Updates on the Evidence-Based Management of Osteoarthritis and Osteoarthritis Pain

Tanezumab Safety

#ACR2020 ~ Abstract # 1482 & 1644

Abstract Tour 3

Social CMEdia

Provided by Integrity Continuing Education, Inc.

This activity is supported by an educational grant from Lilly.
For further information concerning Lilly grant funding visit www.lillygrantoffice.com.
Supported by an educational grant from Pfizer, Inc.

Disclaimer

These slides may not be published, posted online, or used in commercial presentations without permission. Please contact 855-835-4004 or cme@integrityce.com for details

The opinions expressed in this educational activity are those of the faculty and do not necessarily represent the views of any organization associated with this activity. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings

David Hunter MBBS, PhD, FRACP

Florance and Cope Chair of Rheumatology
Professor of Medicine
University of Sydney and Royal North Shore Hospital
Consultant Rheumatologist
@ProfDavidHunter

Disclosures:

Consultant : Tissuegene, TLCBio

Learning Objective

Review clinical trial outcomes and current statuses of emerging therapies for OA and OA pain

Background

- The anti-NGF tanezumab is currently in late-stage development for the treatment of moderate-to-severe OA-associated pain in patients with inadequate relief from or intolerance/contraindications to SOC therapy
- Tanezumab demonstrates **high efficacy, but when combined with chronic NSAIDs, is associated with increased risk for RPOA in a small group of patients**

RPOA, rapidly progressive osteoarthritis; Karsdal et al. *Osteoarthritis Cartilage*. 2019;27(3):484-492. ACR 2020 Abstract: 1644

Background

- Recent phase 3 clinical studies have included comprehensive radiographic eligibility criteria to exclude patients with, or at risk of, RPOA:
  - Rigorous program-level, single-read, radiographic screening process
  - Extensive training for imaging technologists and radiologist central readers

RPOA, rapidly progressive osteoarthritis
Karsdal et al. *Osteoarthritis Cartilage*. 2019;27(3):484-492. ACR 2020 Abstract: 1644

Recent Evaluations of Tanezumab Safety in OA

Guermazi et al.

- Detailed description of the process, frequencies, and nature of the exclusionary radiographic findings observed during screening for 3 phase 3 randomized studies of subcutaneous tanezumab

Carrino et al.

- Analyses of baseline population characteristics, adjudicated joint safety outcomes and sub-group analyses in the combined randomized, controlled, phase 3 OA tanezumab studies

Radiographic Exclusionary Findings During Screening for Three Phase 3 Trials of Subcutaneous Tanezumab in Patients With Moderate to Severe Hip or Knee Osteoarthritis

Ali Guermazi[1], Frank W Roemer[1], Andrew J Kompel[1], Luis E Diaz[2], Michel D Crema[1], Mark T Brown[3], Anne Hickman[3], Glenn C Pixton[4], Lars Viktrup[5], Robert J Fountaine[3], Aimee Burr[3], Sarah P Sherlock[6], Christine R West[3]

[1]Boston University School of Medicine, Boston, MA, USA; [2]Boston Veteran Affairs Healthcare System, Boston, MA, USA; [3]Pfizer Inc, Groton, CT, USA; [4]Pfizer Inc, Morrisville, NC, USA; [5]Eli Lilly and Company, Indianapolis, IN, USA; 6. Pfizer Inc, Cambridge, MA, USA

ACR Convergence 2020; November 5-9, 2020. Abstract 1644

Pooled Analysis

- Radiographic screening data were pooled from 3 large, international, randomized, double-blind, phase 3 studies of subcutaneous tanezumab (2.5 mg or 5 mg every 8 weeks) in patients with OA
  - NCT2697773 was a 40-week placebo-controlled study (16-week treatment and 24-week safety follow-up; planned sample size ~690)[1]
  - NCT2709486 was a 48-week placebo-controlled study (24-week treatment and 24-week safety follow-up; planned sample size ~810)[2]
  - NCT02528188 was an 80-week active-controlled (oral NSAID) study (56-week treatment and 24-week safety follow-up; planned sample size ~3000)[3,4]
- Screening lasted up to 37 days prior to randomization, during which patient underwent two-sage assessments to ascertain their eligibility to enroll

NSAID, nonsteroidal anti-inflammatory drug.

