Efficacy and Safety of Intravenous Tanezumab for the Symptomatic Treatment of Osteoarthritis: 2 Randomized Controlled Trials versus Naproxen

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ABSTRACT. ***Objective.*** Two studies evaluated efficacy and safety of tanezumab versus naproxen for treatment of knee or hip osteoarthritis (OA).

Methods. Randomized controlled studies [NCT00830063 (Study 1015, n = 828) and NCT00863304 (Study 1018, n = 840)] of subjects with hip or knee OA compared intravenous tanezumab (5 mg or 10 mg) to placebo and naproxen (500 mg twice daily). Coprimary outcomes were Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain, WOMAC Physical Function (0–10 numerical rating scale), and patient's global assessment of OA at Week 16.

Results. In both studies, tanezumab reduced pain versus placebo [least squares mean differences, 95% CI, tanezumab 5 mg: –1.21 (–1.72, –0.70); –1.13 (–1.65, –0.62); tanezumab 10 mg: –0.91 (–1.42, –0.40); –0.80 (–1.32, –0.29)], and improved function and global scores. Tanezumab 5 mg produced greater pain reduction [–0.76 (–1.28, –0.25); –0.69 (–1.21, –0.17)], and favorable functional and global outcomes versus naproxen. Pain reductions with tanezumab 10 mg versus naproxen did not reach significance, unlike functional (both studies) and global (1 study) outcomes; thus, tanezumab 10 mg was not superior to naproxen, and predefined statistical testing procedures were not met, allowing for conclusion of superiority of tanezumab 5 mg over naproxen despite replicated favorable coprimary outcomes. Tanezumab was associated with greater incidence of peripheral sensory adverse events (paresthesia, hyperesthesia, hypoesthesia, burning sensation), pain in extremity, peripheral edema, and arthralgia. Overall frequency and discontinuations as a result of adverse events were similar to placebo and naproxen.

Conclusion. Tanezumab provides efficacious treatment of knee or hip OA and may have therapeutic utility in patients with OA who experience inadequate analgesia with nonsteroidal antiinflammatory drugs. (First Release Oct 1 2014; J Rheumatol 2014;41:2249–59; doi:10.3899/jrheum.131294)

Key Indexing Terms:
TANEZUMAB OSTEOARTHRITIS EFFICACY SAFETY NAPROXEN

About 10% to 20% of individuals over age 60 have symptomatic osteoarthritis (OA), a leading cause of disability among nonfatal diseases[1]. Chronic joint pain, the principal complaint, contributes to decreased function, productivity, and quality of life[2,3,4,5]. Treatments include acetaminophen and nonsteroidal antiinflammatory drugs (NSAID)[2,3,4,5]. Although they provide greater effectiveness and patients prefer NSAID over other analgesics, many NSAID have suboptimal effects or poor tolerance[2,6,7]. Patients experiencing inadequate analgesia or NSAID intolerance have limited options.

Nerve growth factor (NGF) is a novel target for pain therapy[8]. Tanezumab, a humanized monoclonal antibody, binds NGF with high affinity and specificity[9,10]. In clinical studies, tanezumab improved pain and function in subjects with knee or hip OA[11,12,13,14,15,16]. To further characterize tanezumab, we conducted 2 studies comparing efficacy and safety of tanezumab versus naproxen in subjects with knee or hip osteoarthritis. Previously reported studies with tanezumab in OA were conducted only against placebo in subjects who were not adequately responding, intolerant to, or unwilling to continue with NSAID treatment. The purpose of our studies was to assess whether subjects with a partial benefit from NSAID would gain additional improvement when treated with tanezumab.

MATERIALS AND METHODS

Two randomized, double-blind, placebo- and active-controlled studies

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[ClinicalTrials.gov identifiers: NCT00830063 (Study 1015) and NCT00863304 (Study 1018)] were conducted at general practice and rheumatology or other specialist study centers in subjects with hip or knee OA receiving some benefit from or considered candidates for NSAID. Study protocols were identical except that Study 1015 enrolled only subjects with knee OA whereas Study 1018 included subjects with knee or hip OA. Studies were conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. Protocols and informed consent documentation were reviewed and approved by institutional review boards. Subjects provided written informed consent before undergoing any procedures.

Study sample. Subjects were aged ≥ 18 years, with body mass index ≤ 39 kg/m^2 and diagnosis of knee OA (Study 1015), or hip or knee OA (Study 1018) based on the American College of Rheumatology criteria and radiographic confirmation (Kellgren-Lawrence grade ≥ 2, 0 to 4 scale)[17,18]. At screening, eligible subjects reported Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain score ≥ 4 (0 to 10 scale) in the index joint, with or without analgesic medication (Supplemental Figure 1, available online at jrheum.org). At baseline, subjects had to report WOMAC Pain score ≥ 5 with an increase ≥ 1 point from screening if they had regularly taken medications (≥ 4 days per week) during the month prior to screening; WOMAC Physical Function score ≥ 4; and a response of fair, poor, or very poor on patient's global assessment of OA to be randomized.

Key exclusion criteria were similar to other tanezumab phase III trials[11,12], but also included a history of naproxen intolerance, or existence of a medical condition or the use of concomitant medication for which naproxen is contraindicated (Supplemental Text 1, available online at jrheum.org).

Study design. Subjects underwent screening within 30 days of randomization (Supplemental Figure 1, available online at jrheum.org). Eligible subjects underwent minimum washout (> 2 days or 5 half-lives, whichever was greater) for prohibited medications (Supplemental Text 2, available online at jrheum.org) prior to baseline assessments. Rescue medication (500 mg acetaminophen as needed, maximum 4000 mg/day) was permitted during screening, but discontinued 48 h before baseline visit (randomization, Day 1). Screening included an initial pain assessment for 3 days prior to randomization, wherein subjects reported pain scores and rescue medication use (prior to its discontinuation) through an interactive voice response system. Baseline efficacy and safety assessments were conducted prior to treatment on Day 1.

Subjects were randomized in equal allocation (stratified by index joint, knee or hip, in Study 1018) to (1) intravenous (IV) tanezumab 5 mg with matching placebo for naproxen, (2) tanezumab 10 mg IV with matching placebo for naproxen, (3) placebo IV (tanezumab vehicle) with naproxen 500 mg twice daily, or (4) placebo IV with matching placebo for naproxen. Tanezumab and matching placebo were administered on Day 1 and Day 57 (Week 8). Naproxen or matching placebo was administered orally twice daily from Weeks 1 to 16, beginning Day 1. Rescue medication (up to 4000 mg acetaminophen/day, up to 3 days/week) was discontinued ≥ 48 h before any scheduled study visit. Study visits were at weeks 2, 4, 8, 12, and 16, during which safety and efficacy assessments, routine laboratory tests, and blood samples were obtained. At Week 16, subjects could enter a longterm extension study (ClinicalTrials.gov identifier: NCT00809783). If subjects did not enter our extension study, oral study medication was discontinued at Week 16 (rescue medication was allowed through Week 24) and safety followup continued through Week 24.

