

Monoclonal Antibodies Targeted Against Nerve Growth Factor For the Treatment of Chronic Pain

Introduction

Ken Verburg, PhD

Medicines Development Group, Pfizer Inc.

Arthritis Advisory Committee Meeting

12 March 2012
FDA White Oak Campus
Silver Spring, MD

Background Narrative

- **Clinical development programs with anti-NGF mAbs and the regulatory process worked to identify a safety signal prior to marketing approval**
 - **Signal was not predicted by 6 decades of research on NGF so a cautionary response was taken**
 - **Concern was justified although it was later learned the initial description of the event as osteonecrosis was incorrect**
 - ◆ **Rapidly progressive osteoarthritis**
 - **Careful examination of the data has allowed for identification of measures that could reduce the risk by 90%**

Decision Point

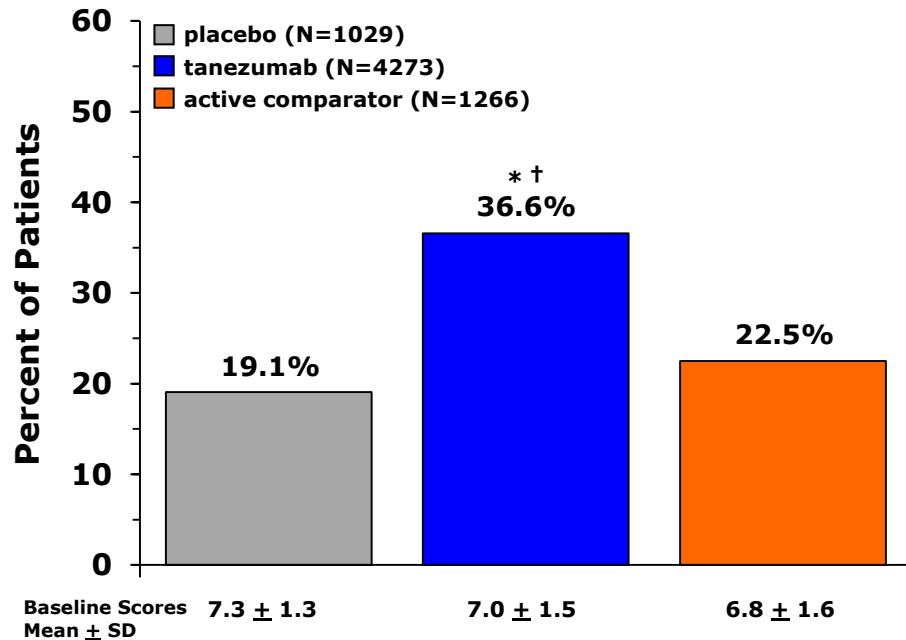
- **Whether to resume clinical development of anti-NGF therapies**
- **If so, how best to proceed**

Why Is it Important to Resume Development?

- **Evidence that anti-NGF therapies hold the promise of bringing a step-change improvement in pain relief**
 - **Need further studies to examine and demonstrate the effectiveness of this therapeutic approach**
- **Opportunities to advance the treatment of pain have been very limited**
 - **Despite decades of research, we have not seen any compounds in the clinic with similar efficacy characteristics**

1 in 3 Patients Treated with Tanezumab Report Minimal to No Pain Over ≥ 4 Consecutive Months¹

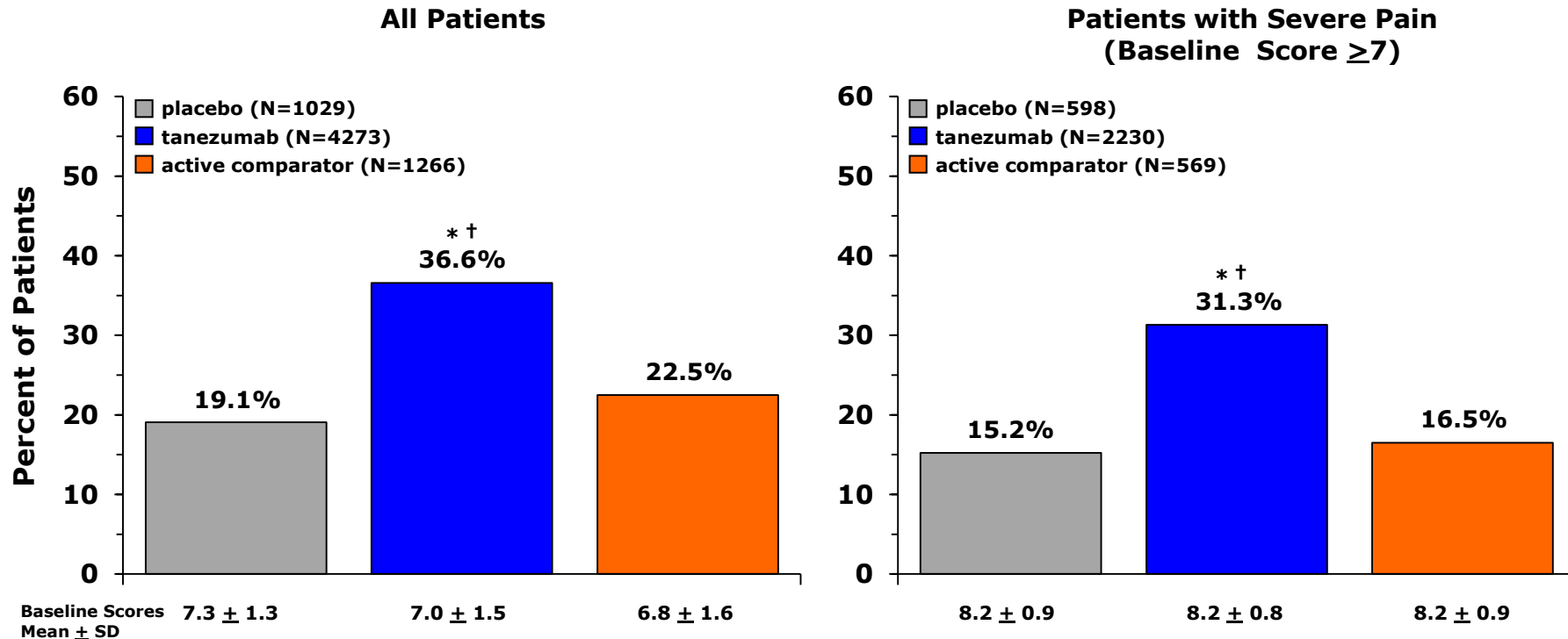
All Patients



WOMAC Pain Scores 0-2 at 2 or more consecutive 8-weekly visits on 0-10 NRS

* $p \leq 0.05$ vs. placebo, † $p \leq 0.05$ vs. active comparator, # $p \leq 0.05$ vs. tanezumab monotherapy

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Sponsor Presentations

- **To confirm with the Arthritis Advisory Committee**
 - **Clinical development of anti-NGF mAbs should resume**
 - **Proposed measures to minimize the risk, protect patient safety, and to characterize the risk further are sufficient**
 - **Chronic pain conditions selected and studies proposed are acceptable approaches for re-initiating the clinical programs**

Agenda

Perspectives on Chronic Pain	Thomas Schnitzer, MD, PhD <i>Professor of Medicine, Northwestern University Feinberg School of Medicine</i>
Tanezumab	Ken Verburg, PhD <i>Sr. VP, Medicines Development Group, Pfizer</i>
Fulranumab	David Upmalis, MD <i>Sr. Director, Neuroscience, Janssen R&D</i>
REGN475	Ned Braunstein, MD <i>Exec. Director, Regulatory, Regeneron</i>
Concluding Remarks	Nathaniel Katz, MD, MS <i>President, Analgesic Solutions</i>

External Delegation

Dr. David Hungerford

Dr. Michael Mont

Dr. Edward McCarthy

Dr. Steve Abramson

Dr. Kenneth Brandt

Dr. Marc Hochberg

Dr. Tom Schnitzer

Dr. Eric Vignon

Dr. David Walsh

Dr. David Cornblath

Dr. Martin Koltzenburg

Dr. Bruce Kneeland

Dr. Pat Mantyh

Orthopedic Surgery

Orthopedic Surgery

Orthopedic Pathology

Rheumatology

Rheumatology

Rheumatology

Rheumatology

Rheumatology

Rheumatology

Neurology

Neurology

Radiology

Pharmacology



Perspectives on Chronic Pain: Current Status and Needs

Thomas J. Schnitzer, MD, PhD

Professor

Departments of Physical Medicine and Rehabilitation
and Internal Medicine/Rheumatology

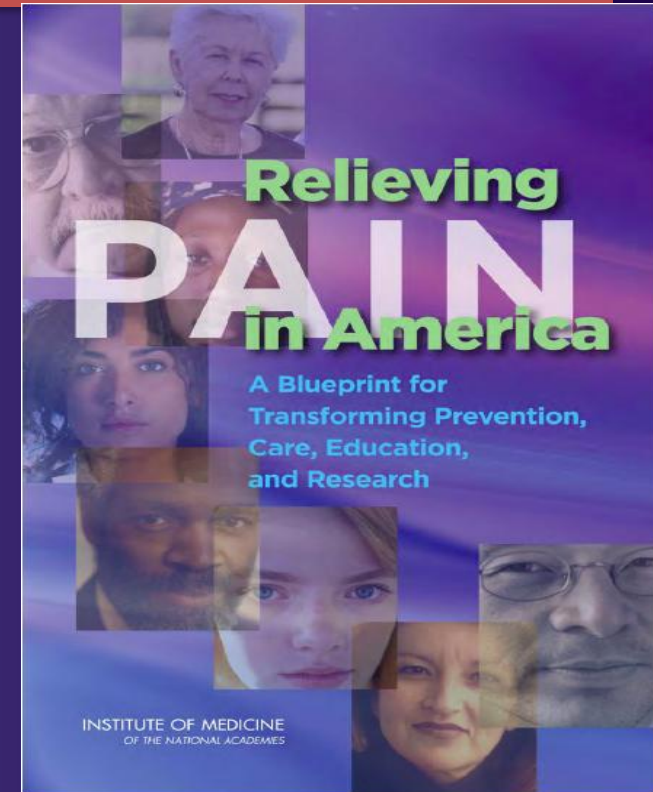


Discussion Outline

- Chronic Pain is prevalent
- Chronic Pain is impactful
- Chronic Pain management paradigms fail many patients
- New therapeutics not available despite serious efforts
- NGF inhibition has shown promise and also raised concerns

Prevalence of Chronic Pain

- 2011 IOM report of the Committee on Advancing Pain Research, Care and Education
- “at least 116 million Americans burdened with chronic pain”
- Most common clinical presentations of chronic pain
 - Musculoskeletal pain¹
 - Low back pain 28% of adults
 - Osteoarthritis 26% of adults
 - Chronic headache/migraine
 - Neuropathic pain
 - Visceral pain
 - Central pain



¹CDC and NCHS, 2010



Impact of Chronic Pain

What is pain?

It is so much more than just pain intensity. Over time, many [patients] find the effects of living with chronic pain impact their ability to work, engage in recreational and social activities, and for some, [perform] the most basic everyday activities that people just take for granted. Not surprisingly, pain begins to chip away at their mood, often leaving them angry, frustrated, anxious, and/or depressed. Our families suffer along with us, and many relationships are forever altered.

--An advocate for people with chronic pain¹

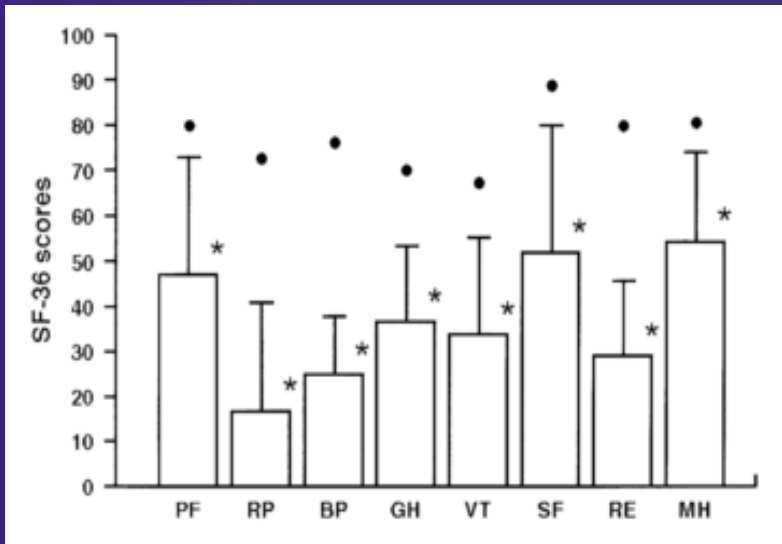
Consequences of pain

- **Poor health-related quality of life & poor self-rated health**
- **Strong link with disability**
- **Likely to seek medical attention**



Impact of Chronic Pain

Quality of Life



Effect of chronic nonmalignant pain on QOL, as indicated by SF-36 subscores, mean (SD) (n=150).^{1,2}

• = population norm values; PF=physical functioning; RP=role-physical; BP=bodily pain; GH=general health; VT=vitality; SF=social functioning; RE=role-emotional; MH=mental health. * p<0.001

Activities/Quality of Life Domains Impaired by Increasing Pain Severity

					Relate
				Walk	Walk
		Sleep	Sleep	Sleep	Sleep
		Active	Active	Active	Active
		Mood	Mood	Mood	Mood
	Work	Work	Work	Work	Work
Enjoy	Enjoy	Enjoy	Enjoy	Enjoy	Enjoy
3	4	5	6	7	8
Worst pain rating					

Boldface indicates an additional dimension that is impaired at the given level of pain

¹Katz N, J Pain Symp Mgmt 2002; 24:S38-47. ²Becker N et al, Pain 1997; 73: 393-400

³Cleland CS and Ryan KM, Ann Acad Med 1994; 23:129-138



Impact of Chronic Pain Disability

Extent of Pain-Related Disability among Adults with Pain in the Last 3 months, United States, 2009¹

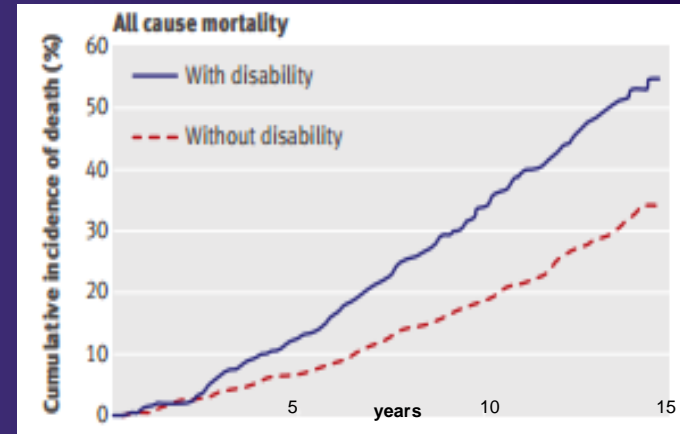
Type of Pain	Difficulty with Basic Activities (%)	Activity Limitations (%)
Low back pain	51.6	55
Neck pain	30.2	34.4
Back pain	37.3	38.6
Shoulder pain	17.7	21.4
Hip pain	15	28.4
Severe headache/migraine	31	33.5

Defined as having difficulties in one or more of the following areas: movement, emotional, seeing, hearing or cognition

Defined as having limitations in one or more of the following areas: self-care, social, work

Source: CDC and NCHS, 2010

All cause mortality in OA Patients with and without disability



¹IOM, 2011: Relieving Pain in America; Nuesch E et al. BMJ 2011; 342d1165



Impact of Chronic Pain

Economic Burden

- Annual Cost of Chronic Pain in the United States¹
 - \$560-635 billion annually
 - \$261-300 billion in health care costs
 - \$297-336 billion in lost productivity
- Expenditures
 - Medicare: \$65.3 billion or 14% of all Medicare costs in 2008
 - All federal & state programs (Medicare, Medicaid, VA, etc) \$99 billion in 2008 for medical expenditures for pain

¹Conservative estimate as excludes cost of pain affecting institutionalized individuals (e.g., long-term care residents, correction inmates), military personnel; excludes lost productivity of personal caregivers, workers <24 and >65 years, and emotional costs of pain.



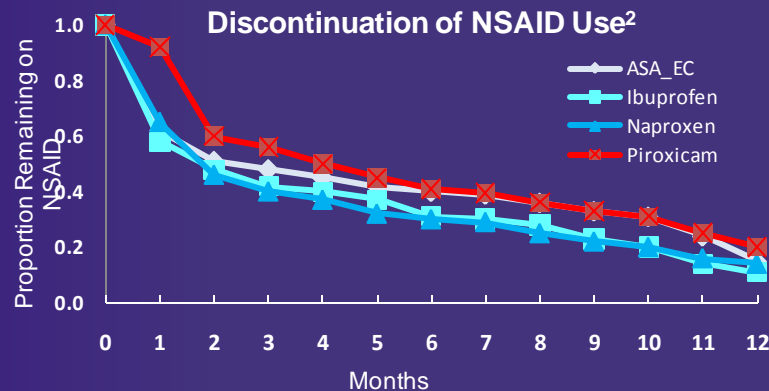
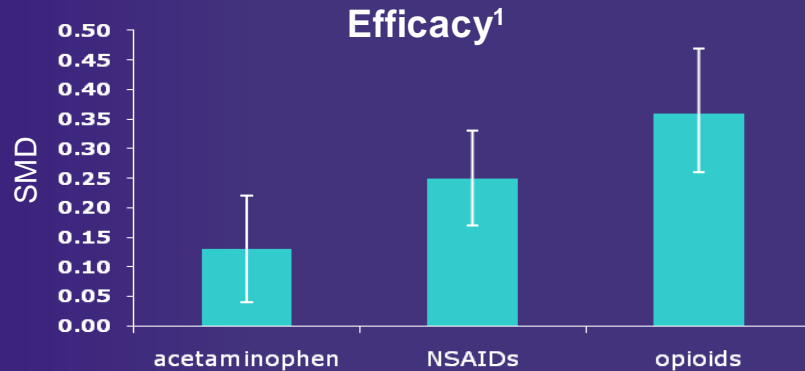
Management of Chronic Pain Fails Too Often

- Significant system and organizational barriers to adequate pain care exist.
- Education is a central part of the necessary cultural transformation of the approach to pain.
- Research to translate advances into effective therapies is a continuing need.

“Academia and industry should develop novel agents for the control of pain. This does not mean simply recycling current drugs. What is required is basic and clinical science research to discover new classes of pain therapeutics and more efficient ways of developing them.”



Existing Pain Medications: NSAID Limitations



NSAID Safety³

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (see WARNINGS).
- Naproxen as NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS or NAPROSYN Suspension is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

Gastrointestinal Risk

- NSAIDs cause an increased risk of gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning. Elderly patients are at greater risk for serious gastrointestinal events (see WARNINGS).

¹Towheed T et al. CDSR 2006; Zhang W et al. OAC 2007;15:981-1000; Nuesch E et al. CDSR 2009; Fransen M, McConnell S. CDSR 2008

²Scholes et al. J. Rheum. 1995; 22: 708-12

³www.accessdata.fda.gov/drugsatfda_docs/label/2008/017581s110,18164s60,18965s18,20067s17lbl.pdf

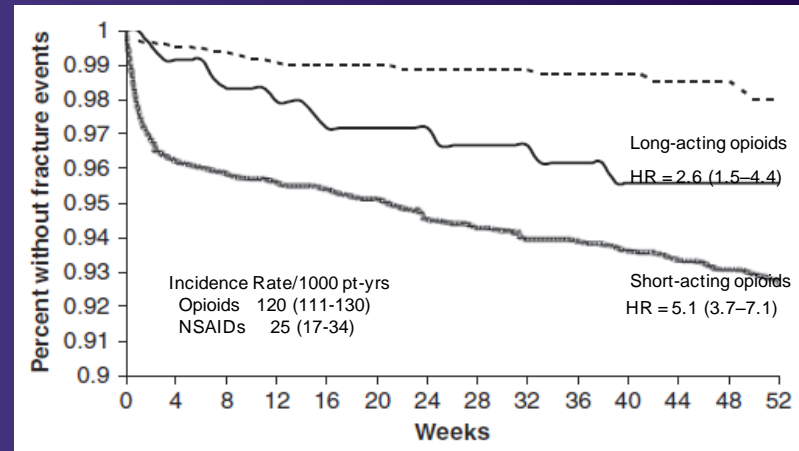


Existing Pain Medications: Opioid Limitations

Adverse Events^{1,2}

- GI:
 - Constipation 40-95%;
 - Nausea 10-40%
- CNS
 - Sedation, drowsiness, cognitive impairment
 - Respiratory depression
 - Dizziness and falls
 - Addiction and dependence
- Others:
 - Hormonal
 - Immunologic
 - Dermatologic

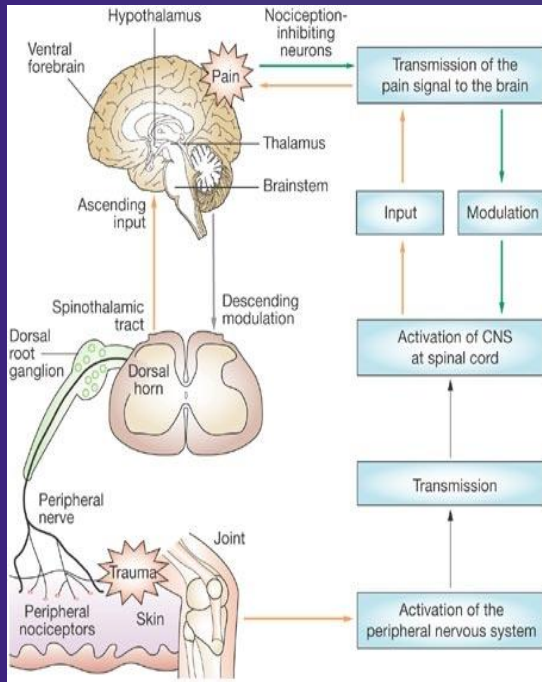
Opioids and Fracture in Older Adults with Arthritis³



Incidence rate highest in first 2 weeks after initiating therapy, especially for short-acting opioid group



Lack of Better Analgesics Not For Lack of Trying



• Multiple Targets Identified

- NMDA receptor blockers
- NK-1 receptor blockers
- FAAH inhibitors
- Na, Ca, K channel modulators
 - TrpV1, V3, V4
 - NaV1.7, NaV1.8
 - ASIC3
- Cannabinoid receptor blockers: CB1, CB2
- Delta opioid agonists
- P2X3 inhibitors
- P38 kinase

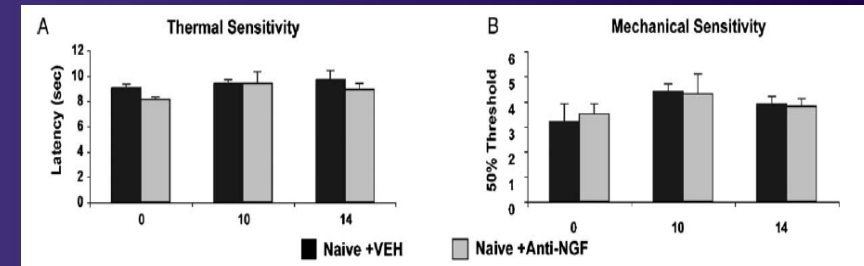
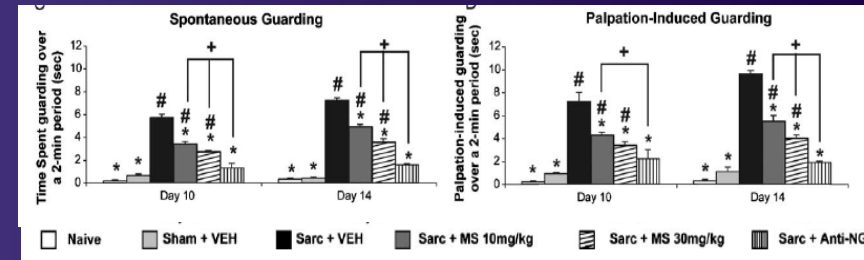
ClinicalTrials.gov
A service of the U.S. National Institutes of Health

539 trials in chronic pain
8 with new molecular entity
2 NCE in musculoskeletal pain



New Target: NGF as a Mediator of Pain

- **Key evidence**
 - NGF causes pain in humans and animals
 - NGF is locally up-regulated in painful conditions
 - NGF inhibition reverses pain in many animal models



Anti-NGF therapy appears to be antihyperalgesic (i.e., normalizing a decreased nociceptive threshold) as opposed to analgesic (i.e., increasing normal and sensitized nociceptive thresholds)



Monoclonal Antibodies Directed Against NGF

- **3 compounds under discussion: tanezumab, fulranumab, REGN475**
 - fully human or humanized monoclonal antibodies
 - picomolar affinity for NGF
 - high selectivity for NGF over other members of the neurotrophin family
 - Inhibit NGF activity at both TrkA and p75 receptors
 - Plasma half-life: 22-25 days
- **Evaluated after IV or SC routes of administration**
 - 4, 8 & 12 wk dosing intervals
 - Doses examined: 3 to 1000 $\mu\text{g/kg}$ (0.003 to 1 mg/kg)



Wide Range of Clinical Conditions Evaluated

Chronic Pain Condition	Efficacy Demonstrated
Osteoarthritis	✓✓
Chronic low back pain	✓✓
Diabetic peripheral neuropathy	✓
Post-herpetic neuralgia	Possible
Interstitial cystitis	Possible
Prostatitis	Possible
Endometriosis	Negative
Cancer pain	On-going

- Efficacy superior to an active comparator has been found repeatedly with tanezumab.



