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Gender, age, disease severity, body mass index and diabetes may not affect response to subcutaneous tanezumab in patients with osteoarthritis after 16 weeks of treatment. A subgroup analysis of placebo-controlled trials.

RUNNING TITLE: Tanezumab subgroup analysis

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DATA SHARING STATEMENT

Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-studys/study-data-and-results for more information), Pfizer will provide

access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer and Lilly will also consider requests for the protocol, data dictionary and statistical analysis plan. Data may be requested from Pfizer studies 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

TITLE: Gender, age, disease severity, body mass index and diabetes do not affect response to subcutaneous tanezumab in patients with osteoarthritis. A subgroup analyses of placebo-controlled trials.

ABSTRACT

Aim: To assess impact of pre-specified patient characteristics on efficacy and safety of subcutaneous tanezumab in patients with osteoarthritis (OA).

Methods: Data were pooled from two (efficacy; N = 1545) or three (safety; N = 1754) phase 3 placebo-controlled trials. Change from baseline to week 16 in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain, WOMAC Physical Function, and patient global assessment of OA (PGA-OA) scores was compared between tanezumab (2.5 and 5 mg) and placebo groups via analysis of covariance. Treatment-emergent adverse events (TEAEs) were summarized descriptively. Analyses were done in patient subgroups (male or female; age <65, ≥65, or ≥75 years; body mass index [BMI] <25, 25 to <30, 30 to <35, or ≥35 kg/m^2; diabetes or no diabetes; baseline WOMAC Pain score <7 or ≥7; and Kellgren-Lawrence [KL] grade 2, 3, or 4 in the index joint) and the overall population).

Results: In all subgroups, improvements in WOMAC Pain were numerically greater and often statistically significant ($P < .05$) for both tanezumab groups compared with placebo. Results were similar for WOMAC Function and PGA-OA. TEAE profiles were generally consistent across subgroups and similar to the overall population (i.e., slightly higher rates of TEAEs, serious TEAEs, and severe TEAEs with tanezumab relative to placebo) with a few exceptions. Exceptions included females reporting slightly more TEAEs with tanezumab than males, and patients with diabetes reporting slightly more severe TEAEs with tanezumab than patients without diabetes. Additionally, TEAEs were more frequent with tanezumab than placebo in the age ≥65 and ≥75 years, but not the age <65 years, subgroups.

Conclusions: Efficacy and safety/tolerability of tanezumab may not be meaningfully impacted by gender, age, BMI, diabetes status, baseline pain severity or KL grade in the index joint. Conclusions are limited by low patient number in some subgroups. Clinicaltrials.gov: NCT02697773, NCT02709486, NCT01089725.

KEY WORDS: osteoarthritis; tanezumab; treatment response, patient characteristics, pooled analysis

What is already known about this topic?

- Response to pharmacological treatment, in terms of both efficacy and safety, can vary across patients with osteoarthritis.
- Variability may be due to differences in patient demographics, disease characteristics, and comorbid conditions.
- Based on large-scale randomized, placebo-controlled clinical trials, treatment with subcutaneous tanezumab has been shown to improve pain and function in patients with moderate-to-severe osteoarthritis and a history of inadequate response to standard analgesics for osteoarthritis.
- Tanezumab, like other nerve growth factor antibodies, is associated with adverse events related to abnormal peripheral sensation (e.g, paresthesia and hypoesthesia) and joint safety events, predominantly rapidly progressive osteoarthritis, in some patients.

What does this article add?

- We show that the efficacy and safety/tolerability of subcutaneous tanezumab after 16 weeks of treatment may not be meaningfully impacted by gender, age, disease severity, body mass index or diabetes in patients with moderate-to-severe osteoarthritis and a history of inadequate response to standard analgesics for osteoarthritis.

1 INTRODUCTION

Osteoarthritis (OA) represents a substantial global burden and is often associated with significant levels of pain and impairment of physical function.[1] Current OA management concentrates on mitigating these symptoms through a combination of non-pharmacologic (eg, weight loss, exercise, education, cognitive behavioral therapy) and pharmacologic (eg, acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], opioids, duloxetine, intra-articular corticosteroids or hyaluronic acid) approaches.[2-5] Managing OA-related pain, however, is difficult and many patients express dissatisfaction with treatment due to inadequate efficacy or tolerability issues, highlighting an unmet need for new safe and effective therapies.[6-8]

Treatment response (efficacy and safety/tolerability) often varies between patients, even in highly controlled clinical trial settings, and may be attributed to differences in disease severity; patient characteristics such as age, weight, and gender; and the presence of certain comorbidities.[9-11] Therefore, examining the efficacy and safety of a particular therapy in subgroups of patients, based on baseline demographic or clinical characteristics, could help identify subgroups of patients that may or may not respond favorably to treatment.

Tanezumab is a monoclonal antibody against nerve growth factor that is in clinical development for the treatment of the signs and symptoms of moderate-to-severe OA in patients with inadequate treatment response or intolerability to standard OA analgesics (eg, acetaminophen, NSAIDs, opioids). Three randomized, placebo-controlled, phase 3 studies have assessed the efficacy and safety of subcutaneous (SC) tanezumab in such patients.[12-14] The current analysis pooled data from these trials to determine whether response (efficacy and safety/tolerability) to SC tanezumab is affected by patient characteristics including gender, age, body mass index (BMI), diabetes status, baseline pain severity, and Kellgren-Lawrence (KL) grade in the index joint.

2 METHODS

2.1 Data sources

Patient-level data were pooled from two (efficacy: NCT02697773 and NCT02709486) or three (safety: NCT02697773, NCT02709486, and NCT01089725) randomized, placebo-controlled, phase 3 trials of SC tanezumab (**Table 1**).[12-14] Study NCT01089725 was terminated early due to a class-wide partial clinical hold on anti-NGF therapies and 90.5% of treated patients received only 8 weeks of treatment (ie, one dose of study medication at baseline). Thus, this study was excluded from the current efficacy analyses (which were based on week 16 data). However, a majority (70.7%) of treated patients remained in study NCT01089725 for >16 weeks for safety evaluation. Therefore, study NCT01089725 is included in the current safety analyses, which were based on the full study (treatment + follow-up) periods and encompasses safety data from all phase 3, placebo-controlled OA studies of SC tanezumab conducted to date. In study NCT02697773, 87.5% and 79.9% of patients completed the treatment and full study (treatment + follow-up) periods, respectively. In study NCT02709486, 88.3% and 82.0% of patients completed the treatment and full study periods, respectively. All studies were conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. Study protocols were approved by an institutional review board at each site and all patients provided written informed consent.

All studies enrolled patients aged ≥18 years with moderate-to-severe OA of the knee or hip and a history of inadequate response to other OA analgesics. Tanezumab was administered every 8 weeks for 16–24 weeks at doses ranging from 2.5–10 mg. Patients in the tanezumab 2.5/5 mg group of study NCT02697773 were included in the tanezumab 5 mg treatment arm in the current efficacy analyses.* The tanezumab 10 mg treatment arm from study NCT01089725 was not included in the current safety analysis since the 10 mg was not assessed in post-2015 trials NCT02697773 and NCT02709486.[15] Co-primary endpoints in each trial were change in Western

* Subjects were grouped according to their randomized treatment for efficacy analyses and according to the actual treatment for safety analyses, consistent with International Council for Harmonisation and United States Food and Drug Administration guidelines. As a result, if a subject was randomized to tanezumab 2.5/5 mg in study NCT02697773 but discontinued prior to receiving a 5 mg dose, then they would be assigned to the 5 mg group for the current efficacy analyses and the 2.5 mg group for the current safety analyses.

Ontario and McMaster Universities Osteoarthritis Index (WOMAC[†]) Pain, WOMAC Physical Function, and patient global assessment of OA (PGA-OA) scores from baseline to end of the treatment period.

2.2 Subgroups of interest

In the current study, efficacy and safety analyses were done in the overall pooled patient populations and in pre-specified subgroups of interest that included male or female; age <65, ≥65, or ≥75 years; BMI of <25, 25 to <30, 30 to <35, or ≥35 kg/m^2; diabetes or no diabetes; baseline WOMAC Pain score <7 or ≥7 (scores range from 0–10 with ≥7 representing severe pain); and KL grade 2, 3, or 4 in the index joint (KL grades of 0, 1, 2, 3, and 4 represent no, doubtful, minimal, moderate, and severe OA, respectively). Index joint was defined as the most painful joint at screening with a qualifying WOMAC Pain score and radiographic KL grade as confirmed by a central reader. Patients were included in the diabetes subgroup if they had a medical history of type 1 or type 2 diabetes mellitus, hyperglycemia, or had a baseline hemoglobin A1c ≥6.5%.

2.3 Efficacy analysis

Efficacy was based on change, from baseline to week 16, in WOMAC Pain, WOMAC Physical Function, and PGA-OA scores using patient-level data derived from studies NCT02697773 and NCT02709486. Week 16 was chosen since it was the longest treatment duration common to both studies. WOMAC Pain and Physical Function scores range from 0–10, with higher score indicating greater pain severity or function impairment, respectively. PGA-OA scores range from 1–5, with higher scores indicating worse disease status.

Least squares (LS) mean changes from baseline to week 16 in these measures were assessed for the placebo, tanezumab 2.5 mg, and tanezumab 5 mg treatment arms using an analysis of covariance (ANCOVA) model including terms for baseline score of the corresponding endpoint, baseline daily average pain score, index joint (hip or knee), treatment, and study. A multiple imputation approach was used for missing data, dependent

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on the reason for missing data. For patients with missing data due to discontinuation prior to week 16 for lack of efficacy, for an adverse event, or death, imputation was based on sampling from a normal distribution using a mean value equal to the patient's baseline efficacy value and the SD (over all treatment groups) of the observed efficacy data at week 16. For patients with missing data for any other reason, imputation was based on sampling from a normal distribution using a mean value of the patient's last observed efficacy value and SD (over all treatment groups) of the observed efficacy data at week 16. The proportion of patients achieving ≥50% (substantial) and ≥30% (moderate) improvement from baseline to week 16 in WOMAC Pain was assessed using a logistic regression method with terms for baseline WOMAC Pain subscale score and baseline daily average pain score, and classification variables of index joint, treatment, and study. A mixed last-observation carried forward/baseline-observation carried forward approach was used for missing data.