1. Schnitzer TJ, et al. *JAMA* 2019;322(1):37-48. 2. Berenbaum F, et al. *Ann Rheum Dis* 2020;79(6):800-10. 3. Hochberg MC, et al. *Arthritis Rheumatol* 2019;71(Suppl 10):1302. 4. Hochberg MC, et al. *Arthritis Rheumatol* 2019;71(Suppl 10):2756.

Key Inclusion Criteria

- A diagnosis of OA of the hip or knee based on the American College of Rheumatology criteria with radiographic confirmation (Kellgren-Lawrence [KL] grade ≥2)
- A Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC*) Pain score ≥5 in the index joint (11-point numeric rating scale from 0 to 10; increasing pain) at baseline
- A WOMAC Physical Function score of ≥5 in the index joint (11-point numeric rating scale from 0 to 10; increasing functional difficulty) at baseline

Key Inclusion Criteria

- A patient's global assessment of OA score of "fair," "poor," or "very poor" at baseline
- A documented history of inadequate response, intolerance, or contraindication to standard of care analgesic for OA pain

Key Radiographic Exclusion Criteria

Key radiographic exclusion criteria applied to all joints and were defined in a program-specific imaging atlas.

- Radiographic exclusion criteria aimed to exclude patients with conditions that may confound efficacy assessments or constitute a potential risk factor for RPOA.
- These included severe malalignment of the knee, severe chondrocalcinosis, other arthropathies, systemic metabolic bone disease, large cystic lesions, primary or metastatic tumor lesions, stress or traumatic fracture, RPOA type 2, atrophic OA, subchondral insufficiency fractures, osteonecrosis, and pathologic fracture

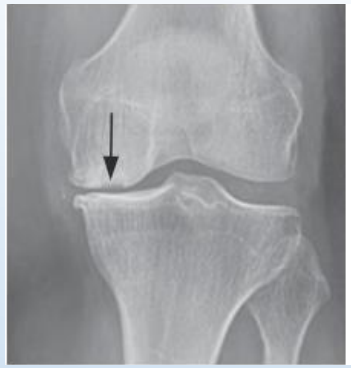
Table 1. Definitions for Selected Key Radiographic Exclusion Criteria

Severe malalignment of the knee	≥10° varus or valgus on the anterior-posterior view.
RPOA type 2	Abnormal bone loss or destruction, including limited or total collapse of at least 1 subchondral surface that is not a feature of conventional advanced OA.
Atrophic OA	Joint space narrowing without relevant osteophyte formation and absence of erosions or other radiographic signs of inflammatory arthritis
Subchondral insufficiency fracture	Focal bone defect, or loss of sphericity of the articular surface and/or focal radiolucency in the subchondral trabecular bone, with or without adjacent cortical defect (observing the sequelae of subchondral insufficiency fracture).
Osteonecrosis	Focal circumscribed or extended region of infarcted bone (avascular necrosis).

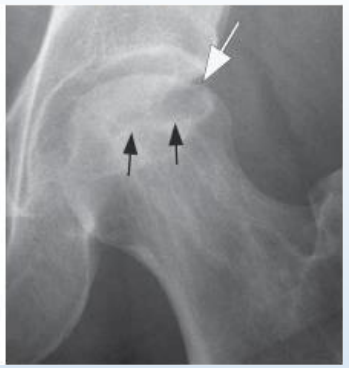
OA, osteoarthritis, RPOA, rapidly progressive OA.

