FDA Arthritis Advisory Committee Meeting July 23, 2013 AM: Introductory Remarks

Adalimumab (Humira®) for active non-radiographic axial spondyloarthritis (nr-axSpA) in adults with objective signs of inflammation by elevated CRP or MRI, who have had inadequate response or are intolerant to NSAIDs

Sarah Yim, M.D.

Associate Director, Division of Pulmonary, Allergy, and Rheumatology Products

Center for Drug Evaluation and Research

Background: Adalimumab

- **Name:**
  - Adalimumab (Humira®)
- **Product:**
  - Monoclonal antibody targeting TNFα
- **Initial Approval:**
  - Treatment of adult patients with moderately to severely active RA (December 2002)
- **Subsequent Approvals**:
  - Multiple subsequent approvals, including signs and symptoms of active AS (August 2006)

TNF=tumor necrosis factor

Proposed indication and dosing

- **Proposed indication**:
  - "Reducing signs and symptoms in adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation by elevated CRP or MRI who have had an inadequate response to or are intolerant to nonsteroidal anti-inflammatory drugs"
- **Proposed dosing**:
  - 40mg every other week (same as AS)

CRP=c-reactive protein
MRI=magnetic resonance imaging

One pivotal trial: M10-791

Study	Design/ Sites	Patient population	Treatment, duration	N	Primary efficacy variable
M10-791	R, DB, PC/ 37 sites	Active non-radiographic axial spondyloarthritis with an inadequate response to NSAIDs or a contraindication to NSAIDs	**12-week controlled period:** •Adalimumab 40mg SC eow •Placebo **144-week open label extension:** •Adalimumab 40mg SC eow	94 (adalimumab) 91 (placebo)	ASAS40 at week 12

R=randomized; DB=double blind; PC=placebo controlled; eow=every other week

- Sponsor submitted 68 weeks of data in the original application

Efficacy Considerations

- Proposed indication is for a subgroup of the axSpA patients studied in M10-791
- M10-791 was intended to enroll nr-axSpA patients and exclude AS patients; however AS patients were included
- Overall treatment difference in the study was impacted by the higher treatment difference observed in AS patients, for whom adalimumab is already approved
- Estimated treatment effect in nr-axSpA patients was modest
  - Use of objective signs of inflammation by elevated CRP or MRI to define a target population resulted in a small numerical increase in treatment difference

Regulatory Considerations

- **Patient population/enrichment**
  - Studied patients *versus* proposed indication
- **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
- **Safety**
  - Framework of known risks associated with TNF inhibitors
- **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

Arthritis Advisory Committee Meeting
Adalimumab (Humira®)
for Non-Radiographic Axial Spondyloarthritis
sBLA 125057/323

Janet Maynard, MD, MHS
Acting Clinical Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products
Center for Drug Evaluation and Research

July 23, 2013

Outline

- Background
- Adalimumab non-radiographic axial spondyloarthritis program
- Trial M10-791 patient population
- Differences between central and local x-ray interpretation
- Efficacy results
- Safety results
- Conclusions

Outline

- Background
- Adalimumab non-radiographic axial spondyloarthritis program
- Trial M10-791 patient population
- Differences between central and local x-ray interpretation
- Efficacy results
- Safety results
- Conclusions

Background on axial spondyloarthritis (SpA)

- **Spectrum of inflammatory diseases of the spine**
  - Ranges from self-limited inflammation to bony destruction of the spine
  - Includes patients with ankylosing spondylitis (AS)
    - Well-recognized and categorized phenotype
  - Variety of classification criteria have been proposed to identify patients in this spectrum
    - Focus: Assessment in Spondyloarthritis international Society (or ASAS) classification criteria

Potential limitations of ASAS classification criteria as the basis of a novel indication

- **Uncertainties**
  - Disease spectrum
    - Important subgroups?
  - Natural history
    - Potentially transitory nature of the diagnosis
  - Prevalence

ASAS classification criteria for axial SpA

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

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

Rudwaleit M. Ann Rheum Dis 2009;68:777.

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)

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

Issues for discussion: nr-axSpA

- **Patient population/enrichment**
  - Studied patients *versus* proposed indication
- **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
- **Safety**
  - Framework of known risks associated with TNF-inhibitors
- **Risk/benefit**
  - How to determine in the context of incomplete long-term characterization of the axial SpA subpopulations

Outline

- Background
- Adalimumab non-radiographic axial spondyloarthritis program
- Trial M10-791 patient population
- Differences between central and local x-ray interpretation
- Efficacy results
- Safety results
- Conclusions

Proposed product: adalimumab

- **Name:**
  - Adalimumab (Humira®)
- **Product:**
  - Monoclonal antibody targeting TNFα
- **Initial Approval:**
  - Treatment of adult patients with moderately to severely active RA (December 2002)
- **Subsequent Approvals**:
  - Multiple subsequent approvals, including signs and symptoms of active AS (August 2006)

TNF=tumor necrosis factor
RA=rheumatoid arthritis

Proposed indication and dosing

- **Proposed indication**:
  - "Reducing signs and symptoms in adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation by elevated CRP or MRI who have had an inadequate response to or are intolerant to nonsteroidal anti-inflammatory drugs"

- **Proposed dosing**:
  - 40mg every other week

CRP=c-reactive protein
MRI=magnetic resonance imaging

Relevant regulatory history

- **EOP2 meeting:** August 2008
  - Sponsor proposed use of ASAS classification criteria (prior to publication)
  - FDA noted it was unclear if the Sponsor would be able to identify a truly distinct patient population
    - In principle, the proposal to study patients with axial spondyloarthritis was felt to be reasonable
- **Pre-sBLA meeting:** June 2011
  - FDA revisited concerns regarding the new axial SpA criteria
- **Type C Meeting:** July 2012
  - Sponsor provided data regarding natural history and prevalence of axial SpA
    - Proposed to narrow the target population further by requiring inflammation on MRI or elevated inflammatory markers
  - FDA remained concerned about the proposed indication
    - 12 weeks of controlled data might not be adequate to support chronic use in a new indication with unclear natural history

