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**GENERIC DRUG NAME and/or COMPOUND NUMBER:** Tanezumab / PF-04383119

**PROTOCOL NO.:** A4091030

**PROTOCOL TITLE:** A Phase 3 Randomized, Double-Blind, Placebo- and Oxycodone-Controlled, Multicenter Study of the Efficacy and Safety of Tanezumab in Patients With Osteoarthritis of the Knee or Hip

**Study Centers:** A total of 74 centers took part in the study and randomized subjects; 3 each in Austria, Poland, Spain and Sweden, 4 in Denmark, 8 in Germany, and 50 in the United States (US).

**Study Initiation and Final Completion Dates:** 30 October 2009 to 04 February 2011
The study was terminated prematurely following a US Food and Drug Administration (FDA) clinical hold for tanezumab osteoarthritis clinical studies which halted dosing and enrollment of subjects on 23 June 2010 for potential safety issues.

**Phase of Development:** Phase 3

**Study Objectives:**

Primary Objectives:

- Demonstrate superior analgesic efficacy of tanezumab 10 mg and 5 mg administered intravenously (IV) every 8 weeks compared to placebo at Week 8;
- Demonstrate noninferiority and, if warranted, superior analgesic efficacy of tanezumab 10 mg and 5 mg administered IV every 8 weeks compared to oxycodone controlled release (CR) tablets (oxycontin) 10 to 40 mg every 12 hours (q12h) at Week 8.

Secondary Objective:

- Evaluate the safety and tolerability up to Week 18 of tanezumab 10 mg and 5 mg administered IV every 8 weeks.

**METHODS**

**Study Design:** This was a randomized, double-blind, placebo- and active-controlled, multicenter, parallel-group, Phase 3 study in subjects with moderate-to-severe osteoarthritis of the knee or hip (as per American College of Rheumatology [ACR] criteria) who required regular analgesic treatment and were unable to take non-opioid pain medications (eg, nonsteroidal anti-inflammatory drugs), for whom non opioid pain medications or limited

amounts of opioids had not provided adequate pain relief, or who were candidates for (or were seeking) invasive interventions such as intra-articular injections, knee or hip arthroplasty, or knee or hip replacement surgery.

Subjects were randomized to 1 of the following 4 treatment groups in a 1:1:1:1 ratio, with randomization stratified by index joint (knee or hip) and by previous opioid use (yes or no):

- Placebo IV, 2 doses (to match tanezumab) at an 8-week interval and oral placebo (to match oxycodone CR) q12h for 16 weeks;
- Tanezumab 5 mg, 2 doses at an 8-week interval and oral placebo q12h for 16 weeks;
- Tanezumab 10 mg, 2 doses at an 8-week interval and oral placebo q12h for 16 weeks;
- Placebo IV, 2 doses (to match tanezumab) at an 8-week interval and oxycodone CR q12h for 16 weeks.

This study was terminated early following the US FDA clinical hold for tanezumab osteoarthritis clinical studies which halted dosing and enrollment of subjects on 23 June 2010 for potential safety issues. Therefore, as of 23 June 2010, all investigators were instructed to stop further dosing with study drug (IV, oral) and no new subjects were to be enrolled into the osteoarthritis studies after this date.

The study consisted of a Screening Period (beginning up to 30 days prior to Randomization), which included a Washout Period (2 to 27 days, allowing for a minimum 2 day washout of prohibited analgesics or at least 5 times the elimination half-life, whichever was greater, prior to entering the Initial Pain Assessment Period), and an Initial Pain Assessment Period (the 3 days prior to Baseline [Randomization]). The Treatment Period was to be 16 weeks, and was followed by an oxycodone CR Taper Period beginning Day 113 (the day of the Week 16 visit) and ending with the End-of-Study visit at Week 18 (Day 127).

As part of the original study design, Week 16 was chosen for the primary treatment comparisons; but, subsequent to the US FDA clinical hold, this assessment was changed to Week 8. The study schedule and evaluations is summarized in Table 1.

## Table 1. Study Schedule and Evaluations

| Study Activity | Screen[a] | Washout[b] | Initial Pain Assessment Period | Treatment[c,d] | | | | | | | Start of Down Taper[d] | End of Study/ Early Term/ Follow-Up[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Baseline[e] | | Week 2 | | Week 4 | Week 8[c] | Week 12 | Week 16[d] | Week 18/24[d] |
| **Study Days:** | **-30 to -1** | **-30 to -3** | **-3 to -1** | **1** | **2-14** | **15 (±2)** | **16-28** | **29 (±2)** | **57 (±2)** | **85 (±2)** | **113 (±2)** | **127 (±2)** |
| Informed consent | X | | | | | | | | | | | |
| Inclusion/exclusion criteria (X-ray, if needed) | X | | | X | | | | | | | | |
| General medical history | X | | | | | | | | | | | |
| Primary diagnosis, demographics | X | | | | | | | | | | | |
| Physical examination | X | | | | | | | | | | | X |
| Radiographic assessment of hips (bilateral X-ray)[f] | | | | | | | | | | | | X[f] |
| Neurological exam/ Neuropathy Impairment Score[g] | X | | | X | | X | | X | X | X | X | X |
| Vital signs (temperature, blood pressure, heart rate, respiratory rate) | X | | | X[h] | | X | | X | X[h] | X | X | X |
| Weight, height, BMI, smoking status, female hormone status, alcohol use | X | | | | | | | | | | | |
| Laboratory | | | | | | | | | | | | |
| Hematology | X | | | X | | | | | X | | X | X |
| Blood chemistry[d] | X | | | X | | | | | X | | X | X |
| Serum/plasma retention samples[d] | | | | X | | | | | | | | X |
| Urinalysis | X | | | X | | | | | X | | X | X |
| Pregnancy test[i] | X | | | X | | | | | X | | | X |
| Serum FSH test[j] | X | | | | | | | | | | | |
| Glycosylated hemoglobin | X | | | X | | | | | X | | | X |
| Hepatitis (B and C) screen | X | | | | | | | | | | | |
| HIV-1 antibody screen | X | | | | | | | | | | | |
| Urine toxicology screen | X | | | | | | | | | | | |
| Serum anti-drug antibody | | | | X | | | | | X | | | X |
| Plasma pharmacokinetic sample | | | | X[h] | | | | | X[h] | | | X |
| De-identified genetic sampling | | | | X | | | | | | | | |
| Serum pharmacodynamic (NGF) sample | | | | X[h] | | | | | X[h] | | | X |
| 12-lead electrocardiogram | X | | | X[h] | | | | | X[h] | | | X |

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| Study Activity | Screen[a] | Washout[b] | Initial Pain Assessment Period | Treatment[c,d] | | | | | | | Start of Down Taper[d] | End of Study/ Early Term/ Follow-Up[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Baseline[e] | | Week 2 | | Week 4 | Week 8[c] | Week 12 | Week 16[d] | Week 18/24[d] |
| **Study Days:** | **-30 to -1** | **-30 to -3** | **-3 to -1** | **1** | **2-14** | **15 (±2)** | **16-28** | **29 (±2)** | **57 (±2)** | **85 (±2)** | **113 (±2)** | **127 (±2)** |
| Discontinue current pain medication | | X | | | | | | | | | | |
| Randomization | | | | X | | | | | | | | |
| Study treatment | | | | | | | | | | | | |
| IV study drug | | | | X | | | | | X | | | |
| Dispense oral study drug | | | | X | | X | | X | X | X | X | |
| Subject-reported assessments at study visits | | | | | | | | | | | | |
| WOMAC Pain Subscale[k] | X | | | X | | X | | X | X | X | X | X |
| WOMAC Physical Function and Stiffness Subscales[k] | | | | X | | X | | X | X | X | X | X |
| Patient Global Assessment of OA[k] | | | | X | | X | | X | X | X | X | X |
| SF-36v2 Health Survey[k] | | | | X | | | | | | X | | |
| EQ-5D[k] | | | | X | | | | | | X | | |
| Other assessments completed at study visits[d] | | | | | | | | | | | | |
| AEs assessment[l] | | | | X[h] | | X | | X | X[h] | X | X | X |
| Review concomitant medications[l] | X | | | X | | X | | X | X | X | X | X |
| Review subject compliance | X | | | X | | X | | X | X | X | X | X |
| Oral study drug compliance[m] | | | | | | X | | X | X | X | X | X |
| Telephone contact[n] | | | | | X | | X | | | | | |
| Dispense rescue medication[o] | X | | | X | | X | | X | X | X | X | |
| Rescue medication return/compliance[o] | | | | X | | X | | X | X | X | X | X |
| Subject Daily Assessments (IVRS) | | | | | | | | | | | | |
| Rescue medication, study drug use | | ◄---------- | | | | | | | | | | ----------► |
| Numeric pain scale rating | | | ◄---------- | | | | | | | | | ----------► |

AEs = adverse events; BMI = body mass index; EuroQol = European Quality of Life Group; EQ-5D = European Quality of Life in Five Dimensions Health Questionnaire; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; IV = intravenous; IVRS = Interactive Voice Response System; NGF = nerve growth factor; SF-36v2 = Medical Outcomes Study Short Form 36 Health Survey, version 2; SAE = serious adverse event; WOMAC = Western Ontario and McMaster Universities (Osteoarthritis Index).

a. The Screening Period began up to 30 days prior to Randomization, allowing for a minimum 48-hour washout of all prohibited medications prior to the Initial Pain Assessment Period. Subjects who did not require washout could have begun the Initial Pain Assessment Period after all laboratory tests and other qualifying tests were evaluated.

## Table 1. Study Schedule and Evaluations

| Study Activity | Screen[a] | Washout[b] | Initial Pain Assessment Period | Treatment[c,d] | | | | | | | Start of Down Taper[d] | End of Study/ Early Term/ Follow-Up[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Baseline[e] | | Week 2 | | Week 4 | Week 8[c] | Week 12 | Week 16[d] | Week 18/24[d] |
| **Study Days:** | **-30 to -1** | **-30 to -3** | **-3 to -1** | **1** | **2-14** | **15 (±2)** | **16-28** | **29 (±2)** | **57 (±2)** | **85 (±2)** | **113 (±2)** | **127 (±2)** |

b. All current analgesic medications were discontinued and the washout was a minimum of 48 hours prior to the start of the Initial Pain Assessment Period (ie, the 3 days prior to Randomization/Baseline) or ≥5 half-lives of the particular analgesic.

c. All subjects who were active at the time of protocol amendment implementation at the site were to be followed for study-specified safety evaluations in the clinic for 16 weeks after their last dose of IV study drug, provided the subject agreed to in-clinic follow-up. If a subject had not agreed to continue with study-specified safety evaluations at clinic visits, efforts were to be made to follow the subject at the defined visit time-points by telephone for 16 weeks after their last dose of IV study drug. Subjects were also reminded about study contraceptive requirements (if applicable).

d. Week 24 follow-up safety assessments replaced the Week 18 visit for subjects who were administered IV study drug at their Week 8 visit, were active in the study on 23 June 2010, and had not had their Week 18 (End-of-Treatment) visit before the implementation of Amendment 4.

e. All study activities at Baseline (Day 1) were performed prior to dosing with study drug, unless otherwise noted.

f. Bilateral X-rays of the hips were to be obtained at End of Study/Early Termination/Follow-up visit.

g. Subjects were to be referred to a neurologist for a full neurologic exam if they experienced an AE suggestive of new or worsening peripheral neuropathy, or if AEs of abnormal peripheral sensation (eg, allodynia, burning sensation, dysesthesia, hyperesthesia, hyperpathia, hypoesthesia, neuralgia, neuritis, neuropathy peripheral, decreased vibratory sense, paresthesia, peripheral sensory neuropathy, sensory disturbance, and sensory loss) were reported. Subjects with pain in the extremities (eg, fingers, hands, feet, soles of feet) that was suggestive of neuropathic pain (eg, pain described as burning, shooting, electric or tingling) were also to be referred to a neurologist. Identification of a new or worsened clinically significant finding on the neurological exam was to be reported as an AE and the subject was also to be referred to a neurologist.

h. Review AEs occurring after signing informed consent (ie, pretreatment AEs), immediately prior to dosing, and 1 hour post-dose at dosing visits. Electrocardiograms were to be obtained pre-dose, at dosing visits and also 1 hour post-dose at the Baseline visit. Pharmacokinetic and pharmacodynamic (NGF) samples and vital signs (temperature, respiratory rate, blood pressure, and heart rate) were obtained pre-dose and 1 hour post-dose (blood pressure and heart rate only) at all dosing visits and at End of Study/Early Termination/Follow-Up visit.

i. For females of childbearing potential: serum pregnancy test at Screening; urine pregnancy tests at Baseline prior to initial dosing, and at Week 8 prior to dosing; serum pregnancy test at Week 18 (End of Study/Early Termination/Follow-Up).

j. Female subjects of nonchildbearing potential who had not had a hysterectomy or bilateral oophorectomy and who had been amenorrheic for <24 months were required to have serum FSH testing at Screening.

k. The WOMAC subscales, Patient Global Assessment of Osteoarthritis, SF-36v2, and EQ-5D were administered using subject worksheets.

l. Subjects who experienced increased joint pain of a severe and persistent nature were not to continue to receive study drug. These subjects were to be followed for study-specified safety evaluations for at least 16 weeks after their last dose of IV study drug. These evaluations were to take place in the clinic, if the subjects agreed. Subjects who did not agree to continue with study-specified safety evaluations at Clinic Visits continued to be followed per protocol-defined visit time points for at least 16 weeks after their last dose of IV study drug. These Follow-Up visits were conducted by telephone to determine if the subject had experienced any SAE or joint replacement surgeries since their previous (in-person at the site or telephone) visit and had used any concomitant corticosteroid medication since the previous (in-person at the site or telephone) visit. Subjects reporting joint replacement during a telephone Follow-Up visit may have been requested to return to the clinic for examination

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| Study Activity | Screen[a] | Washout[b] | Initial Pain Assessment Period | Treatment[c,d] | | | | | | | Start of Down Taper[d] | End of Study/ Early Term/ Follow-Up[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Baseline[e] | | Week 2 | | Week 4 | Week 8[c] | Week 12 | Week 16[d] | Week 18/24[d] |
| **Study Days:** | **-30 to -1** | **-30 to -3** | **-3 to -1** | **1** | **2-14** | **15 (±2)** | **16-28** | **29 (±2)** | **57 (±2)** | **85 (±2)** | **113 (±2)** | **127 (±2)** |

and/or for collection of diagnostic information. Subjects were reminded about study contraceptive requirements (if applicable).

m. Pill counts were to be completed and checked against dosing records to ensure accurate dosing records and to monitor appropriate numbers of returned tablets. For sites within the United States, 'return' or 'collect' meant that the subject and study personnel could perform a compliance review/pill count as follows: drug accountability was to be conducted in the presence of the subject and, after the accounting for unused study drug was completed, the subject was required to retain possession of the study drug.

n. Telephone calls were made from the study site to the subject to evaluate pain relief and tolerability of the oral medication and to counsel the subject regarding dosing. At a minimum, 1 phone call was to be made between the Randomization visit and Week 2 visit and 1 telephone call was to be made between the Week 2 visit and the Week 4 visit. Additional phone calls were to be made as necessary throughout the course of the study

o. Rescue medication was required to be discontinued 48 hours prior to each study visit.

**Number of Subjects (Planned and Analyzed):** A total of 200 subjects per treatment group (800 subjects in total) were planned. Since the study was terminated early due to US FDA clinical hold, this sample size was not reached; a total of 610 subjects were randomized and treated (141 subjects received placebo, 161 subjects received tanezumab 5 mg, 150 subjects received tanezumab 10 mg, and 158 subjects received oxycodone CR).

**Diagnosis and Main Criteria for Inclusion:** Subjects were males or females, 18 to 75 years of age, inclusive, with a diagnosis of osteoarthritis of the knee or hip based on Kellgren Lawrence x-ray grade of ≥2.

Main Exclusion Criteria: Pregnancy or intent to become pregnant; body mass index >39; other severe pain, significant cardiac, neurological or psychiatric disease.

**Study Treatment:** Subjects were randomized to the treatments indicated in Table 2 in a 1:1:1:1 fashion.

**Table 2. Treatment Groups**

| Treatment Group | IV Treatment (Solution) (2 administrations, 8 weeks apart) | Oral Treatment (Tablets) (Every 12 hours for 16 weeks) |
|---|---|---|
| 1 | Placebo (to match tanezumab) | Placebo (to match oxycodone CR) |
| 2 | Tanezumab 5 mg | Placebo (to match oxycodone CR) |
| 3 | Tanezumab 10 mg | Placebo (to match oxycodone CR) |
| 4 | Placebo (to match tanezumab) | Oxycodone CR 10-40 mg |

CR = controlled release; IV = intravenous.

**Efficacy and Safety Endpoints:**

Primary Endpoints:

- The primary endpoint for the tanezumab versus placebo comparison was the change from Baseline to Week 8 in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain subscale;
- The primary endpoint for the tanezumab versus oxycodone CR comparison was the change from Baseline to Week 8 in the WOMAC Pain subscale.

Secondary Endpoints:

- WOMAC Pain subscale change from Baseline to Weeks 2, 4, 12 and 16;
- WOMAC Physical Function subscale change from Baseline to Weeks 2, 4, 8, 12 and 16;
- Patient Global Assessment (PGA) of Osteoarthritis (5-point Likert scale), change from Baseline to Weeks 2, 4, 8, 12 and 16;
- Outcome Measures in Rheumatology Arthritis Clinical Trials (OMERACT) Osteoarthritis Research Society International (OARSI) responder index at Weeks 2, 4, 8, 12 and 16;

- Treatment Response: Reduction in the WOMAC Pain subscale of ≥30%, ≥50%, ≥70% and ≥90%, at Weeks 2, 4, 8, 12 and 16;
- Cumulative distribution of percent change from Baseline in the WOMAC Pain subscale score to Week 16;
- Treatment Response: Improvement of ≥2 points in PGA of Osteoarthritis at Weeks 2, 4, 8, 12 and 16;
- Average daily Numeric Rating Scale (NRS) pain score in the index knee or index hip change from Baseline to Weeks 1, 2, 3, 4, 6, 8, 10, 12 and 16;
- WOMAC stiffness subscale change from Baseline to Weeks 2, 4, 8, 12 and 16;
- WOMAC average change from Baseline to Weeks 2, 4, 8, 12 and 16;
- WOMAC pain subscale item: Pain when walking on a flat surface, change from Baseline to Weeks 2, 4, 8, 12, and 16;
- WOMAC pain subscale item: Pain when going up or down stairs, change from Baseline to Weeks 2, 4, 8, 12, and 16;
- Medical Outcomes Study Short Form 36 Health Survey (SF-36), version 2 change from Baseline to Week 12 (8 domains plus physical component summary and mental component summary);
- EuroQoL 5D Health State Profile Questionnaire (EQ-5D) health state utility and the 5 items (mobility; self-care; usual activities; pain/discomfort; anxiety/depression) change from Baseline to Week 12;
- Incidence and time to discontinuation due to lack of efficacy.

Safety Endpoints:

- Adverse events (AEs);
- Laboratory safety testing (chemistry, hematology, urinalysis);
- Electrocardiogram (ECG);
- Physical examinations;
- Vital signs;
- Neurologic examination (Neuropathy Impairment Score [NIS]).

**Safety Evaluations:** The safety of tanezumab during the study was assessed by blinded data reviews by the Sponsor and unblinded reviews by an independent Data Safety Monitoring

Board (DSMB). The DSMB reviewed unblinded safety data including AEs, serious adverse events (SAEs), vital signs data, and clinical laboratory data on a regular basis throughout the course of the study. AEs were recorded throughout the study. Laboratory safety tests, ECGs, physical examinations, vital sign assessments and neurological examinations were performed at the time points indicated in Table 1.

**Statistical Methods:** The following population sets were analyzed:

Intent-to-treat (ITT): Included all randomized subjects who received at least 1 dose of IV study drug (either tanezumab or placebo).

Modified ITT (mITT): Included all subjects in the ITT analysis set who had a Week 8 (or earlier visit that could be used as the Week 8 last observation carried forward [LOCF]) visit on or before 23 June 2010 (ie, the date of the clinical hold). Subjects who discontinued the study prior to 23 June 2010 were eligible for inclusion in the mITT set.

The main treatment comparisons were tanezumab 10 mg and 5 mg versus placebo and oxycodone CR. Tests for superiority were 2-sided and tests for non-inferiority were 1-sided. The oxycodone CR treatment group was also to be compared to placebo. This test was to be 2-sided at a significance level of 0.05.

All pairwise comparisons for superiority indicated above were to be performed using a significance level of 5%, except where the Hochberg procedure required a reduction in the significance level to 2.5%. The assessments of non-inferiority were made using the upper limit of a 2-sided 95% confidence interval (CI), again with the exception of where the Hochberg procedure required a reduction, and in this case the upper limit of the 2-sided 97.5% CI was used. A combination of a priori fixed-sequence testing procedure and Hochberg procedure was to be used to maintain the Type I error rate to the 5% level for the multiple comparisons within each objective.

The primary efficacy endpoint was the change from Baseline to Week 8 in the WOMAC Pain subscale, with LOCF used for missing data. The analysis of the WOMAC Pain subscale used the analysis of covariance (ANCOVA) model including Baseline score, index joint, previous opioid use, and treatment group as fixed effects, and study site as a random effect. Estimates of treatment effects and pair-wise treatment comparisons were done using least squares (LS) means and 95% CI. The LOCF imputation method was used for missing data at Week 8. The 95% CI for treatment comparisons were calculated. In addition, if required by the Hochberg procedure, the 97.5% CI was to be calculated for tanezumab versus oxycodone CR treatment comparisons.

Secondary efficacy analyses for the primary endpoint included analysis of change from Baseline to Weeks 2, 4, 12 and 16. These analyses used the LOCF imputation method for missing data, and the same (main effects) ANCOVA model as described for the primary analysis. This analysis was performed using the ITT and mITT analysis sets.

Analyses for the change from Baseline to Weeks 2, 4, 8, 12 and 16 in the WOMAC Physical Function subscale, PGA of osteoarthritis, WOMAC Stiffness subscale, WOMAC Average, WOMAC Pain items (pain when walking on a flat surface, and pain when going up or down

stairs) was the same as the main effects efficacy analysis of the WOMAC Pain subscale (ie, ANCOVA model with Baseline score, index joint, previous opioid use and treatment group, and study site as a random effect, using LOCF where necessary). These analyses were performed using both ITT and mITT analysis sets.

The OMERACT-OARSI percentage response rates were summarized by study week up to Week 16, using LOCF imputation for missing data in any of the component scores, using ITT and mITT analysis sets. The output from the analysis of the OMERACT-OARSI response showed odds ratios (with corresponding 95% CI and significance test) for each comparison of tanezumab dose versus placebo and oxycodone, and oxycodone versus placebo.

For the SF-36, the change from Baseline to Week 12 in each of the 8 health dimensions (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) and 2 components (physical component summary and mental component summary) were analyzed using the same (main effects) efficacy analysis of the WOMAC Pain subscale and using LOCF imputation where necessary, using both ITT and mITT analysis sets.

The change from Baseline at Week 12 in the health state utility was analyzed using ANCOVA as for the primary endpoint. The change from Baseline to Week 12 in the EQ-5D health state utility and the 5 individual items were analyzed using observed data, and for the ITT and mITT analysis sets.

The incidence of discontinuation from the study due to lack of efficacy was analyzed using logistic regression.

The incidence of rescue medication use during Weeks 2, 4, 8, 12, and 16 was analyzed using logistic regression for binary data.

Safety data were summarized descriptively.

**RESULTS**

**Subject Disposition and Demography:** Of the 614 subjects who were randomized, 610 received at least 1 dose of IV study medication. As a result, 610 subjects were randomized and treated and by definition composed the ITT population.

Of the 610 treated subjects, overall 109 subjects completed the study (ie, completed treatment at the Week 16 visit). Subject disposition is summarized in Table 3.

## Table 3. Subject Disposition – Number (%) of Subjects

| Category | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|
| | | 5 mg | 10 mg | 10-40 mg q12h |
| Screened 1669 subjects | | | | |
| Assigned to study drug | 142 | 161 | 152 | 159 |
| Randomized, but not treated | 1 | 0 | 2 | 1 |
| Treated[a] | 141 | 161 | 150 | 158 |
| Completed study[b] | 28 (19.7) | 30 (18.6) | 29 (19.1) | 22 (13.8) |
| Discontinued study[c,d] | 113 (79.6) | 131 (81.4) | 121 (79.6) | 136 (85.5) |

CR = controlled release; ITT = intent-to-treat; q12h = every 12 hours.

a. The number of treated subjects was based on intravenous study drug treatment.

b. Completed study: subjects completed the Week 18 visit.

c. Note that the total number of discontinuations is the same for Table 3 and Table 4, but the percentages differ slightly because Table 3 uses all enrolled subjects as the denominator, whereas Table 4 uses the ITT population as the denominator in the calculation of the percentages.

d. Discontinued indicates subjects discontinued from the study and may or may not have been followed through the end of the study.

Table 4 shows study completion and discontinuation rates for the ITT population, which were generally similar across treatment groups.

