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

Recent Guidelines and Emerging Therapies

#ACR2020 ~ Abstract # 1640, 1641, & 1642

Abstract Tour 2

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Disclosures:

Consultant : Tissuegene, TLCBio

Learning Objective

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

Unmet Needs in Chronic Pain Despite Current Treatments and Published Guidelines

Patients with chronic pain and treated with opioids (n=303)[1]

51% Had **little or no control** of their chronic pain

60% Experienced **breakthrough pain** ≥1 time/day

Physicians who treat chronic pain (n=492)[2]

>50% **Lack of therapeutic options** made treatment challenging

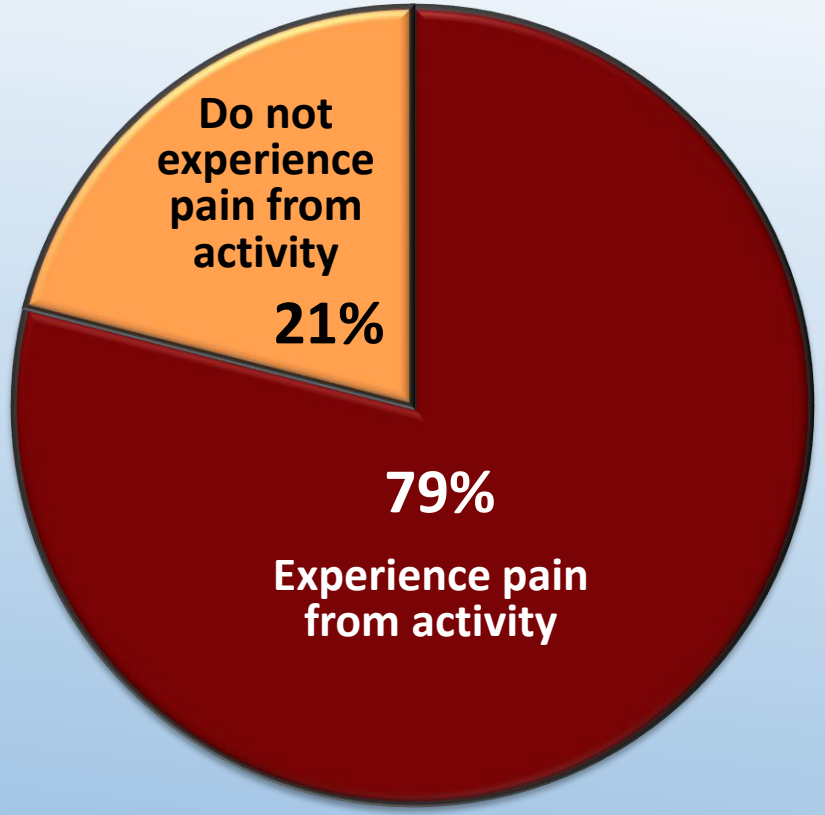
>90% Expressed concern over **addiction and abuse potential**

>90% **Subjective nature of chronic pain** added to treatment challenge

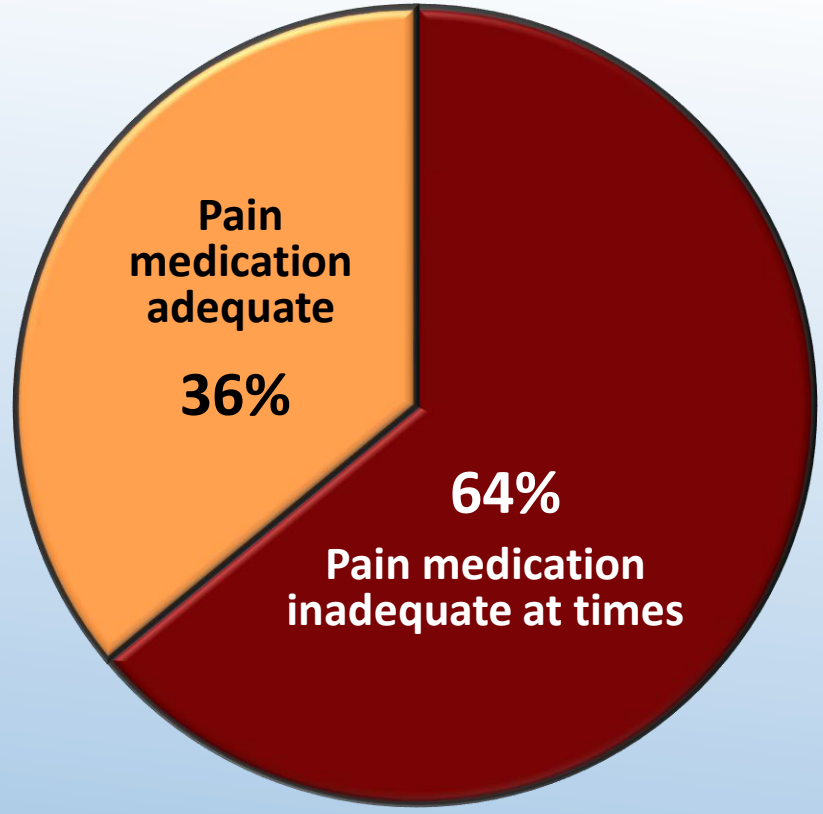
1. 2006 Voices of Chronic Pain Survey. American Pain Society. 2. McCarburg BH, et al. *Am J Therapeutics*. 2008;15:312-320.
Data from 2006 US Survey; physicians included 125 primary care, 241 specialists, and 126 emergency medicine.

Unmet Needs in Chronic Pain Despite Current Treatments and Published Guidelines

Breakthrough Pain From Activity (n=4,787)