Safety Profile Being Defined

- Anti-NGF mAbs do not appear to have cardiovascular or gastrointestinal safety liabilities of NSAIDs
- Anti-NGF mAbs do not appear to have abuse liability or undesirable central effects of opioids
- New safety signal has appeared in clinical development: joint events
- Questions to be addressed:
 - What does this safety signal represent?
 - Under what conditions does this signal occur and at what frequency?
 - Is it advisable to undertake further research with these compounds to define better the benefit:risk?



Summary

- Anti-NGF antibodies first new pain treatment agents in years
 - Efficacy in wide spectrum of pain conditions
 - Magnitude of effect superior to existing agents
- Many people in pain with no effective treatments
- Further research is needed and possible
 - Carefully designed studies
 - Well defined populations
 - Informed consent
 - Risk mitigation strategies

Monoclonal Antibodies Targeted Against Nerve Growth Factor For the Treatment of Chronic Pain

Tanezumab

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Key Points

- **Relieves pain and improves function to a clinically meaningful extent across chronic pain conditions; superior to active comparator treatment**
- **Tanezumab monotherapy does not elevate the risk of all-cause total joint replacements – in contrast to when administered with NSAIDs**
- **Adjudication of total joint replacements showed:**
 - **Tanezumab does not elevate the risk of osteonecrosis**
 - **Associated with a dose-related increase in rapidly progressive OA**
 - ◆ **Further increased >3-fold when administered with NSAIDs**
- **Risk minimization should reduce the risk of rapidly progressive OA in future studies**

Tanezumab Clinical Development

■ Moderate to severe osteoarthritis

– Phase 3 development

- ♦ Monotherapy & NSAID combination therapy
- ♦ 2.5 mg, 5 mg, and 10 mg IV/SC every 8 wks

■ Moderate to severe chronic low back pain

– Phase 2b development

- ♦ Monotherapy
- ♦ 5 mg, 10 mg, and 20 mg IV/SC every 8 wks

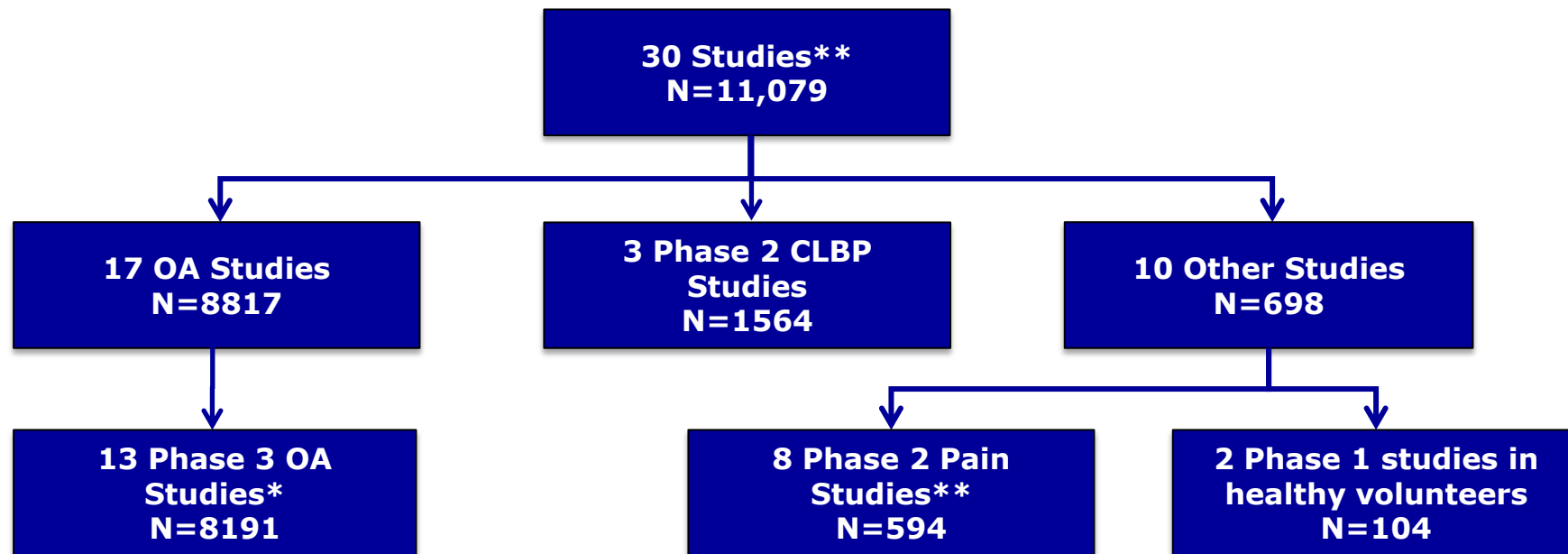
■ Other chronic pain conditions

– Early stage development

- ♦ Cancer, neuropathic, and visceral pain
- ♦ Monotherapy, adjunctive therapy with standard of care
- ♦ Doses up to 20 mg IV/SC (or body-weight adjusted equivalent)

Tanezumab Clinical Program

Number of Studies and Patients



*Includes Studies 1040 and 1032 (total N=22); the Phase 3 osteoarthritis analysis set (N=8169) excludes these 2 studies

**Includes studies of diabetic peripheral neuropathy, post-herpetic neuralgia, interstitial cystitis, prostatitis, endometriosis, chronic pancreatitis, & bunionectomy; excludes 2 ongoing studies in metastatic bone pain

Osteoarthritis (OA); chronic low back pain (CLBP)

Patient Exposure

- **11,079 patients randomized and treated in completed clinical studies**
 - **Placebo = 1649 (exposure up to 6 mo)**
 - **Tanezumab monotherapy = 6410 (exposure up to 2 yrs)**
 - **Tanezumab/NSAID combination therapy = 3400 (exposure up to 2 yrs)**
 - ◆ **Includes patients randomized to combination therapy and concomitant NSAID use in long-term studies**
 - **Active comparator = 1653 (exposure up to 1 yr)**
 - ◆ **naproxen 500 mg BID (N=1083)**
 - ◆ **celecoxib 100 mg BID (N=256)**
 - ◆ **diclofenac SR 75 mg BID (N=152)**
 - ◆ **oxycodone CR 10-40 mg q12h (N=158)**

Presentation Outline

■ Efficacy

- Osteoarthritis
- Chronic Low Back Pain
- Other Chronic Pain Conditions

■ Joint-Related Safety

■ Risk Minimization

Tanezumab Monotherapy vs. Placebo

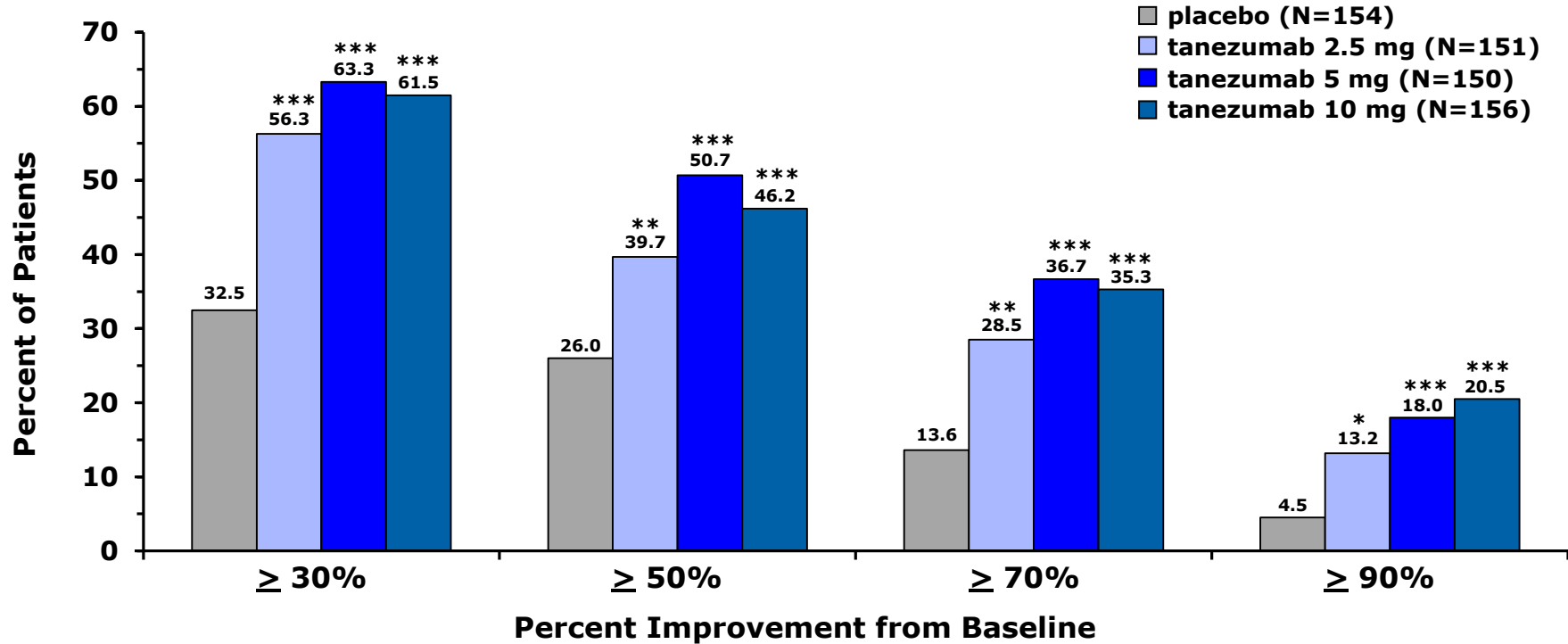
Consistent Improvement with all Doses at Week 16

	WOMAC Pain	WOMAC Physical Function	Patient's Global Assessment
Study 1011 (Knee OA)			
tanezumab 2.5 mg	✓	✓	✓
tanezumab 5 mg	✓	✓	✓
tanezumab 10 mg	✓	✓	✓
Study 1014 (Hip OA)			
tanezumab 2.5 mg	✓	✓	✓
tanezumab 5 mg	✓	✓	✓
tanezumab 10 mg	✓	✓	✓
Study 1015 (Knee OA)			
tanezumab 5 mg	✓	✓	✓
tanezumab 10 mg	✓	✓	✓
Study 1018 (Knee & hip OA)			
tanezumab 5 mg	✓	✓	✓
tanezumab 10 mg	✓	✓	✓

Baseline observation carried forward (BOCF) imputation

WOMAC Pain Response

Tanezumab Improves Response Rates vs. Placebo



* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$ vs. placebo
mITT, BOCF, Study 1014

Tanezumab Monotherapy vs. NSAIDs

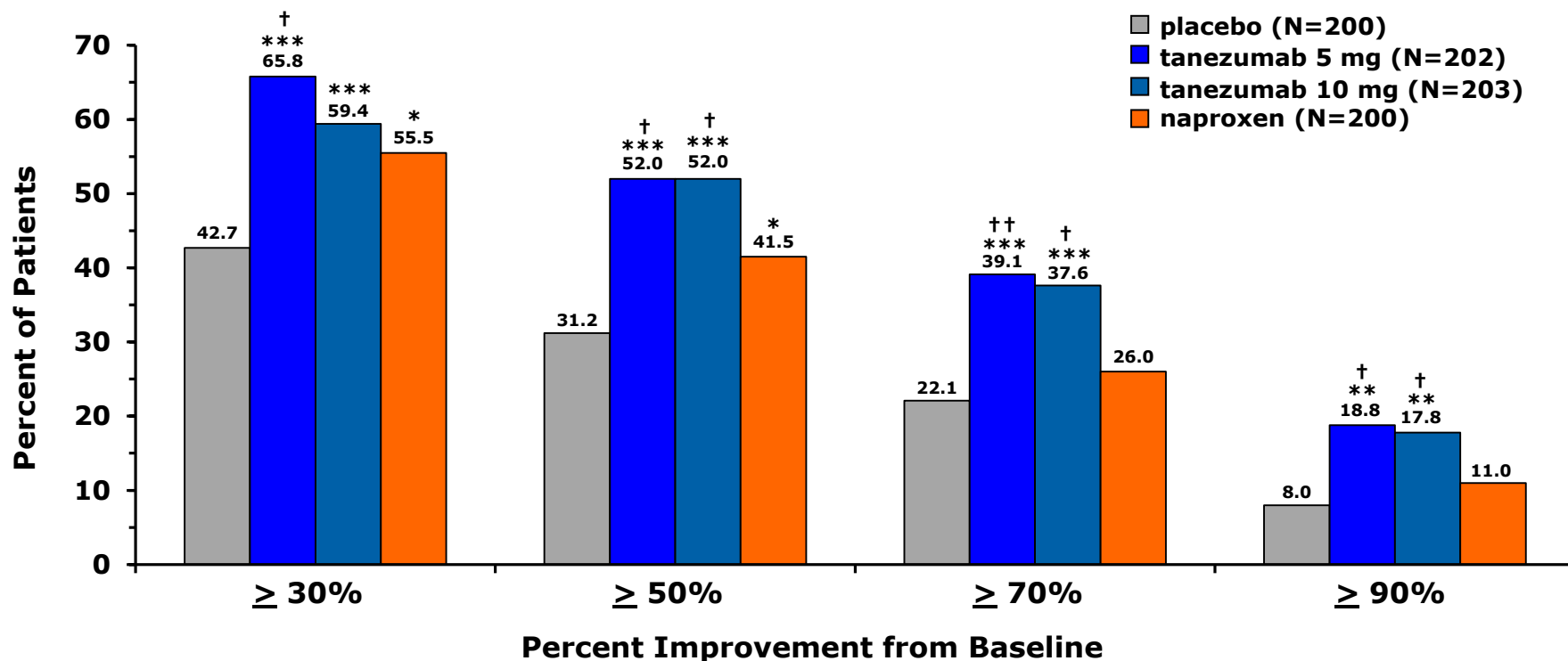
Improved Efficacy at Week 16

	WOMAC Pain	WOMAC Physical Function	Patient's Global Assessment
Study 1015 (Knee OA) vs naproxen			
tanezumab 5 mg	✓	✓	✓
tanezumab 10 mg	--	✓	--
Study 1018 (Knee & hip OA) vs naproxen			
tanezumab 5 mg	✓	✓	✓
tanezumab 10 mg	--	✓	✓
Study 1025 (Knee & hip OA) vs naproxen			
tanezumab 5 mg	✓	✓	--
tanezumab 10 mg	✓	✓	--
Study 1025 (Knee & hip OA) vs celecoxib			
tanezumab 5 mg	✓	✓	--
tanezumab 10 mg	✓	✓	--

Baseline observation carried forward (BOCF) imputation

WOMAC Pain Response

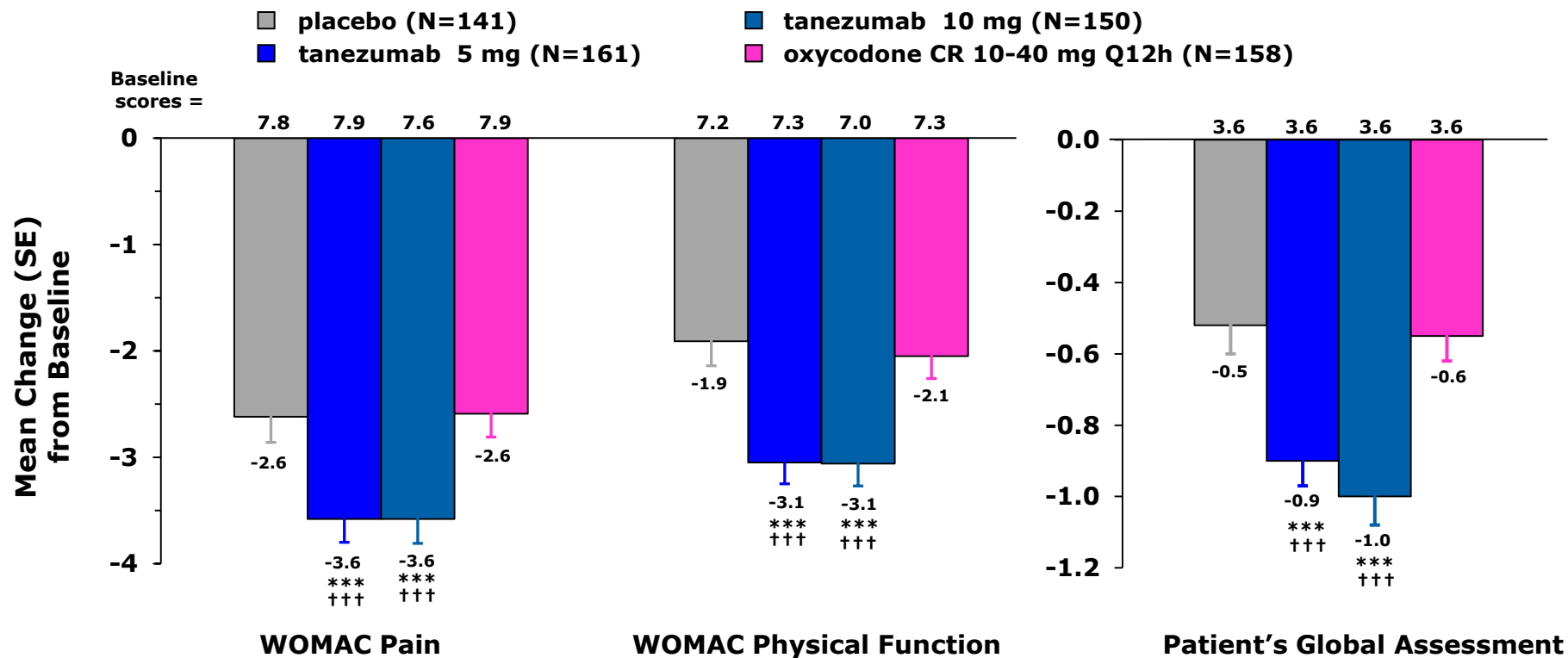
Tanezumab Improves Response Rates vs. Naproxen



* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$ vs. placebo
† $p \leq 0.05$; †† $p \leq 0.01$; ††† $p \leq 0.001$ vs. naproxen 500 mg BID
mITT, BOCF, Study 1015

