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

Certolizumab (Cimzia®) for active axial spondyloarthritis, including ankylosing spondylitis

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Center for Drug Evaluation and Research

Proposed Product: Certolizumab

- **Name:**
  - Certolizumab (Cimzia®)
- **Product:**
  - Humanized fragment antigen binding prime (Fab') conjugated to polyethylene glycol targeting TNFα
- **Initial Approval:**
  - Treatment of Crohn's disease (April 2008)
- **Subsequent Approval**:
  - Rheumatoid arthritis (May 2009)

TNF=tumor necrosis factor

Proposed indication and dosing

- **Proposed indication**:
  - "Treatment of adult patients with active axial spondyloarthritis, including patients with ankylosing spondylitis"

- **Proposed dosing**:
  - 200mg Q2W or 400mg Q4W after an initial loading dose of 400mg at weeks 0, 2, and 4

Q2W=every 2 weeks
Q4W=every 4 weeks

One pivotal trial: AS001

Trial	Design/ Sites	Patient population	Treatment, duration	N†	Primary efficacy variable
AS001	R, DB, PC	Active axial spondyloarthritis with an inadequate response to NSAIDs or a contraindication to NSAIDs	**24-week controlled period‡:** •CZP 200mg Q2W •CZP 400mg Q4W •Placebo **110-week open label extension:** •CZP 200mg Q2W •CZP 400mg Q4W	111 (CZP 200mg Q2W) 107 (CZP 400mg Q4W) 107 (placebo)	ASAS20 at week 12

† Number of patients randomized; ‡ Escape treatment was given to placebo patients who did not achieve a minimal response at both Weeks 14 and 16
R=randomized; DB=double blind; PC=placebo controlled; NSAIDs=non-steroidal anti-inflammatory drugs; CZP=certolizumab; ASAS20=Assessment in Ankylosing Spondylitis 20% Response Criteria
All patients treated with CZP initially received loading doses of CZP 400mg SC at weeks 0, 2, and 4

Source: Adapted from data in AS001 Synopsis (Module 5.3.5.1), submitted 12/14/12

- Sponsor submitted 24 weeks of data in the original application

Efficacy Considerations

- Uncertain if efficacy data are adequate to support proposed indication: axial SpA
  - Efficacy data for **AS** appear reasonable
  - However, unclear if efficacy data for **nr-axSpA** are adequate to support **novel indication**
    - Enriched population
      - Extrapolate to spectrum of patients with axial SpA?
    - Limited study duration
      - Can efficacy be extrapolated to life-long treatment if natural history is unclear?
    - Magnitude of effect
      - Is efficacy sufficient to justify use in context of uncertainty?

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
Certolizumab (Cimzia®)
for Axial Spondyloarthritis, including Ankylosing Spondylitis
sBLA 125160/215

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Division of Pulmonary, Allergy, and Rheumatology Products
Center for Drug Evaluation and Research
July 23, 2013

Outline

- Background
- Certolizumab axial spondyloarthritis program
- Trial AS001 patient population
- Differences between central and local subgroup classification
- Efficacy results
- Safety results
- Conclusions