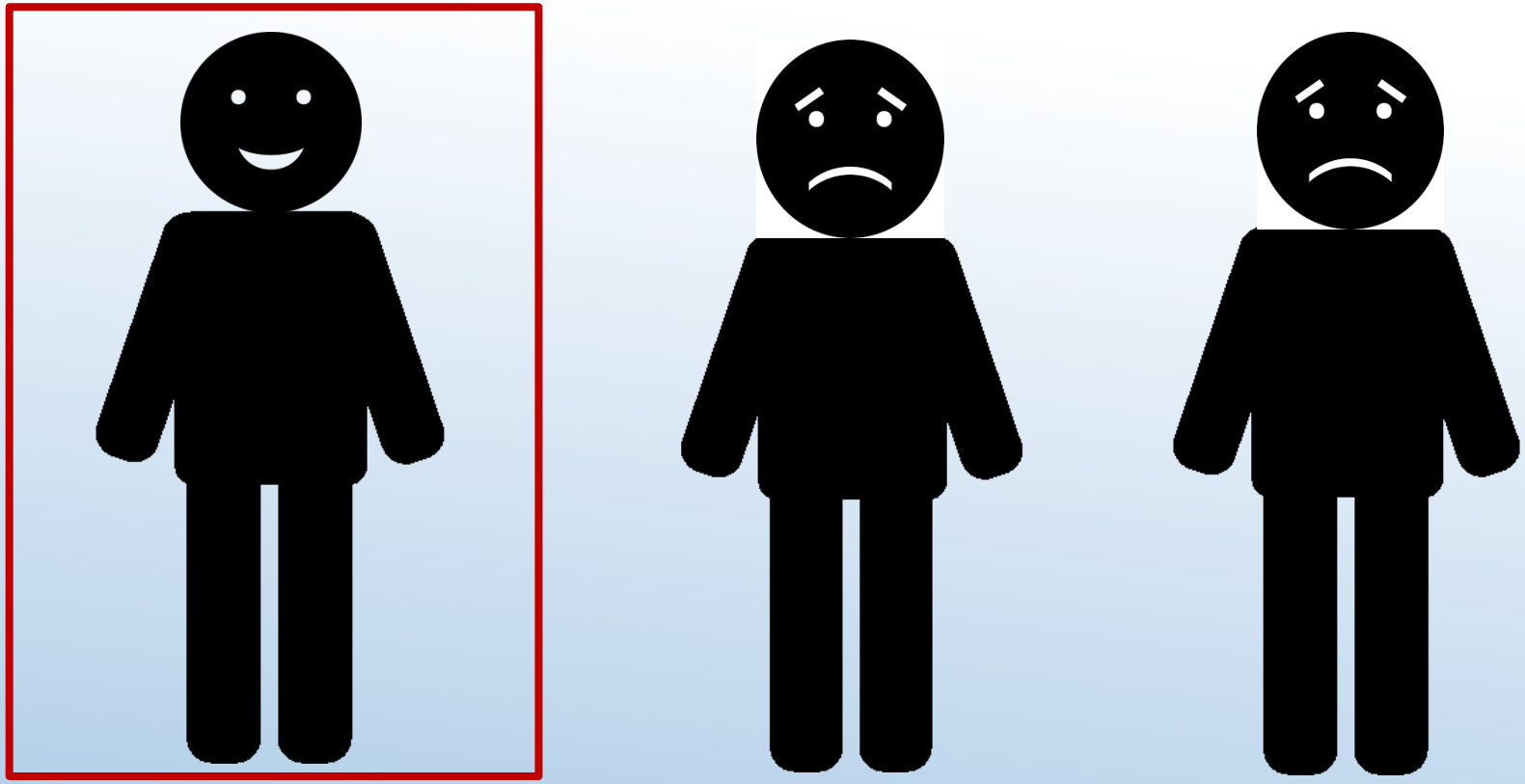


Adequacy of Pain Control From Pain Medication (n=2,450)



Breivik H et al. *Eur J Pain*. 2006;10(4):287-333.

Only One-Third of OA Patients Report High Satisfaction* With Treatment



Satisfaction level was similar across all classes of analgesics† studied

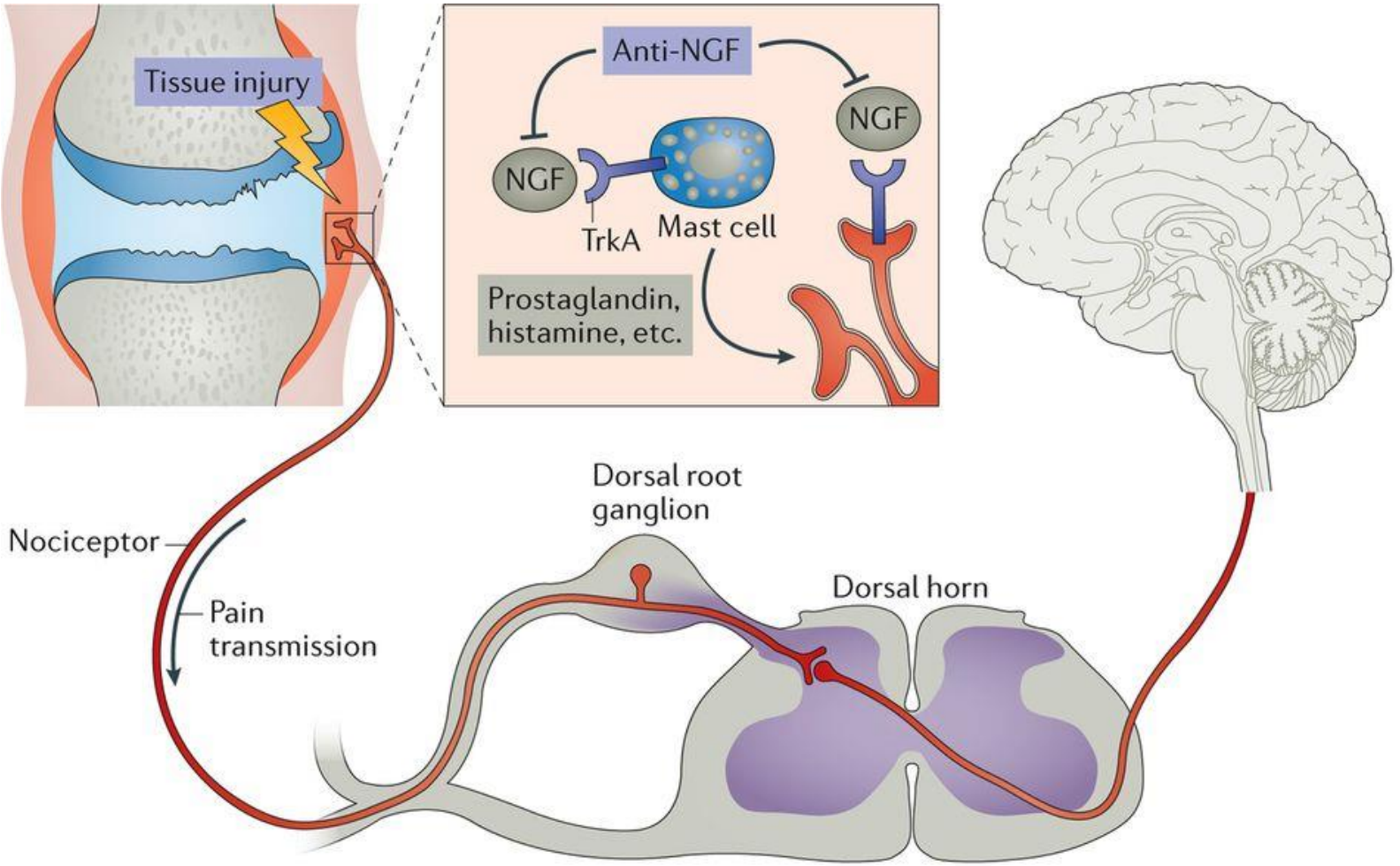
Based on data from the National Health and Wellness Survey conducted in Germany, Spain, France, Italy, and United Kingdom; N=3750.

*Defined as "very satisfied" or "extremely satisfied" with treatment.

†Incl: glucosamine/chondroitin therapy (n=72), opioid (n=626), COX-2 inhibitor (n=116), NSAID + gastroprotective agent (n=75), NSAID (n=1036), paracetamol (n=74).

Kingsbury SR, et al. *Rheumatology*. 2014;53:937-947.

Anti-NGF-Ab: Tanezumab



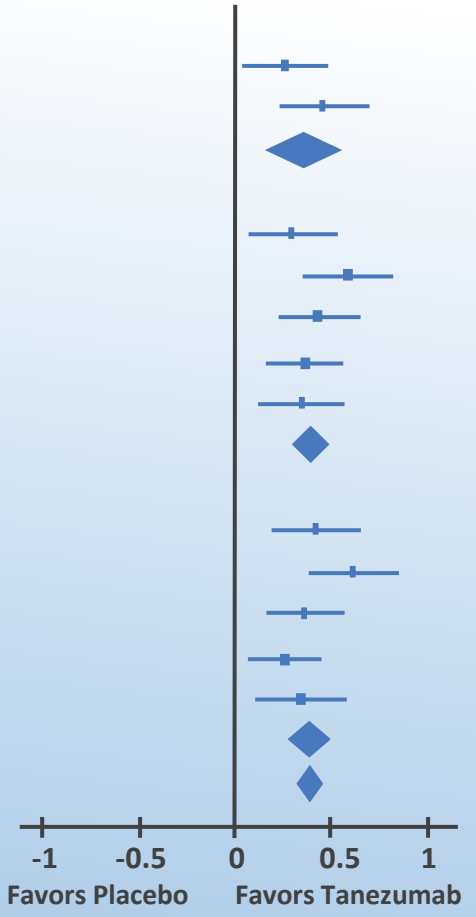
Schnitzer et al. *Osteoarthritis Cartilage*. 2015;23 Suppl 1:S8-17