Treatment comparisons were based on LS mean differences from placebo (or odds ratios for 50% and 30% responder data), associated 95% confidence intervals, and *P*-values. For all comparisons, nominal significance was declared if the two-tailed test for the difference between treatment groups was significant at the 0.05 level.

2.4 Safety analysis

Safety was based on the occurrence of treatment-emergent adverse events (TEAEs) over the full study (treatment + safety follow-up combined) periods in studies NCT02697773 (16-week treatment + 24-week follow-up), NCT02709486 (24-week treatment + 24-week follow-up), and NCT01089725 (16-week treatment + 8-week follow-up). TEAEs were coded using Medical Dictionary for Regulatory Activities v22.0, with severity assessed by site investigators, and were summarized descriptively in the overall patient population and in the subgroups of interest for the placebo, tanezumab 2.5 mg, and tanezumab 5 mg treatment arms.

3 RESULTS

3.1 Efficacy

3.1.1 Patient demographics

The overall efficacy population included 1545 patients (placebo = 514, tanezumab 2.5 mg = 514, tanezumab 5 mg = 517). The population was predominantly female (67.3%), white (80.5%), and had an approximate mean age of 63 years (**Table 2**). OA disease duration ranged from 7.9 to 8.7 years across groups, with a majority (84.1%) of patients having knee as the index joint. Mean baseline WOMAC Pain, WOMAC Physical Function, and PGA-OA scores were 6.9, 7.0, and 3.5, respectively, in all treatment groups.

3.1.2 Change in WOMAC Pain, WOMAC Physical Function, and PGA-OA

Improvements in WOMAC Pain from baseline to week 16 were numerically greater and often statistically significant ($P < .05$) in both tanezumab groups compared with placebo, irrespective of gender, age, BMI, diabetes status, baseline WOMAC Pain score, or KL grade in the index joint (**Figure 1;** the number of patients in each subgroup can be seen within the figure). The only improvements that did not reach the level of significance for tanezumab vs placebo were the 2.5 mg dose in the male subgroup, the 2.5 mg dose in the age ≥75 years subgroup, the 5 mg dose in the <25 kg/m^2 BMI subgroup, both doses in the ≥35 kg/m^2 BMI subgroup, the 2.5 mg dose in the patients with diabetes subgroup, and both doses in the KL grade 2 in the index joint subgroup. In the overall patient population (all subgroups combined), improvements in WOMAC Pain from baseline to week 16 were significantly greater in both tanezumab groups compared with the placebo group. LS mean (standard error) change from baseline was –3.1 (0.12) for tanezumab 2.5 mg and –3.2 (0.12) for tanezumab 5 mg compared with –2.5 (0.12) for placebo (both tanezumab groups $P < .0001$ vs placebo). Improvements in WOMAC Physical Function (**Supplemental Figure 1**) and PGA-OA (**Supplemental Figure 2**) also favored tanezumab over placebo in all the subgroups of interest and often reached the level of significance.

3.1.3 Proportion of patients with ≥50% or ≥30% improvement in WOMAC Pain

The proportion of patients achieving ≥50% improvement in WOMAC Pain from baseline to week 16 was numerically greater and often statistically significant ($P < .05$) in both tanezumab groups compared with placebo, irrespective of gender, age, BMI, diabetes status, baseline WOMAC Pain score, or KL grade in the index joint (**Figure 2**). The only proportion of 50% responders that did not reach the level of significance for tanezumab vs placebo were the 2.5 mg dose in the age ≥75 years subgroup, the 5 mg dose in the <25 kg/m^2 BMI subgroup, both doses in the ≥35 kg/m^2 BMI subgroup, both doses in the patients with diabetes subgroup, and both doses in the KL grade 2 in the index joint subgroup. In the overall patient population (all subgroups combined), the proportion of patients achieving ≥50% improvement in WOMAC Pain was significantly greater in both tanezumab (2.5 mg = 51.9%, 5 mg = 51.8%; both P < .0001) groups compared with the placebo (36.8%) group in the overall population. Similar to the 50% responder threshold, the proportion of patients achieving ≥30% improvement in WOMAC Pain in the tanezumab (2.5 mg = 68.0%, 5 mg = 69.4%; both $P < .0001$) groups was significantly greater than the placebo (55.6%) group in the overall population and in many subgroups of interest (**Supplemental Figure 3**).

3.2 Safety

3.2.1 Patient demographics

The overall safety population included 1754 patients (placebo = 586, tanezumab 2.5 mg = 602, and tanezumab 5 mg = 566). Demographics of the overall safety population (**Table 3**) were similar to those of the overall efficacy population.

3.2.2 Adverse events (AEs)

TEAEs in the overall safety population are summarized in **Table 4**. TEAE rates were largely similar in the tanezumab groups (2.5 mg = 62.8%, 5 mg = 62.0%) relative to the placebo group (60.9%). Rates of serious (placebo = 3.6%, tanezumab 2.5 mg = 5.3%, tanezumab 5 mg = 5.5%) and severe (placebo = 3.9%, tanezumab 2.5 mg = 4.7%, tanezumab 5 mg = 6.4%) TEAEs were slightly higher with tanezumab relative to placebo. Rates of

treatment discontinuations due to TEAEs, however, were lower in the tanezumab groups (2.5 mg = 1.3%, 5 mg = 0.9%) than the placebo group (2.0%). Among common TEAEs (TEAEs occurring in ≥3% of patients in any treatment group), rates of peripheral edema (placebo = 0.3%, tanezumab 2.5 mg = 1.2%, tanezumab 5 mg = 3.2%) and paresthesia (placebo = 1.2%, tanezumab 2.5 mg = 2.5%, tanezumab 5 mg = 3.0%) were at least twice as high in both tanezumab groups than in the placebo group.

A summary of AEs in the subgroups of interest can be found in **Supplemental Tables 1–6**. In general, the profile of TEAEs (proportion of overall TEAEs, serious TEAEs, severe TEAEs, discontinuations due to TEAEs, and common TEAEs) in most subgroups of interest was broadly similar to the profile in the overall patient population, and only a few differences were noted. For example, females reported numerically more TEAEs with tanezumab (2.5 mg = 64.8%, 5 mg = 66.0%) than males (2.5 mg = 58.8%, 5 mg = 54.5%). In addition, overall TEAEs were more frequent in both tanezumab groups than the placebo group in the age ≥65 and age ≥75 years, but not the age <65 years, subgroups. Finally, patients with diabetes reported more severe TEAEs with tanezumab (placebo = 2.2%, tanezumab 2.5 mg = 7.8%, tanezumab 5 mg = 12.0%) than patients without diabetes (placebo = 4.3%, tanezumab 2.5 mg = 4.0%, tanezumab 5 mg = 5.2%), though overall rates of discontinuations due to TEAEs were similar (1.1%–2.2%).

4 DISCUSSION

In this analysis of over 1500 patients with moderate-to-severe OA of the knee and hip and a history of inadequate response to other standard OA analgesics, improvements in pain, function, and PGA-OA favored SC tanezumab (2.5 mg and 5 mg) over placebo irrespective of gender, age, BMI, diabetes status, baseline pain severity, or KL grade in the index joint. The TEAE profile of tanezumab was mostly consistent among the subgroups and broadly similar to the profile in the overall patient population.

The subgroups in these analyses were selected to determine the consistency of treatment response across a number of demographic and clinical variables. Evidence suggests that males and females experience pain, and respond to some treatments, differently.[16-18] Though the underlying mechanisms are unknown, this may be due to inherent differences in drug metabolism, levels of drug receptors, psychological factors, the endocrine system, or processing pathways in males and females.[19-21] Advanced age is also known to affect response to small molecule analgesics due to physiological changes associated with aging, including increased drug absorption due to slowing of the gastrointestinal tract, decreased drug metabolism due to decreased hepatic function, and reduced renal excretion.[22,23] In addition to age, body weight and BMI can also affect the pharmacokinetics of drug therapies by affecting absorption, distribution, and clearance. Likewise, diabetes can potentially affect treatment response via changes in drug pharmacokinetics due to altered drug absorption (via changes in blood flow in subcutaneous adipose tissue or muscle tissue) or excretion (via decreased renal function).[24] The presence of diabetic peripheral neuropathy, which alters nociceptive signaling, could also affect analgesic responses in patients with diabetes.[25] Finally, disease severity may also affect response to treatment. There is some evidence in knee OA, for example, that radiologic severity of disease (assessed by KL grading) may be a possible predictor of efficacy response to intra-articular corticosteroid injection.[26,27] It should be noted, however, that OA severity as assessed by radiographic KL grading does not necessarily correlate with OA-related pain severity.[28,29] Thus, we assessed both objective (KL grade) and subjective (baseline pain scores in the index joint) measures of OA severity.

Improvements in WOMAC Pain, WOMAC Function, and PGA-OA favored tanezumab over placebo in all subgroups and many, but not all, comparisons reached the level of statistical significance. Due to the low number of patients in many of the subgroups, however, it is not surprising that not all comparisons vs placebo were significant. Low patient numbers were particularly evident in the age ≥75 years (56–64), patients with diabetes (86–92), and <25 kg/m^2 BMI (64–72) subgroups. LS mean differences versus placebo in these subgroups with low patient numbers were similar to (and often greater than) the observed LS mean differences

versus placebo observed in subgroups with greater patient numbers, but there was greater variability (i.e. 95% CIs) in the low patient number subgroups that contributed to the lack of statistical significance. In addition, a higher placebo response in the KL grade 2 subgroup (LS mean change from baseline in WOMAC Pain = –2.9) relative to the KL grade 3 subgroup (LS mean change from baseline in WOMAC Pain = –2.6) and, particularly, the KL grade 4 subgroup (LS mean change from baseline in WOMAC Pain = –1.8) may have contributed to the lack of significant effect for both doses of tanezumab in the KL grade 2 subgroup. This observation also suggests that there may be an inverse correlation between the magnitude of the placebo effect and the degree of structural OA severity. The LS mean change for the tanezumab groups was more similar across all KL grades, ranging from –2.9 to –3.4.