EOP2=end of phase 2
sBLA=supplemental biologic license application

One pivotal trial: M10-791

Trial	Design	Patient population	Treatment, duration	N†	Primary efficacy variable
M10-791	R, DB, PC	Active nr-axSpA with an inadequate response to NSAIDs or a contraindication to NSAIDs	**12-week controlled period:** •Adalimumab 40mg SC eow •Placebo **144-week open label extension:** •Adalimumab 40mg SC eow	94 (adalimumab) 91 (placebo)	ASAS40 at week 12

†=number of patients in Full Analysis Set
R=randomized; DB=double blind; PC=placebo controlled; nr-axSpA=non-radiographic axial spondyloarthritis; NSAIDs=nonsteroidal anti-inflammatory drugs; eow=every other week; SC=subcutaneous

- Sponsor submitted 68 weeks of data in the original application

Endpoints in trial M10-791

- Focused on signs and symptoms
  - Patient's global assessment, pain, functional status, and symptoms of stiffness
- Validated for use in AS, not nr-axSpA

Important assessment tools in trial M10-791

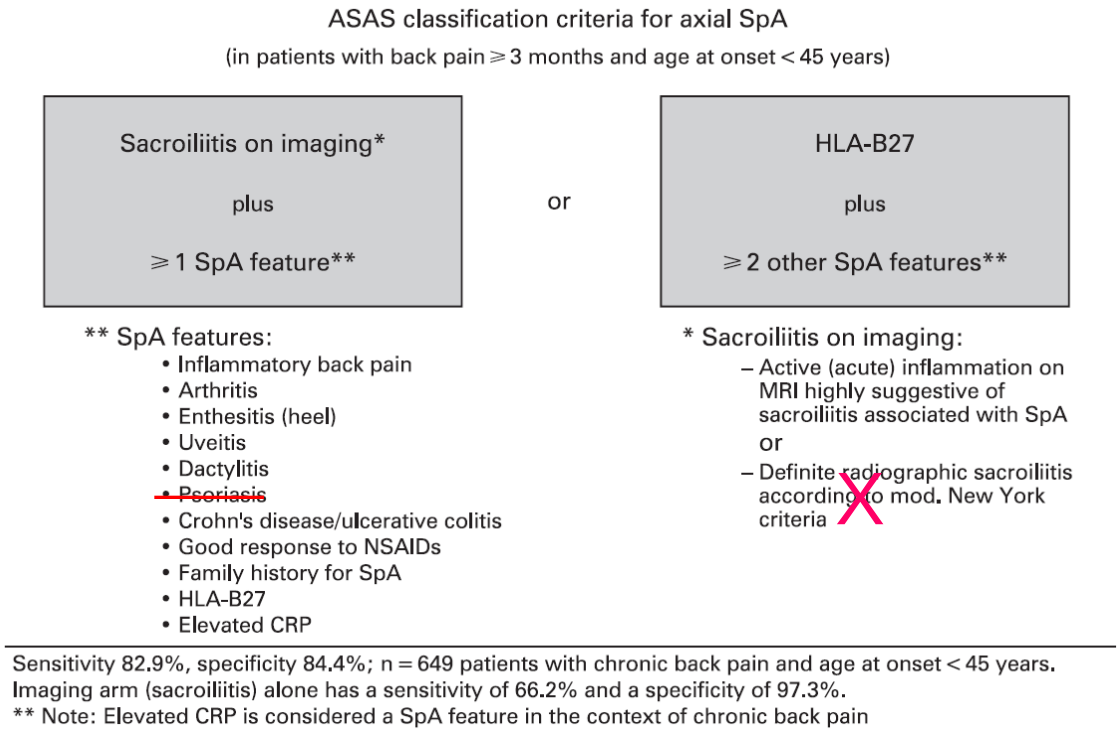
Instrument	Definition
Bath AS Functional Index (BASFI)	Functional instrument based on the patient's assessment of his/her ability to perform 10 selected activities
Bath AS Disease Activity Index (BASDAI)	Summary of 6 self-assessments (fatigue, spinal pain, joint pain, enthesitis, overall level of morning stiffness, and duration of morning stiffness)
ASAS 40% Response (ASAS40)	Improvement of 40% and an absolute improvement of ≥20 units (on a scale of 0 to 100) 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

Outline

- Background
- Adalimumab non-radiographic axial spondyloarthritis program
- Trial M10-791 patient population
- Differences between central and local x-ray interpretation
- Efficacy results
- Safety results
- Conclusions

Trial M10-791: patient population (1)

- Modifications to the ASAS classification criteria for axial SpA



Rudwaleit M, et al. Ann Rheum Dis 2009;68:777-83.