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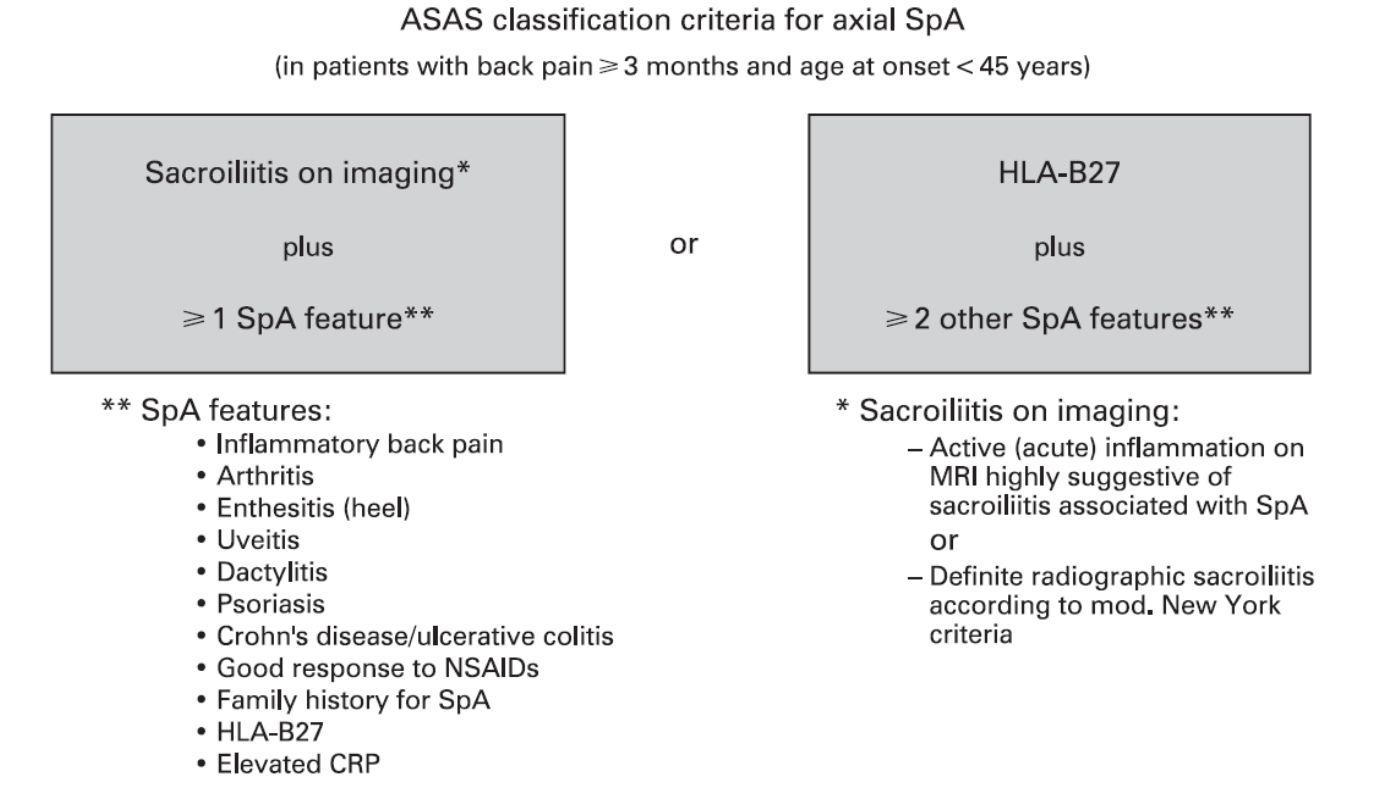
Background on axial spondyloarthritis (SpA)

- **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



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: axial SpA

- **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

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Relevant regulatory history

- **EOP2 meeting:** February 2010
  - Sponsor proposed 1 trial in patients with axial SpA
  - FDA expressed that it might be reasonable to study patients with axial SpA
- **Pre-sBLA meeting:** July 2012
  - FDA raised regulatory concerns regarding use of the new ASAS axial SpA criteria to define a new indication
    - **Specific concerns:**
      - Lack of clarity on the entities the criteria would encompass
      - Whether patients could evolve into other diagnoses for which treatment may have an unfavorable or unknown risk-benefit profile

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

One pivotal trial: AS001

Trial	Design	Patient population	Treatment, duration	N†	Primary efficacy variable
AS001	R, DB, PC	Active axial spondyloarthritis with an inadequate response to NSAIDs or a contraindication to NSAIDs	**24-week controlled period‡:** •CZP 200mg Q2W •CZP 400mg Q4W •Placebo **110-week open label extension:** •CZP 200mg Q2W •CZP 400mg Q4W	111 (CZP 200mg Q2W) 107 (CZP 400mg Q4W) 107 (placebo)	ASAS20 at week 12

† Number of patients randomized; ‡ Escape treatment was given to placebo patients who did not achieve a minimal response at both Weeks 14 and 16
R=randomized; DB=double blind; PC=placebo controlled; NSAIDs=non-steroidal anti-inflammatory drugs; CZP=certolizumab
All patients treated with CZP initially received loading doses of CZP 400mg SC at weeks 0, 2, and 4
Source: Adapted from data in AS001 Synopsis (Module 5.3.5.1), submitted 12/14/12

- Sponsor submitted 24 weeks of data in the original application

Endpoints in trial AS001

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

Important assessment tools in trial AS001

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).
Bath AS Metrology Index (BASMI)	Sum of 5 measures of hip and spine mobility
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

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Trial AS001: patient population (1)

- Chronic back pain ≥3 months and age at onset <45 years

Imaging criteria	Clinical criteria
Sacroiliitis (MRI or radiographs†) plus ≥1 SpA feature	HLA-B27 plus ≥2 other SpA features
SpA features	
Inflammatory back pain	Psoriasis
Arthritis	Crohn's disease/ulcerative colitis
Enthesitis (heel)	HLA-B27
Uveitis	Elevated CRP
Dactylitis	~~Family history~~
	~~Good response to NSAIDs~~

CRP=C-reactive protein; MRI=magnetic resonance imaging; HLA-B27=human leukocyte antigen B27; NSAID=nonsteroidal anti-inflammatory drug; SpA=spondyloarthritis

