Arthritis Care & Research
Vol. 74, No. 6, June 2022, pp 918–928
DOI 10.1002/acr.24637

American College of Rheumatology
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General Safety and Tolerability of Subcutaneous Tanezumab for Osteoarthritis: A Pooled Analysis of Three Randomized, Placebo-Controlled Trials

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Objective. This pooled analysis of 3 randomized, placebo-controlled trials (16–24 week treatment and 8–24 week follow-up) assessed safety of subcutaneous tanezumab (2.5–10 mg every 8 weeks) in 1,840 patients with hip or knee osteoarthritis.

Methods. Overall treatment-emergent adverse events (TEAEs) and TEAEs of abnormal peripheral sensation (APS) were prospectively assessed in 3 trials. Joint safety events (primary osteonecrosis, rapidly progressive osteoarthritis [RPOA], subchondral insufficiency fracture, and pathologic fracture; adjudicated by an independent expert committee) and TEAEs potentially associated with sympathetic neuropathy were prospectively assessed in 2 trials.

Results. During the treatment period, overall TEAE rates were 51.7% for placebo and 39.5–54.8% for tanezumab 2.5–10 mg; treatment discontinuation rates were 2.0% for placebo and 0–1.3% for tanezumab. Rates of composite joint safety events (predominantly RPOA type 1) over the treatment plus follow-up period were 0% for placebo and 0.5–3.2% for tanezumab 2.5–5 mg (5 mg was statistically greater than placebo); total joint replacement rates with tanezumab (5.9–7.0%) were not significantly different from placebo (4.5%). Rates of TEAEs of APS (predominantly paresthesia and hypoesthesia) were 2.2% for placebo and 3.2–12.8% for tanezumab 2.5–10 mg. Rates of TEAEs potentially associated with sympathetic neuropathy (predominantly bradycardia and orthostatic hypotension) were 0.8% for placebo and 0.5–2.8% for tanezumab 2.5–5 mg (exposure-adjusted rates were not significantly different from placebo).

Conclusion. Tanezumab was generally well tolerated. TEAEs of APS (mostly mild and transient) and joint safety events were infrequent but more common with tanezumab than placebo. A tanezumab dose of 2.5 mg demonstrated a more favorable safety profile than higher doses.

INTRODUCTION

Tanezumab, a monoclonal antibody against nerve growth factor (NGF), is in development for the treatment of the signs and symptoms of moderate-to-severe osteoarthritis (OA) (1). Early trials have demonstrated efficacy of intravenous (IV) tanezumab in patients with OA of the knee or hip, but adverse events related to joint safety and abnormal peripheral sensation (APS) were observed in some patients (2–11). Possible changes in sympathetic neuronal morphology were also observed in preclinical studies (12). Following partial clinical holds of all anti-NGF programs in 2010 (due to joint safety observations) and 2012 (due to preclinical sympathetic observations), phase III trials of tanezumab resumed in 2015 with use of subcutaneous

Clinicaltrials.gov identifiers: NCT01089725, NCT02697773, and NCT02709486.

Supported by Pfizer and Eli Lilly and Company.

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Dr. Berenbaum has received consulting and/or speaking fees from Novartis, MSD, Pfizer, Eli Lilly and Company, UCB, AbbVie, Roche, Servier, Sanofi-Aventis, Flexion Therapeutics, Expanscience, GlaxoSmithKline, Biogen, Nordic, Sandoz, Regeneron, Gilead, BoneTherapeutics, Regulaxis, and Peptinov (less than $10,000 each) and from 4P Pharma (greater than $10,000), and has received research support through his institution from TRB Chemedica, MSD, and Pfizer. Dr. Schnitzer has received consulting fees from Eli Lilly and Company, AstraZeneca, and GlaxoSmithKline (less than $10,000 each) and from Pfizer (greater than $10,000). Dr. Kivitz has received consulting and/or speaking fees from Janssen, SUN Pharma Advanced Research, Boehringer Ingelheim, and Merck (less than $10,000 each) and from AbbVie, Novartis, Pfizer, Regeneron, Gilead, Celgene, Horizon, and Flexion Therapeutics (greater than $10,000 each) and owns stock or stock options in Pfizer, Amgen, Gilead, and GlaxoSmithKline. Dr. Viktrup is an employee of and owns stock or stock options in Eli Lilly and Company. Drs. Hickman, Brown, Davignon, and West and Mr. Pixton are employees of and own stock and/or stock options in Pfizer. No other disclosures relevant to this article were reported.

SIGNIFICANCE & INNOVATIONS

- This analysis was the first to summarize safety across all phase 3, placebo-controlled, osteoarthritis trials of subcutaneous tanezumab, a member of a novel and emerging class of anti–nerve growth factor therapies in development for the treatment of the signs and symptoms of osteoarthritis.
- The results demonstrate that tanezumab was generally well tolerated in most patients (rates of treatment discontinuations due to adverse events were 2.0% for placebo and 0–1.3% for tanezumab), and there was no evidence of a sympathetic safety signal in the osteoarthritis population.
- Adverse events of abnormal peripheral sensation occurred more frequently with tanezumab than with placebo during the treatment period but were mostly mild, none were serious, and typically resolved. The frequency of a diagnosis of peripheral polyneuropathy (by a blinded external neurologist) was similar in the tanezumab and placebo treatment groups.
- Joint safety events (most commonly rapidly progressive osteoarthritis type 1) were infrequent overall, but more common with tanezumab than placebo. Rates of joint safety events with low-dose tanezumab (2.5 mg) were not significantly different from placebo.

(SC) administration (for patient convenience), use of lower tanezumab doses, enrollment limited to patients with inadequate response to other OA treatments, restrictions on concomitant nonsteroidal antiinflammatory drug (NSAID) use, and incorporation of comprehensive sympathetic function and joint safety screening and monitoring procedures.

Since resumption of clinical testing, tanezumab has demonstrated significant improvements in pain and function versus placebo in patients with moderate-to-severe OA and a history of inadequate response or intolerance to standard-of-care analgesics (13,14). The current pooled analysis summarizes the general safety and tolerability of SC tanezumab in patients with moderate-to-severe OA by assessing overall treatment-emergent adverse events (TEAEs), joint safety events, TEAEs of APS, and TEAEs potentially associated with sympathetic neuropathy.

PATIENTS AND METHODS

Data sources. Data were derived from all randomized, placebo-controlled trials of SC tanezumab (administered every 8 weeks) in patients with OA of the knee or hip completed to date (n = 3). Tanezumab doses ranged from 2.5 to 10 mg, planned treatment periods ranged from 16 to 24 weeks, and safety follow-up periods ranged from 8 to 24 weeks (Table 1). Studies were conducted in compliance with ethical principles of the Declaration of Helsinki and all International Conference on Harmonization Good Clinical Practice Guidelines, protocols were approved by institutional review boards or independent ethics committees for each site, and all patients provided written informed consent.

