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GENERIC DRUG NAME / COMPOUND NUMBER: Tanezumab / PF-04383119

PROTOCOL NO.: A4091025

PROTOCOL TITLE: A Phase 3, Multi-Center, Randomized, Double-Blind, Controlled Study of the Long-Term Analgesic Efficacy and Safety of Tanezumab Alone or in Combination With Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Versus NSAIDs Alone in Patients With Osteoarthritis of the Knee or Hip

Study Centers: Two hundred and fifty eight (258) centers took part in the study and randomized subjects: 12 in Canada, 4 in Colombia, 8 in India, 5 in the Republic of Korea, 4 in Mexico, 1 in the Netherlands, 6 in the Philippines, 6 in the Russian Federation, 14 in South Africa, 7 in Spain, 8 in the Ukraine, and 183 in the United States (US).

Study Initiation and Final Completion Dates: 12 February 2009 to 12 January 2011

The study was terminated prematurely following a US Food and Drug Adminstration (FDA) clinical hold on 23 June 2010 for tanezumab osteoarthritis (OA) clinical studies which halted dosing and enrollment of subjects for potential safety issues.

Phase of Development: Phase 3

Study Objectives:

Primary Objective:

- Demonstrate superior efficacy of intravenous (IV) tanezumab 10 mg and 5 mg alone and in combination with a NSAID orally (PO) (naproxen 500 mg twice daily [BID] or celecoxib 100 mg BID) versus placebo in combination with an NSAID PO (naproxen 500 mg BID or celecoxib 100 mg BID) at Week 16.

Key Secondary Objectives:

- Demonstrate the long-term safety of IV tanezumab 10 mg and 5 mg alone and in combination with an NSAID PO (naproxen 500 mg BID or celecoxib 100 mg BID) over 56 weeks of treatment;

- Demonstrate the efficacy of IV tanezumab 10 mg and 5 mg alone and in combination with an NSAID PO (naproxen 500 mg BID or celecoxib 100 mg BID) through Week 56.

METHODS

Study Design:

This was a randomized, double-blind, placebo- and active-controlled, multicenter, parallel-group Phase 3 study in subjects with OA of the hip or knee (per American College of Rheumatology [ACR] criteria).

Subjects were randomized to 1 of 5 treatment groups in a 1:1:1:1:1 ratio to receive tanezumab 5 mg, tanezumab 10 mg, tanezumab 5 mg + NSAID, tanezumab 10 mg + NSAID or NSAID alone.

Randomization was stratified by NSAID (naproxen or celecoxib) at study entry and index joint (hip or knee). This resulted in a 4-group stratified randomization scheme as follows:

1. Subjects with OA of the hip previously taking celecoxib;
2. Subjects with OA of the knee previously taking celecoxib;
3. Subjects with OA of the hip previously taking naproxen;
4. Subjects with OA of the knee previously taking naproxen.

Subjects who entered the study taking naproxen (irrespective of whether they received oral naproxen or oral placebo for naproxen during the study) have been referred to as the naproxen cohort, while subjects who entered the study taking celecoxib (irrespective of whether they received oral celecoxib or oral placebo for celecoxib during the study) have been referred to as the celecoxib cohort.

Table 1 presents the schedule of activities for Screening through Week 24 and Table 2 presents the schedule of activities for Weeks 28 through 64 and follow-up.

Table 1. Study Schedule and Evaluations – Screening Through Week 24

Study Activities	Screen[a]	Washout[b]	Treatment							
			BL[c]	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20[d] (Telephone)	Week 24
	Day -30 to Day -1	Day -30 to Day -1	Day 1	Day 15 ±3 days	Day 29 ±3 days	Day 57 ±5 days	Day 85 ±5 days	Day 113 ±5 days	Day 141 ±5 days	Day 169 ±5 days
Informed consent	X									
Inclusion/exclusion criteria	X		X							
General medical history	X									
Primary diagnosis/demographics	X									
Radiograph assessment of index joint (x-ray of knee/hip)	X									
Physical examination	X									X
Assessment of depression by medical history or PHQ-9 (patient work sheet)	X									
Neurological exam[e] NIS	X		X	X	X	X	X	X		X
Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, body temperature, respiratory rate)	X		X[f]	X	X	X	X	X		X
Demographics including weight/height/BMI/smoking status/alcohol history	X									
Laboratory										
Hematology	X		X		X	X		X		X
Blood chemistry	X		X		X	X		X		X
Serum and plasma retention samples			X							X
Urinalysis	X		X		X	X		X		X
Pregnancy test[g]	X		X			X		X		X
Serum FSH test[h]	X									
Hemoglobin A1c	X		X			X		X		X
Hepatitis screen (Hep B & Hep C)	X									
HIV test	X									
Urine toxicology screen	X									

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	Day -30 to Day -1	Day -30 to Day -1	Day 1	Day 15 ±3 days	Day 29 ±3 days	Day 57 ±5 days	Day 85 ±5 days	Day 113 ±5 days	Day 141 ±5 days	Day 169 ±5 days
De-identified genetic sampling			X							
Serum anti-drug antibody (anti-tanezumab)[i]			X					X		X
Plasma pharmacokinetic sample[i]			X					X		X
Electrocardiogram (ECG-12 lead)[j]	X		X[f]		X	X		X		X
Discontinue current pain medication[b]		X								
Randomization			X							
Study Treatments										
Dispense oral study medication for screening period	X									
Inject blinded IV study medication			X			X		X		X
Dispense blinded oral study medication			X	X	X	X	X	X		X
Dispense rescue medication[k]	X		X	X	X	X	X	X		X
On-Site Subject Assessments at Study Visits[l]										
Patient Health Questionnaire (PHQ-9) – optional[m]	X									
WOMAC pain subscale[a]	X[a]		X	X	X	X	X	X		X
WOMAC physical function and stiffness subscales			X	X	X	X	X	X		X
Patient global assessment of osteoarthritis			X	X	X	X	X	X		X
SF-36 v2 health survey			X				X			X
WPAI:SHP			X							X
AE assessment [n, o]			X[f]	X	X	X	X	X	X	X
Concomitant medication review[n, o]	X		X	X	X	X	X	X	X	X
Rescue medication review[k]	X		X	X	X	X	X	X		X

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	Day -30 to Day -1	Day -30 to Day -1	Day 1	Day 15 ±3 days	Day 29 ±3 days	Day 57 ±5 days	Day 85 ±5 days	Day 113 ±5 days	Day 141 ±5 days	Day 169 ±5 days
Study (oral)/rescue medication return/compliance			X	X	X	X	X	X		X

ADA = antidrug antibody, AE = adverse event, BID = twice daily, BL = baseline, BMI = body mass index, ECG = electrocardiogram, FSH = follicle stimulating hormone, Hep = hepatitis, HIV = human immunodeficiency virus, IEC = Independent Ethics Committee, IRB = Institutional Review Board, IV = intravenous(ly), NIS = Neuropathy Impairment Score, NSAID = nonsteroidal anti-inflammatory drug, PHQ-9 = Patient Health Questionnaire-9, PO = orally, QD = once daily, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index, SF-36v2 = Medical Outcomes Study Short Form 36 Version 2, , WPAI:SHP = Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.

a. The Screening Period began up to 30 days prior to Randomization and lasted 14-30 days, allowing for a minimum 2 day washout of prohibited non-study medications (ie, medications other than naproxen 500 mg/day to 1000 mg/day or celecoxib 200 mg/day [either 100 mg BID or 200 mg QD]) prior to the Baseline (Randomization/Day 1) visit. Subjects taking naproxen prior to Screening took naproxen 500 mg BID PO during the Screening Period. Subjects taking celecoxib prior to Screening took celecoxib 100 mg BID PO during the Screening period. All subjects took their oral NSAID medication during the Screening Period for at least 2 consecutive weeks directly prior to the Baseline (Randomization/Day 1) visit. Subjects who did not require washout had their Baseline (Randomization/Day 1) visit the day after completing at least 2 weeks of their oral NSAID medication required during the final 14 days of the Screening Period directly prior to the Baseline (Randomization/Day 1) visit. Subjects were required to take the oral NSAID during Screening Period for an average of at least 5 of 7 days per week (ie, minimum 70% compliance) to qualify for Randomization and entry into the Treatment portion of the study. As part of the Inclusion/Exclusion criteria, the WOMAC Pain subscale was administered in the clinic at Screening and Baseline.

b. All current analgesic medications other than study-permitted celecoxib or naproxen were discontinued and the washout was a minimum of 48 hours prior to Baseline (Randomization/Day 1) visit or ≥5 half-lives of the particular analgesic, whichever was greater.

c. All study activities at Baseline (Randomization/Day 1) were performed prior to dosing with IV study medication, unless otherwise noted.

d. Telephone visits at Week 20. Sites contacted subjects by telephone at Week 20 to check on each subject's general health and well-being as well as to determine if the subject had experienced any AEs during the previous 4-weeks since the last clinic visit.

e. Subjects were to be referred to a neurologist for a full neurological exam if they experienced an AE suggestive of new or worsening of peripheral neuropathy, or if an AE(s) of abnormal peripheral sensation (ie, allodynia, axonal neuropathy, burning sensation, decreased vibratory sense, demyelinating polyneuropathy, dysesthesia, formication, hyperesthesia, hyperpathia, hypoesthesia, hypoesthesia facial, hypoesthesia oral, intercostal neuralgia, neuralgia, neuritis, neuropathy peripheral, paresthesia, paresthesia oral, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy, polyneuropathy chronic, sensory disturbance, sensory loss, and thermohypoesthesia) was reported. Subjects with pain in the extremities (eg, fingers, hands, feet, soles of feet) that was suggestive of neuropathic pain such as pain described as burning, shooting, electric or tingling were also to be referred to a neurologist. A new or worsened clinically significant abnormality on the neurological exam was to be reported as an AE and result in a neurologic evaluation/consult by a neurologist.

f. AEs were reviewed after signing informed consent (ie, pretreatment AEs), immediately prior to dosing, and 1 hour postdose. At Baseline, ECGs and

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vital signs (blood pressure and heart rate) were obtained pre-IV-dose and 1 hour post-IV-dose.

g. For females of childbearing potential: serum pregnancy test at Screening; urine pregnancy tests at Baseline prior to initial dosing, at dosing visits and at Week 64 visit (where applicable); serum pregnancy test at End of Treatment or Early Termination. Pregnancy tests may have also been repeated as per request of IRB/IECs or if required by local regulations.

h. Female subjects of non-child bearing 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.

i. Pharmacokinetic and ADA blood sampling at IV dosing visits (ie, Baseline, Weeks 16 and 24) conducted prior to IV dose administration.

j. If possible, ECGs were collected at the same time each visit.

k. Rescue medication use was required to be discontinued at least 48 hours prior to any study visit.

l. At each visit, on-site subject (self performed) assessments were performed prior to assessments performed by study-site personnel.

m. Use of the PHQ-9 at Screening was optional and may have been used by the Investigator to help determine if active severe major depression was present at Screening: subjects with a hospital admission for depression or suicide attempt within 5 years of Screening, or active severe major depression (determined from medical history; severity of depression may have been assessed using the PHQ-9). A score ≥15 on questions 1-9 of the PHQ-9 at Screening corresponded to severe depression and these subjects were to be excluded from further participation in the study.

n. Subjects who discontinued study medication prematurely (ie, prior to the Week 56 visit) and were not active at the time the study was terminated continued to be followed per study defined visit time points until the completion of the study unless the subject refused to allow this follow-up. These follow-up visits were conducted by telephone to check on the subject's general health and well-being, to determine if the subject had experienced any AEs since their previous (in-person at the site or telephone) visit and had used any concomitant medication since the previous (in-person at the site or telephone) visit. Subjects discontinuing study medication prematurely and reporting (during a telephone follow-up visit) AEs suggestive of peripheral neuropathy may have been requested to return to the clinic for examination and/or may have been referred to a neurologist for further neurological examination and/or consultation. Subjects discontinuing study medication prematurely and reporting (during a telephone follow-up visit) joint replacement may have been requested to return to the clinic for examination and/or for collection of diagnostic information. Subjects were also reminded about study contraceptive requirements (if applicable).

o. All subjects who were active at the time study was terminated were followed for study-specified safety evaluations in the clinic for 16 weeks after their last dose of IV study medication, provided the subjects agreed to in-clinic follow-up. If subjects did not agree to continue with study-specified safety evaluations at clinic visits, efforts were made to follow subjects at the study-defined visit time points by telephone for 16 weeks after the last dose of IV study medication. Subjects were also reminded about study contraceptive requirements (if applicable).

Table 2. Study Schedule and Evaluations – Week 28 Through EOT (Week 56) and Follow-Up (Week 64)

Study Activities	Treatment							EOT/ET	Follow-Up[a]
	Week 28[b] (Telephone)	Week 32	Week 36[b] (Telephone)	Week 40	Week 44[b] (Telephone)	Week 48	Week 52[b] (Telephone)	Week 56	Week 64[c]
	Day 197 ±7 days	Day 225 ±7 days	Day 253 ±7 days	Day 281 ±7 days	Day 309 ±7 days	Day 337 ±7 days	Day 365 ±7 days	Day 393 ±7 days	Day 449 ±7 days
Radiograph assessment of index knee (if applicable)[d]								X	
Radiographic assessment of hips (bilateral x-rays)[d]								X[d]	
Physical examination[e]								X	
Neurological exam[f, e] and NIS		X		X		X		X	X
Vital Signs (systolic blood pressure, diastolic blood pressure, pulse rate, body temperature, respiratory rate)[e]		X				X		X	X
Laboratory									
Hematology[e]		X		X		X		X	X
Blood chemistry[e]		X		X		X		X	X
Serum and plasma retention samples								X	
Urinalysis[e]		X		X		X		X	X
Pregnancy test[g, e]		X		X		X		X	X
Hemoglobin A1c[e]		X		X		X		X	X
Serum anti-drug antibody (anti-tanezumab)[h]				X				X	
Plasma pharmacokinetic sample[h]				X				X	
Electrocardiogram (ECG-12 lead)[i, e]								X	X
Study Treatments									
Inject blinded IV study medication[j, k]		X		X		X			
Dispense blinded oral study medication		X		X		X			
On-Site Subject Assessments at Study Visits[l]									

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Study Activities	Treatment							EOT/ET	Follow-Up[a]
	Week 28[b] (Telephone)	Week 32	Week 36[b] (Telephone)	Week 40	Week 44[b] (Telephone)	Week 48	Week 52[b] (Telephone)	Week 56	Week 64[c]
	Day 197 ±7 days	Day 225 ±7 days	Day 253 ±7 days	Day 281 ±7 days	Day 309 ±7 days	Day 337 ±7 days	Day 365 ±7 days	Day 393 ±7 days	Day 449 ±7 days
WOMAC pain subscale		X		X		X		X	
WOMAC physical function and stiffness subscales		X		X		X		X	
Patient global assessment of osteoarthritis		X		X		X		X	
SF-36 v2 health survey				X				X	
WPAI:SHP								X	
Study Personnel Assessments at Study Visits[l]									
AE Assessment[j, m, e]	X	X	X	X	X	X	X	X	X
Concomitant medication review[m, e]	X	X	X	X	X	X	X	X	X
Rescue medication review[n]		X		X		X			
Study (oral)/rescue medication return/compliance		X		X		X		X	

ADA = antidrug antibody, AE = adverse event, ECG = electrocardiogram, EOT = end of treatment, ET = early termination, IEC = Independent Ethics Committee, IRB = Institutional Review Board, IV = intravenous(ly), NIS = Neuropathy Impairment Score, NSAID = nonsteroidal anti-inflammatory drug, PHQ-9 = Patient Health Questionnaire-9, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index, SF-36v2 = Medical Outcomes Study Short Form 36 Version 2, WPAI:SHP = Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.

a. Week 64 follow-up safety assessments only performed for subjects who were administered IV study medication at their Week 48 visit, were active in the study on 23 June 2010, and have not had their Week 56 (End-of-Treatment) visit before the termination of study.
b. Telephone visits at Weeks 28, 36, 44, and 52. Sites were to contact subjects by telephone at Weeks 28, 36, 44, and 52 to check on each subject's general health and well-being as well as to determine if the subject had experienced any AEs during the previous 4-weeks since their last clinic visit.
c. Week 64 follow-up safety assessments were only performed for subjects who were administered IV study medication at their Week 48 visit, were active in the study on 23 Jun 2010, and had not had their Week 56 (EOT) visit before the study was terminated.
d. Bilateral x-rays of the hips were obtained at the End-of-Treatment/Early Termination visit.
e. All subjects who were active at the time study was terminated were followed for study-specified safety evaluations in the clinic for 16 weeks after their last dose of IV study medication, provided the subjects agreed to in-clinic follow-up. If subjects did not agree to continue with study-specified safety evaluations at clinic visits, efforts were made to follow subjects at the study-defined visit time points by telephone for 16 weeks after the last dose of IV study medication. Subjects were also reminded about study contraceptive requirements (if applicable).
f. Subjects were to be referred to a neurologist for a full neurological exam if they experienced an AE suggestive of new or worsening of peripheral neuropathy, or if an AE(s) of abnormal peripheral sensation (ie, allodynia, axonal neuropathy, burning sensation, decreased vibratory sense,

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Study Activities	Treatment							EOT/ET	Follow-Up[a]
	Week 28[b] (Telephone)	Week 32	Week 36[b] (Telephone)	Week 40	Week 44[b] (Telephone)	Week 48	Week 52[b] (Telephone)	Week 56	Week 64[c]
	Day 197 ±7 days	Day 225 ±7 days	Day 253 ±7 days	Day 281 ±7 days	Day 309 ±7 days	Day 337 ±7 days	Day 365 ±7 days	Day 393 ±7 days	Day 449 ±7 days

demyelinating polyneuropathy, dysesthesia, formication, hyperesthesia, hyperpathia, hypoesthesia, hypoesthesia facial, hypoesthesia oral, intercostal neuralgia, neuralgia, neuritis, neuropathy peripheral, paresthesia, paresthesia oral, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy, polyneuropathy chronic, sensory disturbance, sensory loss, and thermohypoesthesia) was reported. Subjects with pain in the extremities (eg, fingers, hands, feet, soles of feet) that was suggestive of neuropathic pain such as pain described as burning, shooting, electric or tingling were also to be referred to a neurologist. A new or worsened clinically significant abnormality on the neurological exam was to be reported as an AE and result in a neurologic evaluation/consult by a neurologist.

g. For females of childbearing potential: serum pregnancy test at Screening; urine pregnancy tests at Baseline prior to initial dosing, at dosing visits and at Week 64 visit (where applicable); serum pregnancy test at EOT or ET. Pregnancy tests may have also been repeated as per request of IRB/IECs or if required by local regulations.

h. Pharmacokinetic and ADA blood sampling on dosing visits (ie, Weeks 40 and 56) were to be collected prior to IV dose administration.

i. If possible, ECGs were collected at the same time each visit.

j. AEs were reviewed immediately prior to dosing and 1 hour postdose.

k. All subjects who were active at the time the study was terminated were followed for study-specified safety evaluations in the clinic for 16 weeks after their last dose of IV study medication, provided the subjects agreed to in-clinic follow-up. If subjects did not agree to continue with study-specified safety evaluations at clinic visits, efforts were made to follow subjects at the study-defined visit time points by telephone for 16 weeks after the last dose of IV study medication. Subjects were also reminded about study contraceptive requirements (if applicable).

l. At each visit, on-site subject (self performed) assessments were to be performed prior to assessments performed by study-site personnel.

m. Subjects who discontinued study medication prematurely (ie, prior to the Week 56 visit) and were not active at the time the study was terminated continued to be followed per study defined visit time points until the completion of the study unless the subject refused to allow this follow-up. These follow-up visits were conducted by telephone to check on the subject's general health and well-being, to determine if the subject had experienced any AEs since their previous (in-person at the site or telephone) visit and had used any concomitant medication since the previous (in-person at the site or telephone) visit. Subjects discontinuing study medication prematurely and reporting (during a telephone follow-up visit) AEs suggestive of peripheral neuropathy may have been requested to return to the clinic for examination and/or may have been referred to a neurologist for further neurological examination and/or consultation. Subjects discontinuing study medication prematurely and reporting (during a telephone follow-up visit) joint replacement may have been requested to return to the clinic for examination and/or for collection of diagnostic information. Subjects were also reminded about study contraceptive requirements (if applicable).

n. Rescue medication use was discontinued at least 48 hours prior to any study visit.

Number of Subjects (Planned and Analyzed):

A total of 2500 subjects (500 subjects in each of the 5 treatment groups) were planned to be randomized to ensure that a minimum of 210 subjects were available within each separate NSAID cohort and to allow for greater sample size for safety data evaluation over the combined cohorts. A total of 4531 subjects were screened, 2720 subjects randomized, and 2700 subjects (1424 subjects in the naproxen cohort and 1276 subjects in the celecoxib cohort) were treated. A total of 544 subjects were randomized to the tanezumab 5 mg treatment group and 544 to the tanezumab 10 mg treatment group. A total of 543 subjects were randomized to the tanezumab 5 mg + NSAID treatment group and 544 to the tanezumab 10 mg + NSAID treatment group, and 545 subjects to the NSAID alone treatment group.

Diagnosis and Main Criteria for Inclusion: Subjects with OA of the knee or hip according to ACR criteria with Kellgren-Lawrence x-ray grade ≥2; who experienced some benefit from their current stable dose regimen of oral NSAID therapy of either naproxen 500-1000 mg/day or celecoxib 200 mg/day (either 100 mg BID or 200 mg QD) and tolerated their NSAID regimen; with pain level and function levels as required by the study at Screening and Baseline; who were willing to discontinue all non-study pain medications for OA except rescue medication (acetaminophen) and not use prohibited pain medications throughout the duration of the study except as permitted by the study; and who were willing and able to comply with lifestyle guidelines, scheduled visits, treatment plan, laboratory tests and other study procedures were included in the study.

Main Exclusion Criteria: Pregnant women; subjects with body mass index (BMI) >39; subjects with fibromyalgia, regional pain caused by lumbar or cervical compression with radiculopathy or other moderate to severe pain that may have confounded assessments or self-evaluation of the pain associated with OA; with signs and symptoms of clinically significant cardiac disease with 6 months prior to Screening; with diagnosis of transient ischemic attack within 6 months prior to Screening or diagnosis of stroke with residual deficits that would have precluded completion of required study activities; with a history, diagnosis, signs or symptoms of clinically significant neurological and/or psychiatric disease/disorder; with uncontrolled hypertension, hemoglobin A1c ≥10%, alanine aminotransferase or aspartate aminotransferase ≥3× upper limit of normal, creatinine >1.7 mg/dL (men) or >1.5 mg/dL (women) at Screening, with known hypersensitivity to NSAIDs or cyclooxygenase inhibitors; and those on warfarin or other coumadin anticoagulant therapy and/or lithium therapy within 30 days prior to Screening were excluded from the study.

Study Treatment: Tanezumab was provided as 5 mg/mL and 10 mg/mL solution and was administered in the clinic by an IV infusion over 5 minutes without infusion pump (slow IV push) with a 5 mL flush of sodium chloride for injection. Naproxen was provided as 500 mg tablets and celecoxib was provided as 100 mg capsules and were self-administered PO by the subject. Matching placebos were provided for tanezumab solution, naproxen tablets and celecoxib capsules.

