Tanezumab

Monoclonal Antibody Against Nerve Growth Factor

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Senior Vice President, Medicine Team Lead
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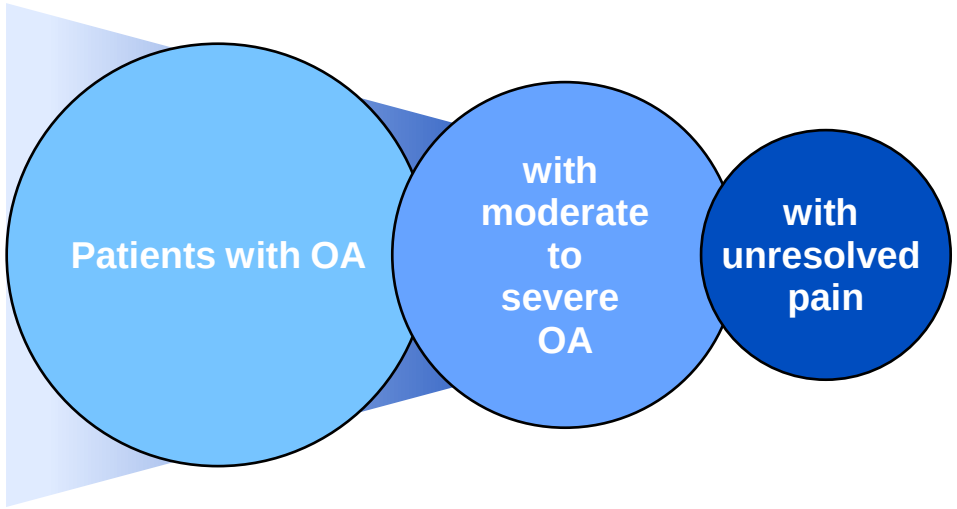
FDA Advisory Committee Meeting
March 24, 2021

Tanezumab

Addressing Critical Unmet Need in Specific Population of Patients with OA

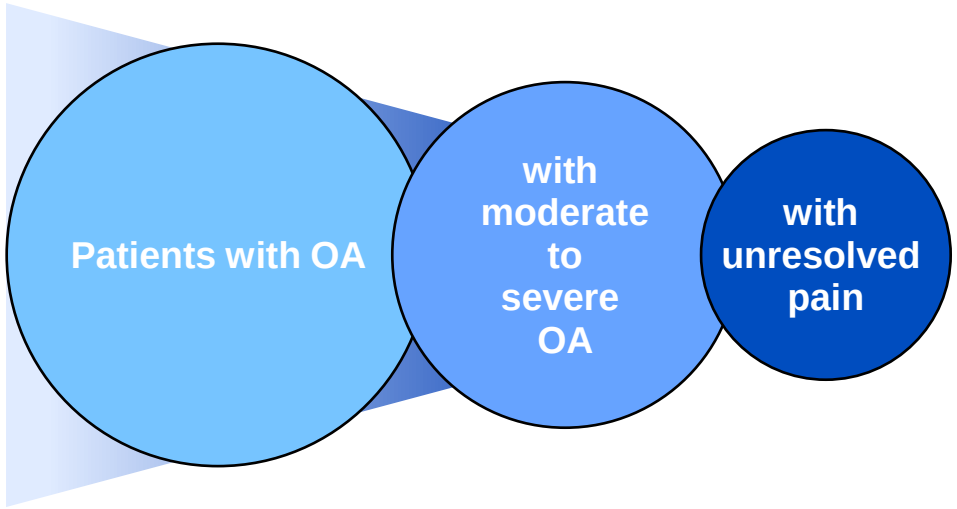


Additional therapeutic options needed for those patients who do not respond or for whom tolerability or safety concerns limit the effectiveness of available treatments

NSAID=Nonsteroidal Anti-Inflammatory Drug; OA=Osteoarthritis

Tanezumab

Addressing Critical Unmet Need in Specific Population of Patients with OA



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Benefits in the Target Population

- Tanezumab is a new approach for treating OA pain and offers the potential for addressing this critical unmet need
- Target population; patients for whom other analgesics are inadequate or not appropriate
  - Clinically meaningful improvement in pain and function
- Mechanism of action is distinct from NSAIDs and opioids
  - Tanezumab may also be of benefit in patients in whom NSAIDs or opioids are not appropriate consistent with our target population

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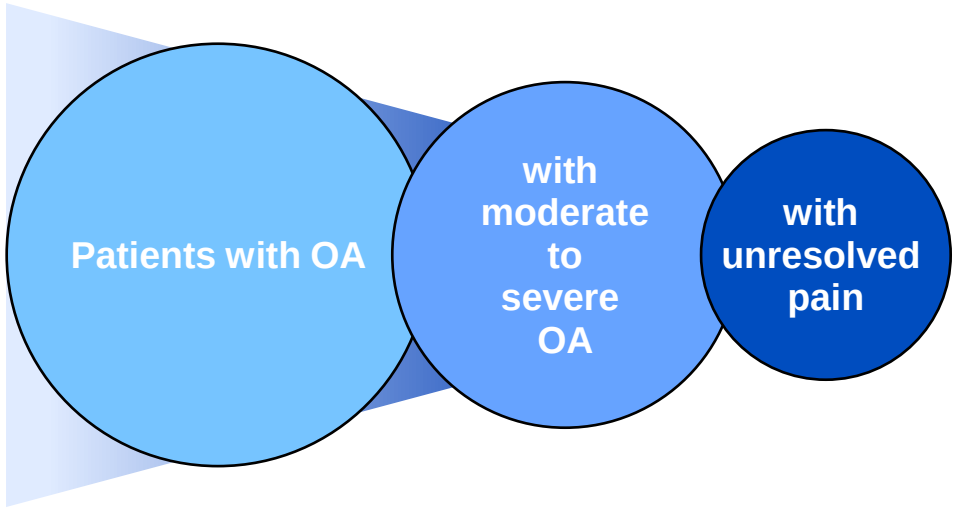
Addressing Critical Unmet Need in Specific Population of Patients with OA



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Risks in the Target Population

- Tanezumab is associated with one serious risk; rapidly progressive osteoarthritis that may necessitate a total joint replacement
- Risk of joint safety events with tanezumab is outweighed by the risks of NSAIDs and opioids
  - Acceptable in context of the unmet medical need of target population and benefits of tanezumab therapy

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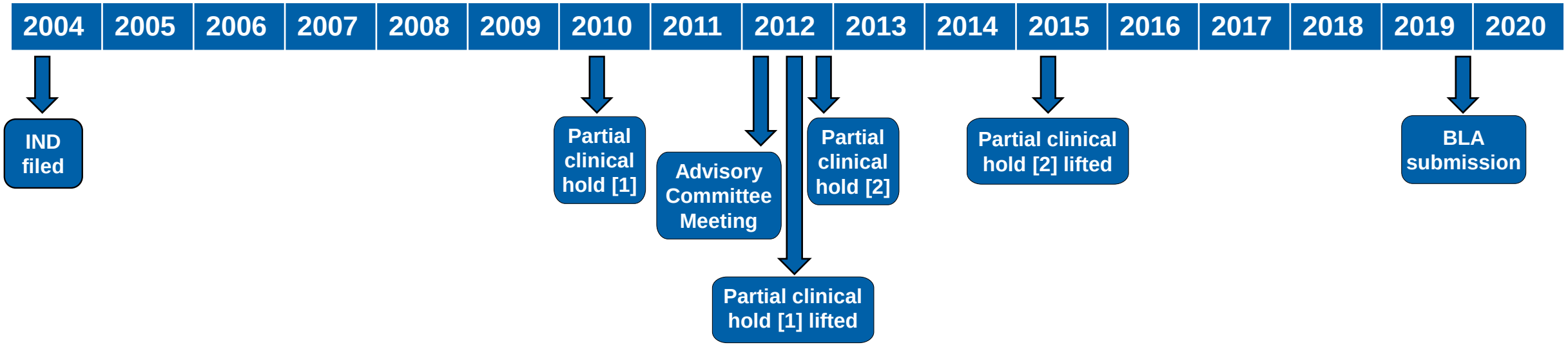
Rapidly Progressive OA

- Rapidly progressive or destructive OA is not a unique term to describe joint damage with tanezumab or other NGF inhibitors
- Idiopathic rapidly progressive OA first reported over 50 years ago
  - Parallel investigations identified “analgesic hip” with NSAIDs; radiologic and clinical profile consistent with idiopathic rapidly progressive OA
- Our program established that analgesic arthropathy manifested as rapidly progressive OA is a risk for both tanezumab and NSAIDs – but more so for tanezumab
  - >50,000 knee and hip radiographs, >3000 patients with advanced structural disease, up to 56 weeks of treatment, and 24 weeks of additional follow-up
- The interesting point is that two very different pain treatment mechanisms can lead to same joint outcome

NGF=Nerve Growth Factor

Clinical Development of Tanezumab for OA



BLA=Biologics License Application; IND=Investigational New Drug; IV=Intravenous; SC=Subcutaneous

Clinical Development of Tanezumab for OA

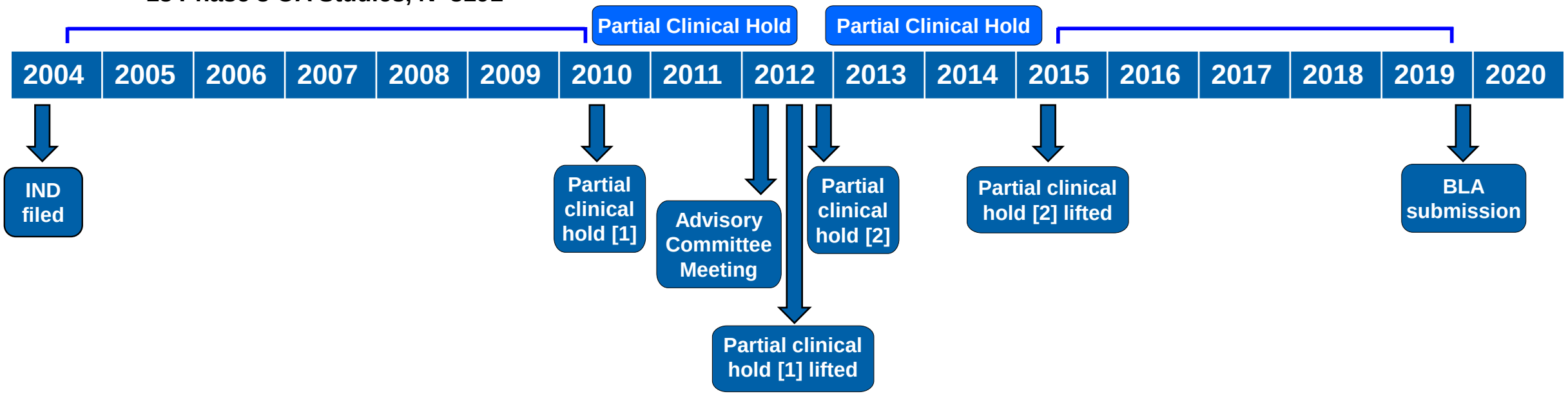
Pre-2015 OA Development (IV + SC)

4 Phase 1 and 2 OA Studies, N=929

13 Phase 3 OA Studies, N=8191

Post-2015 OA Development (SC)

3 Phase 3 OA Studies, N=4541



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Subject	Presenter
Introduction	**Kenneth Verburg, PhD,** *Senior Vice President, Medicine Team Lead Global Product Development, Internal Medicine, Pfizer Inc.*
Update on Osteoarthritis: Current Understanding, Future Needs	**Thomas J. Schnitzer, MD, PhD,** *Professor of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL*
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Safety of Tanezumab in Osteoarthritis	**Christine West, PhD,** *Senior Director, Global Clinical Lead Global Product Development, Internal Medicine, Pfizer Inc.*
Post-Marketing Risk Management	**Anne Hickman, DVM, PhD,** *Senior Director, Global Safety and Risk Management Lead, Worldwide Research and Development, Pfizer Inc.*
Utility of Tanezumab in Clinical Practice and Patient Selection and Monitoring Considerations	**Alan Kivitz, MD, FACR,** *President, Altoona Center for Clinical Research & Altoona Arthritis and Osteoporosis Center*
Benefit-Risk and Conclusions	**Kenneth Verburg, PhD,** *Senior Vice President, Medicine Team Lead Global Product Development, Internal Medicine, Pfizer Inc.*

Presentation Objectives

- To demonstrate that the benefit-risk balance of tanezumab 2.5 mg SC is positive in the context of
  - Unmet medical need
  - Efficacy and safety profile
  - Intended patient population
  - Risk management plan
- To establish that the weight of evidence supports approval of tanezumab 2.5 mg SC for OA

mg=milligrams

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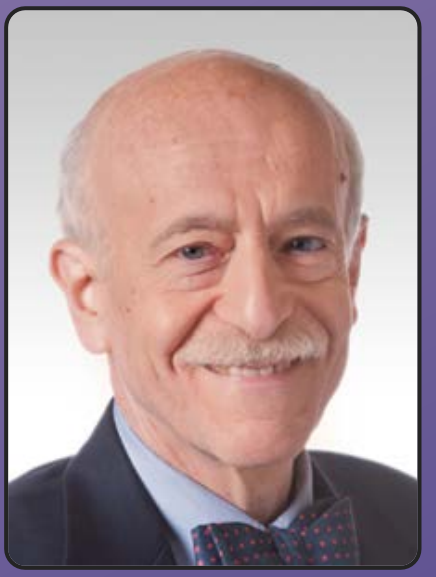


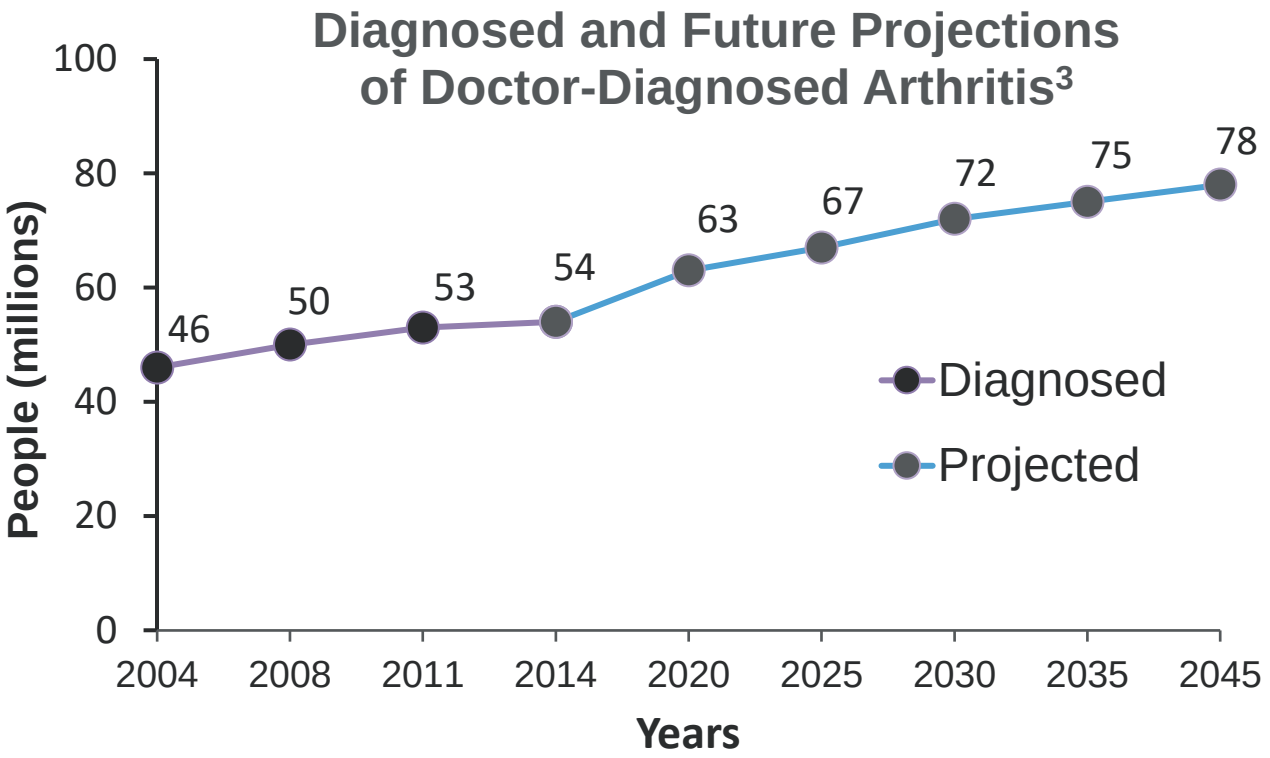
Update on Osteoarthritis: Current Understanding, Future Needs

Thomas J. Schnitzer, MD, PhD
Professor of Medicine
Northwestern University Feinberg School of Medicine, Chicago, IL

MA-11

Osteoarthritis is a Prevalent Disease

- OA: most common form of arthritis
  - Characterized by joint pain, activity limitation, physical disability, reduced health-related QOL and excess mortality
- 32.5 M people in US – 1 in 7 US adults[1,2]
  - Prevalence expected to steadily increase
  - 43% of people >65 years have OA
  - Half of people with OA (18.7 M) of working age
  - Disproportionately affects women overall
  - Knee is the most commonly affected joint



Data from: National Health Interview Survey 2013-2015

1. https://www.cdc.gov/arthritis/basics/osteoarthritis.htm. Accessed 12/29/2020.
2. United States Bone and Joint Initiative: The Burden of Musculoskeletal Diseases in the United States (BMUS), Fourth Edition, 2020. Rosemont, IL. Available at http://www.boneandjointburden.org. Accessed 12/29/2020.

QOL=Quality of Life

3. https://www.cdc.gov/arthritis/data_statistics/national-statistics.html. Accessed 12/29/2020

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Osteoarthritis: Burden on the Individual

- Pain: most prominent clinical presentation of OA
  - 25-50% of OA population has pain levels of ≥4/10 despite treatment[1]
  - One third with 5 or more comorbidities[2]
- Major impact on functional ability
  - 80% with OA have limitations in movement; 25% cannot perform their major ADLs[3]
  - Hip and knee OA - 11th highest contributor to global disability[4]
  - 3rd most rapidly rising cause of YLD just behind diabetes and dementia[5]
- Diminished quality of life and increased mortality
  - QALY lost - 1.9 in OA non-obese; 3.5 in obese, per person[6]
  - Increase in all cause mortality: standardized mortality ratio of 1.55 [95% CI 1.41, 1.70] increase in CV death, associated with disability, pain[7]

1. Collins JE, Osteoarthr Cart 2014; 22:622-630.
2. https://oaaction.unc.edu/oa-module/comorbidities-and-co-occuring-symptoms Accessed 12/29/2020.
3. Neogi T, Osteoarthr Cart 2013; 21:1145-1153.
4. Cross M, Ann Rheum Dis 2013 ; 73:1323-1330.
5. OARSI White Paper_OA Serious Disease, https://oarsi.org/sites/default/files/docs/2016/oarsi_white_paper_oa_serious_disease_121416_1.pdf1, 2016, Accessed 12/29/2020.
6. Losina E, Ann Int Med 2011; 154:217.
7. Hawker GA, PLOSOne 2014; 9:e91286.

ADL=Activity of Daily Living; CI=Confidence Interval; CV=Cardiovascular; QALY=Quality-Adjusted Life-Year; YLD=Years Lived with Disability

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Osteoarthritis is Costly

- 2nd most costly health condition treated in US hospitals in 2013[1]
  - 10% of all hospital admissions; 4.3% of all hospitalization costs[1,2]
- 23.7 million healthcare visits, 2.4% of all healthcare visits for any cause[2]
- Major economic costs to society
  - Total OA incremental costs: $136.8 billion/year[2]
  - $65B in incremental medical expenditures[2]
- Individual's OA-attributable earning loss $4,247[2]
  - Annual total lost work earnings $71.3 billion[2]

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1. https://www.cdc.gov/arthritis/data_statistics/cost.htm. Assessed 12/29/2020.
2. https://www.boneandjointburden.org/fourth-edition/iiib10/osteoarthritis Accessed 12/29/2020.

Current Approaches to OA Management are Failing

General Consensus Among Professional Societies: ACR, AAOS, OARSI

	Medication Utilization
	Initial[1]
Foundational Elements	
Exercise, weight loss, etc.	
OTC therapies as needed	
Clinician medical management, intra-articular modalities	
NSAIDs – topical and oral	39.5%
Intra-articular modalities	12.9%
Non-opioid centrally-acting drugs (SNRIs, tricyclics)	28.3%
If inadequate response	
Joint replacement surgery	
Opioids	54.8%

1. Hansen RA in Pain Week Live Virtual Conference 2020.
2. Shepman PB in Pain Week Live Virtual Conference 2020.
3. Conaghan PG, Rheumatology 2015, 54: 270–277.
4. Collins JE, Osteoarthr Cart 2014; 22:622-630.

AAOS=American Academy of Orthopaedic Surgeons; ACR=American College of Rheumatology; OAI=Osteoarthritis Initiative; OARSI=Osteoarthritis Research Society International; OTC=Over The Counter; SNRI=Serotonin-Norepinephrine Reuptake Inhibitor; SORT=Study of Osteoarthritis Real World Therapies

Current Approaches to OA Management are Failing

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	Medication Utilization	
	Initial[1]	*Ongoing*[2]
Foundational Elements		
Exercise, weight loss, etc.		
OTC therapies as needed		
Clinician medical management, intra-articular modalities		
NSAIDs – topical and oral	39.5%	20.6%
Intra-articular modalities	12.9%	
Non-opioid centrally-acting drugs (SNRIs, tricyclics)	28.3%	3.3%
If inadequate response		
Joint replacement surgery		
Opioids	54.8%	29.1%

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Current Approaches to OA Management are Failing

General Consensus Among Professional Societies: ACR, AAOS, OARSI

	Medication Utilization		Inadequate Pain Relief
	Initial[1]	*Ongoing*[2]	
Foundational Elements			**SORT Data**[3]
Exercise, weight loss, etc.			≥4/10: 54%
OTC therapies as needed			>5/10: 35%
Clinician medical management, intra-articular modalities			**OAI Data**[4]
NSAIDs – topical and oral	39.5%	20.6%	≥4/10: 23%
Intra-articular modalities	12.9%		
Non-opioid centrally-acting drugs (SNRIs, tricyclics)	28.3%	3.3%	
If inadequate response			
Joint replacement surgery			
Opioids	54.8%	29.1%	

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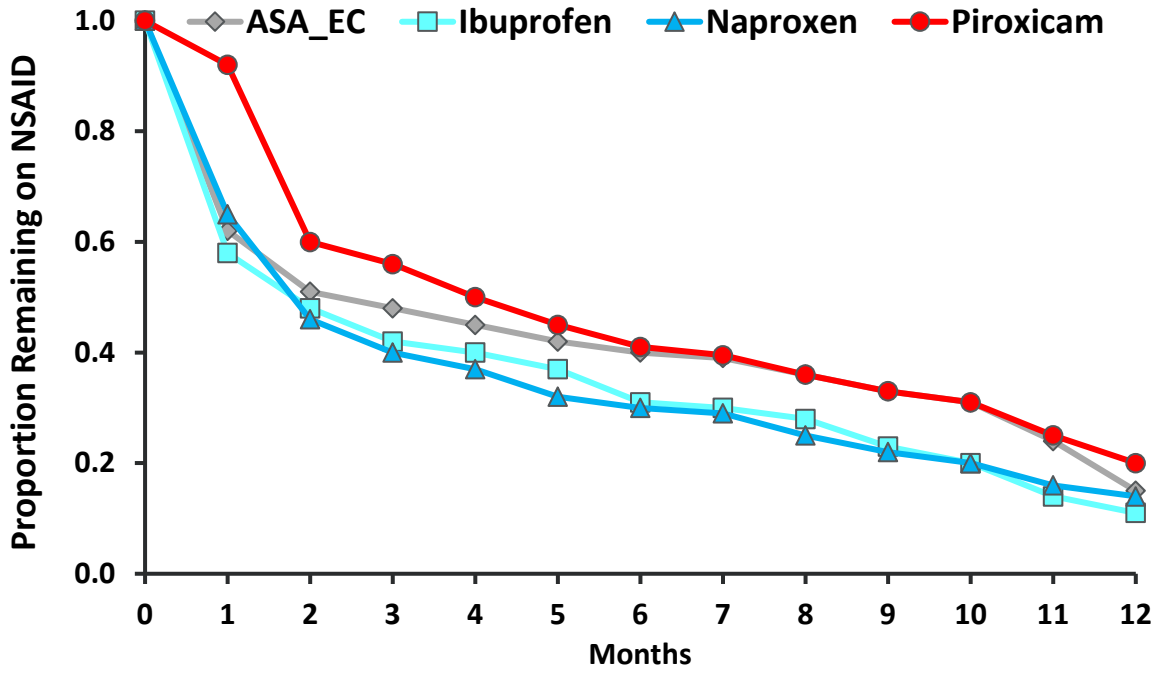
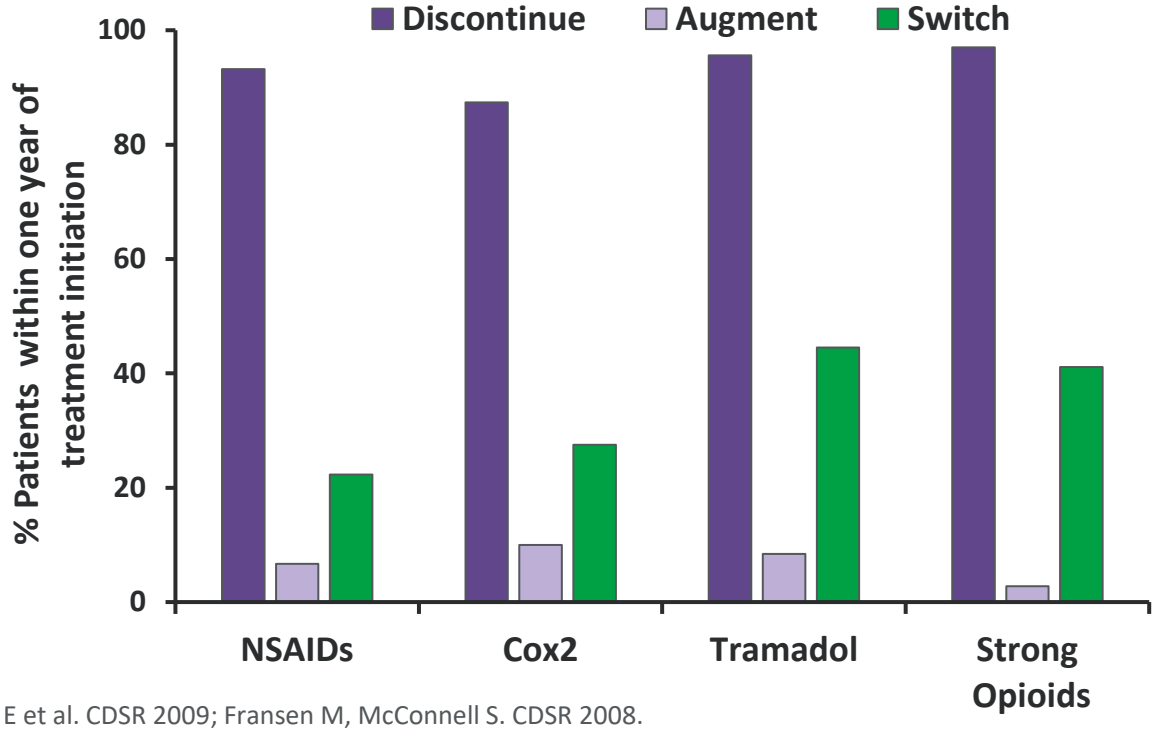
NSAIDs and Opioids: Short-Term Effectiveness Discontinuation and Switching Common

- NSAIDs, weak opioids and strong opioids show similar efficacy in OA in the short term[1,2]; lack of evidence of long-term efficacy with opioids
- Treatment discontinuation, switching suggest lack of efficacy and/or lack of tolerability[3,4]





1. Towheed T, CDSR 2006; Zhang W et al. OAC 2007;15:981-1000.; Nuesch E et al. CDSR 2009; Fransen M, McConnell S. CDSR 2008.
2. Smith SR OAC 2016:24:962.
3. Scholes D, J. Rheum.1995;22:708-12.
4. Gore M, Clin Ther 2011; 33:1914-1931.

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NSAID Safety Limitations

NSAID boxed warnings for CV and GI safety[1]

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.

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.

These confirmed in patient-level meta-analysis by Bhala et al 2013[2]

1. https://www.fdanews.com/articles/73674-fda-releases-black-box-template-for-nsaids#:~:text=The%20black%2Dbox%20risk%20information,increase%20with%20duration%20of%20use. Accessed 03/05/22021
2. Bhala N, Lancet. 2013; 382:769-79.

NSAID Safety Limitations

- Significant proportion of OA population at risk taking NSAIDs
  - Elderly, metabolic syndrome, multiple comorbidities including CV disease
- Congestive heart failure: 10.5% of OA patients from integrated health system[1]
  - OR 2.1 for CHF hospitalization with use of NSAID in week prior
  - OR 10.5 for first admission for CHF if had prior history of heart disease[2]
- Renal insufficiency: 13.1% of OA patients with mod-severe renal insufficiency[1]
  - "Nonsteroidal anti-inflammatory drugs (NSAIDs) have long been regarded as dangerous for use in patients with CKD because of their risk for nephrotoxicity"[3]
  - ↑ OR 1.6-2.1 for AKI[4]; exacerbation of chronic insufficiency
- Using anticoagulants

1. Graham J,. ACR Convergence 2020.
2. Page J, Arch Int Med 2000; 27:777.
3. Baker M, AJKD 2020; 76:546.
4. Cooper C, Drugs Aging 2019; 36:S15-24.
AKI=Acute Kidney Injury; CHF=Congestive Heart Failure; CKD=Chronic Kidney Disease

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Opioids: Drug Class of Last Resort

- Only short-term use if used at all
  - The chances of chronic use begin to increase after the third day supplied and rise rapidly thereafter[1]
- Poorly tolerated[2]

	Prevalence Opioid Treated	NNH
Constipation	13%	9
Nausea	30%	5
Vomiting	13%	9
Dizziness	20%	7
Somnolence	18%	8

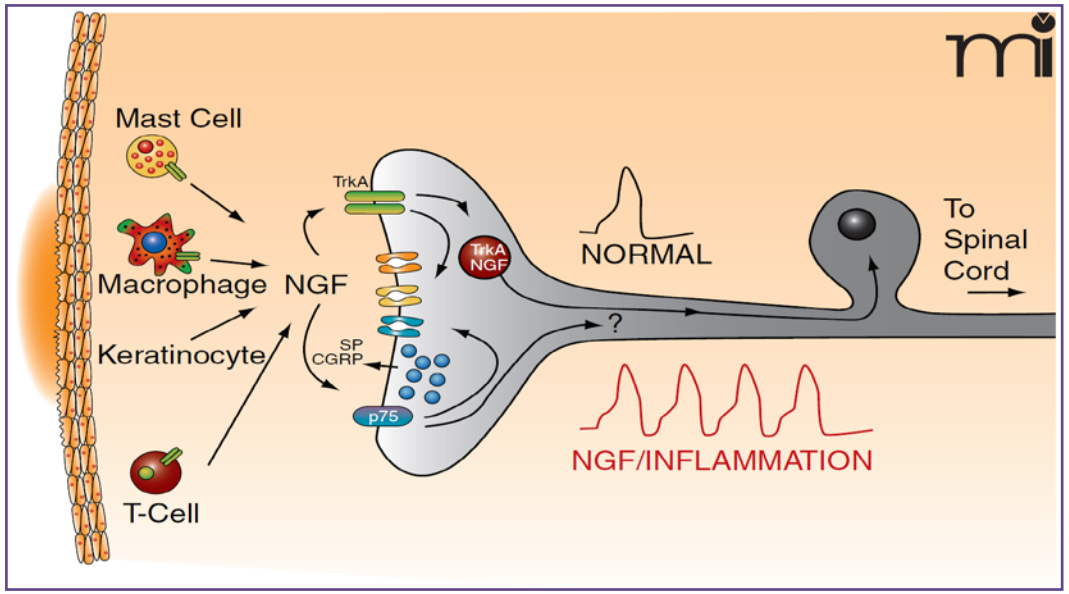
- Dependence, addiction and abuse
  - Patients are unlikely to discontinue opioids after they have received them for 90 days[3]
  - Dependence or abuse in pain patients following opioid treatment 4.7% (95% CI: 2.1-10.4%)[4]
  - Opioid overdose deaths, 2019: >50,000; >12,000 due to prescription opioids[5]

1. Shah A. MMWR 2017: 66:10.
2. Avouac Osteoarthr Cart 2007;15:957-965.
3. Gu GP. MMWR 2017:66:26.
4. Higgens C, BJAnest 2018:1335-1344.
5. CDC per https://www.nytimes.com/interactive/2020/07/15/upshot/drug-overdose-deaths.html

Long Search for Better Analgesics

- Late 20th Century: Neurobiology[1]
  - Multiple Targets Identified
    - NMDA receptor blockers
    - NK-1 receptor blockers
    - FAAH inhibitors
    - NGF 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
  - Genetic Disorders of Pain[2]

- Key evidence for NGF[3]
  - NGF causes pain in humans and animals
  - NGF is locally up-regulated in painful conditions
  - NGF inhibition reverses pain in many animal models



From Nicol GD, Vasko MR. Unraveling the story of NGF-mediated sensitization of nociceptive sensory neurons: ON or OFF the Trks? Mol Interv. 2007 Feb;7(1):26-41

1. Sexton J. Ann Rev Pharmacol Toxidcol 2018, 58:123.
2. Bennett DLH. Lancet Neurol 2014; 13:587-599.
3. Schmelz M. Pain. 2019; 160: 2210–2220.

FAAH=Fatty Acid Amide Hydrolase; NK-1=Neurokinin-1; NMDA=N-Methyl-D-Aspartate

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Summary

- OA is a disease with serious impact
  - Pain and functional limitations negatively affect individuals and society
- Existing therapies have important limitations
- Effective, safe additional treatment options are needed

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Tanezumab

Efficacy of Tanezumab in Osteoarthritis

Kenneth Verburg, PhD
Senior Vice President, Medicine Team Lead
Global Product Development, Internal Medicine
Pfizer Inc.

Efficacy Presentation

- Pre-2015 Phase 3 OA Studies (IV)
  - 2.5 mg, 5 mg and 10 mg vs placebo
  - Maintenance of effect

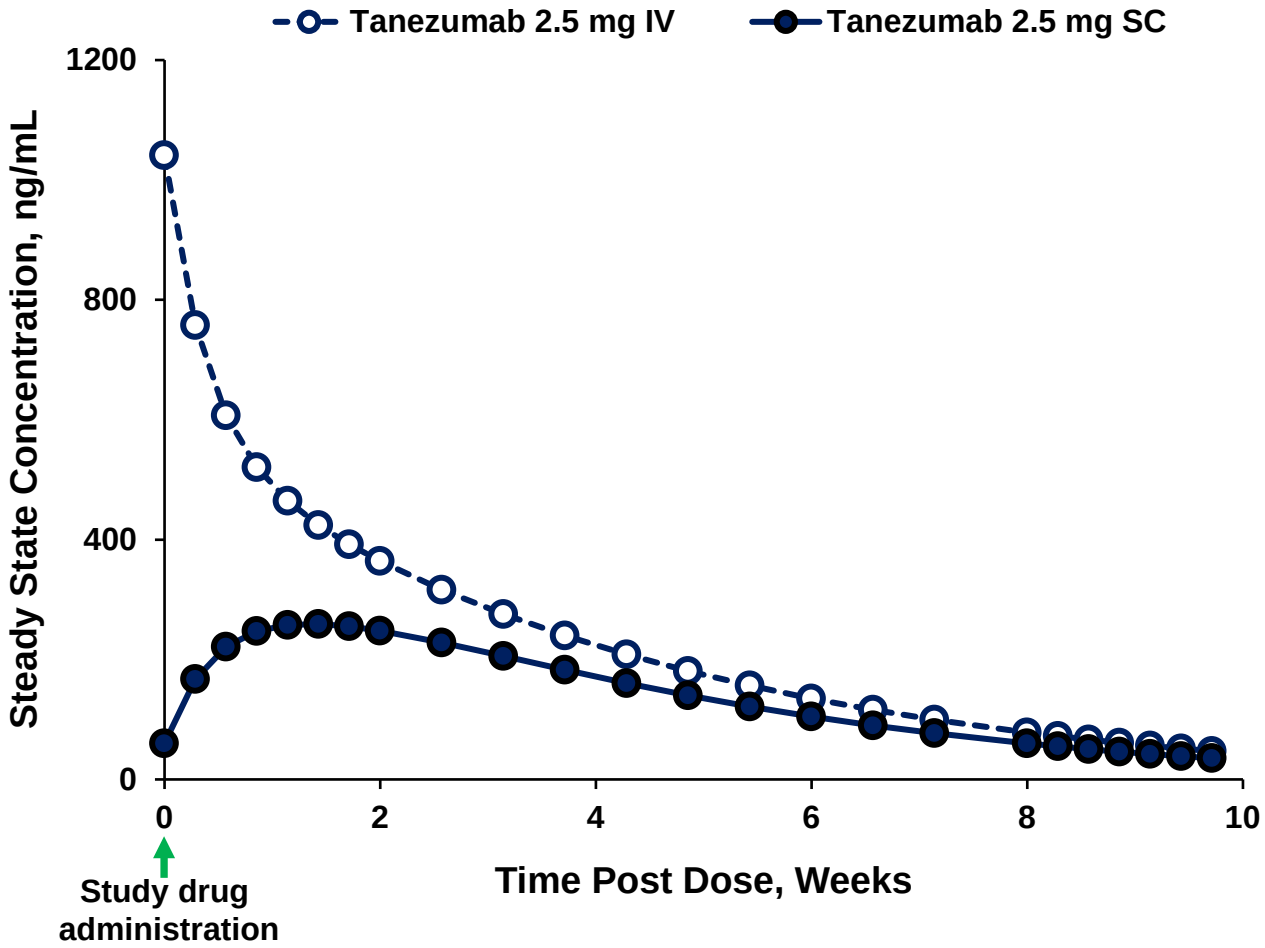
- Post-2015 Phase 3 OA Studies (SC)
  - 2.5 and 5 mg in patients for whom the use of other analgesics is ineffective or not appropriate
  - Sustained efficacy over 8-week dose intervals
  - Clinically important outcomes

Efficacy Profile of Tanezumab in OA

- Tanezumab 2.5 administered SC every 8 weeks provides consistent and clinically important improvement in pain and function
- Efficacy established in patients for whom use of other analgesics is ineffective or not appropriate
  - Similar efficacy across demographic, disease severity, and geographic subgroups
  - No meaningful efficacy differences between tanezumab 2.5 and 5 mg
- Efficacy of tanezumab 2.5 mg durable over long-term treatment

Tanezumab Pharmacokinetics

Tanezumab 2.5 mg; IV vs SC Administration



Parameter	Tanezumab 2.5 mg			
	IV		SC	
	Male	Female	Male	Female
C_{max}, ng/mL	842	962	216	214
$C_{max,ss}$, ng/mL	911	1040	257	259
t_{max}, day	–	–	9.70	10.40
$T_{max,ss}$, day	–	–	8.91	9.40
$t_{1/2,eff}$, day	18.9	19.4	21.4	22.4
C_{min}, ng/mL	57.5	65.0	45.8	50.1
$C_{min,ss}$, ng/mL	68.7	78.5	54.5	60.2
C_{avg}, ng/mL	219	242	131	135
$C_{avg,ss}$, ng/mL	252	279	156	163
R_{Cavg}	1.15	1.16	1.20	1.21

IV and SC Comparison of typical patient profile over 8-week dosing interval (F=0.62) based on final Population Pharmacokinetic Model
N=4423 patients, >18,000 concentrations measurements over 2.5 to 20 mg dose range for up to 7 administrations, with 47.5% receiving SC dose
Cavg=average Concentration; Cmax=maximum Concentration; Cmin=minimum Concentration; ng/mL=nanograms per milliliter; Rcavg=accumulation ratio of the average concentration from single dose to steady state; ss=steady state; t1/2,eff=effective half-life; tmax=time to maximum concentration

Tanezumab vs Placebo in OA

Consistent Improvement with All Doses; Pre-2015 Studies 1011 and 1014

- Tanezumab 2.5, 5 and 10 mg administered by IV injection at 8-week intervals
- Patient population: moderate to severe OA; inadequate/unable/unwilling to take non-opioid pain medications or candidate for invasive intervention
- 3 co-primary endpoints: WOMAC Pain, WOMAC Physical Function and Patient's Global Assessment of OA

Multiple imputation; ✓ indicates p-value <0.05 vs placebo; *p≤0.05; **p≤0.01; ***p≤0.001 vs placebo
LS=Least Squares; NRS=Numerical Rating Scale; SE=Standard Error
WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index; standardized questionnaires targeting pain, function, and joint stiffness efficacy domains in knee or hip OA
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	Pain	Physical Function	Global Assessment of OA
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	✓	✓	✓

Multiple imputation; ✓ indicates p-value <0.05 vs placebo; *p≤0.05; **p≤0.01; ***p≤0.001 vs placebo
LS=Least Squares; NRS=Numerical Rating Scale; SE=Standard Error
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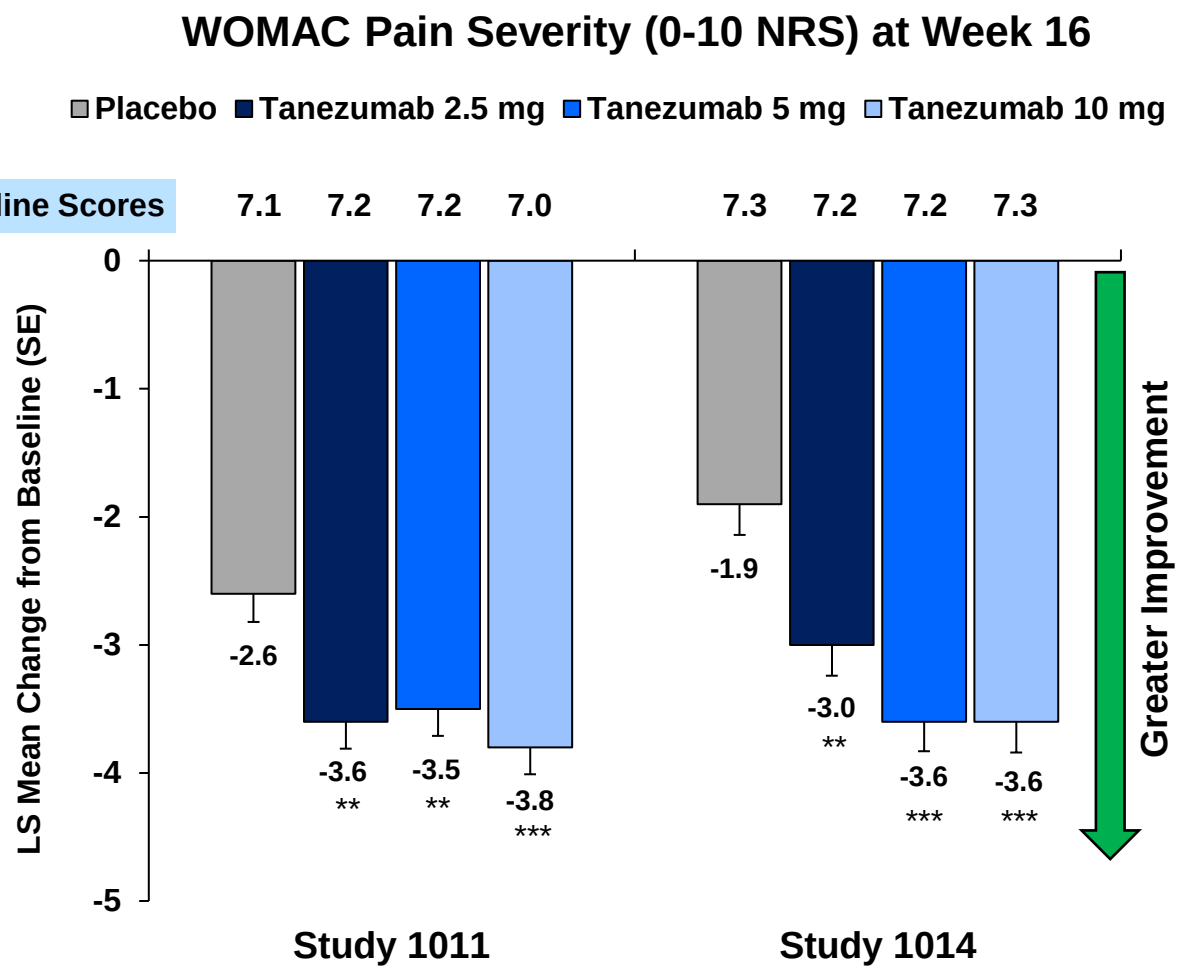
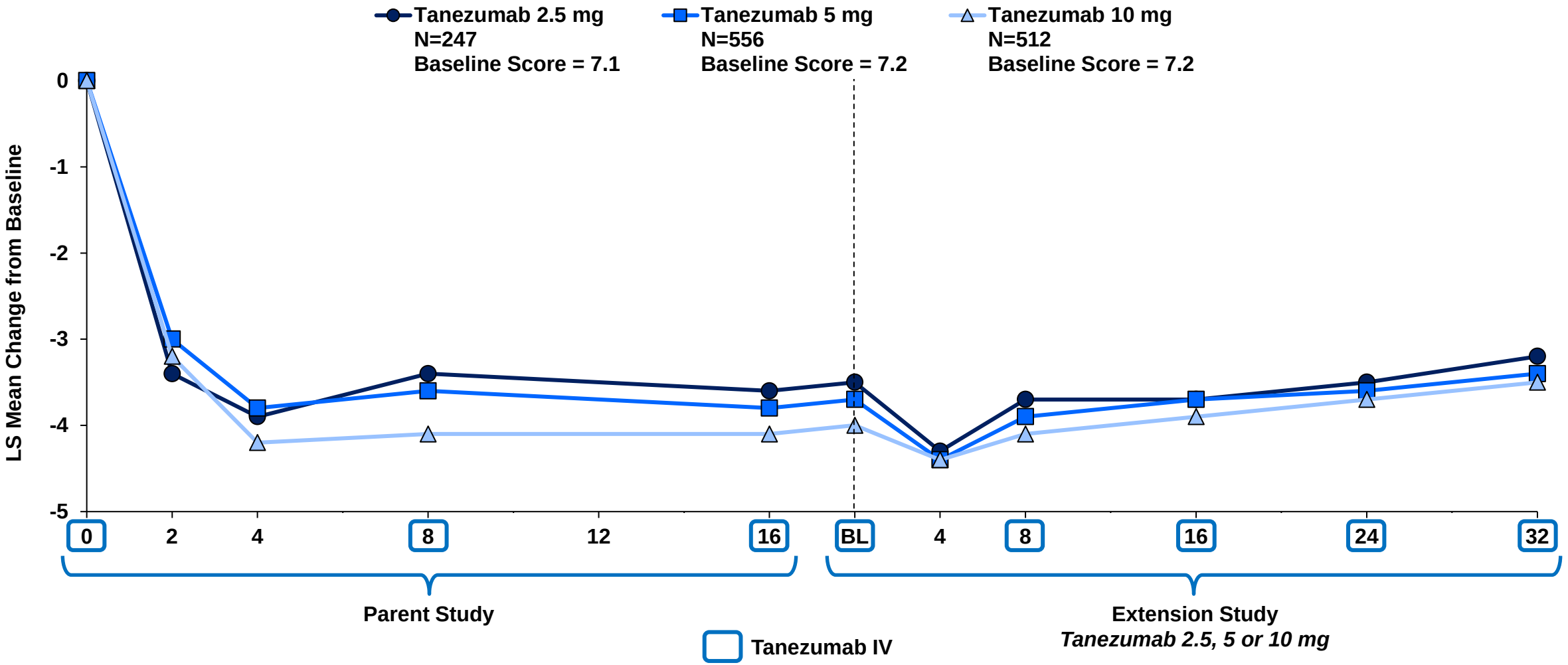
	Pain	Physical Function	Global Assessment of OA
Study 1011: Knee OA			
Tanezumab 2.5 mg	✓	✓	✓
Tanezumab 5 mg	✓	✓	✓
Tanezumab 10 mg	✓	✓	✓
Study 1014: Hip OA			
Tanezumab 2.5 mg	✓	✓	✓
Tanezumab 5 mg	✓	✓	✓
Tanezumab 10 mg	✓	✓	✓