Anti-NGF-Ab: Tanezumab

Study or Subgroup	Weight	Std. Mean Difference IV, Random, 95% Ci
Tanezumab 2.5 mg		
Brown et al, 2012	7.7%	0.26 (0.03, 0.48)
Brown et al, 2013	7.5%	0.45 (0.22, 0.68)
Subtotal (95% CI)	**15.1%**	**0.35 (0.16, 0.54)**
Tanezumab 5 mg		
Brown et al, 2012	7.7%	0.29 (0.07, 0.52)
Brown et al, 2013	7.3%	0.58 (0.35, 0.81)
Ekman et al, 2014 a	9.8%	0.43 (0.23, 0.62)
Ekman et al, 2014 b	10.3%	0.36 (0.16, 0.55)
Spierings et al, 2013	7.4%	0.34 (0.11, 0.57)
Subtotal (95% CI)	**42.5%**	**0.40 (0.30, 0.49)**
Tanezumab 10 mg		
Brown et al, 2012	7.6%	0.42 (0.19, 0.65)
Brown et al, 2013	7.4%	0.61 (0.38, 0.84)
Ekman et al, 2014 a	9.9%	0.35 (0.15, 0.55)
Ekman et al, 2014 b	10.3%	0.25 (0.06, 0.45)
Spierings et al, 2013	7.2%	0.34 (0.11, 0.57)
Subtotal (95% CI)	**42.4%**	**0.39 (0.27, 0.50)**
Total (95% CI)	**100.0%**	**0.38 (0.32, 0.45)**

Test for overall effect: Z = 11.95 ($P < 0.00001$)

Test for subgroup differences: $Chi^2 = 0.17$, df = 2 ($P = 0.92$), $I^2 = 0\%$



Schnitzer et al. *Osteoarthritis Cartilage*. 2015;23 Suppl 1:S8-17

Previous Studies of the Efficacy and Safety of Tanezumab for the Treatment of OA

	Schnitzer et al. 2019	Berenbaum et al. 2020
Study Objective	Assess 2 tanezumab dosing regimens for OA (hip or knee)	Investigate tanezumab for OA (hip or knee) with 24-week treatment and 24-week safety follow-up
Patients	Adults with moderate-to-severe OA, inadequate response to OA analgesics, and no radiographic evidence of prespecified joint safety conditions	Adults with moderate-to-severe OA with inadequate response to or lack of tolerance for SOC analgesics
Treatment Groups	• Tanezumab (2.5 mg at Day 1 & Week 8; n=231) • Tanezumab (2.5 mg at Day 1 & 5 mg at Week 8; n=233) • PBO at Day 1 & Week 8 (n = 232)	• Tanezumab (2.5 mg q8w; n=283) • Tanezumab (5.0 mg q8w; n=284) • PBO q8w (n=282)
Study Findings	• Statistically significant (though modest) improvements with tanezumab vs PBO in WOMAC* Pain and Physical Function, and PGA-OA • More joint safety events and total joint replacements with tanezumab	• Significant improvements in WOMAC Pain and Physical Function, and PGA-OA with tanezumab 5.0 mg vs PBO • Statistically significant improvements in WOMAC Pain and Physical Function, but not PGA-OA, with 2.5 mg dose • More frequent RPOA with the 5.0 mg vs 2.5 mg dose • Similar TJRs across all groups

* WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; PGA-OA, Patient's global assessment of OA; TJRs, total joint replacements. Schnitzer et al. JAMA. 2019;322(1):37-48; Berenbaum et al. Ann Rheum Dis. 2020;79(6):800-810.

Further Characterization of Tanezumab Efficacy in OA: Recent Investigations

Schnitzer et al.

- Randomized NSAID-controlled long-term global safety study
- Exploratory pooled analysis of two phase 3 studies to evaluate clinically meaningful within-patient improvements in pain following tanezumab treatment in patients with OA of the knee or hip

Hunter et al.

- Evaluation of the effect of tanezumab vs NSAID on clinically important improvements in patients with OA

Neogi et al.

- Examination of the time-course and longer-term maintenance of treatment effect of tanezumab vs NSAID on pain and physical function through Week 56

NSAID, nonsteroidal anti-inflammatory drugs

Clinically Important Improvement in Osteoarthritis Pain at Week 16 After Subcutaneous Administration of Tanezumab: Pooled Analysis From International Studies

Thomas J Schnitzer[1], Francis Berenbaum[2], Philip G Conaghan[3], Robert H Dworkin[4], Takaharu Yamabe[5], Isabelle Davignon[5], Stefan Wilhelm[6], Erika Dragon[7], Lars Viktrup[6]

[1]Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [2]Sorbonne Université, INSERM CRSA, AP-HP Hôpital Saint-Antoine, Paris, France; [3]University of Leeds, Leeds, UK; [4]University of Rochester School of Medicine and Dentistry, Rochester, NY, USA; [5]Pfizer Inc, Groton, CT, USA; [6]Eli Lilly and Company, Indianapolis, IN, USA; [7]Pfizer Ltd, Budapest, Hungary

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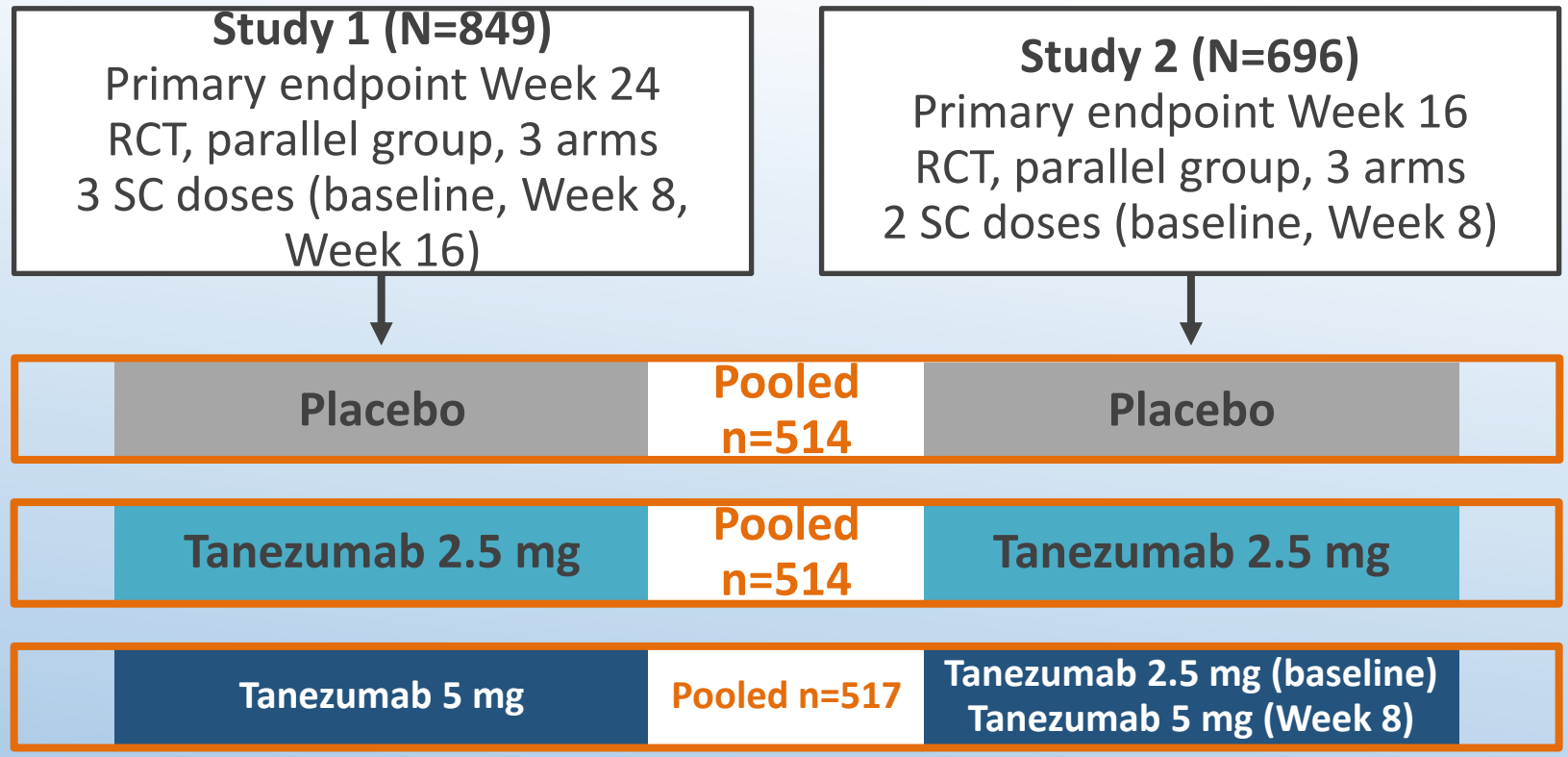
Pooled Analysis Strategy

