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

**PROTOCOL NO.:** A4091029

**PROTOCOL TITLE:** Phase 2 Open Label Safety Extension Study of Tanezumab in Cancer Patients With Pain due to Bone Metastases

**Study Centers:** Nineteen (19) centers took part in the study and enrolled subjects: 1 each in Austria, Bosnia and Herzegovina, Croatia, Hungary and Lativa, 2 each in the Republic of Korea and Slovakia, 3 each in India and the United States, and 4 in Poland.

**Study Initiation and Final Completion Dates:** 29 October 2009 to14 February 2013

**Phase of Development:** Phase 2

**Study Objectives:** To evaluate the safety and efficacy of the 10 mg intravenous (IV) dose of tanezumab in cancer subjects with pain due to bone metastases who participated in the parent double-blind study (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 [NCT00545129]) and who wished to receive open-label tanezumab therapy.

**METHODS**

**Study Design:** This was a 10-month, open-label safety extension of the parent double-blind study. After 8 weeks (and no later than Week 16) in the parent study, subjects had the option of enrolling in the extension study to receive multiple infusions of tanezumab at 8 week intervals under open-label conditions. Subjects who discontinued the parent study prior to Week 8 due to lack of efficacy were eligible to enter the open label study after 8 weeks had elapsed since the last study drug infusion in the parent study. Subjects who discontinued the parent study prior to Week 8 for reasons other than lack of efficacy were not permitted to enroll in this extension study. A Termination Visit in the parent study was to be completed prior to enrolling in this extension study, and most procedures done at that time were considered part of the baseline for this study. If >30 days had elapsed since the Termination Visit, all Baseline procedures were completed. These subjects were eligible to enter this extension study after results of the Baseline laboratory tests were received. During the study, subjects were seen for 6 scheduled clinic visits and 3 telephone contacts. IV infusions of tanezumab were administered at 8 week intervals at Baseline (Day 1), and at Weeks 8, 16 and 24. Following the final infusion, an End of Study Visit was conducted 113 days later (Week 40).

Subjects who elected to terminate from the study prior to Week 40 (End of Study/Early Termination) Visit were continued to be followed for safety monitoring and serious adverse events (SAEs). Subjects who discontinued the study prematurely but did not agree to continue with safety evaluations were advised to report SAEs that occurred during the 112 days following their last dose of IV study medication. They were also advised to continue their contraceptive regimen during that same time period of 112 days after the last dose of study medication.

Subjects in Poland were able to request extended use of tanezumab from Week 40 through Week 80 (Extended-Use Period). For these subjects laboratory test results and bilateral hip x-ray reports were reviewed by the Investigator before administration of the Week 40 dose of tanezumab.

During the Extended-Use Period, subjects were seen for an additional 4 scheduled clinic visits, and 1 telephone contact. IV infusions of tanezumab were administered at 8-week intervals at Weeks 40, 48, 56, and 64. Following the final infusion, an End-of-Study Visit was conducted 112 days later (±5 days) at Week 80. The schedule of activities is presented in Table 1.

## Table 1. Schedule of Activities

| Study Activities | Treatment | | | | | | End-of-Study/Early Termination |
|---|---|---|---|---|---|---|---|
| | Baseline | Week 2 | Week 4 | Weeks 8, 48[a] | Weeks 12, 32, 72[a] | Weeks 16, 24, 56[a], 64[a] | Weeks 40, 80[a] |
| Study Visit/Phone Contact | V1 | V2 | V3 | V4, V10[a] | V5, V8, V13[a] | V6, V7, V11[a] , V12[a] | V9, V14[a] |
| Study Day | Day 1 | (±3 Days) Telephone Contact | Day 29 (±3 Days) | Day 57, Day 337 (±5 Days) | Day 85, Day 225, Day 505 (±5 Days) Telephone Contacts | Day 113, Day 169, Day 393, Day 449 (±5 Days) Dosing Visits | Day 282, Day 561 (±5 Days) |
| Informed consent | X | | | | | | |
| Inclusion/exclusion criteria | X | | | | | | |
| Medical history/cancer history/demographics | X | | | | | | |
| Physical examination | (X) | | | | | | X |
| Radiographic assessment of hips (bilateral x-ray) | (X)[b] | | | | | | X[b] |
| Karnofsky performance scale | (X) | | | | | | X[c] |
| Neurological examination/neuropathy impairment score | (X) | | X | X | | X | X |
| Vital signs (T, BP, HR, RR) | (X)[d] | | X | X[d] | | X[d] | X |
| Weight | (X) | | | | | | X |
| Laboratory | | | | | | | |
| Hematology | (X) | | | X | | X | X |
| Blood Chemistry | (X) | | | X | | X | X |
| Urinalysis | (X) | | | X | | X | X |
| Pregnancy test[e] | (X) | | | X | | X | X |
| Serum anti-drug antibody | (X) | | | | | | X |
| Plasma pharmacokinetic sample | (X) | | | | | | X |
| 12-lead electrocardiogram (ECG) | (X) | | | X | | | X |
| Trial treatment: | | | | | | | |
| Tanezumab 10 mg IV | X | | | X | | X | X[f] |

## Table 1. Schedule of Activities

| Study Activities | Treatment | | | | | | End-of-Study/Early Termination |
|---|---|---|---|---|---|---|---|
| | Baseline | Week 2 | Week 4 | Weeks 8, 48[a] | Weeks 12, 32, 72[a] | Weeks 16, 24, 56[a], 64[a] | Weeks 40, 80[a] |
| Study Visit/Phone Contact | V1 | V2 | V3 | V4, V10[a] | V5, V8, V13[a] | V6, V7, V11[a] , V12[a] | V9, V14[a] |
| Study Day | Day 1 | (±3 Days) Telephone Contact | Day 29 (±3 Days) | Day 57, Day 337 (±5 Days) | Day 85, Day 225, Day 505 (±5 Days) Telephone Contacts | Day 113, Day 169, Day 393, Day 449 (±5 Days) Dosing Visits | Day 282, Day 561 (±5 Days) |
| Subject reported assessments completed at study visits | | | | | | | |
| Brief Pain Inventory Short Form | (X) | | X | X | | X | X |
| Other assessments | | | | | | | |
| Adverse event assessment[g] | (X)[d] | X | X | X[d] | X | X[d] | X |
| Concomitant medication review[g] | (X) | X | X | X | X | X | X |
| Cancer pain medication review | (X) | X | X | X | X | X | X |