Multiple imputation; ✓ indicates p-value <0.05 vs placebo; *p≤0.05; **p≤0.01; ***p≤0.001 vs placebo
LS=Least Squares; NRS=Numerical Rating Scale; SE=Standard Error
WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index; standardized questionnaires targeting pain, function, and joint stiffness efficacy domains in knee or hip OA
© 1996 Nicholas Bellamy. WOMAC® is a registered trademark of Nicholas Bellamy (CDN, EU, USA)

WOMAC Pain: Long-Term Efficacy

Double-Blind Parent Study → Study 1016 (All Tanezumab Doses)



BL=Baseline

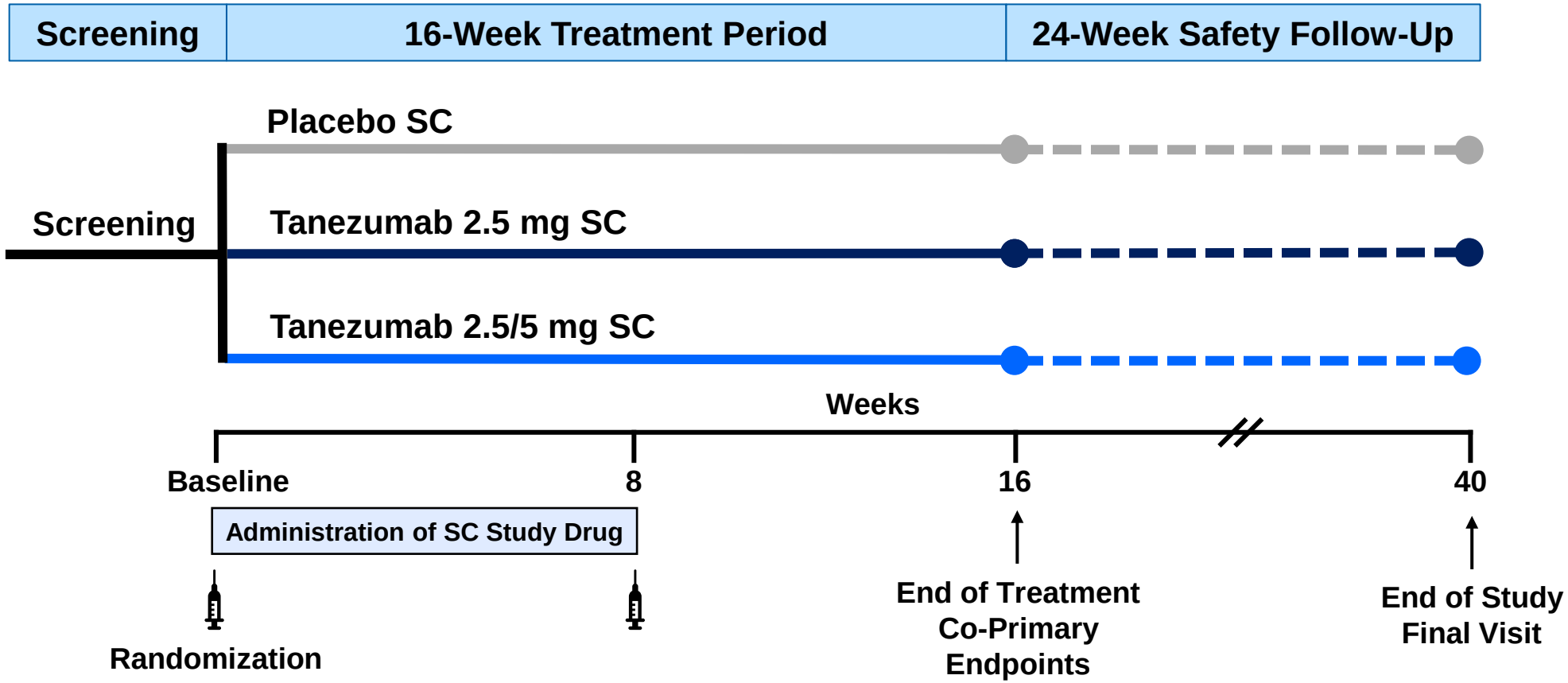
Efficacy Presentation

- Pre-2015 Phase 3 OA Studies (IV)
  - 2.5 mg, 5 mg and 10 mg vs placebo
  - Maintenance of effect

- **Post-2015 Phase 3 OA Studies (SC)**
  - 2.5 and 5 mg in patients for whom the use of other analgesics is ineffective or not appropriate
  - Sustained efficacy over 8-week dose intervals
  - Clinically important outcomes

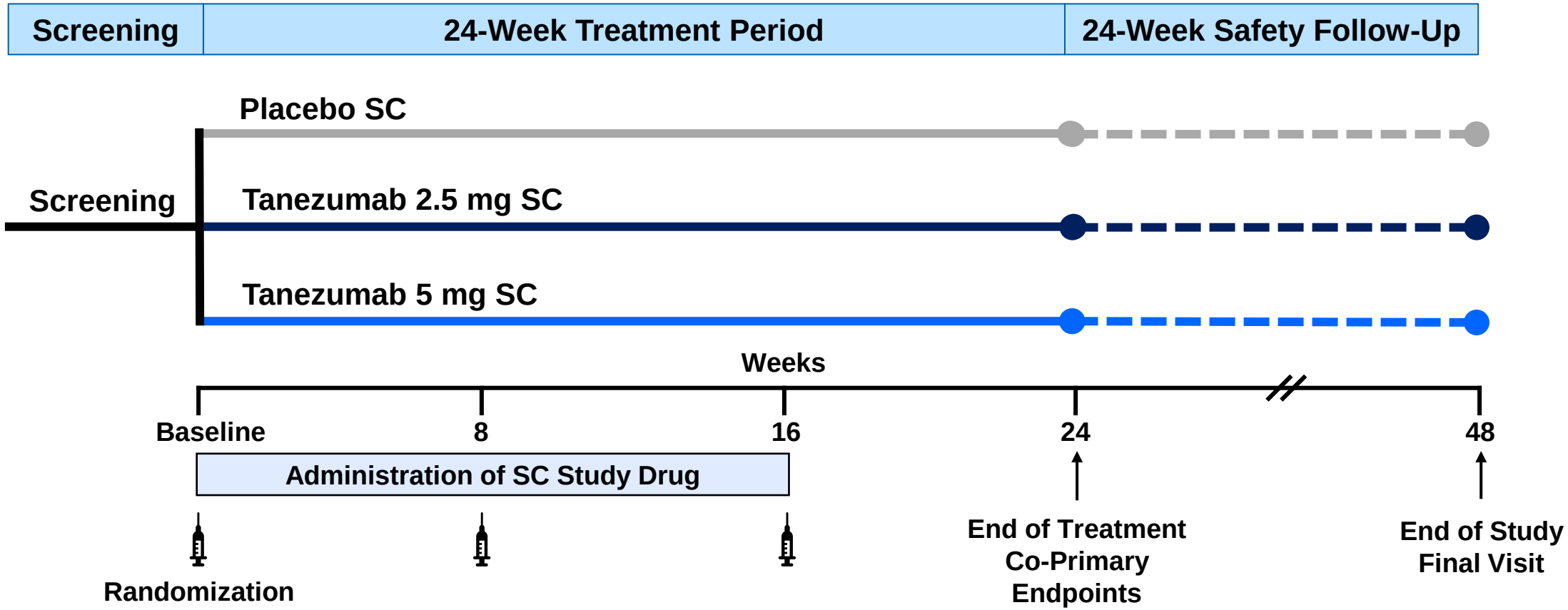
Study Design

Post-2015 Placebo-Controlled SC OA Study 1056



Study Design

Post-2015 Placebo-Controlled SC OA Study 1057



Demographics and Baseline OA Disease Characteristics

Moderate to Severe OA Disease with Multiple Joint Involvement

Post-2015 Placebo-Controlled OA Studies 1056 and 1057 Pooled
N=1545

Demographics Consistent with OA Population
▪ Mean age: 63.1 years
▪ Patients ≥65 years: 45.3%
▪ Patients ≥75 years: 11.6%
▪ Female: 67.3%
▪ Race: White = 80.5%; Black = 9.9%; Asian = 8.5%
▪ Ethnicity: Hispanic or Latino = 10.8%

a. WOMAC Pain ≥7, WOMAC Physical Function ≥7, and PGA-OA, poor or very poor
b. ≥2 knee or hip joints KL grade 2 or greater
KL=Kellgren-Lawrence; PGA-OA=Patient's Global Assessment of Osteoarthritis; SD=Standard Deviation

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Moderate to Severe OA; ~25% Severe Symptoms	
Baseline Symptom Severity, mean (SD)	
WOMAC Pain	6.9 (1.1)
WOMAC Physical Function	7.0 (1.0)
PGA-OA	3.5 (0.6)
Severe Cohort[a], n (%)	
	373 (24.2)

a. WOMAC Pain ≥7, WOMAC Physical Function ≥7, and PGA-OA, poor or very poor
b. ≥2 knee or hip joints KL grade 2 or greater
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WOMAC Physical Function	7.0 (1.0)
PGA-OA	3.5 (0.6)
Severe Cohort[a], n (%)	
	373 (24.2)

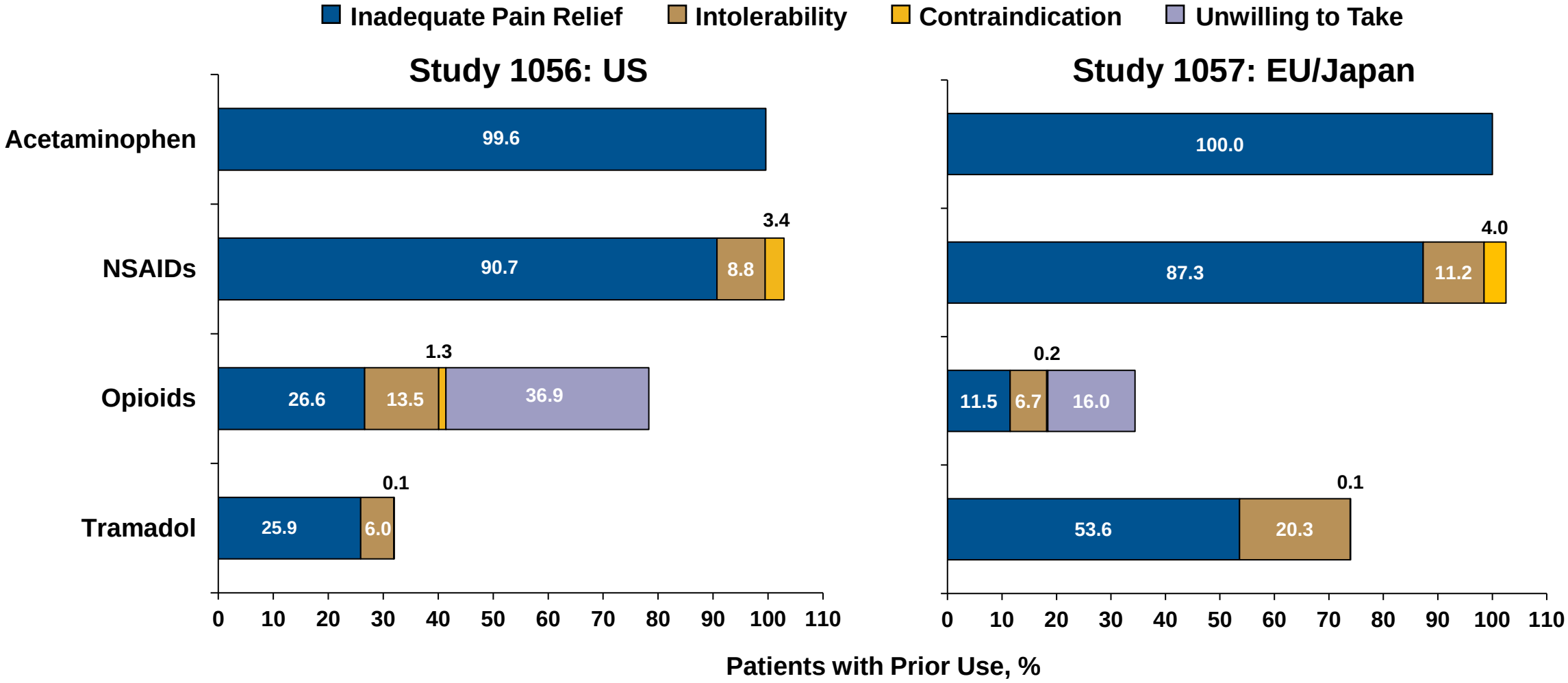
>75% with Advanced OA Disease of Index Joint and Multiple Joints Affected by OA

Duration of OA, years, mean (SD)	
	8.3 (7.7)
Index Joint, n (%)	
Knee	1299 (84.1)
Kellgren-Lawrence Grade of Index Joint, n (%)	
KL Grade 2	350 (22.7)
KL Grade 3	679 (44.0)
KL Grade 4	512 (33.2)
Multiple Joints Affected by OA[b] , n (%)	
	1225 (79.3)

a. WOMAC Pain ≥7, WOMAC Physical Function ≥7, and PGA-OA, poor or very poor
b. ≥2 knee or hip joints KL grade 2 or greater
KL=Kellgren-Lawrence; PGA-OA=Patient's Global Assessment of Osteoarthritis; SD=Standard Deviation

History of Treatment Response Prior to Study Entry

Intended Patient Population; "Other Analgesics are Ineffective or Inappropriate"

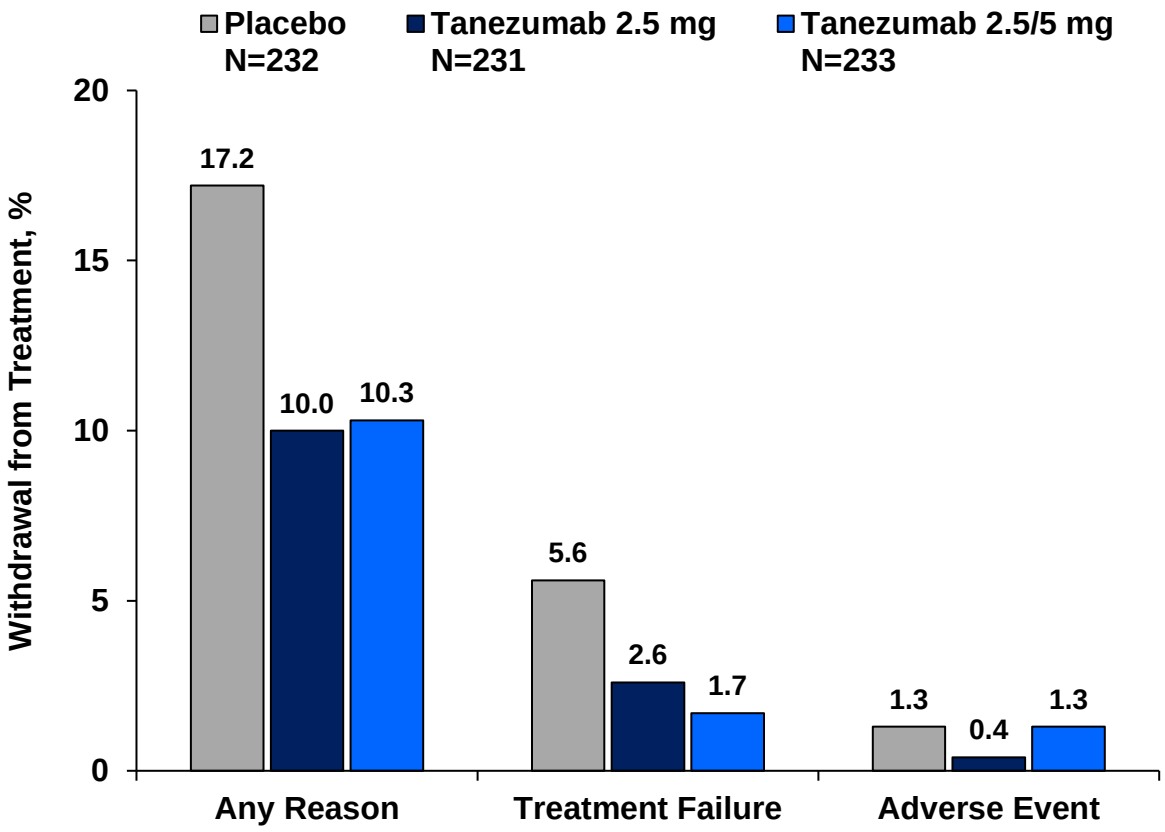


Patients were able to provide more than one reason in an individual class resulting in overall percentages exceeding 100%

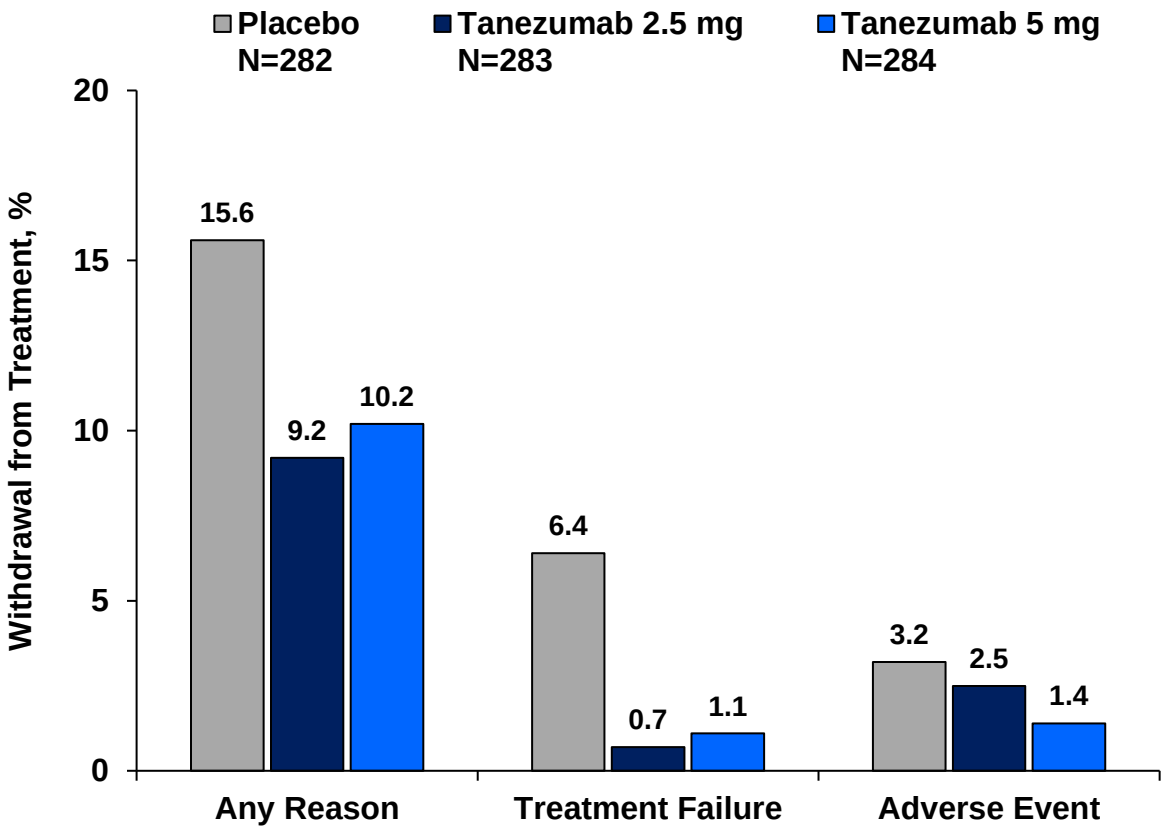
Patient Disposition

Placebo-Controlled Studies 1056 and 1057

Study 1056

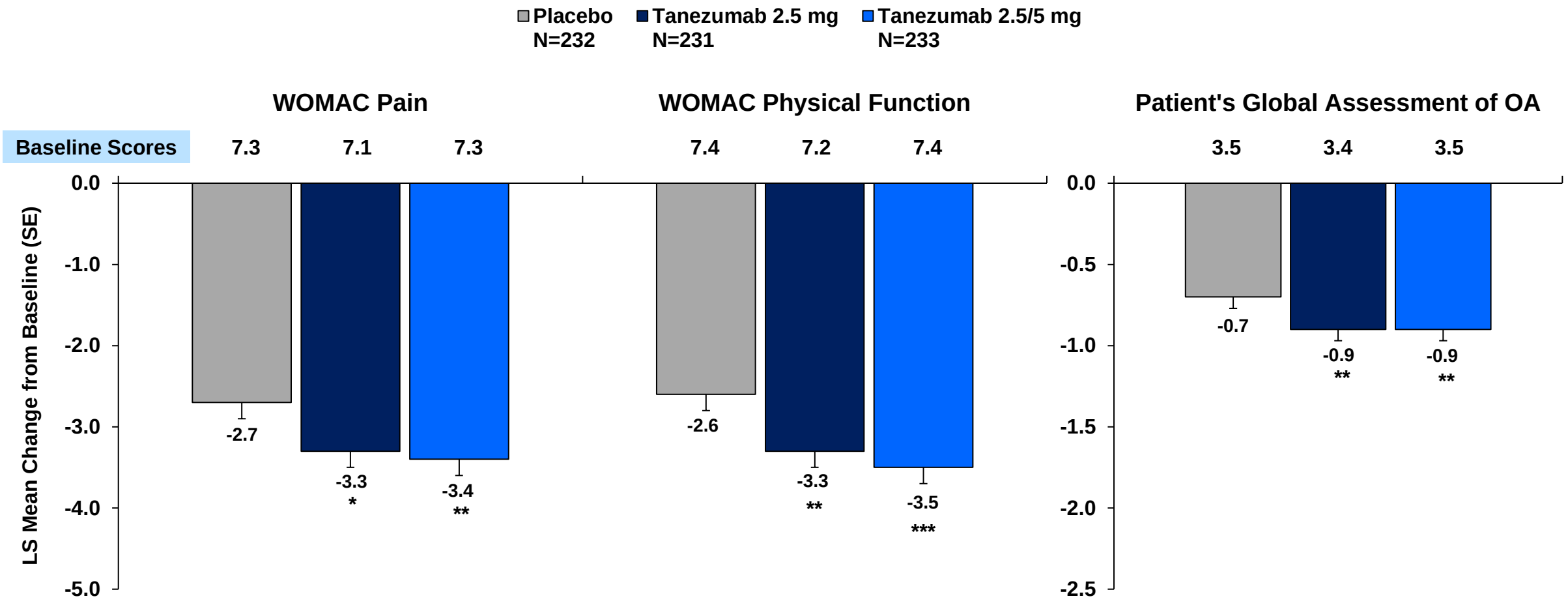


Study 1057



Study 1056: Co-Primary Efficacy Measures

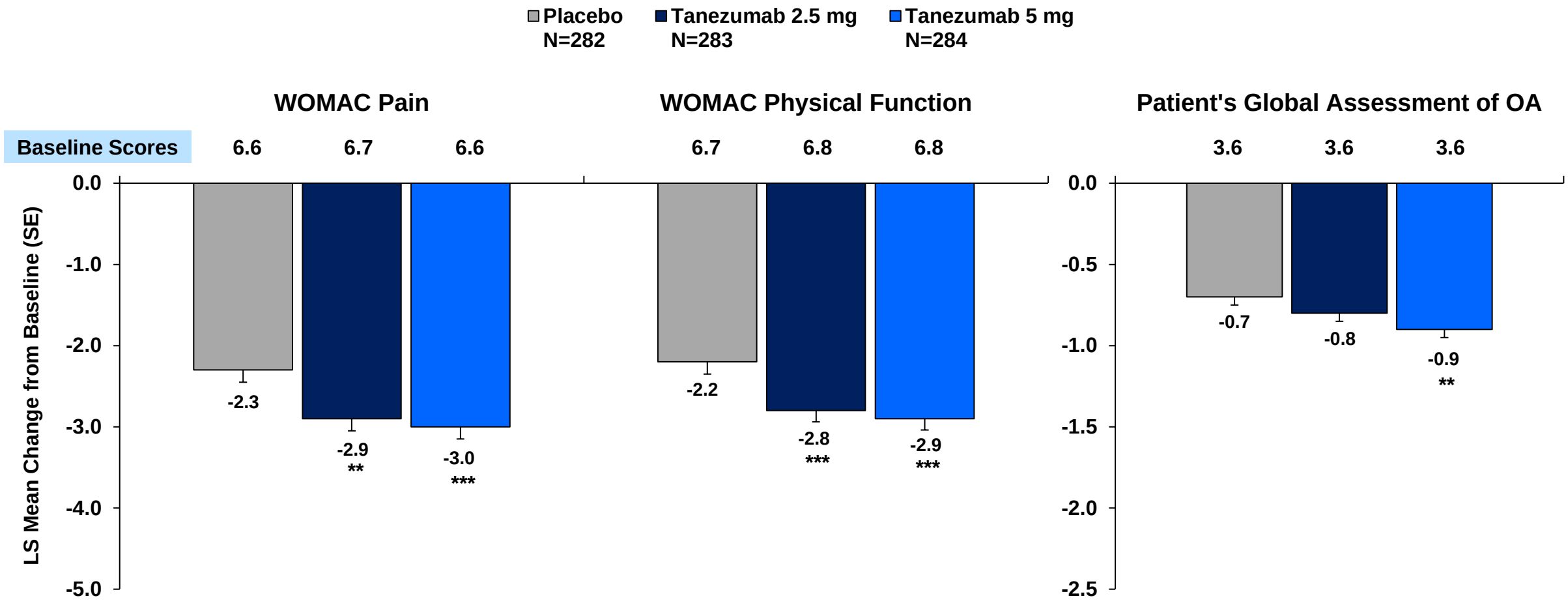
Change from Baseline to Week 16 Landmark Assessment



*p≤0.05; **p≤0.01; ***p≤0.001 vs placebo
Intent-to-treat population, Multiple imputation

Study 1057: Co-Primary Efficacy Measures

Change from Baseline to Week 24 Landmark Assessment

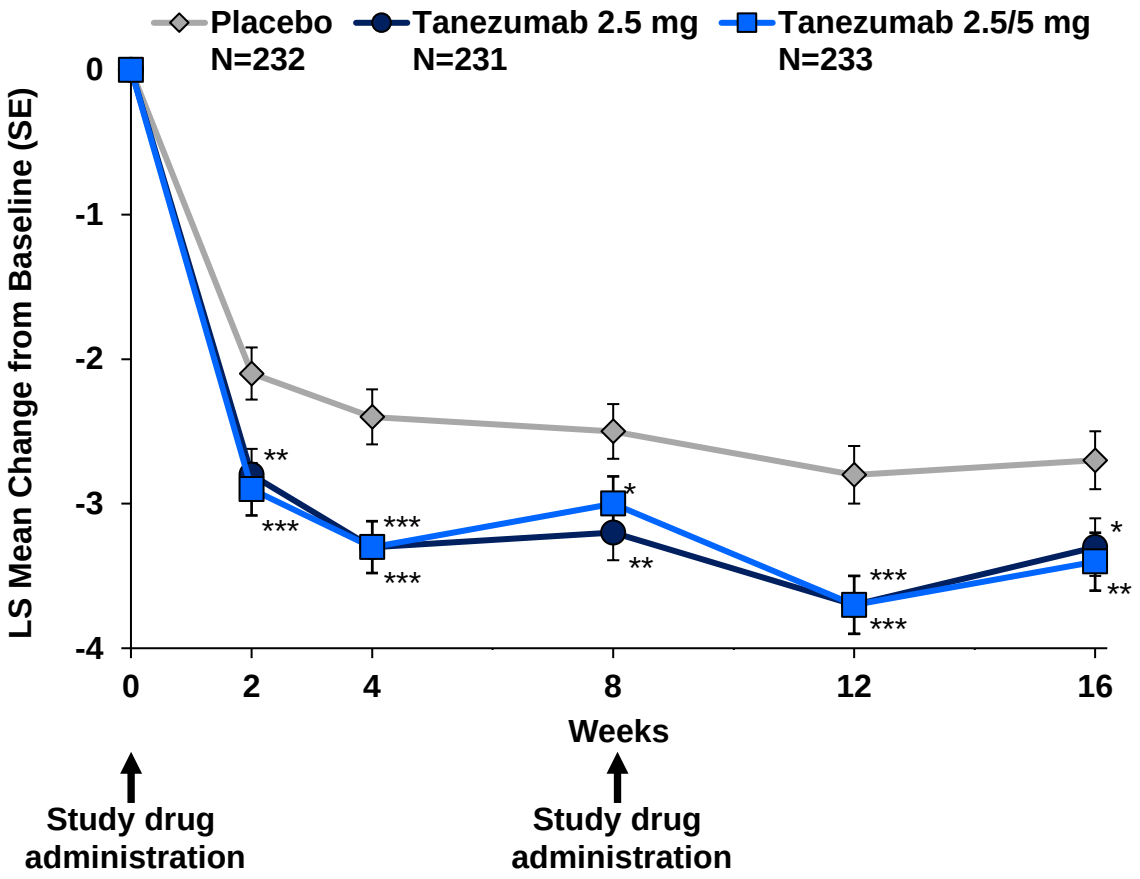


*p≤0.05; **p≤0.01; ***p≤0.001 vs placebo
Intent-to-treat population, Multiple imputation

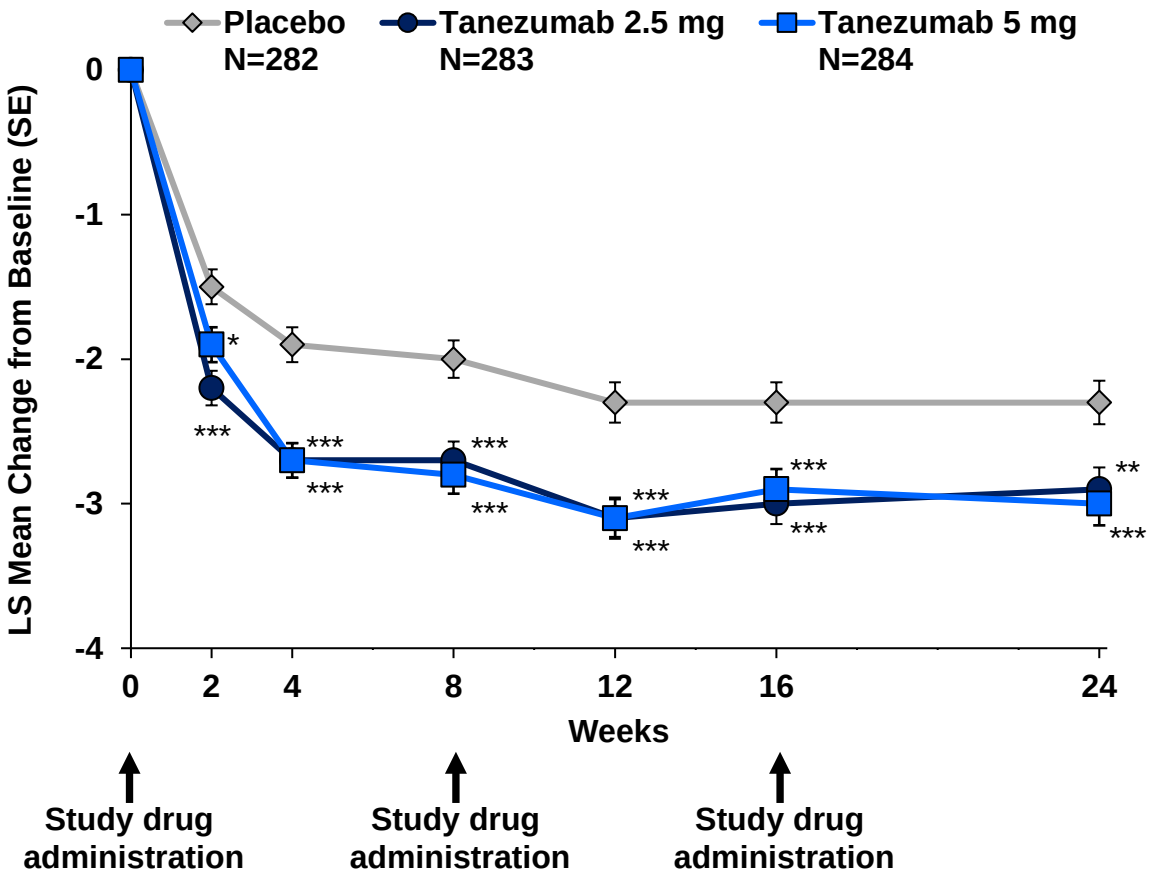
Mean Improvement in WOMAC Pain Over Time

Tanezumab Provides Sustained Efficacy Over Consecutive 8-Week Dosing Intervals

Study 1056



Study 1057

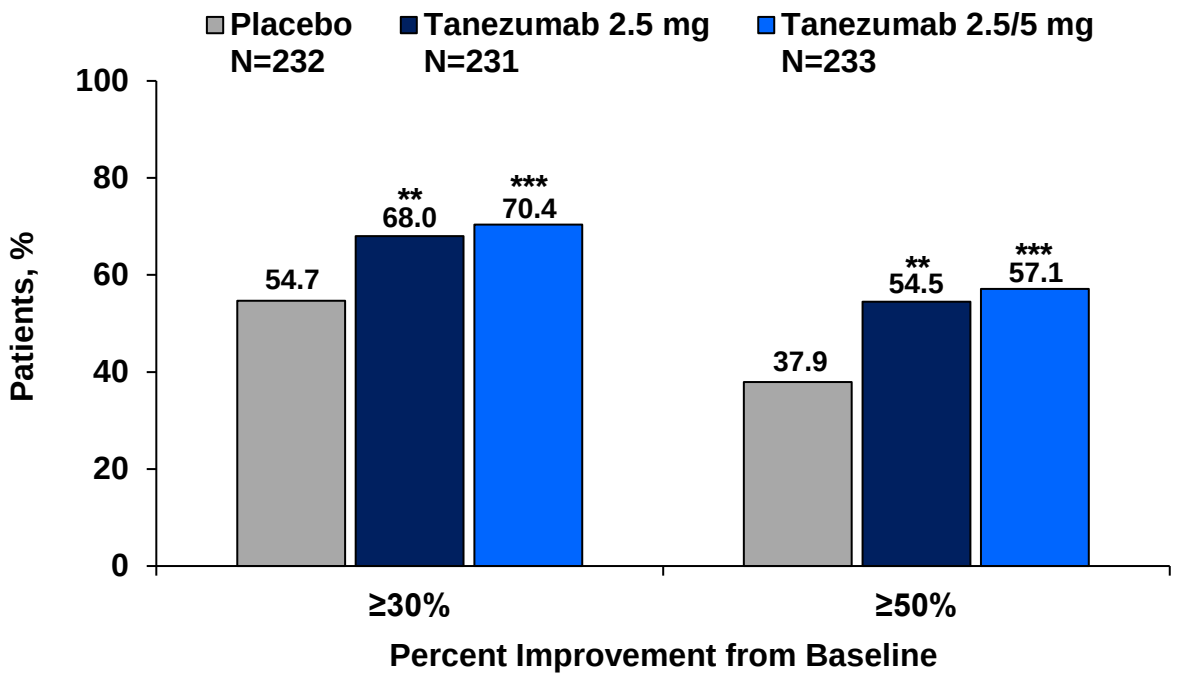


*p≤0.05; **p≤0.01; ***p≤0.001 vs placebo
Multiple imputation

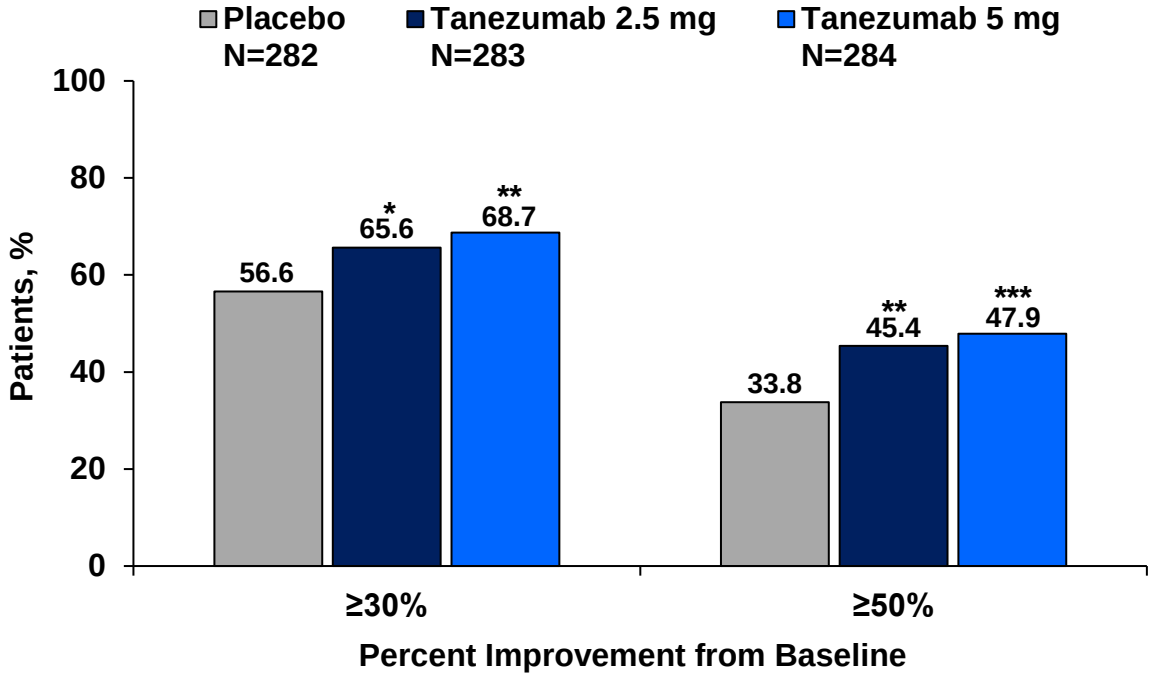
WOMAC Pain: ≥30 and ≥50% Improvements from Baseline

Tanezumab 2.5 mg SC Provides Clinically Important Improvement in OA Pain

Study 1056 at Week 16



Study 1057 at Week 24



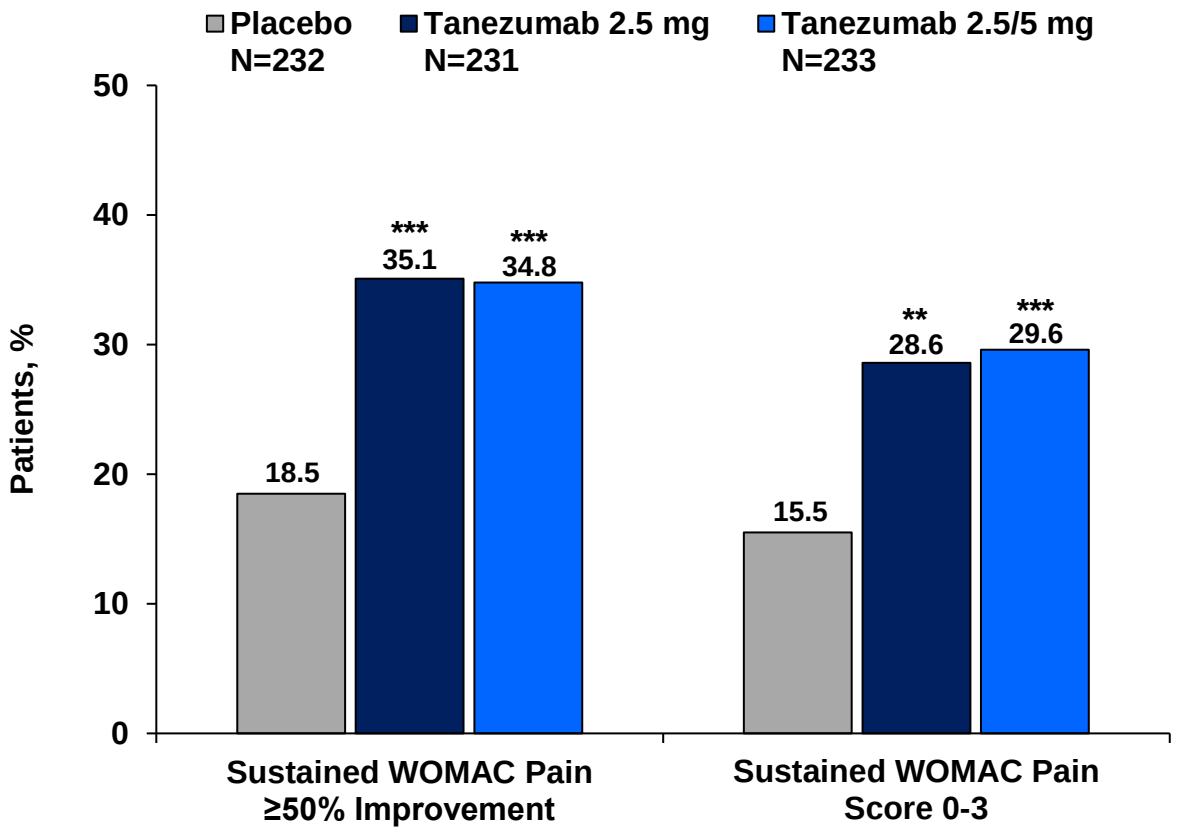
- **45-55% of patients achieved at least a 50% reduction in pain with tanezumab 2.5 mg**
- **Studies have suggested a 50% improvement in pain represents a 'substantial' improvement, corresponds with patient reports of 'very much improved' (Dworkin et al, 2008.)**

*p≤0.05; **p≤0.01; ***p≤0.001 vs placebo
Mixed LOCF/BOCF imputation
Dworkin RH et al. *J Pain* 2008;Feb;9(2):105-121.
BOCF=Baseline Observation Carried Forward; LOCF=Last Observation Carried Forward

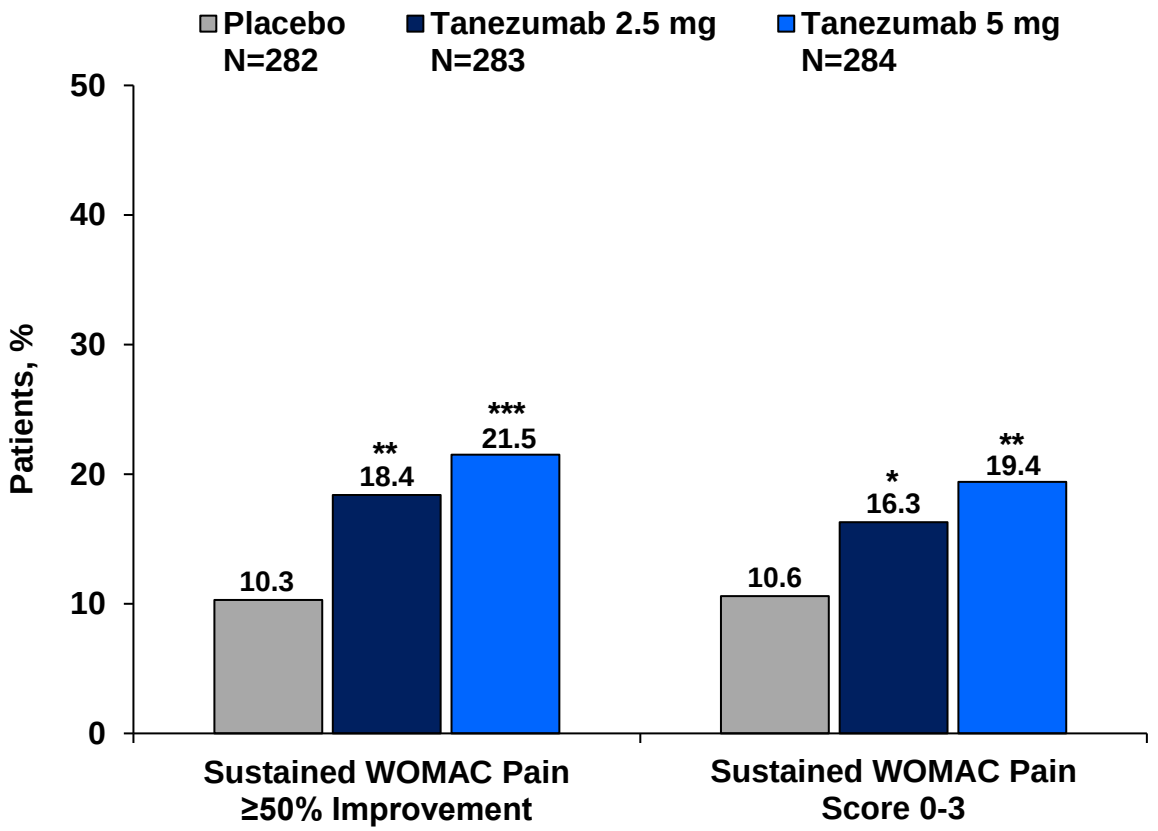
Additional Assessments of Clinically Important Outcomes

Tanezumab 2.5 mg SC Provides Sustained Clinically Important Improvement in OA Pain