## Table 4. Discontinuations From the Study (ITT)

| Category | Number (%) of Subjects | | | |
|---|---|---|---|---|
| | Placebo | Tanezumab | | Oxycodone CR |
| | N=141 | 5 mg N=161 | 10 mg N=150 | 10-40 mg q12h N=158 |
| | n (%) | n (%) | n (%) | n (%) |
| Discontinuation from study | | | | |
| Subject died | 0 | 0 | 0 | 0 |
| AE[a] | 2 (1.4) | 3 (1.9)[a] | 4 (2.7) | 16 (10.1) |
| Insufficient clinical response | 10 (7.1) | 6 (3.7) | 5 (3.3) | 12 (7.6) |
| Lost to follow-up | 2 (1.4) | 3 (1.9) | 4 (2.7) | 4 (2.5) |
| No longer willing to participate in the study | 8 (5.7) | 10 (6.2) | 8 (5.3) | 12 (7.6) |
| Protocol violation | 1 (0.7) | 1 (0.6) | 1 (0.7) | 0 |
| Study terminated by the Sponsor | 89 (63.1) | 108 (67.1) | 99 (66.0) | 92 (58.2) |
| Other reason | 1 (0.7) | 0 | 0 | 0 |
| Total[b] | 113 (80.1) | 131 (81.4) | 121 (80.7) | 136 (86.1) |

AE = adverse event; CR = controlled release; ITT = intent-to-treat; N = number of subjects; n = number of subjects with specified criteria; q12h = every 12 hours.

a. Included both treatment-emergent and non-treatment-emergent AEs; for the tanezumab 5 mg treatment group, 1 subject discontinued from the study due to a non-treatment-emergent AE.

b. Note that the total number of discontinuations is the same for both Table 3 and Table 4, but the percentages differ because Table 3 uses all enrolled subjects as the denominator, whereas Table 4 uses the ITT population as the denominator in the calculation of the percentages.

The Sponsor prematurely discontinued this study due to an FDA-imposed clinical hold. Sites were notified to discontinue randomization and treatment with study medication on 23 June 2010. When the study was discontinued, 614 (76.8%) of the originally planned 800 subjects were randomized, with 610 subjects having received treatment. At the time of the clinical hold 182 (29.8%) of the treated subjects had either already completed or discontinued from the study, or had reached the Week 16 visit, with 428 (70.2%) of treated subjects having not yet reached the Week 16 visit. There are 499 (81.8%) subjects with a WOMAC Pain assessment at Week 8, compared to 244 (40.0%) and 220 (36.1%) at Weeks 12 and 16, respectively. Due to the impact of the clinical hold, resulting in a limited

availability of data for the primary endpoint at Week 16, the timing of the primary endpoint was amended from Week 16 to Week 8.

Table 5 summarizes the number of subjects included in the ITT and mITT analysis sets and in the safety analyses.

**Table 5. Number (%) of Subjects Included in the Analyses**

| | Number (%)[a] of Subjects | | | |
|---|---|---|---|---|
| | Placebo | Tanezumab | | Oxycodone CR |
| | | 5 mg | 10 mg | 10-40 mg q12h |
| Assigned to study drug[a] | 142 | 161 | 152 | 159 |
| Treated (ITT) | 141 | 161 | 150 | 158 |
| mITT analysis set | 137 | 153 | 149 | 156 |
| Analyzed for safety | | | | |
| Adverse events | 141 (99.3) | 161 (100.0) | 150 (98.7) | 158 (99.4) |
| Laboratory data | 136 (95.8) | 155 (96.3) | 147 (96.7) | 146 (91.8) |

The number of treated subjects was based on intravenous study drug treatment. The number of subjects with laboratory data is lower than the total number of treated subjects because some subjects did not return to the clinic for their laboratory tests.
CR = controlled release; ITT = intent-to-treat; mITT = modified ITT; q12h = every 12 hours.

a. Percentages were based on the number of subjects assigned to study drug (ie, the number randomized).

Baseline demographics characteristics were similar across treatment groups (Table 6). Across the 4 treatment groups, 59.6% to 65.2% of subjects were female, 76.6% to 82.6% were White, and the mean age was 57.0 to 57.8 years.

**Table 6. Demographic Characteristics (ITT)**

| | Number (%) of Subjects | | | |
|---|---|---|---|---|
| | Placebo | Tanezumab | | Oxycodone CR |
| | | 5 mg | 10 mg | 10-40 mg q12h |
| | N=141 | N=161 | N=150 | N=158 |
| Gender, n (%) | | | | |
| Male | 49 (34.8) | 65 (40.4) | 56 (37.3) | 59 (37.3) |
| Female | 92 (65.2) | 96 (59.6) | 94 (62.7) | 99 (62.7) |
| Age (years), n (%) | | | | |
| 18–44 | 15 (10.6) | 12 (7.5) | 18 (12.0) | 15 (9.5) |
| 45–64 | 85 (60.3) | 109 (67.7) | 92 (61.3) | 105 (66.5) |
| ≥65 | 41 (29.1) | 40 (24.8) | 40 (26.7) | 38 (24.1) |
| Mean (SD) | 57.2 (10.5) | 57.8 (9.2) | 57.0 (9.8) | 57.6 (9.1) |
| Range | 28-75 | 28-75 | 29-74 | 33-75 |
| Race, n (%) | | | | |
| White | 113 (80.1) | 133 (82.6) | 119 (79.3) | 121 (76.6) |
| Black | 26 (18.4) | 26 (16.1) | 30 (20.0) | 30 (19.0) |
| Asian | 0 | 1 (0.6) | 0 | 4 (2.5) |
| Other | 2 (1.4) | 1 (0.6) | 1 (0.7) | 3 (1.9) |
| Weight (kg) | | | | |
| Mean (SD) | 87.1 (18.8) | 87.6 (18.5) | 88.7 (17.5) | 88.7 (16.8) |
| Range | 45.8-149.7 | 43.1-140.6 | 48.8-132.5 | 46.7-134.7 |
| Body mass index (kg/m$^2$) | | | | |
| Mean (SD) | 30.3 (4.9) | 30.6 (4.9) | 31.2 (4.8) | 31.0 (4.7) |
| Range | 19.1-39.0 | 18.2-38.8 | 19.6-39.0 | 19.4-38.6 |

Body mass index was computed as weight/(height × 0.01)$^2$.
CR = controlled release; ITT = intent-to-treat; N = number of subjects; n = number of subjects with specified criteria; q12h = every 12 hours; SD = standard deviation.

**Efficacy Results:**

Primary Endpoint: The primary efficacy endpoint of change from Baseline to Week 8 in the WOMAC Pain subscale is summarized in Table 7. The primary objective of demonstrating superior efficacy of treatment with tanezumab compared to placebo treatment at Week 8 (ITT) in the WOMAC Pain subscale was met, with p-values <0.001 for both the tanezumab 10 mg and tanezumab 5 mg treatment group comparisons versus placebo-treated subjects. The tanezumab 10 mg and 5 mg treatment groups were also shown to be superior to oxycodone CR treatment.

**Table 7. Summary of Analysis of Primary Efficacy Endpoint (WOMAC Pain Subscale), Change From Baseline to Week 8 (ITT/mITT, LOCF)**

| | Number (%) of Subjects | | | |
|---|---|---|---|---|
| | Placebo | Tanezumab | | Oxycodone CR |
| | N=141 | 5 mg N=161 | 10 mg N=150 | 10-40 mg q12h N=158 |
| **WOMAC Pain Subscale[a], Baseline and Change From Baseline to Week 8 (0-10 NRS)** | | | | |
| **ITT** | | | | |
| N | 141 | 161 | 150 | 158 |
| Baseline mean (SD) | 7.75 (1.21) | 7.85 (1.27) | 7.63 (1.30) | 7.85 (1.27) |
| Change from Baseline LS mean (SE)* | -2.62 (0.24) | -3.58 (0.22) | -3.58 (0.23) | -2.59 (0.22) |
| 95% CI for LS mean | (-3.09, -2.15) | (-4.01, -3.16) | (-4.03, -3.14) | (-3.02, -2.16) |
| Comparison vs placebo | | | | |
| Change from Baseline LS mean (SE)* | | -0.96 (0.27) | -0.97 (0.27) | 0.03 (0.27) |
| 95% CI for LS mean | | (-1.49, -0.44) | (-1.50, -0.43) | (-0.50, 0.56) |
| p-value† | | <0.001 | <0.001 | 0.917 |
| Comparison vs oxycodone CR | | | | |
| Change from Baseline LS mean (SE)* | | -0.99 (0.26) | -0.99 (0.26) | |
| 95% CI for LS mean | | (-1.50, -0.48) | (-1.51, -0.48) | |
| p-value† | | <0.001 | <0.001 | |
| **mITT** | | | | |
| N | 137 | 153 | 149 | 156 |
| Baseline mean (SD) | 7.75 (1.20) | 7.87 (1.26) | 7.64 (1.31) | 7.86 (1.27) |
| Change from Baseline LS mean (SE)* | -2.28 (0.26) | -3.14 (0.24) | -2.81 (0.24) | -2.17 (0.24) |
| 95% CI for LS mean | (-2.79, -1.77) | (-3.61, -2.68) | (-3.28, -2.33) | (-2.64, -1.71) |
| Comparison vs placebo | | | | |
| Change from Baseline LS mean (SE)* | | -0.86 (0.28) | -0.53 (0.28) | 0.11 (0.28) |
| 95% CI for LS mean | | (-1.41, -0.32) | (-1.07, 0.02) | (-0.43, 0.65) |
| p-value† | | 0.002 | 0.058 | 0.700 |
| Comparison vs oxycodone CR | | | | |
| Change from Baseline LS mean (SE)* | | -0.97 (0.27) | -0.63 (0.27) | |
| 95% CI for LS mean | | (-1.49, -0.45) | (-1.16, -0.11) | |
| p-value† | | <0.001 | 0.018 | |

*LS means were estimated from the corresponding ANCOVA model.
†p-value is based on ANCOVA from pairwise comparisons.
ANCOVA model includes treatment as main effect, Baseline value, index joint, previous opioid use as covariates, and study site as a random effect.
ANCOVA = analysis of covariance; CI = confidence interval; CR = controlled release, ITT = intent-to-treat; LOCF = last observation carried forward; LS mean = Least Squares means; mITT = modified ITT, N = number of subjects in each treatment group with Baseline or change from Baseline to Week 8 data; NRS = numeric rating scale; q12h = every 12 hours; SD = standard deviation; SE = standard error; vs = versus; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
a. WOMAC subscale score ranges from 0 to 10, where 0 is the best response. A change from Baseline <0 is an improvement.

Secondary Endpoints:

WOMAC Pain and Physical Function Subscales: Table 8 summarizes change from Baseline to Week 8 in the secondary efficacy endpoint of the WOMAC Physical Function subscale. Superior efficacy of tanezumab compared to placebo treatment at Week 8 (ITT) was demonstrated in the WOMAC Physical Function subscale, with p-values <0.001 for comparisons of both treatment with tanezumab 5 mg and 10 mg versus placebo treatment. Summaries of change from Baseline for the WOMAC Pain and Physical Function subscales using LOCF are provided Table 9 (ITT) and Table 10 (mITT).

For the comparison of tanezumab treatment with oxycodone CR treatment (mITT), there were statistically significant improvements with both tanezumab doses in the WOMAC Physical Function subscale ($p < 0.001$ and $p = 0.002$ for tanezumab 5 mg and 10 mg, respectively). The oxycodone CR treatment group did not show a statistically significant difference from the placebo treatment group in the WOMAC Physical Function subscale (Table 8).

**Table 8. Summary of WOMAC Physical Function Subscale, Change From Baseline to Week 8 (ITT/mITT, LOCF)**

| | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|
| | | 5 mg | 10 mg | 10-40 mg q12h |
| | N=141 | N=161 | N=150 | N=158 |
| **WOMAC Physical Function Subscale[a], Baseline and Change From Baseline to Week 8 (0-10 NRS)** | | | | |
| **ITT** | | | | |
| N | 140 | 161 | 150 | 158 |
| Baseline mean (SD) | 7.19 (1.50) | 7.30 (1.58) | 7.04 (1.54) | 7.25 (1.53) |
| Change from Baseline LS mean (SE)* | -1.91 (0.23) | -3.05 (0.20) | -3.06 (0.21) | -2.05 (0.21) |
| 95% CI for LS mean | (-2.36, -1.47) | (-3.45, -2.65) | (-3.48, -2.64) | (-2.45, -1.64) |
| Comparison vs placebo | | | | |
| Change from Baseline LS mean (SE)* | | -1.14 (0.26) | -1.15 (0.26) | -0.14 (0.26) |
| 95% CI for LS mean | | (-1.65, -0.63) | (-1.67, -0.63) | (-0.65, 0.37) |
| p-value† | | <0.001 | <0.001 | 0.595 |
| Comparison vs oxycodone CR | | | | |
| Change from Baseline LS mean (SE)* | | -1.00 (0.25) | -1.01 (0.25) | |
| 95% CI for LS mean | | (-1.49, -0.51) | (-1.51, -0.51) | |
| p-value† | | <0.001 | <0.001 | |
| **mITT** | | | | |
| N | 136 | 153 | 149 | 156 |
| Baseline mean (SD) | 7.17 (1.51) | 7.32 (1.59) | 7.05 (1.54) | 7.26 (1.53) |
| Change from Baseline LS mean (SE)* | -1.67 (0.24) | -2.78 (0.22) | -2.52 (0.23) | -1.71 (0.22) |
| 95% CI for LS mean | (-2.15, -1.20) | (-3.22, -2.35) | (-2.97, -2.08) | (-2.14, -1.27) |
| Comparison vs Placebo | | | | |
| Change from Baseline LS mean (SE)* | | -1.11 (0.27) | -0.85 (0.27) | -0.03 (0.26) |
| 95% CI for LS mean | | (-1.63, -0.59) | (-1.37, -0.33) | (-0.55, 0.49) |
| p-value† | | <0.001 | 0.002 | 0.898 |
| Comparison vs oxycodone CR | | | | |
| Change from Baseline LS mean (SE)* | | -1.08 (0.26) | -0.82 (0.26) | |
| 95% CI for LS mean | | (-1.58, -0.57) | (-1.32, -0.31) | |
| p-value† | | <0.001 | 0.002 | |

*LS means were estimated from the corresponding ANCOVA model.
†p-value is based on ANCOVA from pairwise comparisons.
ANCOVA model includes treatment as main effect, Baseline value, index joint, previous opioid use as covariates, and study site as a random effect.
ANCOVA = analysis of covariance; CI = confidence interval; CR = controlled release; ITT = intent-to-treat; LOCF = last observation carried forward; LS mean = least squares means; mITT = modified ITT; N = number of subjects in each treatment group with Baseline or change from Baseline to Week 8 data; NRS = numeric rating scale; q12h = every 12 hours; SD = standard deviation; SE = standard error; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
a. WOMAC subscale score ranges from 0 to 10, where 0 is the best response. A change from Baseline of <0 is an improvement.

## Table 9. Summary of Change From Baseline for WOMAC Pain and Physical Function Subscales by Week (ITT, LOCF)

| | | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|---|
| | | | 5 mg | 10 mg | 10-40 mg q12h |
| | | N=141 | N=161 | N=150 | N=158 |
| **WOMAC Pain Subscale Score** | | | | | |
| Baseline | Score | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | 7.75 ( 1.21) | 7.85 ( 1.27) | 7.63 ( 1.30) | 7.85 ( 1.27) |
| | Median | 7.8 | 7.8 | 7.6 | 8.0 |
| | Min, Max | (5.0, 10.0) | (5.0, 10.0) | (2.8, 10.0) | (4.8, 10.0) |
| Week 2 (LOCF) | Change from baseline | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | -2.12 (1.91) | -2.47 (2.23) | -2.29 (2.25) | -2.31 (2.09) |
| | Median | -2.0 | -2.0 | -1.9 | -2.0 |
| | Min, Max | (-8.0, 1.4) | (-8.4, 1.0) | (-9.2, 1.4) | (-8.4, 2.0) |
| Week 4 (LOCF) | Change from baseline | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | -2.55 (2.09) | -3.56 (2.54) | -3.45 (2.62) | -2.87 (2.25) |
| | Median | -2.4 | -3.2 | -3.3 | -2.5 |
| | Min, Max | (-7.6, 1.8) | (-9.4, 1.0) | (-9.6, 3.0) | (-8.6, 2.0) |
| Week 8 (LOCF) | Change from baseline | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | -2.74 (2.26) | -3.71 (2.49) | -3.63 (2.62) | -2.71 (2.36) |
| | Median | -2.6 | -3.4 | -3.6 | -2.1 |
| | Min, Max | (-8.2, 1.8) | (-9.2, 2.6) | (-9.6, 1.6) | (-9.2, 2.4) |
| Week 12 (LOCF) | Change from baseline | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | -2.85 (2.37) | -3.82 (2.62) | -3.64 (2.60) | -2.80 (2.41) |
| | Median | -2.6 | -3.4 | -3.6 | -2.1 |
| | Min, Max | (-9.4, 1.8) | (-9.4, 2.6) | (-9.6, 3.6) | (-9.2, 2.4) |
| Week 16 (LOCF) | Change from baseline | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | -2.95 (2.46) | -3.80 (2.60) | -3.65 (2.51) | -2.79 (2.39) |
| | Median | -2.6 | -3.6 | -3.6 | -2.0 |
| | Min, Max | (-10.0, 1.8) | (-9.4, 2.6) | (-9.6, 1.4) | (-9.2, 2.4) |
| **WOMAC Physical Function Subscale Score** | | | | | |
| Baseline | Score | | | | |
| | N | 140 | 161 | 150 | 158 |
| | Mean (SD) | 7.19 (1.50) | 7.30 (1.58) | 7.04 (1.54) | 7.25 (1.53) |
| | Median | 7.4 | 7.4 | 7.2 | 7.5 |
| | Min, Max | (1.0, 10.0) | (2.7, 10.0) | (2.8, 10.0) | (2.9, 10.0) |
| Week 2 (LOCF) | Change from baseline | | | | |
| | N | 140 | 161 | 150 | 158 |
| | Mean (SD) | -1.51 (1.73) | -2.16 (2.30) | -1.95 (2.08) | -1.71 (1.94) |
| | Median | -1.1 | -1.6 | -1.4 | -1.3 |
| | Min, Max | (-6.7, 1.5) | (-7.8, 2.8) | (-8.2, 2.2) | (-7.0, 2.8) |
| Week 4 (LOCF) | Change from baseline | | | | |
| | N | 140 | 161 | 150 | 158 |
| | Mean (SD) | -1.89 (1.96) | -3.04 (2.59) | -2.94 (2.61) | -2.10 (2.20) |
| | Median | -1.6 | -2.8 | -2.9 | -1.7 |
| | Min, Max | (-7.1, 2.5) | (-9.4, 2.5) | (-8.1, 2.5) | (-8.4, 3.9) |
| Week 8 (LOCF) | Change from baseline | | | | |
| | N | 140 | 161 | 150 | 158 |
| | Mean (SD) | -2.01 (2.09) | -3.18 (2.49) | -3.08 (2.50) | -2.14 (2.30) |
| | Median | -1.7 | -3.2 | -2.9 | -1.7 |
| | Min, Max | (-7.8, 2.2) | (-9.4, 2.9) | (-8.5, 1.5) | (-8.1, 2.9) |
| Week 12 (LOCF) | Change from baseline | | | | |
| | N | 140 | 161 | 150 | 158 |
| | Mean (SD) | -2.17 (2.26) | -3.34 (2.62) | -3.09 (2.45) | -2.17 (2.28) |

## Table 9. Summary of Change From Baseline for WOMAC Pain and Physical Function Subscales by Week (ITT, LOCF)

| | | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|---|
| | | | 5 mg | 10 mg | 10-40 mg q12h |
| | | N=141 | N=161 | N=150 | N=158 |
| | Median | -1.7 | -3.4 | -3.0 | -1.7 |
| | Min, Max | (-8.9, 2.5) | (-9.5, 2.9) | (-8.5, 1.5) | (-7.6, 2.8) |
| Week 16 (LOCF) | Change from baseline | | | | |
| | N | 140 | 161 | 150 | 158 |
| | Mean (SD) | -2.26 (2.37) | -3.27 (2.61) | -3.10 (2.42) | -2.18 (2.26) |
| | Median | -1.7 | -3.1 | -3.1 | -1.7 |
| | Min, Max | (-10.0, 1.9) | (-9.5, 2.9) | (-8.5, 1.5) | (-7.8, 2.8) |

WOMAC subscale scores range from 0 to 10, where 0 is the best response.
CR = controlled release; ITT = intent-to-treat; LOCF = last observation carried forward; Max = maximum; Min = minimum; N = number of subjects in each treatment group; q12h = every 12 hours; SD = standard deviation; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

## Table 10. Summary of Change from Baseline for WOMAC Pain and Physical Function Subscales by Week (mITT, LOCF)

| | | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|---|
| | | | 5 mg | 10 mg | 10-40 mg q12h |
| | | N=137 | N=153 | N=149 | N=156 |
| **WOMAC Pain Subscale Score** | | | | | |
| Baseline | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | 7.75 (1.20) | 7.87 (1.26) | 7.64 (1.31) | 7.86 (1.27) |
| | Median | 7.8 | 8.0 | 7.6 | 8.0 |
| | Min, Max | (5.0, 10.0) | (5.0, 10.0) | (2.8, 10.0) | (4.8, 10.0) |
| Week 2 (LOCF) | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | 5.77 (2.19) | 5.53 (2.52) | 5.59 (2.36) | 5.78 (2.37) |
| | Median | 6.2 | 6.0 | 5.8 | 6.2 |
| | Min, Max | (0.0, 10.0) | (0.0, 10.0) | (0.6, 10.0) | (0.2, 10.0) |
| Week 4 (LOCF) | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | 5.38 (2.31) | 4.60 (2.73) | 4.79 (2.65) | 5.38 (2.43) |
| | Median | 5.8 | 4.6 | 5.2 | 5.5 |
| | Min, Max | (0.0, 9.8) | (0.0, 10.0) | (0.0, 10.0) | (0.0, 9.8) |
| Week 8 (LOCF) | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | 5.17 (2.44) | 4.45 (2.73) | 4.63 (2.62) | 5.45 (2.41) |
| | Median | 5.4 | 4.6 | 4.6 | 5.8 |
| | Min, Max | (0.0, 10.0) | (0.0, 10.0) | (0.0, 10.0) | (0.0, 9.8) |
| Week 12 (LOCF) | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | 5.06 (2.44) | 4.29 (2.78) | 4.58 (2.62) | 5.29 (2.47) |
| | Median | 5.4 | 4.0 | 4.8 | 5.6 |
| | Min, Max | (0.0, 9.8) | (0.0, 10.0) | (0.0, 10.0) | (0.0, 9.8) |
| Week 16 (LOCF) | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | 4.90 (2.52) | 4.24 (2.77) | 4.47 (2.61) | 5.29 (2.46) |
| | Median | 5.0 | 4.0 | 4.4 | 5.6 |
| | Min, Max | (0.0, 9.8) | (0.0, 10.0) | (0.0, 10.0) | (0.0, 9.8) |
| **WOMAC Physical Function Subscale Score** | | | | | |
| Baseline | N | 136 | 153 | 149 | 156 |
| | Mean (SD) | 7.17 (1.51) | 7.32 (1.59) | 7.05 (1.54) | 7.26 (1.53) |
| | Median | 7.3 | 7.4 | 7.2 | 7.5 |
| | Min, Max | (1.0, 10.0) | (2.7, 10.0) | (2.8, 10.0) | (2.9, 10.0) |
| Week 2 (LOCF) | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | 5.74 (2.18) | 5.32 (2.44) | 5.32 (2.32) | 5.70 (2.27) |
| | Median | 5.9 | 5.5 | 5.5 | 5.9 |
| | Min, Max | (0.2, 10.0) | (0.0, 10.0) | (0.3, 10.0) | (0.2, 10.0) |
| Week 4 (LOCF) | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | 5.43 (2.33) | 4.52 (2.62) | 4.58 (2.58) | 5.43 (2.35) |
| | Median | 5.9 | 4.5 | 5.0 | 5.7 |
| | Min, Max | (0.1, 9.9) | (0.0, 10.0) | (0.2, 10.0) | (0.1, 9.9) |
| Week 8 (LOCF) | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | 5.29 (2.40) | 4.32 (2.59) | 4.43 (2.50) | 5.39 (2.35) |
| | Median | 5.8 | 4.2 | 4.5 | 5.7 |
| | Min, Max | (0.1, 9.9) | (0.0, 10.0) | (0.0, 10.0) | (0.3, 9.9) |
| Week 12 (LOCF) | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | 5.13 (2.46) | 4.13 (2.63) | 4.40 (2.49) | 5.31 (2.38) |
| | Median | 5.7 | 3.7 | 4.3 | 5.5 |
| | Min, Max | (0.1, 9.9) | (0.0, 10.0) | (0.0, 10.0) | (0.2, 9.9) |
| Week 16 (LOCF) | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | 4.97 (2.53) | 4.10 (2.65) | 4.28 (2.50) | 5.29 (2.36) |
| | Median | 5.5 | 3.8 | 4.0 | 5.5 |
| | Min, Max | (0.0, 9.9) | (0.0, 10.0) | (0.0, 10.0) | (0.1, 9.9) |

WOMAC subscale scores range from 0 to 10, where 0 is the best response.
CR = controlled release; LOCF = last observation carried forward; mITT = modified intent-to-treat; Max = maximum; Min = minimum; N = number of subjects in each treatment group; q12h = every 12 hours; SD = standard deviation; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Patient Global Assessment of Osteoarthritis: Table 11 summarizes change from Baseline to Week 8 in the secondary efficacy endpoint of PGA of osteoarthritis. Summary of PGA of osteoarthritis is summarized in Table 12 and Table 13. Statistically significant improvements were observed for both tanezumab treatment groups compared to the placebo treatment group (ITT) for the PGA of osteoarthritis (tanezumab 5 mg and 10 mg treatment groups, $p < 0.001$). The oxycodone CR treatment group did not show a statistically significant difference from the placebo treatment group (mITT).

For the comparison of tanezumab treatment with oxycodone CR treatment (mITT) from Baseline to Week 8, there were statistically significant improvements with both tanezumab doses in the PGA of osteoarthritis ($p < 0.001$, both doses; Table 11).