Efficacy. Efficacy was evaluated as change from baseline to Week 16 in 3 predefined coprimary efficacy outcomes: WOMAC Pain, WOMAC Physical Function, and patient's global assessment (PtGA). Changes from baseline to other timepoints (Weeks 2, 4, 8, and 12) were assessed as secondary efficacy measures. WOMAC scores were recorded on 11-point numerical rating scales (NRS; higher scores indicate greater pain or physical function impairment), whereas PtGA was recorded on a 5-point scale (1 = very good to 5 = very poor)[19,20]. Percentages of subjects with ≥ 30%, ≥ 50%, ≥ 70%, and ≥ 90% improvement on the WOMAC Pain subscale were also determined.

Safety. Safety assessments included physical and neurologic examinations using the Neuropathy Impairment Score, a validated standardized instrument for evaluation of peripheral neuropathy signs[21,22], laboratory assessments of blood and urine samples, blood pressure, heart rate, and electrocardiograms. Safety was evaluated at each study visit beginning at baseline and continuing through Week 16 for subjects who entered our extension study or through Week 24 if they did not enter our extension study. Detailed queries of onset, duration, severity, outcome, and relationship to study drug were made for all adverse events. Serious adverse events (resulting in hospitalization or death or that were life-threatening) were reported within 24 h of investigator awareness.

Subjects were referred to a neurologist if an adverse event suggestive of peripheral neuropathy, pain in extremities suggestive of neuropathic pain, or new or worsened clinically significant abnormality were noted. An external neurologist with expertise in peripheral neuropathy and neuromuscular disease reviewed neurologic consultation data for each subject categorized as suggestive of new or worsened peripheral neuropathy based on clinically significant signs or diagnostic tests at final neurological consultation, and provided neuropathy diagnosis.

Because of safety issues identified in other tanezumab clinical trials, an independent Adjudication Committee was formed to review all reported adverse events described by investigators as osteonecrosis, and all reported total joint replacements (TJR) including those unrelated to osteonecrosis[23,24].

Statistical methods. Sample sizes of 200 subjects per treatment (800 subjects per study) were required to achieve 90% power at 5% significance for all 4 contrasts (tanezumab 5 mg and 10 mg versus naproxen and versus placebo) for all coprimary endpoints (Supplemental Text 3, available online at jrheum.org).

Summary and analysis of efficacy and safety data were based on all randomized subjects treated with at least 1 tanezumab or placebo dose (intent-to-treat population). WOMAC Pain, Physical Function, and patient's global assessment results at Week 16 were analyzed separately by ANCOVA for comparisons of tanezumab versus placebo and versus naproxen. Model terms included baseline score, index joint (hip or knee, Study 1018 only), and treatment (as a factor), with study site a random effect. Baseline observation carried forward (BOCF) imputation was used for missing data at Week 16. All treatment comparisons used 2-sided 5% significance except when lower significance was required (Hochberg adjustment).

Testing strategy within each of the 3 coprimary endpoints (analyzed separately, but simultaneously) was first to contrast tanezumab 10 mg versus placebo. If tanezumab 10 mg was superior to placebo at the 2-sided 5% level, then contrasts of tanezumab 5 mg versus placebo and tanezumab 10 mg versus naproxen were tested simultaneously using Hochberg procedure, with both contrasts made initially at 2-sided 5% significance. If both contrasts were significant, then tanezumab 5 mg versus naproxen was tested at 2-sided 5% significance. Statistical comparisons between a given dose of tanezumab to placebo or naproxen were only appropriate to conclude treatment superiority when the prior corresponding contrast was significant for each coprimary endpoint. Regardless of primary outcomes, secondary endpoints were tested. The comparison of naproxen 500 mg BID versus placebo was also made, but this was not part of the testing strategy described above.

RESULTS

Our studies were conducted from May 2009 through August 2010. In Study 1015, 1577 subjects were screened, 832 randomized, and 828 received at least 1 tanezumab or vehicle dose. In Study 1018, 1741 subjects were screened, 849 randomized, and 840 received at least 1 tanezumab or

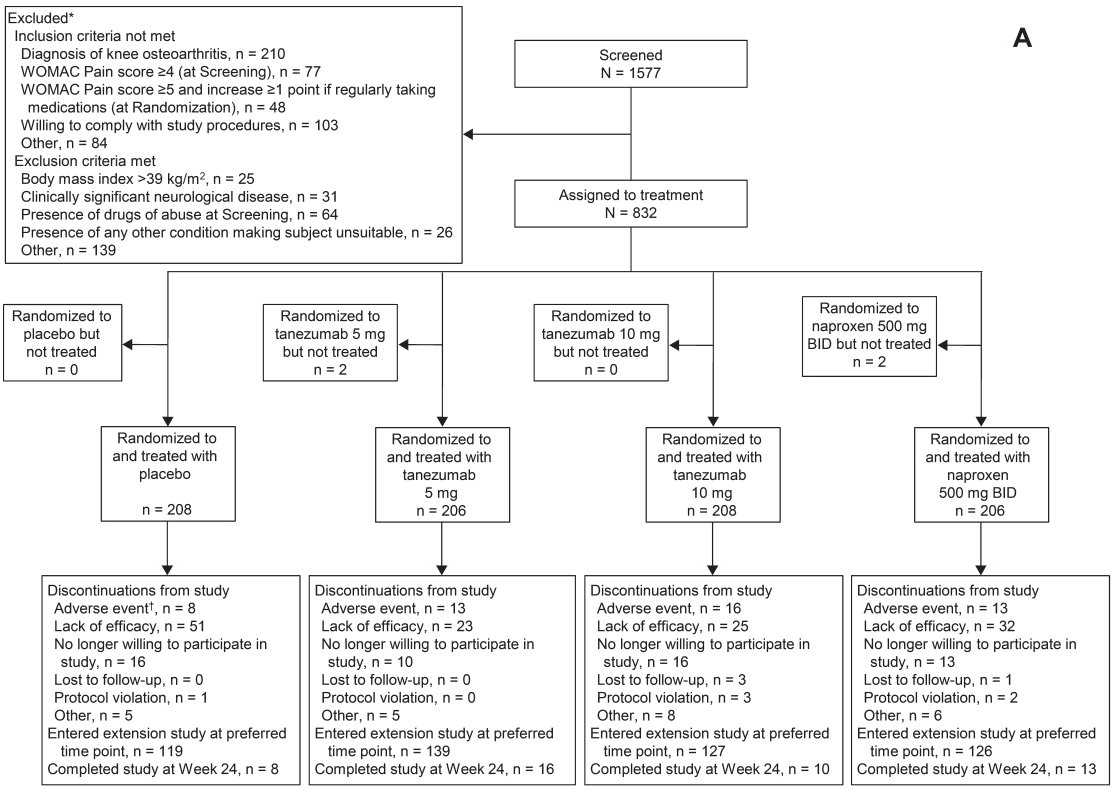

Figure 1. Disposition in (A) subjects with osteoarthritis (OA) of the knee (Study 1015), and (B) subjects with OA of the hip or knee (Study 1018). *More than 1 reason for exclusion could be given, therefore the sums of all reasons is greater than the number of subjects excluded. †Adverse events include 1 placebo-treated subject who died during our study (death not considered related to study medication). WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