Efficacy Endpoints – Preliminary OA Study

Significant Improvement vs. Oxycodone CR

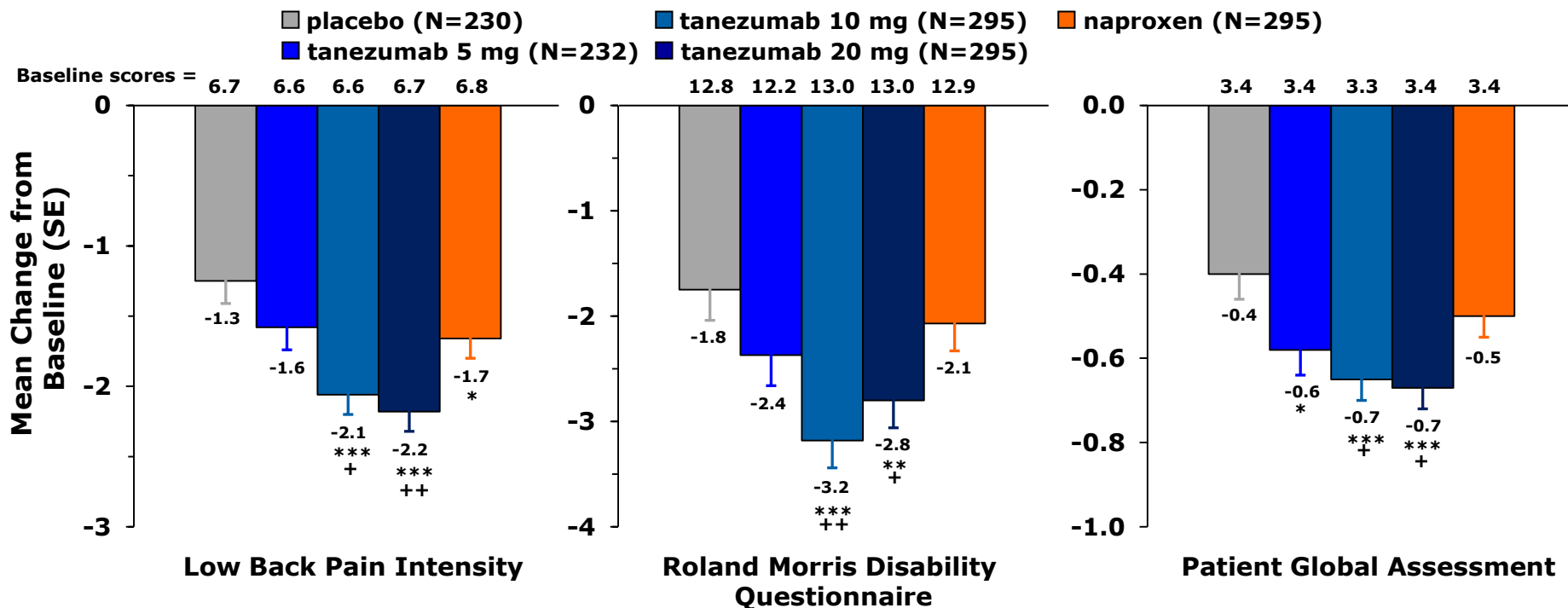


* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$ versus placebo

† $p \leq 0.05$; †† $p \leq 0.01$; ††† $p \leq 0.001$ versus oxycodone CR; ITT, LOCF at Week 8 oxycodone CR dose = 10-40 mg Q12h

Tanezumab in Chronic Low Back Pain

Significant Improvement vs. Placebo and Naproxen



*p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001 versus placebo

+p ≤ 0.05; ++p ≤ 0.01; +++p ≤ 0.001 versus naproxen

ITT, BOCF; naproxen dose = 500 mg BID

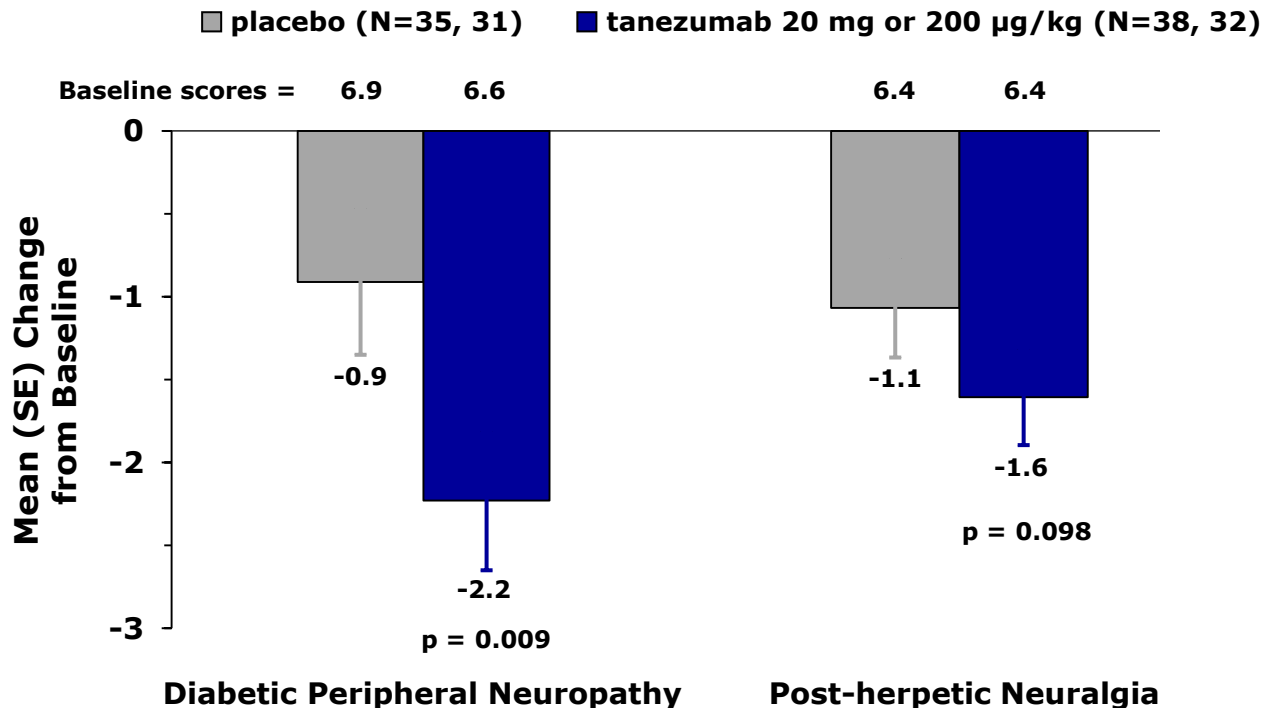
Low Back Pain Intensity assessed with a 0 to 10-point numerical rating scale. Lower scores indicate less pain

Roland-Morris Disability Questionnaire scores range from 0 to 24 points. Lower scores indicate better function

Patient Global Assessment assessed with a 5-point Likert scale. Lower scores indicate better evaluations

Efficacy in Neuropathic Pain

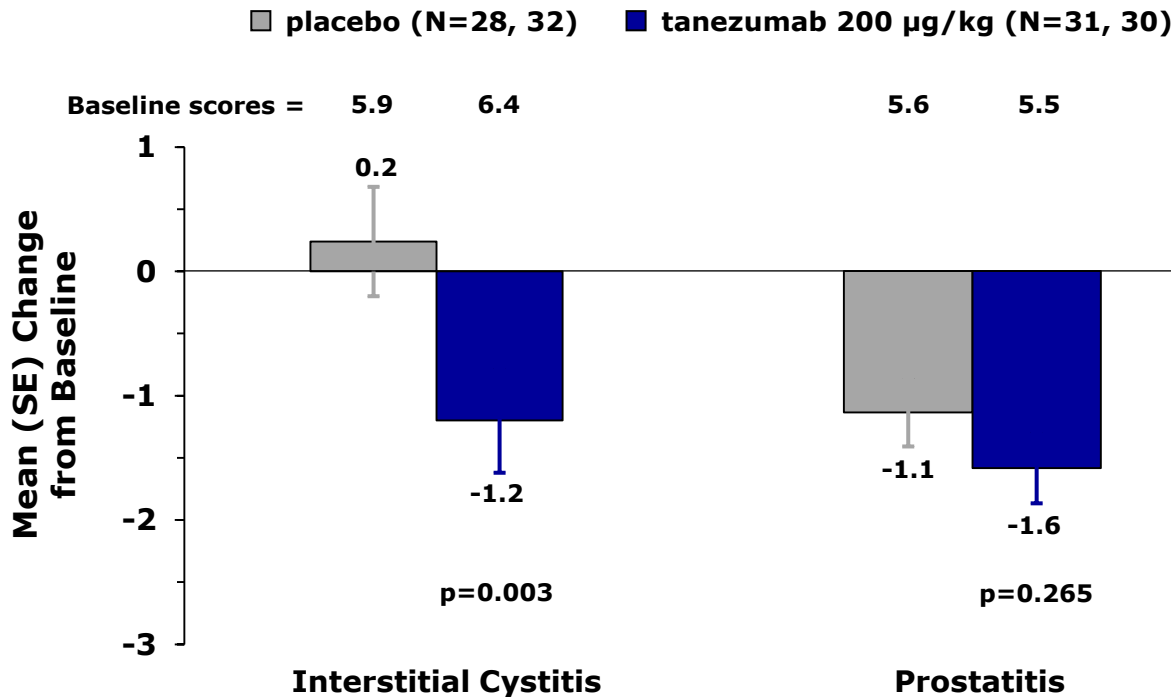
Phase 2; Average Daily Pain at Week 8



Studies 1031 and 1005; ITT, LOCF

Efficacy in Visceral Pain

Phase 2; Average Daily Pain at Week 6



Studies 1010 and 1019; ITT, LOCF

Efficacy Summary — Osteoarthritis

■ Tanezumab monotherapy

- Superior efficacy compared to placebo and NSAIDs
- Favorable efficacy profile compared to oxycodone CR
- Minimal incremental benefit of tanezumab 10 mg vs. 5 mg
- 2.5 mg and 5 mg emerging as therapeutic doses for OA

Efficacy Summary — Chronic Pain

- **Chronic low back pain**
 - Superior efficacy compared to placebo and naproxen
 - Minimal incremental benefit of tanezumab 20 mg vs. 10 mg
- **Neuropathic and visceral pain**
 - Preliminary evidence of analgesic efficacy at doses of 20 mg

Presentation Outline

■ Efficacy

- Osteoarthritis
- Chronic Low Back Pain
- Other Chronic Pain Conditions

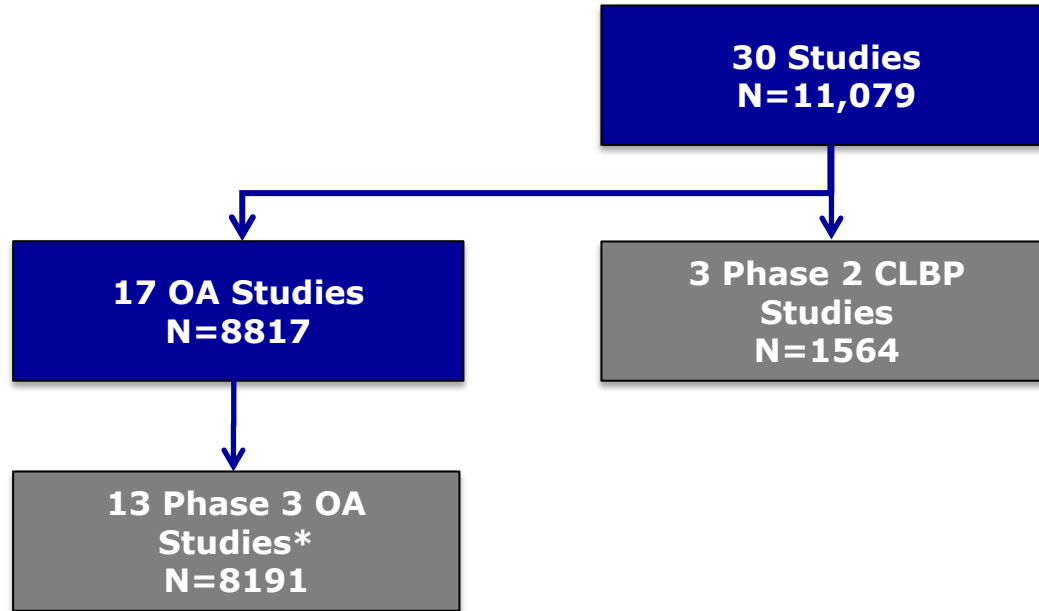
■ Joint-Related Safety

- Total Joint Replacements
- Adjudication Outcomes

■ Risk Minimization

Tanezumab Clinical Program

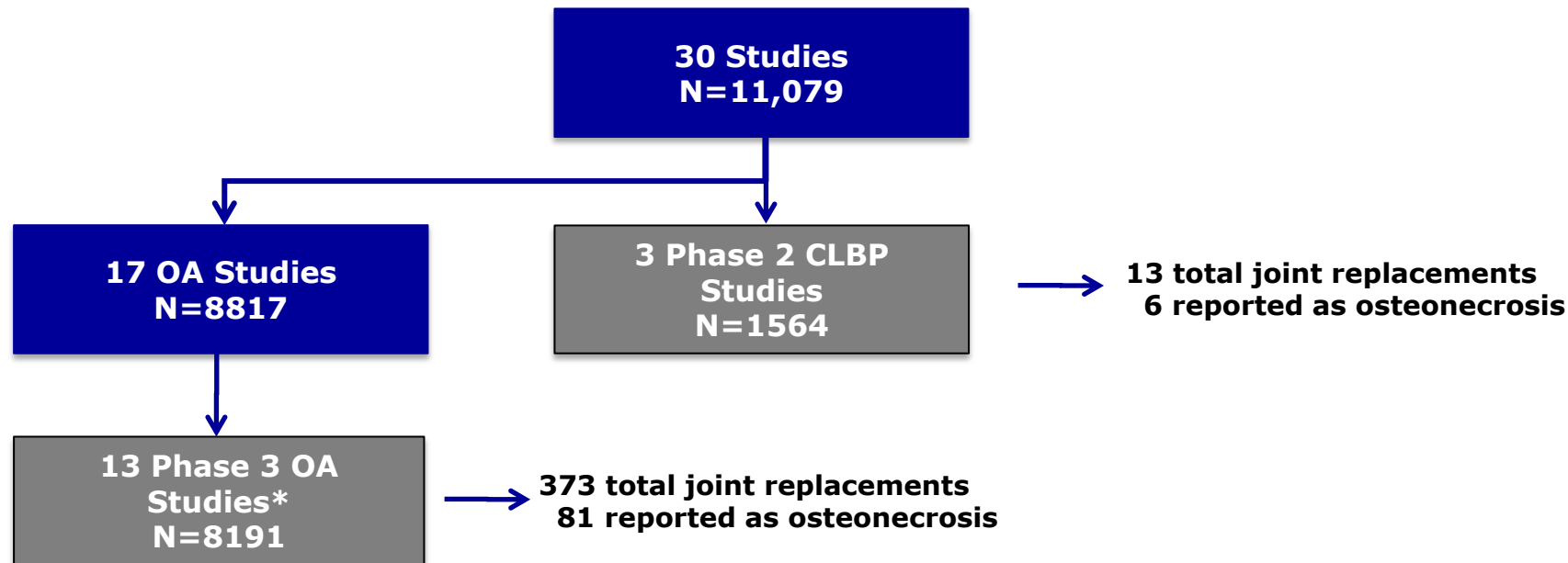
Number of Studies and Patients



*Includes Studies 1040 and 1032 (total N=22); the Phase 3 osteoarthritis analysis set (N=8169) excludes these 2 studies

Tanezumab Clinical Program

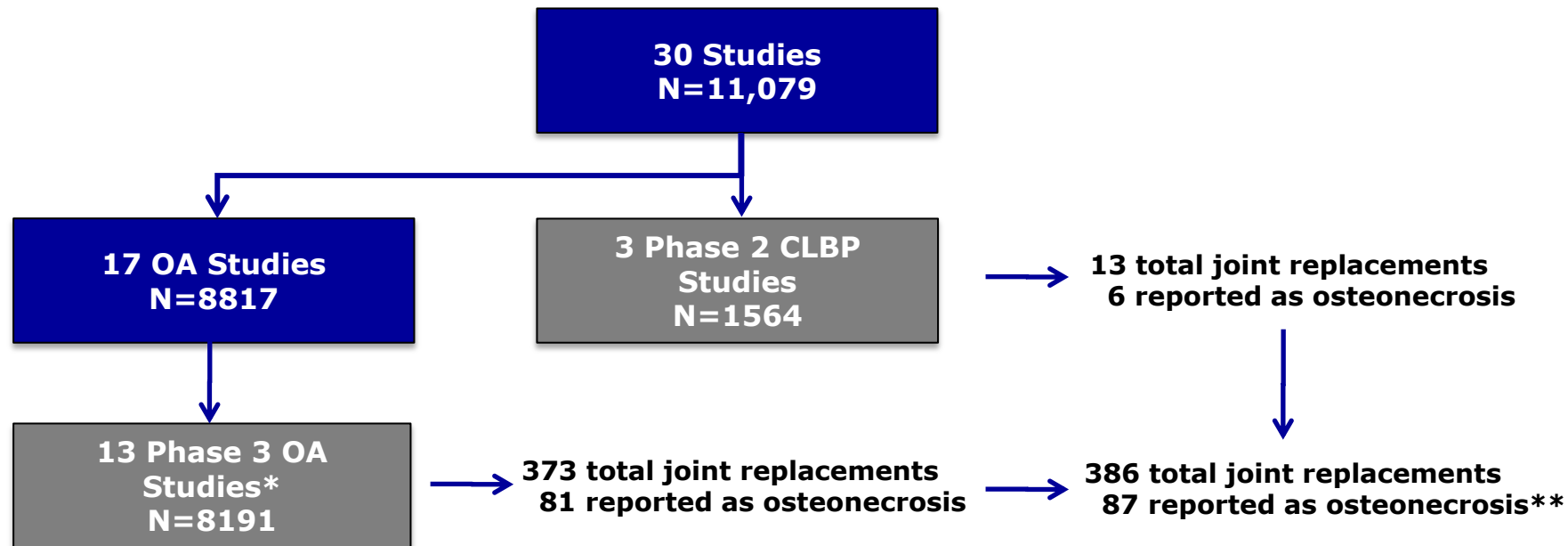
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Tanezumab Clinical Program

Number of Studies and Patients

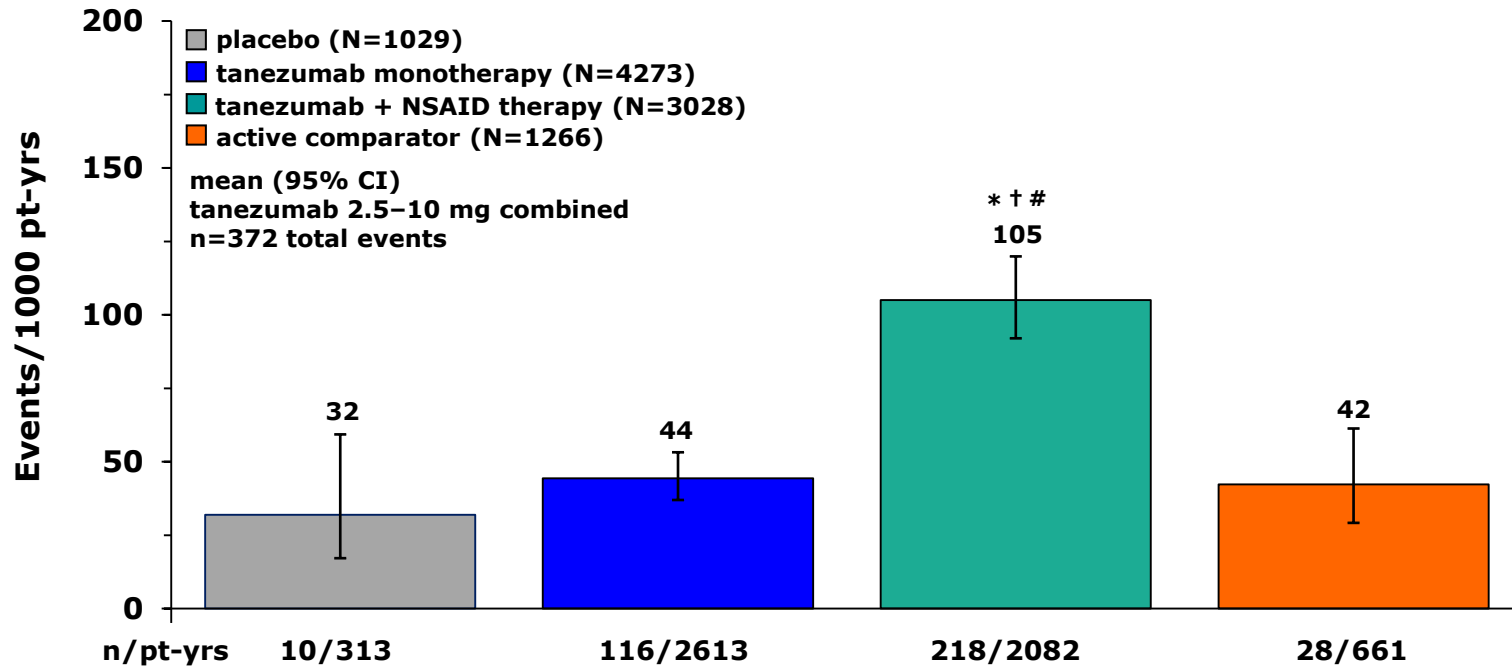


*Includes Studies 1040 and 1032 (total N=22); the Phase 3 osteoarthritis analysis set (N=8169) excludes these 2 studies

**50 patients (57.5%) underwent total joint replacement

All-Cause Total Joint Replacements

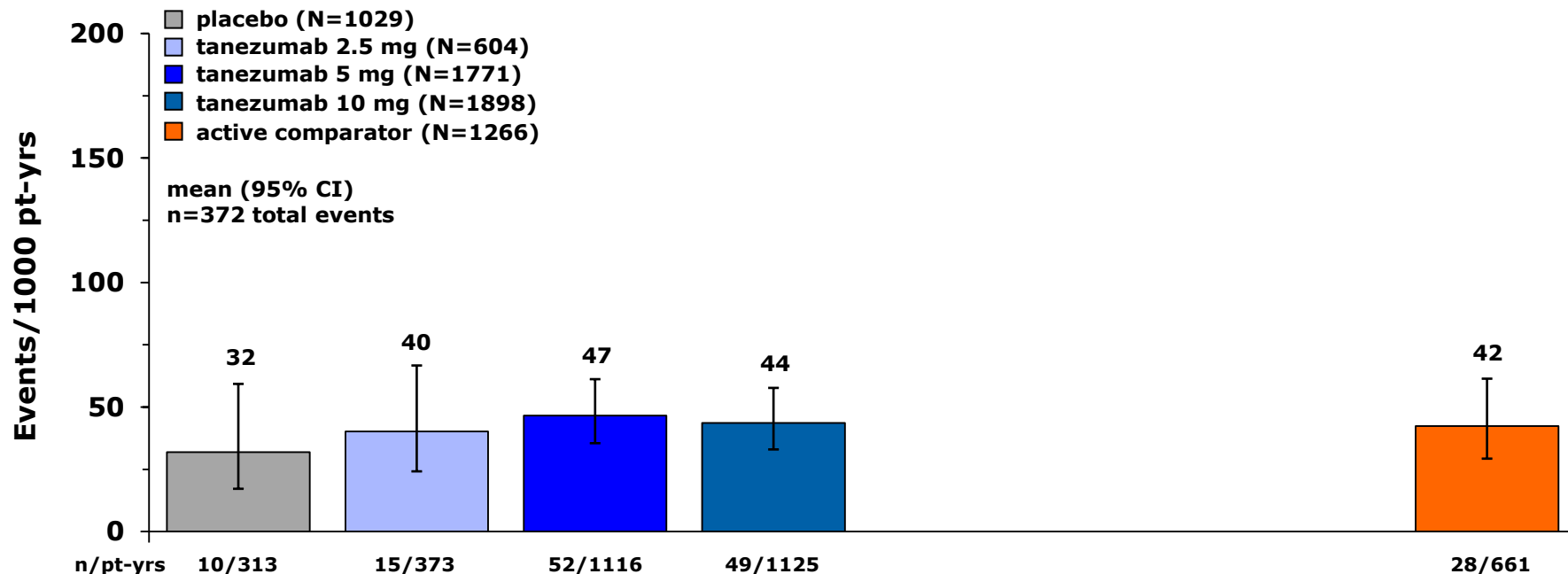
Phase 3 OA Studies



*p≤0.05 vs. placebo, †p ≤ 0.05 vs. active comparator, #p ≤ 0.05 vs. tanezumab monotherapy,

