PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

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

PROTOCOL NO.: A4091003

PROTOCOL TITLE: Phase II Randomized, Double-Blind, Placebo-Controlled Multicenter Efficacy and Safety Study of Tanezumab as Add-on Therapy to Opioid Medication in Patients With Pain due to Bone Metastases

Study Centers: Twenty five (25) centers: 2 in Austria, 2 in Bosnia and Herzegovina, 1 in Croatia, 3 in Hungary, 3 in India, 2 in the Republic of Korea, 1 in Latvia, 1 in Peru, 4 in Poland, 2 in Slovakia and 4 in the United States (US) took part in the study and randomized subjects.

Study Initiation Date and Final Completion Date: 29 April 2009 to 07 February 2012

Phase of Development: Phase 2

Study Objectives:

Primary Objective:

To evaluate the analgesic efficacy of single dose tanezumab 10 mg in combination with opioids (tanezumab 10 mg + opioids) compared with opioids alone (placebo + opioids) in cancer subjects with chronic pain due to bone metastases.

Secondary Objectives:

- To characterize the time course of analgesia associated with tanezumab 10 mg when administered in combination with opioids (tanezumab 10 mg + opioids) compared with opioids alone (placebo + opioids);
- To evaluate opioid consumption, rescue medication use and Opioid-Related Symptom Distress Scale (ORSDS) scores of a single dose of tanezumab 10 mg in combination with opioids (tanezumab 10 mg + opioids) compared with opioids alone (placebo + opioids);
- To examine the effect on subject function of a single dose of tanezumab 10 mg in combination with opioids (tanezumab 10 mg + opioids) compared with opioids alone (placebo + opioids);

- To examine the global assessment scores with a single dose of tanezumab 10 mg in combination with opioids (tanezumab 10 mg + opioids) compared with opioids alone (placebo + opioids);

- To characterize tanezumab 10 mg intravenous (IV) pharmacokinetics in cancer subjects with chronic pain due to bone metastases and treated with opioids;

- To assess the safety and tolerability of single dose tanezumab 10 mg IV in subjects with chronic pain due to bone metastases and treated with opioids.

METHODS

Study Design: This was a randomized, double-blind, placebo-controlled, parallel-group study in cancer subjects with chronic pain due to bone metastases who were being treated with opioids. The study consisted of a pretreatment phase (lasting 3 to 30 days, consisting of a screening period, an opioid dose adjustment phase, and a baseline assessment period) and a treatment phase lasting up to 113 days (with efficacy assessments lasting up to 113 days and total observation on study extending to 113 days). Eligible subjects were randomized in a 1:1 ratio to receive a single IV dose of tanezumab 10 mg IV or matching IV placebo. A summary of study procedures and evaluations is provided in Table 1.

Table 1. Schedule of Activities

Study Activity	Pretreatment Phase			Treatment Phase									
	Screen	Opioid Dose Adjustment	Baseline Assessment Period	Baseline			Week 1 Phone Contact	Week 2	Week 4	Week 6	Week 8 Phone Contact	Week 12	Week 16 End Rx or Early Term[a]
Clinic/Phone Visit	V1			V2			V3	V4	V5	V6	V7	V8	V9
Study Day (±3 Days)	Day -30 to -4	Day -30 to -4	Day -3 to -1	Day 1			Day 8	Day 15	Day 29	Day 43	Day 57	Day 85	Day 113
				1 h Predose	Dose	1 and 2 h Postdose							
Informed consent	X												
Inclusion/ exclusion criteria	X			X									
Medical history	X												
Cancer history[b]	X												
General physical exam	X									X			X
Radiographic assessment of hips (bilateral x-ray)	X[c]												X[c]
Neurologic exam	X			X				X	X	X		X	X
Vital signs (temp, BP, RR, HR)	X			X		X		X	X	X		X	X
Weight	X									X			X
Laboratory tests:													
Hematology	X			X				X	X	X		X	X
Blood chemistry	X			X				X	X	X		X	X
Urinalysis	X			X				X	X	X		X	X
PT/PTT	X			X				X	X	X		X	X
Hepatitis screen (Hep B & Hep C)	X												
HIV test	X												
Pregnancy test[d]	X			X						X			X
Serum FSH test[e]	X												
Urine drug screen	X												

Table 1. Schedule of Activities

Study Activity	Pretreatment Phase			Treatment Phase									
	Screen	Opioid Dose Adjustment	Baseline Assessment Period	Baseline			Week 1 Phone Contact	Week 2	Week 4	Week 6	Week 8 Phone Contact	Week 12	Week 16 End Rx or Early Term[a]
Clinic/Phone Visit	V1			V2			V3	V4	V5	V6	V7	V8	V9
Study Day (±3 Days)	Day -30 to -4	Day -30 to -4	Day -3 to -1	Day 1			Day 8	Day 15	Day 29	Day 43	Day 57	Day 85	Day 113
				1 h Predose	Dose	1 and 2 h Postdose							
Anti-drug antibody test (anti-tanezumab)				X					X	X		X	X
PK sample				X		X		X	X	X		X	X
De-identified genetic sampling				X									
ECG (12-lead triplicate)				X		X[f]			X				X
Bone scan[g]	X												
Randomization				X									
Trial treatment:													
Tanezumab IV or placebo IV					X								
Adjust opioid regimen as needed[h]		X											
Check opioid dose stabilization and randomization criteria[i]			X										
Daily subject diary:													
Dispense/review	X			X			X	X	X	X	X	X	X
Daily average pain (NRS)[j]	----------X----------												

Table 1. Schedule of Activities

Study Activity	Pretreatment Phase			Treatment Phase									
	Screen	Opioid Dose Adjustment	Baseline Assessment Period	Baseline			Week 1 Phone Contact	Week 2	Week 4	Week 6	Week 8 Phone Contact	Week 12	Week 16 End Rx or Early Term[a]
Clinic/Phone Visit	V1			V2			V3	V4	V5	V6	V7	V8	V9
Study Day (±3 Days)	Day -30 to -4	Day -30 to -4	Day -3 to -1	Day 1			Day 8	Day 15	Day 29	Day 43	Day 57	Day 85	Day 113
				1 h Predose	Dose	1 and 2 h Postdose							
Daily worst pain (NRS)[j]	----------X----------												
Total daily opioid dose[j]	----------X----------												
Rescue med total daily dose[j]	----------X----------												
Patient-reported outcomes at study/phone visits													
BPI-sf				X			X	X	X	X	X	X	X
ORSDS				X				X	X	X		X	X
Patient global evaluation of study medication							X	X	X	X	X	X	X
Patient global assessment of cancer pain				X			X	X	X	X	X	X	X
Study personnel-rated instruments at study/phone visits													
Karnofsky performance status	X									X			X
Adverse event assessment[k]		X	X	X	X	X	X	X	X	X	X	X	X

Table 1. Schedule of Activities

Study Activity	Pretreatment Phase			Treatment Phase									
	Screen	Opioid Dose Adjustment	Baseline Assessment Period	Baseline			Week 1 Phone Contact	Week 2	Week 4	Week 6	Week 8 Phone Contact	Week 12	Week 16 End Rx or Early Term[a]
Clinic/Phone Visit	V1			V2			V3	V4	V5	V6	V7	V8	V9
Study Day (±3 Days)	Day -30 to -4	Day -30 to -4	Day -3 to -1	Day 1			Day 8	Day 15	Day 29	Day 43	Day 57	Day 85	Day 113
				1 h Predose	Dose	1 and 2 h Postdose							
Concomitant medication review[k]	X			X			X	X	X	X	X	X	X

Table 1. Schedule of Activities

Study Activity	Pretreatment Phase			Treatment Phase									
	Screen	Opioid Dose Adjustment	Baseline Assessment Period	Baseline			Week 1 Phone Contact	Week 2	Week 4	Week 6	Week 8 Phone Contact	Week 12	Week 16 End Rx or Early Term[a]
Clinic/Phone Visit	V1			V2			V3	V4	V5	V6	V7	V8	V9
Study Day (±3 Days)	Day -30 to -4	Day -30 to -4	Day -3 to -1	Day 1			Day 8	Day 15	Day 29	Day 43	Day 57	Day 85	Day 113
				1 h Predose	Dose	1 and 2 h Postdose							

BP = blood pressure, BPI-sf = Brief Pain Inventory Short Form, CT = computed tomography, ECG = electrocardiogram, FSH = follicle stimulating hormone, Hep = hepatitis, HIV = human immunodeficiency virus, HR = heart rate, IV = intravenous, MRI = magnetic resonance imaging, NRS = numeric rating scale, ORSDS = Opioid Related Symptom Distress Scale, PK = pharmacokinetic, PT = prothrombin time, PTT = partial thromboplastin time, RR = respiratory rate, temp = temperature, term = termination, V = visit.

a. Completed all activities at this visit for subjects who elected to rollover into extension study (Phase II Open-Label Safety Extension Study of Tanezumab In Cancer Patients With Pain due to Bone Metastases [NCT00830180]).
b. Type of cancer, date of initial diagnosis, extent, treatment history.
c. Initial bilateral x-rays of the hips were to occur during the Screening period if the subject had not been randomized. For subjects who had already been randomized, the initial bilateral x-rays of the hips were to occur at the subject's next regularly scheduled clinic visit. Bilateral x-rays of the hips were also to be obtained at End of Study or Early Termination visit If the subject's initial x-rays of the hips were obtained ≤30 days from the End-of-Study/Early Termination visit, the requirement for the End-of-Study/Early Termination x-rays could be waived.
d. For female subjects of child-bearing potential: serum pregnancy test at Screen; urine pregnancy test at Day 1 and Day 43; serum pregnancy test at Day 113 or early termination.
e. Female subjects of non-child bearing potential who have not had a hysterectomy or bilateral oophorectomy were required to have serum FSH testing at Screening.
f. Completed postdose triplicate ECG only at 1 hour postdose.
g. Whole body bone scan for subjects lacking radiographic confirmation (bone scan, MRI, CT or x-ray with corresponding bone scan) of metastasis in 30 days prior to screening.
h. Opioid regimen dose adjustment if needed via telephone contact each day for up to 27 days.
i. Opioid dose stabilization assessment via telephone contact over 3 consecutive days following dose adjustment period.
j. Subject diary was completed each evening, not necessarily at time of the Clinic Visit. .
k. Subjects who experienced increased joint pain of a severe and persistent nature were to be followed for study-specified safety evaluations for as long as their remaining time on study. These evaluations were to take place in the clinic for these subjects provided they agreed. Subjects who did not agree to attend study-specified safety evaluations at clinic visits continued to be contacted by telephone per study-defined visit time-points for their remaining time on study, unless subject decided to rollover into the extension study. These Follow-Up Visits were conducted to determine if the subject had experienced any serious adverse events or joint replacement surgeries since their previous (in-person at the site or telephone) visit and had used any concomitant corticosteroid medication since the previous (in-person at the site or telephone) visit. Subjects reporting joint replacement during a telephone Follow-Up Visit may have been requested to return to the clinic for examination and/or for collection of diagnostic information. Subjects were also to be reminded about study contraceptive requirements (if applicable).

Number of Subjects (Planned and Analyzed): A total of 58 subjects were planned to be enrolled (29 per treatment group) and 59 subjects were randomized (30 in the placebo treatment group and 29 in the tanezumab 10 mg IV treatment group); 4 in Austria, 3 in Bosnia and Herzegovina, 1 in Croatia, 6 each in Hungary, Republic of Korea and the US, 7 in India, 4 in Lativa, 2 in Peru, 15 in Poland and 5 in Slovakia.

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged ≥18 years with prostate cancer, breast cancer, renal cell carcinoma or multiple myeloma that had spread to bone, causing moderate to severe bone pain and which required daily opioid medication were included in the study.

Exclusion Criteria:

Subjects who did not have bone pain caused by cancer, who started chemotherapy <4 weeks prior to the study, or who completed radiotherapy <4 weeks prior to the study were not eligible. Subjects with known history or evidence of osteoarthritis, history of significant trauma to a major joint within 1 year prior to screening or known history of rheumatoid arthritis were also excluded from the study.

Study Treatment:

Study treatment consisted of a single IV infusion of either tanezumab 10 mg or matching placebo on Visit 2, Day 1. Dose preparation required that 1 mL of active or placebo solutions be removed from vials of tanezumab or matching placebo, respectively. The solution was then diluted with saline in a suitable sterile container to a final volume of 5 mL. The final solution was infused over 5 minutes by hand (IV push).

A range of background opioid medications were allowed during the study; the regimen was adjusted during the opioid dose adjustment phase in order to determine the optimal total daily dose based on accepted clinical guidelines. Beginning on Day 1, the average total daily dose of opioids between study clinic visits could not exceed the Baseline total daily opioid dose by >10%. Opioid dose reduction was allowed if subjects experienced intolerable adverse events (AEs), if pain decreased, or if the subject requested the dose reduction. Subjects obtained opioid treatment via prescription through the site's normal prescribing practice.

Efficacy and Safety Endpoints:

Primary Endpoint:

The primary efficacy endpoint was the change from Baseline to Week 6 in the daily average pain intensity measured by the 11-point Pain Intensity Numerical Rating Scale (NRS) where scores range from 0-10. Baseline was defined as the average daily pain NRS score during the baseline assessment period prior to randomization (expected to be 3 days).

Secondary Endpoints:

Secondary pain endpoints:

- Change from Baseline to Weeks 1, 2, 4, 8, 12 and 16 in the daily average pain intensity NRS score;
- Change from Baseline to Weeks 1, 2, 4, 6, 8, 12 and 16 in the daily worst pain intensity NRS score;
- Change from Baseline to Weeks 1, 2, 4, 6, 8, 12 and 16, in the Brief Pain Inventory short-form (BPI-sf) average pain scores obtained at study visits;
- Change from Baseline to Weeks 1, 2, 4, 6, 8, 12 and 16, in the BPI-sf worst pain scores obtained at study visits;
- Response as defined by a ≥30%, ≥50%, ≥70%, and ≥90% reduction from Baseline in the daily average pain intensity NRS score at Weeks 1, 2, 4, 6, 8, 12, and 16.

Opioid use and adverse effects:

- Average daily opioid consumption (up to Week 16);
- Average number of doses of rescue medication required per week (up to Week 16);
- Change in the weekly ORSDS at Weeks 2, 4, 6, 12, and 16.

Subject function:

- Change from Baseline to Weeks 1, 2, 4, 6, 8, 12, and 16, in the Brief Pain Inventory (BPI) Pain Interference with Function Composite Score and individual pain interference item scores obtained at study visits.

Global efficacy measures:

- Patient's Global Evaluation of Study Medication (PGESM) at Weeks 1, 2, 4, 6, 8, 12, and 16;
- Change in Patient's Global Assessment (PGA) of Disease (Cancer Pain) Activity at Weeks 1, 2, 4, 6, 8, 12, and 16;
- Response defined as an improvement of ≥2 points in PGAof Disease (Cancer Pain) Activity at Weeks 1, 2, 4, 6, 8, 12 and 16.

Safety assessments:

- AEs from time of first dose of study treatment through the last subject visit;

- Physical examination at Screening, Week 6 and Week 16 (or at early termination);
- Neurologic examination at Screening, Baseline, and Weeks 2, 4, 6, 12, and 16 (or at early termination);
- Vital sign measurements at Screening, Baseline, and Weeks 2, 4, 6, 12, and 16 (or at early termination);
- Weight measurements at Screening, Week 6 and Week 16 (or at early termination);
- Clinical laboratory assessments (hematology, blood chemistry, prothrombin time/partial thromboplastin time, urinalysis) at Screening, Baseline, and Weeks 2, 4, 6, 12 and 16 (or at early termination);
- Anti-drug antibody (ADA) testing at Baseline and Weeks 4, 6, 12 and 16 (or at early termination);
- Electrocardiogram (ECG) at Baseline (predosing and 1 hour post-dose) and Weeks 4, and 16 (or at early termination).

Safety Evaluations: Safety evaluations included AEs, clinical laboratory tests, 12-lead ECGs, physical examinations, vital signs, neurological examinations (including the neuropathy impairment score [NIS]), neurological consultations (if any AE suggestive of new or worsening peripheral neuropathy or any AE of abnormal peripheral sensation was reported, or in the event of a new or worsened clinically significant abnormality on the neurological exam), and assessment of ADAs against tanezumab.