Inclusion and exclusion criteria. Key inclusion criteria included: age ≥18 years, diagnosis of OA of the knee (A4091027) or of the hip or knee (A4091056 and A4091057) with radiographic confirmation (Kellgren/Lawrence [K/L] grade ≥2), and a Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (15) pain score of ≥5 (from 0 to 10) in the index joint at baseline, a WOMAC physical function score of ≥4 (A4091027) or ≥5 (A4091056 and A4091057) (from 0 to 10) in the index joint at baseline, and a patient global assessment of OA score of fair, poor, or very poor at baseline. Patients were required to exhibit prior inadequate response or intolerance to other OA treatments (Table 1).

Nonanalgesic medications for non-OA, nonpain conditions were permitted if the dose was stable for ≥30 days prior to baseline. Occasional use of analgesics, including acetaminophen (if used for reasons other than rescue) and NSAIDs, was allowed for self-limiting conditions unrelated to OA (Table 1).

Safety assessments. Overall TEAEs were assessed throughout the 3 studies, with severity, seriousness, and relationship to treatment determined by investigators. Comprehensive joint safety screening and monitoring procedures were incorporated into post-2015 studies A4091056 and A4091057. Radiographs of all index and nonindex hips, knees, and shoulders were obtained at screening and during the trials (week 40 for A4091056; weeks 24 and 48 for A4091057). A central reader reviewed images to assess eligibility criteria and possible joint safety events (rapidly progressive OA [RPOA], subchondral insufficiency fractures, osteonecrosis, or pathologic fracture). Musculoskeletal examinations of all major joints and review of

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Submitted for publication December 10, 2020; accepted in revised form April 27, 2021.

Table 1. Description of studies included in the analysis*

Study A4091027 (ClinicalTrials.gov identifier: NCT01089725): Pre-2015 study in the US in patients with osteoarthritis (OA) of the knee. Subcutaneous (SC) treatments: placebo (n = 72) and tanezumab (2.5 mg = 74, 5 mg = 63, 10 mg = 86).† Duration: 16-week treatment (2 SC doses) and 8-week safety follow-up. Previous treatment requirements: unwilling or unable to take nonopiate pain medication, or have a history of inadequate pain relief with nonopiate pain medications, or are candidates for invasive interventions. Rescue medication: acetaminophen ≤3,000 mg/day for up to 3 days/week during treatment period, and no specified limit during follow-up. Nonsteroidal antiinflammatory drug (NSAID) restrictions: as for all analgesics, limited use of NSAIDs was permitted on an occasional basis for self- limiting conditions unrelated to OA. As a result of clinical hold, 90.5% of treated patients received only 1 dose of study medication. A majority of these patients remained in the study for >16 weeks (70.7%).
Study A4091056 (ref. 13) (ClinicalTrials.gov identifier: NCT02697773): Post-2015 study in the US and Canada in patients with OA of the knee or hip. SC treatments: placebo (n = 232) and tanezumab (2.5 mg = 231, 2.5/5 mg = 233).‡ Duration: 16-week treatment (2 SC doses) and 24-week safety follow-up. Previous treatment requirements: a history of inadequate pain relief with acetaminophen; a history of inadequate pain relief with, or contraindication/ intolerability to, oral NSAIDs; and a history of inadequate pain relief with, or contraindication/intolerability to, tramadol or opioids (or unwilling to take opioids). Rescue medication: acetaminophen ≤3,000 mg/day for up to 3 days/week during treatment period and then up to daily during follow-up. NSAID restrictions: limited use of NSAIDs was permitted on an occasional basis for self-limiting conditions unrelated to OA. Aggregate use of NSAIDs during each 8-week SC dosing interval was not to exceed 10 days and total NSAID use was not to exceed 30 days between baseline visit and 16 weeks after last SC dose. Overall, 87.5% and 79.9% of patients completed the treatment and full study (treatment plus follow-up) periods, respectively.
Study A4091057 (ref. 14) (ClinicalTrials.gov identifier: NCT02709486): Post-2015 study in Europe and Japan in patients with OA of the knee or hip. SC treatments: placebo (n = 282) and tanezumab (2.5 mg = 283, 5 mg = 284). Duration: 24-week treatment (3 SC doses) and 24-week safety follow-up. Previous treatment requirements: same as study A4091056. Rescue medication: acetaminophen ≤4,000 mg/day for up to 5 days/ week during treatment period and then up to daily during follow-up. NSAID restrictions: same as study A4091056 except total NSAID use was not to exceed 40 days between baseline visit and 16 weeks after last SC dose. Overall, 88.3% and 82.0% of patients completed the treatment and full study periods, respectively.

* In all trials, SC study medication was administered every 8 weeks.
† This study also included an intravenous tanezumab 10-mg arm that is not included in the current analyses. Patients in SC arms received intravenous doses of placebo to match the intravenous tanezumab arm.
‡ Patients were given a 2.5-mg dose at baseline and a 5-mg dose at week 8. Of the 233 patients randomized to the 2.5/5 mg treatment group, 14 received only the baseline 2.5-mg dose and are therefore included in the tanezumab 2.5 mg treatment group in subsequent analyses/data tables.

pain scores occurred at all study visits. Investigators assessed patients with increased persistent pain to determine whether further evaluation (imaging or orthopedic consultation) was warranted. All possible joint safety events (assessed by the central reader on post-baseline images or reported as a TEAE by an investigator) and total joint replacements (TJRs) were reviewed by a blinded adjudication committee of external experts. Patients with adjudicated outcomes of RPOA type 1 or 2, subchondral insufficiency fractures, primary osteonecrosis, or pathologic fracture were included in a composite joint safety endpoint. RPOA type 1 was defined as a significant loss of joint space width of ≥2 mm (predicated on optimal joint positioning) within approximately 1 year, without gross structural failure. RPOA type 2 was defined as abnormal bone loss or destruction, including limited or total collapse of at least 1 subchondral surface, which is not normally present in conventional end-stage OA (16).

Neurologic examinations, including assessment of muscle strength (head and neck, upper and lower extremities), deep tendon reflexes, and sensation (index fingers and great toes), were performed at screening and all clinic visits during the 3 studies to evaluate patients for signs of peripheral neuropathy. Patients with history, diagnosis, or signs and symptoms of peripheral neuropathy were excluded from enrollment. In studies A4091056 and A4091057, neurologic consultations were performed if a TEAE suggestive of new or worsening peripheral neuropathy or a TEAE of APS was reported and met certain criteria (see footnote to Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24637).