Figure 1. Examples of radiographic exclusionary findings

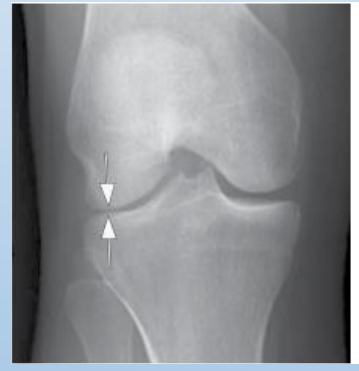
A. Subchondral insufficiency fracture



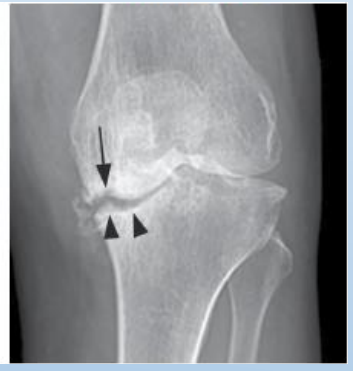
B. Osteonecrosis



C. Atrophic osteoarthritis

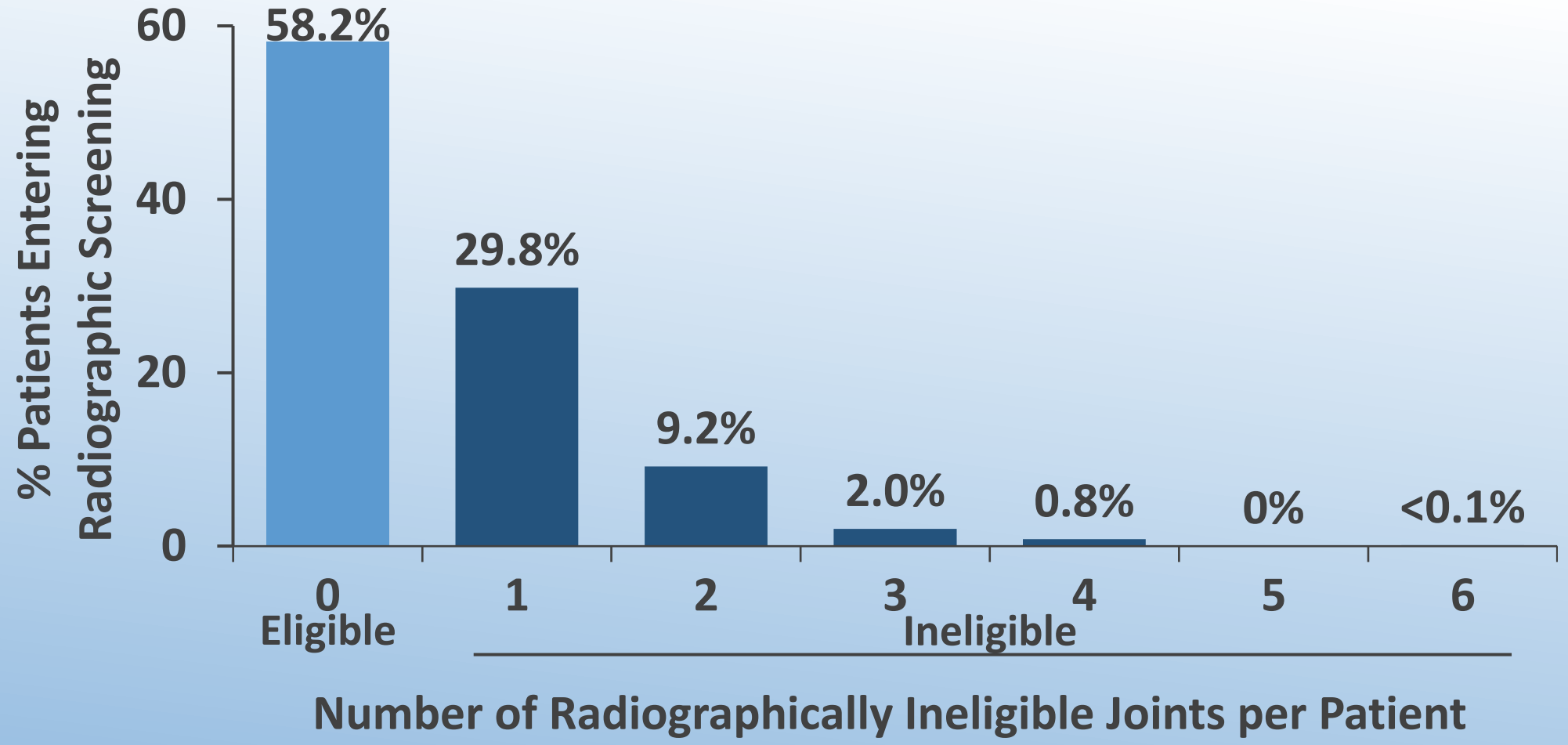


D. Rapidly progressive osteoarthritis type 2



Exclusionary Radiographic Findings

Figure 2. Number of joints with radiographic exclusionary findings in patients who entered radiographic screening