Statistical Methods: The intent-to-treat (ITT) analysis set was the primary efficacy and safety analysis set. It was defined as all randomized subjects who received the Day 1 IV infusion (either tanezumab or placebo). The per-protocol (PP) analysis set was the secondary efficacy set. It was defined as all subjects in the ITT analysis set who were not major protocol deviators.

The change from Baseline for the daily average and worst pain score was summarized for each week and analyzed at Weeks 1, 2, 4, 6, and 8 using analysis of covariance (ANCOVA). The model terms included treatment, study site, type of cancer, and Baseline score. Baseline observation carried forward (BOCF) imputation for missing data was used in these analyses for subjects who discontinued or had missing data at the specific time points. The estimated mean change from Baseline for each treatment group was calculated for Weeks 1, 2, 4, 6, and 8, together with standard errors of the mean and 95% confidence intervals (CI). The estimated mean difference between tanezumab + opioid and opioid alone were shown (with corresponding standard error) and 95% CIs.

The change from Baseline to Weeks 1, 2, 4, 6, and 8 in the BPI-sf average and worst pain scores were also analyzed using an ANCOVA main effects model as described above, with estimated treatment and treatment difference for the change to the individual Weeks 1, 2, 4,

6, and 8. The other BPI-sf endpoints were analyzed in the same way as the BPI-sf pain endpoints.

For the response endpoint ≥30%,≥50%, ≥70%, and ≥90% reduction in the daily average pain NRS score that was maintained for a minimum of 3 consecutive days, the response variables and the response variables at specific time points were analyzed using the Fisher's Exact Test. The odds ratio with 95% 2-sided CI for the treatment contrast was shown.

The daily opioid consumption was converted to the morphine equivalent dosage (MED) and calculated as the sum of MED for each day of the study and summarized for the pre-randomization, opioid dose adjustment phase, baseline assessment period, and the whole post-baseline period. Summaries were shown overall and by treatment group. The summary of post-baseline opioid use was shown as opioids taken as part of the treatment group, opioids taken for rescue medication, and a total amount up to Week 8 and after Week 8 up to Week 16. A second summary showed the post-baseline total opioid dosage divided by the number of days the subject was in the study (up to Week 8). The average daily opioid consumption up to Week 8 and Week 16 was calculated as the daily sum of total opioid dosage from Baseline to the week of interest divided by the number of days the subject was in the study up to that week (or earlier if the subject discontinued). This endpoint was analyzed using the ANCOVA model as described above, with baseline as the total daily dose of opioids determined in the baseline assessment period.

The number of doses of rescue medication was summarized by treatment group for each week in the trial. The total number of doses of rescue medication taken up to the Week 8 visit (or earlier if the subject discontinued) was analyzed using a negative-binomial regression model using the log-total study duration up to the Week 8 visit (or earlier if the subject discontinued), shown in weeks, as the subject offset variable. The resulting analysis showed the estimated rate of opioids taken as rescue medication per week up to Week 8. This estimated rate was shown by treatment group with standard error and 95% CI. The ratio of the opioid usage rate between tanezumab and opioid versus opioid alone was shown (again, with standard error and 95% CI).

The ORSDS was a questionnaire on the frequency, severity, and level of bother of 10 symptoms. For each symptom, the mean of the frequency, severity, and bother was calculated to become the multi-domain average (MDA). These are the 4 dimensions for each symptom. The mean of each dimension over all symptoms was calculated to become the frequency, severity, bother, and MDA composite scores. Each of the 4 dimensions were summarized by treatment and treatment difference for the 10 symptoms and the overall composite, a total of 44 sets of summary measures. The MDA for each symptom and the 4 dimensions for the composite score were analyzed for each time point. The analysis of this data used the mixed effects repeated measures model described above and showed analysis results for the change from Baseline to Weeks 2, 4, and 6.

The Weeks 1, 2, 4, 6, 8, 12, and 16 PGESM and the change from Baseline to Weeks 1, 2, 4, 6, 8, 12, and 16 in the PGA of Disease (Cancer Pain) were summarized by time and treatment group as well as by the percentage of subjects who rated the study medication as at least "good." These endpoints were analyzed using ANCOVA. The model terms included

treatment study site, type of cancer, and Baseline score. In the case of missing data, the PGESM used the LOCF imputation, and the PGA of disease used both the BOCF and LOCF imputations. The PGESM scores range from 1 (poor) to 4 (excellent). The change from Baseline in the PGA of disease scores range from -4 to 4.

All efficacy data were summarized for each week or visit up to Week 16 and analyzed for the time points indicated above up to Week 8 for all subjects with available data at each time point and for the subset of subjects who did not discontinue this study to enter the extension study at the Week 8 visit or later.

All statistical tests used the 2 sided 5% significance level.

RESULTS

Subject Disposition and Demography: A total of 101 subjects were screened and 59 were randomized (30 in the placebo treatment group and 29 in the tanezumab 10 mg IV treatment group), all of whom received study treatment and comprised the ITT population. A total of 41 subjects (22 in the placebo treatment group and 19 in the tanezumab 10 mg IV treatment group) were included in the PP analysis set.

Table 2 summarizes the numbers of subjects screened, randomized, and treated, and the incidence of those who completed or discontinued the study (up to Week 16). Discontinuations from treatment for the ITT population are summarized Table 3.

Table 2. Subject Disposition

Number (%) of Subjects	Placebo IV	Tanezumab 10 mg IV
Screened: 101		
Assigned to study treatment	30	29
Randomized but not treated	0	0
Treated	30	29
Completed treatment	11	13
Completed study	6	12
Discontinued treatment	19	16
Discontinued study	24	17
Analyzed for safety:		
Adverse events	30	29
Laboratory data	29	27

Completed treatment: Subjects completed treatment at Week 8 visit.
Discontinued treatment: Subjects discontinued before Week 8 visit.
Completed study: Subjects completed study at Week 16 visit.
Discontinued study: Subjects discontinued study at or before Week 16 visit.
IV = intravenous.

Table 3. Discontinuations From Study

	Placebo	Tanezumab 10 mg IV
Number (%) of Subjects	**30**	**29**
Discontinuations		
Subject died	1 (3.3)	2 (6.9)
Related to study drug	5 (16.7)	2 (6.9)
Adverse event	0	0
Insufficient clinical response	5 (16.7)	2 (6.9)
Not related to study drug	18 (60.0)	13 (44.8)
Adverse event	1 (3.3)	1 (3.4)
Does not meet entrance criteria	0	0
Lost to follow-up	0	0
Protocol violation	0	0
Study terminated by Sponsor	0	0
Withdrawn due to pregnancy	0	0
Other	17 (56.7)	12 (41.4)
Entering extension study	14 (46.7)	9 (31.0)
Other reasons	3 (10.0)	3 (10.3)
Irrespective of relationship to study drug	23 (76.7)	15 (51.7)
Adverse event	1 (3.3)	1 (3.4)
Does not meet entrance criteria	0	0
Insufficient clinical response	5 (16.7)	2 (6.9)
Lost to follow-up	0	0
Protocol violation	0	0
Study terminated by Sponsor	0	0
Withdrawn due to pregnancy	0	0
Other	17 (56.7)	12 (41.4)
Entering extension study	14 (46.7)	9 (31.0)
Other reasons	3 (10.0)	3 (10.3)
Total	24 (80)	17 (58.6)

Discontinued study: Subjects discontinued before Week 16 visit.

Demographic characteristics were similar between the placebo and the tanezumab 10 mg IV treatment groups: the proportion of female subjects was approximately half (53.3% and 55.2%, respectively), the majority of subjects were White (70.0% and 79.3%, respectively), and the mean age was similar (55.8 years and 62.1 years, respectively), with the proportion of subjects aged ≥65 years at 30.0% and 44.8%, respectively (Table 4).

Table 4. Demography (ITT)

Characteristic	Placebo IV N=30	Tanezumab 10 mg IV N=29
Gender, n (%)		
Male	14 (46.7)	13 (44.8)
Female	16 (53.3)	16 (55.2)
Age in years		
Mean (SD)	55.8 (11.9)	62.1 (11.9)
Min, max	32, 77	40, 90
Categories, n (%):		
<18	0	0
18–44	6 (20.0)	1 (3.4)
45–64	15 (50.0)	15 (51.7)
≥65	9 (30.0)	13 (44.8)
Race, n (%)		
White	21 (70.0)	23 (79.3)
Black	0	0
Asian	9 (30.0)	4 (13.8)
Other	0	2 (6.9)
Weight (kg)		
Mean (SD)	72.6 (17.3)	68.5 (12.0)
Min, max	45.0, 109.8	45.0, 93.0

ITT = intent-to-treat, IV = intravenous, Max = maximum, Min = minimum, N = number of subjects in each treatment group, n = number of subjects with analyzable data at observation, SD = standard deviation.

Efficacy Results:

Primary and Secondary Pain Endpoints:

A descriptive summary of the change from Baseline in average daily pain score by week for the ITT analysis set using BOCF is shown in Table 5.

Table 5. Summary of the Change From Baseline in Average Daily Pain Score (NRS) by Week (ITT, BOCF)

		Placebo (N=30)	Tanezumab 10 mg (N=29)
Baseline	Score		
	Mean (SD)	5.3 (0.98)	5.4 (1.02)
	Median	5.0	5.0
	Min, max	(4.0, 8.0)	(4.0, 8.0)
Week 1	Change from Baseline		
	Mean (SD)	-0.6 (0.86)	-0.8 (0.85)
	Median	-0.3	-0.8
	Min, max	(-2.7, 0.5)	(-2.5, 1.4)
Week 2	Change from Baseline		
	Mean (SD)	-0.8 (1.33)	-0.9 (1.08)
	Median	-0.7	-0.6
	Min, max	(-4.3, 1.6)	(-3.3, 1.0)
Week 4	Change from Baseline		
	Mean (SD)	-1.2 (1.46)	-1.3 (1.58)
	Median	-0.7	-0.9
	Min, max	(-4.0, 0.7)	(-4.3, 1.3)
Week 6	Change from Baseline		
	Mean (SD)	-0.9 (1.52)	-1.3 (1.81)
	Median	-0.3	-1.4
	Min, max	(-5.0, 1.9)	(-5.2, 3.0)
Week 8	Change from Baseline		
	Mean (SD)	-0.9 (1.47)	-1.4 (1.73)
	Median	-0.5	-1.2
	Min, max	(-5.0, 1.0)	(-4.8, 2.0)
Week 12	Change from Baseline		
	Mean (SD)	-0.4 (1.29)	-1.0 (1.56)
	Median	0.0	-0.2
	Min, max	(-5.0, 2.3)	(-4.6, 2.3)
Week 16	Change from Baseline		
	Mean (SD)	-0.4 (1.17)	-0.8 (1.47)
	Median	0.0	0.0
	Min, max	(-5.0, 0.0)	(-5.4, 0.5)

Average Pain score ranges from 0 (no pain) to 10 (worst pain). A change from Baseline <0 is an improvement.
BOCF = baseline observation carried forward, ITT = intent-to-treat, Max = maximum, Min = minimum, N = number of subjects, NRS = numeric rating scale, SD = standard deviation.

The summary of analysis of change from Baseline in average daily pain score to Weeks 1, 2, 4, 6, and 8 analyzed using ANCOVA is presented in Table 6.

Table 6. Summary of Analysis of Change From Baseline for Average Daily Pain Score (NRS) by Week (ITT, BOCF)

		Placebo (N=30)	Tanezumab 10 mg (N=29)
Week 1	LS mean[a] (SE)	-0.39 (0.27)	-0.52 (0.32)
	95% CI for LS mean	(-0.95, 0.17)	(-1.17, 0.13)
	Comparison vs placebo		
	LS mean difference (SE)		-0.13 (0.23)
	95% CI for LS mean difference		(-0.60, 0.34)
	p-value [b]		0.581
Week 2	LS mean[a] (SE)	-0.56 (0.38)	-0.48 (0.44)
	95% CI for LS mean	(-1.34, 0.21)	(-1.38, 0.41)
	Comparison vs placebo		
	LS mean difference (SE)		0.08 (0.32)
	95% CI for LS mean difference		(-0.56, 0.73)
	p-value[b]		0.795
Week 4	LS mean[a] (SE)	-0.71 (0.50)	-0.63 (0.58)
	95% CI for LS mean	(-1.73, 0.31)	(-1.81, 0.56)
	Comparison vs placebo		
	LS mean difference (SE)		0.08 (0.41)
	95% CI for LS mean difference		(-0.76, 0.93)
	p-value[b]		0.843
Week 6	LS mean[a] (SE)	-0.50 (0.55)	-0.76 (0.64)
	95% CI for LS mean	(-1.62, 0.61)	(-2.06, 0.54)
	Comparison vs placebo		
	LS Mean difference (SE)		-0.26 (0.45)
	95% CI for LS mean difference		(-1.18, 0.66)
	p-value[b]		0.569
Week 8	LS mean[a] (SE)	-0.56 (0.52)	-1.02 (0.60)
	95% CI for LS mean	(-1.61, 0.49)	(-2.24, 0.20)
	Comparison vs placebo		
	LS mean difference (SE)		-0.46 (0.43)
	95% CI for LS mean difference		(-1.34, 0.42)
	p-value[b]		0.292

Average Daily Pain score ranges from 0 (no pain) to 10 (worst pain).
ANCOVA model includes treatment and cancer type as fixed effects, baseline value as a covariate and study site as a random effect.
ANCOVA = analysis of covariance, BOCF = baseline observation carried forward, CI = confidence interval, ITT = intent-to-treat, LS = least square, N = number of subjects, NRS = numeric rating scale, SE = standard error, vs = versus.

a. Least squares means were estimated from the corresponding ANCOVA model.
b. The p-value was based on ANCOVA from pairwise comparisons.

A descriptive summary of the change from Baseline in average daily worst pain intensity by week for the ITT analysis set using BOCF is shown Table 7.

Table 7. Summary of the Change From Baseline in Worst Daily Pain Score (NRS) by Week (ITT, BOCF)

		Placebo (N=30)	Tanezumab 10 mg (N=29)
Week 1	Change from Baseline		
	Mean (SD)	-0.6 (0.85)	-0.8 (0.87)
	Median	-0.5	-0.6
	Min, max	(-2.43, 1.17)	(-2.43, 0.38)
Week 2	Change from Baseline		
	Mean (SD)	-1.0 (1.17)	-0.8 (1.32)
	Median	-0.9	-0.6
	Min, max	(-3.14, 1.17)	(-3.67, 1.43)
Week 4	Change from Baseline		
	Mean (SD)	-1.2 (1.40)	-1.2 (1.70)
	Median	-1.2	-0.4
	Min, max	(-4.33, 0.71)	(-4.29, 1.52)
Week 6	Change from Baseline		
	Mean (SD)	-0.9 (1.52)	-1.0 (1.82)
	Median	-0.4	-1
	Min, max	(-3.86, 1.05)	(-5.86, 2.67)
Week 8	Change from Baseline		
	Mean (SD)	-0.9 (1.53)	-1.1 (1.77)
	Median	-0.3	-0.7
	Min, max	(-5.75, 0.81)	(-5.71, 2.67)
Week 12	Change from Baseline		
	Mean (SD)	-0.4 (1.42)	-0.7 (1.40)
	Median	0	0
	Min, max	(-4.86, 2.83)	(-5.71, 1.38)
Week 16	Change from Baseline		
	Mean (SD)	-0.4 (1.16)	-0.5 (1.27)
	Median	0	0
	Min, max	(-4.67, 0.86)	(-5.57, 1.24)

Average Pain score ranges from 0 (no pain) to 10 (worst pain). A change from Baseline <0 is an improvement.
BOCF = baseline observation carried forward, ITT = intent-to-treat, Max = maximum, Min = minimum, N = number of subjects, NRS = numeric rating scale, SD = standard deviation.

The ANCOVA analysis of the change from Baseline in daily worst pain intensity scores by week using BOCF is shown in Table 8.