## Table 11. Summary of Patient Global Assessment of Osteoarthritis, Change From Baseline to Week 8 (ITT/mITT, LOCF)

| | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|
| | | 5 mg | 10 mg | 10-40 mg q12h |
| | N=141 | N=161 | N=150 | N=158 |
| **PGA of OA[a], Baseline and Change From Baseline to Week 8 (0-10 NRS)** | | | | |
| **ITT** | | | | |
| N | 141 | 161 | 150 | 158 |
| Baseline mean (SD) | 3.60 (0.68) | 3.58 (0.65) | 3.57 (0.68) | 3.59 (0.62) |
| Change from Baseline LS mean (SE)* | -0.52 (0.08) | -0.90 (0.07) | -1.00 (0.08) | -0.55 (0.07) |
| 95% CI for LS mean | (-0.68, -0.36) | (-1.04, -0.76) | (-1.14, -0.85) | (-0.69, -0.41) |
| Comparison vs placebo | | | | |
| Change from Baseline LS mean (SE)* | | -0.38 (0.09) | -0.47 (0.09) | -0.03 (0.09) |
| 95% CI for LS mean | | (-0.56, -0.20) | (-0.66, -0.29) | (-0.21, 0.15) |
| p-value† | | <0.001 | <0.001 | 0.760 |
| Comparison vs oxycodone CR | | | | |
| Change from Baseline LS mean (SE)* | | -0.35 (0.09) | -0.45 (0.09) | |
| 95% CI for LS mean | | (-0.52, -0.17) | (-0.62, -0.27) | |
| p-value† | | <0.001 | <0.001 | |
| **mITT** | | | | |
| N | 137 | 153 | 149 | 156 |
| Baseline mean (SD) | 3.59 (0.68) | 3.59 (0.65) | 3.56 (0.68) | 3.59 (0.62) |
| Change from Baseline LS mean (SE)* | -0.51 (0.08) | -0.90 (0.07) | -0.79 (0.08) | -0.50 (0.07) |
| 95% CI for LS mean | (-0.67, -0.35) | (-1.05, -0.76) | (-0.94, -0.64) | (-0.64, -0.35) |
| Comparison vs placebo | | | | |
| Change from Baseline LS mean (SE)* | | -0.39 (0.09) | -0.28 (0.09) | 0.01 (0.09) |
| 95% CI for LS mean | | (-0.57, -0.21) | (-0.46, -0.10) | (-0.16, 0.19) |
| p-value† | | <0.001 | 0.002 | 0.876 |
| Comparison vs oxycodone CR | | | | |
| Change from Baseline LS mean (SE)* | | -0.41 (0.09) | -0.29 (0.09) | |
| 95% CI for LS mean | | (-0.58, -0.23) | (-0.47, -0.12) | |
| p-value† | | <0.001 | <0.001 | |

* LS means were estimated from the corresponding ANCOVA model.
† p-value is based on ANCOVA from pairwise comparisons.
ANCOVA model includes treatment as main effect, Baseline value, index joint, previous opioid use as covariates, and study site as a random effect.
ANCOVA = analysis of covariance; CI = confidence interval; CR = controlled release; ITT = intent-to-treat; LOCF = last observation carried forward; LS mean = least squares means; mITT = modified ITT; N = number of subjects in each treatment group with Baseline or change from Baseline to Week 8 data; NRS = numeric rating scale; PGA of OA = patient global assessment of osteoarthritis; q12h = every 12 hours; SD = standard deviation; SE = standard error; vs = versus.
a. PGA of OA is a 5-point Likert scale, where 1 is "very good" and 5 is "very poor." A change from Baseline <0 is an improvement.

## Table 12. Summary of Patient Global Assessment of Osteoarthritis by Week (ITT, LOCF)

| | | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|---|
| | | | 5 mg | 10 mg | 10-40 mg q12h |
| | | N=141 | N=161 | N=150 | N=158 |
| Baseline | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | 3.60 (0.68) | 3.58 (0.65) | 3.57 (0.68) | 3.59 (0.62) |
| | Median | 3.0 | 3.0 | 3.0 | 4.0 |
| | Min, Max | (3.0, 5.0) | (3.0, 5.0) | (3.0, 5.0) | (2.0, 5.0) |
| Week 2 (LOCF) | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | 3.11 (0.72) | 2.87 (0.81) | 2.94 (0.79) | 3.05 (0.72) |
| | Median | 3.0 | 3.0 | 3.0 | 3.0 |
| | Min, Max | (1.0, 5.0) | (1.0, 5.0) | (1.0, 5.0) | (1.0, 5.0) |
| Week 4 (LOCF) | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | 3.02 (0.75) | 2.59 (0.91) | 2.58 (0.78) | 2.95 (0.73) |
| | Median | 3.0 | 3.0 | 3.0 | 3.0 |
| | Min, Max | (1.0, 5.0) | (1.0, 5.0) | (1.0, 4.0) | (1.0, 5.0) |
| Week 8 (LOCF) | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | 3.04 (0.78) | 2.66 (0.94) | 2.55 (0.89) | 3.01 (0.71) |
| | Median | 3.0 | 3.0 | 3.0 | 3.0 |
| | Min, Max | (1.0, 5.0) | (1.0, 5.0) | (1.0, 5.0) | (1.0, 5.0) |
| Week 12 (LOCF) | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | 2.96 (0.77) | 2.60 (0.95) | 2.49 (0.86) | 2.99 (0.78) |
| | Median | 3.0 | 3.0 | 3.0 | 3.0 |
| | Min, Max | (1.0, 5.0) | (1.0, 5.0) | (1.0, 5.0) | (1.0, 5.0) |
| Week 16 (LOCF) | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | 2.96 (0.76) | 2.62 (0.96) | 2.49 (0.82) | 3.00 (0.77) |
| | Median | 3.0 | 3.0 | 3.0 | 3.0 |
| | Min, Max | (1.0, 5.0) | (1.0, 5.0) | (1.0, 4.0) | (1.0, 5.0) |

Patient Global Assessment score ranges from 1 (Very Good) to 5 (Very Poor).
CR = controlled release; ITT = Intent-to-treat; LOCF = last observation carried forward; Max = maximum; Min = minimum; N = number of subjects in each treatment group; q12h = every 12 hours; SD = standard deviation; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

**Table 13. Summary of Patient Global Assessment of Osteoarthritis by Week (mITT, LOCF)**

| | | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|---|
| | | | 5 mg | 10 mg | 10-40 mg q12h |
| | | N=137 | N=153 | N=149 | N=156 |
| Baseline | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | 3.59 (0.68) | 3.59 (0.65) | 3.56 (0.68) | 3.59 (0.62) |
| | Median | 3.0 | 4.0 | 3.0 | 4.0 |
| | Min, Max | (3.0, 5.0) | (3.0, 5.0) | (3.0, 5.0) | (2.0, 5.0) |
| Week 2 (LOCF) | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | 3.12 (0.75) | 2.89 (0.80) | 3.01 (0.81) | 3.10 (0.72) |
| | Median | 3.0 | 3.0 | 3.0 | 3.0 |
| | Min, Max | (1.0, 5.0) | (1.0, 5.0) | (1.0, 5.0) | (1.0, 5.0) |
| Week 4 (LOCF) | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | 3.09 (0.77) | 2.65 (0.89) | 2.74 (0.85) | 3.04 (0.74) |
| | Median | 3.0 | 3.0 | 3.0 | 3.0 |
| | Min, Max | (1.0, 5.0) | (1.0, 5.0) | (1.0, 5.0) | (1.0, 5.0) |
| Week 8 (LOCF) | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | 3.04 (0.82) | 2.66 (0.90) | 2.76 (0.89) | 3.07 (0.71) |
| | Median | 3.0 | 3.0 | 3.0 | 3.0 |
| | Min, Max | (1.0, 5.0) | (1.0, 5.0) | (1.0, 5.0) | (1.0, 5.0) |
| Week 12 (LOCF) | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | 2.96 (0.83) | 2.61 (0.91) | 2.73 (0.89) | 3.03 (0.77) |
| | Median | 3.0 | 3.0 | 3.0 | 3.0 |
| | Min, Max | (1.0, 5.0) | (1.0, 5.0) | (1.0, 5.0) | (1.0, 5.0) |
| Week 16 (LOCF) | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | 2.92 (0.82) | 2.63 (0.92) | 2.70 (0.87) | 3.04 (0.76) |
| | Median | 3.0 | 3.0 | 3.0 | 3.0 |
| | Min, Max | (1.0, 5.0) | (1.0, 5.0) | (1.0, 5.0) | (1.0, 5.0) |

Patient Global Assessment score ranges from 1 (Very Good) to 5 (Very Poor).
CR = controlled release; LOCF = last observation carried forward; mITT = modified intent-to-treat; Max = maximum; Min = minimum; N = number of subjects in each treatment group; q12h = every 12 hours; SD = standard deviation; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

OMERACT-OARSI Responder Index: Table 14 summarizes OMERACT-OARSI responder rates at Week 8 by treatment group. Summary of OMECART-OARSI responder index at Weeks 2, 4, 8, 12 and 16 for ITT and mITT population is summarized in Table 15 and Table 16. The proportion of responders at Week 8 (ITT) was greater in the tanezumab 5 mg and 10 mg treatment groups compared with the placebo treatment group.

## Table 14. Summary of Analysis of OMERACT-OARSI Response From Baseline to Week 8 (ITT/mITT, LOCF)

| | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|
| | | 5 mg | 10 mg | 10-40 mg q12h |
| | N=141 | N=161 | N=150 | N=158 |
| **ITT** | | | | |
| Yes, n (%) | 81 (57.4%) | 120 (74.5%) | 105 (70.0%) | 93 (58.9%) |
| No, n (%) | 60 (42.6%) | 41 (25.5%) | 45 (30.0%) | 65 (41.1%) |
| Versus placebo | | | | |
| Odds ratio | | 2.13 | 1.73 | 1.06 |
| 95% CI for odds ratio | | (1.30, 3.48) | (1.06, 2.80) | (0.66, 1.68) |
| p-value* | | 0.002 | 0.027 | 0.816 |
| Versus oxycodone CR | | | | |
| Odds ratio | | 2.02 | 1.63 | |
| 95% CI for odds ratio | | (1.25, 3.25) | (1.02, 2.62) | |
| p-value* | | 0.004 | 0.042 | |
| **mITT** | | | | |
| Yes, n (%) | 78 (56.9%) | 108 (70.6%) | 86 (57.7%) | 80 (51.3%) |
| No, n (%) | 59 (43.1%) | 45 (29.4%) | 63 (42.3%) | 76 (48.7%) |
| Versus placebo | | | | |
| Odds ratio | | 1.82 | 1.05 | 0.80 |
| 95% CI for odds ratio | | (1.12, 2.97) | (0.65, 1.68) | (0.50, 1.27) |
| p-value* | | 0.016 | 0.844 | 0.342 |
| Versus oxycodone CR | | | | |
| Odds ratio | | 2.28 | 1.31 | |
| 95% CI for odds ratio | | (1.42, 3.65) | (0.83, 2.07) | |
| p-value* | | <0.001 | 0.240 | |

*p-value (odds ratio and 95% CI) is based on logistic regression model from pairwise comparisons versus placebo. Logistic Regression model includes treatment as a main effect, and Baseline WOMAC Pain subscale score, index joint as covariates.
CI = confidence interval; CR = controlled release; ITT = intent-to-treat; LOCF = last observation carried forward; mITT = modified ITT; n = number of subjects with/without a response; N = number of subjects in each dose group; OARSI = Osteoarthritis Research Society International, OMERACT = Outcome Measures in Rheumatology, q12h = every 12 hours WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

## Table 15. Summary of Analysis of OMERACT-OARSI Response by Week (ITT, LOCF)

| | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|
| | | 5 mg | 10 mg | 10-40 mg q12h |
| | N=141 | N=161 | N=150 | N=158 |
| Week 2 (LOCF) OMERACT-OARSI response | | | | |
| Yes, n (%) | 70 (49.6%) | 89 (55.3%) | 82 (54.7%) | 81 (51.3%) |
| No, n (%) | 71 (50.4%) | 72 (44.7%) | 68 (45.3%) | 77 (48.7%) |
| Versus placebo | | | | |
| Odds ratio | | 1.23 | 1.19 | 1.07 |
| 95% CI for odds ratio | | (0.78, 1.94) | (0.75, 1.89) | (0.67, 1.69) |
| p-value* | | 0.381 | 0.471 | 0.784 |
| Versus oxycodone CR | | | | |
| Odds ratio | | 1.15 | 1.11 | |
| 95% CI for odds ratio | | (0.74, 1.79) | (0.71, 1.75) | |
| p-value* | | 0.534 | 0.644 | |
| Week 4 (LOCF) OMERACT-OARSI response | | | | |
| Yes, n (%) | 87 (61.7%) | 117 (72.7%) | 107 (71.3%) | 97 (61.4%) |
| No, n (%) | 54 (38.3%) | 44 (27.3%) | 43 (28.7%) | 61 (38.6%) |
| Versus placebo | | | | |
| Odds ratio | | 1.61 | 1.53 | 0.98 |
| 95% CI for odds ratio | | (0.99, 2.62) | (0.93, 2.50) | (0.61, 1.56) |
| p-value* | | 0.057 | 0.091 | 0.925 |
| Versus oxycodone CR | | | | |
| Odds ratio | | 1.64 | 1.56 | |
| 95% CI for odds ratio | | (1.02, 2.64) | (0.97, 2.52) | |
| p-value* | | 0.040 | 0.068 | |
| Week 8 (LOCF) OMERACT-OARSI response | | | | |
| Yes, n (%) | 81 (57.4%) | 120 (74.5%) | 105 (70.0%) | 93 (58.9%) |
| No, n (%) | 60 (42.6%) | 41 (25.5%) | 45 (30.0%) | 65 (41.1%) |
| Versus placebo | | | | |
| Odds ratio | | 2.13 | 1.73 | 1.06 |
| 95% CI for odds ratio | | (1.30, 3.48) | (1.06, 2.80) | (0.66, 1.68) |
| p-value* | | 0.002 | 0.027 | 0.816 |
| Versus oxycodone CR | | | | |
| Odds ratio | | 2.02 | 1.63 | |
| 95% CI for odds ratio | | (1.25, 3.25) | (1.02, 2.62) | |
| p-value* | | 0.004 | 0.042 | |
| Week 12 (LOCF) OMERACT-OARSI response | | | | |
| Yes, n (%) | 83 (58.9%) | 120 (74.5%) | 110 (73.3%) | 100 (63.3%) |
| No, n (%) | 58 (41.1%) | 41 (25.5%) | 40 (26.7%) | 58 (36.7%) |
| Versus placebo | | | | |
| Odds ratio | | 2.02 | 1.94 | 1.21 |
| 95% CI for odds ratio | | (1.24, 3.31) | (1.18, 3.19) | (0.76, 1.94) |
| p-value* | | 0.005 | 0.009 | 0.421 |
| Versus oxycodone CR | | | | |
| Odds ratio | | 1.67 | 1.60 | |
| 95% CI for odds ratio | | (1.03, 2.70) | (0.99, 2.61) | |
| p-value* | | 0.037 | 0.057 | |
| Week 16 (LOCF) OMERACT-OARSI response | | | | |
| Yes, n (%) | 84 (59.6%) | 120 (74.5%) | 112 (74.7%) | 95 (60.1%) |
| No, n (%) | 57 (40.4%) | 41 (25.5%) | 38 (25.3%) | 63 (39.9%) |
| Versus placebo | | | | |
| Odds ratio | | 1.96 | 2.02 | 1.04 |
| 95% CI for odds ratio | | (1.20, 3.21) | (1.22, 3.33) | (0.65, 1.65) |
| p-value* | | 0.007 | 0.006 | 0.885 |
| Versus oxycodone CR | | | | |
| Odds ratio | | 1.90 | 1.95 | |
| 95% CI for odds ratio | | (1.18, 3.06) | (1.20, 3.18) | |
| p-value* | | 0.009 | 0.007 | |

## Table 15. Summary of Analysis of OMERACT-OARSI Response by Week (ITT, LOCF)

*p-value is based on logistic regression model from pairwise comparisons. Logistic Regression model includes treatment as a main effect, Baseline value, index joint; previous opioid covariates.
OMERACT response is defined as:

- Change (improvement) from Baseline ≥50% (percentage change) and ≥2 (absolute change) in either the WOMAC Pain or Physical Function subscales, or
- At least 2 of the following 3 being true:
  - Change (improvement) from Baseline ≥20% (percentage change) and ≥1 (absolute change) in the WOMAC Pain subscale.
  - Change (improvement) from Baseline ≥20% (percentage change) and ≥1 (absolute change) in the WOMAC Physical Function subscale.
  - Change (improvement) from Baseline ≥20% (percentage change) and ≥1 (absolute change) in the Patient Global Assessment of Osteoarthritis.

CI = confidence interval; CR = controlled release; ITT = intent-to-treat; LOCF = last observation carried forward; mITT = modified ITT; n = number of subjects with/without a response; N = number of subjects in each dose group; OARSI = Osteoarthritis Research Society International, OMERACT = Outcome Measures in Rheumatology, q12h = every 12 hours; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

## Table 16. Summary of Analysis of OMERACT-OARSI Response by Week (mITT, LOCF)

| | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|
| | | 5 mg | 10 mg | 10-40 mg q12h |
| | N=137 | N=153 | N=149 | N=156 |
| Week 2 (LOCF) OMERACT-OARSI response | | | | |
| Yes, n (%) | 64 (46.7%) | 79 (51.6%) | 74 (49.7%) | 70 (44.9%) |
| No, n (%) | 73 (53.3%) | 74 (48.4%) | 75 (50.3%) | 86 (55.1%) |
| Versus placebo | | | | |
| Odds ratio | | 1.22 | 1.11 | 0.94 |
| 95% CI for odds ratio | | (0.77, 1.95) | (0.69, 1.77) | (0.59, 1.49) |
| p-value* | | 0.397 | 0.669 | 0.791 |
| Versus oxycodone CR | | | | |
| Odds ratio | | 1.30 | 1.18 | |
| 95% CI for odds ratio | | (0.83, 2.04) | (0.75, 1.85) | |
| p-value* | | 0.250 | 0.476 | |
| Week 4 (LOCF) OMERACT-OARSI response | | | | |
| Yes, n (%) | 76 (55.5%) | 105 (68.6%) | 87 (58.4%) | 83 (53.2%) |
| No, n (%) | 61 (44.5%) | 48 (31.4%) | 62 (41.6%) | 73 (46.8%) |
| Versus placebo | | | | |
| Odds ratio | | 1.74 | 1.14 | 0.91 |
| 95% CI for odds ratio | | (1.07, 2.81) | (0.71, 1.82) | (0.57, 1.44) |
| p-value* | | 0.025 | 0.589 | 0.683 |
| Versus oxycodone CR | | | | |
| Odds ratio | | 1.91 | 1.25 | |
| 95% CI for odds ratio | | (1.20, 3.05) | (0.80, 1.98) | |
| p-value* | | 0.006 | 0.329 | |
| Week 8 (LOCF) OMERACT-OARSI response | | | | |
| Yes, n (%) | 78 (56.9%) | 108 (70.6%) | 86 (57.7%) | 80 (51.3%) |
| No, n (%) | 59 (43.1%) | 45 (29.4%) | 63 (42.3%) | 76 (48.7%) |
| Versus placebo | | | | |
| Odds ratio | | 1.82 | 1.05 | 0.80 |
| 95% CI for odds ratio | | (1.12, 2.97) | (0.65, 1.68) | (0.50, 1.27) |
| p-value* | | 0.016 | 0.844 | 0.342 |
| Versus oxycodone CR | | | | |
| Odds ratio | | 2.28 | 1.31 | |
| 95% CI for odds ratio | | (1.42, 3.65) | (0.83, 2.07) | |
| p-value* | | <.001 | 0.240 | |
| Week 12 (LOCF) OMERACT-OARSI response | | | | |
| Yes, n (%) | 80 (58.4%) | 110 (71.9%) | 89 (59.7%) | 87 (55.8%) |
| No, n (%) | 57 (41.6%) | 43 (28.1%) | 60 (40.3%) | 69 (44.2%) |
| Versus placebo | | | | |
| Odds ratio | | 1.85 | 1.09 | 0.90 |
| 95% CI for odds ratio | | (1.13, 3.04) | (0.68, 1.75) | (0.57, 1.44) |
| p-value* | | 0.014 | 0.719 | 0.672 |
| Versus oxycodone CR | | | | |
| Odds ratio | | 2.05 | 1.21 | |
| 95% CI for odds ratio | | (1.27, 3.30) | (0.76, 1.91) | |
| p-value* | | 0.003 | 0.421 | |
| Week 16 (LOCF) OMERACT-OARSI response | | | | |
| Yes, n (%) | 84 (61.3%) | 111 (72.5%) | 93 (62.4%) | 87 (55.8%) |
| No, n (%) | 53 (38.7%) | 42 (27.5%) | 56 (37.6%) | 69 (44.2%) |
| Versus placebo | | | | |
| Odds ratio | | 1.68 | 1.08 | 0.80 |
| 95% CI for odds ratio | | (1.02, 2.77) | (0.67, 1.75) | (0.50, 1.28) |
| p-value* | | 0.041 | 0.752 | 0.344 |
| Versus oxycodone CR | | | | |
| Odds ratio | | 2.11 | 1.36 | |
| 95% CI for odds ratio | | (1.31, 3.41) | (0.86, 2.15) | |
| p-value* | | 0.002 | 0.195 | |

**Table 16. Summary of Analysis of OMERACT-OARSI Response by Week (mITT, LOCF)**

*p-value is based on logistic regression model from pairwise comparisons. Logistic Regression model includes treatment as a main effect, Baseline value, index joint; previous opioid covariates.
OMERACT response is defined as:

- Change (improvement) from Baseline ≥50% (percentage change) and ≥2 (absolute change) in either the WOMAC Pain or Physical Function subscales, or
- At least 2 of the following 3 being true:
  - Change (improvement) from Baseline ≥20% (percentage change) and ≥1 (absolute change) in the WOMAC Pain subscale.
  - Change (improvement) from Baseline ≥20% (percentage change) and ≥1 (absolute change) in the WOMAC Physical Function subscale.
  - Change (improvement) from Baseline ≥20% (percentage change) and ≥1 (absolute change) in the Patient Global Assessment of Osteoarthritis.

CI = confidence interval; CR = controlled release; LOCF = last observation carried forward; mITT = modified ITT; N = number of subjects in each dose group; n = number of subjects with/without a response; OARSI = Osteoarthritis Research Society International, OMERACT = Outcome Measures in Rheumatology; q12h = every 12 hours; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Treatment Response: Reduction in WOMAC Pain subscale: Table 17 summarizes the frequency of subjects who experienced an improvement (reduction) of pain with the WOMAC Pain subscale of ≥30%, ≥50%, ≥70%, and ≥90% from Baseline to Weeks 2, 4, 8, 12, and 16.