† Active inflammatory lesions of sacroiliac joints with definite bone marrow edema/osteitis suggestive of sacroiliitis associated with spondyloarthritis in MRI or radiographic sacroiliitis grade 2 to 4 bilaterally or grade 3 to 4 unilaterally according to modified New York criteria

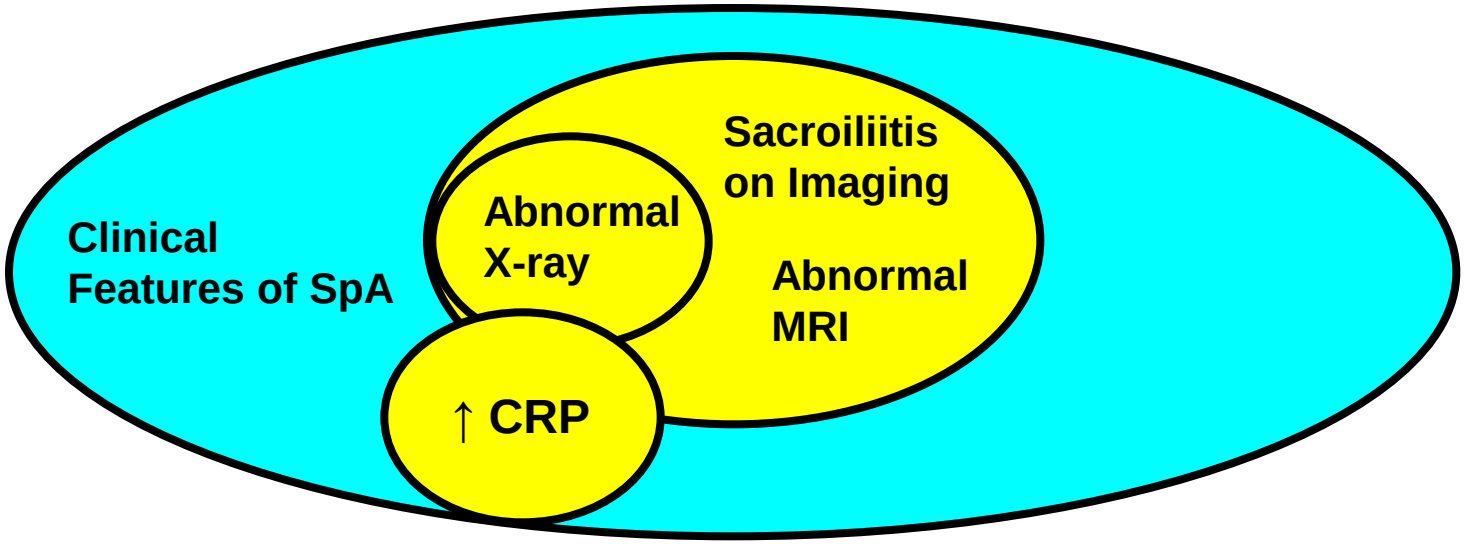
Source: Adapted from Protocol Appendix (Module 5.3.5.1), submitted 12/14/12, table 17:2, page 91

Trial AS001: patient population (2)

- 325 patients with active axial SpA
  - **Active disease**
    - BASDAI ≥4 (0-10)
    - Spinal pain ≥4 (VAS 0-10)
    - CRP>ULN or MRI with evidence of sacroiliitis
- Intolerant to or have had an inadequate response to at least 1 NSAID
- Patients could have taken stable doses of methotrexate, sulfasalazine, or hydroxychloroquine
- No more than 40% of the patients could have been unresponsive to TNF-inhibitors