Study 1056
Sustained Response Over Weeks 4-16

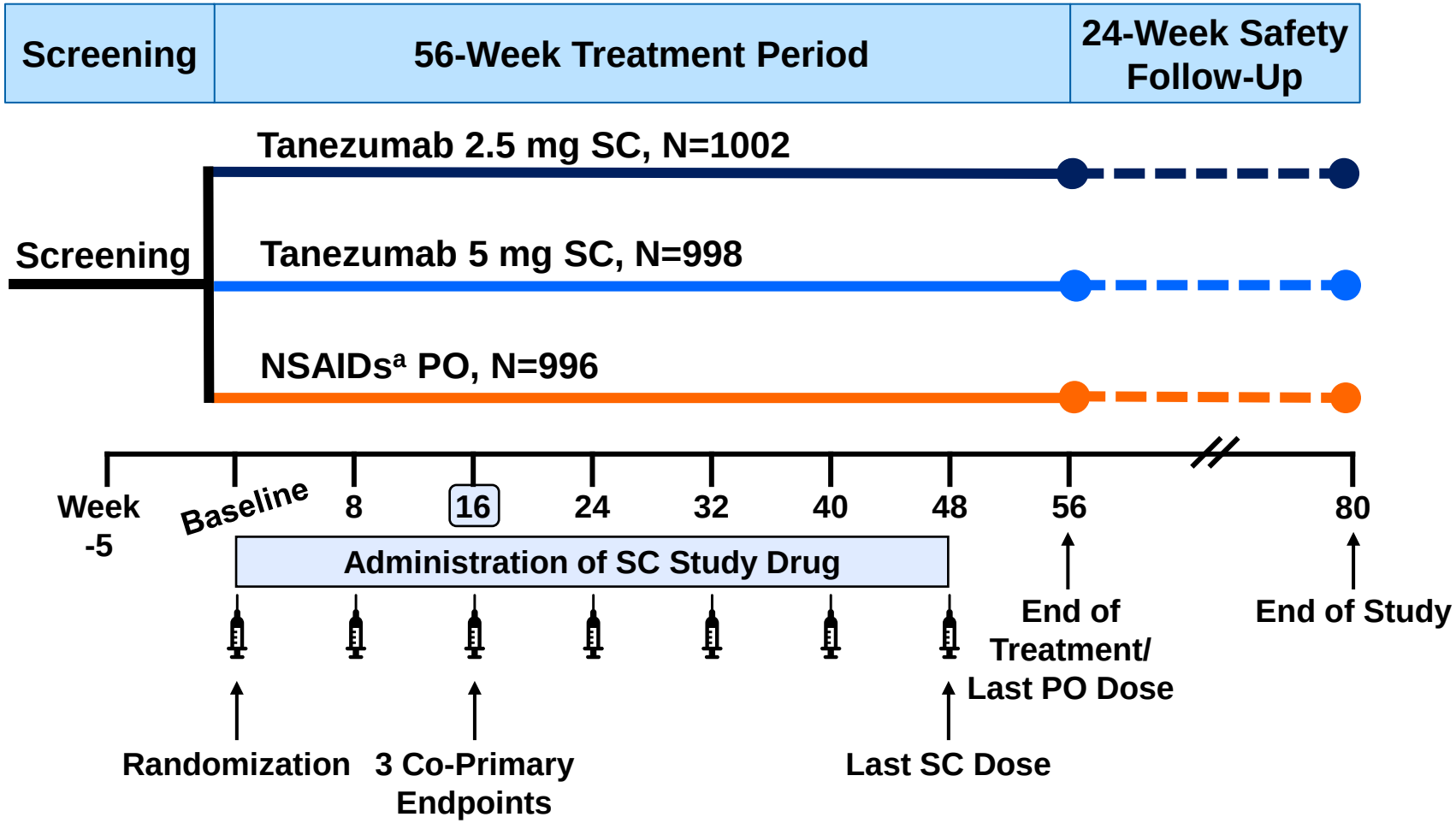


Study 1057
Sustained Response Over Weeks 4-24



*p≤0.05; **p≤0.01; ***p≤0.001 vs placebo
Mixed LOCF/BOCF imputation

Study Design
Study 1058



- NSAIDs were selected to perform this controlled long-term assessment
- Tolerating NSAIDs and receiving benefit
  - ~4 years: average duration of NSAID use
- History of an unsatisfactory outcome with acetaminophen, opioids or tramadol
- Moderate to severe OA at baseline and while taking NSAIDs to be randomized

a. NSAIDs=celecoxib 100 mg BID, naproxen 500 mg BID or diclofenac ER 75 mg BID
Telephone contact at Weeks 12, 20, 28, 36, 44, 52, 60, 68, 72 and 76
BID=twice daily; ER=Extended Release; PO=Per Os/by mouth

Demographics and Baseline OA Disease Characteristics

Moderate to Severe OA Disease with Multiple Joint Involvement

Post-2015 Active-Controlled OA Study 1058
N=2996

Demographics Consistent with OA Population
▪ Mean age: 60.6 years
▪ Patients ≥65 years: 33.7%
▪ Patients ≥75 years: 6.8%
▪ Female: 65.2%
▪ Race: White = 70.0%; Black = 17.2%; Asian = 10.1%
▪ Ethnicity: Hispanic or Latino = 18.4%

a. WOMAC Pain ≥7, WOMAC Physical Function ≥7, and PGA-OA, poor or very poor
b. ≥2 knee or hip joints KL grade 2 or greater

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Moderate to Severe OA; >25% Severe Symptoms	
Baseline Symptom Severity, mean (SD)	
WOMAC Pain	7.0 (1.1)
WOMAC Physical function	7.1 (1.1)
PGA-OA	3.5 (0.6)
Severe Cohort[a], n (%)	
	796 (26.6)

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Demographics and Baseline OA Disease Characteristics

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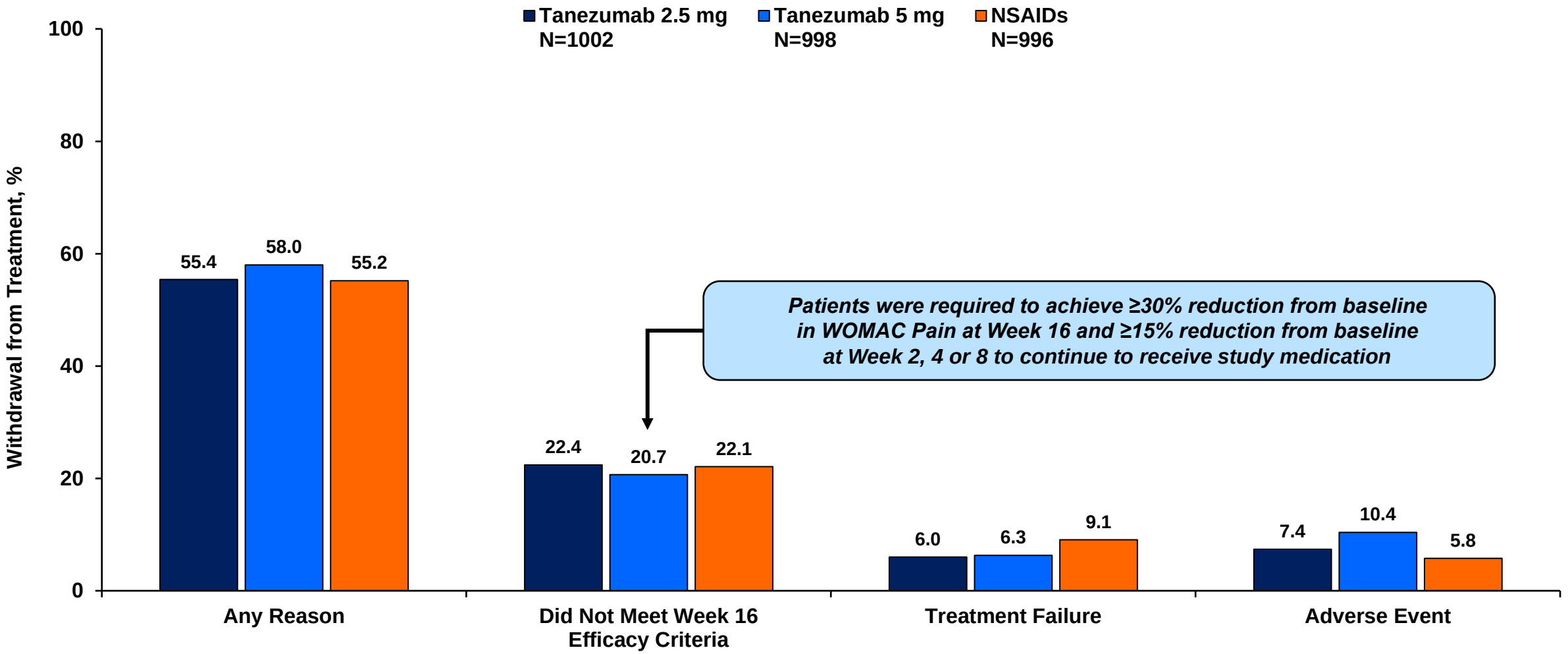
WOMAC Physical function	7.1 (1.1)
PGA-OA	3.5 (0.6)
Severe Cohort[a], n (%)	
	796 (26.6)

≥70% with Advanced OA Disease of Index Joint and Multiple Joints Affected by OA	
Duration of OA, years, mean (SD)	
	8.8 (8.3)
Index Joint, n (%)	
Knee	2553 (85.2)
Kellgren-Lawrence Grade of Index Joint, n (%)	
KL Grade 2	892 (29.8)
KL Grade 3	1425 (47.6)
KL Grade 4	667 (22.3)
Multiple Joints Affected by OA[b] , n (%)	
	2330 (77.8)

a. WOMAC Pain ≥7, WOMAC Physical Function ≥7, and PGA-OA, poor or very poor
b. ≥2 knee or hip joints KL grade 2 or greater

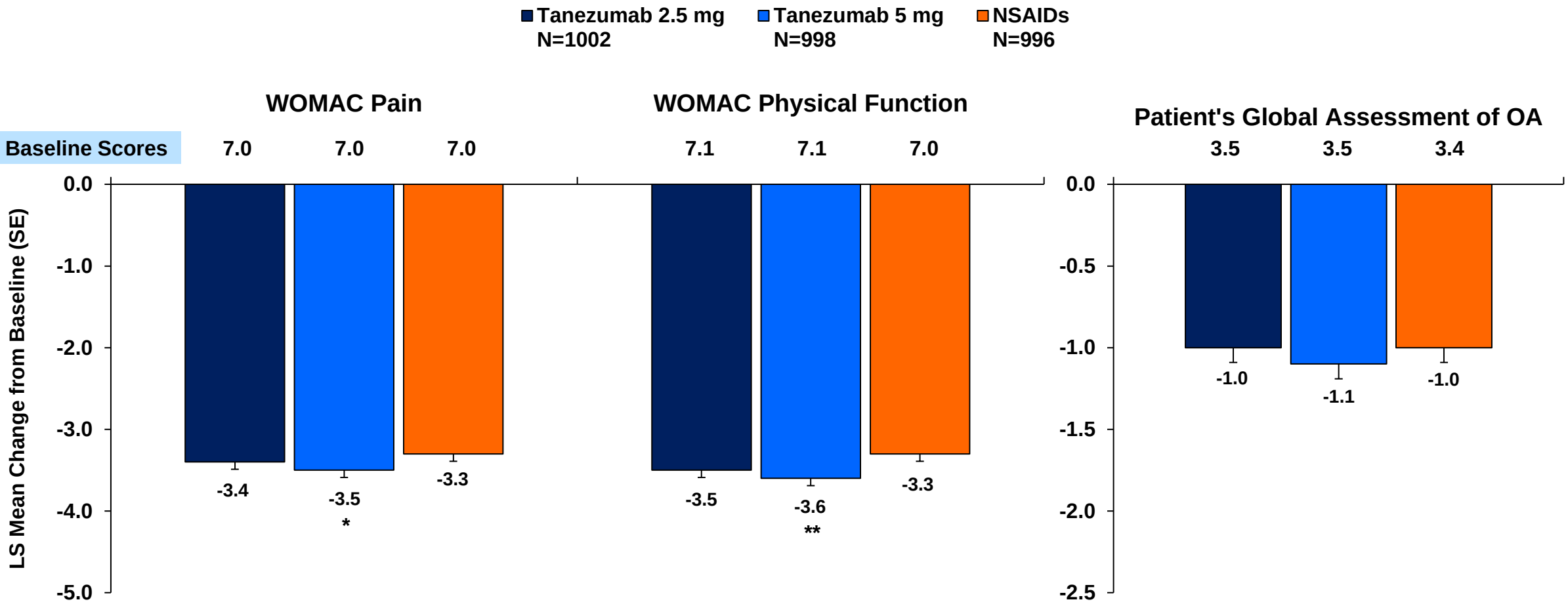
Patient Disposition Over 56-Week Treatment Period

Study 1058



Tanezumab vs NSAIDs: Primary Analysis

Neither Tanezumab Dose Provided Superior Efficacy to NSAID Treatment in Study 1058



Similar efficacy profile observed at Week 56

*p≤0.05; **p≤0.01; ***p≤0.001 vs NSAIDs
Intent-to-treat population, Multiple imputation

Study 1058 Efficacy Outcomes

How do the Results Contribute to the Understanding Tanezumab 2.5 mg Efficacy?

Observed Efficacy of Tanezumab 2.5 mg from Study 1058

Week 16 Co-Primary Efficacy Measures	Week 56 Maintenance of Efficacy
Tanezumab superior to NSAIDs	Durable
X Tanezumab non-inferior to NSAIDs	Waning efficacy
Tanezumab clinically comparable to NSAIDs	Not durable
NSAIDs superior to tanezumab	

MOA=Mechanism Of Action

Study 1058 Efficacy Outcomes

How do the Results Contribute to the Understanding Tanezumab 2.5 mg Efficacy?

Observed Efficacy of Tanezumab 2.5 mg from Study 1058

Week 16
Co-Primary Efficacy Measures

- Tanezumab superior to NSAIDs
- ~~Tanezumab non-inferior to NSAIDs~~
- **Tanezumab clinically comparable to NSAIDs**
- NSAIDs superior to tanezumab

Week 56
Maintenance of Efficacy

- **Durable**
- Waning efficacy
- Not durable

- Interpretation of Outcomes
  - Placebo component to the active treatment efficacy responses may have been larger than anticipated or
  - Efficacy of tanezumab 2.5 mg is not greater than NSAIDs in patients who are tolerating the therapy and receiving benefit
- Tanezumab 2.5 mg does not have to be superior to NSAIDs to be efficacious in the target population
- Given the differences in the MOA, tanezumab 2.5 mg would still offer the potential for benefit in patients who had an inadequate response or cannot tolerate NSAIDs

MOA=Mechanism Of Action

Efficacy Conclusions

- In the treatment of chronic pain associated with osteoarthritis in patients for whom use of other analgesics is ineffective or not appropriate
  - Tanezumab 2.5 mg and 5 mg administered SC every 8 weeks provide consistent and clinically important improvement in pain and physical function in knee or hip OA
  - Tanezumab 2.5 mg SC is fully efficacious dose, no meaningful improvements in the onset, magnitude, or duration of analgesia are evident with escalating doses
  - The efficacy of tanezumab 2.5 mg SC is maintained over long-term treatment

Agenda

Subject	Presenter
Introduction	**Kenneth Verburg, PhD,** *Senior Vice President, Medicine Team Lead Global Product Development, Internal Medicine, Pfizer Inc.*
Update on Osteoarthritis: Current Understanding, Future Needs	**Thomas J. Schnitzer, MD, PhD,** *Professor of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL*
Efficacy of Tanezumab in Osteoarthritis	**Kenneth Verburg, PhD,** *Senior Vice President, Medicine Team Lead Global Product Development, Internal Medicine, Pfizer Inc.*
Safety of Tanezumab in Osteoarthritis	**Christine West, PhD,** *Senior Director, Global Clinical Lead Global Product Development, Internal Medicine, Pfizer Inc.*
Post-Marketing Risk Management	**Anne Hickman, DVM, PhD,** *Senior Director, Global Safety and Risk Management Lead, Worldwide Research and Development, Pfizer Inc.*
Utility of Tanezumab in Clinical Practice and Patient Selection and Monitoring Considerations	**Alan Kivitz, MD, FACR,** *President, Altoona Center for Clinical Research & Altoona Arthritis and Osteoporosis Center*
Benefit-Risk and Conclusions	**Kenneth Verburg, PhD,** *Senior Vice President, Medicine Team Lead Global Product Development, Internal Medicine, Pfizer Inc.*

Tanezumab

Safety of Tanezumab in Osteoarthritis

Christine West, PhD
Senior Director, Global Clinical Lead
Global Product Development, Internal Medicine
Pfizer Inc.

Safety Presentation Topics

- General Safety
- Peripheral Neurological Safety
- Joint Safety

Overview of General Safety

Subcutaneous Administration of Tanezumab 2.5 mg

- No notable differences in overall incidence of adverse events, serious adverse events, discontinuations due to adverse events relative to placebo and NSAID treatments
- Dose-dependent increase in specific types of adverse events vs placebo or NSAIDs
  - Musculoskeletal and connective tissue disorders
  - Nervous system disorders
- No association with increased risk for sympathetic autonomic neuropathy
- No increased risk for adverse events related to cardiovascular, renal, or hepatic systems
  - No increased risk for hypersensitivity
- No association with potential drug abuse, dependence or withdrawal
- Adverse event profile in subgroups consistent with AE profile in overall patient population
- No clinically meaningful changes in laboratory values, vital signs, or ECGs

AE=Adverse Event; ECG=Electrocardiogram

Adverse Events Likely Associated with Tanezumab

Patients Treated with Tanezumab 2.5 mg

System Organ Class	Adverse Drug Reaction Term	Frequency, %
Nervous system disorders	Abnormal peripheral sensation[a]	4.2
	Carpal tunnel syndrome	0.5
Musculoskeletal and connective tissue disorders	Rapidly progressive osteoarthritis[b]	2.7
	Joint swelling	2.5
General disorders and administration site conditions	Peripheral edema[c]	1.7

Event terms that represent the same medical concept or condition were grouped together and reported as a single adverse reaction in the table above
a. Includes: paresthesia, hypoesthesia, and burning sensation
b. Includes: Rapidly Progressive Osteoarthritis Type 1 and Type 2
c. Includes: edema peripheral and peripheral swelling

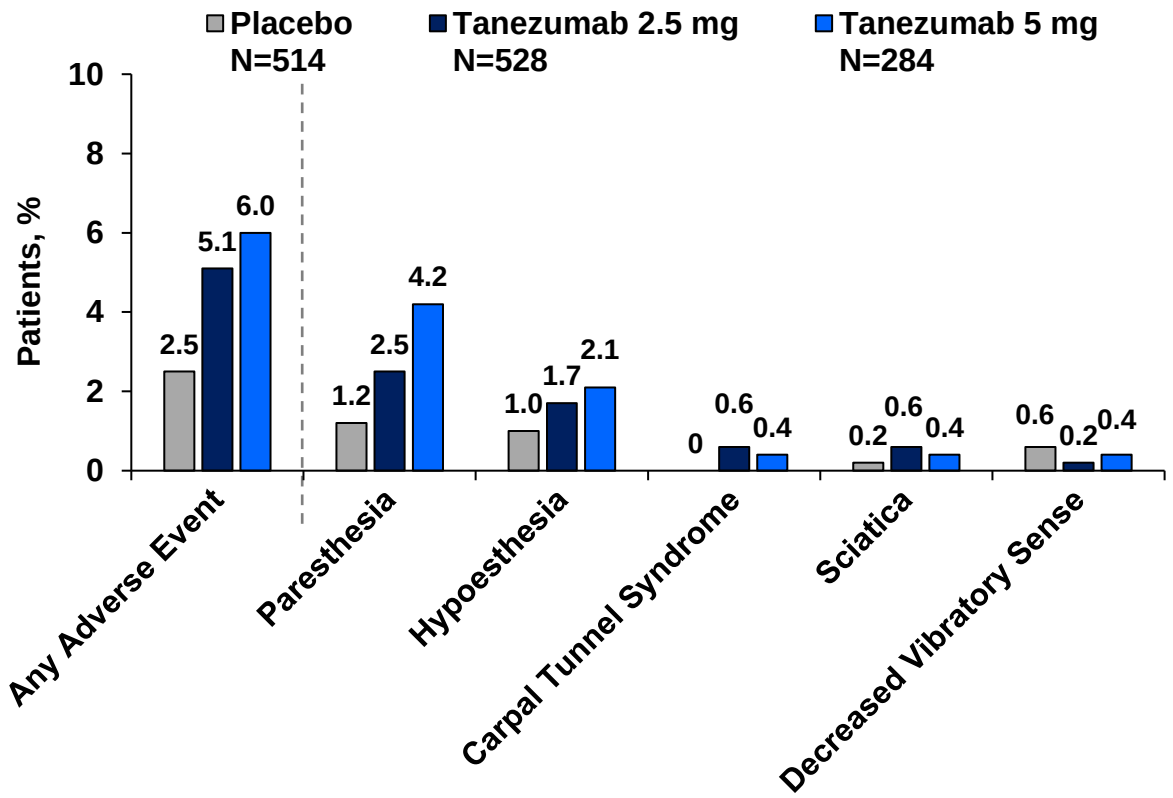
Safety Presentation Topics

- General Safety
- Peripheral Neurological Safety
- Joint Safety

Peripheral Neurological Safety: Post-2015 Placebo-Controlled Studies

Dose Responsive Increase with Tanezumab; Mild or Moderate Severity

Adverse Events of Abnormal Sensation[a]



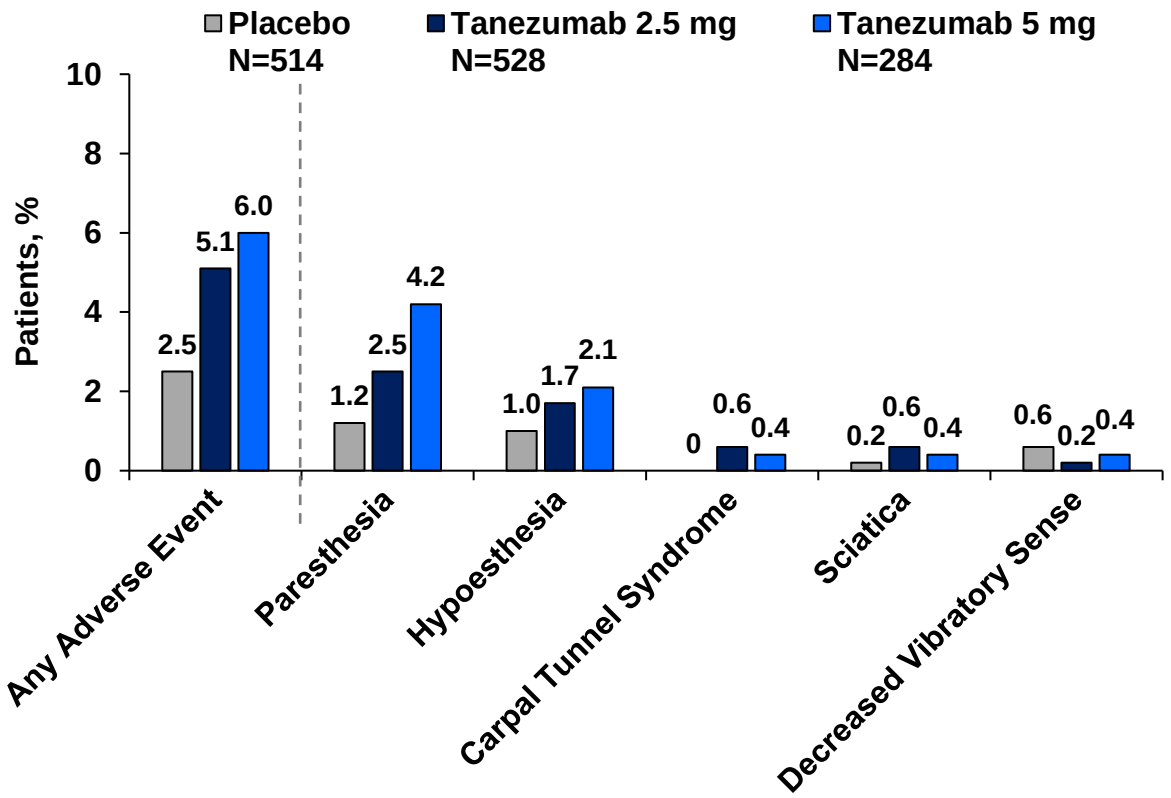
Majority of events were mild to moderate in severity and resolved by end of study

a. Adverse events occurring in ≥0.5% in any treatment group
Studies 1056 and 1057
Data not shown for Study 1056 2.5/5 mg treatment group (N=219)

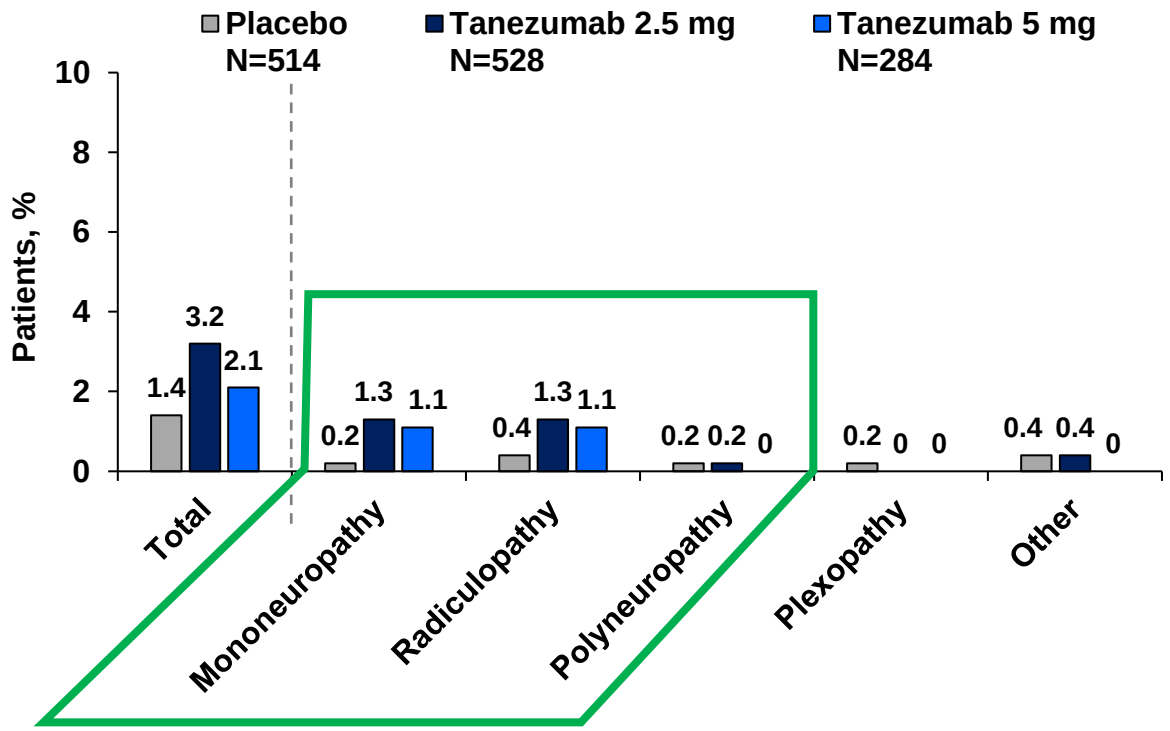
Peripheral Neurological Safety: Post-2015 Placebo-Controlled OA Studies

Incidence of Polyneuropathy was Low at ~0.2%; Similar to Placebo

Adverse Events of Abnormal Sensation[a]



Neurologic Consultations



No evidence for reduction in cutaneous small nerve fiber density with tanezumab treatment relative to placebo

a. Adverse events occurring in ≥0.5% in any treatment group
Studies 1056 and 1057
Data not shown for Study 1056 2.5/5 mg treatment group (N=219)

Safety Presentation Topics

- General Safety
- Peripheral Neurological Safety
- Joint Safety

Imaging Abnormalities Used to Monitor Disease Progression

Visual Assessment of Osteophytes and Joint Space Width (JSW)

- Severity of osteoarthritis commonly estimated by semi-quantitative radiographic scoring systems
  - Kellgren-Lawrence grading[1]
  - Osteoarthritis Research Society International (OARSI) grading system[2]
- Visual assessment of JSW surrogate measure of disease progression
  - Loss of articular cartilage and meniscal changes

1. Kellgren JH, Lawrence JS. *Ann Rheum Dis* 1957;16:494-501.
2. Altman RD, Gold GE. *Osteoarthritis and Cartilage* 2007;15:A1-A56.
3. Guermazi A et al. *J Bone Joint Surg* 2009;91 Suppl 1:54-62.
JSN=Joint Space Narrowing

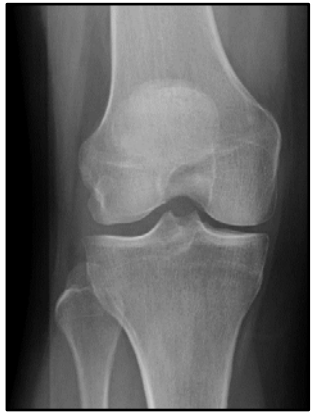
Imaging Abnormalities Used to Monitor Disease Progression

Visual Assessment of Osteophytes and Joint Space Width (JSW)

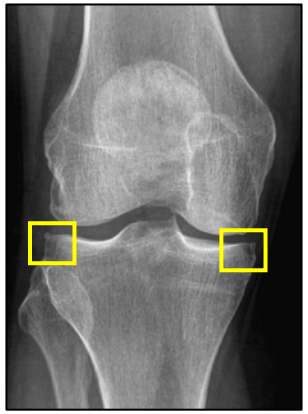
- Severity of osteoarthritis commonly estimated by semi-quantitative radiographic scoring systems
  - Kellgren-Lawrence grading[1]
  - Osteoarthritis Research Society International (OARSI) grading system[2]
- Visual assessment of JSW surrogate measure of disease progression
  - Loss of articular cartilage and meniscal changes

Examples of Kellgren-Lawrence Grades[1,3]

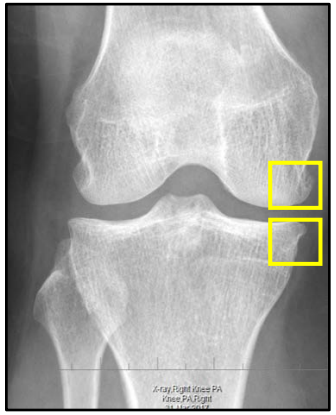
Grade 0
No features of OA



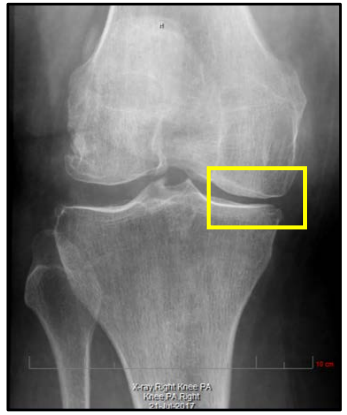
Grade 1
Doubtful JSN,
Possible osteophytic lipping



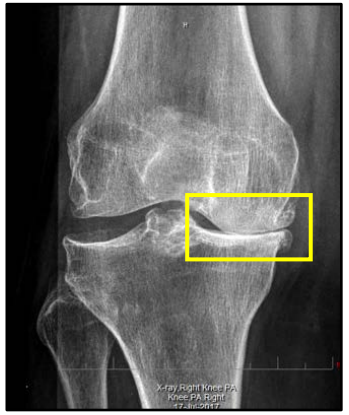
Grade 2
Possible JSN
Definite osteophyte



Grade 3
Definite JSN
Moderate osteophytes, sclerosis, possible deformity of bone ends



Grade 4
Marked JSN
Severe sclerosis, large osteophytes, definite deformity of bone ends



1. Kellgren JH, Lawrence JS. *Ann Rheum Dis* 1957;16:494-501.
2. Altman RD, Gold GE. *Osteoarthritis and Cartilage* 2007;15:A1-A56.
3. Guermazi A et al. *J Bone Joint Surg* 2009;91 Suppl 1:54-62.

JSN=Joint Space Narrowing

Idiopathic Rapidly Progressive Osteoarthritis

- Subset of OA identified in hip[1,2,3,4], knee[5], and shoulder[6]
- Often associated with severe pain, rapid loss of JSW, and subsequent severe progressive atrophic bone destruction
  - Unclear if loss of JSW and progressive bone destruction are a continuum or separate disease processes
- Majority of cases are unilateral; often result in arthroplasty
- Prevalence not well understood, retrospective studies suggested may occur in 1-3% of OA patients[7]

1. Della Torre P et al. *Ital J Orthop Traumatol* 1987;13:187-200.
2. Yamamoto et al. *Skeletal Radiol* 2010;39:189-192.
3. Mitrovic and Riera. *Rheumatol Int* 1992;12:17-22.
4. Rosenberg ZS et al. *Radiology* 1992;182:213-216.
5. Komatsu et al. *Clinical Cases in Mineral and Bone Metabolism* 2014;11:232-235.
6. Cho et al. *Diagnostics* 2020;10:885-896.
7. Pfizer. Tanezumab Arthritis Advisory Committee Briefing Document 8 Feb 2012. https://wayback.archive-it.org/7993/20170404145624/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/ucm295201.htm

Rapidly Progressive Osteoarthritis
Associated with Analgesic Drug Treatment

- Loss of JSW, disease progression and RPOA have been associated with analgesic drug treatment
  - NSAID-associated ‘analgesic hip’[1,2]
  - Intra-articular steroids[3,4,5]
  - Anti-NGF compounds
- Cohort study including patients with mild to moderate knee OA in the OAI study[6]
  - Participants = at least one KL Grade 2 or 3 knee and no reported use of intra-articular corticosteroid (IACS) at baseline
  - Intra-articular corticosteroid use initiated = 148 participants
  - Propensity-score matched participants in comparison cohort = 536 participants
  - Hazard ratio for KL Grade worsening (≥1 grade) or total knee replacement
    - 3.0 (95% CI = 2.25, 4.05) for intra-articular corticosteroid use vs no use

1. Rønningen and Langeland. *Acta Orthop Scand* 1979;50:169-174.
2. Newman and Ling. *Lancet* 1985;2;11-14.
3. Kompel et al. *Radiology* 2019;293:656-663.
4. Simeone et al. *Skeletal Radiology* 2019;48:1417-1426.
5. McAlindon et al. *JAMA* 2017;317:1967-1975.
6. Zeng et al. *Osteoarthritis and Cartilage* 2019;27:855-862.
CI=Confidence Interval; OAI=Osteoarthritis Initiative; RPOA=Rapidly Progressive Osteoarthritis

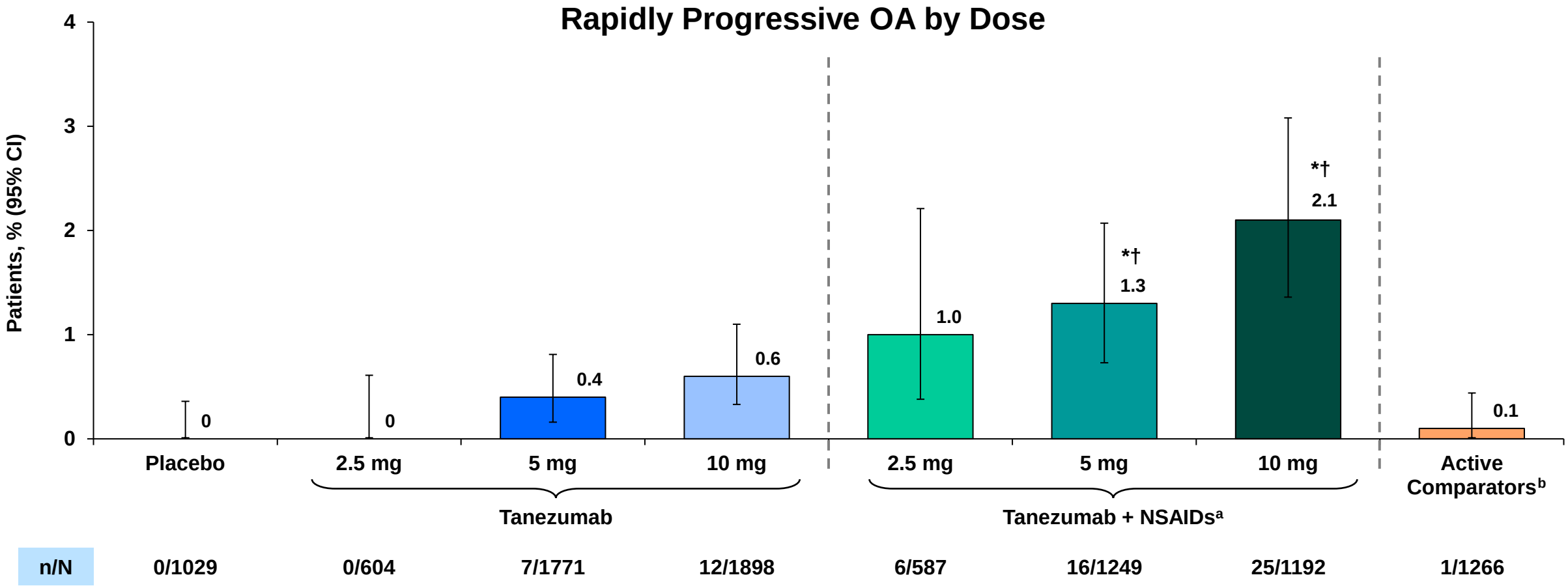
Key Joint Safety Findings with Tanezumab 2.5 mg

- Incidence of Rapidly Progressive OA Type 1 (2.3%) was statistically significantly greater than placebo (0%) or NSAIDs (1.1%)
  - Events most often in the knee; majority (85%) of affected joints did not undergo TJR
- Incidence of Rapidly Progressive OA Type 2 (0.4%) was not significantly elevated relative to NSAIDs (0.1%)
- Risk differences for Rapidly Progressive OA relative to NSAIDs generally similar over time
- Subgroup analyses identified an association between the occurrence of joint safety endpoints and structural severity at baseline
- Incidence of TJR was higher vs NSAIDs and generally associated with normal progression of OA
  - Differences vs placebo did not reach statistical significance

RPOA-1=Rapidly Progressive OA Type 1: Significant loss of joint space width ≥2 mm (predicated on optimal joint positioning) within approximately 1 year, without gross structural failure[1,2]
RPOA-2=Rapidly Progressive OA Type 2: Abnormal bone loss or destruction, including limited or total collapse of at least 1 subchondral surface, which is not normally present in conventional end-stage OA[1]
1. Miller CG, et al. *Osteoarthritis Cartilage* 2015;23:S3-S7.
2. Tanezumab Adjudication Committee Charter
TJR=Total Joint Replacement

Pre-2015 Phase 3 OA Studies – Rapidly Progressive OA (RPOA)

Dose-Responsive Increased Risk of RPOA ~3-Fold Higher with Chronic Concomitant NSAID Use



Includes Studies 1011, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030 and 1043

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

b. Active Comparators = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg Q12H

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

Dose Response: p=0.0048 tanezumab monotherapy, p<0.001 tanezumab + NSAIDs combination therapy

CR=Controlled Release; Q12H=every 12 hours; SR=Sustained Release

Protocol-Specified Imaging in Post-2015 Studies

Screening and Post-Baseline Surveillance

Imaging collected in standardized manner read by Central Reader – Musculoskeletal Radiologists

Screening

- **All Studies**
  - Radiographs of hips, knees and shoulders
- **Study 1058**
  - MRIs of hips and knees
    - MRIs were not used to make eligibility determinations

Post-Baseline ~6-Month Interval

- **Studies 1057 and 1058**
  - Radiographs of hips, knees and shoulders
- **Study 1058**
  - MRIs of hips and knees
    - MRIs were read for cause or for adjudication

End of Treatment and/or End of Study

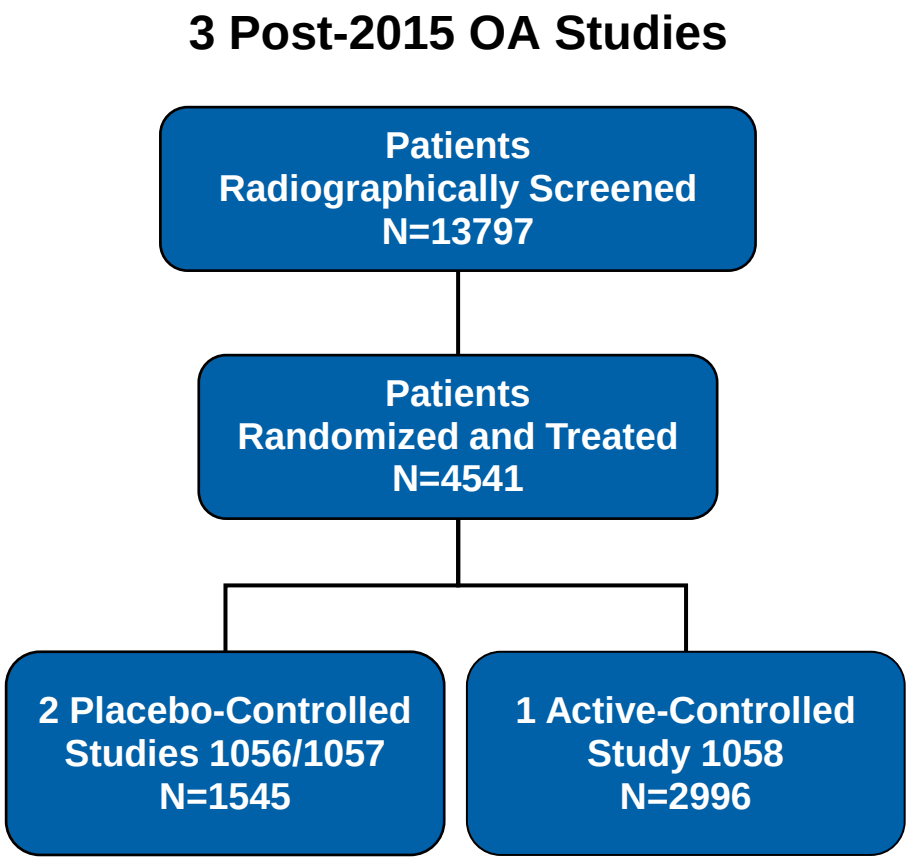
- **All Studies**
  - Radiographs of hips, knees and shoulders
- **Study 1058**
  - MRIs of hips and knees
    - MRIs were read for cause or for adjudication

- At any time, For Cause Radiographs or MRIs could be collected and read
  - Recommended if new-onset persistent pain or swelling was noted to identify the emergence of possible joint safety event

MRIs in Study 1058 were obtained for patients who had at least one hip or knee that was KL Grade 3 or greater at baseline
MRI=Magnetic Resonance Imaging

Radiographic Exclusionary Findings Identified at Screening

Over 13,000 Patients Radiographically Screened at >480 International Sites

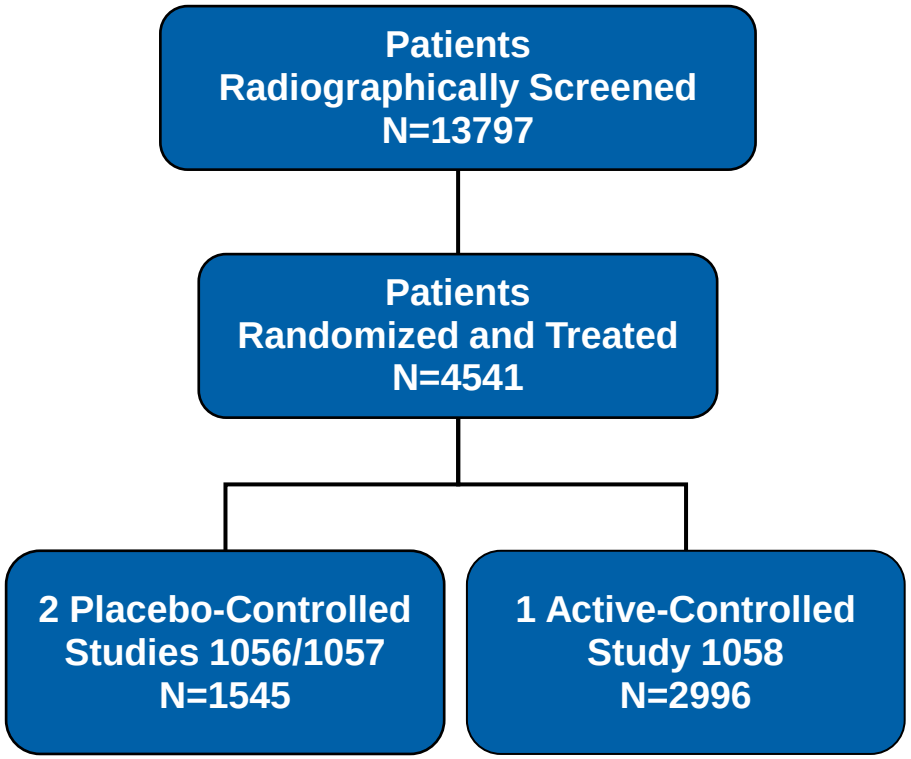


N/A=Not Applicable

Radiographic Exclusionary Findings Identified at Screening

<3% of Joints Screened in Each Exclusionary Category; More Common in Knee vs Hip

3 Post-2015 OA Studies



Exclusions in Patients Radiographically Screened

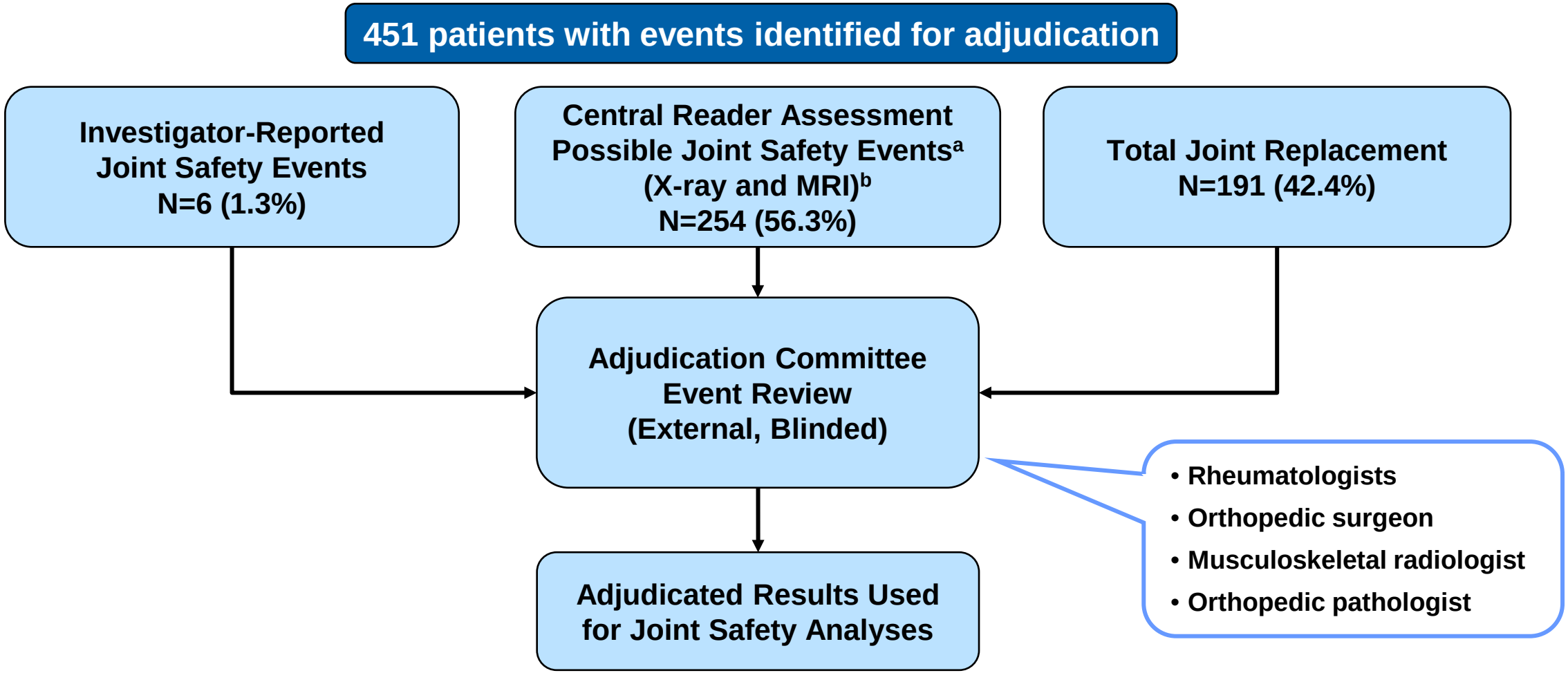
Joint-Level Finding, n (%)	Knee N=26,597	Hip N=26,938
Severe Knee Malalignment	751 (2.8)	N/A
Subchondral Insufficiency Fracture	586 (2.2)	61 (0.2)
Atrophic OA	486 (1.8)	105 (0.4)
Osteonecrosis	119 (0.5)	323 (1.2)
Rapidly Progressive OA Type 2	18 (0.1)	110 (0.4)