Figure 1. The pooling strategy



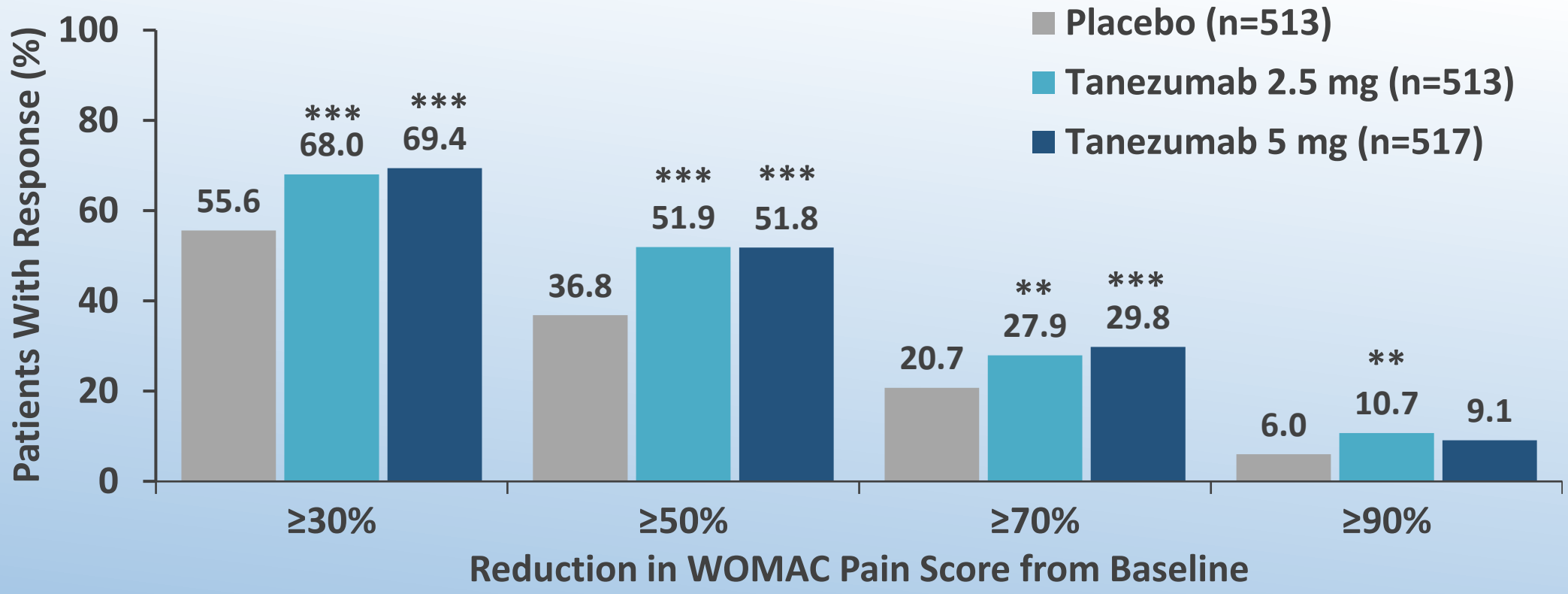
Study 1 was conducted in Europe and Japan (NCT02709486).[1] Study 2 was conducted in North America (NCT02697773).[2] Data from study 2 dose-titration group (tanezumab 2.5 mg at baseline, tanezumab 5 mg at Week 8) were pooled with the study 1 tanezumab 5 mg group for analyses at Week 16.

RCT, randomized controlled trial; SC, subcutaneous.

1. Berenbaum F, et al. *Ann Rheum Dis* 2020;79:800-10. 2. Schnitzer TJ, et al. *JAMA* 2019;322:37-48.

Efficacy Findings: WOMAC

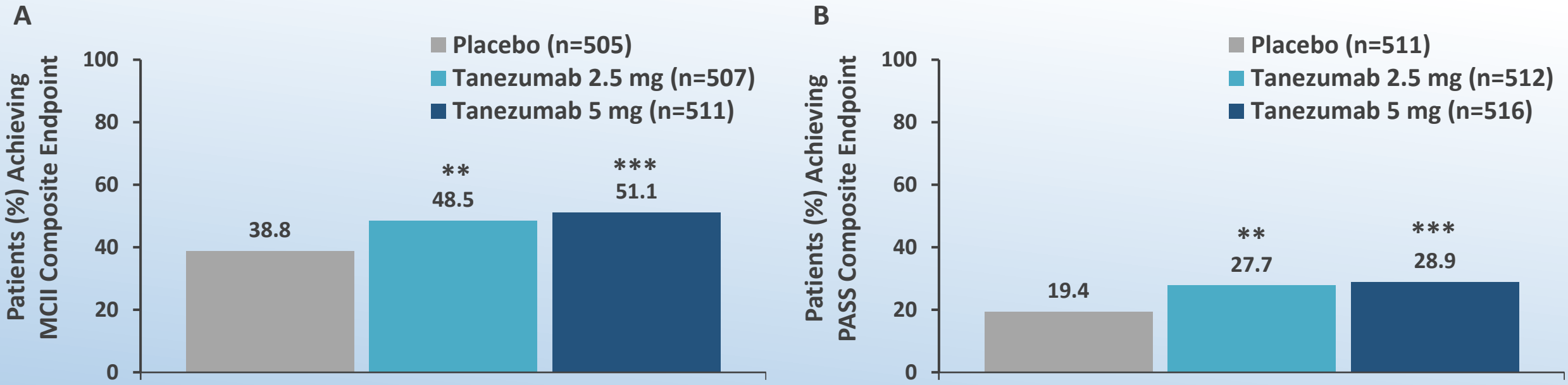
Figure 2. WOMAC Pain responders: proportion of patients achieving ≥30%, ≥50%, ≥70%, or ≥90% improvement in WOMAC Pain subscale at Week 16



**$P \leq 0.01$, *** $P \leq 0.001$ vs placebo. Responder defined as patient achieving specified threshold improvement from baseline at Week 16. Mixed BOCF/LOCF imputation for missing data. Logistic regression model included baseline WOMAC Pain subscale score baseline average pain in the index joint (pain diary) score, index joint (hip or knee), treatment, and study. BOCF, baseline observation carried forward, LOCF, last observation carried forward; WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index.