vehicle dose. About two-thirds of subjects completed our study or enrolled in our extension study at the preferred time [Study 1015: n = 558/828 (67.4%), Study 1018: n = 560/840 (66.7%); Figure 1]. Baseline characteristics and demographics were similar across treatments within each study and between studies (Table 1). About one-half of subjects [Study 1015: n = 466/828 (56.3%), Study 1018: n = 417/840 (49.6%)] had moderate or severe structural OA (Kellgren-Lawrence grades ≥ 3). Baseline mean WOMAC Pain scores were considered severe (≥ 7 on the 11-point NRS) in both studies (Study 1015: 7.17 to 7.29, Study 1018: 7.27 to 7.41).

Efficacy. In Study 1015, tanezumab treatment resulted in significant improvements in all coprimary endpoints versus placebo at Week 16 ($p \leq 0.021$; Figure 2; Supplemental Table 1, available online at jrheum.org). No contrasts between naproxen and placebo were statistically significant at Week 16 ($p \geq 0.056$). All comparisons between tanezumab 5 mg and naproxen favored tanezumab ($p \leq 0.012$), whereas differences between tanezumab 10 mg and naproxen were significant only for WOMAC Physical Function ($p = 0.030$).

For the secondary endpoints, improvements with tanezumab were significantly greater versus placebo at all other timepoints for WOMAC Pain, WOMAC Physical Function, and patient's global assessment, except tanezumab 5 mg versus placebo at Week 2 for WOMAC Pain; naproxen was significant versus placebo for all endpoints. Responses were generally greater with tanezumab than with naproxen beginning at Week 4. Tanezumab resulted in significantly larger percentages of treatment responders versus placebo ($p \leq 0.006$ all levels), while naproxen was only significant versus placebo at the ≥ 30% and ≥ 50% levels ($p \leq 0.049$; Supplemental Figure 2A, available online at jrheum.org). For comparisons of tanezumab versus naproxen, tanezumab 5 mg was significantly greater at all levels ($p \leq 0.017$) and

Table 1. Baseline and demographic characteristics.

	Study 1015				Study 1018			
	Placebo, n = 208	Tanezumab 5 mg*, n = 206	Tanezumab 10 mg*, n = 208	Naproxen 500 mg BID, n = 206	Placebo, n = 209	Tanezumab 5 mg*, n = 211	Tanezumab 10 mg*, n = 209	Naproxen 500 mg BID, n = 211
Sex, n (%)								
Female	120 (57.7)	122 (59.2)	128 (61.5)	129 (62.6)	136 (65.1)	134 (63.5)	128 (61.2)	136 (64.5)
Age, yr								
Mean ± SD	60.9 ± 10.1	61.1 ± 10.1	61.1 ± 10.3	61.4 ± 10.0	60.1 ± 9.4	59.8 ± 9.6	59.2 ± 10.3	60.3 ± 10.5
Range	29–85	37–93	32–85	30–86	33–86	27–89	33–84	32–92
Weight, kg								
Mean ± SD	89.9 ± 16.9	87.9 ± 18.2	88.6 ± 17.9	87.0 ± 16.0	86.1 ± 17.9	86.9 ± 17.1	84.1 ± 16.7	85.8 ± 17.1
Range	51.7–144.7	49.9–148.8	47.6–148.8	48.0–133.8	47.2–142.4	49.0–131.1	47.6–128.8	43.5–133.8
BMI, kg/m^2								
Mean ± SD	31.2 ± 4.4	30.6 ± 4.9	31.0 ± 4.8	30.8 ± 4.6	30.4 ± 4.8	30.5 ± 4.8	29.6 ± 4.9	30.8 ± 4.8
Range	19.1–39.0	19.3–39.9	17.5–39.0	19.9–39.5	16.7–39.2	19.0–39.8	19.1–39.0	18.8–39.3
Kellgren-Lawrence grade, n (%)								
Grade 1	0	0	0	0	1 (0.5)	0	0	0
Grade 2	89 (42.8)	76 (36.9)	98 (47.1)	99 (48.1)	107 (51.2)	104 (49.3)	101 (48.3)	110 (52.1)
Grade 3	91 (43.8)	108 (52.4)	90 (43.3)	89 (43.2)	79 (37.8)	77 (36.5)	72 (34.4)	84 (39.8)
Grade 4	28 (13.5)	22 (10.7)	20 (9.6)	18 (8.7)	22 (10.5)	30 (14.2)	36 (17.2)	17 (8.1)
Duration since diagnosis, yr								
Mean	9.0	7.9	8.5	7.2	6.3	6.4	6.8	7.7
Range	0.0 to 50.7	0.0 to 59.6	0.0 to 37.6	0.0 to 49.8	0.0 to 38.6	0.0 to 33.9	0.0 to 56.9	0.0 to 42.8
Index joint, n (%)								
Knee	208 (100)	206 (100)	208 (100)	206 (100)	168 (80.4)	168 (79.6)	168 (80.4)	172 (81.5)
Hip†	0	0	0	0	41 (19.6)	43 (20.4)	41 (19.6)	39 (18.5)
Prior analgesic treatments for OA pain, n (%)‡	171 (82.2)	170 (82.5)	165 (79.3)	165 (80.1)	153 (73.2)	157 (74.4)	131 (62.7)	139 (65.9)
Ibuprofen	56 (26.9)	43 (20.9)	47 (22.6)	56 (27.2)	57 (27.3)	51 (24.2)	38 (18.2)	48 (22.7)
Acetaminophen	45 (21.6)	44 (21.4)	43 (20.7)	44 (21.4)	20 (9.6)	24 (11.4)	19 (9.1)	22 (10.4)
Naproxen	18 (8.7)	24 (11.7)	22 (10.6)	20 (9.7)	21 (10.0)	23 (10.9)	19 (9.1)	21 (10.0)
Naproxen sodium	21 (10.1)	27 (13.1)	16 (7.7)	18 (8.7)	16 (7.7)	14 (6.6)	19 (9.1)	12 (5.7)
Meloxicam	21 (10.1)	18 (8.7)	11 (5.3)	18 (8.7)	13 (6.2)	12 (5.7)	13 (6.2)	16 (7.6)
Celecoxib	15 (7.2)	14 (6.8)	11 (5.3)	13 (6.3)	11 (5.3)	15 (7.1)	12 (5.7)	9 (4.3)
Vicodin	11 (5.3)	3 (1.5)	6 (2.9)	7 (3.4)	11 (5.3)	9 (4.3)	6 (2.9)	6 (2.8)

*Administered intravenously on Day 1 and Day 57 (Week 8). †All subjects with index joint of hip were in Study 1018. ‡Prior analgesic treatments for OA pain in ≥ 5% of subjects in any treatment (these treatments are separate from rescue medication use); listed by decreasing frequency in the tanezumab 10 mg group from Study 1015. BMI: body mass index; OA: osteoarthritis.