(X) = If completed previously in the parent study (Termination Visit), these test results could be used as baseline for this extension study. If > 30 days had elapsed since the Termination Visit, all Baseline procedures were completed and laboratory results received prior to study drug administration. Blood samples for anti-drug antibody testing and PK sampling were obtained prior to study drug dosing.
BP = blood pressure, ECG = electrocardiogram, HR = heart rate, IEC = Independent Ethics Committee, IRB = Institutional Review Board, PK = pharmacokinetic, RR = respiratory rate, SAE = serious adverse event, T = temperature, V = visit.

a. Only subjects in Poland who entered the Extended-Use Period who went beyond Visit 9 (Week 40).
b. Initial bilateral x-rays of the hips occurred at Baseline if the subject had not been randomized. For subjects who had already been randomized, the initial bilateral x-rays of the hips occurred at the subject's next regularly scheduled clinic visit. Bilateral x-rays of the hips were also obtained at End-of-Study or Early Termination Visit. If a subject's last set of hip x-rays were obtained in the parent double-blind study, the requirement for baseline hip x-rays in this extension study could have been waived. If the subject had x-rays of the hips obtained ≤30 days from the End-of-Study/Early Termination Visit, the requirement for the End-of-Study/Early Termination x-rays could have been waived.
c. Only for subjects in Poland who entered the Extended-Use Period.
d. Vital signs and assessment for adverse events 1 hour postdose as well as predose.
e. For female subjects of childbearing potential: serum and urine pregnancy test prior to dosing at Baseline, predose urine pregnancy test at Weeks 8, 16, and 24, serum pregnancy test at Week 40 or Early Termination. Urine pregnancy test was performed at Baseline if results of serum pregnancy test from the parent study Termination Visit were unknown. If serum pregnancy test from the parent study Termination Visit was known to be negative, urine pregnancy test at Baseline was not necessary. For subjects in Poland entering the Extended-Use Period (Weeks 40 to 80), predose urine pregnancy test was performed at Weeks 40 (as well as serum pregnancy test), 48, 56, and 74, and serum pregnancy test at Week 80 or Early Termination. Pregnancy tests were repeated as per request of the IRB/IEC or if required by local regulations.
f. Only for subjects in Poland who entered the Extended-Use Period at Week 40.
g. Subjects who experienced increased joint pain of a severe and persistent nature were not to continue to receive study medication. These subjects 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 continue with study-specified safety evaluations at clinic visits were to be followed per defined visit time points for as long as their remaining

## Table 1. Schedule of Activities

| Study Activities | Treatment | | | | | | End-of-Study/Early Termination |
|---|---|---|---|---|---|---|---|
| | Baseline | Week 2 | Week 4 | Weeks 8, 48[a] | Weeks 12, 32, 72[a] | Weeks 16, 24, 56[a], 64[a] | Weeks 40, 80[a] |
| Study Visit/Phone Contact | V1 | V2 | V3 | V4, V10[a] | V5, V8, V13[a] | V6, V7, V11[a] , V12[a] | V9, V14[a] |
| Study Day | Day 1 | (±3 Days) Telephone Contact | Day 29 (±3 Days) | Day 57, Day 337 (±5 Days) | Day 85, Day 225, Day 505 (±5 Days) Telephone Contacts | Day 113, Day 169, Day 393, Day 449 (±5 Days) Dosing Visits | Day 282, Day 561 (±5 Days) |

time on study. These Follow-Up Visits were conducted by telephone to determine if the subject had experienced any SAEs 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, could be 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 41 subjects were enrolled in the study including, 2 in Austria, 1 each in Bosnia and Herzegovina, Croatia and Hungary, 5 in India, 4 each in the the Republic of Korea and Lativa, 13 in Poland and 5 each in Slovakia and the US.

**Diagnosis and Main Criteria for Inclusion:** Both male and female subjects of ≥18 years with prostate cancer, breast cancer, renal cell carcinoma or multiple myeloma diagnosed as having metastasized to bone, with the Karnofsky Performance Score ≥40% at Baseline and who were randomized and treated with IV study drug in the parent study.

Exclusion Criteria: Subjects who were withdrawn from the parent study for an adverse event (AE) or SAE or subjects in whom the occurrence of any AE or condition during parent study or since termination from the parent study that, in the opinion of the Investigator, would put the subject at increased safety risk were excluded from this extension study.

**Study Treatment:** Study treatment consisted of a single IV infusion of tanezumab 10 mg administered at Visit 1 (Baseline, Day 1), Visit 4 (Day 57, Week 8), Visit 6 (Day 113, Week 16), and Visit 7 (Day 169, Week 24). For subjects in Poland entering the Extended-Use Period, an IV infusion of tanezumab 10 mg was also administered at Visit 9 (Day 282, Week 40), Visit 10 (Day 337, Week 48), Visit 11 (Day 393, Week 56), and Visit 12 (Day 449, Week 64) with a ±5-day window for each IV infusion.

**Efficacy and Safety Endpoints:**

Efficacy Endpoints:

- Change from study Baseline to Weeks 4, 8, 16, 24, 40, 48, 56, 64 and 80 in the Brief Pain Inventory-Short Form (BPI-sf) pain scores at its ‘worst’, ‘least’, ‘average’ and ‘right now’,
- Change from study Baseline to Weeks 4, 8, 16, 24, 40, 48, 56, 64 and 80 in the BPI-sf Pain Interference with Function Composite Score and individual pain interference item scores obtained at study visits.

Safety Endpoints:

- AEs
- Clinical laboratory tests,
- Electrocardiograms (ECG),
- Neurologic examinations (Neuropathy Impairment Score ),
- Anti-Drug Antibody (ADA) assessments,
- Physical examinations,

- Vital signs.

**Safety Evaluations:** Safety evaluations included clinical monitoring, vital signs (heart rate, blood pressure), 12-lead ECG, AEs and safety laboratory tests.

**Statistical Methods:** This was a non-comparative extension study, no statistical testing was performed.

The Intent-to-Treat (ITT) analysis set included all subjects who received at least 1 dose of IV study medication during this extension study. This analysis set was used for all safety and efficacy data presentations for this study.

The BPI-sf efficacy endpoints were summarized by time point and as change from Baseline to each time point for data from this extension study only. The parent study Baseline was to be summarized for the subjects in the extension study ITT set. Additionally, the change from the parent study Baseline for these endpoints was summarized over both parent and extension study divided by treatment group within the parent study.

Summary tables of continuous endpoints show the number of subjects at that time point, mean (with standard deviation [SD]), median, and the range.