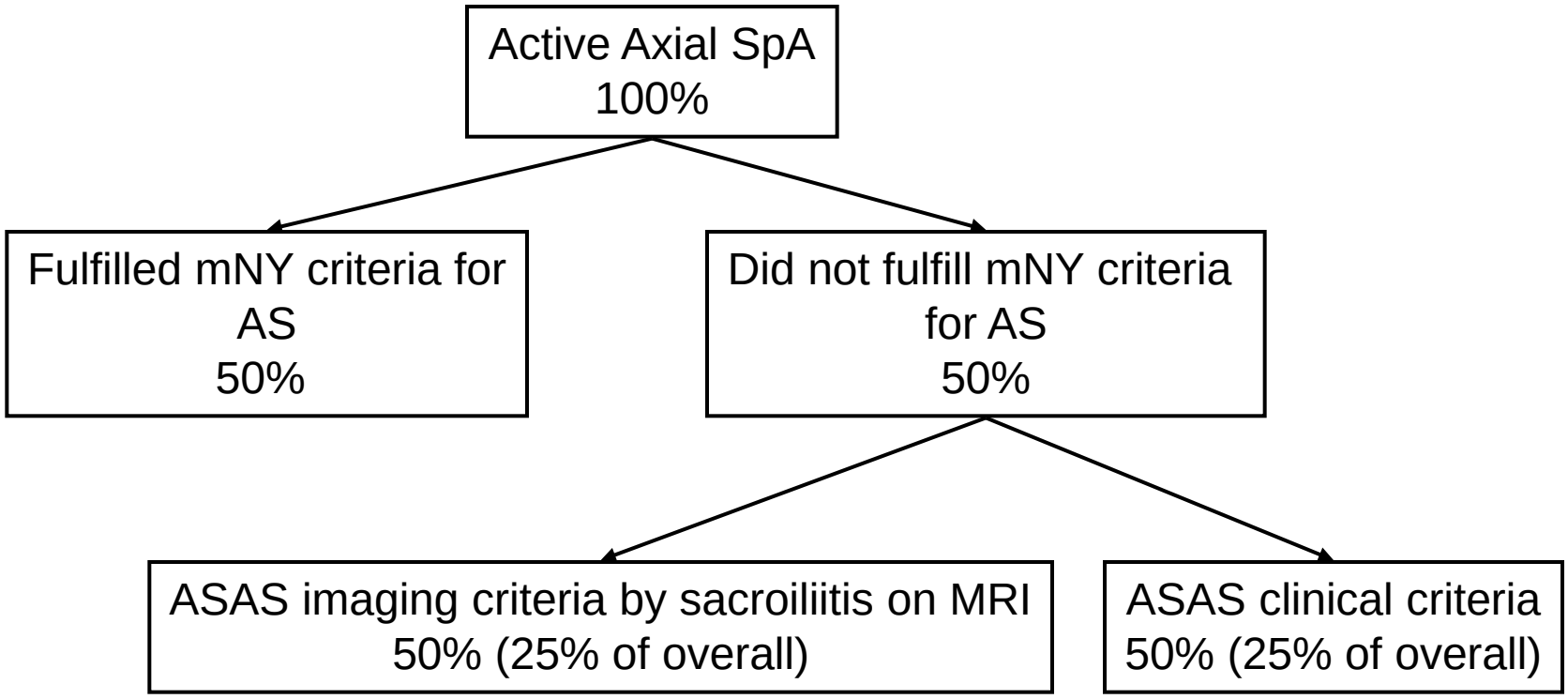
VAS=visual analogue scale
ULN=upper limit of normal

Trial AS001: patient population (3)



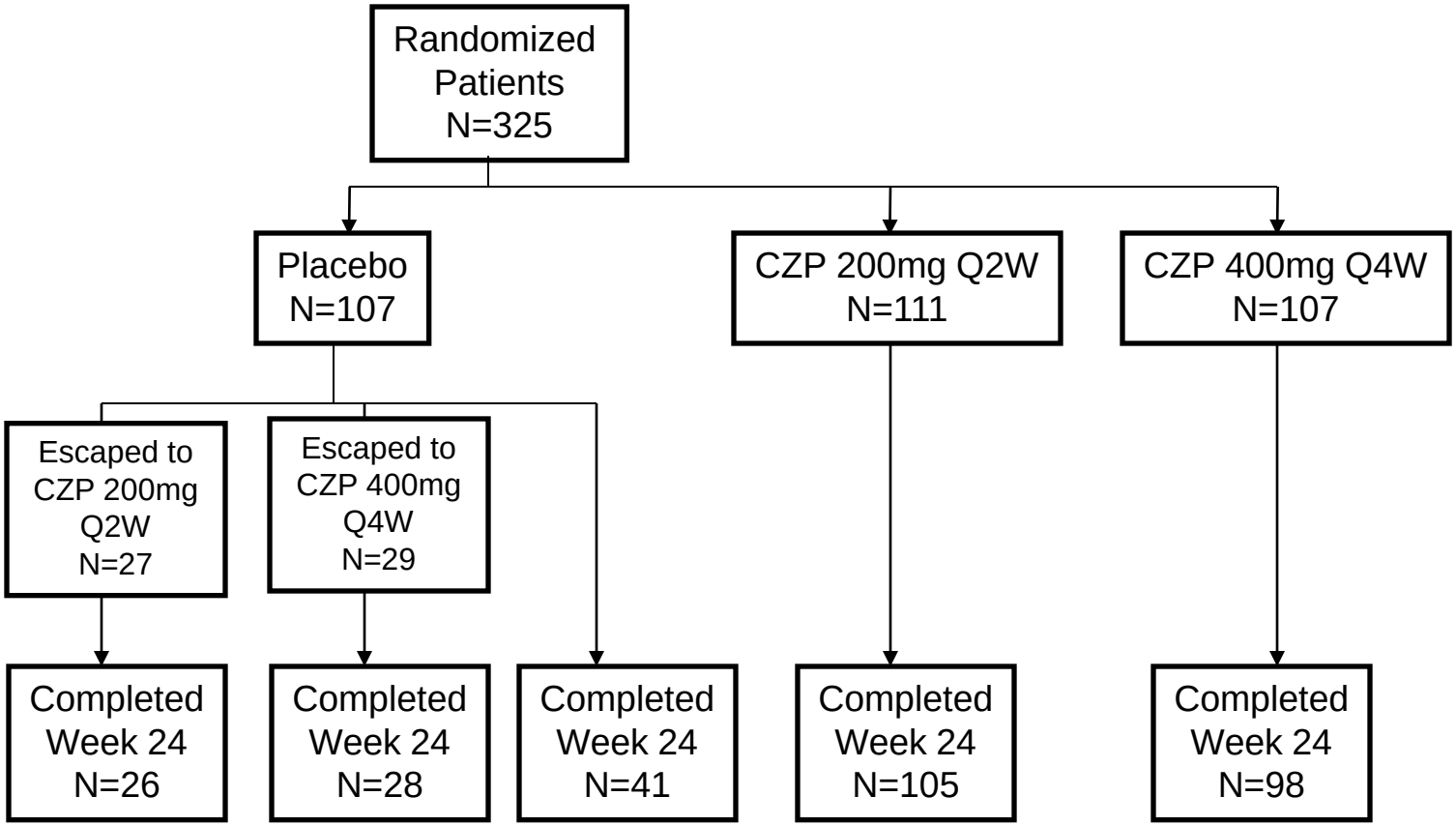
- **Blue**=patients meeting ASAS classification criteria for axial SpA, but excluded from trial AS001
- **Yellow**=patients included in trial AS001