Comprehensive sympathetic function screening and monitoring procedures were incorporated into post-2015 studies A4091056 and A4091057. Patients with a score >7 (scores range from 0 to 55 for women and from 0 to 60 for men) on the Survey of Autonomic Symptoms (a questionnaire assessing the presence of potential autonomic neuropathy), a diagnosis of autonomic neuropathy, or evidence of orthostatic hypotension at screening were excluded from enrollment (17). Sympathetic function was monitored during the studies through TEAE assessment, orthostatic blood pressure assessments at each visit, protocol-specified criteria for reporting TEAEs of bradycardia based on electrocardiograms, Survey of Autonomic Symptoms questionnaires, and consultation with cardiologists and neurologists for prespecified TEAEs potentially associated with sympathetic neuropathy (syncope, bradycardia, orthostatic hypotension, anhidrosis, and hypohidrosis).

Statistical analysis. Patient demographic characteristics, clinical characteristics, and treatment exposure were summarized descriptively. Incidences of overall TEAEs, TEAEs of APS, and TEAEs potentially associated with sympathetic neuropathy were summarized for the treatment and study (treatment plus follow-up) periods. Joint safety was summarized for the study (treatment plus follow-up) period only, as such events were relatively infrequent and an imbalance (between placebo and tanezumab

groups) in these events typically has existed in both treatment and follow-up periods in previous trials of tanezumab. For full statistical methods, see Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24637.

RESULTS

Patients and exposure. Overall, 1,840 patients were included in the analyses (placebo = 586, tanezumab 2.5 mg = 602, tanezumab 2.5/5 mg = 219, tanezumab 5 mg = 347, and tanezumab 10 mg = 86). Patients were predominantly White (80.9%), female (66.6%), and had approximate mean age and disease durations of 62.5 and 8.5 years, respectively (Table 2). A knee was designated as the index joint in 86.6% of patients. In post-2015 studies, 79.3% of participants had ≥2 joints with a K/L grade of ≥2.

The mean ± SD number of doses received in the placebo and tanezumab 2.5-mg, 2.5/5-mg, 5-mg, and 10-mg arms was 2.2 ± 0.7, 2.3 ± 0.7, 2.0 ± 0.0, 2.6 ± 0.8, and 1.1 ± 0.3, respectively, while mean ± SD exposure was 18.1 ± 6.2, 18.6 ± 5.8, 16.2 ± 1.6, 21.3 ± 5.9, and 11.7 ± 2.6 weeks, respectively (tanezumab 10 mg was only used in study A4091027). Exposure calculations were based on study treatment periods, which, due to the pharmacokinetics of tanezumab, ended 8 weeks after the final SC injection. Patient exposure years in the placebo and tanezumab 2.5-mg, 2.5/5-mg, 5-mg, and 10-mg arms were 202.8, 215.1, 67.9, 141.9, and 19.3, respectively.

Overall TEAEs. TEAEs during the treatment and full-study periods are summarized in Table 3 (A4091027, A4091056, and A4091057). TEAE rates during the treatment period were 51.7% for placebo, 52.3% for tanezumab 2.5 mg, 47.0% for tanezumab 2.5/5 mg, 54.8% for tanezumab 5 mg, and 39.5% for tanezumab 10 mg. Among common TEAEs (occurring in ≥2% of patients in any group), injection site reaction (10 mg), edema peripheral (2.5/5 mg; 5 mg), joint stiffness (2.5/5 mg), synovial cyst (10 mg), hypoesthesia (10 mg), and paresthesia (5 mg; 10 mg) had a higher incidence (95% confidence

Table 2. Patient demographic and clinical characteristics with subcutaneous tanezumab treatment or placebo*

Characteristic	Placebo (n = 586)	2.5 mg (n = 602)	2.5/5 mg (n = 219)	5 mg (n = 347)	10 mg (n = 86)
Age, mean ± SD years	62.3 ± 10.2	62.9 ± 9.5	61.3 ± 9.1	64.3 ± 10.5	58.2 ± 8.7
Sex					
Male	186 (31.7)	199 (33.1)	80 (36.5)	118 (34.0)	32 (37.2)
Female	400 (68.3)	403 (66.9)	139 (63.5)	229 (66.0)	54 (62.8)
Race					
White	463 (79.0)	494 (82.1)	159 (72.6)	299 (86.2)	73 (84.9)
Black or African American	70 (11.9)	54 (9.0)	48 (21.9)	8 (2.3)	10 (11.6)
Asian	49 (8.4)	47 (7.8)	8 (3.7)	36 (10.4)	2 (2.3)
Other/unknown	4 (0.7)	7 (1.2)	4 (1.8)	4 (1.2)	1 (1.2)
Body mass index, kg/m^2					
<25	62 (10.6)	88 (14.6)	27 (12.3)	44 (12.7)	7 (8.1)
25 to <30	183 (31.2)	188 (31.2)	71 (32.4)	110 (31.7)	18 (20.9)
30 to <35	191 (32.6)	196 (32.6)	74 (33.8)	129 (37.2)	41 (47.7)
≥35	150 (25.6)	130 (21.6)	47 (21.5)	64 (18.4)	20 (23.3)
Index joint†					
Hip	80 (13.7)	88 (14.6)	30 (13.7)	48 (13.8)	0
Knee	506 (86.3)	514 (85.4)	189 (86.3)	299 (86.2)	86 (100.0)
K/L grade of index joint					
0	0	2 (0.3)	0	0	0
1	0	1 (0.2)	0	0	0
2	157 (26.8)	144 (23.9)	56 (25.6)	83 (23.9)	40 (46.5)
3	247 (42.2)	270 (44.9)	98 (44.7)	152 (43.8)	34 (39.5)
4	182 (31.1)	185 (30.7)	64 (29.2)	112 (32.3)	12 (14.0)
No. of joints (index and nonindex) K/L grade ≥2‡					
0	0	0	0	0	–
1	101 (19.6)	126 (23.9)	45 (20.5)	48 (16.9)	–
2	278 (54.1)	286 (54.2)	116 (53.0)	166 (58.5)	–
3	87 (16.9)	68 (12.9)	34 (15.5)	48 (16.9)	–
4	48 (9.3)	48 (9.1)	24 (11.0)	22 (7.7)	–
OA disease duration, mean ± SD years	8.9 ± 8.4	8.0 ± 7.9	9.0 ± 7.3	8.0 ± 7.6	9.0 ± 10.5
Baseline WOMAC pain score, mean ± SD	7.0 ± 1.1	7.0 ± 1.2	7.3 ± 1.2	6.8 ± 1.1	7.5 ± 1.3
Baseline WOMAC physical function score, mean ± SD	7.0 ± 1.1	7.0 ± 1.1	7.4 ± 1.2	6.8 ± 1.1	7.1 ± 1.4

* Values are the number (%) of patients unless indicated otherwise. K/L = Kellgren/Lawrence; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
† Index joint was defined as the most painful joint at baseline with a qualifying WOMAC pain score and K/L grade as confirmed by a central reader.
‡ K/L grade of nonindex hips and knees was only assessed in studies A4091056 and A4091057.