## RESULTS

**Subject Disposition and Demography:** A total of 42 subjects were screened and 41 subjects were treated with tanezumab 10 mg IV study medication comprising the ITT analysis set. Of these, 19 subjects received tanezumab 10 mg IV in the parent study and 22 subjects received placebo in the parent study. Subject disposition is presented in Table 2.

**Table 2. Summary of Subject Disposition**

| | Tanezumab 10 mg n (%) |
|---|---|
| Number of subjects screened | 42 |
| Number of subjects screened but not treated | 1 (2.4) |
| Number of subjects treated | 41 (100.0) |
| Number of subjects completed | 15 (36.6) |
| Number of subjects discontinued | 26 (63.4) |
| Subject died | 11 (26.8) |
| Adverse event | 6 (14.6) |
| Withdrew consent | 5 (12.2) |
| Progressive disease | 2 (4.9) |
| Insufficient clinical response | 1 (2.4) |
| Other | 1 (2.4) |
| Analyzed for safety: | |
| Adverse events | 41 (100.0) |
| Laboratory data | 34 (82.9) |

n = number of subjects in the treatment group.

Discontinuations from the study are summarized in Table 3.

**Table 3. Discontinuations From Study**

| Reason for Discontinuation | Tanezumab 10 mg (N=41) n (%) |
|---|---|
| Subject died[a] | 11 (26.8) |
| Related to study drug | 1 (2.4) |
| Insufficient clinical response | 1 (2.4) |
| Not related to study drug | 14 (34.1) |
| Adverse event | 6 (14.6) |
| Progressive disease | 2 (4.9) |
| Withdrew consent | 5 (12.2) |
| Other | 1 (2.4) |
| Irrespective of relationship to study drug | 15 (36.6) |
| Adverse event | 6 (14.6) |
| Insufficient clinical response | 1 (2.4) |
| Progressive disease | 2 (4.9) |
| Withdrew consent | 5 (12.2) |
| Other | 1 (2.4) |
| Total | 26 (63.4) |

N = total number of subjects, n = number of subjects meeting prespecified criteria.

a. One (1) subject died after Week 40 and was included as part of the study reporting period, but was not included in this row with the 11 deaths noted above. Four (4) additional subjects died after the study reporting period concluded.

Subject demography is summarized in Table 4. The mean age was 58.7 years. The majority (78.0%) of subjects were White.

**Table 4. Demography and Baseline Characteristics**

| | | Tanezumab 10 mg (N=41) |
|---|---|---|
| Gender, n (%) | Male | 20 (48.8%) |
| | Female | 21 (51.2%) |
| Age (years) | Mean (SD) | 58.7 (12.4) |
| | Range | 32-91 |
| Race, n (%) | White | 32 (78.0%) |
| | Asian | 9 (22.0%) |
| Cancer type, n (%) | Prostate | 18 (43.9%) |
| | Breast | 20 (48.8%) |
| | Multiple myeloma | 2 (4.9%) |
| | Renal cell carcinoma | 1 (2.4%) |
| Baseline average pain score (0-10) | Mean (SD) | 4.21 (2.21) |
| | Range | 0-8 |

N = total number of subjects, n = number of subjects meeting prespecified criteria, SD = standard deviation,

**Efficacy Results:**

Average Pain: The BPI-sf average pain score was rated on a scale of 0-10, where 0 is 'no pain' and 10 is "pain as bad as you can imagine". Table 5 summarizes the change from parent study Baseline in the BPI-sf average pain scores for the parent study and extension study treatment groups, and also the change from extension study Baseline in BPI-sf average pain scores for all subjects from Baseline to Weeks 4, 8, 16, 24, and 40, and for Weeks 48, 56, and 64 for the single subject in the Extended-Use Period (Week 40-Week 80).

The mean change from the extension study Baseline (4.21 [SD 2.21]) in average pain score remained below the Baseline, indicating improvement through Week 40 for all subjects combined, ranging from -0.21 (SD 2.86) at Week 40 to -1.19 (SD 1.75) at Week 24. For subjects who received tanezumab 10 mg in the parent study, improvement in average pain was maintained through Week 40 (-2.44 [SD 2.65]) of the extension study, compared to the parent study Baseline (5.16 [SD 1.01]). For subjects who received placebo in the parent study, the mean average pain score worsened to a change of 0.50 (SD 1.38) at Week 40, compared to the parent study Baseline (5.24 [SD 1.14]), though those data were based on only 6 subjects. To Week 24, though, the mean change from the parent study Baseline in average pain score remained below the Baseline, indicating improvement, ranging from -1.00 (SD 2.16) at the extension study Baseline to -1.67 (SD 2.17) at Week 4. For the single subject in the Extended-Use Period, average pain remained at the extension study Baseline at Weeks 48 and 56 (0.0), and below Baseline at Week 64 (-3.0).

**Table 5. Change From Baseline in BPI-sf Score for Average Pain, Combined Parent Study and Extension Study by Week**

| | Parent Study → Extension Study Treatment | | | | | | Change From Baseline Extension Study All Subjects (N=41) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Placebo → Tanezumab 10 mg IV (N=22) | | | Tanezumab 10 mg IV → Tanezumab 10 mg IV (N=19) | | | | | |
| **Parent Study** | **n** | **Mean (SD)** | **Median** | **n** | **Mean (SD)** | **Median** | **n** | **Mean (SD)** | **Median** |
| Baseline | 21 | 5.24[a] (1.14) | 5.0 | 19 | 5.16[a] (1.01) | 5.0 | - | - | - |
| Week 1 | 16 | -0.69 (1.20) | -1.0 | 16 | -0.94 (1.65) | -1.0 | - | - | - |
| Week 2 | 17 | -0.71 (1.10) | -1.0 | 17 | -1.47 (1.55) | -1.0 | - | - | - |
| Week 4 | 20 | -0.90 (2.07) | 0.0 | 19 | -1.42 (1.68) | -2.0 | - | - | - |
| Week 6 | 20 | -1.15 (1.90) | -1.0 | 17 | -1.47 (1.74) | -2.0 | - | - | - |
| Week 8 | 12 | -1.17 (1.85) | -0.5 | 12 | -1.83 (1.40) | -1.5 | - | - | - |
| Week 12 | 6 | -1.67 (1.86) | -1.5 | 13 | -1.69 (1.18) | -2.0 | - | - | - |
| Week 16 | 3 | -1.33 (1.53) | -1.0 | 4 | -3.25 (1.71) | -3.5 | - | - | - |
| **Extension Study** | | | | | | | | | |
| Baseline | 19 | -1.00 (2.16) | 0.0 | 18 | -1.17 (1.72) | -1.0 | 38[b] | 4.21[a] (2.21) | 5.0 |
| Week 4 | 18 | -1.67 (2.17) | -1.5 | 17 | -1.88 (1.76) | -2.0 | 33[b] | -0.82 (1.55) | -1.0 |
| Week 8 | 15 | -1.33 (1.50) | -1.0 | 15 | -1.87 (1.55) | -2.0 | 29[b] | -0.69 (1.28) | -1.0 |
| Week 16 | 12 | -1.58 (2.02) | -1.0 | 13 | -2.15 (2.41) | -2.0 | 24[b] | -0.67 (2.14) | -1.0 |
| Week 24 | 10 | -1.60 (1.58) | -1.0 | 12 | -2.58 (1.68) | -3.0 | 21[b] | -1.19 (1.75) | -1.0 |
| Week 40 | 6 | 0.50 (1.38) | 0.5 | 9 | -2.44 (2.65) | -3.0 | 14[b] | -0.21 (2.86) | -1.0 |
| Week 48 | - | - | - | 1 | -1.00 (NA) | -1.0 | 1 | 0.00 (NA) | 0.0 |
| Week 56 | - | - | - | 1 | -1.00 (NA) | -1.0 | 1 | 0.00 (NA) | 0.0 |
| Week 64 | - | - | - | 1 | -4.00 (NA) | -4.0 | 1 | -3.00 (NA) | -3.0 |

