The Natural History of Osteoarthritis and Potential Causes of Joint Destruction

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Outline of FDA Presentations

- **Background on Osteoarthritis and Causes of Joint Destruction**
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- **Safety and Efficacy Considerations**
  Anjelina Pokrovnichka, MD
  Medical Officer, DAAAP, CDER, FDA

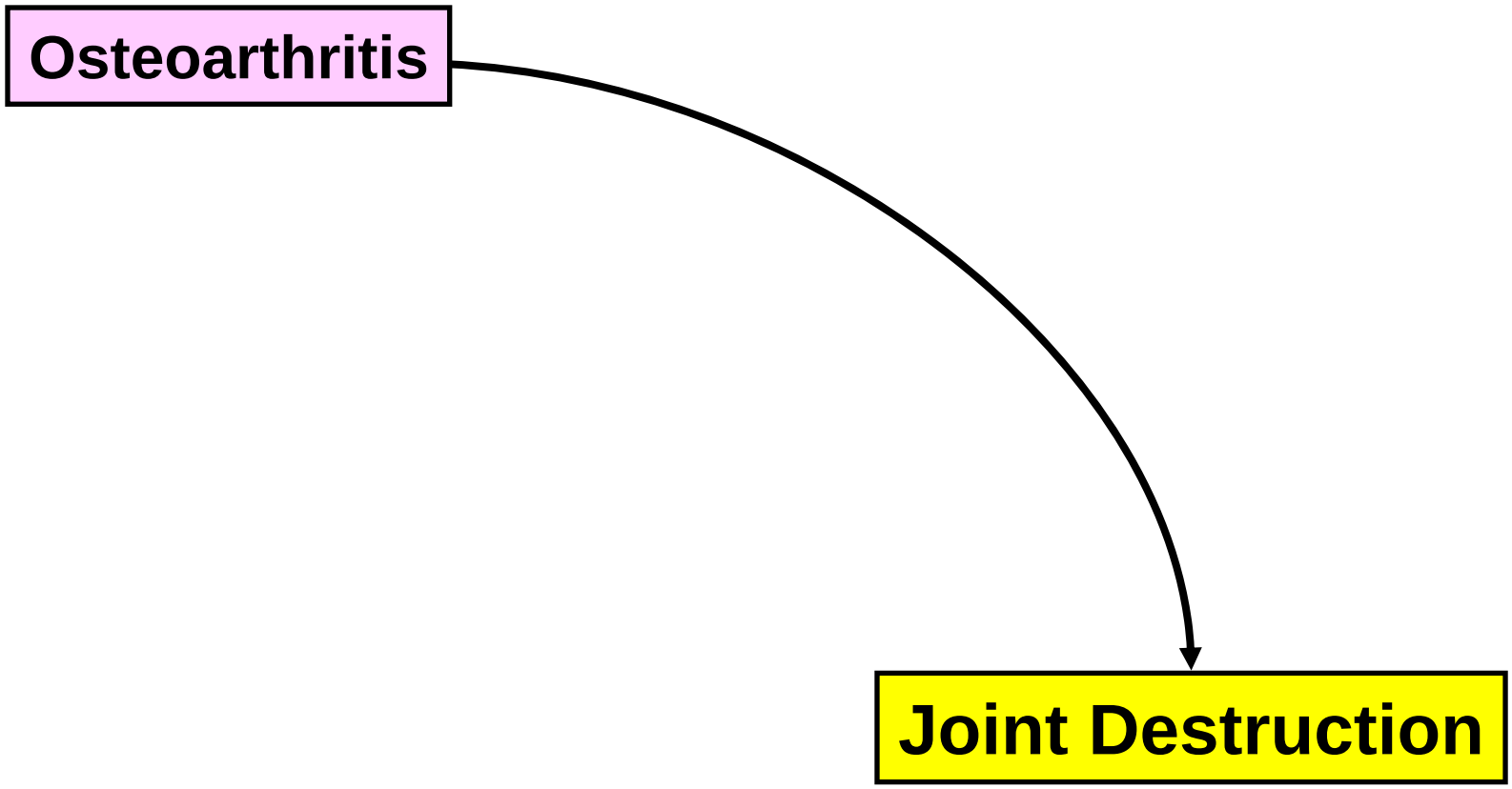
- **FDA Review of Serious Joint Related Adverse Events**
  Nona Colburn, MD
  Clinical Reviewer, CDRH, FDA

- **External Review of Serious Joint Related Adverse Events**
  Joan Bathon, MD
  Director, Division of Rheumatology
  Columbia University College of Physicians and Surgeons

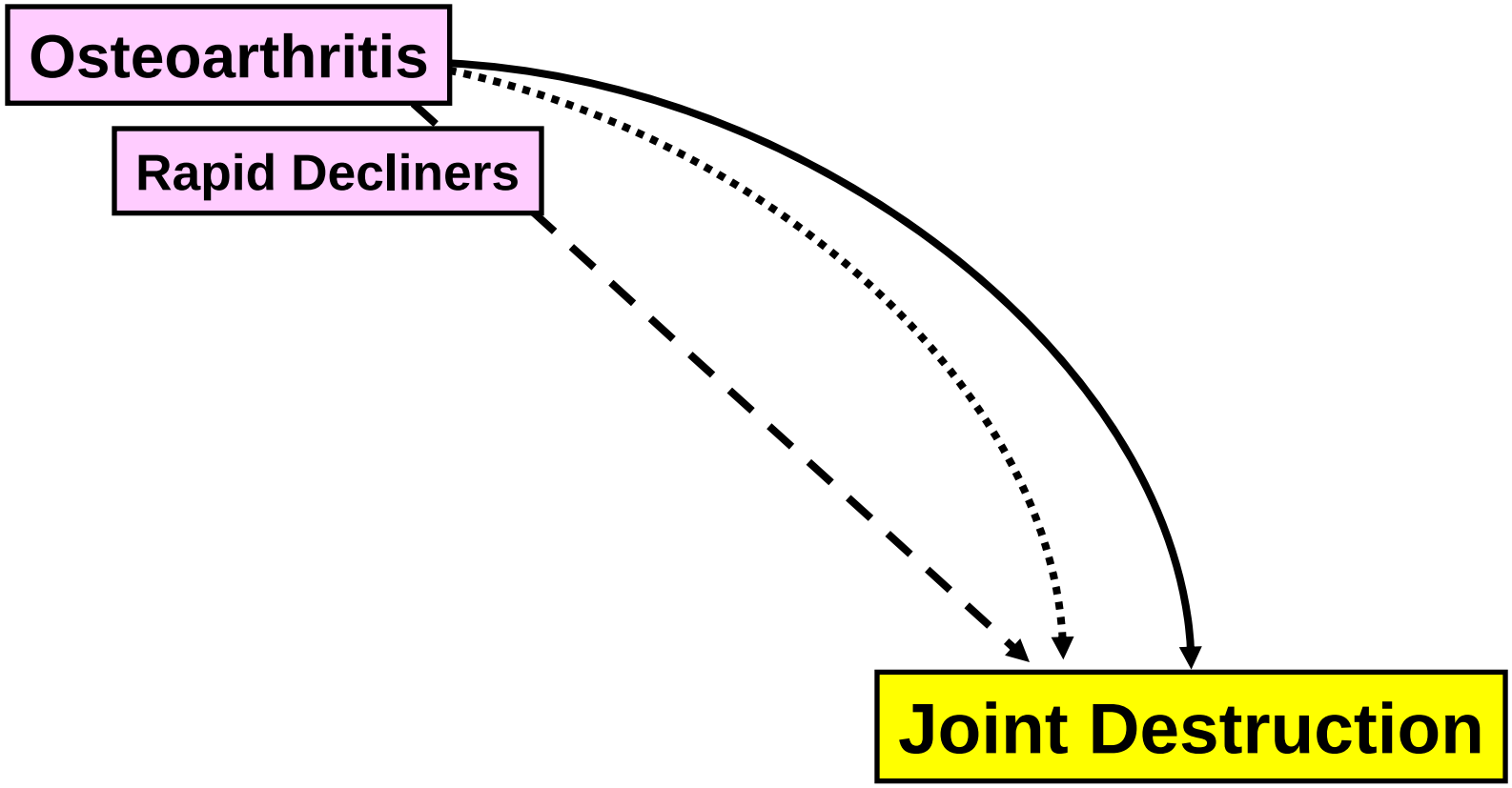
Overview

- Natural history of osteoarthritis (OA)
  - "Rapid decliners"
- Comparison with rapidly destructive arthropathies
  - Clinical
  - Radiographic
  - Pathologic

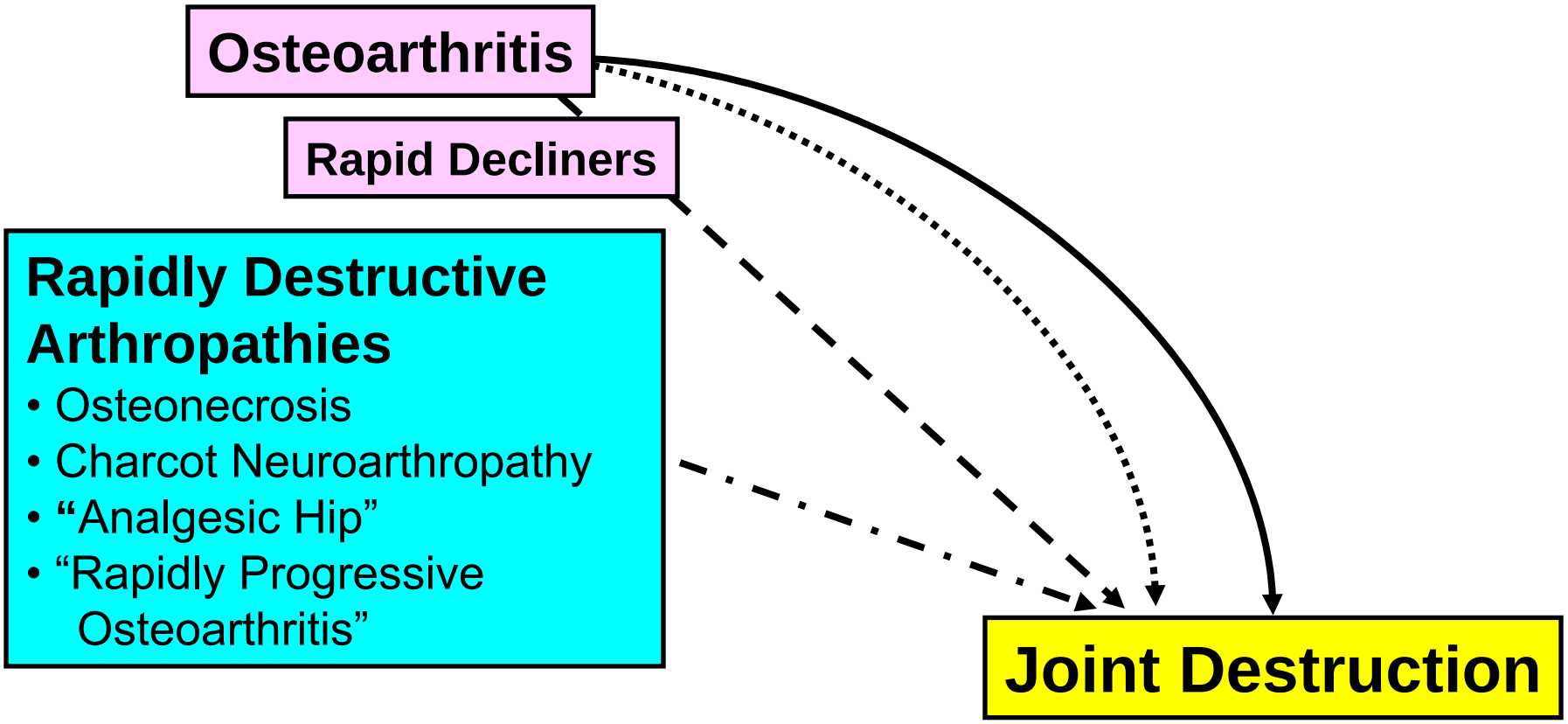
Potential Causes of Joint Destruction



Potential Causes of Joint Destruction



Potential Causes of Joint Destruction



OA: Overview

- Slowly progressive joint degeneration
- **Epidemiology**
  - Most common form of arthritis
    - Prevalence of OA (NHANES I): 12.1%[1]
- **Risk factors[2,3]**
  - Increased age
  - Female gender
  - Obesity
  - Trauma

1. Lawrence RC. Arthritis Rheum 1998;41:778-99.
2. Felson DT. Arthritis Rheum 1987;30:914-8.
3. Sowers M. Curr Opin Rheumatol 2001;13:447-51.

OA: Clinical Features

- **Pain**
  - Correlation between radiographic findings and pain is weak[1]
- **Joints involved**
  - Any joint
  - Weight-bearing joints generally more symptomatic
    - Certain joints are less likely to be affected
- **Pattern of joints involved**[2]
  - Non-random evolution
- **Number of joints involved**
  - Variable

1. Dieppe PA. Lancet 2005;365:965-73.
2. Shakoor N. Arthritis Rheum 2002;46:3185-9.

OA: Radiographic & Pathologic Features

- **Radiographic**
  - Osteophytes, joint space narrowing, sclerosis
- **Pathologic**
  - Degenerative changes
  - Osteonecrosis (ON) can be present
    - Observed grossly in 11.7% of femoral heads removed surgically because of OA[1]

1. Franchi A. J Rheumatol 1992;19:1263-8.

OA: Natural History

- Categorizing OA progression
  - No standard definition
    - Radiographic or clinical
- Total Joint Replacement
  - Frequently used as a surrogate for end-stage OA
    - However, many factors influence joint replacement rates

Hawker GA. N Engl J Med 2000;342:1016-22.