Overall, conclusions on the clinical significance of treatment effect in the various subgroups are difficult to make due to the limited number of patients in some subgroups and the fact that subgroups were not directly compared to each other. It is notable, however, that statistically greater proportions of tanezumab-treated patients achieved ≥30% and ≥50% improvement in WOMAC Pain compared to placebo-treated patients in most subgroups . These 30% and 50% thresholds represent moderate and substantial, respectively, improvements in pain for patients with chronic pain conditions and suggests that the benefits observed in this analysis were clinically meaningful in many of the subgroups.[30]

Though the TEAE profile of tanezumab among the subgroups of interest was broadly consistent with the overall population, there were a few instances where the profile appeared somewhat different across subgroups. Females reported more TEAEs with tanezumab than males. It is possible that this may represent a modest, but real, difference between the genders as patient numbers were high in each subgroup and previous studies suggest that women experience (or report) adverse drug reactions at a higher frequency than men across all drug classes.[31] TEAE rates were higher among tanezumab-treated patients than placebo-treated patients in older (aged ≥65 and ≥75 years) patients, but not in younger (aged <65 years) patients. This could

represent a difference in tanezumab's safety profile among older patients since the risk of AEs to drug treatments in general, as well as the risk for drug-drug interactions, is increased with advanced age.[32] A more likely reason for this discrepancy, however, may be due to the higher TEAE rates among placebo-treated patients in the age <65 years subgroup (65.9%) relative to the age ≥65 years (50.7%) and age ≥75 years (54.7%) subgroups. Further, TEAE rates among tanezumab-treated patients were more comparable across the three age subgroups (58.6–65.7%) and similar to the TEAE rate among all tanezumab-treated patients in the overall safety population (62.0–62.8%).

Joint safety events, particularly rapidly progressive OA, are associated with nerve growth factor antibodies such as tanezumab in some patients.[13-15] Though a detailed analysis of joint safety is beyond the scope of this paper, we note that OA was reported as an AE (representing new [non index joint] or worsening [index joint] cases of OA) more often among tanezumab-treated patients than among placebo-treated patients in the overall safety population and in many subgroups of interest.

Our findings regarding the use of SC tanezumab in patients with moderate-to-severe OA and a history of inadequate response to other analgesics agree with, and build upon, a previous analysis of intravenous (IV) tanezumab in patients with OA.[33] Like the current SC analysis, the previous IV analysis demonstrated that tanezumab provided significant improvement of pain, function, and global disease status in subpopulations of patients based on age, baseline pain severity, diabetes status, and BMI without identifying new safety risks in those subpopulations.[33] Our findings are also in broad agreement with a recent pharmacokinetic analysis of IV and SC data suggesting that tanezumab dosing does not need to be adjusted based on factors such as gender, age, or BMI.[submitted manuscript]

Limitations of this study include the low number of patients in many subgroups and the post-hoc nature of our analyses. In addition, comparisons were with placebo, and different subgroups were not directly

compared with each other (eg, male vs female). Likewise, the two doses of tanezumab were not directly compared with each other and conclusions on relative efficacy are limited. Efficacy was based on changes in pain after 16 weeks (two doses) of treatment and findings should not be generalized to longer treatment durations. Finally, it should be noted that the overall efficacy and safety populations were largely female (approximately two-thirds of all patients) and white (over 80% of patients). This may limit the ability to generalize our findings to other OA populations, particularly those of predominantly non-white racial groups. However, strengths of the study include overall large patient population from which the subgroups were derived and similarity in trial design for the studies included in the analysis.

5 CONCLUSIONS

In summary, treatment with SC tanezumab (at doses of 2.5 or 5 mg) every 8 weeks provided improvements over placebo (often reaching the level of statistical significance) in pain, function, and overall OA disease status in all patient subgroups, which were based on gender, age, BMI, diabetes status, baseline pain severity, or KL grade in the index joint. The overall TEAE profile of tanezumab was mostly consistent among the subgroups, broadly similar to the profile in the overall patient population, and no new safety risks were identified in the subgroups. These findings suggest that tanezumab efficacy is maintained regardless of comorbidity, disease severity, and selected clinical criteria in patients with moderate-to-severe OA and a history of inadequate response to standard OA analgesics. Conclusions, however, are limited by the small number of patients in some subgroups.

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[TABLES]

TABLE 1. Summary of studies included in the analysis

Study	Key inclusion criteria	Duration	Treatment arms (n patients)	Rescue medication	NSAID use
NCT02697773	• Age ≥18 years • OA of the knee or hip[†] • WOMAC Pain ≥5 • WOMAC Physical Function ≥5 • PGA-OA of fair, poor, or very poor • History of inadequate pain relief with acetaminophen, and a history of inadequate pain relief with, or contraindication/intolerability to, oral NSAIDs, and either tramadol or an opioid (or unwilling to take opioids)	• 16-week treatment • 24-week safety follow-up	• Placebo (232) • SC tanezumab 2.5 mg (231) • SC tanezumab 2.5/5 mg[‡] (233)	• Acetaminophen/paracetamol at doses ≤3000 mg/day for up to 3 days/week during the treatment period	• 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
NCT02709486	• Age ≥18 years • OA of the knee or hip[†] • WOMAC Pain ≥5 • WOMAC Physical Function ≥5	• 24-week treatment	• Placebo (282) • SC tanezumab 2.5 mg (283) • SC tanezumab 5 mg (284)	• Acetaminophen/paracetamol at doses ≤4000 mg/day for up to 5 days/week	• 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

	• PGA-OA of fair, poor, or very poor • History of inadequate pain relief with acetaminophen, and a history of inadequate pain relief with, or contraindication/intolerability to, oral NSAIDs, and either tramadol or an opioid (or unwilling to take opioids)	• 24-week safety follow-up		during the treatment period and then daily during safety follow-up	dosing interval was not to exceed 10 days and total NSAID use was not to exceed 40 days between baseline visit and 16 weeks after last SC dose
NCT01089725	• Age ≥18 years • OA of the knee[†] • WOMAC Pain ≥5 • WOMAC Physical Function ≥4 • PGA-OA of fair, poor, or very poor • Unwilling or unable to take non-opiate pain medication, or have a history of inadequate pain relief with non-opiate pain medications, or be candidates for invasive interventions	• 16-week treatment[§] • 8-week safety follow-up	• Placebo (72) • SC tanezumab 2.5 mg (74) • SC tanezumab 5 mg (63) • SC tanezumab 10 mg (86) • IV tanezumab 10 mg (84)	• Acetaminophen/paracetamol at doses ≤3000 mg/day for up to 3 days/week during the treatment period and then daily during safety follow-up	• Limited use of NSAIDs was permitted on an occasional basis for self-limiting conditions unrelated to OA

Abbreviations: IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; PGA-OA, patient global assessment of osteoarthritis; SC, subcutaneous; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

[†]Diagnosed per American College of Rheumatology criteria with radiographic confirmation (Kellgren-Lawrence grade ≥2).

[‡]Patients received 2.5 mg at baseline and 5 mg at week 8. These patients were included in the 5 mg group in the current analyses.

[§]Due to early termination, 90.5% of patients received only 8 weeks of treatment (ie, one dose of study medication at baseline). As a result, study NCT01089725 was included in the current safety analysis but excluded from the 16-week efficacy analysis.

[¶]10 mg SC and IV arms were not included in the current analyses since the 10 mg dose was discontinued prior to studies NCT02697773 and NCT02709486.

TABLE 2. Demographics of the overall efficacy population (NCT02697773 and NCT02709486)

Characteristic	Placebo (n = 514)	Tanezumab 2.5 mg (n = 514)	Tanezumab 5 mg (n = 517)
Gender, n (%)			
Male	161 (31.3)	171 (33.3)	173 (33.5)
Female	353 (68.7)	343 (66.7)	344 (66.5)
Mean (SD) age, years	62.5 (9.8)	63.2 (9.4)	63.4 (9.9)
Race, n (%)			
White	403 (78.4)	423 (82.3)	418 (80.9)
Black or African American	60 (11.7)	43 (8.4)	50 (9.7)
Asian	47 (9.1)	43 (8.4)	42 (8.1)
Other	4 (0.8)	5 (1.0)	7 (1.4)
Mean (SD) disease duration, years	8.7 (8.1)	7.9 (7.8)	8.3 (7.2)
Mean (SD) baseline WOMAC Pain[†]	6.9 (1.1)	6.9 (1.1)	6.9 (1.1)
Mean (SD) baseline WOMAC Physical Function[‡]	7.0 (1.1)	7.0 (1.0)	7.0 (1.1)
Mean (SD) baseline PGA-OA[§]	3.5 (0.6)	3.5 (0.6)	3.5 (0.6)
Index joint, n (%)[¶]			
Hip	80 (15.6)	83 (16.1)	83 (16.1)

Knee	434 (84.4)	431 (83.9)	434 (83.9)

Abbreviations: PGA-OA, patient global assessment of osteoarthritis; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

[†]Scores range from 0–10, with higher scores indicating greater pain severity.

[‡]Scores range from 0–10, with higher scores indicating greater functional impairment.

[§]Scores range from 1 = very good to 5 = very poor.

[¶]Index joint was defined as the most painful joint at baseline with a qualifying WOMAC Pain score and Kellgren-Lawrence grade as confirmed by a central reader.

