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# Effect of Tanezumab on Joint Pain, Physical Function, and Patient Global Assessment of Osteoarthritis Among Patients With Osteoarthritis of the Hip or Knee
## A Randomized Clinical Trial

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**IMPORTANCE** Patients with osteoarthritis (OA) may remain symptomatic with traditional OA treatments.

**OBJECTIVE** To assess 2 subcutaneous tanezumab dosing regimens for OA.

**DESIGN, SETTING, AND PARTICIPANTS** A randomized, double-blind, multicenter trial from January 2016 to May 14, 2018 (last patient visit). Patients enrolled were 18 years or older with hip or knee OA, inadequate response to OA analgesics, and no radiographic evidence of prespecified joint safety conditions.

**INTERVENTIONS** Patients received by subcutaneous administration either tanezumab, 2.5 mg, at day 1 and week 8 (n = 231); tanezumab, 2.5 mg at day 1 and 5 mg at week 8 (ie, tanezumab, 2.5/5 mg; n = 233); or placebo at day 1 and week 8 (n = 232).

**MAIN OUTCOMES AND MEASURES** Co-primary end points were change from baseline to week 16 in Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC) Pain (0-10, no to extreme pain), WOMAC Physical Function (0-10, no to extreme difficulty), and patient global assessment of osteoarthritis (PGA-OA) (1-5, very good to very poor) scores.

**RESULTS** Among 698 patients randomized, 696 received 1 or more treatment doses (mean [SD] age, 60.8 [9.6] years; 65.1% women), and 582 (83.6%) completed the trial. From baseline to 16 weeks, mean WOMAC Pain scores decreased from 7.1 to 3.6 in the tanezumab, 2.5 mg, group; 7.3 to 3.6 in the tanezumab, 2.5/5 mg, group; and 7.3 to 4.4 in the placebo group (least squares mean differences [95% CI] vs placebo were −0.60 [−1.07 to −0.13; $P$ = .01] for tanezumab, 2.5 mg, and −0.73 [−1.20 to −0.26; $P$ = .002] for tanezumab, 2.5/5 mg). Mean WOMAC Physical Function scores decreased from 7.2 to 3.7 in the 2.5-mg group, 7.4 to 3.6 in the 2.5/5-mg group, and 7.4 to 4.5 with placebo (differences vs placebo, −0.66 [−1.14 to −0.19; $P$ = .007] for tanezumab, 2.5 mg, and −0.89 [−1.37 to −0.42; $P$ < .001] for tanezumab, 2.5/5 mg). Mean PGA-OA scores decreased from 3.4 to 2.4 in the 2.5-mg group, 3.5 to 2.4 in the 2.5/5-mg group, and 3.5 to 2.7 with placebo (differences vs placebo, −0.22 [−0.39 to −0.05; $P$ = .01] for tanezumab, 2.5 mg, and −0.25 [−0.41 to −0.08; $P$ = .004] for tanezumab, 2.5/5 mg). Rapidly progressive OA occurred only in tanezumab-treated patients (2.5 mg: n = 5, 2.2%; 2.5/5 mg: n = 1, 0.4%). The incidence of total joint replacements was 8 (3.5%), 16 (6.9%), and 4 (1.7%) in the tanezumab, 2.5 mg; tanezumab, 2.5/5 mg; and placebo groups, respectively.

**CONCLUSIONS AND RELEVANCE** Among patients with moderate to severe OA of the knee or hip and inadequate response to standard analgesics, tanezumab, compared with placebo, resulted in statistically significant improvements in scores assessing pain and physical function, and in PGA-OA, although the improvements were modest and tanezumab-treated patients had more joint safety events and total joint replacements. Further research is needed to determine the clinical importance of these efficacy and adverse event findings.

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Visual Abstract

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Supplemental content

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Nerve growth factor (NGF) is a neurotrophin involved in pain signaling and nociceptor gene expression.[1-3] NGF has been shown to contribute to the clinical symptom of pain hypersensitivity, which is often seen during inflammation and chronic pain conditions.[3-6] NGF is expressed in the subchondral bone of patients with osteoarthritis (OA),[7] consistent with a role in symptomatic OA pain. Additionally, inhibiting NGF blocks increased pain-related behaviors in several animal models of pain, including an arthritis pain model.[4-6,8]

Tanezumab is an IgG2Δa monoclonal antibody that inhibits NGF binding to its receptors, and is under investigation for the treatment of chronic pain conditions, such as OA and chronic low back pain.[9-13] The US Food and Drug Administration placed a partial clinical hold on NGF antibodies in 2010 due to joint safety findings in humans. Adverse changes observed in the sympathetic nervous system of mature animals led to a second hold in 2012. The holds were lifted after detailed investigation of the events (joints) and additional nonclinical studies (neurological). Because some patients in previous tanezumab studies reported transient abnormalities in cutaneous sensation (commonly paresthesia or hypoesthesia), subsequent studies implemented an overall risk minimization strategy and comprehensive assessment of joint and neurological adverse events (AEs).[14,15] These strategies included prohibiting chronic concomitant nonsteroidal anti-inflammatory drug (NSAID) use, prohibiting NGF antibody doses that have no demonstrated benefit over lower doses for the particular condition studied, excluding patients with evidence of or risk factors for rapidly progressive OA, and excluding patients who are not suitable candidates for total joint replacement.

This study assessed the efficacy and AEs associated with tanezumab administered subcutaneously as a fixed dosing regimen or a forced titration dosing regimen in patients with moderate to severe OA who had not responded to or were unable to receive standard pharmacological OA pain treatments.

### Key Points

**Question** Among patients with moderate to severe osteoarthritis of the knee or hip and inadequate treatment response to standard analgesics, what is the effect of subcutaneous tanezumab on joint pain, physical function, and patient global assessment of osteoarthritis?

**Findings** In this randomized clinical trial that enrolled 698 patients, subcutaneous tanezumab administered with fixed doses at 8-week intervals or with a forced titration at week 8, compared with placebo, resulted in statistically significant improvements in joint pain, physical function, and patient global assessment of osteoarthritis over 16 weeks, although the improvements were modest and tanezumab-treated patients had more joint safety events and total joint replacements.

**Meaning** Further research is needed to determine the clinical importance of these efficacy and adverse event findings with regard to use of tanezumab for treatment of osteoarthritis.

## Methods

### Study Design

This was a randomized, double-blind, placebo-controlled, multicenter, parallel-group, dose-titration study (16-week treatment period, 24-week follow-up period) assessing the efficacy and AE profile of subcutaneous tanezumab in patients with moderate to severe hip or knee OA conducted at 89 clinical research sites in the United States, Canada, and Puerto Rico from January 2016 to May 2018. The study was approved by the institutional review board or independent ethics committee at each study center. All patients provided written informed consent before participating. The study was conducted in compliance with the Declaration of Helsinki and all International Conference on Harmonisation Good Clinical Practice guidelines.[16,17] The study protocol and statistical analysis plan can be found in Supplement 1 and Supplement 2, respectively.

The primary objective was to evaluate the efficacy of 2 subcutaneous tanezumab treatment regimens at week 16—fixed dosing (2.5 mg administered at baseline and week 8) and forced dose titration (2.5 mg administered at baseline and 5 mg at week 8)—compared with placebo treatment. The secondary objectives evaluated (1) the efficacy of tanezumab titrated from 2.5 mg to 5 mg at week 8 compared with 2 administrations of tanezumab, 2.5 mg, 8 weeks apart and (2) the AE profile of both tanezumab dosing regimens.