Trial AS001: planned patient population



Source: FDA generated

Patient flow diagram



Source: Adapted from Study Report Body (Module 5.3.5.1), submitted 12/14/12, figure 7-1, page 106

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Classification into subgroups in Trial AS001

- **Trial population:** patients with active axial SpA
  - Subgroups: AS and nr-axSpA
- At screening, **local** rheumatologists or radiologists reviewed x-rays and classified patients as either AS or nr-axSpA
- At baseline, x-rays were repeated and read **centrally**
  - Available for 282 (87%) of patients
  - 36% of patients were reclassified based on the central evaluation

Comparison of investigator's and central reader's sacroiliac x-ray assessment

	Central reader assessment (baseline)†		
Local investigator's assessment (screening)	**mNY-Yes n (%)**	**mNY-No n (%)**	**Total N**
mNY-Yes (N=178)	112 (79)	29 (21)	141
mNY-No (N=147)	72 (51)	69 (49)	141

†Central reads were not performed for 43 patients; mNY=modified New York criteria for ankylosing spondylitis
Source: Adapted from Study Report Body (Module 5.3.5.1), submitted 12/14/12, table 7-11, page 135

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Source: Adapted from Study Report Body (Module 5.3.5.1), submitted 12/14/12, table 7-11, page 135

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Source: Adapted from Study Report Body (Module 5.3.5.1), submitted 12/14/12, table 7-11, page 135

Limitations of analyses based on central x-ray evaluation

- *Post-hoc* analyses
- Non-randomly selected patients
  - Repeat x-rays were not performed at all sites
- 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

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Patient demographics: overall

	Overall N=325
Mean age (SD), years	40 (12)
Female, %	39
White, %	90
Median duration of back pain (years)	8
Prior DMARD use, %	63

SD=standard deviation; DMARD=disease modifying anti-rheumatic drug
Source: Adapted from Study Report Body (Module 5.3.5.1), submitted 12/14/12, tables 7-1 (pages 109-10), 7-6 (124-5), 2.12.1 (474)

Patient demographics: subgroups

	AS N=178	Nr-axSpA N=147
Mean age (SD), years	42 (12)	37 (12)
Female, %	28	52
White, %	89	91
Median duration of back pain (years)	9	6

Local subgroup classification
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, tables 7-2 (pages 111-12), 7-3 (113-4), 7-7 (126-7), 7-8 (128-9)

Baseline disease characteristics: subgroups

	AS N=178	Nr-axSpA N=147
HLA-B27 positive, %	82	75
Mean CRP, mg/L (SD)	21 (26)	16 (20)
Mean BASDAI scores (SD)	6.4 (1.6)	6.5 (1.5)
Mean BASMI scores (SD)	4.4 (1.7)	3.1 (1.5)
Mean BASFI scores (SD)	5.7 (2.2)	4.9 (2.3)

Local subgroup classification
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, tables 7-7 (126-7), and 7-8 (128-9)