TABLE 3. Demographics of the overall safety population (NCT02697773, NCT02709486 and NCT01089725)

Characteristic	Placebo (n = 586)	Tanezumab 2.5 mg (n = 602)	Tanezumab 5 mg (n = 566)
Gender, n (%)			
Male	186 (31.7)	199 (33.1)	198 (35.0)
Female	400 (68.3)	403 (66.9)	368 (65.0)
Mean (SD) age, years	62.3 (10.2)	62.9 (9.5)	63.2 (10.1)
Race, n (%)			
White	463 (79.0)	494 (82.1)	458 (80.9)
Black or African American	70 (11.9)	54 (9.0)	56 (9.9)
Asian	49 (8.4)	47 (7.8)	44 (7.8)
Other	4 (0.7)	7 (1.2)	8 (1.4)
Mean (SD) disease duration, years	8.9 (8.4)	8.0 (7.9)	8.4 (7.5)
Mean (SD) baseline WOMAC Pain[†]	7.0 (1.1)	7.0 (1.2)	7.0 (1.2)
Mean (SD) baseline WOMAC Physical Function[‡]	7.0 (1.1)	7.0 (1.1)	7.0 (1.1)
Mean (SD) baseline PGA-OA[§]	3.5 (0.6)	3.5 (0.6)	3.5 (0.6)
Index joint, n (%)[¶]			
Hip	80 (13.7)	88 (14.6)	78 (13.8)

Knee	506 (86.3)	514 (85.4)	488 (86.2)

Abbreviations: PGA-OA, patient's global assessment of osteoarthritis; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

[†]Scores range from 0–10, with higher scores indicating greater pain severity.

[‡]Scores range from 0–10, with higher scores indicating greater functional impairment.

[§]Scores range from 1 = very good to 5 = very poor.

[¶]Index joint was defined as the most painful joint at baseline with a qualifying WOMAC Pain score and Kellgren-Lawrence grade as confirmed by a central reader.

TABLE 4. Summary of TEAEs the overall safety population over the full study (treatment + follow-up) period[†] (NCT02697773, NCT02709486, and NCT01089725)

Patients, n (%)	Placebo (n = 586)	Tanezumab 2.5 mg (n = 602)	Tanezumab 5 mg (n = 566)
With any TEAE	357 (60.9)	378 (62.8)	351 (62.0)
With any serious TEAE	21 (3.6)	32 (5.3)	31 (5.5)
With any severe TEAE	23 (3.9)	28 (4.7)	36 (6.4)
Discontinued treatment due to TEAE	12 (2.0)	8 (1.3)	5 (0.9)
Discontinued study due to TEAE	5 (0.9)	10 (1.7)	2 (0.4)
Common TEAEs[‡]			
Arthralgia	95 (16.2)	91 (15.1)	83 (14.7)
Nasopharyngitis	49 (8.4)	61 (10.1)	47 (8.3)
Back pain	32 (5.5)	**42 (7.0)**	**34 (6.0)**
Headache	33 (5.6)	34 (5.6)	24 (4.2)
Osteoarthritis	19 (3.2)	**22 (3.7)**	**24 (4.2)**
Pain in extremity	16 (2.7)	**26 (4.3)**	**21 (3.7)**
Musculoskeletal pain	23 (3.9)	31 (5.1)	20 (3.5)
Fall	21 (3.6)	35 (5.8)	19 (3.4)

Upper respiratory tract infection	13 (2.2)	**18 (3.0)**	**19 (3.4)**
Joint swelling	13 (2.2)	**17 (2.8)**	**18 (3.2)**
Peripheral edema	2 (0.3)	**7 (1.2)**	**18 (3.2)**
Paresthesia	7 (1.2)	**15 (2.5)**	**17 (3.0)**

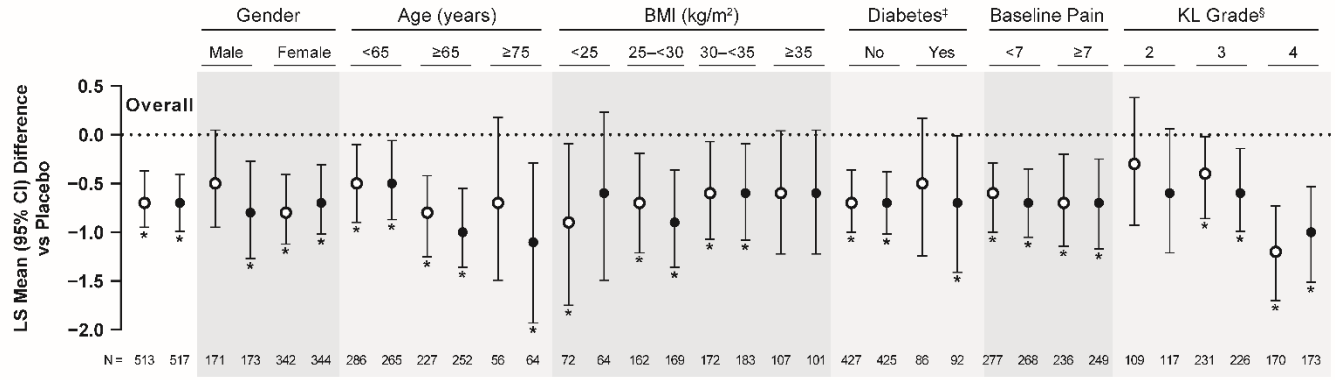
Abbreviations: TEAE, treatment-emergent adverse event.

[†]This is a total of 40, 48, and 24 weeks for NCT02697773, NCT02709486, and NCT01089725, respectively.

[‡]Reported in ≥3% of patients in any treatment group. Bolding indicated the event was reported at a higher frequency in both tanezumab groups relative to the placebo group.

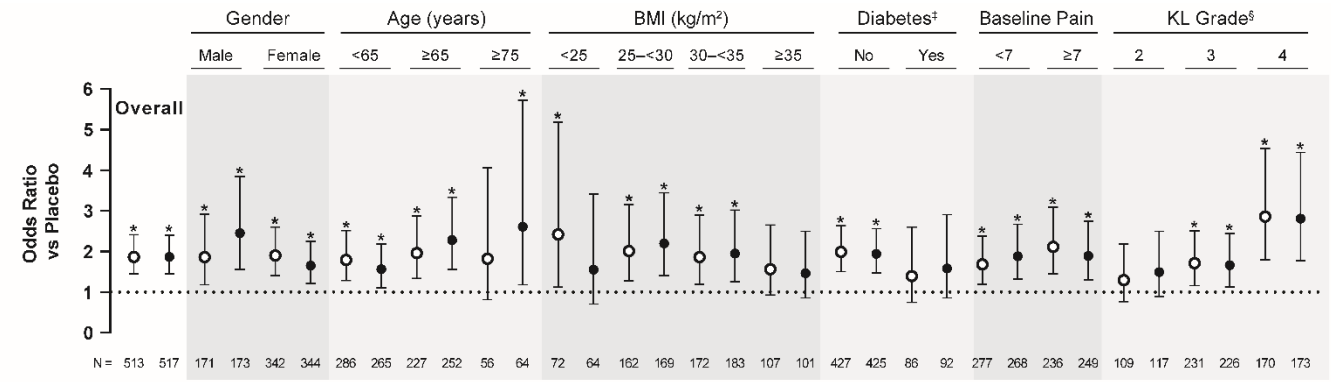
FIGURES

Figure 1. Change in WOMAC Pain[†] from baseline to week 16 (NCT02697773 and NCT02709486).



Symbols: ○ = tanezumab 2.5 mg; ● = tanezumab 5 mg. [†]Scores range from 0–10, with higher scores indicating greater pain severity. [‡]Patients were included in the diabetes group if they had a medical history of hyperglycemia, type 1 or type 2 diabetes mellitus, or a baseline hemoglobin A1c ≥6.5%. [§]In the index joint; defined as the most painful joint at screening with a qualifying WOMAC Pain score and KL grade as confirmed by a central reader. N represents the number of patients, with available baseline data, included in the analysis. *$P < .05$ vs placebo. BMI, body mass index; CI, confidence interval; KL, Kellgren-Lawrence; LS, least squares; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

Figure 2. Proportion of patients achieving ≥50% improvement in WOMAC Pain[†] from baseline to week 16 (NCT02697773 and NCT02709486).



Symbols: ○ = tanezumab 2.5 mg; ● = tanezumab 5 mg. [†]Scores range from 0–10, with higher scores indicating greater pain severity. [‡]Patients were included in the diabetes group if they had a medical history of hyperglycemia, type 1 or type 2 diabetes mellitus, or a baseline hemoglobin A1c ≥6.5%. [§]In the index joint; defined as the most painful joint at screening with a qualifying WOMAC Pain score and KL grade as confirmed by a central reader. N represents the number of patients, with available baseline data, included in the analysis. *P < .05 vs placebo. BMI, body mass index; KL, Kellgren-Lawrence; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

[Supplementary Material]

Supplemental Table 1. Summary of TEAEs over the full study (treatment + follow-up) period[†] in gender subgroups of the safety population (NCT02697773, NCT02709486, and NCT01089725)

	Male			Female		
Patients, n (%)	**Placebo (n = 186)**	**Tanezumab 2.5 mg (n = 199)**	**Tanezumab 5 mg (n = 198)**	**Placebo (n = 400)**	**Tanezumab 2.5 mg (n = 403)**	**Tanezumab 5 mg (n = 368)**
With any TEAE	115 (61.8)	117 (58.8)	108 (54.5)	242 (60.5)	261 (64.8)	243 (66.0)
With any serious TEAE	7 (3.8)	11 (5.5)	9 (4.5)	14 (3.5)	21 (5.2)	22 (6.0)
With any severe TEAE	5 (2.7)	11 (5.5)	13 (6.6)	18 (4.5)	17 (4.2)	23 (6.3)
Discontinued treatment due to TEAE	2 (1.1)	3 (1.5)	1 (0.5)	10 (2.5)	5 (1.2)	4 (1.1)
Discontinued study due to TEAE	0	3 (1.5)	0	5 (1.3)	7 (1.7)	2 (0.5)
Common TEAEs[‡]						
Arthralgia	29 (15.6)	29 (14.6)	22 (11.1)	66 (16.5)	62 (15.4)	61 (16.6)
Nasopharyngitis	16 (8.6)	20 (10.1)	12 (6.1)	33 (8.3)	**41 (10.2)**	**35 (9.5)**
Back pain	12 (6.5)	15 (7.5)	9 (4.5)	20 (5.0)	**27 (6.7)**	**25 (6.8)**
Pain in extremity	5 (2.7)	**9 (4.5)**	**7 (3.5)**	11 (2.8)	**17 (4.2)**	**14 (3.8)**
Diarrhea	3 (1.6)	**6 (3.0)**	**7 (3.5)**	6 (1.5)	4 (1.0)	6 (1.6)
Osteoarthritis	10 (5.4)	9 (4.5)	7 (3.5)	9 (2.3)	**13 (3.2)**	**17 (4.6)**
Upper respiratory tract infection	4 (2.2)	2 (1.0)	7 (3.5)	9 (2.3)	**16 (4.0)**	**12 (3.3)**
Joint swelling	3 (1.6)	**8 (4.0)**	**5 (2.5)**	10 (2.5)	9 (2.2)	13 (3.5)