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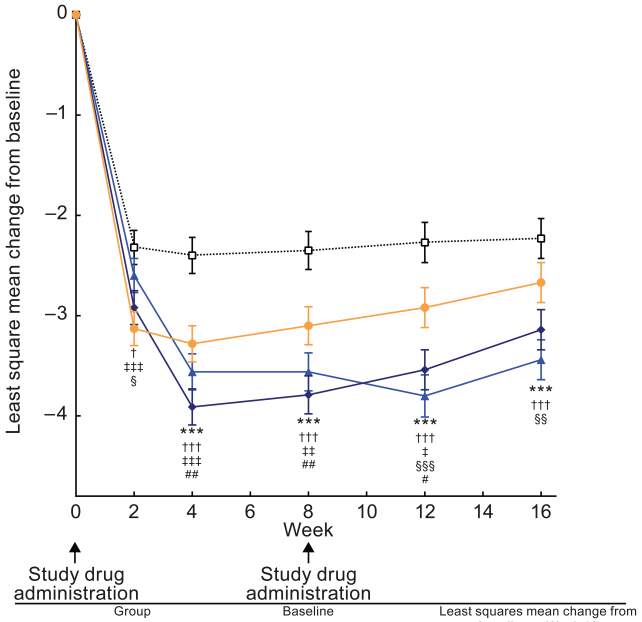

Group	Baseline Mean ± standard deviation	Least squares mean change from baseline to Week 16 Mean ± standard error
Placebo (n = 207)	7.20 ± 1.40	−2.23 ± 0.20
95% CI for LS Mean		[−2.62, −1.83]
Tanezumab 5 mg (n = 206)	7.29 ± 1.46	−3.44 ± 0.20
95% CI for LS Mean		[−3.84, −3.04]
Tanezumab 10 mg (n = 207)	7.23 ± 1.40	−3.14 ± 0.20
95% CI for LS Mean		[−3.54, −2.74]
Naproxen 500 mg BID (n = 206)	7.17 ± 1.35	−2.67 ± 0.20
95% CI for LS Mean		[−3.07, −2.28]

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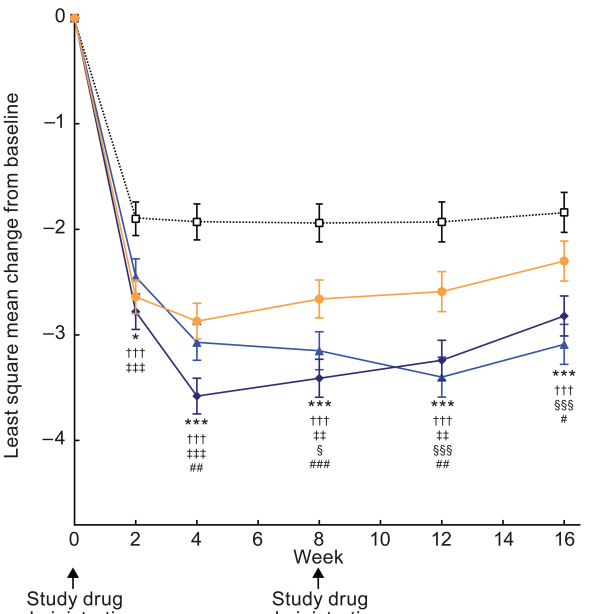

Group	Baseline Mean ± standard deviation	Least squares mean change from baseline to Week 16 Mean ± standard error
Placebo (n = 206)	6.82 ± 1.54	−1.84 ± 0.19
95% CI for LS Mean		[−2.21, −1.48]
Tanezumab 5 mg (n = 206)	6.84 ± 1.71	−3.09 ± 0.19
95% CI for LS Mean		[−3.47, −2.72]
Tanezumab 10 mg (n = 206)	6.82 ± 1.50	−2.82 ± 0.19
95% CI for LS Mean		[−3.19, −2.45]
Naproxen 500 mg BID (n = 206)	6.83 ± 1.57	−2.30 ± 0.19
95% CI for LS Mean		[−2.67, −1.93]

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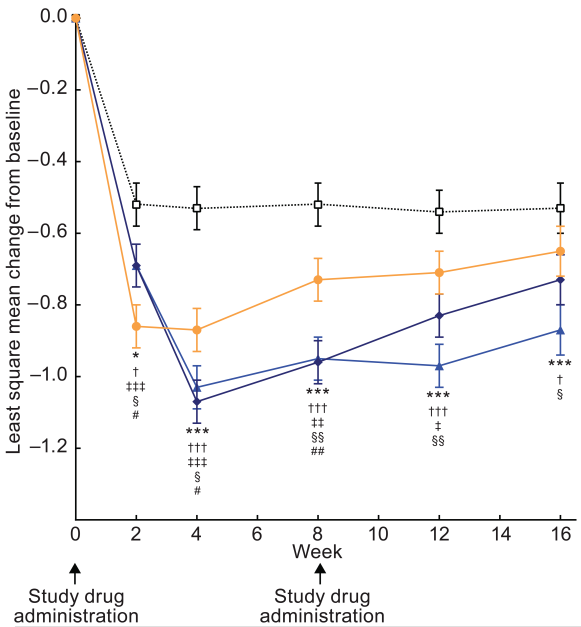


Group	Baseline Mean ± standard deviation	Least squares mean change from baseline to Week 16 Mean ± standard error
Placebo (n = 206)	3.42 ± 0.61	−0.53 ± 0.07
95% CI for LS Mean		[−0.66, −0.40]
Tanezumab 5 mg (n = 205)	3.40 ± 0.58	−0.87 ± 0.07
95% CI for LS Mean		[−1.00, −0.74]
Tanezumab 10 mg (n = 207)	3.39 ± 0.55	−0.73 ± 0.07
95% CI for LS Mean		[−0.86, −0.60]
Naproxen 500 mg BID (n = 206)	3.44 ± 0.61	−0.65 ± 0.07
95% CI for LS Mean		[−0.78, −0.53]

