatory Considerations

- **Patient population/enrichment**
 - Which AxSpA patients should be studied in drug development programs
- **Regulatory standard for evidence of efficacy**
 - Substantial evidence
- **Trial design and duration**
 - Optimal design and duration is unclear as the indication could include conditions with various disease progression and resolution trajectories
- **Risk/benefit**
 - How to determine in the context of incomplete long-term characterization of the AxSpA subpopulations

Purpose of Proceedings Before an Advisory Committee (21 CFR 14.5)

- a) An advisory committee is utilized to conduct public hearing on matters of importance that come before FDA, to review the issues involved, and to provide advice and recommendations to the Commissioner
- b) The Commissioner has sole discretion concerning action to be taken and policy to be expressed on any matter considered by an advisory committee

Regulatory Considerations for the Potential Novel Indication Axial Spondyloarthritis

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Center for Drug Evaluation and Research
July 22, 2013

Outline

- Background on axial spondyloarthritis (SpA)
- Differences between axial SpA subgroups
- Regulatory considerations
 - Overview of drug approval
 - Drug approval for ankylosing spondylitis (AS)
 - Concerns regarding the novel indication axial SpA
- Conclusions

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Background on axial SpA

- **Spectrum of inflammatory diseases of the spine**
 - Ranges from self-limited inflammation to bony destruction of the spine
 - Includes ankylosing spondylitis (AS)
 - Well-recognized and categorized phenotype
 - Focus of research and drug development for the last two decades
 - » Utilized the modified New York Criteria to identify patients
 - Variety of classification criteria have been proposed to identify patients in this spectrum

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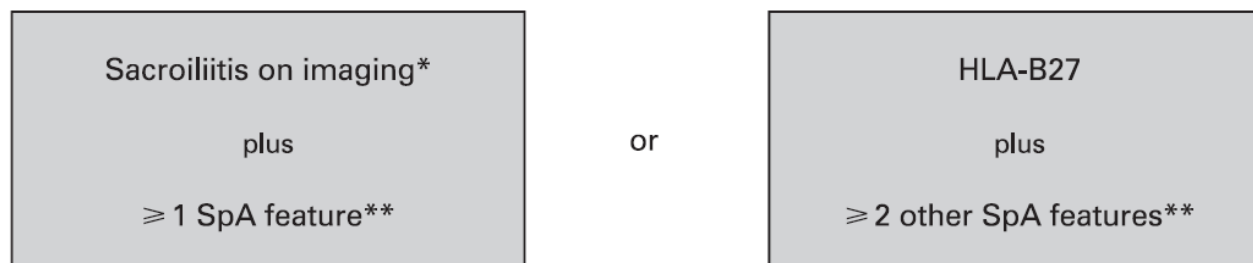
Definitions and terms used in this presentation

Term	Definition as used in this presentation
Axial spondyloarthritis (SpA)	Patients fulfilling the ASAS criteria for axial SpA
Ankylosing spondylitis (AS)	Patients fulfilling the modified New York criteria for AS. Thus, patients with x-ray changes consistent with AS.
Non-radiographic axial spondyloarthritis (nr-axSpA)	Patients fulfilling the ASAS criteria for axial SpA, but without pelvic x-ray changes consistent with AS.