All-Cause Total Joint Replacements

Phase 3 OA Studies, Event Rate by Dose

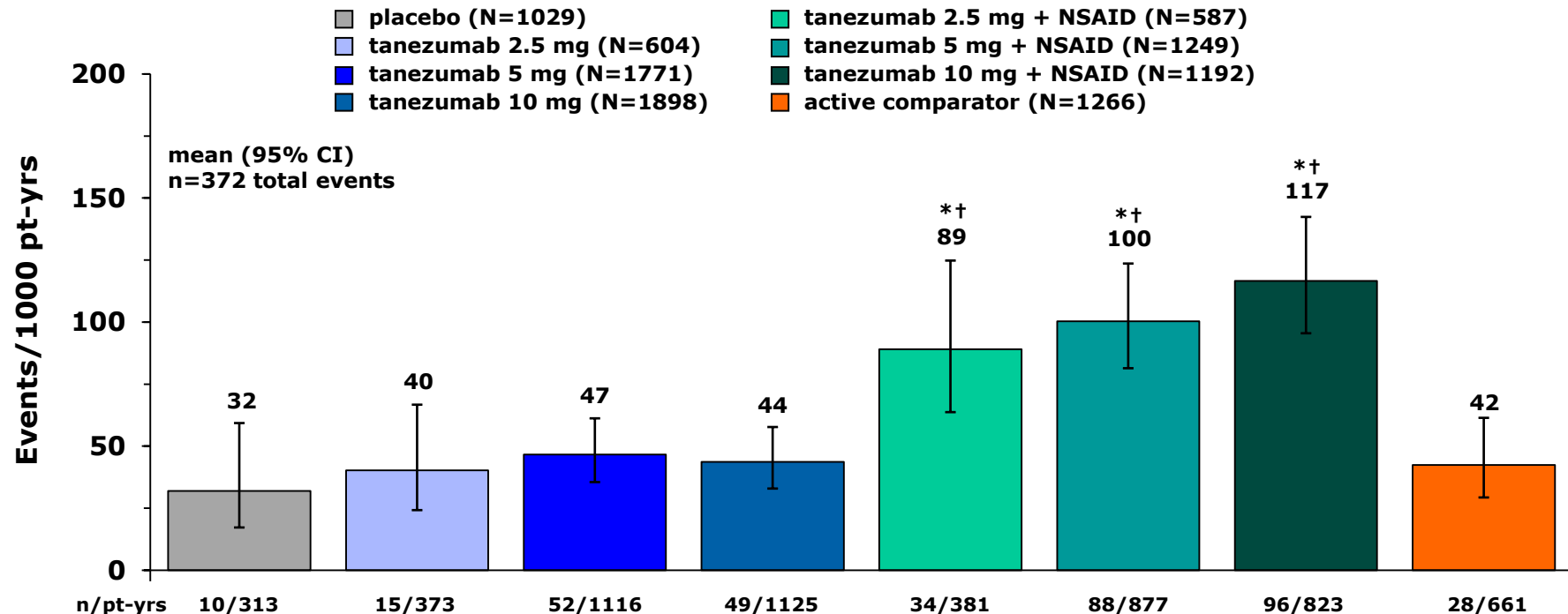


Risk Difference: * $p \leq 0.05$ vs. placebo, † $p \leq 0.05$ vs. active comparator

Dose Response: $p=0.553$ tanezumab monotherapy, $p<0.0001$ tanezumab/NSAID combination therapy

All-Cause Total Joint Replacements

Phase 3 OA Studies, Event Rate by Dose



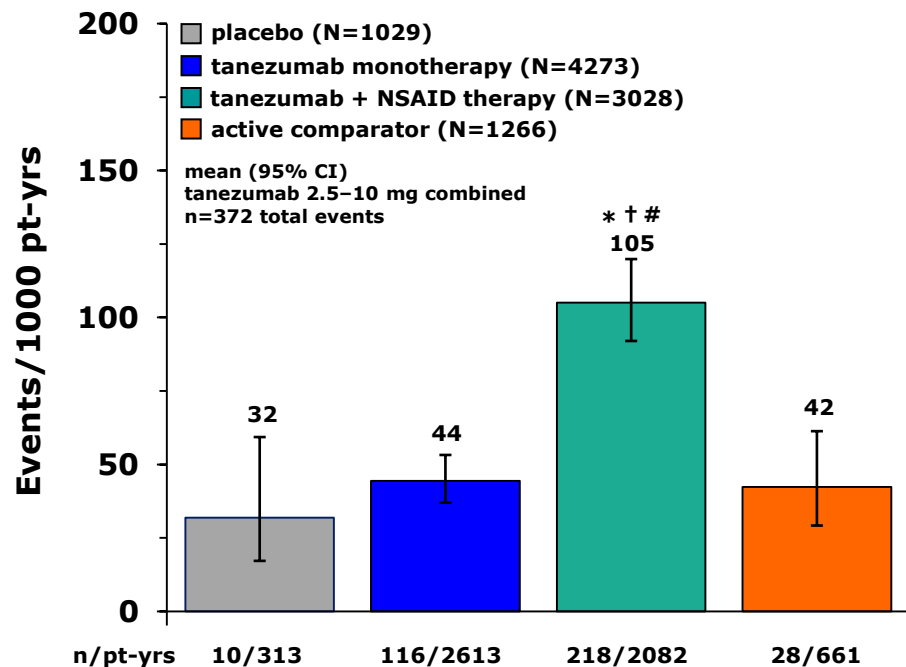
Risk Difference: * $p \leq 0.05$ vs. placebo, † $p \leq 0.05$ vs. active comparator

Dose Response: $p=0.553$ tanezumab monotherapy, $p<0.0001$ tanezumab/NSAID combination therapy

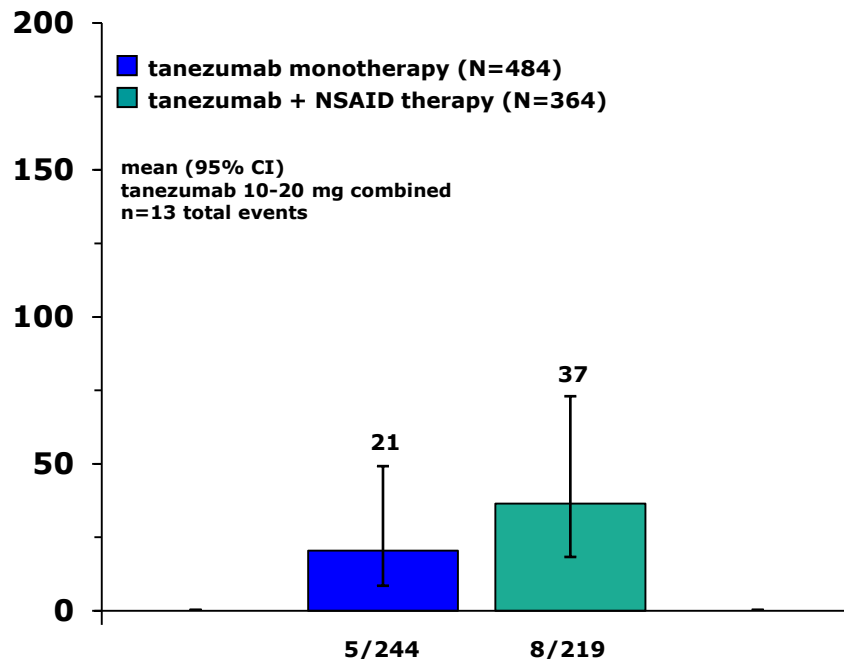
All-Cause Total Joint Replacements

Phase 3 OA & Phase 2 Non-Controlled Long-term CLBP Study

Phase 3 OA Studies



Non-controlled CLBP Study



*p≤0.05 vs. placebo, †p ≤ 0.05 vs. active comparator, #p ≤ 0.05 vs. tanezumab monotherapy,

Summary

■ Tanezumab monotherapy

- No increase in total joint replacements compared to placebo or active comparator
- No observed dose relationship

■ Tanezumab/NSAID combination therapy

- At least 2-fold greater than placebo, tanezumab monotherapy, or active comparator
- Event rate increased with escalating doses of tanezumab

Adjudication Committee

- **Multidisciplinary**
- **Blinded to treatment assignment**
- **Reviewed all total joint replacements with a post-baseline radiology image available within ~9 months of the surgery**
- **Independently reviewed all source documentation prior to Committee meetings**
 - **Clinical summaries, consultation reports, operative reports, radiology & pathology reports, available images & pathology specimens**
- **Each patient was reviewed & discussed at Committee meetings**
- **Each Committee member provided their own final assessment for each patient**

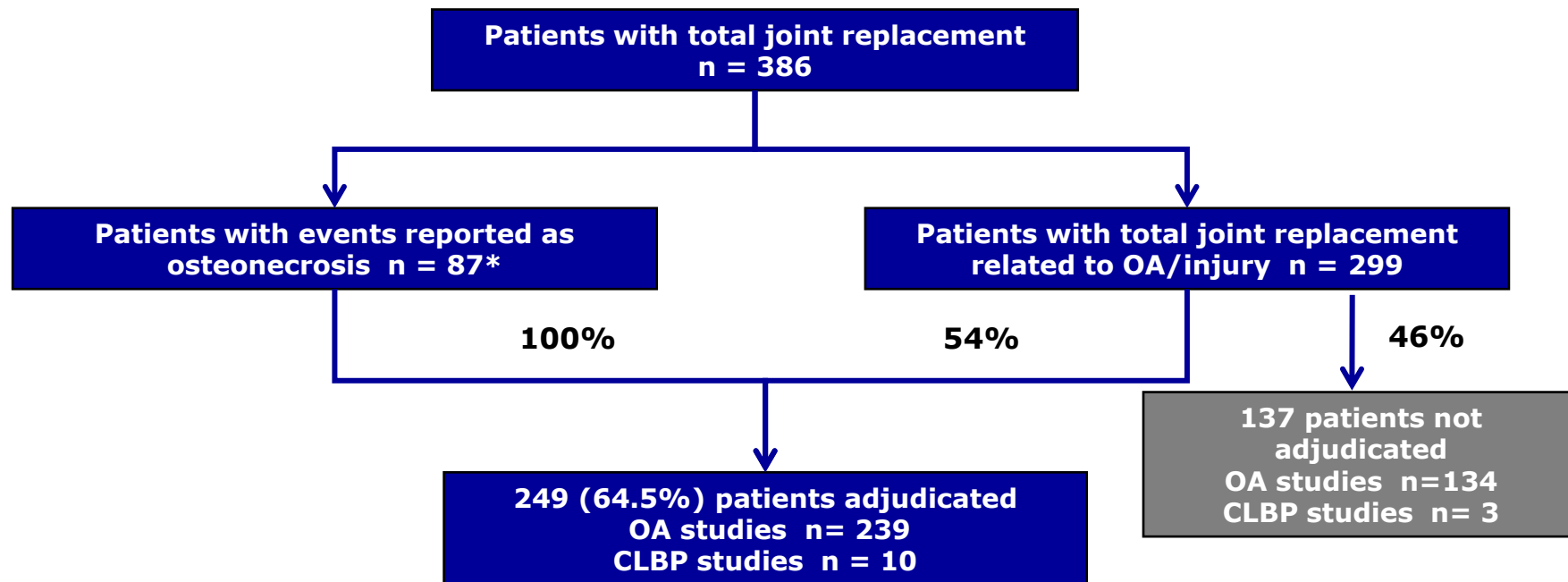
Adjudication Categories

- 1. Primary osteonecrosis**
- 2. Worsening osteoarthritis (OA)**
- 3. Other joint condition/diagnosis**
- 4. Not enough information to distinguish between primary osteonecrosis & worsening OA or to specify another diagnosis**

Adjudication Categories

1. Primary osteonecrosis
2. Worsening osteoarthritis (OA)
 - a. Rapidly progressive OA (type 1 or type 2)
 - i. type 1 – loss of joint space width ≥ 1 mm over approximately 1 year
 - ii. type 2 – abnormal loss/destruction of bone uncommon for end-stage OA
 - b. Normal progression of OA
 - c. Not enough information to distinguish between rapidly progressive and normal progression of OA
3. Other joint condition/diagnosis
4. Not enough information to distinguish between primary osteonecrosis & worsening OA or to specify another diagnosis

Adjudication of Events



*50 patients (57.5%) underwent total joint replacement

Adjudication Results

Summarized by Category

n (%)	Total N=249
Primary osteonecrosis	2 (0.8)
Worsening osteoarthritis	200 (80.3)
Other condition	29 (11.6)
Insufficient information to distinguish osteonecrosis from OA	11 (4.4)
Lack of consensus	7 (2.8)

Adjudication Results

Summarized by Category

n (%)	Total N=249
Primary osteonecrosis	2 (0.8)
Worsening osteoarthritis	200 (80.3)
Other condition	29 (11.6)
Insufficient information to distinguish osteonecrosis from OA	11 (4.4)
Lack of consensus	7 (2.8)

n (%)	
Rapidly progressive	68 (27.3)
Normal progression	119 (47.8)
Insufficient information to distinguish between rapid from normal progression	13 (5.2)

Reported Osteonecrosis

Availability of MRIs and Pathology for Committee Review

n (%)	Total N=87
MRI image(s) available for review	38 (43.7)
Pathology specimen(s) available for review	23 (26.4)
Both MRI and pathology specimen available for review	12 (13.8)

Rapidly Progressive OA

Availability of MRIs and Pathology for Committee Review

n (%)	Total N=68
MRI image(s) available for review	23 (33.8)
Pathology specimen(s) available for review	23 (33.8)
Both MRI and pathology specimen available for review	10 (14.7)

Adjudication Results

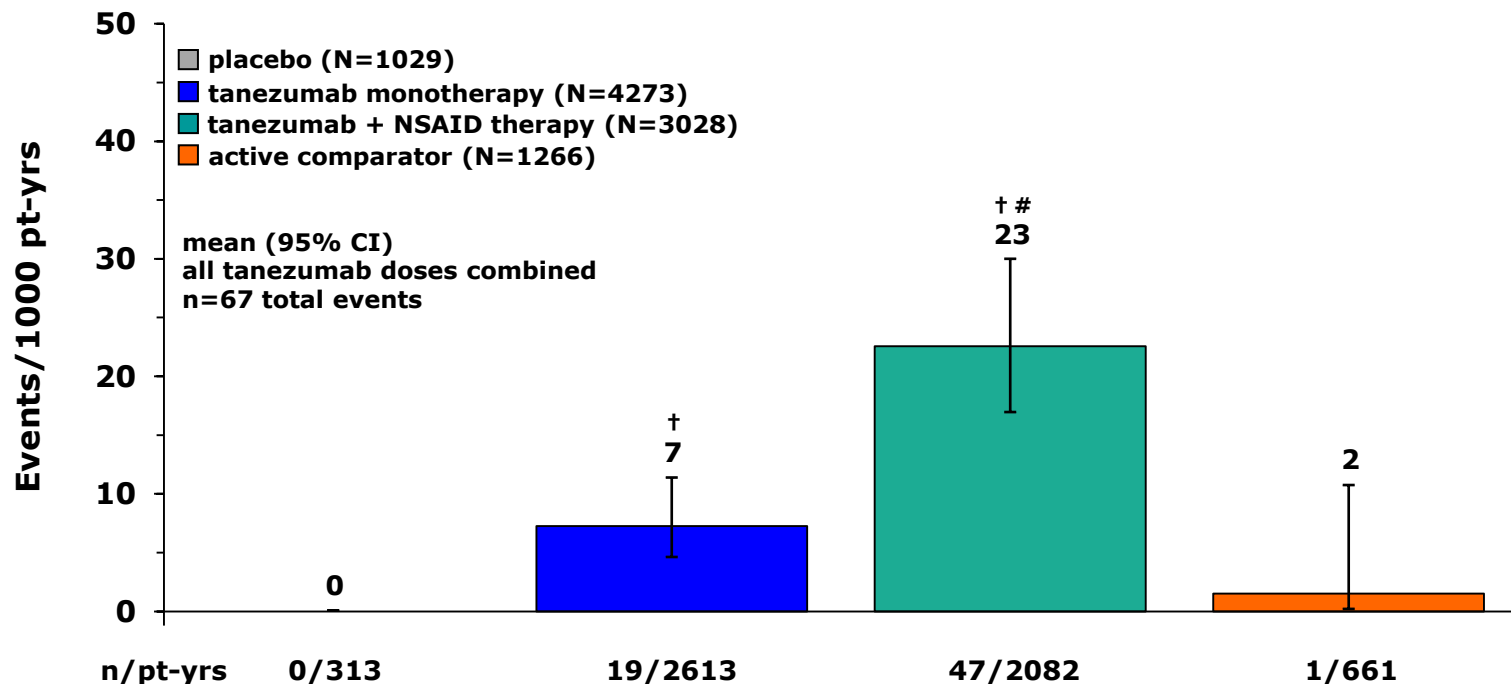
By-Patient vs. By-Joint Analyses

n (%)	Total Patients N=249	Total Joints N=282
Primary osteonecrosis	2 (0.8)	2 (0.7)
Rapidly progressive OA	68 (27.3)	71 (25.2)
Normal progression OA	119 (47.8)	142 (50.4)
Other condition	29 (11.6)	33 (11.7)
Insufficient information*	31 (12.5)	34 (12.1)

* Total for the adjudication categories "Insufficient information to distinguish osteonecrosis from OA", "Lack of consensus" and "Insufficient information to distinguish between rapid from normal progression"

Rapidly Progressive OA

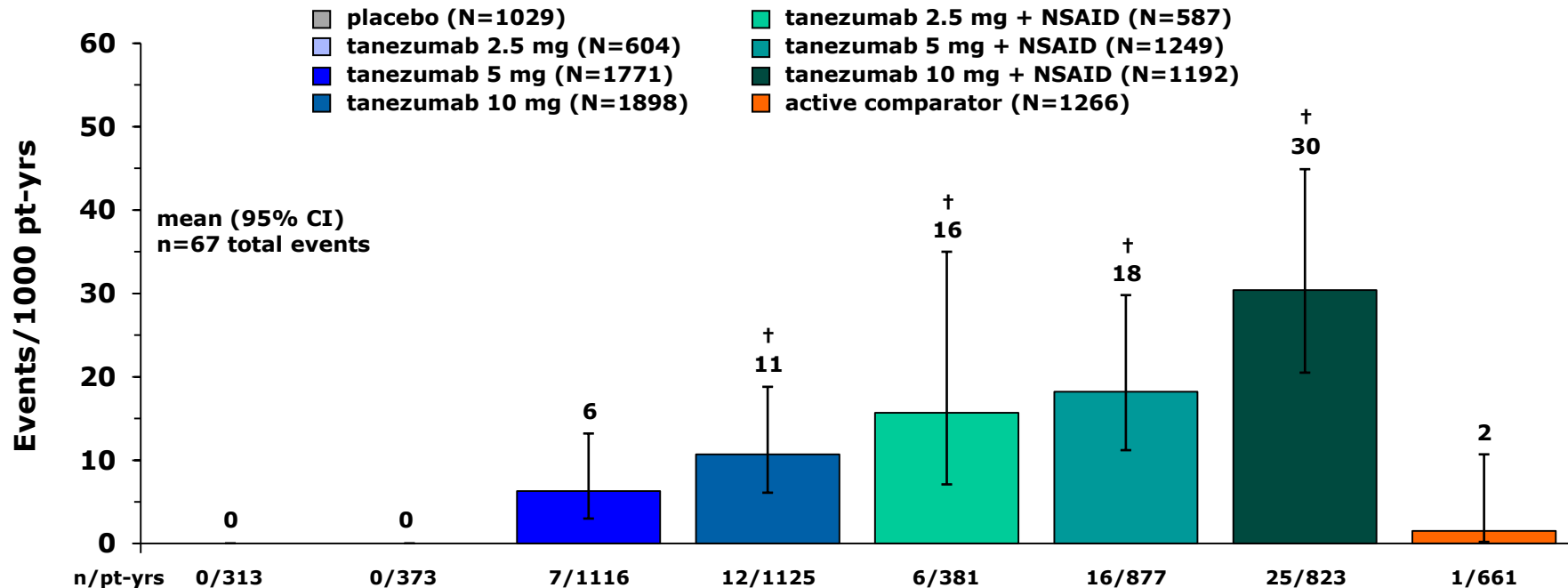
Phase 3 OA Studies



†p ≤ 0.05 vs. active comparator, #p ≤ 0.05 vs. tanezumab, comparisons to placebo (zero events) could not be made