Fall	8 (4.3)	12 (6.0)	4 (2.0)	13 (3.3)	**23 (5.7)**	**15 (4.1)**
Musculoskeletal pain	9 (4.8)	9 (4.5)	3 (1.5)	14 (3.5)	**22 (5.5)**	**17 (4.6)**
Headache	8 (4.3)	6 (3.0)	3 (1.5)	25 (6.3)	28 (6.9)	21 (5.7)
Peripheral edema	0	**2 (1.0)**	**4 (2.0)**	2 (0.5)	**5 (1.2)**	**14 (3.8)**
Hypertension	6 (3.2)	3 (1.5)	3 (1.5)	7 (1.8)	4 (1.0)	5 (1.4)
Paresthesia	2 (1.1)	2 (1.0)	2 (1.0)	5 (1.3)	**13 (3.2)**	**15 (4.1)**
Hypoesthesia	2 (1.1)	4 (2.0)	2 (1.0)	6 (1.5)	**11 (2.7)**	**11 (3.0)**
Bronchitis	0	**3 (1.5)**	**1 (0.5)**	13 (3.3)	13 (3.2)	3 (0.8)
Urinary tract infection	1 (0.5)	2 (1.0)	0	7 (1.8)	**13 (3.2)**	**8 (2.2)**
	-		-			

Abbreviations: TEAE, treatment-emergent adverse event.

[†]This is a total of 40, 48, and 24 weeks for NCT02697773, NCT02709486, and NCT01089725, respectively.

[‡]Reported in ≥3% of patients in any treatment group. Bolding indicated the event was reported at a higher frequency in both tanezumab groups relative to the placebo group.

Supplemental Table 2. Summary of TEAEs over the full study (treatment + follow-up) period[†] in age subgroups of the safety population (NCT02697773, NCT02709486, and NCT01089725)

	Aged <65 years			Aged ≥65 years			Aged ≥75 years		
Patients, n (%)	**Placebo (n = 340)**	**Tanezumab 2.5 mg (n = 346)**	**Tanezumab 5 mg (n = 295)**	**Placebo (n = 246)**	**Tanezumab 2.5 mg (n = 256)**	**Tanezumab 5 mg (n = 271)**	**Placebo (n = 67)**	**Tanezumab 2.5 mg (n = 64)**	**Tanezumab 5 mg (n = 68)**
With any TEAE	224 (65.9)	221 (63.9)	173 (58.6)	133 (54.1)	157 (61.3)	178 (65.7)	34 (50.7)	41 (64.1)	44 (64.7)
With any serious TEAE	13 (3.8)	18 (5.2)	14 (4.7)	8 (3.3)	14 (5.5)	17 (6.3)	3 (4.5)	2 (3.1)	6 (8.8)
With any severe TEAE	14 (4.1)	14 (4.0)	15 (5.1)	9 (3.7)	14 (5.5)	21 (7.7)	3 (4.5)	5 (7.8)	5 (7.4)
Discontinued treatment due to TEAE	8 (2.4)	3 (0.9)	1 (0.3)	4 (1.6)	5 (2.0)	4 (1.5)	0	2 (3.1)	2 (2.9)
Discontinued study due to TEAE	2 (0.6)	5 (1.4)	0	3 (1.2)	5 (2.0)	2 (0.7)	1 (1.5)	1 (1.6)	0
Common TEAEs[‡]									
Arthralgia	63 (18.5)	59 (17.1)	37 (12.5)	32 (13.0)	32 (12.5)	46 (17.0)	9 (13.4)	9 (14.1)	7 (10.3)
Nasopharyngitis	30 (8.8)	35 (10.1)	23 (7.8)	19 (7.7)	**26 (10.2)**	**24 (8.9)**	2 (3.0)	**4 (6.3)**	**7 (10.3)**
Back pain	21 (6.2)	24 (6.9)	16 (5.4)	11 (4.5)	**18 (7.0)**	**18 (6.6)**	4 (6.0)	**7 (10.9)**	**5 (7.4)**
Headache	21 (6.2)	28 (8.1)	14 (4.7)	12 (4.9)	6 (2.3)	10 (3.7)	3 (4.5)	1 (1.6)	1 (1.5)
Osteoarthritis	10 (2.9)	**12 (3.5)**	**13 (4.4)**	9 (3.7)	**10 (3.9)**	**11 (4.1)**	5 (7.5)	4 (6.3)	2 (2.9)
Joint swelling	7 (2.1)	**14 (4.0)**	**11 (3.7)**	6 (2.4)	3 (1.2)	7 (2.6)	2 (3.0)	1 (1.6)	1 (1.5)
Paresthesia	4 (1.2)	**11 (3.2)**	**9 (3.1)**	3 (1.2)	**4 (1.6)**	**8 (3.0)**	0	0	1 (1.5)
Pain in extremity	12 (3.5)	13 (3.8)	9 (3.1)	4 (1.6)	**13 (5.1)**	**12 (4.4)**	1 (1.5)	7 (10.9)	1 (1.5)
Upper respiratory tract infection	7 (2.1)	**11 (3.2)**	**9 (3.1)**	6 (2.4)	**7 (2.7)**	**10 (3.7)**	2 (3.0)	**3 (4.7)**	**3 (4.4)**

Peripheral edema	1 (0.3)	**4 (1.2)**	**8 (2.7)**	1 (0.4)	**3 (1.2)**	**10 (3.7)**	0	**1 (1.6)**	**3 (4.4)**
Fall	12 (3.5)	22 (6.4)	7 (2.4)	9 (3.7)	**13 (5.1)**	**12 (4.4)**	4 (6.0)	**4 (6.3)**	**7 (10.3)**
Hypoesthesia	7 (2.1)	12 (3.5)	6 (2.0)	1 (0.4)	**3 (1.2)**	**7 (2.6)**	1 (1.5)	1 (1.6)	1 (1.5)
Influenza	6 (1.8)	**11 (3.2)**	**6 (2.0)**	4 (1.6)	3 (1.2)	6 (2.2)	0	**3 (4.7)**	**3 (4.4)**
Musculoskeletal pain	15 (4.4)	19 (5.5)	5 (1.7)	8 (3.3)	**12 (4.7)**	**15 (5.5)**	0	**4 (6.3)**	**3 (4.4)**
Dizziness	8 (2.4)	7 (2.0)	5 (1.7)	0	**4 (1.6)**	**5 (1.8)**	0	**2 (3.1)**	**1 (1.5)**
Ligament sprain	2 (0.6)	**6 (1.7)**	**4 (1.4)**	3 (1.2)	2 (0.8)	3 (1.1)	0	2 (3.1)	0
Neck pain	6 (1.8)	5 (1.4)	4 (1.4)	6 (2.4)	4 (1.6)	2 (0.7)	3 (4.5)	1 (1.6)	0
Bronchitis	6 (1.8)	9 (2.6)	3 (1.0)	7 (2.8)	7 (2.7)	1 (0.4)	2 (3.0)	3 (4.7)	0
Hypertension	6 (1.8)	5 (1.4)	3 (1.0)	7 (2.8)	2 (0.8)	5 (1.8)	3 (4.5)	0	1 (1.5)
Urinary tract infection	5 (1.5)	5 (1.4)	2 (0.7)	3 (1.2)	**10 (3.9)**	**6 (2.2)**	1 (1.5)	1 (1.6)	0
Pain	2 (0.6)	0	2 (0.7)	0	**2 (0.8)**	**1 (0.4)**	0	2 (3.1)	0
Peripheral swelling	3 (0.9)	2 (0.6)	2 (0.7)	2 (0.8)	2 (0.8)	6 (2.2)	2 (3.0)	1 (1.6)	2 (2.9)
Orthostatic hypotension	1 (0.3)	2 (0.6)	1 (0.3)	0	**2 (0.8)**	**4 (1.5)**	0	**2 (3.1)**	**1 (1.5)**
Productive cough	0	0	1 (0.3)	2 (0.8)	0	1 (0.4)	2 (3.0)	0	0
Contusion	4 (1.2)	3 (0.9)	1 (0.3)	4 (1.6)	4 (1.6)	7 (2.6)	4 (6.0)	2 (3.1)	3 (4.4)
Joint injury	4 (1.2)	0	1 (0.3)	3 (1.2)	3 (1.2)	2 (0.7)	2 (3.0)	0	1 (1.5)
Dry eye	1 (0.3)	1 (0.3)	1 (0.3)	0	**3 (1.2)**	**1 (0.4)**	0	3 (4.7)	0
Chest pain	0	**2 (0.6)**	**1 (0.3)**	2 (0.8)	0	1 (0.4)	2 (3.0)	0	1 (1.5)
Cataract	2 (0.6)	0	1 (0.3)	4 (1.6)	3 (1.2)	6 (2.2)	2 (3.0)	1 (1.6)	2 (2.9)
Dry mouth	1 (0.3)	1 (0.3)	0	3 (1.2)	2 (0.8)	4 (1.5)	0	**2 (3.1)**	**2 (2.9)**
Atrial fibrillation	0	0	0	3 (1.2)	6 (2.3)	3 (1.1)	0	2 (3.1)	0

Hyperhidrosis	0	1 (0.3)	0	1 (0.4)	**2 (0.8)**	**3 (1.1)**	0	2 (3.1)	0

Abbreviations: TEAE, treatment-emergent adverse event.