Table 3. Summary of overall treatment-emergent adverse events with subcutaneous tanezumab treatment*

AEs	Placebo (n = 586)	2.5 mg (n = 602)	2.5/5 mg (n = 219)	5 mg (n = 347)	10 mg (n = 86)
During the treatment period†					
Number of AEs	647	684	209	482	78
Patients with an AE	303 (51.7)	315 (52.3)	103 (47.0)	190 (54.8)	34 (39.5)
Patients with serious AE‡	9 (1.5)	13 (2.2)	3 (1.4)	9 (2.6)	0
Patients with severe AE§	10 (1.7)	13 (2.2)	6 (2.7)	13 (3.7)	0
Patients discontinuing treatment due to an AE¶	12 (2.0)	8 (1.3)	1 (0.5)	4 (1.2)	0
Common AEs#					
Arthralgia	67 (11.4)	52 (8.6)	19 (8.7)	30 (8.6)	4 (4.7)
Nasopharyngitis	33 (5.6)	44 (7.3)	11 (5.0)	23 (6.6)	0
Back pain	22 (3.8)	28 (4.7)	6 (2.7)	18 (5.2)	0
Headache	27 (4.6)	26 (4.3)	7 (3.2)	14 (4.0)	5 (5.8)
Paresthesia	6 (1.0)	14 (2.3)	3 (1.4)	14 (4.0)	6 (7.0)
Osteoarthritis	10 (1.7)	13 (2.2)	1 (0.5)	13 (3.7)	0
Joint swelling	10 (1.7)	15 (2.5)	4 (1.8)	10 (2.9)	2 (2.3)
Influenza	7 (1.2)	7 (1.2)	0	9 (2.6)	1 (1.2)
Fall	14 (2.4)	26 (4.3)	4 (1.8)	8 (2.3)	0
Musculoskeletal pain	15 (2.6)	14 (2.3)	2 (0.9)	8 (2.3)	1 (1.2)
Hypoesthesia	5 (0.9)	11 (1.8)	3 (1.4)	8 (2.3)	5 (5.8)
Pain in extremity	10 (1.7)	14 (2.3)	7 (3.2)	7 (2.0)	3 (3.5)
Upper respiratory tract infection	9 (1.5)	14 (2.3)	3 (1.4)	7 (2.0)	0
Edema peripheral	1 (0.2)	6 (1.0)	6 (2.7)	6 (1.7)	0
Peripheral swelling	5 (0.9)	4 (0.7)	2 (0.9)	5 (1.4)	2 (2.3)
Diarrhea	7 (1.2)	9 (1.5)	5 (2.3)	4 (1.2)	0
Bronchitis	8 (1.4)	7 (1.2)	0	3 (0.9)	2 (2.3)
Synovial cyst	2 (0.3)	3 (0.5)	1 (0.5)	3 (0.9)	2 (2.3)
Joint stiffness	1 (0.2)	4 (0.7)	5 (2.3)	2 (0.6)	0
Urinary tract infection	4 (0.7)	10 (1.7)	3 (1.4)	2 (0.6)	2 (2.3)
Injection site reaction	3 (0.5)	2 (0.3)	0	1 (0.3)	4 (4.7)
During the full study period**					
Number of AEs	959	1,041	339	676	95
Patients with an AE	357 (60.9)	378 (62.8)	130 (59.4)	221 (63.7)	36 (41.9)
Patients with serious AE	21 (3.6)	32 (5.3)	8 (3.7)	23 (6.6)	0
Patients with severe AE	23 (3.9)	28 (4.7)	13 (5.9)	23 (6.6)	1 (1.2)
Common AEs#					
Arthralgia	95 (16.2)	91 (15.1)	30 (13.7)	53 (15.3)	5 (5.8)
Nasopharyngitis	49 (8.4)	61 (10.1)	16 (7.3)	31 (8.9)	0
Back pain	32 (5.5)	42 (7.0)	8 (3.7)	26 (7.5)	1 (1.2)
Osteoarthritis	19 (3.2)	22 (3.7)	2 (0.9)	22 (6.3)	1 (1.2)
Headache	33 (5.6)	34 (5.6)	8 (3.7)	16 (4.6)	5 (5.8)
Paresthesia	7 (1.2)	15 (2.5)	3 (1.4)	14 (4.0)	6 (7.0)
Musculoskeletal pain	23 (3.9)	31 (5.1)	7 (3.2)	13 (3.7)	2 (2.3)
Joint swelling	13 (2.2)	17 (2.8)	6 (2.7)	12 (3.5)	3 (3.5)
Pain in extremity	16 (2.7)	26 (4.3)	9 (4.1)	12 (3.5)	4 (4.7)
Edema peripheral	2 (0.3)	7 (1.2)	7 (3.2)	11 (3.2)	2 (2.3)
Influenza	10 (1.7)	14 (2.3)	1 (0.5)	11 (3.2)	1 (1.2)
Fall	21 (3.6)	35 (5.8)	9 (4.1)	10 (2.9)	1 (1.2)
Upper respiratory tract infection	13 (2.2)	18 (3.0)	10 (4.6)	9 (2.6)	0
Cough	9 (1.5)	9 (1.5)	2 (0.9)	9 (2.6)	0
Rapidly progressive osteoarthritis	0	7 (1.2)	1 (0.5)	8 (2.3)	0
Hypoesthesia	8 (1.4)	15 (2.5)	5 (2.3)	8 (2.3)	6 (7.0)
Respiratory tract infection	0	2 (0.3)	0	7 (2.0)	0
Cataract	6 (1.0)	3 (0.5)	0	7 (2.0)	0
Hypertension	13 (2.2)	7 (1.2)	2 (0.9)	6 (1.7)	1 (1.2)
Diarrhea	9 (1.5)	10 (1.7)	8 (3.7)	5 (1.4)	0
Peripheral swelling	5 (0.9)	4 (0.7)	3 (1.4)	5 (1.4)	2 (2.3)
Neck pain	12 (2.0)	9 (1.5)	2 (0.9)	4 (1.2)	0
Bronchitis	13 (2.2)	16 (2.7)	0	4 (1.2)	2 (2.3)
Urinary tract infection	8 (1.4)	15 (2.5)	4 (1.8)	4 (1.2)	2 (2.3)
Joint stiffness	2 (0.3)	5 (0.8)	5 (2.3)	4 (1.2)	0
Synovial cyst	3 (0.5)	4 (0.7)	1 (0.5)	4 (1.2)	2 (2.3)
Muscle spasms	6 (1.0)	8 (1.3)	5 (2.3)	3 (0.9)	1 (1.2)