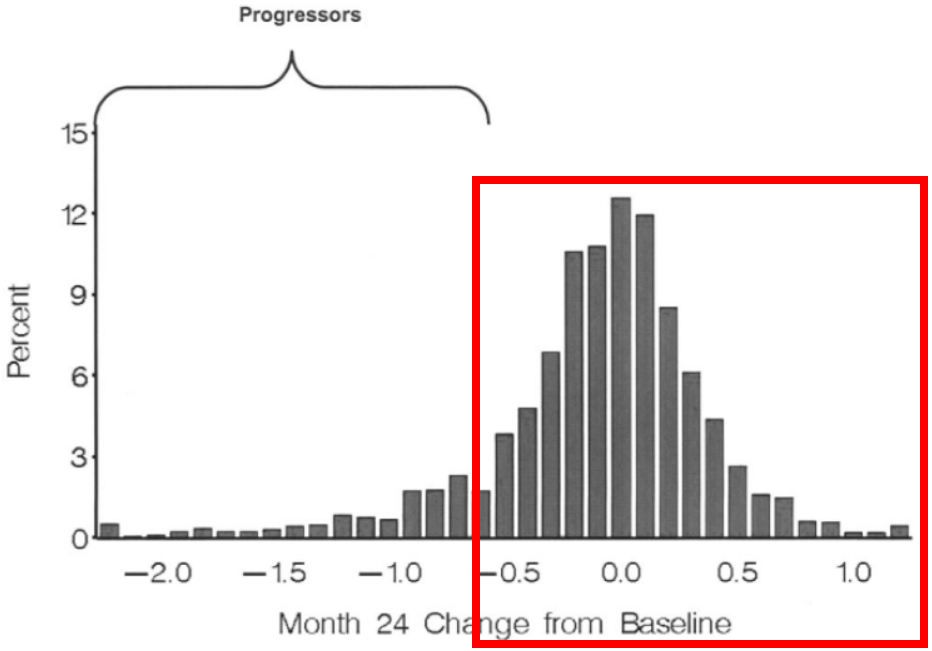
Kellgren-Lawrence (KL) Grade

Radiographic Outcomes for Knee Joints	Grade
Normal	0
Possible osteophytes Doubtful narrowing of joint space	1
Definite osteophytes Absent or questionable narrowing of joint space	2
Moderate osteophytes Moderate narrowing of joint space Some sclerosis Possible deformity	3
Large osteophytes Marked narrowing of joint space Severe sclerosis Definite deformity	4

Kellgren JH. Ann Rheum Dis 1957;16:494-502.

Radiographic Progression: Knee OA Structural Arthritis (KOSTAR) Study

- 2-year study of risedronate in knee OA
  - 2,483 patients
  - Progressors: joint space (JS) width decrease ≥0.6mm
- Majority of patients were not progressors
  - 87%



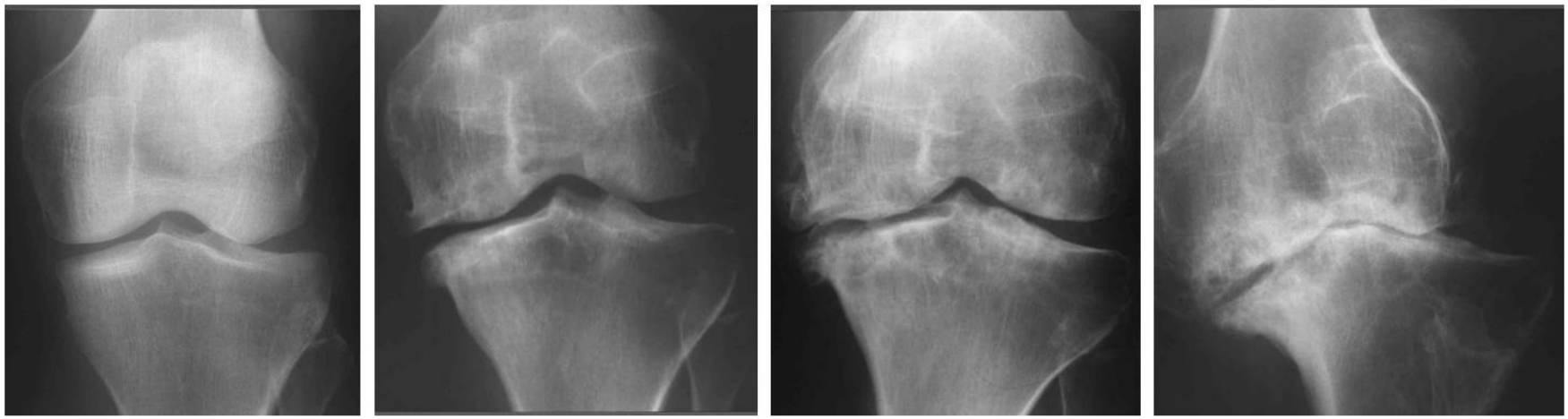
Bingham CO. Arthritis Rheum 2006;54:3494-3507.

Knee OA: Natural History in the Framingham Cohort

- 869 subjects
  - **Incident radiographic knee OA:**
    - ~2% per year in women
  - **Incident symptomatic knee OA:**
    - ~1% per year in women
  - **Progressive knee OA:**
    - ~4% per year in women

Felson DT. Arthritis Rheum 1995;38:1500-5.

OA: Natural History



Occurrence of Total Knee Replacements in OA Initiative Study

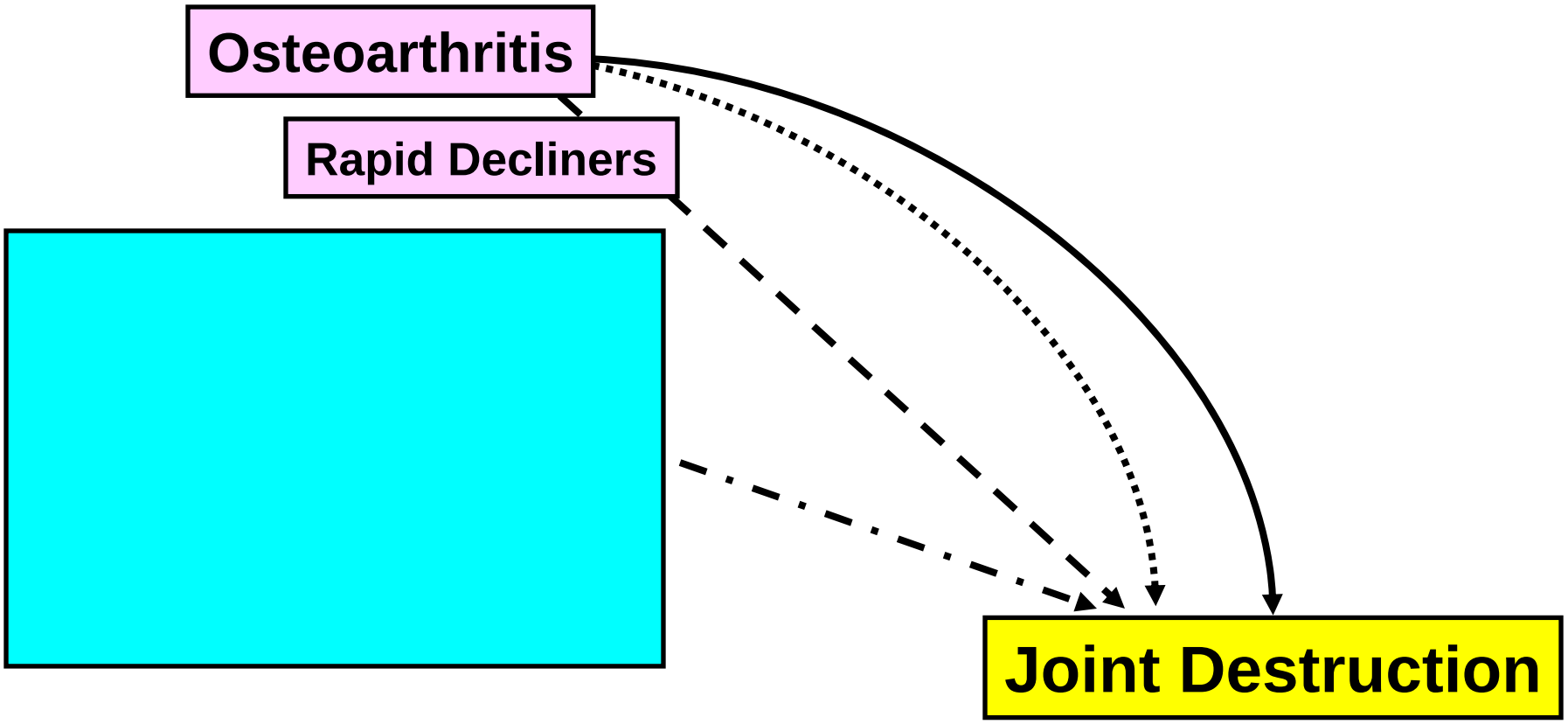
	Subjects with knee replacements n (%)
2-year follow-up (Progression Cohort)	
All subjects with available data (N=778)	29 (3.7)
Subjects with baseline end-stage OA (KL grade 4) (N=227)	22 (9.7)
3-year follow-up (Progression & Incidence Cohorts)	
Subjects with baseline end-stage OA (KL grade 4) (N=554)	67 (12.1)

Riddle DL. The Knee 2009;16:494-500.
Riddle DL. Joint Bone Spine 2011;epub.

Natural History of OA: Conclusions

- Slow evolution of OA over time
  - Majority of subjects remain stable
- However, there is a spectrum of disease progression
  - Depends on many factors, including patient population

Potential Causes of Joint Destruction



Rapidly Destructive Arthopathies

- Rapid and unexpected joint destruction
  - Variety of potential causes
    - Overlapping features: necrosis and degeneration
      - Poor outcomes
  - Well-defined phenotypes
    - Osteonecrosis
    - Charcot neuroarthropathy
  - Potential phenotypes
    - “Analgesic arthropathy”
    - “Rapidly progressive osteoarthritis”

Osteonecrosis: Overview

- Death of bone→collapse of the architectural bony structure
  - Can be a primary or secondary process
- **Epidemiology**[1]
  - Incidence: 3/100,000 persons in 2003 (United Kingdom)
- **Risk Factors**[2]
  - Associated with a variety of conditions & medications

1. Cooper C. Osteoporos Int 2010;21:569-77.
2. Mankin HJ. N Engl J Med 1992;326:1473.

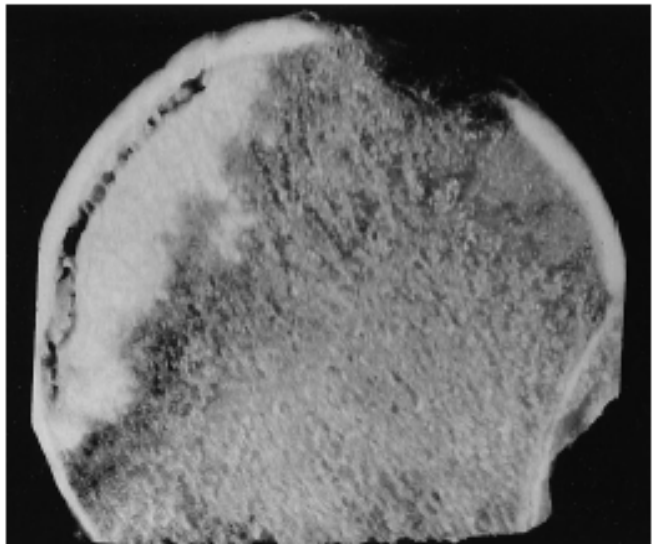
Osteonecrosis: Clinical Features

- **Pain**
  - Depends on location and size of lesion
- **Joints involved**
  - Femoral head is most common location
    - Can affect any skeletal site
- **Pattern of joints involved**
  - No clear pattern
- **Number of joints involved**
  - Variable

Assouline-Dayan Y. Semin Arthritis Rheum 2002;32:94-124.

Osteonecrosis: Radiographic & Pathologic Features

- **Radiographic**
  - "Crescent sign", femoral head collapse
- **Pathologic**
  - Necrosis
  - Secondary degenerative changes



Imhof H. Eur Radiol 1997;7:180-6.