Rapidly Progressive OA

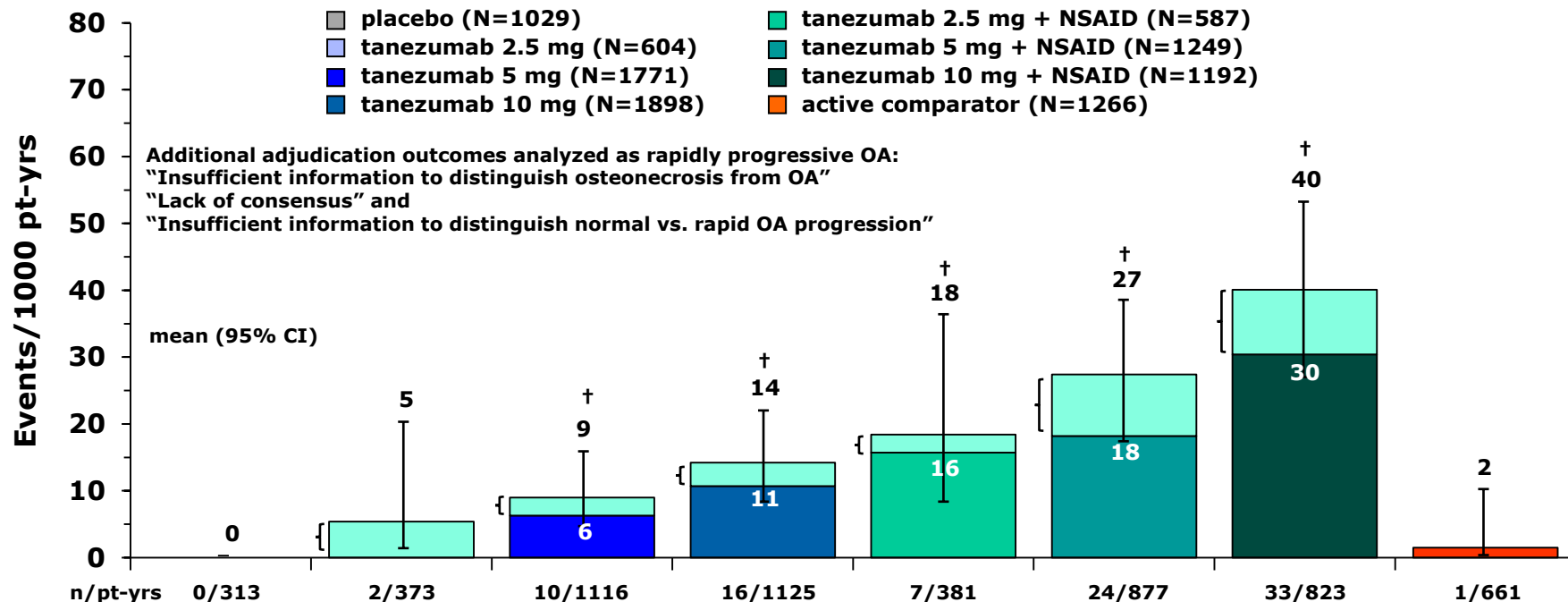
Phase 3 OA Studies, Event Rate by Dose



Risk Difference: †p ≤ 0.05 vs. active comparator, analyses vs. placebo (zero events) could not be made
Dose Response: p=0.0124 tanezumab monotherapy, p<0.0001 tanezumab/NSAID combination therapy

Rapidly Progressive OA

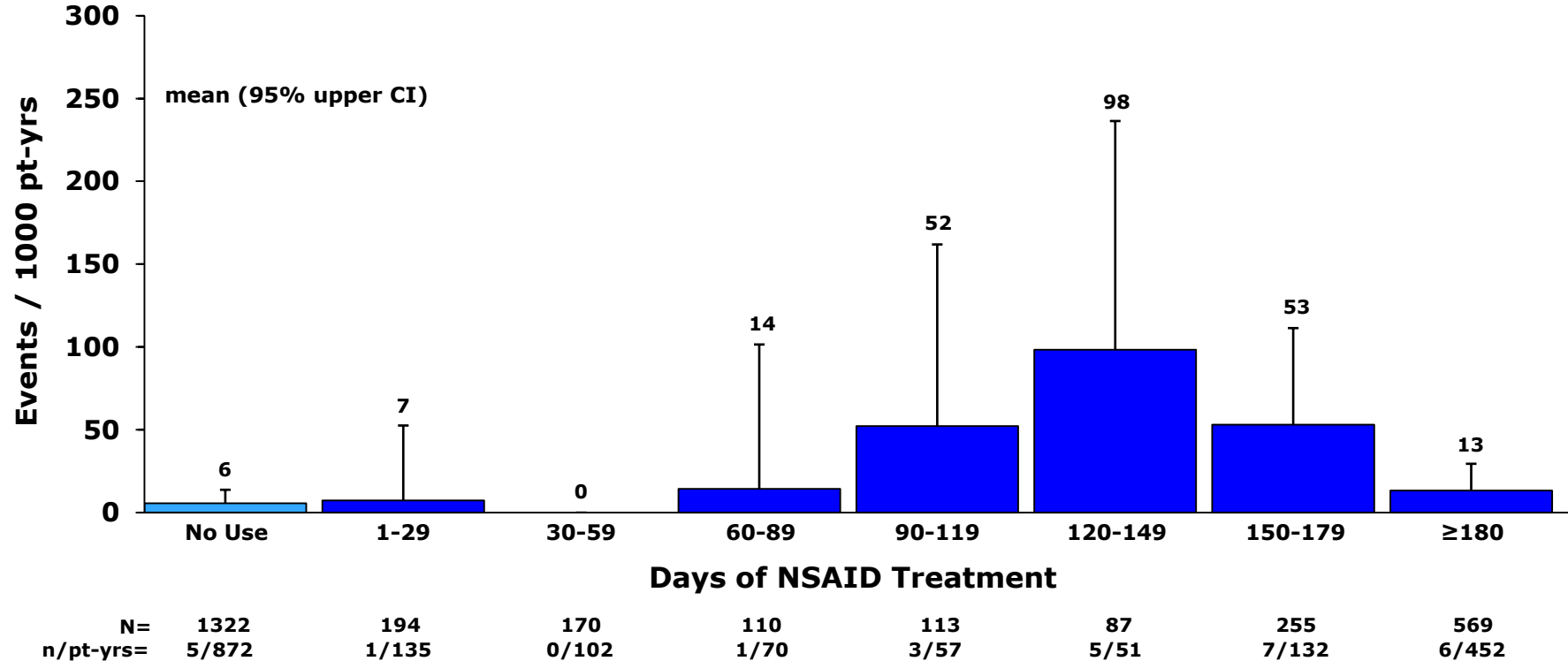
Phase 3 OA Studies¹ - Sensitivity Analysis



Risk Difference: † $p \leq 0.05$ vs. active comparator, analyses vs. placebo (zero events) could not be made
 Dose Response: $p=0.0164$ tanezumab monotherapy, $p<0.0001$ tanezumab/NSAID combination therapy

Effect of Duration of NSAID Use

Rapidly Progressive OA – Event Rate



Mean (95% upper CI); tanezumab 2.5-10 mg combined
Non-controlled, long-term Phase 3 OA Studies 1016 & 1043

Rapidly Progressive OA

- Well recognized in orthopedic, radiology, and pathology literature by various names including:
 - Rapidly destructive OA, rapidly destructive arthrosis, or destructive arthropathy
 - Initially described in 1957 (Forestier)
 - Over 100 publications since 1970
- Predominantly occurs in the hip; less commonly in the knee or shoulder
 - Occurs in up to one-sixth of patients with hip OA
- Severe progressive joint destruction with focal joint space narrowing and extensive subchondral bone loss in femoral head, acetabulum or both

Lequesne. La Presse Med 1970; 78:1425-26

Postel and Kerboull. Clin Orthop Rel Res 1970; 72:138-44

Rosenberg et al. Radiology 1992; 182:213-6

Yamamoto and Bullough. Arthritis Rheum 2000; 43:2423-7

Osteoarthritis 2nd edition, 2003. Ed by KD Brandt, M Doherty and LS Lohmander

Batra et al. J Orthop Surg Res 2008, 3:3-8

Walker et al. Magn Reson Imaging Clin N Am 2011; 19:283-94

Rapidly Progressive OA

Example from Literature

Skeletal Radiol (2010) 39:189–192
DOI 10.1007/s00256-009-0834-3

CASE REPORT

Bilateral rapidly destructive arthrosis of the hip joint resulting from subchondral fracture with superimposed secondary osteonecrosis

Takuaki Yamamoto • Robert Schneider •
Yukihide Iwamoto • Peter G. Bullough

- **57-year old woman**
- **14-month history of bilateral hip pain**
- **Rapid hip destruction over 10 months**
- **Progressive severe pain both hips**
- **Bilateral total hip replacement**



Rapidly Progressive OA

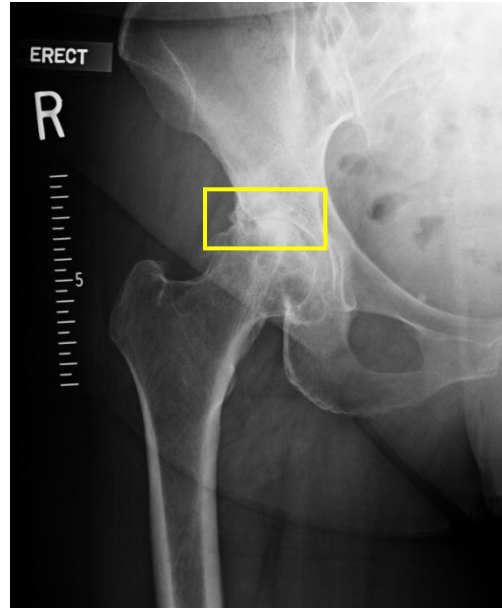
Pre-existing Event from Tanezumab Clinical Program

- 63-year old woman
- KL Grade 4 OA right hip at baseline
- 5-year history of generalized OA

- Increased right hip pain 7 months post-baseline
- Right hip total joint replacement



4 months pre-baseline



2 weeks pre-baseline



9 months post-baseline

Rapidly Progressive OA Characterization

- **Evidence of OA in the affected joint
prior to study = 61 patients (90%)**
 - **Including patient with CLBP**

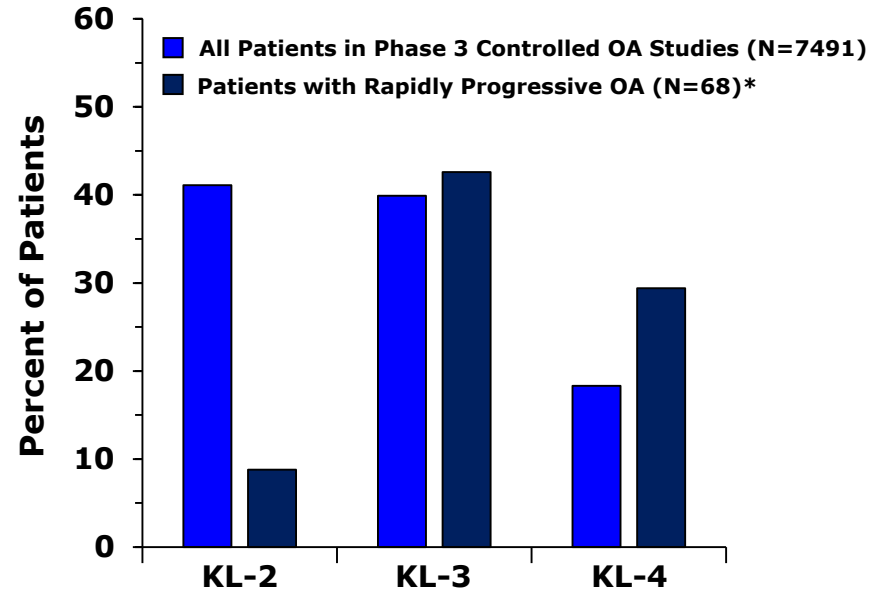
Rapidly Progressive OA

Characterization

- **Evidence of OA in the affected joint prior to study = 61 patients (90%)**
 - **Including patient with CLBP**
- **A majority of patients had rapidly progressive OA in the hip - 56%**
 - **21% patients in the overall study population with hip as the index joint**

Rapidly Progressive OA Characterization

- Evidence of OA in the affected joint prior to study = 61 patients (90%)
 - Including patient with CLBP
- A majority of patients had rapidly progressive OA in the hip - 56%
 - 21% patients in the overall study population with hip as the index joint
- Fewer patients with rapidly progressive OA in joints that were KL Grade 2 vs. the overall study population
 - ◆ 9% vs. 41%



* 13 patients (19.1%) KL Grade unknown

Rapidly Progressive OA & anti-NGF mAbs

Considerations of Mechanism – Clinical Observations

- **No patients with loss of protective sensation; neurologic characteristics did not differ from the overall treated population**

Rapidly Progressive OA & anti-NGF mAbs

Considerations of Mechanism – Clinical Observations

- **No patients with loss of protective sensation; neurologic characteristics did not differ from the overall treated population**
- **A direct link of greater pain relief to rapidly progressive OA could not be established**

Rapidly Progressive OA & anti-NGF mAbs

Considerations of Mechanism – Clinical Observations

- **No patients with loss of protective sensation; neurologic characteristics did not differ from the overall treated population**
- **A direct link of greater pain relief to rapidly progressive OA could not be established**
- **However, the findings do not exclude that pain relief may contribute or accelerate further damage in a susceptible joint**
 - **Greater subchondral bone pathology, and/or susceptibility for subchondral insufficiency fractures or atrophic OA**

Rapidly Progressive OA & anti-NGF mAbs

Considerations of Mechanism – Clinical Observations

- **No patients with loss of protective sensation; neurologic characteristics did not differ from the overall treated population**
- **A direct link of greater pain relief to rapidly progressive OA could not be established**
- **However, the findings do not exclude that pain relief may contribute or accelerate further damage in a susceptible joint**
 - **Greater subchondral bone pathology, and/or susceptibility for subchondral insufficiency fractures or atrophic OA**
- **There was no evidence that greater pain relief accounted for the greater risk of rapidly progressive OA with tanezumab/NSAID combination therapy**

Summary of Adjudication Results

- **Adjudication confirmed 2 patients with primary osteonecrosis**
- **Rapidly progressive OA**
 - **Observed in OA patients (and joints with moderate to severe OA)**
 - **Dose-related increase with tanezumab monotherapy over active comparator**
 - **Rate further increased >3-fold with tanezumab/NSAID combination therapy**
 - **NSAID use up to 90 days did not appear to elevate risk**
 - **Some events were pre-existing**

Presentation Outline

■ Efficacy

- Osteoarthritis
- Chronic Low Back Pain
- Other Chronic Pain Conditions

■ Joint-Related Safety

- Total Joint Replacements and Events Reported as Osteonecrosis
- Adjudication Outcomes

■ Risk minimization to reduce the risk of rapidly progressive OA in future studies

Rationale for Risk Minimization

- **The risk of rapidly progressive OA increases with chronic concomitant NSAID use**
- **In OA, tanezumab 10 mg did not provide additional benefit over tanezumab 5 mg**
- **Preliminary review of the data suggest most patients who respond to tanezumab do so after 1-2 doses**
- **Expert review of baseline radiographs indicate that some patients had rapidly progressive OA at study entry**

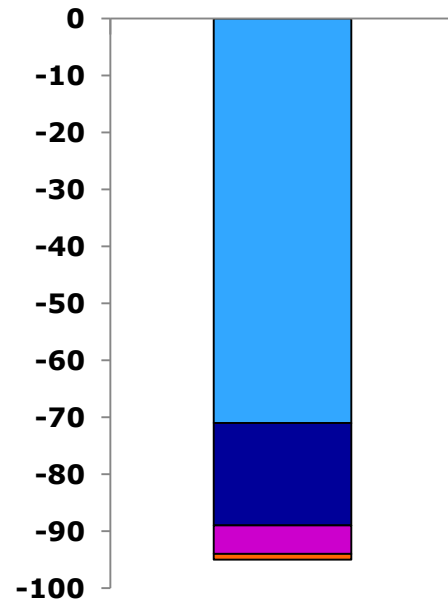
This evidence was used to define the risk minimization plan

Application of Risk Minimization Measures

Rapidly Progressive OA – Phase 3 OA Studies

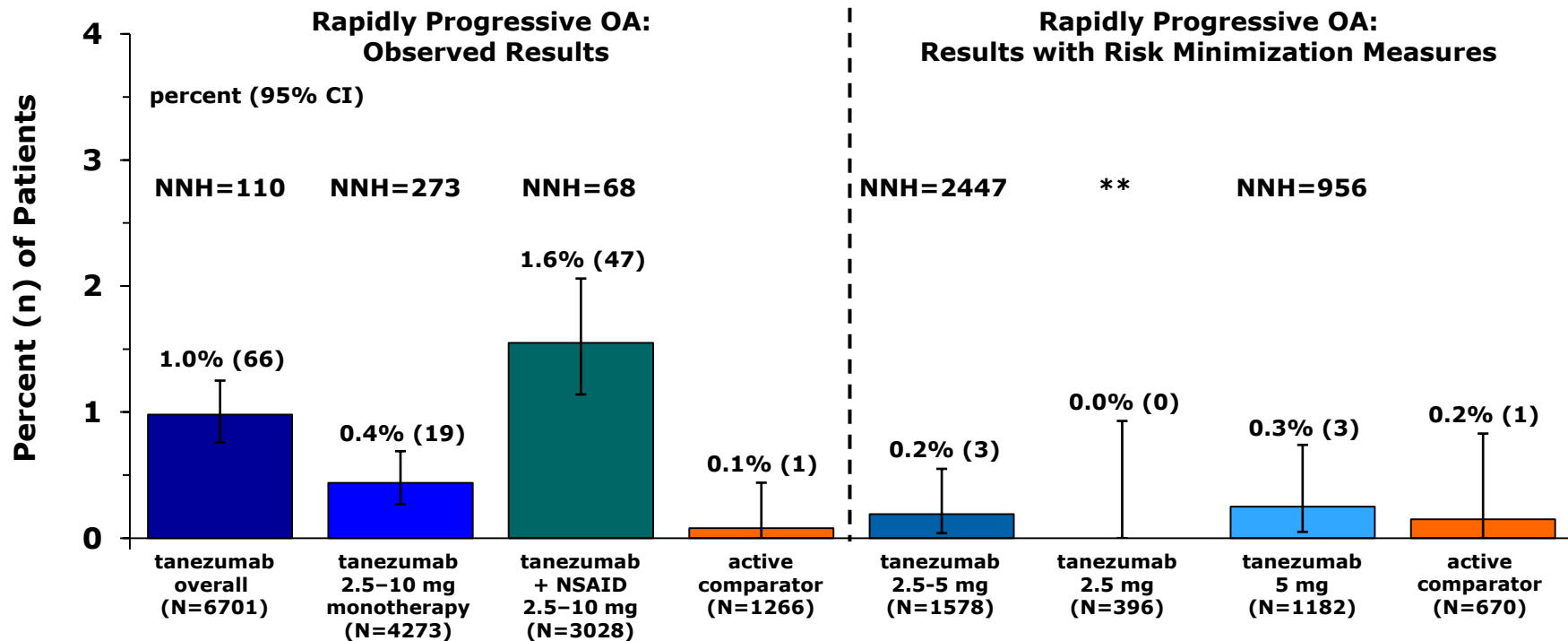
N=66 patients	Patients with Rapidly Progressive OA Impacted by the Risk Minimization Measure (n) Cumulative Reduction in Rapidly Progressive OA events (%)
Excluding chronic concomitant NSAID use with anti-NGF therapy	47 patients; 71% reduction <div data-bbox="1039 565 1097 598" style="display: inline-block; width: 20px; height: 10px; background-color: #00AEEF; border: 1px solid black; margin-left: 10px;"></div>
Careful selection of anti-NGF doses for further clinical investigation - Discontinue further study of tanezumab 10 mg in OA	12 patients: 89% reduction <div data-bbox="1039 680 1097 713" style="display: inline-block; width: 20px; height: 10px; background-color: #002060; border: 1px solid black; margin-left: 10px;"></div>
Discontinuing patients who do not respond adequately to initial dose(s) of anti-NGF therapy	3 patients: 94% reduction <div data-bbox="1039 816 1097 849" style="display: inline-block; width: 20px; height: 10px; background-color: #E91E63; border: 1px solid black; margin-left: 10px;"></div>
Excluding patients with pre-existing rapidly progressive OA from study participation	1 patient: 95% reduction <div data-bbox="1039 936 1097 969" style="display: inline-block; width: 20px; height: 10px; background-color: #FF9800; border: 1px solid black; margin-left: 10px;"></div>

Cumulative Reduction in the Rapidly Progressive OA events (%)



Application of Risk Minimization Measures

Rapidly Progressive OA – Phase 3 OA Studies

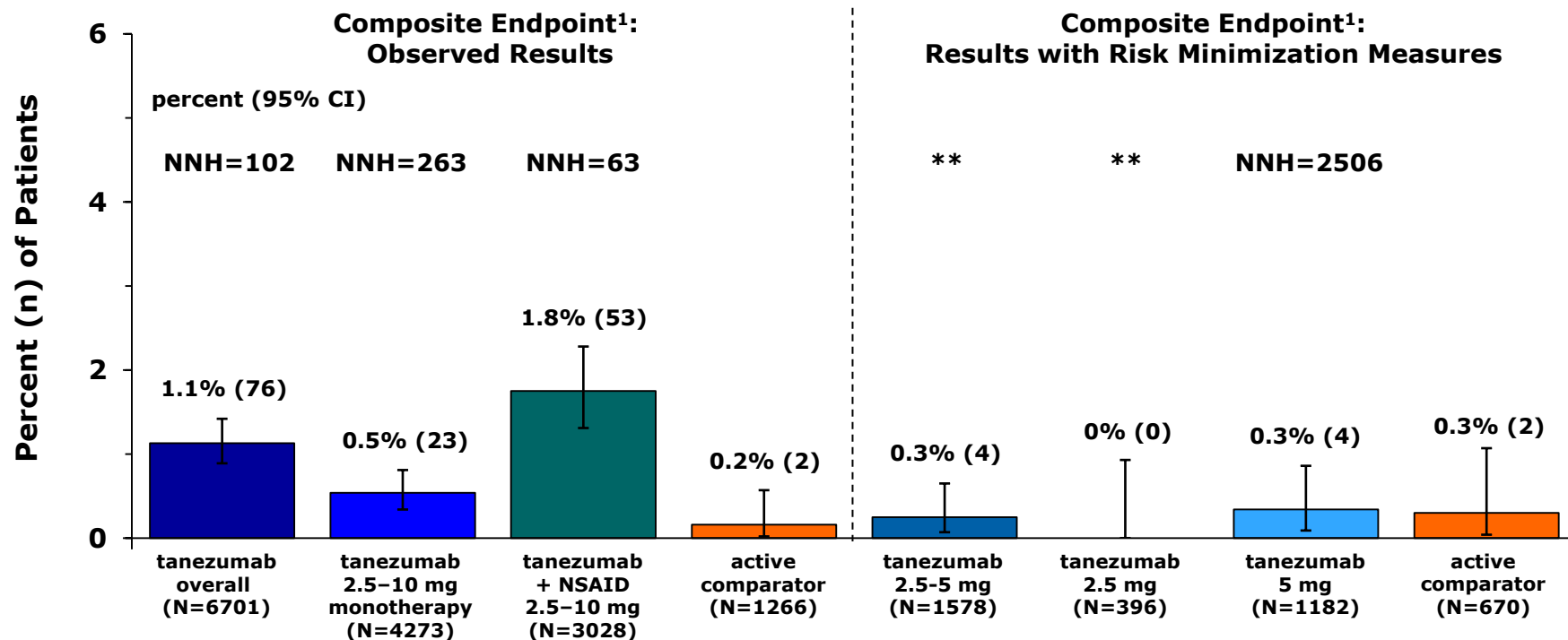


NNH = Number of patients treated with tanezumab instead of active comparator to observe 1 additional event