[†]This is a total of 40, 48, and 24 weeks for NCT02697773, NCT02709486, and NCT01089725, respectively.

[‡]Reported in ≥3% of patients in any treatment group. Bolding indicated the event was reported at a higher frequency in both tanezumab groups relative to the placebo group.

Supplemental Table 3. Summary of TEAEs over the full study (treatment + follow-up) period[†] in BMI subgroups of the safety population (NCT02697773, NCT02709486, and

	<25 kg/m²			25–<30 kg/m²			30–<35 kg/m²			
Patients, n (%)	**Placebo (n = 62)**	**Tanezumab 2.5 mg (n = 88)**	**Tanezumab 5 mg (n = 71)**	**Placebo (n = 183)**	**Tanezumab 2.5 mg (n = 188)**	**Tanezumab 5 mg (n = 181)**	**Placebo (n = 191)**	**Tanezumab 2.5 mg (n = 196)**	**Tanezumab 5 mg (n = 203)**	**Plac (n = 1**
With any TEAE	41 (66.1)	52 (59.1)	45 (63.4)	108 (59.0)	119 (63.3)	102 (56.4)	112 (58.6)	123 (62.8)	127 (62.6)	96 (6
With any serious TEAE	2 (3.2)	5 (5.7)	2 (2.8)	5 (2.7)	11 (5.9)	12 (6.6)	8 (4.2)	10 (5.1)	10 (4.9)	6 (4
With any severe TEAE	2 (3.2)	7 (8.0)	1 (1.4)	4 (2.2)	9 (4.8)	14 (7.7)	9 (4.7)	8 (4.1)	13 (6.4)	8 (5
Discontinued treatment due to TEAE	0	0	0	2 (1.1)	4 (2.1)	0	6 (3.1)	2 (1.0)	3 (1.5)	4 (2
Discontinued study due to TEAE	0	2 (2.3)	0	0	2 (1.1)	2 (1.1)	2 (1.0)	2 (1.0)	0	3 (2
Common TEAEs[‡]										
Arthralgia	5 (8.1)	**9 (10.2)**	**13 (18.3)**	25 (13.7)	24 (12.8)	23 (12.7)	30 (15.7)	40 (20.4)	23 (11.3)	35 (2
Nasopharyngitis	5 (8.1)	**8 (9.1)**	**9 (12.7)**	14 (7.7)	20 (10.6)	13 (7.2)	16 (8.4)	**24 (12.2)**	**19 (9.4)**	14 (9
Back pain	3 (4.8)	4 (4.5)	5 (7.0)	10 (5.5)	20 (10.6)	9 (5.0)	11 (5.8)	**13 (6.6)**	**13 (6.4)**	8 (5
Musculoskeletal pain	0	**6 (6.8)**	**5 (7.0)**	7 (3.8)	6 (3.2)	6 (3.3)	8 (4.2)	17 (8.7)	6 (3.0)	8 (5
Osteoarthritis	1 (1.6)	**3 (3.4)**	**4 (5.6)**	5 (2.7)	**6 (3.2)**	**8 (4.4)**	6 (3.1)	**8 (4.1)**	**10 (4.9)**	7 (4
Muscle spasms	0	**1 (1.1)**	**3 (4.2)**	4 (2.2)	5 (2.7)	2 (1.1)	1 (0.5)	1 (0.5)	1 (0.5)	1 (0
Upper respiratory tract infection	4 (6.5)	1 (1.1)	2 (2.8)	3 (1.6)	**9 (4.8)**	**7 (3.9)**	0	**5 (2.6)**	**7 (3.4)**	6 (4
Influenza	1 (1.6)	**2 (2.3)**	**2 (2.8)**	4 (2.2)	3 (1.6)	5 (2.8)	1 (0.5)	4 (2.0)	1 (0.5)	4 (2
Peripheral edema	0	**1 (1.1)**	**2 (2.8)**	1 (0.5)	**3 (1.6)**	**3 (1.7)**	0	**2 (1.0)**	**7 (3.4)**	1 (0
Neck pain	1 (1.6)	0	2 (2.8)	4 (2.2)	6 (3.2)	1 (0.6)	6 (3.1)	3 (1.5)	1 (0.5)	1 (0

Contusion	2 (3.2)	2 (2.3)	2 (2.8)	2 (1.1)	0	1 (0.6)	2 (1.0)	**3 (1.5)**	**3 (1.5)**	2 (1
Headache	4 (6.5)	4 (4.5)	2 (2.8)	11 (6.0)	11 (5.9)	9 (5.0)	8 (4.2)	**12 (6.1)**	**9 (4.4)**	10 (6
Dizziness	0	0	1 (1.4)	2 (1.1)	2 (1.1)	4 (2.2)	5 (2.6)	5 (2.6)	5 (2.5)	1 (0
Paresthesia	1 (1.6)	1 (1.1)	1 (1.4)	1 (0.5)	**4 (2.1)**	**4 (2.2)**	2 (1.0)	**7 (3.6)**	**5 (2.5)**	3 (2
Hypertension	0	0	1 (1.4)	7 (3.8)	2 (1.1)	2 (1.1)	4 (2.1)	4 (2.0)	4 (2.0)	2 (1
Fall	2 (3.2)	8 (9.1)	1 (1.4)	7 (3.8)	8 (4.3)	6 (3.3)	8 (4.2)	10 (5.1)	6 (3.0)	4 (2
Joint swelling	0	**3 (3.4)**	**1 (1.4)**	5 (2.7)	5 (2.7)	4 (2.2)	3 (1.6)	**6 (3.1)**	**7 (3.4)**	5 (3
Hypoesthesia	0	**3 (3.4)**	**1 (1.4)**	0	**9 (4.8)**	**3 (1.7)**	4 (2.1)	1 (0.5)	7 (3.4)	4 (2
Nausea	0	0	0	2 (1.1)	3 (1.6)	0	1 (0.5)	7 (3.6)	1 (0.5)	5 (3
Bronchitis	1 (1.6)	1 (1.1)	0	4 (2.2)	6 (3.2)	1 (0.6)	4 (2.1)	6 (3.1)	3 (1.5)	4 (2
Urinary tract infection	2 (3.2)	2 (2.3)	0	2 (1.1)	**4 (2.1)**	**5 (2.8)**	2 (1.0)	7 (3.6)	2 (1.0)	2 (1
Arthritis	2 (3.2)	0	0	1 (0.5)	1 (0.5)	1 (0.6)	2 (1.0)	0	0	0
Viral infection	2 (3.2)	0	0	1 (0.5)	1 (0.5)	1 (0.6)	0	**1 (0.5)**	**2 (1.0)**	0
Diarrhea	1 (1.6)	3 (3.4)	0	2 (1.1)	2 (1.1)	6 (3.3)	5 (2.6)	2 (1.0)	5 (2.5)	1 (0
Pain in extremity	1 (1.6)	3 (3.4)	0	6 (3.3)	6 (3.2)	7 (3.9)	6 (3.1)	**17 (8.7)**	**7 (3.4)**	3 (2
Myalgia	0	1 (1.1)	0	2 (1.1)	2 (1.1)	0	2 (1.0)	2 (1.0)	1 (0.5)	3 (2
Eczema	2 (3.2)	0	0	0	**1 (0.5)**	**1 (0.6)**	0	0	0	0
Cough	1 (1.6)	2 (2.3)	0	1 (0.5)	**5 (2.7)**	**7 (3.9)**	4 (2.1)	1 (0.5)	3 (1.5)	3 (2

Abbreviations: BMI, body mass index; TEAE, treatment-emergent adverse event.

[†]This is a total of 40, 48, and 24 weeks for NCT02697773, NCT02709486, and NCT01089725, respectively.

[‡]Reported in ≥2% of patients in any treatment group. Bolding indicates the event was reported at a higher frequency in both tanezumab groups relative to the placebo group.

Supplemental Table 4. Summary of TEAEs over the full study (treatment + follow-up) period[†] in diabetes subgroups of the safety population (NCT02697773, NCT02709486, and NCT01089725)

	No diabetes			Diabetes[‡]		
Patients, n (%)	**Placebo (n = 493)**	**Tanezumab 2.5 mg (n = 500)**	**Tanezumab 5 mg (n = 466)**	**Placebo (n = 93)**	**Tanezumab 2.5 mg (n = 102)**	**Tanezumab 5 mg (n = 100)**
With any TEAE	305 (61.9)	313 (62.6)	293 (62.9)	52 (55.9)	65 (63.7)	58 (58.0)
With any serious TEAE	19 (3.9)	25 (5.0)	25 (5.4)	2 (2.2)	7 (6.9)	6 (6.0)
With any severe TEAE	21 (4.3)	20 (4.0)	24 (5.2)	2 (2.2)	8 (7.8)	12 (12.0)
Discontinued treatment due to TEAE	10 (2.0)	6 (1.2)	5 (1.1)	2 (2.2)	2 (2.0)	0
Discontinued study due to TEAE	5 (1.0)	8 (1.6)	2 (0.4)	0	2 (2.0)	0
Common TEAEs[§]						
Arthralgia	79 (16.0)	77 (15.4)	72 (15.5)	16 (17.2)	14 (13.7)	11 (11.0)
Nasopharyngitis	38 (7.7)	**48 (9.6)**	**41 (8.8)**	11 (11.8)	13 (12.7)	6 (6.0)
Back pain	27 (5.5)	**37 (7.4)**	**26 (5.6)**	5 (5.4)	5 (4.9)	8 (8.0)
Headache	31 (6.3)	30 (6.0)	22 (4.7)	2 (2.2)	4 (3.9)	2 (2.0)
Osteoarthritis	14 (2.8)	**18 (3.6)**	**21 (4.5)**	5 (5.4)	4 (3.9)	3 (3.0)
Pain in extremity	15 (3.0)	**24 (4.8)**	**18 (3.9)**	1 (1.1)	**2 (2.0)**	**3 (3.0)**
Musculoskeletal pain	18 (3.7)	29 (5.8)	16 (3.4)	5 (5.4)	2 (2.0)	4 (4.0)
Upper respiratory tract infection	10 (2.0)	**13 (2.6)**	**15 (3.2)**	3 (3.2)	**5 (4.9)**	**4 (4.0)**
Paresthesia	7 (1.4)	**10 (2.0)**	**14 (3.0)**	0	**5 (4.9)**	**3 (3.0)**