Osteonecrosis: FDA Analysis of Four Large Clinical Trials of NSAIDs

Patient Characteristics	**Patients with osteoarthritis N = 52,945**
Age in years, mean (SD)	63.7 (8.9)
Women, % / Caucasian, %	74 / 79
Treatment duration, patient-years	52,729
Osteonecrosis events	11
Events, per 1,000 patient-years	0.2

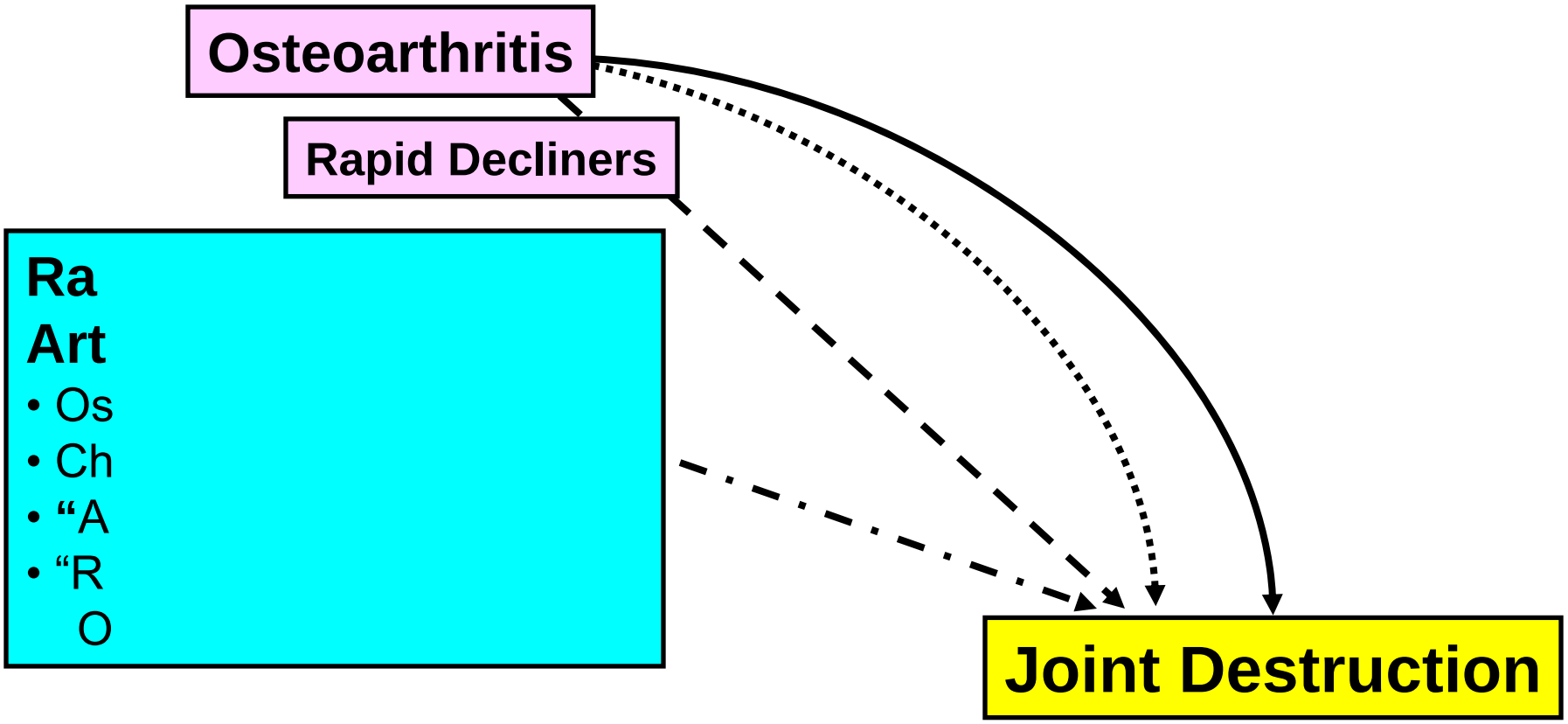
Source: FDA analysis

Osteonecrosis: Natural History

- High rate of progression
  - Retrospective review of 50 osteonecroitc femoral heads[1]
    - 67% progressed to femoral head collapse
    - 68% required replacement within a mean of 16 months
- However, progression rates depend on size and site of lesion[2]

1. Musso ES. Clin Orthop Relat Res 1986;207:209-15.
2. Sugano N. Clin Orthop Relat Res 1994;303;155-64.

Potential Causes of Joint Destruction



Charcot Neuroarthropathy: Overview

- Potentially rapid and destructive
- **Epidemiology**
  - Exact prevalence is difficult to determine
- **Risk factors**
  - Sensory neurological disorders
    - But, 32% of cases had no documented neurological disease in one retrospective case series

Brower AC. Radiology 1981;139:349-54.

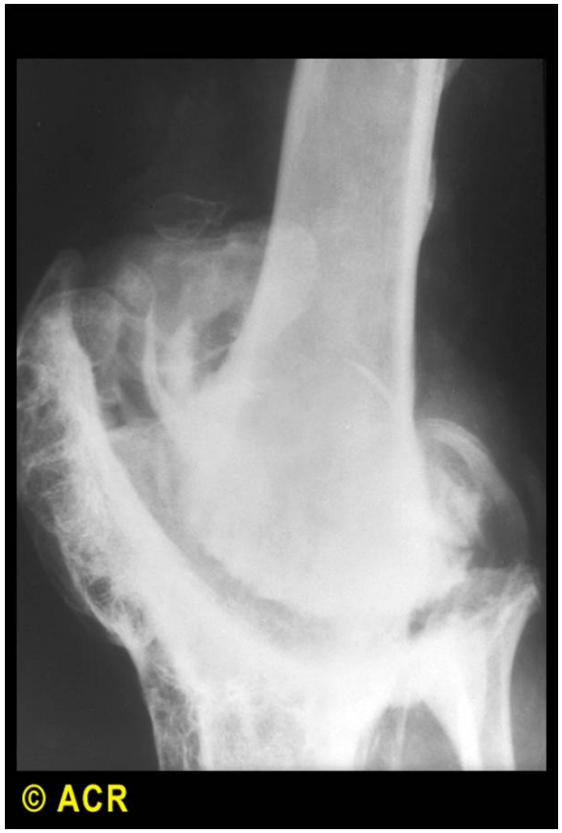
Charcot Neuroarthropathy: Clinical Features

- **Pain**
  - Variable
    - 76% diabetic patients reported pain, even though they were insensate[1]
- **Joints involved**
  - Depends on the underlying neuropathy
    - Diabetes mellitus: foot and ankle
- **Pattern of joints involved**
  - Depends on the underlying neuropathy
- **Number of joints involved**
  - Variable

1. Armstrong DG. Diabet Med 1997;14:357-63.

Charcot Neuroarthropathy: Radiographic & Pathologic Features

- **Radiographic**
  - Bone erosion, resorption, & formation
  - Fractures, free fragments of bone
- **Pathologic**
  - Fragments of bone & cartilage debris embedded in the synovium[1]



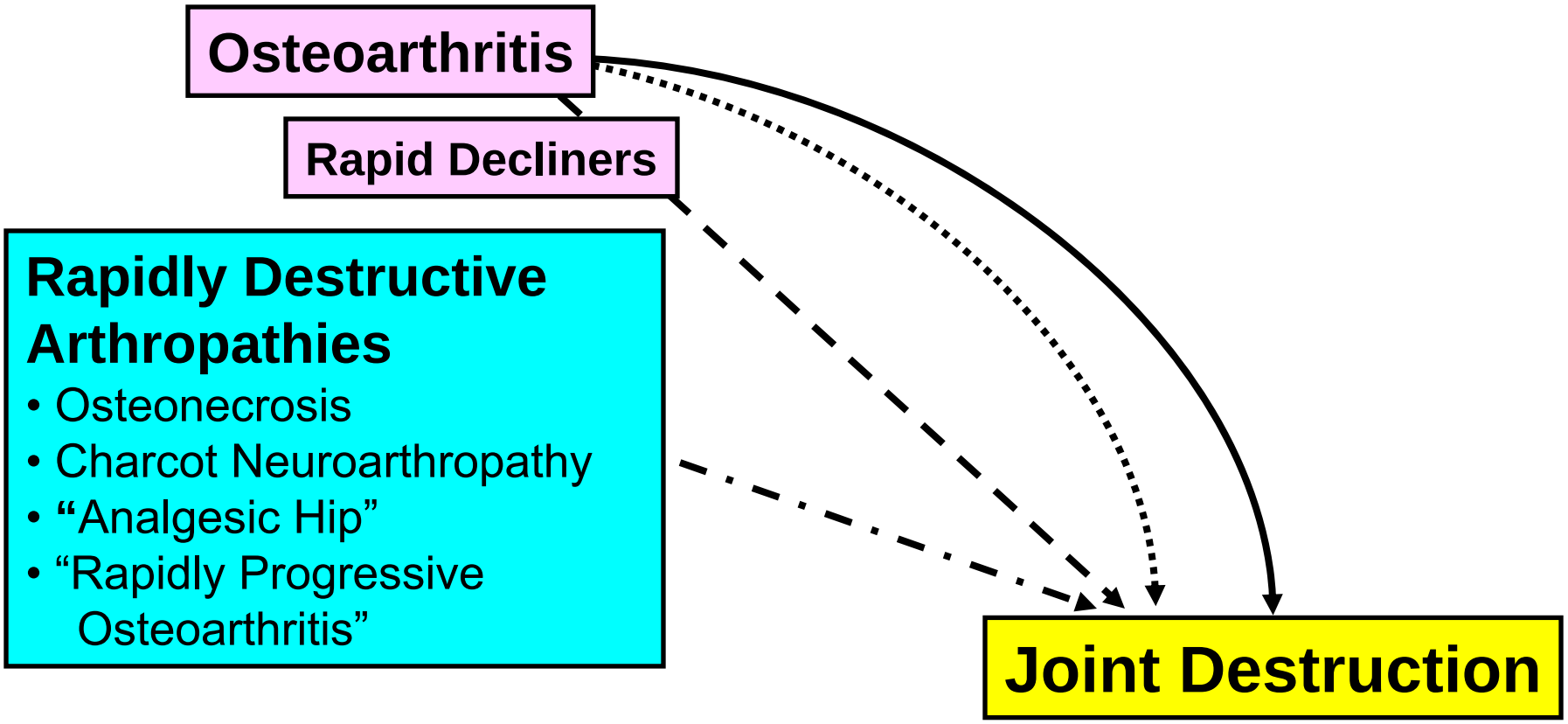
1. Horwitz T. J Bone Joint Surg (Am) 1948;30:579-88.

Charcot Neuroarthropathy: Natural History

- **Natural history**
  - Phases of disease:
    - Acute
      - Warm, swollen, tender
    - Chronic
      - Established deformity
  - Progression can be rapid
    - Dependent on many factors, including when treatment is started

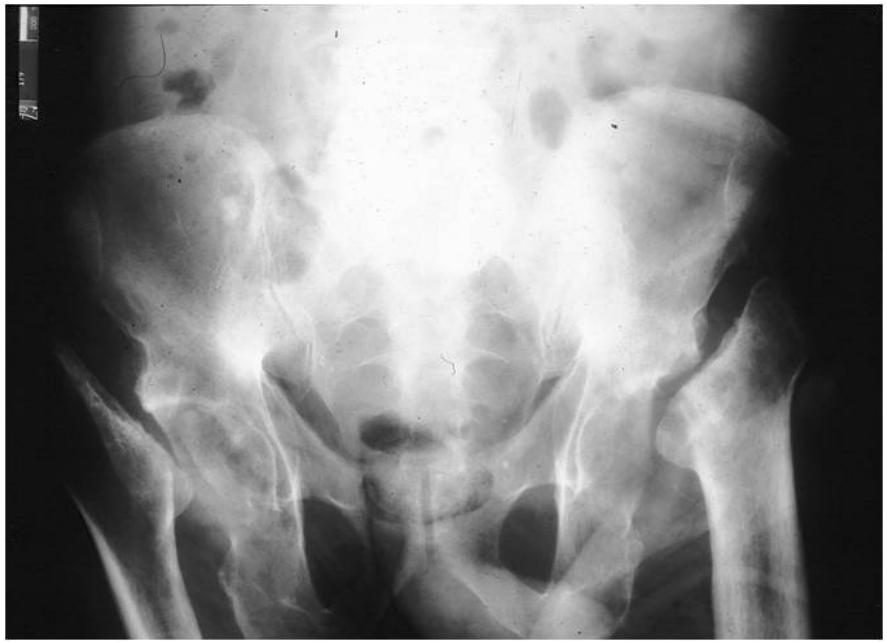
Rajbhandari SM. Diabetologia 2002;45:1085-96.

Potential Causes of Joint Destruction



"Analgesic Hip"

- Case series and case reports
  - Most frequently of the hip in patients with OA
    - Initially thought to be related to NSAIDs
    - However, occurred in the absence of NSAIDs



Doherty MI. Ann Rheum Dis 1986;45:272-6.

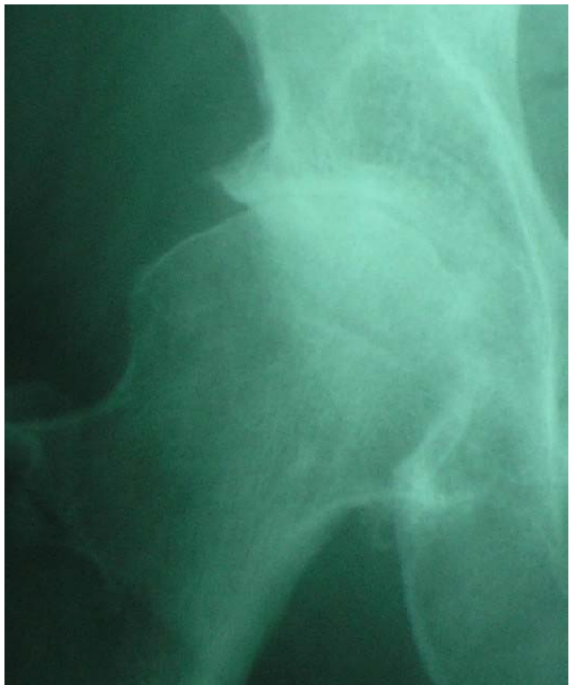
"Rapidly Progressive OA"

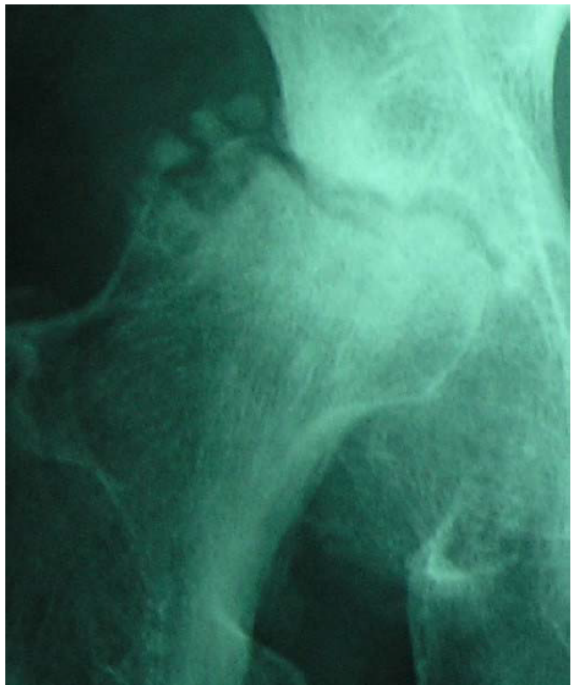
- Rapidly destructive arthropathy
  - Case series and case reports
    - Hip described most frequently
  - Variety of different names
    - Rapidly progressive osteoarthritis
    - Rapidly destructive arthritis, osteoarthritis, or hip disease
  - No validated criteria
    - No standard definition used in the literature
      - Criteria frequently descriptive or focus on rapid loss of joint space

"Rapidly Progressive OA": Sponsor Definitions

Type 1: ≥1mm joint space narrowing in less than approximately 1 year Type 2: abnormal loss/destruction of bone that is **not normally present in end-stage OA** which in the most severe form was catastrophic bone failure and joint destruction	Required baseline films Initial radiograph: KL grade 0-3 Follow-up radiographs: • Focal JS narrowing of ≥50% or 2mm per year • Flattening of femoral head • Flattening of the femoral/tibial condyle or tibial plateau Histopathology Evidence: • Consistent with totality of clinical and radiographic findings • If ON present, evidence of focal ON only	1. Normal OA: consistent with normal progression of OA 2. Other: ***not* consistent with the normal progression of OA** 3. Insufficient information: the information provided was insufficient to make a determination

"Rapidly Destructive OA": Hip Radiographs





Batra S, et al. J Orthop Surg Res 2008;3:3.