IV = intravenous, N = total number of subjects, n = number of subjects meeting prespecified criteria, NA = not applicable, SD = standard deviation.

a. Baseline shown.

b. The total of the columns showing parent study treatments does not match the column showing extension study treatment alone for the extension study Baseline and Weeks 4 to 40. This is because of the absence of either a parent study or extension study Baseline value. One (1) subject did not have an extension study Baseline value for 'average pain', and so was excluded from last column showing change from extension study Baseline (affects extension study Baseline to Week 40 rows); Three (3) subjects did not have a parent study Baseline value for 'average pain', and so are excluded from the first 2 columns showing change from parent study Baseline (2 subjects affect Weeks 4 to 40; 1 subject affects Week 4 only).

Worst Pain: Table 6 summarizes the change from the parent study Baseline in the BPI-sf worst pain scores for the parent study and extension study treatment groups, and also the change from extension study baseline in BPI-sf worst pain scores for all subjects from Baseline to Weeks 4, 8, 16, 24, and 40, and for Weeks 48, 56, and 64 for the single subject in the Extended-Use Period.

The mean change from extension study Baseline in worst pain indicated improvement from Baseline (5.34 [SD 2.63]) through Week 40 for all subjects combined, ranging from -0.25 (SD 2.92) at Week 16 to -1.14 (SD 2.20) at Week 24. For subjects who received tanezumab 10 mg in the parent study, mean change in worst pain indicated improvement compared to the parent study Baseline (5.79 [SD 1.58]) at all visits in the extension study, ranging from -0.87 (SD 1.92) at Week 8 to -2.17 (SD 1.99) at Week 24. For subjects who received placebo in the parent study, the mean change in worst pain improved in the extension study compared to the parent study Baseline (6.14 [SD 1.15]), ranging from -0.33 (SD 2.07) at Week 40 to -1.22 (SD 2.44) at Week 4 in extension study. For the single subject in the Extended-Use Period, worst pain remained unchanged at Weeks 48 and 56 and improved by -3.00 at Week 64 compared with the extension study Baseline.

**Table 6. Change From Baseline in BPI-sf Score for Worst Pain, Combined Parent Study and Extension Study by Week**

| | Parent Study → Extension Study Treatment | | | | | | Change From Baseline Extension Study All Subjects (N=41) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Placebo → Tanezumab 10 mg IV (N=22) | | | Tanezumab 10 mg IV → Tanezumab 10 mg IV (N=19) | | | | | |
| **Parent Study** | **n** | **Mean (SD)** | **Median** | **n** | **Mean (SD)** | **Median** | **n** | **Mean (SD)** | **Median** |
| Baseline | 21 | 6.14[a] (1.15) | 6.0 | 19 | 5.79[a] (1.58) | 6.0 | - | - | - |
| Week 1 | 16 | -0.63 (1.75) | -1.0 | 16 | -0.69 (1.85) | 0.0 | - | - | - |
| Week 2 | 17 | -0.94 (1.98) | -1.0 | 17 | -0.88 (1.73) | -1.0 | - | - | - |
| Week 4 | 20 | -0.75 (2.15) | 0.0 | 19 | -0.84 (1.80) | -1.0 | - | - | - |
| Week 6 | 20 | -1.00 (2.36) | -1.0 | 17 | -1.00 (2.47) | -1.0 | - | - | - |
| Week 8 | 12 | -1.25 (1.66) | -1.5 | 12 | -1.50 (2.11) | -1.0 | - | - | - |
| Week 12 | 6 | -2.67 (1.97) | -3.0 | 13 | -0.92 (2.02) | -1.0 | - | - | - |
| Week 16 | 3 | -2.67 (0.58) | -3.0 | 4 | -2.00 (2.16) | -1.5 | - | - | - |
| **Extension Study** | | | | | | | | | |
| Baseline | 19 | -0.68 (2.69) | 0.0 | 18 | -0.72 (2.08) | -0.5 | 38 | 5.34[a] (2.63) | 6.0 |
| Week 4 | 18 | -1.22 (2.44) | -0.5 | 17 | -1.24 (1.71) | -1.0 | 33 | -0.82 (1.83) | -1.0 |
| Week 8 | 15 | -0.87 (2.17) | 0.0 | 15 | -0.87 (1.92) | -1.0 | 29 | -0.48 (1.72) | 0.0 |
| Week 16 | 12 | -0.67 (2.96) | -1.0 | 13 | -1.23 (2.68) | -1.0 | 24 | -0.25 (2.92) | 0.0 |
| Week 24 | 10 | -1.20 (2.10) | -1.0 | 12 | -2.17 (1.99) | -2.0 | 21 | -1.14 (2.20) | -1.0 |
| Week 40 | 6 | -0.33 (2.07) | 0.0 | 9 | -2.11 (2.62) | -3.0 | 14 | -0.36 (2.87) | -1.0 |
| Week 48 | - | - | - | 1 | -2.0 (NA) | -2.0 | 1 | 0.00 (NA) | 0.0 |
| Week 56 | - | - | - | 1 | -2.0 (NA) | -2.0 | 1 | 0.00 (NA) | 0.0 |
| Week 64 | - | - | - | 1 | -5.0 (NA) | -5.0 | 1 | -3.00 (NA) | -3.0 |

IV = intravenous, N = total number of subjects, n = number of subjects meeting prespecified criteria, NA = not applicable, SD = standard deviation.

a. Baseline shown.