Figure 2. Least squares mean changes in (A) WOMAC Pain, (B) WOMAC Physical Function, and (C) patient's global assessment of osteoarthritis (OA) over time in subjects with OA of the knee (Study 1015). WOMAC assessed with 0 to 10-point numerical rating scale. Patient's global assessment of OA measured with 5-point Likert scale. A change from baseline < 0 is an improvement. Error bars represent standard error. Baseline observation carried forward imputation was applied for missing data. *$p < 0.05$, **$p \le 0.01$, ***$p \le 0.001$ tanezumab 5 mg versus placebo. $^{\dagger}p < 0.05$, $^{\dagger\dagger}p \le 0.01$, $^{\dagger\dagger\dagger}p < 0.001$ tanezumab 10 mg versus placebo. $^{\ddagger}p < 0.05$, $^{\ddagger\ddagger}p \le 0.01$, $^{\ddagger\ddagger\ddagger}p \le 0.001$ naproxen versus placebo. $^{\S}p < 0.05$, $^{\S\S}p \le 0.01$, $^{\S\S\S}p \le 0.001$ tanezumab 5 mg versus naproxen. $^{\#}p < 0.05$, $^{\#\#}p \le 0.01$, $^{\#\#\#}p \le 0.001$ tanezumab 10 mg versus naproxen. WOMAC: Western Ontario McMaster Universities Osteoarthritis Index; LS: least squares.

tanezumab 10 mg was significant at the ≥ 50%, ≥ 70%, and ≥ 90% levels ($p \leq 0.049$).

In Study 1018, tanezumab doses provided significant improvements versus placebo at Week 16 for all coprimary endpoints ($p \leq 0.002$; Figure 3; Supplemental Table 1, available online at jrheum.org). Differences between placebo and naproxen were not significant for any endpoint at Week 16 ($p \geq 0.067$). Tanezumab 5 mg provided significantly greater improvement than naproxen for all endpoints ($p \leq 0.019$) while improvements in WOMAC Physical Function and PtGA were significantly greater with tanezumab 10 mg than with naproxen ($p \leq 0.031$).

Improvements with tanezumab were significantly greater than with placebo for every secondary assessment time except Week 2 for WOMAC Pain and PtGA for tanezumab 10 mg. For naproxen, differences versus placebo were significant at all other timepoints except Week 2 for WOMAC Pain and Week 12 for patient's global assessment. Responses were generally greater with tanezumab than with naproxen beginning at Week 4. Tanezumab resulted in significantly larger percentages of treatment responders at the ≥ 30%, ≥ 50%, and ≥ 70% levels versus placebo ($p \leq 0.022$), whereas naproxen was only significant versus placebo at the ≥ 30% and ≥ 50% levels ($p \leq 0.015$; Supplemental Figure 2B, available online at jrheum.org). Tanezumab 5 mg provided significantly greater percentages of subjects at the ≥ 30%, ≥ 50%, and ≥ 70% levels versus naproxen ($p \leq 0.029$), but differences between tanezumab 10 mg and naproxen were not significant.

Safety. In Study 1015, the overall rate of adverse events was highest with tanezumab 10 mg; rates were generally similar across the other groups (Table 2). Rates of serious adverse events were low and consistent across treatments (Supplemental Text 4, available online at jrheum.org). One death unrelated to study medication (cardiac arrest preceded by traumatic brain injury from fall as a result of alcohol consumption) was reported for a placebo-treated subject. The number of subjects discontinuing because of an adverse event was higher in all active treatments than in the placebo group. No meaningful differences were identified in blood, urine, other laboratory, electrocardiogram, or blood pressure assessments.

In Study 1018, more subjects receiving active treatment reported an adverse event with the highest rates occurring in naproxen-treated subjects (Table 2). Rates of serious adverse events were generally low across all treatments, although they were higher among subjects in the naproxen group (Supplemental Text 5, available online at jrheum.org). More subjects in the naproxen and tanezumab 10 mg groups discontinued because of an adverse event. No meaningful differences were identified in blood, urine, other laboratory, electrocardiogram, or blood pressure assessments.

In both studies, adverse events of abnormal peripheral sensation were reported more frequently with tanezumab treatment than with naproxen or placebo; incidence was highest with tanezumab 10 mg (Table 2; Supplemental Text 6, available online at jrheum.org). This treatment-related difference was driven primarily by greater reporting of paresthesia, hyperesthesia, hypoesthesia, and burning sensation. Adverse events of abnormal peripheral sensation generally resolved before study end.

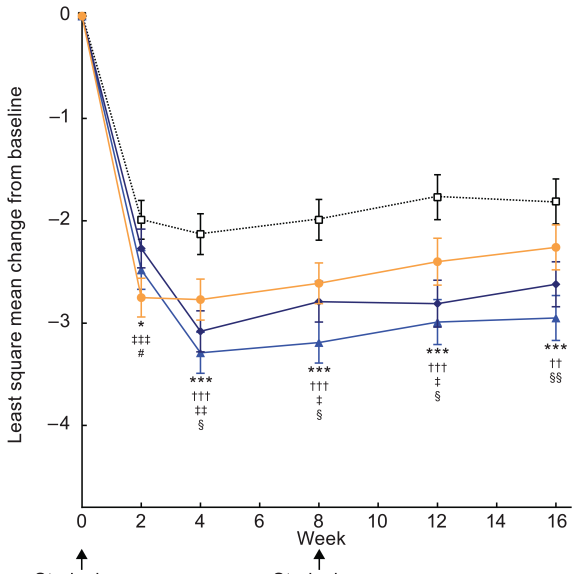
Few subjects had clinically significant new or worsened abnormality at last neurologic examination (≤ 0.5% in any group; both studies) with no meaningful differences among treatments (Table 3). In Study 1015, more tanezumab-treated subjects were referred for neurologic consultation than those receiving naproxen or placebo, with almost twice as many subjects referred for consultation from the tanezumab 10 mg group than from the tanezumab 5 mg group. Results of final neurologic consultations for subjects categorized as suggestive of new or worsened peripheral neuropathy based on clinically significant signs or diagnostic tests were mononeuropathy (n = 9; 8 had carpal tunnel syndrome), radiculopathy (n = 5), and polyneuropathy (n = 3) with tanezumab; carpal tunnel syndrome (n = 1) and radiculopathy (n = 1) with naproxen; and carpal tunnel syndrome (n = 1) with placebo. Only the placebo-treated subject had worsening of an ongoing carpal tunnel syndrome. The other subjects had evidence suggestive of a new peripheral neuropathy.