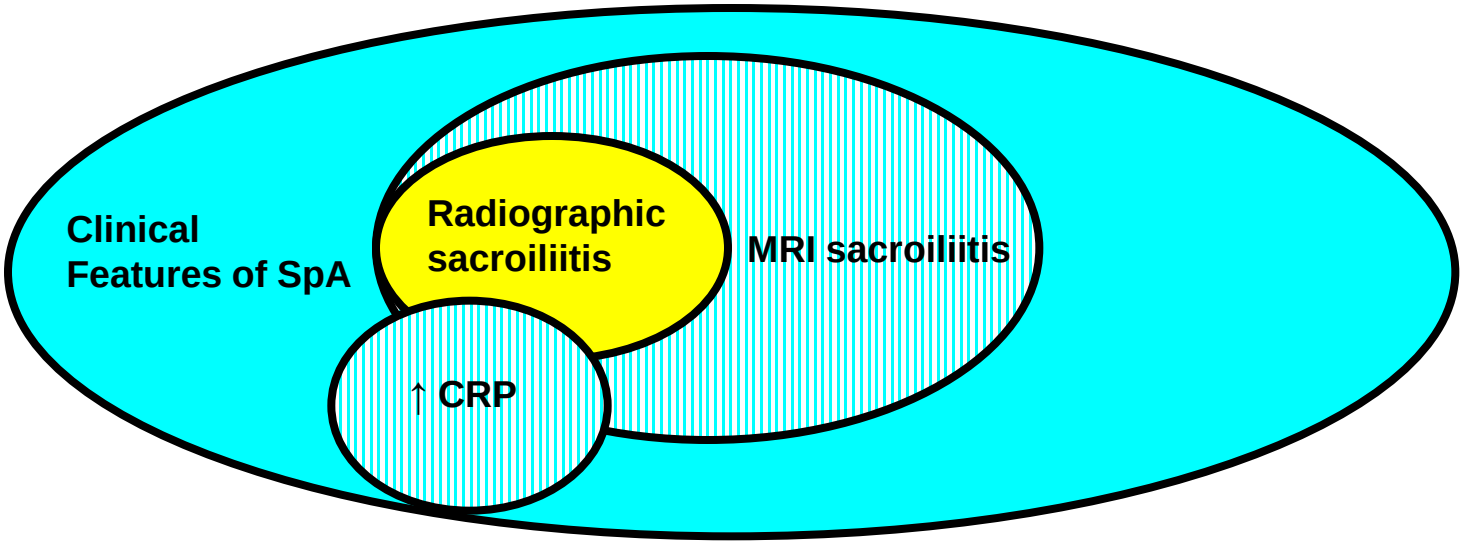
Trial M10-791: patient population (2)

- 192 patients with **active** nr-axSpA
  - BASDAI ≥4 (0-10)
  - Total back pain ≥40 (VAS 0-100)
- Inadequate response to NSAIDs, intolerant to ≥1 NSAID, or contraindication to NSAIDs
- Patients could continue stable concomitant DMARDs, including methotrexate, sulfasalazine, and hydroxychloroquine
  - Patients with prior use of a TNF-inhibitor were excluded

VAS=visual analogue scale

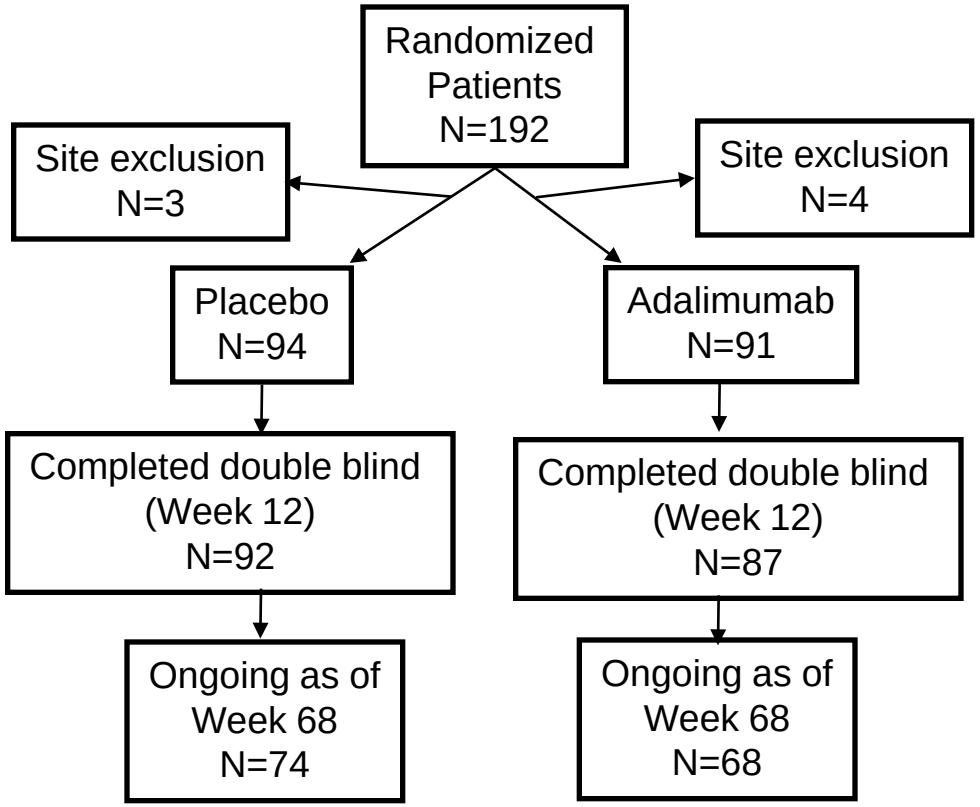
Adalimumab target population (ATP)

- Subgroup defined *post-hoc*



- **Yellow**=AS, intended to be excluded from studied
- **Blue (solid + stripe)**=nr-axSpA, study population (if evidence of active disease)
- **Blue stripe**=adalimumab target population (patients with nr-ax-SpA with objective evidence of inflammation based on abnormal MRI or elevated CRP)

Patient flow diagram



Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 11/29/12, figure 3, page 282

ATP Subgroup

- 142 patients
  - 77% of full analysis set

Outline

- Background
- Adalimumab non-radiographic axial spondyloarthritis program
- Trial M10-791 patient population
- Differences between central and local x-ray interpretation
- Efficacy results
- Safety results
- Conclusions