ASAS classification criteria for axial SpA

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



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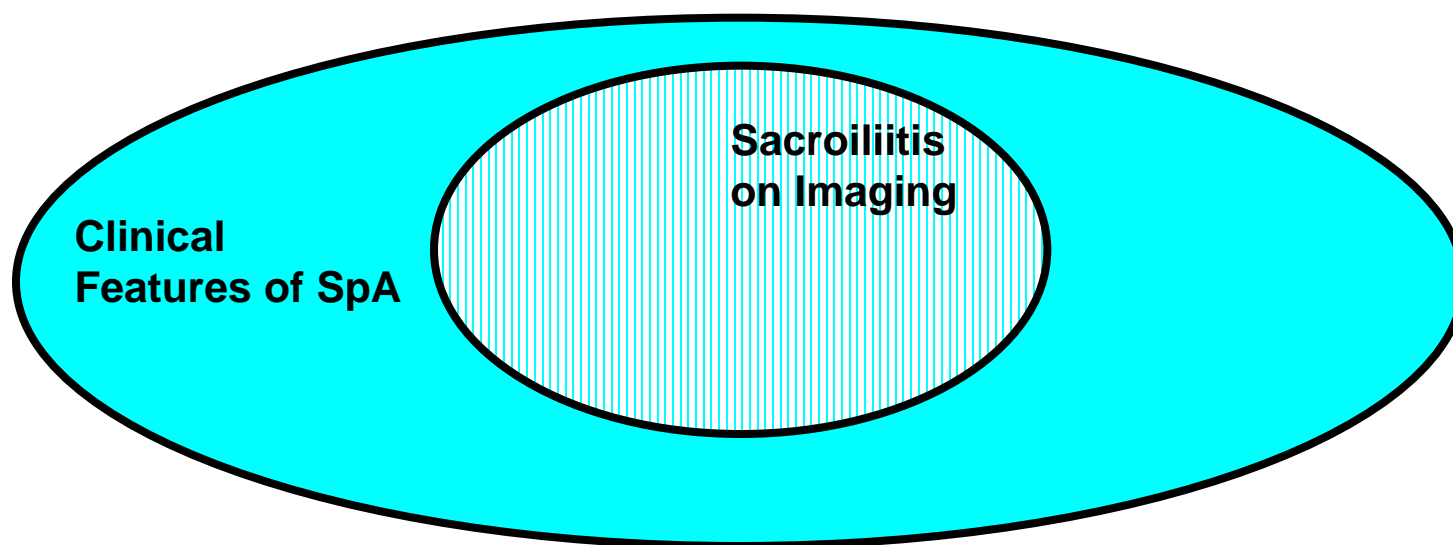
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Axial spondyloarthritis