More tanezumab-treated subjects from Study 1018 were referred for neurologic consultation than those receiving naproxen or placebo; referral rates for the tanezumab 10 mg and 5 mg groups were similar. Results of final neurologic consultations for subjects categorized as suggestive of new or worsened peripheral neuropathy based on clinically significant signs or diagnostic tests were mononeuropathy (n = 5; 4 had carpal tunnel syndrome), radiculopathy (n = 1), polyneuropathy (n = 2), and other diagnosis (numbness in the feet without reflex or sensory findings, n = 1) with tanezumab; carpal tunnel syndrome (n = 1) and radiculopathy (n = 1) with naproxen; and carpal tunnel syndrome (n = 1) with placebo. The subject with numbness in the feet without reflex or sensory findings had worsening of a baseline sensory neuropathy. The other subjects had evidence suggestive of a new peripheral neuropathy.

Six subjects reported TJR across both studies. In Study 1015, 2 subjects who received placebo (1 unilateral and 1 bilateral knee replacement) and 1 who received tanezumab 5 mg (left hip replacement from worsening degenerative joint disease with prior right hip injury and replacement) reported TJR. In Study 1018, no subjects treated with tanezumab reported TJR, but 1 naproxen- and 2 placebo-treated subjects (all index joint) underwent TJR.

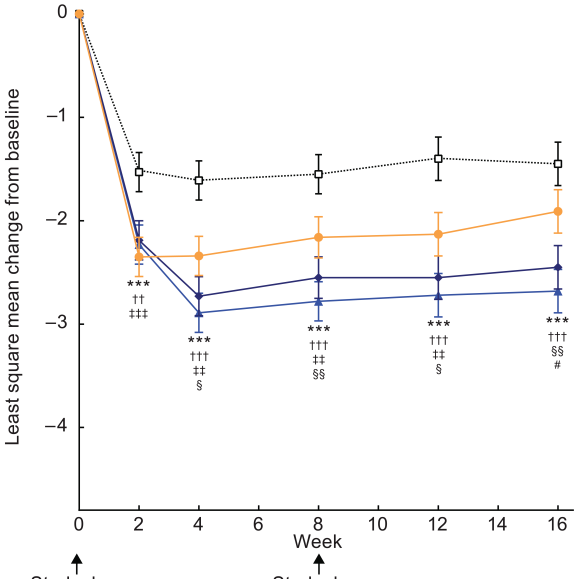
Radiographs were available for the Adjudication Committee to examine 3 subjects, including the subject who received tanezumab 5 mg, the naproxen-treated subject, and 1 placebo-treated subject (total left hip arthroplasty). The

A



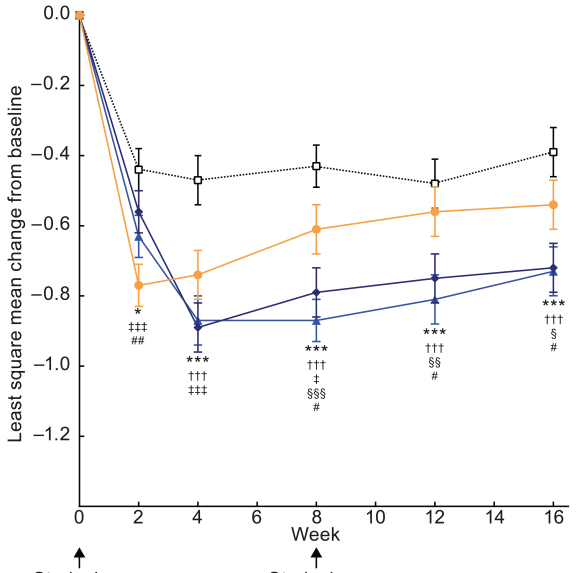
Group	Baseline Mean ± standard deviation	Least squares mean change from baseline to Week 16 Mean ± standard error
Placebo (n = 209)	7.41 ± 1.38	−1.81 ± 0.22
95% CI for LS Mean		[−2.25, −1.38]
Tanezumab 5 mg (n = 211)	7.27 ± 1.38	−2.95 ± 0.22
95% CI for LS Mean		[−3.39, −2.51]
Tanezumab 10 mg (n = 208)	7.37 ± 1.39	−2.62 ± 0.22
95% CI for LS Mean		[−3.06, −2.18]
Naproxen 500 mg BID (n = 207)	7.30 ± 1.41	−2.26 ± 0.22
95% CI for LS Mean		[−2.70, −1.82]

B



Group	Baseline Mean ± standard deviation	Least squares mean change from baseline to Week 16 Mean ± standard error
Placebo (n = 209)	7.04 ± 1.49	−1.45 ± 0.21
95% CI for LS Mean		[−1.86, −1.04]
Tanezumab 5 mg (n = 211)	6.83 ± 1.56	−2.68 ± 0.21
95% CI for LS Mean		[−3.10, −2.27]
Tanezumab 10 mg (n = 208)	7.09 ± 1.52	−2.45 ± 0.21
95% CI for LS Mean		[−2.86, −2.03]
Naproxen 500 mg BID (n = 207)	6.95 ± 1.64	−1.91 ± 0.21
95% CI for LS Mean		[−2.33, −1.49]

C



Group	Baseline Mean ± standard deviation	Least squares mean change from baseline to Week 16 Mean ± standard error
Placebo (n = 209)	3.46 ± 0.65	−0.39 ± 0.07
95% CI for LS Mean		[−0.53, −0.26]
Tanezumab 5 mg (n = 211)	3.36 ± 0.56	−0.73 ± 0.07
95% CI for LS Mean		[−0.86, −0.60]
Tanezumab 10 mg (n = 208)	3.40 ± 0.61	−0.72 ± 0.07
95% CI for LS Mean		[−0.85, −0.58]
Naproxen 500 mg BID (n = 207)	3.48 ± 0.61	−0.54 ± 0.07
95% CI for LS Mean		[−0.67, −0.40]

Figure 3. Least squares mean changes in (A) WOMAC Pain, (B) WOMAC Physical Function, and (C) patient's global assessment of osteoarthritis (OA) over time in subjects with OA of the hip or knee (Study 1018). WOMAC assessed with 0 to 10-point numerical rating scale. Patient's global assessment of OA measured with 5-point Likert scale. A change from baseline < 0 is an improvement. Error bars represent standard error. Baseline observation carried forward imputation was applied for missing data. *$p < 0.05$, **$p \le 0.01$, ***$p \le 0.001$ tanezumab 5 mg versus placebo. $^{\dagger}p < 0.05$, $^{\dagger\dagger}p \le 0.01$, $^{\dagger\dagger\dagger}p \le 0.001$ tanezumab 10 mg versus placebo. $^{\ddagger}p < 0.05$, $^{\ddagger\ddagger}p \le 0.01$, $^{\ddagger\ddagger\ddagger}p \le 0.001$ naproxen versus placebo. $^{\S}p < 0.05$, $^{\S\S}p \le 0.01$, $^{\S\S\S}p \le 0.001$ tanezumab 5 mg versus naproxen. $^{\#}p < 0.05$, $^{\#\#}p \le 0.01$, $^{\#\#\#}p \le 0.001$ tanezumab 10 mg versus naproxen. WOMAC: Western Ontario McMaster Universities Osteoarthritis Index; LS: least squares.