Joint swelling	9 (1.8)	**15 (3.0)**	**14 (3.0)**	4 (4.3)	2 (2.0)	4 (4.0)
Peripheral edema	2 (0.4)	**7 (1.4)**	**14 (3.0)**	0	0	4 (4.0)
Fall	19 (3.9)	29 (5.8)	12 (2.6)	2 (2.2)	**6 (5.9)**	**7 (7.0)**
Diarrhea	8 (1.6)	5 (1.0)	8 (1.7)	1 (1.1)	**5 (4.9)**	**5 (5.0)**
Hypertension	10 (2.0)	6 (1.2)	7 (1.5)	3 (3.2)	1 (1.0)	1 (1.0)
Neck pain	9 (1.8)	8 (1.6)	6 (1.3)	3 (3.2)	1 (1.0)	0
Peripheral swelling	5 (1.0)	2 (0.4)	5 (1.1)	0	**2 (2.0)**	**3 (3.0)**
Contusion	8 (1.6)	6 (1.2)	5 (1.1)	0	**1 (1.0)**	**3 (3.0)**
Oropharyngeal pain	2 (0.4)	**4 (0.8)**	**3 (0.6)**	2 (2.2)	2 (2.0)	3 (3.0)
Limb injury	5 (1.0)	2 (0.4)	1 (0.2)	3 (3.2)	0	1 (1.0)
Bronchitis	13 (2.6)	15 (3.0)	3 (0.6)	0	**1 (1.0)**	**1 (1.0)**

Abbreviations: TEAE, treatment-emergent adverse event.

[†]This is a total of 40, 48, and 24 weeks for NCT02697773, NCT02709486, and NCT01089725, respectively.

[‡]Patients were included in the yes diabetes group if they had a medical history of type 1 or type 2 diabetes mellitus, hyperglycemia, or who had a baseline hemoglobin A1c ≥6.5%.

[§] Reported in ≥3% of patients in any treatment group. Bolding indicated the event was reported at a higher frequency in both tanezumab groups relative to the placebo group.

Supplemental Table 5. Summary of TEAEs over the full study (treatment + follow-up) period[†] in baseline pain subgroups of the safety population (NCT02697773, NCT02709486, and NCT01089725)

	Baseline pain <7			Baseline pain ≥7		
Patients, n (%)	**Placebo (n = 296)**	**Tanezumab 2.5 mg (n = 305)**	**Tanezumab 5 mg (n = 283)**	**Placebo (n = 289)**	**Tanezumab 2.5 mg (n = 296)**	**Tanezumab 5 mg (n = 283)**
With any TEAE	185 (62.5)	179 (58.7)	177 (62.5)	172 (59.5)	198 (66.9)	174 (61.5)
With any serious TEAE	12 (4.1)	18 (5.9)	22 (7.8)	9 (3.1)	14 (4.7)	9 (3.2)
With any severe TEAE	10 (3.4)	14 (4.6)	21 (7.4)	13 (4.5)	14 (4.7)	15 (5.3)
Discontinued treatment due to TEAE	7 (2.4)	3 (1.0)	4 (1.4)	5 (1.7)	5 (1.7)	1 (0.4)
Discontinued study due to TEAE	4 (1.4)	2 (0.7)	1 (0.4)	1 (0.3)	8 (2.7)	1 (0.4)
Common TEAEs[‡]						
Arthralgia	52 (17.6)	50 (16.4)	39 (13.8)	43 (14.9)	40 (13.5)	44 (15.5)
Nasopharyngitis	32 (10.8)	31 (10.2)	28 (9.9)	17 (5.9)	**29 (9.8)**	**19 (6.7)**
Back pain	24 (8.1)	22 (7.2)	22 (7.8)	8 (2.8)	**19 (6.4)**	**12 (4.2)**
Osteoarthritis	10 (3.4)	7 (2.3)	15 (5.3)	9 (3.1)	**15 (5.1)**	**9 (3.2)**
Peripheral edema	1 (0.3)	**2 (0.7)**	**13 (4.6)**	1 (0.3)	**5 (1.7)**	**5 (1.8)**
Headache	18 (6.1)	15 (4.9)	13 (4.6)	15 (5.2)	19 (6.4)	11 (3.9)
Musculoskeletal pain	16 (5.4)	14 (4.6)	11 (3.9)	7 (2.4)	**16 (5.4)**	**9 (3.2)**
Paresthesia	3 (1.0)	**7 (2.3)**	**11 (3.9)**	4 (1.4)	**8 (2.7)**	**6 (2.1)**
Pain in extremity	11 (3.7)	11 (3.6)	10 (3.5)	5 (1.7)	**15 (5.1)**	**11 (3.9)**

Fall	12 (4.1)	15 (4.9)	10 (3.5)	9 (3.1)	**20 (6.8)**	**9 (3.2)**
Upper respiratory tract infection	4 (1.4)	**6 (2.0)**	**10 (3.5)**	9 (3.1)	**12 (4.1)**	**9 (3.2)**
Hypoesthesia	0	**5 (1.6)**	**7 (2.5)**	8 (2.8)	10 (3.4)	6 (2.1)
Influenza	7 (2.4)	4 (1.3)	7 (2.5)	3 (1.0)	**10 (3.4)**	**5 (1.8)**
Joint swelling	7 (2.4)	8 (2.6)	6 (2.1)	6 (2.1)	**9 (3.0)**	**12 (4.2)**
Urinary tract infection	5 (1.7)	**9 (3.0)**	**5 (1.8)**	3 (1.0)	**6 (2.0)**	**3 (1.1)**
Bronchitis	6 (2.0)	6 (2.0)	3 (1.1)	7 (2.4)	10 (3.4)	1 (0.4)

Abbreviations: TEAE, treatment-emergent adverse event.

[†]This is a total of 40, 48, and 24 weeks for NCT02697773, NCT02709486, and NCT01089725, respectively.

[‡]Reported in ≥3% of patients in any treatment group. Bolding indicated the event was reported at a higher frequency in both tanezumab groups relative to the placebo group.

Supplemental Table 6. Summary of TEAEs over the full study (treatment + follow-up) period[†] in KL subgroups of the safety population (NCT02697773, NCT02709486, and NCT01089725)

	KL grade 2 in index joint			KL grade 3 in index joint			KL grade 4 in index joint		
Patients, n (%)	**Placebo (n = 157)**	**Tanezumab 2.5 mg (n = 144)**	**Tanezumab 5 mg (n = 139)**	**Placebo (n = 247)**	**Tanezumab 2.5 mg (n = 270)**	**Tanezumab 5 mg (n = 250)**	**Placebo (n = 182)**	**Tanezumab 2.5 mg (n = 185)**	**Tanezumab 5 mg (n = 176)**
With any TEAE	100 (63.7)	90 (62.5)	91 (65.5)	147 (59.5)	175 (64.8)	156 (62.4)	110 (60.4)	111 (60.0)	104 (59.1)
With any serious TEAE	3 (1.9)	7 (4.9)	9 (6.5)	10 (4.0)	13 (4.8)	13 (5.2)	8 (4.4)	12 (6.5)	9 (5.1)
With any severe TEAE	4 (2.5)	6 (4.2)	9 (6.5)	8 (3.2)	12 (4.4)	15 (6.0)	11 (6.0)	10 (5.4)	12 (6.8)
Discontinued treatment due to TEAE	2 (1.3)	2 (1.4)	1 (0.7)	9 (3.6)	2 (0.7)	3 (1.2)	1 (0.5)	4 (2.2)	1 (0.6)
Discontinued study due to TEAE	0	1 (0.7)	0	5 (2.0)	4 (1.5)	1 (0.4)	0	5 (2.7)	1 (0.6)
Common TEAEs[‡]									
Arthralgia	26 (16.6)	22 (15.3)	19 (13.7)	43 (17.4)	49 (18.1)	40 (16.0)	26 (14.3)	20 (10.8)	24 (13.6)
Nasopharyngitis	14 (8.9)	16 (11.1)	9 (6.5)	24 (9.7)	29 (10.7)	24 (9.6)	11 (6.0)	**16 (8.6)**	**14 (8.0)**
Back pain	6 (3.8)	**15 (10.4)**	**8 (5.8)**	14 (5.7)	**18 (6.7)**	**18 (7.2)**	12 (6.6)	9 (4.9)	8 (4.5)
Pain in extremity	2 (1.3)	**4 (2.8)**	**7 (5.0)**	9 (3.6)	**16 (5.9)**	**11 (4.4)**	5 (2.7)	6 (3.2)	3 (1.7)
Osteoarthritis	2 (1.3)	**5 (3.5)**	**5 (3.6)**	9 (3.6)	9 (3.3)	9 (3.6)	8 (4.4)	8 (4.3)	10 (5.7)
Peripheral edema	1 (0.6)	**1 (0.7)**	**5 (3.6)**	0	**4 (1.5)**	**6 (2.4)**	1 (0.5)	**2 (1.1)**	**7 (4.0)**
Joint swelling	2 (1.3)	1 (0.7)	5 (3.6)	7 (2.8)	**12 (4.4)**	**9 (3.6)**	4 (2.2)	4 (2.2)	4 (2.3)
Hypoesthesia	1 (0.6)	**4 (2.8)**	**4 (2.9)**	3 (1.2)	**5 (1.9)**	**4 (1.6)**	4 (2.2)	**6 (3.2)**	**5 (2.8)**
Diarrhea	0	**5 (3.5)**	**4 (2.9)**	5 (2.0)	3 (1.1)	6 (2.4)	4 (2.2)	2 (1.1)	3 (1.7)