Local and central x-ray interpretation

- **Planned patient population: non-radiographic axial SpA**
  - Thus, patients meeting radiographic modified New York criteria for AS at screening were intended to be excluded
  - Screening pelvis x-rays were read by **local rheumatologists or radiologists**
  - Sponsor added analyses in which x-rays at screening and week 104 were read **centrally** after the study was unblinded
    - Post-hoc central reads were performed to assess for radiographic progression

Differences between local and central x-ray interpretation

- **Of the 192 patients enrolled in Study M10-791, 102 patients had x-rays at screening and week 104**
  - 37% of patients classified as non-radiographic axial SpA at screening were re-classified as fulfilling the radiographic modified New York criteria
    - Thus, only 64 patients had non-radiographic axial SpA according to central x-ray interpretation

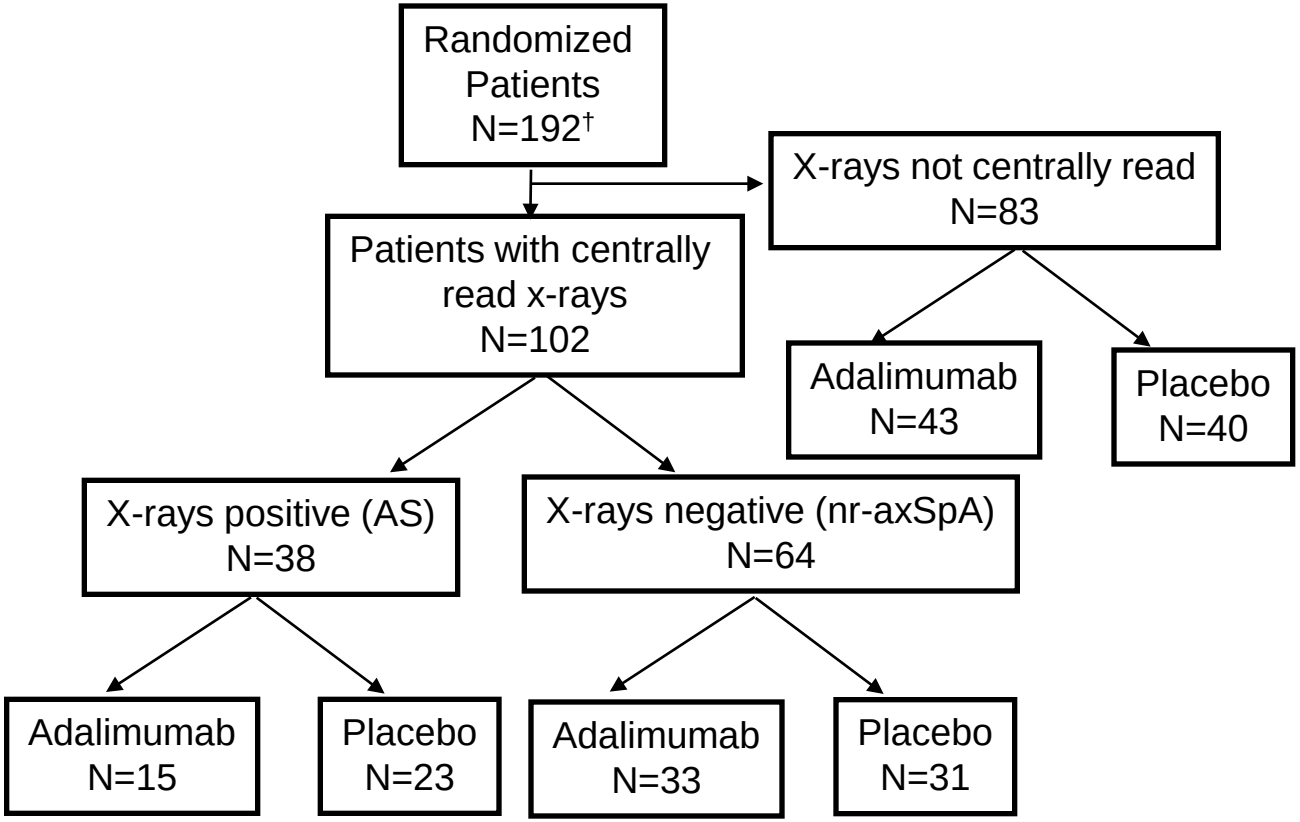
Limitations of analyses based on central x-ray evaluation

- *Post-hoc* analyses
- Non-randomly selected patients
  - Patients who discontinued prior to week 104 or were at sites where repeat x-rays were not performed did not have centrally evaluated screening x-rays
- Missing data