The study was divided into 3 periods: screening (≤37 days), treatment (16 weeks), and follow-up (24 weeks). Screening procedures included a washout period of prohibited medications and an initial pain assessment period (3-7 days prior to randomization/baseline).

### Study Population

Patients were aged 18 years and older and diagnosed as having hip or knee OA according to American College of Rheumatology criteria with radiographic confirmation at screening (Kellgren-Lawrence grade ≥2). Entry criteria included an index joint Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC) Pain subscale score of 5 or greater (on an 11-point numerical rating scale from 0 = no pain to 10 = extreme pain) at both screening and baseline, a baseline WOMAC Physical Function subscale score of 5 or greater (on an 11-point numerical rating scale from 0 = no difficulty to 10 = extreme difficulty), and a baseline patient global assessment of osteoarthritis (PGA-OA) rating of fair, poor, or very poor (on a scale from 1 = very good to 5 = very poor). Index joint was defined as the most painful hip or knee at screening. Patients had a documented history of (1) insufficient pain relief from acetaminophen; (2) insufficient pain relief, intolerance to, or contraindication to NSAIDs; and (3) insufficient pain relief, intolerance to, or contraindication to either tramadol or opioids (or were unwilling to take opioids). To characterize the study population, race (4 fixed categories with an open-ended option for a response of "other") and ethnicity (2 fixed categories) data were provided to the study site staff by patients.

Main exclusion criteria included evidence of prespecified joint safety conditions (eg, rapidly progressive OA, subchondral insufficiency fracture, osteonecrosis, pathologic fracture) in any major joint on screening radiographs as determined by the central reader; a history of diseases that could confound index joint efficacy assessments (eg, rheumatoid arthritis, seronegative spondyloarthropathies, gout, chondrocalcinosis/pseudogout); significant trauma or surgery in a hip, knee, or shoulder in the previous year; any planned surgery during the study; any recent intra-articular corticosteroid or hyaluronic acid injection in the index joint; a history of neurological conditions (eg, peripheral or autonomic neuropathy, Alzheimer disease, multiple sclerosis); a Survey of Autonomic Symptoms[18] score greater than 7 at screening; and pregnancy or breastfeeding.

## Intervention

Using a computer-generated randomization code, patients were randomized in equal allocation to 1 of 3 subcutaneous treatment regimens: tanezumab, 2.5 mg, at baseline and week 8 (ie, tanezumab, 2.5 mg); tanezumab, 2.5 mg at baseline and 5 mg at week 8 (ie, tanezumab, 2.5/5 mg); and placebo at baseline and week 8 (ie, placebo) (eFigure in Supplement 3). Randomization was stratified by index joint and highest Kellgren-Lawrence grade. Placebo (identical in composition [color, volume, pH] to the drug product, but without the active pharmaceutical ingredient) was administered in a manner matching subcutaneous tanezumab.

Permitted concomitant treatments included aspirin less than or equal to 325 mg/d for cardiovascular prophylaxis and stable doses of medications for other non-OA, nonpain conditions. Analgesics were prohibited except as follows: NSAIDs for non-OA conditions were permitted for up to 10 days per 8-week period between baseline and week 24, but not within 48 hours of a study visit. Rescue medication (acetaminophen) was allowed up to 3000 mg/d and for 3 or fewer days per week during the treatment period, but not within 24 hours of a study visit, and usage was recorded by the patient via a handheld electronic diary (eDiary; Trial Collector version 3.2.0.1; CRF Health). Standard of care treatment for OA pain was permitted 16 weeks after the last study drug dose.

## Efficacy Assessments

The co-primary efficacy end points were change from baseline to week 16 in WOMAC Pain subscale, WOMAC Physical Function subscale, and PGA-OA scores.[19,20] WOMAC Pain and WOMAC Physical Function subscales measured symptoms within the last 48 hours using an 11-point numeric rating scale (0 = no pain/no difficulty to 10 = extreme pain/extreme difficulty). For PGA-OA, patients answered the question, "Considering all the ways your osteoarthritis in your hip/knee affects you, how are you doing today?" on a scale from 1 = very good to 5 = very poor.

A key secondary efficacy end point was the WOMAC Pain responder rate of 50% or greater at week 16, defined as the proportion of patients with a 50% or greater reduction from baseline in WOMAC Pain score at week 16. Other secondary efficacy end points were WOMAC Pain responder rates (≥30%, ≥70%, and ≥90% reductions from baseline) at week 16 and patient-reported rescue medication use during weeks 2, 4, 8, 12, and 16. All prespecified secondary end points can be found in eTable 1 in Supplement 3.

A recent systematic review of minimal clinically important difference values for improvement in OA by the OMERACT Rasch group reported results that ranged from −29.9 to −7.5 for WOMAC Pain and from −33.5 to −5.3 for WOMAC function, both reported on a scale of 0 to 100.[21] The minimal clinically important difference for improvement in PGA has been reported as 0.4 on a Likert scale of 0 to 4 and −15.2 (hip) and −18.3 (knee) on a 0 to 100 visual analog scale.[22,23]

## Adverse Event Assessments

AE assessments included AE reporting; laboratory testing; 12-lead electrocardiogram; sitting vital signs; orthostatic blood pressure assessments; physical examinations; musculoskeletal examinations; neurological examinations reported using the Neuropathy Impairment Score[24]; Survey of Autonomic Symptoms scores[18]; adjudication of joint safety events including total joint replacements; and antidrug antibody assessments. AEs were coded using the Medical Dictionary for Regulatory Activities version 21.0 (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use). AE severity and relationship to study treatment were assessed by the investigator.

### Neurological Assessments

Patients meeting protocol-specified criteria were further evaluated for peripheral neuropathy and/or sympathetic autonomic neuropathy. Neurological examinations were conducted at all clinic visits by investigators or designated physicians who received protocol-required training, and findings were recorded using the Neuropathy Impairment Score.[24] Patients were referred to a consulting neurologist if an AE of peripheral neuropathy or abnormal peripheral sensation was reported as (1) serious, (2) of severe intensity, (3) resulted in study withdrawal, or (4) was ongoing at the end of study participation. Patients with reported AEs suggestive of sympathetic autonomic neuropathy (ie, bradycardia, orthostatic hypotension, syncope, anhidrosis, or hypohidrosis) of any seriousness or severity were further evaluated by a cardiologist or neurologist.

### Joint Safety Events

Investigators performed musculoskeletal examinations of all major joints at each study visit. Radiographs of both knees, hips, and shoulders, as well as other major joints exhibiting signs or symptoms of OA, were obtained at screening and week 40 (or early discontinuation). Images were evaluated by a central reader for the presence of exclusionary conditions. Patients recorded daily average index joint pain and weekly average nonindex joint(s) pain via eDiary during the treatment period using an 11-point numeric rating scale (0 to 10, indicating no to worst possible pain). Weekly average pain was recorded for all joints during the safety follow-up period.