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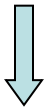
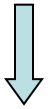
Efficacy analyses: trial AS001

Primary analyses: overall axial SpA population



Supportive analyses: AS and nr-axSpA subgroups (local classification)



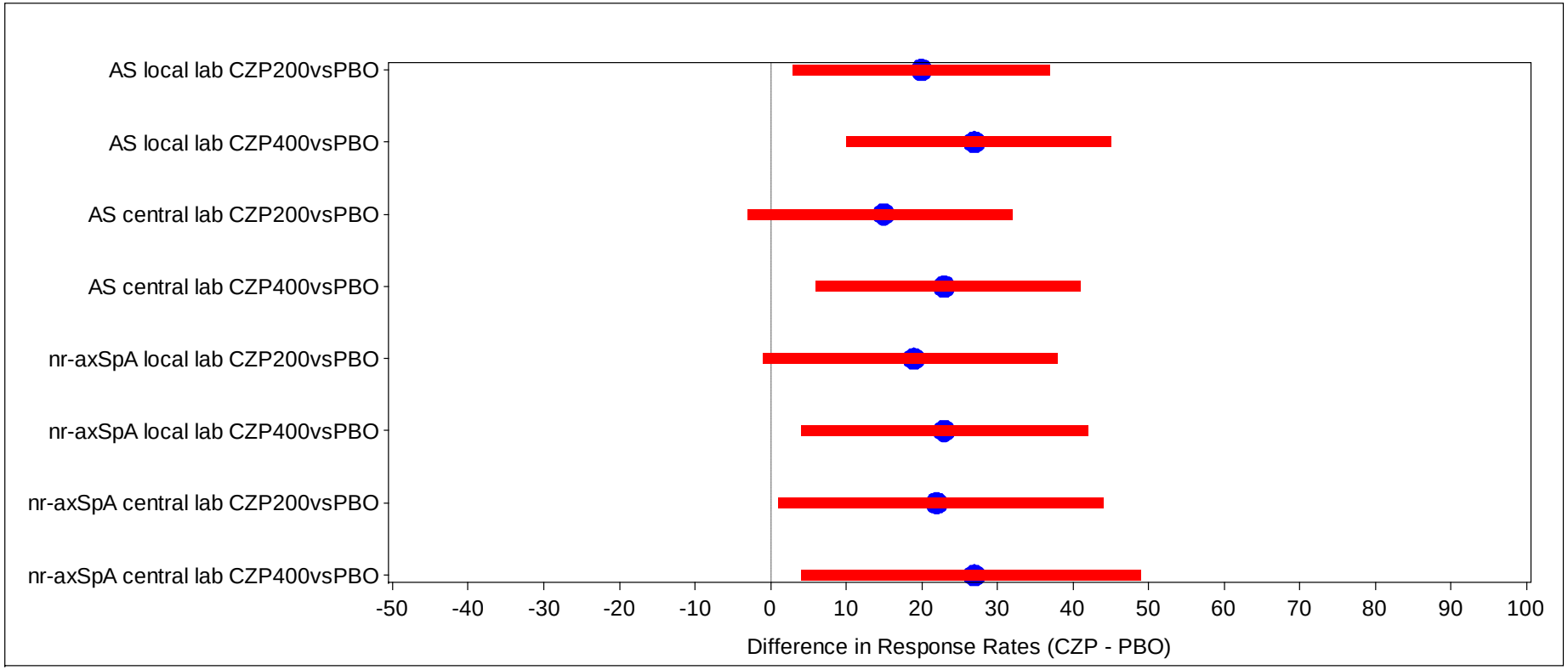
Additional supportive analyses: AS and nr-axSpA subgroups (central classification)

ASAS20 response at weeks 12 and 24 in overall population

ASAS20 responders, %	Placebo N=107	CZP 200mg Q2W N=111	CZP 400mg Q4W N=107
Week 12	38	58	64
Difference to placebo	---	19	25
P-value	---	0.004	<0.001
Week 24	29	67	70
Difference to placebo	---	38	41
P-value	---	<0.001	<0.001

Source: Adapted from Study Report Body (Module 5.3.5.1), submitted 12/14/12, table 8.2-3, pages 140-2

ASAS20 response at week 12 in subgroups based on method of x-ray classification



Source: FDA generated

ASAS20 response at week 12 in AS and nr-axSpA subgroups (by central evaluation)

	Placebo	CZP 200mg Q2W	CZP 400mg Q4W
AS subgroup, N	57	66	61
Responders, %	46	61	69
Difference to placebo, % (95% CI)	---	15 (-3, 33)	23 (6, 41)
Nr-axSpA subgroup, N	35	33	30
Responders, %	20	42	47
Difference to placebo, % (95% CI)	---	22 (1, 44)	27 (4, 49)