## Table 17. WOMAC Pain Subscale Reduction: ≥30%, ≥50%, ≥70%, and ≥90% Improvement From Baseline to Weeks 2, 4, 8, 12, and 16 (ITT/mITT, LOCF)

| | Response, n (%) | | | |
|---|---|---|---|---|
| | Placebo | Tanezumab | | Oxycodone CR |
| | N = 141 | 5 mg N = 161 | 10 mg N = 150 | 10-40 mg q12h N = 158 |
| WOMAC Pain Subscale, improvement ≥30% from Baseline | | | | |
| Intent to Treat | | | | |
| Week 2 | 59 (41.8) | 75 (46.6) | 66 (44.0) | 71 (44.9) |
| Week 4 | 72 (51.1) | 98 (60.9) | 97 (64.7)* | 86 (54.4) |
| Week 8 | 78 (55.3) | 109 (67.7)*§ | 99 (66.0)‡ | 75 (47.5) |
| Week 12 | 80 (56.7) | 107 (66.5)‡ | 102 (68.0)*‡ | 81 (51.3) |
| Week 16 | 78 (55.3) | 107 (66.5)‡ | 103 (68.7)*§ | 78 (49.4) |
| Modified Intent to Treat | | | | |
| Week 2 | 54 (39.4) | 67 (43.8) | 58 (38.9) | 63 (40.4) |
| Week 4 | 62 (45.3) | 88 (57.5)* | 78 (52.3) | 74 (47.4) |
| Week 8 | 73 (53.3) | 94 (61.4)‡ | 81 (54.4) | 69 (44.2) |
| Week 12 | 76 (55.5) | 97 (63.4)‡ | 83 (55.7) | 76 (48.7) |
| Week 16 | 78 (56.9) | 97 (63.4)‡ | 87 (58.4) | 75 (48.1) |
| WOMAC Pain Subscale, improvement ≥50% from Baseline | | | | |
| Intent to Treat | | | | |
| Week 2 | 30 (21.3) | 46 (28.6) | 42 (28.0) | 33 (20.9) |
| Week 4 | 44 (31.2) | 72 (44.7)*‡ | 68 (45.3)*‡ | 48 (30.4) |
| Week 8 | 47 (33.3) | 71 (44.1)‡ | 73 (48.7)*§ | 47 (29.7) |
| Week 12 | 44 (31.2) | 75 (46.6)*‡ | 77 (51.3)†§ | 51 (32.3) |
| Week 16 | 47 (33.3) | 76 (47.2)*‡ | 75 (50.0)*‡ | 51 (32.3) |
| Modified Intent to Treat | | | | |
| Week 2 | 28 (20.4) | 41 (26.8) | 37 (24.8) | 31 (19.9) |
| Week 4 | 39 (28.5) | 61 (39.9)*‡ | 55 (36.9) | 40 (25.6) |
| Week 8 | 43 (31.4) | 63 (41.2)‡ | 57 (38.3)‡ | 38 (24.4) |
| Week 12 | 41 (29.9) | 68 (44.4)*‡ | 61 (40.9)*‡ | 43 (27.6) |
| Week 16 | 44 (32.1) | 71 (46.4)*‡ | 63 (42.3)‡ | 44 (28.2) |
| WOMAC Pain Subscale, improvement ≥70% from Baseline | | | | |
| Intent to Treat | | | | |
| Week 2 | 10 (7.1) | 23 (14.3)* | 15 (10.0) | 13 (8.2) |
| Week 4 | 15 (10.6) | 48 (29.8)†‡ | 47 (31.3)†‡ | 25 (15.8) |
| Week 8 | 21 (14.9) | 44 (27.3)*‡ | 47 (31.3)†‡ | 27 (17.1) |
| Week 12 | 26 (18.4) | 48 (29.8)*‡ | 44 (29.3)*‡ | 26 (16.5) |
| Week 16 | 29 (20.6) | 47 (29.2)‡ | 43 (28.7)‡ | 28 (17.7) |
| Modified Intent to Treat | | | | |
| Week 2 | 9 (6.6) | 21 (13.7)* | 12 (8.1) | 13 (8.3) |
| Week 4 | 13 (9.5) | 40 (26.1)†‡ | 37 (24.8)*‡ | 22 (14.1) |
| Week 8 | 16 (11.7) | 43 (28.1)†‡ | 39 (26.2)*‡ | 22 (14.1) |
| Week 12 | 21 (15.3) | 45 (29.4)*§ | 38 (25.5)*‡ | 21 (13.5) |
| Week 16 | 25 (18.2) | 47 (30.7)*§ | 40 (26.8)*‡ | 21 (13.5) |
| WOMAC Pain Subscale, improvement ≥90% from Baseline | | | | |
| Intent to Treat | | | | |
| Week 2 | 1 (<1.0) | 5 (3.1) | 4 (2.7) | 5 (3.2) |
| Week 4 | 3 (2.1) | 20 (12.4)*‡ | 14 (9.3)* | 7 (4.4) |
| Week 8 | 5 (3.5) | 20 (12.4)*‡ | 16 (10.7)*‡ | 4 (2.5) |
| Week 12 | 6 (4.3) | 25 (15.5)*§ | 18 (12.0)*‡ | 6 (3.8) |
| Week 16 | 8 (5.7) | 24 (14.9)*§ | 19 (12.7)*‡ | 3 (1.9) |
| Modified Intent to Treat | | | | |
| Week 2 | 1 (<1.0) | 4 (2.6) | 2 (1.3) | 5 (3.2) |
| Week 4 | 3 (2.2) | 17 (11.1)*‡ | 9 (6.0) | 6 (3.8) |
| Week 8 | 5 (3.6) | 19 (12.4)*‡ | 8 (5.4) | 4 (2.6) |
| Week 12 | 6 (4.4) | 24 (15.7)*‡ | 9 (6.0) | 7 (4.5) |
| Week 16 | 8 (5.8) | 23 (15.0)*§ | 10 (6.7) | 5 (3.2) |

**Table 17. WOMAC Pain Subscale Reduction: ≥30%, ≥50%, ≥70%, and ≥90% Improvement From Baseline to Weeks 2, 4, 8, 12, and 16 (ITT/mITT, LOCF)**

* Statistically significant (p ≤0.05) decrease from Baseline compared with placebo.
† Statistically significant (p <0.001) decrease from Baseline compared with placebo.
‡ Statistically significant (p ≤0.05) decrease from Baseline compared with oxycodone CR.
§ Statistically significant (p <0.001) decrease from Baseline compared with oxycodone CR.
p-value based on pairwise comparisons from logistic regression versus placebo and oxycodone CR.
CR = controlled release; ITT = intent-to-treat; LOCF = last observation carried forward; mITT = modified ITT; q12h = every 12 hours; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Changes from Baseline to Week 8 in cumulative reduction in pain recorded with the WOMAC Pain subscale for the ITT and mITT populations are presented in Table 18 and Table 19, respectively, using LOCF imputation for missing data.

**Table 18. Summary of Cumulative Reduction in WOMAC Pain Subscale for Change From Baseline to Week 8 (ITT, LOCF)**

| Reduction Cut-off Values | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|
| | N=141 | 5 mg N=161 | 10 mg N=150 | N=158 |
| | n (%) | n (%) | n (%) | n (%) |
| >0% | 121 (85.8%) | 149 (92.5%) | 134 (89.3%) | 139 (88.0%) |
| ≥10% | 109 (77.3%) | 138 (85.7%) | 127 (84.7%) | 125 (79.1%) |
| ≥20% | 91 (64.5%) | 125 (77.6%) | 110 (73.3%) | 101 (63.9%) |
| ≥30% | 78 (55.3%) | 109 (67.7%) | 99 (66.0%) | 75 (47.5%) |
| ≥40% | 54 (38.3%) | 93 (57.8%) | 86 (57.3%) | 57 (36.1%) |
| ≥50% | 47 (33.3%) | 71 (44.1%) | 73 (48.7%) | 47 (29.7%) |
| ≥60% | 31 (22.0%) | 62 (38.5%) | 61 (40.7%) | 38 (24.1%) |
| ≥70% | 21 (14.9%) | 44 (27.3%) | 47 (31.3%) | 27 (17.1%) |
| ≥80% | 11 (7.8%) | 30 (18.6%) | 28 (18.7%) | 10 (6.3%) |
| ≥90% | 5 (3.5%) | 20 (12.4%) | 16 (10.7%) | 4 (2.5%) |
| =100% | 0 | 12 (7.5%) | 5 (3.3%) | 2 (1.3%) |
| Total | 141 | 161 | 150 | 158 |

CR = controlled release; ITT = intent-to-treat; LOCF = last observation carried forward; N = number of subjects; n = number of subjects with specified criteria; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

**Table 19. Summary of Cumulative Reduction in WOMAC Pain Subscale for Change From Baseline to Week 8 (mITT, LOCF)**

| Reduction Cut-off Values | Placebo N=137 | Tanezumab 5 mg N=153 | Tanezumab 10 mg N=149 | Oxycodone CR N=156 |
|---|---|---|---|---|
| | n (%) | n (%) | n (%) | n (%) |
| >0% | 108 (78.8%) | 127 (83.0%) | 115 (77.2%) | 119 (76.3%) |
| ≥10% | 94 (68.6%) | 119 (77.8%) | 111 (74.5%) | 105 (67.3%) |
| ≥20% | 83 (60.6%) | 106 (69.3%) | 92 (61.7%) | 92 (59.0%) |
| ≥30% | 73 (53.3%) | 94 (61.4%) | 81 (54.4%) | 69 (44.2%) |
| ≥40% | 51 (37.2%) | 80 (52.3%) | 67 (45.0%) | 51 (32.7%) |
| ≥50% | 43 (31.4%) | 63 (41.2%) | 57 (38.3%) | 38 (24.4%) |
| ≥60% | 29 (21.2%) | 54 (35.3%) | 47 (31.5%) | 31 (19.9%) |
| ≥70% | 16 (11.7%) | 43 (28.1%) | 39 (26.2%) | 22 (14.1%) |
| ≥80% | 14 (10.2%) | 26 (17.0%) | 22 (14.8%) | 11 (7.1%) |
| ≥90% | 5 (3.6%) | 19 (12.4%) | 8 (5.4%) | 4 (2.6%) |
| =100% | 1 (<1.0%) | 11 (7.2%) | 3 (2.0%) | 1 (<1.0%) |
| Total | 137 | 153 | 149 | 156 |

CR = controlled release; LOCF = last observation carried forward; mITT = modified intent-to-treat; N = number of subjects; n = number of subjects with specified criteria; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Treatment Response: Improvement of ≥2 points in PGA of Osteoarthritis: Table 20 summarizes the PGA of osteoarthritis response for Weeks 2, 4, 8, 12, and 16, where there was an improvement from Baseline ≥2 grades on the 5-point Likert scale (eg, "fair" to "very good"). Table 21 summarizes the results at Week 8 for PGA of osteoarthritis.

**Table 20. Summary of Patient Global Assessment of Osteoarthritis Response by Week: ≥2 Grade Improvement From Baseline (ITT/mITT, LOCF)**

| | Response, n (%) | | | |
|---|---|---|---|---|
| | Placebo | Tanezumab | | Oxycodone CR |
| Improvement ≥2 Grades | N = 141 | 5 mg N = 161 | 10 mg N = 150 | 10-40 mg q12h N = 158 |
| | n (%) | n (%) | n (%) | n (%) |
| **ITT** | | | | |
| Week 2 | 16 (11.3) | 24 (14.9) | 19 (12.7) | 17 (10.8) |
| Week 4 | 17 (12.1) | 45 (28.0)†§ | 37 (24.7)*‡ | 19 (12.0) |
| Week 8 | 13 (9.2) | 36 (22.4)†‡ | 42 (28.0)†§ | 17 (10.8) |
| Week 12 | 17 (12.1) | 40 (24.8)*‡ | 47 (31.3)†§ | 23 (14.6) |
| Week 16 | 18 (12.8) | 38 (23.6)*‡ | 44 (29.3)†§ | 18 (11.4) |
| **mITT** | | | | |
| Week 2 | 15 (10.9) | 23 (15.0) | 17 (11.4) | 16 (10.3) |
| Week 4 | 16 (11.7) | 39 (25.5)†§ | 32 (21.5)*‡ | 15 (9.6) |
| Week 8 | 14 (10.2) | 38 (24.8)†§ | 31 (20.8)*‡ | 14 (9.0) |
| Week 12 | 18 (13.1) | 39 (25.5)*‡ | 33 (22.1)*‡ | 19 (12.2) |
| Week 16 | 21 (15.3) | 39 (25.5)*§ | 35 (23.5)*‡ | 16 (10.3) |

p-value based on pairwise comparisons from logistic regression versus placebo and oxycodone CR.
Logistic regression model includes treatment, Baseline value, index joint, and previous opioid use as fixed effects.
CR = controlled release; ITT = intent-to-treat; LOCF = last observation carried forward; mITT = modified ITT; n = number of subjects with response; N = number of subjects in each treatment group; q12h = every 12 hours.
*Statistically significant ($p \leq 0.05$) decrease from Baseline compared with placebo.
†Statistically significant ($p < 0.001$) decrease from Baseline compared with placebo.
‡Statistically significant ($p \leq 0.05$) decrease from Baseline compared with oxycodone CR.
§Statistically significant ($p < 0.001$) decrease from Baseline compared with oxycodone CR.

**Table 21. Summary of Analysis of Patient Global Assessment of Osteoarthritis Response by Week 8: ≥2 Grade Improvement From Baseline Comparison With Placebo (ITT/mITT, LOCF)**

| | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|
| **Improvement ≥2 Grades** | | **5 mg** | **10 mg** | **10-40 mg q12h** |
| **ITT Population** | **N=141** | **N=161** | **N=150** | **N=158** |
| **mITT Population** | **N=137** | **N=153** | **N=149** | **N=156** |
| **ITT** | | | | |
| ≥2 Point improvement | | | | |
| Yes, n (%) | 13 (9.2) | 36 (22.4) | 42 (28.0) | 17 (10.8) |
| No, n (%) | 128 (90.8) | 125 (77.6) | 108 (72.0) | 141 (89.2) |
| Versus placebo | | | | |
| Odds ratio | | 3.43 | 4.91 | 1.30 |
| 95% ci for odds ratio | | (1.65, 7.12) | (2.37, 10.18) | (0.58, 2.90) |
| p-value* | | <0.001 | <0.001 | 0.518 |
| Versus oxycodone CR | | | | |
| Odds ratio | | 2.63 | 3.77 | |
| 95% CI for odds ratio | | (1.36, 5.11) | (1.95, 7.29) | |
| p-value* | | 0.004 | <0.001 | |
| **mITT** | | | | |
| ≥2 Point improvement | | | | |
| Yes, n (%) | 14 (10.2) | 38 (24.8) | 31 (20.8) | 14 (9.0) |
| No, n (%) | 123 (89.8) | 115 (75.2) | 118 (79.2) | 142 (91.0) |
| Versus placebo | | | | |
| Odds ratio | | 3.54 | 2.77 | 0.94 |
| 95% CI for odds ratio | | (1.73, 7.26) | (1.33, 5.77) | (0.41, 2.13) |
| p-value* | | <0.001 | 0.007 | 0.878 |
| Versus oxycodone CR | | | | |
| Odds ratio | | 3.78 | 2.95 | |
| 95% CI for odds ratio | | (1.88, 7.60) | (1.44, 6.05) | |
| p-value* | | <0.001 | 0.003 | |

*p-value (odds ratio and 95% CI) was based on logistic regression model from pairwise comparisons versus placebo and oxycodone CR.
Logistic regression model includes treatment, Baseline value, index joint, and previous opioid use as fixed effects.
CI = confidence interval; CR = controlled release; ITT = intent-to-treat; LOCF = last observation carried forward; mITT = modified ITT; n = number of subjects with improvement; N = number of subjects in each treatment group; q12h = every 12 hours.

Average Daily NRS Pain Score: The average NRS pain scores in the index joint change from Baseline to Weeks 2, 4, 8, 12 and 16 for ITT and mITT populations are summarized in Table 22 and Table 23 respectively.

## Table 22. Summary of Change From Baseline in Average Pain Score in the Index Joint by Week (ITT, LOCF)

| | | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|---|
| | | | 5 mg | 10 mg | 10-40 mg q12h |
| | | N=141 | N=161 | N=150 | N=158 |
| Baseline | Score | | | | |
| | N | 138 | 160 | 148 | 155 |
| | Mean (SD) | 7.18 (1.80) | 7.28 (1.62) | 6.98 (1.84) | 7.03 (1.72) |
| | Median | 7.7 | 7.3 | 7.3 | 7.3 |
| | Min, Max | (1.3, 10.0) | (3.0, 10.0) | (1.0, 10.0) | (1.0, 10.0) |
| Week 1 (LOCF) | Change from Baseline | | | | |
| | N | 138 | 160 | 148 | 155 |
| | Mean (SD) | -0.79 (1.30) | -1.71 (1.93) | -1.47 (1.84) | -1.15 (1.65) |
| | Median | -0.5 | -1.4 | -1.3 | -1.0 |
| | Min, Max | (-5.4, 2.5) | (-8.7, 3.7) | (-6.5, 3.5) | (-6.1, 3.0) |
| Week 2 (LOCF) | Change from Baseline | | | | |
| | N | 138 | 160 | 148 | 155 |
| | Mean (SD) | -1.26 (1.63) | -1.96 (2.23) | -1.43 (2.13) | -1.54 (1.99) |
| | Median | -1.0 | -1.9 | -1.3 | -1.4 |
| | Min, Max | (-6.3, 2.5) | (-9.0, 4.3) | (-7.3, 3.5) | (-7.0, 3.0) |
| Week 3 (LOCF) | Change from Baseline | | | | |
| | N | 138 | 160 | 148 | 155 |
| | Mean (SD) | -1.57 (1.73) | -2.27 (2.42) | -1.71 (2.29) | -1.67 (2.08) |
| | Median | -1.3 | -2.1 | -1.5 | -1.5 |
| | Min, Max | (-6.7, 1.6) | (-9.0, 4.3) | (-7.3, 4.3) | (-7.9, 3.0) |
| Week 4 (LOCF) | Change from Baseline | | | | |
| | N | 138 | 160 | 148 | 155 |
| | Mean (SD) | -1.70 (1.81) | -2.65 (2.49) | -2.28 (2.60) | -1.76 (2.10) |
| | Median | -1.4 | -2.6 | -2.1 | -1.4 |
| | Min, Max | (-6.0, 1.5) | (-10.0, 3.3) | (-9.7, 4.3) | (-8.3, 3.0) |
| Week 5 (LOCF) | Change from Baseline | | | | |
| | N | 138 | 160 | 148 | 155 |
| | Mean (SD) | -1.77 (1.85) | -2.79 (2.50) | -2.39 (2.66) | -1.94 (2.18) |
| | Median | -1.5 | -2.8 | -2.0 | -1.5 |
| | Min, Max | (-7.0, 1.8) | (-9.0, 3.3) | (-9.3, 4.3) | (-7.9, 3.0) |
| Week 6 (LOCF) | Change from Baseline | | | | |
| | N | 138 | 160 | 148 | 155 |
| | Mean (SD) | -1.91 (1.95) | -2.87 (2.55) | -2.43 (2.66) | -1.94 (2.18) |
| | Median | -1.5 | -3.0 | -2.0 | -1.7 |
| | Min, Max | (-7.3, 1.3) | (-9.0, 3.3) | (-9.5, 4.3) | (-8.0, 3.0) |
| Week 7 (LOCF) | Change from Baseline | | | | |
| | N | 138 | 160 | 148 | 155 |
| | Mean (SD) | -1.99 (2.03) | -2.85 (2.62) | -2.45 (2.72) | -1.89 (2.14) |
| | Median | -1.7 | -2.8 | -2.0 | -1.5 |
| | Min, Max | (-9.0, 1.3) | (-10.0, 3.3) | (-9.7, 4.3) | (-7.8, 3.0) |
| Week 8 (LOCF) | Change from Baseline | | | | |
| | N | 138 | 160 | 148 | 155 |
| | Mean (SD) | -1.96 (1.99) | -2.82 (2.54) | -2.38 (2.72) | -1.83 (2.18) |
| | Median | -1.7 | -2.7 | -2.0 | -1.4 |
| | Min, Max | (-9.0, 1.3) | (-9.3, 3.3) | (-9.9, 4.3) | (-8.2, 3.0) |
| Week 9 (LOCF) | Change from Baseline | | | | |
| | N | 138 | 160 | 148 | 155 |
| | Mean (SD) | -2.02 (2.05) | -2.95 (2.58) | -2.41 (2.73) | -1.91 (2.25) |
| | Median | -1.7 | -3.0 | -2.0 | -1.5 |
| | Min, Max | (-7.8, 1.3) | (-9.1, 3.3) | (-9.4, 4.3) | (-7.4, 3.0) |
| Week 10 (LOCF) | Change from Baseline | | | | |
| | N | 138 | 160 | 148 | 155 |
| | Mean (SD) | -2.06 (2.16) | -2.92 (2.62) | -2.39 (2.72) | -1.89 (2.23) |
| | Median | -1.7 | -3.0 | -2.0 | -1.5 |
| | Min, Max | (-9.0, 1.9) | (-10.0, 3.3) | (-9.3, 4.3) | (-8.5, 3.0) |

## Table 22. Summary of Change From Baseline in Average Pain Score in the Index Joint by Week (ITT, LOCF)

| | | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|---|
| | | | 5 mg | 10 mg | 10-40 mg q12h |
| | | N=141 | N=161 | N=150 | N=158 |
| Week 11 (LOCF) | Change from Baseline | | | | |
| | N | 138 | 160 | 148 | 155 |
| | Mean (SD) | -2.06 (2.24) | -2.88 (2.62) | -2.39 (2.68) | -1.93 (2.32) |
| | Median | -1.7 | -2.9 | -2.0 | -1.3 |
| | Min, Max | (-9.0, 1.3) | (-10.0, 3.3) | (-9.0, 4.3) | (-8.1, 3.0) |
| Week 12 (LOCF) | Change from Baseline | | | | |
| | N | 138 | 160 | 148 | 155 |
| | Mean (SD) | -2.07 (2.27) | -2.94 (2.60) | -2.38 (2.67) | -1.88 (2.33) |
| | Median | -1.7 | -3.0 | -2.0 | -1.5 |
| | Min, Max | (-9.0, 1.3) | (-9.4, 3.3) | (-9.2, 4.3) | (-7.8, 3.0) |
| Week 13 (LOCF) | Change from Baseline | | | | |
| | N | 138 | 160 | 148 | 155 |
| | Mean (SD) | -2.15 (2.31) | -2.92 (2.60) | -2.42 (2.69) | -1.91 (2.32) |
| | Median | -1.7 | -3.0 | -2.0 | -1.5 |
| | Min, Max | (-9.0, 1.3) | (-9.0, 3.3) | (-10.0, 4.3) | (-8.7, 3.0) |
| Week 14 (LOCF) | Change from Baseline | | | | |
| | N | 138 | 160 | 148 | 155 |
| | Mean (SD) | -2.12 (2.28) | -2.91 (2.58) | -2.40 (2.65) | -1.91 (2.29) |
| | Median | -1.7 | -3.0 | -2.0 | -1.5 |
| | Min, Max | (-9.0, 1.3) | (-9.2, 3.3) | (-10.0, 4.3) | (-8.7, 3.0) |
| Week 15 (LOCF) | Change from Baseline | | | | |
| | N | 138 | 160 | 148 | 155 |
| | Mean (SD) | -2.16 (2.33) | -2.93 (2.63) | -2.39 (2.68) | -1.88 (2.31) |
| | Median | -1.7 | -3.0 | -2.0 | -1.5 |
| | Min, Max | (-9.0, 1.3) | (-9.0, 3.3) | (-10.0, 4.3) | (-8.5, 3.0) |
| Week16 (LOCF) | Change from Baseline | | | | |
| | N | 138 | 160 | 148 | 155 |
| | Mean (SD) | -2.09 (2.31) | -2.90 (2.63) | -2.39 (2.68) | -1.86 (2.28) |
| | Median | -1.7 | -2.9 | -2.0 | -1.5 |
| | Min, Max | (-9.0, 1.3) | (-9.5, 3.3) | (-10.0, 4.3) | (-8.5, 3.0) |

Average Pain score ranges from 0 (No Pain) to 10 (Worst Pain). A change from Baseline < 0 is an improvement.
CR = controlled release; ITT = intent-to-treat; LOCF = last observation carried forward; Max = maximum; Min = minimum; N = number of subjects in each treatment group; q12h = every 12 hours; SD = standard deviation.

## Table 23. Summary of Change From Baseline in Average Pain Score in the Index Joint by Week (mITT, LOCF)

| | | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|---|
| | | | 5 mg | 10 mg | 10-40 mg q12h |
| | | N=137 | N=153 | N=149 | N=156 |
| Baseline | Score | | | | |
| | N | 134 | 152 | 147 | 153 |
| | Mean (SD) | 7.16 (1.81) | 7.31 (1.62) | 6.98 (1.84) | 7.05 (1.71) |
| | Median | 7.7 | 7.3 | 7.3 | 7.3 |
| | Min, Max | (1.3, 10.0) | (3.0, 10.0) | (1.0, 10.0) | (1.0, 10.0) |
| Week 1 (LOCF) | Change from Baseline | | | | |
| | N | 134 | 152 | 147 | 153 |
| | Mean (SD) | -0.79 (1.24) | -1.71 (1.96) | -1.50 (1.81) | -1.16 (1.64) |
| | Median | -0.5 | -1.3 | -1.3 | -1.0 |
| | Min, Max | (-5.4, 1.6) | (-8.7, 3.7) | (-6.5, 3.5) | (-6.1, 3.0) |
| Week 2 (LOCF) | Change from Baseline | | | | |
| | N | 134 | 152 | 147 | 153 |
| | Mean (SD) | -1.23 (1.59) | -1.99 (2.19) | -1.51 (2.10) | -1.46 (1.96) |
| | Median | -1.0 | -1.9 | -1.4 | -1.0 |
| | Min, Max | (-6.3, 1.8) | (-9.0, 4.3) | (-7.3, 3.5) | (-7.0, 3.0) |
| Week 3 (LOCF) | Change from Baseline | | | | |
| | N | 134 | 152 | 147 | 153 |
| | Mean (SD) | -1.54 (1.74) | -2.28 (2.31) | -1.73 (2.20) | -1.58 (2.07) |
| | Median | -1.2 | -2.1 | -1.5 | -1.0 |
| | Min, Max | (-6.7, 1.5) | (-9.0, 4.3) | (-7.3, 4.3) | (-7.9, 3.0) |
| Week 4 (LOCF) | Change from Baseline | | | | |
| | N | 134 | 152 | 147 | 153 |
| | Mean (SD) | -1.63 (1.85) | -2.70 (2.42) | -2.21 (2.52) | -1.70 (2.10) |
| | Median | -1.3 | -2.6 | -2.0 | -1.3 |
| | Min, Max | (-6.3, 1.5) | (-10.0, 4.3) | (-9.7, 4.3) | (-8.3, 3.0) |
| Week 5 (LOCF) | Change from Baseline | | | | |
| | N | 134 | 152 | 147 | 153 |
| | Mean (SD) | -1.68 (1.87) | -2.83 (2.42) | -2.31 (2.57) | -1.86 (2.17) |
| | Median | -1.3 | -2.7 | -1.9 | -1.4 |
| | Min, Max | (-6.5, 1.8) | (-9.0, 4.3) | (-9.3, 4.3) | (-7.9, 3.0) |
| Week 6 (LOCF) | Change from Baseline | | | | |
| | N | 134 | 152 | 147 | 153 |
| | Mean (SD) | -1.78 (1.96) | -2.92 (2.48) | -2.37 (2.58) | -1.85 (2.17) |
| | Median | -1.3 | -2.8 | -2.0 | -1.5 |
| | Min, Max | (-6.9, 1.5) | (-9.0, 4.3) | (-9.5, 4.3) | (-8.0, 3.0) |
| Week 7 (LOCF) | Change from Baseline | | | | |
| | N | 134 | 152 | 147 | 153 |
| | Mean (SD) | -1.86 (2.05) | -2.94 (2.56) | -2.41 (2.62) | -1.81 (2.13) |
| | Median | -1.4 | -2.8 | -1.9 | -1.3 |
| | Min, Max | (-9.0, 1.5) | (-10.0, 4.3) | (-9.7, 4.3) | (-7.8, 3.0) |
| Week 8 (LOCF) | Change from Baseline | | | | |
| | N | 134 | 152 | 147 | 153 |
| | Mean (SD) | -1.82 (2.00) | -2.88 (2.50) | -2.36 (2.63) | -1.78 (2.16) |
| | Median | -1.3 | -2.7 | -2.0 | -1.4 |
| | Min, Max | (-9.0, 1.5) | (-9.3, 4.3) | (-9.9, 4.3) | (-8.2, 3.0) |
| Week 9 (LOCF) | Change from Baseline | | | | |
| | N | 134 | 152 | 147 | 153 |
| | Mean (SD) | -1.91 (2.08) | -3.00 (2.52) | -2.39 (2.64) | -1.86 (2.21) |
| | Median | -1.4 | -2.9 | -2.0 | -1.4 |
| | Min, Max | (-7.8, 1.5) | (-9.1, 4.3) | (-9.4, 4.3) | (-7.3, 3.0) |
| Week 10 (LOCF) | Change from Baseline | | | | |
| | N | 134 | 152 | 147 | 153 |
| | Mean (SD) | -1.95 (2.17) | -2.98 (2.56) | -2.40 (2.63) | -1.83 (2.20) |
| | Median | -1.4 | -2.9 | -2.1 | -1.4 |
| | Min, Max | (-9.0, 1.9) | (-10.0, 4.3) | (-9.3, 4.3) | (-8.5, 3.0) |