Investigators evaluated patients reporting increased severe (score of 7-10 out of 10) persistent pain via eDiary lasting 2 or more weeks to determine whether additional follow-up was needed. Postbaseline radiographs (scheduled or for cause) were assessed by the central reader for possible or probable rapidly progressive OA, subchondral insufficiency fracture, primary osteonecrosis, or pathologic fracture. If warranted, magnetic resonance imaging scans were performed and/or patients were referred to an orthopedic surgeon. All cases of possible or probable joint safety events or cases of total joint replacements for any reason were adjudicated by an external, blinded adjudication committee consisting of orthopedic surgery, rheumatology, orthopedic pathology, and musculoskeletal radiology experts.

### Statistics

A sample size of approximately 230 patients per treatment group was determined to provide 90% power to achieve statistical significance at the 5% 2-sided level for comparisons of tanezumab, 2.5 mg, and tanezumab, 2.5/5 mg, vs placebo across all 3 co-primary end points. This was based on estimates from a combined analysis of 2 previous studies (treatment difference of −1.0 for WOMAC Pain and Physical Function subscales and −0.32 for PGA-OA, and SDs of 2.73, 2.58, and 0.92, respectively).[12,13] Co-primary end points were analyzed using an analysis of covariance model, with terms for baseline score, baseline patient diary mean pain, index joint, Kellgren-Lawrence grade, and treatment group, and study site as a random effect. The efficacy analysis set was analyzed by randomization group and included all patients who received 1 or more study medication doses. Missing data were handled with a multiple imputation strategy dependent on the reason for discontinuation. Missing data at week 16 due to discontinuation for lack of efficacy, AE, or death were based on sampling from a normal distribution using a mean value equal to the patient's baseline efficacy value; missing data at week 16 due to other reasons were based on sampling from a normal distribution using a mean value of the patient's last observed efficacy value. Final results were calculated using the combined sets of results from each imputation data set analysis. All statistical testing was 2-sided.

The co-primary end points used a stepdown strategy designed to maintain type I error at 5% or less for multiple comparisons, defined as first testing tanezumab, 2.5/5 mg, vs placebo and, if statistically significant at the 5% level, testing tanezumab, 2.5 mg, vs placebo at the 5% level. Tanezumab treatment groups were considered more effective than placebo if all 3 co-primary end points were statistically significant. The key secondary efficacy end point was tested using the Hochberg procedure for both tanezumab regimens vs placebo, contingent on successful primary comparisons. Comparisons for other secondary end points were unadjusted. Comparisons between the tanezumab dose regimens were descriptive only. A planned exploratory analysis assessed WOMAC Pain response (percentage of patients with a reduction from baseline of ≥15%, ≥30%, and ≥50%) at week 16 according to response at week 8, using a logistic regression model including baseline WOMAC Pain subscale, baseline diary average pain and classification variables of index joint, highest Kellgren-Lawrence grade, and treatment. AEs were summarized by treatment group as percentages of the treatment group population. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory. Statistical software used was SAS version 9.4 (SAS Institute).

## Results

### Patients

Randomization included 698 patients, and 696 received 1 or more study treatment doses (2 randomized patients who did not meet eligibility criteria were discontinued prior to dosing; **Figure 1**). All patients who received 1 or more study treatment doses were analyzed for efficacy and AEs. Eighty-three percent of patients had observations at all planned time points between baseline and week 16. An additional 6% of patients had observations at least at baseline and week 16. Patient baseline characteristics were similar across treatment groups (**Table 1**).

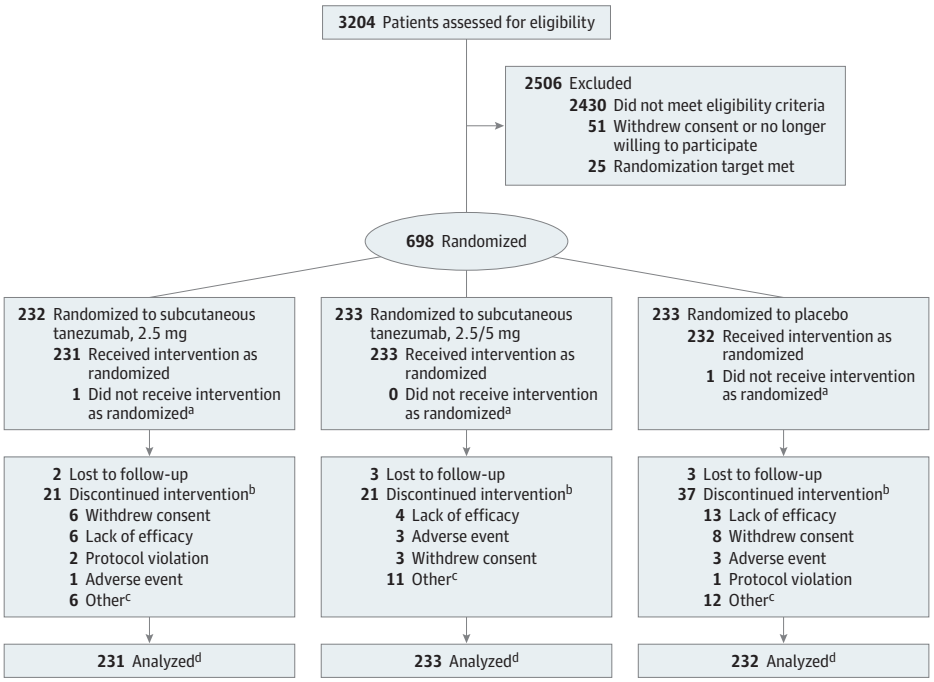
### Efficacy

Baseline mean (SD) WOMAC Pain scores were 7.1 (1.2), 7.3 (1.3), and 7.3 (1.2) for the tanezumab, 2.5 mg; tanezumab, 2.5/5 mg; and placebo groups, respectively. Baseline mean (SD) WOMAC Physical Function scores were 7.2 (1.1), 7.4 (1.2), and 7.4 (1.1) for the tanezumab, 2.5 mg; tanezumab, 2.5/5 mg; and placebo groups, respectively. Baseline mean (SD) PGA-OA scores were 3.4 (0.6), 3.5 (0.6), and 3.5 (0.6) in the tanezumab, 2.5 mg; tanezumab, 2.5/5 mg; and placebo groups, respectively. Both tanezumab 2.5 mg and 2.5/5 mg demonstrated statistically significant improvement in WOMAC Pain, WOMAC Physical Function, and PGA-OA scores compared with placebo at week 16 (**Table 2** and **Figure 2**); thus, both tanezumab dosing regimens met the co-primary end points.

At 16 weeks, mean (SD) WOMAC Pain scores were 3.6 (2.6) in the tanezumab, 2.5 mg, group; 3.6 (2.7) in the tanezumab, 2.5/5 mg, group; and 4.4 (2.7) in the placebo group. Mean (SD) WOMAC Physical Function scores were 3.7 (2.7) in the 2.5-mg group, 3.6 (2.7) in the 2.5/5-mg group, and 4.5 (2.7) with placebo. Mean (SD) PGA-OA scores were 2.4 (0.9) in the 2.5-mg group, 2.4 (1.0) in the 2.5/5-mg group, and 2.7 (0.9) with placebo. Least squares mean differences vs placebo were as follows: WOMAC Pain scores were −0.60 (95% CI, −1.07 to −0.13; $P = .01$) for tanezumab, 2.5 mg, and −0.73 (95% CI, −1.20 to −0.26; $P = .002$) for tanezumab, 2.5/5 mg; WOMAC Physical Function scores were -0.66 (95% CI, −1.14 to −0.19; $P = .007$) for tanezumab, 2.5 mg, and −0.89 (95% CI, −1.37 to −0.42; $P < .001$) for tanezumab, 2.5/5 mg; and PGA-OA scores were -0.22 (95% CI, −0.39 to −0.05; $P = .01$) for tanezumab, 2.5 mg, and −0.25 (95% CI, −0.41 to −0.08; $P = .004$) for tanezumab, 2.5/5 mg.