Subjects were randomized at the Baseline visit to 1 of the following 5 treatments:

- Tanezumab 5 mg: Tanezumab 5 mg IV once every 8 weeks (up to a maximum of 7 administrations) plus naproxen 500 mg BID PO or celecoxib 100 mg BID PO beginning at Screening that was tapered down to naproxen 0 mg BID or celecoxib 0 mg BID, respectively, from the Baseline (Randomization/Day 1) visit over 2 weeks (ie, through the Week 2 visit). During the first week (Study Days 1 to 7) after the Baseline visit, each subject in this treatment group remained on their respective NSAID regimen of naproxen 500 mg BID PO or celecoxib 100 mg BID PO. During the second week (Study Days 8 to 14) after the Baseline visit, subjects in this treatment group were tapered down on their respective NSAID regimen to naproxen 500 mg QD in the morning (QAM) and matching placebo QD in the evening (QPM) or celecoxib 100 mg QAM and matching placebo QPM to maintain blinded BID oral study medication. Beginning on Study Day 15, subjects in this treatment group received placebo matching naproxen or celecoxib BID to maintain blinded BID oral study medication administration for the remaining 54 weeks of the study (to Week 56). Subjects in this treatment group received tanezumab 5 mg IV once every 8 weeks beginning at the Baseline (Randomization/Day 1) visit through the last IV dose at the Week 48 visit;

- Tanezumab 10 mg: Tanezumab 10 mg IV once every 8 weeks (up to a maximum of 7 administrations) plus naproxen 500 mg BID PO or celecoxib 100 mg BID PO beginning at Screening that was tapered down to naproxen 0 mg BID or celecoxib 0 mg BID, respectively, from the Baseline (Randomization/Day 1) visit over 2 weeks (ie, through the Week 2 visit). During the first week (Study Days 1 to 7) after the Baseline visit, each subject in this treatment group remained on the respective NSAID regimen of naproxen 500 mg BID PO or celecoxib 100 mg BID PO. During the second week (Study Days 8 to 14) after the Baseline visit, subjects in this treatment group were tapered down on the respective NSAID regimen to naproxen 500 mg QAM and matching placebo QPM or celecoxib 100 mg QAM and matching placebo QPM to maintain blinded BID oral study medication. Beginning on Study Day 15, subjects in this treatment group received placebo matching naproxen or celecoxib BID to maintain blinded oral study medication for the remaining 54 weeks of the study (to Week 56). Subjects in this treatment group received tanezumab 10 mg IV once every 8 weeks beginning at the Baseline (Randomization/Day 1) visit through the last IV dose at the Week 48 visit;

- Tanezumab 5 mg + NSAID: Tanezumab 5 mg IV once every 8 weeks (up to a maximum of 7 administrations) plus naproxen 500 mg BID PO or celecoxib 100 mg BID PO (note: NSAID BID PO dosing continued through the Week 56 visit);

- Tanezumab 10 mg + NSAID: Tanezumab 10 mg IV once every 8 weeks (up to a maximum of 7 administrations) plus naproxen 500 mg BID PO or celecoxib 100 mg BID PO (note: NSAID BID PO dosing continued through the Week 56 visit);

- NSAID alone: IV doses of placebo (to match tanezumab) once every 8 weeks (up to a maximum of 7 administrations) plus naproxen 500 mg BID PO or celecoxib 100 mg BID PO (note: NSAID BID PO dosing continued through the Week 56 visit).

Efficacy, Pharmacokinetic and Safety Endpoints:

Co-Primary Efficacy Endpoints:

The 3 co-primary efficacy endpoints were:

- Change from Baseline to Week 16 in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain subscale;
- Change from Baseline to Week 16 in the WOMAC Physical Function subscale; and
- Change from Baseline to Week 16 in the Patient Global Assessment (PGA) of OA.

Secondary Efficacy Endpoints:

- WOMAC Pain subscale change from Baseline to Weeks 2, 4, 8, 12, 24, 32, 40, 48, and 56 (End-of-Treatment [EOT]/Early Termination [ET]);
- WOMAC Physical Function subscale change from Baseline to Weeks 2, 4, 8, 12, 24, 32, 40, 48, and 56 (EOT/ET);
- PGA of OA change from Baseline to Weeks 2, 4, 8, 12, 24, 32, 40, 48, and 56 (EOT/ET);
- Outcome Measures in Rheumatology (OMERACT) OA Research Society International (OARSI) responder index at Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, and 56 (EOT/ET);
- Treatment Response: Reductions in the WOMAC Pain subscale of ≥30%, ≥50%, ≥70%, and ≥90% at Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, and 56 (EOT/ET);
- Cumulative distribution of percent change from Baseline in the WOMAC Pain subscale score to Week 16 (endpoint for summary only);
- Treatment Response: Improvement of ≥2 points in the PGA of OA at Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, and 56 (EOT/ET);
- WOMAC Stiffness subscale change from Baseline to Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, and 56 (EOT/ET);
- WOMAC Average score change from Baseline to Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48 and 56 (EOT/ET);
- WOMAC Pain subscale item: Pain When Walking on a Flat Surface, change from Baseline to Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, and 56 (EOT/ET);
- WOMAC Pain subscale item: Pain When Going Up or Down Stairs, change from Baseline to Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, and 56 (EOT/ET);

- Medical Outcomes Study Short Form 36 Health Survey version 2 (SF-36v2) change from Baseline to Weeks 12, 24, 40, and 56 (EOT/ET) (8 domains plus Physical Component Summary and Mental Component Summary);

- Time to discontinuation due to Lack of Efficacy;

- Incidence of discontinuation due to Lack of Efficacy;

- Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) change from Baseline to Weeks 24 and 56 (EOT/ET) in the percent work time missed due to OA;

- WPAI:SHP change from Baseline to Weeks 24 and 56 (EOT/ET) in the percent impairment while working due to OA;

- WPAI:SHP change from Baseline to Weeks 24 and 56 (EOT/ET) in the percent overall work impairment due to OA;

- WPAI:SHP change from Baseline to Weeks 24 and 56 (EOT/ET) in the percent activity impairment due to OA.

Usage of Rescue Medication:

- Incidence of subjects who used rescue medication during Weeks 1-2, 3-4, 5-8, 9-12, 13-16, 17-24, 25-32, 33-40, 41-48, and 49-56 (EOT/ET);

- Amount (mg) of rescue medication taken during Weeks 1-2, 3-4, 5-8, 9-12, 13-16, 17-24, 25-32, 33-40, 41-48, and 49-56 (EOT/ET).

Radiographic Assessments (Safety):

- Change from Baseline to Week 56 (EOT/ET) in Medial Minimum Joint Space Width (JSW) (mm) of the index knee (for subjects with OA of the knee);

- Change from Baseline to Week 56 (EOT/ET) in Minimum JSW (mm) of the index hip (for subjects with OA of the hip).

Safety Measures:

- Adverse events (AEs);

- Safety laboratory testing (chemistry, hematology, urinalysis);

- Vital signs;

- Electrocardiogram (ECG);

- Neurologic exam (Neuropathy Impairment Score [NIS]);

- Serum anti-drug antibody (ADA) assessments;
- Physical examination.

Pharmacokinetics:

- Measurement of plasma tanezumab concentrations.

Safety Evaluations: The safety of tanezumab 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 AEs (SAEs), vital signs data, and clinical laboratory data on a regular basis throughout the course of this study. Blood and urine samples for clinical laboratory testing were collected at Screening, Baseline, and at Weeks 4, 8, 16, 24, 32, 40, 48, 56 (or at EOT/ET), and 64 (where applicable). Twelve-lead ECGs were performed at Screening, Baseline (predose and 1 hour postdose) and at Weeks 4, 8, 16, 24, 56, and 64 (where applicable). If possible, ECGs were collected at the same time each visit. Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) were measured after the subject had been sitting for 5 minutes at Screening, Baseline (predose and 1 hour postdose on Day 1), and at Weeks 2, 4, 8, 12, 16, 24, 32, 48, 56 (EOT/ET), and 64 (where applicable). Each subject underwent a physical examination at Screening, Week 24, and at the last study visit (Week 56 or EOT/ET). Additional safety assessments included radiographic assessments: changes from Baseline to Week 56 in the medial minimum JSW of the index knee for subjects with knee OA and changes from Baseline to Week 56 in the minimum JSW of the index hip for subjects with hip OA.

Neurological examinations were performed at Screening, Baseline, and at Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, 56 (or EOT/ET), and 64 (where applicable). The Investigator was to complete the NIS at these time points based on the neurological exam.

Blood samples for the assessment of ADAs against tanezumab (anti-tanezumab antibodies) were collected at Baseline (predose) and at Weeks 16, 24, 40, and 56 (or EOT/ET).

Statistical Methods:

The intent to treat (ITT) analysis set was used for the primary analysis of efficacy and safety. It consisted of all randomized subjects who received at least 1 dose of randomized IV study medication (either tanezumab or placebo IV). The ITT population was used for all presentations of efficacy and safety data and all data listings. Subjects who received oral study medication but not IV study medication were excluded from the ITT analysis set.

The secondary efficacy analysis set was the per protocol (PP) analysis set and included all subjects in the ITT analysis population who had no major protocol deviations potentially affecting efficacy.

The testing strategy within each primary endpoint was: first test contrast (1) tanezumab 10 mg + NSAID versus NSAID alone. If this was significant at the 2-sided 5% level (where tanezumab 10 mg + NSAID was superior to NSAID alone), then both contrasts (2) tanezumab 5 mg + NSAID versus NSAID alone and (3) tanezumab 10 mg versus NSAID

alone were tested simultaneously using the Hochberg procedure (with both contrasts being initially made at the 2-sided 5% significance level). If both of these contrasts were significant (with tanezumab 5 mg + NSAID and tanezumab 10 mg both being superior to NSAID alone), then the final treatment contrast (4) tanezumab 5 mg versus NSAID alone was made, also at the 2-sided 5% significance level.

The assessment of statistical significance for each treatment contrast given above was then made over all co-primary endpoints, in order to declare each treatment contrast as significant for all co-primary endpoints.

All statistical comparisons were 2-sided, and were made at the 5% level of significance (except under the Hochberg adjustment described above). The assessment of significance for the treatment contrasts used the stepdown testing strategy described above to maintain the Type 1 error to ≤5% within each of the co-primary efficacy endpoints, and to <5% for all 3 co-primary efficacy endpoints. The primary analysis used Baseline observation carried forward (BOCF) for missing data.

The 3 co-primary efficacy endpoints were change from Baseline to Week 16 in the WOMAC Pain subscale, the WOMAC Physical Function subscale, and the PGA of OA, and these were analyzed using an analysis of covariance (ANCOVA) model. Additional analysis models for the 3 co-primary endpoints were used to examine the interaction of a range of effects with treatment group. These effects included Baseline score, index joint (knee or hip), country, and study center.

All analyses of the co-primary efficacy endpoints used change from Baseline as the response efficacy value, and estimated the treatment group response and treatment group differences with corresponding standard errors (SE) of the mean, and 95% confidence intervals (CIs), as well as p-values for treatment differences.

Secondary efficacy analyses of the 3 co-primary endpoints included analysis of change from Baseline to Weeks 2, 4, 8, 12, 24, 32, 40, 48, and 56. These analyses used BOCF (up to Week 24 only) and last observation carried forward (LOCF) imputation methods for missing data, and the same (main effects) ANCOVA model as described for the primary analyses.

RESULTS

Subject Disposition and Demography: A total of 4531 subjects were screened, 2720 subjects randomized, and 2700 subjects (1424 subjects in the naproxen cohort and 1276 subjects in the celecoxib cohort) treated; a total of 20 subjects did not receive IV study medication and were excluded from the ITT population (Table 3).

The percentage of subjects completing the study (Week 56) overall was similar across all treatment groups. Approximately 50% of all ITT subjects discontinued from the treatment portion of the study due to implementation of the FDA clinical hold on 23 June 2010. The study was terminated by the Sponsor as a result.

Table 3. Subject Disposition

	Tanezumab		Tanezumab + NSAID		NSAIDs
	5 mg	10 mg	5 mg	10 mg	
Screened 4531					
Assigned to study drug	544	544	543	544	545
Randomized but not treated	3	2	7	2	6
Randomized and treated	541	542	536	542	539
Analyzed for efficacy					
Intent to treat	541	542	536	542	539
Per protocol	451	474	450	442	436
Analyzed for safety[a]:					
Adverse events	541 (99.4)	542 (99.6)	536 (98.7)	542 (99.6)	539 (98.9)
Laboratory data	530 (97.4)	532 (97.8)	529 (97.4)	529 (97.2)	527 (96.7)
Completed, n (%)[a]	64 (11.8)	63 (11.6)	51 (9.4)	60 (11.0)	63 (11.6)
Discontinued, n (%)[b]	477 (88.2)	479 (88.4)	485 (90.5)	482 (88.9)	476 (883)
Subject died	0	0	1 (0.2)	0	0
Adverse event	65 (12.0)[c]	89 (16.4)	77 (14.4)[d]	99 (18.3)[e]	52 (9.6)
Lack of efficacy	42 (7.8)	44 (8.1)	37 (6.9)	33 (6.1)	78 (14.5)
Lost to follow-up	12 (2.2)	11 (2.0)	13 (2.4)	17 (3.1)	6 (1.1)
Other	13 (2.4)	4 (0.7)	10 (1.9)	14 (2.6)	8 (1.5)
Protocol violation	13 (2.4)	18 (3.3)	20 (3.7)	21 (3.9)	17 (3.2)
Study terminated by sponsor	271 (50.1)	258 (47.6)	277 (51.7)	247 (45.6)	261 (48.4)
Subject no longer willing to participate in study	61 (11.3)	54 (10.0)	50 (9.3)	51 (9.4)	54 (10.0)
Withdrawn due to pregnancy	0	1 (0.2)	0	0	0

n = number of subjects in each category, NSAID = nonsteroidal anti-inflammatory drug.
a. Denominator for percentages was number of subjects assigned to study drug.
b. Denominator for percentages was number of subjects randomized and treated.
c. Two (2) subjects (both in the celecoxib cohort) later died of the adverse events that led to their withdrawal.
d. One (1) subject (in the naproxen cohort) later died of the adverse event that led to her withdrawal.
e. One (1) subject (in the celecoxib cohort) later died of the adverse event that led to her withdrawal.

Table 4 and Table 5 summarize the subject disposition for the naproxen and celecoxib cohorts, respectively. Subject disposition was similar for the treatment groups within the naproxen cohort and for the tanezumab monotherapy, celecoxib alone, and tanezumab 10 mg + celecoxib treatment groups in the celecoxib cohort; a lower percentage of subjects in the the tanezumab 5 mg + celecoxib treatment group completed the study.

Table 4. Subject Disposition – Number (%) of Subjects – Naproxen Cohort

	Tanezumab		Tanezumab + Naproxen		Naproxen
	5 mg	10 mg	5 mg	10 mg	500 mg BID
Assigned to study drug	288	289	286	288	288
Randomized but not treated	3	1	6	0	5
Randomized and treated	285	288	280	288	283
Completed[a]	33 (11.5)	31 (10.7)	32 (11.2)	32 (11.1)	32 (11.1)
Discontinued[a]	252 (87.5)	257 (88.9)	248 (86.7)	256 (88.9)	251 (87.2)

BID = twice daily.
a. Denominator for percentages was number of subjects assigned to study drug.

Table 5. Subject Disposition – Number (%) of Subjects – Celecoxib Cohort

	Tanezumab		Tanezumab + Celecoxib		Celecoxib
	5 mg	10 mg	5 mg	10 mg	100 mg BID
Assigned to study drug	256	255	257	256	257
Randomized but not treated	0	1	1	2	1
Randomized and treated	256	254	256	254	256
Completed[a]	31 (12.1)	32 (12.5)	19 (7.4)	28 (10.9)	31 (12.1)
Discontinued[a]	225 (87.9)	222 (87.1)	237 (92.2)	226 (88.3)	225 (87.5)

BID = twice daily.
a. Denominator for percentages was number of subjects assigned to study drug.

Table 6 and Table 7 summarize the number of subjects included in the analyses for the naproxen and celecoxib cohorts, respectively.

Table 6. Number of Subjects Included in the Analyses – Naproxen Cohort

	Tanezumab		Tanezumab + Naproxen		Naproxen
	5 mg	10 mg	5 mg	10 mg	500 mg BID
Assigned to study treatment	288	289	286	288	288
Treated	285	288	280	288	283
Analyzed for efficacy[a]					
Intent to treat, n (%)	285 (99.0)	288 (99.7)	280 (97.9)	288 (100.0)	283 (98.3)
Per protocol, n (%)	233 (80.9)	254 (87.9)	238 (83.2)	233 (80.9)	227 (78.8)
Analyzed for safety[a]					
Adverse events, n (%)	285 (99.0)	288 (99.7)	280 (97.9)	288 (100.0)	283 (98.3)
Laboratory data, n (%)	279 (96.9)	282 (97.6)	275 (96.2)	279 (96.9)	274 (95.1)

BID = twice daily, n = number of subjects in category.
a. Percentages were calculated using the number of subjects assigned to study treatment as the denominator.

Table 7. Number of Subjects Included in the Analyses – Celecoxib Cohort

	Tanezumab		Tanezumab + Celecoxib		Celecoxib
	5 mg	10 mg	5 mg	10 mg	100 mg BID
Assigned to study treatment	256	255	257	256	257
Treated	256	254	256	254	256
Analyzed for efficacy[a]					
Intent to treat, n (%)	256 (100.0)	254 (99.6)	256 (99.6)	254 (99.2)	256 (99.6)
Per protocol, n (%)	218 (95.2)	220 (86.3)	212 (82.5)	209 (81.6)	209 (81.3)
Analyzed for safety[a]					
Adverse events, n (%)	256 (100.0)	254 (99.6)	256 (99.6)	254 (99.2)	256 (99.6)
Laboratory data, n (%)	251 (98.0)	250 (98.0)	254 (98.8)	250 (97.7)	253 (98.4)

BID = twice daily, n = number of subjects in category.
a. Percentages were calculated using the number of subjects assigned to study treatment as the denominator.

Demographic characteristics at Baseline were similar across the treatment groups (Table 8). Across the 5 treatment groups, the majority of subjects (67.7% to 72.5%) were female and White (65.2% to 70.7%), and the mean age ranged from 61.3 years to 62.0 years. Mean BMI at Baseline ranged from 30.0 kg/m^2 to 30.7 kg/m^2 across the treatment groups, indicating that in general the study population was overweight. In general, demographic characteristics in

the naproxen and celecoxib cohorts were similar to those in the overall population and to each other.

Table 8. Demographic Characteristics (ITT)

	Tanezumab		Tanezumab + NSAID		NSAIDs
	5 mg N[a]=541	10 mg N[a]=542	5 mg N[a]=536	10 mg N[a]=542	N[a]=539
Gender, n (%)					
Male	149 (27.5)	150 (27.7)	173 (32.3)	173 (31.9)	151 (28.0)
Female	392 (72.5)	392 (72.3)	363 (67.7)	369 (68.1)	388 (72.0)
Age (years), n (%)					
18–44	28 (5.2)	19 (3.5)	29 (5.4)	25 (4.6)	17 (3.2)
45–64	302 (55.8)	298 (55.0)	296 (55.2)	304 (56.1)	339 (62.9)
≥65	211 (39.0)	225 (41.5)	211 (39.4)	213 (39.3)	183 (34.0)
>75	40 (7.4)	51 (9.4)	40 (7.5)	40 (7.4)	38 (7.1)
Mean (SD)	61.9 (9.7)	62.0 (10.0)	61.7 (10.2)	61.3 (10.0)	61.3 (9.3)
Range	28-86	20-92	29-93	28-86	28-89
Race, n (%)					
White	353 (65.2)	375 (69.2)	369 (68.8)	356 (65.7)	381 (70.7)
Black	60 (11.1)	69 (12.7)	59 (11.0)	65 (12.0)	62 (11.5)
Asian	71 (13.1)	56 (10.3)	67 (12.5)	70 (12.9)	53 (9.8)
Other	57 (10.5)	42 (7.7)	41 (7.6)	51 (9.4)	43 (8.0)
Weight (kg)					
Mean (SD)	83.4 (18.1)	82.1 (17.6)	82.0 (17)	83.2 (17.7)	83.1 (16.2)
Range	36.5-148.3	33.0-134.2	40.8-136.2	41.9-137.0	45.5-139.0
N[b] (%)	541 (100.0)	541 (99.8)	536 (100.0)	542 (100.0)	539 (100.0)
Body mass index (kg/m^2)					
Mean (SD)	30.7 (4.9)	30.2 (4.9)	30.0 (4.8)	30.4 (5.0)	30.5 (4.8)
Range	17.2-50.5	17.3-39.2	18.3-39.1	16.5-42.3	16.3-39.0
N[b] (%)	541 (100.0)	541 (99.8)	536 (100.0)	542 (100.0)	539 (100.0)

Body mass index computed as weight/(height/100)^2.
ITT = intent to treat, n = number of subjects in category, NSAID = nonsteroidal anti-inflammatory drug, SD = standard deviation.
a. Number of subjects treated in treatment group.
b. Number of subjects providing data.

Efficacy Results:

The study was terminated prematurely following a US FDA clinical hold on 23 June 2010 for tanezumab OA clinical studies which halted dosing and enrollment of subjects for potential safety issues.

Primary Efficacy Results:

Table 9 summarizes the 3 co-primary efficacy endpoints for the naproxen cohort.

The comparison for tanezumab 10 mg + naproxen versus naproxen was declared as statistically significant across the 3 co-primary endpoints, as significance was achieved for all of these efficacy measures. The comparisons for tanezumab 5 mg + naproxen, tanezumab 10 mg, and tanezumab 5 mg versus naproxen alone were statistically significant for the WOMAC Pain and Physical Function subscales, but not for the PGA of OA.

Table 9. Summary of Co-Primary Efficacy Endpoints, Change From Baseline to Week 16 (ITT, BOCF) – Naproxen Cohort

	Tanezumab		Tanezumab + Naproxen		Naproxen
	5 mg N[a]=285	10 mg N[a]=288	5 mg N[a]=280	10 mg N[a]=288	500 mg BID N[a]=283
WOMAC pain subscale (0-10 NRS)					
N[b]	285	287	280	286	282
Baseline mean (SD)	6.39 (1.61)	6.50 (1.57)	6.52 (1.65)	6.33 (1.65)	6.32 (1.64)
LS mean change from Baseline (SE)	-1.88 (0.14)	-2.02 (0.14)	-2.13 (0.14)	-2.36 (0.14)	-1.44 (0.14)
Comparison vs naproxen					
LS mean change from Baseline (95% CI)	-0.45 (-0.81, -0.09)	-0.58 (-0.94, -0.23)	-0.70 (-1.06, -0.33)	-0.92 (-1.28, -0.57)	
p-Value	0.015	0.001	<0.001	<0.001	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			-0.25 (-0.61, 0.11)	-0.34 (-0.70, 0.02)	
p-Value			0.177	0.062	
Comparison of T10 versus T5		**vs TZB 5 mg**		**vs TZB 5 mg + Naproxen**	
LS mean change from Baseline (95% CI)		-0.14 (-0.49, 0.22)		-0.23 (-0.59, 0.13)	
p-Value		0.453		0.212	
WOMAC physical function subscale (0-10 NRS)					
N[b]	284	287	280	286	282
Baseline mean (SD)	6.46 (1.72)	6.47 (1.61)	6.57 (1.67)	6.39 (1.62)	6.32 (1.62)
LS mean change from Baseline (SE)	-1.86 (0.13)	-1.90 (0.13)	-2.16 (0.14)	-2.26 (0.13)	-1.38 (0.13)
Comparison vs naproxen					
LS mean change from Baseline (95% CI)	-0.48 (-0.83, -0.13)	-0.52 (-0.87, -0.17)	-0.78 (-1.13, -0.43)	-0.88 (-1.23, -0.53)	
p-Value	0.007	0.003	<0.001	<0.001	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			-0.29 (-0.64, 0.06)	-0.36 (-0.70, -0.01)	
p-Value			0.100	0.044	
Comparison of T10 versus T5		**vs TZB 5 mg**		**vs TZB 5 mg + Naproxen**	
LS mean change from Baseline (95% CI)		-0.04 (-0.39, 0.31)		-0.10 (-0.45, 0.25)	
p-Value		0.824		0.565	

Table 9. Summary of Co-Primary Efficacy Endpoints, Change From Baseline to Week 16 (ITT, BOCF) – Naproxen Cohort

	Tanezumab		Tanezumab + Naproxen		Naproxen
	5 mg N[a]=285	10 mg N[a]=288	5 mg N[a]=280	10 mg N[a]=288	500 mg BID N[a]=283
PGA of OA (5-point Likert)					
N[b]	284	288	280	285	283
Baseline mean (SD)	3.39 (0.63)	3.41 (0.62)	3.39 (0.63)	3.39 (0.66)	3.38 (0.63)
LS mean change from Baseline (SE)	-0.54 (0.05)	-0.61 (0.05)	-0.62 (0.05)	-0.72 (0.05)	-0.54 (0.05)
Comparison vs naproxen					
LS mean change from Baseline (95% CI)	-0.00 (-0.14, 0.13)	-0.08 (-0.22, 0.06)	-0.08 (-0.22, 0.06)	-0.18 (-0.32, -0.05)	
p-Value	0.961	0.251	0.251	0.008	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			-0.08 (-0.21, 0.06)	-0.11 (-0.24, 0.03)	
p-Value			0.271	0.128	
Comparison of T10 versus T5		**vs TZB 5 mg**		**vs TZB 5 mg + Naproxen**	
LS mean change from Baseline (95% CI)		-0.08 (-0.21, 0.06)		-0.10 (-0.24, 0.03)	
p-Value		0.272		0.133	

A change from Baseline <0 is an improvement.
ANCOVA model includes treatment, Baseline value, index joint (knee or hip) as covariates. LS means were estimated from the corresponding ANCOVA model.
p-Value is based on ANCOVA from pairwise comparisons.
ANCOVA = analysis of covariance, BID = twice daily, BOCF = baseline observation carried forward, CI = confidence interval, ITT = intent to treat, LS mean = least squares means, NRS = numeric rating scale, OA = osteoarthritis, PGA = Patient Global Assessment, SD= standard deviation, SE = standard error, T5 = tanezumab 5 mg, T10 = tanezumab 10 mg, TZB = tanezumab, vs = versus, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

a. Number of subjects in treatment group.
b. Number of subjects providing data.