Source: Adapted from Response to FDA information request, submitted 5/16/13, table 1-2, page 3

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Efficacy conclusions (1)

- Not possible to drawn definitive conclusions from *post-hoc* subgroup analyses
- Suggest overall results in patients with axial spondyloarthritis were not driven by a single subgroup

Secondary endpoints in AS and nr-axSpA subgroups

- Showed similar trends to those seen in the overall population
  - Regardless of whether subgroup classification was based on local or central x-ray interpretation
- Magnitude of the treatment difference varied somewhat by method of classification

Efficacy conclusions (2)

- Uncertain if efficacy data are adequate to support proposed indication: axial SpA
  - Efficacy data for **AS** appear reasonable
  - However, unclear if efficacy data for **nr-axSpA** are adequate to support **novel indication**
    - Enriched population
      - Extrapolate to spectrum of patients with axial SpA?
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    - Magnitude of effect
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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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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

Safety database: placebo controlled period

	Placebo†	CZP 200mg Q2W	CZP 400mg Q4W	All CZP‡
N	107	111	107	274

†=Placebo exposure ended with the date of first CZP injection for patients escaping from placebo to CZP;
‡=includes CZP 200mg Q2W, CZP 400mg Q4W and escaped placebo patients
Source: Adapted from Study Report Body (Module 5.3.5.1), submitted 12/14/12, table 11-1, page 225

Safety database: placebo controlled period

	Placebo† N=107	All CZP‡ N=274
N	107	274

†=Placebo exposure ended with the date of first CZP injection for patients escaping from placebo to CZP;
‡=includes CZP 200mg Q2W, CZP 400mg Q4W and escaped placebo patients
Source: Adapted from Study Report Body (Module 5.3.5.1), submitted 12/14/12, table 11-1, page 225

Serious adverse events

System Organ Class	Placebo† N=107 %	All CZP‡ N=274 %
SAE	4.7	4.7
Blood and lymphatic system	0	0.4
Cardiac disorders	0	0.4
Eye disorders	0	0.4
Gastrointestinal disorders	0.9	0.4
General disorders & administration site conditions	1.9	0
Hepatobiliary disorders	0	0.7
Immune system disorders	0.9	0.4
Infections and infestations	0	1.1
Investigations	0	0.4
Metabolism and nutrition	0	0.4
Neoplasms	0	0.4
Renal and urinary disorders	0.9	0.4
Respiratory, thoracic, and mediastinal disorders	0	0.4

†=Placebo exposure ended with the date of first CZP injection for patients escaping from placebo to CZP; ‡=includes CZP 200mg Q2W, CZP 400mg Q4W and escaped placebo patients
Source: Adapted from Study Report Body (Module 5.3.5.1), submitted 12/14/12, table 11-6, page 232-33

Serious adverse events

System Organ Class	Placebo† N=107 %	All CZP‡ N=274 %
SAE	4.7	4.7
Blood and lymphatic system	0	0.4
Cardiac disorders	0	0.4
Eye disorders	0	0.4
Gastrointestinal disorders	0.9	0.4
General disorders & administration site conditions	1.9	0
Hepatobiliary disorders	0	0.7
Immune system disorders	0.9	0.4
Infections and infestations	0	1.1
Investigations	0	0.4
Metabolism and nutrition	0	0.4
Neoplasms	0	0.4
Renal and urinary disorders	0.9	0.4
Respiratory, thoracic, and mediastinal disorders	0	0.4

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Source: Adapted from Study Report Body (Module 5.3.5.1), submitted 12/14/12, table 11-6, page 232-33

Discontinuations secondary to AEs

Preferred term	Placebo† N=107 %	All CZP‡ N=274 %
Discontinuation secondary to AE	**1.9**	**2.2**
Non-cardiac chest pain	0.9	0
Cholelithiasis	0	0.4
Hepatitis	0.9	0
Hypersensitivity	0	0.4
Folliculitis	0	0.4
Upper respiratory tract infection	0	0.4
C-reactive protein increased	0	0.4
Gynaecomastia	0	0.4

†=Placebo exposure ended with the date of first CZP injection for patients escaping from placebo to CZP;
‡=includes CZP 200mg Q2W, CZP 400mg Q4W and escaped placebo patients
Source: Adapted from Study Report Body (Module 5.3.5.1), submitted 12/14/12, table 11-7, page 234

Discontinuations secondary to AEs

Preferred term	Placebo† N=107 %	All CZP‡ N=274 %
Discontinuation secondary to AE	**1.9**	**2.2**
Non-cardiac chest pain	0.9	0
Cholelithiasis	0	0.4
Hepatitis	0.9	0
Hypersensitivity	0	0.4
Folliculitis	0	0.4
Upper respiratory tract infection	0	0.4
C-reactive protein increased	0	0.4
Gynaecomastia	0	0.4