Table 8. Summary of Analysis of Change From Baseline for the Worst Daily Pain Score (NRS) by Week (ITT, BOCF)

		Placebo (N=30)	Tanezumab 10 mg (N=29)
Week 1	LS mean (SE)[a]	-0.69 (0.28)	-0.94 (0.33)
	95% CI for LS mean	(-1.27, -0.11)	(-1.60, -0.27)
	Comparison vs placebo		
	LS mean difference (SE)		-0.24 (0.23)
	95% CI for LS mean difference		(-0.72, 0.23)
	p-value[b]		0.299
Week 2	LS mean (SE)[a]	-0.75 (0.41)	-0.53 (0.48)
	95% CI for LS mean	(-1.60, 0.09)	(-1.51, 0.44)
	Comparison vs placebo		
	LS mean difference (SE)		0.22 (0.34)
	95% CI for LS mean difference		(-0.47, 0.91)
	p-value[b]		0.519
Week 4	LS mean (SE)[a]	-0.89 (0.52)	-0.77 (0.60)
	95% CI for LS mean	(-1.95, 0.16)	(-1.99, 0.45)
	Comparison vs placebo		
	LS mean difference (SE)		0.12 (0.42)
	95% CI for LS mean difference		(-0.74, 0.98)
	p-value[b]		0.776
Week 6	LS mean (SE)[a]	-0.63 (0.55)	-0.65 (0.64)
	95% CI for LS mean	(-1.76, 0.50)	(-1.96, 0.67)
	Comparison vs placebo		
	LS mean difference (SE)		-0.01 (0.45)
	95% CI for LS mean difference		(-0.93, 0.91)
	p-value[b]		0.978
Week 8	LS mean (SE)[a]	-0.79 (0.55)	-0.98 (0.63)
	95% CI for LS mean	(-1.91, 0.32)	(-2.27, 0.31)
	Comparison vs placebo		
	LS mean difference (SE)		-0.18 (0.45)
	95% CI for LS mean difference		(-1.10, 0.73)
	p-value[b]		0.689

A change from Baseline <0 is an improvement.
ANCOVA model includes treatment and cancer type as fixed effects, baseline value as a covariate and study site as a random effect.
ANCOVA = analysis of covariance, BOCF = baseline observation carried forward, CI = confidence interval, ITT = intent-to-treat, LS = least square, N = number of subjects, NRS = numeric rating scale SE = standard error, vs = versus.

a. Least squares means were estimated from the corresponding ANCOVA model.
b. The p-value was based on ANCOVA from pairwise comparisons.

The summary of the change from Baseline in BPI-sf score for average pain by week using BOCF is presented in Table 9.

Table 9. Summary of Change From Baseline in BPI-sf Score for Average Pain by Week (ITT, BOCF)

		Placebo (N=30)	Tanezumab 10 mg (N=29)
Baseline	Score		
	N	27	27
	Mean (SD)	5.1 (1.14)	5.2 (1.15)
	Median	5	5
	Min, max	(3.00, 8.00)	(3.00, 8.00)
Week 1	Change from Baseline		
	N	27	27
	Mean(SD)	-0.4 (1.12)	-0.4 (1.65)
	Median	0	0
	Min, max	(-4.00, 2.00)	(-4.00, 4.00)
Week 2	Change from Baseline		
	N	27	27
	Mean (SD)	-0.8 (1.15)	-0.9 (1.99)
	Median	-1	-1
	Min, max	(-4.00, 1.00)	(-5.00, 6.00)
Week 4	Change from Baseline		
	N	27	27
	Mean (SD)	-1.0 (1.84)	-1.0 (1.97)
	Median	0	-1
	Min, max	(-5.00, 2.00)	(-5.00, 5.00)
Week 6	Change from Baseline		
	N	27	27
	Mean(SD)	-0.9 (1.78)	-1.0 (1.54)
	Median	0	0
	Min, max	(-5.00, 2.00)	(-4.00, 2.00)
Week 8	Change from Baseline		
	N	27	27
	Mean(SD)	-0.9 (1.84)	-1.0 (1.43)
	Median	0	0
	Min, max	(-5.00, 2.00)	(-4.00, 1.00)
Week 12	Change from Baseline		
	N	27	27
	Mean (SD)	-0.5 (1.40)	-0.9 (1.17)
	Median	0	0
	Min, max	(-5.00, 2.00)	(-3.00, 0.00)
Week 16	Change from Baseline		
	N	27	27
	Mean (SD)	-0.4 (1.22)	-0.7 (1.39)
	Median	0	0
	Min, max	(-5.00, 0.00)	(-5.00, 1.00)

A change from Baseline <0 is an improvement.
BOCF = baseline observation carried forward, BPI-sf = Brief Pain Inventory - short form, ITT = intent-to-treat, Max = maximum, Min = minimum, N = number of subjects, SD = standard deviation.

The summary of the analysis of change from Baseline in BPI-sf for average pain by week using BOCF is provided in Table 10.

Table 10. Summary of Analysis of Change From Baseline in BPI-sf for Average Pain by Week (ITT, BOCF)

		Placebo (N=30)	Tanezumab 10 mg (N=29)
Week 1	LS mean (SE)[a]	-0.64 (0.45)	-0.60 (0.52)
	95% CI for LS mean	(-1.56, 0.28)	(-1.66, 0.46)
	Comparison vs placebo		
	LS mean difference (SE)		0.04 (0.34)
	95% CI for LS mean difference		(-0.66, 0.74)
	p-value[b]		0.906
Week 2	LS mean (SE) [a]	-0.91 (0.58)	-0.96 (0.65)
	95% CI for LS mean	(-2.10, 0.28)	(-2.31, 0.38)
	Comparison vs placebo		
	LS mean difference (SE)		-0.05 (0.44)
	95% CI for LS mean difference		(-0.95, 0.85)
	p-value[b]		0.906
Week 4	LS mean (SE) [a]	-0.68 (0.67)	-0.42 (0.77)
	95% CI for LS mean	(-2.05, 0.69)	(-2.02, 1.17)
	Comparison vs placebo		
	LS mean difference (SE)		0.26 (0.50)
	95% CI for LS mean difference		(-0.78, 1.29)
	p-value[b]		0.613
Week 6	LS mean (SE) [a]	-0.72 (0.61)	-0.73 (0.69)
	95% CI for LS mean	(-1.97, 0.53)	(-2.15, 0.69)
	Comparison vs placebo		
	LS mean difference (SE)		-0.01 (0.46)
	95% CI for LS mean difference		(-0.95, 0.94)
	p-value[b]		0.988
Week 8	LS mean (SE)[a]	-0.48 (0.62)	-0.53 (0.70)
	95% CI for LS mean	(-1.76, 0.80)	(-1.97, 0.91)
	Comparison vs placebo		
	LS mean difference (SE)		-0.05 (0.47)
	95% CI for LS mean difference		(-1.01, 0.92)
	p-value[b]		0.922

ANCOVA model includes treatment and cancer type as fixed effects, baseline value as a covariate and study site as a random effect.
ANCOVA = analysis of covariance, BOCF = baseline observation carried forward, BPI-sf = Brief Pain Inventory - short form, CI = confidence interval, ITT = intent-to-treat, LS = least square, N = number of subjects, SE = standard error, vs = versus.

a. Least squares means were estimated from the corresponding ANCOVA model.
b. The p-value was based on ANCOVA from pairwise comparisons.

The summary of the change from Baseline in BPI-sf score for worst pain by week using BOCF is presented in Table 11.

Table 11. Summary of Change From Baseline in BPI-sf Score for Worst Pain by Week (ITT, BOCF)

		Placebo (N=30)	Tanezumab 10 mg (N=29)
Baseline	Score		
	N	27	27
	Mean (SD)	6.0 (1.09)	6.1 (1.54)
	Median	6.0	6.0
	Min, max	(4.00, 8.00)	(4.00, 9.00)
Week 1	Change from Baseline		
	N	27	27
	Mean(SD)	-0.4 (1.42)	-0.8 (1.76)
	Median	0.0	0.0
	Min, max	(-4.00, 4.00)	(-5.00, 3.00)
Week 2	Change from Baseline		
	N	27	27
	Mean (SD)	-1.0 (1.74)	-1.0 (1.74)
	Median	-1.0	-1.0
	Min, max	(-4.00, 5.00)	(-6.00, 2.00)
Week 4	Change from Baseline		
	N	27	27
	Mean (SD)	-0.8 (1.92)	-1.2 (2.01)
	Median	0.0	-1.0
	Min, max	(-5.00, 3.00)	(-6.00, 2.00)
Week 6	Change from Baseline		
	N	27	27
	Mean(SD)	-0.7 (2.25)	-0.7 (2.02)
	Median	0.0	0.0
	Min, max	(-6.00, 5.00)	(-6.00, 3.00)
Week 8	Change from Baseline		
	N	27	27
	Mean(SD)	-0.7 (1.98)	-1.1 (2.09)
	Median	0.0	0.0
	Min, max	-6.00, 4.00)	(-8.00, 1.00)
Week 12	Change from Baseline		
	N	27	27
	Mean (SD)	-0.7 (1.77)	-0.4 (1.48)
	Median	0.0	0.0
	Min, max	(-5.00, 3.00)	(-4.00, 4.00)
Week 16	Change from Baseline		
	N	27	27
	Mean (SD)	-0.6 (1.34)	-0.5 (1.09)
	Median	0.0	0.0
	Min, max	(-5.00, 0.00)	(-5.00, 0.00)

A change from Baseline <0 is an improvement.
BOCF = baseline observation carried forward, BPI-sf = Brief Pain Inventory - short form, ITT = intent-to-treat, Max = maximum, Min = minimum, N = number of subjects, SD = standard deviation.

The summary of the analysis of change from Baseline in BPI-sf for worst pain by week using BOCF is provided in Table 12.

Table 12. Summary of Analysis of Change From Baseline in BPI-sf for Worst Pain by Week (ITT, BOCF)

		Placebo (N=30)	Tanezumab 10 mg (N=29)
Week 1	LS mean (SE)[a]	-0.34 (0.54)	-0.65 (0.61)
	95% CI for LS mean	(-1.45, 0.78)	(-1.91, 0.61)
	Comparison vs placebo		
	LS mean difference (SE)		-0.32 (0.41)
	95% CI for LS mean difference		(-1.16, 0.52)
	p-value[b]		0.445
Week 2	LS mean (SE)	-1.16 (0.64)	-1.15 (0.74)
	95% CI for LS mean	(-2.48, 0.16)	(-2.68, 0.37)
	Comparison vs placebo		
	LS mean difference (SE)		0.00 (0.49)
	95% CI for LS mean difference		(-1.00, 1.00)
	p-value		0.992
Week 4	LS mean (SE)	-0.14 (0.70)	-0.38 (0.80)
	95% CI for LS mean	(-1.59, 1.31)	(-2.02, 1.26)
	Comparison vs placebo		
	LS mean difference (SE)		-0.24 (0.53)
	95% CI for LS mean difference		(-1.34, 0.86)
	p-value		0.655
Week 6	LS mean (SE)	-0.76 (0.77)	-0.66 (0.87)
	95% CI for LS mean	(-2.34, 0.82)	(-2.45, 1.13)
	Comparison vs placebo		
	LS mean difference (SE)		0.10 (0.58)
	95% CI for LS mean difference		(-1.09, 1.30)
	p-value		0.860
Week 8	LS mean (SE)	-0.43 (0.77)	-0.74 (0.89)
	95% CI for LS mean	(-2.02, 1.16)	(-2.58, 1.10)
	Comparison vs placebo		
	LS mean difference (SE)		-0.31 (0.59)
	95% CI for LS mean difference		(-1.52, 0.89)
	p-value		0.595

ANCOVA model includes treatment and cancer type as fixed effects, baseline value as a covariate and study site as a random effect.
ANCOVA = analysis of covariance, BOCF = baseline observation carried forward, BPI-sf = Brief Pain Inventory - short form, CI = confidence interval, ITT = intent-to-treat, LS = least square, N = number of subjects, SE = standard error, vs = versus.

a. Least squares means were estimated from the corresponding ANCOVA model.
b. The p-value was based on ANCOVA from pairwise comparisons.

A summary of the analysis of daily average pain reduction ≥30%, ≥50%, ≥70% and ≥90% from Baseline by week using BOCF is displayed in Table 13.

Table 13. Summary of Analysis of Average Daily Pain Reduction: ≥30%, ≥50%, ≥70% and ≥90% Improvement From Baseline (ITT, BOCF)

		Placebo (N=30) n (%)	Tanezumab 10mg (N=29) n (%)
Week 1	≥30% reduction		
	Yes	4 (13.3%)	3 (10.3%)
	No	26 (86.7%)	26 (89.7%)
	Vs placebo		
	Odds ratio		0.75
	95% CI for odds ratio		(0.10, 4.94)
	p-value[a]		1.000
	≥50% reduction		
	Yes	0	1 (3.4%)
	No	30 (100.0%)	28 (96.6%)
	Vs placebo		
	Odds ratio		-
	95% CI for odds ratio		(0.05, -)
	p-value[a]		0.492
	≥70% reduction		
	Yes	0	0
	No	30 (100.0%)	29 (100.0%)
	Vs placebo		
	Odds ratio		-
	95% CI for odds ratio		-
	p-value[a]		-
	≥90% reduction		
	Yes	0	0
	No	30 (100.0%)	29 (100.0%)
	Vs placebo		
	Odds ratio		-
	95% CI odds ratio		-
	p-value[a]		-
Week 2	≥30% reduction		
	Yes	8 (26.7%)	7 (24.1%)
	No	22 (73.3%)	22 (75.9%)
	Vs placebo		
	Odds ratio		0.88
	95% CI for odds ratio		(0.23, 3.32)
	p-value[a]		1.000
	≥50% reduction		
	Yes	3 (10.0%)	2 (6.9%)
	No	27 (90.0%)	27 (93.1%)
	Vs placebo		
	Odds ratio		0.67
	95% CI for odds ratio		(0.05, 6.35)
	p-value[a]		1.000
	≥70% reduction		
	Yes	0	0
	No	30 (100.0%)	29 (100.0%)
	Vs placebo		
	Odds ratio		-
	95% CI for odds ratio		-
	p-value[a]		-

Table 13. Summary of Analysis of Average Daily Pain Reduction: ≥30%, ≥50%, ≥70% and ≥90% Improvement From Baseline (ITT, BOCF)

		Placebo (N=30) n (%)	Tanezumab 10mg (N=29) n (%)
	≥90% reduction		
	Yes	0	0
	No	30 (100.0%)	29 (100.0%)
	Vs placebo		
	Odds ratio		-
	95% CI odds ratio		-
	p-value[a]		-
Week 4	≥30% reduction		
	Yes	11 (36.7%)	13 (44.8%)
	No	19 (63.3%)	16 (55.2%)
	Vs placebo		
	Odds ratio		1.40
	95% CI for odds ratio		(0.44, 4.53)
	p-value[a]		0.601
	≥50% reduction		
	Yes	5 (16.7%)	8 (27.6%)
	No	25 (83.3%)	21 (72.4%)
	Vs placebo		
	Odds Ratio		1.90
	95% CI for odds ratio		(0.46, 8.51)
	p-value[a]		0.360
	≥70% reduction		
	Yes	2 (6.7%)	1 (3.4%)
	No	28 (93.3%)	28 (96.6%)
	Vs placebo		
	Odds ratio		0.50
	95% CI for odds ratio		(0.01, 10.24)
	p-value[o]		1.000
	≥90% reduction		
	Yes	0	0
	No	30 (100.0%)	29 (100.0%)
	Vs placebo		
	Odds ratio		-
	95% CI odds ratio		-
	p-value[a]		-
Week 6	≥30% reduction		
	Yes	10 (33.3%)	12 (41.4%)
	No	20 (66.7%)	17 (58.6%)
	Vs placebo		
	Odds ratio		1.41
	95% CI for odds ratio		(0.43, 4.66)
	p-value[a]		0.596
	≥50% reduction		
	Yes	6 (20.0%)	8 (27.6%)
	No	24 (80.0%)	21 (72.4%)
	Vs placebo		
	Odds ratio		1.52
	95% CI for odds ratio		(0.39, 6.24)
	p-value[a]		0.552

Table 13. Summary of Analysis of Average Daily Pain Reduction: ≥30%, ≥50%, ≥70% and ≥90% Improvement From Baseline (ITT, BOCF)

		Placebo (N=30) n (%)	Tanezumab 10mg (N=29) n (%)
	≥70% reduction		
	Yes	1 (3.3%)	2 (6.9%)
	No	29 (96.7%)	27 (93.1%)
	Vs placebo		
	Odds ratio		2.15
	95% CI for odds ratio		(0.10, 131.03)
	p-value[a]		0.612
	≥90% reduction		
	Yes	1 (3.3%)	0
	No	29 (96.7%)	29 (100.0%)
	Vs placebo		
	Odds ratio		0.00
	95% CI odds ratio		(0.00, 19.66)
	p-value[a]		1.000
Week 8	≥30% Reduction		
	Yes	6 (20.0%)	14 (48.3%)
	No	24 (80.0%)	15 (51.7%)
	Vs placebo		
	Odds ratio		3.73
	95% CI for odds ratio		(1.04, 14.32)
	p-value[a]		0.029
	≥50% reduction		
	Yes	5 (16.7%)	10 (34.5%)
	No	25 (83.3%)	19 (65.5%)
	Vs placebo		
	Odds ratio		2.63
	95% CI for odds ratio		(0.67, 11.36)
	p-value[a]		0.143
	≥70% reduction		
	Yes	2 (6.7%)	2 (6.9%)
	No	28 (93.3%)	27 (93.1%)
	Vs placebo		
	Odds ratio		1.04
	95% CI for odds ratio		(0.07, 15.25)
	p-value[a]		1.000
	≥90% reduction		
	Yes	2 (6.7%)	0
	No	28 (93.3%)	29 (100.0%)
	Vs placebo		
	Odds ratio		0.00
	95% CI odds ratio		(0.00, 3.57)
	p-value[a]		0.492

BOCF = baseline observation carried forward, CI = confidence interval, ITT = intent-to–treat, N = total number of subjects, n = number of subjects in prespecified criteria, vs = versus.

a. The p-value was based on Fisher's Exact Test.