(Continued)

Table 3. (*Cont'd*)

AEs	Placebo (n = 586)	2.5 mg (n = 602)	2.5/5 mg (n = 219)	5 mg (n = 347)	10 mg (n = 86)
Injection site reaction	3 (0.5)	2 (0.3)	0	1 (0.3)	4 (4.7)
Rotator cuff syndrome	4 (0.7)	6 (1.0)	5 (2.3)	1 (0.3)	0

* Values are the number (%) unless indicated otherwise. AE = adverse event.
† Treatment period was 16, 16, and 24 weeks for studies A4091027, A4091056, and A4091057, respectively.
‡ Osteoarthritis (OA) was the only serious AE that occurred in >1 patient in any treatment group (2 patients each in the placebo, tanezumab 2.5-mg, and tanezumab 5-mg groups).
§ Arthralgia was the only AE reported as severe in >1 patient in any group (placebo n = 3; tanezumab 2.5 mg n = 1; tanezumab 5 mg n = 7).
¶ The only treatment-emergent AEs that led to discontinuation of treatment and/or study in >1 patient in any group were arthralgia (placebo n = 7; tanezumab 2.5 mg n = 2; tanezumab 2.5/5 mg n = 1) and OA (tanezumab 2.5 mg n = 3).
# Occurring in ≥2% of patients in any treatment group.
** Full study comprised both the treatment plus safety follow-up periods. These periods were 16 + 8, 16 + 24, and 24 + 24 weeks for studies A40901027, A4091056, and A4091057, respectively.

interval [95% CI] of the risk difference versus placebo excluded 0) in a tanezumab group relative to placebo (data not shown). Five deaths were reported (tanezumab 2.5 mg: cerebrovascular incident [informed by family after patient was lost to follow-up]; tanezumab 2.5/5 mg: lung cancer and suicide in follow-up period; tanezumab 5 mg: nasopharyngitis [severe cold with probable influenza virus infection] and cardiorespiratory arrest in treatment period); none were deemed treatment-related (13,14).

Joint safety events. Joint safety findings for the full study period are summarized in Table 4 (A4091056 and A4091057). The proportion of patients included in the composite joint safety endpoint was 0% for placebo, 1.9% for tanezumab 2.5 mg, 0.5% for tanezumab 2.5/5 mg, and 3.2% for tanezumab 5 mg. Risk difference versus placebo was significantly greater for tanezumab 5 mg (3.17 [95% CI 0.56, 7.18]; $P = 0.037$) but not for tanezumab 2.5 mg (1.89 [95% CI –0.05, 4.71]; $P = 0.084$) or tanezumab 2.5/5 mg (0.46 [95% CI –1.63, 4.47]; $P = 0.696$). Observation time-adjusted incidence rates (patients with events/1,000 patient-years) for the composite joint safety endpoint were 24.1, 6.2, and 37.5 for tanezumab 2.5 mg, 2.5/5 mg, and 5 mg, respectively. The most common adjudicated joint safety event was RPOA (2.5 mg = 1.7%, 2.5/5 mg = 0.5%, and 5 mg = 2.8%), mostly RPOA type 1.

Among 20 tanezumab-treated patients included in the composite joint safety end point, 11 (55%) had the joint safety event in a knee and 9 (45%) had it in a hip. Eleven (55%) had the safety event in an index joint and 9 (45%) had it in a nonindex joint. Baseline K/L grade in the affected joint was 0, 1, 2, 3, or 4 for 2 patients (10%), 1 patient (5%), 7 patients (35%), 7 patients (35%), and 3 patients (15%), respectively. Joint safety events occurred during the treatment period (n = 3; 15%), after discontinuing the treatment period (n = 1; 5%), and after completing the treatment period (n = 16; 80%). Six (30%) of 20 patients included in the composite joint safety end point underwent a TJR.

TJR rates observed with tanezumab (2.5 mg = 5.9%, 2.5/5 mg = 6.8%, and 5 mg = 7.0%) were not significantly different

Table 4. Summary of joint safety with subcutaneous tanezumab treatment or placebo during the full study period*

Patients†	Placebo (n = 514)	2.5 mg (n = 528)	2.5/5 mg (n = 219)	5 mg (n = 284)
Analyzed by the adjudication committee‡	24 (4.7)	41 (7.8)	17 (7.8)	33 (11.6)
Included in the composite joint safety end point‡	0	10 (1.9)	1 (0.5)	9 (3.2)
Rapidly progressive osteoarthritis§	0	9 (1.7)	1 (0.5)	8 (2.8)
Type 1	0	6 (1.1)	1 (0.5)	5 (1.8)
Type 2	0	3 (0.6)	0	3 (1.1)
Primary osteonecrosis	0	0	0	1 (0.4)
Subchondral insufficiency fracture	0	1 (0.2)	0	0
Normal progression of osteoarthritis	22 (4.3)	30 (5.7)	16 (7.3)	19 (6.7)
Other joint outcome‡	2 (0.4)	1 (0.2)	0	5 (1.8)
With ≥1 total joint replacement	23 (4.5)	31 (5.9)	15 (6.8)	20 (7.0)

* Values are the number (%) of patients. Full study comprised both the treatment plus follow-up periods. These periods were 16 + 24 and 24 + 24 weeks for studies A4091056 and A4091057, respectively.
† Data are for studies A4091056 and A4091057 only; A4091027 was not included in the analysis. See Methods section for details.
‡ Other joint outcomes included 2 instances of preexisting conditions in the placebo group; 1 instance of preexisting conditions in the tanezumab 2.5-mg group; and 2 instances of preexisting conditions, 2 instances of no change in joint, and 1 instance of posttraumatic condition in the tanezumab 5-mg group.
§ Rapidly progressive osteoarthritis type 1 was defined as a significant loss of joint space width ≥2 mm (predicated on optimal joint positioning) within approximately 1 year, without gross structural failure. Rapidly progressive osteoarthritis type 2 was defined as abnormal bone loss or destruction, including limited or total collapse of at least 1 subchondral surface, which is not normally present in conventional end-stage osteoarthritis (ref. 16).

from placebo (4.5%); risk difference versus placebo was 1.40 (95% CI –2.17, 5.73) for tanezumab 2.5 mg ($P = 0.443$), 2.37 (95% CI –2.24, 8.60) for tanezumab 2.5/5 mg ($P = 0.333$), and 2.57 (95% CI –1.72, 8.10) for tanezumab 5 mg ($P = 0.253$).