Efficacy Findings: MCII, and PASS

Figure 3. Proportion of patients achieving A) MCII composite endpoint and B) PASS composite endpoint at Week 16



**$P \leq 0.01$, *** $P \leq 0.001$ vs placebo. Published 100-mm VAS-based thredholds[7,8] were adapted for the current analyses of average pain in the index joint (pain diary) score (assessed on 11-point NRS, 0-10), WOMAC Physical Function score (NRS, 0-10), and PGA-OA scores (5-point Likert scale). For average pain in the index (pain diary) score and WOMAN Physical Function score, the published mean VAS (0-100 mm) thresholds for pain and function,[7,8] respectively, were extrapolated to NRS (0-10) equivalent by dividing by 10. For PGA-OA, the published mean VAS (0-100 mm) threshold was categorized as 10/30/50/70/90 and 0/25/50/75/100 to extrapolate to a 5-point Likert scale: an improvement of at least 18.3 mm (knee)[7] and 15.2 mm (hip)[7] was considered closest to an improvement of as least 1 category on the 5-point scale (MCII), ad scores of 32.mm (knee)[8] and 34.6 mm (hip)[8] were considered to correspond to "good" or "very good" on the 5-point scale (PASS). For the current analyses, MCII and PASS were defined as composite endpoints, such that an individual patient must achieve all 3 thresholds (pain, function, and global assessment). MCII composite endpoint defined as: improvement from baseline in average pain in the index joint (pain diary) (≥–1.53 for hip). WOMAC Physical Function (≥–0.91 for knee, ≥–0.79 for hip), and PGA-OA (improvement of at least 1 category scores. PASS composite endpoint defined as: average pain in the index joint (pain diary) scores ≤3.23 for knee or ≤3.50 for hip; and WOMAC Physical Function score ≤3.10 for knee or ≤3.44 for hip; and PGA-OA score "good" or "very good." Mixed BOCF/LOCF imputation for missing data. Logistic regression model included baseline WOMAN Pain subscale score, baseline average pain in the index joint (pain diary) score, index joint (hip or knee), treatment and study.

BOCF, baseline observation carried forward, LOCF, last observation carried forward; MCII, minimal clinically important improvement; NRS, numeric rating scale; PASS, patient acceptable symptom state; VAS, visual analog scale; WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index.

Efficacy Findings: Use of Rescue Medication

Use of Rescue Medication During Week 16

		Placebo (n=514)	Tanezumab 2.5 mg (n=514)	Tanezumab 5 mg (n= 517)
Rescue medication, incidence of use in Week 16[a]	Rescue medication taken, n (%)	254 (49.4)	231 (44.9)	218 (42.2)
	Odds ratio (95% CI vs placebo)		0.83 (0.65, 1.06)	0.74 (0.58, 0.94)
	P value		0.1363	0.0157
Rescue medication, days of use in Week 16[b]	LS mean (SE)	1.8 (0.16)	1.6 (0.14)	1.6 (0.13)
	LS mean ratio		0.89 (0.72, 1.09)	0.86 (0.69, 1.06)
	P value		0.2605	

Rescue medication (acetaminophen) was allowed in the US (≤3000 mg/day, ≤3 days per week) and Europe and Japan (≤4000 mg/day, ≤5 days per week), but could not be used within 24 hours of clinic efficacy assessments. Patients recorded any use of rescue medication electronically each day, with bottles returned at each clinic visit for assessment of compliance. Analysis included all patients who took rescue medication on 1 or more days during Week 16 of treatment. LOCF imputation for missing data.

[a]Logistic regression model including baseline WOMAC Pain subscale score, baseline average pain the index joint (pain diary) score, index joint (hip or knee), treatment, and study.

[b]Negative binomial model using the same model covariates as in the logistic regression model to get estimates and treatment differences; exponentiation of the estimates and the differences render the LS means and their difference not additive.

CI, confidence interval, LOCF, last observation carried forward; LS, least squares; SE, standard error; WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index.

Study Conclusions

The proportion of patients with a clinically meaningful improvement was significantly higher with tanezumab (both treatment groups) compared with placebo across several measures, including composite measures encompassing pain, function, and the patients assessment of disease.

Clinically Important Improvements in Patients With Osteoarthritis Treated With Subcutaneous Tanezumab: Results From a 56-Week Randomized NSAID-Controlled Study

David J Hunter[1], Tuhina Neogi[2], Melvin Churchill[3], Ivan Shirinsky[4], Masanari Omata[5], Alexander White[6], Ali Guermazi[2], Robert J Fountaine[7], Glenn Pixton[8], Lars Viktrup[9], Mark T Brown[7], Christine R West[7], Kenneth M Verburg[7]

[1]University of Sydney, Sydney, Australia; [2]Boston University School of Medicine, Boston, MA, USA; [3]Arthritis Center of Nebraska, Lincoln, NE, USA; [4]Federal State Budgetary Scientific Institution Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russia; [5]Ohimachi Orthopaedic Clinic, Tokyo, Japan; [6]Progressive Medical Research, Port Orange, FL, USA; [7]Pfizer Inc, Groton, CT, USA; [8]Pfizer Inc, Morrisville, NC, USA; 9. Eli Lilly and Company, Indianapolis, IN, USA

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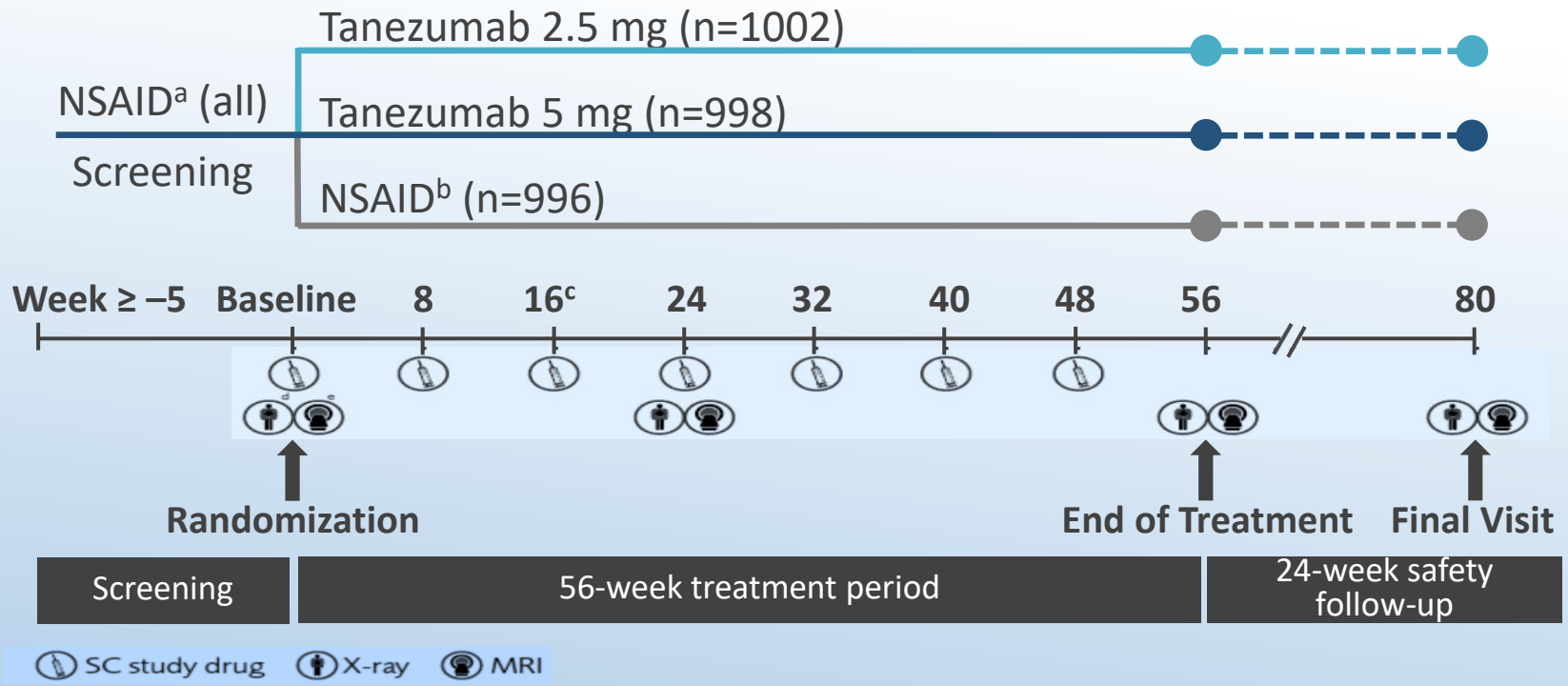
Study Design