**Table 23. Summary of Change From Baseline in Average Pain Score in the Index Joint by Week (mITT, LOCF)**

| | | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|---|
| | | | 5 mg | 10 mg | 10-40 mg q12h |
| | | N=137 | N=153 | N=149 | N=156 |
| Week 11 (LOCF) | Change from Baseline | | | | |
| | N | 134 | 152 | 147 | 153 |
| | Mean (SD) | -1.94 (2.25) | -2.94 (2.55) | -2.39 (2.60) | -1.86 (2.27) |
| | Median | -1.4 | -2.8 | -2.1 | -1.3 |
| | Min, Max | (-9.0, 1.5) | (-10.0, 4.3) | (-9.0, 4.3) | (-8.1, 3.0) |
| Week 12 (LOCF) | Change from Baseline | | | | |
| | N | 134 | 152 | 147 | 153 |
| | Mean (SD) | -1.96 (2.27) | -3.00 (2.53) | -2.36 (2.61) | -1.83 (2.27) |
| | Median | -1.4 | -2.9 | -2.1 | -1.4 |
| | Min, Max | (-9.0, 1.5) | (-9.4, 4.3) | (-9.2, 4.3) | (-7.8, 3.0) |
| Week 13 (LOCF) | Change from Baseline | | | | |
| | N | 134 | 152 | 147 | 153 |
| | Mean (SD) | -2.01 (2.33) | -2.99 (2.54) | -2.39 (2.63) | -1.86 (2.25) |
| | Median | -1.4 | -2.9 | -2.1 | -1.4 |
| | Min, Max | (-9.0, 1.5) | (-9.0, 4.3) | (-10.0, 4.3) | (-8.7, 3.0) |
| Week 14 (LOCF) | Change from Baseline | | | | |
| | N | 134 | 152 | 147 | 153 |
| | Mean (SD) | -1.99 (2.28) | -2.98 (2.52) | -2.37 (2.59) | -1.87 (2.22) |
| | Median | -1.4 | -2.9 | -2.1 | -1.4 |
| | Min, Max | (-9.0, 1.5) | (-9.2, 4.3) | (-10.0, 4.3) | (-8.7, 3.0) |
| Week 15 (LOCF) | Change from Baseline | | | | |
| | N | 134 | 152 | 147 | 153 |
| | Mean (SD) | -2.02 (2.32) | -2.99 (2.55) | -2.38 (2.61) | -1.86 (2.24) |
| | Median | -1.5 | -2.9 | -2.1 | -1.4 |
| | Min, Max | (-9.0, 1.5) | (-9.0, 4.3) | (-10.0, 4.3) | (-8.5, 3.0) |
| Week16 (LOCF) | Change from Baseline | | | | |
| | N | 134 | 152 | 147 | 153 |
| | Mean (SD) | -1.96 (2.31) | -2.97 (2.55) | -2.40 (2.63) | -1.84 (2.23) |
| | Median | -1.4 | -2.9 | -2.1 | -1.4 |
| | Min, Max | (-9.0, 1.5) | (-9.5, 4.3) | (-10.0, 4.3) | (-8.5, 3.0) |

Average Pain score ranges from 0 (No Pain) to 10 (Worst Pain). A change from Baseline < 0 is an improvement.
CR = controlled release; mITT = modified intent-to-treat; LOCF = last observation carried forward; Max = maximum; Min = minimum; N = number of subjects in each treatment group; q12h = every 12 hours; SD = standard deviation; mITT = modified intent-to-treat; N = number of subjects in each treatment group.

Other WOMAC Assessments: The change from Baseline to Week 8 for the other WOMAC assessments are summarized in Table 24 (WOMAC Stiffness subscale), Table 27 (WOMAC average score), Table 30 (WOMAC Pain subscale item "pain when walking on a flat surface"), and Table 33 (WOMAC Pain subscale item "pain when going up or down stairs").

The change from Baseline to Weeks 2, 4, 8, 12 and 16 for the other WOMAC assessments for ITT and mITT populations are summarized in Table 25 and Table 26 (WOMAC Stiffness subscale), Table 28 and Table 29 (WOMAC average score), Table 31 and Table 32 (WOMAC Pain subscale item "pain when walking on a flat surface"), and Table 34 and Table 35 (WOMAC Pain subscale item "pain when going up or down stairs").

## Table 24. Summary of WOMAC Stiffness Subscale, Change From Baseline to Week 8 (ITT/mITT, LOCF)

| | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|
| | | 5 mg | 10 mg | 10-40 mg q12h |
| | N=141 | N=161 | N=150 | N=158 |
| **WOMAC Stiffness Subscale[a], Baseline and Change From Baseline to Week 8 (0-10 NRS)** | | | | |
| **ITT** | | | | |
| N | 141 | 161 | 150 | 158 |
| Baseline mean (SD) | 7.22 (1.67) | 7.30 (1.92) | 7.15 (1.82) | 7.39 (1.72) |
| Change from Baseline LS mean (SE)* | -1.85 (0.23) | -3.01 (0.21) | -3.27 (0.22) | -2.07 (0.21) |
| 95% CI for LS mean | (-2.32, -1.39) | (-3.43, -2.60) | (-3.70, -2.83) | (-2.49, -1.65) |
| Comparison vs placebo | | | | |
| Change from Baseline LS mean (SE)* | | -1.16 (0.27) | -1.42 (0.27) | -0.21 (0.27) |
| 95% CI for LS mean | | (-1.69, -0.63) | (-1.95, -0.88) | (-0.75, 0.32) |
| p-value† | | <0.001 | <0.001 | 0.435 |
| Comparison vs oxycodone CR | | | | |
| Change from Baseline LS mean (SE)* | | -0.95 (0.26) | -1.20 (0.27) | |
| 95% CI for LS mean | | (-1.46, -0.43) | (-1.73, -0.68) | |
| p-value† | | <0.001 | <0.001 | |
| **mITT** | | | | |
| N | 137 | 153 | 149 | 156 |
| Baseline mean (SD) | 7.22 (1.69) | 7.29 (1.93) | 7.16 (1.82) | 7.39 (1.72) |
| Change from Baseline LS mean (SE)* | -1.54 (0.25) | -2.77 (0.23) | -2.58 (0.24) | -1.69 (0.23) |
| 95% CI for LS mean | (-2.03, -1.04) | (-3.22, -2.31) | (-3.04, -2.11) | (-2.14, -1.24) |
| Comparison vs placebo | | | | |
| Change from Baseline LS mean (SE)* | | -1.23 (0.28) | -1.04 (0.28) | -0.16 (0.28) |
| 95% CI for LS mean | | (-1.77, -0.68) | (-1.59, -0.49) | (-0.70, 0.39) |
| p-value† | | <0.001 | <0.001 | 0.568 |
| Comparison vs oxycodone CR | | | | |
| Change from Baseline LS mean (SE)* | | -1.07 (0.27) | -0.88 (0.27) | |
| 95% CI for LS mean | | (-1.60, -0.55) | (-1.41, -0.36) | |
| p-value† | | <0.001 | 0.001 | |

*LS means were estimated from the corresponding ANCOVA model.
†p-value is based on ANCOVA from pairwise comparisons.
ANCOVA model includes treatment as main effect, Baseline value, index joint, previous opioid use as covariates, and study site as a random effect. .
ANCOVA = analysis of covariance; CI = confidence interval; CR = controlled release; ITT = intent-to-treat; LOCF = last observation carried forward; LS mean = least squares means; mITT = modified ITT; N = number of subjects in each treatment group with Baseline or change from Baseline to Week 8 data; NRS = numeric rating scale; q12h = every 12 hours; SD = standard deviation, SE = standard error; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
a. WOMAC subscale score ranges from 0 to 10, where 0 is the best response. A change from Baseline of <0 is an improvement.

## Table 25. Summary of Change From Baseline for WOMAC Stiffness Subscale by Week (ITT, LOCF)

| | | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|---|
| | | | 5 mg | 10 mg | 10-40 mg q12h |
| | | N=141 | N=161 | N=150 | N=158 |
| Baseline | Score | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | 7.22 (1.67) | 7.30 (1.92) | 7.15 (1.82) | 7.39 (1.72) |
| | Median | 7.5 | 7.5 | 7.5 | 7.5 |
| | Min, Max | (1.5, 10.0) | (0.0, 10.0) | (1.0, 10.0) | (2.0, 10.0) |
| Week 2 (LOCF) | Change from Baseline | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | -1.49 (1.83) | -2.24 (2.50) | -2.19 (2.41) | -1.78 (2.16) |
| | Median | -1.0 | -1.5 | -2.0 | -1.0 |
| | Min, Max | (-6.0, 2.0) | (-8.5, 2.5) | (-10.0, 3.5) | (-8.0, 4.0) |
| Week 4 (LOCF) | Change from Baseline | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | -1.88 (1.95) | -3.12 (2.70) | -3.08 (2.91) | -2.16 (2.35) |
| | Median | -1.5 | -3.0 | -3.0 | -2.0 |
| | Min, Max | (-7.0, 3.0) | (-10.0, 2.0) | (-10.0, 6.5) | (-9.5, 4.0) |
| Week 8 (LOCF) | Change from Baseline | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | -1.92 (2.17) | -3.09 (2.60) | -3.28 (2.77) | -2.19 (2.43) |
| | Median | -1.5 | -3.0 | -3.0 | -2.0 |
| | Min, Max | (-8.0, 2.5) | (-9.0, 3.0) | (-10.0, 4.5) | (-10.0, 4.0) |
| Week 12 (LOCF) | Change from Baseline | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | -2.15 (2.35) | -3.33 (2.75) | -3.31 (2.72) | -2.25 (2.45) |
| | Median | -2.0 | -3.0 | -3.0 | -2.0 |
| | Min, Max | (-9.0, 2.0) | (-10.0, 3.0) | (-10.0, 2.5) | (-10.0, 4.0) |
| Week 16 (LOCF) | Change from Baseline | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | -2.20 (2.50) | -3.24 (2.73) | -3.25 (2.66) | -2.19 (2.40) |
| | Median | -2.0 | -3.0 | -3.0 | -2.0 |
| | Min, Max | (-10.0, 2.0) | (-10.0, 3.0) | (-10.0, 2.5) | (-10.0, 4.0) |

WOMAC subscale scores range from 0 to 10, where 0 is the best response.
CR = controlled release; ITT = intent-to-treat; LOCF = last observation carried forward; Max = maximum; Min = minimum; N = number of subjects in each treatment group; SD = standard deviation; q12h = every 12 hours; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

## Table 26. Summary of Change From Baseline for WOMAC Stiffness Subscale by Week (mITT, LOCF)

| | | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|---|
| | | | 5 mg | 10 mg | 10-40 mg q12h |
| | | N=137 | N=153 | N=149 | N=156 |
| Baseline | Score | | | | |
| | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | 7.22 (1.69) | 7.29 (1.93) | 7.16 (1.82) | 7.39 (1.72) |
| | Median | 7.5 | 7.5 | 7.5 | 7.5 |
| | Min, Max | (1.5, 10.0) | (0.0, 10.0) | (1.0, 10.0) | (2.0, 10.0) |
| Week 2 (LOCF) | Change from Baseline | | | | |
| | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | -1.38 (1.87) | -2.08 (2.53) | -1.90 (2.26) | -1.57 (2.13) |
| | Median | -1.0 | -1.5 | -1.5 | -1.0 |
| | Min, Max | (-6.0, 2.0) | (-8.5, 2.5) | (-8.0, 3.5) | (-8.0, 4.0) |
| Week 4 (LOCF) | Change from Baseline | | | | |
| | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | -1.71 (2.02) | -2.91 (2.82) | -2.61 (2.90) | -1.92 (2.36) |
| | Median | -1.5 | -2.5 | -2.5 | -1.5 |
| | Min, Max | (-7.0, 3.0) | (-10.0, 2.0) | (-10.0, 6.5) | (-9.5, 4.0) |
| Week 8 (LOCF) | Change from Baseline | | | | |
| | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | -1.77 (2.14) | -2.97 (2.74) | -2.72 (2.88) | -1.92 (2.34) |
| | Median | -1.0 | -3.0 | -2.5 | -1.5 |
| | Min, Max | (-7.5, 2.5) | (-9.0, 3.0) | (-10.0, 6.5) | (-8.0, 4.0) |
| Week 12 (LOCF) | Change from Baseline | | | | |
| | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | -2.01 (2.32) | -3.24 (2.88) | -2.77 (2.85) | -2.06 (2.40) |
| | Median | -1.5 | -3.0 | -2.5 | -1.5 |
| | Min, Max | (-9.0, 2.0) | (-10.0, 3.0) | (-10.0, 6.5) | (-7.5, 4.0) |
| Week 16 (LOCF) | Change from Baseline | | | | |
| | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | -2.14 (2.47) | -3.24 (2.83) | -2.83 (2.87) | -2.06 (2.37) |
| | Median | -1.5 | -3.0 | -2.5 | -1.5 |
| | Min, Max | (-10.0, 2.0) | (-10.0, 3.0) | (-9.5, 6.5) | (-8.5, 4.0) |

WOMAC subscale scores range from 0 to 10, where 0 is the best response.
CR = controlled release; LOCF = last observation carried forward; mITT =modified intent-to-treat; Max = maximum; Min = minimum; N = number of subjects in each treatment group; q12h = every 12 hours; SD = standard deviation; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

## Table 27. Summary of WOMAC Average Score, Change From Baseline to Week 8 (ITT/mITT, LOCF)

| | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|
| | | 5 mg | 10 mg | 10-40 mg q12h |
| | N=141 | N=161 | N=150 | N=158 |
| **WOMAC Stiffness Subscale Average Score[a], Baseline and Change From Baseline to Week 8 (0-10 NRS)** | | | | |
| **ITT** | | | | |
| N | 141 | 161 | 150 | 158 |
| Baseline mean (SD) | 7.39 (1.32) | 7.48 (1.43) | 7.27 (1.40) | 7.50 (1.33) |
| Change from Baseline LS mean (SE)[*] | -2.14 (0.22) | -3.22 (0.20) | -3.31 (0.21) | -2.25 (0.20) |
| 95% CI for LS mean | (-2.58, -1.70) | (-3.62, -2.82) | (-3.72, -2.89) | (-2.66, -1.85) |
| Comparison vs placebo | | | | |
| Change from Baseline LS mean (SE)[*] | | -1.08 (0.26) | -1.17 (0.26) | -0.11 (0.26) |
| 95% CI for LS mean | | (-1.58, -0.58) | (-1.68, -0.66) | (-0.62, 0.39) |
| p-value[†] | | <0.001 | <0.001 | 0.659 |
| Comparison vs oxycodone CR | | | | |
| Change from Baseline LS mean (SE)[*] | | -0.97 (0.25) | -1.05 (0.25) | |
| 95% CI for LS mean | | (-1.45, -0.48) | (-1.55, -0.56) | |
| p-value[†] | | <0.001 | <0.001 | |
| **mITT** | | | | |
| N | 137 | 153 | 149 | 156 |
| Baseline mean (SD) | 7.38 (1.34) | 7.50 (1.44) | 7.28 (1.40) | 7.51 (1.33) |
| Change from Baseline LS mean (SE)[*] | -1.84 (0.24) | -2.91 (0.22) | -2.64 (0.23) | -1.87 (0.22) |
| 95% CI for LS mean | (-2.32, -1.37) | (-3.34, -2.47) | (-3.09, -2.20) | (-2.31, -1.44) |
| Comparison vs placebo | | | | |
| Change from Baseline LS mean (SE)[*] | | -1.07 (0.26) | -0.80 (0.27) | -0.03 (0.26) |
| 95% CI for LS mean | | (-1.59, -0.55) | (-1.32, -0.28) | (-0.55, 0.49) |
| p-value[†] | | <0.001 | 0.003 | 0.906 |
| Comparison vs oxycodone CR | | | | |
| Change from Baseline LS mean (SE)[*] | | -1.03 (0.25) | -0.77 (0.26) | |
| 95% CI for LS mean | | (-1.53, -0.54) | (-1.27, -0.27) | |
| p-value[†] | | <0.001 | 0.003 | |

[*]LS means were estimated from the corresponding ANCOVA model.
[†]p-value is based on ANCOVA from pairwise comparisons.
ANCOVA model includes treatment as main effect, Baseline value, index joint, previous opioid use as covariates, and study site as a random effect.
ANCOVA = analysis of covariance; CI = confidence interval; CR = controlled release; ITT = intent-to-treat; LOCF = last observation carried forward; LS mean = least squares means; mITT = modified ITT; N = number of subjects in each treatment group with Baseline or change from Baseline to Week 8 data; NRS = numeric rating scale; q12h = every 12 hours; SD = standard deviation; SE = standard error; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
a. WOMAC subscale score ranges from 0 to 10, where 0 is the best response. A change from Baseline of <0 is an improvement.

## Table 28. Summary of Change From Baseline for the WOMAC Average Score by Week (ITT, LOCF)

| | | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|---|
| | | | 5 mg | 10 mg | 10-40 mg q12h |
| | | N=141 | N=161 | N=150 | N=158 |
| Baseline | Score | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | 7.39 (1.32) | 7.48 (1.43) | 7.27 (1.40) | 7.50 (1.33) |
| | Median | 7.5 | 7.5 | 7.4 | 7.7 |
| | Min, Max | (3.5, 10.0) | (3.7, 10.0) | (3.5, 10.0) | (3.8, 10.0) |
| Week 2 (LOCF) | Change from Baseline | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | -1.71 (1.67) | -2.29 (2.21) | -2.15 (2.04) | -1.94 (1.91) |
| | Median | -1.3 | -1.8 | -1.9 | -1.5 |
| | Min, Max | (-5.8, 1.2) | (-8.2, 1.5) | (-8.1, 2.1) | (-7.5, 1.7) |
| Week 4 (LOCF) | Change from Baseline | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | -2.11 (1.88) | -3.24 (2.49) | -3.16 (2.58) | -2.38 (2.12) |
| | Median | -2.0 | -2.9 | -3.1 | -2.1 |
| | Min, Max | (-7.0, 2.2) | (-9.0, 1.3) | (-8.7, 2.2) | (-8.5, 3.0) |
| Week 8 (LOCF) | Change from Baseline | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | -2.23 (2.05) | -3.32 (2.40) | -3.33 (2.49) | -2.35 (2.22) |
| | Median | -2.0 | -3.2 | -3.4 | -2.0 |
| | Min, Max | (-7.7, 1.5) | (-9.0, 2.8) | (-9.1, 1.5) | (-8.9, 2.0) |
| Week 12 (LOCF) | Change from Baseline | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | -2.39 (2.20) | -3.49 (2.55) | -3.35 (2.45) | -2.41 (2.23) |
| | Median | -2.1 | -3.3 | -3.4 | -2.0 |
| | Min, Max | (-8.6, 1.4) | (-9.5, 2.8) | (-8.7, 1.8) | (-8.9, 1.7) |
| Week 16 (LOCF) | Change from Baseline | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | -2.47 (2.33) | -3.42 (2.53) | -3.34 (2.39) | -2.39 (2.20) |
| | Median | -2.0 | -3.3 | -3.4 | -2.0 |
| | Min, Max | (-10.0, 1.2) | (-9.5, 2.8) | (-8.7, 1.5) | (-8.9, 1.7) |

WOMAC subscale scores range from 0 to 10, where 0 is the best response.
CR = controlled release; ITT = intent-to-treat; LOCF = last observation carried forward; Max = maximum; Min = minimum; N = number of subjects in each treatment group; q12h = every 12 hours; SD = standard deviation; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

## Table 29. Summary of Change From Baseline for the WOMAC Average Score by Week (mITT, LOCF)

| | | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|---|
| | | | 5 mg | 10 mg | 10-40 mg q12h |
| | | N=137 | N=153 | N=149 | N=156 |
| Baseline | Score | | | | |
| | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | 7.38 (1.34) | 7.50 (1.44) | 7.28 (1.40) | 7.51 (1.33) |
| | Median | 7.5 | 7.6 | 7.4 | 7.7 |
| | Min, Max | (3.5, 10.0) | (3.7, 10.0) | (3.5, 10.0) | (3.8, 10.0) |
| Week 2 (LOCF) | Change from Baseline | | | | |
| | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | -1.60 (1.70) | -2.14 (2.25) | -1.90 (1.96) | -1.74 (1.94) |
| | Median | -1.2 | -1.6 | -1.4 | -1.2 |
| | Min, Max | (-5.8, 1.2) | (-8.2, 1.5) | (-7.9, 2.0) | (-7.5, 1.7) |
| Week 4 (LOCF) | Change from Baseline | | | | |
| | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | -1.94 (1.93) | -2.99 (2.61) | -2.64 (2.61) | -2.08 (2.13) |
| | Median | -1.9 | -2.7 | -2.1 | -1.8 |
| | Min, Max | (-7.0, 2.2) | (-9.0, 1.3) | (-8.7, 2.2) | (-8.5, 1.7) |
| Week 8 (LOCF) | Change from Baseline | | | | |
| | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | -2.08 (2.03) | -3.13 (2.59) | -2.79 (2.60) | -2.07 (2.16) |
| | Median | -2.0 | -3.0 | -2.5 | -1.6 |
| | Min, Max | (-7.4, 1.5) | (-9.0, 2.8) | (-9.1, 2.2) | (-7.6, 2.0) |
| Week 12 (LOCF) | Change from Baseline | | | | |
| | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | -2.25 (2.19) | -3.34 (2.72) | -2.83 (2.60) | -2.20 (2.21) |
| | Median | -2.1 | -3.2 | -2.5 | -1.8 |
| | Min, Max | (-8.6, 1.4) | (-9.5, 2.8) | (-8.6, 2.2) | (-7.9, 1.7) |
| Week 16 (LOCF) | Change from Baseline | | | | |
| | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | -2.40 (2.36) | -3.36 (2.71) | -2.92 (2.62) | -2.20 (2.19) |
| | Median | -2.2 | -3.2 | -2.8 | -1.8 |
| | Min, Max | (-10.0, 1.4) | (-9.5, 2.8) | (-8.7, 2.2) | (-8.0, 1.7) |

WOMAC subscale scores range from 0 to 10, where 0 is the best response.
CR = controlled release; LOCF = last observation carried forward; mITT = modified intent-to-treat; Max = maximum; Min = minimum; N = number of subjects in each treatment group; q12h = every 12 hours; SD = standard deviation.
WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

## Table 30. Summary of WOMAC Pain Subscale Item When Walking on a Flat Surface, Change From Baseline to Week 8 (ITT/mITT, LOCF)

| | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|
| | | 5 mg | 10 mg | 10-40 mg q12h |
| | N=141 | N=161 | N=150 | N=158 |
| **WOMAC Pain Subscale Item[a], Baseline and Change From Baseline to Week 8 (0-10 NRS)** | | | | |
| **ITT** | | | | |
| N | 141 | 161 | 150 | 158 |
| Baseline mean (SD) | 7.58 (1.57) | 7.80 (1.45) | 7.67 (1.54) | 7.70 (1.66) |
| Change from Baseline LS mean (SE)* | -2.62 (0.25) | -3.57 (0.22) | -3.71 (0.23) | -2.63 (0.23) |
| 95% CI for LS mean | (-3.11, -2.13) | (-4.01, -3.13) | (-4.17, -3.25) | (-3.07, -2.18) |
| Comparison vs placebo | | | | |
| Change from Baseline LS mean (SE)* | | -0.95 (0.28) | -1.09 (0.28) | -0.01 (0.28) |
| 95% CI for LS mean | | (-1.51, -0.40) | (-1.65, -0.53) | (-0.56, 0.55) |
| p-value† | | <0.001 | <0.001 | 0.979 |
| Comparison vs oxycodone CR | | | | |
| Change from Baseline LS mean (SE)* | | -0.95 (0.27) | -1.09 (0.28) | |
| 95% CI for LS mean | | (-1.48, -0.41) | (-1.63, -0.54) | |
| p-value† | | <0.001 | <0.001 | |
| **mITT** | | | | |
| N | 137 | 153 | 149 | 156 |
| Baseline mean (SD) | 7.60 (1.56) | 7.80 (1.46) | 7.68 (1.54) | 7.72 (1.62) |
| Change from Baseline LS mean (SE)* | -2.25 (0.27) | -3.07 (0.24) | -2.94 (0.25) | -2.19 (0.24) |
| 95% CI for LS mean | (-2.77, -1.73) | (-3.55, -2.59) | (-3.43, -2.45) | (-2.67, -1.71) |
| Comparison vs Placebo | | | | |
| Change from Baseline LS mean (SE)* | | -0.82 (0.29) | -0.69 (0.29) | 0.06 (0.29) |
| 95% CI for LS mean | | (-1.39, -0.26) | (-1.26, -0.13) | (-0.50, 0.62) |
| p-value† | | 0.004 | 0.017 | 0.840 |
| Comparison vs oxycodone CR | | | | |
| Change from Baseline LS mean (SE)* | | -0.88 (0.28) | -0.75 (0.28) | |
| 95% CI for LS mean | | (-1.42, -0.34) | (-1.30, -0.20) | |
| p-value† | | 0.002 | 0.007 | |

*LS means were estimated from the corresponding ANCOVA model.
†p-value is based on ANCOVA from pairwise comparisons.
ANCOVA model includes treatment as main effect, Baseline value, index joint, previous opioid use as covariates, and study site as a random effect.
ANCOVA = analysis of covariance; CI = confidence interval; CR = controlled release; ITT = intent-to-treat; LOCF = last observation carried forward; LS mean = least squares means; mITT = modified ITT; N = number of subjects in each treatment group with Baseline or change from Baseline to Week 8 data; NRS = numeric rating scale; q12h = every 12 hours; SD = standard deviation; SE = standard error; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
a. WOMAC subscale score ranges from 0 to 10, where 0 is the best response. A change from Baseline of <0 is an improvement.