At week 16, a greater proportion of patients in each tanezumab regimen (54.5% and 57.1% in the tanezumab,

Figure 1. CONSORT Diagram




[a] Two randomized patients did not meet eligibility criteria and therefore did not receive the study drug.

[b] During the 16-week treatment period.

[c] Other reasons for treatment discontinuation were typically personal such as patient moving, loss of transportation to visits, and family illness.

[d] Efficacy and safety analysis sets were identical and included all patients who received at least 1 dose of study treatment.

2.5 mg, and tanezumab, 2.5/5 mg, groups, respectively) reported 50% or more reduction from baseline in WOMAC Pain subscale score compared with placebo (37.9%, $P = .001$ for tanezumab, 2.5 mg, vs placebo; $P < .001$ for tanezumab, 2.5/5 mg, vs placebo; **Table 3**). A greater proportion of patients in both tanezumab groups also reported 30% or more and 70% or more (but not ≥90%) reductions from baseline in WOMAC Pain subscale scores compared with placebo at week 16 (Table 3). Both tanezumab dosing regimens demonstrated statistically significant differences in WOMAC Pain and WOMAC Physical Function at first assessment (week 2) vs placebo (WOMAC Pain mean changes from baseline: -2.87 [95% CI, -3.28 to -2.46], -2.89 [95% CI, -3.29 to -2.48], and -2.20 [95% CI, -2.62 to -1.79] in the tanezumab, 2.5 mg; tanezumab, 2.5/5 mg; and placebo groups, respectively, *P*. = 002 for tanezumab, 2.5 mg, vs placebo, $P = .001$ for tanezumab, 2.5/5 mg, vs placebo; WOMAC Physical Function mean changes: -2.89 [95% CI, -3.30 to -2.48], -3.05 [95% CI, -3.46 to -2.65], and -2.14 [95% CI, -2.55 to -1.72] in the tanezumab, 2.5 mg; tanezumab, 2.5/5 mg; and placebo groups, respectively, $P < .001$ for each tanezumab group vs placebo).

In a planned exploratory analysis, most patients who did not achieve 15% or greater, 30% or greater, or 50% or greater reduction from baseline at week 8 also did not respond at week 16 (eTable 2 in Supplement 3). However, of patients who did not achieve a 50% or greater reduction from baseline in WOMAC Pain at week 8, a higher proportion (33%) experienced 50% or greater improvement relative to baseline at week 16 after receiving tanezumab, 5 mg, at week 8 compared with those receiving another 2.5-mg dose (22%) or those treated with placebo (19%).

The proportion of patients who took rescue medication was not significantly different between the 2 tanezumab treatment groups and placebo, except at week 2, in which 160 placebo-treated patients (69.0%) reported taking rescue medication compared with 138 patients (59.2%) in the tanezumab, 2.5/5 mg, group ($P = .03$) and at week 4, in which 143 placebo-treated patients (61.6%) reported taking rescue medication vs 119 patients (51.5%) in the tanezumab, 2.5 mg, group and 110 patients (47.2%) in the tanezumab, 2.5/5 mg, group ($P = .03$ for tanezumab, 2.5 mg, vs placebo; $P = .001$ for tanezumab, 2.5/5 mg, vs placebo). The total amount of rescue medication used was not significantly different in the tanezumab groups vs placebo at all weeks tested (eTable 3 in Supplement 3).

## Adverse Events

During the treatment period, 55.4%, 46.8%, and 49.6% of patients experienced a treatment-emergent AE in the tanezumab, 2.5 mg; tanezumab, 2.5/5 mg; and placebo groups, respectively (**Table 4**). A total of 0.9%, 2.6%, and 2.2% of patients in the tanezumab, 2.5 mg; tanezumab, 2.5/5 mg; and placebo groups, respectively, had severe AEs. Nasopharyngitis, pain in extremity, and paresthesia occurred in 3% or more of patients in any treatment group and more frequently in tanezumab-treated patients compared with placebo during the treatment period. Seven patients were discontinued due to AEs. One death due to non-small-cell lung cancer stage IV and 1 due to suicide were reported during the follow-up

Table 1. Patient Demographic Characteristics and Baseline Measurements

| Characteristic | No. (%) | | |
|---|---|---|---|
| | Tanezumab | | |
| | 2.5 mg (n = 231) | 2.5/5 mg (n = 233) | Placebo (n = 232) |
| Sex | | | |
| Men | 86 (37.2) | 82 (35.2) | 75 (32.3) |
| Women | 145 (62.8) | 151 (64.8) | 157 (67.7) |
| Age, mean (range), y | 60.9 (27-84) | 61.2 (32-83) | 60.4 (31-85) |
| Race | | | |
| White | 178 (77.1) | 170 (73.0) | 156 (67.2) |
| Black or African American | 43 (18.6) | 50 (21.5) | 60 (25.9) |
| Asian | 5 (2.2) | 8 (3.4) | 13 (5.6) |
| Other[a] | 5 (2.2) | 5 (2.1) | 3 (1.3) |
| Ethnicity | | | |
| Not Hispanic or Latino | 188 (81.4) | 193 (82.8) | 196 (84.5) |
| Hispanic or Latino | 43 (18.6) | 40 (17.2) | 36 (15.5) |
| History of inadequate pain relief from or intolerance to classes of pain medication | | | |
| Acetaminophen/paracetamol | 230 (99.6) | 232 (99.6) | 232 (100) |
| Inadequate pain relief | 230 (99.6) | 231 (99.1) | 232 (100) |
| Intolerability | 0 | 1 (0.4) | 0 |
| Oral nonsteroidal anti-inflammatory drugs | 230 (99.6) | 233 (100) | 232 (100) |
| Inadequate pain relief | 209 (90.5) | 211 (90.6) | 211 (90.9) |
| Intolerability | 16 (6.9) | 22 (9.4) | 23 (9.9) |
| Contraindication | 12 (5.2) | 7 (3.0) | 5 (2.2) |
| Opioids | 172 (74.5) | 180 (77.3) | 179 (77.2) |
| Unwilling to take | 78 (33.8) | 89 (38.2) | 90 (38.8) |
| Inadequate pain relief | 69 (29.9) | 58 (24.9) | 58 (25.0) |
| Intolerability | 28 (12.1) | 33 (14.2) | 33 (14.2) |
| Contraindication | 5 (2.2) | 3 (1.3) | 1 (0.4) |
| Tramadol | 73 (31.6) | 79 (33.9) | 71 (30.6) |
| Inadequate pain relief | 53 (22.9) | 65 (27.9) | 62 (26.7) |
| Intolerability | 19 (8.2) | 14 (6.0) | 9 (3.9) |
| Contraindication | 1 (0.4) | 0 | 0 |
| Time since osteoarthritis diagnosis, median (IQR), y | 6.4 (3.2-11.7) | 7.2 (3.5-11.8) | 6.9 (3.4-12.6) |
| Index joint | | | |
| Knee | 197 (85.3) | 198 (85.0) | 199 (85.8) |
| Hip | 34 (14.7) | 35 (15.0) | 33 (14.2) |
| WOMAC Pain subscale score, median (IQR)[b] | 7.0 (6.2-7.8) | 7.2 (6.4-8.2) | 7.4 (6.4-8.0) |
| WOMAC Physical Function subscale score, median (IQR)[c] | 7.2 (6.4-7.9) | 7.2 (6.5-8.3) | 7.5 (6.5-8.1) |
| Patient global assessment of osteoarthritis[d] | | | |
| Good (2) | 1 (0.4) | 0 | 0 |
| Fair (3) | 144 (62.3) | 125 (53.6) | 134 (57.8) |
| Poor (4) | 74 (32.0) | 92 (39.5) | 89 (38.4) |
| Very poor (5) | 12 (5.2) | 16 (6.9) | 9 (3.9) |
| Mean (range) | 3.42 (2-5) | 3.53 (3-5) | 3.46 (3-5) |
| Kellgren-Lawrence grade of index joint[e] | | | |
| 1 (least affected) | 1 (0.4) | 0 | 0 |
| 2 | 60 (26.0) | 59 (25.4) | 65 (28.0) |
| 3 | 101 (43.7) | 105 (45.3) | 98 (42.2) |
| 4 (most affected) | 69 (29.9) | 68 (29.3) | 69 (29.7) |