**Indicates that a negative number is needed to harm, lower risk with tanezumab than active comparator

Application of Risk Minimization Measures

Composite Endpoint – Phase 3 OA Studies



¹ Includes all-cause total joint replacement, adjudicated osteonecrosis or RPOA and 10 patients with subchondral insufficiency fracture

**Indicates that a negative number is needed to harm, lower risk with tanezumab than active comparator

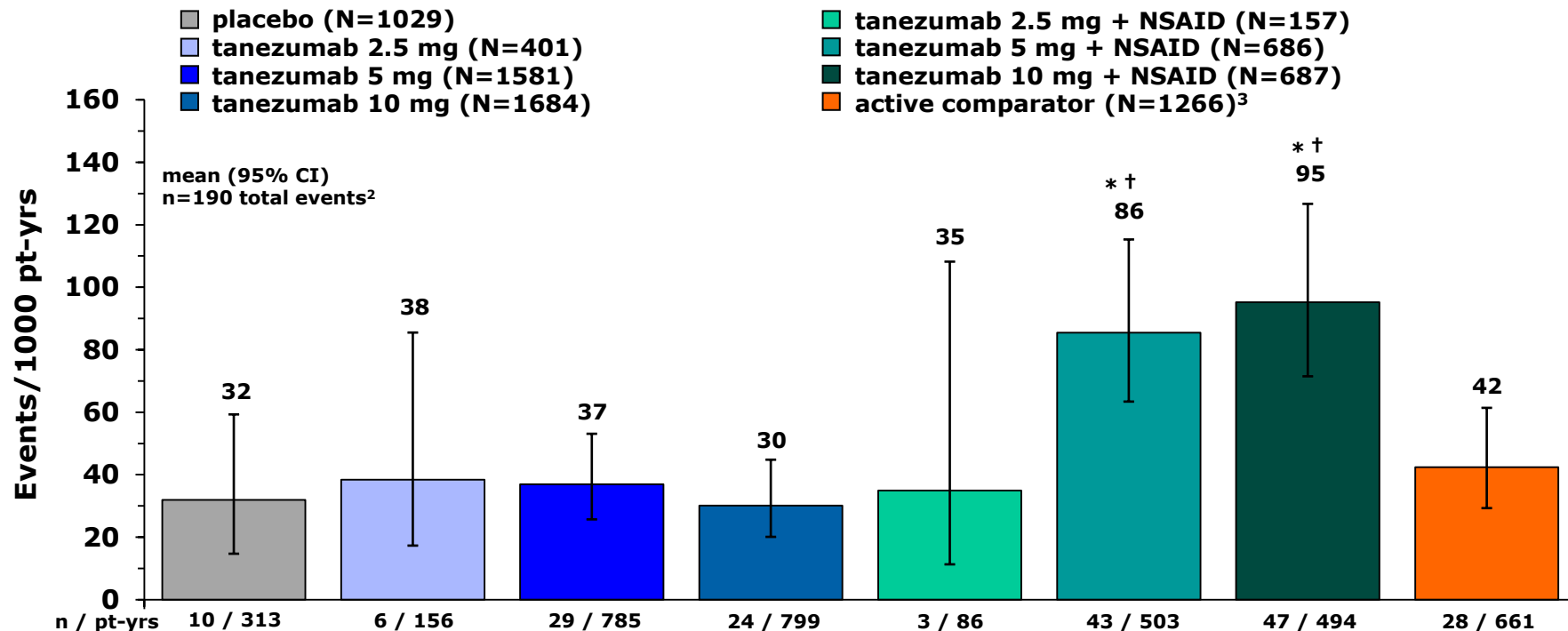
NNH = Number of patients treated with tanezumab instead of active comparator to observe 1 additional event

Conclusions

- **Relieves pain and improves function to a clinically meaningful extent across chronic pain conditions; superior to active comparator treatment**
- **Tanezumab monotherapy does not elevate the risk of all-cause total joint replacements – in contrast to when administered with NSAIDs**
- **Adjudication of total joint replacements showed:**
 - **Tanezumab does not elevate the risk of osteonecrosis**
 - **Associated with a dose-related increase in rapidly progressive OA**
 - ◆ **Further increased >3-fold when administered with NSAIDs**
- **Risk minimization should reduce the risk of rapidly progressive OA in future studies**

All-Cause Total Joint Replacements

Controlled Phase 3 OA Studies¹: Event Rate by Dose



¹ Includes Studies 1011, 1014, 1015, 1017, 1018, 1025, 1026, 1027, & 1030

² Includes all reported osteonecrosis adverse events with or without total joint replacement

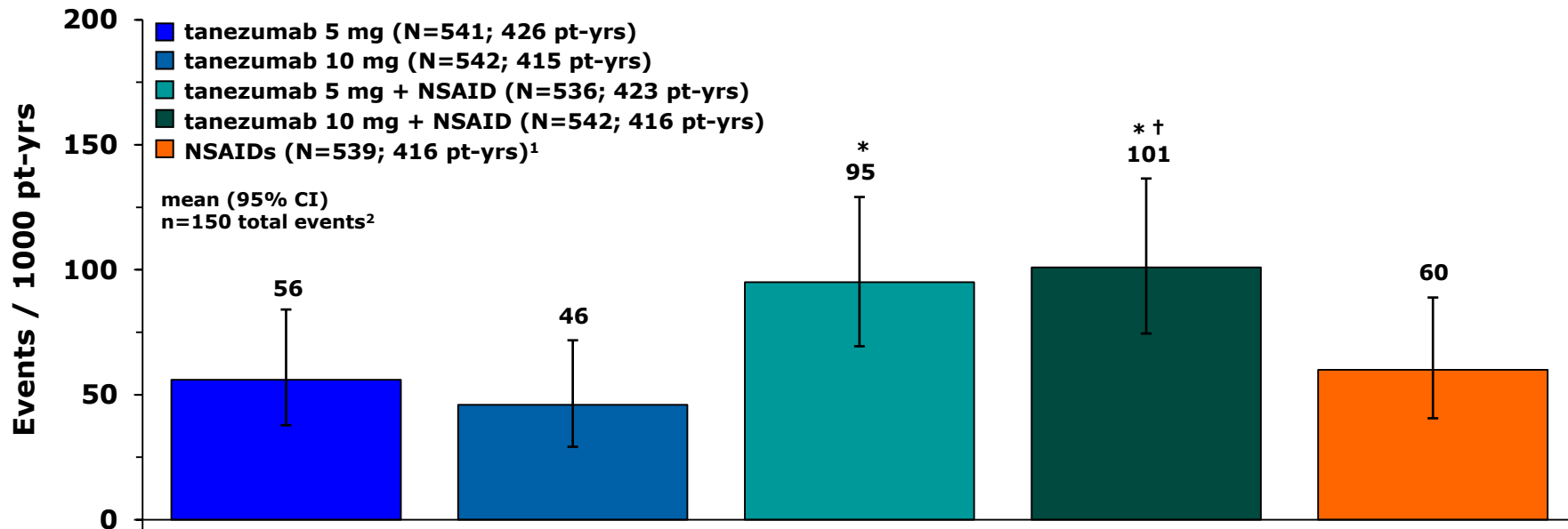
³ Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID

Risk Difference: *p≤0.05 vs. placebo, †p ≤ 0.05 vs. active comparator

Dose Response: p=0.655 tanezumab monotherapy, p=0.0004 tanezumab/NSAID combination therapy

All-Cause Total Joint Replacements

Phase 3 OA Study 1025, Event Rate by Treatment



¹ NSAIDs = naproxen 500 mg BID, celecoxib 100 mg BID

² Includes all reported osteonecrosis adverse events with or without total joint replacement

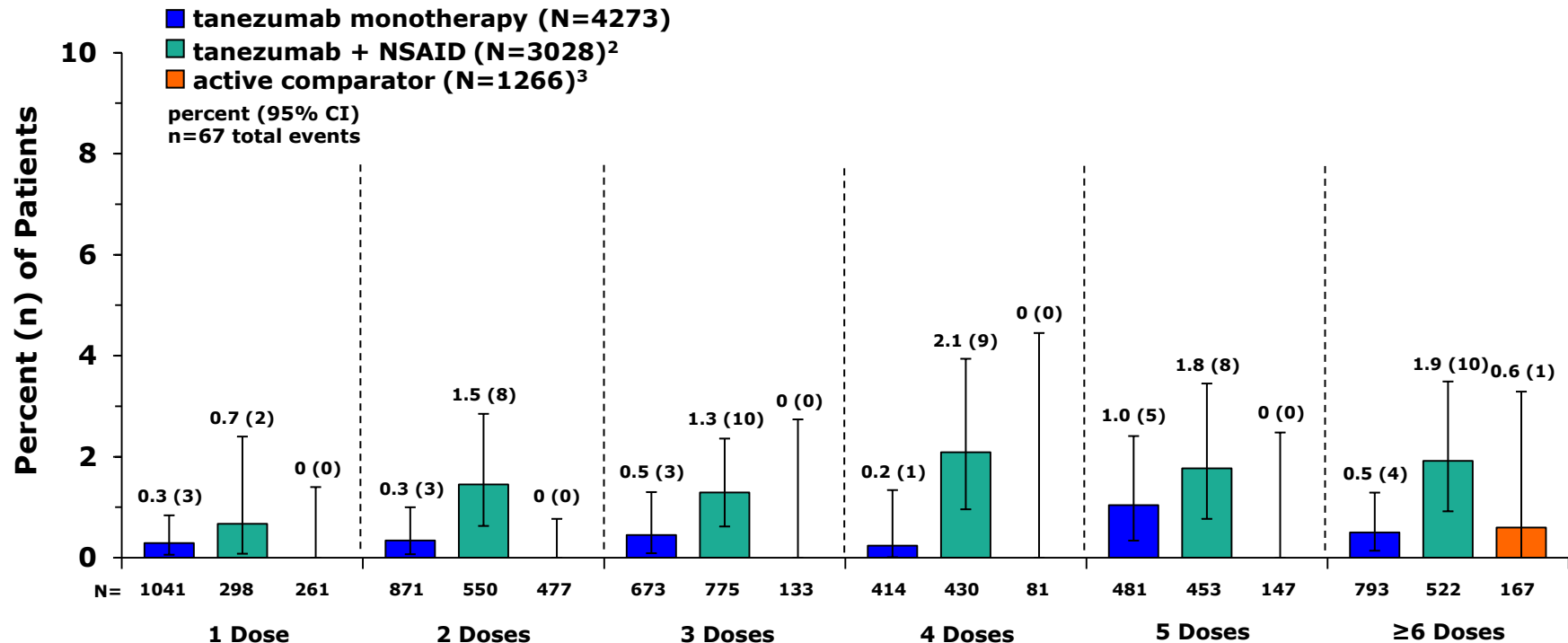
Risk difference: *p≤0.05 vs. tanezumab 5 or 10 mg, †p≤0.05 vs. NSAID

Adjudicated vs. Non-Adjudicated Patients

	Adjudicated Patients N = 249	Non-Adjudicated Patients N = 137
Treatment Assignments		
placebo	4 (1.6)	6 (4.4)
tanezumab (2.5 – 10 mg)	161 (64.7)	94 (68.6)
tanezumab (2.5 - 10 mg) + NSAID	65 (26.1)	28 (20.4)
active comparator	19 (7.6)	9 (6.6)
tanezumab treatment duration median / mean (no. of injections)	4 / 4.7	5 / 4.6
Time to reported osteonecrosis or total joint replacement (days)		
From 1 st administration of study medication (median / mean)	286 / 297.4	291 / 286.6
From last administration of study medication (median / mean)	83 / 87.4	76 / 77.9

Rapidly Progressive OA

Incidence by Number of Doses – Phase 3 OA Studies¹



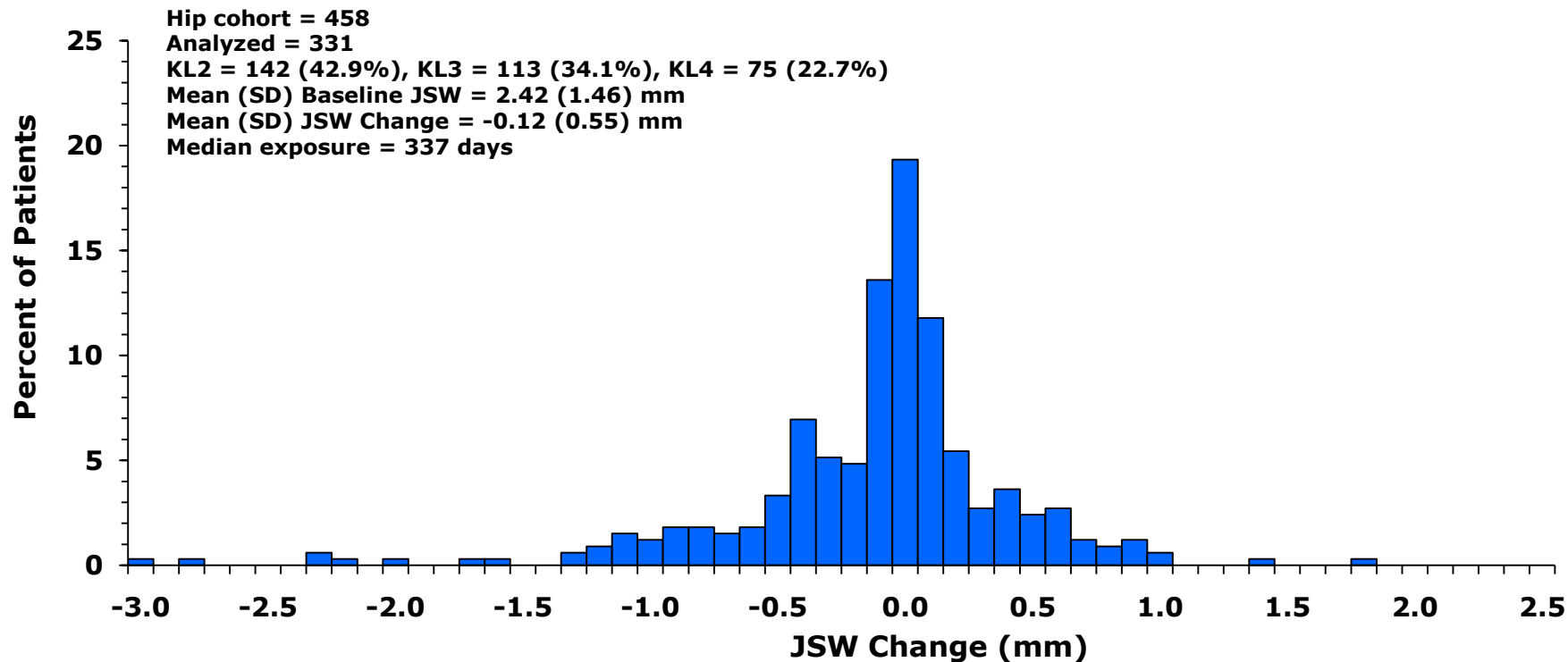
¹ Studies 1011, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030 & 1043. The placebo treatment group is not shown.

² Patients receiving concomitant NSAID treatment with tanezumab in long-term studies are included in the tanezumab + NSAID treatment groups

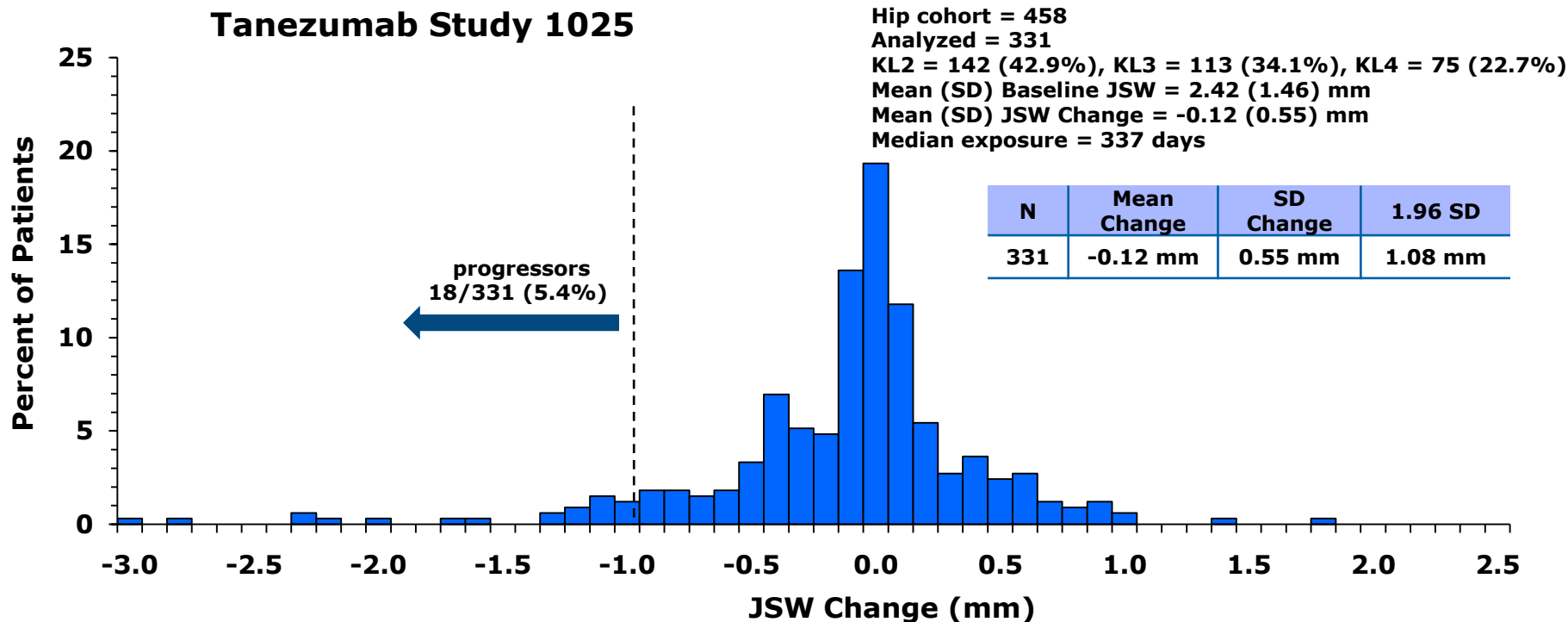
³ Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID

Distribution of Hip JSW Changes

Tanezumab 1025 Study



Patients with Hip JSW Change Exceeding the Experimental Measurement Threshold¹



¹ Threshold above which a change in JSW can be considered relevant based on the evaluation of the measurement error; Ornetti et al. OARSI-OMERACT Definition of Relevant Radiological Progression in Hip/Knee Osteoarthritis. Osteoarthritis and Cartilage. 2009; 17:856-863. Bland-Altman technique was used.

Patients with Hip JSW Change Exceeding Experimental Measurement Threshold¹

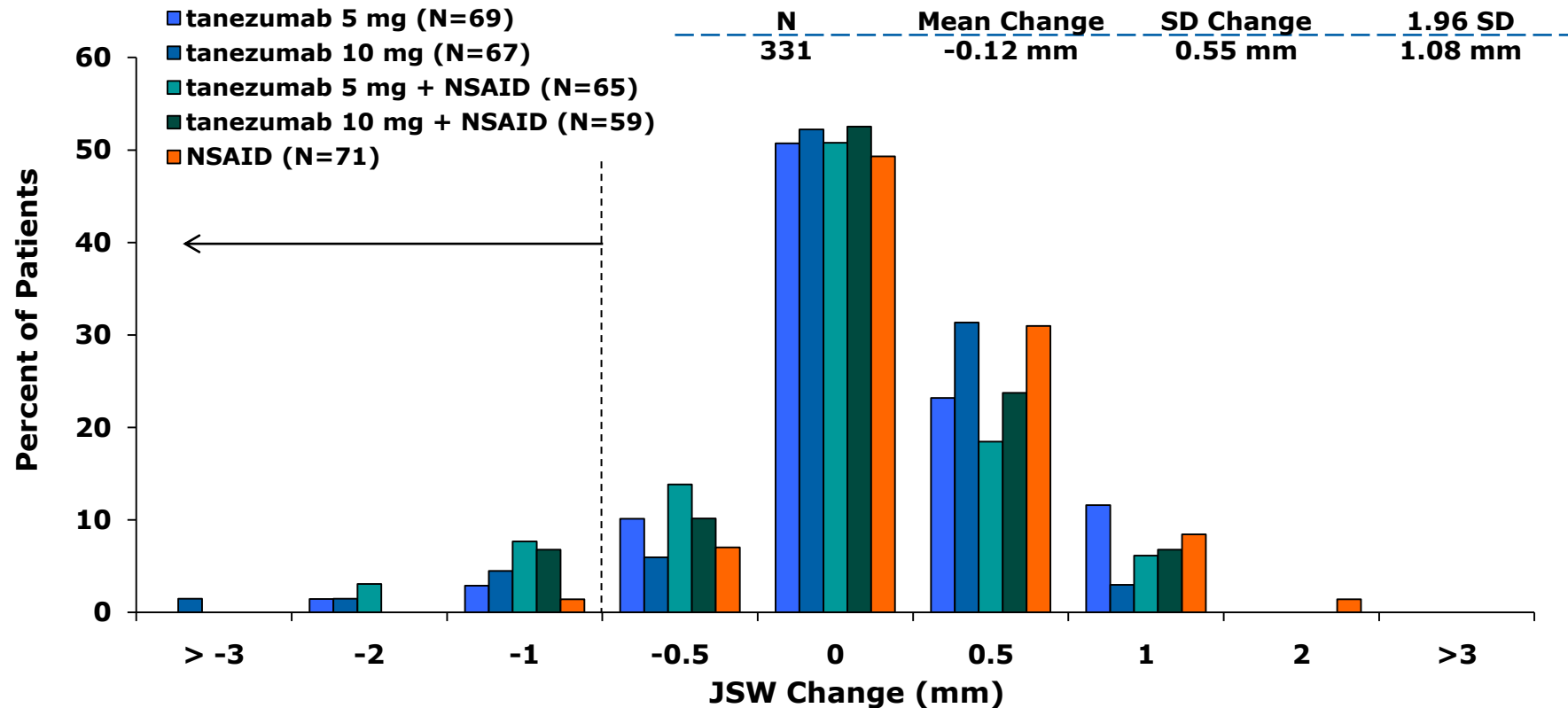
	tanezumab		tanezumab + NSAID		NSAID N = 446
	5 mg N = 92	10 mg N = 93	5 mg N = 446	10 mg N = 452	
Patients Analyzed, N	69	67	65	59	71
Patients with JSN \geq -1.08 mm n (%)	2 (2.9%)	5 (7.5%)	6 (9.2%)	3 (5.1%)	2 (2.8%)
Risk Difference vs NSAID [95% CI]	0.1% [-13.0, 17.2]	4.7% [-8.7, 21.6]	6.4% [-7.5, 24.0]	2.3% [-11.4, 20.3]	-
p-value	1.00	0.51	0.41	0.77	-

¹ Threshold above which a change in JSW can be considered relevant based on the evaluation of the measurement error; Ornetti et al. OARSI-OMERACT Definition of Relevant Radiological Progression in Hip/Knee Osteoarthritis. Osteoarthritis and Cartilage. 2009; 17:856-863. Bland-Altman technique was used.