Table 10 summarizes the 3 co-primary efficacy endpoints for the celecoxib cohort.

The comparisons for both tanezumab 10 mg + celecoxib and tanezumab 5 mg + celecoxib versus celecoxib alone were declared statistically significant, as significance was achieved for all 3 co-primary efficacy endpoints. The comparisons for tanezumab 10 mg and tanezumab 5 mg versus celecoxib alone were statistically significant for the WOMAC Pain and Physical Function subscales, but not for the PGA of OA.

Table 10. Summary of Co-Primary Efficacy Endpoints, Change From Baseline to Week 16 (ITT, BOCF) – Celecoxib Cohort

	Tanezumab		Tanezumab + Celecoxib		Celecoxib
	5 mg N[a]=256	10 mg N[a]=254	5 mg N[a]=256	10 mg N[a]=254	100 mg BID N[a]=256
WOMAC pain subscale (0-10 NRS)					
N[b]	254	254	256	254	255
Baseline mean (SD)	6.49 (1.55)	6.44 (1.53)	6.41 (1.66)	6.27 (1.64)	6.29 (1.60)
LS mean change from Baseline (SE)	-2.02 (0.16)	-2.05 (0.16)	-2.22 (0.16)	-2.41 (0.16)	-1.47 (0.15)
Comparison vs celecoxib					
LS mean change from Baseline (95% CI)	-0.55 (-0.95, -0.15)	-0.58 (-0.98, -0.18)	-0.75 (-1.15, -0.35)	-0.94 (-1.34, -0.54)	
p-Value	0.007	0.004	<0.001	<0.001	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			-0.20 (-0.60, 0.20)	-0.35 (-0.75, 0.05)	
p-Value			0.330	0.083	
Comparison of T10 versus T5		**vs TZB 5 mg**		**vs TZB 5 mg + Celecoxib**	
LS mean change from Baseline (95% CI)		-0.03 (-0.43, 0.37)		-0.19 (-0.59, 0.21)	
p-Value		0.879		0.360	
WOMAC physical function subscale (0-10 NRS)					
N[b]	255	253	255	253	254
Baseline mean (SD)	6.67 (1.60)	6.58 (1.58)	6.57 (1.72)	6.39 (1.62)	6.47 (1.59)
LS mean change from Baseline (SE)	-2.05 (0.15)	-2.04 (0.15)	-2.22 (0.15)	-2.42 (0.15)	-1.42 (0.15)
Comparison vs celecoxib					
LS mean change from Baseline (95% CI)	-0.63 (-1.02, -0.24)	-0.63 (-1.02, -0.24)	-0.81 (-1.20, -0.42)	-1.01 (-1.40, -0.62)	
p-Value	0.002	0.002	<0.001	<0.001	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			-0.17 (-0.56, 0.22)	-0.38 (-0.77, 0.01)	
p-Value			0.383	0.057	
Comparison of T10 versus T5		**vs TZB 5 mg**		**vs TZB 5 mg + Celecoxib**	
LS mean change from Baseline (95% CI)		0.01 (-0.39, 0.40)		-0.20 (-0.59, 0.19)	
p-Value		0.980		0.312	

Table 10. Summary of Co-Primary Efficacy Endpoints, Change From Baseline to Week 16 (ITT, BOCF) – Celecoxib Cohort

	Tanezumab		Tanezumab + Celecoxib		Celecoxib
	5 mg N[a]=256	10 mg N[a]=254	5 mg N[a]=256	10 mg N[a]=254	100 mg BID N[a]=256
PGA of OA (5-Point Likert)					
N[b]	256	254	255	253	254
Baseline mean (SD)	3.44 (0.65)	3.48 (0.63)	3.45 (0.67)	3.41 (0.64)	3.37 (0.59)
LS mean change from Baseline (SE)	-0.67 (0.05)	-0.59 (0.05)	-0.74 (0.05)	-0.75 (0.05)	-0.54 (0.05)
Comparison vs celecoxib					
LS mean change from Baseline (95% CI)	-0.13 (0.27, 0.00)	-0.06 (-0.20, 0.08)	-0.20 (-0.34, -0.06)	-0.21 (-0.35, -0.08)	
p-Value	0.057	0.414	0.004	0.002	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change From Baseline (95% CI)			-0.07 (-0.21, 0.07)	-0.16 (-0.30, -0.02)	
p-Value			0.328	0.026	
Comparison of T10 versus T5		**vs TZB 5 mg**		**vs TZB 5 mg + Celecoxib**	
LS mean change From Baseline (95% CI)		0.08 (-0.06, 0.21)		-0.01 (-0.15, 0.13)	
p-Value		0.277		0.864	

A change from Baseline <0 is an improvement.
ANCOVA model includes treatment, Baseline value, index joint (knee or hip) as covariates. LS means were estimated from the corresponding ANCOVA model.
p-Value is based on ANCOVA from pairwise comparisons.
ANCOVA = analysis of covariance, BID = twice daily, BOCF = baseline observation carried forward, CI = confidence interval, ITT = intent to treat, LS mean = least squares means, NRS = numeric rating scale, OA = osteoarthritis, PGA = Patient Global Assessment, SD = standard deviation, SE = standard error, TZB = tanezumab, T5 = tanezumab 5 mg, T10 = tanezumab 10 mg, vs = versus, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

a. Number of subjects in treatment group.
b. Number of subjects providing data.

Secondary Efficacy Results:

Changes From Baseline in WOMAC Pain and Physical Function Subscales and PGA of OA:

Table 11 and Table 12 summarize changes from Baseline with the WOMAC Pain subscale at Weeks 2 through 24 (ITT, BOCF) in the naproxen cohort and in the celecoxib cohort, respectively.

Table 13 and Table 14 summarize changes from Baseline with the WOMAC Physical Function subscale at Weeks 2 through 24 (ITT, BOCF) in the naproxen cohort and in the celecoxib cohort, respectively.

Table 15 and Table 16 summarize changes from Baseline with the PGA of OA at Weeks 2 through 24 (ITT, BOCF) in the naproxen cohort and in the celecoxib cohort, respectively.

Overall, for all three endpoints there was a consistent pattern of efficacy with tanezumab monotherapy and tanezumab/celecoxib combination therapy compared to treatment with celecoxib alone through Week 24, and with tanezumab monotherapy and tanezumab/naproxen combination therapy compared to treatment with naproxen alone through Week 24.

Table 11. Summary of Change From Baseline in WOMAC Pain Subscale at Weeks 2, 4, 8, 12, and 24 (ITT, BOCF) – Naproxen Cohort

	Tanezumab		Tanezumab + Naproxen		Naproxen
	5 mg N=285	10 mg N=288	5 mg N=280	10 mg N=288	100 mg BID N=256
Week 2					
LS mean change from Baseline (SE)	-1.20 (0.12)	-1.20 (0.12)	-1.47 (0.13)	-1.14 (0.12)	-1.16 (0.12)
Comparison versus naproxen					
LS mean change from Baseline (95% CI)	-0.04 (-0.36, 0.28)	-0.05 (-0.37, 0.28)	-0.31 (-0.64, 0.01)	0.01 (-0.31, 0.34)	
p-Value	0.798	0.779	0.057	0.927	
Week 4					
LS mean change from Baseline (SE)	-1.79 (0.13)	-1.95 (0.13)	-2.16 (0.13)	-2.11 (0.13)	-1.28 (0.13)
Comparison versus naproxen					
LS mean change from Baseline (95% CI)	-0.52 (-0.85, -0.18)	-0.68 (-1.01, -0.34)	-0.89 (-1.22, -0.55)	-0.84 (-1.17, -0.50)	
p-Value	0.003	<0.001	<0.001	<0.001	
Week 8					
LS mean change from Baseline (SE)	-1.68 (0.14)	-2.05 (0.14)	-2.06 (0.14)	-2.20 (0.14)	-1.15 (0.14)
Comparison versus naproxen					
LS mean change from Baseline (95% CI)	-0.53 (-0.88, -0.17)	-0.90 (-1.25, -0.55)	-0.91 (-1.27, -0.56)	-1.05 (-1.40, -0.69)	
p-Value	0.003	<0.001	<0.001	<0.001	
Week 12					
LS mean change from Baseline (SE)	-1.91 (0.14)	-1.96 (0.14)	-2.26 (0.14)	-2.40 (0.14)	-1.29 (0.14)
Comparison versus naproxen					
LS mean change from Baseline (95% CI)	-0.62 (-0.98, -0.26)	-0.67 (-1.03, -0.31)	-0.97 (-1.33, -0.60)	-1.11 (-1.47, -0.75)	
p-Value	<0.001	<0.001	<0.001	<0.001	
Week 24					
LS mean change from Baseline (SE)	-1.69 (0.14)	-1.83 (0.14)	-1.85 (0.14)	-2.01 (0.14)	-1.38 (0.14)
Comparison versus naproxen					
LS mean change from Baseline (95% CI)	-0.31 (-0.68, 0.06)	-0.45 (-0.84, -0.09)	-0.46 (-0.84, -0.09)	-0.62 (-0.99, -0.25)	
p-Value	0.098	0.016	0.014	<0.001	

A change from Baseline <0 is an improvement.
ANCOVA model includes treatment, Baseline value, index joint (knee or hip) as covariates. LS means were estimated from the corresponding ANCOVA model. p-Value is based on ANCOVA from pairwise comparisons.
ANCOVA = analysis of covariance, BID = twice daily, BOCF = baseline observation carried forward, CI = confidence interval, ITT = intent to treat, LS mean = least squares means, N = number of subjects in each treatment group, SE = standard error, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Table 12. Summary of Change From Baseline in WOMAC Pain Subscale at Weeks 2, 4, 8, 12, and 24 (ITT, BOCF) – Celecoxib Cohort

	Tanezumab		Tanezumab + Celecoxib		Celecoxib
	5 mg N=256	10 mg N=254	5 mg N=256	10 mg N=254	100 mg BID N=256
Week 2					
LS mean change from Baseline (SE)	-1.13 (0.13)	-0.88 (0.13)	-1.23 (0.13)	-1.04 (0.13)	-1.11 (0.13)
Comparison versus celecoxib					
LS mean change from Baseline (95% CI)	-0.02 (-0.36, 0.33)	0.23 (-0.11, 0.58)	-0.12 (-0.46, 0.23)	0.06 (-0.28, 0.41)	
p-Value	0.919	0.183	0.504	0.710	
Week 4					
LS mean change from Baseline (SE)	-1.69 (0.14)	-1.80 (0.14)	-2.10 (0.14)	-2.12 (0.14)	-1.17 (0.14)
Comparison versus celecoxib					
LS mean change from Baseline (95% CI)	-0.52 (-0.88, -0.15)	-0.63 (-0.99, -0.26)	-0.93 (-1.29, -0.56)	-0.95 (-1.31, -0.58)	
p-Value	0.005	<0.001	<0.001	<0.001	
Week 8					
LS mean change from Baseline (SE)	-1.79 (0.15)	-2.00 (0.15)	-2.23 (0.15)	-2.41 (0.15)	-1.20 (0.14)
Comparison versus celecoxib					
LS mean change from Baseline (95% CI)	-0.59 (-0.97, -0.22)	-0.80 (-1.17, -0.43)	-1.03 (-1.40, -0.65)	-1.21 (-1.59, -0.84)	
p-Value	0.002	<0.001	<0.001	<0.001	
Week 12					
LS mean change from Baseline (SE)	-2.07 (0.15)	-2.15 (0.15)	-2.23 (0.15)	-2.50 (0.15)	-1.42 (0.15)
Comparison versus celecoxib					
LS mean change from Baseline (95% CI)	-0.65 (-1.04, -0.26)	-0.73 (-1.12, -0.34)	-0.81 (-1.20, -0.42)	-1.08 (-1.47, -0.69)	
p-Value	0.001	<0.001	<0.001	<0.001	
Week 24					
LS mean change from Baseline (SE)	-1.73 (0.16)	-1.99 (0.16)	-2.05 (0.16)	-2.29 (0.16)	-1.62 (0.16)
Comparison versus celecoxib					
LS mean change from Baseline (95% CI)	-0.11 (-0.51, 0.29)	-0.36 (-0.76, 0.04)	-0.43 (-0.83, -0.03)	-0.43 (-1.07, -0.26)	
p-Value	0.597	0.078	0.037	0.001	

A change from Baseline <0 is an improvement.
ANCOVA model includes treatment, Baseline value, index joint (knee or hip) as covariates. LS means were estimated from the corresponding ANCOVA model. p-Value is based on ANCOVA from pairwise comparisons.
ANCOVA = analysis of covariance, BID = twice daily, BOCF = baseline observation carried forward, CI = confidence interval, ITT = intent to treat, LS mean = least squares means, N = number of subjects in each treatment group, SE = standard error, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Table 13. Summary of Change From Baseline in WOMAC Physical Function Subscale at Weeks 2, 4, 8, 12, and 24 (ITT, BOCF) – Naproxen Cohort

	Tanezumab		Tanezumab + Naproxen		Naproxen
	5 mg N=285	10 mg N=288	5 mg N=280	10 mg N=288	100 mg BID N=256
Week 2					
LS mean change from Baseline (SE)	-1.31 (0.12)	-1.33 (0.12)	-1.63 (0.12)	-1.29 (0.12)	-1.15 (0.12)
Comparison versus naproxen					
LS mean change from Baseline (95% CI)	-0.17 (-0.47, 0.14)	-0.19 (-0.50, 0.12)	-0.48 (-0.79, -0.17)	-0.14 (-0.45, 0.16)	
p-Value	0.284	0.224	0.002	0.355	
Week 4					
LS mean change from Baseline (SE)	-1.83 (0.12)	-1.91 (0.12)	-2.13 (0.13)	-2.14 (0.12)	-1.17 (0.12)
Comparison versus naproxen					
LS mean change from Baseline (95% CI)	-0.67 (-0.99, -0.34)	-0.74 (-1.06, -0.42)	-0.96 (-1.29, -0.64)	-0.97 (-1.29, -0.65)	
p-Value	<0.001	<0.001	<0.001	<0.001	
Week 8					
LS mean change from Baseline (SE)	-1.67 (0.13)	-2.05 (0.13)	-2.06 (0.13)	-2.21 (0.13)	-1.14 (0.13)
Comparison versus naproxen					
LS mean change from Baseline (95% CI)	-0.52 (-0.86, -0.18)	-0.90 (-1.24, -0.56)	-0.92 (-1.26, -0.57)	-1.07 (-1.41, -0.73)	
p-Value	0.003	<0.001	<0.001	<0.001	
Week 12					
LS mean change from Baseline (SE)	-1.91 (0.14)	-1.92 (0.13)	-2.21 (0.14)	-2.37 (0.13)	-1.32 (0.14)
Comparison versus naproxen					
LS mean change from Baseline (95% CI)	-0.58 (-0.93, -0.23)	-0.60 (-0.95, -0.25)	-0.88 (-1.24, -0.53)	-1.05 (-1.40, -0.70)	
p-Value	0.001	<0.001	<0.001	<0.001	
Week 24					
LS mean change from Baseline (SE)	-1.72 (0.14)	-1.82 (0.14)	-1.80 (0.14)	-2.03 (0.14)	-1.39 (0.14)
Comparison versus naproxen					
LS mean change from Baseline (95% CI)	-0.33 (-0.69, 0.03)	-0.43 (-0.77, -0.06)	-0.41 (-0.77, -0.06)	-0.64 (-1.00, -0.29)	
p-Value	0.070	0.018	0.024	<0.001	

A change from Baseline <0 is an improvement.
ANCOVA model includes treatment, Baseline value, index joint (knee or hip) as covariates. LS means were estimated from the corresponding ANCOVA model. p-Value is based on ANCOVA from pairwise comparisons.
ANCOVA = analysis of covariance, BID = twice daily, BOCF = baseline observation carried forward, CI = confidence interval, ITT = intent to treat, LS mean = least squares means, N = number of subjects in each treatment group, SE = standard error, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Table 14. Summary of Change From Baseline in WOMAC Physical Function Subscale at Weeks 2, 4, 8, 12, and 24 (ITT, BOCF) – Celecoxib Cohort

	Tanezumab		Tanezumab + Celecoxib		Celecoxib
	5 mg N=256	10 mg N=254	5 mg N=256	10 mg N=254	100 mg BID N=256
Week 2					
LS mean change from Baseline (SE)	-1.22 (0.13)	-1.01 (0.13)	-1.28 (0.13)	-1.13 (0.13)	-0.99 (0.13)
Comparison versus celecoxib					
LS mean change from Baseline (95% CI)	-0.23 (-0.57, 0.10)	-0.03 (-0.36, 0.31)	-0.29 (-0.63, 0.04)	-0.14 (-0.47, 0.19)	
p-Value	0.172	0.882	0.084	0.405	
Week 4					
LS mean change from Baseline (SE)	-1.73 (0.14)	-1.80 (0.14)	-1.99 (0.14)	-2.08 (0.14)	-1.13 (0.14)
Comparison versus celecoxib					
LS mean change from Baseline (95% CI)	-0.60 (-0.95, -0.25)	-0.67 (-1.02, -0.32)	-0.87 (-1.22, -0.51)	-0.95 (-1.31, -0.60)	
p-Value	<0.001	<0.001	<0.001	<0.001	
Week 8					
LS mean change from Baseline (SE)	-1.86 (0.14)	-2.00 (0.14)	-2.16 (0.14)	-2.36 (0.14)	-1.16 (0.14)
Comparison versus celecoxib					
LS mean change from Baseline (95% CI)	-0.70 (-1.06, -0.33)	-0.84 (-1.21, -0.47)	-0.99 (-1.36, -0.63)	-1.19 (-1.56, -0.83)	
p-Value	<0.001	<0.001	<0.001	<0.001	
Week 12					
LS mean change from Baseline (SE)	-2.15 (0.15)	-2.09 (0.15)	-2.30 (0.15)	-2.49 (0.15)	-1.36 (0.15)
Comparison versus celecoxib					
LS mean change from Baseline (95% CI)	-0.79 (-1.17, -0.40)	-0.72 (-1.11, -0.34)	-0.94 (-1.32, -0.56)	-1.13 (-1.51, -0.75)	
p-Value	<0.001	<0.001	<0.001	<0.001	
Week 24					
LS mean change from Baseline (SE)	-1.85 (0.15)	-1.96 (0.15)	-2.04 (0.15)	-2.34 (0.15)	-1.56 (0.15)
Comparison versus celecoxib					
LS mean change from Baseline (95% CI)	-0.29 (-0.69, 0.10)	-0.40 (-0.87, -0.09)	-0.48 (-0.87, -0.09)	-0.78 (-1.17, -0.39)	
p-Value	0.141	0.044	0.016	<0.001	

A change from Baseline <0 is an improvement.
ANCOVA model includes treatment, Baseline value, index joint (knee or hip) as covariates. LS means were estimated from the corresponding ANCOVA model. p-Value is based on ANCOVA from pairwise comparisons.
ANCOVA = analysis of covariance, BID = twice daily, BOCF = baseline observation carried forward, CI=confidence interval, ITT = intent to treat, LS mean = least squares means, N = number of subjects in each treatment group, SE = standard error, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Table 15. Summary of Change From Baseline in PGA of OA at Weeks 2, 4, 8, 12, and 24 (ITT, BOCF) – Naproxen Cohort

	Tanezumab		Tanezumab + Naproxen		Naproxen
	5 mg N=285	10 mg N=288	5 mg N=280	10 mg N=288	100 mg BID N=256
Week 2					
LS mean change from Baseline (SE)	-0.50 (0.05)	-0.46 (0.05)	-0.55 (0.05)	-0.45 (0.05)	-0.44 (0.05)
Comparison versus naproxen					
LS mean change from Baseline (95% CI)	-0.06 (-0.18, 0.06)	-0.01 (-0.13, 0.11)	-0.11 (-0.23, 0.01)	-0.00 (-0.12, 0.12)	
p-Value	0.360	0.845	0.076	0.957	
Week 4					
LS mean change from Baseline (SE)	-0.59 (0.05)	-0.67 (0.05)	-0.74 (0.05)	-0.67 (0.05)	-0.43 (0.05)
Comparison versus naproxen					
LS mean change from Baseline (95% CI)	-0.16 (-0.28, -0.04)	-0.24 (-0.36, -0.11)	-0.30 (-0.43, -0.18)	-0.24 (-0.36, -0.12)	
p-Value	0.011	<0.001	<0.001	<0.001	
Week 8					
LS mean change from Baseline (SE)	-0.55 (0.05)	-0.67 (0.05)	-0.67 (0.05)	-0.79 (0.05)	-0.43 (0.05)
Comparison versus naproxen					
LS mean change from Baseline (95% CI)	-0.12 (-0.25, 0.01)	-0.23 (-0.37, -0.10)	-0.24 (-0.37, -0.10)	-0.36 (-0.49, -0.23)	
p-Value	0.074	<0.001	<0.001	<0.001	
Week 12					
LS mean change from Baseline (SE)	-0.60 (0.05)	-0.67 (0.05)	-0.69 (0.05)	-0.84 (0.05)	-0.47 (0.05)
Comparison versus naproxen					
LS mean change from Baseline (95% CI)	-0.13 (-0.26, 0.01)	-0.20 (-0.33, -0.07)	-0.22 (-0.36, -0.09)	-0.37 (-0.51, -0.24)	
p-Value	0.059	0.003	0.001	<0.001	
Week 24					
LS mean change from Baseline (SE)	-0.61 (0.05)	-0.55 (0.05)	-0.53 (0.05)	-0.62 (0.05)	-0.53 (0.05)
Comparison versus naproxen					
LS mean change from Baseline (95% CI)	-0.08 (-0.22, 0.06)	-0.03 (-0.17, 0.11)	-0.00 (-0.15, 0.14)	-0.10 (-0.24, 0.04)	
p-Value	0.253	0.716	0.945	0.171	

A change from Baseline <0 is an improvement.
ANCOVA model includes treatment, Baseline value, index joint (knee or hip) as covariates. LS means were estimated from the corresponding ANCOVA model. p-Value is based on ANCOVA from pairwise comparisons.
ANCOVA = analysis of covariance, BID = twice daily, BOCF = baseline observation carried forward, CI = confidence interval, ITT = intent to treat, LS mean = least squares means, N = number of subjects in each treatment group, OA = osteoarthritis, PGA = Patient Global Assessment, SE = standard error.