Rationale for analyses based on central x-ray evaluation

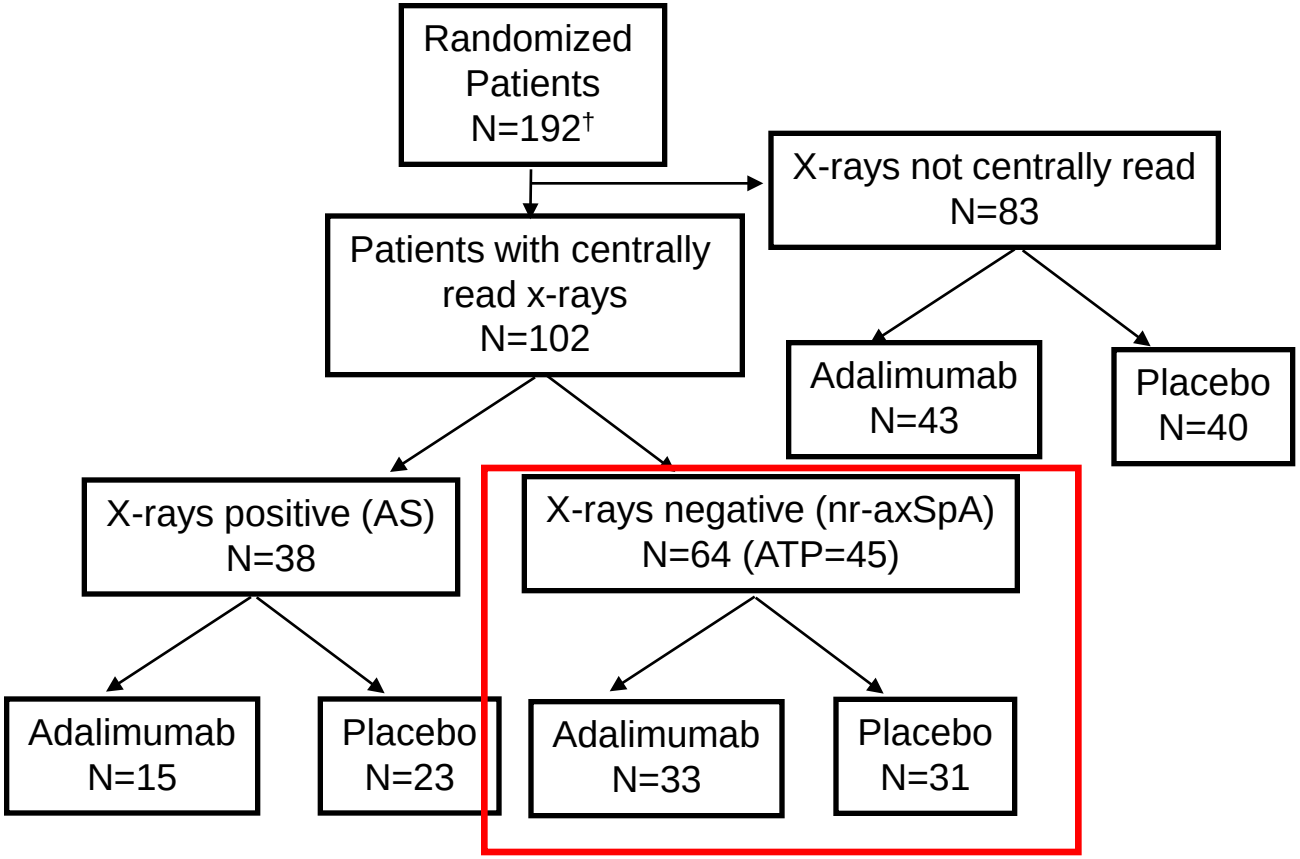
- Axial SpA represents of spectrum of inflammatory diseases
  - Includes important subgroups
    - Presence or absence of x-ray changes consistent with AS may help define different subgroups
  - Unclear if treatment effect is the same across these subgroups
    - Thus, unclear if risk/benefit profile is the same

Patient flow diagram: centrally read x-rays



† 7 patients from 192 patients excluded from efficacy analyses due to investigator non-compliance
Source: FDA generated

Patient flow diagram: centrally read x-rays (ATP subgroup)



ATP Subgroup of centrally read x-rays

- 45 patients (20 placebo, 25 adalimumab)

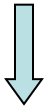
† 7 patients from 192 patients excluded from efficacy analyses due to investigator non-compliance
Source: FDA generated

Outline

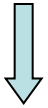
- Background
- Adalimumab non-radiographic axial spondyloarthritis program
- Trial M10-791 patient population
- Differences between central and local x-ray interpretation
- Efficacy results
- Safety results
- Conclusions

Efficacy analyses: trial M10-791

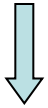
Primary analyses: overall population



Supportive *post-hoc* analyses: ATP subgroup



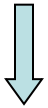
Additional FDA analyses: subgroups based on central x-ray interpretation



Additional FDA analyses: subgroups based on central x-ray interpretation in ATP subgroup

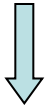
Efficacy analyses: trial M10-791

Primary analyses: overall population



Supportive *post-hoc* analyses: ATP subgroup

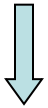
Additional FDA analyses: subgroups based on central x-ray interpretation



Additional FDA analyses: subgroups based on central x-ray interpretation in ATP subgroup

Efficacy analyses: trial M10-791

Primary analyses: overall population



Supportive *post-hoc* analyses: ATP subgroup

Additional FDA analyses: Subgroups based on central x-ray interpretation

Additional FDA analyses: Subgroups based on central x-ray interpretation in ATP subgroup

ASAS40 response based on centrally-read screening x-rays (1)

	X-rays Negative			X-rays Positive			X-rays Not Read		
At Week 12	**PBO N=31**	**ADA N=33**	**Diff**	**PBO N=23**	**ADA N=15**	**Diff**	**PBO N=40**	**ADA N=43**	**Diff**
ASAS40, %	26	30	5	17	73	**56****	5	28	**23***

Difference is **bolded** if $p<0.05$
**$p<0.001$
*$p<0.05$
PBO=placebo; ADA=adalimumab; Diff=difference
Source: FDA generated

ASAS40 response based on centrally-read screening x-rays (2)

	X-rays Negative			X-rays Positive			X-rays Not Read		
At Week 12	**PBO N=31**	**ADA N=33**	**Diff**	**PBO N=23**	**ADA N=15**	**Diff**	**PBO N=40**	**ADA N=43**	**Diff**
ASAS40, %	26	30	5	17	73	**56****	5	28	**23***

Difference is **bolded** if p<0.05
**p<0.001
*p<0.05
PBO=placebo; ADA=adalimumab; Diff=difference
Source: FDA generated

ASAS40 response based on centrally-read screening x-rays (3)

	X-rays Negative			X-rays Positive			X-rays Not Read		
At Week 12	PBO N=31	ADA N=33	Diff	PBO N=23	ADA N=15	Diff	PBO N=40	ADA N=43	Diff
ASAS40, %	26	30	5	17	73	**56****	5	28	**23***

Difference is **bolded** if p<0.05
**p<0.001
*p<0.05
PBO=placebo; ADA=adalimumab; Diff=difference
Source: FDA generated