"Rapidly Progressive OA": Comparison with OA

- **Similarities**
  - Degenerative changes on histology
- **Differences**
  - Occurrence in a normal joint that is not painful
  - Rate and severity of joint destruction
  - Radiographic features

"Rapidly Progressive OA": Occurrence in Two Patient Populations

"Rapidly Progressive OA"	Osteoarthritis Initiative Study (N=1,174)	2-year Pfizer study of radiographic progression (not involving anti-nerve growth factor agents) (N=1,457)
Type 1, n (%)	39 (3.3)	14 (1.0)
Type 2, n (%)	2 (0.2)	2 (0.1)
Total (Type 1 and 2), n (%)	41 (3.5)	16 (1.1)

Pfizer's definitions of Rapidly Progressive OA:
Type 1: ≥1mm joint space narrowing over the course of 1 year
Type 2: abnormal loss/destruction of bone that is **not normally present in end-stage OA** which in the most severe form was catastrophic bone failure and joint destruction

Pfizer submission, AC briefing book, Section 6.5.7, pg. 62.

Rapidly Destructive Arthropathies: Pathogenesis

- Overlapping features
  - Difficult to assess what is the primary process
    - Central concern is poor outcome
- Hypothesized mechanisms:
  - Drug toxicity
  - Subchondral insufficiency fractures[1]

1. Yamamoto T. Arthritis Rheum 2000;43:2423-7.

Conclusions

- Majority of patients with OA have slowly progressive disease
  - Subset may progressive more rapidly
    - However, this is rare
  - Rapidly destructive arthopathies cause joint destruction not normally seen in OA

Outline of FDA Presentations

- **Background on Osteoarthritis and Causes of Joint Destruction**
  Janet Maynard, MD, MHS
  Clinical Reviewer, DPARP, CDER, FDA

- **Safety and Efficacy Considerations**
  Anjelina Pokrovnichka, MD
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  Joan Bathon, MD
  Director, Division of Rheumatology
  Columbia University, College of Physicians and Surgeons

Anti-NGF Drug Class Efficacy and Safety

Anjelina Pokrovnichka, M.D.

Medical Officer
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II

Presentation Outline

- Investigational products and regulatory history
- Safety profile of anti-NGF products
- Joint-related events with anti-NGF products
- Efficacy of anti-NGF products

Investigational Products

- Tanezumab (Pfizer) - humanized IgG_2 monoclonal antibody directed against NGF
- Fulranumab (Janssen Research & Development, L.L.C.) - fully human, recombinant IgG2 monoclonal antibody directed against NGF
- REGN475 (Regeneron) – fully human IgG4 monoclonal antibody directed against NGF

Regulatory History

- April 2010
  - Potential osteonecrosis (ON) safety signal detected
  - Additional data requested and reviewed
- June 2010
  - Tanezumab osteoarthritis (OA) and chronic low back pain (CLBP) programs placed on hold
  - Adequate informed consent, appropriate I/E criteria, strict joint-related safety assessments, monitoring and stopping criteria for ongoing trials
- December 2010
  - All active INDs for the anti-NGF agents placed on hold
    - Histopathologically confirmed AVN in non-OA patient
  - Only trials in terminal cancer patients allowed to proceed

Regulatory History

- AC scheduled September 2011
- Response to clinical hold submitted July 1, 2011 (~500 cases from Pfizer, Janssen)
- AC re-scheduled for March 12, 2012
- Janssen – Another response to hold submitted Jan. 31, 2012 to restart studies in diabetic peripheral neuropathy (DPN)

Clinical Trials

- Variety of chronic painful conditions
  - OA, CLBP, DPN, postherpetic neuralgia, chronic pancreatitis, chronic prostatitis, interstitial cystitis, endometriosis, cancer pain, vertebral fracture, thermal injury
- Pfizer
  - In Phase 3 of development for OA
  - >10,000 patients
- Janssen and Regeneron
  - In Phase 2 of development

Safety Profile

Common Adverse Events (AEs)

- Higher incidence with anti-NGF treatment
  - Neurosensory symptoms
  - Arthralgia
  - Pain in extremity
  - Peripheral edema
- Described for all three anti-NGF drugs
- Long-term consequences of these are unknown

Neurosensory Symptoms

- Abnormal peripheral sensation:
  - Paresthesia, hypoesthesia, and hyperesthesia
  - Dose-related
  - Generally resolve during the 1st month
  - Reported cases of persistent symptoms at last follow-up visit (some over 5 months)

Selected AEs ≥ 2% - Tanezumab OA

N(%)	Tanezumab			Placebo	Naproxen
	2.5mg N=327	5mg N=743	10mg N=748	N=744	500mg BID N=417
Edema peripheral	2.8%	3.5%	6.3%	0.5%	1.9%
Arthralgia	5.5%	4.4%	6.4%	3.0%	3.6%
Pain in extremity	2.8%	2.0%	6.7%	2.2%	0.7%
Paresthesias	4.0%	4.7%	6.3%	1.9%	2.6%

Adapted from Pfizer response to clinical hold – July 2011
Placebo-controlled OA studies 1011, 1014, 1015, 1018

Selected AEs ≥2% - Fulranumab

All studies							
	Placebo (N=285) n (%)	**Oxy CR** BID (N=50) n (%)	**Fulranumab**				
			1mg Q4wk (N=183)	3mg Q4wk (N=232) n (%)	6mg Q8wk (N=78) n (%)	9mg Q4wk (N=64) n (%)	10mg Q4wk (N=142) n (%)
Arthralgia	12%	4%	16%	16%	22%	13%	12%
Pain in extremities	7%	2%	10%	3%	14%	5%	12%
Paresthesia	6%	8%	4%	13%	21%	3%	8%

Adapted from Janssen submission – February 10, 2012

Joint-related Events

- Joint replacements
- Osteonecrosis
- Rapid Joint Destruction
- Atraumatic fractures

Baseline Disease Characteristics in Anti-NGF OA Studies

Disease characteristic	Tanezumab OA studies	Fulranumab OA studies	REGN475 OA study	OAI Progression cohort
Kellgren-Lawrence Grade	Gr. 2 ~ 40% Gr. 3 ~ 40-45% Gr. 4 ~ 15-20%	Gr. 2 ~ 43% Gr. 3 ~ 40% Gr. 4 ~ 17%	Not captured in the CRF	Gr. 2 ~ 28% Gr. 3 ~ 40% Gr. 4 ~ 17%
Median disease duration	~ 5 years	~ 5 to 6 years	~ 8 years	Not collected

Total Joint Replacement (TJR)

- In studies with placebo and active comparators, the total number of JRs appear comparable across treatment groups
- Across tanezumab doses, appears to be a dose response
- Some cases in non-OA patients

TJR Events – Tanezumab Studies

Treatment Group	Events/100 patient-years
All Controlled Osteoarthritis Studies – Monotherapy	
Placebo	3.19
Tanezumab 2.5 mg	3.84
Tanezumab 5 mg	3.69
Tanezumab 10 mg	3.01
Tanezumab 2.5 – 10 mg combined	3.39
Active Comparator	4.24
All Controlled Osteoarthritis Studies – Combination Therapy	
Tanezumab 2.5 mg + NSAID	3.49
Tanezumab 5 mg + NSAID	8.55
Tanezumab 10 mg + NSAID	9.52
Tanezumab 5 – 10 mg combined + NSAID	8.59
Randomized Non-Controlled Long-Term Osteoarthritis Studies	
Tanezumab 2.5 mg	7.81
Tanezumab 5 mg	9.65
Tanezumab 10 mg	11.30
Tanezumab 2.5 – 10 mg combined	9.72
Randomized Non-Controlled Chronic Low Back Study	
Tanezumab 10 – 20 mg combined	1.51

TJR with Tanezumab – Joints Affected

Table 9. All-Cause Total Joint Replacements in the Phase 3 Osteoarthritis Studies and the Phase 2 Chronic Low Back Pain Studies; Affected Joints

joints affected; n (%)	placebo (N=1300)	tanezumab monotherapy[1] (N=5183)	tanezumab[1] + NSAID[2] (N=3400)	active comparator[3] (N=1653)
All-cause total joint replacements	11	143	259	32
Knee	6 (54.5)	68 (47.6)	164 (63.3)	22 (68.8)
Hip	5 (45.5)	69 (48.3)	79 (30.5)	10 (31.2)
Shoulder[4]	0 (0.0)	6 (4.2)	13 (5.0)	0 (0.0)
Other (foot, ankle, wrist)[5]	0 (0.0)	0 (0.0)	3 (1.2)	0 (0.0)

TJR with Fulranumab – OA Studies

Pain condition	Subjects treated	TJR Rate in 1000 person year (n/exposure)		
		Placebo	Fulranumab	Oxycodone CR
Knee or hip OA	466	**98** (8/82)	**139** (63/455)	**N/A**
Knee OA	196	**0** (0/28)	**38** (2/53)	**40** (1/25)

Adapted from Fulranumab AC briefing book

Reported Events of Osteonecrosis

- Signal first suggested by investigator reports
- Diagnosis based on imaging and surgical reports
- Histopathology available in small number of cases
- Cases included
  - Several patients with multiple joints ON
  - Non-index joints
  - Unusual joints
  - Patients with no history of OA

Index vs. Affected Joint for Reported ON Cases

		OA N=239		CLBP N=10	Total
Index joint	**Affected joint**	Reported ON n (%)		Reported ON n (%)	
N		81		6	87
Hip or knee	Index hip or knee	41 (51%)			
Hip or knee	Non-index total	40 (50%)			
		Hip or knee	31 (38%)		
		Shoulder	8 (10%)		
		Foot	1 (1%)		
NA	Hip or knee			5 (83%)	
NA	Ankle			1 (17%)	

Adapted from Pfizer response to hold submission – July 2011

Reported Cases of ON

- Majority of cases received anti-NGF drug
  - Tanezumab (89 patients)
    - 85 tanezumab +/- NSAIDs
    - 4 comparator drug
  - Fulranumab (19 patients)
    - 17 fulranumab +/- NSAIDs
    - 2 placebo
  - REGN475: no cases

Based on updated information submitted February 2012

Adjudication of Joint Replacements

Adjudication

- Internal FDA adjudicator
- External FDA adjudicator
- Adjudication based on sponsors' data
- Similar but not identical adjudication protocols
- Limitations
  - Available baseline imaging and histopathology
  - External adjudicator did not have access to electronic imaging files

Rapid Joint Destruction

- Rapidly Progressive Osteoarthritis (RPOA)
  - Adjudication diagnosis used by sponsors
  - Descriptive term, not uniformly recognized
- Incidence rate:
  - Anti-NGF +NSAID > Anti-NGF monotherapy > placebo
- Time to event:
  - Late, usually after several doses
- Not restricted to advanced OA cases

Sponsor-Adjudicated RPOA (Tanezumab Ph3 OA Trials)

	Placebo N=1026 n (%)	Active comparator N=1266 n (%)	Tanezumab monotherapy N=4273 n (%)	Tanezumab + NSAIDs N=3028 n (%)	Total # pts N=8963 n (%)
RPOA Type 1	0	0	5 (0.1)	6 (0.2)	11 (0.1)
RPOA Type 2	0	1 (0.1)	19 (0.4)	41 (1.4)	56 (0.7)
RPOA Type 1 and 2	0	1 (0.1)	24 (0.6)	47 (1.6)	67 (0.8)

Adapted from Pfizer submission – March 2012

RPOA Comparison

RPOA	Tanezumab Ph3 OA N=8963	OAI N=1174	2-year Pfizer study of radiographic progression (not involving anti-NGF agents) N=1457
Type 1 n (%)	11 (0.1)	39 (3.3)	14 (1.0)
Type 2 n (%)	56 (0.7)	2 (0.2)	2 (0.1)
Total (Type1 and 2) n (%)	67 (0.8)	41 (3.5)	16 (1.1)

Definitions of RPOA

Type 1: ≥1mm joint space narrowing over the course of 1 year

Type 2: abnormal loss/destruction of bone that is **not normally present in end-stage OA**

Kellgren-Lawrence Grade- Study 1025 Tanezumab

Outcome	KL Gr. Affected joint	Tanezumab rate /1000 pts N=1083	NSAID rate /1000 pts N=539	NSAID+tanezumab rate /1000 patients N=1078
Adjudicated RPOA (Type 1 and 2)	2	2	0	1
	3	4	2	6
	4	2	0	8
	Unknown	3	0	5
	Total	10	2	20
Combined Adjudicated ON & RPOA	2	2	0	1
	3	4	2	6
	4	2	0	8
	Unknown	4	0	5
	Total	11	2	20

Adapted from Pfizer submission November 11, 2011

Joint Replacements – Fulranumab

Treatment	Number of adjudicated JR	Adjudicated case definition					
		ON	**RPOA**	RPOA with features of ON	OA normal progression	NA	Insufficient information
Placebo	12	0	0	0	10	1	1
Fulranumab	88	0	18	0	55	3	12
Oxycodone CR	1	0	0	0	0	0	1
Total	101	0	18	0	65	4	14