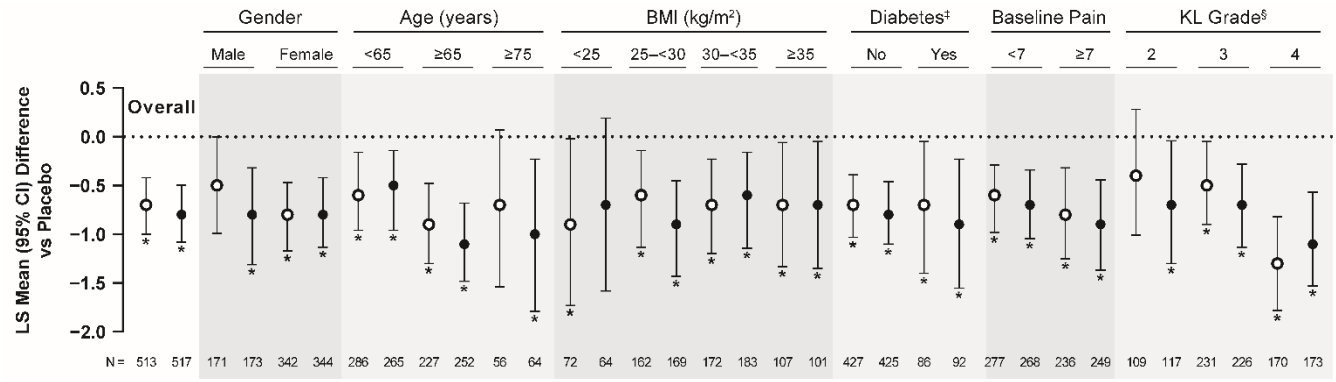
Musculoskeletal pain	4 (2.5)	**11 (7.6)**	**4 (2.9)**	12 (4.9)	12 (4.4)	6 (2.4)	7 (3.8)	**8 (4.3)**	**10 (5.7)**
Headache	8 (5.1)	10 (6.9)	4 (2.9)	17 (6.9)	14 (5.2)	14 (5.6)	8 (4.4)	10 (5.4)	6 (3.4)
Urinary tract infection	3 (1.9)	**5 (3.5)**	**4 (2.9)**	4 (1.6)	9 (3.3)	4 (1.6)	1 (0.5)	1 (0.5)	0
Fall	6 (3.8)	10 (6.9)	3 (2.2)	7 (2.8)	14 (5.2)	7 (2.8)	8 (4.4)	**11 (5.9)**	**9 (5.1)**
Upper respiratory tract infection	3 (1.9)	**4 (2.8)**	**3 (2.2)**	6 (2.4)	**9 (3.3)**	**9 (3.6)**	4 (2.2)	**5 (2.7)**	**7 (4.0)**
Bronchitis	6 (3.8)	4 (2.8)	1 (0.7)	4 (1.6)	8 (3.0)	1 (0.4)	3 (1.6)	4 (2.2)	2 (1.1)
		-	-	-	-	-	-	-	-

Abbreviations: KL, Kellgren-Lawrence; TEAE, treatment-emergent adverse event.

[†]This is a total of 40, 48, and 24 weeks for NCT02697773, NCT02709486, and NCT01089725, respectively.

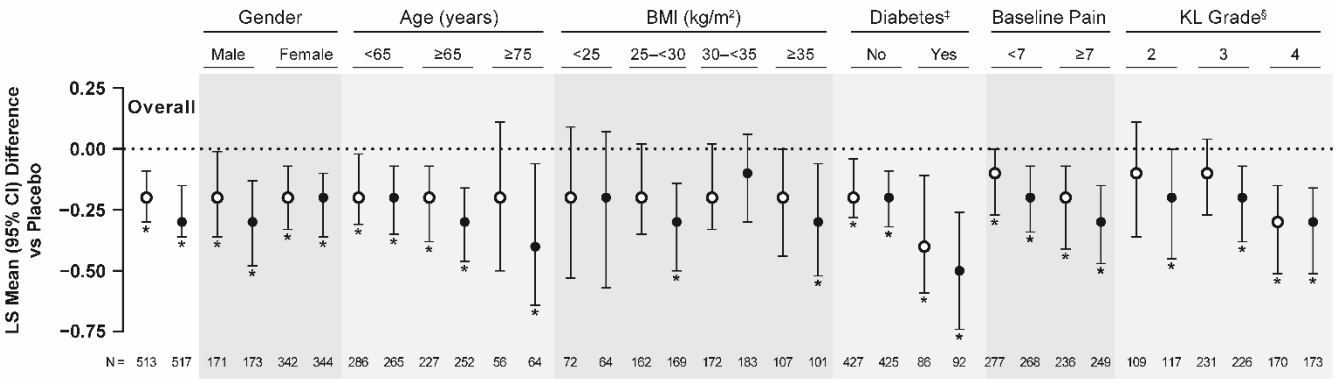
[‡]Reported in ≥3% of patients in any treatment group. Bolding indicated the event was reported at a higher frequency in both tanezumab groups relative to the placebo group.

Supplemental Figure 1. Change in WOMAC Physical Function[†] from baseline to week 16 (NCT02697773 and NCT02709486).



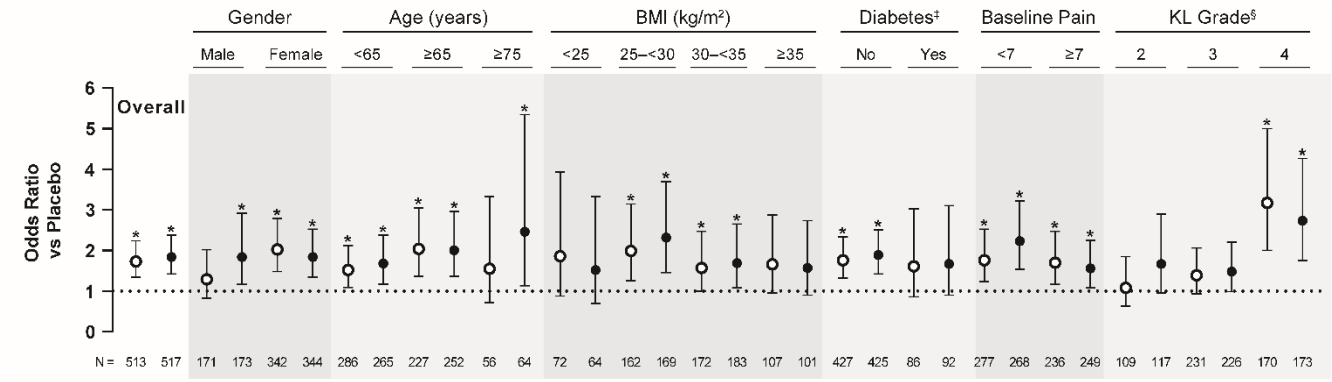
Symbols: ○ = tanezumab 2.5 mg; ● = tanezumab 5 mg. [†]Scores range from 0–10, with higher scores indicating greater difficulty with function. [‡]Patients were included in the diabetes group if they had a medical history of hyperglycemia, type 1 or type 2 diabetes mellitus, or a baseline hemoglobin A1c ≥6.5%. [§]In the index joint; defined as the most painful joint at screening with a qualifying WOMAC Pain score and KL grade as confirmed by a central reader. N represents the number of patients, with available baseline data, included in the analysis. *P < .05 vs placebo. BMI, body mass index; CI, confidence interval; KL, Kellgren-Lawrence; LS, least squares; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

Supplemental Figure 2. Change in PGA-OA[†] from baseline to week 16 (NCT02697773 and NCT02709486).



Symbols: ○ = tanezumab 2.5 mg; ● = tanezumab 5 mg. [†]Scores range from 1 = "very good" to 5 = "very poor". [‡]Patients were included in the diabetes group if they had a medical history of hyperglycemia, type 1 or type 2 diabetes mellitus, or a baseline hemoglobin A1c ≥6.5%. [§]In the index joint; defined as the most painful joint at screening with a qualifying WOMAC Pain score and KL grade as confirmed by a central reader. N represents the number of patients, with available baseline data, included in the analysis. *P < .05 vs placebo. BMI, body mass index; CI, confidence interval; KL, Kellgren-Lawrence; LS, least squares; PGA-OA, Patient's Global Assessment of Osteoarthritis; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

Supplemental Figure 3. Proportion of patients achieving ≥30% improvement in WOMAC Pain[†] from baseline to week 16 (NCT02697773 and NCT02709486).



Symbols: ○ = tanezumab 2.5 mg; ● = tanezumab 5 mg. [†]Scores range from 0–10, with higher scores indicating greater pain severity. [‡]Patients were included in the diabetes group if they had a medical history of hyperglycemia, type 1 or type 2 diabetes mellitus, or a baseline hemoglobin A1c ≥6.5%. [§]In the index joint; defined as the most painful joint at screening with a qualifying WOMAC Pain score and KL grade as confirmed by a central reader. N represents the number of patients, with available baseline data, included in the analysis. *P < .05 vs placebo. BMI, body mass index; KL, Kellgren-Lawrence; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

GRAPHICAL ABSTRACT Per the journal, this section should contain the title, authors, ≤ 80-word summary of key findings, and 1 representative figure (no legends) to be included in our table of contents for the issue upon publication.

Title: Gender, age, disease severity, body mass index and diabetes do not affect response to subcutaneous tanezumab in patients with osteoarthritis. A subgroup analyses of placebo-controlled trials.

Authors: Francis Berenbaum*, Thomas Schnitzer, Alan Kivitz, Lars Viktrup, Elizabeth Johnston, Ruoyong Yang, Ed Whalen, Leslie Tive, David Semel

Summary: Data were pooled from two (efficacy) or three (safety) phase 3, randomized, placebo-controlled trials to assess the impact of pre-specified patient characteristics on the efficacy and safety of subcutaneous tanezumab (2.5 and 5 mg) in patients with osteoarthritis. The efficacy and safety of tanezumab were not meaningfully impacted by gender, age, body mass index, diabetes status, baseline pain severity or Kellgren-Lawrence grade in the index joint, though conclusions are limited by low numbers of patients in some subgroups.