ASAS40 response based on centrally-read screening x-rays (4)

	X-rays Negative			X-rays Positive			X-rays Not Read		
At Week 12	**PBO N=31**	**ADA N=33**	**Diff**	**PBO N=23**	**ADA N=15**	**Diff**	**PBO N=40**	**ADA N=43**	**Diff**
ASAS40, %	26	30	5	17	73	**56****	5	28	**23***

Difference is **bolded** if $p<0.05$
**$p<0.001$
*$p<0.05$
PBO=placebo; ADA=adalimumab; Diff=difference
Source: FDA generated

ASAS40 response based on centrally-read screening x-rays (5)

	X-rays Negative			X-rays Positive			X-rays Not Read		
At Week 12	PBO N=31	ADA N=33	Diff	PBO N=23	ADA N=15	Diff	PBO N=40	ADA N=43	Diff
ASAS40, %	26	30	5	17	73	**56****	5	28	**23***

Difference is **bolded** if p<0.05
**p<0.001
*p<0.05
PBO=placebo; ADA=adalimumab; Diff=difference
Source: FDA generated

ASAS40 response based on centrally-read screening x-rays (6)

	X-rays Negative			X-rays Positive			X-rays Not Read		
At Week 12	PBO N=31	ADA N=33	Diff	PBO N=23	ADA N=15	Diff	PBO N=40	ADA N=43	Diff
ASAS40, %	26	30	5	17	73	**56****	5	28	**23***

Difference is **bolded** if p<0.05
**p<0.001
*p<0.05
PBO=placebo; ADA=adalimumab; Diff=difference
Source: FDA generated

ASAS40 response based on centrally-read screening x-rays: sensitivity analyses (1)

	X-rays Negative or Not Read			X-rays Positive		
At Week 12	PBO N=71	ADA N=76	Diff (95% CI)	PBO N=23	ADA N=15	Diff (95% CI)
ASAS40, %	14	29	15 (2, 28)	17	73	56 (29, 83)

PBO=placebo; ADA=adalimumab; Diff=difference; CI=confidence interval
Source: FDA generated

ASAS40 response based on centrally-read screening x-rays: sensitivity analyses (2)

	X-rays Negative or Not Read			X-rays Positive		
At Week 12	PBO N=71	ADA N=76	Diff (95% CI)	PBO N=23	ADA N=15	Diff (95% CI)
ASAS40, %	14	29	15 (2, 28)	17	73	56 (29, 83)

PBO=placebo; ADA=adalimumab; Diff=difference; CI=confidence interval
Source: FDA generated

Secondary endpoints by centrally-read screening x-ray subgroups

- A similar pattern of differential efficacy based on centrally-read screening x-ray subgroup was seen for the ranked secondary endpoints
  - ASAS20 response
  - BASDAI50 response
  - SF-36 physical component score
  - ASAS partial remission
  - ASAS5/6 response
  - HAQ-S total score
  - Hs-CRP
  - SPARCC MRI score for sacroiliac joints and spine

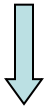
SF-36=short form-36; HAQ-S=Health Assessment Questionnaire for Spondyloarthropathies; hs-CRP=high sensitivity c-reactive protein; SPARCC=Spondyloarthritis Research Consortium of Canada

Summary: differential efficacy according to central x-ray subgroup

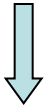
- Differential efficacy based on centrally-read screening x-ray subgroup for the primary and secondary endpoints
  - Patients with nr-axSpA had a lower higher magnitude of effect than patients with AS
- While there are limitations to these analyses, they suggest that inclusion of patients with AS (by central evaluation) in the study appears to increase the apparent treatment effect of adalimumab in the overall study population

Efficacy analyses: trial M10-791

Primary analyses: overall population



Supportive *post-hoc* analyses: ATP subgroup



Additional FDA analyses: Subgroups based on central x-ray interpretation

Additional FDA analyses: Subgroups based on central x-ray interpretation in ATP subgroup

ASAS40 response based on centrally-read screening x-rays in overall population and ATP subgroup (1)

Overall Population									
	X-rays Negative			X-rays Positive			X-rays not read		
At Week 12	PBO N=31	ADA N=33	Diff (95% CI)	PBO N=23	ADA N=15	Diff (95% CI)	PBO N=40	ADA N=43	Diff (95% CI)
ASAS40, %	26	30	5 (-18, 27)	17	73	56 (29, 83)	5	28	23 (9, 38)
ATP Subgroup									
	X-rays Negative			X-rays Positive			X-rays not read		
At Week 12	PBO N=20	ADA N=25	Diff (95% CI)	PBO N=22	ADA N=14	Diff (95% CI)	PBO N=31	ADA N=30	Diff (95% CI)
ASAS40, %	25	36	11 (-16, 38)	14	79	65 (39, 91)	6	27	20 (2, 28)

PBO=placebo; ADA=adalimumab; Diff=difference; CI=confidence interval
Source: FDA generated

ASAS40 response based on centrally-read screening x-rays in overall population and ATP subgroup (2)

Overall Population									
	X-rays Negative			X-rays Positive			X-rays not read		
At Week 12	PBO N=31	ADA N=33	Diff (95% CI)	PBO N=23	ADA N=15	Diff (95% CI)	PBO N=40	ADA N=43	Diff (95% CI)
ASAS40, %	26	30	5 (-18, 27)	17	73	56 (29, 83)	5	28	23 (9, 38)

ATP Subgroup									
	X-rays Negative			X-rays Positive			X-rays not read		
At Week 12	PBO N=20	ADA N=25	Diff (95% CI)	PBO N=22	ADA N=14	Diff (95% CI)	PBO N=31	ADA N=30	Diff (95% CI)
ASAS40, %	25	36	11 (-16, 38)	14	79	65 (39, 91)	6	27	20 (2, 38)