## Table 31. Summary of Change From Baseline for the WOMAC Item: Pain When Walking on a Flat Surface by Week (ITT, LOCF)

| | | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|---|
| | | | 5 mg | 10 mg | 10-40 mg q12h |
| | | N=141 | N=161 | N=150 | N=158 |
| Baseline | Score | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | 7.58 (1.57) | 7.80 (1.45) | 7.67 (1.54) | 7.70 (1.66) |
| | Median | 8.0 | 8.0 | 8.0 | 8.0 |
| | Min, Max | (4.0, 10.0) | (4.0, 10.0) | (3.0, 10.0) | (3.0, 10.0) |
| Week 2 (LOCF) | Change from Baseline | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | -2.01 (2.17) | -2.61 (2.53) | -2.43 (2.39) | -2.27 (2.17) |
| | Median | -2.0 | -2.0 | -2.0 | -2.0 |
| | Min, Max | (-8.0, 3.0) | (-10.0, 2.0) | (-10.0, 2.0) | (-9.0, 2.0) |
| Week 4 (LOCF) | Change from Baseline | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | -2.46 (2.30) | -3.54 (2.72) | -3.58 (2.86) | -2.91 (2.42) |
| | Median | -2.0 | -3.0 | -3.5 | -3.0 |
| | Min, Max | (-8.0, 2.0) | (-10.0, 2.0) | (-10.0, 4.0) | (-9.0, 3.0) |
| Week 8 (LOCF) | Change from Baseline | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | -2.70 (2.63) | -3.75 (2.64) | -3.82 (2.86) | -2.72 (2.50) |
| | Median | -3.0 | -4.0 | -3.5 | -2.0 |
| | Min, Max | (-10.0, 4.0) | (-9.0, 2.0) | (-10.0, 2.0) | (-9.0, 4.0) |
| Week 12 (LOCF) | Change from Baseline | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | -2.85 (2.72) | -3.84 (2.80) | -3.85 (2.80) | -2.80 (2.58) |
| | Median | -3.0 | -4.0 | -4.0 | -3.0 |
| | Min, Max | (-10.0, 4.0) | (-10.0, 2.0) | (-10.0, 4.0) | (-10.0, 4.0) |
| Week 16 (LOCF) | Change from Baseline | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | -2.91 (2.73) | -3.79 (2.75) | -3.76 (2.76) | -2.72 (2.48) |
| | Median | -3.0 | -4.0 | -4.0 | -2.0 |
| | Min, Max | (-10.0, 4.0) | (-10.0, 2.0) | (-10.0, 2.0) | (-9.0, 4.0) |

WOMAC subscale scores range from 0 to 10, where 0 is the best response.
CR = controlled release; ITT = intent-to-treat; LOCF = last observation carried forward; Max = maximum; Min = minimum; N = number of subjects in each treatment group; q12h = every 12 hours; SD = standard deviation; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

## Table 32. Summary of Change From Baseline for the WOMAC Item: Pain When Walking on a Flat Surface by Week (mITT, LOCF)

| | | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|---|
| | | | 5 mg | 10 mg | 10-40 mg q12h |
| | | N=137 | N=153 | N=149 | N=156 |
| Baseline | Score | | | | |
| | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | 7.60 (1.56) | 7.80 (1.46) | 7.68 (1.54) | 7.72 (1.62) |
| | Median | 8.0 | 8.0 | 8.0 | 8.0 |
| | Min, Max | (4.0, 10.0) | (4.0, 10.0) | (3.0, 10.0) | (3.0, 10.0) |
| Week 2 (LOCF) | Change from Baseline | | | | |
| | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | -1.85 (2.15) | -2.47 (2.55) | -2.19 (2.28) | -1.99 (2.15) |
| | Median | -1.0 | -2.0 | -2.0 | -1.5 |
| | Min, Max | (-8.0, 2.0) | (-10.0, 2.0) | (-10.0, 2.0) | (-9.0, 2.0) |
| Week 4 (LOCF) | Change from Baseline | | | | |
| | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | -2.26 (2.34) | -3.20 (2.73) | -2.98 (2.84) | -2.50 (2.37) |
| | Median | -2.0 | -3.0 | -3.0 | -2.0 |
| | Min, Max | (-8.0, 2.0) | (-10.0, 2.0) | (-10.0, 4.0) | (-9.0, 1.0) |
| Week 8 (LOCF) | Change from Baseline | | | | |
| | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | -2.50 (2.59) | -3.36 (2.77) | -3.19 (2.92) | -2.39 (2.33) |
| | Median | -2.0 | -3.0 | -3.0 | -2.0 |
| | Min, Max | (-10.0, 3.0) | (-9.0, 2.0) | (-10.0, 2.0) | (-9.0, 1.0) |
| Week 12 (LOCF) | Change from Baseline | | | | |
| | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | -2.66 (2.75) | -3.54 (2.92) | -3.23 (2.88) | -2.56 (2.44) |
| | Median | -3.0 | -3.0 | -3.0 | -2.0 |
| | Min, Max | (-10.0, 3.0) | (-10.0, 2.0) | (-10.0, 2.0) | (-10.0, 3.0) |
| Week 16 (LOCF) | Change from Baseline | | | | |
| | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | -2.83 (2.81) | -3.57 (2.90) | -3.32 (2.90) | -2.51 (2.37) |
| | Median | -3.0 | -3.0 | -3.0 | -2.0 |
| | Min, Max | (-10.0, 3.0) | (-10.0, 2.0) | (-10.0, 2.0) | (-9.0, 3.0) |

WOMAC subscale scores range from 0 to 10, where 0 is the best response.
CR = controlled release; LOCF = last observation carried forward; mITT = modified intent-to-treat; Max = maximum; Min = minimum; N = number of subjects in each treatment group; q12h = every 12 hours; SD = standard deviation.WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

## Table 33. Summary of WOMAC Pain Subscale Item When Going Up or Down Stairs, Change From Baseline to Week 8 (ITT/mITT, LOCF)

| | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|
| | | 5 mg | 10 mg | 10-40 mg q12h |
| | N=141 | N=161 | N=150 | N=158 |
| **WOMAC Pain Subscale Item[a], Baseline and Change from Baseline to Week 8 (0-10 NRS)** | | | | |
| **ITT** | | | | |
| N | 141 | 161 | 150 | 158 |
| Baseline mean (SD) | 8.59 (1.20) | 8.39 (1.29) | 8.45 (1.42) | 8.53 (1.37) |
| Change from Baseline LS mean (SE)* | -2.62 (0.25) | -3.55 (0.23) | -3.68 (0.24) | -2.44 (0.23) |
| 95% CI for LS mean | (-3.12, -2.13) | (-4.00, -3.11) | (-4.15, -3.21) | (-2.89, -1.99) |
| Comparison vs placebo | | | | |
| Change from Baseline LS mean (SE)* | | -0.93 (0.29) | -1.06 (0.29) | 0.18 (0.29) |
| 95% CI for LS mean | | (-1.49, -0.37) | (-1.63, -0.49) | (-0.38, 0.74) |
| p-value† | | 0.001 | <0.001 | 0.530 |
| Comparison vs oxycodone CR | | | | |
| Change from Baseline LS mean (SE)* | | -1.11 (0.28) | -1.24 (0.28) | |
| 95% CI for LS mean | | (-1.65, -0.57) | (-1.79, -0.69) | |
| p-value† | | <0.001 | <0.001 | |
| **mITT** | | | | |
| N | 137 | 153 | 149 | 156 |
| Baseline mean (SD) | 8.59 (1.20) | 8.42 (1.27) | 8.44 (1.42) | 8.55 (1.35) |
| Change from Baseline LS mean (SE)* | -2.34 (0.27) | -3.09 (0.25) | -2.85 (0.26) | -2.04 (0.25) |
| 95% CI for LS mean | (-2.87, -1.81) | (-3.58, -2.60) | (-3.36, -2.35) | (-2.53, -1.55) |
| Comparison vs placebo | | | | |
| Change from Baseline LS mean (SE)* | | -0.75 (0.29) | -0.51 (0.29) | 0.30 (0.29) |
| 95% CI for LS mean | | (-1.32, -0.17) | (-1.09, 0.06) | (-0.27, 0.87) |
| p-value† | | 0.011 | 0.081 | 0.299 |
| Comparison vs oxycodone CR | | | | |
| Change from Baseline LS mean (SE)* | | -1.05 (0.28) | -0.81 (0.28) | |
| 95% CI for LS mean | | (-1.60, -0.50) | (-1.37, -0.26) | |
| p-value† | | <0.001 | 0.004 | |

*LS means were estimated from the corresponding ANCOVA model.
†p-value is based on ANCOVA from pairwise comparisons.
ANCOVA model includes treatment as main effect, Baseline value, index joint, previous opioid use as covariates, and study site as a random effect.
ANCOVA = analysis of covariance; CI = confidence interval; CR = controlled release; ITT = intent-to-treat; LOCF = last observation carried forward; LS mean = least squares means; mITT = modified ITT; N = number of subjects in each treatment group with Baseline or change from Baseline to Week 8 data; NRS = numeric rating scale; q12h = every 12 hours; SD = standard deviation; SE = standard error; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
a. WOMAC subscale score ranges from 0 to 10, where 0 is the best response. A change from Baseline of <0 is an improvement.

## Table 34. Summary of Change From Baseline for the WOMAC Item: Pain When Going Up or Down Stairs by Week (ITT, LOCF)

| | | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|---|
| | | | 5 mg | 10 mg | 10-40 mg q12h |
| | | N=141 | N=161 | N=150 | N=158 |
| Baseline | Score | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | 8.59 (1.20) | 8.39 (1.29) | 8.45 (1.42) | 8.53 (1.37) |
| | Median | 9.0 | 9.0 | 9.0 | 9.0 |
| | Min, Max | (4.0, 10.0) | (5.0, 10.0) | (4.0, 10.0) | (5.0, 10.0) |
| Week 2 (LOCF) | Change from Baseline | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | -2.06 (1.99) | -2.34 (2.45) | -2.39 (2.40) | -2.08 (2.10) |
| | Median | -2.0 | -2.0 | -2.0 | -2.0 |
| | Min, Max | (-8.0, 2.0) | (-9.0, 3.0) | (-10.0, 2.0) | (-8.0, 1.0) |
| Week 4 (LOCF) | Change from Baseline | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | -2.64 (2.12) | -3.39 (2.78) | -3.48 (2.84) | -2.64 (2.31) |
| | Median | -3.0 | -3.0 | -3.0 | -2.0 |
| | Min, Max | (-8.0, 2.0) | (-10.0, 2.0) | (-9.0, 3.0) | (-9.0, 2.0) |
| Week 8 (LOCF) | Change from Baseline | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | -2.77 (2.34) | -3.58 (2.81) | -3.74 (2.86) | -2.51 (2.37) |
| | Median | -2.0 | -3.0 | -4.0 | -2.0 |
| | Min, Max | (-9.0, 2.0) | (-10.0, 2.0) | (-10.0, 2.0) | (-9.0, 3.0) |
| Week 12 (LOCF) | Change from Baseline | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | -2.87 (2.38) | -3.70 (2.98) | -3.76 (2.87) | -2.68 (2.48) |
| | Median | -3.0 | -3.0 | -4.0 | -2.0 |
| | Min, Max | (-9.0, 2.0) | (-10.0, 2.0) | (-10.0, 4.0) | (-9.0, 3.0) |
| Week 16 (LOCF) | Change from Baseline | | | | |
| | N | 141 | 161 | 150 | 158 |
| | Mean (SD) | -3.02 (2.55) | -3.61 (2.86) | -3.75 (2.80) | -2.66 (2.45) |
| | Median | -3.0 | -4.0 | -4.0 | -2.0 |
| | Min, Max | (-10.0, 2.0) | (-10.0, 2.0) | (-10.0, 2.0) | (-9.0, 3.0) |

WOMAC subscale scores range from 0 to 10, where 0 is the best response.
CR = controlled release; ITT = intent-to-treat; LOCF = last observation carried forward; Max = maximum; Min = minimum; N = number of subjects in each treatment group; q12h = every 12 hours; SD = standard deviation; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

**Table 35. Summary of Change From Baseline for the WOMAC Item: Pain When Going Up or Down Stairs by Week (mITT, LOCF)**

| | | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|---|
| | | | 5 mg | 10 mg | 10-40 mg q12h |
| | | N=137 | N=153 | N=149 | N=156 |
| Baseline | Score | | | | |
| | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | 8.59 (1.20) | 8.42 (1.27) | 8.44 (1.42) | 8.55 (1.35) |
| | Median | 9.0 | 9.0 | 9.0 | 9.0 |
| | Min, Max | (4.0, 10.0) | (5.0, 10.0) | (4.0, 10.0) | (5.0, 10.0) |
| Week 2 (LOCF) | Change from Baseline | | | | |
| | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | -1.90 (1.98) | -2.21 (2.45) | -2.06 (2.26) | -1.87 (2.16) |
| | Median | -2.0 | -2.0 | -1.0 | -1.0 |
| | Min, Max | (-8.0, 1.0) | (-9.0, 3.0) | (-9.0, 2.0) | (-8.0, 1.0) |
| Week 4 (LOCF) | Change from Baseline | | | | |
| | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | -2.44 (2.19) | -3.10 (2.82) | -2.81 (2.79) | -2.24 (2.28) |
| | Median | -2.0 | -3.0 | -2.0 | -2.0 |
| | Min, Max | (-8.0, 2.0) | (-10.0, 2.0) | (-9.0, 3.0) | (-8.0, 1.0) |
| Week 8 (LOCF) | Change from Baseline | | | | |
| | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | -2.62 (2.36) | -3.25 (2.86) | -3.04 (2.86) | -2.21 (2.29) |
| | Median | -2.0 | -3.0 | -3.0 | -2.0 |
| | Min, Max | (-8.0, 2.0) | (-10.0, 2.0) | (-10.0, 2.0) | (-8.0, 1.0) |
| Week 12 (LOCF) | Change from Baseline | | | | |
| | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | -2.71 (2.45) | -3.40 (2.99) | -3.11 (2.88) | -2.40 (2.44) |
| | Median | -2.0 | -3.0 | -3.0 | -2.0 |
| | Min, Max | (-9.0, 2.0) | (-10.0, 2.0) | (-10.0, 2.0) | (-9.0, 1.0) |
| Week 16 (LOCF) | Change from Baseline | | | | |
| | N | 137 | 153 | 149 | 156 |
| | Mean (SD) | -2.91 (2.64) | -3.42 (2.92) | -3.24 (2.89) | -2.40 (2.42) |
| | Median | -2.0 | -3.0 | -3.0 | -2.0 |
| | Min, Max | (-10.0, 2.0) | (-10.0, 2.0) | (-10.0, 2.0) | (-8.0, 1.0) |

WOMAC subscale scores range from 0 to 10, where 0 is the best response.
CR = controlled release; LOCF = last observation carried forward; mITT = modified intent-to-treat; Max = maximum; Min = minimum; N = number of subjects in each treatment group; q12h = every 12 hours; SD = standard deviation.
WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Medical Outcomes Study Short Form 36 (SF 36v2): Table 36 summarizes the change from Baseline at Week 12 for the health survey SF-36 dimensions of physical function, role physical, bodily pain, vitality, and physical component summary.

## Table 36. Summary of Change From Baseline to Week 12 in SF-36 Dimensions (ITT/mITT, Observed Data)

| | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|
| | | 5 mg | 10 mg | 10-40 mg q12h |
| **ITT Population** | **N=141** | **N=161** | **N=150** | **N=158** |
| **mITT Population** | **N=137** | **N=153** | **N=149** | **N=156** |
| | **n=57** | **n=62** | **n=57** | **n=59** |
| General health | | | | |
| Baseline, ITT (mean [SD]) | 56.14 (24.44) | 60.37 (18.32) | 58.93 (21.68) | 57.03 (17.71) |
| Week 12, ITT | | | | |
| LS mean (SE)* | 4.17 (2.34) | 6.55 (2.09) | 8.03 (2.26) | 3.09 (2.10) |
| 95% CI for LS mean | (-0.44, 8.78) | (2.43, 10.66) | (3.57, 12.49) | (-1.04, 7.23) |
| Comparison to placebo | | | | |
| LS mean difference (SE)* | | 2.38 (2.65) | 3.86 (2.69) | -1.08 (2.73) |
| 95% CI for LS mean difference | | (-2.84, 7.60) | (-1.44, 9.16) | (-6.47, 4.32) |
| p-value† | | 0.370 | 0.153 | 0.694 |
| Comparison to oxycodone CR | | | | |
| LS mean difference (SE)* | | 3.45 (2.63) | 4.93 (2.67) | |
| 95% CI for LS mean difference | | (-1.73, 8.64) | (-0.34, 10.21) | |
| p-value† | | 0.190 | 0.067 | |
| Week 12, mITT | | | | |
| LS mean (SE)* | 4.17 (2.34) | 6.55 (2.09) | 8.03 (2.26) | 3.09 (2.10) |
| 95% CI for LS mean | (-0.44, 8.78) | (2.43, 10.66) | (3.57, 12.49) | (-1.04, 7.23) |
| Comparison to placebo | | | | |
| LS mean difference (SE)* | | 2.38 (2.65) | 3.86 (2.69) | -1.08 (2.73) |
| 95% CI for LS mean difference | | (-2.84, 7.60) | (-1.44, 9.16) | (-6.47, 4.32) |
| p-value† | | 0.370 | 0.153 | 0.694 |
| Comparison to oxycodone CR | | | | |
| LS mean difference (SE)* | | 3.45 (2.63) | 4.93 (2.67) | |
| 95% CI for LS mean difference | | (-1.73, 8.64) | (-0.34, 10.21) | |
| p-value† | | 0.190 | 0.067 | |
| Physical Function | | | | |
| Baseline, ITT(mean [SD]) | 29.30 (19.85) | 29.92 (20.64) | 34.21 (22.44) | 29.24 (20.32) |
| Week 12, ITT | | | | |
| LS mean (SE)* | 11.08 (3.27) | 25.69 (2.91) | 14.13 (3.17) | 8.92 (2.94) |
| 95% CI for LS mean | (4.62, 17.53) | (19.95, 31.43) | (7.88, 20.38) | (3.13, 14.71) |
| Comparison to placebo | | | | |
| LS mean difference (SE)* | | 14.61 (3.75) | 3.05 (3.83) | -2.16 (3.88) |
| 95% CI for LS mean difference | | (7.22, 22.00) | (-4.50, 10.60) | (-9.81, 5.49) |
| p-value† | | <0.001 | 0.426 | 0.578 |
| Comparison to oxycodone CR | | | | |
| LS mean difference (SE)* | | 16.77 (3.72) | 5.21 (3.80) | |
| 95% CI for LS mean difference | | (9.43, 24.11) | (-2.29, 12.71) | |
| p-value† | | <0.001 | 0.172 | |
| Week 12, mITT | | | | |
| LS mean (SE)* | 11.08 (3.27) | 25.69 (2.91) | 14.13 (3.17) | 8.92 (2.94) |
| 95% CI for LS mean | (4.62, 17.53) | (19.95, 31.43) | (7.88, 20.38) | (3.13, 14.71) |
| Comparison to placebo | | | | |
| LS mean difference (SE)* | | 14.61 (3.75) | 3.05 (3.83) | -2.16 (3.88) |
| 95% CI for LS mean difference | | (7.22, 22.00) | (-4.50, 10.60) | (-9.81, 5.49) |
| p-value† | | <0.001 | 0.426 | 0.578 |
| Comparison to oxycodone CR | | | | |
| LS mean difference (SE)* | | 16.77 (3.72) | 5.21 (3.80) | |
| 95% CI for LS mean difference | | (9.43, 24.11) | (-2.29, 12.71) | |
| p-value† | | <0.001 | 0.172 | |
| Role physical | | | | |
| Baseline, ITT(mean [SD]) | 37.50 (23.39) | 40.12 (25.85) | 41.67 (23.69) | 36.33 (24.74) |
| Week 12, ITT | | | | |
| LS mean (SE)* | 15.64 (3.73) | 27.71 (3.33) | 16.16 (3.60) | 12.93 (3.35) |
| 95% CI for LS mean | (8.27, 23.00) | (21.14, 34.29) | (9.05, 23.27) | (6.32, 19.54) |

## Table 36. Summary of Change From Baseline to Week 12 in SF-36 Dimensions (ITT/mITT, Observed Data)

| | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|
| | | 5 mg | 10 mg | 10-40 mg q12h |
| **ITT Population** | **N=141** | **N=161** | **N=150** | **N=158** |
| **mITT Population** | **N=137** | **N=153** | **N=149** | **N=156** |
| | **n=57** | **n=62** | **n=57** | **n=59** |
| Comparison to placebo | | | | |
| LS mean difference (SE)* | | 12.08 (4.14) | 0.52 (4.21) | -2.70 (4.28) |
| 95% CI for LS mean difference | | (3.91, 20.24) | (-7.79, 8.83) | (-11.14, 5.74) |
| p-value† | | 0.004 | 0.902 | 0.528 |
| Comparison to oxycodone CR | | | | |
| LS mean difference (SE)* | | 14.78 (4.11) | 3.22 (4.19) | |
| 95% CI for LS mean difference | | (6.67, 22.89) | (-5.03, 11.48) | |
| p-value† | | <0.001 | 0.442 | |
| Week 12, mITT | | | | |
| LS mean (SE)* | 15.64 (3.73) | 27.71 (3.33) | 16.16 (3.60) | 12.93 (3.35) |
| 95% CI for LS mean | (8.27, 23.00) | (21.14, 34.29) | (9.05, 23.27) | (6.23, 19.54) |
| Comparison to placebo | | | | |
| LS mean difference (SE)* | | 12.08 (4.14) | 0.52 (4.21) | -2.70 (4.28) |
| 95% CI for LS mean difference | | (3.91, 20.24) | (-7.79, 8.83) | (-11.14, 5.74) |
| p-value† | | 0.004 | 0.902 | 0.528 |
| Comparison to oxycodone CR | | | | |
| LS mean difference (SE)* | | 14.78 (4.11) | 3.22 (4.19) | |
| 95% CI for LS mean difference | | (6.67, 22.89) | (-5.03, 11.48) | |
| p-value† | | <0.001 | 0.442 | |
| Bodily Pain | | | | |
| Baseline, ITT (mean [SD]) | 30.30 (15.32) | 28.84 (12.85) | 30.60 (15.98) | 28.73 (13.94) |
| Week 12, ITT | | | | |
| LS mean (SE)* | 13.98 (3.14) | 30.19 (2.80) | 20.70 (3.04) | 15.53 (2.83) |
| 95% CI for LS mean | (7.78, 20.17) | (24.68, 35.71) | (14.70, 26.69) | (9.95, 21.12) |
| Comparison to placebo | | | | |
| LS mean difference (SE)* | | 16.21 (3.64) | 6.72 (3.70) | 1.56 (3.77) |
| 95% CI for LS mean difference | | (9.03, 23.39) | (-0.58, 14.01) | (-5.87, 8.98) |
| p-value† | | <0.001 | 0.071 | 0.680 |
| Comparison to oxycodone CR | | | | |
| LS mean difference (SE)* | | 14.66 (3.62) | 5.16 (3.69) | |
| 95% CI for LS mean difference | | (7.53, 21.79) | (-2.12, 12.44) | |
| p-value† | | <0.001 | 0.164 | |
| Week 12, mITT | | | | |
| LS mean (SE)* | 13.98 (3.14) | 30.19 (2.80) | 20.70 (3.04) | 15.53 (2.83) |
| 95% CI for LS mean | (7.78, 20.17) | (24.68, 35.71) | (14.70, 26.69) | (9.95, 21.12) |
| Comparison to placebo | | | | |
| LS mean difference (SE)* | | 16.21 (3.64) | 6.72 (3.70) | 1.56 (3.77) |
| 95% CI for LS mean difference | | (9.03, 23.39) | (-0.58, 14.01) | (-5.87, 8.98) |
| p-value† | | <0.001 | 0.071 | 0.68 |
| Comparison to oxycodone CR | | | | |
| LS mean difference (SE)* | | 14.66 (3.62) | 5.16 (3.69) | |
| 95% CI for LS mean difference | | (7.53, 21.79) | (-2.12, 12.44) | |
| p-value† | | <0.001 | 0.164 | |
| Vitality | | | | |
| Baseline, ITT (mean [SD]) | 45.72 (18.27) | 48.08 (21.90) | 49.34 (22.77) | 48.41 (22.43) |
| Week 12, ITT | | | | |
| LS mean (SE)* | 7.08 (2.51) | 11.44 (2.22) | 9.57 (2.41) | 6.98 (2.24) |
| 95% CI for LS mean | (2.14, 12.03) | (7.07, 15.80) | (4.82, 14.33) | (2.56, 11.39) |
| Comparison to placebo | | | | |
| LS mean difference (SE)* | | 4.35 (2.89) | 2.49 (2.94) | -0.11 (3.00) |
| 95% CI for LS mean difference | | (-1.35, 10.06) | (-3.32, 8.29) | (-6.02, 5.80) |
| p-value† | | 0.134 | 0.399 | 0.971 |
| Comparison to oxycodone CR | | | | |