[a]Patients received stable doses of NSAID for ≥2 weeks during screening and before randomization: naproxen 500 mg BID, celecoxib 100 mg BID, or diclofenac ER 75 mg BID.
[b]Patients randomized to oral NSAID group received same NSAID regimen as before randomization.
[c]Only responders continued to receive treatment after Week 16; nonresponders entered 24-week safety follow-up.
[d]X-rays of knees, hips, and shoulders in all patients at all timepoints.
[e]MRIs of knees and hips in all patients at screening and in patients with screening Kellgren-Lawrence grade ≥3 at other timepoints.
BID, twice daily; ER, extended release; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; SC, subcutaneous.

Study Patients: Key Inclusion Criteria[1,2]

- Aged ≥18 years and body mass index ≤39kg/m^2
- Diagnosis of hip or knee OA based on ACR criteria with X-ray confirmation
- Baseline WOMAC Pain and Physical Function subscale scores ≥5
- PGA-OA baseline rating of “fair,” “poor,” or “very poor”
- History of inadequate pain relief with acetaminophen and inadequate pain relief with/intolerance to/contraindication to tramadol or opioids, or unwillingness to take opioids
- Received and tolerated a qualifying, stable dose of oral NSAID therapy for ≥30 days prior to screening

ACR, American College of Rheumatology.

1. Hochberg M, et al. *Arthritis Rheumatol* 2019;71(Suppl 10):4888. 2. Hochberg M, et al. *Arthritis Rheumatol* 2019;71(Suppl 10):2243.

Study Patients: Key Exclusion Criteria[1,2]

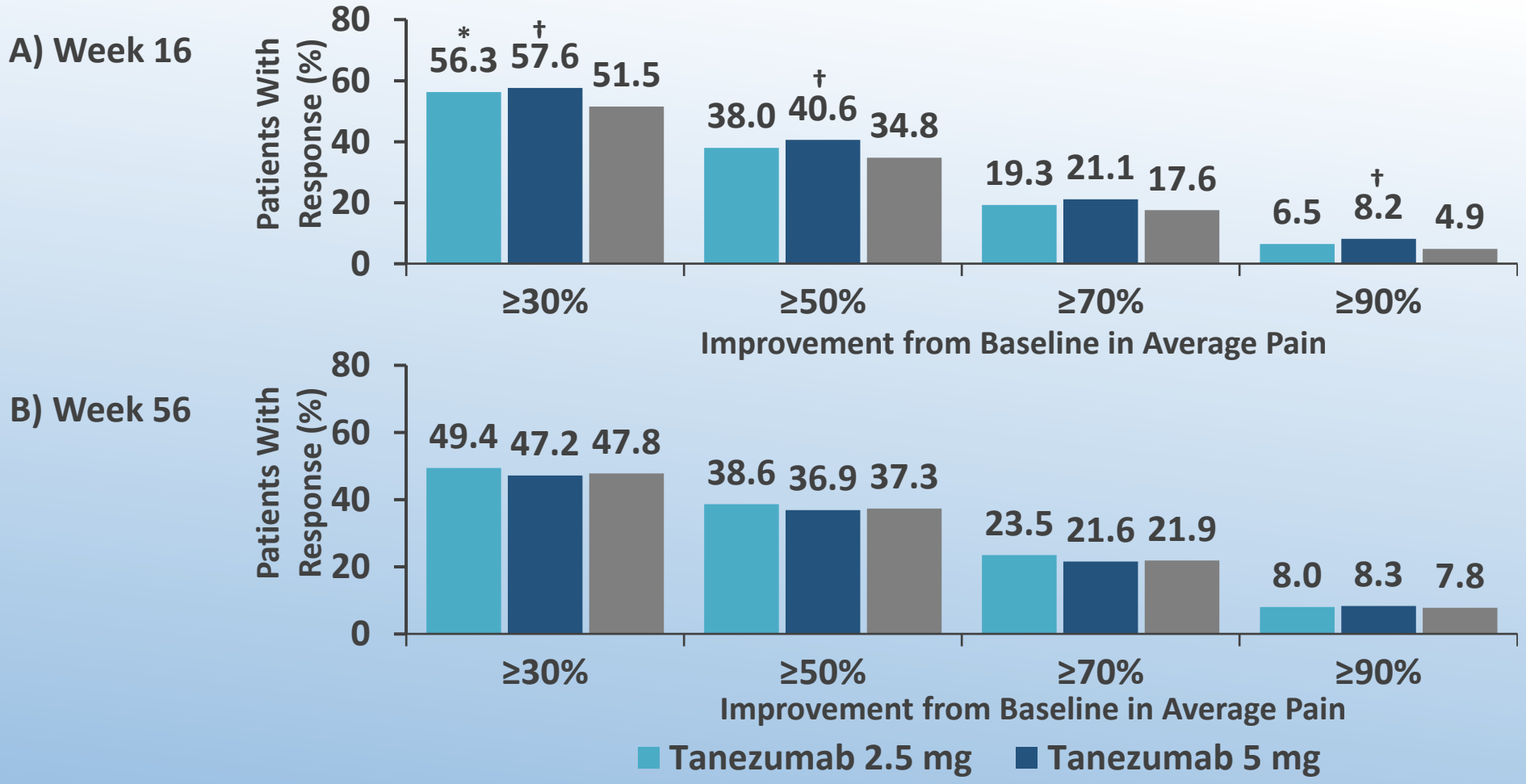
- Radiographic evidence (any joint) of prespecified bone or joint conditions (ie, RPOA, atrophic or hypotrophic OA, SIF, primary osteonecrosis, or pathologic fracture) at screening.
- History of osteonecrosis or osteoporotic fracture, or significant trauma or surgery to a knee, hip, or shoulder within the previous year.
- History or presence of clinically significant neurologic, CV, or psychiatric disorders; cancer (except certain skin cancers); fibromyalgia; or sciatica.
- Corticosteroid within 30 days or intra-articular corticosteroid injection in the index joint within 12 weeks or in any other joint within ~30 days of randomization.
- Intra-articular hyaluronic acid injection in the index joint within 30 days or long-acting hyaluronic acid formulation injection in the index joint within ~18 weeks of randomization.

*RPOA, rapidly progressive OA; SIF, subchondral insufficiency fractures; CV, cardiovascular.

1. Hochberg M, et al. *Arthritis Rheumatol* 2019;71(Suppl 10):4888. 2. Hochberg M, et al. *Arthritis Rheumatol* 2019;71(Suppl 10):2243.