TEAEs of APS. TEAEs of APS during the treatment and full study periods are summarized in Table 5 (A4091027, A4091056, and A4091057). Rates of these TEAEs during the treatment period were higher with tanezumab (2.5 mg = 5.1%, 2.5/5 mg = 3.2%, 5 mg = 6.1%, and 10 mg = 12.8%) than placebo (2.2%) and increased with increasing tanezumab dose. Paresthesia and hypoesthesia were the most common adverse events and were reported more frequently in all tanezumab groups than in the placebo group.

Among patients experiencing a TEAE of APS during the treatment period, most had a mild adverse event (placebo = 92.3%, tanezumab 2.5 mg = 74.2%, tanezumab 2.5/5 mg = 85.7%, tanezumab 5 mg = 76.2%, and tanezumab 10 mg = 81.8%), none had a severe or serious event, and only 1 (hypoesthesia in the tanezumab 5-mg group) discontinued treatment as a result.

The mean ± SD/median day of onset for TEAEs of APS during the treatment period was 45.2 ± 37.4/57.0 for placebo, 57.3 ± 46.9/57.0 for tanezumab 2.5 mg, 44.1 ± 36.6/41.0 for tanezumab 2.5/5 mg, 71.3 ± 55.3/61.0 for tanezumab 5 mg, and 53.0 ± 28.5/62.0 for tanezumab 10 mg. The mean ± SD/median duration of these TEAEs was 109.9 ± 148.9/29.0 days for placebo, 66.8 ± 81.3/31.0 days for tanezumab 2.5 mg, 76.9 ± 44.2/54.0 days for tanezumab 2.5/5 mg, 41.7 ± 77.0/16.0 days for

Table 5. Summary of treatment-emergent AEs of abnormal peripheral sensation with subcutaneous tanezumab treatment or placebo*

AEs	Placebo (n = 586)	2.5 mg (n = 602)	2.5/5 mg (n = 219)	5 mg (n = 347)	10 mg (n = 86)
During the treatment period†					
Patients with an AE	13 (2.2)	31 (5.1)	7 (3.2)	21 (6.1)	11 (12.8)
Patients with serious AE	0	0	0	0	0
Patients with severe AE	0	0	0	0	0
Patients discontinuing treatment due to an AE	0	0	0	1 (0.3)	0
Specific AEs					
Paresthesia	6 (1.0)	14 (2.3)	3 (1.4)	14 (4.0)	6 (7.0)
Hypoesthesia	5 (0.9)	11 (1.8)	3 (1.4)	8 (2.3)	5 (5.8)
Burning sensation	1 (0.2)	1 (0.2)	0	2 (0.6)	0
Carpal tunnel syndrome	0	3 (0.5)	0	1 (0.3)	0
Sciatica	1 (0.2)	3 (0.5)	0	1 (0.3)	0
Decreased vibratory sense	3 (0.5)	1 (0.2)	1 (0.5)	1 (0.3)	1 (1.2)
Neuralgia	0	1 (0.2)	0	1 (0.3)	0
Neuropathy peripheral	0	0	0	1 (0.3)	1 (1.2)
Paresthesia oral	0	0	0	1 (0.3)	0
Hypoesthesia oral	1 (0.2)	0	0	0	0
Sensory disturbance	0	0	0	0	1 (1.2)
During the full study period‡					
Patients with an AE	19 (3.2)	41 (6.8)	9 (4.1)	24 (6.9)	12 (14.0)
Patients with serious AE	1 (0.2)	0	0	0	0
Patients with severe AE	1 (0.2)	2 (0.3)	0	0	0
Specific AEs					
Paresthesia	7 (1.2)	15 (2.5)	3 (1.4)	14 (4.0)	6 (7.0)
Hypoesthesia	8 (1.4)	15 (2.5)	5 (2.3)	8 (2.3)	6 (7.0)
Sciatica	4 (0.7)	6 (1.0)	0	3 (0.9)	0
Burning sensation	1 (0.2)	1 (0.2)	0	2 (0.6)	0
Decreased vibratory sense	3 (0.5)	2 (0.3)	1 (0.5)	2 (0.6)	1 (1.2)
Carpal tunnel syndrome	0	4 (0.7)	0	1 (0.3)	0
Neuralgia	0	1 (0.2)	0	1 (0.3)	0
Neuropathy peripheral	0	0	0	1 (0.3)	1 (1.2)
Paresthesia oral	0	0	0	1 (0.3)	0
Sensory loss	1 (0.2)	1 (0.2)	0	0	0
Dysesthesia	0	1 (0.2)	0	0	0
Hypoesthesia oral	1 (0.2)	0	0	0	0
Sensory disturbance	0	0	0	0	1 (1.2)

* Values are the number (%). Events of abnormal peripheral sensation could include the terms of 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, or thermal hypoesthesia. AE = adverse event.
† Treatment period was 16, 16, and 24 weeks for studies A4091027, A4091056, and A4091057, respectively.
‡ Full study comprised both the treatment plus safety follow-up periods. These periods were 16 + 8, 16 + 24, and 24 + 24 weeks for studies A40901027, A4091056, and A4091057, respectively.

tanezumab 5 mg, and 35.3 ± 40.7/17.0 days for tanezumab 10 mg. Except for patients in the tanezumab 10-mg group, a majority of patients had resolution of the adverse event by the end of the study (placebo = 12 of 13 [92.3%], tanezumab 2.5 mg = 25 of 31 [80.6%], tanezumab 2.5/5 mg = 6 of 7 [85.7%], tanezumab 5 mg = 19 of 21 [90.5%], and tanezumab 10 mg = 3 of 11 [27.3%]). Notably, particularly regarding resolution, data for the 10-mg dose were derived only from study A4091027, in which safety follow-up was shorter (8 weeks) than in the other studies (24 weeks). The overall profile of TEAEs of APS over the full study period was similar to that of the treatment period.

At the final neurologic examination, ≥92% of patients (across all groups in all 3 trials) had no new or worsened abnormalities, <1.0% had new or worsened abnormalities deemed clinically significant, and overall findings were similar in the tanezumab and placebo groups. In studies A4091056 and A4091057, tanezumab-treated patients required neurologic consultation more frequently (1.8–3.2%) than placebo-treated patients (1.4%) (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24637). Radiculopathy, mononeuropathy, and peripheral polyneuropathy were the most common diagnoses among patients with a consultation, but none occurred in >1.3% of patients in any group, and a dose-dependent response was not observed among tanezumab-treated patients. Radiculopathy and mononeuropathy were more frequent in tanezumab-treated patients (0.5–1.3% and 0–1.3%, respectively) than in placebo-treated patients (0.4% and 0.2%, respectively), though the frequency of peripheral polyneuropathy was similar in the tanezumab group (0–0.5%) and the placebo group (0.2%).