Table 2. Treatment-emergent adverse events (AE). Data are n (%).

	Study 1015				Study 1018			
	Placebo, n = 208	Tanezumab 5 mg*, n = 206	Tanezumab 10 mg*, n = 208	Naproxen 500 mg BID, n = 206	Placebo, n = 209	Tanezumab 5 mg*, n = 211	Tanezumab 10 mg*, n = 209	Naproxen 500 mg BID, n = 211
Any adverse event (AE)†	99 (47.6)	107 (51.9)	122 (58.7)	104 (50.5)	85 (40.7)	101 (47.9)	101 (48.3)	110 (52.1)
Any serious AE*	8 (3.8)	7 (3.4)	6 (2.9)	5 (2.4)	4 (1.9)	3 (1.4)	4 (1.9)	9 (4.3)
Study discontinuations because of AE	7 (3.4)	13 (6.3)	16 (7.7)	13 (6.3)	10 (4.8)	4 (1.9)	14 (6.7)	16 (7.6)
AE ≥ 3% of subjects in any treatment group‡								
Arthralgia	8 (3.8)	12 (5.8)	14 (6.7)	6 (2.9)	2 (1.0)	12 (5.7)	12 (5.7)	9 (4.3)
Back pain	4 (1.9)	5 (2.4)	3 (1.4)	7 (3.4)	1 (0.5)	6 (2.8)	3 (1.4)	1 (0.5)
Blood creatine phosphokinase increased	0 (0.0)	8 (3.9)	3 (1.4)	4 (1.9)	1 (0.5)	4 (1.9)	6 (2.9)	1 (0.5)
Constipation	0	1 (0.5)	1 (0.5)	7 (3.4)	1 (0.5)	2 (0.9)	0	6 (2.8)
Dyspepsia	2 (1.0)	2 (1.0)	2 (1.0)	4 (1.9)	4 (1.9)	3 (1.4)	2 (1.0)	10 (4.7)
Fall	8 (3.8)	5 (2.4)	2 (1.0)	2 (1.0)	5 (2.4)	6 (2.8)	4 (1.9)	5 (2.4)
Headache	11 (5.3)	7 (3.4)	5 (2.4)	9 (4.4)	6 (2.9)	9 (4.3)	7 (3.3)	6 (2.8)
Hypoesthesia	2 (1.0)	4 (1.9)	10 (4.8)	8 (3.9)	0	7 (3.3)	2 (1.0)	2 (0.9)
Joint swelling	1 (0.5)	7 (3.4)	8 (3.8)	5 (2.4)	0	4 (1.9)	3 (1.4)	0
Nasopharyngitis	4 (1.9)	2 (1.0)	6 (2.9)	8 (3.9)	2 (1.0)	8 (3.8)	4 (1.9)	5 (2.4)
Pain in extremity	6 (2.9)	6 (2.9)	20 (9.6)	1 (0.5)	1 (0.5)	4 (1.9)	11 (5.3)	2 (0.9)
Paresthesia	3 (1.4)	12 (5.8)	18 (8.7)	6 (2.9)	2 (1.0)	13 (6.2)	12 (5.7)	5 (2.4)
Peripheral edema	0	9 (4.4)	15 (7.2)	4 (1.9)	2 (1.0)	4 (1.9)	11 (5.3)	4 (1.9)
Sinusitis	10 (4.8)	6 (2.9)	6 (2.9)	7 (3.4)	3 (1.4)	3 (1.4)	3 (1.4)	4 (1.9)
Upper respiratory tract infection	10 (4.8)	12 (5.8)	6 (2.9)	4 (1.9)	2 (1.0)	8 (3.8)	6 (2.9)	5 (2.4)
Urinary tract infection	2 (1.0)	6 (2.9)	7 (3.4)	7 (3.4)	6 (2.9)	6 (2.8)	6 (2.9)	6 (2.8)
AE of abnormal peripheral sensation‡								
Allodynia	0	0	5 (2.4)	0	0	0	0	0
Burning sensation	1 (0.5)	2 (1.0)	3 (1.4)	1 (0.5)	0	2 (0.9)	5 (2.4)	2 (0.9)
Decreased vibratory sense	1 (0.5)	2 (1.0)	2 (1.0)	1 (0.5)	0	0	0	0
Dysesthesia	1 (0.5)	0	2 (1.0)	0	0	0	1 (0.5)	0
Facial hypoesthesia	0	0	0	1 (0.5)	0	0	0	0
Hyperesthesia	1 (0.5)	1 (0.5)	2 (1.0)	0	0	0	5 (2.4)	0
Hypoesthesia	2 (1.0)	4 (1.9)	10 (4.8)	8 (3.9)	0	7 (3.3)	2 (1.0)	2 (0.9)
Neuralgia	0	1 (0.5)	0	0	0	0	0	0
Paresthesia	3 (1.4)	12 (5.8)	18 (8.7)	6 (2.9)	2 (1.0)	13 (6.2)	12 (5.7)	5 (2.4)
Peripheral neuropathy	0	1 (0.5)	1 (0.5)	0	0	0	1 (0.5)	0
Peripheral sensory neuropathy	0	0	0	0	0	1 (0.5)	0	0
Sensory disturbance	0	1 (0.5)	1 (0.5)	0	0	0	0	0

*Administered intravenously on Day 1 and Day 57 (Week 8). †All causality. ‡Listed in alphabetical order.

tanezumab-treated subject was adjudicated to the classification of worsening OA with insufficient information to distinguish normal versus rapid progression. The other 2 subjects were adjudicated to worsening OA of normal progression.

DISCUSSION

The results of 2 similar active- and placebo-controlled clinical trials confirmed and extended observations regarding tanezumab efficacy in symptomatic treatment of knee or hip OA[11,12,13,14,15,16]. Both tanezumab doses, administered at 8-week intervals, provided significant improvements versus placebo across all 3 coprimary efficacy domains over 16 weeks of treatment, whereas naproxen 500 mg twice daily (the maximum dose for OA management) resulted in no significant improvements versus placebo. No compelling evidence suggested tanezumab 10 mg provided greater efficacy than tanezumab 5 mg in OA pain treatment because tanezumab 5 mg was associated with greater improvement across efficacy domains in the landmark Week 16 analysis.

A primary objective of each study was to compare tanezumab 5 mg and 10 mg efficacy versus naproxen. Pain reductions with tanezumab 10 mg versus naproxen did not reach significance whereas functional (both studies) and global (1 study) outcomes did; thus, tanezumab 10 mg was not superior to naproxen and predefined statistical testing procedures were not met, allowing for conclusion of superiority of tanezumab 5 mg over naproxen despite replicated favorable coprimary outcomes. Predefined sensitivity

Table 3. Summary of final neurologic examinations and neurologic consultations. Neurological examinations were performed per protocol by study investigators. Data are n (%).