MRIs not used for screening assessments
~10% joints had pain inconsistent with radiographic findings; led to exclusion

N/A=Not Applicable

Review of Joint Safety Events and Total Joint Replacements

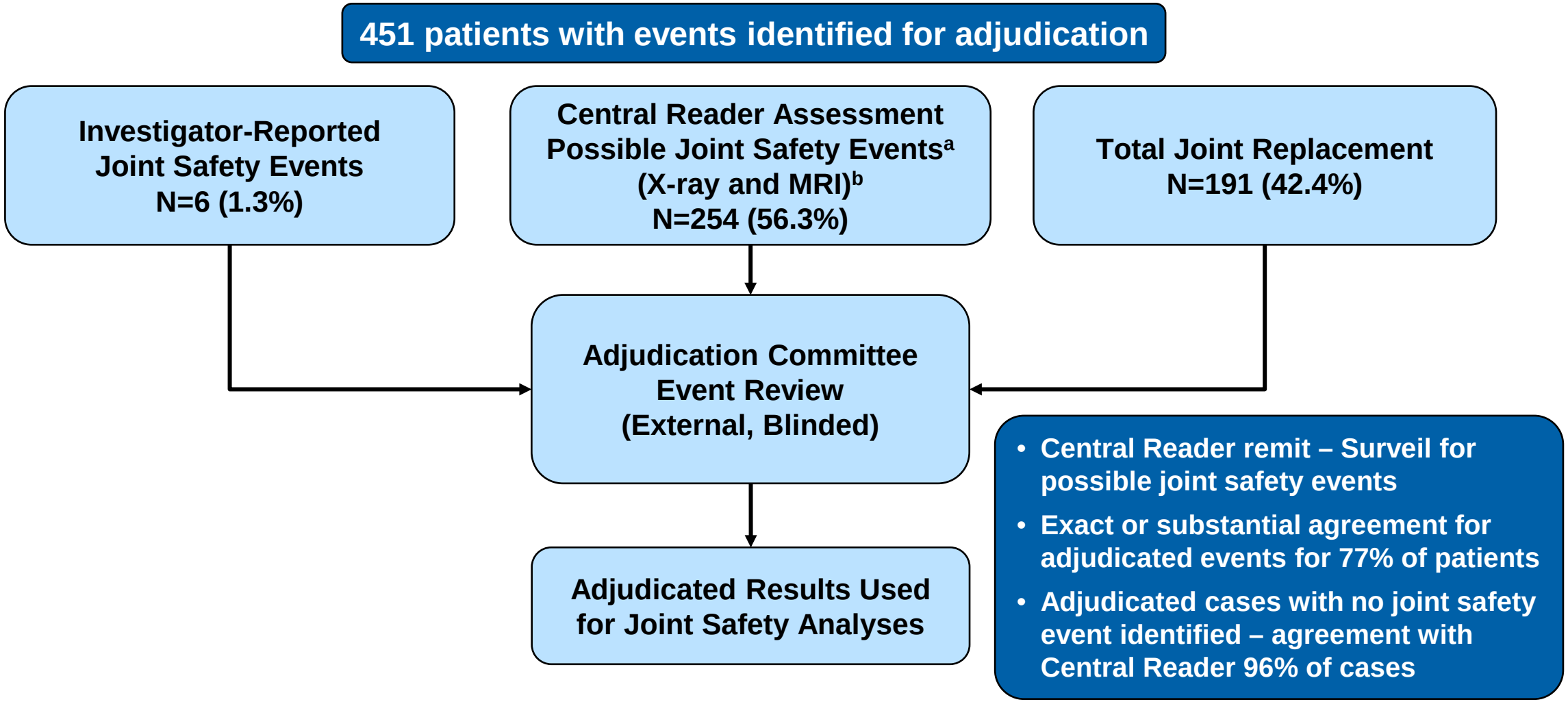
Post-Baseline Surveillance During Treatment Period and 24-Week Safety Follow-Up



a. Rapidly Progressive OA Type 1 or Rapidly Progressive OA Type 2, primary osteonecrosis, subchondral insufficiency fracture, or pathologic fracture
b. Based on a program level imaging atlas

Review of Joint Safety Events and Total Joint Replacements

Post-Baseline Surveillance During Treatment Period and 24-Week Safety Follow-Up



a. Rapidly Progressive OA Type 1 or Rapidly Progressive OA Type 2, primary osteonecrosis, subchondral insufficiency fracture, or pathologic fracture
b. Based on a program level imaging atlas

Joint Safety Outcomes: Post-2015 Studies

Adjudication Categories	Primary Composite Endpoint
Primary Osteonecrosis	Yes
Worsening Osteoarthritis	
Rapidly Progressive OA (Type 1 or 2)	Yes
Normal Progression of OA	
Not enough information to distinguish rapidly progressive OA	
Subchondral Insufficiency Fracture	Yes
Pathologic Fracture	Yes
Other (with diagnosis specified)	
Not enough information to specify a diagnosis	

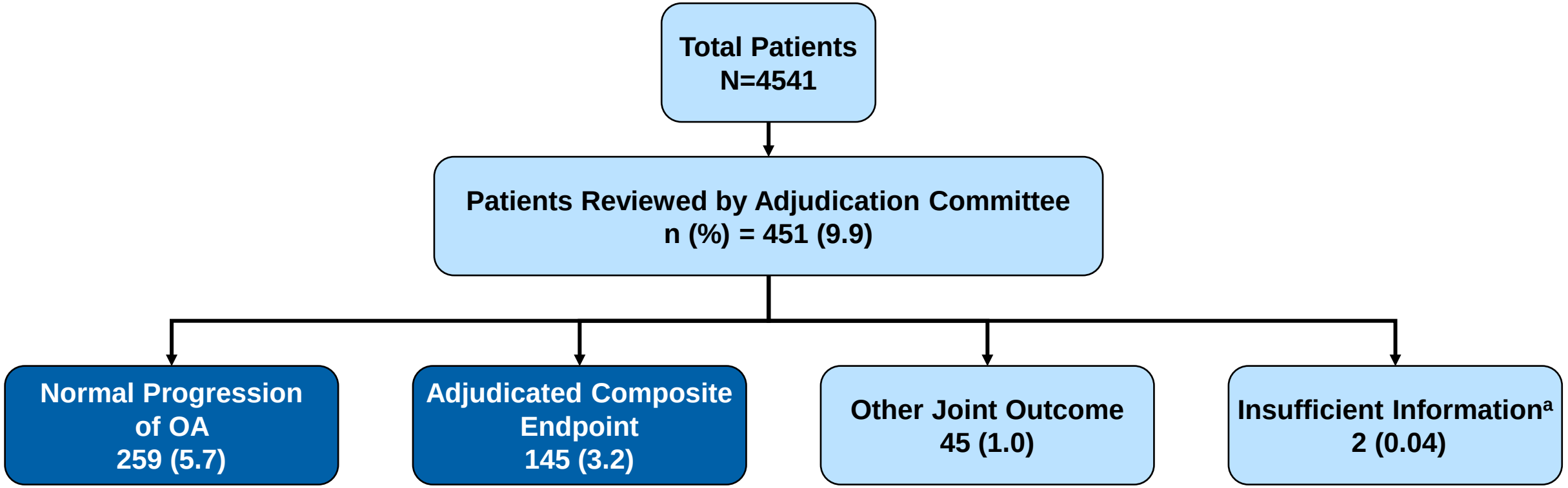
- Rapidly Progressive OA Type 1: Significant loss of joint space width ≥2 mm (predicated on optimal joint positioning) within approximately 1 year, without gross structural failure[1,2]
- Rapidly Progressive OA Type 2: Abnormal bone loss or destruction, including limited or total collapse of at least one subchondral surface, which is not normally present in conventional end-stage OA[1]

1. Miller CG, et al. *Osteoarthritis Cartilage* 2015;23:S3-S7.
2. Tanezumab Adjudication Committee Charter

mm=milimeter

Identification of and Adjudication of Joint Safety Events

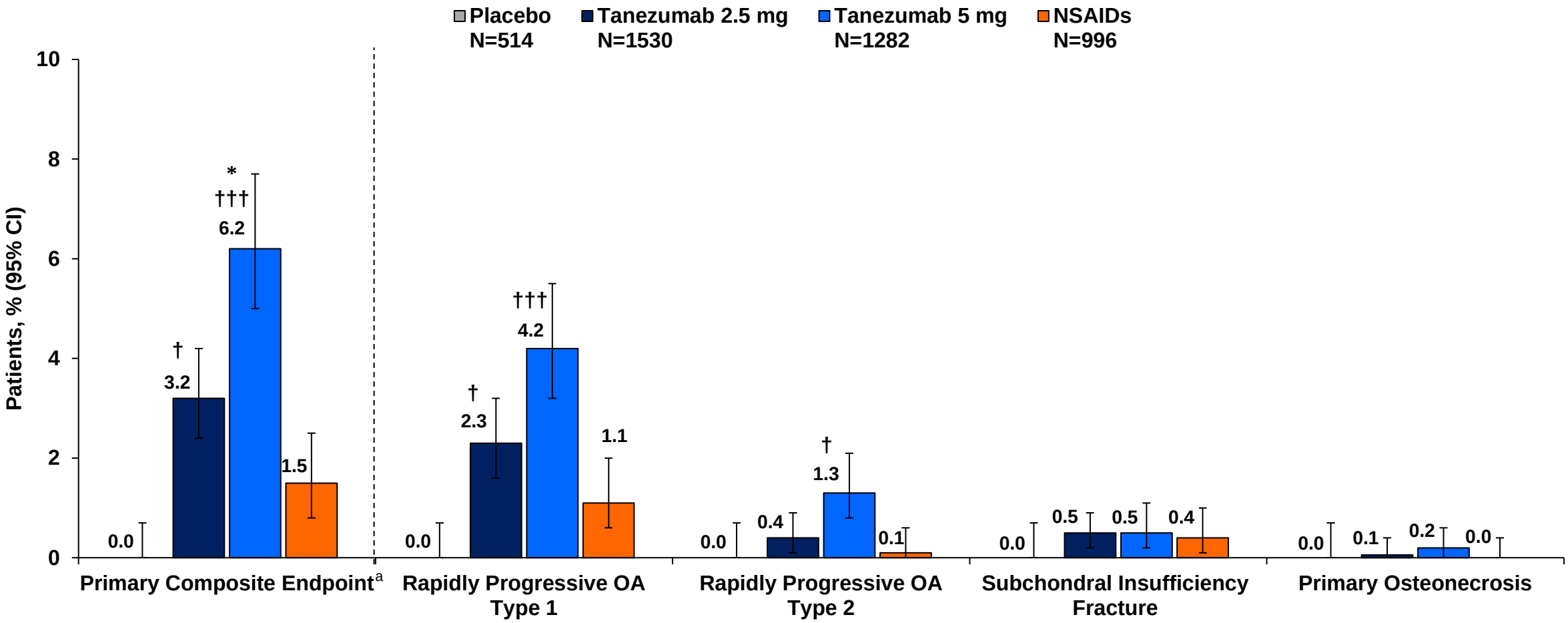
~10% of Patients Met Criteria for Adjudication; ~6% of Patients with Normal Progression of OA



a. Not enough information to distinguish rapid from normal progression of OA
Includes Studies 1056, 1057 and 1058 (Composite Endpoint-Primary Outcome; Individual Components-All Outcomes)

Post-2015 Phase 3 OA Studies: Adjudication Outcomes

Rapidly Progressive OA Type 1 Most Common Adjudicated Endpoint



a. No patients adjudicated with pathological fracture

Data not shown for Study 1056 2.5/5 mg treatment group: Composite endpoint, 0.5%; RPOA-1, 0.5%; RPOA-2, 0%; Subchondral Insufficiency Fracture, 0%; Osteonecrosis, 0%

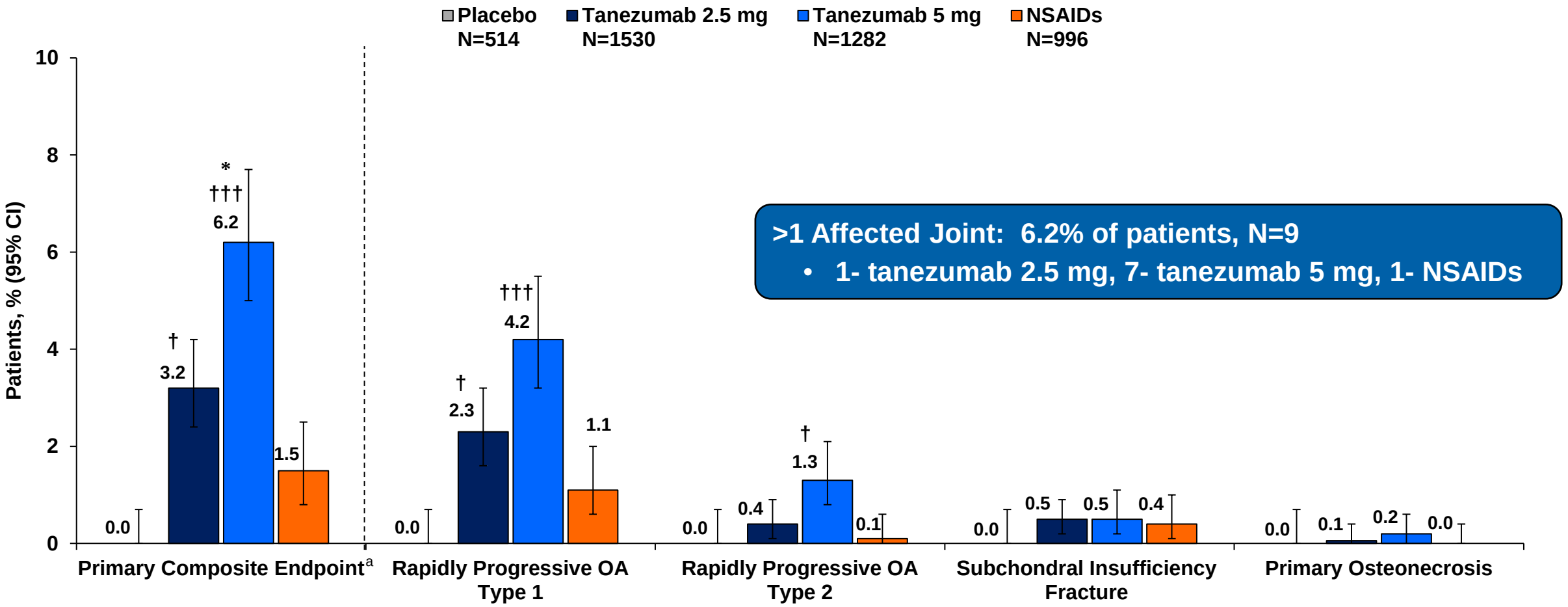
*p≤0.05; **p≤0.01; ***p≤0.001 vs placebo (based on comparison of data from Studies 1056/1057)

†p≤0.05; ††p≤0.01; †††p≤0.001 vs NSAIDs (based on comparisons of data from Study 1058)

Studies 1056, 1057 and 1058 (Composite Endpoint-Primary Outcome; Individual Components-All Outcomes)

Post-2015 Phase 3 OA Studies: Adjudication Outcomes

Rapidly Progressive OA Type 1 Most Common Adjudicated Endpoint



>1 Affected Joint: 6.2% of patients, N=9

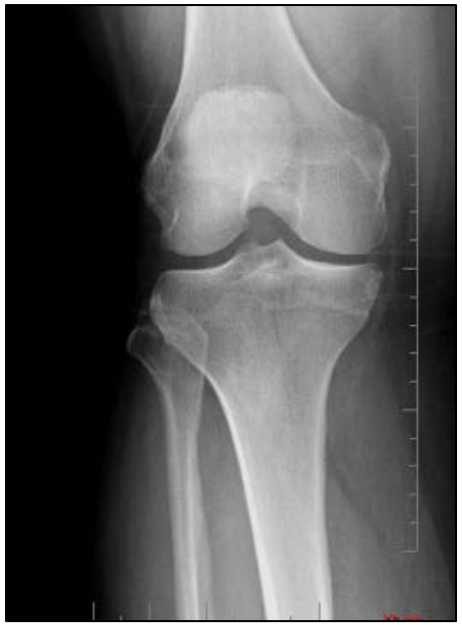
- **1- tanezumab 2.5 mg, 7- tanezumab 5 mg, 1- NSAIDs**

a. No patients adjudicated with pathological fracture
Data not shown for Study 1056 2.5/5 mg treatment group: Composite endpoint, 0.5%; RPOA-1, 0.5%; RPOA-2, 0%; Subchondral Insufficiency Fracture, 0%; Osteonecrosis, 0%
*p≤0.05; **p≤0.01; ***p≤0.001 vs placebo (based on comparison of data from Studies 1056/1057)
†p≤0.05; ††p≤0.01; †††p≤0.001 vs NSAIDs (based on comparisons of data from Study 1058)
Studies 1056, 1057 and 1058 (Composite Endpoint-Primary Outcome; Individual Components-All Outcomes)

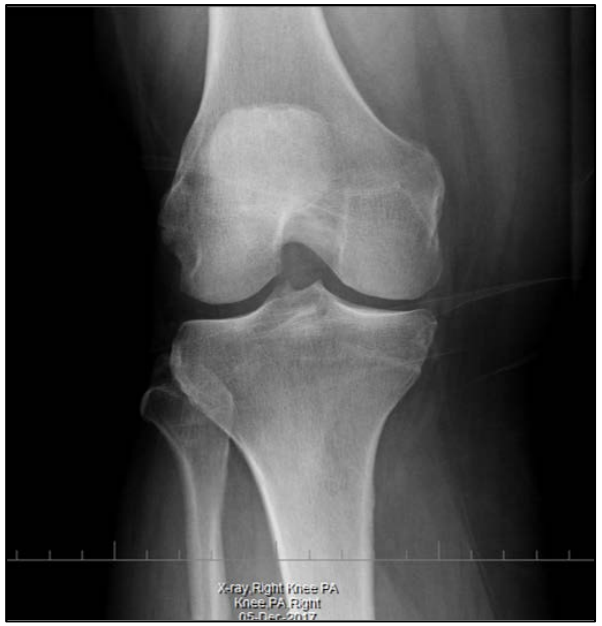
Example of Progression: Rapidly Progressive OA Type 1 in Knee

Loss of ≥2 mm of Joint Space Width

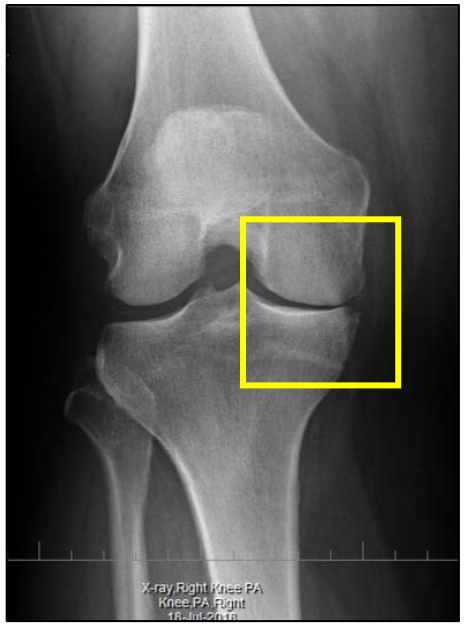
Rapidly Progressive OA Type 1: Significant loss of joint space width ≥2 mm (predicated on optimal joint positioning) within approximately 1 year, without gross structural failure[a]



Screening
Medial JSW = 3.4 mm



6 Months
Medial JSW = 3.2 mm



13 Months
Medial JSW = 1.0 mm

Example case: Loss of 2.4 mm JSW in medial compartment

Extrusion and/or maceration of meniscus and some changes in cartilage associated with identification of Rapidly Progressive OA Type 1

a. Predicated on optimal positioning and other technical issues associated with the radiological assessment

Rapidly Progressive OA Type 1 Characterization

~77% of RPOA-1 Events in KL Grade 2/3 Joints; 15% of RPOA-1 Events Led to TJR

Characteristics % of Joints with Rapidly Progressive OA Type 1	N=101 Patients (106 Joints) Tanezumab 2.5 mg = 35 Patients
Affected Joint	Knee: 83% Hip: 16% Shoulder: 1% (Tanezumab 5 mg = 1 patient)
Baseline Kellgren-Lawrence Grade of Affected Joint	KL Grade 2 or 3: ~77% KL Grade 1: 18% KL Grade 0: 4%
TJR in Affected Joint	15% (KL Grade 2 or 3 joints: 15/16) (Tanezumab 2.5 mg = 4 patients) (NSAIDs = 2 patients)
Patients with ≥1 Rapidly Progressive OA Type 1 Joint	5 patients (Tanezumab 2.5 mg = 1 patient)

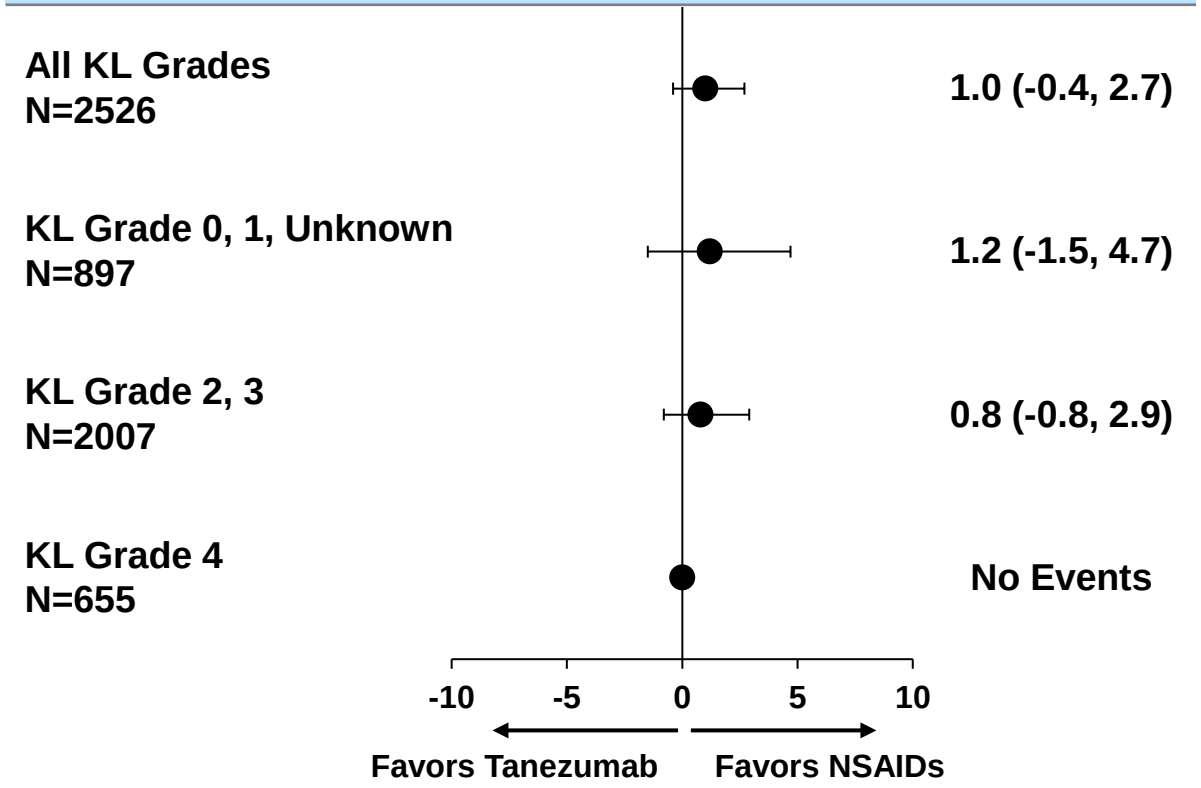
Studies 1056, 1057 and 1058; all treatment groups
During treatment period or 24-week post-treatment follow-up period

Rapidly Progressive OA Type 1: Tanezumab 2.5 mg vs NSAIDs

Risk Differences Similar Across Patients with KL Grade ≤3 Joints

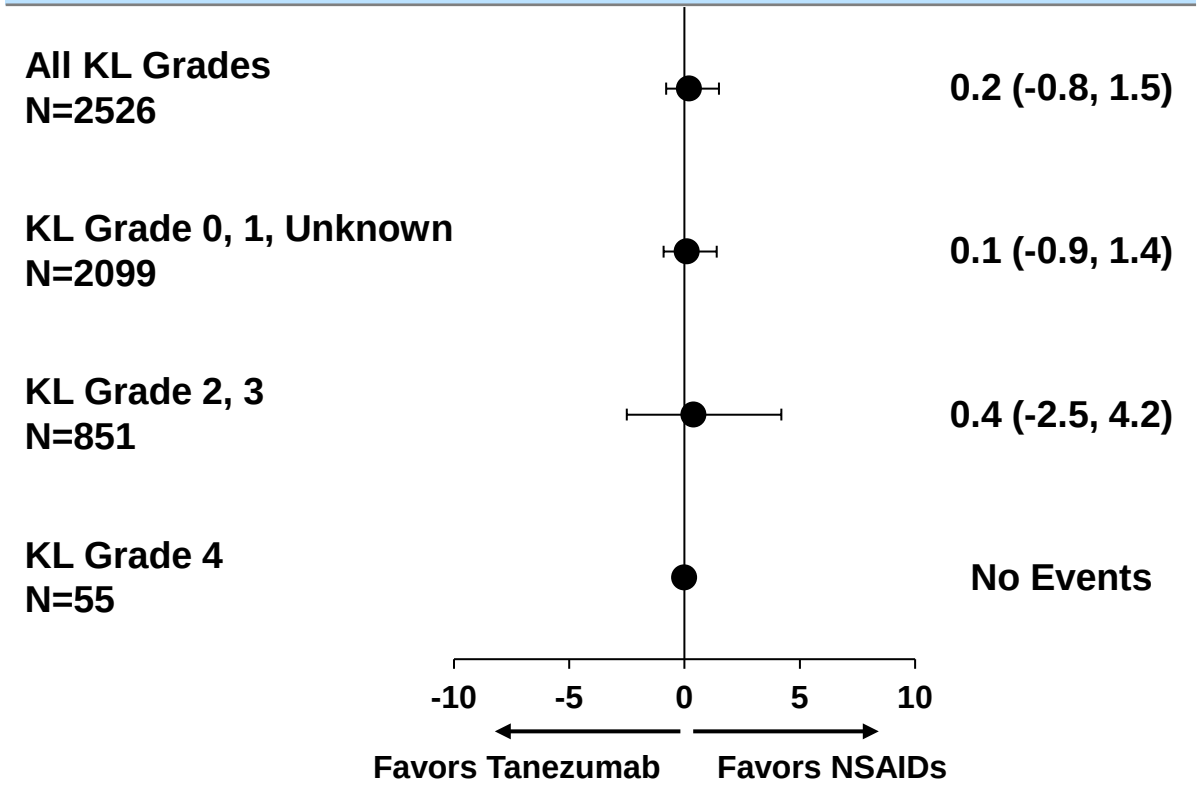
Knee Joints

Risk Difference for Incidence for Patients with ≥1 Affected Joint % (95% CI)



Hip Joints

Risk Difference for Incidence for Patients with ≥1 Affected Joint % (95% CI)



Studies 1056, 1057 and 1058
Patient-level analysis
Patients can be represented in more than one KL subcategory

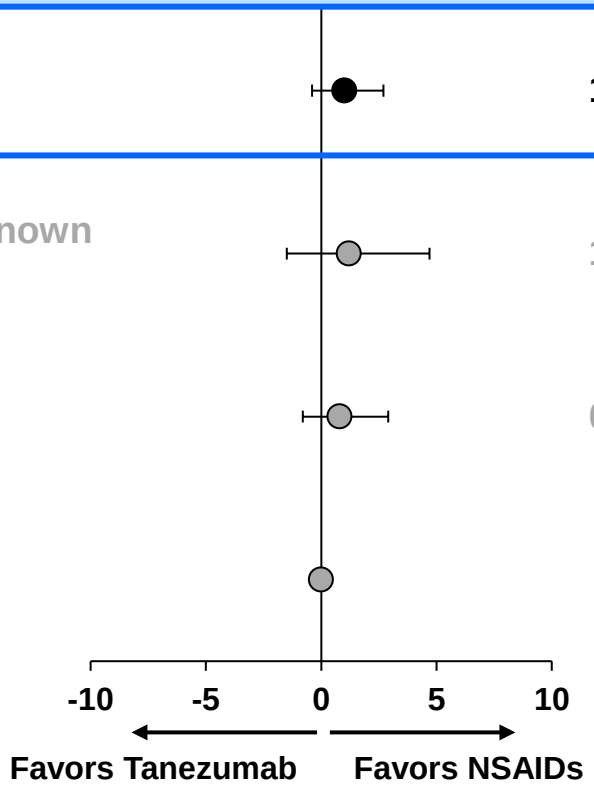
Rapidly Progressive OA Type 1: Tanezumab 2.5 mg vs NSAIDs

Risk Differences Similar Across Patients with KL Grade ≤3 Joints

Knee Joints

Risk Difference for Incidence for Patients with ≥1 Affected Joint % (95% CI)

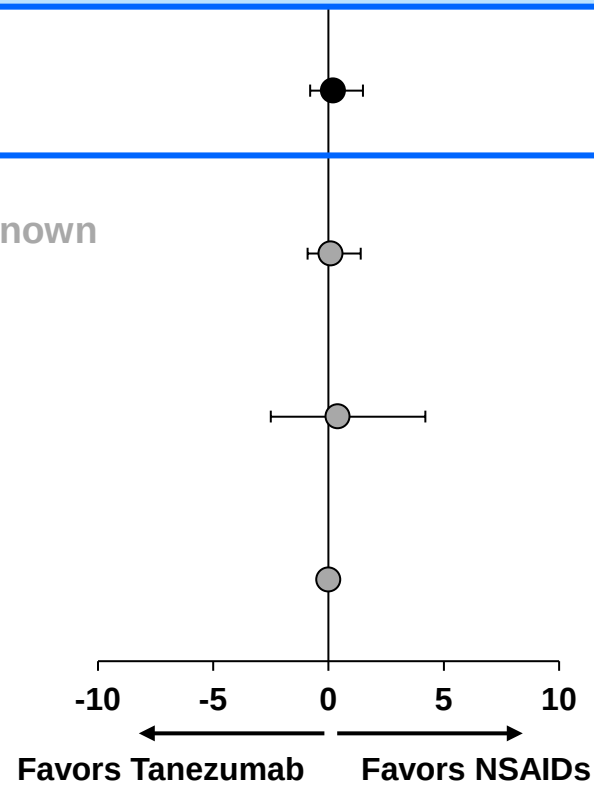
All KL Grades N=2526	**1.0 (-0.4, 2.7)**
KL Grade 0, 1, Unknown N=897	1.2 (-1.5, 4.7)
KL Grade 2, 3 N=2007	0.8 (-0.8, 2.9)
KL Grade 4 N=655	No Events



Hip Joints

Risk Difference for Incidence for Patients with ≥1 Affected Joint % (95% CI)

All KL Grades N=2526	**0.2 (-0.8, 1.5)**
KL Grade 0, 1, Unknown N=2099	0.1 (-0.9, 1.4)
KL Grade 2, 3 N=851	0.4 (-2.5, 4.2)
KL Grade 4 N=55	No Events



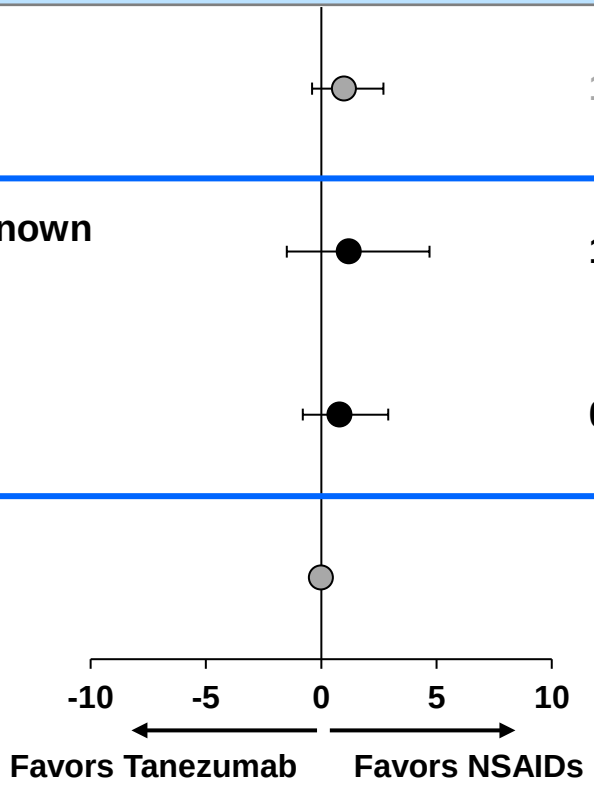
Studies 1056, 1057 and 1058
Patient-level analysis
Patients can be represented in more than one KL subcategory

Rapidly Progressive OA Type 1: Tanezumab 2.5 mg vs NSAIDs

Risk Differences Similar Across Patients with KL Grade ≤3 Joints

Knee Joints

Risk Difference for Incidence for Patients with ≥1 Affected Joint % (95% CI)



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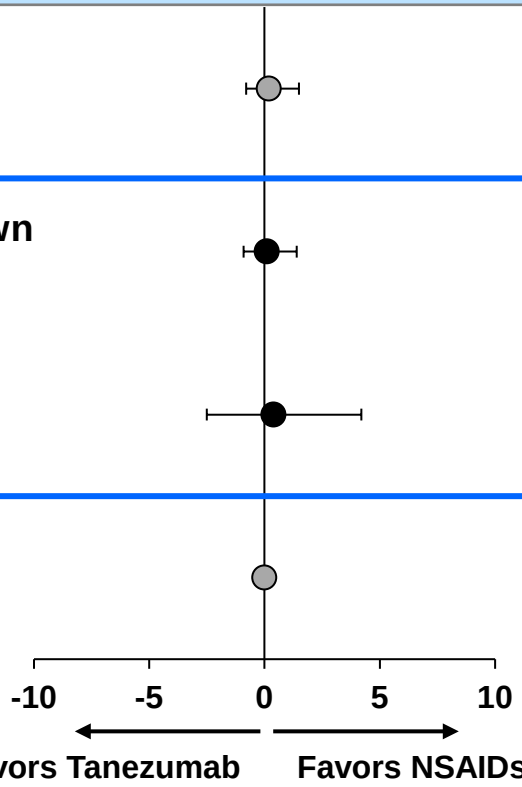
Hip Joints

Risk Difference for Incidence for Patients with ≥1 Affected Joint % (95% CI)



All KL Grades N=2526	0.2 (-0.8, 1.5)
KL Grade 0, 1, Unknown N=2099	**0.1 (-0.9, 1.4)**
KL Grade 2, 3 N=851	**0.4 (-2.5, 4.2)**
KL Grade 4 N=55	No Events

Studies 1056, 1057 and 1058
Patient-level analysis
Patients can be represented in more than one KL subcategory

Comparison of RPOA-1 and Normal Progression of OA Events

Many Similarities in Musculoskeletal Profile

Joint-Level Summary Knee and Hip Joints, n (%)	Tanezumab 2.5 mg N=133 Patients	
	Rapidly Progressive OA Type 1 N=35 Patients n=36 Affected Joints	Normal Progression of OA N=98 Patients n=106 Affected Joints
Affected Joint: Knee	30 (83.3)	73 (68.9)
Total Joint Replacement	4 (11.1)	80 (75.5)
Index Joint	19 (52.8)	80 (75.5)
KL Grade	KL Grade 2/3: 27 (75.0) KL Grade 4: 0 (0)	KL Grade 2/3: 53 (50.0) KL Grade 4: 52 (48.1)

a. Includes MSK exam results up to and including the date of the adjudicated outcome
Studies 1056, 1057 and 1058
MSK=Musculoskeletal

Comparison of RPOA-1 and Normal Progression of OA Events

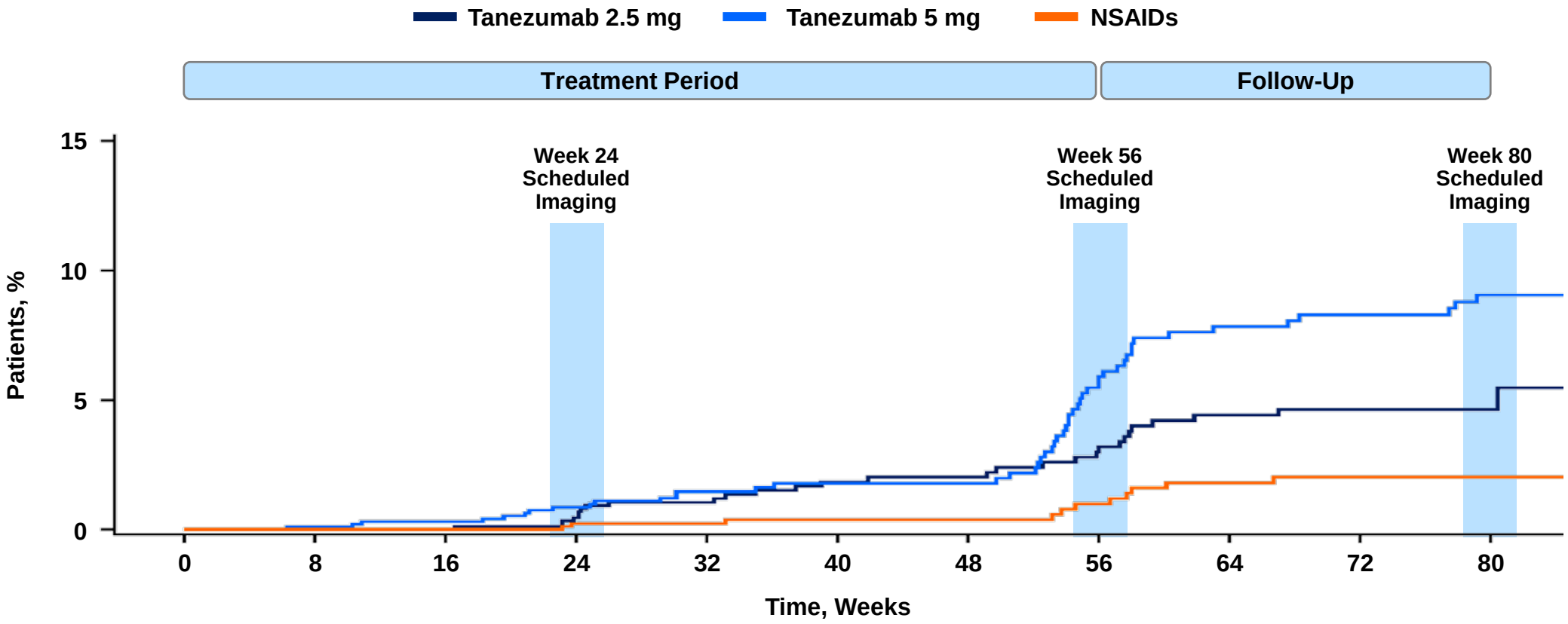
Many Similarities in Musculoskeletal Profile; Change in MSK Exam in RPOA-1 More Common

Joint-Level Summary Knee and Hip Joints, n (%)	Tanezumab 2.5 mg N=133 Patients	
	Rapidly Progressive OA Type 1 N=35 Patients n=36 Affected Joints	Normal Progression of OA N=98 Patients n=106 Affected Joints
Affected Joint: Knee	30 (83.3)	73 (68.9)
Total Joint Replacement	4 (11.1)	80 (75.5)
Index Joint	19 (52.8)	80 (75.5)
KL Grade	KL Grade 2/3: 27 (75.0) KL Grade 4: 0 (0)	KL Grade 2/3: 53 (50.0) KL Grade 4: 52 (48.1)
Abnormal MSK Exam at Baseline	28 (77.8)	93 (87.7)
Pain on motion	19 (52.8)	70 (66.0)
Crepitus	19 (52.8)	45 (42.5)
Tenderness	11 (30.6)	42 (39.6)
Decreased range of motion	9 (25.0)	48 (45.3)
Change in MSK Exam Post-Baseline[a]	14 (38.9)	22 (20.8)
Clinically significant	6 (16.7)	15 (14.2)

a. Includes MSK exam results up to and including the date of the adjudicated outcome
Studies 1056, 1057 and 1058
MSK=Musculoskeletal

Rapidly Progressive OA Type 1: Time to Event in Study 1058

Most Events Identified at Week 56 Imaging Visit



Week		0	24	56	80
Patients	2.5 mg	1002	855	489	259
	5 mg	998	873	450	238
	NSAIDs	996	866	489	254

Tanezumab 2.5 mg vs NSAIDs p=0.0043
Tanezumab 5 mg vs NSAIDs p<0.0001

Rapidly Progressive OA Type 1 by Study Interval

Most RPOA-1 Events Occurred After Week 24 Through Week 56 in Study 1058

Incidence of Rapidly Progressive OA Type 1 by Interval

	Tanezumab 2.5 mg N=1002 n/N (%)	NSAID N=996 n/N (%)
All RPOA-1 Events	29/1002 (2.9)	11/996 (1.1)
Through Week 24	9/1002 (0.9)	2/996 (0.2)
After Week 24 through Week 56	17/822 (2.1)	8/815 (1.0)
After Week 56	3/466 (0.6)	1/473 (0.2)

Week 24 and Week 56 imaging visits defined as Study Days 169 and 393, respectively, +/- 4 weeks

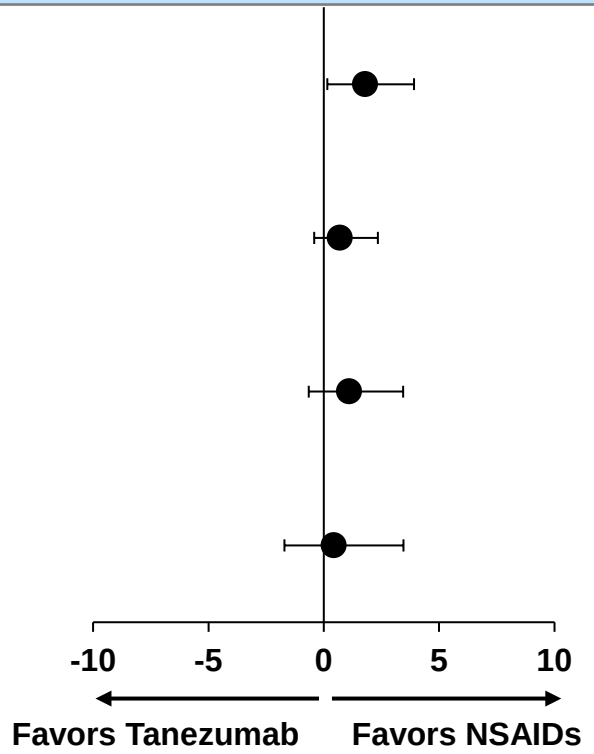
Rapidly Progressive OA Type 1 by Study Interval

Risk Differences for Tanezumab 2.5 mg vs NSAIDs ≤1.8% Across Intervals in Study 1058

Incidence of Rapidly Progressive OA Type 1 by Interval

	Tanezumab 2.5 mg N=1002 n/N (%)	NSAID N=996 n/N (%)	Patients with ≥1 Affected Joint % (95% CI)
All RPOA-1 Events	29/1002 (2.9)	11/996 (1.1)	1.8 (0.2, 3.9)
Through Week 24	9/1002 (0.9)	2/996 (0.2)	0.7 (-0.4, 2.4)
After Week 24 through Week 56	17/822 (2.1)	8/815 (1.0)	1.1 (-0.7, 3.4)
After Week 56	3/466 (0.6)	1/473 (0.2)	0.4 (-1.7, 3.5)

Risk Differences for Tanezumab 2.5 mg vs NSAIDs Rapidly Progressive OA Type 1 by Interval



Week 24 and Week 56 imaging visits defined as Study Days 169 and 393, respectively, +/- 4 weeks