Table 16. Summary of Change From Baseline in PGA of OA at Weeks 2, 4, 8, 12, and 24 (ITT, BOCF) – Celecoxib Cohort

	Tanezumab		Tanezumab + Celecoxib		Celecoxib
	5 mg N=256	10 mg N=254	5 mg N=256	10 mg N=254	100 mg BID N=256
Week 2					
LS mean change from Baseline (SE)	-0.47 (0.05)	-0.31 (0.05)	-0.45 (0.05)	-0.29 (0.05)	-0.41 (0.05)
Comparison versus celecoxib					
LS mean change from Baseline (95% CI)	-0.06 (-0.19, 0.08)	0.10 (-0.03, 0.23)	-0.04 (-0.17, 0.09)	0.12 (-0.01, 0.25)	
p-Value	0.404	0.128	0.577	0.068	
Week 4					
LS mean change from Baseline (SE)	-0.66 (0.05)	-0.71 (0.05)	-0.78 (0.05)	-0.76 (0.05)	-0.53 (0.05)
Comparison versus celecoxib					
LS mean change from Baseline (95% CI)	-0.14 (-0.27, -0.00)	-0.18 (-0.31, -0.05)	-0.25 (-0.38, -0.12)	-0.23 (-0.36, -0.10)	
p-Value	0.043	0.007	<0.001	<0.001	
Week 8					
LS mean change from Baseline (SE)	-0.60 (0.05)	-0.63 (0.05)	-0.77 (0.05)	-0.78 (0.05)	-0.52 (0.05)
Comparison versus celecoxib					
LS mean change from Baseline (95% CI)	-0.08 (-0.21, 0.05)	-0.11 (-0.24, 0.02)	-0.24 (-0.38, -0.11)	-0.26 (-0.39, -0.12)	
p-Value	0.236	0.112	<0.001	<0.001	
Week 12					
LS mean change from Baseline (SE)	-0.69 (0.05)	-0.71 (0.05)	-0.75 (0.05)	-0.84 (0.05)	-0.56 (0.05)
Comparison versus celecoxib					
LS mean change from Baseline (95% CI)	-0.13 (-0.27, 0.00)	-0.15 (-0.28, -0.01)	-0.19 (-0.33, -0.05)	-0.28 (-0.42, -0.14)	
p-Value	0.055	0.038	0.007	<0.001	
Week 24					
LS mean change from Baseline (SE)	-0.54 (0.05)	-0.53 (0.05)	-0.63 (0.05)	-0.72 (0.05)	-0.55 (0.05)
Comparison versus celecoxib					
LS mean change from Baseline (95% CI)	0.01 (-0.13, 0.16)	0.03 (-0.12, 0.17)	-0.07 (-0.21, 0.07)	-0.16 (-0.31, -0.02)	
p-Value	0.838	0.717	0.309	0.023	

A change from Baseline <0 is an improvement.
ANCOVA model includes treatment, Baseline value, index joint (knee or hip) as covariates. LS means were estimated from the corresponding ANCOVA model.
p-Value is based on ANCOVA from pairwise comparisons.
ANCOVA = analysis of covariance, BID = twice daily, BOCF = baseline observation carried forward, CI=confidence interval, ITT = intent to treat,
LS mean = least squares means, N = number of subjects in each treatment group, OA = osteoarthritis, PGA = Patient Global Assessment, SE = standard error.

OMERACT-OARSI Treatment Response:

Table 17 and Table 18 summarize OMERACT-OARSI responses at Week 16 (ITT, BOCF imputation) in the naproxen cohort and in the celecoxib cohort, respectively.

In the naproxen cohort at Week 16, the tanezumab/naproxen combination treatments provided the greatest response rates (56.8% and 60.1% in the 5 mg and 10 mg treatment groups, respectively), followed by the tanezumab monotherapy treatment groups (52.3% and 53.0% in the 5 mg and 10 mg treatment groups, respectively) and then the naproxen alone treatment group (45.2%). The odds ratios for achieving an OMERACT-OARSI response were significantly greater with all tanezumab monotherapy and tanezumab/naproxen combination treatments compared with naproxen alone at Weeks 4 through 12 ($p \leq 0.012$) and with both tanezumab + naproxen combination treatments compared with naproxen alone at Weeks 4 through 24. In the celecoxib cohort at Week 16, the tanezumab/celecoxib combination treatments provided the greatest response rates (59.8% and 63.4% in the 5 mg and 10 mg treatment groups, respectively), followed by the tanezumab monotherapy treatments (55.1% and 55.9% in the 5 mg and 10 mg treatment groups, respectively) and then celecoxib alone treatment (47.3%). The odds ratios for achieving an OMERACT-OARSI response were significantly greater for the tanezumab monotherapy and tanezumab/celecoxib combination treatments compared with celecoxib alone treatment for Weeks 4 through 12 ($p \leq 0.022$).

Table 17. Summary of Analysis of OMERACT-OARSI Response Rates at Week 16 (ITT, BOCF) – Naproxen Cohort

	Tanezumab		Tanezumab + Naproxen		Naproxen
	5 mg N=285	10 mg N=288	5 mg N=280	10 mg N=288	500 mg BID N=283
Yes, n (%)	149 (52.3)	152 (53.0)	159 (56.8)	173 (60.1)	128 (45.2)
No, n (%)	136 (47.7)	135 (47.0)	121 (43.2)	115 (39.9)	155 (54.8)
Comparison vs naproxen					
Odds ratio (95% CI)	1.34 (0.96, 1.86)	1.38 (0.99, 1.92)	1.61 (1.15, 2.24)	1.82 (1.30, 2.53)	
p-Value	0.084	0.057	0.005	<0.001	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
Odds ratio (95% CI)			1.20 (0.86, 1.67)	1.32 (0.95, 1.84)	
p-Value			0.279	0.102	

Logistic regression model includes treatment as a main effect, and Baseline WOMAC Pain score and index joint (knee or hip) as covariates.
BID = twice daily, BOCF = baseline observation carried forward, CI = confidence interval, ITT = intent to treat, n = number of subjects with/without a response, N = number of subjects, OARSI = Osteoarthritis Research Society International, OMERACT = Outcome Measures in Rheumatology, TZB = tanezumab, vs = versus, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Table 18. Summary of Analysis of OMERACT-OARSI Response Rates at Week 16 (ITT, BOCF) – Celecoxib Cohort

	Tanezumab		Tanezumab + Celecoxib		Celecoxib
	5 mg N=256	10 mg N=254	5 mg N=256	10 mg N=254	100 mg BID N=256
Yes, n (%)	141 (55.1)	142 (55.9)	153 (59.8)	161 (63.4)	121 (47.3)
No, n (%)	115 (44.9)	112 (44.1)	103 (40.2)	93 (36.6)	135 (52.7)
Comparison vs celecoxib					
Odds ratio (95% CI)	1.35 (0.95, 1.91)	1.42 (1.00, 2.01)	1.66 (1.17, 2.36)	1.95 (1.37, 2.78)	
p-Value	0.092	0.049	0.005	<0.001	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
Odds ratio (95% CI)			1.23 (0.87, 1.75)	1.37 (0.96, 1.96)	
p-Value			0.246	0.082	

Logistic regression model includes treatment as a main effect, and Baseline WOMAC Pain score and index joint (knee or hip) as covariates.
BID = twice daily, BOCF = baseline observation carried forward, CI = confidence interval, ITT = intent to treat, n = number of subjects with/without a response, N = number of subjects, OMERACT = Outcome Measures in Rheumatology, OARSI = Osteoarthritis Research Society International, TZB = tanezumab, vs = versus, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

WOMAC Pain Subscale Reduction Treatment Response and Categorical Analysis:

In the naproxen cohort, tanezumab 5 mg and tanezumab 10 mg alone or in combination with naproxen resulted in significant improvement in the percentages of subjects achieving the WOMAC Pain subscale response levels (≥30%, ≥50%, ≥70%, and ≥90%) at Week 16 compared to naproxen alone (odds ratios 1.43 to 4.03, p ≤0.041; Table 19). In the celecoxib cohort, tanezumab 5 mg and tanezumab 10 mg alone or in combination with celecoxib demonstrated significant improvements in the WOMAC Pain subscale response levels (≥30%, ≥50%, ≥70%, and ≥90%) at Week 16 compared to celecoxib alone (odds ratios 1.44 to 5.10, p ≤0.044), with the exception of 90% reduction for the tanezumab 10 mg treatment group (odds ratio 2.23, p=0.086; Table 20).

Table 19. Categorical Analysis of the WOMAC Pain Subscale: Response Rates ≥30%, ≥50%, ≥70%, and ≥90% From Baseline at Week 16 (ITT, BOCF) – Naproxen Cohort

	Tanezumab		Tanezumab + Naproxen		Naproxen
	5 mg N=285	10 mg N=288	5 mg N=280	10 mg N=288	500 mg BID N=283
≥30% Reduction					
Yes, n (%)	127 (44.6)	135 (47.0)	139 (49.6)	154 (54.0)	102 (36.2)
No, n (%)	158 (55.4)	152 (53.0)	141 (50.4)	131 (46.0)	180 (63.8)
Comparison vs naproxen					
Odds ratio (95% CI)	1.43 (1.02, 2.00)	1.58 (1.13, 2.22)	1.76 (1.25, 2.47)	2.08 (1.49, 2.92)	
p-Value	0.040	0.007	0.001	<0.001	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
Odds ratio (95% CI)			1.23 (0.89, 1.72)	1.32 (0.95, 1.83)	
p-Value			0.213	0.102	
≥50% Reduction					
Yes, n (%)	78 (27.4)	94 (32.8)	96 (34.3)	104 (36.5)	56 (19.9)
No, n (%)	207 (72.6)	193 (67.2)	184 (65.7)	181 (63.5)	226 (80.1)
Comparison vs naproxen					
Odds ratio (95% CI)	1.53 (1.03, 2.26)	1.99 (1.35, 2.91)	2.13 (1.45, 3.13)	2.33 (1.59, 3.40)	
p-Value	0.034	<0.001	<0.001	<0.001	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
Odds ratio (95% CI)			1.39 (0.97, 2.00)	1.17 (0.83, 1.66)	
p-Value			0.070	0.365	
≥70% Reduction					
Yes, n (%)	43 (15.1)	50 (17.4)	42 (15.0)	71 (24.9)	22 (7.8)
No, n (%)	242 (84.9)	237 (82.6)	238 (85.0)	214 (75.1)	260 (92.2)
Comparison vs naproxen					
Odds ratio (95% CI)	2.15 (1.24, 3.70)	2.61 (1.53, 4.45)	2.18 (1.26, 3.77)	4.03 (2.41, 6.73)	
p-Value	0.006	<0.001	0.005	<0.001	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
Odds ratio (95% CI)			1.02 (0.64, 1.62)	1.55 (1.03, 2.33)	
p-Value			0.945	0.037	

Table 19. Categorical Analysis of the WOMAC Pain Subscale: Response Rates ≥30%, ≥50%, ≥70%, and ≥90% From Baseline at Week 16 (ITT, BOCF) – Naproxen Cohort

	Tanezumab		Tanezumab + Naproxen		Naproxen
	5 mg N=285	10 mg N=288	5 mg N=280	10 mg N=288	500 mg BID N=283
≥90% Reduction					
Yes, n (%)	17 (6.0)	18 (6.3)	19 (6.8)	24 (8.4)	7 (2.5)
No, n (%)	268 (94.0)	269 (93.7)	261 (93.2)	261 (91.6)	275 (97.5)
Comparison vs naproxen					
Odds ratio (95% CI)	2.55 (1.04, 6.26)	2.76 (1.13, 6.73)	3.01 (1.24, 7.30)	3.70 (1.56, 8.75)	
p-Value	0.041	0.026	0.015	0.003	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
Odds ratio (95% CI)			1.18 (0.60, 2.33)	1.34 (0.71, 2.53)	
p-Value			0.631	0.368	

Logistic regression model includes treatment as a main effect, Baseline WOMAC Pain score, index joint (knee or hip) as covariates.
Odds ratio and 95% CI estimated from logistic regression model.
p-Value is based on logistic regression model from pairwise comparisons versus naproxen.
BID = twice daily, BOCF = baseline observation carried forward, CI = confidence interval, ITT = intent to treat, N = number of subjects, n = number of subjects in category, TZB = tanezumab, vs = versus, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Table 20. Categorical Analysis of the WOMAC Pain Subscale: Response Rates ≥30%, ≥50%, ≥70%, and ≥90% From Baseline at Week 16 (ITT, BOCF) – Celecoxib Cohort

	Tanezumab		Tanezumab + Celecoxib		Celecoxib
	5 mg N=256	10 mg N=254	5 mg N=256	10 mg N=254	100 mg BID N=256
≥30% Reduction					
Yes, n (%)	122 (48.0)	124 (48.8)	135 (52.9)	138 (54.3)	100 (39.2)
No, n (%)	132 (52.0)	130 (51.2)	120 (47.1)	116 (45.7)	155 (60.8)
Comparison vs celecoxib					
Odds ratio (95% CI)	1.44 (1.01, 2.04)	1.48 (1.04, 2.11)	1.75 (1.23, 2.48)	1.84 (1.29, 2.62)	
p-Value	0.044	0.029	0.002	<0.001	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
Odds ratio (95% CI)			1.22 (0.86, 1.72)	1.24 (0.88, 1.76)	
p-Value			0.271	0.222	
≥50% Reduction					
Yes, n (%)	89 (35.0)	89 (35.0)	96 (37.6)	108 (42.5)	62 (24.3)
No, n (%)	165 (65.0)	165 (65.0)	159 (62.4)	146 (57.5)	193 (75.7)
Comparison vs celecoxib					
Odds ratio (95% CI)	1.68 (1.14, 2.47)	1.68 (1.14, 2.47)	1.88 (1.28, 2.76)	2.30 (1.57, 3.36)	
p-Value	0.008	0.008	0.001	<0.001	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
Odds ratio (95% CI)			1.12 (0.78, 1.61)	1.37 (0.96, 1.96)	
p-Value			0.545	0.087	
≥70% Reduction					
Yes, n (%)	51 (20.1)	46 (18.1)	56 (22.0)	63 (24.8)	25 (9.8)
No, n (%)	203 (79.9)	208 (81.9)	199 (78.0)	191 (75.2)	230 (90.2)
Comparison vs celecoxib					
Odds ratio (95% CI)	2.32 (1.39, 3.88)	2.04 (1.21, 3.44)	2.60 (1.56, 4.32)	3.04 (1.84, 5.02)	
p-Value	0.001	0.007	<0.001	<0.001	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
Odds ratio (95% CI)			1.12 (0.73, 1.72)	1.49 (0.97, 2.28)	
p-Value			0.604	0.068	

Table 20. Categorical Analysis of the WOMAC Pain Subscale: Response Rates ≥30%, ≥50%, ≥70%, and ≥90% From Baseline at Week 16 (ITT, BOCF) – Celecoxib Cohort

	Tanezumab		Tanezumab + Celecoxib		Celecoxib
	5 mg N=256	10 mg N=254	5 mg N=256	10 mg N=254	100 mg BID N=256
≥90% Reduction					
Yes, n (%)	19 (7.5)	15 (5.9)	20 (7.8)	32 (12.6)	7 (2.7)
No, n (%)	235 (92.5)	239 (94.1)	235 (92.2)	222 (87.4)	248 (97.3)
Comparison vs celecoxib					
Odds ratio (95% CI)	2.87 (1.18, 6.96)	2.23 (0.89, 5.56)	3.02 (1.25, 7.27)	5.10 (2.21, 11.78)	
p-Value	0.020	0.086	0.014	<0.001	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
Odds ratio (95% CI)			1.05 (0.55, 2.02)	2.29 (1.21, 4.34)	
p-Value			0.881	0.011	

Logistic regression model includes treatment as a main effect, Baseline WOMAC Pain score, index joint (knee or hip) as covariates.
Odds ratio and 95% CI estimated from logistic regression model.
p-Value is based on logistic regression model from pairwise comparisons versus celecoxib.
BID = twice daily, BOCF = baseline observation carried forward, CI = confidence interval, ITT = intent to treat, N=number of subjects, n = number of subjects in category, TZB=Tanezumab, vs = versus, WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

Table 21 and Table 22 summarize the cumulative (categorical) responder analysis of the WOMAC Pain subscale reductions from Baseline at Week 16 (ITT, BOCF imputation) in the naproxen cohort and celecoxib cohort, respectively. The percentage of subjects who experienced a treatment response in the WOMAC Pain subscale at Week 16 was greater with tanezumab monotherapy, tanezumab/naproxen combination treatment and tanezumab/celecoxib combination treatment than with naproxen or celecoxib alone treatment, for all classifications of response over the range of >0% to ≥90%.

Table 21. Summary of Cumulative Reduction in WOMAC Pain Subscale for Change From Baseline at Week 16 (ITT, BOCF) – Naproxen Cohort

Number (%) of Subjects	Tanezumab		Tanezumab + Naproxen		Naproxen
	5 mg N=285	10 mg N=287	5 mg N=280	10 mg N=285	500 mg BID N=282
>0%	198 (69.5)	201 (70.0)	199 (71.1)	203 (71.2)	172 (61.0)
≥10%	179 (62.8)	184 (64.1)	183 (65.4)	194 (68.1)	153 (54.3)
≥20%	148 (51.9)	162 (56.4)	158 (56.4)	174 (61.1)	130 (46.1)
≥30%	127 (44.6)	135 (47.0)	139 (49.6)	154 (54.0)	102 (36.2)
≥40%	103 (36.1)	117 (40.8)	118 (42.1)	132 (46.3)	81 (28.7)
≥50%	78 (27.4)	94 (32.8)	96 (34.3)	104 (36.5)	56 (19.9)
≥60%	53 (18.6)	75 (26.1)	61 (21.8)	82 (28.8)	39 (13.8)
≥70%	43 (15.1)	50 (17.4)	42 (15.0)	71 (24.9)	22 (7.8)
≥80%	29 (10.2)	29 (10.1)	31 (11.1)	45 (15.8)	14 (5.0)
≥90%	17 (6.0)	18 (6.3)	19 (6.8)	24 (8.4)	7 (2.5)
100%	4 (1.4)	11 (3.8)	12 (4.3)	10 (3.5)	3 (1.1)
Total	285	287	280	285	282

BID = twice daily, BOCF = baseline observation carried forward, ITT = intent to treat, N = total number of subjects, WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

Table 22. Summary of Cumulative Reduction in WOMAC Pain Subscale for Change From Baseline at Week 16 (ITT, BOCF) – Celecoxib Cohort

Number (%) of Subjects	Tanezumab		Tanezumab + Celecoxib		Celecoxib
	5 mg N=256	10 mg N=254	5 mg N=256	10 mg N=254	100 mg BID N=256
>0%	177 (69.7)	182 (71.7)	193 (75.7)	194 (76.4)	170 (66.7)
≥10%	162 (63.8)	167 (65.7)	176 (69.0)	184 (72.4)	150 (58.8)
≥20%	142 (55.9)	150 (59.1)	151 (59.2)	162 (63.8)	124 (48.6)
≥30%	122 (48.0)	124 (48.8)	135 (52.9)	138 (54.3)	100 (39.2)
≥40%	108 (42.5)	114 (44.9)	115 (45.1)	123 (48.4)	81 (31.8)
≥50%	89 (35.0)	89 (35.0)	96 (37.6)	108 (42.5)	62 (24.3)
≥60%	70 (27.6)	68 (26.8)	72 (28.2)	79 (31.1)	44 (17.3)
≥70%	51 (20.1)	46 (18.1)	56 (22.0)	63 (24.8)	25 (9.8)
≥80%	31 (12.2)	34 (13.4)	36 (14.1)	50 (19.7)	13 (5.1)
≥90%	19 (7.5)	15 (5.9)	20 (7.8)	32 (12.6)	7 (2.7)
100%	5 (2.0)	8 (3.1)	7 (2.7)	11 (4.3)	5 (2.0)
Total	254	254	255	254	255

BID = twice daily, BOCF = baseline observation carried forward, ITT = intent to treat, N = total number of subjects, WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

PGA of OA Treatment Response:

Table 23 and Table 24 summarize the percentages of subjects with a ≥2 grade improvement from Baseline (and defined as responders) in the PGA of OA at Week 16 (ITT, BOCF imputation) in the naproxen cohort and in the celecoxib cohort, respectively.

In the naproxen cohort at Week 16, the response rates (percentages of subjects with a ≥2 grade improvement from Baseline) with tanezumab 10 mg, tanezumab 5 mg + naproxen, and tanezumab 10 mg + naproxen were significantly higher than with naproxen alone. In the celecoxib cohort at Week 16, the percentages of subjects responding in any of the tanezumab treatment groups were not significantly different than the percentages of subjects responding in the celecoxib alone treatment group.

Table 23. Analysis of PGA of Osteoarthritis Response: ≥2 Grade Improvement From Baseline at Week 16 (ITT, BOCF) – Naproxen Cohort

	Tanezumab		Tanezumab + Naproxen	
	5 mg N=285	10 mg N=288	5 mg N=280	10 mg N=288
Subjects with data at Week 16	284	288	280	285
Subjects with response, n (%)[a]				
Yes	42 (14.8)	55 (19.1)	46 (16.4)	64 (22.5)
No	242 (85.2)	233 (80.9)	234 (83.6)	221 (77.5)
Versus naproxen				
Odds ratio	1.50	2.08	1.74	2.67
95% CI for odds ratio	(0.89, 2.55)	(1.25, 3.46)	(1.03, 2.94)	(1.62, 4.41)
p-Value	0.131	0.005	0.038	<0.001

Logistic regression model includes treatment, Baseline PGA score, index joint (knee or hip) as covariates.
Odds ratio and 95% CI estimated from logistic regression model.
p-Value based on logistic regression model from pairwise comparisons versus naproxen alone.
BOCF = baseline observation carried forward, CI = confidence interval, ITT = intent to treat, N = number of subjects, n = number of subjects meeting criterion, PGA = Patient Global Assessment.
a. Response for naproxen alone-treated subjects=30/283 (10.6%).

Table 24. Analysis of PGA of Osteoarthritis Response: ≥2 Grade Improvement From Baseline at Week 16 (ITT, BOCF) – Celecoxib Cohort

	Tanezumab		Tanezumab + Celecoxib	
	5 mg N=256	10 mg N=254	5 mg N=256	10 mg N=254
Subjects with data at Week 16	256	254	255	253
Subjects with response, n (%)[a]				
Yes	47 (18.4)	39 (15.4)	51 (20.0)	46 (18.2)
No	209 (81.6)	215 (84.6)	204 (80.0)	207 (81.8)
Versus celecoxib				
Odds ratio	1.35	0.99	1.47	1.40
95% CI for odds ratio	(0.81, 2.26)	(0.58, 1.69)	(0.88, 2.45)	(0.84, 2.35)
p-Value	0.255	0.974	0.141	0.200

Logistic regression model includes treatment, Baseline PGA score, index joint (knee or hip) as covariates.
Odds ratio and 95% CI estimated from logistic regression model.
p-Value based on logistic regression model from pairwise comparisons versus celecoxib alone.
BOCF = baseline observation carried forward, CI = confidence interval, ITT = intent to treat, N = number of subjects, n = number of subjects meeting criterion, PGA = Patient Global Assessment.
a. Response for celecoxib alone-treated subjects=34/254 (13.4%).

Other WOMAC Endpoints:

In the naproxen cohort, all tanezumab monotherapy and tanezumab/naproxen combination treatments significantly improved the 4 secondary WOMAC endpoints (WOMAC Stiffness subscale, WOMAC Average Score, WOMAC Pain Walking on a Flat Surface, and WOMAC Pain When Going Up or Down Stairs) at Week 16 (Table 25) compared to naproxen alone ($p \leq 0.048$). The tanezumab monotherapy and tanezumab/naproxen combination treatment groups had numerically greater improvement than naproxen alone in all 4 secondary WOMAC endpoints through Week 24. In the celecoxib cohort, all tanezumab monotherapy and tanezumab/celecoxib combination treatment groups significantly improved the 4 secondary WOMAC endpoints (WOMAC Stiffness subscale, WOMAC Average Score, WOMAC Pain Walking on a Flat Surface, and WOMAC Pain When Going Up or Down Stairs) at Week 16 (Table 26) compared to celecoxib alone ($p \leq 0.044$). The tanezumab monotherapy and tanezumab/celecoxib combination treatment groups resulted in numerically larger improvements than celecoxib alone in all 4 secondary WOMAC endpoints through Week 24.