Least Pain: Table 7 summarize the change from the parent study Baseline in the BPI-sf least pain scores for the parent study and extension study treatment groups, and also the change from the extension study Baseline in BPI-sf least pain scores for all subjects from Baseline to Weeks 4, 8, 16, 24, and 40, and for Weeks 48, 56, and 64 for the single subject in the Extended-Use Period.

The mean change from the extension study Baseline in least pain indicated improvement compared to Baseline (3.34 [SD 2.20]) at all visits in the extension study for all subjects combined, ranging from -1.00 (SD 1.36) at Week 8 to -1.81 (SD 1.60) at Week 24. For subjects who received tanezumab 10 mg in the parent study, the mean change in least pain indicated improvement, remaining below the parent study Baseline (4.21 [SD 1.08]) at all visits, ranging from -2.18 (SD 2.07) at Week 4 to -3.31 (SD 2.32) at Week 16. For subjects who received placebo in the parent study, the mean change in least pain remained below the parent study Baseline (4.52 [SD 1.69]) at all visits, ranging from -1.00 (SD 1.67) at Week 40 to -2.50 (SD 1.84) at Week 24.

For the single subject in the Extended-Use Period, least pain remained below Baseline at Week 48 (-1.0), Week 56 (-1.0), and Week 64 (-1.0), compared with the extension study Baseline.

**Table 7. Change From Baseline in BPI-sf Score for Least Pain, Combined Parent Study and Extension Study by Week**

| | Parent Study → Extension Study Treatment | | | | | | Change From Baseline Extension Study All Subjects (N=41) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Placebo → Tanezumab 10 mg IV (N=22) | | | Tanezumab 10 mg IV → Tanezumab 10 mg IV (N=19) | | | | | |
| **Parent Study** | **n** | **Mean (SD)** | **Median** | **n** | **Mean (SD)** | **Median** | **n** | **Mean (SD)** | **Median** |
| Baseline | 21 | 4.52[a](1.69) | 4.0 | 19 | 4.21[a] (1.08) | 4.0 | - | - | - |
| Week 1 | 16 | -0.50 (1.51) | -0.5 | 16 | -1.06 (1.91) | -1.0 | - | - | - |
| Week 2 | 17 | -0.94 (1.14) | -1.0 | 17 | -1.41 (2.40) | -2.0 | - | - | - |
| Week 4 | 20 | -0.70 (2.05) | 0.0 | 19 | -1.47 (2.22) | -1.0 | - | - | - |
| Week 6 | 20 | -1.15 (-1.95) | -1.0 | 17 | -1.76 (2.25) | -2.0 | - | - | - |
| Week 8 | 12 | -0.83 (2.08) | 0.0 | 12 | -1.92 (2.27) | -3.0 | - | - | - |
| Week 12 | 6 | -0.67 (2.34) | 0.0 | 13 | -1.92 (1.93) | -2.0 | - | - | - |
| Week 16 | 3 | -1.00 (2.00) | -1.0 | 4 | -3.50 (1.29) | -3.5 | - | - | - |
| **Extension Study** | | | | | | | | | |
| Baseline | 19 | -1.05 (2.04) | 0.0 | 18 | -1.28 (2.14) | -1.0 | 38 | 3.34[a] (2.20) | 3.0 |
| Week 4 | 18 | -2.28 (1.96) | -2.0 | 17 | -2.18 (2.07) | -2.0 | 33 | -1.15 (1.46) | -1.0 |
| Week 8 | 15 | -1.40 (1.76) | -1.0 | 15 | -2.60 (1.64) | -3.0 | 29 | -1.00 (1.36) | -1.0 |
| Week 16 | 12 | -1.67 (2.53) | -1.5 | 13 | -3.31 (2.32) | -3.0 | 24 | -1.08 (1.93) | -1.0 |
| Week 24 | 10 | -2.50 (1.84) | -2.5 | 12 | -3.25 (1.82) | -3.0 | 21 | -1.81 (1.60) | -1.0 |
| Week 40 | 6 | -1.00 (1.67) | -1.0 | 9 | -2.67 (2.83) | -3.0 | 14 | -1.00 (2.11) | -1.0 |
| Week 48 | - | - | - | 1 | -3.0 (NA) | -3.0 | 1 | -1.00 (NA) | -1.0 |
| Week 56 | - | - | - | 1 | -3.0 (NA) | -3.0 | 1 | -1.00 (NA) | -1.0 |
| Week 64 | - | - | - | 1 | -3.0 (NA) | -3.0 | 1 | -1.00 (NA) | -1.0 |

IV = intravenous, N = total number of subjects, n = number of subjects meeting prespecified criteria, NA = not applicable, SD = standard deviation.
a. Baseline shown.

Pain Right Now: Table 8 summarizes the change from the parent study Baseline in the BPI-sf scores for pain right now for the parent study and extension study treatment groups, and also the change from the extension study Baseline in BPI-sf score for pain right now for all subjects from Baseline to Weeks 4, 8, 16, 24, and 40, and for Weeks 48, 56, and 64 for the single subject in the Extended-Use Period.

The mean change from the extension study Baseline in pain right now indicated improvement compared to the Baseline (3.84 [SD 2.27]) at all visits in the extension study for all subjects combined, ranging from -0.21 (SD 3.49) at Week 40 to -0.95 (SD 1.72) at Week 24. For subjects who received tanezumab 10 mg in the parent study, mean change in least pain indicated improvement in the extension study, remaining below the parent study Baseline (5.00 [SD 1.53]) at all visits, ranging from -1.61 (SD 1.85) at Baseline in the extension study to -2.75 (SD 2.56) at Week 24. For subjects who received placebo in the parent study the mean change in least pain in the extension study remained at or below the parent study Baseline (4.86 [SD 1.68]) through Week 24, ranging from 0.0 (SD 1.10) at Week 40 to -1.67 (SD 1.94) at Week 4.

For the single subject in the Extended-Use Period, the pain right now score was below the extension study Baseline at Week 48 (-1.0), Week 56 (-3.0), and Week 64 (-3.0).