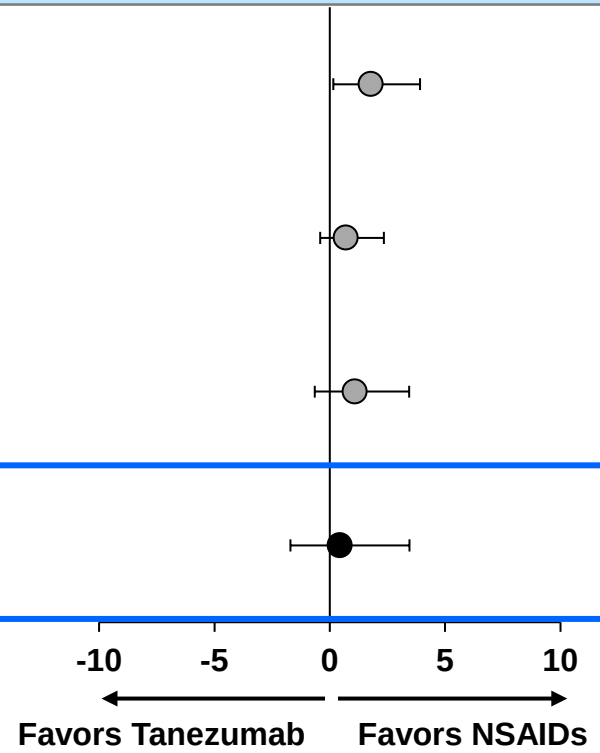
Rapidly Progressive OA Type 1 by Study Interval

Risk Differences for Tanezumab 2.5 mg vs NSAIDs ≤1.8% Across Intervals in Study 1058

Incidence of Rapidly Progressive OA Type 1 by Interval

	Tanezumab 2.5 mg N=1002 n/N (%)	NSAID N=996 n/N (%)	Patients with ≥1 Affected Joint % (95% CI)
All RPOA-1 Events	29/1002 (2.9)	11/996 (1.1)	1.8 (0.2, 3.9)
Through Week 24	9/1002 (0.9)	2/996 (0.2)	0.7 (-0.4, 2.4)
After Week 24 through Week 56	17/822 (2.1)	8/815 (1.0)	1.1 (-0.7, 3.4)
After Week 56	**3/466 (0.6)**	**1/473 (0.2)**	**0.4 (-1.7, 3.5)**

Risk Differences for Tanezumab 2.5 mg vs NSAIDs Rapidly Progressive OA Type 1 by Interval

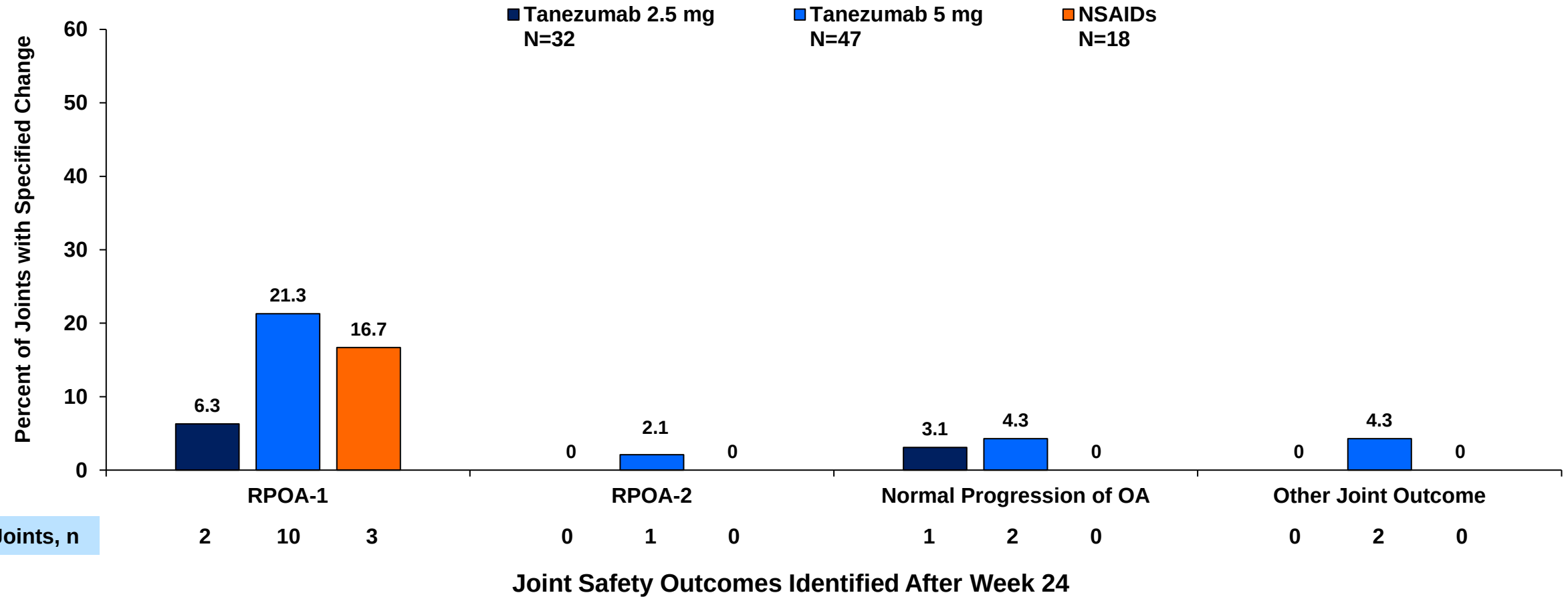


Week 24 and Week 56 imaging visits defined as Study Days 169 and 393, respectively, +/- 4 weeks

Adjudicated Joint Safety Outcomes Identified After Week 24 in Patients who Received 48 to 56 Weeks of Study Medication Treatment

Joints with Loss of JSW from 1 mm to <2 mm at Week 24

No patients subsequently developed RPOA-2 with continued treatment with tanezumab 2.5 mg



Study 1058; All KL Grades

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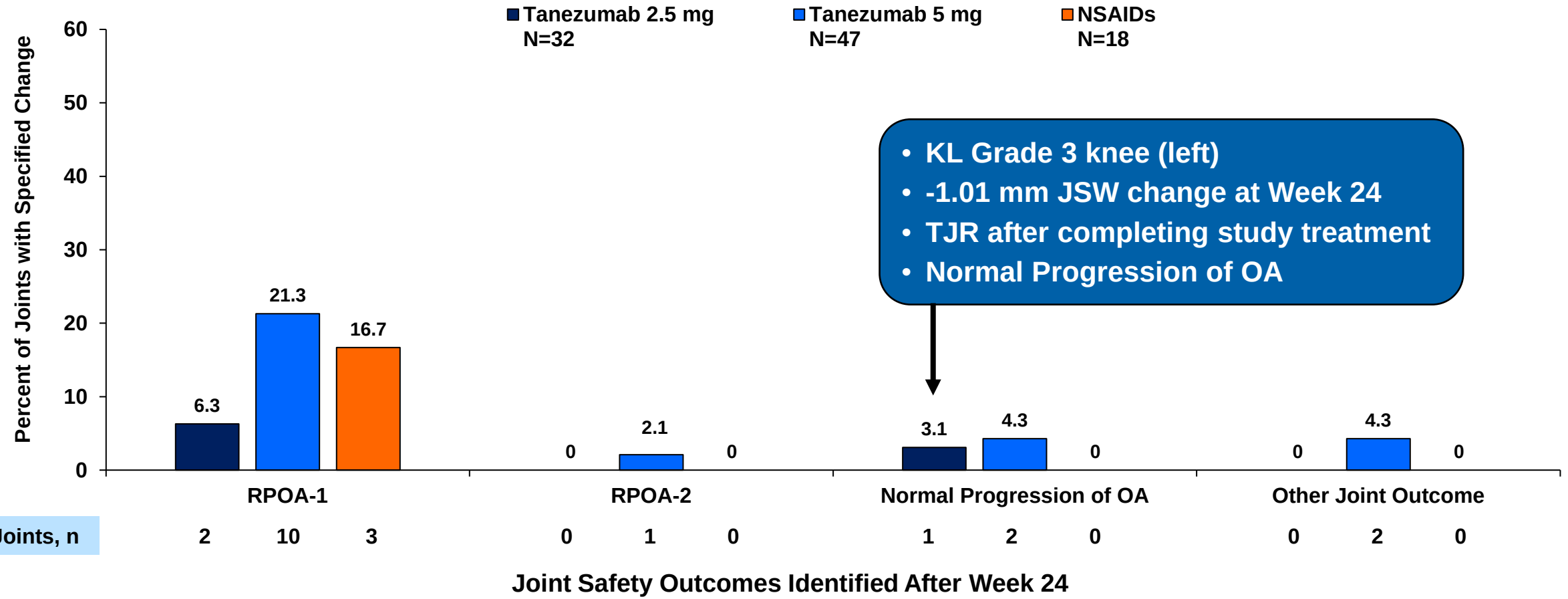
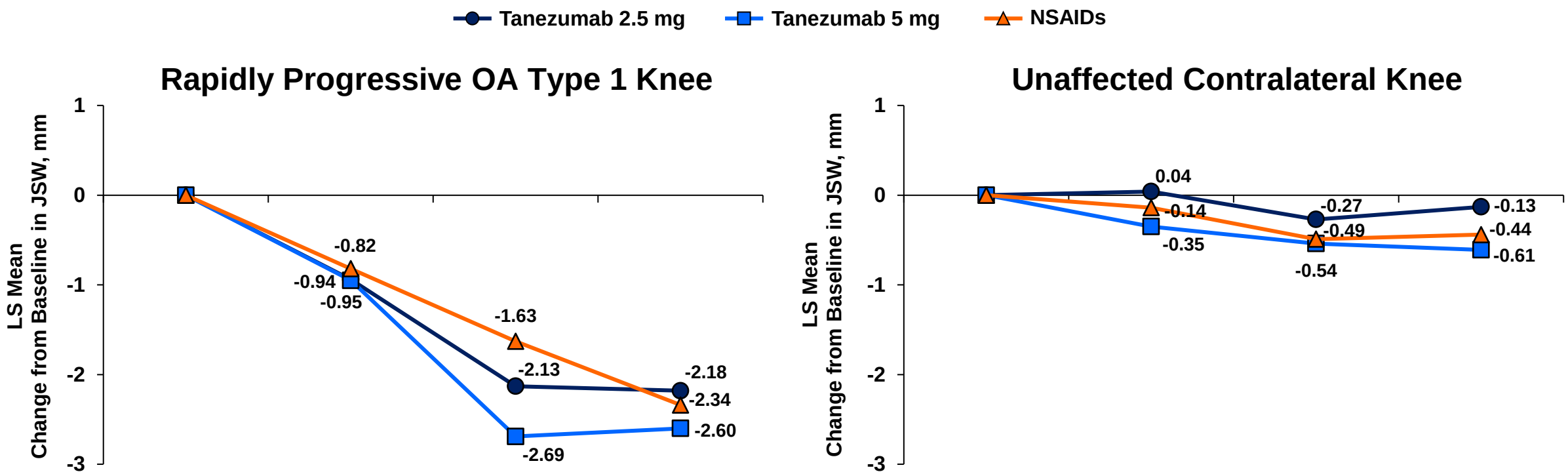


Study 1058; All KL Grades

Medial Knee JSW: Rapidly Progressive OA Type 1 Knee vs Contralateral Knee

Decreases in JSW Observed in RPOA-1 Knees not Observed in Contralateral Knee



	Baseline (Medial JSW Median)	Number of Knees		
		Week 24	Week 56	Week 80
2.5 mg	24 (3.9 mm)	22	13	9
5 mg	38 (3.5 mm)	36	28	16
NSAIDs	8 (3.9 mm)	7	5	2

	Baseline (Medial JSW Median)	Number of Knees		
		Week 24	Week 56	Week 80
2.5 mg	22 (4.0 mm)	21	12	8
5 mg	33 (2.3 mm)	32	26	14
NSAIDs	7 (2.1 mm)	6	4	2

Study 1058; Includes all baseline KL Grades except for KL Grade 4

Rapidly Progressive OA Type 1 Key Findings

- Incidence of RPOA-1 (2.3%) was statistically significantly greater than placebo (0%) or NSAIDs (1.1%)
- Most events occurred in knees (83%), KL Grade 2 or 3 joints (77%), and did not lead to TJR (85%)
- The pattern of occurrence of RPOA-1 during treatment with tanezumab 2.5 mg was similar to NSAID treatment
- After the treatment period, the risk of RPOA-1 relative to NSAIDs decreased
- Continued treatment of patients with potentially important joint space narrowing (1 mm to <2 mm) did not result in increased joint safety events
- Increased risk of developing RPOA-1 appears to be at the joint-level rather than at the patient-level
  - Significant decreases in JSW not observed in contralateral knee joints of patients with RPOA-1

Rapidly Progressive OA Type 2 Characterization

~77% of RPOA-2 Events in KL Grade 3/4 Joints; 54% of RPOA-2 Events Led to TJR

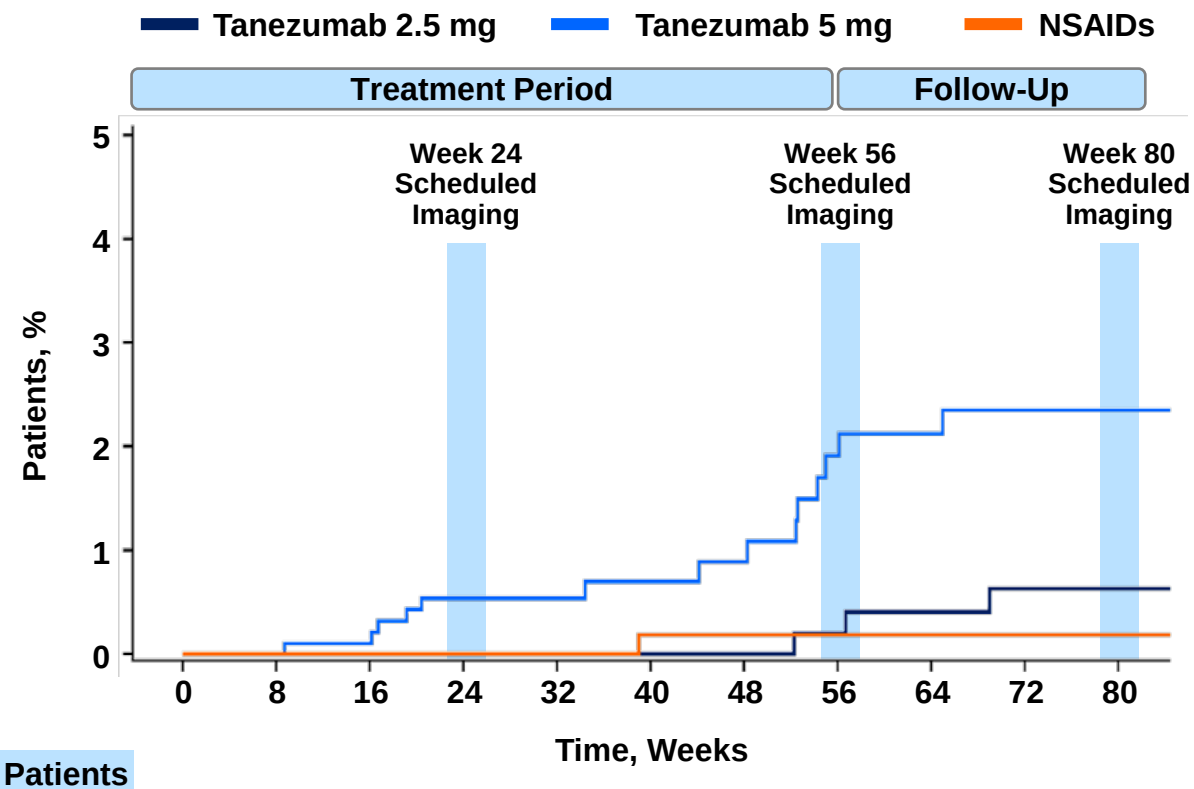
Characteristics % of Joints with Rapidly Progressive OA Type 2	N=24 Patients (26 Joints) Tanezumab 2.5 mg = 6 Patients
Affected Joint	Knee: 42% Hip: 50% Shoulder: 8% (No tanezumab 2.5 mg)
Baseline Kellgren-Lawrence Grade of Affected Joint	KL Grade 3 or 4: ~77% KL Grade 1/2: 8% (No tanezumab 2.5 mg) KL Grade 0: 8% (No tanezumab 2.5 mg)
TJR in Affected Joint	54% (Tanezumab 2.5 mg = 3/3 were KL Grade 4)
Patients with ≥1 Rapidly Progressive OA Type 2 Joint	2 patients (No tanezumab 2.5 mg)

Studies 1056, 1057 and 1058; all treatment groups
During treatment period or 24-week post-treatment follow-up period

Rapidly Progressive OA Type 2: Time to Event and By Period

Timing of Tanezumab 2.5 mg and NSAIDs Events Generally Similar

Time to Event



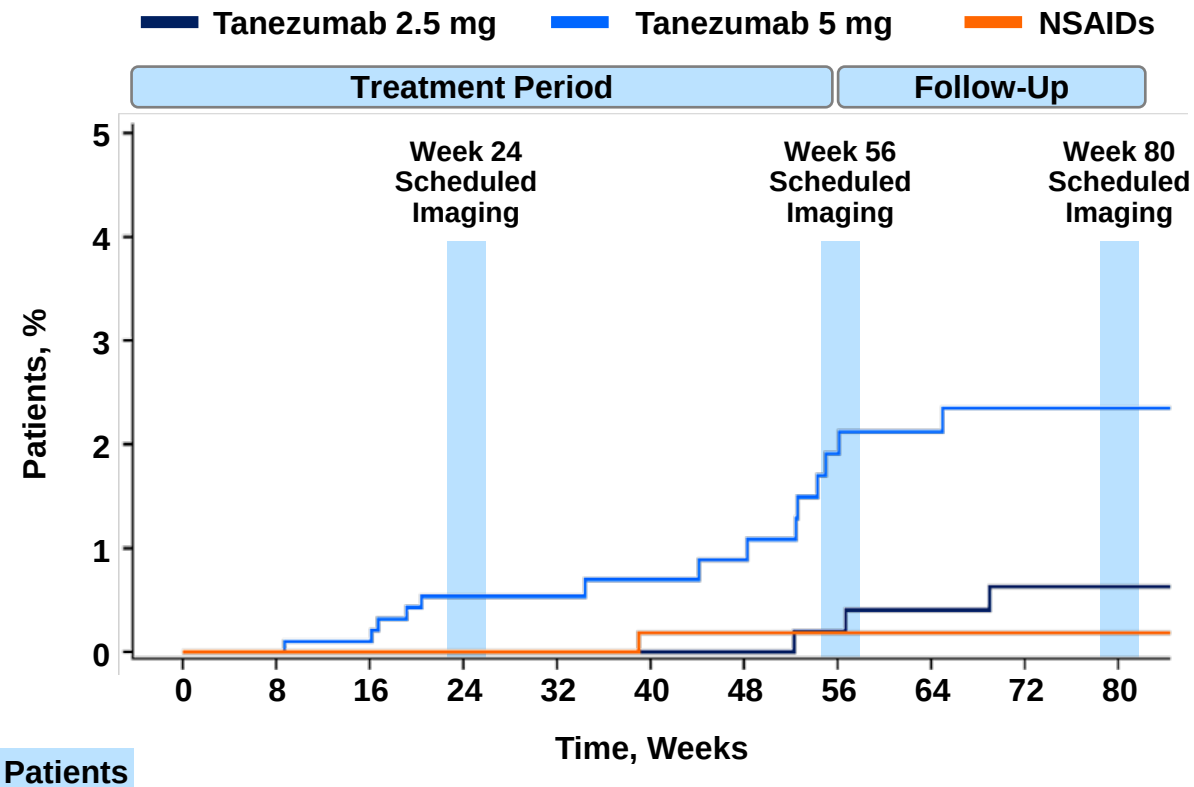
Patients				
2.5 mg	1002	859	494	264
5 mg	998	877	465	249
NSAIDs	996	868	492	259

Study 1058
Tanezumab 2.5 mg vs NSAIDs p=0.1261; Tanezumab 5 mg vs NSAIDs p=0.0006
Forest Plot: Week 24 and Week 56 imaging visits defined as Study Days 169 and 393, respectively, +/- 4 weeks

Rapidly Progressive OA Type 2: Time to Event and By Period

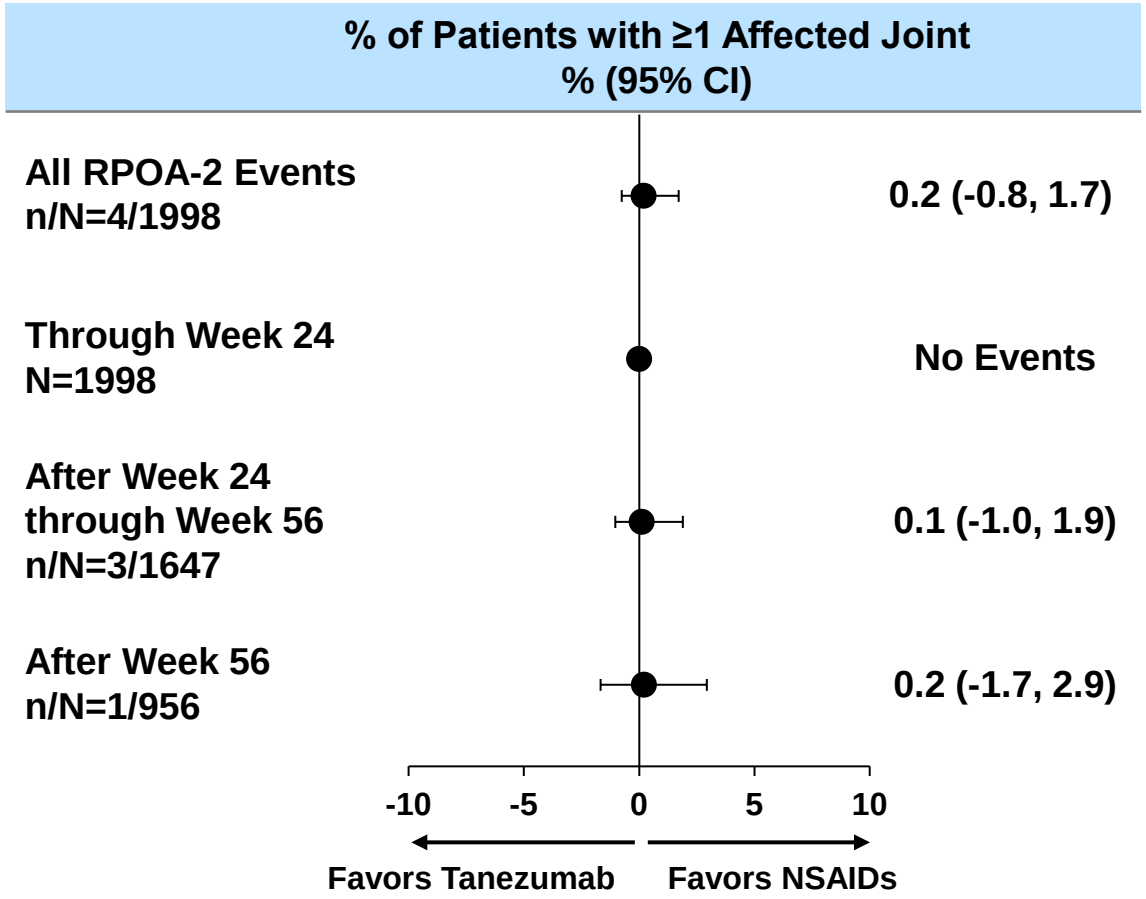
Timing of Tanezumab 2.5 mg and NSAIDs Events Generally Similar

Time to Event



Patients				
2.5 mg	1002	859	494	264
5 mg	998	877	465	249
NSAIDs	996	868	492	259

Risk Differences for Tanezumab 2.5 mg vs NSAIDs Rapidly Progressive OA Type 2 by Period



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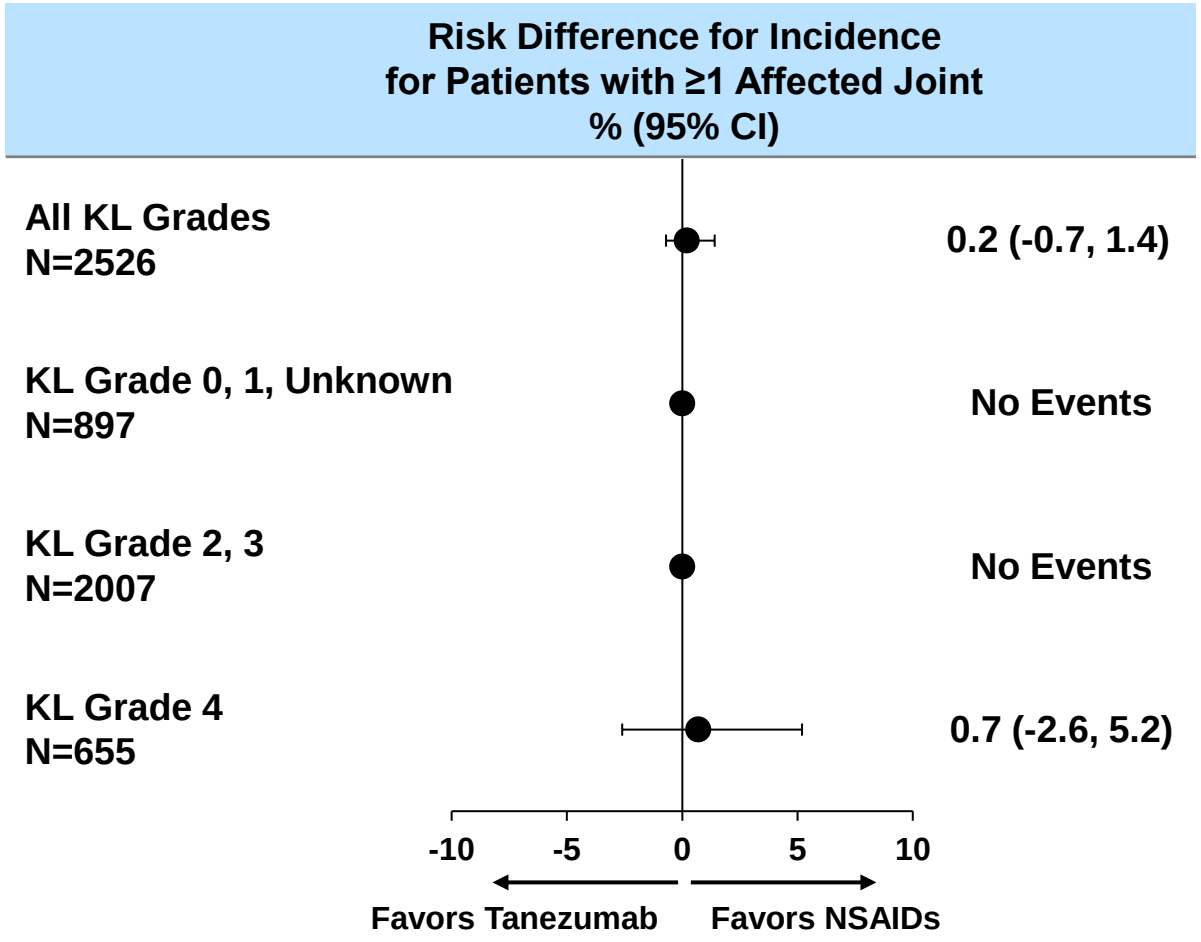
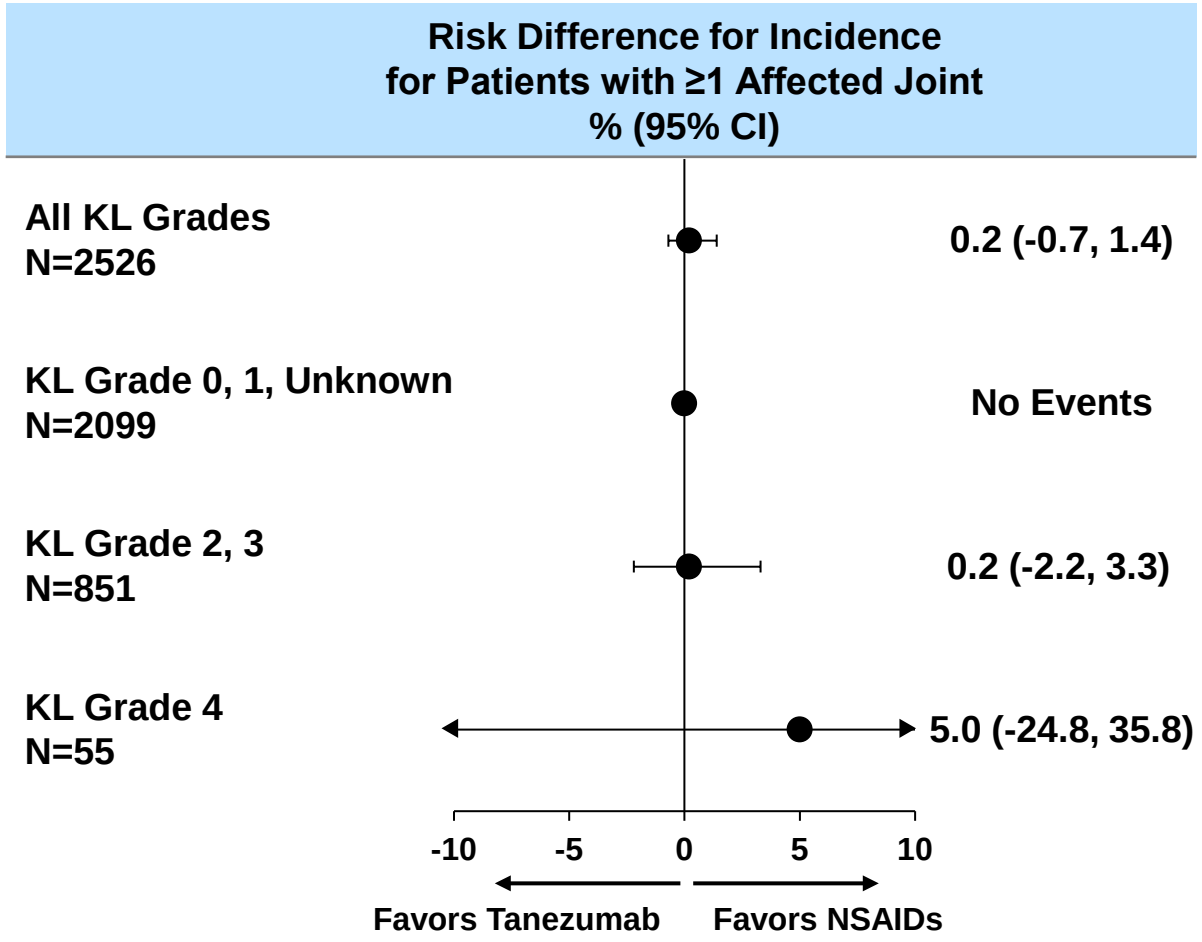
Rapidly Progressive OA Type 2: Tanezumab 2.5 mg vs NSAIDs

6 Total Events; Risk Difference Least Favorable for KL Grade 4 Hips

Knee Joints (n=3 Events)



Hip Joints (n=3 Events)



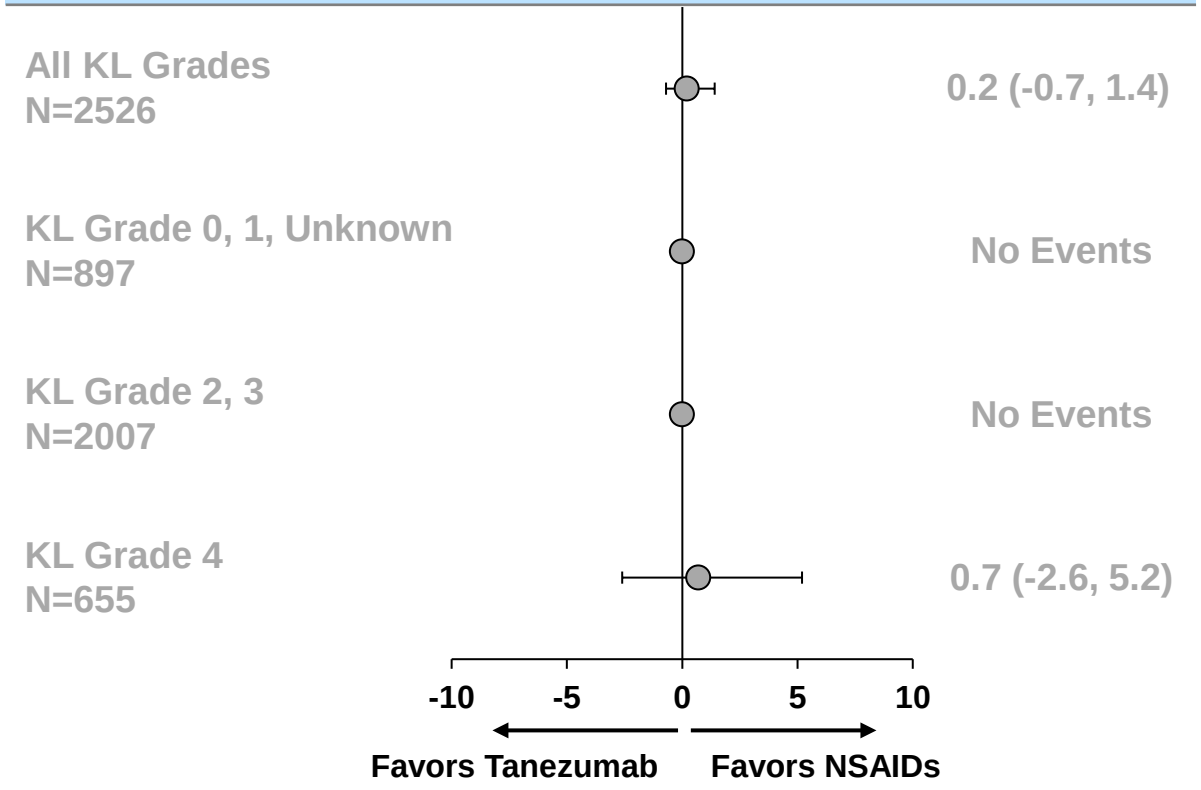
Studies 1056, 1057 and 1058
Patient-level analyses

Rapidly Progressive OA Type 2: Tanezumab 2.5 mg vs NSAIDs

6 Total Events; Risk Difference Least Favorable for KL Grade 4 Hips

Knee Joints (n=3 Events)

Risk Difference for Incidence for Patients with ≥1 Affected Joint % (95% CI)



Hip Joints (n=3 Events)

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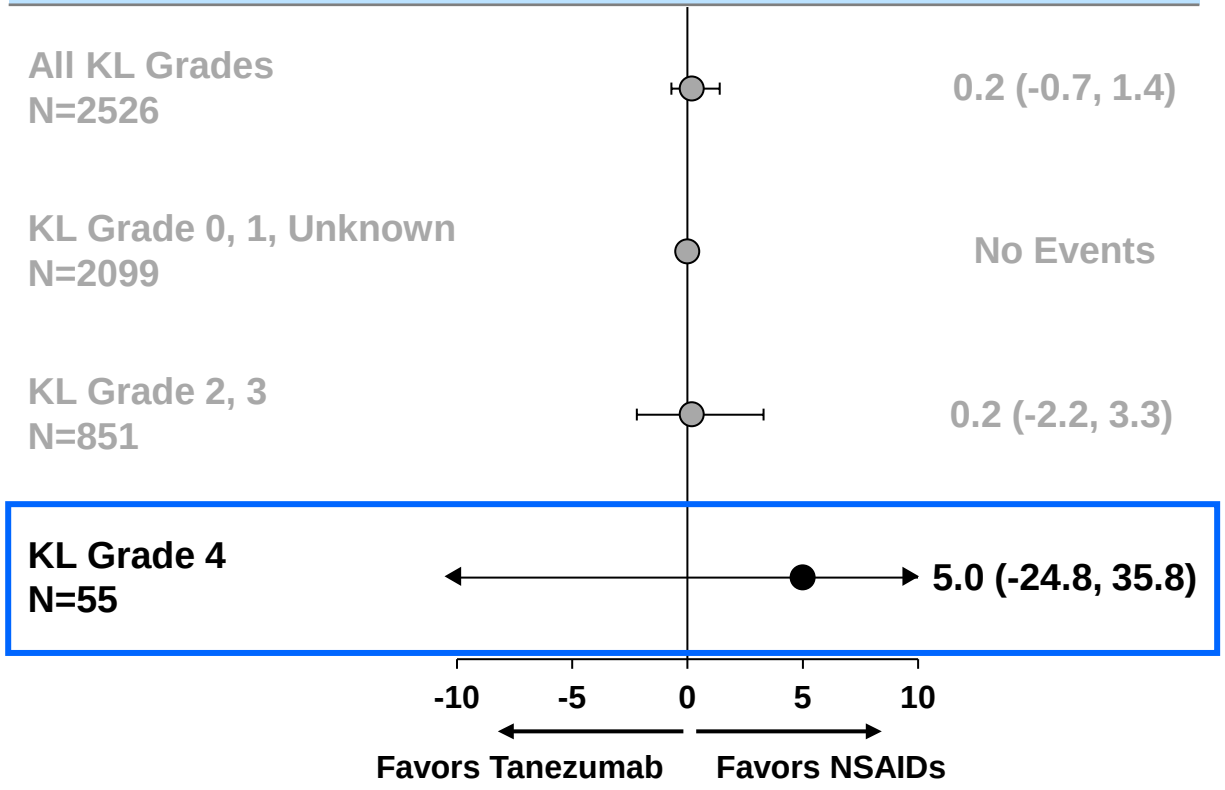
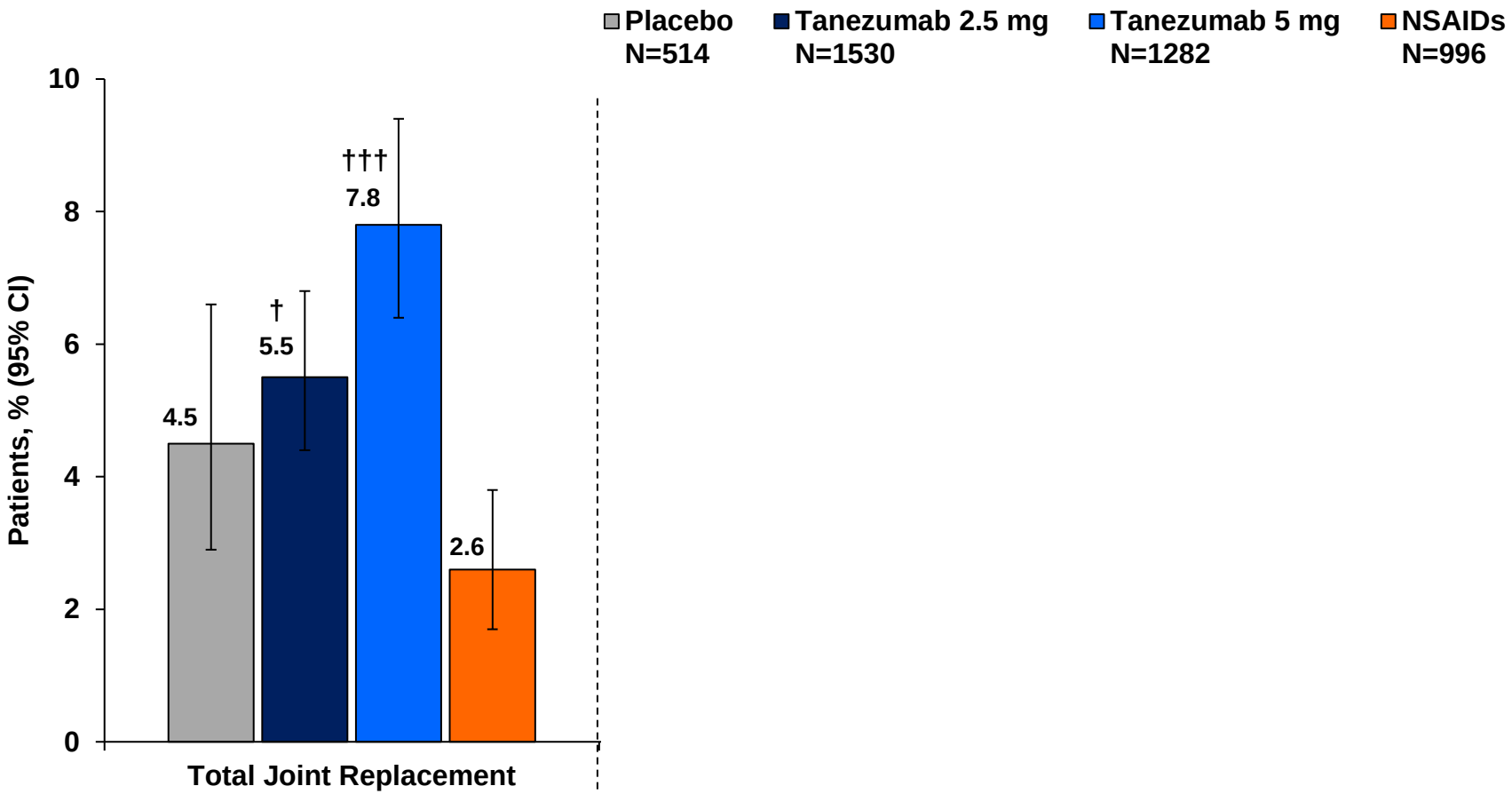


Studies 1056, 1057 and 1058
Patient-level analyses

Total Joint Replacements

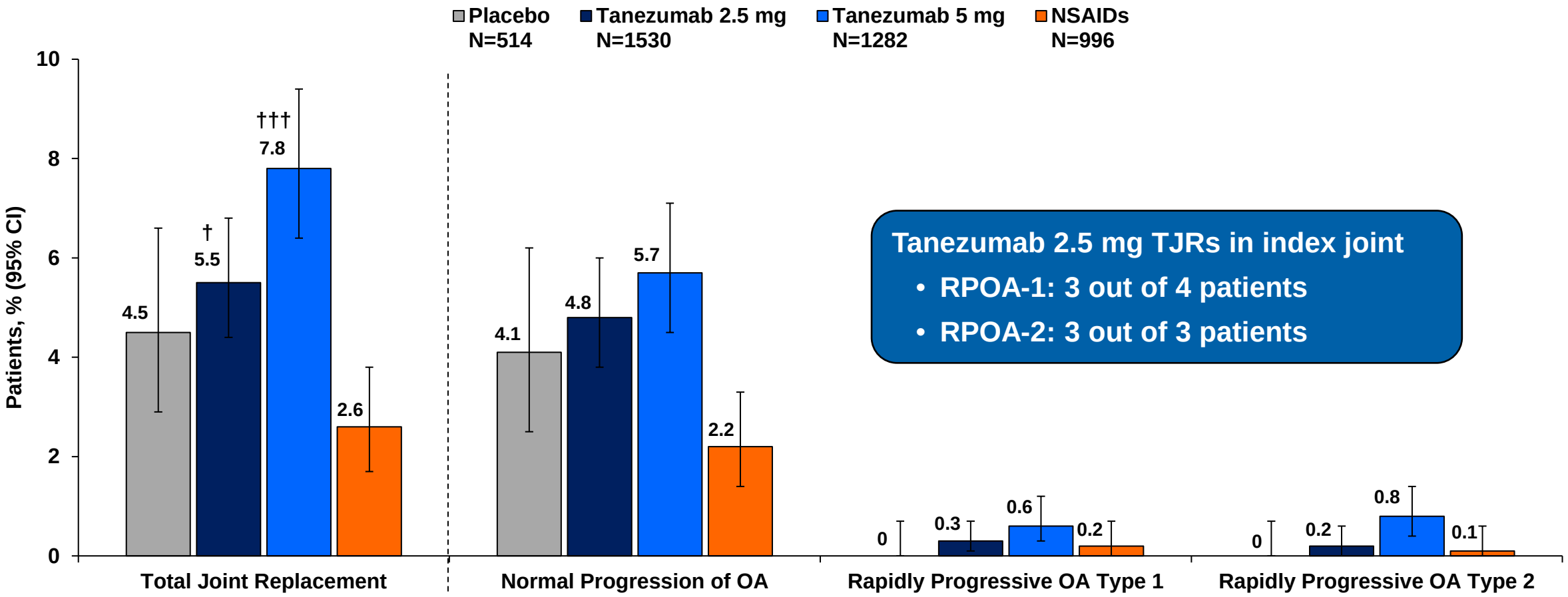
~85% of TJRs in KL Grade ≥3 Joints at Baseline



Studies 1056, 1057 and 1058
Data not shown for Study 1056 2.5/5 mg treatment group: 15 TJRs/219 patients (6.8%); 14 Normal Progression of OA and 1 RPOA-1
Statistical comparisons apply to incidence of TJR
*p≤0.05; **p≤0.01; ***p≤0.001 vs placebo (based on comparison of data from Studies 1056/1057)
†p≤0.05; ††p≤0.01; †††p≤0.001 vs NSAIDs (based on comparisons of data from Study 1058)

Total Joint Replacements

~85% of TJRs in KL Grade ≥3 Joints at Baseline; Most TJRs Associated with Normal Progression