Opioid Use and Adverse Effects:

Average Daily Opioid Consumption: A summary of average daily around-the-clock opioid use (in mg/day MED) is provided by study phase and treatment group in Table 14 and through Week 8 and Week 16 in Table 15. At Week 8, the average daily around-the-clock opioid dosage was numerically similar between the placebo and the tanezumab 10 mg IV treatment groups and not statistically significant (p=0.429).

Table 14. Summary of Average Daily Around the Clock Opioid (Morphine Equivalent) Dosage by Study Phase and Treatment Group

		Placebo (N=30)	Tanezumab 10 mg (N=29)
Dose adjust period	N	27	28
	Mean (SD)	86.4 (99.78)	96.7 (103.66)
	Median	36.3	55.0
	Min, max	(9.0, 380.0)	(9.0, 450.0)
Baseline assessment period	N	30	29
	Mean (SD)	90.3 (104.87)	97.5 (114.60)
	Median	40.0	60.0
	Min, max	(4.5, 360.0)	(9.0, 600.0)
Post baseline period	N	30	29
	Mean (SD)	90.5 (104.98)	99.4 (116.57)
	Median	39.7	50.0
	Min, max	(4.4, 360.0)	(3.6, 600.0)

Max = maximum, Min = minimum, N = number of subjects, SD = standard deviation.

Table 15. Summary of Average Daily Around the Clock Opioid (Morphine Equivalent) Dosage Through Week 8 and Week 16

		Placebo (N=30)	Tanezumab 10 mg (N=29)
Week 8	N	30	29
	Mean (SD)	90.52 (105.00)	99.96 (116.26)
	Median	40	54
	Min, max	(4, 360)	(4, 600)
Week 16	N	22	21
	Mean (SD)	85.85 (99.05)	106.75 (129.99)
	Median	50	60
	Min, max	(4, 360)	(1, 600)

Max = maximum, Min = minimum, N = number of subjects, SD = standard deviation.

A summary of average daily rescue medication opioid mediation use (in mg/day MED) is provided by study phase and treatment group in Table 16 and through Week 8 and Week 16 in Table 17. Analysis showed no statistically significant difference between the treatment groups at Week 8 (p=0.139).

Table 16. Summary of Average Daily Rescue Medication (Morphine Equivalent) by Study Phase and Treatment Group

		Placebo (N=30)	Tanezumab 10 mg (N=29)
Dose adjust period	N	19	25
	Mean (SD)	17.0 (22.21)	18.1 (23.64)
	Median	8.3	9.0
	Min, max	(0.0, 84.7)	(0.0, 90.0)
Baseline assessment period	N	22	26
	Mean (SD)	16.0 (25.67)	15.9 (23.72)
	Median	6.8	13.3
	Min, max	(0.0, 112.5)	(0.0, 120.0)
Post baseline period	N	22	26
	Mean (SD)	16.6 (31.33)	13.9 (24.97)
	Median	6.0	8.4
	Min, max	(0.0, 146.0)	(0.0, 129.0)

Max = maximum, Min = minimum, N = number of subjects, SD = standard deviation.

Table 17. Summary of Average Daily Rescue Medication (Morphine Equivalent) Dosage through Week 8 and Week 16

		Placebo (N=30)	Tanezumab 10 mg (N=29)
Week 8	N	22	26
	Mean (SD)	16.65 (31.27)	13.86 (23.46)
	Median	6	8
	Min, max	(0, 146)	(0, 121)
Week 16	N	15	19
	Mean (SD)	22.17 (40.06)	14.64 (31.38)
	Median	9	7
	Min, max	(0, 158)	(0, 140)

Max = maximum, Min = minimum, N = number of subjects, SD = standard deviation.

A summary of total average daily opioid dosage use (the sum of around-the-clock and rescue opioid use expressed as mg/day MED) is provided by study phase and treatment group in Table 18 and through Week 8 and Week 16 in Table 19. Analysis showed no statistically significant difference between the treatment groups at Week 8 (p=0.744).

Table 18. Summary of Average Daily Total Opioid (Morphine Equivalent) Dosage by Study Phase and Treatment Group

		Placebo (N=30)	Tanezumab 10 mg (N=29)
Dose adjust period	N	27	28
	Mean (SD)	98.3 (107.42)	112.8 (123.22)
	Median	40.0	65.0
	Min, max	(9.0, 417.8)	(9.0,540.0)
Baseline assessment period	N	30	29
	Mean (SD)	102.0 (112.78)	111.8 (134.59)
	Median	40.0	70.0
	Min, max	(4.5, 400)	(11.5, 720)
Post baseline period	N	30	29
	Mean (SD)	102.7 (111.83)	111.9 (137.22)
	Median	39.7	61.0
	Min, max	(9.0, 386.2)	(3.6, 729.0)

Daily total opioid (MED) = rescue medication + around the clock medication.
Max = maximum, MED = morphine equivalent dosage, Min = minimum, N = number of subjects, SD = standard deviation.

Table 19. Summary of Average Daily Total Opioid (Morphine Equivalent) Dosage Through Week 8 and Week 16

		Placebo (N=30)	Tanezumab 10 mg (N=29)
Week 8	N	30	29
	Mean (SD)	102.7 (111.79)	112.4 (135.78)
	Median	39.7	61.1
	Min, max	(9.0, 385.4)	(4.1, 720.7)
Week 16	N	22	21
	Mean (SD)	101.0 (109.66)	120.0 (157.14)
	Median	49.7	60.0
	Min, max	(9.0, 410.0)	(1.1, 740.0)

Daily total opioid (MED) = rescue medication + around the clock medication.
Max = maximum, MED = morphine equivalent dosage, Min = minimum, N = number of subjects, SD = standard deviation.

Average Number of Doses of Rescue Medication: A summary of number of doses of rescue medication required per week is provided in Table 20.

Table 20. Summary of Number of Doses of Rescue Medication by Week

		Placebo (N=30)	Tanezumab 10 mg (N=29)
Week 1	N	21	26
	Mean (SD)	5.6 (6.21)	9.5 (16.16)
	Median	3	6
	Min, max	(0, 20)	(0, 82)
Week 2	N	20	25
	Mean (SD)	5.0 (6.24)	9.0 (16.57)
	Median	3	6
	Min, max	(0, 21)	(0, 84)
Week 3	N	19	25
	Mean (SD)	5.2 (6.88)	8.9 (17.46)
	Median	2	3
	Min, max	(0, 21)	(0, 86)
Week 4	N	20	24
	Mean (SD)	6.6 (10.82)	9.0 (17.24)
	Median	2	6
	Min, max	(0, 44)	(0, 86)
Week 5	N	20	23
	Mean (SD)	7.1 (10.47)	5.5 (5.62)
	Median	3	4
	Min, max	(0, 41)	(0, 21)
Week 6	N	20	22
	Mean (SD)	8.0 (11.25)	4.8 (5.59)
	Median	5	4
	Min, max	(0, 46)	(0, 21)
Week 7	N	18	22
	Mean (SD)	9.0 (12.49)	5.9 (5.96)
	Median	6	6
	Min, max	(0, 50)	(0, 21)
Week 8	N	18	22
	Mean (SD)	9.9 (12.04)	5.8 (6.08)
	Median	8	7
	Min, max	(0, 48)	(0, 21)
Week 9	N	15	18
	Mean (SD)	3.8 (4.23)	5.2 (5.61)
	Median	3	3
	Min, max	(0, 12)	(0, 18)
Week 10	N	6	17
	Mean (SD)	3.3 (3.98)	11.0 (23.22)
	Median	2	6
	Min, max	(0, 9)	(0, 98)
Week 11	N	6	16
	Mean (SD)	4.7 (5.50)	12.1 (23.75)
	Median	4	7
	Min, max	(0, 13)	(0, 98)
Week 12	N	6	15
	Mean (SD)	4.7 (4.46)	12.6 (24.22)
	Median	5	7
	Min, max	(0, 9)	(0, 98)
Week 13	N	5	11
	Mean (SD)	4.0 (3.81)	5.8 (6.06)
	Median	5	5
	Min, max	(0, 8)	(0, 19)

Table 20. Summary of Number of Doses of Rescue Medication by Week

		Placebo (N=30)	Tanezumab 10 mg (N=29)
Week 14	N	4	11
	Mean (SD)	2.5 (3.00)	5.9 (7.30)
	Median	2	1
	Min, max	(0, 6)	(0, 18)
Week 15	N	3	11
	Mean (SD)	3.0 (5.20)	4.9 (6.55)
	Median	0	2
	Min, max	(0, 9)	(0, 18)
Week 16	N	3	10
	Mean (SD)	2.3 (4.04)	6.6 (8.35)
	Median	0	2
	Min, max	(0, 7)	(0, 21)

Max = maximum, Min = minimum, N = number of subjects, SD = standard deviation.

A summary of the analysis of number of doses of rescue medication up to Week 8 is presented in Table 21.

Table 21. Summary of Analysis of Number of Doses of Rescue Medication up to Week 8

		Placebo (N=30)	Tanezumab 10 mg (N=29)
Week 1	LS mean (SE)[a]	5.62 (1.70)	9.55 (2.54)
	95% CI for LS mean	(3.11, 10.16)	(5.67, 16.07)
	Comparison vs placebo		
	LS mean ratio (SE)		1.70 (0.68)
	95% CI for LS mean ratio		(0.77, 3.73)
	p-value[b]		0.188
Week 2	LS mean (SE)[a]	4.98 (1.76)	9.00 (2.79)
	95% CI for LS mean	(2.49, 9.94)	(4.90, 16.52)
	Comparison vs placebo		
	LS mean ratio (SE)		1.81 (0.85)
	95% CI for LS mean ratio		(0.72, 4.54)
	p-value[b]		0.207
Week 3	LS mean (SE)[a]	5.21 (2.13)	8.94 (3.14)
	95% CI for LS mean	(2.34, 11.60)	(4.49, 17.79)
	Comparison vs placebo		
	LS mean ratio (SE)		1.71 (0.92)
	95% CI for LS mean ratio		(0.60, 4.93)
	p-value[b]		0.317
Week 4	LS mean (SE)[a]	6.64 (2.53)	9.00 (3.10)
	95% CI for LS mean	(3.15, 14.00)	(4.58, 17.70)
	Comparison vs placebo		
	LS mean ratio (SE)		1.36 (0.70)
	95% CI for LS mean ratio		(0.50, 3.71)
	p-value[b]		0.554
Week 5	LS mean (SE) [a]	7.05 (2.32)	5.50 (1.70)
	95% CI for LS mean	(3.70, 13.46)	(2.99, 10.09)
	Comparison vs placebo		
	LS mean ratio (SE)		0.78 (0.35)
	95% CI for LS mean ratio		(0.32, 1.89)
	p-value[b]		0.581
Week 6	LS mean (SE)[a]	7.95 (2.50)	4.81 (1.47)
	95% CI for LS mean	(4.30, 14.71)	(2.64, 8.76)
	Comparison vs placebo		
	LS mean ratio (SE)		0.61 (0.27)
	95% CI for LS mean ratio		(0.26, 1.43)
	p-value[b]		0.252
Week 7	LS mean (SE)[a]	9.00 (3.12)	5.87 (1.87)
	95% CI for LS mean	(4.56, 17.77)	(3.15, 10.96)
	Comparison vs placebo		
	LS mean ratio (SE)		0.65 (0.31)
	95% CI for LS mean ratio		(0.26, 1.64)
	p-value[b]		0.365
Week 8	LS mean (SE)[a]	9.94 (3.16)	5.80 (1.70)
	95% CI for LS mean	(5.33, 18.55)	(3.26, 10.30)
	Comparison vs placebo		
	LS mean ratio (SE) [a]		0.58 (0.25)
	95% CI for LS mean ratio		(0.25, 1.36)
	p-value[b]		0.212

Table 21. Summary of Analysis of Number of Doses of Rescue Medication up to Week 8

CI = confidence interval, LS = least square, N = number of subjects per treatment group, SE = standard error, vs = versus.
a. Negative binomial regression model with model terms for treatment as a main effect.
b. The p-value was based on negative binomial regression model from pairwise comparisons.

Opioid-Related Symptom Distress Scale: A summary of change from Baseline in all ORSDS individual symptom MDAs and in the dimension (frequency, severity and bother) and MDA composite scores by week (ITT, observed data) is presented in Table 22. The summaries of repeated measures analysis of the change from Baseline in ORSDS scores by week to Week 8 is presented in Table 23.