N	Mean Change	SD Change	1.96 SD
331	-0.12 mm	0.55 mm	1.08 mm

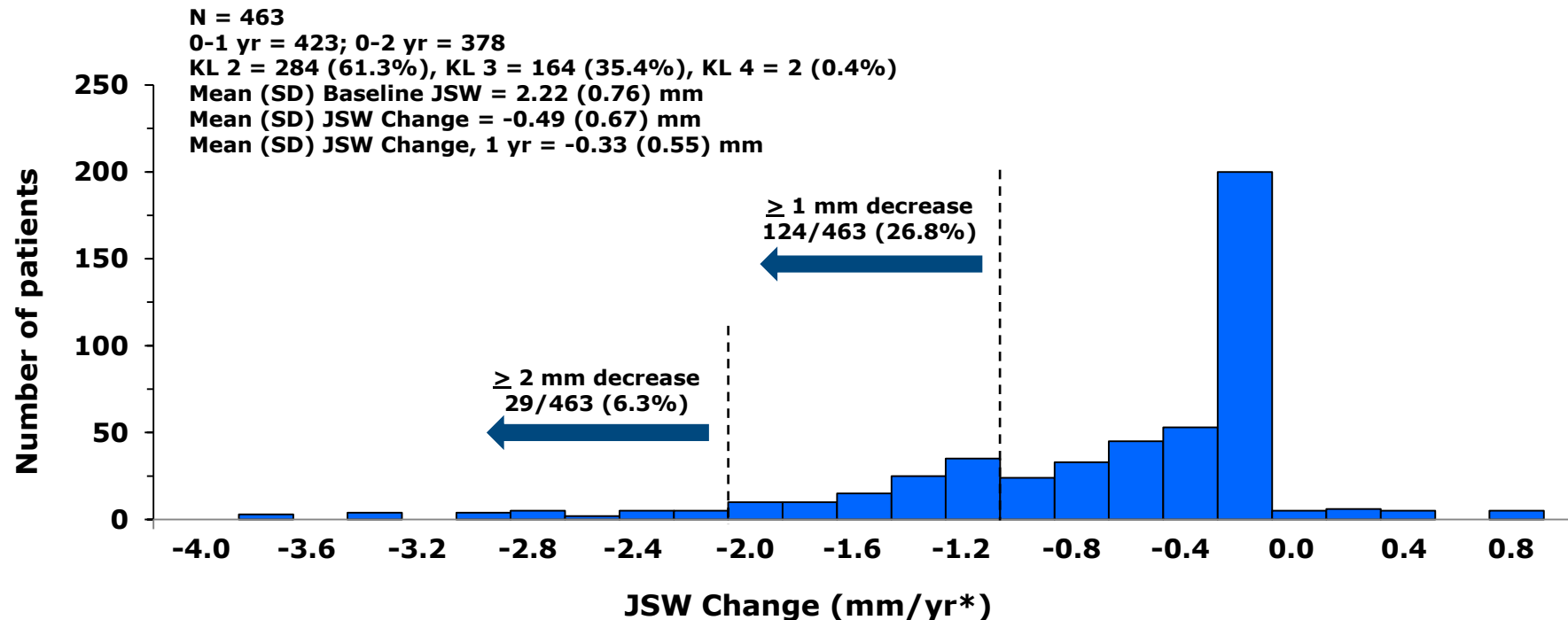
Distribution of Hip JSW Changes

Tanezumab Study 1025



Distribution of Hip JSW Changes

Dougados et al. Echodiah Study



*Rate of change between the first and last available radiograph during the two-year study period.
Dougados et al. Radiographic features predictive of radiographic progression of hip osteoarthritis.
Rev Rhum (Engl. ed) 1997;64:795-803.

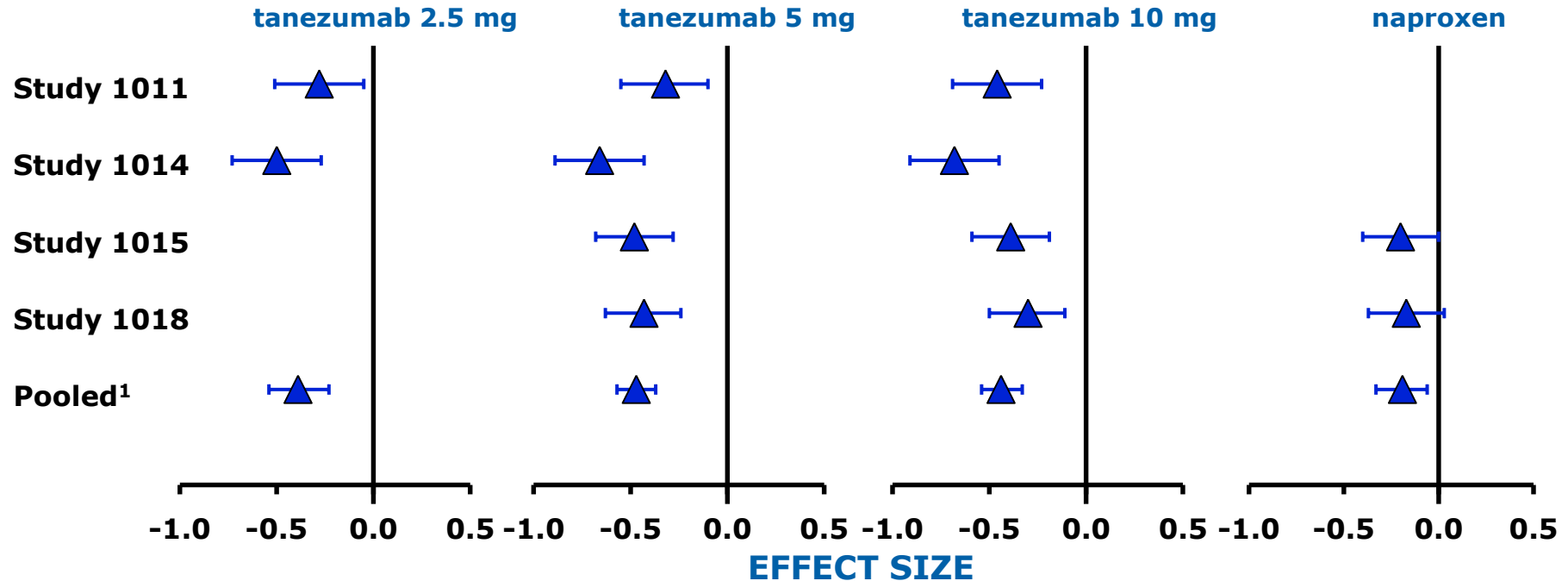
Change in Hip Joint Space Width

Tanezumab Study 1025

	tanezumab		tanezumab + NSAID		NSAID N = 93
	5 mg N = 92	10 mg N = 93	5 mg N = 90	10 mg N = 90	
Patients Analyzed, n (%)	69 (75.0)	67 (72.0)	65 (72.2)	59 (65.6)	71 (76.3)
Baseline Mean (SD) JSW(mm)	2.45 (1.36)	2.37 (1.43)	2.35 (1.42)	2.20 (1.56)	2.72 (1.53)
Mean (SE) JSW Change (mm)	-0.08 (0.07)	-0.14 (0.07)	-0.24 (0.07)	-0.14 (0.07)	-0.02 (0.07)
Comparison vs NSAID Mean JSW Change [95% CI]	-0.06 [-0.24, 0.13]	-0.12 [-0.30, 0.07]	-0.22 [-0.40, -0.03]	-0.12 [-0.31, 0.07]	-
p-value	0.54	0.20	0.02	0.21	-

WOMAC Pain

Tanezumab Provides Consistent Pain Relief vs. Placebo

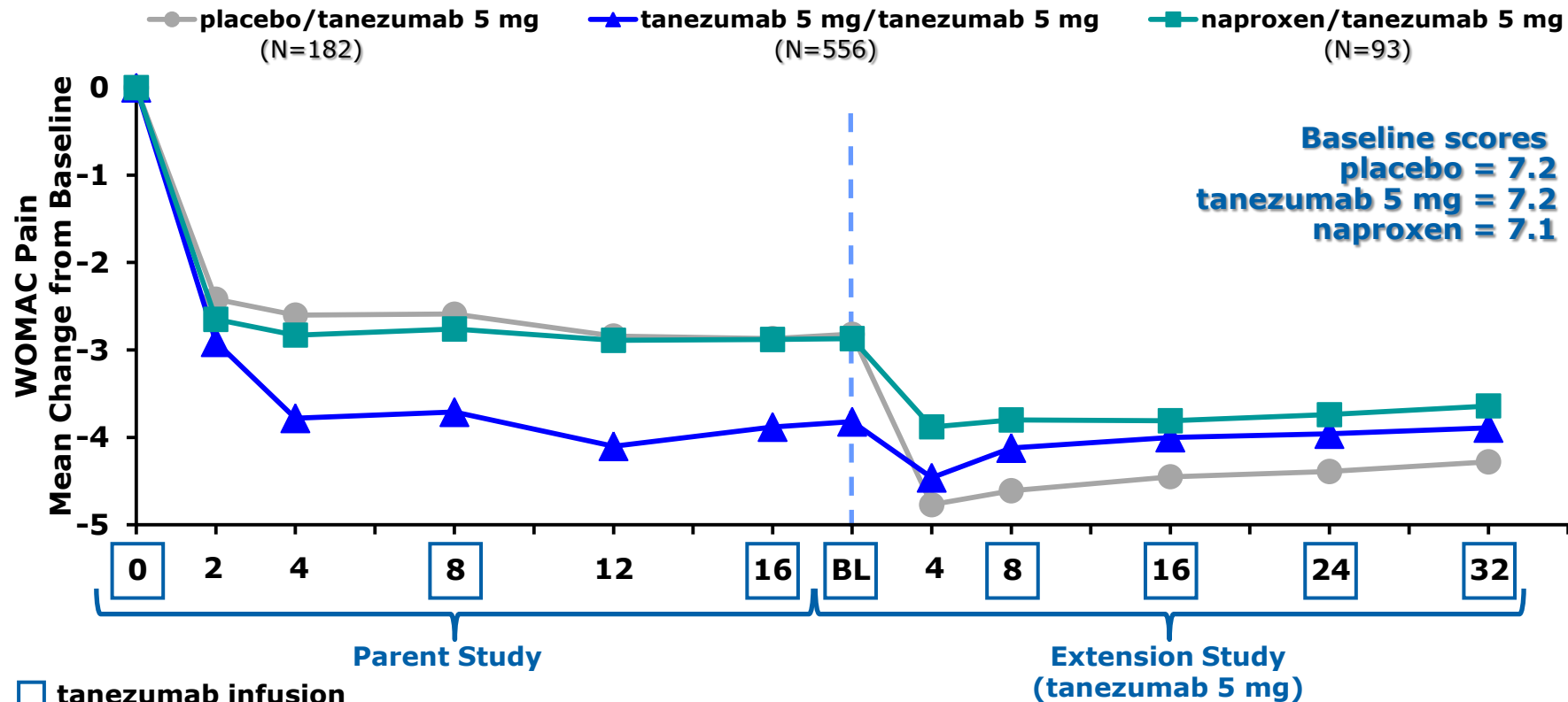


▲ Effect size (95% CI); LS mean difference/SD of difference vs. placebo at Week 16; WOMAC Pain Subscale (0-10 NRS)

¹Studies 1011, 1014, 1015, and 1018 combined; ITT, BOCF; naproxen dose = 500 mg BID

WOMAC Pain: Long-Term Efficacy

Double-Blind Parent Study → Study 1016 (5 mg)



Sensory Examinations in Lower Extremities for RPOA vs Non-RPOA: Phase 3 Controlled and Long-term OA Studies* (Combined Doses)

	All Tanezumab Treated	
	With RPOA	Without RPOA
	N=66	N=6635
NIS Sensory Score in Great Toes**		
Baseline (mean)	0.24	0.32
p-value for Baseline means	0.530	
LS Mean Change from Baseline	-0.02	-0.08
LS Mean Difference (SE)	0.07 (0.11)	
p-value	0.522	

RPOA= rapidly progressive osteoarthritis

*Studies 1011, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030, & 1043;

** NIS= Neuropathy Impairment Score; Patient score can range from 0 (normal sensory exam) to 12 (absent joint position, vibration and pinprick in both great toes).

Expert Neurological Consult Review of Joint Safety

- For patients with a joint safety adjudication and a neurological consultation, (N=54) an expert external neurologist reviewed patients' neurological consultation data
- Neurological consultations were reviewed without knowledge of study treatment assignment or adjudication outcome
- Neurologist provided a diagnosis for each case where possible

Neurological Diagnoses in Patients with both Joint Safety Adjudication and Neurological Consult

249 Patients with Joint Safety Adjudication

195 (78%) – Adjudication but No Neurological Consultation Required

54 (22%) - Both Adjudication and Neurological Consultation

Adjudication Outcomes		Neurological Diagnoses					
		Normal	Carpal Tunnel Syndrome	Other Mono-neuropathy	Radiculopathy	Other / No Diagnosis	Poly-neuropathy
Osteonecrosis	n= 1	1	0	0	0	0	0
Rapidly Progressive Osteoarthritis	n=17	7	5	2	2	0	1
Osteoarthritis – Normal Progression	n=25	13	4	2	1	2	3
All Other Adjudication Outcomes	n=11	4	1	0	2	2	2
Total	N=54	25	10	4	5	4	6

Only one RPOA or ON patient had polyneuropathy and carpal tunnel reported by nerve conduction study

Meta-Analysis – All-Cause Total Joint Replacements

Tanezumab 5 mg vs. Placebo

Study (weight ¹)	Number of Patients with Event [Treatment Group N/Treatment Exposure (pt-yrs)]		OR (95% CI) ² Eliminating Studies with 0 events	OR (95% CI) ² With Correction for Studies with 0 events ³
	Comparison Group 1	Comparison Group 2		
	Tanezumab 5 mg	Placebo		
1011 (32.7)	1 [172/70]	0 [172/61]	7.4 [0.2, 372.4]	7.4 [0.2, 372.4]
1014 (27.2)	2 [154/64]	3 [155/48]	0.7 [0.1, 3.9]	0.7 [0.1, 3.9]
1015 (29.2)	1 [206/62]	2 [208/55]	0.5 [0.05, 5.0]	0.5 [0.05, 5.0]
1018 (29.0)	0 [211/64]	2 [209/53]	0.1 [0.01, 2.1]	0.1 [0.01, 2.1]
1026 (14.9)	0 [73/29]	0 [72/30]	NA	1.0 [0.02, 50.4]
1027 (10.2)	0 [63/19]	2 [72/22]	0.2 [0.01, 2.5]	0.2 [0.01, 2.5]
1030 (23.7)	1 [161/52]	1 [141/44]	0.9 [0.05, 14.1]	0.9 [0.05, 14.1]
Combined Studies	-	-	0.7 [0.2, 2.5]	0.8 [0.2, 2.5]

¹ Study weight is calculated as $(1/[\text{Comparison Group 1 exposure}] + 1/[\text{Comparison Group 2 exposure}])^{-1}$

² Odds ratios and 95% confidence intervals calculated using the Peto odds ratio method.

³ Correction for studies with 0 events is the addition of ni/N in each group so that 1 patient in total is added and the OR is 1.0 for that study. (ITT, All Placebo-Controlled Studies)



Perspectives on Chronic Pain: Current Status and Needs

Thomas J. Schnitzer, MD, PhD

Professor

Departments of Physical Medicine and Rehabilitation
and Internal Medicine/Rheumatology

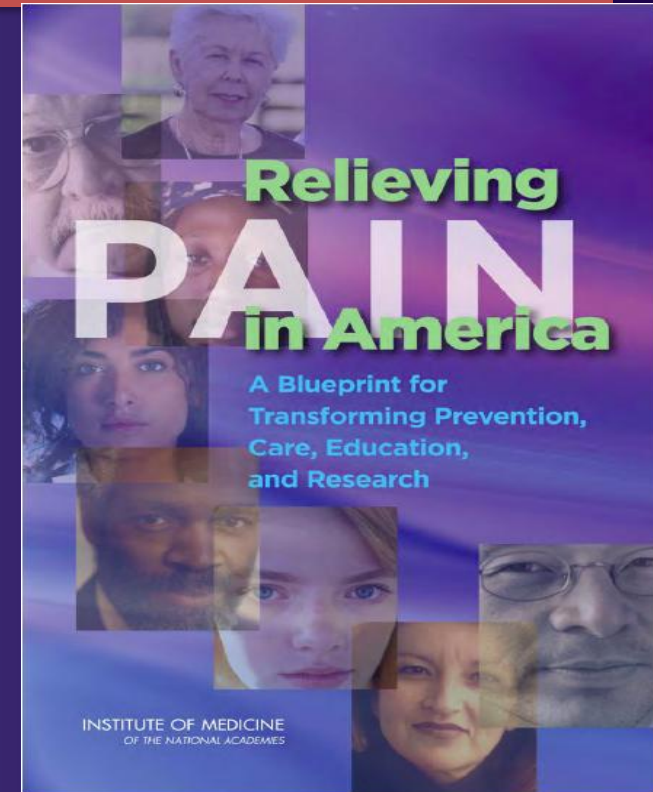


Discussion Outline

- Chronic Pain is prevalent
- Chronic Pain is impactful
- Chronic Pain management paradigms fail many patients
- New therapeutics not available despite serious efforts
- NGF inhibition has shown promise and also raised concerns

Prevalence of Chronic Pain

- 2011 IOM report of the Committee on Advancing Pain Research, Care and Education
- “at least 116 million Americans burdened with chronic pain”
- Most common clinical presentations of chronic pain
 - Musculoskeletal pain¹
 - Low back pain 28% of adults
 - Osteoarthritis 26% of adults
 - Chronic headache/migraine
 - Neuropathic pain
 - Visceral pain
 - Central pain



¹CDC and NCHS, 2010



Impact of Chronic Pain

What is pain?

It is so much more than just pain intensity. Over time, many [patients] find the effects of living with chronic pain impact their ability to work, engage in recreational and social activities, and for some, [perform] the most basic everyday activities that people just take for granted. Not surprisingly, pain begins to chip away at their mood, often leaving them angry, frustrated, anxious, and/or depressed. Our families suffer along with us, and many relationships are forever altered.

--An advocate for people with chronic pain¹

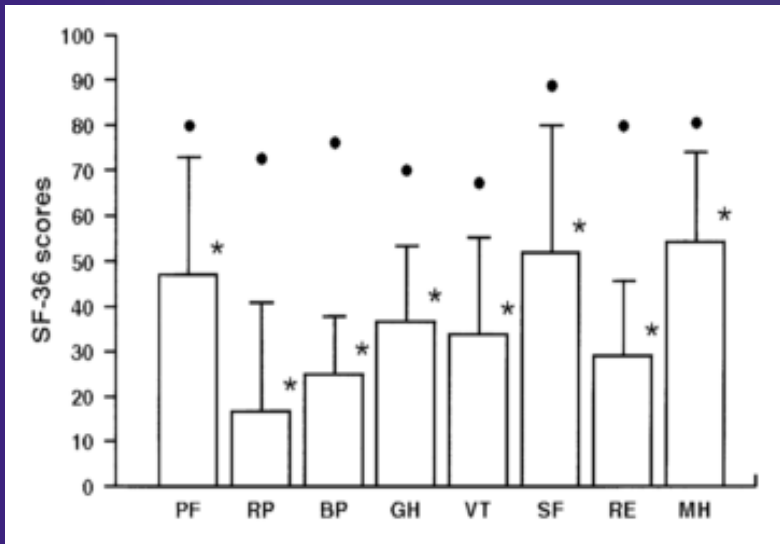
Consequences of pain

- **Poor health-related quality of life & poor self-rated health**
- **Strong link with disability**
- **Likely to seek medical attention**



Impact of Chronic Pain

Quality of Life



Effect of chronic nonmalignant pain on QOL, as indicated by SF-36 subscores, mean (SD) (n=150).^{1,2}

• = population norm values; PF=physical functioning; RP=role-physical; BP=bodily pain; GH=general health; VT=vitality; SF=social functioning; RE=role-emotional; MH=mental health. * p<0.001

Activities/Quality of Life Domains Impaired by Increasing Pain Severity

					Relate
				Walk	Walk
		Sleep	Sleep	Sleep	Sleep
		Active	Active	Active	Active
		Mood	Mood	Mood	Mood
	Work	Work	Work	Work	Work
Enjoy	Enjoy	Enjoy	Enjoy	Enjoy	Enjoy
3	4	5	6	7	8
Worst pain rating					

Boldface indicates an additional dimension that is impaired at the given level of pain

¹Katz N, J Pain Symp Mgmt 2002; 24:S38-47. ²Becker N et al, Pain 1997; 73: 393-400

³Cleland CS and Ryan KM, Ann Acad Med 1994; 23:129-138



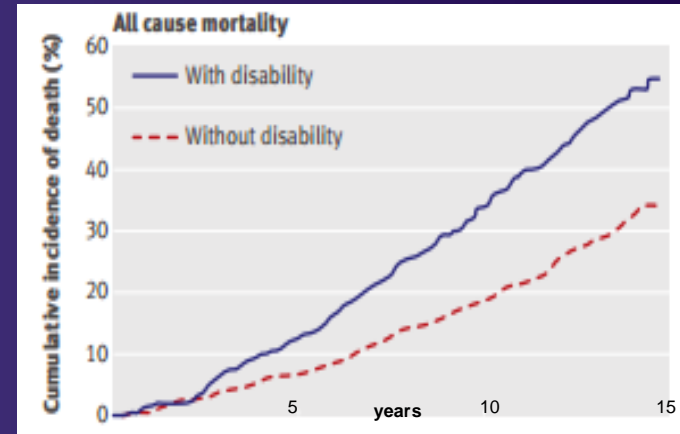
Impact of Chronic Pain Disability

Extent of Pain-Related Disability among Adults with Pain in the Last 3 months, United States, 2009¹

Type of Pain	Difficulty with Basic Activities (%)	Activity Limitations (%)
Low back pain	51.6	55
Neck pain	30.2	34.4
Back pain	37.3	38.6
Shoulder pain	17.7	21.4
Hip pain	15	28.4
Severe headache/migraine	31	33.5

Defined as having difficulties in one or more of the following areas: movement, emotional, seeing, hearing or cognition
Defined as having limitations in one or more of the following areas: self-care, social, work
Source: CDC and NCHS, 2010

All cause mortality in OA Patients with and without disability



¹IOM, 2011: Relieving Pain in America; Nuesch E et al. BMJ 2011; 342d1165



Impact of Chronic Pain

Economic Burden

- Annual Cost of Chronic Pain in the United States¹
 - \$560-635 billion annually
 - \$261-300 billion in health care costs
 - \$297-336 billion in lost productivity
- Expenditures
 - Medicare: \$65.3 billion or 14% of all Medicare costs in 2008
 - All federal & state programs (Medicare, Medicaid, VA, etc) \$99 billion in 2008 for medical expenditures for pain

¹Conservative estimate as excludes cost of pain affecting institutionalized individuals (e.g., long-term care residents, correction inmates), military personnel; excludes lost productivity of personal caregivers, workers <24 and >65 years, and emotional costs of pain.