**Table 8. Change From Baseline in BPI-sf Score for Pain Right Now, Combined Parent Study and Extension Study by Week**

| | Parent Study → Extension Study Treatment | | | | | | Change From Baseline Extension Study All Subjects (N=41) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Placebo → Tanezumab 10 mg IV (N=22) | | | Tanezumab 10 mg IV → Tanezumab 10 mg IV (N=19) | | | | | |
| **Parent Study** | **n** | **Mean (SD)** | **Median** | **n** | **Mean (SD)** | **Median** | **n** | **Mean (SD)** | **Median** |
| Baseline | 21 | 4.86[a](1.68) | 5.0 | 19 | 5.00[a] (1.53) | 5.0 | - | - | - |
| Week 1 | 16 | -0.88 (1.86) | -1.0 | 16 | -1.13 (2.09) | -2.0 | - | - | - |
| Week 2 | 17 | -0.41 (1.97) | 0.0 | 17 | -1.53 (1.97) | -1.0 | - | - | - |
| Week 4 | 20 | -0.45 (2.11) | 0.0 | 19 | -1.63 (1.61) | -1.0 | - | - | - |
| Week 6 | 20 | -1.10 (2.02) | 0.0 | 17 | -1.71 (2.31) | -2.0 | - | - | - |
| Week 8 | 12 | -0.50 (1.78) | 0.0 | 12 | -1.83 (2.21) | -2.0 | - | - | - |
| Week 12 | 6 | -1.33 (1.51) | -1.0 | 13 | -1.46 (1.66) | -2.0 | - | - | - |
| Week 16 | 3 | -1.67 (2.89) | 0.0 | 4 | -3.50 (1.73) | -3.5 | - | - | - |
| **Extension Study** | | | | | | | | | |
| Baseline | 19 | -0.68 (2.73) | 0.0 | 18 | -1.61 (1.85) | -1.0 | 38 | 3.84[a] (2.27) | 4.0 |
| Week 4 | 18 | -1.67 (1.94) | -1.0 | 17 | -2.24 (2.31) | -2.0 | 33 | -0.82 (1.61) | -1.0 |
| Week 8 | 15 | -1.20 (1.82) | -1.0 | 15 | -2.40 (2.16) | -3.0 | 29 | -0.72 (1.62) | -1.0 |
| Week 16 | 12 | -1.08 (2.64) | -1.0 | 13 | -2.54 (3.04) | -3.0 | 24 | -0.67 (2.62) | -1.0 |
| Week 24 | 10 | -1.20 (1.48) | -1.0 | 12 | -2.75 (2.56) | -3.0 | 21 | -0.95 (1.72) | -1.0 |
| Week 40 | 6 | 0.00 (1.10) | 0.0 | 9 | -2.11 (3.76) | -3.0 | 14 | -0.21 (3.49) | -1.0 |
| Week 48 | - | - | - | 1 | -2.00 (NA) | -2.0 | 1 | -1.00 (NA) | -1.0 |
| Week 56 | - | - | - | 1 | -4.00 (NA) | -4.0 | 1 | -3.00 (NA) | -3.0 |
| Week 64 | - | - | - | 1 | -4.00 (NA) | -4.0 | 1 | -3.00 (NA) | -3.0 |

IV = intravenous, N = total number of subjects, n = number of subjects meeting prespecified criteria, NA = not applicable, SD = standard deviation.
a. Baseline shown.

Pain Interference With Function: Table 9 summarizes the change from the parent study Baseline in the BPI-sf scores for pain interference with function for the parent study and extension study treatment groups, and also the change from the extension study Baseline in BPI-sf score for pain interference with function for all subjects from Baseline to Weeks 4, 8, 16, 24, and 40, and for Weeks 48, 56, and 64 for the single subject in the Extended-Use Period.

The mean change from the extension study Baseline to Week 40 in pain interference with function score indicated improvement, remaining below the Baseline (4.05 [SD 2.41]) at all visits in the extension study for all subjects combined, ranging from -0.29 (SD 2.46) at Week 16 to -0.88 (SD 1.77) at Week 24. For subjects who received tanezumab 10 mg in the parent study, mean change in pain interference with function indicated improvement compared to the parent study Baseline (4.74 [SD 1.52]) at all visits in the extension study, ranging from -1.10 (SD 2.11) at Baseline in the extension study to -2.38 (SD 2.89) at Week 40. For subjects who received placebo in the parent study, the mean change in pain interference with function improved compared to the parent study Baseline (5.45 [SD 1.64]) at all visits, ranging from -0.90 (SD 2.04) at Week 40 to -2.03 (SD 2.02) at Week 4. For the single subject in the Extended-Use Period, pain interference with function remained below the extension study Baseline at Week 48 (-1.71), Week 56 (-2.00), and Week 64 (-4.14).

Similar results were reported for pain interference with general activity, mood, walking ability, normal work, relations with other people, and, sleep, and enjoyment of life.

**Table 9. Change From Baseline in BPI-sf Score for Pain Interference with Function (Composite Score), Combined Parent Study and Extension Study by Week**

| | Parent Study → Extension Study Treatment | | | | | | Change From Baseline Extension Study All Subjects (N=41) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Placebo → Tanezumab 10 mg IV (N=22) | | | Tanezumab 10 mg IV → Tanezumab 10 mg IV (N=19) | | | | | |
| **Parent Study** | **n** | **Mean (SD)** | **Median** | **n** | **Mean (SD)** | **Median** | **n** | **Mean (SD)** | **Median** |
| Baseline | 20 | 5.45[a] (1.64) | 5.2 | 19 | 4.74[a](1.52) | 5.3 | - | - | - |
| Week 1 | 16 | -1.46 (2.37) | -0.9 | 16 | -0.69 (1.43) | -0.4 | - | - | - |
| Week 2 | 17 | -1.40 (2.11) | -1.1 | 17 | -1.02 (1.55) | -0.7 | - | - | - |
| Week 4 | 19 | -1.21 (2.16) | -0.7 | 19 | -1.26 (1.64) | -1.4 | - | - | - |
| Week 6 | 19 | -1.51 (1.92) | -0.7 | 17 | -1.55 (1.51) | -1.6 | - | - | - |
| Week 8 | 11 | -1.65 (1.54) | -1.4 | 12 | -1.88 (1.56) | -1.6 | - | - | - |
| Week 12 | 5 | -0.63 (1.47) | -0.6 | 13 | -1.69 (1.93) | -1.4 | - | - | - |
| Week 16 | 3 | -1.67 (1.80) | -1.4 | 4 | -3.04 (1.57) | -2.8 | - | - | - |
| **Extension Study** | | | | | | | | | |
| Baseline | 18 | -0.81 (2.32) | -0.1 | 18 | -1.10 (2.11) | -1.4 | 38 | 4.05[a] (2.41) | 4.2 |
| Week 4 | 17 | -2.03 (2.02) | -1.1 | 17 | -1.26 (1.91) | -1.6 | 33 | -0.69 (1.33) | -0.6 |
| Week 8 | 14 | -1.22 (1.49) | -0.6 | 15 | -1.61 (2.13) | -1.9 | 29 | -0.79 (1.90) | -0.3 |
| Week 16 | 11 | -1.05 (2.35) | -0.7 | 13 | -1.38 (2.56) | -1.4 | 24 | -0.29 (2.46) | 0.0 |
| Week 24 | 10 | -1.41 (1.84) | -1.3 | 12 | -1.94 (1.87) | -1.6 | 21 | -0.88 (1.77) | -0.6 |
| Week 40 | 6 | -0.90 (2.04) | -1.4 | 8 | -2.38 (2.89) | -3.1 | 13 | -0.56 (2.81) | -1.1 |
| Week 48 | - | - | - | 1 | -3.00 (NA) | -3.0 | 1 | -1.71 (NA) | -1.7 |
| Week 56 | - | - | - | 1 | -3.29 (NA) | -3.3 | 1 | -2.00 (NA) | -2.0 |
| Week 64 | - | - | - | 1 | -5.43 (NA) | -5.4 | 1 | -4.14 (NA) | -4.1 |