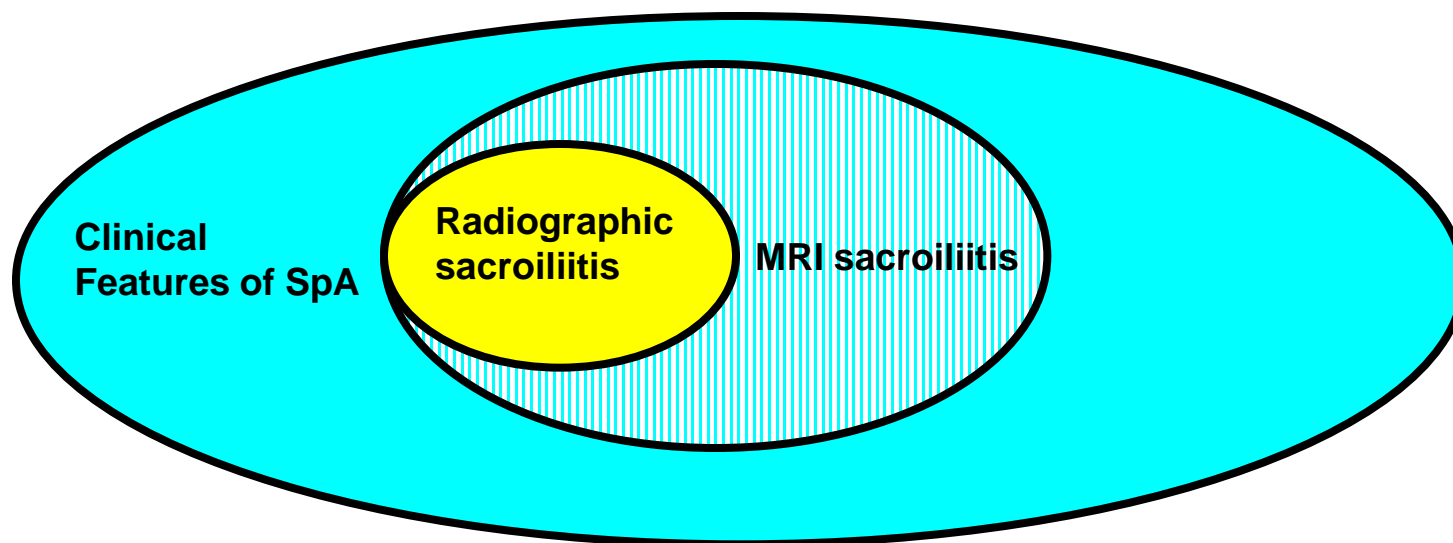


**Clinical
Features of SpA**

Axial spondyloarthritis



Axial spondyloarthritis



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Axial SpA subgroups

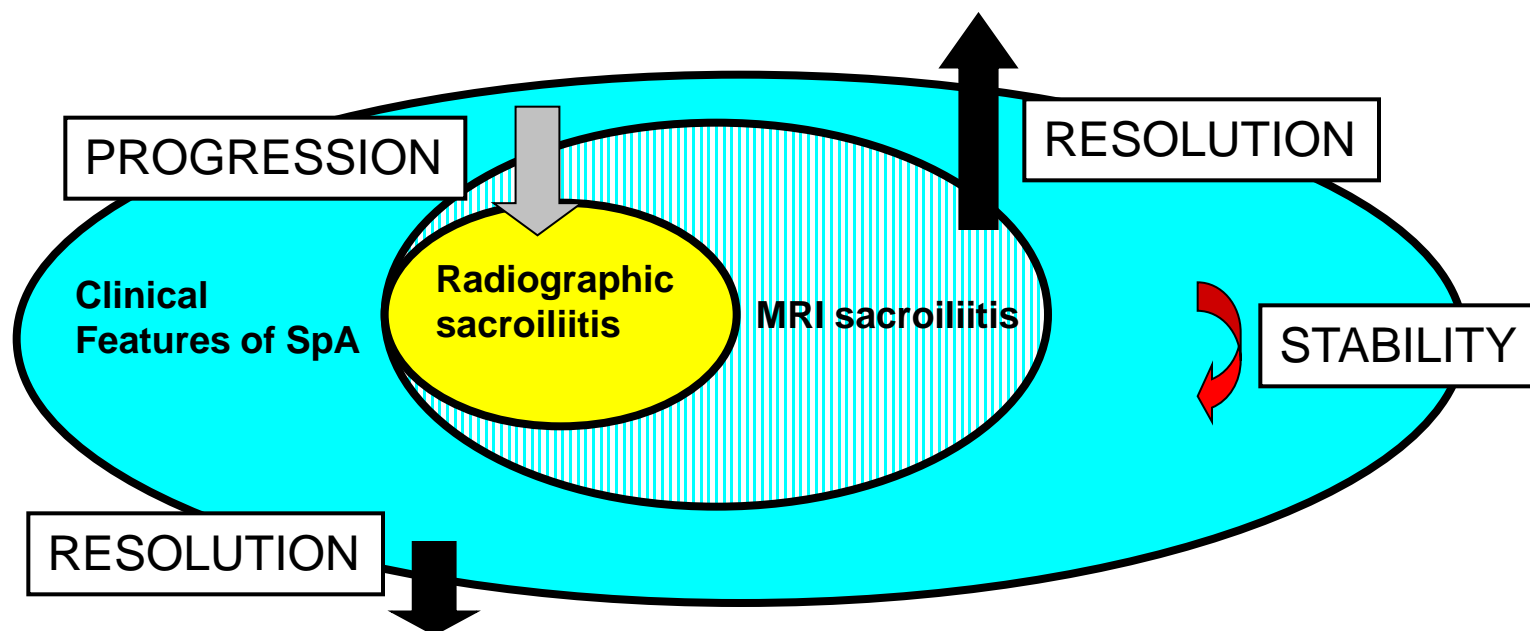
- From a drug development perspective, it is important to understand whether there are important subgroups within axial SpA
 - AS and nr-axSpA
- Potential differences identified in published literature:
 - Demographics (age, gender)
 - Genetics
 - Severity of disease signs and symptoms
 - Disease duration

Kiltz. Arthritis Care Res 2012;64:1415-22.
Poddubnyy. Ann Rheum Dis 2011;70:1369-74.
Rudwaleit. Arthritis Rheum 2009;60:717-27.