Exclusionary Radiographic Findings

Table 2. Exclusionary Radiographic Findings in Patients Who Entered Radiographic Screening – Patient Level	
n (%) Patients	**Patients Entering Radiographic Screening (n=13,797)**
Number of patients with ≥1 exclusionary finding	5773 (41.8)
Discordant pain to x-ray	3773 (27.4)
Severe malalignment of the knee	666 (4.8)
Subchondral insufficiency fracture	597 (4.3)
Atrophic OA	513 (3.7)
Osteonecrosis	454 (3.3)
RPOA type 2	125 (0.9)
Large cystic lesion	119 (0.9)

1 or more exclusionary radiographical finding may have been reported for each patient. Other findings reported in ≤0.5% of patients entering radiographic screening were severe chondrocalcinosis, stress or recent fracture, system metabolic bone disease, pathological fracture, and primary or metastatic tumor. OA, osteoarthritis; RPOA, rapidly progressive OA.

Exclusionary Radiographic Findings

Table 3. Exclusionary Radiographic Findings in Patients Who Entered Radiographic Screening – Joint Level

	Knee Radiographs (n=26,597)		Hip Radiographs (n=26,938)		Shoulder Radiographs (n=27,520)	
Exclusionary Radiographic Finding	n Radiographs (%)	Observed Frequency During Screening	n Radiographs (%)	Observed Frequency During Screening	n Radiographs (%)	Observed Frequency During Screening
Discordant pain to x-ray	2508 (9.4)	~1 in 10 x-rays	2612 (9.7)	~1 in 10 x-rays	N/A	N/A
Severe malalignment of the knee	751 (2.8)	~1 in 35 x-rays	N/A	N/A	N/A	N/A
Subchondral insufficiency fracture	586 (2.2)	~1 in 50 x-rays	61 (0.23)	~1 in 500 x-rays	10 (0.4)	~1 in 2500 x-rays
Atrophic OA	486 (1.8)	~1 in 50 x-rays	105 (0.39)	~1 in 250 x-rays	3 (0.01)	~1 in 10,000 x-rays
Osteonecrosis	119 (0.45)	~1 in 250 x-rays	323 (1.2)	~1 in 100 x-rays	82 (0.30)	~1 in 325 x-rays
RPOA type 2	18 (0.07)	~1 in 1500 x-rays	110 (0.41)	~1 in 250 x-rays	14 (0.05)	~1 in 2000 x-rays

1 or more exclusionary radiographical finding may have been reported for each patient or from each radiograph. OA, osteoarthritis; RPOA, rapidly progressive OA.

Conclusions

- The phase 3 subcutaneous tanezumab clinical trial program included comprehensive radiographic screening.
- Among patients who entered radiographs screening, the most common exclusionary finding in knees and hips was pain discordant to x-ray (~1 in 10 screening x-rays). Findings for defined joint conditions were less common.
- Exclusionary finding in more than 1 joint per patient were uncommon.
- Defined joint conditions were each identified in <5% of radiographically screened patients.

Joint Safety with Tanezumab: Integrated Analyses from Randomized Controlled Phase 3 Studies in Patients with Osteoarthritis

John Carrino[1], Timothy McAlindon[2], Eric Vignon[3], Mark Brown[4], Aimee Burr[4], Robert Fountaine[4], Glenn Pixton[5], Lars Viktrup[6], Christine West[7] and Kenneth Verburg[8]

[1]Hospital for Special Surgery, Hackensack, NJ, [2]Tufts Medical Center, Boston, MA, [3]Université Claude Bernard Lyon 1, Pierre Benite, France, [4]Pfizer Inc., Groton, CT, [5]Pfizer Inc., Morrisville, NC, [6]Eli Lilly and Company, Indianapolis, IN, [7]Pfizer Inc, Groton, CT, [8]Pfizer Inc, Groton