IV = intravenous, N = total number of subjects, n = number of subjects meeting prespecified criteria, NA = not applicable, SD = standard deviation.
a. Baseline shown.

**Safety Results:**

For this study, treatment emergent adverse events (TEAEs) were defined as any AE which began in the extension study, or began in the parent study and worsened in severity during the extension study. Table 10 presents the non-serious TEAEs by system organ class and preferred term.

**Table 10. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in ≥5% of Subjects**

| Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v15.1) Preferred Term | Tanezumab 10 mg | |
|---|---|---|
| | n (%) | n1 |
| Number (%) of subjects: | | |
| Evaluable for adverse events | 41 | |
| With adverse events | 18 (43.9) | |
| Gastrointestinal disorders | 11 (26.8) | 25 |
| Constipation | 3 (7.3) | 4 |
| Nausea | 8 (19.5) | 12 |
| Vomiting | 4 (9.8) | 9 |
| General disorders and administration site conditions | 12 (29.3) | 18 |
| Asthenia | 6 (14.6) | 7 |
| Oedema peripheral | 5 (12.2) | 5 |
| Pyrexia | 5 (12.2) | 6 |
| Investigations | 3 (7.3) | 4 |
| Weight decreased | 3 (7.3) | 4 |
| Metabolism and nutrition disorders | 3 (7.3) | 6 |
| Decreased appetite | 3 (7.3) | 6 |
| Musculoskeletal and connective tissue disorders | 3 (7.3) | 4 |
| Arthralgia | 3 (7.3) | 4 |
| Respiratory, thoracic and mediastinal disorder | 7 (17.1) | 9 |
| Cough | 3 (7.3) | 3 |
| Dyspnoea | 5 (12.2) | 6 |

Except for 'n1' subjects were only counted once per treatment for each row. Included data up to 9999 days after last dose of study drug. MedDRA (v15.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities, n = the number of subjects in this reporting group affected by any occurrence of this adverse event, all-causalities, n1 = the number of occurrences of treatment emergent all causalities adverse events, v = version.

The incidence of treatment-emergent treatment-related AEs is presented in Table 11.

**Table 11. Incidence of Treatment-Emergent Adverse Events (Treatment Related)**

| Number of Subjects With Adverse Events by: System Organ Class and MedDRA (v15.1) Preferred Term | Tanezumab 10 mg N=41 |
|---|---|
| Number of subjects: | |
| Evaluable for adverse events | 41 |
| With adverse events | 5 |
| Discontinued due to adverse events | 0 |
| Blood and lymphatic system disorders | 1 |
| Anaemia | 1 |
| Thrombocytopenia | 1 |
| Gastrointestinal disorders | 1 |
| Nausea | 1 |
| General disorders and administration site conditions | 1 |
| Influenza like illness | 1 |
| Injury, poisoning and procedural complications | 1 |
| Tendon rupture | 1 |
| Investigations | 1 |
| Platelet count decreased | 1 |
| Nervous system disorders | 1 |
| Neuropathy peripheral | 1 |
| Respiratory, thoracic and mediastinal disorders | 1 |
| Dyspnoea | 1 |

Non-SAEs and SAEs are not separated out.
Subjects were only counted once per treatment for each row. Included data up to 9999 days after last dose of study drug. MedDRA (v15.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities, N = total number of subjects, SAEs = serious adverse events, v = version.

SAEs were reported in 23 subjects (56.1%), though none of those SAEs were considered by the Investigators to be related to tanezumab. The majority of these SAEs were attributed to the subjects' underlying cancer. Table 12 presents the SAEs reported for this study.

**Table 12. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term**

| Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v15.1) Preferred Term | Tanezumab 10 mg | | |
|---|---|---|---|
| | n (%) | n1 | n2 |
| Number (%) of subjects: | | | |
| Evaluable for adverse events | 41 | | |
| With adverse events | 23 (56.1) | | |
| Blood and lymphatic system disorders | 6 (14.6) | 8 | 0 |
| Anaemia | 4 (9.8) | 5 | 0 |
| Aplastic anaemia | 1 (2.4) | 1 | 0 |
| Disseminated intravascular coagulation | 1 (2.4) | 1 | 0 |
| Thrombocytopenia | 1 (2.4) | 1 | 0 |
| Cardiac disorders | 1 (2.4) | 2 | 0 |
| Cardiovascular insufficiency | 1 (2.4) | 2 | 0 |
| General disorders and administration site conditions | 3 (7.3) | 3 | 0 |
| Disease progression | 3 (7.3) | 3 | 0 |
| Hepatobiliary disorders | 1 (2.4) | 1 | 0 |
| Hepatorenal failure | 1 (2.4) | 1 | 0 |
| Infections and infestations | 2 (4.9) | 2 | 0 |
| Bronchopneumonia | 1 (2.4) | 1 | 0 |
| Pneumonia | 1 (2.4) | 1 | 0 |
| Metabolism and nutrition disorders | 1 (2.4) | 1 | 0 |
| Hypercalcaemia | 1 (2.4) | 1 | 0 |
| Musculoskeletal and connective tissue disorders | 3 (7.3) | 3 | 0 |
| Muscular weakness | 1 (2.4) | 1 | 0 |
| Pathological fracture | 2 (4.9) | 2 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps | 12 (29.3) | 12 | 0 |
| Breast cancer | 1 (2.4) | 1 | 0 |
| Malignant neoplasm progression | 1 (2.4) | 1 | 0 |
| Meningioma | 1 (2.4) | 1 | 0 |
| Metastatic neoplasm | 2 (4.9) | 2 | 0 |
| Multiple myeloma | 1 (2.4) | 1 | 0 |
| Prostate cancer | 3 (7.3) | 3 | 0 |
| Prostate cancer metastatic | 2 (4.9) | 2 | 0 |
| Renal cancer | 1 (2.4) | 1 | 0 |
| Nervous system disorders | 1 (2.4) | 1 | 0 |
| Cerebral infarction | 1 (2.4) | 1 | 0 |
| Renal and urinary disorders | 1 (2.4) | 1 | 0 |
| Renal failure acute | 1 (2.4) | 1 | 0 |
| Respiratory, thoracic and mediastinal disorders | 2 (4.9) | 3 | 0 |
| Dyspnoea | 1 (2.4) | 2 | 0 |
| Pulmonary embolism | 1 (2.4) | 1 | 0 |