Axial SpA: natural history (1)

- No longitudinal studies using the ASAS classification criteria
 - Epidemiologic data utilizing other classification criteria for axial SpA suggest a **heterogeneous natural history**
- Multiple potential pathways
 - Symptoms may:
 - Spontaneously remit
 - Continue without clear structural progression
 - Continue with clear structural progression

Axial SpA: natural history (2)



Axial SpA: natural history (3)

- Heterogeneous disease, varied natural history
 - Only a small subgroup of patients appear to have “early AS”

Treatment of axial SpA

- AS
 - NSAIDs are first-line
 - Four TNF-inhibitor are approved therapies
- Nr-axSpA
 - No approved therapies in the United States
- ASAS society recommendations
 - Active disease and positive expert opinion
 - Recommend consideration of a TNF-inhibitor in a subgroup of patients with certain levels of disease activity

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Efficacy standard

- CFR 314.125 Refusal to Approve an Application

(b) (5) “... 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 the conditions of use prescribed, recommended, or suggested in the proposed labeling.”

Meaning of substantial evidence†

- Well-designed, well-controlled studies demonstrating an efficacy finding
 - 2 studies, appropriate endpoint, both win statistically and clinically
- One study may be sufficient if:
 - Excellent design, multicenter study shows highly reliable, statistically strong evidence on an important clinical benefit, such as survival
 - Demonstrates statistically and clinically meaningful benefit in multiple unrelated, pre-specified endpoints
 - Independent substantiation from study data in related uses
 - Generally for an approved drug product for a new, related indication

†Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (1998)

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Drug approval for AS

- Since 1998, four drugs have been approved for the treatment of active AS
 - Infliximab
 - Etanercept
 - Adalimumab
 - Golimumab
 - All TNF-inhibitors

General framework for drug approval for AS

- ***Study population***
- ***Duration/exposure***
- ***Primary efficacy endpoints***
- ***Risk/benefit in AS***

General framework for drug approval for AS

- ***Study population***
 - Adult patients with active AS
 - Modified New York criteria
- ***Duration/exposure***
- ***Primary efficacy endpoints***
- ***Risk/benefit in AS***

General framework for drug approval for AS

- ***Study population***
 - Adult patients with active AS
 - Modified New York criteria
- ***Duration/exposure***
 - Primary efficacy and safety data from one randomized, placebo-controlled, double-blind study of 24 weeks duration
- ***Primary efficacy endpoints***
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 - Signs and symptoms of AS, predominantly patient-reported outcomes
 - No radiographic outcomes
- ***Risk/benefit in AS***

General framework for drug approval for AS

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 - Primary efficacy and safety data from one randomized, placebo-controlled, double-blind study of 24 weeks duration
- ***Primary efficacy endpoints***
 - Signs and symptoms of AS, predominantly patient-reported outcomes
 - No radiographic outcomes
- ***Risk/benefit in AS***
 - Context of a chronic, progressive, and severe disease