Table 25. Summary of Other WOMAC Endpoints, Change From Baseline to Week 16 (ITT, BOCF) – Naproxen Cohort

	Tanezumab		Tanezumab + Naproxen		Naproxen
	5 mg N=285	10 mg N=288	5 mg N=280	10 mg N=288	500 mg BID N=283
WOMAC Stiffness Subscale[a] (0-10 NRS)					
Baseline Mean (SD)	6.50 (2.00)	6.66 (1.85)	6.70 (1.88)	6.42 (2.05)	6.60 (1.73)
LS mean change from Baseline (SE)	-2.04 (0.15)	-2.19 (0.15)	-2.34 (0.15)	-2.54 (0.15)	-1.49 (0.15)
Comparison vs naproxen					
LS mean change from Baseline (95% CI)	-0.56 (-0.94, -0.17)	-0.70 (-1.09, -0.31)	-0.85 (-1.24, -0.46)	-1.05 (-1.44, -0.66)	
p-Value	0.005	<0.001	<0.001	<0.001	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			-0.30 (-0.68, 0.09)	-0.35 (-0.74, 0.03)	
p-Value			0.135	0.074	
WOMAC average score[a] (0-10 NRS)					
Baseline mean (SD)	6.45 (1.62)	6.54 (1.53)	6.60 (1.58)	6.38 (1.63)	6.41 (1.51)
Change from Baseline LS mean (SE)	-1.92 (0.14)	-2.04 (0.13)	-2.22 (0.14)	-2.38 (0.13)	-1.43 (0.14)
Comparison vs naproxen					
LS mean change from Baseline (95% CI)	-0.50 (-0.85, -0.15)	-0.61 (-0.96, -0.26)	-0.79 (-1.14, -0.44)	-0.95 (-1.30, -0.60)	
p-Value	0.006	<0.001	<0.001	<0.001	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			-0.29 (-0.64, 0.06)	-0.34 (-0.69, 0.01)	
p-Value			0.101	0.058	
WOMAC pain when walking on a flat surface[a] (0-10 NRS)					
Baseline mean (SD)	6.22 (1.83)	6.37 (1.97)	6.34 (1.87)	6.13 (1.96)	6.12 (2.08)
LS mean change from Baseline (SE)	-1.82 (0.15)	-1.82 (0.15)	-2.02 (0.15)	-2.34 (0.15)	-1.39 (0.15)
Comparison vs naproxen					
LS mean change from Baseline (95% CI)	-0.44 (-0.82, -0.05)	-0.43 (-0.82, -0.05)	-0.63 (-1.02, -0.24)	-0.95 (-1.34, -0.57)	
p-Value	0.026	0.027	0.001	<0.001	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			-0.19 (-0.58, 0.19)	-0.52 (-0.90, -0.14)	
p-Value			0.327	0.008	

Table 25. Summary of Other WOMAC Endpoints, Change From Baseline to Week 16 (ITT, BOCF) – Naproxen Cohort

	Tanezumab		Tanezumab + Naproxen		Naproxen
	5 mg N=285	10 mg N=288	5 mg N=280	10 mg N=288	500 mg BID N=283
WOMAC pain when going up or down stairs[a] (0-10 NRS)					
Baseline mean (SD)	7.55 (1.80)	7.68 (1.78)	7.72 (1.69)	7.50 (1.73)	7.40 (1.87)
Change from Baseline LS mean (SE)	-2.08 (0.16)	-2.24 (0.16)	-2.37 (0.16)	-2.64 (0.16)	-1.68 (0.16)
Comparison vs naproxen					
LS mean change from Baseline (95% CI)	-0.41 (-0.81, -0.00)	-0.57 (-0.97, -0.16)	-0.70 (-1.10, -0.29)	-0.97 (-1.37, -0.57)	
p-Value	0.048	0.006	<0.001	<0.001	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)[a]			-0.29 (-0.69, 0.12)	-0.40 (-0.81, -0.00)	
p-Value			0.162	0.049	

ANCOVA model includes treatment, baseline value, index joint (knee or hip) as covariates. LS means were estimated from the corresponding ANCOVA model. p-Value is based on ANCOVA from pairwise comparisons.
ANCOVA = analysis of covariance, BID = twice daily, BOCF = baseline observation carried forward, CI = confidence interval, ITT = intent to treat, LS mean = least squares means, N = number of subjects, NRS = numeric rating scale, TZB = tanezumab, SD = standard deviation, SE = standard error, vs = versus, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
a. Score ranges from 0 to 10, where 0 is the best response. A change from Baseline <0 is an improvement.

Table 26. Summary of Other WOMAC Endpoints, Change From Baseline to Week 16 (ITT, BOCF) – Celecoxib Cohort

	Tanezumab		Tanezumab + Celecoxib		Celecoxib
	5 mg N=256	10 mg N=254	5 mg N=256	10 mg N=254	100 mg BID N=256
WOMAC stiffness subscale[a] (0-10 NRS)					
Baseline mean (SD)	6.62 (2.14)	6.58 (2.04)	6.47 (2.14)	6.33 (2.01)	6.39 (1.89)
LS mean change from Baseline (SE)	-2.05 (0.16)	-2.21 (0.16)	-2.33 (0.16)	-2.68 (0.16)	-1.36 (0.16)
Comparison vs celecoxib					
LS mean change from Baseline (95% CI)	-0.69 (-1.10, -0.28)	-0.85 (-1.26, -0.44)	-0.96 (-1.38, -0.55)	-1.31 (-1.73, -0.90)	
p-Value	0.001	<0.001	<0.001	<0.001	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			-0.27 (-0.68, 0.14)	-0.46 (-0.88, 0.05)	
p-Value			0.197	0.028	
WOMAC average score[a] (0-10 NRS)					
Baseline mean (SD)	6.60 (1.58)	6.54 (1.54)	6.48 (1.70)	6.33 (1.59)	6.38 (1.55)
Change from Baseline LS mean (SE)	-2.06 (0.15)	-2.11 (0.15)	-2.26 (0.15)	-2.50 (0.15)	-1.42 (0.15)
Comparison vs celecoxib					
LS mean change from Baseline (95% CI)	-0.64 (-1.02, -0.25)	-0.69 (-1.08, -0.31)	-0.84 (-1.23, -0.46)	-1.08 (-1.47, -0.69)	
p-Value	0.001	<0.001	<0.001	<0.001	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			-0.21 (-0.60, 0.18)	-0.39 (-0.77, 0.00)	
p-Value			0.291	0.051	
WOMAC pain when walking on a flat surface[a] (0-10 NRS)					
Baseline mean (SD)	6.28 (1.83)	6.30 (1.88)	6.21 (1.97)	6.14 (1.97)	6.10 (1.83)
LS mean change from Baseline (SE)	-1.85 (0.16)	-1.81 (0.16)	-2.02 (0.16)	-2.20 (0.16)	-1.38 (0.16)
Comparison vs celecoxib					
LS mean change from Baseline (95% CI)	-0.47 (-0.90, -0.05)	-0.43 (-0.86, -0.01)	-0.64 (-1.06, -0.22)	-0.83 (-1.25, -0.40)	
p-Value	0.029	0.044	0.003	<0.001	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			-0.17 (-0.59, 0.25)	-0.39 (-0.81, 0.03)	
p-Value			0.431	0.071	

Table 26. Summary of Other WOMAC Endpoints, Change From Baseline to Week 16 (ITT, BOCF) – Celecoxib Cohort

	Tanezumab		Tanezumab + Celecoxib		Celecoxib
	5 mg N=256	10 mg N=254	5 mg N=256	10 mg N=254	100 mg BID N=256
WOMAC pain when going up or down stairs[a] (0-10 NRS)					
Baseline mean (SD)	7.80 (1.71)	7.59 (1.77)	7.55 (1.77)	7.54 (1.78)	7.52 (1.70)
Change from Baseline LS mean (SE)	-2.27 (0.17)	-2.32 (0.17)	-2.50 (0.17)	-2.74 (0.17)	-1.66 (0.17)
Comparison vs celecoxib					
LS mean change from Baseline (95% CI)	-0.62 (-1.06, -0.18)	-0.66 (-1.10, -0.22)	-0.84 (-1.28, -0.40)	-1.09 (-1.53, -0.65)	
p-Value	0.006	0.003	<0.001	<0.001	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			-0.23 (-0.67, 0.21)	-0.43 (-0.87, 0.01)	
p-Value			0.313	0.056	

ANCOVA model includes treatment, Baseline value, index joint (knee or hip) as covariates. LS means were estimated from the corresponding ANCOVA model. p-Value is based on ANCOVA from pairwise comparisons.

ANCOVA = analysis of covariance, BID = twice daily, BOCF = baseline observation carried forward, CI = confidence interval, ITT = intent to treat, LS mean = least squares means, N = number of subjects, NRS = numeric rating scale, SD = standard deviation, SE = standard error, TZB = tanezumab, vs = versus, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

a. Score ranges from 0 to 10, where 0 is the best response. A change from Baseline <0 is an improvement.

Medical Outcomes Study Short-Form 36 Health Survey (SF-36v2):

Table 27 and Table 28 summarize the changes from Baseline at Week 24 with the SF-36 dimensions of Physical Function, Role Physical, Bodily Pain, Vitality, and Physical Component Summary using BOCF imputation in the naproxen cohort and in the celecoxib cohort, respectively (ITT).

In the naproxen cohort at Week 24, treatment with tanezumab 5 mg resulted in significant improvements in the Physical Function and Vitality dimensions of the SF-36 compared to naproxen alone. Treatment with tanezumab 5 mg + naproxen or tanezumab 10 mg + naproxen resulted in significant improvements in the dimensions of Physical Function, Vitality, and the Physical Component Summary compared to naproxen alone at Week 24. Treatment with tanezumab 10 mg + naproxen resulted in significant improvements in the Bodily Pain dimension compared to naproxen alone at Week 24. In the celecoxib cohort at Week 24, treatment with tanezumab 5 mg + celecoxib or tanezumab 10 mg + celecoxib resulted in significant improvements in the Physical Function and Bodily Pain dimensions of the SF-36 compared to celecoxib alone, and treatment with tanezumab 10 mg + celecoxib resulted in significant improvement in the Physical Component Summary compared to celecoxib alone.

Table 27. Summary and Analyses of Change From Baseline in SF-36 Dimensions at Week 24 (ITT, BOCF) – Naproxen Cohort

SF-36 Dimension	Tanezumab		Tanezumab + Naproxen		Naproxen
	5 mg N=285	10 mg N=288	5 mg N=280	10 mg N=288	500 mg BID N=283
Physical function					
Baseline mean (SD)	32.82 (19.12)	32.74 (21.34)	34.79 (20.63)	33.88 (18.66)	35.46 (19.94)
LS mean change from Baseline (SE)	10.09 (1.32)	9.04 (1.31)	10.20 (1.32)	12.30 (1.31)	6.39 (1.32)
Comparison vs naproxen					
LS mean change from Baseline (95% CI)	3.70 (0.28, 7.12)	2.65 (-0.75, 6.06)	3.81 (0.38, 7.24)	5.91 (2.50, 9.32)	
p-Value	0.034	0.127	0.029	<0.001	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			0.11 (-3.31, 3.53)	3.26 (-0.13, 6.64)	
p-Value			0.950	0.059	
Role physical					
Baseline mean (SD)	43.29 (25.54)	43.88 (23.81)	44.58 (23.90)	44.69 (23.60)	46.09 (24.57)
LS mean change from Baseline (SE)	9.01 (1.43)	7.29 (1.42)	9.74 (1.44)	11.75 (1.43)	8.10 (1.44)
Comparison vs naproxen					
LS mean change from Baseline (95% CI)	0.91 (-2.81, 4.64)	-0.81 (-4.51, 2.90)	1.65 (-2.09, 5.38)	3.66 (-0.06, 7.37)	
p-Value	0.630	0.669	0.387	0.054	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			0.73 (-2.99, 4.45)	4.46 (0.77, 8.15)	
p-Value			0.700	0.018	
Bodily pain					
Baseline mean (SD)	36.91 (17.91)	35.90 (17.87)	37.80 (17.49)	37.67 (17.89)	35.72 (16.34)
LS mean change from Baseline (SE)	11.09 (1.28)	9.56 (1.27)	11.15 (1.28)	13.73 (1.27)	8.73 (1.29)
Comparison vs naproxen					
LS mean change from Baseline (95% CI)	2.37 (-0.95, 5.68)	0.83 (-2.47, 4.14)	2.42 (-0.90, 5.75)	5.00 (1.69, 8.31)	
p-Value	0.161	0.621	0.153	0.003	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			0.06 (-3.26, 3.37)	4.17 (0.88, 7.46)	
p-Value			0.974	0.013	

Table 27. Summary and Analyses of Change From Baseline in SF-36 Dimensions at Week 24 (ITT, BOCF) – Naproxen Cohort

SF-36 Dimension	Tanezumab		Tanezumab + Naproxen		Naproxen
	5 mg N=285	10 mg N=288	5 mg N=280	10 mg N=288	500 mg BID N=283
Vitality					
Baseline mean (SD)	51.58 (19.45)	51.28 (20.10)	53.73 (19.83)	52.57 (19.76)	50.78 (18.94)
LS mean change from Baseline (SE)	6.17 (0.97)	4.06 (0.96)	4.72 (0.97)	5.08 (0.97)	1.86 (0.97)
Comparison vs naproxen					
LS mean change from Baseline (95% CI)	4.31 (1.80, 6.82)	2.19 (-0.31, 4.70)	2.85 (0.33, 5.38)	3.22 (0.71, 5.72)	
p-Value	<0.001	0.085	0.027	0.012	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			-1.46 (-3.97, 1.05)	1.02 (-1.47, 3.51)	
p-Value			0.255	0.422	
Physical component summary					
Baseline mean (SD)	-1.80 (0.76)	-1.80 (0.75)	-1.72 (0.75)	-1.75 (0.76)	-1.74 (0.77)
LS mean change from Baseline (SE)	0.42 (0.05)	0.39 (0.05)	0.47 (0.05)	0.56 (0.05)	0.31 (0.05)
Comparison vs naproxen					
LS mean change from Baseline (95% CI)	0.10 (-0.02, 0.23)	0.07 (-0.05, 0.20)	0.15 (0.03, 0.28)	0.24 (0.12, 0.37)	
p-Value	0.107	0.252	0.017	<0.001	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			0.05 (-0.08, 0.18)	0.17 (0.04, 0.29)	
p-Value			0.436	0.009	

A change from Baseline >0 is an improvement.
ANCOVA model includes treatment, Baseline value, index joint (knee or hip) as covariates. LS means were estimated from the corresponding ANCOVA model.
p-Value is based on ANCOVA from pairwise comparisons.
ANCOVA = analysis of covariance, BID = twice daily, BOCF = baseline observation carried forward, CI = confidence interval, ITT = intent to treat, LS mean = least squares means, N = number of subjects, SD = standard deviation, SE = standard error, SF-36 = Medical Outcomes Study Short Form 36, TZB =Tanezumab, vs = versus.

Table 28. Summary and Analyses of Change From Baseline in SF-36 Dimensions at Week 24 (ITT, BOCF) – Celecoxib Cohort

SF-36 Dimension	Tanezumab		Tanezumab + Celecoxib		Celecoxib
	5 mg N=256	10 mg N=254	5 mg N=256	10 mg N=254	100 mg BID N=256
Physical function					
Baseline mean (SD)	33.43 (20.62)	34.79 (19.21)	33.41 (22.07)	35.11 (20.48)	32.81 (19.57)
LS mean change from Baseline (SE)	9.93 (1.37)	9.37 (1.37)	11.34 (1.37)	12.16 (1.38)	7.29 (1.37)
Comparison vs celecoxib					
LS mean change from Baseline (95% CI)	2.63 (-0.90, 6.17)	2.08 (-1.45, 5.61)	4.05 (0.52, 7.57)	4.87 (1.33, 8.41)	
p-Value	0.143	0.248	0.025	0.007	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			1.41 (-2.12, 4.94)	2.79 (-0.74, 6.32)	
p-Value			0.433	0.122	
Role physical					
Baseline mean (SD)	42.59 (23.69)	42.86 (23.46)	42.65 (24.90)	45.60 (22.57)	43.55 (22.70)
LS mean change from Baseline (SE)	9.23 (1.46)	9.57 (1.46)	9.93 (1.47)	10.83 (1.47)	7.12 (1.46)
Comparison vs celecoxib					
LS mean change from Baseline (95% CI)	2.10 (-1.67, 5.87)	2.45 (-1.33, 6.22)	2.81 (-0.96, 6.57)	3.71 (-0.07, 7.48)	
p-Value	0.275	0.204	0.144	0.054	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			0.70 (-3.07, 4.47)	1.26 (-2.52, 5.04)	
p-Value			0.714	0.513	
Bodily pain					
Baseline mean (SD)	34.14 (16.39)	35.57 (18.00)	34.11 (16.66)	36.47 (16.93)	36.96 (17.60)
LS mean change from Baseline (SE)	9.52 (1.37)	9.70 (1.37)	12.82 (1.37)	13.36 (1.38)	8.84 (1.37)
Comparison vs celecoxib					
LS mean change from Baseline (95% CI)	0.68 (-2.85, 4.22)	0.86 (-2.67, 4.39)	3.98 (0.45, 7.51)	4.52 (0.99, 8.05)	
p-Value	0.704	0.632	0.027	0.012	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			3.30 (-0.23, 6.82)	3.66 (0.12, 7.19)	
p-Value			0.067	0.043	

Table 28. Summary and Analyses of Change From Baseline in SF-36 Dimensions at Week 24 (ITT, BOCF) – Celecoxib Cohort

SF-36 Dimension	Tanezumab		Tanezumab + Celecoxib		Celecoxib
	5 mg N=256	10 mg N=254	5 mg N=256	10 mg N=254	100 mg BID N=256
Vitality					
Baseline mean (SD)	50.52 (18.21)	51.52 (21.07)	51.45 (19.16)	53.63 (18.42)	51.52 (17.90)
LS mean change from Baseline (SE)	5.18 (1.08)	3.82 (1.08)	2.63 (1.08)	4.69 (1.08)	2.69 (1.07)
Comparison vs celecoxib					
LS mean change from Baseline (95% CI)	2.50 (-0.27, 5.26)	1.13 (-1.64, 3.90)	-0.05 (-2.82, 2.71)	2.00 (-0.77, 4.77)	
p-Value	0.077	0.423	0.970	0.157	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			-2.55 (-5.32, 0.22)	0.87 (-1.91, 3.65)	
p-Value			0.071	0.539	
Physical component summary					
Baseline mean (SD)	-1.82 (0.74)	-1.77 (0.72)	-1.78 (0.77)	-1.71 (0.70)	-1.77 (0.71)
LS mean change from Baseline (SE)	0.41 (0.05)	0.43 (0.05)	0.50 (0.05)	0.55 (0.05)	0.38 (0.05)
Comparison vs celecoxib					
LS mean change from Baseline (95% CI)	0.03 (-0.10, 0.17)	0.05 (-0.09, 0.18)	0.12 (-0.01, 0.25)	0.17 (0.04, 0.30)	
p-Value	0.636	0.483	0.075	0.012	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			0.09 (-0.04, 0.22)	0.12 (-0.01, 0.26)	
p-Value			0.190	0.069	

A change from Baseline >0 is an improvement.
ANCOVA model includes treatment, Baseline value, index joint (knee or hip) as covariates. LS means were estimated from the corresponding ANCOVA model.
p-Value is based on ANCOVA from pairwise comparisons.
ANCOVA = analysis of covariance, BID = twice daily, BOCF = baseline observation carried forward, CI = confidence interval, ITT = intent to treat, LS mean = least squares means, N = number of subjects, SD = standard deviation, SE = standard error, SF-36 = Medical Outcomes Study Short Form 36, TZB = tanezumab, vs = versus.

Discontinuation due to Lack of Efficacy: In the naproxen cohort, significantly more subjects treated with naproxen alone discontinued due to lack of efficacy compared to subjects who received tanezumab monotherapy or tanezumab/naproxen combination treatment ($p \leq 0.023$; Table 29). In the celecoxib cohort, significantly more subjects treated with celecoxib alone discontinued due to lack of efficacy compared to subjects who received tanezumab monotherapy or tanezumab/celecoxib combination treatment ($p \leq 0.022$; Table 30).

Table 29. Analysis of Subjects Who Discontinued From the Study due to Lack of Efficacy (ITT) – Naproxen Cohort

	Tanezumab		Tanezumab + Naproxen		Naproxen
	5 mg N=285	10 mg N=288	5 mg N=280	10 mg N=288	500 mg BID N=283
Discontinued due to lack of efficacy, n (%)					
Yes	23 (8.1)	23 (8.0)	22 (7.9)	15 (5.2)	40 (14.1)
No	262 (91.9)	265 (92.0)	258 (92.1)	273 (94.8)	243 (85.9)
Comparison versus naproxen					
Odds ratio	0.53	0.53	0.52	0.33	
95% CI for odds ratio	(0.31, 0.92)	(0.31, 0.91)	(0.30, 0.90)	(0.18, 0.62)	
p-Value	0.023	0.021	0.019	<0.001	

Logistic regression model includes treatment as a main effect. Odds ratio and 95% CI estimated from logistic regression model.
p-Value is based on logistic regression model from pairwise comparisons.
BID = twice daily, CI = confidence interval, ITT = intent to treat, N = number of subjects, n = number of subjects meeting criterion.

Table 30. Analysis of Subjects Who Discontinued From the Study due to Lack of Efficacy (ITT) – Celecoxib Cohort

	Tanezumab		Tanezumab + Celecoxib		Celecoxib
	5 mg N=256	10 mg N=254	5 mg N=256	10 mg N=254	100 mg BID N=256
Discontinued due to lack of efficacy					
Yes, n (%)	19 (7.4)	21 (8.3)	15 (5.9)	18 (7.1)	38 (14.8)
No, n (%)	237 (92.6)	233 (91.7)	241 (94.1)	236 (92.9)	218 (85.2)
Comparison versus celecoxib					
Odds ratio	0.46	0.52	0.36	0.44	
95% CI for odds ratio	(0.26, 0.82)	(0.29, 0.91)	(0.19, 0.67)	(0.24, 0.79)	
p-Value	0.009	0.022	0.001	0.006	

Logistic regression model includes treatment as a main effect. Odds ratio and 95% CI estimated from logistic regression model.
p-Value is based on logistic regression model from pairwise comparisons.
BID = twice daily, CI = confidence interval, ITT = intent to treat, N = number of subjects, n = number of subjects meeting criterion.

Based on the time to event analysis, subjects receiving tanezumab monotherapy or tanezumab/naproxen combination treatment discontinued due to lack of efficacy after a longer period of time in treatment compared to subjects treated with naproxen alone ($p \leq 0.021$; Table 31). In the celecoxib cohort, the time to discontinuation due to lack of efficacy was statistically significantly longer for subjects receiving tanezumab monotherapy

or tanezumab/celecoxib combination treatment than for subjects treated with celecoxib alone ($p \leq 0.037$; Table 32).

Table 31. Summary of Analysis of Time to Discontinuation due to Lack of Efficacy (ITT) – Naproxen Cohort

	Tanezumab		Tanezumab + Naproxen		Naproxen
	5 mg N=285	10 mg N=288	5 mg N=280	10 mg N=288	500 mg BID N=283
Number of subjects withdrawn	23	23	22	15	40
Number of subjects censored	262	265	258	273	243
Discontinuation time (days)					
Min, max	(15, 337)	(34, 348)	(20, 418)	(14, 281)	(6, 337)
Time to percentiles (days)					
1st	27	76	61	23	36
5th	170	169	168	224	91
10th	N/A	342	418	N/A	170
Comparison to naproxen					
p-Value	0.021	0.011	0.013	0.001	

Analysis was of time to discontinuation due to lack of efficacy. Censored observations included subjects completed study and discontinuation for other reasons.
p-Value based on Wilcoxon Test.
BID=twice daily, ITT = intent to treat, Max = maximum, Min = minimum, N = number of subjects in each treatment group, N/A = not applicable.

Table 32. Summary of Analysis of Time to Discontinuation due to Lack of Efficacy (ITT) – Celecoxib Cohort

	Tanezumab		Tanezumab + Celecoxib		Celecoxib
	5 mg N=256	10 mg N=254	5 mg N=256	10 mg N=254	500 mg BID N=256
Number of subjects withdrawn	19	21	15	18	38
Number of subjects censored	237	233	241	236	218
Discontinuation time (days)					
Min, max	(15, 344)	(15, 332)	(16, 345)	(22, 337)	(16, 334)
Time to percentiles (days)					
1st	28	29	27	79	36
5th	177	148	283	225	88
10th	N/A	N/A	N/A	N/A	149
Comparison to naproxen					
p-Value	0.006	0.037	<0.001	0.004	

Analysis was of time to discontinuation due to lack of efficacy. Censored observations included subjects completed study and discontinuation for other reasons.
p-Value based on Wilcoxon Test.
BID=twice daily, ITT = intent to treat, Max = maximum, Min = minimum, N = number of subjects in each treatment group, N/A = not applicable.

Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP):

Table 33 and Table 34 summarize changes from Baseline in the 4 components of the WPAI:SHP at Week 24 (ITT, BOCF) in the naproxen cohort and in the celecoxib cohort, respectively.

In the naproxen cohort at Week 24, tanezumab monotherapy and tanezumab/naproxen combination treatment resulted in improvement from Baseline in all 4 scales of the WPAI:SHP; treatment with tanezumab 10 mg + naproxen provided significantly greater improvement in the Activity Impairment scale compared to naproxen alone. In the celecoxib cohort at Week 24, treatment with tanezumab monotherapy or tanezumab/celecoxib combination therapy significantly improved the Activity Impairment scale compared to celecoxib alone with the exception of tanezumab 5 mg monotherapy, for which the improvement was not statistically significant. At Week 24 treatment with tanezumab 5 mg significantly improved the Impairment While Working and Overall Work Impairment scales compared to celecoxib alone.