Except for 'n1' and 'n2' subjects were only counted once per treatment for each row. Includes data up to 9999 days after last dose of study drug. MedDRA (v15.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities, n = the number of subjects in this reporting group affected by any occurrence of this adverse event, all causalities, n1= the number of occurrences of treatment emergent all causalities adverse events, n2 = the number of occurrences of treatment emergent causally related to treatment adverse events, v = version.

A total of 8 subjects discontinued the study due to an AE (Table 13). All AEs leading to discontinuation were considered to be unrelated to tanezumab.

**Table 13. Incidence of Treatment-Emergent Adverse Events Leading to Discontinuation (All Causalities)**

| Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v15.1) Preferred Term | Tanezumab 10 mg N=41 n |
|---|---|
| Investigations | 1 |
| Blood glucose increase | 1 |
| Musculoskeletal and connective tissue disorder | 3 |
| Arthralgia | 2 |
| Osteoarthritis | 1 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 3 |
| Malignant neoplasm progression | 1 |
| Prostate cancer | 1 |
| Prostate cancer metastatic | 1 |
| Nervous system disorders | 1 |
| Cerebral infarction | 1 |
| Total preferred term events | 8 |

Subjects were only counted once per treatment for each row.
Included data upto 9999 days after last dose of study drug. MedDRA (v15.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities, N = total number of subjects, n = number of subjects with adverse event, v = version.

Overall, 16 deaths were reported. Twelve (12) deaths, including the death of the single subject in the Extended-Use Period, occurred during the study period, while the remaining 4 deaths occurred after the study period. Twelve (12) of the 16 deaths had AEs leading to a fatal outcome in which the AE was the subject's cancer at study entry or progression of the same. None of the deaths were considered by the Investigator to be related to tanezumab.

**Table 14. All Subject Deaths**

| Serial Number | Sex/Age (Years) | Event With Fatal Outcome MedDRA Preferred Term | Day of Death | Causality |
|---|---|---|---|---|
| 1 | M/76 | Prostate cancer | 60 | Unrelated to study drug |
| 2 | M/73 | Hepatorenal failure | 258 | Unrelated to study drug |
| 3 | M/63 | Prostate cancer metastatic | 123 | Unrelated to study drug |
| 4 | M/66 | Prostate cancer metastatic | 10 | Unrelated to study drug |
| 5 | M/54 | Pulmonary embolism | 8 | Unrelated to study drug |
| 6 | F/48 | Cardiovascular insufficiency | 493 | Unrelated to study drug |
| 7 | M/68 | Prostate cancer | 249 | Unrelated to study drug |
| 8 | M/34 | Renal cancer | 4 | Unrelated to study drug |
| 9 | F/66 | Metastatic neoplasm | 53 | Unrelated to study drug |
| 10 | F/65 | Metastatic neoplasm | 38 | Unrelated to study drug |
| 11 | F/32 | Disseminated intravascular coagulation | 61 | Unrelated to study drug |
| 12 | F/55 | Disease progression | 201 | Unrelated to study drug |
| 13 | M/66 | Malignant neoplasm progression | 283 | Unrelated to study drug |
| 14 | F/58 | Plasma cell myeloma | 14 | Unrelated to study drug |
| 15 | M/75 | Prostate cancer | 4 | Unrelated to study drug |
| 16 | M/67 | Breast cancer | 107 | Unrelated to study drug |

MedDRA (v15.1) coding dictionary applied.
F = female, M = male, MedDRA = Medical Dictionary for Regulatory Activities, v = version.

Only 3 subjects reported 4 AEs of abnormal peripheral sensation, including hypoaesthesia (2 subjects), hypoaesthesia oral and peripheral neuropathy (1 subject each). The incidence of subjects with AEs of abnormal peripheral sensation was 3/41 (7.3%) which was comparable to the incidence in subjects treated with tanezumab in the parent study.

A large majority of subjects (86.5%) had final neurological examinations that were not worsened compared to Baseline. This was comparable to the previous study where 85.7% in the placebo treatment group and 89.3% in the tanezumab 10 mg treatment group had no new or worsened abonormality at the final neurologic examination. Five (5) subjects reported new or worsened abnormality (13.5%) on the final neurological examination, the findings were not considered clinically significant for any subject. No subject had a clinically significant neurological examination on consecutive study visits.

There was no clear evidence of an effect of tanezumab on vital signs, ECG, or laboratory safety data. None of the ADA serum samples were found to be positive for the development of antibodies against tanezumab in this extension study. None of the subjects who entered into the extension study had tested positive for ADA previously in the parent study.

There were no reported events of osteonecrosis or total joint replacements.

**CONCLUSIONS:**

- Multiple doses of tanezumab 10 mg IV in subjects with chronic pain due to bone metastases and treated with opioids were well-tolerated in this study, and no new safety issues were identified in this extension safety study. The AE profile was consistent with the subject population and previous tanezumab studies; the most commonly reported AE (nausea) likely reflects the use of background opioids.

- In the study, there was no comparator and therefore statistical analyses of analgesic efficacy was not performed, but changes from the parent study and extension study Baselines in the 4 pain scores of average, worst, least, and pain right now in the BPI-sf demonstrated reduction in pain until at least Week 24, and for most until Week 40, as well as for pain interference with function (composite score) from the BPI-sf until Week 40.