Important assessment tools in AS

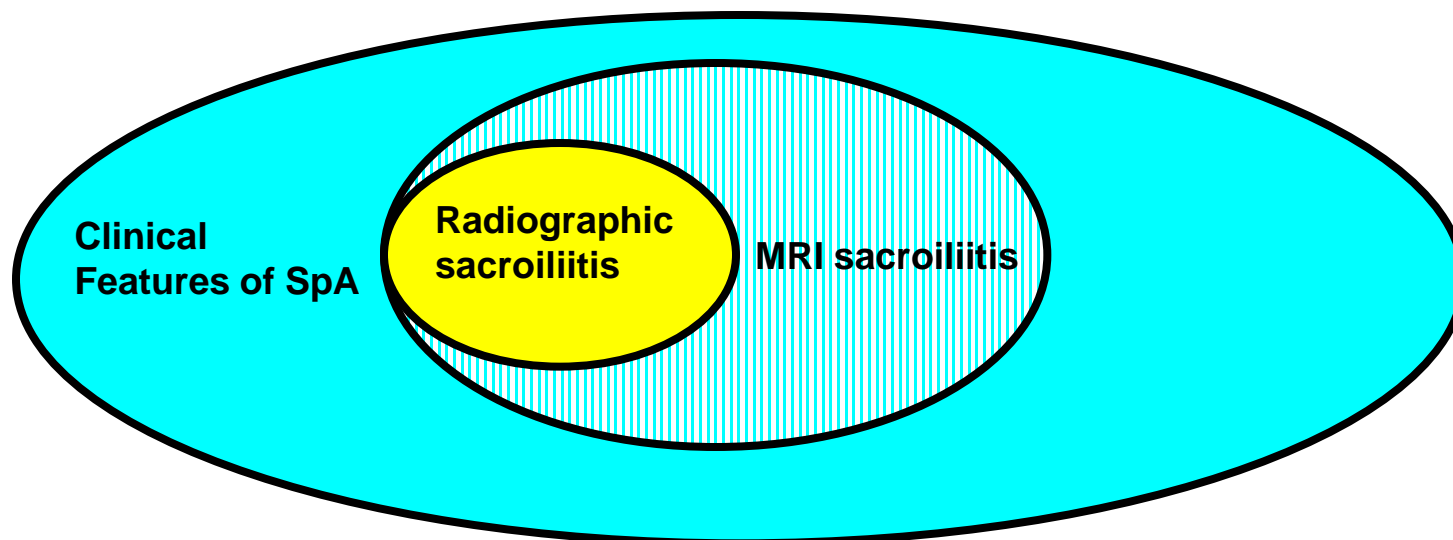
Instrument	Definition	Range
Bath AS Functional Index (BASFI)	Functional instrument based on the patient's assessment of his/her ability to perform 10 selected activities	0 to 10
Bath AS Disease Activity Index (BASDAI)	Summary of 6 self-assessments (fatigue, spinal pain, joint pain, enthesitis, overall level of morning stiffness, and duration of morning stiffness).	0 to 10
Bath AS Metrology Index (BASMI)	Sum of 5 measures of hip and spine mobility	0 to 10
ASAS 20% response (ASAS20)	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, total back pain, function (BASFI), and inflammation (questions 5 and 6 of BASDAI) with an absence of deterioration from baseline in the potential remaining domain	Yes or No

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Potential impact of ASAS classification criteria on drug development