PBO=placebo; ADA=adalimumab; Diff=difference; CI=confidence interval
Source: FDA generated

ASAS40 response based on centrally-read screening x-rays in overall population and ATP subgroup (3)

Overall Population									
	X-rays Negative			X-rays Positive			X-rays not read		
At Week 12	PBO N=31	ADA N=33	Diff (95% CI)	PBO N=23	ADA N=15	Diff (95% CI)	PBO N=40	ADA N=43	Diff (95% CI)
ASAS40, %	26	30	5 (-18, 27)	17	73	56 (29, 83)	5	28	23 (9, 38)
ATP Subgroup									
	X-rays Negative			X-rays Positive			X-rays not read		
At Week 12	PBO N=20	ADA N=25	Diff (95% CI)	PBO N=22	ADA N=14	Diff (95% CI)	PBO N=31	ADA N=30	Diff (95% CI)
ASAS40, %	25	36	11 (-16, 38)	14	79	65 (39, 91)	6	27	20 (2, 38)

PBO=placebo; ADA=adalimumab; Diff=difference; CI=confidence interval
Source: FDA generated

ASAS40 response based on centrally-read screening x-rays in overall population and ATP subgroup (4)

Overall Population									
	X-rays Negative			X-rays Positive			X-rays not read		
At Week 12	PBO N=31	ADA N=33	Diff (95% CI)	PBO N=23	ADA N=15	Diff (95% CI)	PBO N=40	ADA N=43	Diff (95% CI)
ASAS40, %	26	30	5 (-18, 27)	17	73	56 (29, 83)	5	28	23 (9, 38)
ATP Subgroup									
	X-rays Negative			X-rays Positive			X-rays not read		
At Week 12	PBO N=20	ADA N=25	Diff (95% CI)	PBO N=22	ADA N=14	Diff (95% CI)	PBO N=31	ADA N=30	Diff (95% CI)
ASAS40, %	25	36	11 (-16, 38)	14	79	65 (39, 91)	6	27	20 (2, 38)

PBO=placebo; ADA=adalimumab; Diff=difference; CI=confidence interval
Source: FDA generated

ASAS40 response based on centrally-read screening x-rays in overall population and ATP subgroup (5)

Overall Population									
	X-rays Negative			X-rays Positive			X-rays not read		
At Week 12	PBO N=31	ADA N=33	Diff (95% CI)	PBO N=23	ADA N=15	Diff (95% CI)	PBO N=40	ADA N=43	Diff (95% CI)
ASAS40, %	26	30	5 (-18, 27)	17	73	56 (29, 83)	5	28	23 (9, 38)
ATP Subgroup									
	X-rays Negative			X-rays Positive			X-rays not read		
At Week 12	PBO N=20	ADA N=25	Diff (95% CI)	PBO N=22	ADA N=14	Diff (95% CI)	PBO N=31	ADA N=30	Diff (95% CI)
ASAS40, %	25	36	11 (-16, 38)	14	79	65 (39, 91)	6	27	20 (2, 38)

PBO=placebo; ADA=adalimumab; Diff=difference; CI=confidence interval
Source: FDA generated

Efficacy conclusions

- The magnitude of adalimumab's treatment difference varied according to the presence of x-ray changes consistent with AS according to central evaluation
  - Patients with AS had the largest magnitude of effect
  - Patients with nr-axSpA had the smallest magnitude of effect
    - Use of the ATP criteria was associated with only modest numerical increases in the treatment difference between adalimumab and placebo
  - Unclear if the magnitude of effect is clinically meaningful for nr-axSpA patients

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)

Outline

- Background
- Adalimumab non-radiographic axial spondyloarthritis program
- Trial M10-791 patient population
- Differences between central and local x-ray interpretation
- Efficacy results
- Safety results
- Conclusions

Overview of safety concerns with TNF-inhibitors

Boxed Warnings:

- **Serious infections**, including bacterial sepsis, tuberculosis, invasive fungal infections, histoplasmosis, and other opportunistic infections
- **Malignancies**, including hepatosplenic T-cell lymphoma, lymphoma, and other malignancies in children and adolescents

Warnings/Precautions

- Infections
- Hepatitis B reactivation
- Invasive fungal infections
- Malignancies
- Hepatotoxicity
- Hypersensitivity disorders
- Demyelinating disorders
- Adverse outcomes in patients with heart failure
- Pancytopenia, leukopenia, neutropenia, thrombocytopenia
- Autoimmune disorders
- Injection-site reactions

All TNF-inhibitor labels do not contain all safety concerns. Generated from prescribing information data

Extent of exposure by study period

12-week double blind period		**68-week open label period**
Placebo N=97	Adalimumab N=95	Adalimumab N=190

Source: FDA generated

Safety database: placebo-controlled period

	Safety analysis set		Centrally-read negative baseline x-rays		ATP Centrally-read negative baseline x-rays	
	Placebo	**Adalimumab**	**Placebo**	**Adalimumab**	**Placebo**	**Adalimumab**
N	97	95	31	33	20	25

ATP=adalimumab target population
Source: FDA generated

Deaths through 68 weeks

	12-week double blind period		**68-week open label period**
	Placebo N=97 n	Adalimumab N=95 n	Adalimumab N=190 n (%)
Death, n (%)	0	0	2 (1)
Cause of death			• Suicide • Opiate toxicity

Serious adverse events through Week 12

Preferred term	Placebo N=97 n (%)	Adalimumab N=95 n (%)
Any SAE	1 (1.0)	3 (3.2)
Nausea	1 (1.0)	0
Vomiting	1 (1.0)	0
Chills	1 (1.0)	0
Pyrexia	1 (1.0)	0
Hepatitis acute	0	1 (1.1)
Dizziness	1 (1.0)	0
Breast dysplasia	0	1 (1.1)
Abortion induced	0	1 (1.1)