Tanezumab 2.5 mg TJRs in index joint

- **RPOA-1: 3 out of 4 patients**
- **RPOA-2: 3 out of 3 patients**

Studies 1056, 1057 and 1058
Data not shown for Study 1056 2.5/5 mg treatment group: 15 TJRs/219 patients (6.8%); 14 Normal Progression of OA and 1 RPOA-1
Statistical comparisons apply to incidence of TJR
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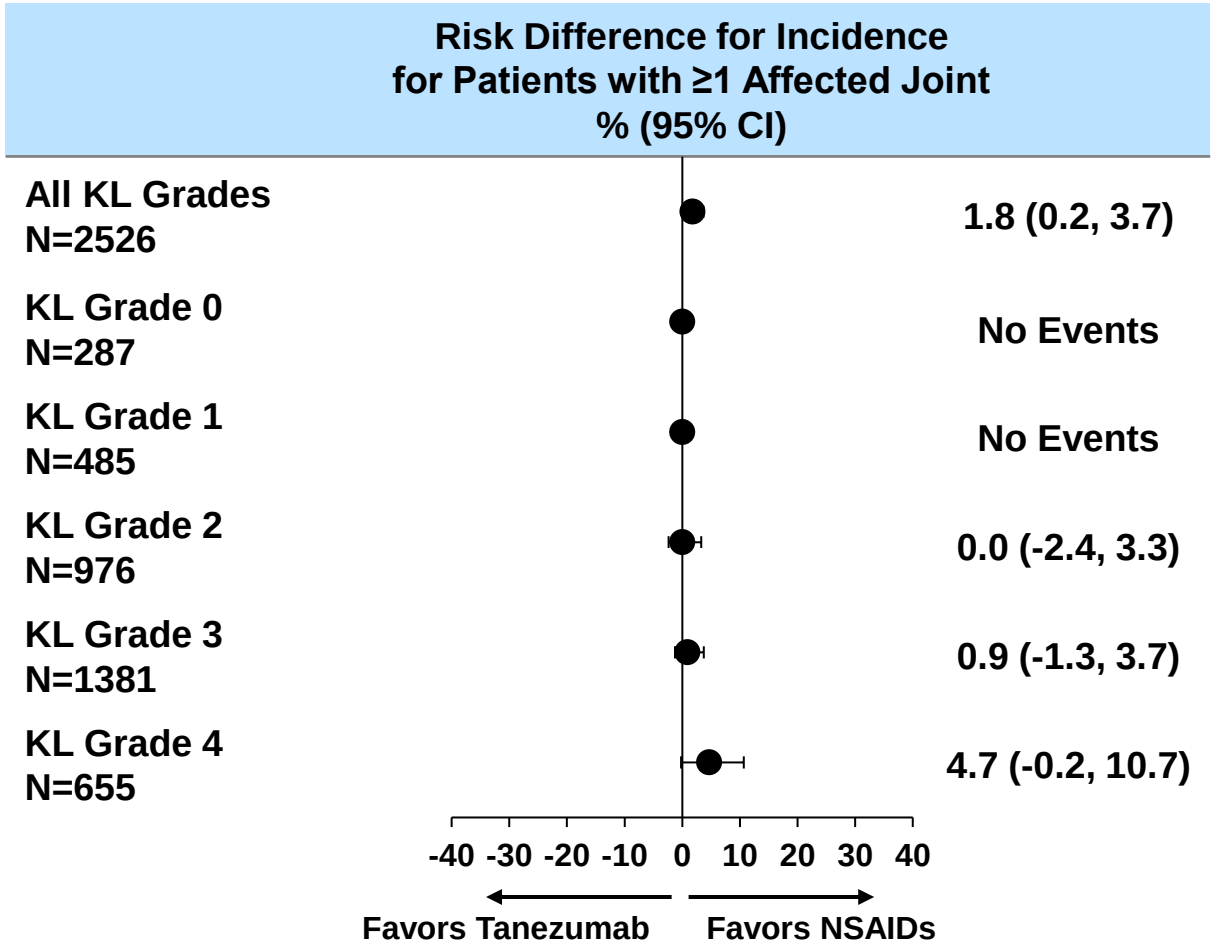
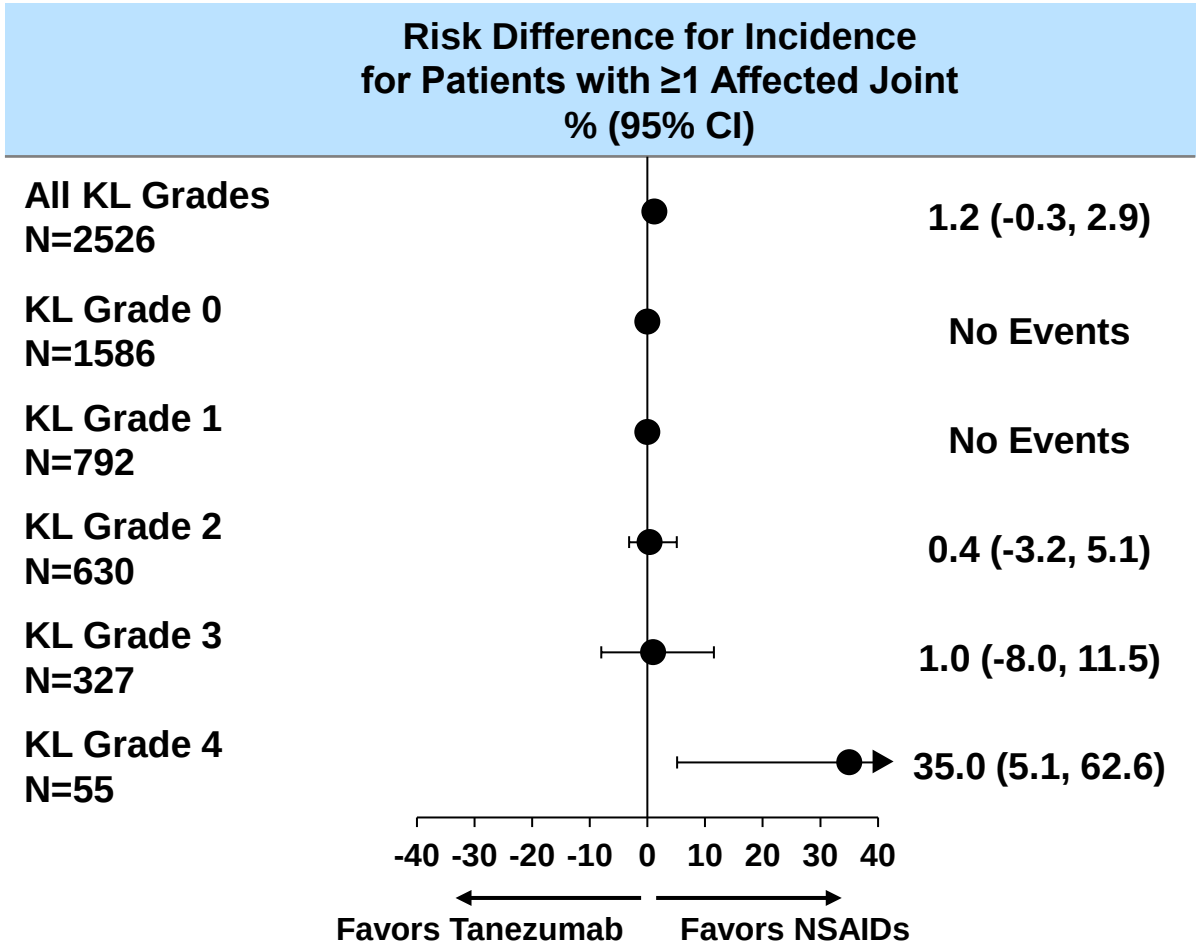
Total Joint Replacement: Tanezumab 2.5 mg vs NSAIDs

Knee Joints vs Hip Joints

Knee Joints



Hip Joints

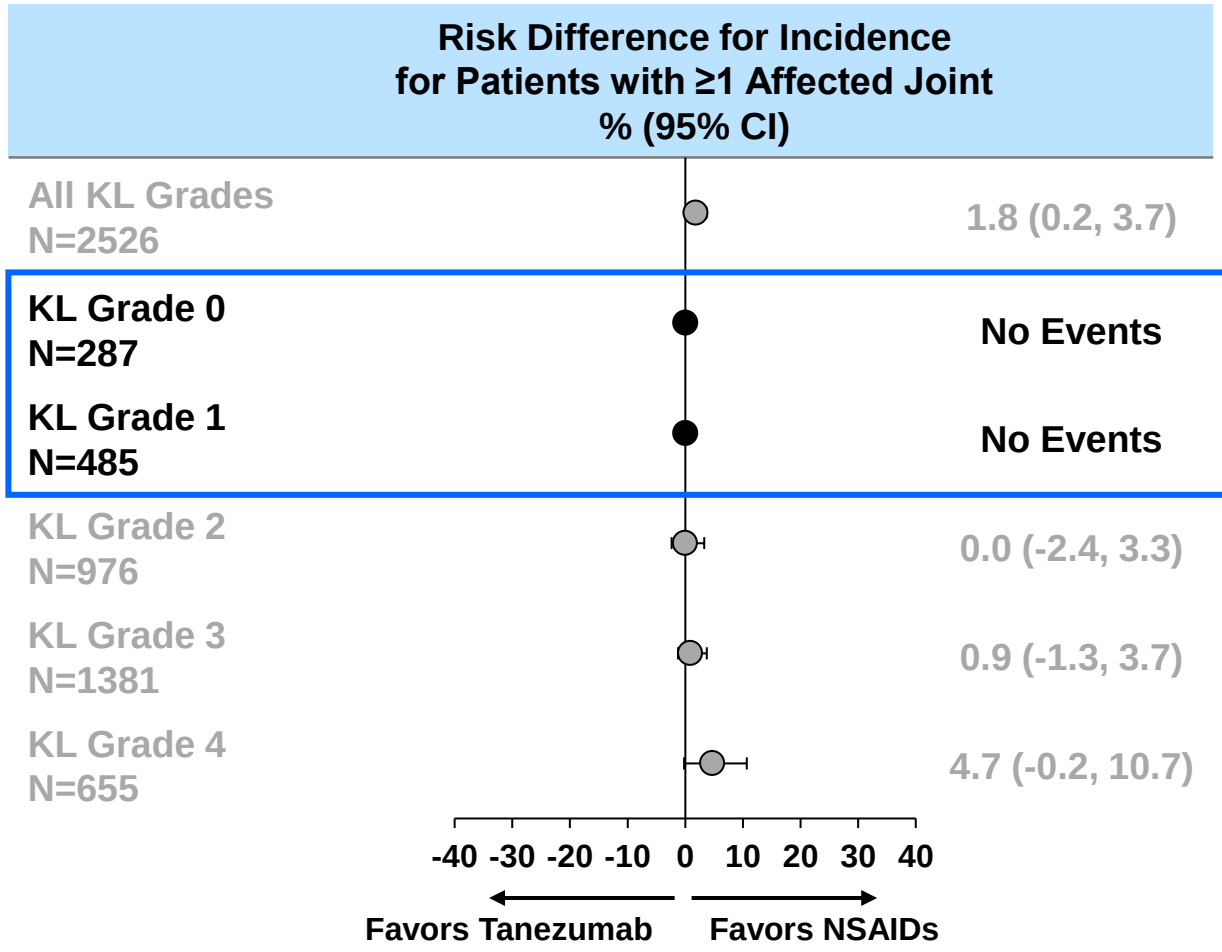


Studies 1056, 1057 and 1058
Patient-level analysis
Patients can be represented in more than one KL subcategory

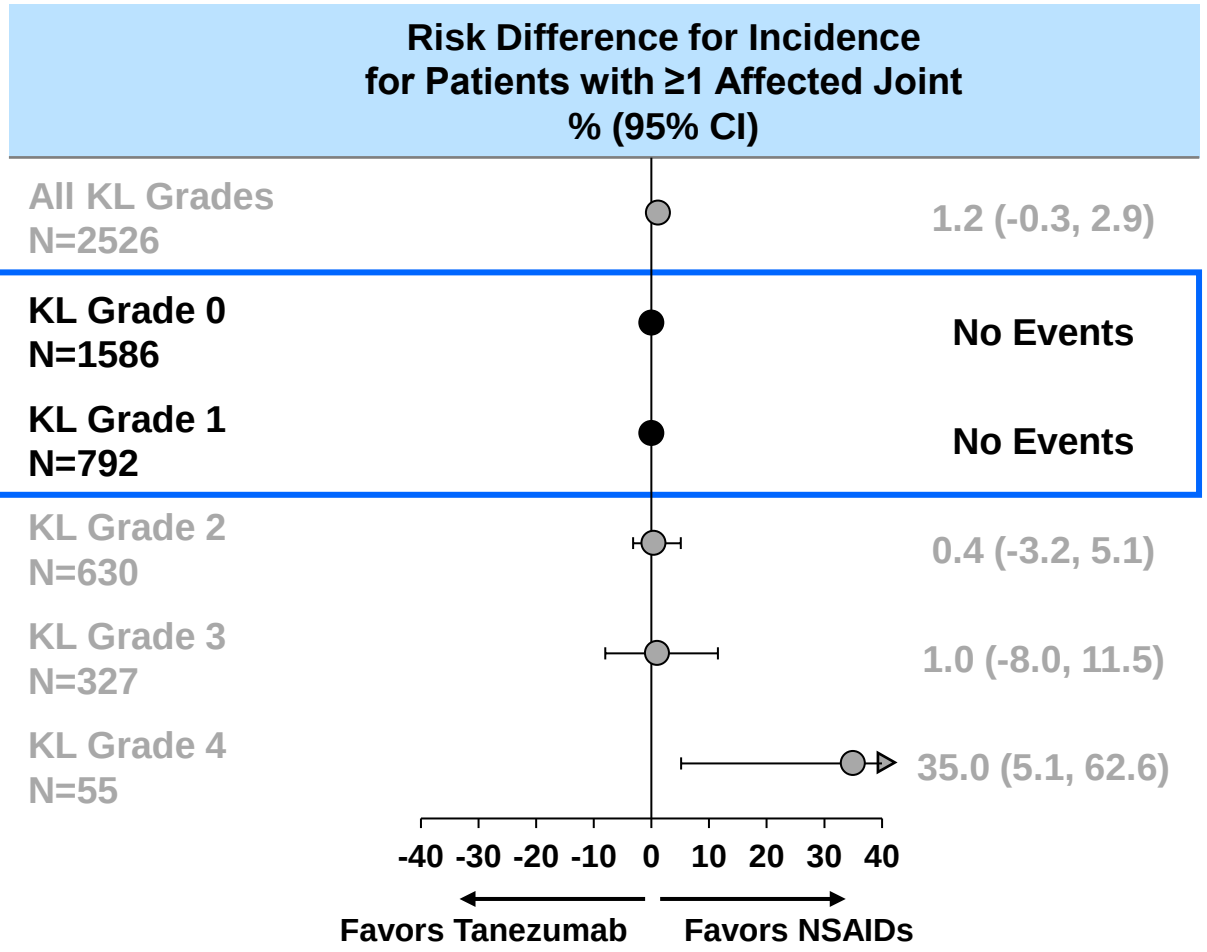
Total Joint Replacement: Tanezumab 2.5 mg vs NSAIDs

No TJRs Occurred in Kellgren-Lawrence Grade 0 or 1 Joints

Knee Joints



Hip Joints



Studies 1056, 1057 and 1058
Patient-level analysis
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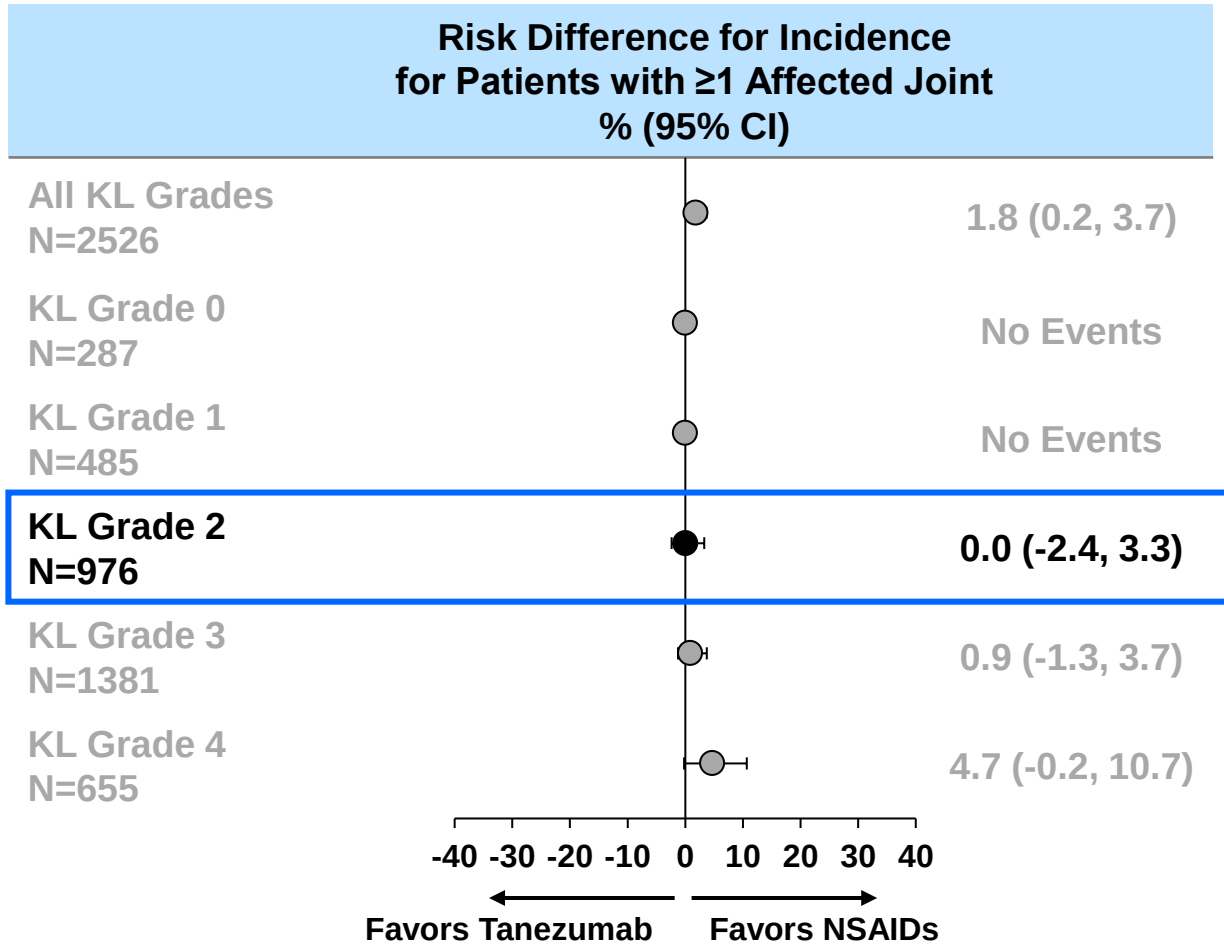
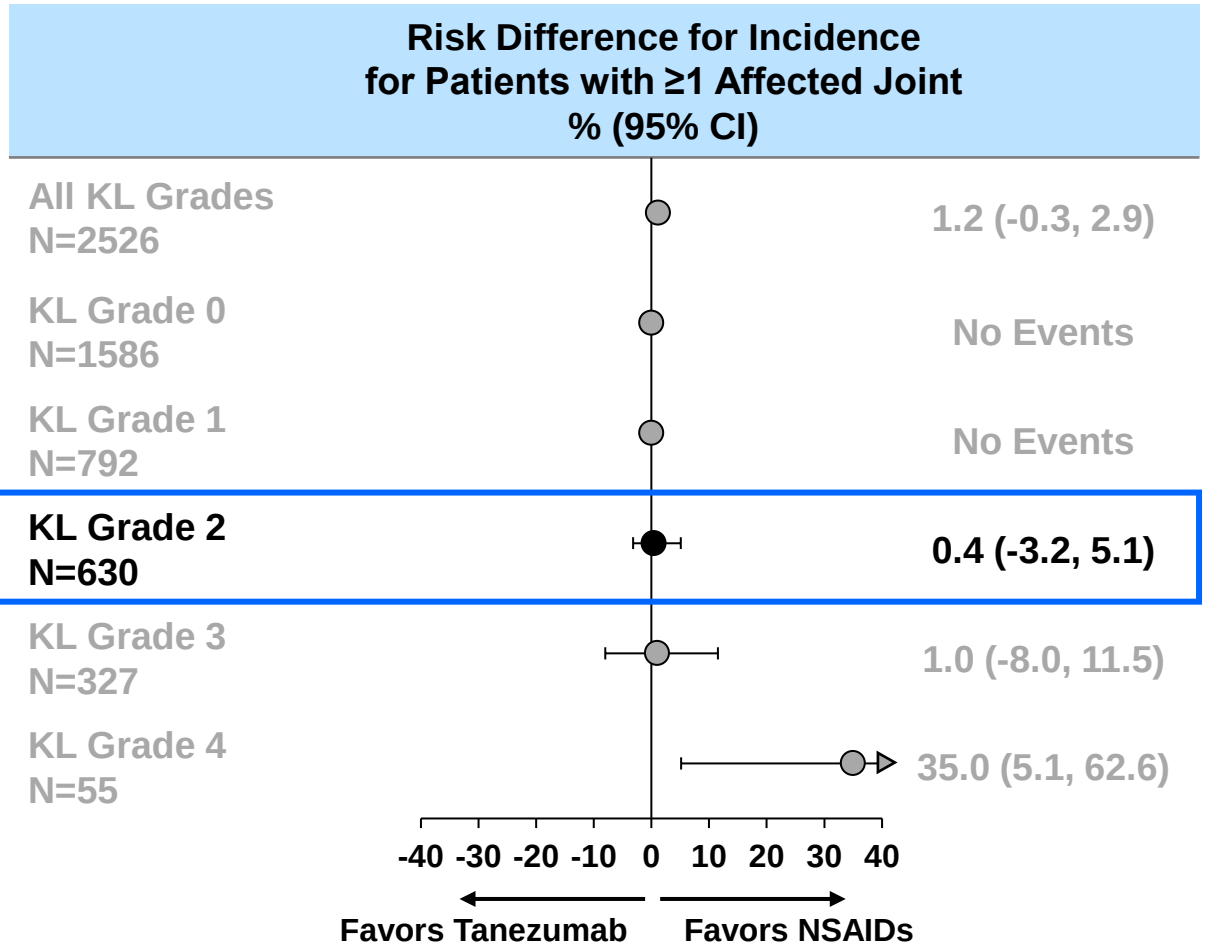
Total Joint Replacement: Tanezumab 2.5 mg vs NSAIDs

Risk Differences were Low in Kellgren-Lawrence Grade 2 Joints

Knee Joints



Hip Joints

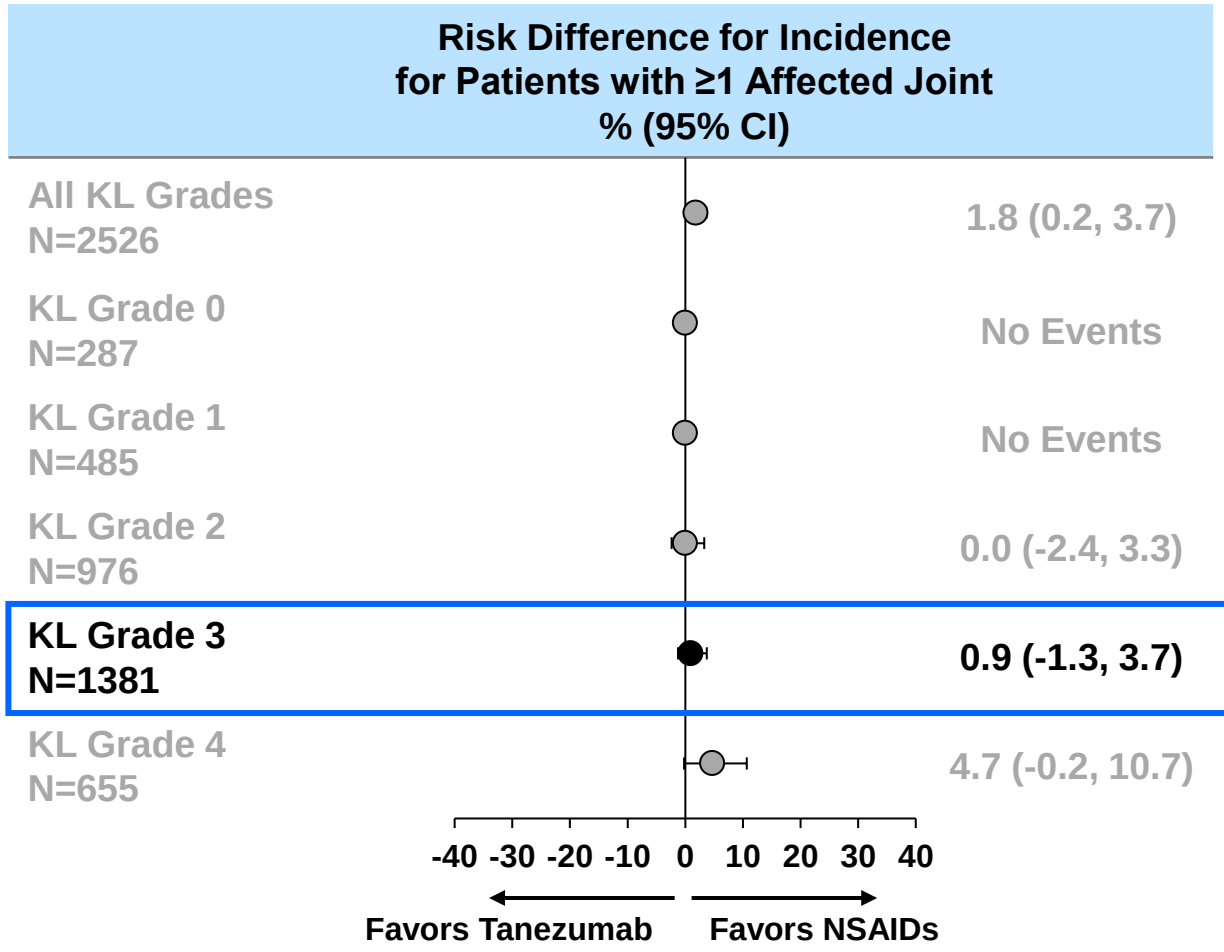


Studies 1056, 1057 and 1058
Patient-level analysis
Patients can be represented in more than one KL subcategory

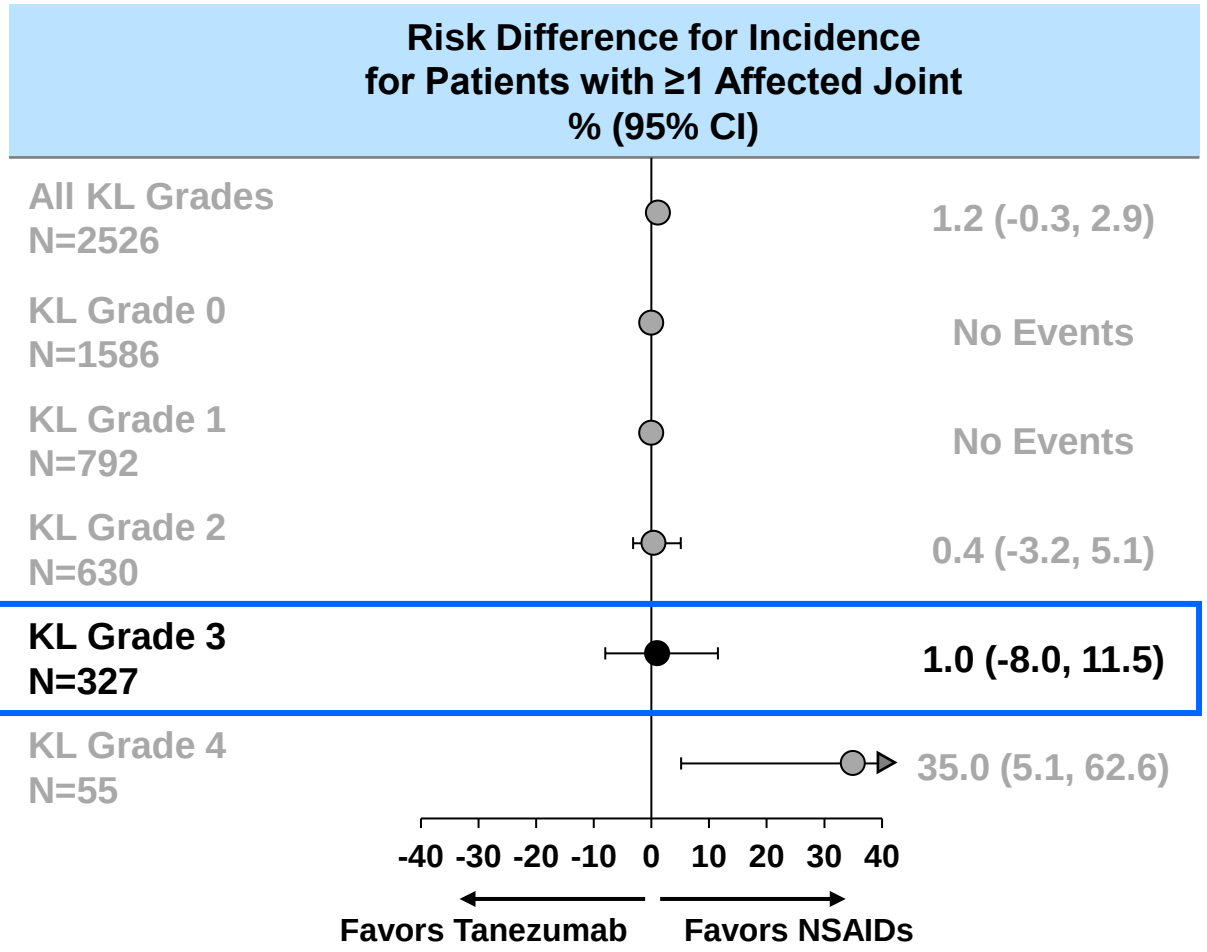
Total Joint Replacement: Tanezumab 2.5 mg vs NSAIDs

Risk Difference of ~1% in Kellgren-Lawrence Grade 3 Joints

Knee Joints



Hip Joints



Studies 1056, 1057 and 1058
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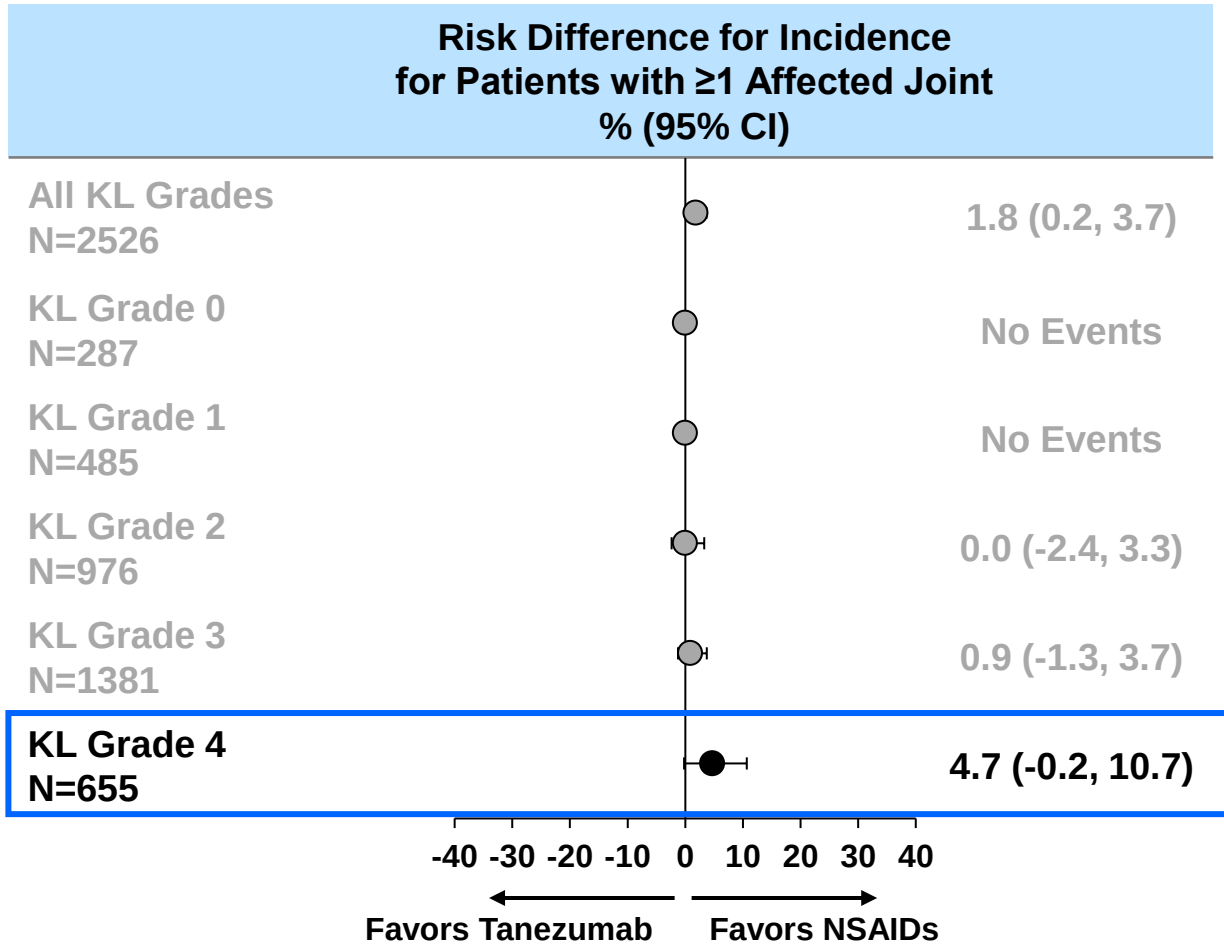
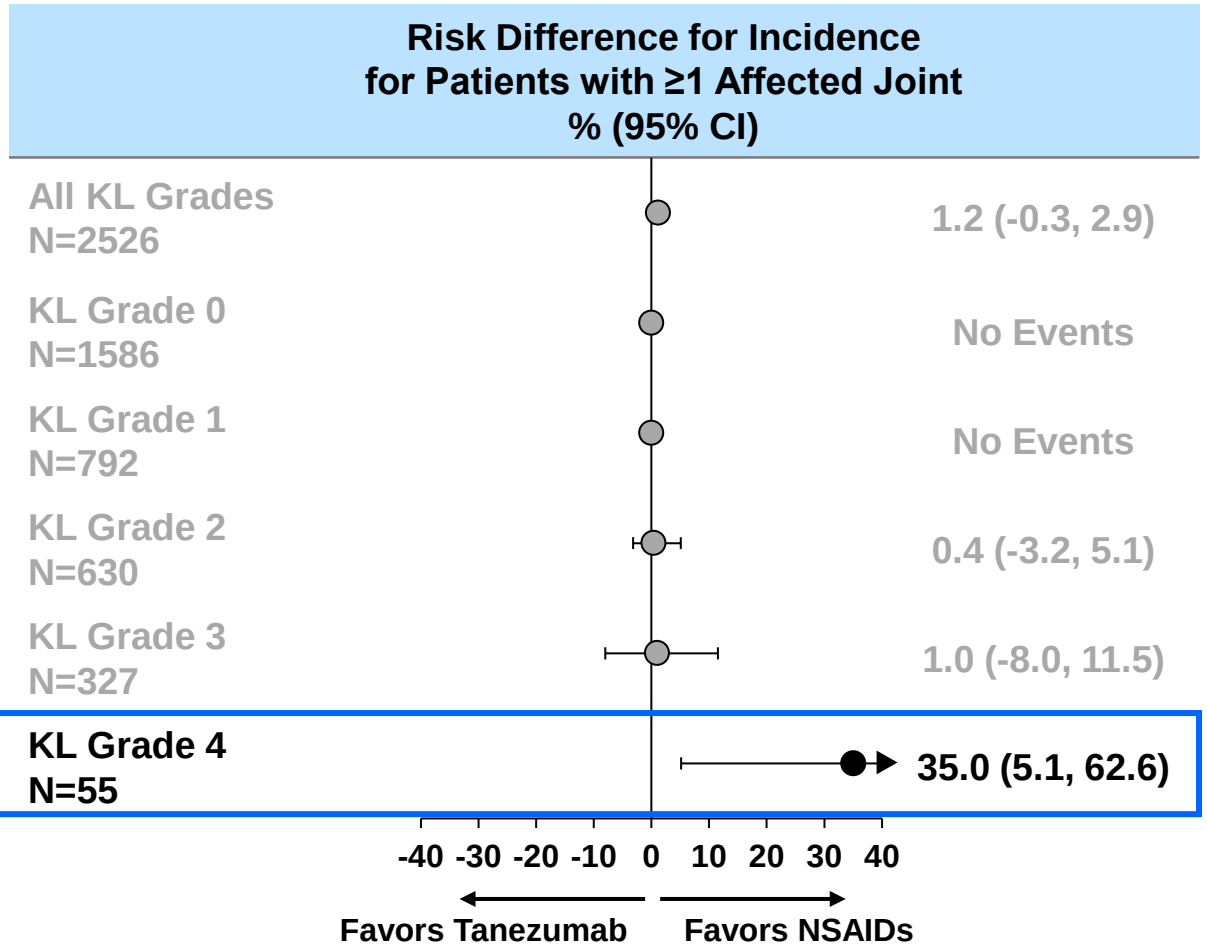
Total Joint Replacement: Tanezumab 2.5 mg vs NSAIDs

Risk Difference Least Favorable for Kellgren-Lawrence Grade 4 Hips at Baseline

Knee Joints



Hip Joints



Studies 1056, 1057 and 1058
Patient-level analysis
Patients can be represented in more than one KL subcategory

Key Safety Findings with Tanezumab 2.5 mg

- No increased risk for adverse events related to cardiovascular, renal, or hepatic systems
- No association with increased risk for peripheral or sympathetic autonomic neuropathy
- No association with potential drug abuse, dependence or withdrawal
- Incidence of Rapidly Progressive OA Type 1 was increased vs placebo and NSAIDs
- Incidence of Rapidly Progressive OA Type 2 was not significantly elevated relative to NSAIDs
- Risk differences for Rapidly Progressive OA relative to NSAIDs generally similar over time
- Subgroup analyses identified an association between the occurrence of joint safety endpoints and structural severity at baseline
- Incidence of total joint replacement was higher vs NSAIDs

Agenda

Subject	Presenter
Introduction	**Kenneth Verburg, PhD,** *Senior Vice President, Medicine Team Lead Global Product Development, Internal Medicine, Pfizer Inc.*
Update on Osteoarthritis: Current Understanding, Future Needs	**Thomas J. Schnitzer, MD, PhD,** *Professor of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL*
Efficacy of Tanezumab in Osteoarthritis	**Kenneth Verburg, PhD,** *Senior Vice President, Medicine Team Lead Global Product Development, Internal Medicine, Pfizer Inc.*
Safety of Tanezumab in Osteoarthritis	**Christine West, PhD,** *Senior Director, Global Clinical Lead Global Product Development, Internal Medicine, Pfizer Inc.*
Post-Marketing Risk Management	**Anne Hickman, DVM, PhD,** *Senior Director, Global Safety and Risk Management Lead, Worldwide Research and Development, Pfizer Inc.*
Utility of Tanezumab in Clinical Practice and Patient Selection and Monitoring Considerations	**Alan Kivitz, MD, FACR,** *President, Altoona Center for Clinical Research & Altoona Arthritis and Osteoporosis Center*
Benefit-Risk and Conclusions	**Kenneth Verburg, PhD,** *Senior Vice President, Medicine Team Lead Global Product Development, Internal Medicine, Pfizer Inc.*

Post-Marketing Risk Management

Anne Hickman, DVM, PhD
Senior Director, Global Safety and Risk Management Lead
Worldwide Research and Development
Pfizer Inc.

Post-Marketing Risk Management

Comprehensive Risk Minimization and Pharmacovigilance

- Risk minimization
  - US Prescribing Information (USPI) and Patient Medication Guide
    - Boxed warning for Rapidly Progressive OA and total joint replacement
  - Risk Evaluation and Mitigation Strategy (REMS) program for Rapidly Progressive OA
    - Includes Elements to Ensure Safe Use (ETASU)
  - Imaging resources for prescribers and radiologists

- Pharmacovigilance
  - AE monitoring, signal detection and evaluation
  - Safety surveillance study to assess long-term safety (i.e., >than 1 year of controlled treatment)

Key Risk Minimization Measures

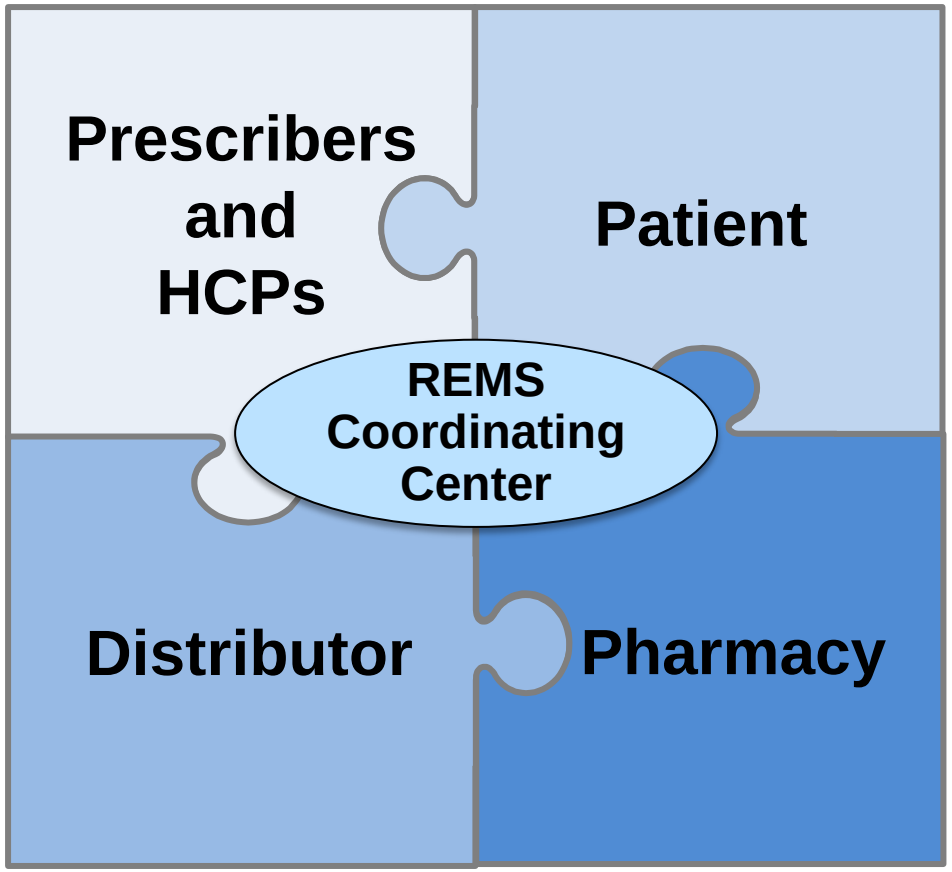
Translation from Clinical Program

- Overall REMS goal – minimize the risk for Rapidly Progressive OA
  - Ensure incidence does not increase in real-world use
- Minimize use in at risk patients
  - Treatment should not be initiated in patients with pre-existing Rapidly Progressive OA, subchondral insufficiency fracture, osteonecrosis, or atrophic OA
- Minimize use in patients not receiving benefit
  - Patients without a satisfactory clinical response after 2 doses should not continue treatment, as no additional benefit is anticipated
- Minimize exposure to known risk factor
  - Use of concomitant NSAIDs is not recommended, as chronic use increased risk 3-fold
- Minimize further joint damage
  - Monitor patients for development of Rapidly Progressive OA and discontinue if diagnosed

A REMS Is Proposed to Ensure Safe Use of Tanezumab

The education requirements are considered beyond what can be communicated in routine labelling (US Prescribing Information, Package Leaflet and Medication Guide)

- Designed to mitigate the risk of Rapidly Progressive OA by ensuring
  - Prescribers, healthcare settings and pharmacies are educated and certified
    - Educational materials for each stakeholder
    - Knowledge assessment test for prescribers



Subject to FDA review and discussion with Sponsor
HCP=Healthcare Professional

A REMS Is Proposed to Ensure Safe Use of Tanezumab

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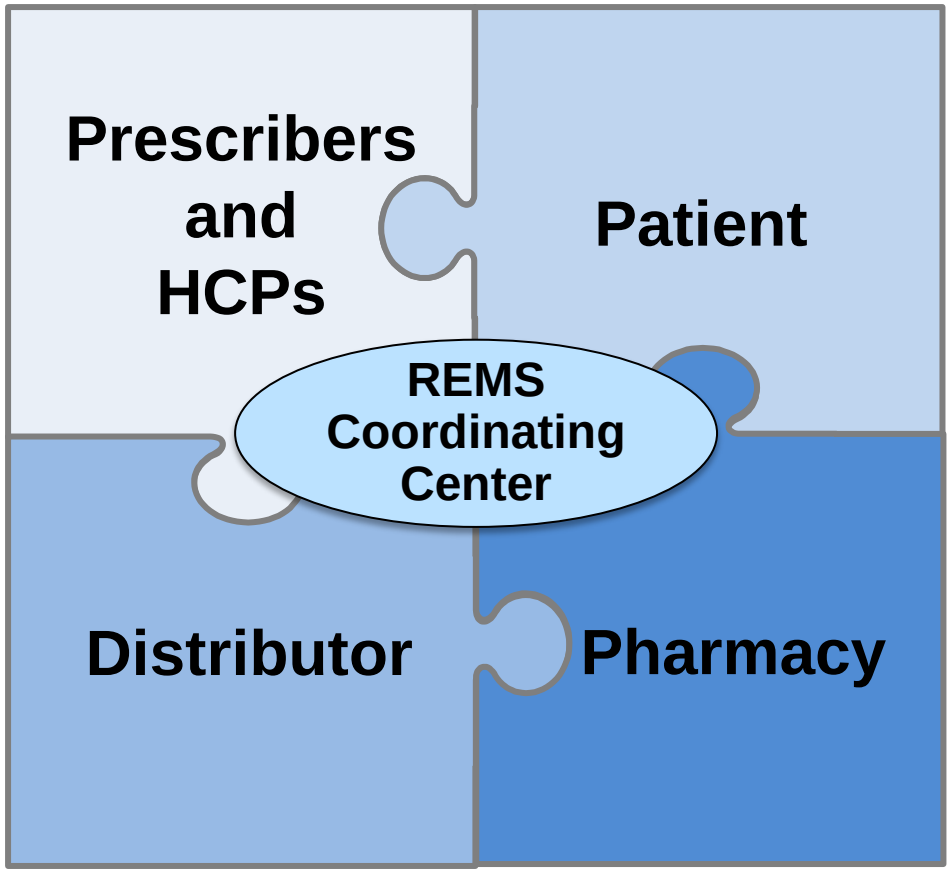
- Designed to mitigate the risk of Rapidly Progressive OA by ensuring
  - Prescribers, healthcare settings and pharmacies are educated and certified
    - Educational materials for each stakeholder
    - Knowledge assessment test for prescribers
  - Certified prescribers adhere to the baseline and periodic monitoring requirements
  - Patients are counseled
  - All cases of Rapidly Progressive OA are reported



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Patient Journey Through the REMS Program

Treatment Initiation

Patient/Prescriber Discussion, Patient Guide

Hip and Knee Radiographs

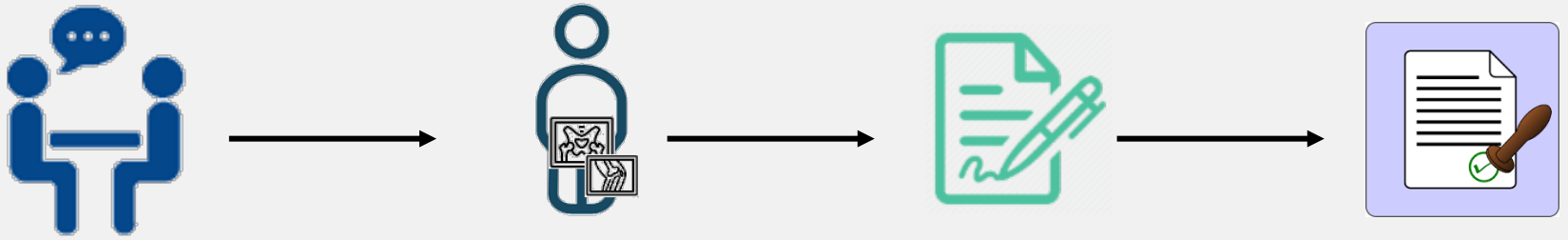
Patient/Prescriber both Sign Patient Enrollment Form