Table 22. Summary of Opioid Related Symptom Distress Scale Change From Baseline by Week (ITT, Observed Data)

			Placebo N=30	Tanezumab 10 mg N=29
Fatigue MDA	Week 2	Change from Baseline		
		n	21	17
		Mean (SD)	-0.3 (0.56)	0.1 (0.46)
		Median	0	0
		Min, max	(-2.0, 0.3)	(-0.7, 1.0)
	Week 4	Change from Baseline		
		n	21	11
		Mean (SD)	-0.2 (0.57)	-0.2 (0.58)
		Median	-0.3	-0.3
		Min, max	(-1.0, 1.0)	(-1.0, 0.7)
	Week 6	Change from Baseline		
		n	21	9
		Mean (SD)	-0.2 (0.43)	-0.3 (0.62)
		Median	-0.3	0
		Min, max	(-1.3, 0.3)	(-1.7, 0.3)
	Week 8	Change from Baseline		
		n	13	3
		Mean (SD)	-0.2 (0.62)	-0.4 (1.07)
		Median	-0.3	0
		Min, max	(-1.0, 1.0)	(-1.7, 0.3)
	Week 12	Change from Baseline		
		n	5	5
		Mean (SD)	-0.4 (0.76)	-0.3 (0.53)
		Median	-0.3	-0.3
		Min, max	(-1.7, 0.3)	(-1.0, 0.3)
	Week 16	Change from Baseline		
		n	5	4
		Mean (SD)	-0.4 (0.15)	-0.5 (0.58)
		Median	-0.3	-0.7
		Min, max	(-0.7, -0.3)	(-1.0, 0.3)

Table 22. Summary of Opioid Related Symptom Distress Scale Change From Baseline by Week (ITT, Observed Data)

			Placebo N=30	Tanezumab 10 mg N=29
Drowsiness MDA	Week 2	Change from Baseline		
		n	17	12
		Mean (SD)	-0.4 (0.84)	-0.1 (0.66)
		Median	-0.3	0
		Min, max	(-2.0, 1.0)	(-1.3, 1.0)
	Week 4	Change from Baseline		
		n	17	10
		Mean (SD)	-0.2 (0.65)	0.1 (0.89)
		Median	-0.3	0
		Min, max	(-1.3, 1.3)	(-1.0, 1.3)
	Week 6	Change from Baseline		
		n	14	8
		Mean (SD)	-0.3 (0.76)	0.0 (0.62)
		Median	-0.3	0
		Min, max	(-1.3, 1.3)	(-1.0, 1.0)
	Week 8	Change from Baseline		
		n	10	3
		Mean (SD)	-0.1 (0.63)	0.0 (0.67)
		Median	0.2	0
		Min, max	(-1.3, 0.7)	(-0.7, 0.7)
	Week 12	Change from Baseline		
		n	6	7
		Mean (SD)	-0.9 (0.96)	-0.3 (0.77)
		Median	-0.7	0
		Min, max	(-2.7, 0.0)	(-1.7, 0.7)
	Week 16	Change from Baseline		
		N	4	4
		Mean (SD)	-0.5 (0.64)	-0.6 (0.92)
		Median	-0.3	-0.5
		Min, max	(-1.3, 0.0)	(-1.7, 0.3)

Table 22. Summary of Opioid Related Symptom Distress Scale Change From Baseline by Week (ITT, Observed Data)

			Placebo N=30	Tanezumab 10 mg N=29
Inability to concentrate MDA	Week 2	Change from Baseline		
		n	12	8
		Mean (SD)	-0.2 (0.46)	0.2 (0.40)
		Median	-0.2	0.2
		Min, max	(-1.0, 0.7)	(-0.3, 1.0)
	Week 4	Change from Baseline		
		n	7	7
		Mean (SD)	-0.3 (0.23)	0.1 (0.98)
		Median	-0.3	0
		Min, max	(-0.7, 0.0)	(-1.7, 1.3)
	Week 6	Change from Baseline		
		n	7	6
		Mean (SD)	-0.1 (0.38)	0.2 (0.81)
		Median	-0.3	0.2
		Min, max	(-0.7, 0.3)	(-0.7, 1.7)
	Week 8	Change from Baseline		
		n	4	2
		Mean (SD)	-0.4 (0.50)	-0.2 (1.65)
		Median	-0.3	-0.2
		Min, max	(-1.0, 0.0)	(-1.3, 1.0)
	Week 12	Change from Baseline		
		n	3	4
		Mean (SD)	-0.3 (0.33)	-0.2 (0.84)
		Median	-0.3	0
		Min, max	(-0.7, 0.0)	(-1.3, 0.7)
	Week 16	Change from Baseline		
		n	2	3
		Mean (SD)	-0.5 (0.24)	-0.1 (1.07)
		Median	-0.5	0.3
		Min, max	(-0.7, -0.3)	(-1.3, 0.7)

Table 22. Summary of Opioid Related Symptom Distress Scale Change From Baseline by Week (ITT, Observed Data)

			Placebo N=30	Tanezumab 10 mg N=29
Nausea MDA	Week 2	Change from baseline		
		n	6	8
		Mean (SD)	0.0 (0.67)	-0.0 (0.77)
		Median	0	0
		Min, max	(-1.0, 1.0)	(-1.7, 0.8)
	Week 4	Change from Baseline		
		n	3	6
		Mean (SD)	-0.2 (0.38)	0.1 (0.34)
		Median	0	0
		Min, max	(-0.7, 0.0)	(-0.3, 0.7)
	Week 6	Change from Baseline		
		n	3	3
		Mean (SD)	0.6 (0.77)	-0.7 (0.67)
		Median	1	-0.7
		Min, max	(-0.3, 1.0)	(-1.3, 0.0)
	Week 8	Change from Baseline		
		n	3	2
		Mean (SD)	-0.1 (0.38)	-0.2 (0.24)
		Median	-0.3	-0.2
		Min, max	(-0.3, 0.3)	(-0.3, 0.0)
Dizziness MDA	Week 2	Change from Baseline		
		n	7	6
		Mean (SD)	0.0 (0.36)	0.5 (0.46)
		Median	0	0.5
		Min, max	(-0.3, 0.7)	(0.0, 1.0)
	Week 4	Change from Baseline		
		n	6	5
		Mean (SD)	-0.3 (0.37)	0.5 (0.80)
		Median	-0.3	0.7
		Min, max	(-0.7, 0.3)	(-0.7, 1.3)

Table 22. Summary of Opioid Related Symptom Distress Scale Change From Baseline by Week (ITT, Observed Data)

			Placebo N=30	Tanezumab 10 mg N=29
	Week 6	Change from Baseline		
		n	3	2
		Mean (SD)	-0.2 (0.38)	0.5 (0.24)
		Median	0	0.5
		Min, max	(-0.7, 0.0)	(0.3, 0.7)
	Week 8	Change from Baseline		
		n	2	2
		Mean (SD)	-0.3 (0.47)	0.0 (0.47)
		Median	-0.3	-0.0
		Min, max	(-0.7, 0.0)	(-0.3, 0.3)
	Week 12	Change from Baseline		
		n	2	0
		Mean (SD)	-0.3 (0.47)	
		Median	-0.3	
		Min, max	(-0.7, 0.0)	
	Week 16	Change from Baseline		
		N	3	0
		Mean (SD)	-0.2 (0.51)	
		Median	-0.3	
		Min, max	(-0.7, 0.3)	
Constipation	Week 2	Change from baseline		
		n	11	10
		Mean (SD)	0.1 (1.32)	-0.1 (1.31)
		Median	0	-0.3
		Min, max	(-3.0, 2.0)	(-2.0, 2.3)
	Week 4	Change from Baseline		
		n	10	7
		Mean (SD)	-0.2 (0.67)	0.5 (0.88)
		Median	0	0.7
		Min, max	(-1.3, 0.7)	(-1.0, 1.7)

Table 22. Summary of Opioid Related Symptom Distress Scale Change From Baseline by Week (ITT, Observed Data)

			Placebo N=30	Tanezumab 10 mg N=29
	Week 6	Change from Baseline		
		n	10	5
		Mean (SD)	0.0 (0.52)	0.5 (0.90)
		Median	0	0.3
		Min, max	(-0.7,1.0)	(-0.7,1.7)
	Week 8	Change from Baseline		
		n	6	3
		Mean (SD)	0.0 (0.37)	-0.9 (0.51)
		Median	0	-1
		Min, max	(-0.7, 0.3)	(-1.3, -0.3)
	Week 12	Change from Baseline		
		n	4	5
		Mean (SD)	-0.5 (1.73)	-0.2 (0.80)
		Median	0	0
		Min, max	(-3.0, 1.0)	(-1.3, 0.7)
	Week 16	Change from Baseline		
		n	1	2
		Mean (SD)	0.0 (.)	1.2 (1.65)
		Median	0	1.2
		Min, max	(0.0, 0.0)	(0.0, 2.3)
Itching MDA	Week 2	Change from Baseline		
		n	4	2
		Mean (SD)	-0.2 (0.33)	0.0 (0.00)
		Median	0	0
		Min, max	(-0.7, 0.0)	(0.0, 0.0)
	Week 4	Change from Baseline		
		n	3	1
		Mean (SD)	0.2 (0.19)	-1.0 (.)
		Median	0.3	-1
		Min, max	(0.0, 0.3)	(-1.0, -1.0)

Table 22. Summary of Opioid Related Symptom Distress Scale Change From Baseline by Week (ITT, Observed Data)

			Placebo N=30	Tanezumab 10 mg N=29
	Week 6	Change from Baseline		
		n	2	2
		Mean (SD)	0.3 (0.00)	-0.7 (0.94)
		Median	0.3	-0.7
		Min, max	(0.3, 0.3)	(-1.3, 0.0)
	Week 8	Change from Baseline		
		N	2	2
		Mean (SD)	1.0 (0.94)	0.3 (1.41)
		Median	1	0.3
		Min, max	(0.3, 1.7)	(-0.7, 1.3)
Difficulty with urination MDA	Week 2	Change from Baseline		
		n	4	4
		Mean (SD)	0.0 (0.27)	0.5 (0.79)
		Median	0	0.5
		Min, max	(-0.3, 0.3)	(-0.3, 1.3)
	Week 4	Change from Baseline		
		n	1	4
		Mean (SD)	0.0 (.)	0.9 (1.10)
		Median	0	0.8
		Min, max	(0.0, 0.0)	(-0.3, 2.3)
	Week 6	Change from Baseline		
		n	2	2
		Mean (SD)	-0.8 (0.24)	0.3 (0.94)
		Median	-0.8	0.3
		Min, max	(-1.0, -0.7)	(-0.3, 1.0)
	Week 8	Change from Baseline		
		n	1	2
		Mean (SD)	0.0 (.)	0.5 (0.71)
		Median	0	0.5
		Min, max	(0.0, 0.0)	(0.0, 1.0)

Table 22. Summary of Opioid Related Symptom Distress Scale Change From Baseline by Week (ITT, Observed Data)

			Placebo N=30	Tanezumab 10 mg N=29
	Week 12	Change from Baseline		
		n	1	1
		Mean (SD)	0.0 (.)	-0.3 (.)
		Median	0	-0.3
		Min, max	(0.0, 0.0)	(-0.3, -0.3)
	Week 16	Change from Baseline		
		n	1	
		Mean (SD)	-0.7 (.)	
		Median	-0.7	
		Min, max	(-0.7, -0.7)	
Confusion MDA	Week 2	Change from Baseline		
		n	3	1
		Mean (SD)	-0.4 (0.51)	-0.7 (.)
		Median	-0.3	-0.7
		Min, max	(-1.0, 0.0)	(-0.7, -0.7)
	Week 4	Change from Baseline		
		n	3	1
		Mean (SD)	-0.2 (0.38)	-0.7 (.)
		Median	0	-0.7
		Min, max	(-0.7, 0.0)	(-0.7, -0.7)
	Week 6	Change from Baseline		
		n	2	1
		Mean (SD)	0.3 (0.47)	-0.7 (.)
		Median	0.3	-0.7
		Min, max	(0.0, 0.7)	(-0.7, -0.7)
	Week 8	Change from Baseline		
		n	1	0
		Mean (SD)	-0.7 (.)	
		Median	-0.7	
		Min, max	(-0.7, -0.7)	

Table 22. Summary of Opioid Related Symptom Distress Scale Change From Baseline by Week (ITT, Observed Data)

			Placebo N=30	Tanezumab 10 mg N=29
	Week 12	Change from Baseline		
		n		1
		Mean (SD)		-0.7 (.)
		Median		-0.7
		Min, max		(-0.7, -0.7)
	Week 16	Change from Baseline		
		n	1	
		Mean (SD)	0.3 (.)	
		Median	0.3	
		Min, max	(0.3, 0.3)	
Retching/vomiting MDA	Week 2	Change from Baseline		
		n	3	2
		Mean (SD)	-0.7 (0.33)	0.2 (0.24)
		Median	-0.7	0.2
		Min, max	(-1.0, -0.3)	(0.0, 0.3)
	Week 4	Change from Baseline		
		n	3	2
		Mean (SD)	0.0 (0.33)	-0.7 (0.47)
		Median	0	-0.7
		Min, max	(-0.3, 0.3)	(-1.0, -0.3)
	Week 6	Change from Baseline		
		n	2	1
		Mean (SD)	0.7 (0.94)	-0.3 (.)
		Median	0.7	-0.3
		Min, max	(0.0, 1.3)	(-0.3, -0.3)
	Week 8	Change from Baseline		
		n	1	1
		Mean (SD)	-0.7 (.)	0.0 (.)
		Median	-0.7	0
		Min, max	(-0.7, -0.7)	(0.0, 0.0)

Table 22. Summary of Opioid Related Symptom Distress Scale Change From Baseline by Week (ITT, Observed Data)

			Placebo N=30	Tanezumab 10 mg N=29
	Week 12	Change from Baseline		
		n	0	
		Mean (SD)		
		Median		
		Min, max		
	Week 16	Change from Baseline		
		n	0	
		Mean (SD)		
		Median		
		Min, max		
Frequency composite scores	Week 2	Change from Baseline		
		n	27	25
		Mean (SD)	-0.2 (0.66)	-0.0 (0.55)
		Median	-0.2	0
		Min, max	(-2.3, 1.0)	(-1.5, 1.1)
	Week 4	Change from Baseline		
		n	24	21
		Mean (SD)	-0.0 (0.69)	-0.0 (0.76)
		Median	0	-0.0
		Min, max	(-1.0, 2.0)	(-1.7, 1.3)
	Week 6	Change from Baseline		
		n	22	16
		Mean (SD)	-0.1 (0.48)	-0.3 (0.55)
		Median	-0.2	-0.2
		Min, max	(-1.3, 1.0)	(-1.5, 0.7)
	Week 8	Change from Baseline		
		n	14	6
		Mean (SD)	-0.1 (0.50)	-0.6 (0.73)
		Median	-0.2	-0.5
		Min, max	(-0.8, 1.0)	(-1.5, 0.2)

Table 22. Summary of Opioid Related Symptom Distress Scale Change From Baseline by Week (ITT, Observed Data)

			Placebo N=30	Tanezumab 10 mg N=29
	Week 12	Change from Baseline		
		n	7	10
		Mean (SD)	-0.4 (0.55)	-0.3 (0.48)
		Median	-0.4	-0.3
		Min, max	(-1.1, 0.3)	(-1.0, 0.7)
	Week 16	Change from Baseline		
		n	5	6
		Mean (SD)	-0.2 (0.46)	-0.2 (0.88)
		Median	-0.1	-0.5
		Min, max	(-0.9, 0.3)	(-1.0, 1.5)
Severity composite score	Week 2	Change from Baseline		
		n	26	25
		Mean (SD)	0.0 (0.51)	0.0 (0.53)
		Median	0	0
		Min, max	(-1.0, 1.5)	(-1.3, 1.0)
	Week 4	Change from Baseline		
		n	24	21
		Mean (SD)	-0.1 (0.50)	0.1 (0.62)
		Median	0	0
		Min, max	(-1.0, 1.4)	(-1.3, 1.5)
	Week 6	Change from Baseline		
		n	22	16
		Mean (SD)	-0.1 (0.44)	-0.0 (0.44)
		Median	0	0
		Min, max	(-1.0, 0.6)	(-1.0, 0.7)
	Week 8	Change from Baseline		
		n	14	6
		Mean (SD)	0.0 (0.45)	-0.5 (0.49)
		Median	0	-0.4
		Min, max	(-1.0, 0.7)	(-1.0, 0.0)
	Week 12	Change from Baseline		
		n	7	10
		Mean (SD)	-0.3 (0.52)	0.0 (0.31)
		Median	0	0

Table 22. Summary of Opioid Related Symptom Distress Scale Change From Baseline by Week (ITT, Observed Data)

			Placebo N=30	Tanezumab 10 mg N=29
		Min, max	(-1.4, 0.2)	(-0.5, 0.7)
	Week 16	Change from Baseline		
		n	5	6
		Mean (SD)	-0.1 (0.24)	0.0 (0.97)
		Median	0	-0.3
		Min, max	(-0.4, 0.1)	(-0.5, 2.0)
Bother composite score	Week 2	Change from Baseline		
		n	26	25
		Mean (SD)	-0.1 (0.70)	-0.0 (0.61)
		Median	0	0
		Min, max	(-1.5, 1.5)	(-1.1, 1.4)
	Week 4	Change from Baseline		
		n	24	21
		Mean (SD)	-0.1 (0.85)	-0.0 (0.79)
		Median	-0.2	0
		Min, max	(-1.7, 2.4)	(-1.7, 1.3)
	Week 6	Change from Baseline		
		n	22	16
		Mean (SD)	-0.2 (0.59)	-0.1 (0.62)
		Median	-0.3	-0.3
		Min, max	(-1.6, 0.9)	(-1.0, 1.0)
	Week 8	Change from Baseline		
		n	14	6
		Mean (SD)	-0.2 (0.54)	-0.6 (0.75)
		Median	-0.1	-0.4
		Min, max	(-1.0, 0.9)	(-2.0, 0.0)
	Week 12	Change from Baseline		
		n	7	10
		Mean (SD)	-0.5 (0.85)	-0.1 (1.05)
		Median	-0.2	-0.1
		Min, Max	(-1.9, 0.6)	(-2.0, 1.7)