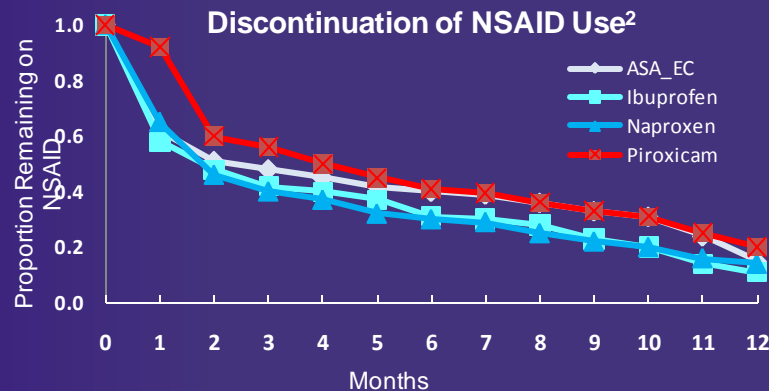
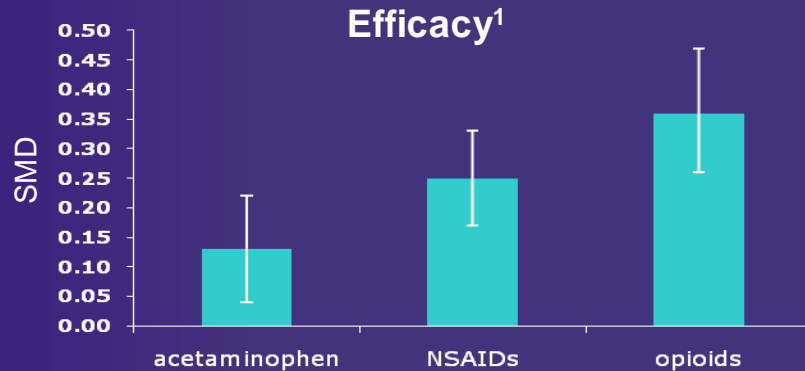
Management of Chronic Pain Fails Too Often

- Significant system and organizational barriers to adequate pain care exist.
- Education is a central part of the necessary cultural transformation of the approach to pain.
- Research to translate advances into effective therapies is a continuing need.

“Academia and industry should develop novel agents for the control of pain. This does not mean simply recycling current drugs. What is required is basic and clinical science research to discover new classes of pain therapeutics and more efficient ways of developing them.”



Existing Pain Medications: NSAID Limitations



NSAID Safety³

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (see WARNINGS).
- Naproxen as NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS or NAPROSYN Suspension is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

Gastrointestinal Risk

- NSAIDs cause an increased risk of gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning. Elderly patients are at greater risk for serious gastrointestinal events (see WARNINGS).

¹Towheed T et al. CDSR 2006; Zhang W et al. OAC 2007;15:981-1000; Nuesch E et al. CDSR 2009; Fransen M, McConnell S. CDSR 2008

²Scholes et al. J. Rheum. 1995; 22: 708-12

³www.accessdata.fda.gov/drugsatfda_docs/label/2008/017581s110,18164s60,18965s18,20067s17lbl.pdf

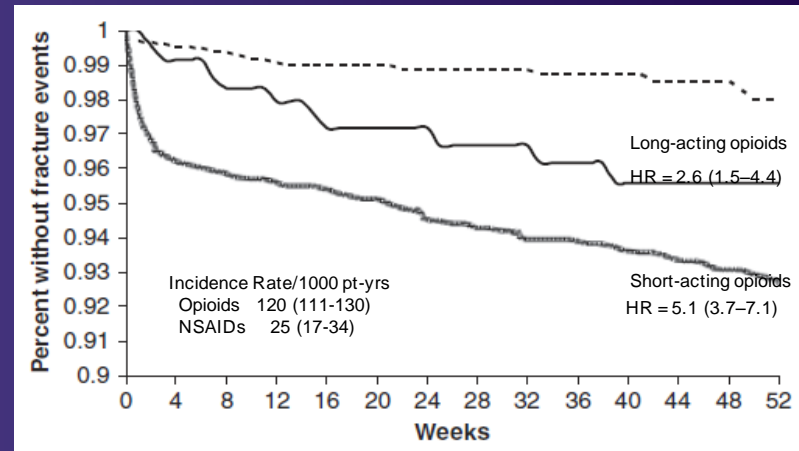


Existing Pain Medications: Opioid Limitations

Adverse Events^{1,2}

- GI:
 - Constipation 40-95%;
 - Nausea 10-40%
- CNS
 - Sedation, drowsiness, cognitive impairment
 - Respiratory depression
 - Dizziness and falls
 - Addiction and dependence
- Others:
 - Hormonal
 - Immunologic
 - Dermatologic

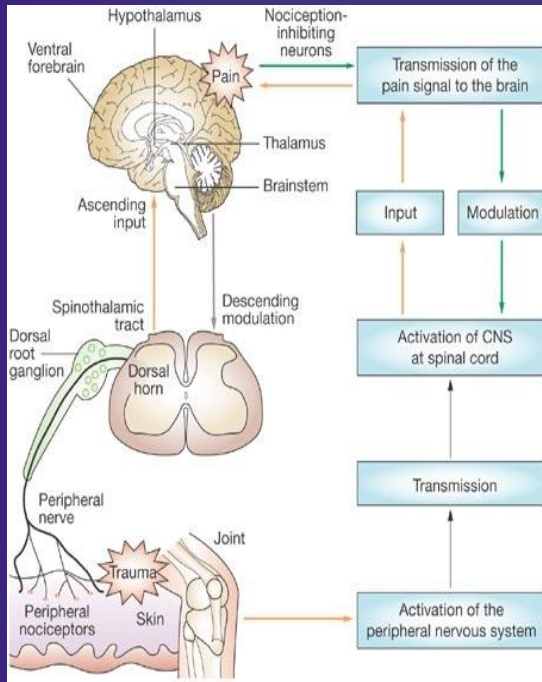
Opioids and Fracture in Older Adults with Arthritis³



Incidence rate highest in first 2 weeks after initiating therapy, especially for short-acting opioid group



Lack of Better Analgesics Not For Lack of Trying



• Multiple Targets Identified

- NMDA receptor blockers
- NK-1 receptor blockers
- FAAH inhibitors
- Na, Ca, K channel modulators
 - TrpV1, V3, V4
 - NaV1.7, NaV1.8
 - ASIC3
- Cannabinoid receptor blockers: CB1, CB2
- Delta opioid agonists
- P2X3 inhibitors
- P38 kinase

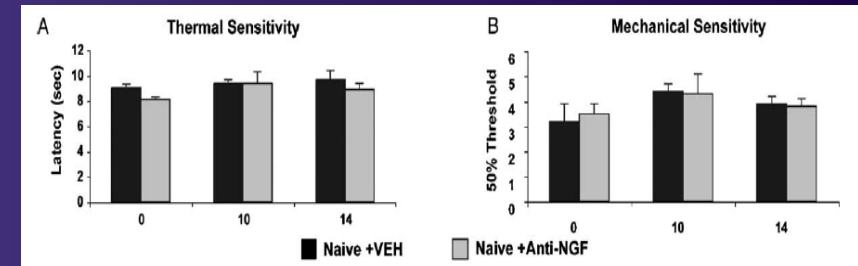
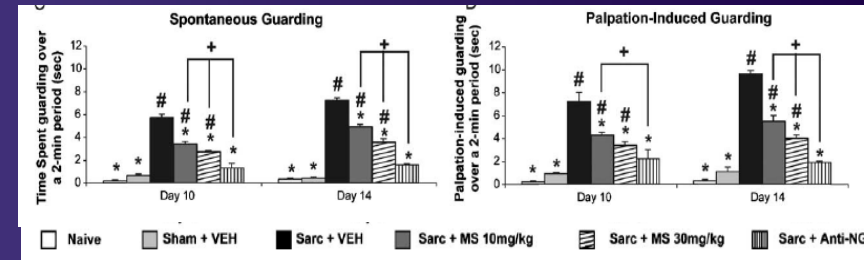
ClinicalTrials.gov
A service of the U.S. National Institutes of Health

539 trials in chronic pain
8 with new molecular entity
2 NCE in musculoskeletal pain



New Target: NGF as a Mediator of Pain

- **Key evidence**
 - NGF causes pain in humans and animals
 - NGF is locally up-regulated in painful conditions
 - NGF inhibition reverses pain in many animal models



Anti-NGF therapy appears to be antihyperalgesic (i.e., normalizing a decreased nociceptive threshold) as opposed to analgesic (i.e., increasing normal and sensitized nociceptive thresholds)



Monoclonal Antibodies Directed Against NGF

- **3 compounds under discussion: tanezumab, fulranumab, REGN475**
 - fully human or humanized monoclonal antibodies
 - picomolar affinity for NGF
 - high selectivity for NGF over other members of the neurotrophin family
 - Inhibit NGF activity at both TrkA and p75 receptors
 - Plasma half-life: 22-25 days
- **Evaluated after IV or SC routes of administration**
 - 4, 8 & 12 wk dosing intervals
 - Doses examined: 3 to 1000 $\mu\text{g/kg}$ (0.003 to 1 mg/kg)



Wide Range of Clinical Conditions Evaluated

Chronic Pain Condition	Efficacy Demonstrated
Osteoarthritis	✓✓
Chronic low back pain	✓✓
Diabetic peripheral neuropathy	✓
Post-herpetic neuralgia	Possible
Interstitial cystitis	Possible
Prostatitis	Possible
Endometriosis	Negative
Cancer pain	On-going

- Efficacy superior to an active comparator has been found repeatedly with tanezumab.



Safety Profile Being Defined

- Anti-NGF mAbs do not appear to have cardiovascular or gastrointestinal safety liabilities of NSAIDs
- Anti-NGF mAbs do not appear to have abuse liability or undesirable central effects of opioids
- New safety signal has appeared in clinical development: joint events
- Questions to be addressed:
 - What does this safety signal represent?
 - Under what conditions does this signal occur and at what frequency?
 - Is it advisable to undertake further research with these compounds to define better the benefit:risk?



Summary

- Anti-NGF antibodies first new pain treatment agents in years
 - Efficacy in wide spectrum of pain conditions
 - Magnitude of effect superior to existing agents
- Many people in pain with no effective treatments
- Further research is needed and possible
 - Carefully designed studies
 - Well defined populations
 - Informed consent
 - Risk mitigation strategies

Anti-NGF Antibody Clinical Development

Contextual Factors and Policy Implications

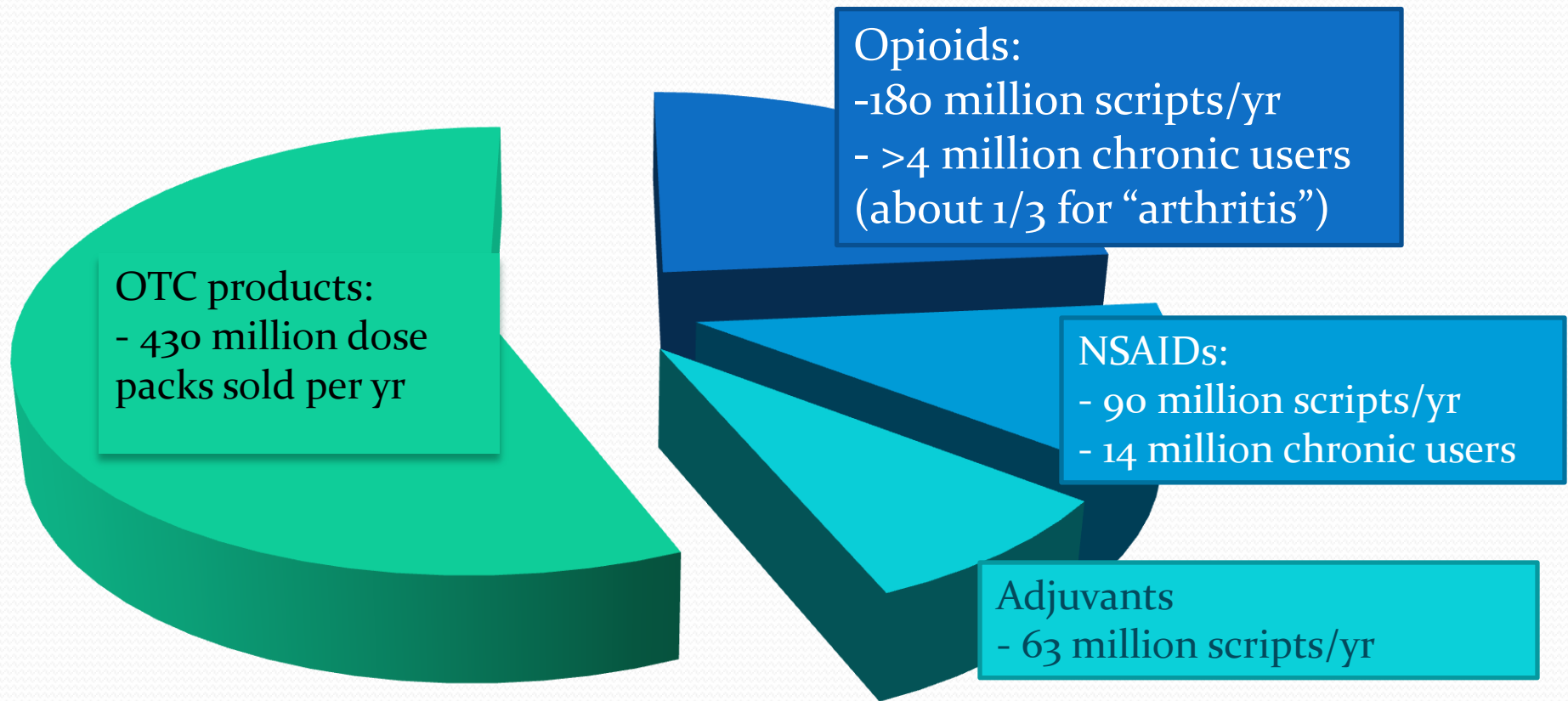
Nathaniel Katz, MD, MS
Analgesic Solutions, Inc.
Tufts University School of Medicine
March 12, 2012

Chronic Pain in America

- National survey of 500,000 US households
- 9% of adult U.S. population estimated to have chronic moderate-to-severe pain (17,482,410)
- 64% of these have either arthritis or back pain
- Most have had it for over 5 years
- 64% of patients with “arthritis” rate their pain as “severe” or “very severe” despite treatment

Roadblocks to Pain Relief, Roper Starch, 1998

US Annual Analgesic Use



ACPM, 2011; IMS, 2005; Laine 2002; Parsells Kelly 2008

Risks of opioids

- Patients on long-term opioid therapy have a 0.2-1.8% risk of overdose per year.
- About 12,000 deaths in the US per year from prescription opioids (2/day in MA)
- About 5% of primary care patients prescribed hydrocodone will develop abuse or addiction
- 1.7 million prescription opioid addicts in the US
- The majority of patients on long-term opioid therapy develop clinically significant endocrinopathy

Risks of NSAIDs

- Thousands of deaths per year from NSAID-associated GI bleeds
- Approximately 1-2% of regular NSAID users will develop serious GI adverse events
- Over 80% have no warning
- NSAIDs double the risk of CHF admissions and increase risk of recurrent MI and death in patients with prior MI
- NSAIDs double risk of hospitalization for ARF

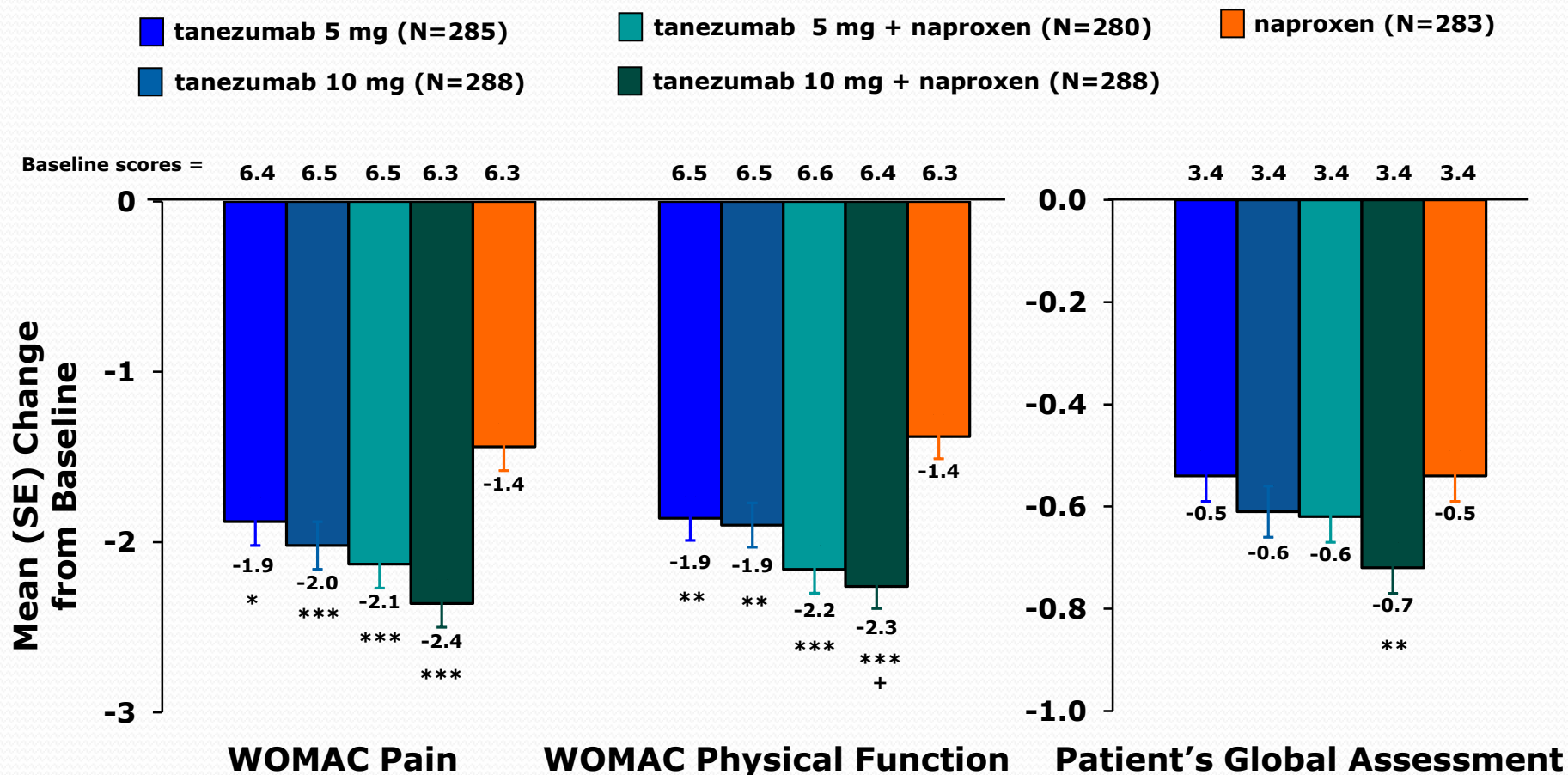


Can we do better?

A personal career in analgesic drug development

- NMDA antagonists
- Glycine antagonists
- Opioid-NMDA combinations
- Ultra-low-dose antagonists
- Vanilloid-receptor antagonists
- NK-1 antagonists
- N-Ca Channel Blockers
- GABA agonists

Figure 21. WOMAC Pain and Physical Function Subscales and Patient's Global Assessment of Osteoarthritis: Change from Baseline to Week 16 in Study 1025 – Naproxen Cohort



*p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001 versus naproxen

+p ≤ 0.05; ++p ≤ 0.01; +++p ≤ 0.001 vs. tanezumab 10 mg

Study 1025; Week 16; ITT, BOCF; naproxen dose = 500 mg BID

Risks of tanezumab monotherapy vs. comparators (NSAIDs/opioids)

	Placebo	Comparators	Tanezumab monotherapy
AE dropout (%)	2.8	7.9	7.0
SAE/1000 pt-yrs	80	107	110
All TJR/1000 pt-yrs	32	42	44
RPOA/1000 pt-yrs	0	2	7
Expected RPOA after mitigation (%)	0	.2	.2

Options

- Continue with cautious development
- Study only risk-free medications
- Only accept risks for “serious diseases”
- Accept our current treatment options
- Wait for something better to come along



Primum non nocere

Beneficence