## Table 36. Summary of Change From Baseline to Week 12 in SF-36 Dimensions (ITT/mITT, Observed Data)

| | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|
| | | 5 mg | 10 mg | 10-40 mg q12h |
| **ITT Population** | **N=141** | **N=161** | **N=150** | **N=158** |
| **mITT Population** | **N=137** | **N=153** | **N=149** | **N=156** |
| | **n=57** | **n=62** | **n=57** | **n=59** |
| LS mean difference (SE)* | | 4.46 (2.87) | 2.60 (2.93) | |
| 95% CI for LS mean difference | | (-1.20, 10.12) | (-3.18, 8.37) | |
| p-value† | | 0.122 | 0.376 | |
| Week 12, mITT | | | | |
| LS mean (SE)* | 7.08 (2.51) | 11.44 (2.22) | 9.57 (2.41) | 6.98 (2.24) |
| 95% CI for LS mean | (2.14, 12.03) | (7.07, 15.80) | (4.82, 14.33) | (2.56, 11.39) |
| Comparison to placebo | | | | |
| LS mean difference (SE)* | | 4.35 (2.89) | 2.49 (2.94) | -0.11 (3.00) |
| 95% CI for LS mean difference | | (-1.35, 10.06) | (-3.32, 8.29) | (-6.02, 5.80) |
| p-value† | | 0.134 | 0.399 | 0.971 |
| Comparison to oxycodone CR | | | | |
| LS mean difference (SE)* | | 4.46 (2.87) | 2.60 (2.93) | |
| 95% CI for LS mean difference | | (-1.20, 10.12) | (-3.18, 8.37) | |
| p-value† | | 0.122 | 0.376 | |
| Social function | | | | |
| Baseline, ITT (mean [SD]) | 53.51 (25.20) | 61.90 (27.67) | 62.28 (27.90) | 58.05 (26.64) |
| Week 12, ITT | | | | |
| LS mean (SE)* | 10.41 (3.46) | 15.13 (3.06) | 13.75 (3.32) | 10.86 (3.08) |
| 95% CI for LS mean | (3.58, 17.23) | (9.09, 21.17) | (7.20, 20.31) | (4.77, 16.94) |
| Comparison to placebo | | | | |
| LS mean difference (SE)* | | 4.72 (3.89) | 3.35 (3.96) | 0.45 (4.02) |
| 95% CI for LS mean difference | | (-2.96, 12.40) | (-4.46, 11.16) | (-7.47, 8.37) |
| p-value† | | 0.227 | 0.399 | 0.911 |
| Comparison to oxycodone CR | | | | |
| LS mean difference (SE)* | | 4.27 (3.84) | 2.90 (3.91) | |
| 95% CI for LS mean difference | | (-3.31, 11.85) | (-4.82, 10.61) | |
| p-value† | | 0.268 | 0.460 | |
| Week 12, mITT | | | | |
| LS mean (SE)* | 10.41 (3.46) | 15.13 (3.06) | 13.75 (3.32) | 10.86 (3.08) |
| 95% CI for LS mean | (3.58, 17.23) | (9.09, 21.17) | (7.20, 20.31) | (4.77, 16.94) |
| Comparison to placebo | | | | |
| LS mean difference (SE)* | | 4.72 ( 3.89) | 3.35 ( 3.96) | 0.45 ( 4.02) |
| 95% CI for LS mean difference | | (-2.96, 12.40) | (-4.46, 11.16) | (-7.47, 8.37) |
| p-value† | | 0.227 | 0.399 | 0.911 |
| Comparison to oxycodone CR | | | | |
| LS mean difference (SE)* | | 4.27 ( 3.84) | 2.90 ( 3.91) | |
| 95% CI for LS mean difference | | (-3.31, 11.85) | (-4.82, 10.61) | |
| p-value† | | 0.268 | 0.460 | |
| Role emotional | | | | |
| Baseline, ITT (mean [SD]) | 56.29 (31.07) | 59.68 (32.26) | 65.06 (32.33) | 63.42 (30.48) |
| Week 12, ITT | | | | |
| LS mean (SE)* | 11.01 (3.90) | 14.84 (3.47) | 10.71 (3.76) | 4.94 (3.49) |
| 95% CI for LS mean | (3.31, 18.71) | (8.00, 21.69) | (3.31, 18.12) | (-1.94, 11.81) |
| Comparison to placebo | | | | |
| LS mean difference (SE)* | | 3.83 (4.37) | -0.30 (4.47) | -6.07 (4.55) |
| 95% CI for LS mean difference | | (-4.80, 12.46) | (-9.11, 8.51) | (-15.05, 2.90) |
| p-value† | | 0.382 | 0.947 | 0.183 |
| Comparison to oxycodone CR | | | | |
| LS mean difference (SE)* | | 9.91 (4.35) | 5.78 (4.42) | |
| 95% CI for LS mean difference | | (1.32, 18.49) | (-2.93, 14.49) | |
| p-value† | | 0.024 | 0.192 | |
| Week 12, mITT | | | | |
| LS mean (SE)* | 11.01 (3.90) | 14.84 (3.47) | 10.71 (3.76) | 4.94 (3.49) |

## Table 36. Summary of Change From Baseline to Week 12 in SF-36 Dimensions (ITT/mITT, Observed Data)

| | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|
| | | 5 mg | 10 mg | 10-40 mg q12h |
| **ITT Population** | **N=141** | **N=161** | **N=150** | **N=158** |
| **mITT Population** | **N=137** | **N=153** | **N=149** | **N=156** |
| | **n=57** | **n=62** | **n=57** | **n=59** |
| 95% CI for LS mean | (3.31, 18.71) | (8.00, 21.69) | (3.31, 18.12) | (-1.94, 11.81) |
| Comparison to placebo | | | | |
| LS mean difference (SE)* | | 3.83 (4.37) | -0.30 (4.47) | -6.07 (4.55) |
| 95% CI for LS mean difference | | (-4.80, 12.46) | (-9.11, 8.51) | (-15.05, 2.90) |
| p-value† | | 0.382 | 0.947 | 0.183 |
| Comparison to oxycodone CR | | | | |
| LS mean difference (SE)* | | 9.91 (4.35) | 5.78 (4.42) | |
| 95% CI for LS mean difference | | (1.32, 18.49) | (-2.93, 14.49) | |
| p-value† | | 0.024 | 0.192 | |
| Mental health | | | | |
| Baseline, ITT (mean [SD]) | 64.91 (21.08) | 68.71 (20.16) | 67.54 (23.49) | 68.56 (19.32) |
| Week 12, ITT | | | | |
| LS mean (SE)* | 1.96 (2.44) | 4.50 (2.17) | 6.66 (2.36) | 3.41 (2.19) |
| 95% CI for LS mean | (-2.86, 6.78) | (0.21, 8.78) | (2.01, 11.32) | (-0.91, 7.73) |
| Comparison to placebo | | | | |
| LS mean difference (SE)* | | 2.54 ( 2.80) | 4.71 ( 2.84) | 1.45 ( 2.89) |
| 95% CI for LS mean difference | | (-2.97, 8.05) | (-0.89, 10.30) | (-4.26, 7.15) |
| p-value† | | 0.365 | 0.099 | 0.617 |
| Comparison to oxycodone CR | | | | |
| LS mean difference (SE)* | | 1.09 (2.77) | 3.26 (2.82) | |
| 95% CI for LS mean difference | | (-4.38, 6.55) | (-2.31, 8.83) | |
| p-value† | | 0.695 | 0.250 | |
| Week 12, mITT | | | | |
| LS mean (SE)* | 1.96 (2.44) | 4.50 (2.17) | 6.66 (2.36) | 3.41 (2.19) |
| 95% CI for LS mean | (-2.86, 6.78) | (0.21, 8.78) | (2.01, 11.32) | (-0.91, 7.73) |
| Comparison to placebo | | | | |
| LS mean difference (SE)* | | 2.54 (2.80) | 4.71 (2.84) | 1.45 (2.89) |
| 95% CI for LS mean difference | | (-2.97, 8.05) | (-0.89, 10.30) | (-4.26, 7.15) |
| p-value† | | 0.365 | 0.099 | 0.617 |
| Comparison to oxycodone CR | | | | |
| LS mean difference (SE)* | | 1.09 (2.77) | 3.26 (2.82) | |
| 95% CI for LS mean difference | | (-4.38, 6.55) | (-2.31, 8.83) | |
| p-value† | | 0.695 | 0.250 | |
| Mental component aggregate | | | | |
| Baseline, ITT (mean [SD]) | -0.51 (1.30) | -0.24 (1.29) | -0.20 (1.45) | -0.18 (1.28) |
| Week 12, ITT | | | | |
| LS mean (SE)* | 0.25 (0.14) | 0.22 (0.13) | 0.36 (0.14) | 0.18 (0.13) |
| 95% CI for LS mean | (-0.03, 0.53) | (-0.03, 0.47) | (0.09, 0.64) | (-0.07, 0.43) |
| Comparison to placebo | | | | |
| LS mean difference (SE)* | | -0.03 ( 0.16) | 0.12 ( 0.16) | -0.07 ( 0.17) |
| 95% CI for LS mean difference | | (-0.35, 0.29) | (-0.21, 0.44) | (-0.40, 0.26) |
| p-value† | | 0.870 | 0.486 | 0.691 |
| Comparison to oxycodone CR | | | | |
| LS mean difference (SE)* | | 0.04 (0.16) | 0.18 (0.16) | |
| 95% CI for LS mean difference | | (-0.28, 0.36) | (-0.14, 0.50) | |
| p-value† | | 0.802 | 0.266 | |
| Week 12, mITT | | | | |
| LS mean (SE)* | 0.25 (0.14) | 0.22 (0.13) | 0.36 (0.14) | 0.18 (0.13) |
| 95% CI for LS mean | (-0.03, 0.53) | (-0.03, 0.47) | (0.09, 0.64) | (-0.07, 0.43) |
| Comparison to placebo | | | | |
| LS mean difference (SE)* | | -0.03 ( 0.16) | 0.12 ( 0.16) | -0.07 ( 0.17) |
| 95% CI for LS mean difference | | (-0.35, 0.29) | (-0.21, 0.44) | (-0.40, 0.26) |
| p-value† | | 0.870 | 0.486 | 0.691 |

**Table 36. Summary of Change From Baseline to Week 12 in SF-36 Dimensions (ITT/mITT, Observed Data)**

| | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|
| | | 5 mg | 10 mg | 10-40 mg q12h |
| **ITT Population** | **N=141** | **N=161** | **N=150** | **N=158** |
| **mITT Population** | **N=137** | **N=153** | **N=149** | **N=156** |
| | **n=57** | **n=62** | **n=57** | **n=59** |
| Comparison to oxycodone CR | | | | |
| LS mean difference (SE)* | | 0.04 (0.16) | 0.18 (0.16) | |
| 95% CI for LS mean difference | | (-0.28, 0.36) | (-0.14, 0.50) | |
| p-value† | | 0.802 | 0.266 | |
| Physical component aggregate | | | | |
| Baseline, ITT (mean [SD]) | -1.88 (0.80) | -1.88 (0.65) | -1.81 (0.77) | -2.01 (0.71) |
| Week 12, ITT | | | | |
| LS mean (SE)* | 0.53 (0.12) | 1.12 (0.11) | 0.66 (0.12) | 0.48 (0.11) |
| 95% CI for LS mean | (0.29, 0.77) | (0.91, 1.34) | (0.43, 0.90) | (0.26, 0.70) |
| Comparison to placebo | | | | |
| LS mean difference (SE)* | | 0.60 (0.14) | 0.14 (0.14) | -0.05 (0.14) |
| 95% CI for LS mean difference | | (0.32, 0.87) | (-0.14, 0.41) | (-0.33, 0.24) |
| p-value† | | <0.001 | 0.332 | 0.750 |
| Comparison to oxycodone CR | | | | |
| LS mean difference (SE)* | | 0.64 (0.14) | 0.18 (0.14) | |
| 95% CI for LS mean difference | | (0.37, 0.91) | (-0.09, 0.46) | |
| p-value† | | <0.001 | 0.195 | |
| Week 12, mITT | | | | |
| LS mean (SE)* | 0.53 (0.12) | 1.12 (0.11) | 0.66 (0.12) | 0.48 (0.11) |
| 95% CI for LS mean | (0.29, 0.77) | (0.91, 1.34) | (0.43, 0.90) | (0.26, 0.70) |
| Comparison to placebo | | | | |
| LS mean difference (SE)* | | 0.60 (0.14) | 0.14 (0.14) | -0.05 (0.14) |
| 95% CI for LS mean difference | | (0.32, 0.87) | (-0.14, 0.41) | (-0.33, 0.24) |
| p-value† | | <0.001 | 0.332 | 0.750 |
| Comparison to oxycodone CR | | | | |
| LS mean difference (SE)* | | 0.64 (0.14) | 0.18 (0.14) | |
| 95% CI for LS mean difference | | (0.37, 0.91) | (-0.09, 0.46) | |
| p-value† | | <0.001 | 0.195 | |

*LS means were estimated from the corresponding ANCOVA model.
†p-value is based pairwise comparisons.
ANCOVA model includes treatment as main effect, Baseline value and index joint as covariates, and study site as a random effect. SF-36 domain score ranges from 0 to 100, where 100 is the best response, and a change from Baseline >0 is an improvement.
ANCOVA = analysis of covariance; CI = confidence interval; CR = controlled release; ITT = intent-to-treat; LOCF = last observation carried forward; LS = least squares; mITT = modified ITT; n = number of subjects with a change from baseline to Week 12 observed values; N = number of subjects in each treatment group; q12h = every 12 hours; SD = standard deviation; SE = standard error; SF-36 = Medical Outcomes Study Short Form 36 Health Survey.

EuroQol 5D Health State Profile (EQ-5D): Table 37 summarizes the change from Baseline to Week 12 for the EQ-5D (health state utility and individual dimensions) for the ITT and mITT populations (observed values).

## Table 37. Summary of Change From Baseline to Week 12 in the EuroQol 5D – Individual Dimension Scores and Health State Utility (ITT/mITT, Observed Data)

| | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|
| | | 5 mg | 10 mg | 10-40 mg q12h |
| **ITT Population** | **N=141** | **N=161** | **N=150** | **N=158** |
| **mITT Population** | **N=137** | **N=153** | **N=149** | **N=156** |
| **EQ-5D item** | | | | |
| **Individual Dimension Scores** | **Number (%) of Subjects** | | | |
| Health state utility | | | | |
| ITT | n=56 | n=61 | n=57 | n=59 |
| Mean baseline (SD) | 0.39 (0.31) | 0.41 (0.31) | 0.43 (0.29) | 0.38 (0.30) |
| Change from Baseline LS mean (SE)* | 0.19 (0.04) | 0.31 (0.03) | 0.24 (0.03) | 0.15 (0.03) |
| 95% CI for LS mean | (0.12, 0.26) | (0.24, 0.37) | (0.17, 0.30) | (0.09, 0.21) |
| Comparison vs placebo | | | | |
| LS mean difference (SE) | | 0.12 (0.04) | 0.05 (0.04) | -0.04 (0.04) |
| 95% CI for LS mean difference | | (0.04, 0.20) | (-0.04, 0.13) | (-0.12, 0.05) |
| p-value† | | 0.005 | 0.262 | 0.382 |
| Comparison vs oxycodone CR | | | | |
| LS mean difference (SE) | | 0.16 (0.04) | 0.09 (0.04) | |
| 95% CI for LS mean difference | | (0.07, 0.24) | (0.00, 0.17) | |
| p-value† | | <0.001 | 0.043 | |
| mITT | n=56 | n=61 | n=57 | n=59 |
| Mean baseline (SD) | 0.40 (0.31) | 0.41 (0.31) | 0.43 (0.30) | 0.38 (0.30) |
| Change from Baseline LS mean (SE)* | 0.19 (0.04) | 0.31 (0.03) | 0.24 (0.03) | 0.15 (0.03) |
| 95% CI for LS mean | (0.12, 0.26) | (0.24, 0.37) | (0.17, 0.35) | (0.09, 0.21) |
| Comparison vs placebo | | | | |
| LS mean difference (SE) | | 0.12 (0.04) | 0.05 (0.04) | -0.04 (0.04) |
| 95% CI for LS mean difference | | (0.04, 0.20) | (-0.04, 0.13) | (-0.12, 0.05) |
| p-value† | | 0.005 | 0.262 | 0.382 |
| Comparison vs oxycodone CR | | | | |
| LS mean difference (SE) | | 0.16 (0.04) | 0.09 (0.04) | |
| 95% CI for LS mean difference | | (0.07, 0.24) | (0.00, 0.17) | |
| p-value† | | <0.001 | 0.043 | |
| Mobility | | | | |
| ITT | n=56 | n=61 | n=57 | n=59 |
| Improved | 12 (21.4) | 29 (47.5) | 17 (29.8) | 4 (6.8) |
| No change | 43 (76.8) | 31 (50.8) | 39 (68.4) | 53 (89.8) |
| Worsened | 1 (1.8) | 1 (1.6) | 1 (1.8) | 2 (3.4) |
| Total | 56 (100.0) | 61 (100.0) | 57 (100.0) | 59 (100.0) |
| p-value‡ vs placebo | | 0.005 | 0.387 | 0.060 |
| p-value‡ vs oxycodone CR | | <0.001 | 0.002 | |
| mITT | n=56 | n=61 | n=57 | n=59 |
| Improved | 12 (21.4) | 29 (47.5) | 17 (29.8) | 4 (6.8) |
| No change | 43 (76.8) | 31 (50.8) | 39 (68.4) | 53 (89.8) |
| Worsened | 1 (1.8) | 1 (1.6) | 1 (1.8) | 2 (3.4) |
| Total | 56 (100.0) | 61 (100.0) | 57 (100.0) | 59 (100.0) |
| p-value‡ vs placebo | | 0.005 | 0.387 | 0.060 |
| p-value‡ vs oxycodone CR | | <0.001 | 0.002 | |
| Self-care | | | | |
| ITT | n=56 | n=61 | n=57 | n=59 |
| Improved | 15 (26.8) | 12 (19.7) | 17 (29.8) | 10 (16.9) |
| No change | 39 (69.6) | 46 (75.4) | 38 (66.7) | 44 (74.6) |
| Worsened | 2 (3.6) | 3 (4.9) | 2 (3.5) | 5 (8.5) |
| Total | 56 (100.0) | 61 (100.0) | 57 (100.0) | 59 (100.0) |
| p-value‡ vs placebo | | 0.412 | 0.534 | 0.284 |
| p-value‡ vs oxycodone CR | | 0.410 | 0.141 | |
| mITT | n=56 | n=61 | n=57 | n=59 |
| Improved | 15 (26.8) | 12 (19.7) | 17 (29.8) | 10 (16.9) |

## Table 37. Summary of Change From Baseline to Week 12 in the EuroQol 5D – Individual Dimension Scores and Health State Utility (ITT/mITT, Observed Data)

| | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|
| | | 5 mg | 10 mg | 10-40 mg q12h |
| **ITT Population** | **N=141** | **N=161** | **N=150** | **N=158** |
| **mITT Population** | **N=137** | **N=153** | **N=149** | **N=156** |
| **EQ-5D item** | | | | |
| **Individual Dimension Scores** | **Number (%) of Subjects** | | | |
| No change | 39 (69.6) | 46 (75.4) | 38 (66.7) | 44 (74.6) |
| Worsened | 2 (3.6) | 3 (4.9) | 2 (3.5) | 5 (8.5) |
| Total | 56 (100.0) | 61 (100.0) | 57 (100.0) | 59 (100.0) |
| p-value‡ vs placebo | | 0.412 | 0.534 | 0.284 |
| p-value‡ vs oxycodone CR | | 0.410 | 0.141 | |
| Usual activities | | | | |
| ITT | n=56 | n=61 | n=57 | n=59 |
| Improved | 15 (26.8) | 27 (44.3) | 15 (26.3) | 21 (35.6) |
| No change | 36 (64.3) | 32 (52.5) | 41 (71.9) | 36 (61.0) |
| Worsened | 5 (8.9) | 2 (3.3) | 1 (1.8) | 2 (3.4) |
| Total | 56 (100.0) | 61 (100.0) | 57 (100.0) | 59 (100.0) |
| p-value‡ vs placebo | | 0.027 | 0.582 | 0.196 |
| p-value‡ vs oxycodone CR | | 0.401 | 0.369 | |
| mITT | n=56 | n=61 | n=57 | n=59 |
| Improved | 15 (26.8) | 27 (44.3) | 15 (26.3) | 21 (35.6) |
| No change | 36 (64.3) | 32 (52.5) | 41 (71.9) | 36 (61.0) |
| Worsened | 5 (8.9) | 2 (3.3) | 1 (1.8) | 2 (3.4) |
| Total | 56 (100.0) | 61 (100.0) | 57 (100.0) | 59 (100.0) |
| p-value‡ vs placebo | | 0.027 | 0.582 | 0.196 |
| p-value‡ vs oxycodone CR | | 0.401 | 0.369 | |
| Pain/discomfort | | | | |
| ITT | n=55 | n=61 | n=57 | n=59 |
| Improved | 23 (41.8) | 32 (52.5) | 21 (36.8) | 17 (28.8) |
| No change | 29 (52.7) | 28 (45.9) | 35 (61.4) | 39 (66.1) |
| Worsened | 3 (5.5) | 1 (1.6) | 1 (1.8) | 3 (5.1) |
| Total | 55 (100.0) | 61 (100.0) | 57 (100.0) | 59 (100.0) |
| p-value‡ vs placebo | | 0.115 | 0.841 | 0.192 |
| p-value‡ vs oxycodone CR | | 0.001 | 0.167 | |
| mITT | n=55 | n=61 | n=57 | n=59 |
| Improved | 23 (41.8) | 32 (52.5) | 21 (36.8) | 17 (28.8) |
| No change | 29 (52.7) | 28 (45.9) | 35 (61.4) | 39 (66.1) |
| Worsened | 3 (5.5) | 1 (1.6) | 1 (1.8) | 3 (5.1) |
| Total | 55 (100.0) | 61 (100.0) | 57 (100.0) | 59 (100.0) |
| p-value‡ vs placebo | | 0.115 | 0.841 | 0.192 |
| p-value‡ vs oxycodone CR | | 0.001 | 0.167 | |
| Anxiety/depression | | | | |
| ITT | n=56 | n=61 | n=57 | n=59 |
| Improved | 16 (28.6) | 16 (26.2) | 12 (21.1) | 9 (15.3) |
| No change | 35 (62.5) | 40 (65.6) | 37 (64.9) | 42 (71.2) |
| Worsened | 5 (8.9) | 5 (8.2) | 8 (14.0) | 8 (13.6) |
| Total | 56 (100.0) | 61 (100.0) | 57 (100.0) | 59 (100.0) |
| p-value‡ vs placebo | | 0.903 | 0.246 | 0.177 |
| p-value‡ vs oxycodone CR | | 0.156 | 0.885 | |
| mITT | n=56 | n=61 | n=57 | n=59 |
| Improved | 16 (28.6) | 16 (26.2) | 12 (21.1) | 9 (15.3) |
| No change | 35 (62.5) | 40 (65.6) | 37 (64.9) | 42 (71.2) |
| Worsened | 5 (8.9) | 5 (8.2) | 8 (14.0) | 8 (13.6) |
| Total | 56 (100.0) | 61 (100.0) | 57 (100.0) | 59 (100.0) |
| p-value‡ vs placebo | | 0.903 | 0.246 | 0.177 |
| p-value‡ vs oxycodone CR | | 0.156 | 0.885 | |

**Table 37. Summary of Change From Baseline to Week 12 in the EuroQol 5D – Individual Dimension Scores and Health State Utility (ITT/mITT, Observed Data)**

| | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|
| | | 5 mg | 10 mg | 10-40 mg q12h |
| **ITT Population** | **N=141** | **N=161** | **N=150** | **N=158** |
| **mITT Population** | **N=137** | **N=153** | **N=149** | **N=156** |
| **EQ-5D item** | | | | |
| **Individual Dimension Scores** | **Number (%) of Subjects** | | | |

*LS means were estimated from the corresponding ANCOVA model. ANCOVA model included treatment as main effect, Baseline value, index joint, and previous opioid use as covariates.
†p-value was based on ANCOVA from pairwise comparisons.
‡ p-value was based on pairwise comparisons and is derived from Cochran–Mantel–Haenszel test controlling for index joint and previous opioid use.
The Health State Utility has a maximum value of 1, which indicates no impairment of health state, with lower values indicating increased impairment. .
CR = controlled release; EQ-5D = EuroQol 5D Health State Profile; ITT = intent-to-treat; mITT = modified ITT; n = number of subjects with a change from Baseline to Week 12 observed values; N = number of subjects in each treatment group; q12h = every 12 hours; vs = versus.

Incidence and Time to Discontinuation due to Lack of Efficacy: Table 38 summarizes the statistical analysis of the incidence of subjects who discontinued from the study due to lack of efficacy.