Table 22. Summary of Opioid Related Symptom Distress Scale Change From Baseline by Week (ITT, Observed Data)

			Placebo N=30	Tanezumab 10 mg N=29
	Week 16	Change from Baseline		
		n	5	6
		Mean (SD)	-0.6 (0.84)	-0.4 (1.13)
		Median	-0.1	0.1
		Min, max	(-2.0, 0.0)	(-2.0, 0.8)
MDA composite score	Week 2	Change from Baseline		
		n	27	25
		Mean (SD)	-0.1 (0.51)	-0.0 (0.46)
		Median	0	-0.1
		Min, max	(-1.5, 1.2)	(-0.8, 1.0)
	Week 4	Change from Baseline		
		n	24	21
		Mean (SD)	-0.1 (0.61)	0.0 (0.62)
		Median	-0.1	-0.1
		Min, max	(-1.1, 1.8)	(-1.2, 1.3)
	Week 6	Change from Baseline		
		n	22	16
		Mean (SD)	-0.1 (0.41)	-0.1 (0.42)
		Median	-0.2	-0.1
		Min, max	(-1.1, 0.7)	(-0.8, 0.5)
	Week 8	Change from Baseline		
		n	14	6
		Mean (SD)	-0.1 (0.33)	-0.6 (0.51)
		Median	-0.2	-0.6
		Min, max	(-0.6, 0.4)	(-1.4, 0.0)
	Week 12	Change from Baseline		
		n	7	10
		Mean (SD)	-0.4 (0.50)	-0.1 (0.57)
		Median	-0.2	-0.1
		Min, max	(-1.4, 0.1)	(-1.0, 1.0)

Table 22. Summary of Opioid Related Symptom Distress Scale Change From Baseline by Week (ITT, Observed Data)

		Placebo N=30	Tanezumab 10 mg N=29
Week 16	Change from Baseline		
	n	5	6
	Mean (SD)	-0.3 (0.25)	-0.2 (0.88)
	Median	-0.2	-0.2
	Min, max	(-0.7, -0.0)	(-1.0, 1.4)

ITT = intent-to-treat, Max = maximum, MDA = multi domain average, Min = minimum, N = total number of subjects, n = number of evaluable subjects, SD = standard deviation.

Table 23. Summary of Repeated Measures Analysis of Change From Baseline to Week 8 in Opioid Related Symptom Distress Scale (OR-SDS) by Week (ITT, Observed Data)

			Placebo (N=30)	Tanezumab 10 mg (N=29)
Fatigue MDA	Week 2	LS mean (SE)[a]	-0.50 (0.14)	-0.29 (0.17)
		95% CI for LS mean	(-0.78, -0.22)	(-0.63, 0.05)
		Comparison vs placebo		
		LS mean difference (SE)		0.21 (0.17)
		95% CI for LS mean difference		(-0.13, 0.55)
		p-value[b]		0.215
	Week 4	LS mean (SE)[a]	-0.06 (0.20)	-0.07 (0.27)
		95% CI for LS mean	(-0.47, 0.36)	(-0.63, 0.49)
		Comparison vs placebo		
		LS mean difference (SE)		-0.01 (0.21)
		95% CI for LS mean difference		(-0.45, 0.42)
		p-value[b]		0.947
	Week 6	LS mean (SE) [a]	-0.21 (0.17)	-0.38 (0.24)
		95% CI for LS mean	(-0.56, 0.14)	(-0.88, 0.11)
		Comparison vs. placebo		
		LS mean difference (SE)		-0.18 (0.18)
		95% CI for LS mean difference		(-0.56, 0.20)
		p-value[b]		0.341
	Week 8	LS mean (SE) [a]	-0.31 (0.22)	-0.55 (0.44)
		95% CI for LS mean	(-0.80, 0.18)	(-1.52, 0.41)
		Comparison vs placebo		
		LS mean difference (SE)		-0.24 (0.45)
		95% CI for LS mean difference		(-1.24, 0.75)
		p-value[b]		0.600
Drowsiness MDA	Week 2	LS mean (SE) [a]	-0.20 (0.18)	-0.53 (0.27)
		95% CI for LS mean	(-0.57, 0.17)	(-1.09, 0.03)
		Comparison vs placebo		
		LS mean difference (SE)		-0.33 (0.24)
		95% CI for LS mean difference		(-0.83, 0.17)
		p-value[b]		0.180
	Week 4	LS mean (SE) [a]	-0.10 (0.26)	0.11 (0.36)
		95% CI for LS mean	(-0.65, 0.45)	(-0.65, 0.86)
		Comparison vs placebo		
		LS mean difference (SE)		0.20 (0.30)
		95% CI for LS mean difference		(-0.43, 0.84)
		p-value[b]		0.509
	Week 6	LS mean (SE) [a]	-0.22 (0.27)	-0.12 (0.36)
		95% CI for LS mean	(-0.78, 0.33)	(-0.89, 0.65)
		Comparison vs placebo		
		LS mean difference (SE)		0.10 (0.34)
		95% CI for LS mean difference		(-0.62, 0.82)
		p-value[b]		0.767
	Week 8	Comparison vs placebo		
		LS mean difference (SE)		-
		95% CI for LS mean difference		-
		p-value[b]		-

Table 23. Summary of Repeated Measures Analysis of Change From Baseline to Week 8 in Opioid Related Symptom Distress Scale (OR-SDS) by Week (ITT, Observed Data)

			Placebo (N=30)	Tanezumab 10 mg (N=29)
Inability to concentrate MDA	Week 2	LS mean (SE) [a]	-0.24 (0.15)	0.19 (0.22)
		95% CI for LS mean	(-0.56, 0.09)	(-0.28, 0.66)
		Comparison vs placebo		
		LS mean difference (SE)		0.42 (0.25)
		95% CI for LS mean difference		(-0.11, 0.95)
		p-value [b]		0.108
	Week 4	LS mean (SE) [a]	0.19 (0.32)	-0.23 (0.30)
		95% CI for LS mean	(-0.55, 0.94)	(-0.93, 0.46)
		Comparison vs placebo		
		LS mean difference (SE)		-0.43 (0.37)
		95% CI for LS mean difference		(-1.26, 0.41)
		p-value [b]		0.280
	Week 6	LS mean (SE) [a]	0.11 (0.31)	-0.08 (0.54)
		95% CI for LS mean	(-0.60, 0.82)	(-1.44, 1.27)
		Comparison vs placebo		
		LS mean difference (SE)		-0.19 (0.57)
		95% CI for LS mean difference		(-1.53, 1.15)
		p-value [b]		0.747
	Week 8	Comparison vs placebo		
		LS mean difference (SE)		-
		95% CI for LS mean difference		-
		p-value [b]		-
Nausea MDA	Week 2	LS Mean (SE) [a]	-0.01 (0.30)	-0.01 (0.26)
		95% CI for LS mean	(-0.67, 0.65)	(-0.58, 0.56)
		Comparison vs placebo		
		LS mean difference (SE)		0.00 (0.39)
		95% CI for LS mean difference		(-0.87, 0.88)
		p-value [b]		0.991
	Week 4	LS mean (SE) [a]	-0.20 (0.21)	0.09 (0.16)
		95% CI for LS mean	(-0.76, 0.35)	(-0.31, 0.49)
		Comparison vs placebo		
		LS mean difference (SE)		0.29 (0.27)
		95% CI for LS mean difference		(-0.41, 0.99)
		p-value [b]		0.335
	Week 6	LS mean (SE) [a]	0.72 (0.47)	-0.83 (0.47)
		95% CI for LS mean	(-1.29, 2.72)	(-2.84, 1.18)
		Comparison vs placebo		
		LS mean difference (SE)		-1.55 (0.70)
		95% CI for LS mean difference		(-4.57, 1.48)
		p-value [b]		0.159
	Week 8	Comparison vs placebo		
		LS mean difference (SE)		-
		95% CI for LS mean difference		-
		p-value [b]		-

Table 23. Summary of Repeated Measures Analysis of Change From Baseline to Week 8 in Opioid Related Symptom Distress Scale (OR-SDS) by Week (ITT, Observed Data)

			Placebo (N=30)	Tanezumab 10 mg (N=29)
Dizziness MDA	Week 2	LS mean (SE) [a]	0.05 (0.19)	0.44 (0.23)
		95% CI for LS mean	(-0.40, 0.50)	(-0.09, 0.98)
		Comparison vs placebo		
		LS mean difference (SE)		0.39 (0.23)
		95% CI for LS mean difference		(-0.16, 0.94)
		p-value[b]		0.136
	Week 4	Comparison vs placebo		
		LS mean difference (SE)		-
		95% CI for LS mean difference		-
		p-value[b]		-
	Week 6	LS mean (SE) [a]	-0.62 (0.28)	0.60 (0.20)
		95% CI for LS mean	(-4.21, 2.97)	(-1.95, 3.15)
		Comparison vs placebo		
		LS mean difference (SE)		1.22 (0.37)
		95% CI for LS mean difference		(-3.46, 5.90)
		p-value[b]		0.186
	Week 8	Comparison vs placebo		
		LS mean difference (SE)		-
		95% CI for LS mean difference		-
		p-value[b]		-
Constipation MDA	Week 2	LS mean (SE) [a]	0.25 (0.33)	-0.27 (0.34)
		95% CI for LS mean	(-0.44, 0.94)	(-0.98, 0.45)
		Comparison vs placebo		
		LS mean difference (SE)		-0.52 (0.48)
		95% CI for LS mean difference		(-1.52, 0.49)
		p-value[b]		0.292
	Week 4	LS mean (SE) [a]	-0.13 (0.26)	0.36 (0.29)
		95% CI for LS mean	(-0.75, 0.50)	(-0.26, 0.98)
		Comparison vs placebo		
		LS mean difference (SE)		0.48 (0.38)
		95% CI for LS mean difference		(-0.34, 1.30)
		p-value[b]		0.225
	Week 6	LS mean (SE) [a]	0.06 (0.26)	0.31 (0.31)
		95% CI for LS mean	(-0.52, 0.64)	(-0.39, 1.00)
		Comparison vs placebo		
		LS mean difference (SE)		0.25 (0.36)
		95% CI for LS mean difference		(-0.58, 1.07)
		p-value[b]		0.517
	Week 8	LS mean (SE) [a]	-0.09 (0.16)	-0.80 (0.23)
		95% CI for LS mean	(-0.52, 0.33)	(-1.38, -0.22)
		Comparison vs placebo		
		LS mean difference (SE)		-0.71 (0.29)
		95% CI for LS mean difference		(-1.45, 0.04)
		p-value		0.058

Table 23. Summary of Repeated Measures Analysis of Change From Baseline to Week 8 in Opioid Related Symptom Distress Scale (OR-SDS) by Week (ITT, Observed Data)

			Placebo (N=30)	Tanezumab 10 mg (N=29)
Itching MDA	Week 2	LS mean (SE) [a]	-0.17 (0.20)	-0.17 (0.46)
		95% CI for LS mean	(-1.05, 0.71)	(-2.13, 1.80)
		Comparison vs placebo		
		LS mean difference (SE)		-0.00 (0.58)
		95% CI for LS mean difference		(-2.48, 2.48)
		p-value[b]		1.000
	Week 4	LS mean (SE) [a]	0.17 (0.00)	-0.83 (0.00)
		95% CI for LS mean	(0.16, 0.17)	(-0.84, -0.83)
		Comparison vs placebo		
		LS mean difference (SE)		-1.00 (0.00)
		95% CI for LS mean difference		(-1.01, -0.99)
		p-value[b]		<.001
	Week 6	Comparison vs placebo		
		LS mean difference (SE)		-
		95% CI for LS mean difference		-
		p-value[b]		-
	Week 8	LS mean (SE) [a]	0.72 (0.00)	0.61 (0.00)
		95% CI for LS mean	(, -)	(, -)
		Comparison vs placebo		
		LS mean difference (SE)		-0.11 (0.00)
		95% CI for LS mean difference		(, -)
		p-value[b]		-
Difficulty with urination MDA	Week 2	LS mean (SE) [a]	-0.18 (0.30)	0.26 (0.32)
		95% CI for LS mean	(-1.01, 0.65)	(-0.63, 1.16)
		Comparison vs placebo		
		LS mean difference (SE)		0.44 (0.43)
		95% CI for LS mean difference		(-0.75, 1.63)
		p-value[b]		0.362
	Week 4	LS mean (SE) [a]	0.18 (3.24)	0.18 (1.14)
		95% CI for LS mean	(-40.92, 41.29)	(-14.30, 14.66)
		Comparison vs placebo		
		LS mean difference (SE)		-0.00 (4.08)
		95% CI for LS mean difference		(-51.87, 51.87)
		p-value[b]		1.000
	Week 6	Comparison vs placebo		
		LS mean difference (SE)		-
		95% CI for LS mean difference		-
		p-value[b]		-
	Week 8	Comparison vs placebo		
		LS mean difference (SE)		-
		95% CI for LS mean difference		-
		p-value[b]		-
Confusion MDA	Week 2	Comparison vs placebo		
		LS mean difference (SE)		-
		95% CI for LS mean difference		-
		p-value[b]		-
	Week 4	Comparison vs placebo		
		LS mean difference (SE)		-
		95% CI for LS mean difference		-

Table 23. Summary of Repeated Measures Analysis of Change From Baseline to Week 8 in Opioid Related Symptom Distress Scale (OR-SDS) by Week (ITT, Observed Data)

			Placebo (N=30)	Tanezumab 10 mg (N=29)
		p-value[b]		-
	Week 6	Comparison vs placebo		
		LS mean difference (SE)		-
		95% CI for LS mean difference		-
		p-value[b]		-
	Week 8	Comparison vs placebo		
		LS mean difference (SE)		-
		95% CI for LS mean difference		-
		p-value[b]		-
Retching / vomiting MDA	Week 2	Comparison vs placebo		
		LS mean difference (SE)		-
		95% CI for LS mean difference		-
		p-value[b]		-
	Week 4	LS mean (SE)[a]	0.41 (0.04)	-1.62 (0.09)
		95% CI for LS mean	(-0.15, 0.97)	(-2.70, -0.54)
		Comparison vs placebo		
		LS mean difference (SE)		-2.03 (0.10)
		95% CI for LS mean difference		(-3.30, -0.76)
		p-value[b]		0.031
	Week 6	LS mean (SE)[a]	( )	( )
		95% CI for LS mean	(, -)	(, -)
		Comparison vs placebo		
		LS mean difference (SE)		( )
		95% CI for LS mean difference		(, -)
		p-value[b]		-
	Week 8	Comparison vs placebo		
		LS mean difference (SE)		-
		95% CI for LS mean difference		-
		p-value[b]		-
Frequency composite scores	Week 2	LS mean (SE)[a]	-0.23 (0.17)	-0.20 (0.19)
		95% CI for LS mean	(-0.56, 0.11)	(-0.60, 0.19)
		Comparison vs placebo		
		LS mean difference (SE)		0.02 (0.15)
		95% CI for LS mean difference		(-0.28, 0.32)
		p-value[b]		0.886
	Week 4	LS mean (SE)[a]	0.05 (0.25)	-0.05 (0.28)
		95% CI for LS mean	(-0.46, 0.55)	(-0.63, 0.53)
		Comparison vs placebo		
		LS mean difference (SE)		-0.09 (0.21)
		95% CI for LS mean difference		(-0.52, 0.33)
		p-value[b]		0.660
	Week 6	LS mean (SE)[a]	-0.26 (0.18)	-0.47 (0.21)
		95% CI for LS mean	(-0.64, 0.11)	(-0.90, -0.03)
		Comparison vs placebo		
		LS mean difference (SE)		-0.20 (0.17)
		95% CI for LS mean difference		(-0.54, 0.14)
		p-value[b]		0.238

Table 23. Summary of Repeated Measures Analysis of Change From Baseline to Week 8 in Opioid Related Symptom Distress Scale (OR-SDS) by Week (ITT, Observed Data)