- Adapted from Janssen AC briefing book
- Joint replacements in fulranumab clinical studies adjudicated as of July 8, 2011

Fractures

Fractures – Ph3 OA Tanezumab

	Placebo	Tanezumab	Tanezumab + NSAID	Active comparator
N	1029	4273	3028	1266
Total exposure (pt-yrs)	313	2614	2081	661
Traumatic n (%)	7 (0.7)	56 (1.3)	60 (2.0)	8 (0.6)
Pathologic n (%)	0	0	0	0
Unspecified/other				
n (%)	1 (0.1)	20 (0.5)	42 (1.4)	3 (0.2)
Osteoporotic				
n (%)	0	4 (0.1)	4 (0.1)	0
All-Cause				
n (%)	8 (0.8)	80 (1.9)	106 (3.5)	11 (0.9)
Events/1000 pt-yrs	26	31	49	17

- Adapted from Pfizer AC briefing book
- Includes OA studies 1011, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030, and 1043

Fractures-Fulranumab

Fracture type	Placebo (N=285) n (%)	Fulranumab (N=931) n (%)	Oxycodone (N=50) n (%)
Total no. subjects with fracture	4 (1)	34 (4)	0
Traumatic	2 (1)	14 (2)	0
Osteoporotic	0	4 (<1)	0
Unspecified/unknown	2 (1)	15 (2)	0
Pathologic	0	2 (<1)	0

- Adapted from Janssen AC briefing book
- Includes studies PAI-2003, PAI-2004, PAI-2005, PAI-2002, NPP-2001, and NPP-2002

Tanezumab Efficacy

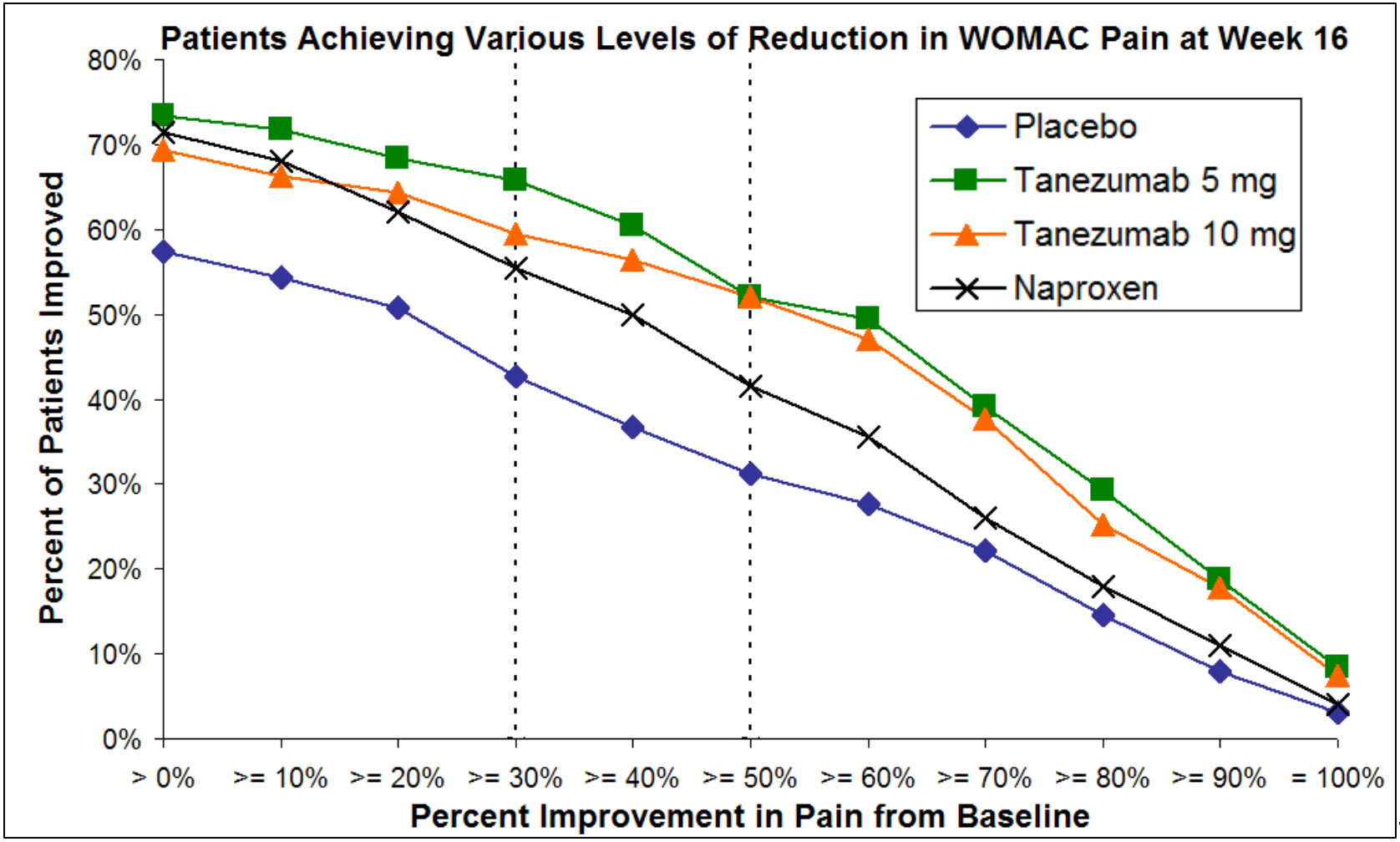
Tanezumab Efficacy

- Evaluated five Phase 3 trials for OA
- Preliminary assessment suggests analyses were appropriate
- Tanezumab appears to be efficacious

Study 1015 – Patient Population

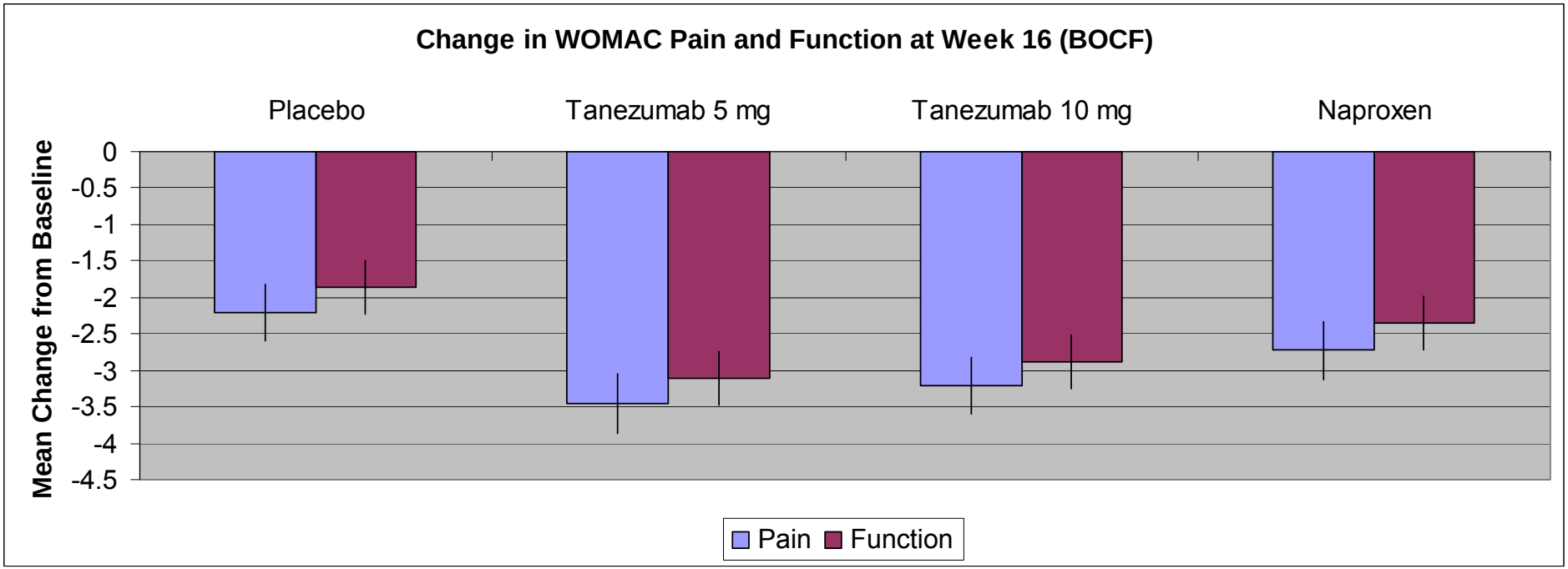
- OA of the knee and candidate for NSAID therapy
  - KL Gr. ≥ 2
  - Western Ontario and McMaster Universities Arthritis Index (WOMAC) Pain ≥5
  - WOMAC Physical Function ≥4
  - Patient Global Assessment - fair to very poor
- 4 treatment groups:
  - Placebo - Tanezumab IV 5 mg q 8wks
  - Naproxen - Tanezumab IV 10 mg q 8wks
- Primary efficacy: Change in WOMAC pain, function, and global from baseline to Week 16

Study 1015



Source: Adapted from Pfizer's results

Study 1015

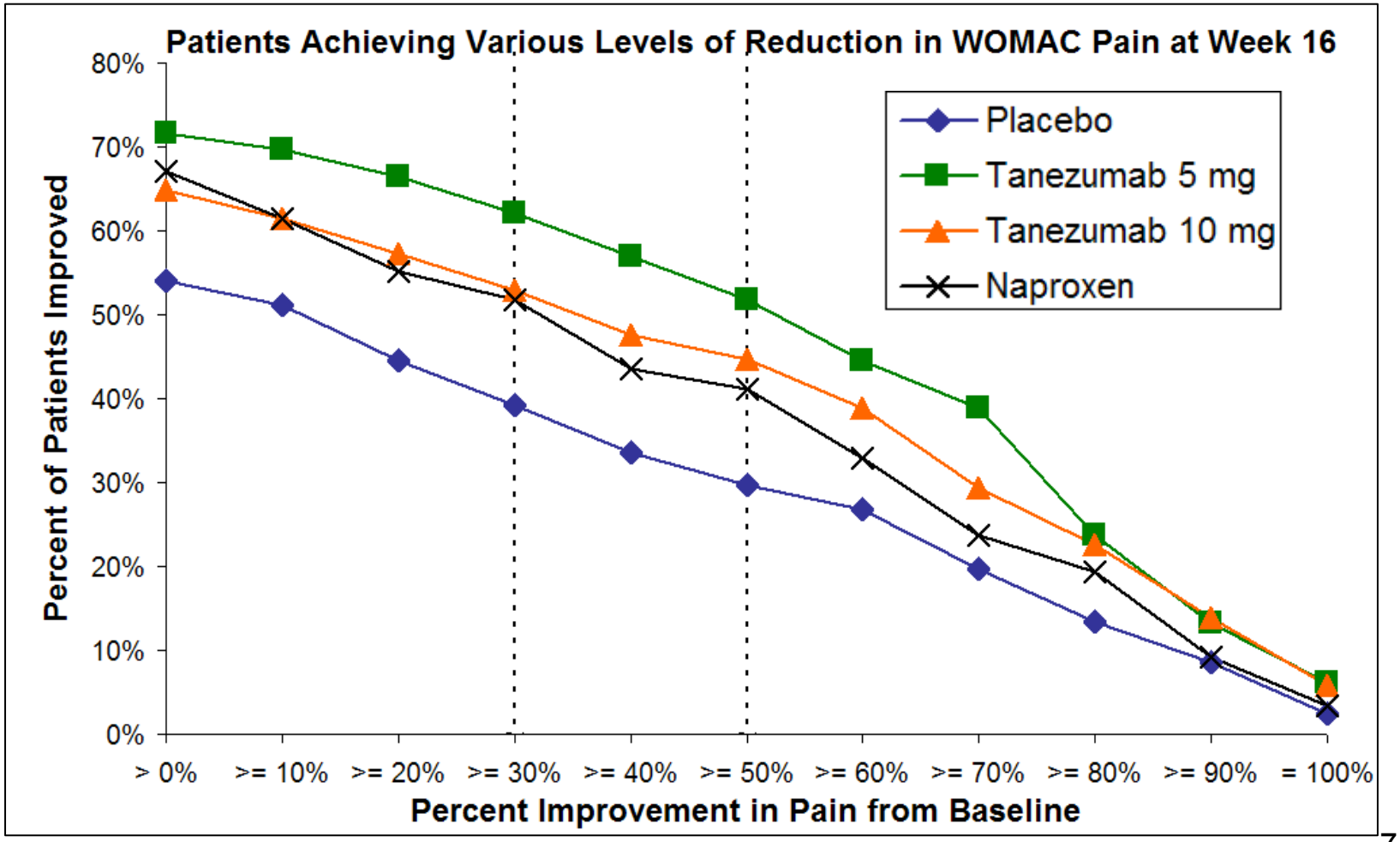


*Comparisons of tanezumab to placebo were statistically significant.