Results: Improvements in Average Pain

Figure 2. Proportion of patients with ≥30%, ≥50%, ≥70%, and ≥90% improvement from baseline in average pain at A) Week 16 and B) Week 56

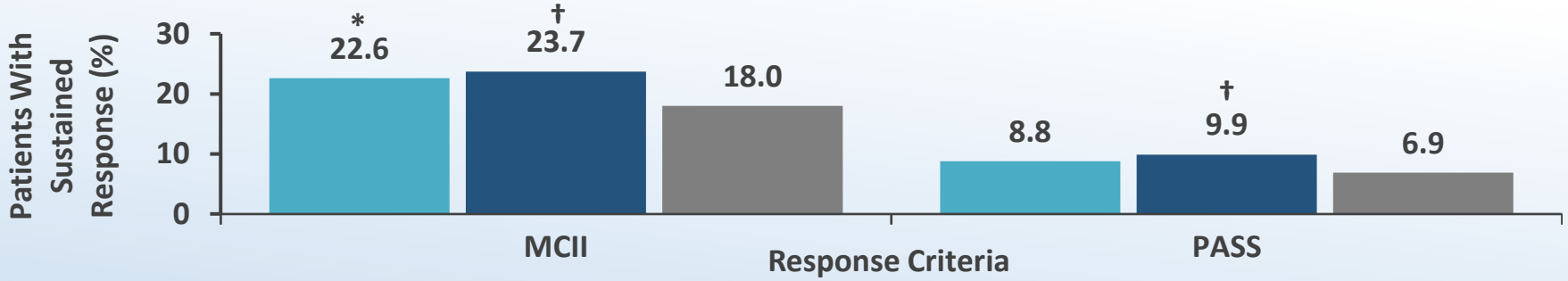


*Unadjusted *P*≤0.05 for tanezumab 2.5 mg vs NSAID. †Unadjusted *P*≤0.05 for tanezumab 5 mg vs NSAID. NSAID, nonsteroidal anti-inflammatory drug.

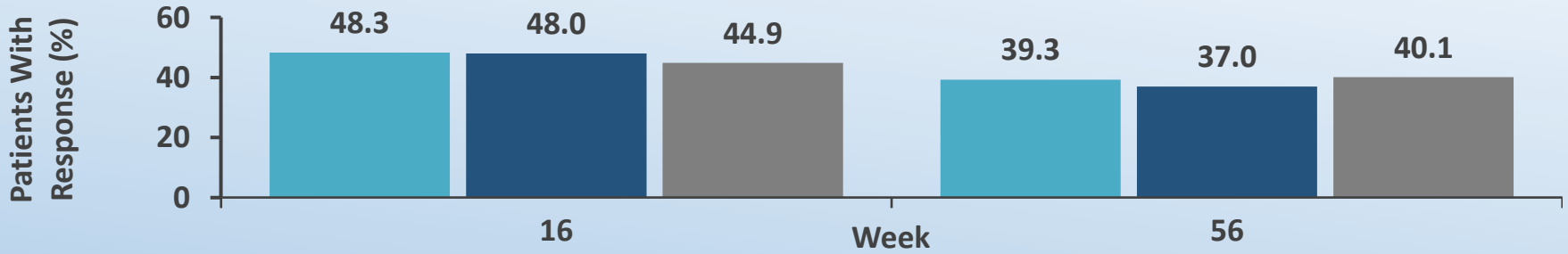
Results: Clinically Important Improvements

Figure 3. Proportion of patients with clinically important improvement: A) sustained MCII and PASS response from Week 4 to 16, and B) MCII and C) PASS at Weeks 16 and 56

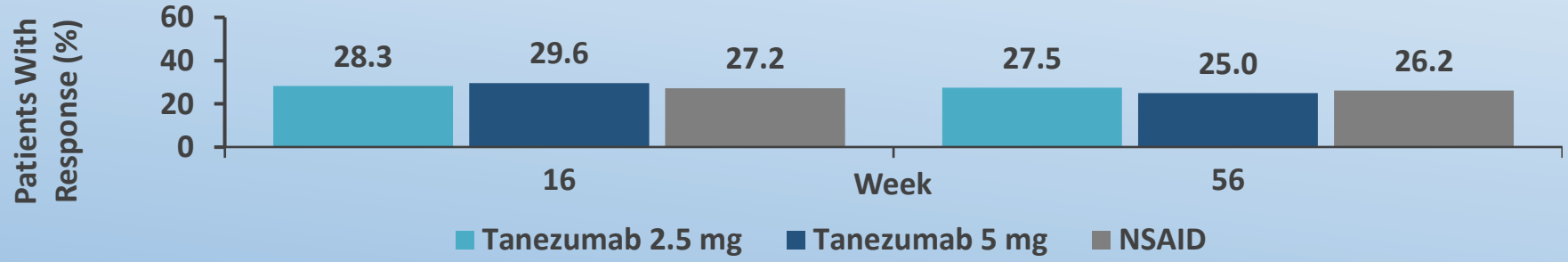
A) Sustained MCII and PASS response from Week 4 to 16



B) MCII at Weeks 16 and 56



C) PASS at Weeks 16 and 56



*Unadjusted *P*≤0.05 for tanezumab 2.5 mg vs NSAID. †Unadjusted *P*≤0.05 for tanezumab 5 mg vs NSAID. MCII, Minimum Important Improvement; NSAID, nonsteroidal anti-inflammatory drug; PASS, Patient Acceptable Symptom State.

Study Conclusions

- The majority of patients treated with tanezumab or NSAID had a clinically important improvement (≥30%) at Week 16, with a greater (unadjusted $P \leq 0.05$) proportion of patients achieving this level of improvement with tanezumab compared with NSAID.
- Patients treated with tanezumab vs NSAID more consistently had a meaningful response (MCII or PASS) at Week 4 that was sustained to Week 16; however, the proportion of patients achieving MCII and PASS at Week 16 and 56 did not differ between treatment groups.
- These results suggest clinically meaningful efficacy across all groups.

Observed Efficacy With Subcutaneous Tanezumab is Early and Maintained in Patients With Osteoarthritis: Results From a 56-Week Randomized NSAID-Controlled Study

Tuhina Neogi[1], David J Hunter[2], Melvin Churchill[3], Ivan Shirinsky[4], Masanari Omata[5], Alexander White[6], Ali Guermazi[1], Robert J Fountaine[7], Glenn Pixton[8], Lars Viktrup[9], Mark T Brown[7], Christine R West[7], Kenneth M Verburg[7]

[1]Boston University School of Medicine, Boston, MA, USA; [2]University of Sydney, Sydney, Australia; [3]Arthritis Center of Nebraska, Lincoln, NE, USA; [4]Federal State Budgetary Scientific Institution Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russia; [5]Ohimachi Orthopaedic Clinic, Tokyo, Japan; [6]Progressive Medical Research, Port Orange, FL, USA; [7]Pfizer Inc, Groton, CT, USA; 8. Pfizer Inc, Morrisville, NC, USA; 9. Eli Lilly and Company, Indianapolis, IN, USA