Table 33. Summary and Analyses of Change From Baseline in WPAI:SHP Components at Week 24 (ITT, BOCF) – Naproxen Cohort

WPAI:SHP Component	Tanezumab		Tanezumab + Naproxen		Naproxen
	5 mg N=285	10 mg N=288	5 mg N=280	10 mg N=288	500 mg BID N=283
Work time missed (percentage)					
Baseline mean (SD)	5.74 (14.23)	4.94 (12.83)	4.12 (11.39)	5.51 (14.60)	2.95 (9.97)
LS mean change from Baseline (SE)	-0.89 (1.11)	-0.30 (1.10)	-0.06 (1.13)	-0.79 (1.00)	0.03 (1.04)
Comparison vs naproxen					
LS mean change from Baseline (95% CI)	-0.92 (-3.72, 1.89)	-0.33 (-3.11, 2.46)	-0.09 (-2.90, 2.73)	-0.82 (-3.49, 1.86)	
p-Value	0.521	0.818	0.952	0.549	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			0.83 (-2.06, 3.73)	-0.49 (-3.24, 2.26)	
p-Value			0.573	0.726	
Impairment while working (percentage)					
Baseline mean (SD)	54.60 (26.11)	53.27 (25.69)	49.49 (27.86)	52.00 (24.89)	50.80 (27.16)
Change from Baseline LS mean (SE)	-12.12 (2.58)	-12.43 (2.57)	-7.83 (2.64)	-14.00 (2.32)	-8.93 (2.42)
Comparison vs naproxen					
LS mean change from Baseline (95% CI)	-3.19 (-9.69, 3.32)	-3.50 (-9.98, 2.98)	1.10 (-5.44, 7.64)	-5.07 (-11.28, 1.13)	
p-Value	0.336	0.289	0.742	0.109	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			4.28 (-2.45, 11.02)	-1.57 (-7.97, 4.83)	
p-Value			0.212	0.629	
Overall work impairment (percentage)					
Baseline mean (SD)	17.26 (33.25)	14.69 (30.52)	12.23 (28.04)	13.94 (29.98)	8.81 (26.17)
LS mean change from Baseline (SE)	-5.01 (2.50)	-2.28 (2.48)	-2.83 (2.55)	-2.23 (2.25)	1.32 (2.34)
Comparison vs naproxen					
LS mean change from Baseline (95% CI)	-3.69 (-9.99, 2.61)	-0.96 (-7.22, 5.29)	-1.51 (-7.83, 4.81)	-0.91 (-6.91, 5.09)	
p-Value	0.250	0.762	0.640	0.766	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			2.19 (-4.32, 8.69)	0.05 (-6.11, 6.22)	
p-Value			0.509	0.987	

Table 33. Summary and Analyses of Change From Baseline in WPAI:SHP Components at Week 24 (ITT, BOCF) – Naproxen Cohort

WPAI:SHP Component	Tanezumab		Tanezumab + Naproxen		Naproxen
	5 mg N=285	10 mg N=288	5 mg N=280	10 mg N=288	500 mg BID N=283
Activity impairment (percentage)					
Baseline mean (SD)	62.65 (23.13)	64.98 (21.68)	64.41 (22.14)	62.96 (21.77)	61.54 (22.64)
Change from Baseline LS mean (SE)	-13.15 (1.55)	-15.33 (1.54)	-13.62 (1.56)	-15.68 (1.54)	-11.34 (1.55)
Comparison vs naproxen					
LS mean change from Baseline (95% CI)	-1.81 (-5.82, 2.20)	-3.99 (-8.00, 0.01)	-2.28 (-6.32, 1.75)	-4.34 (-8.35, -0.33)	
p-Value	0.377	0.051	0.267	0.034	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			-0.47 (-4.49, 3.55)	-0.35 (-4.34, 3.63)	
p-Value			0.817	0.862	

ANCOVA model includes treatment, Baseline value, index joint (knee or hip) as covariates. LS means were estimated from the corresponding ANCOVA model.
p-Value is based on ANCOVA from pairwise comparisons.
Change from Baseline <0 is an improvement.
ANCOVA = analysis of covariance, BID = twice daily, BOCF = baseline observation carried forward, CI = confidence interval, ITT = intent to treat, LS mean = least squares means, N = number of subjects, SD = standard deviation, SE = standard error, TZB = tanezumab, vs = versus, WPAI:SHP = Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.

Table 34. Summary and Analyses of Change From Baseline in WPAI:SHP Components at Week 24 (ITT, BOCF) – Celecoxib Cohort

WPAI:SHP Component	Tanezumab		Tanezumab + Celecoxib		Celecoxib
	5 mg N=256	10 mg N=254	5 mg N=256	10 mg N=254	100 mg BID N=256
Work time missed (percentage)					
Baseline mean (SD)	6.32 (14.35)	4.61 (12.70)	2.72 (8.59)	3.78 (12.52)	6.82 (15.45)
LS mean change from Baseline (SE)	-2.07 (1.15)	-0.29 (1.15)	0.91 (1.07)	-1.83 (1.11)	0.33 (1.04)
Comparison vs celecoxib					
LS mean change from Baseline (95% CI)	-2.40 (-5.24, 0.45)	-0.62 (-3.46, 2.23)	0.58 (-2.14, 3.30)	-2.16 (-4.94, 0.62)	
p-Value	0.098	0.670	0.675	0.127	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			2.98 (0.14, 5.82)	-1.54 (-4.42, 1.33)	
p-Value			0.040	0.292	
Impairment while working (percentage)					
Baseline mean (SD)	51.64 (23.75)	50.82 (28.37)	50.56 (26.81)	49.13 (24.14)	47.21 (27.85)
Change from Baseline LS mean (SE)	-17.13 (2.76)	-12.61 (2.76)	-9.01 (2.53)	-9.79 (2.64)	-6.62 (2.51)
Comparison vs celecoxib					
LS mean change from Baseline (95% CI)	-10.51 (-17.31, -3.71)	-5.99 (-12.78, 0.81)	-2.39 (-8.84, 4.06)	-3.17 (-9.79, 3.46)	
p-Value	0.003	0.084	0.467	0.348	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			8.12 (1.40, 14.85)	2.82 (-4.07, 9.72)	
p-Value			0.018	0.421	
Overall work impairment (percentage)					
Baseline mean (SD)	17.76 (31.83)	13.14 (29.56)	9.28 (24.44)	10.29 (25.84)	18.18 (32.17)
LS mean change from Baseline (SE)	-8.89 (2.57)	-1.20 (2.57)	-1.57 (2.38)	-6.62 (2.47)	-0.68 (2.32)
Comparison vs celecoxib					
LS mean change from Baseline (95% CI)	-8.21 (-14.54, -1.88)	-0.52 (-6.84, 5.80)	-0.90 (-6.96, 5.16)	-5.95 (-12.14, 0.24)	
p-Value	0.011	0.872	0.771	0.060	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			7.31 (1.00, 13.63)	-5.43 (-11.83, 0.98)	
p-Value			0.023	0.096	

Table 34. Summary and Analyses of Change From Baseline in WPAI:SHP Components at Week 24 (ITT, BOCF) – Celecoxib Cohort

WPAI:SHP Component	Tanezumab		Tanezumab + Celecoxib		Celecoxib
	5 mg N=256	10 mg N=254	5 mg N=256	10 mg N=254	100 mg BID N=256
Activity impairment (percentage)					
Baseline mean (SD)	66.73 (20.33)	65.48 (22.49)	64.63 (22.30)	61.61 (22.50)	62.92 (22.36)
Change from Baseline LS mean (SE)	-15.95 (1.62)	-17.08 (1.63)	-17.64 (1.62)	-18.20 (1.64)	-12.23 (1.62)
Comparison vs celecoxib					
LS mean change from Baseline (95% CI)	-3.72 (-7.90, 0.47)	-4.85 (-9.05, -0.65)	-5.40 (-9.58, -1.23)	-5.97 (-10.17, -1.76)	
p-Value	0.082	0.024	0.011	0.005	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean change from Baseline (95% CI)			-1.69 (-5.86, 2.48)	-1.12 (-5.34, 3.10)	
p-Value			0.427	0.604	

ANCOVA model includes treatment, Baseline value, index joint (knee or hip) as covariates. LS means were estimated from the corresponding ANCOVA model. p-Value is based on ANCOVA from pairwise comparisons.
Change from Baseline <0 is an improvement.
ANCOVA = analysis of covariance, BID = twice daily, BOCF = baseline observation carried forward, CI = confidence interval, ITT = intent to treat, LS mean = least squares means, N = number of subjects, SD = standard deviation, SE = standard error, TZB = tanezumab, vs = versus, WPAI:SHP = Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.

Rescue Medication:

Table 35 and Table 36 summarizes the incidence of subjects taking rescue medication (acetaminophen) and the mean amounts (mg) of rescue medication taken per week during Weeks 13-16 in the naproxen cohort and in the celecoxib cohort, respectively.

Overall rates of rescue medication use during the study were fairly stable in all treatment groups. In the naproxen cohort, the incidence of rescue medication use was generally lower in subjects who received tanezumab monotherapy or tanezumab/naproxen combination treatment compared to those treated with naproxen alone, including all time points from Weeks 5-8 through Weeks 49-56. Significantly fewer subjects receiving tanezumab 5 mg + naproxen (p=0.012) or tanezumab 10 mg + naproxen (p=0.003) treatment took rescue medication during Weeks 13-16 than subjects who received naproxen alone. In the celecoxib cohort, rates of rescue medication use were generally lower in subjects receiving tanezumab monotherapy or tanezumab/celecoxib combination treatment compared with those treated with celecoxib alone, with the exception subjects receiving tanezumab 5 mg monotherapy. Significantly fewer subjects receiving tanezumab 10 mg (p=0.030), tanezumab 5 mg + celecoxib (p=0.035), or tanezumab 10 mg + celecoxib (p=0.008) took rescue medication during Weeks 13-16 than subjects treated with celecoxib alone.

Table 35. Summary of Analysis of Rescue Medication Taken During Weeks 13-16 (Through Clinical Hold, ITT, LOCF) – Naproxen Cohort

	Tanezumab		Tanezumab + Naproxen		Naproxen
	5 mg N=285	10 mg N=288	5 mg N=280	10 mg N=288	500 mg BID N=283
Number of Subjects Taking Rescue Medication[a]					
Yes, n (%)	186 (65.3)	180 (62.5)	168 (60.0)	166 (57.8)	195 (69.4)
No, n (%)	99 (34.7)	108 (37.5)	112 (40.0)	121 (42.2)	86 (30.6)
Comparison vs naproxen					
Odds ratio (95% CI)[b]	0.82 (0.57, 1.17)	0.72 (0.51, 1.02)	0.64 (0.45, 0.91)	0.59 (0.42, 0.84)	
p-Value[c]	0.272	0.067	0.012	0.003	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
Odds ratio (95% CI) [b]			1.08 (0.55, 1.10)	1.29 (0.59, 1.16)	
p-Value[c]			0.672	0.153	
Amount (mg) Total per Week of Rescue Medication Taken					
LS mean (SE)[d]	2704.25 (475.01)	2453.18 (434.85)	2298.75 (409.31)	2480.02 (432.24)	2713.63 (478.70)
Comparison vs naproxen					
LS mean ratio (95% CI) [d]	1.00 (0.63,1.57)	0.90 (0.57,1.43)	0.85 (0.54,1.34)	0.91 (0.58,1.44)	
p-Value[e]	0.988	0.666	0.478	0.699	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean ratio (95% CI) [d]			1.07 (0.68, 1.68)	1.01 (0.64, 1.60)	
p-Value[e]			0.780	0.963	

For any period which overlapped 23 Jun 2010 and any periods beginning on or after 23 Jun 2010, rescue medication use was excluded from analyses.
This table summarizes rescue medications which began from day of first IV dose up to 23 Jun 2010.
Results shown as estimated amount of rescue medication used per week, and ratio of estimated amount of rescue medication for comparisons.
BID = twice daily, CI = confidence interval, ITT = intent to treat, IV = intravenous, LOCF = last observation carried forward, LS mean = least squares means, N = number of subjects, n = number of subjects in category, SE = standard error, TZB = tanezumab, vs = versus, WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

a. Logistic regression model includes treatment as a main effect, Baseline WOMAC Pain score and index joint as a covariate.
b. Odds ratio and 95% CI estimated from logistic regression model.
c. p-Value is based on logistic regression model from pairwise comparisons.
d. Negative binomial regression model with model terms for treatment as a main effect, Baseline WOMAC Pain score and Index joint as a covariate.
e. p-Value is based on pairwise comparisons.

Table 36. Summary of Analysis of Rescue Medication Taken During Weeks 13-16 (Through Clinical Hold, ITT, LOCF) – Celecoxib Cohort

	Tanezumab		Tanezumab + Celecoxib		Celecoxib
	5 mg N=256	10 mg N=254	5 mg N=256	10 mg N=254	100 mg BID N=256
Number of Subjects Taking Rescue Medication					
Yes, n (%)	172 (67.5)	157 (62.3)	160 (62.5)	151 (59.7)	181 (70.7)
No, n (%)	83 (32.5)	95 (37.7)	96 (37.5)	102 (40.3)	75 (29.3)
Comparison vs celecoxib					
Odds ratio (95% CI)[a]	0.83 (0.57, 1.22)	0.66 (0.45, 0.96)	0.67 (0.46, 0.97)	0.61 (0.42, 0.88)	
p-Value[b]	0.345	0.030	0.035	0.008	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
Odds ratio (95% CI)[a]			1.11 (0.56, 1.16)	1.24 (0.64, 1.31)	
p-Value[b]			0.579	0.245	
Amount (mg) Total per Week of Rescue Medication Taken					
LS mean (SE)[c]	2626.59 (472.43)	3218.01 (581.96)	2359.96 (420.78)	2671.40 (490.19)	3556.02 (637.34)
Comparison vs celecoxib					
LS mean ratio (95% CI) [d]	0.74 (0.46, 1.17)	0.90 (0.57, 1.44)	0.66 (0.42, 1.05)	0.75 (0.47, 1.19)	
p-Value[e]	0.200	0.673	0.082	0.226	
Comparison vs tanezumab			**vs TZB 5 mg**	**vs TZB 10 mg**	
LS mean ratio (95% CI) [d]			1.36 (0.86, 2.17)	0.83 (0.52, 1.32)	
p-Value[e]			0.190	0.432	

For any period which overlapped 23 Jun 2010 and any periods beginning on or after 23 Jun 2010, rescue medication use was excluded from analyses.
This table summarizes rescue medications which began from day of first IV dose up to 23 Jun 2010.
Results shown as estimated amount of rescue medication used per week, and ratio of estimated amount of rescue medication for comparisons.
BID = twice daily, CI = confidence interval, ITT = intent to treat, IV = intravenous, LOCF = last observation carried forward, LS mean = least squares means, N = number of subjects, n = number of subjects in category, SE = standard error, TZB = tanezumab, vs = versus, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

a. Logistic regression model includes treatment as a main effect, Baseline WOMAC Pain score and index joint as a covariate.
b. Odds ratio and 95% CI estimated from logistic regression model.
c. p-Value is based on logistic regression model from pairwise comparisons.
d. Negative binomial regression model with model terms for treatment as a main effect, Baseline WOMAC Pain score and Index joint as a covariate.
e. p-Value is based on pairwise comparisons.

Pharmacokinetic Results:

The increase in trough concentrations from 5 mg to 10 mg was approximately dose-proportional. There were also no obvious differences noted in the median exposures for tanezumab combined with naproxen or celecoxib.

Safety Results:

Adverse Events:

The incidence of the most frequently reported (all causalities) treatment-emergent AEs (AEs reported by ≥2% of subjects in any treatment group) for the study overall is shown in Table 37. The 6 most frequently reported AEs (arthralgia, paresthesia, peripheral edema, OA, hypoesthesia, and pain in extremity) were all experienced by ≥2% more subjects in 1 or more of the tanezumab monotherapy or tanezumab/NSAID combination treatment groups compared to the NSAID alone treatment group. Among the AEs reported in ≥5% of subjects in at least 1 treatment group, in general the incidence rates were higher for the tanezumab/naproxen combination treatment groups than the tanezumab monotherapy or NSAID alone treatment groups, and higher among subjects treated with tanezumab 10 mg (alone or in combination with NSAID) than among subjects treated with tanezumab 5 mg (alone or in combination with NSAID). Among infection-related AEs reported in ≥5% of subjects in at least 1 treatment group (urinary tract infection, upper respiratory tract infection, and nasopharyngitis), the incidence rates among subjects in the tanezumab monotherapy and tanezumab/naproxen combination treatment groups were comparable or lower than the incidence rates in the NSAID alone treatment group. Upper respiratory tract infection, hypertension, and sinusitis occurred in a greater percentage of subjects in the NSAID alone treatment group than in any of the tanezumab monotherapy or tanezumab/NSAID combination treatment groups.

Table 37. Incidence of Most Frequent (≥2% of Subjects in Any Treatment Group) Adverse Events (All Causalities, ITT)

Number (%) of Subjects MedDRA Preferred Term	Tanezumab		Tanezumab + NSAID		NSAIDs
	5 mg N=541	10 mg N=542	5 mg N=536	10 mg N=542	N=539
Subjects with adverse events	405 (74.9)	399 (73.6)	390 (72.8)	400 (73.8)	364 (67.5)
Arthralgia	72 (13.3)	89 (16.4)	73 (13.6)	61 (11.3)	48 (8.9)
Paresthesia	33 (6.1)	39 (7.2)	48 (9.0)	60 (11.1)	17 (3.2)
Edema peripheral	33 (6.1)	27 (5.0)	38 (7.1)	50 (9.2)	12 (2.2)
Osteoarthritis	31 (5.7)	37 (6.8)	45 (8.4)	37 (6.8)	28 (5.2)
Hypoesthesia	25 (4.6)	31 (5.7)	35 (6.5)	35 (6.5)	14 (2.6)
Pain in extremity	19 (3.5)	36 (6.6)	21 (3.9)	30 (5.5)	18 (3.3)
Fall	18 (3.3)	20 (3.7)	25 (4.7)	25 (4.6)	16 (3.0)
Urinary tract infection	31 (5.7)	27 (5.0)	25 (4.7)	24 (4.4)	30 (5.6)
Upper respiratory tract infection	22 (4.1)	19 (3.5)	22 (4.1)	24 (4.4)	30 (5.6)
Back pain	31 (5.7)	22 (4.1)	21 (3.9)	24 (4.4)	20 (3.7)
Nasopharyngitis	22 (4.1)	19 (3.5)	30 (5.6)	21 (3.9)	23 (4.3)
Joint swelling	22 (4.1)	27 (5.0)	18 (3.4)	17 (3.1)	7 (1.3)
Headache	30 (5.5)	31 (5.7)	22 (4.1)	16 (3.0)	21 (3.9)
Diarrhea	15 (2.8)	11 (2.0)	19 (3.5)	16 (3.0)	12 (2.2)
Musculoskeletal pain	16 (3.0)	17 (3.1)	20 (3.7)	15 (2.8)	17 (3.2)
Myalgia	12 (2.2)	15 (2.8)	10 (1.9)	15 (2.8)	2 (0.4)
Hypertension	13 (2.4)	16 (3.0)	19 (3.5)	13 (2.4)	22 (4.1)
Joint effusion	9 (1.7)	11 (2.0)	12 (2.2)	13 (2.4)	2 (0.4)
Blood creatine phosphokinase increased	13 (2.4)	15 (2.8)	18 (3.4)	12 (2.2)	14 (2.6)
Muscle spasms	14 (2.6)	8 (1.5)	16 (3.0)	12 (2.2)	10 (1.9)
Rash	7 (1.3)	9 (1.7)	13 (2.4)	12 (2.2)	7 (1.3)
Cough	14 (2.6)	13 (2.4)	12 (2.2)	12 (2.2)	11 (2.0)
Joint injury	9 (1.7)	5 (0.9)	6 (1.1)	12 (2.2)	4 (0.7)
Rotator cuff syndrome	6 (1.1)	7 (1.3)	6 (1.1)	12 (2.2)	1 (0.2)
Dizziness	17 (3.1)	14 (2.6)	16 (3.0)	11 (2.0)	12 (2.2)
Carpal tunnel syndrome	9 (1.7)	23 (4.2)	11 (2.1)	11 (2.0)	4 (0.7)
Bronchitis	15 (2.8)	12 (2.2)	11 (2.1)	11 (2.0)	10 (1.9)
Abdominal pain upper	3 (0.6)	3 (0.6)	7 (1.3)	11 (2.0)	6 (1.1)
Burning sensation	7 (1.3)	5 (0.9)	7 (1.3)	11 (2.0)	4 (0.7)
Sinusitis	14 (2.6)	12 (2.2)	11 (2.1)	10 (1.8)	21 (3.9)
Influenza	16 (3.0)	16 (3.0)	10 (1.9)	10 (1.8)	16 (3.0)
Synovial cyst	7 (1.3)	11 (2.0)	6 (1.1)	7 (1.3)	2 (0.4)
Nausea	15 (2.8)	3 (0.6)	12 (2.2)	6 (1.1)	12 (2.2)
Fatigue	4 (0.7)	5 (0.9)	11 (2.1)	6 (1.1)	3 (0.6)

MedDRA (version 13.1) coding dictionary applied.
Subjects are only counted once for each row.
Adverse events sorted in decreasing frequency by tanezumab 10 mg + NSAID treatment group and then tanezumab 5 mg + NSAID treatment group.
ITT=intent to treat, MedDRA=Medical Dictionary for Regulatory Activities, N=number of subjects, NSAID=nonsteroidal anti-inflammatory drug.

Table 38 provides a summary of treatment-related AEs reported in ≥2% of subjects in any treatment group; paresthesia and hypoesthesia were the most frequent treatment-related AEs. For all of these most frequent AEs except OA, pain in extremity, and headache, the incidences in the tanezumab monotherapy and tanezumab/NSAID combination treatment groups were greater than the incidence in the NSAID alone treatment group. The incidence

rates of treatment-related AEs overall were low (all events reported in ≤7.9% subjects in all 5 treatment groups). Among the most frequent treatment-related AEs, the incidence rates of individual events were generally higher for subjects in the tanezumab/NSAID combination treatment groups than for subjects in the tanezumab monotherapy or NSAID alone treatment groups.

Table 38. Incidence of Most Frequent (≥2% of Subjects in Any Treatment Group) Treatment-Related Adverse Events (ITT)

Number (%) of Subjects MedDRA Preferred Term	Tanezumab		Tanezumab + NSAID		NSAIDs
	5 mg N=541	10 mg N=542	5 mg N=536	10 mg N=542	N=539
Paresthesia	24 (4.4)	27 (5.0)	35 (6.5)	43 (7.9)	11 (2.0)
Hypoesthesia	15 (2.8)	15 (2.8)	24 (4.5)	22 (4.1)	8 (1.5)
Edema peripheral	11 (2.0)	7 (1.3)	19 (3.5)	22 (4.1)	4 (0.7)
Osteoarthritis	11 (2.0)	7 (1.3)	16 (3.0)	14 (2.6)	8 (1.5)
Pain in extremity	6 (1.1)	15 (2.8)	6 (1.1)	14 (2.6)	6 (1.1)
Headache	7 (1.3)	16 (3.0)	10 (1.9)	12 (2.2)	9 (1.7)
Arthralgia	17 (3.1)	23 (4.2)	19 (3.5)	11 (2.0)	8 (1.5)
Carpal tunnel syndrome	3 (0.6)	11 (2.0)	2 (0.4)	3 (0.6)	1 (0.2)

Subjects are only counted once for each row.
MedDRA (version 13.1) coding dictionary applied.
Adverse events sorted in decreasing frequency by tanezumab 10 mg + NSAID treatment group.
ITT = intent to treat, MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects, NSAID = nonsteroidal anti-inflammatory drug.

SAEs:

Table 39 summarizes the SAEs (all causalities). Among all SAEs (all causalities), only OA was reported at a frequency ≥2% in any treatment group. The incidence rates of SAEs overall were low (all events reported in ≤3.3% subjects in all 5 treatment groups). Among the most frequent SAEs, the incidence rates of individual events were generally higher for subjects in the tanezumab/NSAID combination treatment groups than for subjects in the tanezumab monotherapy or NSAID alone treatment groups.