†=Placebo exposure ended with the date of first CZP injection for patients escaping from placebo to CZP;
‡=includes CZP 200mg Q2W, CZP 400mg Q4W and escaped placebo patients
Source: Adapted from Study Report Body (Module 5.3.5.1), submitted 12/14/12, table 11-7, page 234

Adverse events occurring in ≥2% of the all CZP group

System Organ Class	Placebo† N=107 %	All CZP‡ N=274 %
AE	63	70
Gastrointestinal disorders	14	14
General disorders and administration site conditions	8	12
Infections and infestations	23	35
Investigations	7	14
Nervous system disorders	11	10
Respiratory, thoracic and mediastinal disorders	6	7
Vascular disorders	6	5

†=Placebo exposure ended with the date of first CZP injection for patients escaping from placebo to CZP;
‡=includes CZP 200mg Q2W, CZP 400mg Q4W and escaped placebo patients
Source: Adapted from Study Report Body (Module 5.3.5.1), submitted 12/14/12, table 11-3, pages 227-8

Adverse events occurring in ≥2% of the all CZP group

System Organ Class	Placebo† N=107 %	All CZP‡ N=274 %
AE	63	70
Gastrointestinal disorders	14	14
General disorders and administration site conditions	8	12
Infections and infestations	23	35
Investigations	7	14
Nervous system disorders	11	10
Respiratory, thoracic and mediastinal disorders	6	7
Vascular disorders	6	5

†=Placebo exposure ended with the date of first CZP injection for patients escaping from placebo to CZP;
‡=includes CZP 200mg Q2W, CZP 400mg Q4W and escaped placebo patients
Source: Adapted from Study Report Body (Module 5.3.5.1), submitted 12/14/12, table 11-3, pages 227-8

Adverse event of interest: infections

	Placebo† N=107 %	All CZP‡ N=274 %
Any AE in the infections and infestations SOC, %	23	35
Severe AE, %	0	0.4
Serious AE, %	0	1

†=Placebo exposure ended with the date of first CZP injection for patients escaping from placebo to CZP;
‡=includes CZP 200mg Q2W, CZP 400mg Q4W and escaped placebo patients
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, table 11-9, page 236

- One case of active tuberculosis reported in 120-day safety update

Safety summary

- Safety profile of certolizumab in axial SpA 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 certolizumab safety profile

Outline

- Background
- Certolizumab axial spondyloarthritis program
- Trial AS001 patient population
- Differences between central and local subgroup classification
- Demographics
- Efficacy results
- Safety results
- Conclusions

Context for risk/benefit assessment

- Axial SpA includes subgroups of patients
  - Therapeutic options exist for AS, but not nr-axSpA
    - Axial SpA 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: axial SpA

- **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 PM: Charge to the Committee

Certolizumab (Cimzia®) for active axial spondyloarthritis, including ankylosing spondylitis

Sarah Yim, M.D.

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

Center for Drug Evaluation and Research

Efficacy Considerations

- Uncertain if efficacy data are adequate to support proposed indication: axial SpA
  - Efficacy data for **AS** appear reasonable
  - However, unclear if efficacy data for **nr-axSpA** are adequate to support **novel indication**
    - Enriched population
      - Extrapolate to spectrum of patients with axial SpA?
    - Limited study duration
      - Can efficacy be extrapolated to life-long treatment if natural history is unclear?
    - Magnitude of effect
      - Is efficacy sufficient to justify use in context of uncertainty?

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 certolizumab
  - a) Discuss the treatment effect of certolizumab for axial spondyloarthritis, with consideration of the subgroups of AS and nr-axSpA
  - b) Discuss whether the submitted data are adequate to determine the treatment effect of certolizumab in AS and nr-axSpA or whether additional data are needed
    - If the latter, please explain what additional data should be required

Question 2 (Discussion)

- Discuss the safety data for certolizumab
  - 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
  - b) Discuss whether the safety data for the AS subgroup 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 certolizumab provides a clinically meaningful beneficial effect in the treatment of active axial spondyloarthritis, including patients with ankylosing spondylitis?
  - If no, what additional data are necessary?

Question 4 (Voting)

- Is the safety profile of certolizumab adequate to support approval of certolizumab for the treatment of active axial spondyloarthritis, including patients with ankylosing spondylitis?
  - If no, what additional data are necessary?

Question 5 (Voting)

- Does the Committee recommend approval of certolizumab for the proposed indication of active axial spondyloarthritis, including patients with ankylosing spondylitis?
  - If no, what additional data are necessary?