Treatment Authorization First Dose

- Avoid NSAIDs
- Know signs and symptoms
- Contact prescriber

Patient Journey Through the REMS Program

Treatment Initiation



Patient/Prescriber Discussion, Patient Guide

Hip and Knee Radiographs

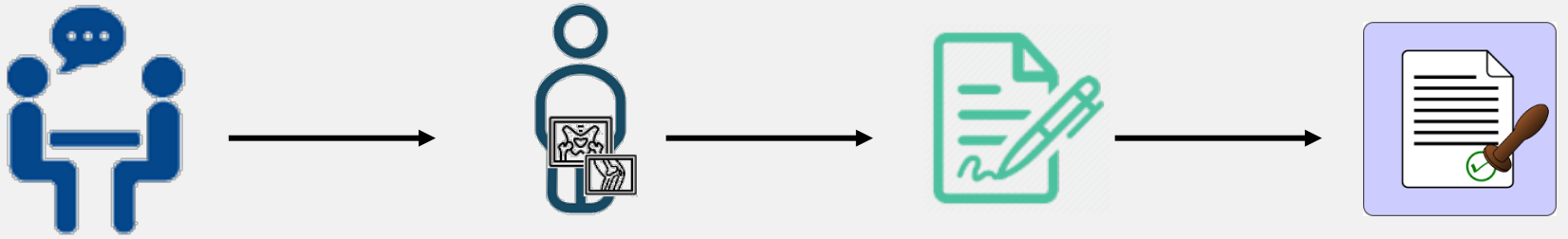
Patient/Prescriber both Sign Patient Enrollment Form

Treatment Authorization First Dose

- Identify risk factors
- Exclude at risk patients

Patient Journey Through the REMS Program

Treatment Initiation



Patient/Prescriber Discussion, Patient Guide

Hip and Knee Radiographs

Patient/Prescriber both Sign Patient Enrollment Form

Treatment Authorization First Dose

- Document radiographs and shared decision making
- Attest to REMS requirements

Patient Journey Through the REMS Program

Treatment Initiation

Patient/Prescriber Discussion

Hip and Knee Radiographs

Patient/Prescriber both Sign Patient Enrollment Form

Treatment Authorization First Dose

Treatment Continuation

Visit Every 8 Weeks

- Monitor for Signs and Symptoms
- Obtain Treatment Authorization
- New Patient Wallet Card

Patient Journey Through the REMS Program

Treatment Initiation

Patient/Prescriber Discussion

Hip and Knee Radiographs

Patient/Prescriber both Sign Patient Enrollment Form

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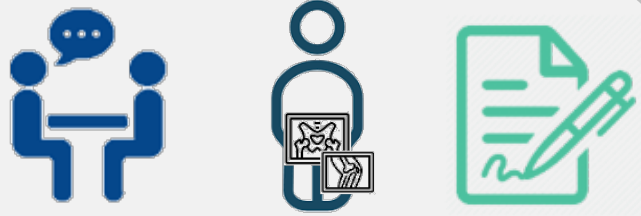
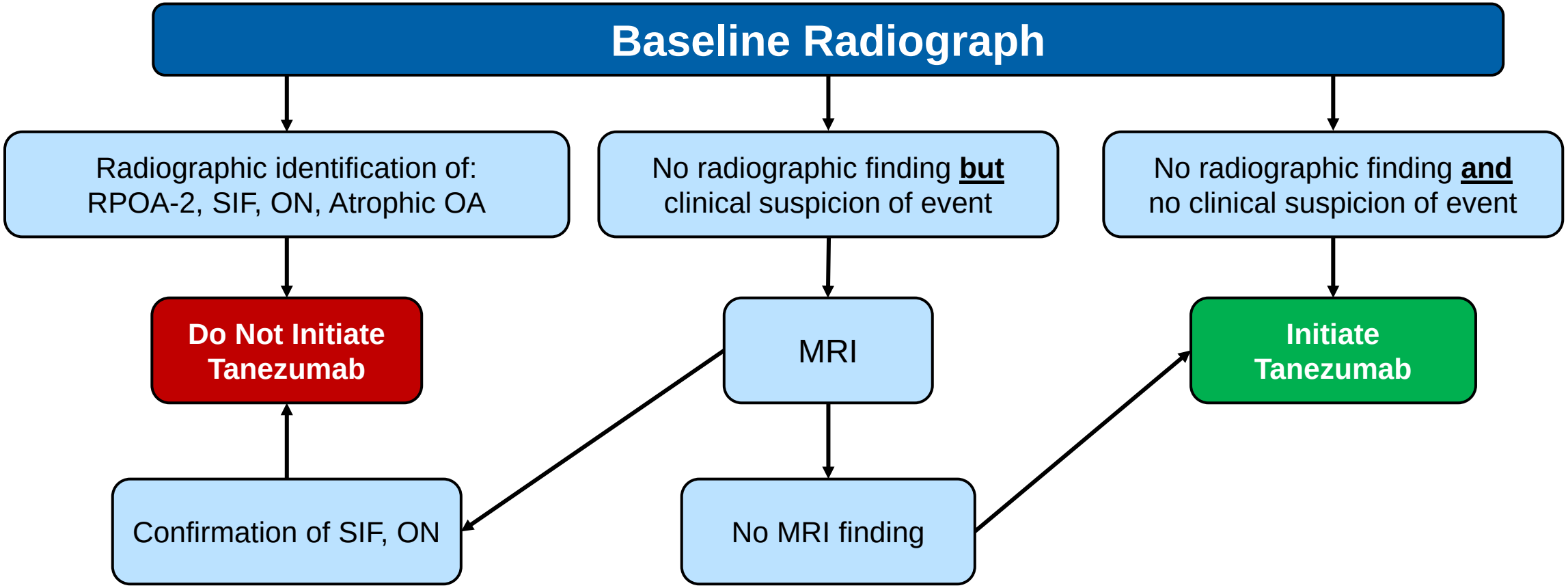


Annual Benefit-Risk Assessment

- Benefit-Risk Discussion
- Repeat Radiographs
- Sign Patient Continuation Form

Baseline Treatment Decision Tree

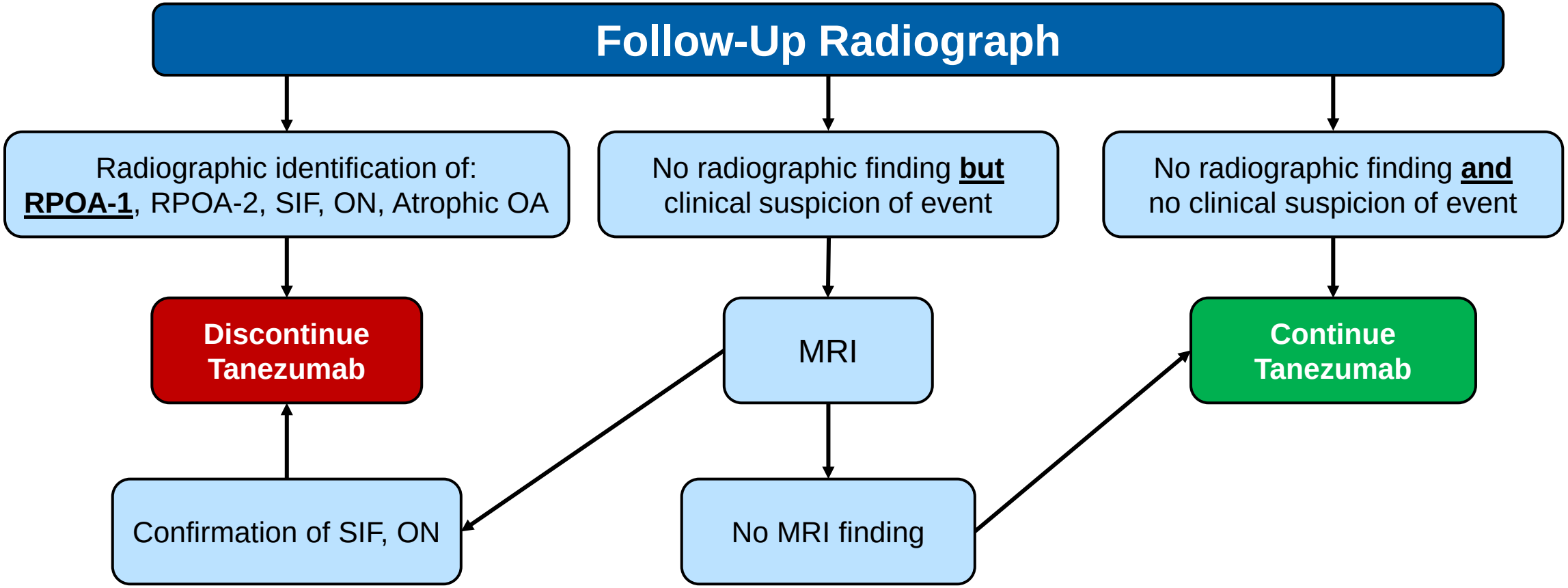
Clear Imaging Guidance for Prescribers



Adapted from Guermazi et al. Radiology 2020;297(3):503-512.
Subject to FDA review and discussion with Sponsor
ON=Osteonecrosis; SIF=Subchondral Insufficiency Fracture

Monitoring Treatment Decision Tree

Clear Imaging Guidance for Prescribers

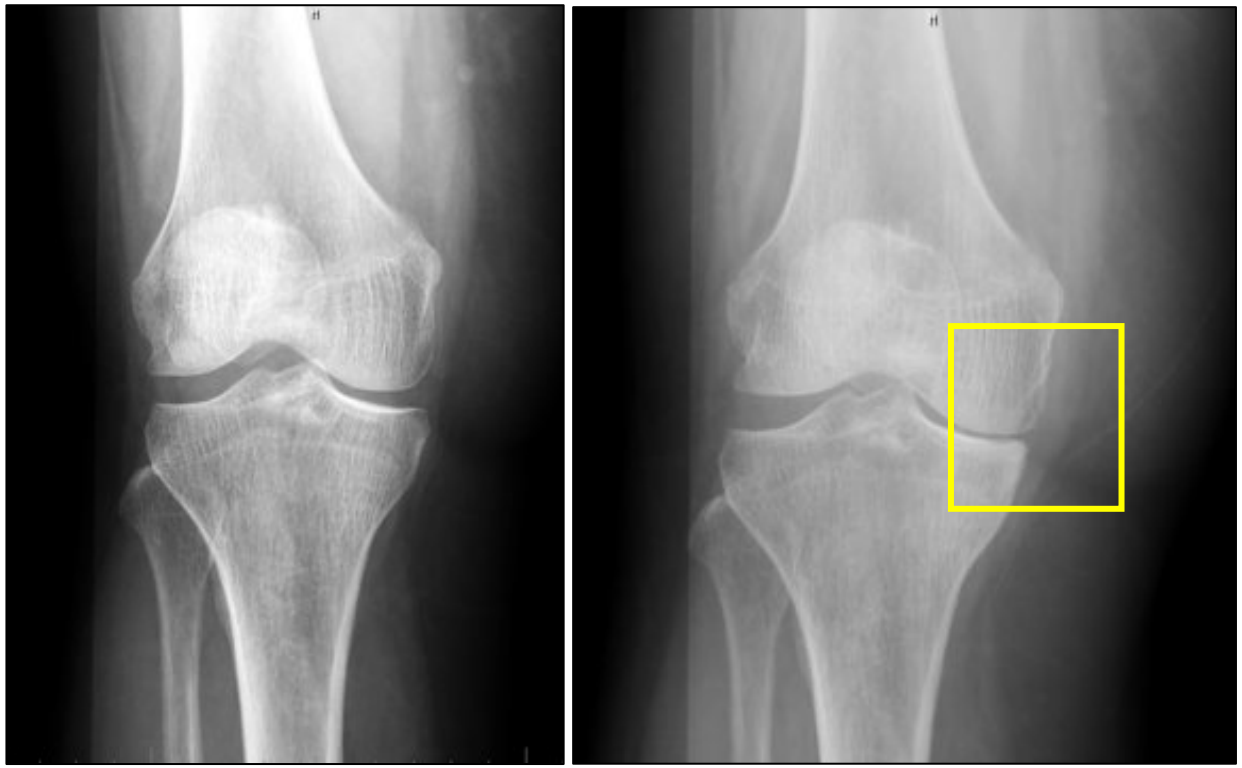


Adapted from Guermazi et al. Radiology 2020;297(3):503-512.
Subject to FDA review and discussion with Sponsor
ON=Osteonecrosis; SIF=Subchondral Insufficiency Fracture

Translating Learnings from Clinical Studies to Clinical Practice

Identification of Significant Amount of Loss of Joint Space Width

- Precise definition of Rapidly Progressive OA Type 1 was required in clinical trials
- The objective in clinical practice will be different
- Joint space width (JSW) loss can be visually assessed on serial images
  - Used routinely to access OA severity
- JSW loss was mapped to transitions in KL Grade using data from the Osteoarthritis Initiative[1]
  - KL Grade changes equivalent to ~1-2 mm of JSW loss were identified
- In clinical practice, KL Grade changes can be monitored to determine rapid losses of JSW



Screening
Medial JSW = 4.7 mm

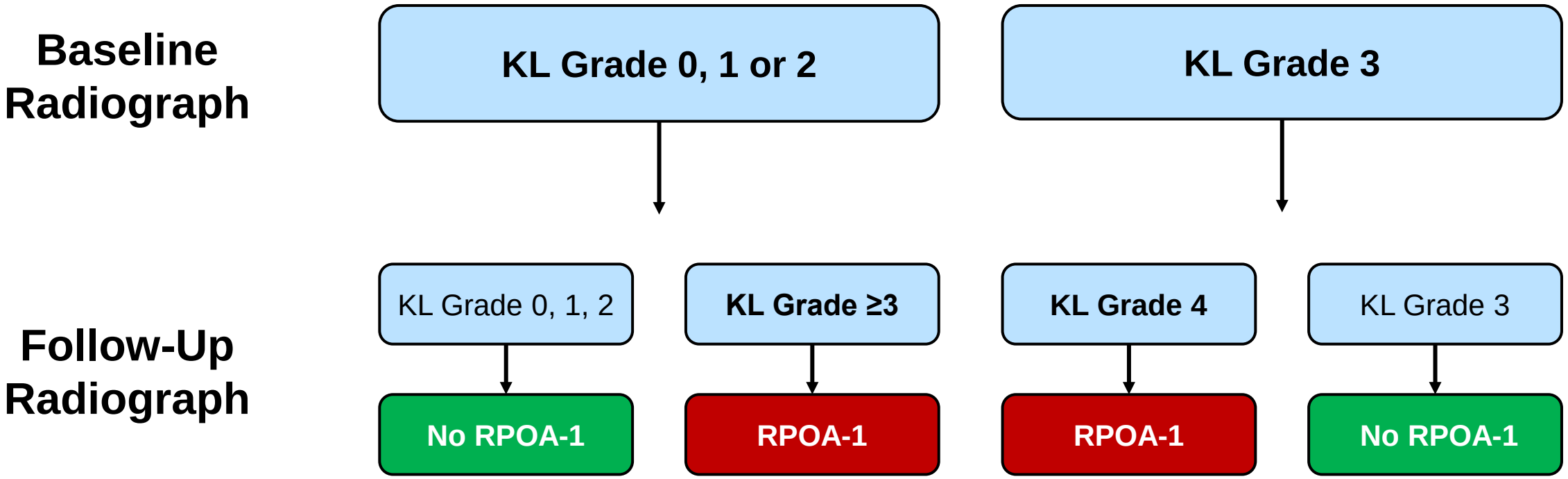
10 Months
Medial JSW = 2.0 mm

1. Ratzlaff et al. *OAC* 2018;26(9):1215-1224.

Subject to FDA review and discussion with Sponsor

Potential RPOA-1 Decision Tree

Clear Guidance Based on KL Grade

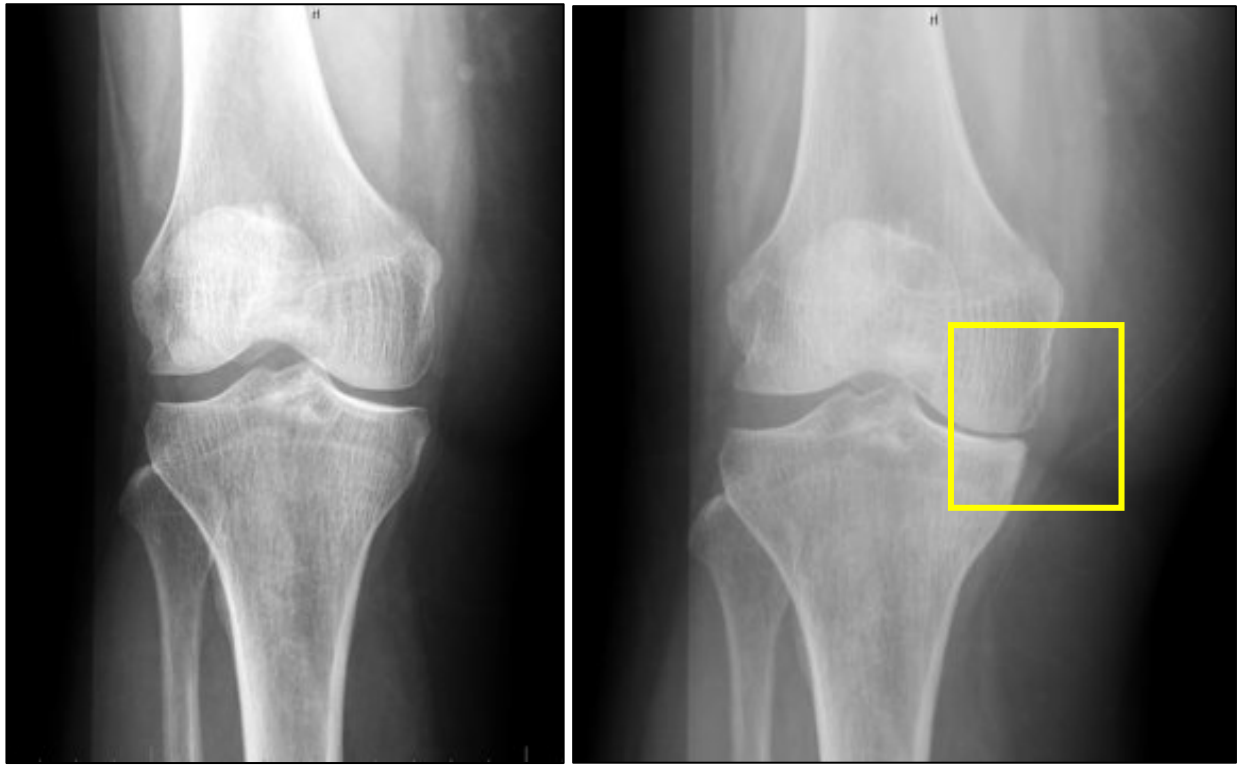


Subject to FDA review and discussion with Sponsor

Translating Learnings from Clinical Studies to Clinical Practice

Identification of Significant Amount of Loss of Joint Space Width

- Acknowledge difficulties in standardizing joint position for sequential radiographs
  - Expect some false positives and false negatives for Rapidly Progressive OA Type 1
  - If needed, request additional radiographs to confirm diagnosis



Screening
Medial JSW = 4.7 mm

10 Months
Medial JSW = 2.0 mm

Assessment of REMS Effectiveness

Ensure High Quality Program

- Categories for assessment
  - Program implementation and operations, safe use behaviors, stakeholder knowledge, health outcomes, access/burden
- Plan includes both process and outcome indicators with metrics
  - Multiple data sources including REMS database; prescriber, healthcare setting and patient surveys; electronic healthcare data
- Periodic audits of healthcare settings, pharmacies and wholesale distributors
  - Ensure that REMS processes and procedures are implementing and functioning
  - Noncompliance plan with corrective actions as needed
- Assessment report submitted 6 and 12 months after approval and annually thereafter – REMS program will be modified if needed

Imaging Resources for Prescribers and Radiologists

Supportive Tool

- Imaging materials for prescribers and radiologists will be available to ensure that tanezumab can be incorporated into current standard of care practices
  - Definitions and radiographic images of Rapidly Progressive OA including case studies
  - Definitions and radiographic images of key baseline risk factors such as osteonecrosis and subchondral insufficiency fracture
  - Guide to optimal positioning and radiographic image collection
    - Key for determining changes in joint space width over time
  - Guide to when additional imaging modalities should be considered (e.g., CT, MRI)
  - Radiology request form with specific tanezumab requirements
- Comprehensive outreach and educational program

Subject to FDA review and discussion with Sponsor
CT=Computerized Tomography

Post-Marketing Pharmacovigilance

Comprehensive Safety Surveillance

- Routine Pharmacovigilance
  - Adverse event reporting
    - Includes specific data capture aid to obtain additional information on joint safety events
  - Periodic safety data summary reports
    - Clinical trial data, post-marketing data, scientific literature information
  - Signal detection and evaluation

Post-Marketing Pharmacovigilance

Comprehensive Safety Surveillance

- Routine Pharmacovigilance
  - Adverse event reporting
    - Includes specific data capture aid to obtain additional information on joint safety events
  - Periodic safety data summary reports
    - Clinical trial data, post-marketing data, scientific literature information
  - Signal detection and evaluation

- Long-Term Post-Marketing Safety Study – extend safety knowledge
  - Safety surveillance study using real-world electronic healthcare data
    - Primary objective: Estimate the real-world incidence rate of Rapidly Progressive OA Type 2 (and subsequent occurrence of Total Joint Replacement) in patients receiving tanezumab and in an appropriate comparison group
    - Data source: Innovation in Medical Evidence and Development Surveillance (IMEDS) data network, which includes a subset of FDA Sentinel data partners

Agenda

Subject	Presenter
Introduction	**Kenneth Verburg, PhD,** *Senior Vice President, Medicine Team Lead Global Product Development, Internal Medicine, Pfizer Inc.*
Update on Osteoarthritis: Current Understanding, Future Needs	**Thomas J. Schnitzer, MD, PhD,** *Professor of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL*
Efficacy of Tanezumab in Osteoarthritis	**Kenneth Verburg, PhD,** *Senior Vice President, Medicine Team Lead Global Product Development, Internal Medicine, Pfizer Inc.*
Safety of Tanezumab in Osteoarthritis	**Christine West, PhD,** *Senior Director, Global Clinical Lead Global Product Development, Internal Medicine, Pfizer Inc.*
Post-Marketing Risk Management	**Anne Hickman, DVM, PhD,** *Senior Director, Global Safety and Risk Management Lead, Worldwide Research and Development, Pfizer Inc.*
Utility of Tanezumab in Clinical Practice and Patient Selection and Monitoring Considerations	**Alan Kivitz, MD, FACR,** *President, Altoona Center for Clinical Research & Altoona Arthritis and Osteoporosis Center*
Benefit-Risk and Conclusions	**Kenneth Verburg, PhD,** *Senior Vice President, Medicine Team Lead Global Product Development, Internal Medicine, Pfizer Inc.*

Alan J Kivitz MD, FACR

President, Altoona Center for Clinical Research
&
Altoona Arthritis and Osteoporosis Center

Real Patient Experience: “Robert”

- 76-year-old white male
- Referred by orthopedics to help manage bilateral knee OA of 2 years duration
- History of coronary artery disease with stents 2019
- Treatment by orthopedics has included
  - NSAIDs before the stent (now on Plavix)
  - Intraarticular steroid injections
  - Intraarticular viscosupplement injections
  - Physical therapy
- BMI 35
- X-ray KL Grade 3 bilaterally
- Was scheduled for TKR in 2019 but cancelled due to requirement of coronary stent
- Now prefers to look at other nonsurgical options, considers TKR a last resort
- Does not wish opioid therapy

TKR=Total Knee Replacement

Treatment is Individualized

- Patient goals
- Past successful and unsuccessful treatments
- Comorbidities
- Which joints are involved: one knee, both knees, other areas?

Tanezumab as a Treatment Option for OA

- **Efficacy**
- **Risks**
- **Which patients might benefit?**
- **What toxicities are avoided?**
- **What is the potential upside?**

Safety Considerations/REMS

- Radiographs before as screening
- Radiographs for monitoring during treatment
- How does this differ from current practice
- For cause imaging
- Types 1 and 2 Rapidly Progressive Osteoarthritis
- Concomitant NSAID: how to monitor

Conclusions

- **Limited treatment options and increased unmet need (active ageing)**
- **Treatment needs to be individualized based on shared decision-making and the patient's preferences**
- **Tanezumab may not be for everyone, but is may be an important option for some patients**
- **HCP and patient education is critical, but Tanezumab can be successfully implemented in the clinical setting**

HCP=Health Care Provider

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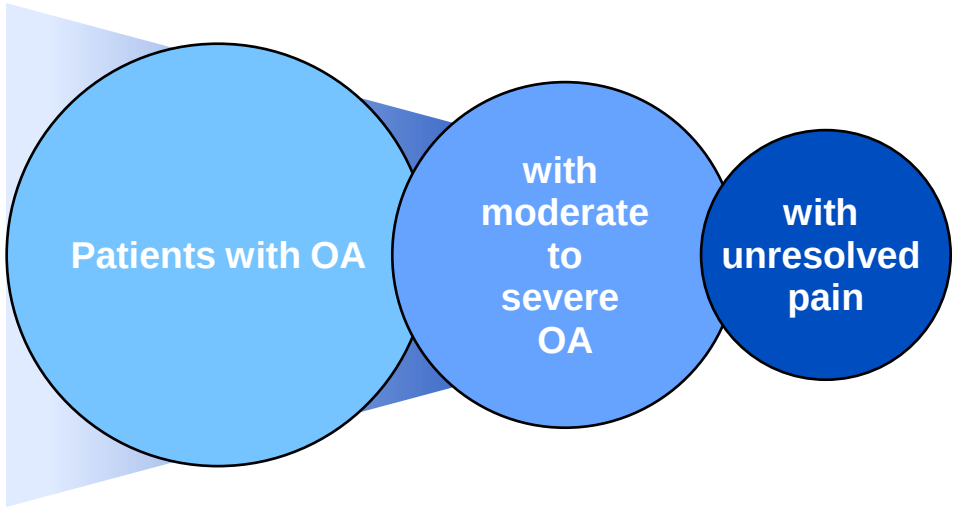
Tanezumab

Benefit-Risk and Conclusions

Kenneth Verburg, PhD
Senior Vice President, Medicine Team Lead
Global Product Development, Internal Medicine
Pfizer Inc.

Tanezumab

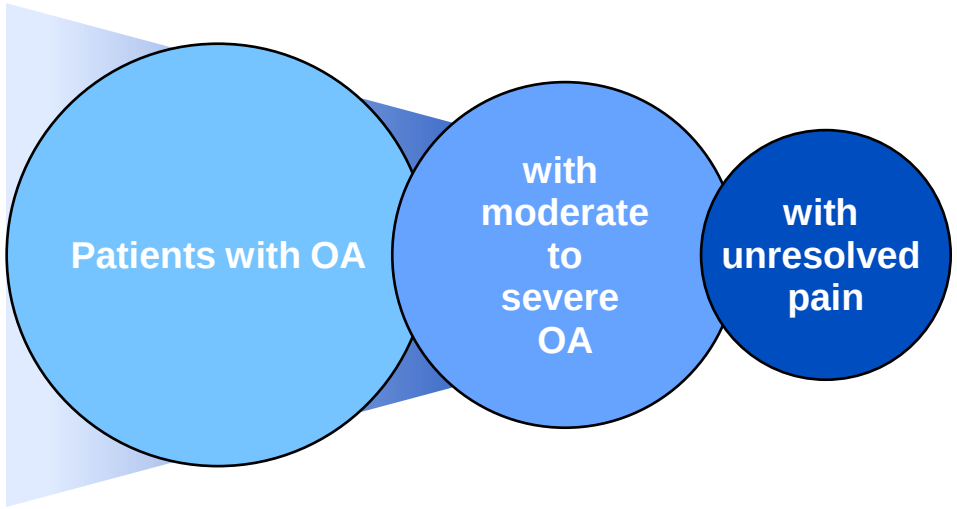
Addressing Critical Unmet Need in Specific Population of Patients with OA



Additional therapeutic options needed for those patients who do not respond or for whom tolerability or safety concerns limit the effectiveness of available treatments

Tanezumab

Addressing Critical Unmet Need in Specific Population of Patients with OA

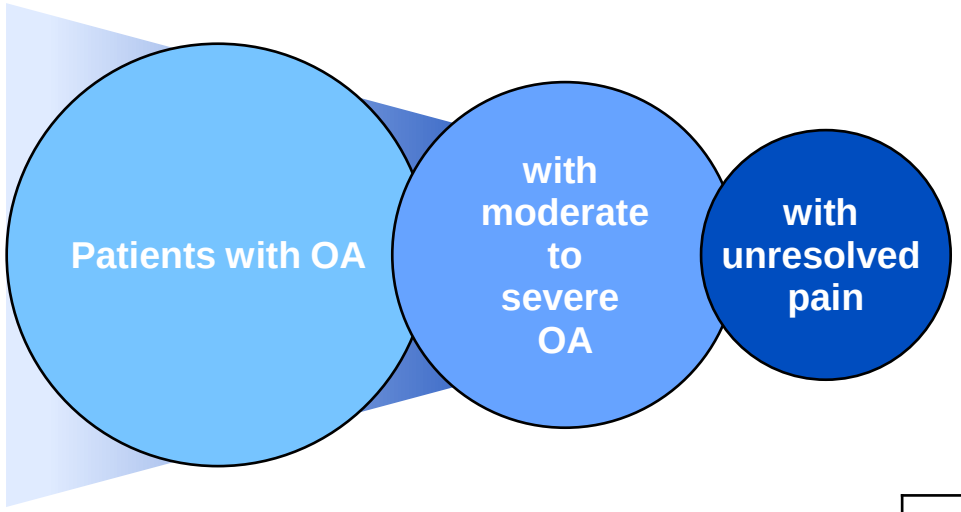


Additional therapeutic options needed for those patients who do not respond or for whom tolerability or safety concerns limit the effectiveness of available treatments

- Tanezumab was developed to treat OA pain and offers the potential for addressing this critical unmet need
- Tanezumab is not intended for patients who are benefiting from existing treatment options
- The proposed indication is restricted to patients who have had inadequate pain relief, cannot tolerate or are unable to take currently approved analgesics
- The benefit-risk of tanezumab is considered in the context of this target population
- Tanezumab 2.5 mg is associated with the optimal benefit-risk profile vs 5 mg

Tanezumab

Addressing Critical Unmet Need in Specific Population of Patients with OA



Additional therapeutic options needed for those patients who do not respond or for whom tolerability or safety concerns limit the effectiveness of available treatments

Studies 1056 and 1057

Acetaminophen	Inadequate pain relief
NSAIDs	Inadequate pain relief, intolerability, or contraindication
Opioids, tramadol	Inadequate pain relief, intolerability, or contraindication
Opioids	Unwilling to take

Studies 1011 and 1014

Non-opioid pain medications	Inadequate pain relief or unable, unwilling to take
Candidate for total joint replacement or other invasive intervention	

Efficacy Benefit

Tanezumab 2.5 mg SC in the Target Treatment Population

- The clinical benefit of tanezumab 2.5 mg is clearly evident from
  - Improvements in physical function and global well-being associated with reductions in pain
  - Responder analyses for substantial clinical improvement and sustained improvement in pain
  - Multi-domain responder indices
  - Efficacy in patients with severe symptoms and across demographic, disease severity and geographic subpopulations
- This benefit is seen in patients for whom current treatments are not efficacious or clinically appropriate
- These patients are not served by current therapies and their unmet medical need is undeniable

Number Needed to Treat (NNT)

Clinically Important Outcomes, NNT = 9 for Tanezumab 2.5 mg SC

Replacing Placebo with Tanezumab 2.5 mg

	Week(s)	Treatment Difference vs Placebo Patients, %	NNT
Studies 1056 and 1057 Pooled (SC)			
≥30% WOMAC Pain Improvement	16	12.5	9
≥50% WOMAC Pain Improvement	16	16.6	7
Sustained ≥50% WOMAC Pain Improvement	4-16	12.9	8
Sustained WOMAC Pain Score 0-3	4-16	13.1	10
Studies 1011 and 1014 Pooled (IV)			
≥30% WOMAC Pain Improvement	16	18.6	5
≥50% WOMAC Pain Improvement	16	15.0	7
Sustained ≥50% WOMAC Pain Improvement	4-16	16.2	6
Sustained WOMAC Score 0-3	4-16	15.0	7

Benefit of Novel Mechanism of Action

Patients at Risk for NSAID- or Opioid-Related Adverse Outcomes

- Mechanism of action is distinct from NSAIDs and opioids; tanezumab lacks the risks characteristic of these medications
- No serious safety concerns were identified with tanezumab 2.5 mg treatment for the following
  - Cardiovascular
  - Gastrointestinal
  - Renal
  - Bleeding or anemia
  - Abuse, addiction or overdose
- Tanezumab 2.5 mg may be an appropriate alternative therapy for patients at risk or contraindicated for NSAID- or opioid-related serious toxicities

NSAIDs	Opioids
• CV thrombotic events • UGI ulcer complication • Heart failure/fluid retention • Bleeding/anemia • Renal decompensation • Hypertension	• Abuse • Addiction • Overdose

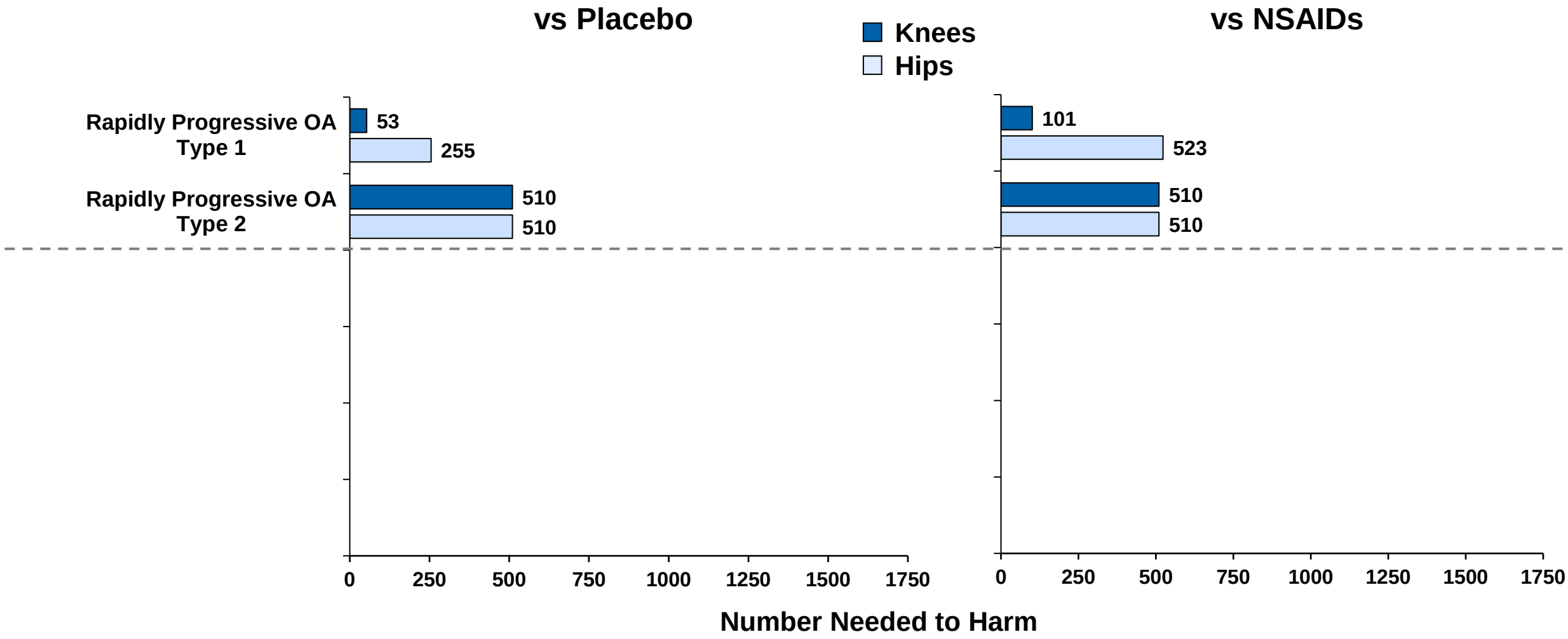
CV=Cardiovascular; UGI=Upper Gastrointestinal

Joint Safety Risks

Tanezumab 2.5 mg SC in the Target Treatment Population

- Evaluation of joint safety was carried out in patients with advanced OA as indicated by
  - Degree of structural joint damage of the index joint
  - Multiple joints affected by OA
  - ~10% of patients with history of TJR prior to study entry
- Rapidly Progressive Osteoarthritis Type 1: tanezumab 2.5 mg (2.3%), NSAIDs (1.1%), placebo (0.0%)
- Rapidly Progressive Osteoarthritis Type 2: tanezumab 2.5 mg (0.4%), NSAIDs (0.1%), placebo (0.0%)
- Total Joint Replacements: tanezumab 2.5 mg (5.5%), NSAIDs (2.6%), placebo (4.5%)
- In general, neither tanezumab 2.5 mg nor NSAIDs accelerated the underlying progression of osteoarthritis
  - Over 96% patients treated with either agent were unaffected
- The risk of an adverse joint outcome is typically isolated to a single joint even within an affected patient

Number Needed to Harm; Use of Tanezumab 2.5 mg Rather than Placebo or NSAIDs in OA



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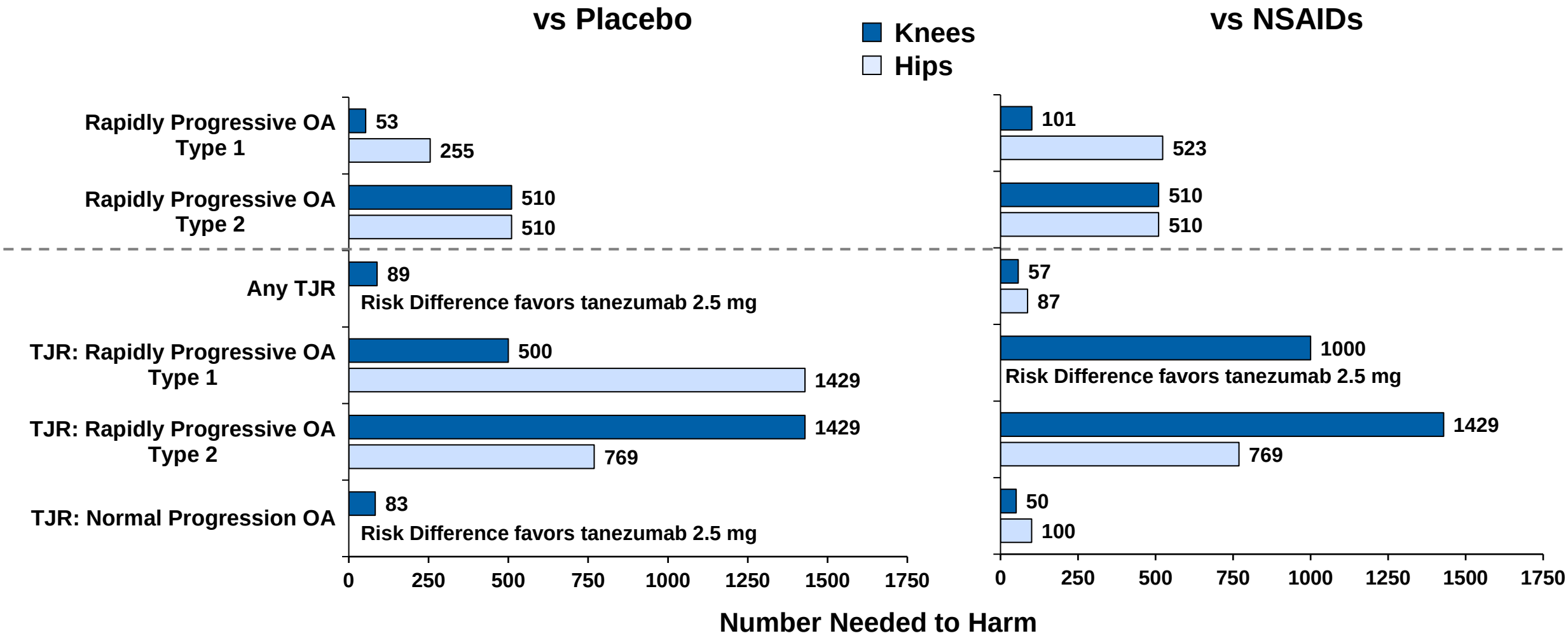
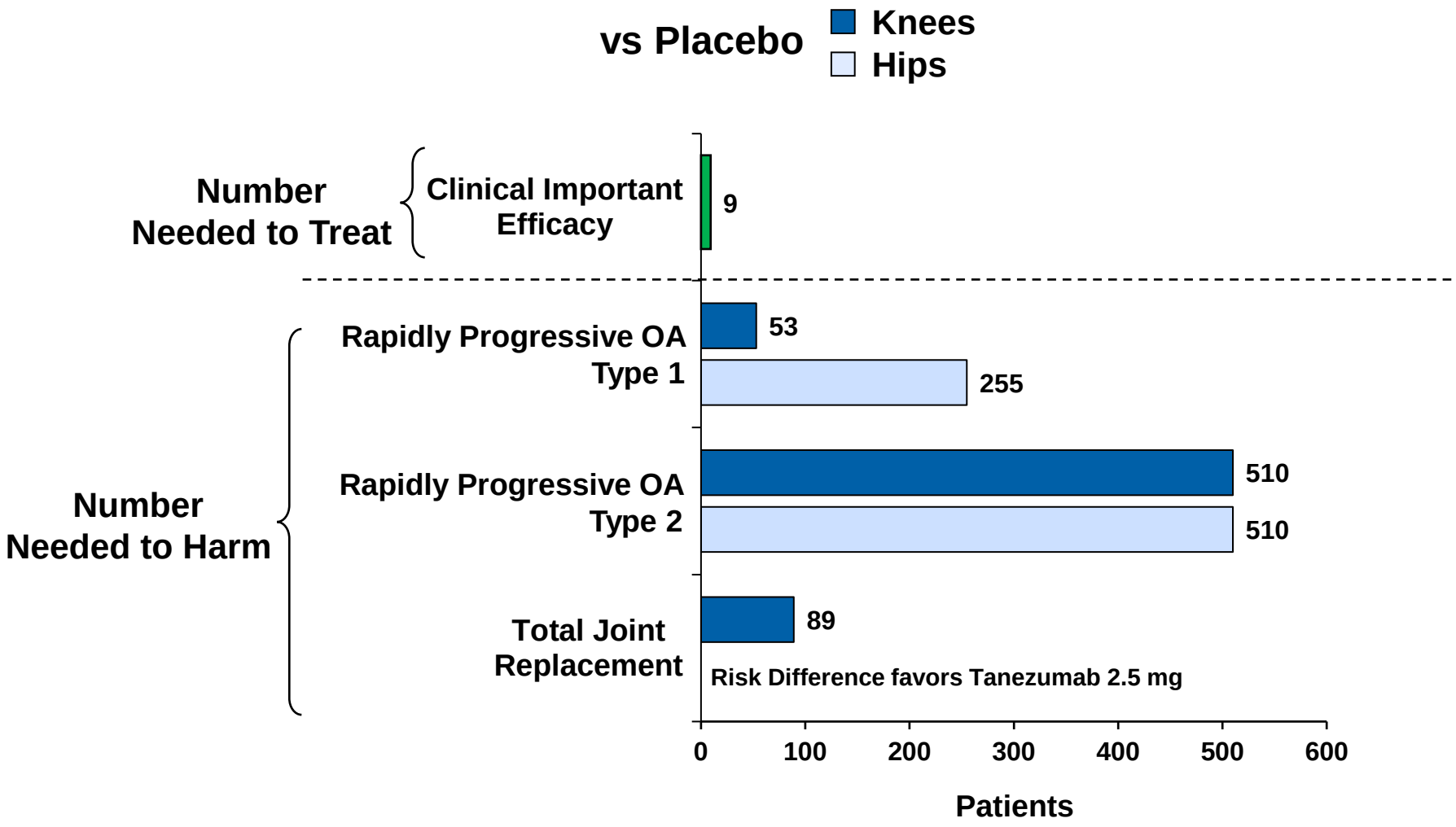


Clinical Outcomes with Tanezumab 2.5 mg SC

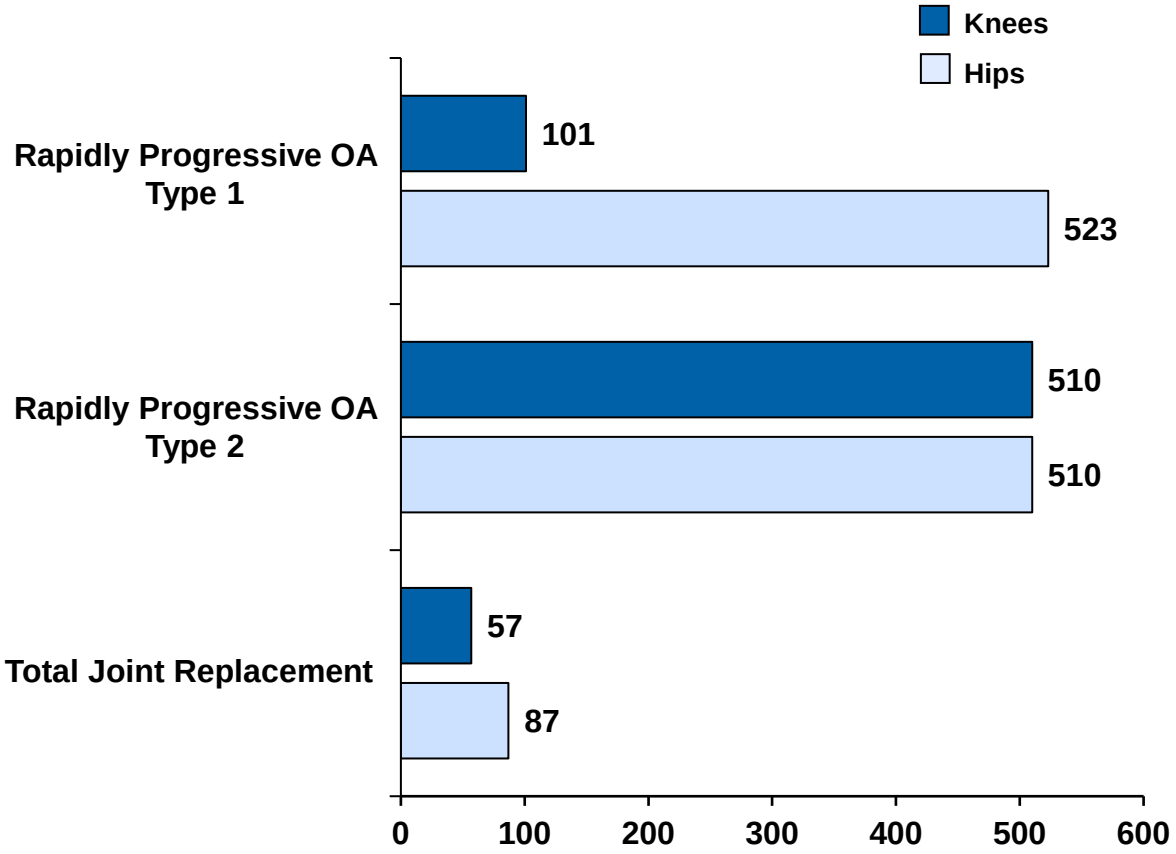
NNT to NNH Ratio Indicates Favorable Benefit-Risk Profile