TEAEs potentially associated with sympathetic neuropathy. TEAEs potentially associated with sympathetic neuropathy during the treatment and full study periods are summarized in Table 6 (A4091056 and A4091057). Rates of these TEAEs during the treatment period were 0.8% for placebo, 1.5% for tanezumab 2.5 mg, 0.5% for tanezumab 2.5/5 mg, and 2.8% for tanezumab 5 mg. Exposure-adjusted incidence rates (the number of patients with events/1,000 patient-years) were not significantly different for tanezumab (2.5 mg = 40.4, 2.5/5 mg = 14.7, and 5 mg = 63.2) compared with placebo (21.4); risk difference versus placebo was 19 (95% CI −15.9, 54.0) for tanezumab 2.5 mg (P = 0.286), −6.6 (95% CI −42.3, 29.1) for tanezumab 2.5/5 mg (P = 0.716), and 41.8 (95% CI −6.7, 90.4) for tanezumab 5 mg (P = 0.091). Reports consisted mostly of bradycardia or orthostatic hypotension.

Among patients experiencing a TEAE potentially associated with sympathetic neuropathy during the treatment period, most had a mild adverse event (placebo = 100%, tanezumab 2.5 mg = 87.5%, tanezumab 2.5/5 mg = 100.0%, tanezumab 5 mg = 87.5%), and none had an event that was severe, serious, or led to treatment discontinuation.

Table 6. Summary of treatment-emergent AEs potentially associated with sympathetic neuropathy subcutaneous tanezumab treatment or placebo*

AEs	Placebo (n = 514)†	2.5 mg (n = 528)	2.5/5 mg (n = 219)	5 mg (n = 284)
During the treatment period‡				
Patients with an AE	4 (0.8)	8 (1.5)	1 (0.5)	8 (2.8)
Patients with serious AE	0	0	0	0
Patients with severe AE	0	0	0	0
Patients discontinuing treatment due to an AE	0	0	0	0
Specific AEs				
Bradycardia	3 (0.6)	4 (0.8)	0	4 (1.4)
Orthostatic hypotension	1 (0.2)	3 (0.6)	1 (0.5)	3 (1.1)
Syncope	0	0	0	1 (0.4)
Hypohidrosis	0	1 (0.2)	0	0
Anhidrosis	0	0	0	0
During the full study period§				
Patients with an AE	8 (1.6)	12 (2.3)	2 (0.9)	11 (3.9)
Patients with serious AE	0	0	0	0
Patients with severe AE	0	0	0	0
Specific AEs				
Bradycardia	7 (1.4)	7 (1.3)	1 (0.5)	6 (2.1)
Orthostatic hypotension	1 (0.2)	4 (0.8)	1 (0.5)	4 (1.4)
Syncope	0	0	0	1 (0.4)
Hypohidrosis	0	1 (0.2)	0	0
Anhidrosis	0	0	0	0

* Values are the number (%). AE = adverse event.
† Data are for studies A4091056 and A4091057 only; A4091027 was not included in the analysis. See Methods section for details.
‡ Treatment period was 16 and 24 weeks for studies A4091056 and A4091057, respectively.
§ Full study comprised both the treatment plus safety follow-up periods. These periods were 16 + 24 weeks and 24 + 24 weeks for studies A4091056 and A4091057, respectively.

The mean ± SD/median day of onset for these TEAEs during the treatment period was 127.3 ± 48.2/128.0 for placebo (n = 4), 93.0 ± 59.2/101.5 for tanezumab 2.5 mg (n = 8), 85.0 (NA)/85.0 for tanezumab 2.5/5 mg (n = 1), and 111.1 ± 71.7/141.5 for tanezumab 5 mg (n = 8). The mean ± SD/median duration for these TEAEs was 47.8 ± 24.1/45.5 days for placebo, 40.1 ± 55.5/18.5 days for tanezumab 2.5 mg, 30.0 (NA)/30.0 days for tanezumab 2.5/5 mg, and 44.9 ± 49.0/16.0 days for tanezumab 5 mg. All patients had resolution of the adverse event.

The overall profile of TEAEs potentially associated with sympathetic neuropathy over the full study period was similar to that of the treatment period. The number of patients having a consultation due to a TEAE potentially associated with sympathetic neuropathy was 11 (2.1%) for placebo, 7 (1.3%) for tanezumab 2.5 mg, 5 (2.3%) for tanezumab 2.5/5 mg, and 5 (1.8%) for tanezumab 5 mg. None were diagnosed with a sympathetic neuropathy.

DISCUSSION

This pooled analysis of data from over 1,800 patients in 3 placebo-controlled studies demonstrates that SC tanezumab was well tolerated in most patients with moderate-to-severe OA of the hip or knee, and no new safety concerns were identified. TEAEs of APS were more common with tanezumab than placebo, though such events were infrequent, predominantly mild, and typically resolved without discontinuing treatment. Joint safety events, predominantly RPOA type 1, were also infrequent but were more common with tanezumab than placebo. Joint safety events, TEAEs of APS, and TEAEs potentially associated with sympathetic neuropathy were generally dose-dependent, with tanezumab 2.5 mg exhibiting a more favorable safety profile than higher doses.

Overall TEAEs during the treatment period occurred at similar rates in the tanezumab groups (39.5–54.8%) and placebo group (51.7%), and most were mild. The only TEAEs that were severe, serious, or led to discontinuation during the treatment period in >1 patient in any tanezumab group were arthralgia and OA. These particular TEAEs are not unexpected given that the studies enrolled patients with moderate-to-severe OA and a history of inadequate response to pharmacologic OA treatment. TEAEs associated with tanezumab in this study (e.g., edema peripheral, hypoesthesia, and paresthesia) have been frequently reported in previous studies of tanezumab. Injection-site reaction and synovial cyst were more often reported with tanezumab 10 mg than placebo, but this dose had relatively few patients since it was discontinued in post-2015 studies.