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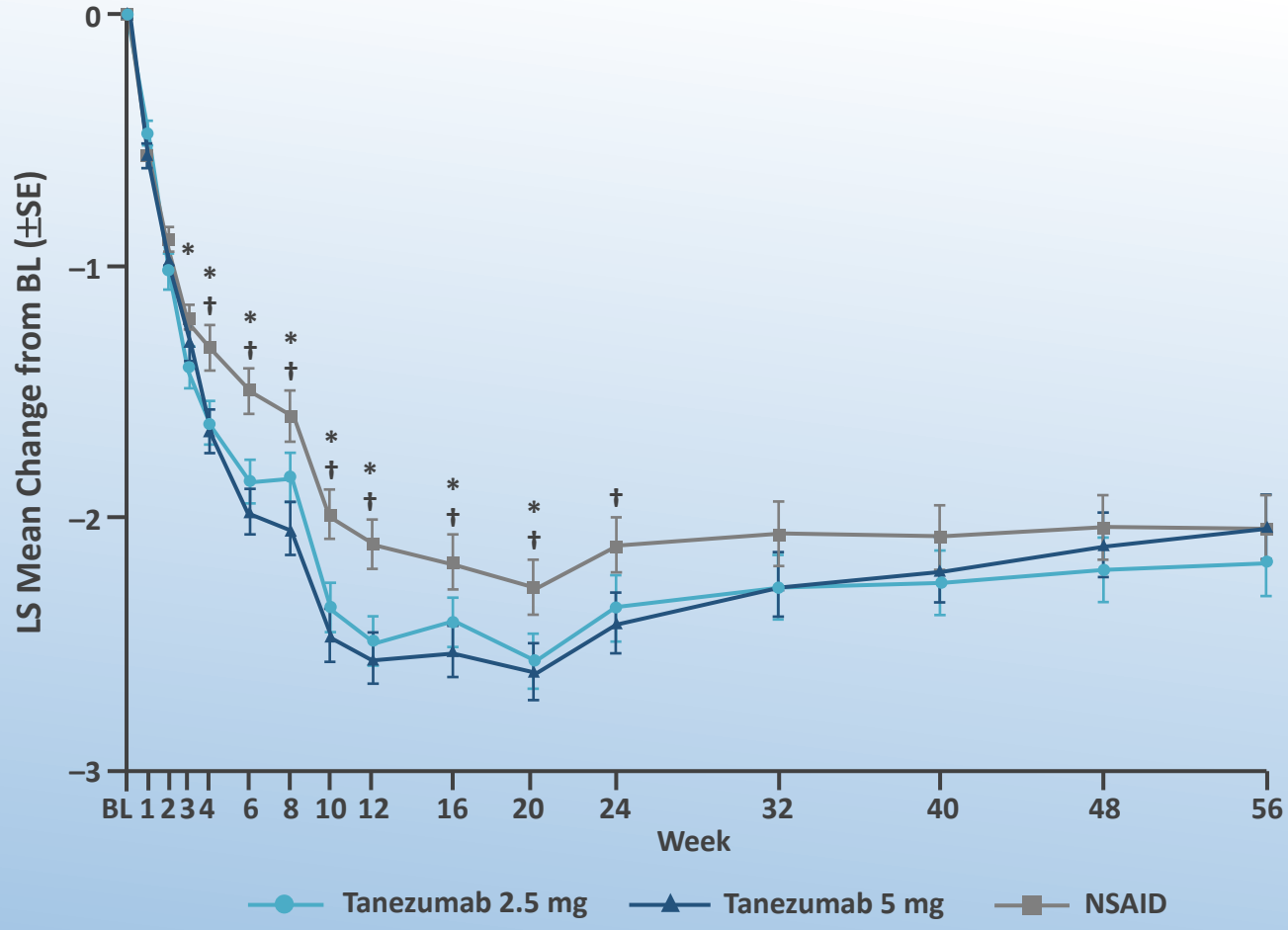
Time Course of Tanezumab Efficacy: Average Pain

Figure 2. Change from baseline in average pain in index joint through Week 56



*Unadjusted *P*≤0.05 for tanezumab 2.5 mg vs NSAID. †Unadjusted *P*≤0.05 for tanezumab 5 mg vs NSAID. BL, baseline; LS, least squares; NSAID, nonsteroidal anti-inflammatory drug; SE, standard error.

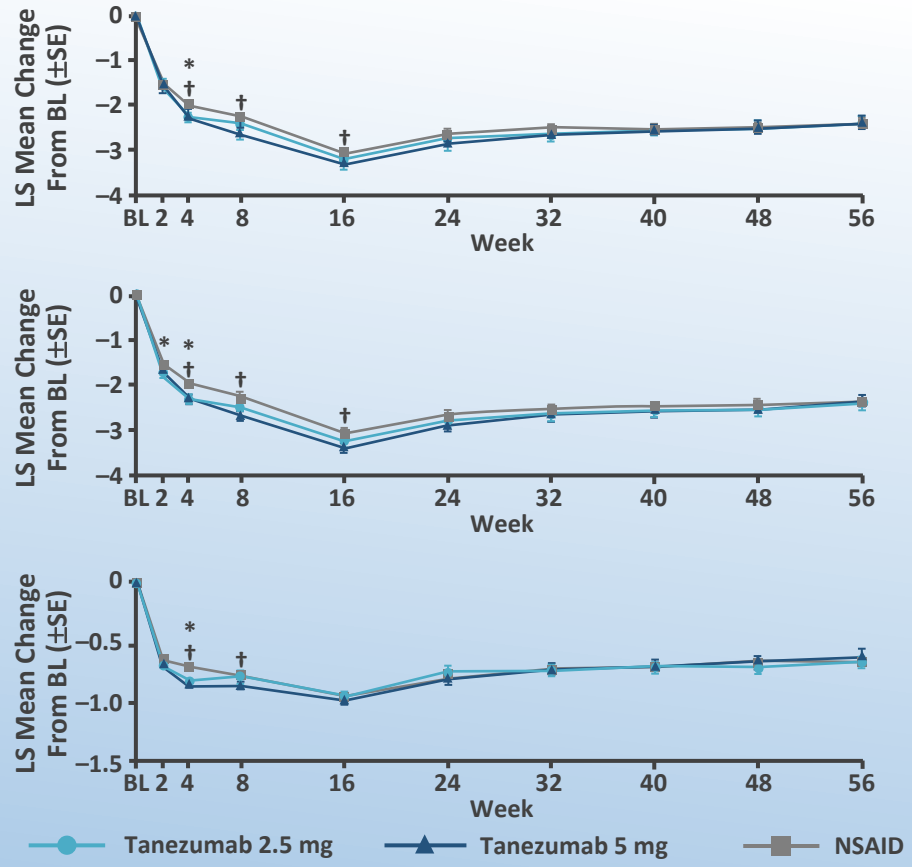
Time Course of Tanezumab Efficacy: WOMAC Pain and Physical Function, and PGA-OA

Figure 3. Change from baseline up to Week 56

A) WOMAC Pain

B) WOMAC Physical Function

C) PGA-OA



*Unadjusted $P \leq 0.05$ for tanezumab 2.5 mg vs NSAID. †Unadjusted $P \leq 0.05$ for tanezumab 5 mg vs NSAID. BL, baseline; LS, least squares; NSAID, nonsteroidal anti-inflammatory drug; PGA-OA, patient's global assessment of osteoarthritis; SE, standard error; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Study Conclusions

- Patients with moderate-to-severe hip or knee OA treated with tanezumab or NSAID experienced an early improvement within the first few weeks in pain and function that was maintained throughout the treatment period.
- Patients receiving tanezumab vs NSAID had similar or greater (unadjusted $P \leq 0.05$) improvement in pain and function scores at all timepoints during the treatment period.
- The magnitude of change from baseline in pain and function scores observed with tanezumab was largely comparable to those observed in recent 16- and 24-week placebo-controlled studies of tanezumab.[1,2]

1. Schnitzer TJ, et al. *JAMA* 2019;322(1):37-48. 2. Berenbaum F, et al. *Ann Rheum Dis* 2020;79(6):800-10.