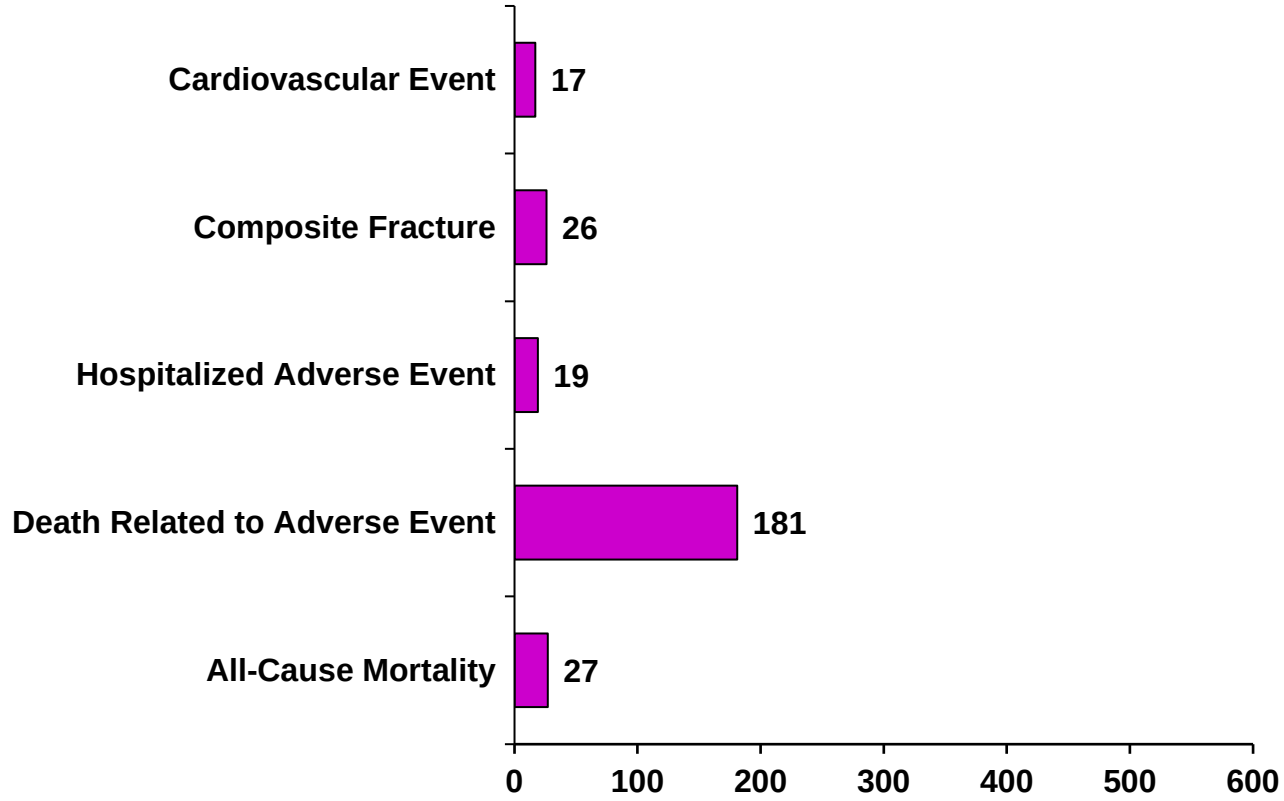
Significant Risks Associated with Tanezumab 2.5 mg and Opioids

Comparison of NNH for Joint Safety Events and Opioids

Tanezumb 2.5 mg vs NSAIDs



Opioids vs nsNSAIDs[1]

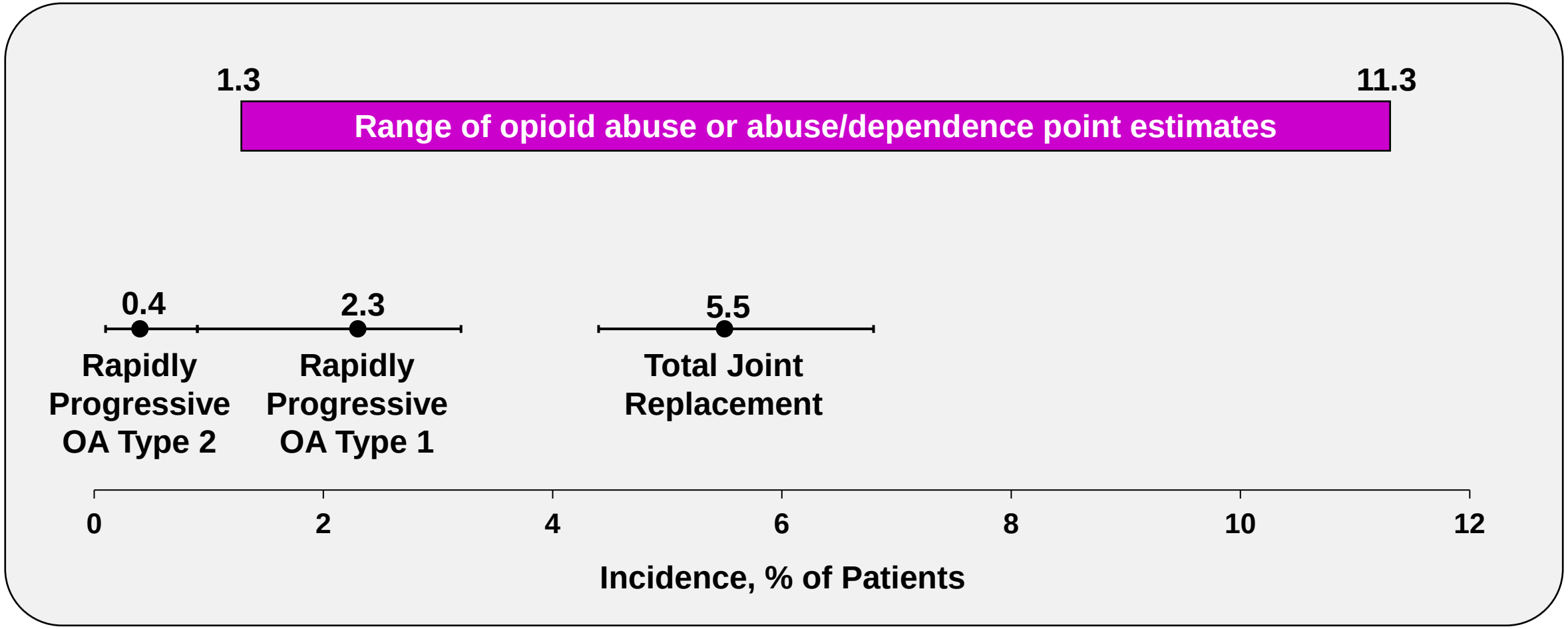


Number Needed to Harm

1. Solomon DH et al. *Arch Intern Med* 2010 Dec 13;170(22):1968-76.
nsNSAID=non-selective Nonsteroidal Anti-Inflammatory Drug

Significant Risks Associated with Tanezumab 2.5 mg and Opioids

Comparison of Joint Safety Events to Abuse-Related Events and Overdose



Conclusions

- If approved, tanezumab will be the first in a new pharmacologic class of pain therapy
  - Mechanism of action is distinct from that of NSAIDs and opioids
  - Devoid of risks of abuse, addiction, or overdose or other serious safety concerns associated with opioid or NSAID use
- Tanezumab addresses a significant unmet medical need in the treatment of OA pain, specifically
  - Patients in whom other analgesic medications are inadequate or not appropriate
- The benefit-risk balance of tanezumab 2.5 mg SC is positive in the context of
  - Unmet medical need
  - Efficacy and safety profile
  - Intended patient population
  - Risk management plan
- The weight of evidence supports approval of tanezumab 2.5 mg within the current therapeutic context of managing patients with OA

Backup Slides Presented

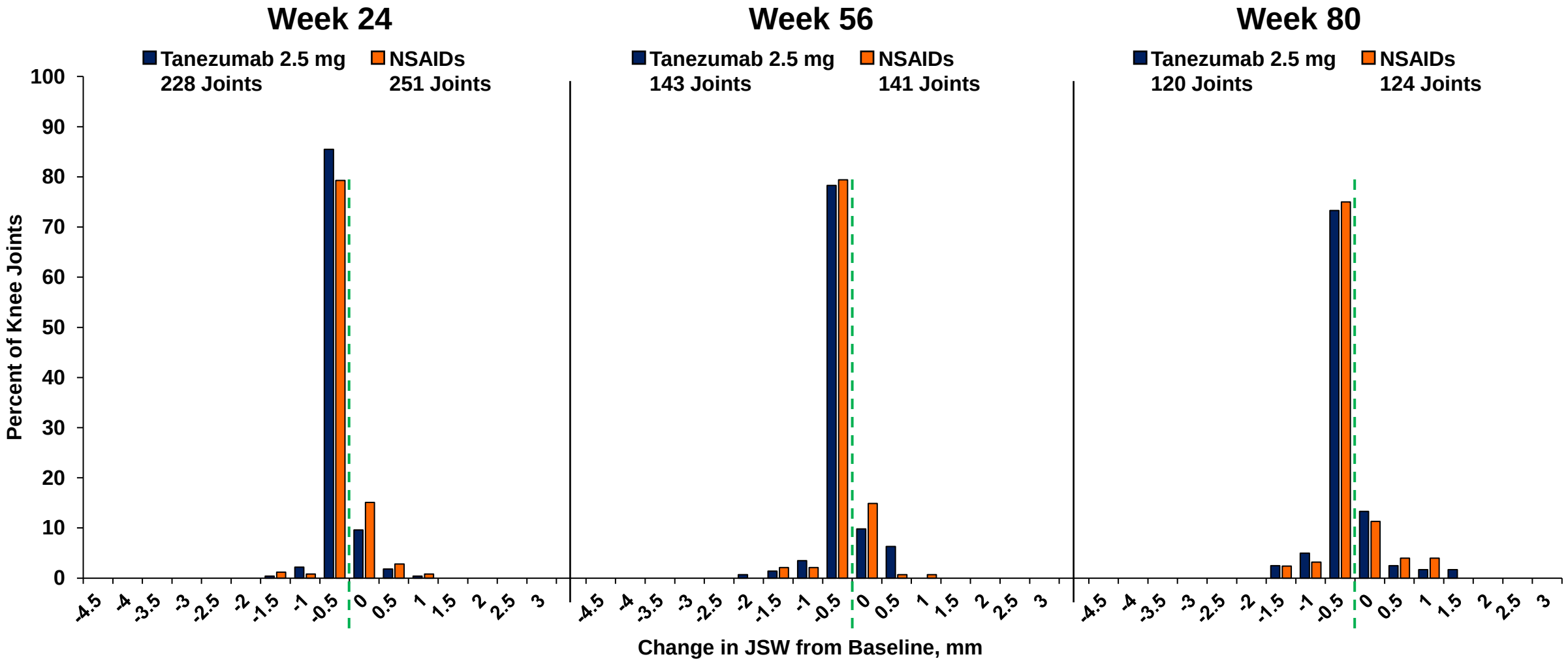
Adjudicated Joint Safety Outcomes: Patient Level Assessment

Classification of All Outcomes in Post-2015 OA Studies 1056, 1057, 1058

n (%)	Placebo N=514	Tanezumab			NSAIDs N=996
		2.5 mg N=1530	2.5/5 mg N=219	5 mg N=1282	
Patients assessed by Adjudication Committee	24 (4.7)	157 (10.3)	17 (7.8)	204 (15.9)	49 (4.9)
Composite joint safety endpoint	0	49 (3.2)	1 (0.5)	80 (6.2)	15 (1.5)
RPOA-1	0	35 (2.3)	1 (0.5)	54 (4.2)	11 (1.1)
RPOA-2	0	6 (0.4)	0	17 (1.3)	1 (0.1)
Primary osteonecrosis	0	1 (0.1)	0	2 (0.2)	0
Pathological fracture	0	0	0	0	0
Subchondral insufficiency fracture	0	7 (0.5)	0	7 (0.5)	4 (0.4)
Normal progression of OA	22 (4.3)	96 (6.3)	16 (7.3)	98 (7.6)	27 (2.7)
Other joint outcome	2 (0.4)	10 (0.7)	0	26 (2.0)	7 (0.7)
Not enough information to determine rapid vs normal progression of OA	0	2 (0.1)	0	0	0

Categorical Changes in Medial Knee JSW

Study 1058: Baseline KL Grade 4



Factors Assessed in Subgroup Analyses

- Evaluations based on subgroup analyses, logistic regressions and machine learning to identify potential risk factors that may be associated with primary composite endpoint, RPOA-1 or RPOA-2
- Baseline characteristics
  - Demographics
  - Disease severity at baseline (KL Grade, WOMAC Pain, WOMAC Physical Function)
  - Bone health at Baseline (medical history, DXA, vitamin D, parathyroid hormone)
  - Prior use of IA corticosteroid or hyaluronic acid
- Post-baseline responses
  - Selected adverse events
  - Standardized neurological exams
  - Efficacy response
  - Concomitant medications – CV prophylactic aspirin, bisphosphonate, acetaminophen

DXA=Dual-Energy X-ray Absorptiometry; IA=Intra-Articular

Joint Safety Events in Patients with Baseline KL Grade 0 Joints

OA Studies 1056, 1057 and 1058: Patient-Level

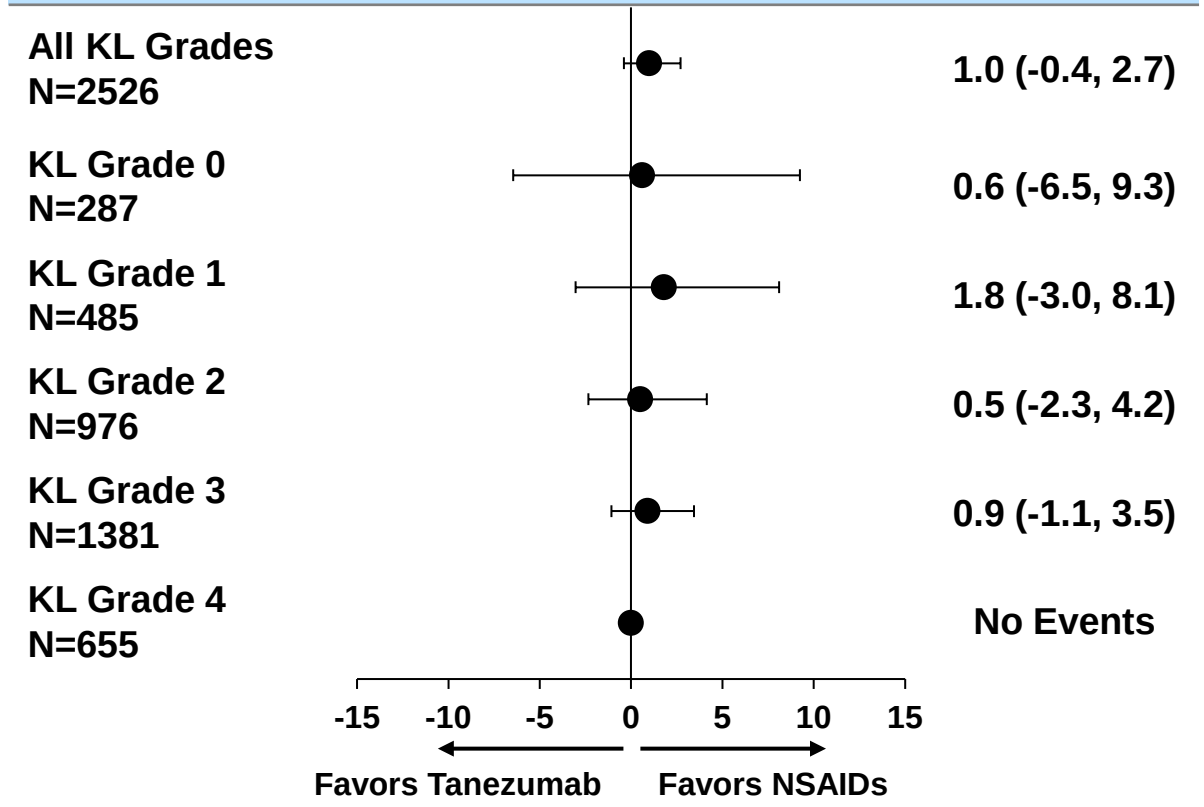
	Placebo N=514	Tanezumab 2.5 mg N=1530	Tanezumab 5 mg N=1282	NSAIDs N=996
At Least One KL Grade 0 Joint n (% of total patients)	351 (68.3)	1047 (68.4)	885 (69.0)	689 (69.2)
Adjudication Outcome n (% of patients with KL Grade 0 joint)				
RPOA-1	0	2 (0.19)	2 (0.23)	0
RPOA-2	0	0	2 (0.23)	0
TJR	0	0	2 (0.23)	0

Risk Differences – Rapidly Progressive OA Type 1: Tanezumab 2.5 mg vs NSAIDs

Similar Across Patients with KL Grade ≤3 Joints

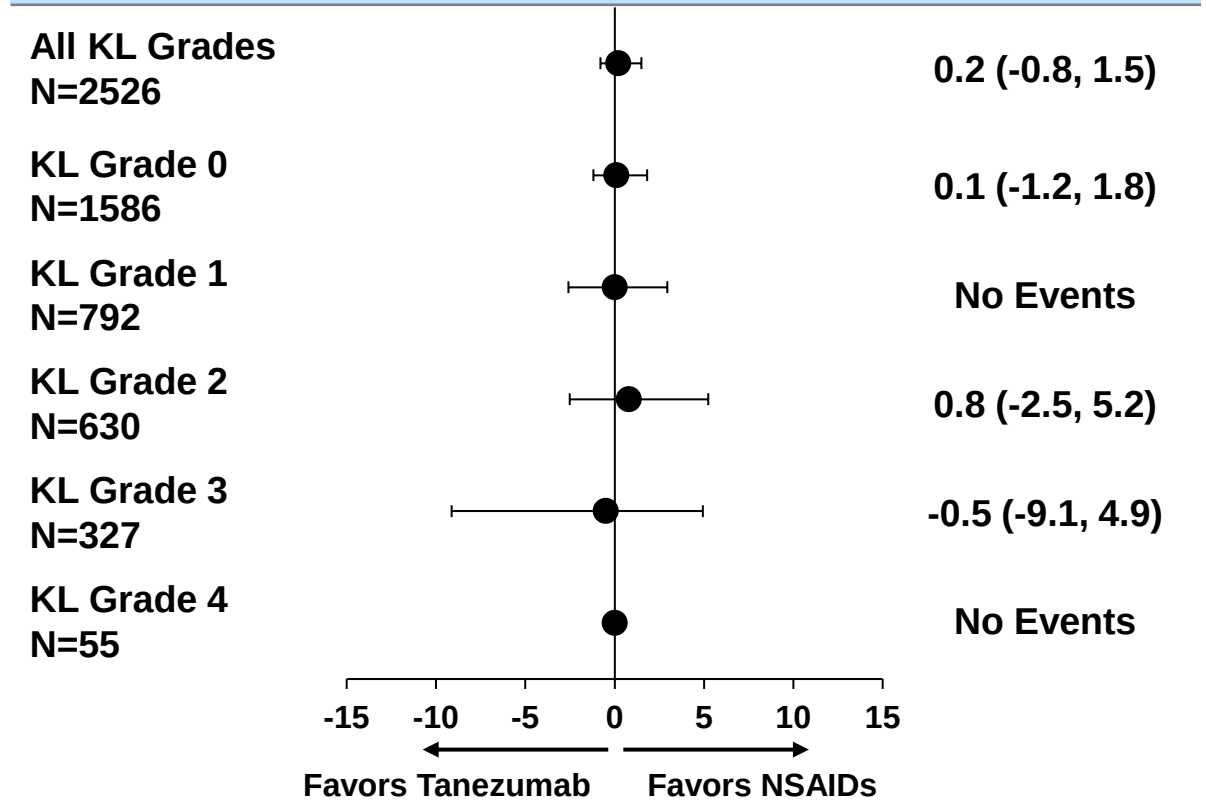
Knee Joints

Risk Difference for Incidence for Patients with ≥1 Affected Joint % (95% CI)



Hip Joints

Risk Difference for Incidence for Patients with ≥1 Affected Joint % (95% CI)

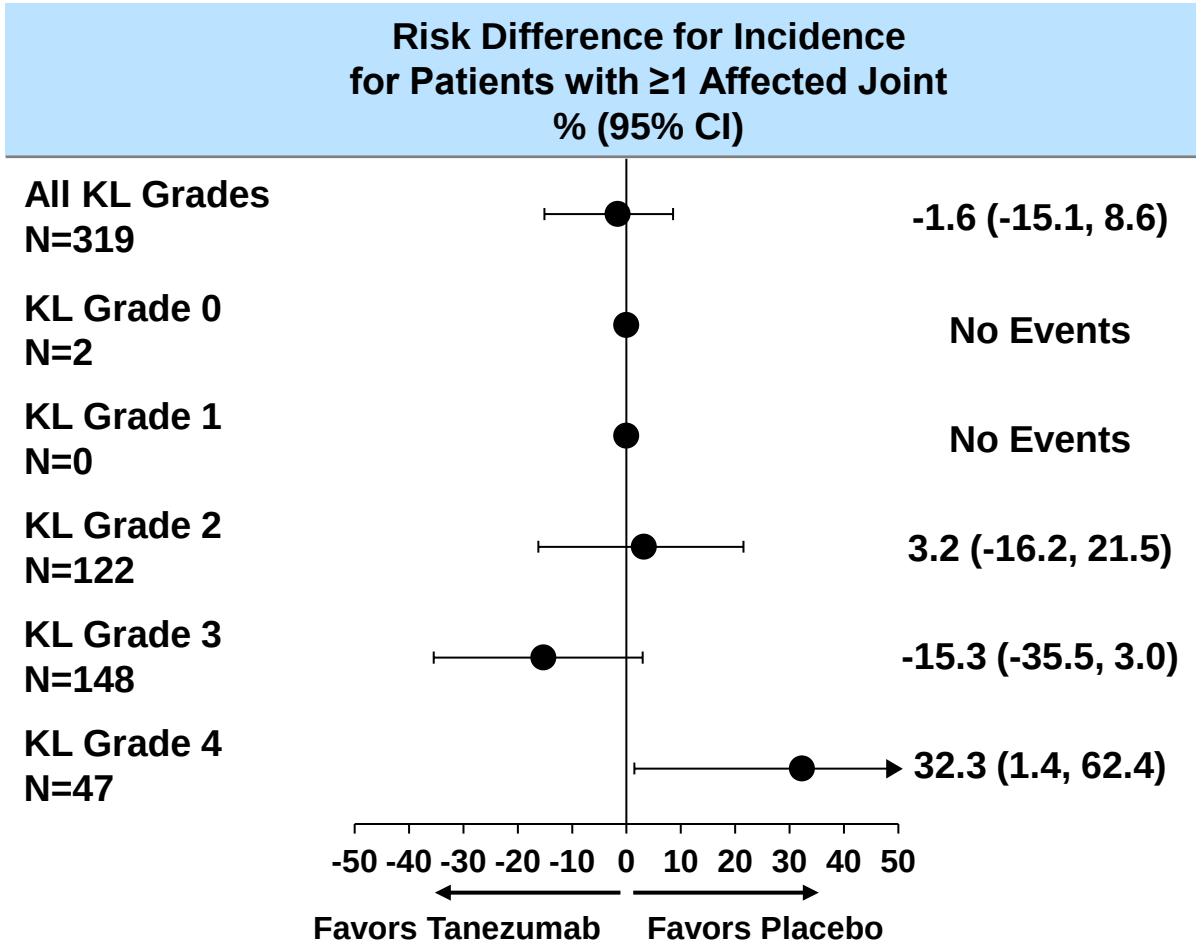


Patient-level analysis
Patients can be represented in more than one KL subcategory
Studies 1056, 1057 and 1058

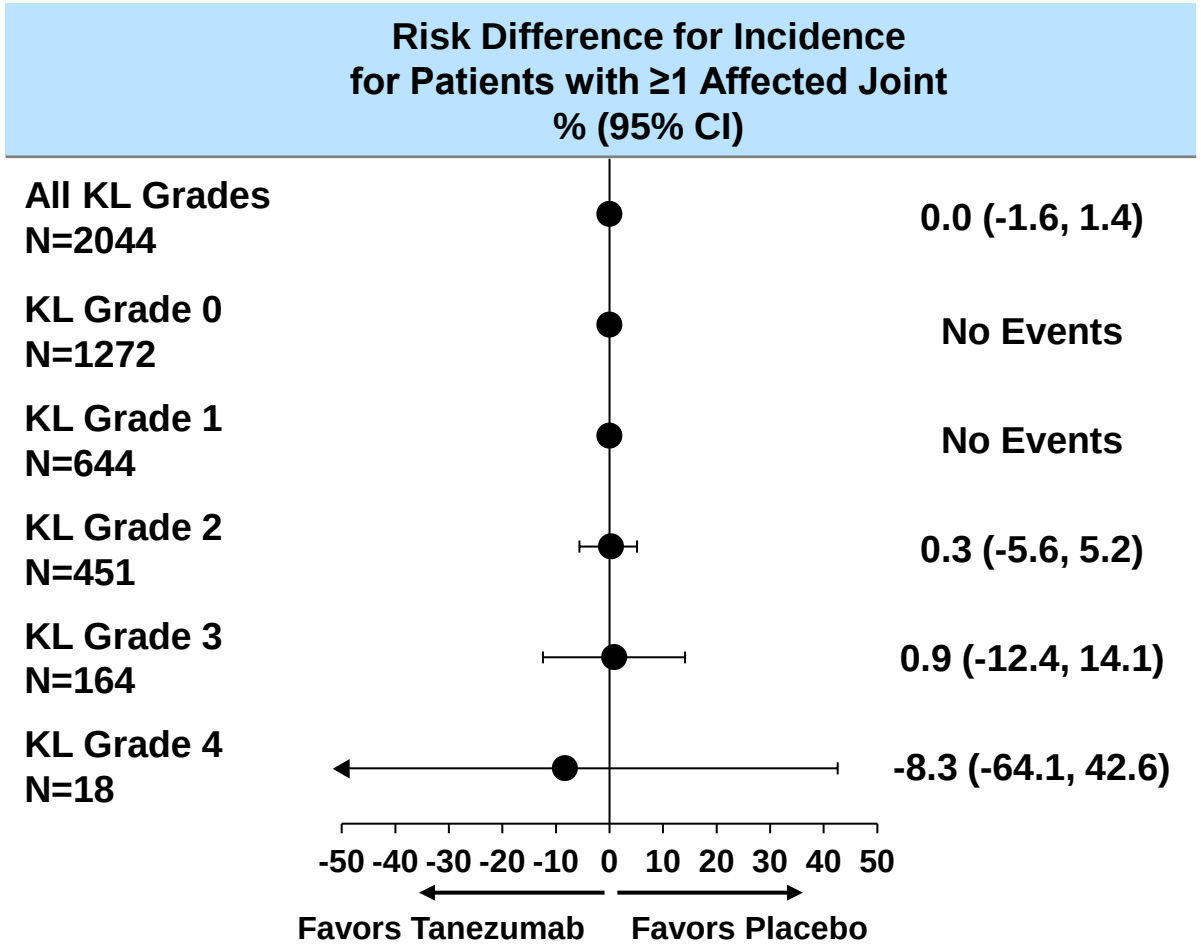
Risk Differences for TJR: Tanezumab 2.5 mg vs Placebo

Index Hips vs Non-Index Hips

Index Hip Joints



Non-Index Hip Joints



Patient-level analysis
Patients can be represented in more than one KL subcategory
Studies 1056, 1057 and 1058

RPOA-1/NPOA
Index Joint, Shoulder OA at Baseline
Studies 1056, 1057, 1058

n (%)	Placebo		Tanezumab						NSAIDs	
			2.5 mg		2.5/5 mg		5 mg			
	RPOA-1 N=0	NPOA N=22	RPOA-1 N=35	NPOA N=98	RPOA-1 N=1	NPOA N=16	RPOA-1 N=54	NPOA N=114	RPOA-1 N=11	NPOA N=28
Index joint										
Hip	–	11 (50.0)	4 (11.4)	32 (32.7)	1 (100.0)	5 (31.3)	9 (16.7)	31 (27.2)	2 (18.2)	8 (28.6)
Knee	–	11 (50.0)	31 (88.6)	66 (67.3)	0	11 (68.8)	45 (83.3)	83 (72.8)	9 (81.8)	20 (71.4)
Shoulder OA at baseline	–	1 (4.5)	2 (5.7)	9 (9.2)	0	0	4 (7.4)	9 (7.9)	1 (9.1)	3 (10.7)

Slide 17 of FDA Safety Presentation

Annotated to Include Specific KL Grade 0 vs 1

FDA Analysis of Composite Joint Safety Events focused only on Affected Joints

n (%)	Study 1058					
	NSAID N=996		Tanezumab 2.5 mg N=1002		Tanezumab 5 mg N=998	
CJSE in Any Joint	15 (1.5)		39 (3.9)		72 (7.2)	
	KL Grade 0	KL Grade 1	KL Grade 0	KL Grade 1	KL Grade 0	KL Grade 1
CJSE in KL Grade 0/1 Joint	1 (0.1)	1 (0.1)	2 (0.2)	6 (0.6)	5 (0.5)	14 (1.4)
RPOA-1	0	1 (0.1)	1 (0.1)	6 (0.6)	2 (0.2)	11 (1.1)
RPOA-2	0	0	0	0	2 (0.2)	1 (0.1)
SIF	1 (0.1)	0	0	0	1 (0.1)	1 (0.1)
ON	0	0	1 (0.1)	0	0	1 (0.1)

After presentation during the FDA Advisory Committee meeting on 25 March 2021, the Sponsor noted an error in data summarized for patients who received tanezumab 5 mg and had a primary composite joint safety event in a joint with KL Grade 0. The data have been corrected in this slide.

- *The slide shown indicated 7 patients with KL Grade 0 who had a CJSE, 5 is correct*
- *The Slide shown indicated 3 patients with KL Grade 0 who had RPOA-1, 2 is correct*
- *The Slide shown indicated 1 patient with KL Grade 0 who had ON, 0 is correct*

Adapted from https://www.fda.gov/media/146924/download

Joint Safety Events in Patients with Baseline KL Grade 0 or 1 Joints

OA Studies 1056, 1057 and 1058: Patient-Level

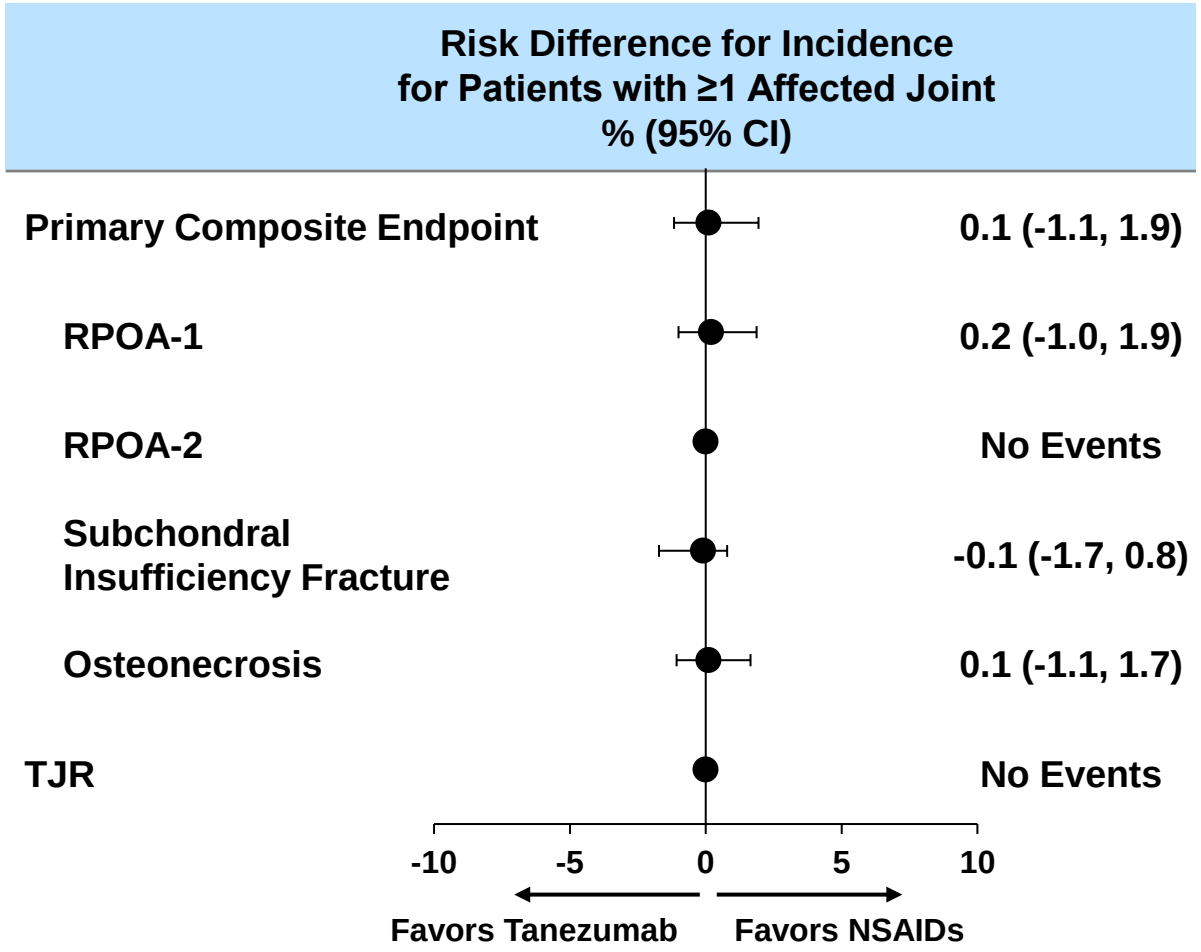
Pfizer Analysis of Composite Joint Safety Events focused on all patients with at-risk KL Grade 0 (n=2087) and 1 (n=1363) joints

	Placebo N=514		Tanezumab 2.5 mg N=1530		NSAIDs N=996	
	KL Grade 0	KL Grade 1	KL Grade 0	KL Grade 1	KL Grade 0	KL Grade 1
≥1 KL Grade 0 or 1 Joint n (% of total patients)	351 (68.3)	229 (44.6)	1047 (68.4)	691 (45.2)	689 (69.2)	443 (44.5)
Primary Composite Endpoint	0	0	3 (0.3)	7 (1.0)	1 (0.1)	1 (0.2)
RPOA-1	0	0	2 (0.2)	7 (1.0)	0	1 (0.2)
RPOA-2	0	0	0	0	0	0
SIF	0	0	0	0	1 (0.1)	0
ON	0	0	1 (0.1)	0	0	0
TJR	0	1 (0.4)	0	0	0	0

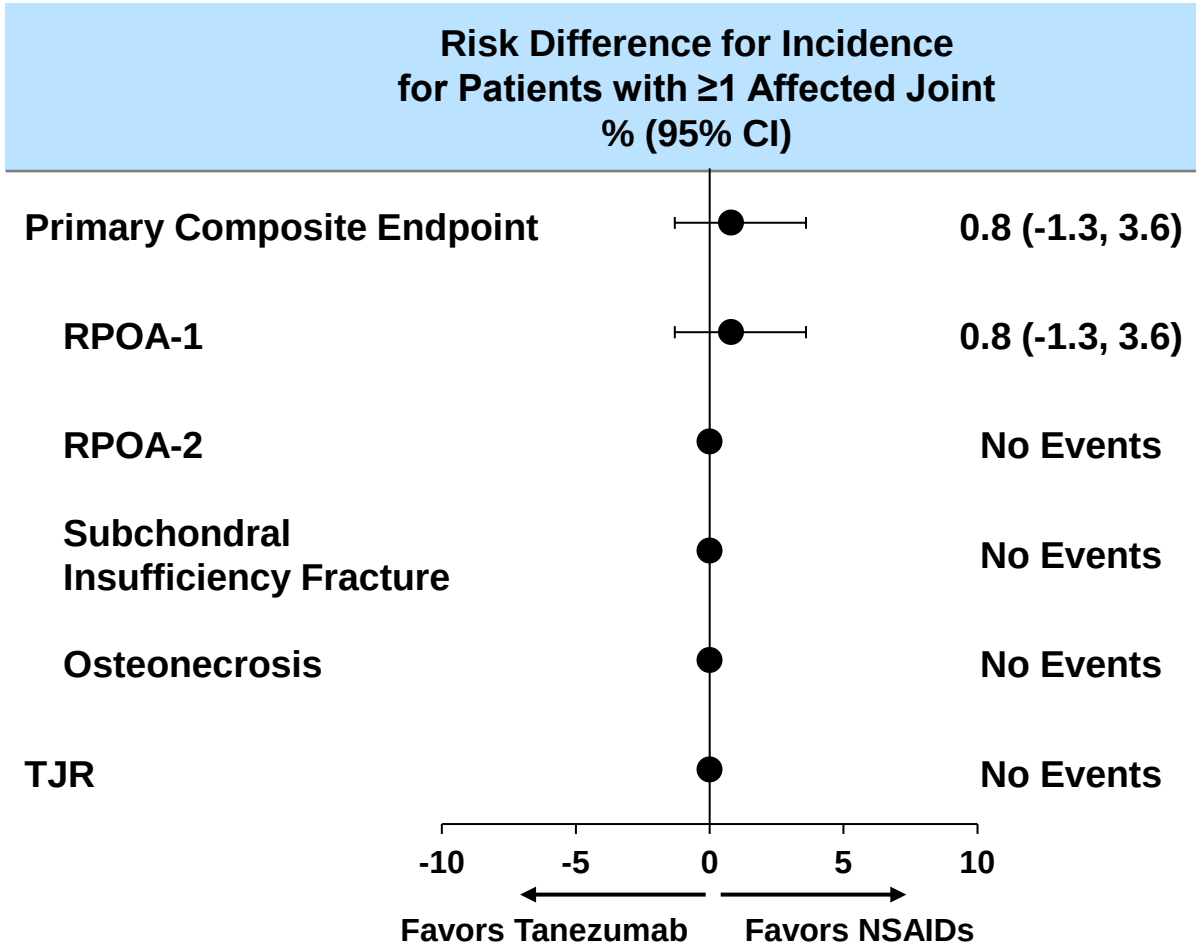
Tanezumab 2.5 mg patient with osteonecrosis had history of alcoholic liver disease which could have predisposed the patient to ON

Risk Differences for Joint Safety Endpoints in KL Grade 0 and 1 Joints: Tanezumab 2.5 mg vs NSAIDs

KL Grade 0 Joints



KL Grade 1 Joints



Patient-level analysis
Patients can be represented in more than one component of the primary composite endpoint
Studies 1056, 1057 and 1058

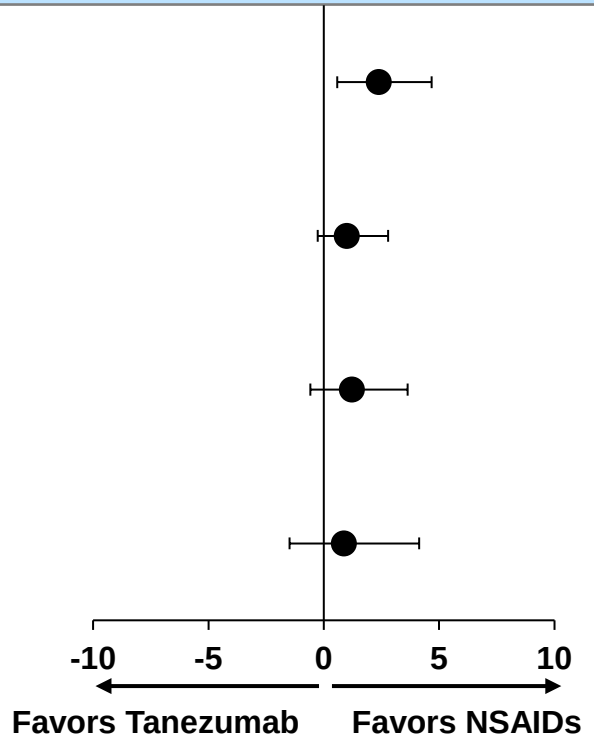
Risk Differences for Primary Composite Endpoint by Study Period

Study 1058

Incidence of Primary Composite Endpoint by Period

	Tanezumab 2.5 mg N=1002 n/N (%)	NSAID N=996 n/N (%)	Patients with ≥1 Affected Joint % (95% CI)
All Primary Composite Endpoint Events	39/1002 (3.9)	15/996 (1.5)	2.4 (0.6, 4.7)
Through Week 24	14/1002 (1.4)	4/996 (0.4)	1.0 (-0.3, 2.8)
After Week 24 through Week 56	19/818 (2.3)	9/813 (1.1)	1.2 (-0.6, 3.6)
After Week 56	6/464 (1.3)	2/473 (0.4)	0.9 (-1.5, 4.1)

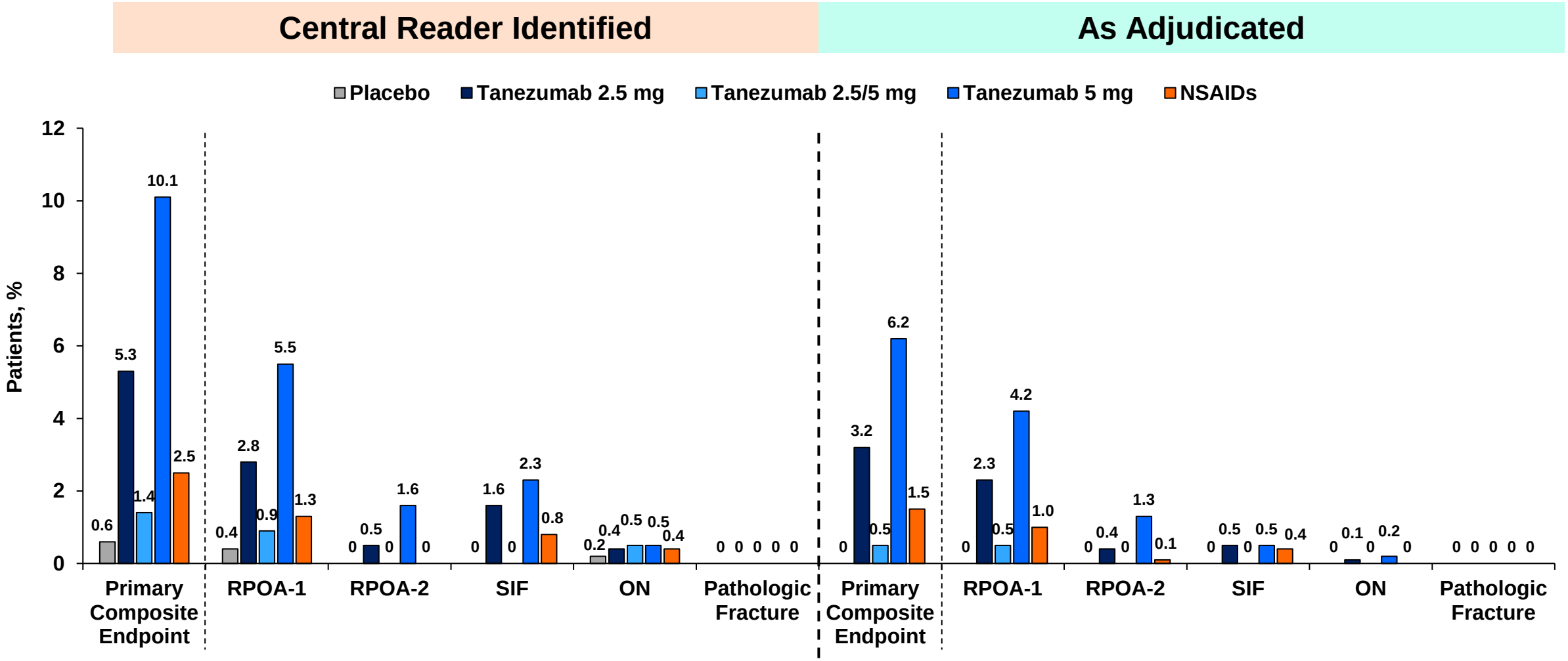
Risk Differences for Tanezumab 2.5 mg vs NSAIDs Primary Composite Endpoint by Period



4-week window

Joint Safety Outcomes Included in Primary Composite Endpoint

Comparison of Central Reader and Adjudication Committee Classification



Studies 1056, 1057, 1058

RPOA-1 Analyses – At-Risk Set of Patients

Follow-up for Day 1 Question

- Did the at-risk set of patients used for KM (and other) analysis of RPOA-1 data include patients who would not have the opportunity to have an RPOA-1 event because of baseline severity (KL grade 4, JSW <2)?

- Hip, knee, and shoulder joints could be at risk for RPOA-1, as not only the index joint is at risk

- There was only one patient (tanezumab 5 mg) who had severe enough OA across all four major joints (hip and knee) to preclude getting classified as an RPOA-1 event, so no new analyses were performed

Clinical Trial Risk Minimization Measures Informed REMS Strategy[a]

- Not recommended for patients with pre-existing RPOA, subchondral insufficiency fracture, osteonecrosis, or atrophic OA
  - REMS requirement for baseline radiographs of knees and hips
- Patients without a satisfactory clinical response after 2 doses should stop treatment
- Concomitant administration with NSAIDs is not recommended
  - Acute use should be limited to 10 days in an 8-week period
- Patients should be monitored for RPOA and radiographs repeated as needed
- Annual re-assessment of benefit risk
  - REMS requirement for annual radiographs of knees and hips

a. Strategy developed from clinical trial data with tanezumab, published literature and guidance from external experts

Elevated Risk of Rapidly Progressive OA with Tanezumab

Working Hypothesis Most Consistent with Preclinical and Clinical Evidence

Tanezumab

Reduced pain severity and improved function

Altered gait mechanics, increased joint loading

Joint-specific condition, e.g.

- **Structural OA disease severity**
- **Reduced subchondral bone mass**
  - **Osteoporosis/osteopenia**
- **Subchondral insufficiency fracture**
- **Subchondral bone defects**
  - **Accumulating microfractures**
- **Meniscal pathology (knee)**

RPOA