In post-2015 placebo-controlled studies analyzed here, joint safety events were more common with tanezumab (2.5 mg = 1.9%, 2.5/5 mg = 0.5%, and 5 mg = 3.2%) than placebo (0%). The risk difference for the composite joint safety end point versus placebo was significantly greater for the tanezumab 5-mg group. Rates of TJRs, though numerically higher with tanezumab than placebo, were not significantly different among treatment groups. Rates of the composite joint safety end point and of TJRs were numerically lower with 2.5 mg of tanezumab than with 5 mg of tanezumab. Due to extensive joint safety screening and monitoring procedures, comparing the rate of joint safety events in post-2015 studies with pre-2015 studies is difficult. Similar to pre-2015 studies (where adjudication was conducted retrospectively), however, most tanezumab-treated patients analyzed by the adjudication committee in this post-2015 analysis had an outcome of normal progression of OA (71.4%), and the most common event included in the composite joint safety end point was RPOA. In contrast to pre-2015 studies, RPOA type 1 was more frequently reported than RPOA type 2 in the current analysis, likely due to increased surveillance in post-2015 studies (10). In the current analysis, joint safety events included in the composite joint safety end point occurred primarily in joints that had K/L grade evidence of OA at baseline, with similar frequency in both index (55%) and nonindex (45%) joints. Only 3 events (15%) occurred in a joint with a baseline K/L grade of <2. Most events in the composite joint safety end point (80%) occurred after completion of the treatment period, and 30% led to a TJR. Additional details on these joint events have been described previously (13,14).

Repeated administration of high-dose NGF antibody does not affect healthy bone or joint tissue in monkeys or rodents (18). NGF antibody has not been associated with RPOA in preclinical studies, and the mechanism underlying increased rates of RPOA with tanezumab in human trials is unclear (10,19,20). Several mechanisms have been proposed that may explain the increased risk for joint safety events reported in tanezumab studies, including neuropathic and analgesic arthropathy, preexisting deficits in bone integrity, and NGF-related effects on cartilage repair and load-induced bone formation (10,21). However, patients receiving tanezumab do not exhibit a loss of protective pain sensitivity, which suggests neuropathic arthropathy is an unlikely mechanism. A description of joint safety in a long-term study of tanezumab was recently published (22), and further details of the systematic assessment of joint safety in the tanezumab clinical program will be addressed in future publications.

Due to NGF's ability to modulate nociceptor function, assessment of TEAEs of APS (e.g., hypoesthesia and paresthesia) is pertinent to agents targeting NGF (21,23). TEAEs of APS occurred more frequently during the treatment period with tanezumab (3.2–12.8%) than placebo (2.2%), and occurred in a dose-dependent manner. The rates observed in this study were similar to those observed in previous trials of IV tanezumab at doses of 2.5 mg to 10 mg (typically <5% to 10%) (11,24). However, the current analysis demonstrates that TEAEs of APS among tanezumab-treated patients during the treatment period were mostly mild (none were serious), they rarely led to treatment discontinuation, and except for the 10-mg dose (discontinued in post-2015 trials), they typically resolved. Further, neurologic

examinations and consultations did not provide evidence that tanezumab increases the risk of peripheral polyneuropathy.

In a 24-week study in patients with painful OA, IV tanezumab (5 or 10 mg every 8 weeks) did not produce significant structural changes in Aδ and C fibers (assessed by intraepidermal nerve fiber density [IENF]) or changes in nerve conduction parameters compared with placebo (12). Similarly, in a 16-week study in patients with diabetic peripheral neuropathy, IV tanezumab (20 mg every 8 weeks) was not associated with significant changes in IENF density, and quantitative sensory testing demonstrated that function of small and large sensory fibers of the lower extremities was not altered (25). Though completion of these previous studies was impacted by clinical hold, the studies support the current pooled analysis suggesting that tanezumab treatment, though associated with increased rates of transient and typically mild events of APS versus placebo, may not lead to irreversible changes in peripheral sensory function.

Possible changes in sympathetic neuronal morphology in rodents have been observed with tanezumab (26). In the current analysis, rates of TEAEs potentially associated with sympathetic neuropathy during the treatment period were higher with tanezumab (0.5–2.8%) than placebo (0.8%). These adverse events were almost exclusively bradycardia and orthostatic hypotension. However, since the number of patients with TEAEs potentially associated with sympathetic neuropathy was low (no specific event occurred in >4 patients per group), making conclusions based solely on raw incidence rates is difficult. Exposure-adjusted rates were not significantly different between tanezumab and placebo groups. Further, TEAEs potentially associated with sympathetic neuropathy in tanezumab-treated patients during the treatment period were mostly mild, and all resolved without treatment discontinuation. Notably, while the TEAEs included here are potentially associated with sympathetic neuropathy, they may have etiologies unrelated to sympathetic neuropathy, and no patient was diagnosed with a sympathetic neuropathy following neurologic consultation.

Three studies have assessed the effects of tanezumab (clinically relevant and supratherapeutic doses) on the sympathetic nervous system of adult nonhuman primates. They showed that 6-month exposure to tanezumab decreased sympathetic ganglion volume and neuron size, but such changes were not associated with clinical signs of sympathetic dysfunction and completely reversed when treatment was discontinued (27). No adverse effects on the sympathetic control of cardiovascular function were associated with tanezumab exposure (27). These studies concluded that tanezumab administration (up to 6 months) had no adverse effects on sympathetic neuronal morphology or function and did not cause cell death in adult nonhuman primates (27). These findings, along with results from the current pooled analysis, support a conclusion that tanezumab is not associated with any significant sympathetic safety concerns.

The findings of this pooled analysis are limited by the relatively short trial durations. Most patients received only 1 dose of SC study medication in study A4091027 due to partial clinical hold, while treatment duration was 16–24 weeks (2–3 doses) in post-2015 studies. Thus, our findings may not represent long-term safety of tanezumab treatment, which will be better evaluated in comparator studies of extended duration. In addition, clinical trial settings are strictly controlled and may not fully represent real-world treatment settings. Finally, because clinical development of tanezumab 10 mg was discontinued and not included in post-2015 studies, the 10-mg arm was small (n = 86) compared with other groups (n = 219 to 602), making conclusions about this dose less robust. However, the strength of this analysis resides in the large data set (>1,200) of tanezumab-treated patients. Additionally, the 2 post-2015 trials incorporated extensive neurologic and joint safety monitoring procedures and lengthy follow-up periods (24 weeks), allowing for comprehensive assessment of tanezumab's neurologic and joint safety during and after treatment. Overall, SC tanezumab was well tolerated in most patients. TEAEs of APS (mostly mild and transient) and joint safety events were infrequent but more common with tanezumab (particularly at doses of >2.5 mg) than placebo.

ACKNOWLEDGMENT

Editorial support was provided by Matt Soulsby, PhD, CMPP of Engage Scientific Solutions, and was funded by Pfizer and Eli Lilly and Company.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Berenbaum 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.

Study conception and design. Viktrup, Hickman, Pixton, Brown, Davignon, West.

Analysis and interpretation of data. Berenbaum, Schnitzer, Kivitz, Viktrup, Hickman, Pixton, Brown, Davignon, West.

ROLE OF THE STUDY 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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