Abbreviations: IQR, interquartile range; WOMAC, Western Ontario and McMasters Universities Osteoarthritis Index.

[a] Other races self-reported by patients were mixed race, American Indian, Middle Eastern/Indian, Hispanic, Pacific Islander, African American, Spanish, white and Native American, biracial, and Mexican.

[b] WOMAC Pain subscale on an 11-point numerical rating scale, from 0 = no pain to 10 = extreme pain.

[c] WOMAC Physical Function subscale on an 11-point numerical rating scale, from 0 = no difficulty to 10 = extreme difficulty.

[d] Patient global assessment of osteoarthritis scale ranged from 1 = very good to 5 = very poor.

[e] Kellgren-Lawrence grades ranged from 0 = no radiographic features of osteoarthritis to 4 = complete loss of joint space with large osteophytes, marked joint space narrowing, severe sclerosis, and definite deformity of bone contour.

Table 2. Change From Baseline to Week 16 in WOMAC Pain Subscale, WOMAC Physical Function Subscale, and Patient Global Assessment of Osteoarthritis (Co-primary End Points)[a]

| | Tanezumab | | |
|---|---|---|---|
| Scale | 2.5 mg (n = 231) | 2.5/5 mg (n = 233) | Placebo (n = 232) |
| **WOMAC Pain[b]** | | | |
| Baseline Pain score, mean (range) | 7.1 (4.8 to 10.0) | 7.3 (5.0 to 10.0) | 7.3 (4.2 to 10.0) |
| Least squares change from baseline, mean (95% CI) | −3.23 (−3.67 to −2.79) | −3.37 (−3.81 to −2.93) | −2.64 (−3.08 to −2.19) |
| Difference of least squares vs placebo, mean (95% CI) | −0.60 (−1.07 to −0.13) | −0.73 (−1.20 to −0.26) | |
| *P* value | .01 | .002 | |
| **WOMAC Physical Function[c]** | | | |
| Baseline Physical Function score, mean (range) | 7.2 (5.1 to 9.9) | 7.4 (3.2 to 9.9) | 7.4 (4.4 to 10.0) |
| Least squares change from baseline, mean (95% CI) | −3.22 (−3.66 to −2.79) | −3.45 (−3.88 to −3.03) | −2.56 (−3.00 to −2.12) |
| Difference of least squares vs placebo, mean (95% CI) | −0.66 (−1.14 to −0.19) | −0.89 (−1.37 to −0.42) | |
| *P* value | .007 | <.001 | |
| **Patient Global Assessment of Osteoarthritis[d]** | | | |
| Baseline score, mean (range) | 3.4 (2 to 5) | 3.5 (3 to 5) | 3.5 (3 to 5) |
| Least squares change from baseline, mean (95% CI) | −0.87 (−1.02 to −0.72) | −0.90 (−1.05 to −0.75) | −0.65 (−0.80 to −0.50) |
| Difference of least squares vs placebo, mean (95% CI) | −0.22 (−0.39 to −0.05) | −0.25 (−0.41 to −0.08) | |
| *P* value | .01 | .004 | |

Abbreviation: WOMAC, Western Ontario and McMasters Universities Osteoarthritis Index.

[a] Analysis of the co-primary end points used a stepdown strategy (described in the Methods section) designed to maintain type I error at ≤5% for multiple comparisons.

[b] WOMAC Pain subscale on an 11-point numerical rating scale, from 0 = no pain to 10 = extreme pain.

[c] WOMAC Physical Function subscale on an 11-point numerical rating scale, from 0 = no difficulty to 10 = extreme difficulty.

[d] Patient global assessment of osteoarthritis scale ranged from 1 = very good to 5 = very poor.

period in the tanezumab, 2.5/5 mg, group; neither was considered treatment related.