Source: Adapted from Pfizer's results

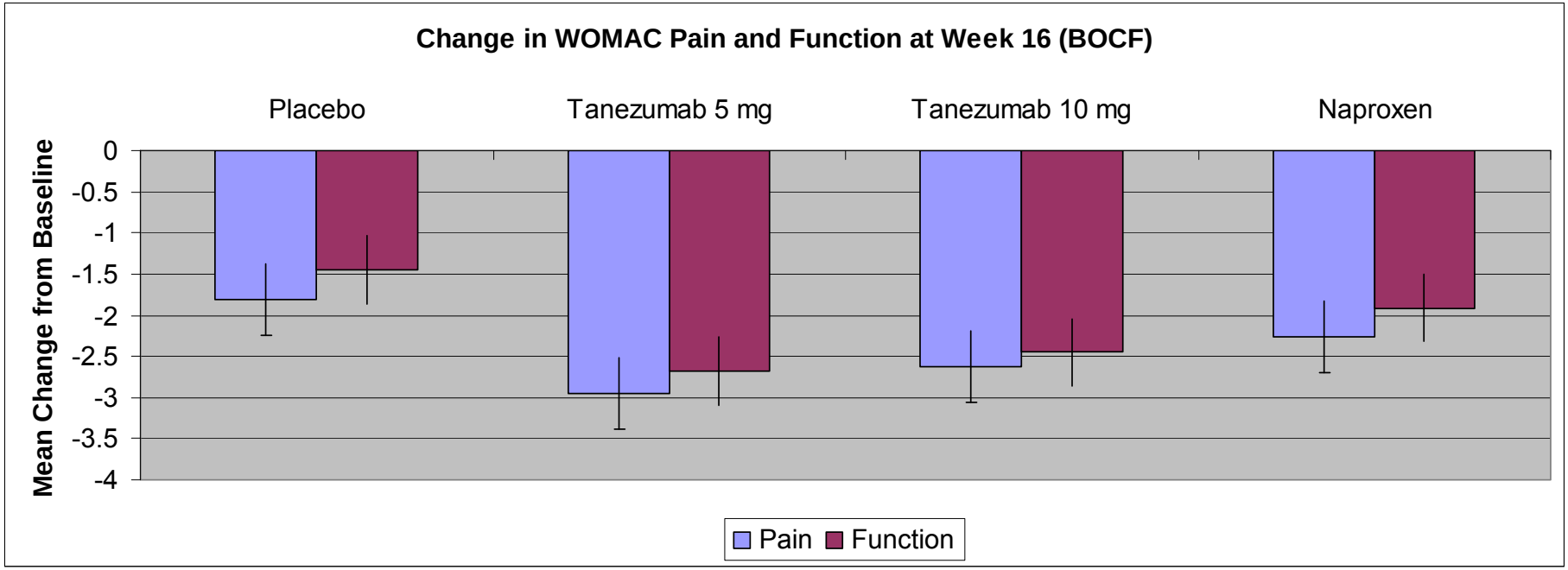
BOCF - Baseline Observation Carried Forward

Study 1018



Source: Adapted from Pfizer's results

Study 1018



*Comparisons of tanezumab to placebo were statistically significant.
Source: Adapted from Pfizer's results

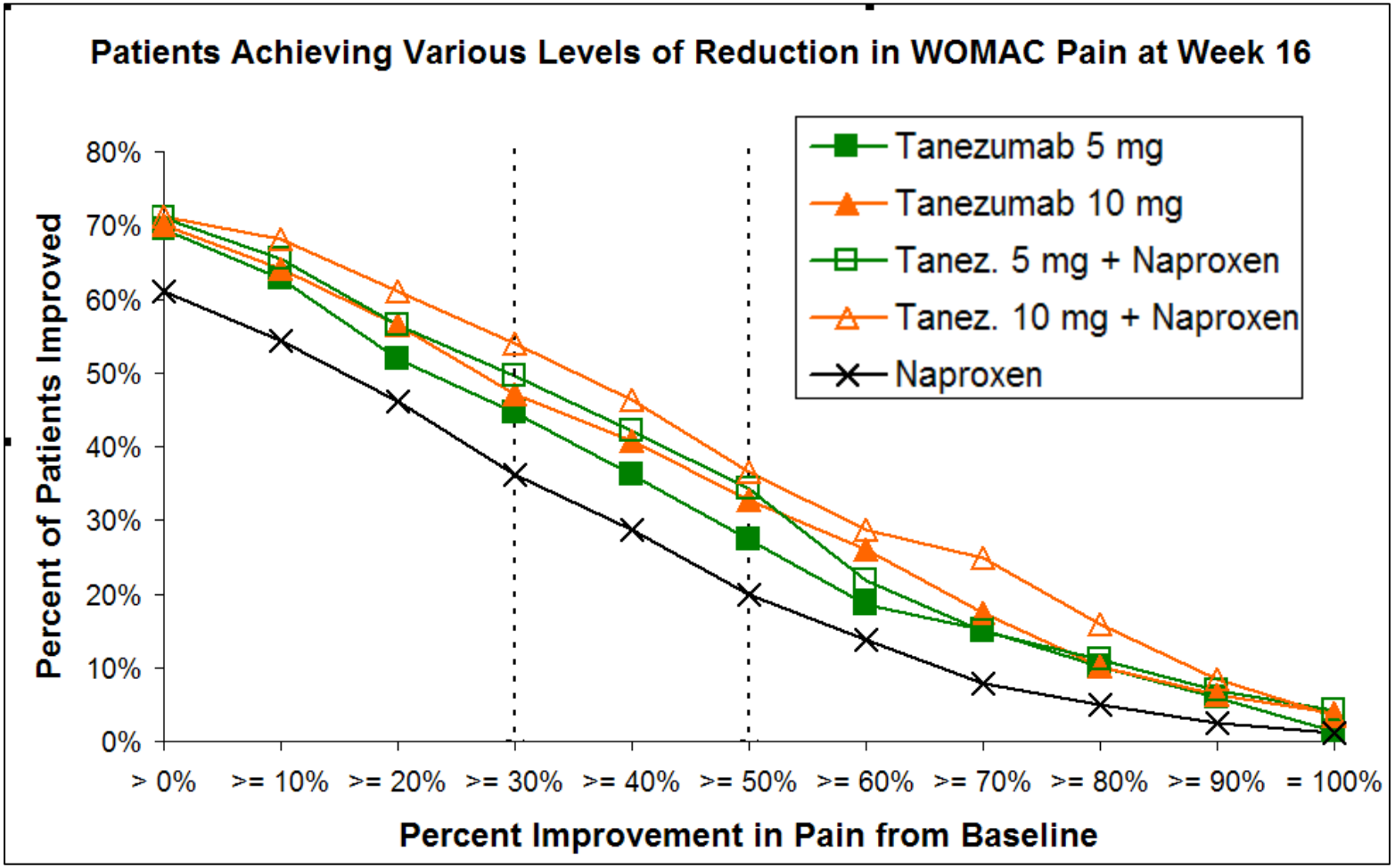
Study 1025 – Patient Population

- OA of hip or knee
- On stable dose of naproxen or celecoxib for 30 days, require additional pain relief
  - KL Gr. ≥2
  - WOMAC Pain numerical rating scale (NRS) ≥4
- 5 treatment groups
  - NSAID
  - Tanezumab 5 mg
  - Tanezumab 10 mg
  - Tanezumab 5 mg + NSAID
  - Tanezumab 10 mg + NSAID
- Primary Efficacy: Change from baseline to Week 16 in WOMAC pain, function, and global

Study 1025

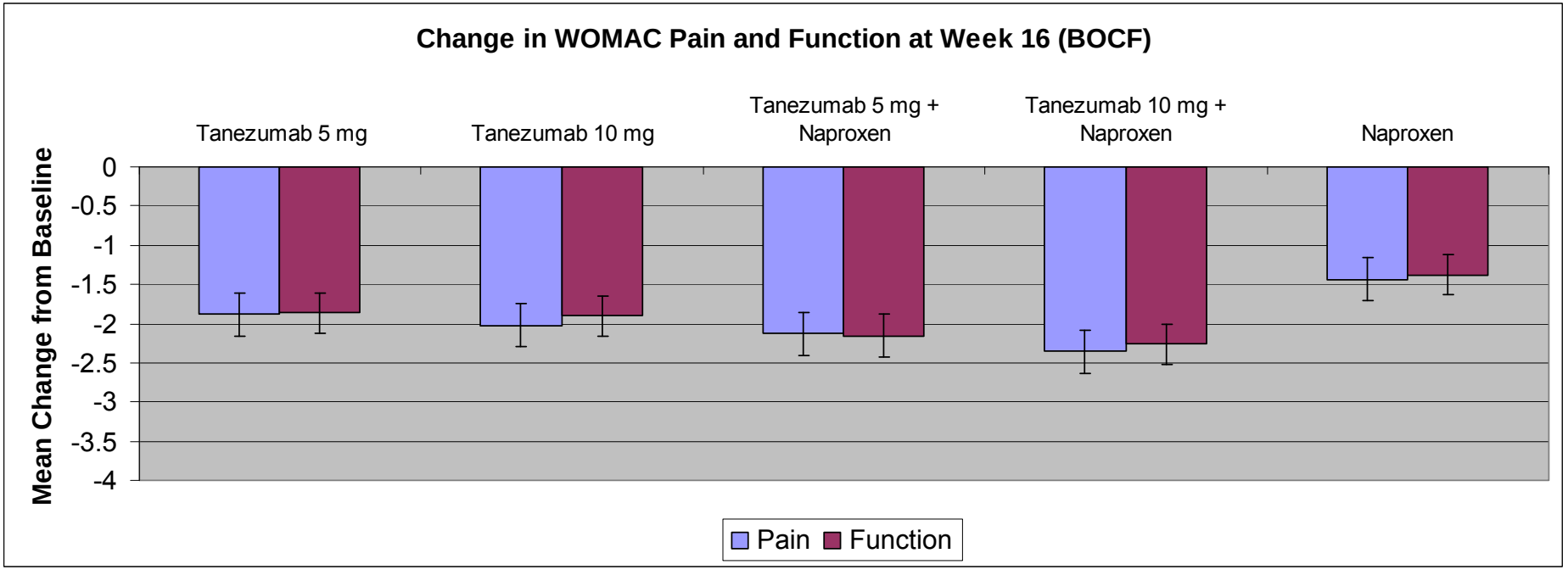
- Study was put on clinical hold, but primary efficacy analysis at Week 16 was not affected.

Study 1025



Source: Adapted from Pfizer's results

Study 1025



Comparisons of tanezumab 10mg + naproxen to naproxen were statistically significant.

Source: Adapted from Pfizer's results

Conclusion

- Safety signal for joint destruction with the administration of anti-NGF agents
- This rapidly destructive arthropathy occurs following exposure to anti-NGF agents alone at doses associated with efficacy
- The signal is greater with concurrent NSAID use
- The efficacy data suggest a numerically larger effect size for tanezumab relative to NSAIDs

Outline of FDA Presentations

- **Background on Osteoarthritis and Causes of Joint Destruction**
  Janet Maynard, MD, MHS
  Clinical Reviewer, DPARP, CDER, FDA

- **Safety and Efficacy Considerations**
  Anjelina Pokrovnichka, MD
  Medical Officer, DAAAP, CDER, FDA

- **FDA Review of Serious Joint Related Adverse Events**
  Nona Colburn, MD
  Clinical Reviewer, CDRH, FDA

- **External Review of Serious Joint Related Adverse Events**
  Joan Bathon, MD
  Director, Division of Rheumatology
  Columbia University, College of Physicians and Surgeons

CDRH ADJUDICATION REVIEW

Nona T. Colburn, M.D.

Arthritis Advisory Committee Meeting

March 12, 2012

Overview

- Multi-center, prospective, randomized, concurrently controlled trials of therapeutic anti-NGF for pain relief
  - patients with KL graded OA of the hip and/or knee
  - one study of patients with chronic low back pain
- Trial designs of either placebo, NSAIDS, and/ or one of three therapeutic recombinant anti-NGF
  - tanezumab [Pfizer] (284 joints)
  - fulranumab [Janssen] (105 joints)
  - or REGN475 [Regeneron] (12 joints)

Overview

- FDA adjudication of 355 cases (401 joints) of total joint replacements (TJR) and osteonecrosis (ON)
- Blinded assessment
  - To the treatment
  - To the sponsors' adjudicated diagnoses
- Joints assigned five adjudication categories
  - Normal Progression of Osteoarthritis (NPOA)
  - Rapid Progression of Osteoarthritis (RPOA)
  - Osteonecrosis (ON)
  - Other (with diagnosis specified)
  - Insufficient Information

	NPOA	RPOA	ON	Other	Insufficient Info	NA
Total Joints	**196 (49%)**	**83 (21%)**	**30 (7%)**	**21 (5%)**	**66 (17%)**	**5 (1%)**

Source Materials Reviewed

- Digital imaging and imaging reports
- Digital pathology and pathology reports
- Medical history narratives
  - Operative reports
  - Consultation reports
  - History and physical
- MedWatch reports
- Case Report Forms

Normal Progression of Osteoarthritis (NPOA): Clinical

- By definition a slowly progressive joint degeneration
- PMH consistent with long standing disease and absence of confounding comorbidities
- Patient demographics considered
  - Age
  - Obesity
  - Prior history of trauma

NPOA: Radiographic & Pathologic Features

- **Radiographic**
  - Osteophytes, joint space narrowing, sclerosis
  - Kellgren and Lawrence scores pre- and post-event
- **Pathologic**
  - Evidence of degenerative changes
  - Concomitant Osteonecrosis seen on 6-38% of pathology specimens
    - Adjudicated as NPOA with predominant features of OA
    - Adjudicated as ON with predominant features of ON

Rapid Progressive Osteoarthritis (RPOA): Clinical

- Time of occurrence compared to study entrance
  - Rapid rate of destruction
- Severe pain
- Diagnosis of exclusion, evaluate confounding diagnoses and risk factors
  - Steroid use
  - Neuropathic osteoarthropathy
  - Rheumatoid and seronegative arthritis
  - Septic arthritis
  - Primary osteonecrosis
  - Chondrocalcinosis

RPOA: Radiographic Features

- Diagnosis **requires** the availability of comparator X-rays and/or radiology reports
  - Studies often lacked pre- and/or post study films
- X-rays often demonstrated characteristic features
  - >50% joint-space narrowing in 1 year
  - Abnormal marked bony resorption and bone loss
  - Flattening of the femoral head/condyles or tibial plateau
  - Lack of a line of demarcation between necrotic and healthy bone
  - MRI shows subchondral insufficiency fractures

RPOA: Pathologic Features

- Lack of inflammation
- No evidence for ON
- Severe degenerative changes in articular cartilage
- Subchondral detritus and bone fragmentation
- Reactive synovitis