	Study 1015				Study 1018			
	Placebo, n = 208	Tanezumab 5 mg†, n = 206	Tanezumab 10 mg†, n = 208	Naproxen 500 mg BID, n = 206	Placebo, n = 209	Tanezumab 5 mg†, n = 211	Tanezumab 10 mg†, n = 209	Naproxen 500 mg BID, n = 211
Final neurological examination assessments								
New or worsened abnormality								
Clinically significant	0	1 (0.5)	1 (0.5)	1 (0.5)	0	1 (0.5)	1 (0.5)	1 (0.5)
Not clinically significant	27 (13.0)	24 (11.8)	23 (11.2)	14 (6.8)	14 (6.9)	17 (8.2)	19 (9.3)	20 (9.9)
No new or worsened abnormality	180 (87.0)	179 (87.7)	181 (88.3)	191 (92.7)	189 (93.1)	190 (91.3)	184 (90.2)	181 (89.6)
Final neurological consultation categorization‡								
Subjects referred for consultation	10 (4.8)	20 (9.7)	38 (18.3)	10 (4.9)	3 (1.4)	20 (9.5)	25 (12.0)	9 (4. 3)
Symptoms, clinically significant signs, or diagnostic tests suggestive of new or worsened peripheral neuropathy	1 (0.5)	6 (2.9)	19 (9.1)	2 (1.0)	2 (1.0)	4 (1.9)	7 (3.3)	3 (1.4)
Other neurological symptoms or signs	3 (1.4)	4 (1.9)	8 (3.8)	3 (1.5)	1 (0.4)	11 (5.2)	9 (4.3)	2 (0.9)
No neurological symptoms or signs	6 (2.9)	10 (4.9)	11 (5.3)	5 (2.4)	0	5 (2.4)	9 (4.3)	4 (1.9)

†Administered intravenously on Day 1 and Day 57 (Week 8). ‡Neurological consultations were performed by neurologists following a neurological adverse event report or after significant neurological examination abnormalities were detected by investigators.

analyses examined the degree that BOCF imputation affected outcomes because differential discontinuation rates across treatments led to varied amounts of imputed baseline ("no improvement") scores. Alternative methodologies (mixed model for repeated measurements and imputation using multiple imputation and last observation carried forward) were consistent with analyses using BOCF, and therefore are not presented in this manuscript. Regardless of analysis, both tanezumab doses were associated with consistently greater efficacy versus placebo over all coprimary endpoints, whereas naproxen was not.

It is customary in assessment of daily oral medications for OA to evaluate efficacy responses across multiple domains after 12 weeks of treatment[25]. At Week 12 in our current studies, a time consistent with observed benefit in other naproxen OA studies[26], naproxen provided significantly greater improvements versus placebo in WOMAC Pain and Physical Function regardless of analysis (both studies) and PtGA (1 study).

Improvements observed with tanezumab were clinically meaningful as judged by several different methods of assessment, including the magnitude of mean improvement observed, analysis of WOMAC Pain 30% and 50% response rates (Supplemental Figure 2, available online at jrheum.org), and response rates determined by minimally clinical important improvement or patient acceptable symptom score (Supplemental Text 7; Supplemental Table 2, available online at jrheum.org). Effect sizes observed in our studies were also determined, and based on general estimates, were small to moderate in magnitude (Supplemental Table 3, available online at jrheum.org).

Taken together, the safety results indicate that overall incidence of adverse events and serious adverse events were generally similar among subjects receiving tanezumab or naproxen, with fewer adverse events reported with placebo than with active treatments. Rates and reporting pattern of adverse events were similar across both studies and were comparable to previous tanezumab clinical studies[11,12,13,14,15,16]. Fewer subjects withdrew because of adverse events with placebo or tanezumab 5 mg treatment versus naproxen or tanezumab 10 mg. In both studies, most adverse events leading to withdrawals in subjects treated with tanezumab were peripheral sensory or musculoskeletal adverse events, whereas naproxen withdrawals generally were the result of gastrointestinal or cardiovascular adverse events. Few serious adverse events occurred in either study and rates of discontinuations because of an adverse event were low. There was no indication that tanezumab treatment produced meaningful changes in clinical or laboratory assessments.

As in other tanezumab studies, we observed a generally dose-related incidence of adverse events of abnormal peripheral sensation in subjects treated with tanezumab[11,12,13,16]. The mechanism for these effects is unknown. Most subjects treated with tanezumab with final neurologic consultations suggestive of new or worsening peripheral neuropathy based on clinical signs or diagnostic tests were diagnosed with some form of mononeuropathy, predominantly carpal tunnel syndrome (a common median nerve mononeuropathy); fewer subjects were diagnosed with radiculopathy or polyneuropathy. These results are not consistent with the expected pattern associated with a neurotoxic compound, which typically causes length-dependent

polyneuropathy in most affected individuals. Animal studies do not indicate evidence of peripheral sensory neurotoxicity with tanezumab, and we saw no strong evidence for such in previous clinical studies[11,12,13,14,15,16,27]. Most subjects report transient abnormalities and few had clinically relevant findings on neurologic examination.

Near the completion of our studies, the US Food and Drug Administration (FDA) placed all NGF-inhibitor therapies in development on partial clinical hold (for all indications except cancer pain) because of adverse events initially described as osteonecrosis. Many required TJR. Extensive analysis of these reports and other TJR were conducted[23]. On March 12, 2012, the FDA Arthritis Advisory Committee reviewed these results, as well as those prepared by the FDA[23,28,29]. The committee endorsed continued clinical development of the NGF-inhibitor class of compounds with inclusion of additional measures to minimize risk and protect subject safety. On August 28, 2012, the FDA lifted the partial clinical hold on tanezumab related to joint safety. Neither of our current studies were affected by the clinical hold, and both studies were completed as planned. TJR were infrequent, incidence was similar across treatments, and no osteonecrosis events were reported in either study.

In 2 clinical trials, tanezumab was associated with significant improvements in WOMAC Pain, WOMAC Physical Function, and patient's global assessment versus placebo. Tanezumab provided consistently greater improvement versus naproxen, and replicate evidence indicated that both doses provided greater improvement than naproxen for physical function. Safety of tanezumab was similar to previous reports. Overall incidence of adverse events, serious adverse events, and withdrawals because of adverse events were generally similar between tanezumab and naproxen. Tanezumab appears efficacious in treatment of knee or hip OA with greater magnitude of symptomatic improvement than with NSAID such as naproxen. These results suggest tanezumab may have clinical utility in treatment of patients experiencing inadequate analgesia with NSAID and the potential to affect clinical practice significantly.

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ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

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