**Table 38. Analysis of Incidence of Discontinuations From the Study due to Lack of Efficacy (ITT)**

| Discontinued due to Lack of Efficacy | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|
| | | 5 mg | 10 mg | 10-40 mg q12h |
| | N=141 | N=161 | N=150 | N=158 |
| Yes, n (%) | 10 (7.1) | 6 (3.7) | 5 (3.3) | 12 (7.6) |
| No, n (%) | 131 (92.9) | 155 (96.3) | 145 (96.7) | 146 (92.4) |
| Versus placebo | | | | |
| Odds ratio | | 0.51 | 0.45 | 1.08 |
| 95% CI for odds ratio | | (0.18, 1.43) | (0.15, 1.36) | (0.45, 2.57) |
| p-value* | | 0.200 | 0.156 | 0.868 |
| Versus oxycodone CR | | | | |
| Odds ratio | | 0.47 | 0.42 | |
| 95% CI for odds ratio | | (0.17, 1.29) | (0.14, 1.22) | |
| p-value* | | 0.142 | 0.111 | |

*p-value is based on logistic regression model from pairwise comparisons versus placebo and oxycodone CR.
Logistic regression model includes treatment as a main effect. Odds ratio and 95% CI estimated from logistic regression model.
CI = confidence interval; CR = controlled release; ITT = intent-to-treat; N = number of subjects in each treatment group; q12h = every 12 hours.

## Safety Results:

The overall incidence of subjects with all-causality and treatment-related AEs is summarized in Table 39.

## Table 39. Incidence of Adverse Events

| | Placebo | Tanezumab | | Oxycodone CR |
|---|---|---|---|---|
| | | 5 mg | 10 mg | 10-40 mg q12h |
| | N=141 | N=161 | N=150 | N=158 |
| All-causality AEs | | | | |
| Number of AEs | 96 | 155 | 140 | 230 |
| Subjects with AEs | 50 (35.5) | 72 (44.7) | 61 (40.7) | 100 (63.3) |
| Subjects with SAEs | 2 (1.4) | 4 (2.5) | 3 (2.0) | 4 (2.5) |
| Subjects with severe AEs | 4 (2.8) | 5 (3.1) | 2 (1.3) | 6 (3.8) |
| Subjects discontinued due to AEs[a] | 2 (1.4) | 2 (1.2) | 4 (2.7) | 16 (10.1) |
| Subjects with dose reduced or temporary discontinuation due to AEs[b] | 1 (0.7) | 3 (1.9) | 2 (1.3) | 7 (4.4) |
| Treatment-related AEs | | | | |
| Number of AEs | 25 | 47 | 46 | 127 |
| Subjects with AEs | 15 (10.6) | 25 (15.5) | 26 (17.3) | 65 (41.1) |
| Subjects with SAE | 0 | 1 (0.6) | 1 (0.7) | 0 |
| Subjects with severe AEs | 0 | 2 (1.2) | 1 (0.7) | 1 (0.6) |
| Subjects discontinued due to AEs[a] | 1 (0.7) | 2 (1.2) | 0 | 15 (9.5) |
| Subjects with dose reduced or temporary discontinuation due to AEs[b] | 0 | 2 (1.2) | 1 (0.7) | 5 (3.2) |

Table includes data up to 9999 days after last dose of study drug.
Except for the number of AEs, subjects are counted only once per treatment in each row.
SAEs were according to the Investigator's assessment.
MedDRA (version 13.1) coding applied.
AEs = adverse events; CR = controlled release; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in each treatment group; q12h = every 12 hours; SAEs = serious adverse events.
a. Discontinued study.
b. In response to an AE, blinded oral study medication dosing may have been temporarily reduced or interrupted and/or the second dosing of blinded intravenous study medication may have been delayed.

The incidence of the most frequently reported all-causality AEs (those reported by ≥2% of subjects in any treatment group) is presented in Table 40.

**Table 40. Incidence of Most Frequent All-Causality Adverse Events (≥2% Subjects in any Treatment Group) (ITT)**

| MedDRA Preferred Term | Number (%) of Subjects | | | |
|---|---|---|---|---|
| | Placebo | Tanezumab | | Oxycodone CR |
| | | 5 mg | 10 mg | 10-40 mg q12h |
| | N=141 | N=161 | N=150 | N=158 |
| | n (%) | n (%) | n (%) | n (%) |
| Any adverse event | 50 (35.5) | 72 (44.7) | 61 (40.7) | 100 (63.3) |
| Arthralgia | 4 (2.8) | 3 (1.9) | 8 (5.3) | 2 (1.3) |
| Headache | 7 (5.0) | 5 (3.1) | 5 (3.3) | 8 (5.1) |
| Edema peripheral | 3 (2.1) | 4 (2.5) | 4 (2.7) | 3 (1.9) |
| Nasopharyngitis | 6 (4.3) | 3 (1.9) | 4 (2.7) | 3 (1.9) |
| Musculoskeletal pain | 2 (1.4) | 3 (1.9) | 4 (2.7) | 3 (1.9) |
| Pain in extremity | 2 (1.4) | 3 (1.9) | 4 (2.7) | 3 (1.9) |
| Nausea | 0 | 6 (3.7) | 3 (2.0) | 25 (15.8) |
| Paresthesia | 1 (0.7) | 6 (3.7) | 3 (2.0) | 1 (0.6) |
| Hypoesthesia | 0 | 4 (2.5) | 3 (2.0) | 2 (1.3) |
| Dizziness | 2 (1.4) | 2 (1.2) | 3 (2.0) | 10 (6.3) |
| Diarrhea | 2 (1.4) | 2 (1.2) | 3 (2.0) | 1 (0.6) |
| Back pain | 2 (1.4) | 1 (0.6) | 3 (2.0) | 3 (1.9) |
| Joint swelling | 1 (0.7) | 1 (0.6) | 3 (2.0) | 0 |
| Urinary tract infection | 4 (2.8) | 4 (2.5) | 2 (1.3) | 4 (2.5) |
| Insomnia | 1 (0.7) | 0 | 2 (1.3) | 4 (2.5) |
| Fall | 3 (2.1) | 4 (2.5) | 1 (0.7) | 1 (0.6) |
| Bronchitis | 1 (0.7) | 4 (2.5) | 1 (0.7) | 2 (1.3) |
| Osteoarthritis | 0 | 3 (1.9) | 1 (0.7) | 4 (2.5) |
| Constipation | 2 (1.4) | 2 (1.2) | 1 (0.7) | 24 (15.2) |
| Fatigue | 1 (0.7) | 2 (1.2) | 1 (0.7) | 7 (4.4) |
| Hypertension | 2 (1.4) | 2 (1.2) | 1 (0.7) | 5 (3.2) |
| Pruritus | 1 (0.7) | 2 (1.2) | 0 | 10 (6.3) |
| Vomiting | 1 (0.7) | 1 (0.6) | 0 | 15 (9.5) |
| Somnolence | 0 | 0 | 0 | 7 (4.4) |

MedDRA (version 13.1) coding applied. Adverse events are sorted by decreasing frequency in the tanezumab 10 mg treatment group and then in the tanezumab 5 mg treatment group. Table includes data up to 9999 days after last dose of study drug. Subjects are only counted once per treatment for each row.
CR = controlled release; ITT = intent-to-treat, MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects in each treatment group; n = number of subjects with specified criteria; q12h = every 12 hours.

The incidence of the most frequently reported treatment-related AEs (those reported by ≥2% of subjects in any treatment group) is presented in Table 41.

## Table 41. Incidence of Most Frequent Treatment-Related Adverse Events (≥2% Subjects in any Treatment Group) (ITT)

| MedDRA Preferred Term | Number (%) of Subjects | | | |
|---|---|---|---|---|
| | Placebo | Tanezumab | | Oxycodone CR |
| | | 5 mg | 10 mg | 10-40 mg q12h |
| | N = 141 | N = 161 | N = 150 | N = 158 |
| | n (%) | n (%) | n (%) | n (%) |
| Any AE | 15 (10.6) | 25 (15.5) | 26 (17.3) | 65 (41.1) |
| Headache | 4 (2.8) | 3 (1.9) | 3 (2.0) | 7 (4.4) |
| Nausea | 0 | 4 (2.5) | 2 (1.3) | 24 (15.2) |
| Dizziness | 1 (0.7) | 2 (1.2) | 2 (1.3) | 9 (5.7) |
| Paresthesia | 1 (0.7) | 4 (2.5) | 1 (0.7) | 0 |
| Constipation | 2 (1.4) | 2 (1.2) | 1 (0.7) | 22 (13.9) |
| Pruritus | 1 (0.7) | 2 (1.2) | 0 | 8 (5.1) |
| Fatigue | 1 (0.7) | 1 (0.6) | 0 | 6 (3.8) |
| Vomiting | 0 | 0 | 0 | 13 (8.2) |
| Somnolence | 0 | 0 | 0 | 7 (4.4) |

MedDRA (version 13.1) coding applied. AEs are sorted by decreasing frequency in the tanezumab 10 mg treatment group and then in the tanezumab 5 mg treatment group. Table includes data up to 9999 days after last dose of study drug. Subjects were only counted once per treatment for each row.
AE = adverse event; CR = controlled release; ITT = intent-to-treat; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in each treatment group; n = number of subjects with specified criteria; q12h = every 12 hours.

Serious Adverse Events (SAEs): Treatment-emergent SAEs are summarized in Table 42.

## Table 42. Treatment-Emergent Serious Adverse Events

| Treatment Group | Serial Number | SAE MedDRA Preferred Term | Severity | Outcome |
|---|---|---|---|---|
| Placebo | 1 | Clostridial infection | Moderate | Resolved |
| | 2 | Unintended pregnancy | Severe | Still present |
| | | Drug exposure in utero | Mild | Still present |
| | | Drug ineffective[a] | Severe | Still present |
| Tanezumab 5 mg | 1 | Road traffic accident | Severe | Resolved |
| | | Clavicle fracture | Severe | Resolved |
| | | Hand fracture | Severe | Resolved |
| | | Lumbar vertebral fracture | Severe | Resolved |
| | | Fractured coccyx | Severe | Resolved |
| | 2 | Pneumonia primary atypical | Moderate | Resolved |
| | 3 | Guillain-Barre Syndrome[b] | Severe | Resolved |
| | | Cervical myelopathy | Severe | Resolved |
| | 4 | Chest pain | Moderate | Resolved |
| Tanezumab 10 mg | 1 | Osteonecrosis | Severe | Resolved |
| | 2 | Osteonecrosis[b] | Severe | Resolved |
| | 3 | Cholestasis | Mild | Resolved |
| Oxycodone CR 10-40 mg q12h | 1 | Colitis | Severe | Resolved |
| | | Suicide attempt | Severe | Resolved |
| | 2 | Head injury | Severe | Resolved |
| | | Limb injury (stabbing) | Severe | Resolved |
| | 3 | Intervertebral disc protrusion | Severe | Resolved |
| | 4 | Osteoarthritis[c] | Severe | Resolved |

MedDRA (v13.1) coding applied.
Note that an additional 3 SAEs occurred among prerandomized subjects.
CR = controlled release; MedDRA = Medical Dictionary for Regulatory Activities; q12h = every 12 hours; SAEs = serious adverse events; v = version.
a. Verbatim term from source table was "lack of efficacy (ortho evra)".
b. Investigator "causality" was related.
c. Verbatim terms was "worsening osteoarthritis of right knee requiring (total right knee replacement)."

Permanent Discontinuations due to AEs: Table 43 summarizes AEs leading to discontinuation from the study.

**Table 43. Adverse Events Leading to Discontinuation From the Study (All-Causalities)**

| MedDRA Preferred Term | Number (%) of Subjects | | | |
|---|---|---|---|---|
| | Placebo | Tanezumab | | Oxycodone CR |
| | N = 141 | 5 mg N = 161 | 10 mg N = 150 | 10-40 mg q12h N = 158 |
| Any AE resulting in discontinuation | 2 (1.4) | 2 (1.2) | 4 (2.7) | 16 (10.1) |
| Arthralgia | 0 | 0 | 1 (0.7) | 0 |
| Osteonecrosis | 0 | 0 | 1 (0.7)[a] | 0 |
| Disorientation | 0 | 0 | 1 (0.7) | 0 |
| Rash | 0 | 0 | 1 (0.7) | 0 |
| Guillain-Barre syndrome | 0 | 1 (0.6)[a,b] | 0 | 0 |
| Urticaria | 0 | 1 (0.6)[b] | 0 | 0 |
| Gastroesophageal reflux disease | 1 (0.7)[b] | 0 | 0 | 0 |
| Nausea | 0 | 0 | 0 | 3 (1.9)[b] |
| Vomiting | 0 | 0 | 0 | 5 (3.2)[b] |
| Constipation | 0 | 0 | 0 | 2 (1.3) |
| Hypersensitivity | 0 | 0 | 0 | 1 (0.6)[b] |
| Musculoskeletal pain | 1 (0.7) | 0 | 0 | 0 |
| Dizziness | 0 | 0 | 0 | 2 (1.3)[b] |
| Libido decreased | 0 | 0 | 0 | 1 (0.6)[b] |
| Suicide attempt | 0 | 0 | 0 | 1 (0.6)[a,c] |
| Pruritus generalized | 0 | 0 | 0 | 1 (0.6)[b] |

MedDRA (v 13.1) coding applied. AEs are sorted by decreasing frequency in the tanezumab 10 mg treatment group and then in the tanezumab 5 mg treatment group. Table includes data up to 9999 days after last dose of study drug. Subjects were only counted once per treatment for each row.
In addition to the AEs reported on this table, 1 additional subject had a treatment-emergent AE that resulted in discontinuation from the study.
AE = adverse event; CR = controlled release; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in each treatment group; q12h = every 12 hours; v = version.

a. Serious AE in at least 1 subject.
b. Treatment-related event in at least 1 subject.
c. This subject discontinued from the study due to suicide attempt; however, colitis resulted in discontinuation for this subject because colitis was part of this serious case.

Dose Reductions or Temporary Discontinuations due to AEs: Thirteen (13) subjects across all treatment groups had a dose reduction or temporary discontinuation due to an AE; of these 13 subjects, 7 were in the oxycodone CR treatment group. Overall, treatment-related AEs resulting in dose reduction or temporary discontinuation were reported for 8 subjects, including 5 subjects, 2 subjects, and 1 subject in the oxycodone CR, tanezumab 5 mg, and tanezumab 10 mg treatment groups, respectively.

Deaths: No deaths occurred among subjects who participated in this study.

Laboratory Evaluations: The incidence of abnormal laboratory tests was similar across treatment groups.

ECG: Mean changes from Baseline were small and no trends were observed over time. QT corrected for heart rate using Bazett's formula, and QT corrected for heart rate using Fridericia's formula data were similar across treatment groups. Clinically significant ECG results were captured as AEs; among these AEs, 4 AEs were considered treatment-related (cardiac murmur and bradycardia in the tanezumab 5 mg treatment group, ECG ST-segment

depression in the placebo treatment group, and tachycardia in the oxycodone CR treatment group.

Physical Examination: Summary of physical examination findings at Screening is summarized in Table 44.

Neurological Examination: Summary of neurological examination findings by Visit is provided in Table 45.

## Table 44. Physical Examination Findings at Screening

| Number of Subjects | Number (%) of Subjects | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo | | Tanezumab | | | | Oxycodone CR | |
| | | | 5 mg | | 10 mg | | | |
| | 141 | | 161 | | 150 | | 158 | |
| Site | Number Examined | Abnormal N% | Number Examined | Abnormal N% | Number Examined | Abnormal N% | Number Examined | Abnormal N% |
| Abdomen | 140 | 3 (2.1) | 161 | 8 (5.0) | 150 | 7 (4.7) | 158 | 9 (5.7) |
| Ears | 140 | 2 (1.4) | 161 | 0 | 150 | 1 (0.7) | 158 | 0 |
| Extremities | 138 | 42 (30.4) | 158 | 45 (28.5) | 147 | 50 (34.0) | 156 | 38 (24.4) |
| Eyes | 140 | 7 (5.0) | 161 | 9 (5.6) | 150 | 3 (2.0) | 158 | 5 (3.2) |
| General | 140 | 6 (4.3) | 161 | 5 (3.1) | 150 | 11 (7.3) | 158 | 7 (4.4) |
| Head | 140 | 1 (0.7) | 161 | 1 (0.6) | 150 | 0 | 158 | 0 |
| Heart | 140 | 3 (2.1) | 161 | 3 (1.9) | 150 | 3 (2.0) | 158 | 4 (2.5) |
| Lungs | 140 | 1 (0.7) | 161 | 4 (2.5) | 150 | 2 (1.3) | 157 | 1 (0.6) |
| Musculoskeletal | 140 | 47 (33.6) | 161 | 53 (32.9) | 150 | 59 (39.3) | 158 | 58 (36.7) |
| Neck | 140 | 0 | 161 | 2 (1.2) | 150 | 1 (0.7) | 158 | 1 (0.6) |
| Nose | 140 | 0 | 161 | 0 | 150 | 1 (0.7) | 157 | 0 |
| Other | 21 | 4 (19.0) | 19 | 4 (21.1) | 18 | 3 (16.7) | 22 | 7 (31.8) |
| Skin | 140 | 11 (7.9) | 161 | 12 (7.5) | 150 | 12 (8.0) | 157 | 15 (9.6) |
| Throat | 140 | 0 | 161 | 0 | 149 | 0 | 158 | 0 |
| Thyroid | 140 | 1 (0.7) | 161 | 1 (0.6) | 150 | 1 (0.7) | 158 | 4 (2.5) |

CR = controlled release; N = number of subjects.

## Table 45. Summary of Neurological Examinations by (Study) Visit

| | Treatment Group | New or Worsened Neurological Examination Abnormality | | | No New or Worsened Neurological Examination Abnormality n (%) | Total n (%) |
|---|---|---|---|---|---|---|
| | | Clinically Significant n (%) | Not Clinically Significant n (%) | Total n (%) | | |
| Week 2 | Placebo (N=141) | 0 | 4 (3.1%) | 4 (3.1%) | 127 (96.9%) | 131 (100.0%) |
| | Tanezumab 5 mg (N=161) | 0 | 2 (1.3%) | 2 (1.3%) | 150 (98.7%) | 152 (100.0%) |
| | Tanezumab 10 mg (N=150) | 1 (0.7%) | 3 (2.1%) | 4 (2.9%) | 136 (97.1%) | 140 (100.0%) |
| | Oxycodone CR (N=158) | 0 | 7 (5.1%) | 7 (5.1%) | 130 (94.9%) | 137 (100.0%) |
| Week 4 | Placebo (N=141) | 0 | 5 (4.0%) | 5 (4.0%) | 119 (96.0%) | 124 (100.0%) |
| | Tanezumab 5 mg (N=161) | 1 (0.7%) | 3 (2.0%) | 4 (2.7%) | 146 (97.3%) | 150 (100.0%) |
| | Tanezumab 10 mg (N=150) | 0 | 1 (0.7%) | 1 (0.7%) | 137 (99.3%) | 138 (100.0%) |
| | Oxycodone CR (N=158) | 0 | 6 (4.7%) | 6 (4.7%) | 121 (95.3%) | 127 (100.0%) |
| Week 8 | Placebo (N=141) | 0 | 4 (3.4%) | 4 (3.4%) | 113 (96.6%) | 117 (100.0%) |
| | Tanezumab 5 mg (N=161) | 1 (0.7%) | 7 (4.9%) | 8 (5.6%) | 136 (94.4%) | 144 (100.0%) |
| | Tanezumab 10 mg (N=150) | 0 | 5 (3.7%) | 5 (3.7%) | 129 (96.3%) | 134 (100.0%) |
| | Oxycodone CR (N=158) | 0 | 8 (6.8%) | 8 (6.8%) | 109 (93.2%) | 117 (100.0%) |
| Week 12 | Placebo (N=141) | 0 | 5 (4.6%) | 5 (4.6%) | 103 (95.4%) | 108 (100.0%) |
| | Tanezumab 5 mg (N=161) | 1 (0.8) | 4 (3.0%) | 5 (3.8%) | 127 (96.2%) | 132 (100.0%) |
| | Tanezumab 10 mg (N=150) | 0 | 4 (3.2%) | 4 (3.2%) | 122 (96.8%) | 126 (100.0%) |
| | Oxycodone CR (N=158) | 0 | 2 (1.8%) | 2 (1.8%) | 110 (98.2%) | 112 (100.0%) |
| Week 16 | Placebo (N=141) | 0 | 2 (3.4%) | 2 (3.4%) | 57 (96.6%) | 59 (100.0%) |
| | Tanezumab 5 mg (N=161) | 1 (1.5%) | 4 (6.1%) | 5 (7.6%) | 61 (92.4%) | 66 (100.0%) |
| | Tanezumab 10 mg (N=150) | 0 | 1 (1.7%) | 1 (1.7%) | 59 (98.3%) | 60 (100.0%) |
| | Oxycodone CR (N=158) | 0 | 1 (1.9%) | 1 (1.9%) | 51 (98.1%) | 52 (100.0%) |
| Early termination/Week 18 | Placebo (N=141) | 0 | 5 (3.8%) | 5 (3.8%) | 125 (96.2%) | 130 (100.0%) |
| | Tanezumab 5 mg (N=161) | 2 (1.4%) | 5 (3.4%) | 7 (4.7%) | 141 (95.3%) | 148 (100.0%) |
| | Tanezumab 10 mg (N=150) | 2 (1.4%) | 5 (3.6%) | 7 (5.0%) | 132 (95.0%) | 139 (100.0%) |
| | Oxycodone CR (N=158) | 0 | 11 (7.7%) | 11 (7.7%) | 132 (92.3%) | 143 (100.0%) |
| Unplanned | Placebo (N=141) | 0 | 0 | 0 | 7 (100.0%) | 7 (100.0%) |
| | Tanezumab 5 mg (N=161) | 0 | 0 | 0 | 8 (100.0%) | 8 (100.0%) |
| | Tanezumab 10 mg (N=150) | 0 | 0 | 0 | 6 (100.0%) | 6 (100.0%) |
| | Oxycodone CR (N=158) | 0 | 2 (33.3%) | 2 (33.3%) | 4 (66.7%) | 6 (100.0%) |
| Last assessment | Placebo (N=141) | 0 | 6 (4.3%) | 6 (4.3%) | 133 (95.7%) | 139 (100.0%) |
| | Tanezumab 5 mg (N=161) | 2 (1.3%) | 5 (3.2%) | 7 (4.4%) | 151 (95.6%) | 158 (100.0%) |
| | Tanezumab 10 mg (N=150) | 2 (1.3%) | 6 (4.0%) | 8 (5.4%) | 141 (94.6%) | 149 (100.0%) |
| | Oxycodone CR (N=158) | 0 | 11 (7.1%) | 11 (7.1%) | 145 (92.9%) | 156 (100.0%) |

## Table 45. Summary of Neurological Examinations by (Study) Visit

Conclusions from the neurological examination were based on the Investigator's assessment.
The number of subjects shown next to each treatment group is the number of subjects in the ITT analysis set.
The number of subjects shown in the total column includes subjects with a neurological consultation at each respective timepoint, and this is less than the number shown in the ITT set.
The number of subjects in the total column (number with neurological examination data) is used as the denominator for calculation of percentages in this table.
CR = controlled release; ITT = intent-to-treat; N = number of subjects in each treatment group; n = number of subjects with specified criteria.

Vital Signs: Mean changes from Baseline were small and no trends were observed over time. Clinically significant vital sign results were captured as AEs; among these AEs, only the 2 AEs of hypotension were considered treatment-related.

**CONCLUSIONS:**

Sponsor prematurely discontinued this study due to an FDA-imposed clinical hold and the conclusions below are based on the available data, which is less complete than if the study had been allowed to continue to its planned conclusion.

- Superior efficacy was demonstrated with tanezumab 5 mg and 10 mg treatments compared to placebo and oxycodone CR treatments at Week 8 in the WOMAC Pain subscale.

- Tanezumab 5 mg and 10 mg provided superior pain relief, improvement in physical function, and PGA of disease activity versus placebo and versus oxycodone CR treatment.

- The efficacy responses to tanezumab 5 mg were marginally, but consistently, greater than tanezumab 10 mg in this study for the mITT population. The efficacy responses to tanezumab 5 mg and 10 mg were similar in this study for the ITT population.

- The analgesic efficacy of tanezumab 5 mg and 10 mg was clinically meaningful as determined by significant effects across efficacy domains, multiple assessments of categorical response rates, and the efficacy response relative to oxycodone CR.

- Only marginal separation of oxycodone CR treatment from placebo treatment at Week 8 was observed.

- Across the tanezumab treatment groups, the rate of SAEs and the rate of discontinuation due to AEs were low. No deaths were reported in this study.

- The most frequently reported AEs in the tanezumab treatment groups (≥2% in any treatment group) and higher in frequency than oxycodone CR and placebo were arthralgia and paresthesia.

- Among the most frequently reported AEs, gastrointestinal AEs (ie, nausea, constipation, and vomiting) and other AEs commonly reported by subjects taking opioids (ie, dizziness, fatigue and pruritus) were reported more frequently for oxycodone CR treated subjects than for tanezumab treated subjects.

- A higher proportion of tanezumab-treated subjects reported AEs of abnormal peripheral sensation than oxycodone CR- or placebo-treated subjects. In addition, a higher proportion of subjects treated with tanezumab underwent neurological consultations with findings suggestive of new or worsened peripheral neuropathy than the other treatment groups.

- Two AEs of osteonecrosis were reported in the tanezumab 10 mg treatment group. A blinded external Adjudication Committee did not confirm primary osteonecrosis in either of the subjects. The committee identified rapidly progressive osteoarthritis in 1 of the subjects and normal progression of osteoarthritis in the other subject.

- Overall, tanezumab was generally well-tolerated in this study.