### Neurological Assessments

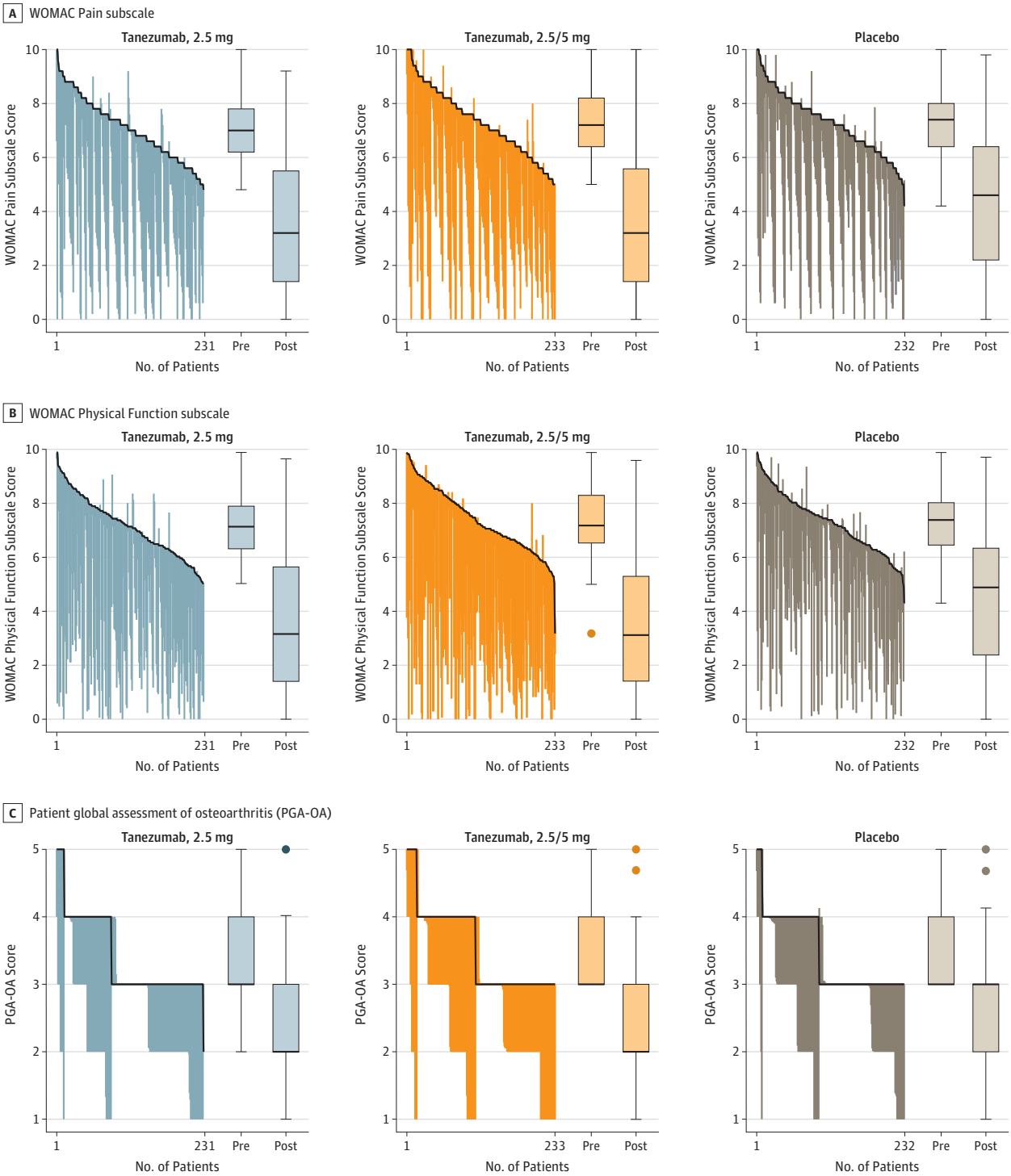
The incidences of patients with AEs of abnormal peripheral sensation during the treatment period were 6.1%, 3.0%, and 2.2% in the tanezumab, 2.5 mg; tanezumab, 2.5/5 mg; and placebo groups, respectively, and all events were mild or moderate in severity. A total of 90.9%, 94.1%, and 91.7% of new or worsened abnormalities in the tanezumab, 2.5 mg; tanezumab, 2.5/5 mg; and placebo groups, respectively, at the final neurological examination were deemed not clinically significant. There was no significant difference in Neuropathy Impairment Score change from baseline between tanezumab-treated patients and placebo at any time point (eTable 4 in Supplement 3). No diagnoses of sympathetic neuropathy were reported by the principal investigator in patients evaluated by cardiology or neurology specialists.

### Joint Safety Events

Thirty-seven patients had adjudicated joint safety events. Most patients (30/37, 81%) had joint safety events adjudicated as normal OA progression. Adjudicated rapidly progressive OA cases were classified by the predefined terms: type 1 (defined as a significant loss of joint space width ≥2 mm [predicated on optimal joint positioning] within approximately 1 year, without gross structural failure; n = 4) or type 2 (defined as abnormal bone loss or destruction, including limited or total collapse of at least 1 subchondral surface that is not normally present in conventional end-stage OA; n = 2), and were seen only in tanezumab-treated patients (6/464; 1.3%; Table 4).[25] Events adjudicated as rapidly progressive OA (types 1 and 2) occurred more frequently in the tanezumab, 2.5 mg, group (2.2%) compared with tanezumab, 2.5/5 mg (0.4%). Both rapidly progressive OA type 2 events occurred in index joints that were Kellgren-Lawrence grade 4 at screening, and neither patient reported NSAID use during the study. In 1 rapidly progressive OA type 2 case, the screening radiographs adjudicated after study completion suggested that this patient had atrophic OA and possible osteonecrosis before tanezumab treatment.

Most adjudicated joint safety events were total joint replacements (28/37 patients; 75.7%). Eight tanezumab, 2.5 mg-treated patients (3.5%); 16 tanezumab, 2.5/5 mg-treated patients (6.9%); and 4 placebo-treated patients (1.7%) underwent total joint replacements. All total joint replacements occurred in joints that were Kellgren-Lawrence grade 3 to 4 at screening. Most patients underwent total joint replacements that were of the index joint (26/28 patients; 92.9%), elective (ie, there was no associated AE and the total

Figure 2. Change From Baseline to Week 16 in WOMAC Pain, WOMAC Physical Function, and Patient Global Assessment of Osteoarthritis at the Patient Level




The black lines represent baseline values for each individual patient, sorted by severity. Individual colored lines represent the change from baseline at week 16 for each individual patient (colored lines extending below the black line indicate lower score and, thus, improvement at week 16). The pre (baseline) and post (week 16) boxplots show median (middle horizontal line in the box), and quartiles 1 and 3 (bottom and top lines of the box). Lines extend from the box to the smallest and largest observations no further than 1.5 times the interquartile range from quartile 1 and quartile 3, respectively, and any data beyond this range are plotted individually. WOMAC Pain subscale ranges from 0 = no pain to 10 = extreme pain. WOMAC Physical Function subscale ranges from 0 = no difficulty to 10 = extreme difficulty. PGA-OA scale ranges from 1 = very good to 5 = very poor. WOMAC indicates Western Ontario and McMasters Universities Osteoarthritis.

Table 3. Proportion of Patients With ≥30%, ≥50%, ≥70%, and ≥90% Reduction From Baseline in WOMAC Pain at Week 16

| | Tanezumab | | |
|---|---|---|---|
| | 2.5 mg (n = 231) | 2.5/5 mg (n = 233) | Placebo (n = 232) |
| **≥30% Reduction** | | | |
| Patients, No. (%) | 157 (68.0) | 164 (70.4) | 127 (54.7) |
| Difference from placebo, % | 13.2 | 15.6 | |
| Odds ratio (95% CI) vs placebo[a] | 1.72 (1.17-2.52) | 1.95 (1.33-2.88) | |
| *P* value | .006 | <.001 | |
| **≥50% Reduction** | | | |
| Patients, No. (%) | 126 (54.5) | 133 (57.1) | 88 (37.9) |
| Difference from placebo, % | 16.6 | 19.2 | |
| Odds ratio (95% CI) vs placebo[a] | 1.89 (1.29-2.76) | 2.17 (1.48-3.16) | |
| *P* value | .001 | <.001 | |
| **≥70% Reduction** | | | |
| Patients, No. (%) | 80 (34.6) | 85 (36.5) | 58 (25.0) |
| Difference from placebo, % | 9.6 | 11.5 | |
| Odds ratio (95% CI) vs placebo[a] | 1.53 (1.02-2.31) | 1.72 (1.14-2.57) | |
| *P* value | .04 | .009 | |
| **≥90% Reduction** | | | |
| Patients, No. (%) | 34 (14.7) | 33 (14.2) | 22 (9.5) |
| Difference from placebo, % | 5.2 | 4.7 | |
| Odds ratio (95% CI) vs placebo[a] | 1.60 (0.89-2.86) | 1.56 (0.87-2.79) | |
| *P* value | .11 | .14 | |

Abbreviation: WOMAC, Western Ontario and McMasters Universities Osteoarthritis Index.