Source: Adapted from Study Report Body (Module 5.3.5.1), submitted 11/29/12, table 93, page 571-4

Adverse events experienced by ≥3% of patients through Week 12

	Safety analysis set	
Preferred term	**Placebo N=97 n (%)**	**Adalimumab N=95 n (%)**
Any adverse event	57 (59)	55 (58)
Nasopharyngitis	3 (3)	11 (12)
Nausea	8 (8)	7 (7)
Headache	3 (3)	6 (6)
Diarrhea	7 (7)	4 (4)
Injection site reaction	0	4 (4)
Upper respiratory tract infection	4 (4)	3 (3)
Asthenia	2 (2)	3 (3)
Fatigue	0	3 (3)
Injection site erythema	0	3 (3)
Pharyngitis	0	3 (3)
Gastroenteritis	3 (3)	2 (2)
Vomiting	3 (3)	2 (2)
Constipation	3 (3)	1 (1)
Injection site pain	3 (3)	1 (1)

Source: Adapted from Study Report Body (Module 5.3.5.1), submitted 11/29/12, table 87, page 556

Serious infections through 68 weeks

	12-week double blind period		68-week open label period
	Placebo N=97 n	Adalimumab N=95 n	Adalimumab N=190 n (%)
Serious infections, n (%)	0	0	3 (2)
Types of infection			• Postoperative wound infection • Disseminated tuberculosis • Sinusitis

Source: Adapted from Study Report Body (Module 5.3.5.1), submitted 11/29/12, table 98, page 590

Safety summary

- Safety profile of adalimumab in nr-axSpA is consistent with its known safety profile
  - However, data are limited
    - Short double, blind-placebo controlled period
    - Relatively small number of patients exposed
- Risk/benefit needs to be considered in the context of well-characterized adalimumab safety profile

Outline

- Background
- Adalimumab non-radiographic axial spondyloarthritis program
- Trial M10-791 patient population
- Differences between central and local x-ray interpretation
- Efficacy results
- Safety results
- Conclusions

Context for risk/benefit assessment

- Nr-axSpA can cause severe symptoms
- There is unmet need for patients with nr-axSpA

- For approval: efficacy and safety must be defined for the proposed indication

Risk/benefit assessment: nr-axSpA

- **Patient population/enrichment**
  - Studied patients *versus* proposed indication
- **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
- **Safety**
  - Framework of known risks associated with TNF-inhibitors
- **Risk/benefit**
  - How to determine in the context of incomplete long-term characterization of the axial SpA subpopulations

FDA Arthritis Advisory Committee Meeting July 23, 2013 AM: Charge to the Committee

Adalimumab (Humira®) for active non-radiographic axial spondyloarthritis (nr-axSpA) in adults with objective signs of inflammation by elevated CRP or MRI, who have had inadequate response or are intolerant to NSAIDs

Sarah Yim, M.D.

Associate Director, Division of Pulmonary, Allergy, and Rheumatology Products

Center for Drug Evaluation and Research

Efficacy Considerations

- Proposed indication is for a subgroup of the axSpA patients studied in M10-791
- M10-791 was intended to enroll nr-axSpA patients and exclude AS patients; however AS patients were included
- Overall treatment difference in the study was impacted by the higher treatment difference observed in AS patients, for whom adalimumab is already approved
- Estimated treatment effect in nr-axSpA patients was modest
  - Use of objective signs of inflammation by elevated CRP or MRI to define a target population resulted in a small numerical increase in treatment difference

Regulatory Considerations

- **Patient population/enrichment**
  - Studied patients *versus* proposed indication
- **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
- **Safety**
  - Framework of known risks associated with TNF inhibitors
- **Risk/benefit**
  - How to determine in the context of incomplete long-term characterization of the AxSpA subpopulations

Approval of an Application 21 CFR 314.105 (c)

- "FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling."

Efficacy Standard
21 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."

Safety Standard
21 CFR 314.125 Refusal to Approve an Application

(b)(2) "…do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling."

(b)(3) "The results of the test show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions."

(b)(4) "There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling."

Question 1 (Discussion)

- Discuss the efficacy data for adalimumab
  - a) Discuss the treatment effect of adalimumab for ankylosing spondylitis (AS) patients versus non-radiographic axial spondyloarthritis (nr-axSpA) patients
  - b) Discuss whether the data for the subpopulation with “objective signs of inflammation by elevated c-reactive protein (CRP) or magnetic resonance imaging (MRI)” supports specifying this population in the proposed indication

Question 2 (Discussion)

- Discuss the safety data for adalimumab
  - a) Discuss whether nr-axSpA may include disease entities that are not chronic and progressive. In light of your position, discuss whether the currently available safety data are adequate or whether additional data are needed
    - If the latter, please explain what additional data should be required

Question 3 (Voting)

- Overall, do the data provide substantial evidence that adalimumab provides a clinically meaningful beneficial effect in the treatment of active nr-axSpA in adults with objective signs of inflammation by elevated CRP or MRI, who have had inadequate response or are intolerant to NSAIDs?
  - If no, what additional data are necessary?

Question 4 (Voting)

- Is the safety profile of adalimumab adequate to support approval of adalimumab for the treatment of active nr-axSpA in adults with objective signs of inflammation by elevated CRP or MRI, who have had inadequate response or are intolerant to NSAIDs?
  - If no, what additional data are necessary?

Question 5 (Voting)

- Does the Committee recommend approval of adalimumab for the proposed indication of active nr-axSpA in adults with objective signs of inflammation by elevated CRP or MRI, who have had inadequate response or are intolerant to NSAIDs?
  - If no, what additional data are necessary?