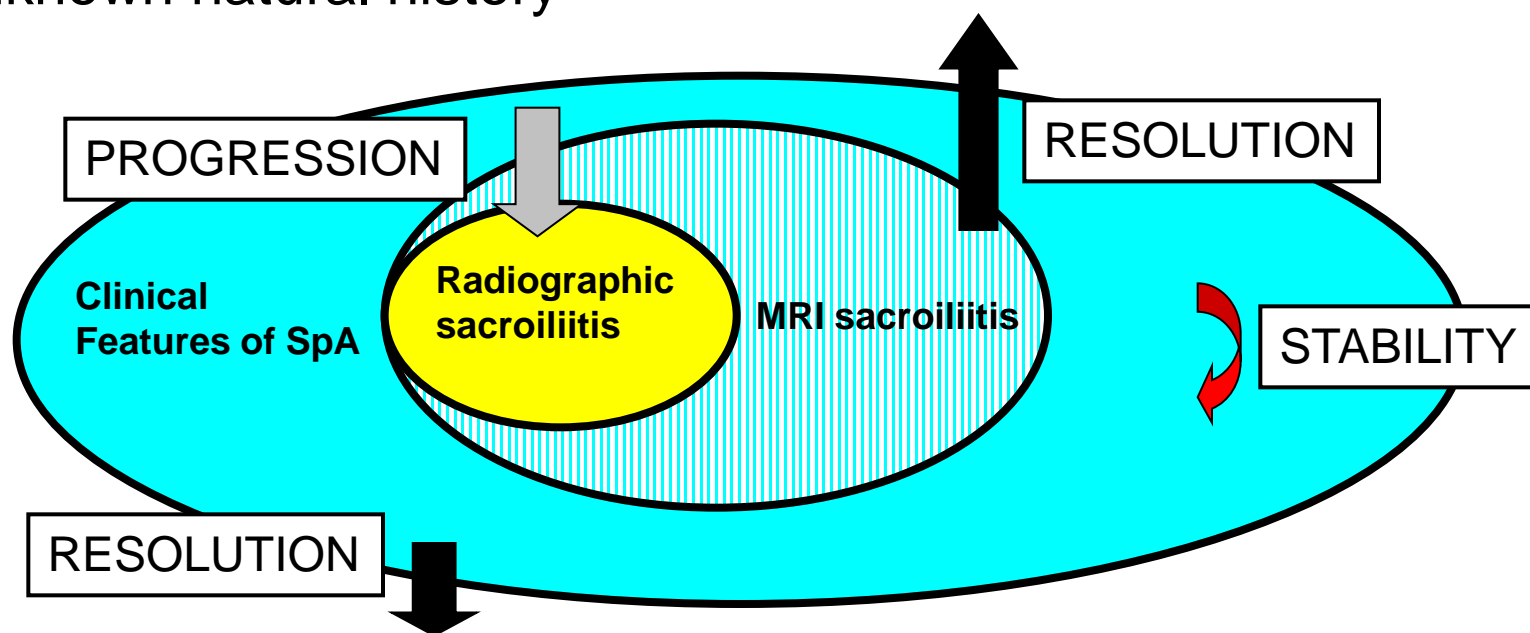
- Expanded population
 - Unknown prevalence



- **Yellow**=AS (meeting modified NY criteria), currently approved indication
- **Blue (solid + stripe)**=non-AS axial SpA or non-radiographic SpA (nr-axSpA)
- **Yellow + Blue (solid + stripe)**=potential new indication

Potential impact of ASAS classification criteria on drug development: defining risk/benefit

- Unknown natural history



- Unclear subgroups

Potential limitations of axial SpA as identified by ASAS classification criteria

- More inclusive than modified New York criteria for AS
 - Increased heterogeneity of resulting population
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 - Possible transitory nature of the diagnosis
- Potential for misclassification

Potential misclassification

- Back pain is very common
 - Only a small percentage of patients with back pain have axial spondyloarthritis
- Data suggest potential misclassification using ASAS classification criteria
 - Low to moderate agreement in classification of individual patients when using the ASAS criteria and rheumatology experts
 - 63% of patients diagnosed with axial spondyloarthritis according to the ASAS classification criteria, were not diagnosed by rheumatology expert

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Risk/benefit assessment

- Considers risks inherent in the underlying disease
 - Balancing those risks with both the risks and benefits of the proposed treatment

Conclusions: axial SpA

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Discussion Question 1

- Given the existing data available on the natural history of the subgroups of patients with axial spondyloarthritis (axSpA) as defined by the ASAS criteria, discuss whether additional data are needed before implementing axSpA 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

Discussion Question 2

- Discuss the pros and cons of using the ASAS classification criteria to define a population of patients with axSpA, as the basis of a new indication for product labels
 - a) Discuss the subgroups, such as ankylosing spondylitis (AS) and nonradiographic axSpA, differences in disease progression and the impact of this heterogeneity on the risk/benefit assessment
 - b) Discuss whether certain parameters, such as elevated inflammatory markers or MRI inflammation, should be used to define a subgroup of axSpA patients as the basis for a broadened indication

Discussion Question 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 axSpA as defined by the ASAS criteria
 - a) Include whether efficacy data expectations should be 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

Discussion Question 4

- Discuss the safety data that would be needed to support the indication of axial spondyloarthritis