ACR Convergence 2020; November 5-9, 2020. Abstract 1482

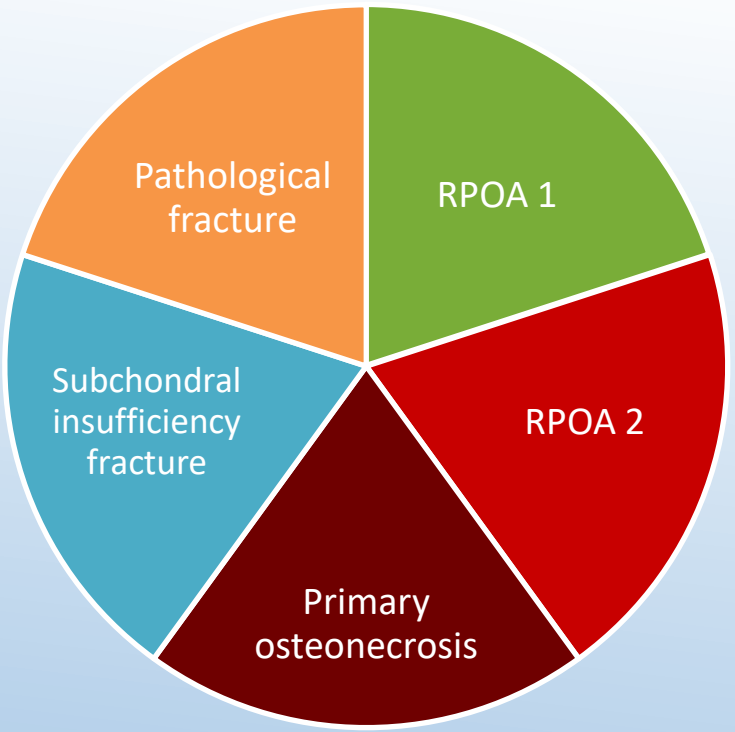
Integrated Analysis

Included Studies

Study 1	Study 2	Study 3

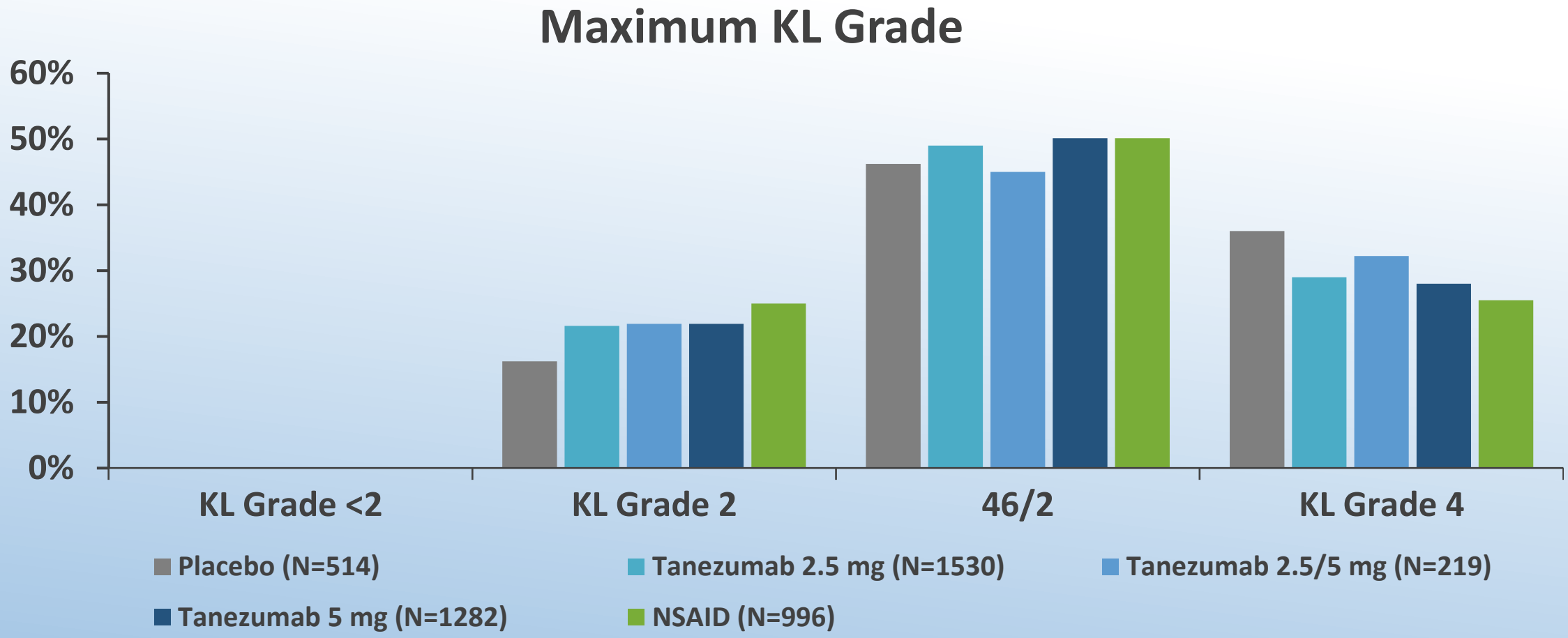
• Treatment groups:
  • Placebo
  • Tanezumab 2.5 mg SC
  • Tanezumab 2.5 mg then 5mg SC
• Treatment duration: 16 weeks
• Study duration: 40 weeks
• Randomized and treated: N=696
	• Treatment groups:
	  • Placebo
	  • Tanezumab 2.5 mg SC
	  • Tanezumab 5mg SC
	• Treatment duration: 24 weeks
	• Study duration: 48 weeks
	• Randomized and treated: N=849
		• Treatment groups:
		  • Oral NSAID bid
		  • Tanezumab 2.5 mg SC
		  • Tanezumab 2.5 mg then 5mg SC
		• Treatment duration: 56 weeks
		• Study duration: 80 weeks
		• Randomized and treated: N=2996