[a] Odds ratio and *P* values vs placebo using a logistic regression model including baseline WOMAC Pain subscale, baseline diary average pain and classification variables of index joint, highest Kellgren-Lawrence grade, and treatment.

joint replacement was adjudicated as normal OA progression; 21/28 patients; 75%), adjudicated as normal OA progression (26/28 patients; 92.9%), and occurred after the treatment period (19/28 patients; 67.9%). Two tanezumab-treated patients had total joint replacements and adjudicated rapidly progressive OA.

## Discussion

In this clinical trial of patients with moderate to severe OA of the knee or hip and inadequate treatment response to standard analgesics, subcutaneous tanezumab demonstrated statistically significant improvements over placebo in pain, physical function, and PGA-OA at week 16; approximately 85% of patients had knee index joints. Forced titration of tanezumab from 2.5 mg to 5 mg resulted in nominally greater improvements compared with patients who continued taking tanezumab, 2.5 mg.

A significantly greater proportion of patients treated with tanezumab, 2.5 mg and 2.5/5 mg, had an improvement of 50% or greater reduction in WOMAC Pain score from baseline to week 16 compared with placebo.

The efficacy results at week 16 in this study were similar to the prior OA study in patients with index knee OA treated with intravenous tanezumab, 2.5 mg, or intravenous tanezumab, 5 mg, every 8 weeks[12] and in patients with index knee or hip OA (approximately 80% knee and 20% hip) treated with tanezumab, 5 mg, every 8 weeks.[26] Importantly, patients in the current dose-titration study had more radiographically severe OA and failed more treatments than patients in prior tanezumab OA studies.[12,26]

Across treatment groups, more AEs occurred during the treatment period vs the follow-up period. The observed pattern for paresthesia and pain in extremity, which were among the most common AEs in this study, is consistent with data from previous controlled phase 3 tanezumab studies of OA.[27] In the present study, several of the most common AEs overall (eg, arthralgia and paresthesia) were also among the most common AEs in previous tanezumab studies of OA.[12,13,28] However, in the present study, arthralgia was less common in tanezumab-treated patients than in placebo-treated patients, a pattern that differed from previous tanezumab studies.[12,13,28]

In this study, few patients overall (37/696; 5.3%) experienced joint safety events that warranted adjudication, and most events (30/37; 81.1%) were adjudicated as normal OA progression. Overall, rapidly progressive OA (types 1 and 2) occurred in 6 tanezumab-treated patients (1.3%) and no placebo-treated patients.[25] No joint safety events were adjudicated as osteonecrosis, subchondral insufficiency fracture, or pathologic fracture. Rapidly progressive OA (types 1 and 2) occurred more frequently in the tanezumab, 2.5 mg, group (2.2%) compared with tanezumab, 2.5/5 mg (0.4%). There was no consistent pattern of pain relief or of severe increase in pain associated with rapidly progressive OA cases.

All total joint replacements occurred in joints that were considered radiographically moderate to severe at screening (Kellgren-Lawrence grade 3-4). Most total joint replacements occurred after the treatment period (67.9% of patients) and were elective (75.0% of patients), ie, the total joint replacement was not associated with an AE and the events were adjudicated as normal OA progression. Substantially more total joint replacements occurred in the tanezumab groups than in the placebo group. Most previous studies with tanezumab have

Table 4. Summary of Overall Adverse Events, Neurological Adverse Events (AEs), and Joint Safety Outcomes

| | Treatment Period (0-16 wk), No. (%) | | | Up to End of Study (0-40 wk), No. (%) | | |
|---|---|---|---|---|---|---|
| | Tanezumab | | | Tanezumab | | |
| | 2.5 mg (n = 231) | 2.5/5 mg (n = 233) | Placebo (n = 232) | 2.5 mg (n = 231) | 2.5/5 mg (n = 233) | Placebo (n = 232) |
| **Overall Treatment-Emergent AEs** | | | | | | |
| Patients with AEs | 128 (55.4) | 109 (46.8) | 115 (49.6) | 156 (67.5) | 143 (61.4) | 145 (62.5) |
| Patients with treatment-related AEs | 29 (12.6) | 22 (9.4) | 24 (10.3) | 40 (17.3) | 33 (14.2) | 31 (13.4) |
| Patients discontinued treatment due to AEs | 1 (0.4) | 3 (1.3) | 3 (1.3) | 1 (0.4) | 3 (1.3) | 3 (1.3) |
| Patients with serious AEs | 4 (1.7) | 4 (1.7) | 4 (1.7) | 7 (3.0) | 11 (4.7) | 9 (3.9) |
| **Most Common Treatment-Emergent AEs**[a] | | | | | | |
| Arthralgia | 19 (8.2) | 22 (9.4) | 29 (12.5) | 34 (14.7) | 34 (14.6) | 40 (17.2) |
| Nasopharyngitis | 12 (5.2) | 11 (4.7) | 8 (3.4) | 20 (8.7) | 17 (7.3) | 16 (6.9) |
| Fall | 11 (4.8) | 5 (2.1) | 6 (2.6) | 13 (5.6) | 10 (4.3) | 9 (3.9) |
| Back pain | 10 (4.3) | 6 (2.6) | 7 (3.0) | 13 (5.6) | 8 (3.4) | 9 (3.9) |
| Joint swelling | 8 (3.5) | 4 (1.7) | 4 (1.7) | 9 (3.9) | 6 (2.6) | 5 (2.2) |
| Paresthesia | 8 (3.5) | 3 (1.3) | 1 (0.4) | 8 (3.5) | 3 (1.3) | 1 (0.4) |
| Upper respiratory tract infection | 7 (3.0) | 3 (1.3) | 6 (2.6) | 11 (4.8) | 10 (4.3) | 9 (3.9) |
| Musculoskeletal pain | 7 (3.0) | 2 (0.9) | 8 (3.4) | 17 (7.4) | 8 (3.4) | 11 (4.7) |
| Headache | 6 (2.6) | 7 (3.0) | 7 (3.0) | 9 (3.9) | 9 (3.9) | 10 (4.3) |
| Pain in extremity | 4 (1.7) | 7 (3.0) | 2 (0.9) | 9 (3.9) | 9 (3.9) | 3 (1.3) |
| **Treatment-Emergent Neurological AEs** | | | | | | |
| Abnormal peripheral sensation AEs occurring in ≥2% in any treatment group[b] | | | | | | |
| Paresthesia | 8 (3.5) | 3 (1.3) | 1 (0.4) | 8 (3.5) | 3 (1.3) | 1 (0.4) |
| Hypoesthesia | 5 (2.2) | 3 (1.3) | 3 (1.3) | 5 (2.2) | 6 (2.6) | 6 (2.6) |
| Sympathetic nervous system AEs occurring in ≥1% in any treatment group[c] | | | | | | |
| Diarrhea | 5 (2.2) | 5 (2.1) | 3 (1.3) | 5 (2.2) | 8 (3.4) | 4 (1.7) |
| Nausea | 3 (1.3) | 1 (0.4) | 3 (1.3) | 4 (1.7) | 1 (0.4) | 4 (1.7) |
| Orthostatic hypotension | 3 (1.3) | 1 (0.4) | 1 (0.4) | 3 (1.3) | 1 (0.4) | 1 (0.4) |
| Urinary incontinence | 2 (0.9) | 1 (0.4) | 3 (1.3) | 2 (0.9) | 3 (1.3) | 4 (1.7) |
| Sinus bradycardia | 1 (0.4) | 3 (1.3) | 2 (0.9) | 1 (0.4) | 3 (1.3) | 4 (1.7) |
| **Joint Safety Outcomes** | | | | | | |
| Patients with adjudicated joint safety events | | | | | | |
| Normal osteoarthritis progression | | | | 8 (3.5) | 17 (7.3) | 5 (2.2) |
| Rapidly progressive OA type 1[d] | | | | 3 (1.3) | 1 (0.4) | 0 |
| Rapidly progressive OA type 2[e] | | | | 2 (0.9) | 0 | 0 |
| Other (eg, preexisting subchondral insufficiency fracture)[f] | | | | 1 (0.4) | 0 | 0 |
| Patients with ≥1 total joint replacement | | | | 8 (3.5) | 16 (6.9)[g] | 4 (1.7) |
| Joints replaced | | | | | | |
| Knee | | | | 3 | 10 | 4 |
| Hip | | | | 5 | 7 | 0 |