			Placebo (N=30)	Tanezumab 10 mg (N=29)
	Week 8	LS mean (SE) [a]	-0.17 (0.14)	-0.67 (0.20)
		95% CI for LS mean	(-0.47, 0.12)	(-1.10, -0.25)
		Comparison vs placebo		
		LS mean difference (SE)		-0.50 (0.21)
		95% CI for LS mean difference		(-0.96, -0.04)
		p-value [b]		0.035
Severity composite scores	Week 2	LS mean (SE) [a]	-0.04 (0.16)	-0.17 (0.19)
		95% CI for LS mean	(-0.36, 0.28)	(-0.55, 0.21)
		Comparison vs placebo		
		LS mean difference (SE)		-0.13 (0.14)
		95% CI for LS mean difference		(-0.42, 0.16)
		p-value [b]		0.360
	Week 4	LS mean (SE) [a]	-0.02 (0.20)	0.17 (0.23)
		95% CI for LS mean	(-0.43, 0.39)	(-0.31, 0.64)
		Comparison vs placebo		
		LS mean difference (SE)		0.19 (0.17)
		95% CI for LS mean difference		(-0.16, 0.54)
		p-value [b]		0.278
	Week 6	LS mean (SE) [a]	-0.06 (0.16)	-0.10 (0.19)
		95% CI for LS mean	(-0.39, 0.27)	(-0.48, 0.28)
		Comparison vs placebo		
		LS mean difference (SE)		-0.04 (0.15)
		95% CI for LS mean difference		(-0.34, 0.27)
		p-value		0.809
	Week 8	LS mean (SE) [a]	-0.00 (0.12)	-0.48 (0.18)
		95% CI for LS mean	(-0.26, 0.25)	(-0.87, -0.09)
		Comparison vs placebo		
		LS mean difference (SE)		-0.47 (0.22)
		95% CI for LS mean difference		(-0.93, -0.01)
		p-value [b]		0.044
Bother composite scores	Week 2	LS mean (SE) [a]	0.06 (0.20)	0.07 (0.24)
		95% CI for LS mean	(-0.34, 0.46)	(-0.41, 0.56)
		Comparison vs placebo		
		LS mean difference (SE)		0.01 (0.18)
		95% CI for LS mean difference		(-0.35, 0.38)
		p-value [b]		0.944
	Week 4	LS mean (SE) [a]	0.05 (0.30)	0.08 (0.35)
		95% CI for LS mean	(-0.56, 0.66)	(-0.62, 0.79)
		Comparison vs placebo		
		LS mean difference (SE)		0.03 (0.26)
		95% CI for LS mean difference		(-0.48, 0.55)
		p-value [b]		0.892
	Week 6	LS mean (SE) [a]	-0.19 (0.22)	-0.16 (0.27)
		95% CI for LS mean	(-0.65, 0.27)	(-0.70, 0.38)
		Comparison vs placebo		
		LS mean difference (SE)		0.03 (0.21)
		95% CI for LS mean difference		(-0.39, 0.45)
		p-value [b]		0.884
	Week 8	LS mean (SE) [a]	-0.11 (0.15)	-0.59 (0.23)

Table 23. Summary of Repeated Measures Analysis of Change From Baseline to Week 8 in Opioid Related Symptom Distress Scale (OR-SDS) by Week (ITT, Observed Data)

			Placebo (N=30)	Tanezumab 10 mg (N=29)
		95% CI for LS mean	(-0.45, 0.22)	(-1.09, -0.08)
		Comparison vs placebo		
		LS mean difference (SE)		-0.47 (0.26)
		95% CI for LS mean difference		(-1.03, 0.09)
		p-value[b]		0.095
MDA composite scores	Week 2	LS mean (SE) [a]	-0.08 (0.15)	-0.07 (0.18)
		95% CI for LS mean	(-0.38, 0.21)	(-0.43, 0.29)
		Comparison vs placebo		
		LS mean difference (SE)		0.01 (0.13)
		95% CI for LS mean difference		(-0.26, 0.28)
		p-value[b]		0.919
	Week 4	LS mean (SE) [a]	0.00 (0.23)	0.07 (0.26)
		95% CI for LS mean	(-0.45, 0.46)	(-0.47, 0.60)
		Comparison vs placebo		
		LS mean difference (SE)		0.06 (0.19)
		95% CI for LS mean difference		(-0.33, 0.45)
		p-value[b]		0.752
	Week 6	LS mean (SE) [a]	-0.19 (0.15)	-0.24 (0.18)
		95% CI for LS mean	(-0.50, 0.12)	(-0.61, 0.13)
		Comparison vs placebo		
		LS mean difference (SE)		-0.05 (0.14)
		95% CI for LS mean difference		(-0.34, 0.24)
		p-value[b]		0.715
	Week 8	LS mean (SE) [a]	-0.09 (0.10)	-0.60 (0.15)
		95% CI for LS mean	(-0.32, 0.13)	(-0.92, -0.28)
		Comparison vs placebo		
		LS mean difference (SE)		-0.50 (0.17)
		95% CI for LS mean difference		(-0.87, -0.14)
		P-value[b]		0.011

ANCOVA = analysis of covariance, CI = confidence interval, LS = least square, MDA = multi-domain average, OR-SDS = Opioid-Related Symptom Distress Scale, SE = standard error, vs = versus.
OR-SDS is a questionnaire on the frequency, severity and level of bother of 10 symptoms. For each symptom the mean of the frequency, severity and bother is calculated to become the MDA. The mean of frequency, severity and bother scores across the symptoms is defined as the frequency, severity, bother composite scores.
Repeated Measures ANCOVA model includes treatment and week as main effects, treatment-by-week as an interaction term, cancer type and baseline value as a covariate, and study site as a random effect.
Negative change from Baseline in OR-SDS means symptom improvement.
a. Least squares means were estimated from the corresponding Repeated Measures ANCOVA model.
b. The p-value was based on ANCOVA from pairwise comparisons.

Subject Function:

Change from Baseline to Weeks 1, 2, 4, 6, 8, 12, and 16, in the BPI-sf Pain Interference with Function composite score obtained at study visits using BOCF is presented in Table 24. The summary of analysis of change from Baseline in BPI-sf Pain Interference with Function composite score by week through Week 8 using BOCF is provided in Table 25. There were no statistically significant differences between treatment groups for any of the individual items of general activity, walking ability, and normal work at any time.

Table 24. Summary of Change From Baseline in BPI-sf Score for Pain Interference With Function (Composite Score) by Week (ITT, BOCF)

		Placebo (N=30)	Tanezumab 10 mg (N=29)
Baseline	Score		
	N	26	27
	Mean (SD)	5.19 (1.66)	4.90 (1.56)
	Median	5.1	5.3
	Min, max	(2.71, 8.29)	1.71, 8.71)
Week 1	Change from Baseline		
	N	26	27
	Mean (SD)	-0.8 (2.17)	-0.3 (1.49)
	Median	0.0	0.0
	Min, max	(-8.00, 2.57)	(-3.86, 2.86)
Week 2	Change from Baseline		
	N	26	27
	Mean (SD)	-1.1 (1.98)	-0.9 (1.41)
	Median	-0.9	-0.7
	Min, max	(-4.71, 3.14)	(-4.00, 2.14)
Week 4	Change from Baseline		
	N	26	27
	Mean (SD)	-1.2 (1.83)	-1.3 (1.56)
	Median	-1.1	-1.3
	Min, max	(-5.14, 3.29)	(-4.43, 2.43)
Week 6	Change from Baseline		
	N	26	27
	Mean (SD)	-0.9 (1.98)	-1.1 (1.53)
	Median	-0.2	-1.0
	Min, max	(-6.00, 3.43)	(-4.29, 2.14)
Week 8	Change from Baseline		
	N	26	27
	Mean (SD)	-0.8 (1.98)	-1.0 (1.92)
	Median	0.0	0.0
	Min, max	(-5.14, 4.43)	(-5.14, 3.00)
Week 12	Change from Baseline		
	N	26	27
	Mean (SD)	-0.1 (0.89)	-0.8 (1.56)
	Median	0.0	0.0
	Min, max	(-2.57, 1.71)	(-4.57, 1.86)
Week 16	Change from Baseline		
	N	26	27
	Mean (SD)	-0.2 (0.80)	-0.9 (1.50)
	Median	0.0	0.0
	Min, max	(-3.57, 0.29)	(-5.00, 0.71)

A change from Baseline <0 is an improvement.
BOCF = baseline observation carried forward, BPI-sf = Brief Pain Inventory - short form, ITT = intent-to-treat, Max = maximum, Min = minimum, N = number of subjects, SD = standard deviation.

Table 25. Summary of Analysis of Change From Baseline in BPI-sf Score for Pain Interference With Function (Composite Score) by Week (ITT, BOCF)

		Placebo (N=30)	Tanezumab 10 mg (N=29)
Week 1	LS mean (SE)[a]	-1.11 (0.63)	-0.90 (0.73)
	95% CI for LS mean	(-2.40, 0.18)	(-2.41, 0.61)
	Comparison vs placebo		
	LS mean difference (SE)		0.21 (0.47)
	95% CI for LS mean difference		(-0.77, 1.18)
	p-value[b]		0.666
Week 2	LS mean (SE) [a]	-1.56 (0.64)	-1.40 (0.74)
	95% CI for LS mean	(-2.89, -0.23)	(-2.93, 0.13)
	Comparison vs placebo		
	LS mean difference (SE)		0.16 (0.49)
	95% CI for LS mean difference		(-0.86, 1.18)
	p-value		0.745
Week 4	LS mean (SE) [a]	-1.34 (0.62)	-1.49 (0.71)
	95% CI for LS mean	(-2.62, -0.05)	(-2.95, -0.03)
	Comparison vs placebo		
	LS mean difference (SE)		-0.15 (0.48)
	95% CI for LS mean difference		(-1.14, 0.83)
	p-value[b]		0.749
Week 6	LS mean (SE) [a]	-0.66 (0.65)	-0.79 (0.74)
	95% CI for LS mean	(-2.00, 0.68)	(-2.32, 0.74)
	Comparison vs placebo		
	LS mean difference (SE)		-0.13 (0.50)
	95% CI for LS mean difference		(-1.16, 0.90)
	p-value[b]		0.794
Week 8	LS mean (SE) [a]	-0.45 (0.74)	-0.62 (0.84)
	95% CI for LS mean	(-1.97, 1.06)	(-2.35, 1.11)
	Comparison vs placebo		
	LS mean difference (SE)		-0.17 (0.56)
	95% CI for LS mean difference		(-1.33, 1.00)
	p-value[b]		0.772

ANCOVA model included treatment and cancer type as fixed effects, baseline value as a covariate and study site as a random effect.
ANCOVA = analysis of covariance, BOCF = baseline observation carried forward, BPI-sf = Brief Pain Inventory - short form, CI = confidence interval, ITT = intent-to-treat, LS = least square, N = number of subjects, SE = standard error, vs = versus.
a. Least squares means were estimated from the corresponding ANCOVA model.
b. The p-value was based on ANCOVA from pairwise comparison.

Global Efficacy Measures:

Table 26 provides a summary of analysis of PGESM using LOCF including time point results.

Table 26. Summary of Analysis of Patient Global Evaluation of Study Medication (ITT, LOCF)

		Placebo (N=30) n (%)	Tanezumab 10 mg (N=29) n (%)
Week 1	Poor	5 (20.8%)	1 (4.8%)
	Fair	7 (29.2%)	10 (47.6%)
	Good	12 (50.0%)	5 (23.8%)
	Excellent	0	5 (23.8%)
	Total	24 (100.0%)	21 (100.0%)
	p-value vs placebo[a]		0.399
	Time point results		
	Poor/Fair	12 (50.0%)	11 (52.4%)
	Good/Excellent	12 (50.0%)	10 (47.6%)
Week 2	Poor	6 (23.1%)	2 (8.0%)
	Fair	6 (23.1%)	10 (40.0%)
	Good	12 (46.2%)	10 (40.0%)
	Excellent	2 (7.7%)	3 (12.0%)
	Total	26 (100.0%)	25 (100.0%)
	p-value vs placebo[a]		0.779
	Time point results		
	Poor/Fair	12 (46.2%)	12 (48.0%)
	Good/Excellent	14 (53.8%)	13 (52.0%)
Week 4	Poor	5 (17.2%)	0
	Fair	12 (41.4%)	17 (63.0%)
	Good	9 (31.0%)	8 (29.6%)
	Excellent	3 (10.3%)	2 (7.4%)
	Total	29 (100.0%)	27 (100.0%)
	p-value vs placebo[a]		0.922
	Time point results		
	Poor/Fair	17 (58.6%)	17 (63.0%)
	Good/Excellent	12 (41.4%)	10 (37.0%)
Week 6	Poor	5 (17.2%)	2 (7.4%)
	Fair	12 (41.4%)	11 (40.7%)
	Good	9 (31.0%)	12 (44.4%)
	Excellent	3 (10.3%)	2 (7.4%)
	Total	29 (100.0%)	27 (100.0%)
	p-value vs placebo[a]		0.811
	Time point results		
	Poor/Fair	17 (58.6%)	13 (48.1%)
	Good/Excellent	12 (41.4%)	14 (51.9%)

Table 26. Summary of Analysis of Patient Global Evaluation of Study Medication (ITT, LOCF)

		Placebo (N=30) n (%)	Tanezumab 10 mg (N=29) n (%)
Week 8	Poor	6 (20.7%)	2 (7.4%)
	Fair	13 (44.8%)	9 (33.3%)
	Good	8 (27.6%)	12 (44.4%)
	Excellent	2 (6.9%)	4 (14.8%)
	Total	29 (100.0%)	27 (100.0%)
	p-value vs placebo[a]		0.237
	Time point results		
	Poor/Fair	19 (65.5%)	11 (40.7%)
	Good/Excellent	10 (34.5%)	16 (59.3%)

N = total number of subjects, n = number of subjects meeting prespecified criteria, vs = versus.
a. The p-value was based on Cochran-Mantel-Haenszel test.

A summary of the change from Baseline in PGA by week using BOCF is provided in Table 27.

Table 27. Summary of the Change From Baseline for the Patient Global Assessment of Cancer Pain by Week (ITT, BOCF)

		Placebo (N=30)	Tanezumab 10 mg (N=29)
Week 1	Change from Baseline		
	N	26	27
	Mean (SD)	0.2 (0.94)	-0.3 (0.62)
	Median	0	0
	Min, max	(-2.00, 3.00)	(-2.00, 1.00)
Week 2	Change from Baseline		
	N	26	27
	Mean (SD)	0.0 (0.85)	-0.4 (0.57)
	Median	0	0
	Min, max	(-2.00, 3.00)	(-1.00,1.00)
Week 4	Change from Baseline		
	N	26	27
	Mean (SD)	-0.2 (0.86)	-0.5 (0.75)
	Median	0	-1
	Min, max	(-3.00, 1.00)	(-2.00, 1.00)
Week 6	Change from Baseline		
	N	26	27
	Mean (SD)	-0.3 (0.92)	-0.4 (0.80)
	Median	0	0
	Min, max	(-3.00, 1.00)	(-2.00, 1.00)
Week 8	Change from Baseline		
	N	26	27
	Mean (SD)	-0.1 (1.02)	-0.3 (0.91)
	Median	0	0
	Min, max	(-3.00, 2.00)	(-2.00, 1.00)
Week 12	Change from Baseline		
	N	26	27
	Mean (SD)	-0.1 (0.48)	-0.4 (0.63)
	Median	0	0
	Min, max	(-1.00, 1.00)	(-2.00, 0.00)
Week 16	Change from Baseline		
	N	26	27
	Mean (SD)	-0.0 (0.34)	-0.2 (0.51)
	Median	0	0
	Min, max	(-1.00, 1.00)	(-2.00, 0.00)

BOCF = baseline observation carried forward, Max = maximum, Min = minimum, N = number of subjects, SD = standard deviation.

The summary of analysis of change from Baseline in PGA by week using BOCF is given in Table 28.