Composite Joint Safety Endpoint



Note: For all three studies, SC dosing of tanezumab or matching placebo was once every 8 weeks

Baseline Patient Characteristics: Kellgren-Lawrence Grade of Any Joint



The maximum KL grade of any joint was similar across treatment groups

KL, Kellgren-Lawrence

Adjudicated Joint Safety Endpoints

- RPOA1 accounted for the majority of adjudicated outcomes in the CJSE

	Placebo (N=514)	Tanezumab 2.5 mg (N=1530)	Tanezumab 2.5/5 mg (N=219)	Tanezumab 5 mg (N=1282)	NSAID (N=996)
Patient adjudicated	24 (4.7)	157 (10.3)	17 (7.8)	204 (15.9)	49 (4.9)
CISE	0	49 (3.2)	1 (0.5)	80 (6.2)	15 (1.5)
RPOA1	0	35 (2.3)	1 (0.5)	54 (4.2)	10 (1.0)
RPOA2	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
SIF	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)
Insufficient information to determine rapid vs normal progression of OA	0	2 (0.1)	0	0	0

*Includes patients who did not meet the criteria for one of the other adjudicated joint safety endpoints or who the committee could not assign to a particular outcome.
†Includes joint outcomes such as post-traumatic/post-procedure events and pre-existing conditions.
CJSE, composite joint safety endpoint; RPOA, rapidly progressive osteoarthritis; SIF, subchondral insufficiency fracture; OA, osteoarthritis.

Subgroup Analysis

- Subgroups were analyzed to assess any association with composite joint safety endpoints
- Subgroups included:
  - Baseline demographics and disease characteristics
  - Adverse events
  - Efficacy response
  - Sensory examinations
  - And concomitant medications
- Possible associations were noted for:
- Baseline structural OA severity
- Adverse events of arthralgia and joint swelling

Study Conclusions

- The proportion of patients with adjudicated CJSE was higher in tanezumab-treated patients relative to placebo or NSAID.
- The incidence of adjudicated CJSE increased with increasing dose of tanezumab.
- Subgroup analyses did not reveal an association of CJSE with efficacy response.
- Possible associations were noted for baseline structural OA severity and adverse events of arthralgia and joint swelling.