[a] Those occurring in ≥3% in any treatment group during the treatment period.

[b] AEs of abnormal peripheral sensation include the following terms: allodynia, axonal neuropathy, burning sensation, carpal tunnel syndrome, decreased vibratory sense, demyelinating polyneuropathy, dysesthesia, formication, hyperesthesia, hyperpathia, hypoesthesia, hypoesthesia oral, intercostal neuralgia, neuralgia, neuritis, neuropathy peripheral, paresthesia, paresthesia oral, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy, polyneuropathy chronic, sciatica, sensory disturbance, sensory loss, tarsal tunnel syndrome, and thermohypoesthesia.

[c] Sympathetic nervous system AEs included abdominal discomfort, anal incontinence, anhidrosis, blood pressure orthostatic decreased, bradycardia, diarrhea, dizziness postural, early satiety, ejaculation delayed, ejaculation disorder, ejaculation failure, heart rate decreased, hypertonic bladder, hypohidrosis, micturition urgency, nausea, orthostatic hypotension, nocturia, pollakiuria, presyncope, respiratory distress, respiratory failure, sinus bradycardia, syncope, urinary hesitation, urinary incontinence, and vomiting.

[d] Rapidly progressive osteoarthritis (OA) type 1 is defined as a significant loss of joint space width ≥2 mm (predicated on optimal joint positioning) within approximately 1 year, without gross structural failure. One patient with rapidly progressive OA type 1 in the tanezumab, 2.5/5 mg, treatment group had a total joint replacement.

[e] Rapidly progressive OA type 2 is defined as abnormal bone loss or destruction, including limited or total collapse of at least 1 subchondral surface, that is not normally present in conventional end-stage osteoarthritis. One patient with rapidly progressive OA type 2 in the tanezumab, 2.5 mg, treatment group had a total joint replacement.

[f] A condition was adjudicated as "preexisting" if it was not identified by the central reader at screening but the adjudication committee determined it to be preexisting after reviewing all available postbaseline clinical and imaging information for the joint safety event in question.

[g] One patient had 2 joint replacements.

not demonstrated such differences in total joint replacement rates when compared with active comparators or placebo, though the current study used a longer posttreatment observation period.[12,13] However, in a recently completed 1-year, NSAID-controlled study of tanezumab in patients with OA, the incidence of rapidly progressive OA was 6.3% in the tanezumab, 5 mg, group; 3.2% in the tanezumab, 2.5 mg, group; and 1.2% in the NSAID group. The incidence of total joint replacement was 8.0% in the tanezumab, 5 mg, group; 5.3% in the tanezumab, 2.5 mg, group; and 2.6% in the NSAID group (ClinicalTrial.gov Identifier: NCT02528188).[29]

### Limitations

This study has several limitations. First, the 16-week treatment period is too short to assess the ability to maintain efficacy in treating symptomatic OA pain with repeated tanezumab dosing over longer periods. Second, while the study population is appropriate for evaluating efficacy, larger patient populations studied over longer durations are required for more precise estimates of adverse events. Other recently completed OA studies of tanezumab, 2.5 mg and 5 mg, subcutaneously over 6- and 12-month treatment periods will provide additional efficacy and AE data (ClinicalTrial.gov Identifiers: NCT02709486 and NCT02528188).

## Conclusions

Among patients with moderate to severe OA of the knee or hip and inadequate response to standard analgesics, tanezumab, compared with placebo, resulted in statistically significant improvements in scores assessing pain and physical function, and in PGA-OA, although the improvements were modest and tanezumab-treated patients had more joint safety events and total joint replacements. Further research is needed to determine the clinical importance of these efficacy and AE findings.


### ARTICLE INFORMATION

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**Author Contributions:** Dr Schnitzer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
*Concept and design:* Pixton, Viktrup, Davignon, Brown, West, Verburg.
*Acquisition, analysis, or interpretation of data:* Schnitzer, Easton, Pang, Levinson, Pixton, Viktrup, Davignon, Brown, West.
*Drafting of the manuscript:* Easton, Levinson, Pixton, Viktrup, Brown, West, Verburg.
*Critical revision of the manuscript for important intellectual content:* Schnitzer, Easton, Pang, Pixton, Viktrup, Davignon, Brown, West.
*Statistical analysis:* Pixton.
*Administrative, technical, or material support:* Easton, Levinson.
*Supervision:* Easton, Pang, Viktrup, Davignon, Brown, West, Verburg.

**Conflict of Interest Disclosures:** Dr Schnitzer reported receiving nonfinancial support from Pfizer during the conduct of the study and grants, personal fees, and nonfinancial support from Pfizer, Regeneron, AbbVie, and Kolon TissueGene; personal fees from Vertex, Sanofi, Astellas, and Calibr; grants and personal fees from Flexion; personal fees and nonfinancial support from GlaxoSmithKline and Aptinyx; and grants from Galapagos and Grunenthal outside the submitted work. Dr Schnitzer also reported performing clinical research for Pfizer Inc and Eli Lilly and Company and has received consulting fees from Pfizer Inc and Eli Lilly and Company. Dr Easton reported receiving compensation for participation in multiple Pfizer-sponsored clinical trials. Dr Pang reported receiving consulting fees from Pfizer Inc. Dr Levinson reported receiving grants from Pfizer during the conduct of the study and grants from Amgen, Regeneron, and AbbVie outside the submitted work. Mr Pixton and Drs Davignon, Brown, Verburg, and West are employees of Pfizer Inc and own stock. Dr Viktrup is an employee of Eli Lilly and Company. Drs Brown and West reported having tanezumab method of treatment patents pending. No other disclosures were reported.

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**Role of the Funder/Sponsor:** Pfizer Inc and Eli Lily and Company contributed to the study design; Pfizer contributed to the management and collection of data. In their role as authors, employees of Pfizer and Eli Lilly were involved in the interpretation of data, preparation, review, and approval of the manuscript and the decision to submit for publication, along with their co-authors. The study sponsors approved the manuscript from an intellectual property perspective but had no right to veto the publication.

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**Data Sharing Statement:** See Supplement 4.

**Additional Information:** Pfizer Inc, in collaboration with Eli Lilly and Company, is the manufacturer of tanezumab, which is being investigated for the treatment of chronic pain.


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