Table 28. Summary of Analysis of Change From Baseline in Patient Global Assessment of Cancer Pain by Week (ITT, BOCF)

		Placebo (N=30)	Tanezumab 10 mg (N=29)
Week 1	LS mean (SE)[a]	-0.07 (0.29)	-0.44 (0.32)
	95% CI for LS mean	(-0.66, 0.52)	(-1.10, 0.22)
	Comparison vs placebo		
	LS mean difference (SE)		-0.37 (0.22)
	95% CI for LS mean difference		(-0.82, 0.09)
	p-value[b]		0.108
Week 2	LS mean (SE)[a]	-0.14 (0.27)	-0.41 (0.30)
	95% CI for LS mean	(-0.69, 0.41)	(-1.03, 0.21)
	Comparison vs placebo		
	LS mean difference (SE)		-0.27 (0.21)
	95% CI for LS mean difference		(-0.70, 0.16)
	p-value[b]		0.202
Week 4	LS mean (SE) [a]	-0.57 (0.27)	-0.69 (0.29)
	95% CI for LS mean	(-1.12, -0.02)	(-1.29, -0.09)
	Comparison vs placebo		
	LS mean difference (SE)		-0.12 (0.20)
	95% CI for LS mean difference		(-0.54, 0.30)
	p-value[b]		0.571
Week 6	LS mean (SE)[a]	-0.53 (0.31)	-0.58 (0.34)
	95% CI for LS mean	(-1.17, 0.11)	(-1.29, 0.12)
	Comparison vs placebo		
	LS mean difference (SE)		-0.06 (0.24)
	95% CI for LS mean difference		(-0.55, 0.43)
	p-value[b]		0.808
Week 8	LS mean (SE) [a]	-0.25 (0.34)	-0.28 (0.38)
	95% CI for LS mean	(-0.96, 0.46)	(-1.06, 0.50)
	Comparison vs placebo		
	LS mean difference (SE)		-0.03 (0.26)
	95% CI for LS mean difference		(-0.57, 0.51)
	p-value[b]		0.913

ANCOVA model included treatment and cancer type as fixed effects, baseline value as a covariate and study site as a random effect.
ANCOVA = analysis of covariance, BOCF = baseline observation carried forward, BPI-sf = Brief Pain Inventory - short form, CI = confidence interval, ITT = intent-to-treat, LS = least square, SE = standard error.
a. Least squares means were estimated from the corresponding ANCOVA model.
b. The p-value was based on ANCOVA from pairwise comparisons.

Treatment response, as measured by improvement from Baseline in PGA of ≥2, is summarized in Table 29.

Table 29. Summary of Analysis of Patient Global Assessment of Cancer Pain ≥2 Improvement From Baseline (ITT, BOCF)

	Response ≥2	Placebo (N=30) n (%)	Tanezumab 10 mg (N=29) n (%)
Week 1	Yes	1 (3.8%)	1 (3.7%)
	No	25 (96.2%)	26 (96.3%)
	Comparison vs placebo		
	Odds ratio		0.58
	95% CI for odds ratio		(0.03, 12.27)
	p-value[a]		0.724
Week 2	Yes	1 (3.8%)	0
	No	25 (96.2%)	27 (100.0%)
	Comparison vs placebo		
	Odds ratio		0
	95% CI for odds ratio		(0.00, I)
	p-value[a]		0.947
Week 4	Yes	1 (3.8%)	2 (7.4%)
	No	25 (96.2%)	25 (92.6%)
	Comparison vs placebo		
	Odds Ratio		0.5
	95% CI for Odds ratio		(0.03, 8.71)
	p-value[a]		0.634
Week 6	Yes	2 (7.7%)	4 (14.8%)
	No	24 (92.3%)	23 (85.2%)
	Comparison vs placebo		
	Odds ratio		1.03
	95% CI for odds ratio		(0.14, 7.74)
	p-value[a]		0.975
Week 8	Yes	1 (3.8%)	3 (11.1%)
	No	25 (96.2%)	24 (88.9%)
	Comparison vs placebo		
	Odds ratio		1.49
	95% CI for odds ratio		(0.12, 18.86)
	p-value[a]		0.759

BOCF = baseline observation carried forward, CI = confidence interval, ITT = intent-to-treat, N = number of subjects, n = number of subjects with pre-specified criteria, vs = versus.
a. The p-value is based on Fisher's Exact Test.

Safety Results:

Adverse Events: The incidence of the most frequently reported all-causality non-serious AEs (≥5% of subjects in either treatment group) is summarized in Table 30 and the treatment-related non-serious AEs are provided in Table 31.

Table 30. Treatment Emergent Non Serious Adverse Events for Events Having a Frequency Rate ≥5%

	Placebo n (%)	Tanezumab 10 mg n (%)
Number (%) of Subjects:		
Evaluable for Adverse Events	**30**	**29**
With Adverse Events	**16 (53.3)**	**14 (48.3)**
System organ class and MedDRA (v14.1) preferred term		
Blood and lymphatic system disorders	2 (6.7)	2 (6.9)
Anaemia	0	2 (6.9)
Lymphadenopathy	2 (6.7)	0
Gastrointestinal disorders	5 (16.7)	8 (27.6)
Constipation	2 (6.7)	3 (10.3)
Diarrhoea	1 (3.3)	2 (6.9)
Dyspepsia	2 (6.7)	0
Nausea	2 (6.7)	5 (17.2)
Vomiting	2 (6.7)	2 (6.9)
General disorders and administration site conditions	7 (23.3)	5 (17.2)
Asthenia	2 (6.7)	0
Fatigue	3 (10.0)	1 (3.4)
Oedema peripheral	2 (6.7)	2 (6.9)
Pyrexia	0	2 (6.9)
Infections and infestations	0	2 (6.9)
Urinary tract infection	0	2 (6.9)
Metabolism and nutrition disorders	2 (6.7)	0
Decreased appetite	2 (6.7)	0
Musculoskeletal and connective tissue disorders	2 (6.7)	2 (6.9)
Back pain	2 (6.7)	2 (6.9)
Nervous system disorders	3 (10.0)	2 (6.9)
Headache	2 (6.7)	0
Somnolence	1 (3.3)	2 (6.9)
Renal and urinary disorders	2 (6.7)	0
Dysuria	2 (6.7)	0
Skin and subcutaneous tissue disorders	3 (10.0)	3 (10.3)
Decubitus ulcer	0	2 (6.9)
Pruritus	2 (6.7)	1 (3.4)
Rash	2 (6.7)	0

Subjects are only counted once per treatment for each row.
Includes data up to 9999 days after last dose of study drug.
MedDRA = Medical Dictionary for Regulatory Activities, n = number of subjects with adverse event, v = version.

Table 31. Treatment Emergent Adverse Events (Treatment Related)

	Placebo n (%)	Tanezumab 10 mg n (%)
Number (%) of Subjects: Evaluable for Adverse Events	**30**	**29**
System organ class and MedDRA (v14.1) preferred term		
General disorders and administration site conditions	1 (3.3)	2 (6.9)
Fatigue	1 (3.3)	0
Influenza like illness	0	1 (3.4)
Pain	0	1 (3.4)
Musculoskeletal and connective tissue disorders	1 (3.3)	0
Bone pain	1 (3.3)	0
Nervous system disorders	3 (10.0)	2 (6.9)
Headache	2 (6.7)	0
Hyperesthesia	0	1 (3.4)
Neuropathy peripheral	0	1 (3.4)
Somnolence	1 (3.3)	1 (3.4)
Psychiatric disorders	0	1 (3.4)
Hallucination	0	1 (3.4)
Total preferred term events	5	6

Subjects are only counted once per treatment for each row.
Includes data up to 9999 days after last dose of study drug.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with adverse event, SAE = serious adverse event, v = version.

Serious Adverse Events (SAEs): The incidence of SAEs is presented in Table 32. No SAEs in either treatment group were considered to be treatment related.

Table 32. Treatment Emergent Serious Adverse Events

	Placebo n (%)	Tanezumab 10 mg n (%)
Number (%) of Subjects:		
Evaluable for Adverse Events	**30**	**29**
With Adverse Events	**4 (13.3)**	**7 (24.1)**
System organ class and MedDRA (v14.1) preferred term		
Cardiac disorders	0	1 (3.4)
Cardiac failure acute	0	1 (3.4)
Gastrointestinal disorders	0	1 (3.4)
Proctitis haemorrhagic	0	1 (3.4)
General disorders and administration site conditions	2 (6.7)	1 (3.4)
Disease progression	2 (6.7)	0
Malaise	0	1 (3.4)
Infections and infestations	1 (3.3)	2 (6.9)
Septic shock	0	1 (3.4)
Urinary tract infection	1 (3.3)	1 (3.4)
Injury, poisoning and procedural complications	0	1 (3.4)
Femur fracture	0	1 (3.4)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (3.3)	1 (3.4)
Metastatic neoplasm	1 (3.3)	0
Neoplasm malignant	0	1 (3.4)
Nervous system disorders	0	1 (3.4)
Embolic stroke	0	1 (3.4)
Respiratory, thoracic and mediastinal disorders	1 (3.3)	1 (3.4)
Lung disorder	0	1 (3.4)
Pleural effusion	1 (3.3)	0

Subjects are only counted once per treatment for each row.
Includes data up to 9999 days after last dose of study drug.
MedDRA = Medical Dictionary for Regulatory Activities, n = number of subjects with adverse events, v = version.

Discontinuations due to Adverse Events: One (1) subject in the tanezumab 10 mg IV treatment group (embolic stroke; 3.3%) and 1 subject in the placebo treatment group (disease progression; 3.4%) permanently discontinued from the study due to an AE, neither of which was attributed to study drug.

Deaths: All deaths are summarized in Table 33.

Table 33. All Subject Deaths

Treatment Group Serial Number	Sex/Age (Years)	Event With Fatal Outcome MedDRA Preferred Term	Severity	Event Start Day/Day of Death[a]	Causality
Placebo					
1	Female/52	Sepsis	unk	unk/89[b]	Unrelated to study drug[c]
2	Female/43	Disease progression	Severe	90/97[b]	Disease under study
		Pleural effusion	Severe	94/97[b]	Other (disease progression and side effect of docetaxel)
3	Female/48	Disease progression	Severe	7/unk	Disease under study
4	Male/77	Neoplasm malignant (verbatim term: progression of metastatic disease)	Severe	37/40	Disease under study
Tanezumab 10 mg IV					
5	Female/61	Cardiac failure (verbatim: acute cardial failure)	Severe	84/84	Concomitant treatment-new Chemotherapeutic regime Taxan gemcytabin
6	Male/85	Septic shock	Severe	83/84[b]	Disease under study
7	Male/54	Disease progression/ prostate cancer	Severe	28/31	Disease under study
8	Male/75	NA	NA	NA/123[d]	Disease progression

MedDRA (v14.1) coding dictionary applied.
One (1) additional subject died due to disease progression during the pre-randomization phase. Age reflects age at time of screening.
MedDRA = Medical Dictionary for Regulatory Activities, NA = not applicable, unk = unknown, v = version.

a. First day of study treatment = Day 1. Day of death day is calculated as the death date minus treatment period start date +1.
b. Subject died after having permanently discontinued study participation for other reasons.
c. The event of sepsis was unrelated to study drug, according to the Investigator's assessment; source information states it stemmed from decubitus.
d. Subject died due to disease progression after having completed the study; the death was not associated with an adverse event.

Clinical Laboratory Assessments: Overall, the incidence of subjects experiencing abnormal laboratory test values that met criteria for potential clinical concern was higher in the tanezumab 10 mg IV treatment group (93%) than in the placebo treatment group (72%). Among the most frequently reported laboratory abnormalities (≥20% in either treatment group) were lymphocytes (absolute), urine protein and urine bilirubin (qualitative), urine nitrite, and urine leukocyte esterase. Median clinical laboratory test result changes from Baseline to last observation while on study drug were generally small and not clinically meaningful in the subject population under study. A total of 13 treatment-emergent clinical laboratory AEs were reported: 6 events in 4 subjects in the placebo treatment group and 7 events in 5 subjects in the tanezumab 10 mg IV treatment group.

Other Safety Results:

No statistically significant differences in change from Baseline in NIS were observed at any visit for either treatment group. Two (2) subjects in each treatment group experienced a change from Baseline NIS ≥2.

For vital sign data (systolic blood pressure, diastolic blood pressure, heart rate, body temperature, and respiration rate) at each visit from Baseline through Week 16, mean and

maximum changes from Baseline were small, and no trends toward relevant changes from Baseline or clinically meaningful differences between treatment groups were observed over time. Overall, the distribution of maximum changes from Baseline in vital sign measurements was not remarkably different between the 2 treatment groups. No individual vital sign measurements were reported as AEs.

Mean changes from Baseline in ECG measurements were small, and no trends or clinically meaningful differences between treatment groups were observed over time. One (1) subject in the placebo treatment group had a QT interval corrected for heart rate using Bazett's formula (QTcB interval) that was both ≥500 msec and represented a maximum change from Baseline that was ≥60 msec, and 1 subject in the tanezumab 10 mg IV treatment group had a maximum QTcB interval that was ≥500 msec. No subjects experienced a QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥500 msec or a change in QTcF ≥60 msec. One (1) clinically significant ECG measurement was captured as an AE in a placebo-treated subject: moderate, non-serious tachycardia starting on Study Day 2, attributed to the disease under study.

No pattern of changes in physical examination results was noted.

Two (2) serum samples from 1 subject receiving tanezumab 10 mg IV tested positive for anti-tanezumab antibodies. These antibodies were detected as early as Week 4 and were still present in the early termination sample approximately 8 weeks after dosing. The pharmacokinetic (PK) and the efficacy profiles for this subject did not differ significantly from the PK and efficacy profiles for subjects who did not develop anti-tanezumab antibodies. There was also no clear link between the AE profile for this subject, including the SAEs of cardioembolic stroke (attributed to atrial fibrillation) and acute pneumopathy (attributed to hospitalization), and the subject's immunogenicity profile. Because the antibodies were present at low levels in both samples and were non-neutralizing in nature, a clinical consequence attributable to the presence of anti-tanezumab antibodies was unlikely.

CONCLUSIONS:

- Analgesic efficacy of a single dose of tanezumab 10 mg IV compared with placebo IV in cancer subjects taking background opioids for chronic pain due to bone metastases was not demonstrated in this study, based on the prespecified primary comparison of change in daily average pain from Baseline to Week 6 and on the additional comparison at Week 8.

- Among secondary endpoints, there was evidence of efficacy at the 30% response level at Week 8 for response defined as reduction in daily average pain, when 48.3% of subjects in the tanezumab 10 mg IV treatment group and 20.0% of subjects in the placebo IV treatment group experienced ≥30% reduction in daily average pain.

- Although differences between the 2 treatment groups did not reach statistical significance in this small study, changes from Baseline suggesting efficacy in the tanezumab 10 mg IV treatment group, when compared to the placebo IV treatment group, in cancer subjects

taking background opioids for chronic pain due to bone metastases increased numerically toward the end of the 8 week period postdose.

- Opioid consumption and rescue medication use with a single dose of tanezumab 10 mg IV in combination with opioids when compared with opioids alone (placebo IV plus opioids) was similar for both treatment groups, and differences were not statistically significant. Differences in the change from Baseline in the ORSDS composite score, frequency, severity, bother, and MDA composite scores, and individual symptom scores were small and not statistically significant, except for itching and vomiting/retching at Week 4, when the tanezumab 10 mg IV treatment group showed statistically significant improvement when compared to the placebo IV treatment group.

- The effect on subject function of a single dose of tanezumab 10 mg IV compared with placebo IV in cancer subjects taking background opioids was small and not statistically significant.

- The effect on global assessment of disease (cancer pain) scores and on global evaluation of study medication scores of a single dose of tanezumab 10 mg IV compared with placebo IV in cancer subjects taking background opioids was small and not statistically significant.

- The AE profile in this study of a single dose of tanezumab 10 mg IV compared with placebo IV in cancer subjects taking background opioids for chronic pain due to bone metastases was consistent with the subject population and previous tanezumab studies; the most commonly reported AEs likely reflect the use of background opioids in all subjects.

- A single dose of tanezumab 10 mg IV in subjects with chronic pain due to bone metastases and treated with opioids was well-tolerated in this study. No new safety issues were identified in this study.