Osteonecrosis (ON): Clinical

- Death of bone can be a primary or secondary process
  - Primary ON: an idiopathic vascular process where no pre-deposing etiology can be defined. Applied to cases of post-traumatic or repeated microfracture ON (such as Spontaneous Osteonecrosis of the Knee-SPONK)
  - Secondary ON: occurs in the setting of a defined etiology. All cases of ON felt to be drug related are considered secondary
- Consider risk factors
  - Concomitant at risk comorbidities
  - Concomitant at risk medications

ON: Characteristic X-Ray

- Cystic or sclerotic changes
- Collapse or change in contour of the femoral head/condyles or tibial plateau
- “Crescent Sign”
  - A pathognomonic radiolucent line
  - Early collapse of cancellous bone beneath subchondral plate

ON: Characteristic MRI

- Well defined margins surround a focus of fat or fluid-like signal or low signal intensity +/- surrounding edema
- Collapse or change in contour of the femoral head/condyles or tibial plateau
- Bone marrow with high-signal intensity in both T1 and T2
- Subchondral bone appears as dark striations
- **Line of decreased signal** on both T1 and T2 images
- Demarcation between live regenerating bone and necrotic tissue
- Characteristic **serpiginous pattern** with combined signals

Osteonecrosis: Pathology

- "Gold standard" of diagnosis
- Necrosis
- Histologically proven dead bone may stand alone to make the diagnosis
- Secondary degenerative changes

Other

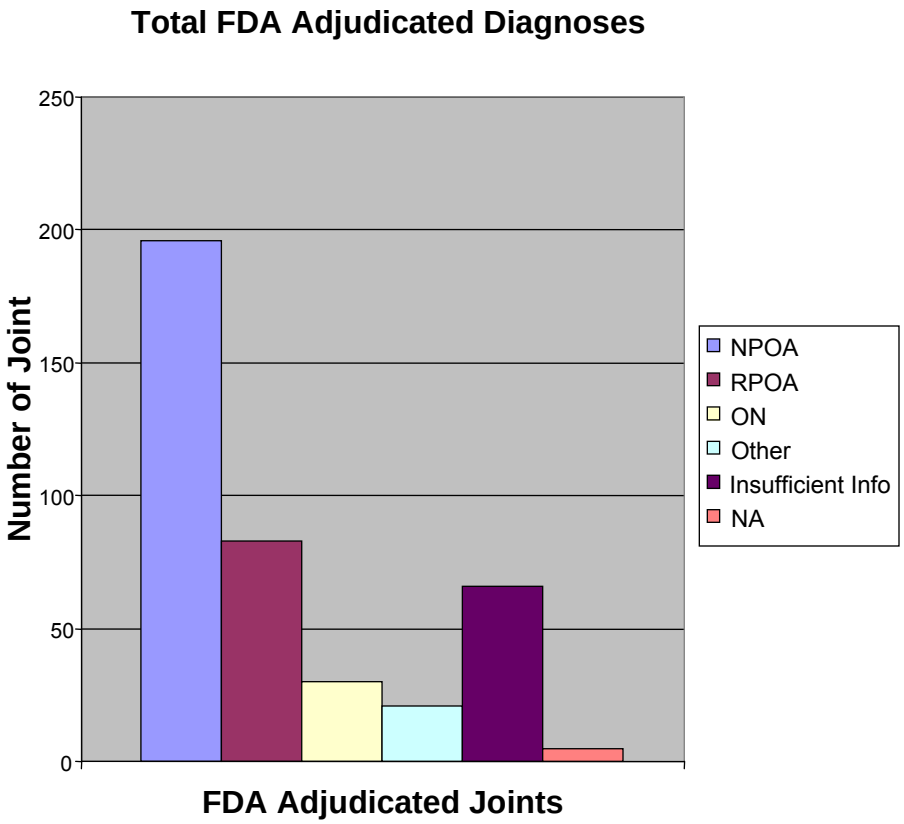
- Another diagnosis not definitely assessed as any of the other 3 categories
  - Failed lumbar hardware
  - Fractures
  - Rotator Cuff tendinopathy
  - End stage OA associated with severe cystic disease and chronic ON

Insufficient Information

- When no baseline and/or post study imaging and/or report were available

Adjudication Results

- 355 cases from 3 sponsors
- 401 joints
- Majority of joints involved the adjudicated diagnosis of NPOA
- A significant number of RPOA and ON joint involvement (28%)

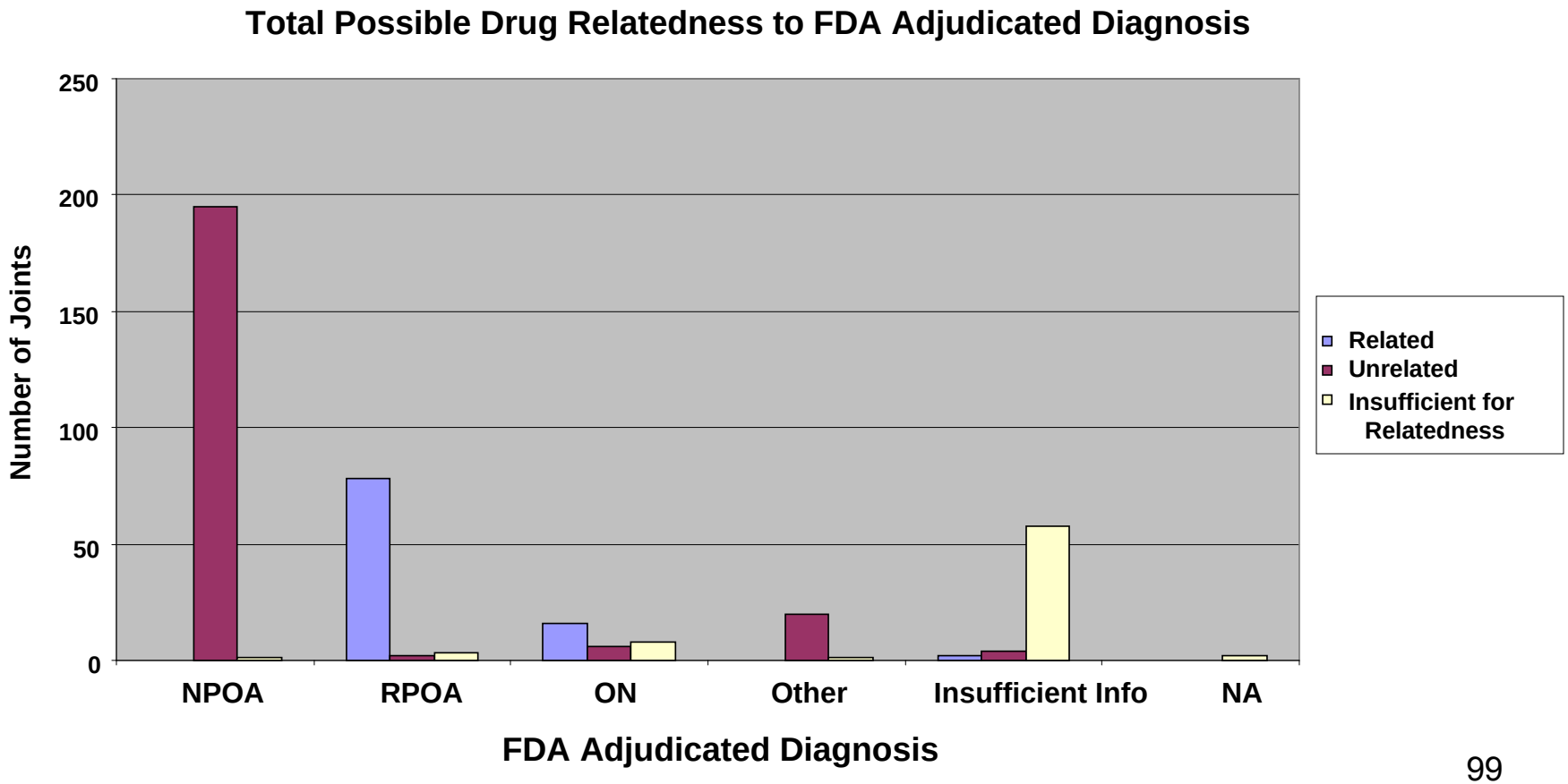


Relationship of Study Drug to Joint Event

- Possible relatedness of study drug to the adjudicated diagnosis determined by considering all components of the clinical presentation
- Drug contribution
  - more likely in cases of RPOA and ON
  - less likely in cases of NPOA

	NPOA	RPOA	ON	Other	Insufficient Info	NA
Related	0	78	16	0	2	0
Unrelated	195	2	6	20	4	0
Insufficient	1	3	8	1	58	2

Relationship of Study Drug to Joint Event



Adjudication of Cases by Treatment Assignment

- Drug dosages, administration, and trial design differed among the three sponsors
- Lower doses and/or less frequent administration of anti-NGF, as well as placebo, more likely associated with NPOA
- Higher doses, and the addition of NSAIDS with higher doses, more likely associated with RPOA and ON

Pfizer Treatment Groups

	NP OA	RPOA	ON	Other	Insufficient Info
Placebo	**4**	**0**	**0**	**0**	**0**
placebo/ ext study tanez 10 mg	5	0	0	0	0
placebo/ ext study tanez 5 mg	0	1	0	3	2
placebo/ ext study tanez 2.5 mg	1	1	0	0	0
placebo/blinded tanez dose ext study	0	0	0	0	1
tanez 20 mg	0	0	2	0	0
tanez 10mg	**21**	**23**	**7**	**4**	**11**
tanez 5 mg	35	14	4	5	10
tanez 2.5 mg	15	4	2	0	6
tanez 10 mg + diclofenac	0	2	1	0	0
tanez 5 mg + diclofenac	0	0	0	0	2
tanez 2.5 mg + diclofenac	0	0	1	0	1
tanez 10mg + nsaid	**13**	**13**	**2**	**1**	**2**
tanez 5 mg + nsaid	14	7	4	1	10
naproxen	1	0	0	0	0
naproxen/ ext study tanez 10mg	1	0	0	1	2
naproxen/ext study tanez 5 mg	2	1	0	0	0
NSAID	16	2	1	1	1
Totals	128	68	24	16	48

Janssen Treatment Groups

	NPOA	RPOA	ON	Other Dx	Insufficient Info
Treatment assignment Total N= 100) (100%)	62 (62%)	15 (15%)	4 (4%)	4 (4%)	15 (15%)
Placebo	8	0	0	0	1
Ful 3 mg Q8W	5	3	0	0	2
Ful 6 mg Q8W	7	2	1	3	1
Ful 10 mg Q8W	13	4	1	1	3
Ful 3 mg Q4W	14	5	2	0	0
Ful 6 mg LD +3 mg Q4W	2	0	0	0	0
Ful 9 mg Q4W	2	0	0	0	2
Ful 10 mg Q4W	4	0	0	0	1
Ful 20 mg Q4W	0	0	0	0	2
Oxycodone CR	0	0	0	0	1

Regeneron Treatment Groups

	NPOA	RPOA	ON	Other Dx	Insufficient Info
Treatment assignment (Total N=12) (100%)	**6 (50%)**	**0 (0%)**	**2 (16.67%)**	**1 (18.33%)**	**3 (25%)**
Placebo (N=2)	1	0	0	0	1
1 mg/kg IV SD (N=1)	**1**	**0**	**0**	**0**	**0**
0.3 mg/kg IV Q8w, 2 doses (N=3)	**3**	**0**	**0**	**0**	**0**
0.3 mg/kg IV, SD (N=2)	**0**	**0**	**1**	**0**	**1**
0.1 mg/kg IV Q8w, 2 doses (N=2)	**1**	**0**	**1**	**0**	**0**
0.03 mg/kg IV Q8w, 2 doses (N=2)	**0**	**0**	**0**	**1**	**1**

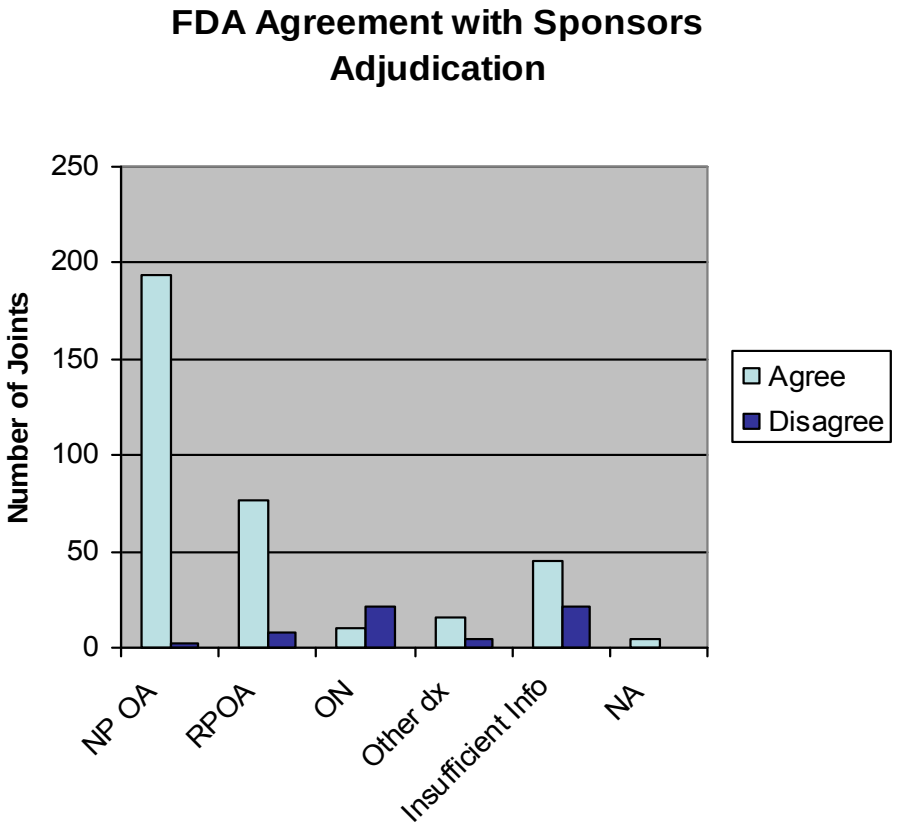
Level of Agreement

- To determine the level of agreement between FDA's adjudication and that of the sponsors
  - Unblinded to each sponsor's own adjudication responses
  - Assigned binomial determinations of Agree or Disagree
- A breakdown of the level of agreement:

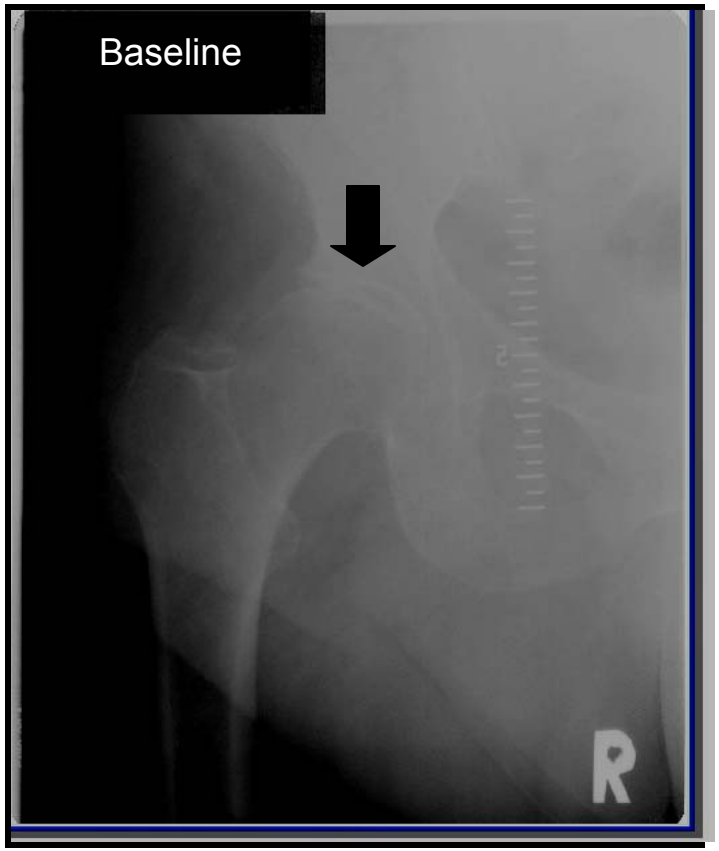
	NPOA	RPOA	ON	Other	Insufficient Info
Agree	194	77	10	16	45
Disagree	2	8	21	5	21

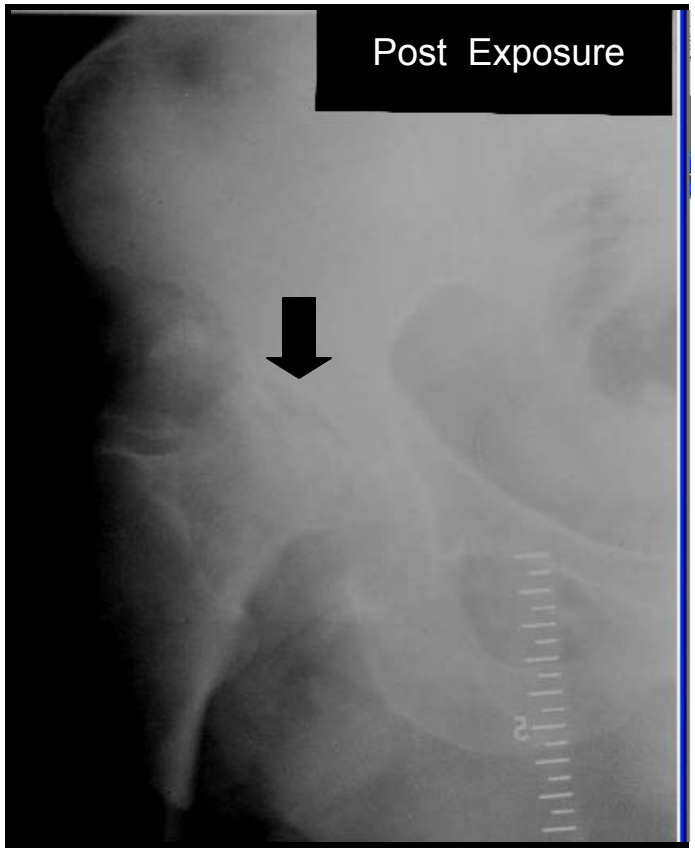
FDA/Sponsor Adjudication Agreement

- Overall considerable agreement between the FDA and sponsors' adjudications
- Two major areas of divergence
  - ON
  - Insufficient Information
- Major reasons for the divergences
  - 1) ON was diagnosed by FDA if there were clear pathological and/or imaging criteria met
  - 2) Insufficient information was the adjudicated response if no baseline or post study imaging or imaging reports were available
- Pfizer more likely to consider the diagnosis of RPOA and SPONK over that of ON



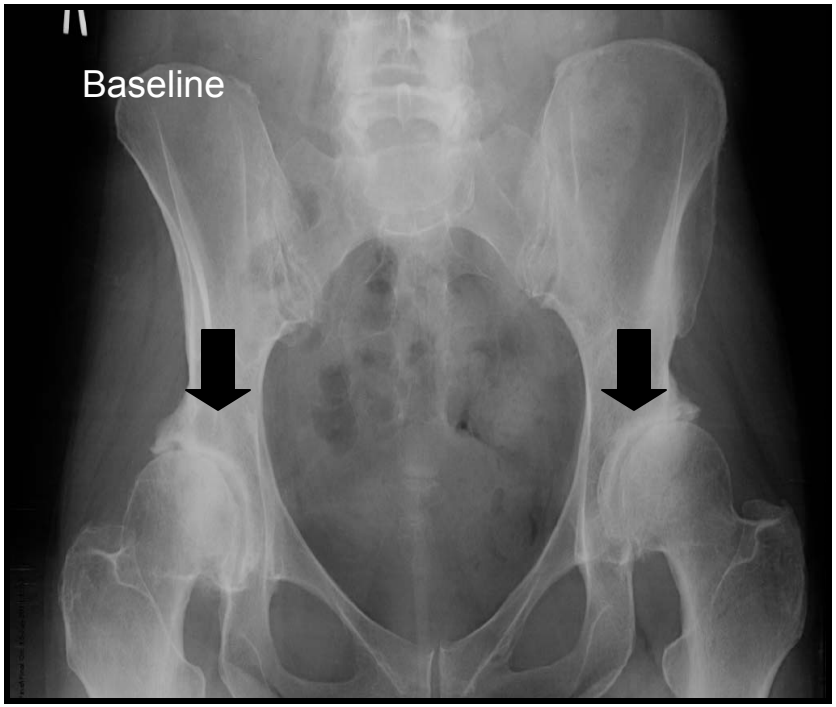
RPOA within 8 months

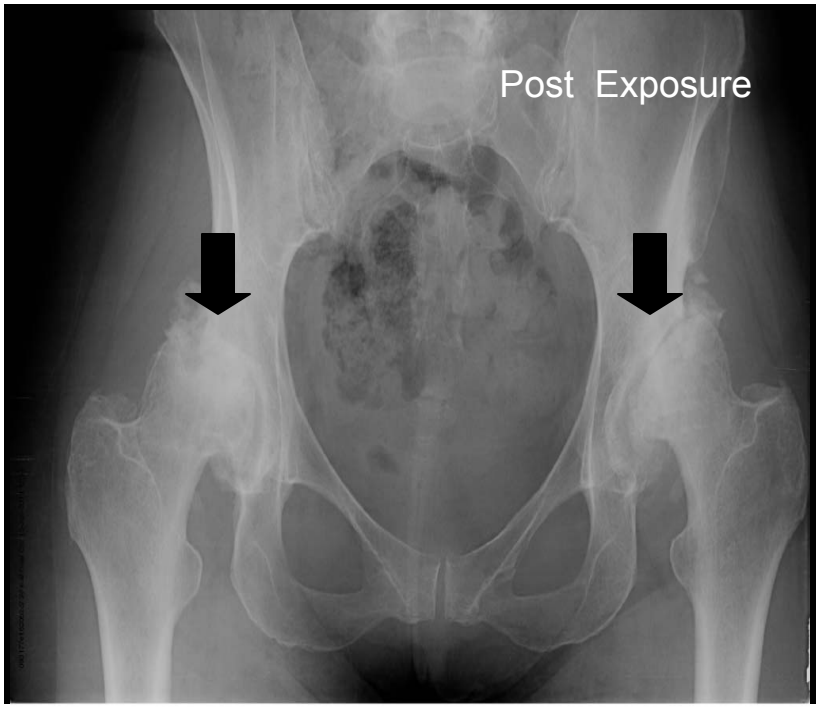




tanezumab 10 mg + NSAID

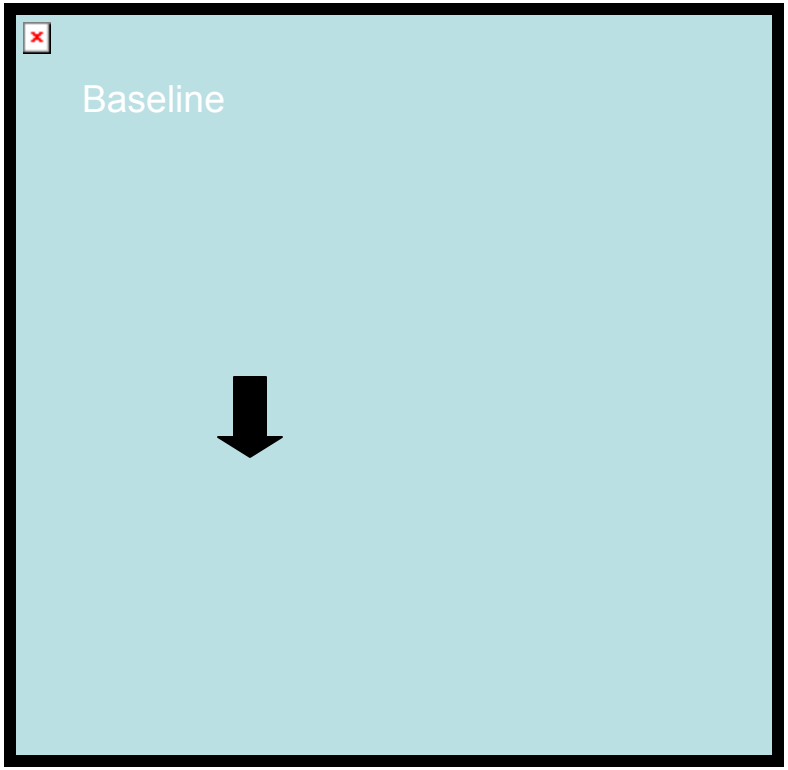
Bilateral RPOA within 10 months

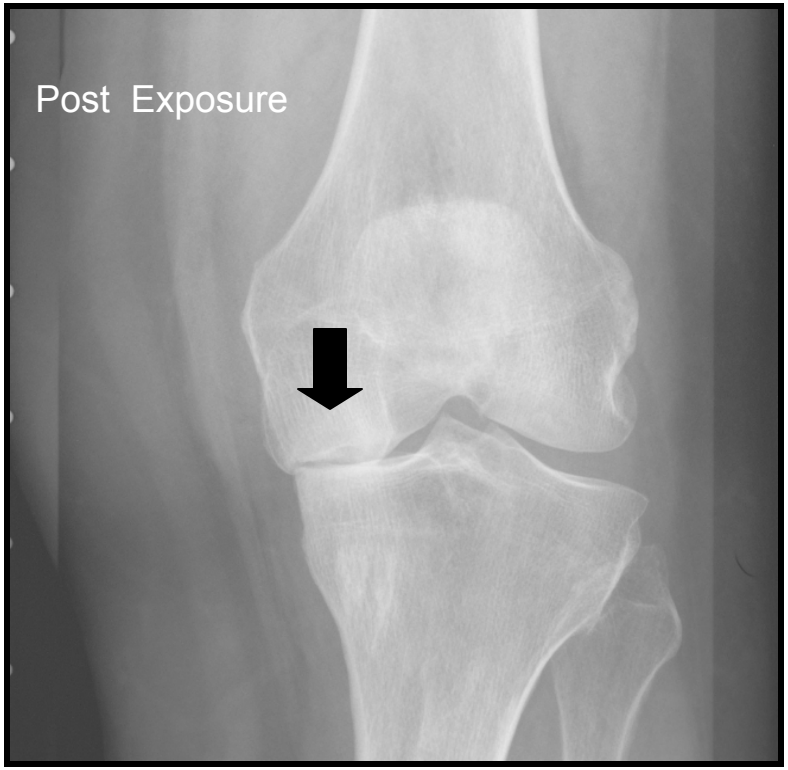




tanezumab 10 mg + medical history of ongoing diclofenac use

ON within 6 months





tanezumab 10 mg + NSAID

Bony Pathogenesis of Anti-NGF

- Cases adjudicated to RPOA demonstrated considerable and rapid destruction
  - Most often within 6 to 12 months post-exposure
  - Femoral head flattening to complete destruction
  - Medial femoral condyle often with subchondral fractures
- Associated with diffuse edema, joint effusions, and marked pain
  - Begins in an abnormal joint (KL graded OA)
  - Differs from previous literature where normal joints involved

Bony Pathogenesis of Anti-NGF

- Plausible mechanisms
  - "Analgesic" hip
  - "ON"-like with subchondral insufficiency fractures
  - "Charcot"-like joint
- Possible drug toxicity
  - Maybe synergistic with NSAIDs

Conclusion

- RPOA seen with drug exposure to anti-NGF is a unique clinical form of rapidly destructive arthropathy