Table 39. Summary of Serious Adverse Events by Decreasing Frequency (All Causalities) - Overall

Number (%) of Subjects	Tanezumab		Tanezumab + NSAID		NSAIDs
MedDRA Preferred Term	**5 mg N=541**	**10 mg N=542**	**5 mg N=536**	**10 mg N=542**	**N=539**
Osteoarthritis	7 (1.3)	11 (2.0)	16 (3.0)	18 (3.3)	8 (1.5)
Osteonecrosis	6 (1.1)	4 (0.7)	10 (1.9)	7 (1.3)	4 (0.7)
Arthralgia	2 (0.4)	1 (0.2)	4 (0.7)	4 (0.7)	6 (1.1)
Tibia fracture	0	1 (0.2)	0	3 (0.6)	0
Arthritis	0	0	0	2 (0.4)	1 (0.2)
Chest pain	1 (0.2)	1 (0.2)	2 (0.4)	2 (0.4)	3 (0.6)
Femur fracture	0	0	0	2 (0.4)	0
Intervertebral disc protrusion	0	1 (0.2)	0	2 (0.4)	1 (0.2)
Abdominal pain	0	0	0	1 (0.2)	0
Acute left ventricular failure	0	0	0	1 (0.2)	0
Adenocarcinoma	0	0	0	1 (0.2)	0
Aortic stenosis	0	0	0	1 (0.2)	0
Asthma	0	0	0	1 (0.2)	0
Atrial fibrillation	3 (0.6)	0	2 (0.4)	1 (0.2)	0
Bone disorder	0	0	0	1 (0.2)	0
Bronchitis chronic	0	0	0	1 (0.2)	0
Cardiac failure congestive	0	0	0	1 (0.2)	0
Cardio-respiratory arrest	0	0	0	1 (0.2)	0
Cellulitis	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Cerebrovascular accident	1 (0.2)	1 (0.2)	0	1 (0.2)	1 (0.2)
Cervical myelopathy	0	0	0	1 (0.2)	0
Colitis	0	0	0	1 (0.2)	0
Coronary artery disease	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Diarrhoea	0	0	0	1 (0.2)	0
Diverticulitis	0	0	0	1 (0.2)	0
Dyspnoea	1 (0.2)	0	0	1 (0.2)	0
Endometrial cancer	1 (0.2)	0	0	1 (0.2)	0
Foot fracture	0	0	0	1 (0.2)	0
Gallbladder pain	0	0	0	1 (0.2)	1 (0.2)
Gastritis	0	0	0	1 (0.2)	1 (0.2)
Hepatic neoplasm malignant	0	0	0	1 (0.2)	0
Hiatus hernia	0	0	0	1 (0.2)	0
Intracranial aneurysm	0	0	0	1 (0.2)	0
Knee deformity	0	0	0	1 (0.2)	0
Left ventricular hypertrophy	0	0	0	1 (0.2)	0
Ligament rupture	0	0	0	1 (0.2)	0
Lower limb fracture	0	0	0	1 (0.2)	0
Lumbar vertebral fracture	0	0	0	1 (0.2)	0
Lung carcinoma cell type unspecified stage IV	0	0	0	1 (0.2)	0
Muscular weakness	0	0	0	1 (0.2)	0
Oedema peripheral	0	0	0	1 (0.2)	0
Paraesthesia	0	0	0	1 (0.2)	0
Peptic ulcer perforation	0	0	0	1 (0.2)	0
Pericardial effusion	0	0	0	1 (0.2)	0
Pulmonary embolism	2 (0.4)	0	1 (0.2)	1 (0.2)	0
Pulmonary oedema	0	0	0	1 (0.2)	0
Rash	0	0	0	1 (0.2)	0
Rotator cuff syndrome	1 (0.2)	1 (0.2)	2 (0.4)	1 (0.2)	0

Table 39. Summary of Serious Adverse Events by Decreasing Frequency (All Causalities) - Overall

Number (%) of Subjects	Tanezumab		Tanezumab + NSAID		NSAIDs
MedDRA Preferred Term	5 mg N=541	10 mg N=542	5 mg N=536	10 mg N=542	N=539
Skeletal injury	0	0	0	1 (0.2)	0
Spinal column stenosis	0	0	1 (0.2)	1 (0.2)	0
Subcutaneous abscess	0	0	0	1 (0.2)	0
Subdural haematoma	0	0	0	1 (0.2)	0
Synovitis	0	0	0	1 (0.2)	0
Transient ischaemic attack	0	0	0	1 (0.2)	0
Upper respiratory tract infection	0	0	0	1 (0.2)	0
Vomiting	0	0	0	1 (0.2)	0
Anaemia	0	1 (0.2)	2 (0.4)	0	0
Ankle fracture	1 (0.2)	0	1 (0.2)	0	0
Aphasia	0	0	1 (0.2)	0	0
Appendicitis	1 (0.2)	0	0	0	0
Arteriosclerosis coronary artery	1 (0.2)	0	0	0	0
Arthritis bacterial	0	1 (0.2)	0	0	0
Arthritis infective	0	0	0	0	1 (0.2)
Atelectasis	0	0	0	0	1 (0.2)
Atrial flutter	0	0	1 (0.2)	0	0
Atrioventricular block	0	1 (0.2)	0	0	0
Back pain	0	1 (0.2)	1 (0.2)	0	0
Bile duct obstruction	0	0	0	0	1 (0.2)
Blood pressure increased	0	1 (0.2)	0	0	0
Bradycardia	0	0	0	0	1 (0.2)
Breast cancer	0	1 (0.2)	0	0	1 (0.2)
Bronchitis	0	1 (0.2)	1 (0.2)	0	0
Bursitis infective	0	0	0	0	1 (0.2)
Calculus ureteric	0	1 (0.2)	0	0	0
Cardiac tamponade	0	1 (0.2)	0	0	0
Central nervous system lymphoma	0	0	1 (0.2)	0	0
Cerebral ischaemia	0	1 (0.2)	0	0	0
Cervicobrachial syndrome	0	0	1 (0.2)	0	0
Chemical peritonitis	0	0	0	0	1 (0.2)
Cholecystitis	0	0	0	0	1 (0.2)
Cholecystitis acute	0	0	1 (0.2)	0	0
Cholelithiasis	0	0	0	0	2 (0.4)
Colon cancer	1 (0.2)	0	0	0	0
Contusion	0	1 (0.2)	1 (0.2)	0	0
Convulsion	0	0	1 (0.2)	0	0
Deep vein thrombosis	1 (0.2)	0	1 (0.2)	0	0
Dehydration	1 (0.2)	0	0	0	0
Depression	0	0	1 (0.2)	0	0
Dizziness	2 (0.4)	0	0	0	0
Duodenal ulcer	1 (0.2)	0	0	0	0
Dysphagia	0	1 (0.2)	0	0	0
Ear pain	1 (0.2)	0	0	0	0
Enteritis	1 (0.2)	0	0	0	0
Extradural haematoma	0	1 (0.2)	0	0	0
Fall	0	2 (0.4)	1 (0.2)	0	1 (0.2)
Food poisoning	0	0	0	0	1 (0.2)
Fracture	0	0	1 (0.2)	0	0

Table 39. Summary of Serious Adverse Events by Decreasing Frequency (All Causalities) - Overall

Number (%) of Subjects	Tanezumab		Tanezumab + NSAID		NSAIDs
MedDRA Preferred Term	5 mg N=541	10 mg N=542	5 mg N=536	10 mg N=542	N=539
Fractured sacrum	0	1 (0.2)	0	0	0
Gangrene	1 (0.2)	0	0	0	1 (0.2)
Gastric cancer	0	0	2 (0.4)	0	0
Gastric ulcer	0	0	0	0	1 (0.2)
Headache	1 (0.2)	0	0	0	0
Hip fracture	0	0	0	0	1 (0.2)
Humerus fracture	1 (0.2)	0	0	0	0
Hyperhidrosis	1 (0.2)	0	0	0	0
Hypertension	2 (0.4)	0	0	0	0
Incisional hernia	1 (0.2)	0	0	0	0
Influenza	0	0	0	0	1 (0.2)
Intervertebral disc degeneration	0	0	1 (0.2)	0	0
Intervertebral disc disorder	1 (0.2)	1 (0.2)	0	0	0
Intestinal perforation	0	0	1 (0.2)	0	0
Ischaemic stroke	0	0	1 (0.2)	0	0
Joint dislocation	1 (0.2)	0	2 (0.4)	0	0
Joint injury	1 (0.2)	0	1 (0.2)	0	1 (0.2)
Localised infection	0	0	0	0	1 (0.2)
Lumbar spinal stenosis	0	1 (0.2)	0	0	0
Lung adenocarcinoma	0	0	1 (0.2)	0	0
Metastases to lung	1 (0.2)	0	0	0	0
Metastases to spine	1 (0.2)	0	0	0	0
Multiple fractures	1 (0.2)	0	0	0	0
Muscle rupture	0	1 (0.2)	0	0	0
Myocardial ischaemia	0	0	0	0	1 (0.2)
Nausea	1 (0.2)	0	0	0	0
Nerve root compression	0	1 (0.2)	0	0	0
Osteomyelitis	0	1 (0.2)	0	0	0
Ovarian cancer	1 (0.2)	0	0	0	0
Oxygen saturation decreased	1 (0.2)	0	0	0	0
Pain in extremity	0	1 (0.2)	0	0	0
Pancreatic carcinoma	1 (0.2)	0	0	0	0
Paralysis	0	0	1 (0.2)	0	0
Pelvic fracture	1 (0.2)	0	0	0	0
Peripheral ischaemia	0	0	0	0	1 (0.2)
Pituitary tumour benign	0	0	0	0	1 (0.2)
Pneumonia	0	1 (0.2)	1 (0.2)	0	1 (0.2)
Pneumonia pneumococcal	0	1 (0.2)	0	0	0
Pneumonitis	1 (0.2)	0	0	0	0
Pneumothorax	1 (0.2)	0	0	0	0
Prostate cancer	0	1 (0.2)	0	0	1 (0.2)
Radiculopathy	0	1 (0.2)	0	0	0
Renal cancer	0	0	0	0	1 (0.2)
Renal cancer stage II	0	1 (0.2)	0	0	0
Renal failure acute	0	0	0	0	1 (0.2)
Retinal detachment	1 (0.2)	0	0	0	0
Right ventricular failure	1 (0.2)	0	0	0	0
Road traffic accident	0	1 (0.2)	0	0	0
Sepsis	1 (0.2)	1 (0.2)	0	0	1 (0.2)

Table 39. Summary of Serious Adverse Events by Decreasing Frequency (All Causalities) - Overall

Number (%) of Subjects	Tanezumab		Tanezumab + NSAID		NSAIDs
MedDRA Preferred Term	5 mg N=541	10 mg N=542	5 mg N=536	10 mg N=542	N=539
Septic shock	0	0	0	0	1 (0.2)
Spinal fracture	0	2 (0.4)	0	0	0
Spinal osteoarthritis	0	1 (0.2)	0	0	0
Spondylolisthesis	0	1 (0.2)	0	0	0
Staphylococcal infection	1 (0.2)	0	0	0	0
Stress fracture	0	0	1 (0.2)	0	0
Synovial cyst	1 (0.2)	2 (0.4)	0	0	1 (0.2)
Synovial rupture	1 (0.2)	0	0	0	0
Tendon rupture	0	1 (0.2)	2 (0.4)	0	1 (0.2)
Thrombocytopenia	0	0	0	0	1 (0.2)
Thyroid neoplasm	0	0	1 (0.2)	0	0
Upper gastrointestinal haemorrhage	0	0	2 (0.4)	0	0
Urinary tract infection	1 (0.2)	0	0	0	1 (0.2)
Uterine cancer	0	0	0	0	1 (0.2)
Uterine leiomyoma	0	1 (0.2)	0	0	0
VIIth nerve paralysis	0	0	0	0	1 (0.2)
Ventricular tachycardia	0	0	1 (0.2)	0	0
Viral infection	0	1 (0.2)	0	0	0
Wound sepsis	0	1 (0.2)	0	0	0

MedDRA (version 13.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities, N = total number of subjects, NSAID = nonsteroidal anti-inflammatory drug.

Discontinuations due to AEs:

AEs leading to discontinuation in the study occurred most frequently in the musculoskeletal and connective tissue disorders and nervous system disorders system organ classes (SOCs) (Table 40). Muscle spasms resulted in discontinuation in a greater percentage of subjects in the NSAID alone treatment group than in any of the tanezumab monotherapy or tanezumab/NSAID combination treatment groups (the incidence rate of discontinuation due to muscle spasms was ≤0.4% in all 5 treatment groups). The incidence rates of AEs resulting in discontinuation overall were low (all events reported in ≤3.4% subjects in all 5 treatment groups). Among the most frequent AEs resulting in discontinuation, the incidence rates of individual events were generally higher for subjects in the tanezumab/NSAID combination treatment groups than for subjects in the tanezumab monotherapy or NSAID alone treatment groups, and generally higher for subjects receiving tanezumab 10 mg (alone or in combination with NSAID) than for subjects receiving tanezumab 5 mg (alone or in combination with NSAID).

Table 40. Incidence of Treatment-Emergent Adverse Events Leading to Discontinuation (All Causalities) - Overall

Number (%) of Subjects	Tanezumab		Tanezumab + NSAID		NSAIDs
System Organ Class MedDRA Preferred Term	5 mg n (%)	10 mg n (%)	5 mg n (%)	10 mg n (%)	n (%)
Evaluable for adverse events	541	542	536	542	539
With adverse events	405 (74.9)	399 (73.6)	390 (72.8)	400 (73.8)	364 (67.5)
Discontinued due to adverse events	65 (12.0)	86 (15.9)	77 (14.4)	99 (18.3)	49 (9.1)
Blood and lymphatic system disorders	0	0	1 (0.2)	0	0
Anaemia	0	0	1 (0.2)	0	0
Cardiac disorders	3 (0.6)	5 (0.9)	3 (0.6)	4 (0.7)	1 (0.2)
Arteriosclerosis coronary artery	1 (0.2)	0	0	0	0
Atrial fibrillation	2 (0.4)	0	2 (0.4)	1 (0.2)	0
Atrial flutter	0	0	1 (0.2)	0	0
Atrioventricular block	0	1 (0.2)	0	0	0
Bundle branch block right	0	1 (0.2)	0	1 (0.2)	0
Coronary artery disease	0	1 (0.2)	0	1 (0.2)	0
Palpitations	0	0	0	1 (0.2)	1 (0.2)
Supraventricular tachycardia	0	1 (0.2)	0	0	0
Ventricular extrasystoles	0	1 (0.2)	0	0	0
Endocrine disorders	0	0	1 (0.2)	0	0
Hypothyroidism	0	0	1 (0.2)	0	0
Gastrointestinal disorders	2 (0.4)	2 (0.4)	3 (0.6)	3 (0.6)	3 (0.6)
Abdominal pain	0	1 (0.2)	0	0	0
Gastric ulcer	0	1 (0.2)	0	0	1 (0.2)
Gastritis	0	0	1 (0.2)	1 (0.2)	1 (0.2)
Glossodynia	0	0	0	0	1 (0.2)
Intestinal perforation	0	0	1 (0.2)	0	0
Pancreatic disorder	1 (0.2)	0	0	0	0
Peptic ulcer perforation	0	0	0	1 (0.2)	0
Rectal haemorrhage	0	0	0	1 (0.2)	0
Upper gastrointestinal haemorrhage	0	0	1 (0.2)	0	0
Vomiting	1 (0.2)	0	0	0	0
General disorders and administration site conditions	1 (0.2)	5 (0.9)	4 (0.7)	3 (0.6)	2 (0.4)
Chest discomfort	0	0	1 (0.2)	0	0
Chest pain	0	0	0	1 (0.2)	0
Fatigue	0	2 (0.4)	0	0	0
Feeling of body temperature change	0	0	0	0	1 (0.2)
Oedema peripheral	1 (0.2)	3 (0.6)	3 (0.6)	2 (0.4)	1 (0.2)
Hepatobiliary disorders	0	0	1 (0.2)	0	0
Hepatomegaly	0	0	1 (0.2)	0	0
Immune system disorders	0	1 (0.2)	1 (0.2)	0	0
Hypersensitivity	0	1 (0.2)	1 (0.2)	0	0
Infections and infestations	2 (0.4)	4 (0.7)	0	1 (0.2)	1 (0.2)
Appendicitis	1 (0.2)	0	0	0	0
Arthritis bacterial	0	1 (0.2)	0	0	0
Cellulitis	0	1 (0.2)	0	0	0
Gastroenteritis	0	0	0	1 (0.2)	0
H1N1 influenza	0	1 (0.2)	0	0	0
Influenza	1 (0.2)	0	0	0	0
Pneumonia pneumococcal	0	1 (0.2)	0	0	0
Sepsis	0	0	0	0	1 (0.2)

Table 40. Incidence of Treatment-Emergent Adverse Events Leading to Discontinuation (All Causalities) - Overall

Number (%) of Subjects	Tanezumab		Tanezumab + NSAID		NSAIDs
System Organ Class MedDRA Preferred Term	5 mg n (%)	10 mg n (%)	5 mg n (%)	10 mg n (%)	n (%)
Injury, poisoning and procedural complications	3 (0.6)	5 (0.9)	4 (0.7)	7 (1.3)	1 (0.2)
Ankle fracture	0	0	1 (0.2)	0	0
Fall	0	1 (0.2)	1 (0.2)	0	0
Femur fracture	0	0	1 (0.2)	1 (0.2)	0
Hip fracture	0	0	0	0	1 (0.2)
Humerus fracture	1 (0.2)	0	0	0	0
Ligament rupture	0	0	0	1 (0.2)	0
Lower limb fracture	0	0	0	1 (0.2)	0
Meniscus lesion	1 (0.2)	3 (0.6)	0	0	0
Radius fracture	0	0	0	1 (0.2)	0
Skeletal injury	0	0	0	1 (0.2)	0
Stress fracture	0	0	1 (0.2)	0	0
Subdural haematoma	0	0	0	1 (0.2)	0
Tendon rupture	1 (0.2)	0	0	0	0
Tibia fracture	0	1 (0.2)	0	1 (0.2)	0
Investigations	1 (0.2)	0	0	3 (0.6)	3 (0.6)
Bleeding time prolonged	0	0	0	1 (0.2)	0
Blood creatinine increased	1 (0.2)	0	0	1 (0.2)	0
Blood pressure increased	0	0	0	1 (0.2)	0
Electrocardiogram change	0	0	0	0	1 (0.2)
Gamma-glutamyltransferase increased	0	0	0	0	1 (0.2)
Laboratory test abnormal	0	0	0	0	1 (0.2)
Metabolism and nutrition disorders	0	1 (0.2)	0	1 (0.2)	0
Decreased appetite	0	1 (0.2)	0	0	0
Type 2 diabetes mellitus	0	0	0	1 (0.2)	0
Musculoskeletal and connective tissue disorders	24 (4.4)	34 (6.3)	33 (6.2)	48 (8.9)	25 (4.6)
Arthralgia	10 (1.8)	6 (1.1)	7 (1.3)	16 (3.0)	7 (1.3)
Arthritis	0	3 (0.6)	0	0	1 (0.2)
Back pain	0	3 (0.6)	0	0	1 (0.2)
Bone disorder	0	0	0	1 (0.2)	0
Bursitis	0	0	0	1 (0.2)	0
Exostosis	1 (0.2)	0	0	0	0
Intervertebral disc disorder	1 (0.2)	0	0	0	0
Intervertebral disc protrusion	0	1 (0.2)	0	1 (0.2)	1 (0.2)
Joint effusion	0	0	0	2 (0.4)	0
Joint swelling	1 (0.2)	4 (0.7)	1 (0.2)	0	0
Medial tibial stress syndrome	0	0	0	1 (0.2)	0
Muscle spasms	0	0	1 (0.2)	1 (0.2)	2 (0.4)
Muscular weakness	0	0	1 (0.2)	0	0
Musculoskeletal pain	0	0	1 (0.2)	0	0
Myalgia	0	0	0	3 (0.6)	0
Osteoarthritis	8 (1.5)	13 (2.4)	18 (3.4)	9 (1.7)	9 (1.7)
Osteonecrosis	2 (0.4)	3 (0.6)	1 (0.2)	5 (0.9)	2 (0.4)
Pain in extremity	0	1 (0.2)	2 (0.4)	1 (0.2)	1 (0.2)
Rheumatoid arthritis	0	0	0	2 (0.4)	0
Rotator cuff syndrome	0	0	1 (0.2)	0	0

Table 40. Incidence of Treatment-Emergent Adverse Events Leading to Discontinuation (All Causalities) - Overall

Number (%) of Subjects	Tanezumab		Tanezumab + NSAID		NSAIDs
System Organ Class MedDRA Preferred Term	5 mg n (%)	10 mg n (%)	5 mg n (%)	10 mg n (%)	n (%)
Sacroiliitis	0	0	0	1 (0.2)	0
Synovial cyst	0	0	0	2 (0.4)	1 (0.2)
Synovitis	0	0	0	2 (0.4)	0
Tendonitis	1 (0.2)	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (0.7)	2 (0.4)	3 (0.6)	3 (0.6)	3 (0.6)
Adenocarcinoma	0	0	0	1 (0.2)	0
Breast cancer	0	1 (0.2)	0	0	0
Central nervous system lymphoma	0	0	1 (0.2)	0	0
Colon cancer	1 (0.2)	0	0	0	0
Endometrial cancer	1 (0.2)	0	0	1 (0.2)	0
Gastric cancer	0	0	1 (0.2)	0	0
Hepatic neoplasm malignant	0	0	0	1 (0.2)	0
Lung adenocarcinoma	0	0	1 (0.2)	0	0
Metastases to lung	1 (0.2)	0	0	0	0
Ovarian cancer	1 (0.2)	0	0	0	0
Pituitary tumour benign	0	0	0	0	1 (0.2)
Prostate cancer	0	1 (0.2)	0	0	0
Renal cancer	0	0	0	0	1 (0.2)
Uterine cancer	0	0	0	0	1 (0.2)
Nervous system disorders	16 (3.0)	22 (4.1)	19 (3.5)	20 (3.7)	5 (0.9)
Amnesia	0	0	0	0	1 (0.2)
Axonal neuropathy	0	0	0	0	1 (0.2)
Burning sensation	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	0
Carpal tunnel syndrome	0	6 (1.1)	3 (0.6)	1 (0.2)	0
Cerebrovascular accident	1 (0.2)	1 (0.2)	0	1 (0.2)	0
Cervical myelopathy	0	0	0	1 (0.2)	0
Cervicobrachial syndrome	0	0	1 (0.2)	0	0
Diabetic neuropathy	0	0	0	1 (0.2)	0
Dysaesthesia	0	1 (0.2)	0	0	0
Headache	2 (0.4)	0	1 (0.2)	0	0
Hyperaesthesia	0	1 (0.2)	0	0	0
Hypoaesthesia	2 (0.4)	3 (0.6)	4 (0.7)	3 (0.6)	0
Intracranial aneurysm	0	0	0	1 (0.2)	0
Ischaemic stroke	0	0	1 (0.2)	0	0
Lumbar radiculopathy	1 (0.2)	0	0	0	0
Mononeuropathy	0	0	1 (0.2)	0	0
Neuropathy peripheral	3 (0.6)	0	1 (0.2)	2 (0.4)	0
Paraesthesia	4 (0.7)	6 (1.1)	5 (0.9)	7 (1.3)	2 (0.4)
Peripheral sensory neuropathy	0	1 (0.2)	0	0	0
Peroneal nerve palsy	0	0	1 (0.2)	0	0
Polyneuropathy	0	0	0	1 (0.2)	1 (0.2)
Radiculopathy	0	1 (0.2)	0	1 (0.2)	0
Sciatica	1 (0.2)	0	0	0	0
Sensory disturbance	1 (0.2)	0	0	0	0
Toxic neuropathy	0	1 (0.2)	0	0	0
Psychiatric disorders	1 (0.2)	2 (0.4)	0	0	0
Anxiety	1 (0.2)	0	0	0	0
Depression	0	1 (0.2)	0	0	0

Table 40. Incidence of Treatment-Emergent Adverse Events Leading to Discontinuation (All Causalities) - Overall

Number (%) of Subjects	Tanezumab		Tanezumab + NSAID		NSAIDs
System Organ Class MedDRA Preferred Term	5 mg n (%)	10 mg n (%)	5 mg n (%)	10 mg n (%)	n (%)
Restlessness	0	1 (0.2)	0	0	0
Renal and urinary disorders	0	0	0	0	2 (0.4)
Nephrolithiasis	0	0	0	0	1 (0.2)
Renal impairment	0	0	0	0	1 (0.2)
Reproductive system and breast disorders	0	0	1 (0.2)	0	0
Erectile dysfunction	0	0	1 (0.2)	0	0
Respiratory, thoracic and mediastinal disorders	3 (0.6)	0	1 (0.2)	1 (0.2)	0
Dyspnoea	0	0	1 (0.2)	0	0
Pneumonitis	1 (0.2)	0	0	0	0
Pneumothorax	1 (0.2)	0	0	0	0
Pulmonary embolism	1 (0.2)	0	0	1 (0.2)	0
Skin and subcutaneous tissue disorders	1 (0.2)	3 (0.6)	2 (0.4)	4 (0.7)	2 (0.4)
Dermatitis allergic	0	1 (0.2)	0	0	0
Erythema	0	0	0	1 (0.2)	0
Hyperhidrosis	0	1 (0.2)	0	0	0
Neurodermatitis	0	0	0	0	1 (0.2)
Photosensitivity reaction	0	0	1 (0.2)	0	0
Pruritus	0	0	0	0	1 (0.2)
Rash	0	0	0	2 (0.4)	0
Skin burning sensation	0	0	1 (0.2)	0	0
Skin hyperpigmentation	0	0	0	1 (0.2)	0
Skin irritation	1 (0.2)	0	0	0	0
Skin ulcer	0	1 (0.2)	0	0	0
Vascular disorders	4 (0.7)	0	0	1 (0.2)	1 (0.2)
Deep vein thrombosis	2 (0.4)	0	0	0	0
Hypertension	1 (0.2)	0	0	1 (0.2)	0
Hypotension	0	0	0	0	1 (0.2)
Vasculitis	1 (0.2)	0	0	0	0

Subjects are only counted once per treatment for each row.
Includes data up to 9999 days after last dose of study drug.
MedDRA (version 13.1) coding dictionary applied.
MedDRA=Medical Dictionary for Regulatory Activities, n=number of subjects, NSAID=nonsteroidal anti-inflammatory drug.

Deaths:

Five subjects died during the study: 2 in the tanezumab 5 mg treatment group, and 1 each in the tanezumab 5 mg + naproxen, tanezumab 5 mg + celecoxib, and tanezumab 10 mg + celecoxib treatment groups.

- One (1) subject (tanezumab 5 mg) died as a result of a pulmonary thromboembolism, approximately 9 weeks after her last dose of IV study medication. The Investigator stated there was not a reasonable possibility the event was related to tanezumab.

- One (1) subject (tanezumab 5 mg) died as a result of pancreatic cancer metastasized to the lungs and bones, approximately 8 months after her only dose of IV study medication (on Day 1). The Investigator stated that the cause of death was pancreatic carcinoma.

- One (1) subject (tanezumab 5 mg + naproxen) died as a result of central nervous system lymphoma, approximately 5 months after her only dose of IV study medication (on Day 1). The Investigator stated that the cause of death was metastatic non-Hodgkins lymphoma and nodular (B-cell) lymphoma.

- One (1) subject (tanezumab 5 mg + celecoxib) died as a result of gastric cancer, approximately 10 weeks after her last (fifth dose; Week 32) dose of IV study medication. The Investigator stated that the cause of death was gastric cancer.

- One (1) subject (tanezumab 10 mg + celecoxib) died as a result of cardiorespiratory arrest and liver and lung cancer (lung neoplasm malignant), approximately 3 months after her only dose of IV study medication (on Day 1). The Investigator stated that the cause of death was lung cancer and cardiopulmonary arrest.

Radiographic Results (Joint Space Width):

Minimum Medial JSW of the Index Knee: The mean (SD) Baseline medial tibiofemoral JSW in the index knee ranged from 2.77 (2.08) mm in the tanezumab 5 mg treatment group to 3.02 (2.09) mm in the NSAID alone treatment group (Table 41). LS mean (SE) changes from Baseline in medial JSW of the index knee were observed in all treatment groups, ranging from -0.03 (0.06) mm in the NSAID treatment group to -0.22 (0.06) mm in the tanezumab 10 mg treatment group. The mean change in JSW was greater across the tanezumab treatment groups compared to the NSAID alone treatment group and larger in subjects receiving tanezumab monotherapy compared to subjects receiving tanezumab/NSAID combination therapy. There were no differences noted between tanezumab 5 mg and 10 mg administered as monotherapy or combination therapy. The treatment differences in mean change of JSW reached statistical significance for the comparisons of tanezumab 5 mg and tanezumab 10 mg versus NSAID treatment (p=0.040 and 0.028, respectively).

In an additional analysis, the duration between the Baseline and end of study x-ray was not a significant covariate in the analysis (p=0.8795), and there was no indication from an evaluation of mean change in JSW by time interval to suggest an increasing JSW reduction with duration of exposure in any of the treatment groups.

The mean (SD) Baseline JSW in subjects with index hip OA ranged from 2.20 (1.56) mm in the tanezumab 10 mg + NSAID combination treatment group to 2.72 (1.53) mm in the NSAID alone treatment group (Table 42). LS mean (SE) changes in JSW of the index hip from Baseline were observed in all treatment groups, ranging from -0.02 (0.07) mm in the NSAID alone treatment group to -0.24 (0.07) mm in the tanezumab 5 mg + NSAID combination treatment group. The mean change in JSW was greater across the tanezumab treatment groups compared to the NSAID alone treatment group and larger in subjects receiving tanezumab/NSAID combination therapy compared to subjects receiving tanezumab

monotherapy. There were no differences detected between tanezumab 5 mg and 10 mg administered as monotherapy or combination therapy. The treatment differences in mean changes in JSW reached statistical significance for the comparison of tanezumab 5 mg + NSAID combination therapy versus NSAID alone treatment (p=0.021). The duration between the Baseline and end of study x-ray was not a significant covariate in the analysis (p=0.5482) and there was no indication from an evaluation of mean change in JSW by time interval to suggest an increasing hazard rate for JSW reduction with duration of exposure in any of the treatment groups.

Table 41. Analysis of Change From Baseline to End of Study for Minimum Medial Joint Space Width (mm) of the Index Knee (ITT, Observed Data)

	Tanezumab		Tanezumab + NSAID		NSAIDs
	5 mg N[a]=448	10 mg N[a]=449	5 mg N[a]=446	10 mg N[a]=452	N[a]=446
Baseline JSW (mm)					
N[b]	371	370	369	368	375
Mean (SD)	2.77 (2.08)	2.85 (2.08)	3.01 (2.07)	2.98 (2.11)	3.02 (2.09)
Change from Baseline in JSW (mm)					
N[c]	255	256	262	239	275
Mean (SD)	-0.189 (0.970)	-0.213 (1.069)	-0.162 (1.069)	-0.172 (1.096)	-0.041 (0.850)
LS Mean[d] (SE)	-0.21 (0.06)	-0.22 (0.06)	-0.15 (0.06)	-0.17 (0.06)	-0.03 (0.06)
Comparison versus NSAID					
LS Mean change from Baseline (mm) (95% CI)	-0.18 (0.35, -0.01)	-0.19 (-0.36, -0.02)	-0.12 (-0.29, 0.05)	-0.14 (-0.31, 0.03)	
p-Value[e]	0.040	0.028	0.155	0.113	

ANCOVA model includes treatment and Baseline value as covariates.

ANCOVA = analysis of covariance, CI = confidence interval, ITT = intent to treat, JSW = joint space width, LS = least squares, NSAID = nonsteroidal anti-inflammatory drug, SD = standard deviation, SE = standard error.

a. N=number of subjects in each treatment group with index joint=knee.
b. N=number of subjects with Baseline x-ray.
c. N=number of subjects with end of study x-ray.
d. LS means were estimated from the corresponding ANCOVA model.
e. p-Value is based on ANCOVA from pairwise comparisons.

Table 42. Analysis of Change From Baseline to End of Study for Minimum Joint Space Width (mm) of the Index Hip (ITT, Observed Data)

	Tanezumab		Tanezumab + NSAID		NSAIDs
	5 mg N[a]=92	10 mg N[a]=93	5 mg N[a]=90	10 mg N[a]=90	N[a]=93
Baseline JSW (mm)					
N[b]	91	92	87	87	90
Mean (SD)	2.45 (1.36)	2.37 (1.43)	2.35 (1.42)	2.20 (1.56)	2.72 (1.53)
Change from Baseline in JSW (mm)					
N[c]	69	67	65	59	71
Mean (SD)	-0.075 (0.587)	-0.137 (-0.619)	-0.240 (0.599)	-0.136 (0.437)	-0.028 (0.477)
LS Mean[d] (SE)	-0.08 (0.07)	-0.14 (0.07)	-0.24 (0.07)	-0.14 (0.07)	-0.02 (0.07)
Comparison versus NSAID					
LS Mean change From Baseline (mm) (95% CI)	-0.06 (-0.24, 0.13)	-0.12 (-0.30, 0.07)	-0.22 (-0.40, -0.03)	-0.12 (-0.31, 0.07)	
p-Value[e]	0.538	0.204	0.021	0.208	

ANCOVA model includes treatment and Baseline value as covariates.

ANCOVA = analysis of covariance, CI = confidence interval, ITT = intent to treat, JSW = joint space width, LS = least squares, NSAID = nonsteroidal anti-inflammatory drug, SD = standard deviation, SE = standard error.

a. N=number of subjects in each treatment group with index joint=hip.
b. N=number of subjects with Baseline x-ray.
c. N=number of subjects with end of study x-ray.
d. LS means were estimated from the corresponding ANCOVA model.
e. p-Value is based on ANCOVA from pairwise comparisons.

Laboratory Tests: There was no indication of more frequent abnormalities for tanezumab-treated subjects vs NSAID-alone-treated subjects. The most frequently reported clinical laboratory abnormalities (≥10% of subjects in each treatment group) were urine epithelial cells, urine casts, urine hyaline casts, urine crystals, urine bacteria, urine WBC/high-powered field (HPF), urine leukocyte esterase, urine nitrite, urine bilirubin, and urine specific gravity. Clean catch urine specimens were not requested for this study. Other abnormalities reported by ≥10% of subjects in at least 1 of the treatment groups were red blood cell (RBC) distribution width, eosinophils (%), urine blood/hemoglobin, and urine RBC/HPF. The median changes from Baseline for clinical laboratory tests were not clinically significant.

Vital Signs and ECGs: Most subjects' systolic and diastolic blood pressure increased or decreased from Baseline between 0 mm Hg and 10 mm Hg. The proportion of subjects within a category of change was similar across the treatment groups. Thirteen subjects overall had QT corrected for heart rate using Fridericia's formula (QTcF) values ≥500 msec: 5, 1, 2, and 3 subjects in the tanezumab 5 mg, tanezumab 10 mg, tanezumab 5 mg + NSAID, and tanezumab 10 mg + NSAID treatment groups, respectively, and 2 subjects in the NSAID alone treatment group. QTcF intervals increased from Baseline by ≥60 msec in 20 subjects overall: 2, 6, 4, and 4 subjects in the tanezumab 5 mg, tanezumab 10 mg, tanezumab 5 mg + NSAID, and tanezumab 10 mg + NSAID treatment groups, respectively, and 4 subjects in the NSAID alone treatment group. The occurrence of QTcF values ≥500 msec and increases ≥60 msec from Baseline in QTcF values did not appear to have a relationship to the study treatment administered.

Adverse Events of Abnormal Peripheral Sensation: Table 43 summarizes the incidence of AEs of abnormal peripheral sensation (all causalities). Among the AEs of abnormal peripheral sensation, paresthesia, hypoesthesia, burning sensation, peripheral neuropathy, decreased vibratory sense, and hyperesthesia were reported by ≥1% more subjects treated with tanezumab monotherapy or tanezumab/NSAID combination treatment than in the NSAID alone treatment group. Overall, the tanezumab 10 mg + NSAID and tanezumab 5 mg + NSAID treatment groups had more AEs of abnormal peripheral sensation than the tanezumab 5 mg and tanezumab 10 mg treatment groups, which in turn had a higher frequency of these AEs than the NSAID alone treatment group. The great majority of AEs of abnormal peripheral sensation across all treatment groups were either mild or moderate in intensity. The incidence rates of AEs of abnormal peripheral sensation overall were low (all events reported in ≤11.1% subjects in all 5 treatment groups).

Table 43. Number (%) of Subjects With AEs of Abnormal Peripheral Sensation (All Causalities, ITT)

MedDRA Preferred Term	Tanezumab		Tanezumab + NSAID		NSAIDs
	5 mg N=541	10 mg N=542	5 mg N=536	10 mg N=542	N=539
Paresthesia	33 (6.1)[a]	39 (7.2)[a]	48 (9.0)[a]	60 (11.1)[b]	17 (3.2)
Hypoesthesia	25 (4.6)	31 (5.7)[c]	35 (6.5)[a]	35 (6.5)	14 (2.6)
Burning sensation	7 (1.3)[a]	5 (0.9)	7 (1.3)	11 (2.0)[a]	4 (0.7)
Neuropathy peripheral	9 (1.7)	8 (1.5)	4 (0.7)	8 (1.5)	3 (0.6)
Decreased vibratory sense	10 (1.8)	1 (0.2)	6 (1.1)	7 (1.3)	1 (0.2)
Hyperesthesia	3 (0.6)	5 (0.9)[a]	3 (0.6)	6 (1.1)	0
Dysesthesia	2 (0.4)	6 (1.1)	3 (0.6)	5 (0.9)[c]	2 (0.4)
Polyneuropathy	2 (0.4)[a]	1 (0.2)	3 (0.6)	3 (0.6)	1 (0.2)
Sensory disturbance	2 (0.4)	1 (0.2)	2 (0.4)	2 (0.4)	1 (0.2)
Allodynia	2 (0.4)	4 (0.7)[a]	1 (0.2)	2 (0.4)[a]	1 (0.2)
Demyelinating polyneuropathy	2 (0.4)	1 (0.2)	0	2 (0.4)	0
Neuritis	0	0	0	2 (0.4)	1 (0.2)
Sensory loss	0	0	2 (0.4)	1 (0.2)	0
Neuralgia	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)[a]	1 (0.2)
Formication	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	0
Hypoesthesia facial	0	0	0	1 (0.2)	0
Hypoesthesia oral	0	0	1 (0.2)	0	0
Peripheral sensory neuropathy	0	1 (0.2)	0	0	0
Axonal neuropathy	0	0	0	0	1 (0.2)

MedDRA (version 13.1) coding dictionary applied.
AEs sorted in decreasing frequency by tanezumab 10 mg + NSAID treatment group.
AEs of abnormal peripheral sensation are allodynia, axonal neuropathy, burning sensation, decreased vibratory sense, demyelinating polyneuropathy, dysesthesia, formication, hyperesthesia, hyperpathia, hypoesthesia, hypoesthesia facial, hypoesthesia oral, intercostal neuralgia, neuralgia, neuritis, neuropathy peripheral, paresthesia, paresthesia oral, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy, polyneuropathy chronic, sensory disturbance, sensory loss, and thermohypoesthesia.
AE = adverse event, ITT = intent to treat, MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects, NSAID = nonsteroidal anti-inflammatory drug.
a. One (1) of these AEs was severe in intensity.
b. Three (3) of these AEs were severe in intensity.
c. Two (2) of these AEs were severe in intensity.

Neurological Examinations: A large majority of subjects participating in the study (85.8% to 88.3% across the treatment groups) had no new or worsened abnormalities in their final neurological examination. The proportion of subjects with clinically significant changes in their final neurological examination ranged from 1.3% to 2.4% in the tanezumab monotherapy and tanezumab/NSAID combination treatment groups, compared to 0.9% of subjects in the NSAID alone treatment group.

Neurological Consultations: The percentages of subjects referred for a neurological consultation were greater in the the tanezumab monotherapy and tanezumab/NSAID combination treatment groups (range 15.9% to 20.8%) than in the NSAID alone treatment group (10.0%). The incidence of a categorization suggestive of new or worsened peripheral neuropathy was similar across the tanezumab monotherapy and tanezumab/NSAID

combination treatment groups (ranging from 6.8% to 8.7% of treated subjects) and more common than in subjects receiving NSAID alone (2.6% of treated subjects).

Osteonecrosis and Total Joint Replacements: There were 33 cases of reported osteonecrosis in this study. The incidence of subjects (number [%]) with reported osteonecrosis across the treatment groups was 7 (1.29%) with tanezumab 5 mg, 4 (0.74%) with tanezumab 10 mg, 10 (1.87%) with tanezumab 5 mg + NSAID, 8 (1.48%) with tanezumab 10 mg + NSAID, and 4 (0.74%) with NSAID treatment alone. The difference [95% CI] versus NSAID treatment alone in the incidence of subjects with reported osteonecrosis was 0.55% [-1.61%, 3.71%] with tanezuamb 5 mg, 0% [-2.94%, 2.22%] with tanezumab 10 mg, 1.12% [-1.26%, 4.20%] with tanezumab 5 mg + NSAID, and 0.73% [-1.46%, 3.90%] with tanezumab 10 mg + NSAID.

There were a total of 150 total joint replacements for any cause, which included subjects who underwent a total joint replacement and those with reported osteonecrosis but no record of undergoing a total joint replacement. The incidences and exposure adjusted-event rates of all-cause total joint replacement were similar with tanezumab administered as monotherapy and in combination with an NSAID active comparator in this study. However, there was a consistent trend for increasing incidence and exposure-adjusted event rates with tanezumab + NSAID therapy compared to tanezumab monotherapy. The incidences (difference versus NSAID with 95% CI) of all-cause total joint replacements were as follows: 4.44% (Δ=-0.20% [-4.27%, 3.25%]) with tanezumab 5 mg; 3.51% (Δ=-1.13% [-5.07%, 2.17%]) with tanezumab 10 mg; 7.46% (Δ=2.82% [-0.88%, 7.13%] with tanezumab 5 mg + NSAID; 7.75% (Δ=3.11% [-0.48%, 7.52%]) with tanezumab 10 mg + NSAID; 4.64% with NSAID alone.

An Adjudication Committee consisting of external orthopedic surgeons, rheumatologists, and an orthopedic pathologist with expertise in patients with end-stage OA and osteonecrosis was assembled to review blinded joint safety data from the tanezumab clinical program.

The adjudication categories for the events were the following:

1. Primary osteonecrosis;
2. Worsening OA;

   For events of worsening OA, the event was further categorized:

   a. Rapid progression of OA (type 1 or type 2);

   b. Normal progression of OA;

   c. Not enough information to distinguish between rapidly progressive OA and normal progression of OA.

3. Other (with diagnosis specified);

4. Not enough information to distinguish between primary osteonecrosis and worsening OA or another specified diagnosis.

For events assessed as worsening OA-rapid progression (rapidly progressive OA), the Adjudication Committee further classified these cases as type 1 or type 2. Type 1 events were those that the Adjudication Committee considered to have significant loss of JSW (≥1 mm) in less than approximately 1 year. Type 2 events were those which were considered to have abnormal loss/destruction of bone that is not normally present in end-stage OA which in the most severe form was catastrophic bone failure and joint destruction. One (1) event was adjudicated as primary osteonecrosis in the study.

Table 44 summarizes the adjudication results.

Table 44. Summary of Adjudication Outcomes

	Tanezumab			Tanezumab + NSAID			NSAIDs
	5 mg	10 mg	5 mg + 10 mg combined	5 mg	10 mg	5 mg + 10 mg combined	
N	541	542	1083	536	542	1078	539
Total exposure (pt-yrs)	426	415	841	423	416	839	416
All-cause total joint replacements n (%)	24 (4.4)	19 (3.5)	43 (4.0)	40 (7.5)	42 (7.8)	82 (7.6)	25 (4.6)
Subjects adjudicated, n (%)	17 (70.8)	13 (68.4)	30 (69.8)	29 (72.5)	29 (69.0)	58 (70.7)	18 (72.0)
Primary Osteonecrosis (1)							
n (%)	0	1 (0.2)[a]	1 (0.1)[a]	0	0	0	0
Events/ 1000 pt-yrs	0	2.4	1.2	0	0	0	0
Worsening Osteoarthritis (2)							
n (%)	15 (2.8)	10 (1.8)	25 (2.3)	23 (4.3)	27 (5.0)	50 (4.6)	17 (3.2)
Events/ 1000 pt-yrs	35.2	24.1	29.7	54.4	64.8	59.6	40.9
Other (3)							
n (%)	2 (0.4)	2 (0.4)	4 (0.4)	3 (0.6)	2 (0.4)	5 (0.5)	1 (0.2)
Events/ 1000 pt-yrs	4.7	4.8	4.8	7.1	4.8	6.0	2.4
Insufficient Information to Distinguish Osteonecrosis From Worsening Osteoarthritis (4)							
n (%)	0	0	0	3 (0.6)	0	3 (0.3)	0
Events/ 1000 pt-yrs	0	0	0	7.1	0	3.6	0

Events/1000 pt-yrs=10×events/100 pt-yrs.
NSAID = nonsteroidal anti-inflammatory drug, N = number of subjects in treatment group, n = number of subjects in category, pt-yrs = patient-years.
a. Case diagnosis = end stage osteoarthritis.

The crude incidence rates of worsening OA for tanezumab monotherapy (5 mg and 10 mg doses combined), tanezumab/NSAID combination therapy (tanezumab 5 mg and 10 mg doses combined), and NSAID alone treatment were 2.3%, 4.6%, and 3.2%, respectively, and event rates normalized for treatment exposure were 29.7, 59.6, and 40.9 events/1000 patient

years (pt-yrs), respectively. Three (3) subjects in the tanezumab 5 mg + NSAID treatment group were adjudicated to not have enough information to distinguish between primary osteonecrosis and worsening OA (Category 4).

Anti-Tanezumab Antibodies: Fifty-three serum samples from 25 different subjects receiving 5 mg or 10 mg tanezumab alone or in combination with oral NSAID tested positive for anti-tanezumab antibodies. These antibodies were either pre-existing (n=11), transient (n=8), or developing (n=6). In all 53 samples the level of antibody was relatively low. Eight of the 53 anti-tanezumab-positive samples were tested as being neutralizing in nature. Based on all available data, there was no evidence supporting a consistent change in the individual pharmacokinetic and efficacy profiles between the subjects who developed antibodies against tanezumab and those who did not.

CONCLUSIONS:

- Tanezumab monotherapy and tanezumab/NSAID combination therapy provided significant reductions in pain and improvements in physical function compared to NSAID monotherapy in subjects with OA of the knee or hip at Week 16, the primary analysis time point.

- Tanezumab monotherapy and tanezumab/NSAID combination therapy provided improvements in PGA in subjects with OA of the knee or hip at Week 16, but tanezumab treatment (alone or in combination with NSAID) generally failed to reach statistical significance compared to NSAID monotherapy.

- Minimal differences in efficacy were evident between tanezumab monotherapy and tanezumab/NSAID combination therapy, and minimal differences in efficacy were evident between tanezumab 5 mg and 10 mg (alone or in combination with NSAID).

- The improvements in pain and function seen with tanezumab treatment were clinically meaningful and consistently observed across multiple measures of efficacy.

- The efficacy results seen with tanezumab treatment (alone or in combination with NSAID) were robust, as indicated by replication across 2 different NSAIDs and multiple methods of imputation for missing data.

- The incidence rates of AEs, SAEs, and AEs causing discontinuations were generally higher with tanezumab/NSAID combination treatment than with tanezumab monotherapy or NSAID monotherapy.

- A higher proportion of tanezumab-treated subjects reported AEs of abnormal peripheral sensation than subjects treated with NSAID monotherapy, and a higher proportion of tanezumab-treated subjects underwent neurological consultations with findings suggestive of new or worsened peripheral neuropathy than subjects treated with NSAID monotherapy. Most of the new or worsened peripheral neuropathies were diagnosed as mononeuropathies (generally carpal tunnel syndrome) rather than polyneuropathies, as would have been expected in response to a neurotoxic agent.

- Rates of Investigator reports of osteonecrosis and all-cause total joint replacements were similar in the tanezumab monotherapy and NSAID alone treatment groups and were greater in the tanezumab + NSAID combination treatment groups, although the differences from NSAID alone were generally not statistically different.

- Only 1 reported osteonecrosis SAE was adjudicated as primary osteonecrosis, indicating that an association with nerve growth factor inhibition is unlikely.

- Rapidly progressive OA was identified in some subjects who received tanezumab monotherapy. The incidence appeared to be dose-related, and the incidence with tanezumab 10 mg monotherapy exceeded the incidence with NSAID monotherapy. Treatment with tanezumab in combination with NSAID increased the incidence of rapidly progressive OA by 2-fold compared with NSAID monotherapy.

- No significant treatment effects on blood pressure, other vital signs, or ECG parameters were observed.

- The early termination of the study limits the ability to draw firm conclusions about the efficacy and safety of 56 weeks of tanezumab treatment.