A Randomized Placebo-Controlled Trial of the Anti-Nerve Growth Factor Antibody Tanezumab in Subjects With Cancer Pain Due to Bone Metastasis

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Abstract

Background: This phase III, randomized, double-blind, placebo-controlled, parallel-group study assessed the efficacy and safety of tanezumab in subjects with cancer pain predominantly due to bone metastasis receiving background opioid therapy.

Methods: Subjects were randomized (stratified by (1) tumor aggressiveness and (2) presence/absence of concomitant anticancer treatment) to placebo or tanezumab 20 mg. Treatment was administered by subcutaneous injection every 8 weeks for 24 weeks (3 doses) followed by a 24-week safety follow-up period. The primary outcome was change in daily average pain in the index bone metastasis cancer pain site (from 0 = no pain to 10 = worst possible pain) from baseline to week 8.

Results: LS mean (SE) change in pain at week 8 was −1.25 (0.35) for placebo (n = 73) and –2.03 (0.35) for tanezumab 20 mg (n = 72). LS mean (SE) [95% CI] difference from placebo was –0.78 (0.37) [–1.52, –0.04]; P = .0381 with α = 0.0478. The number of subjects with a treatment-emergent adverse event during the treatment period was 50 (68.5%) for placebo and 53 (73.6%) for tanezumab 20 mg. The number of subjects with a prespecified joint safety event was 0 for placebo and 2 (2.8%) for tanezumab 20 mg (pathologic fracture; n = 2).

Conclusion: Tanezumab 20 mg met the primary efficacy endpoint at week 8. Conclusions on longer-term efficacy are limited since the study was not designed to evaluate the durability of the effect beyond 8 weeks. Safety findings were consistent with adverse events expected in subjects with cancer pain due to bone metastasis and the known safety profile of tanezumab. Clinicaltrials.gov identifier: NCT02609828.

Key words: tanezumab; cancer pain; nerve growth factor; randomized controlled trial.

Implications for Practice

This phase III placebo-controlled study demonstrates the potential of anti-nerve growth factor therapies such as tanezumab to reduce pain caused by bone metastases, though adjudicated intra-articular pathologic fractures were only observed among tanezumab-treated subjects. Further, since the durability of efficacy beyond 8 weeks was not demonstrated, future research should evaluate the durability of anti-NGF therapy efficacy over longer durations.

Introduction

Bone metastasis is the most common form of cancer-related pain.1-3 Approximately 60%-80% of subjects with bone metastasis report moderate-to-severe pain that can substantially impact physical function and quality of life.4,5 Treatment focuses on the alleviation of pain, prevention of pathological fractures, and improvement in mobility and function via a multidisciplinary approach that may include palliative radiotherapy, osteoprotective agents, surgery, analgesics, and treatment of primary cancer.6 Management of chronic pain associated with bone metastasis, however, remains a challenge as it is relatively resistant to analgesics.6 Consequently, opioid use has increased despite questionable efficacy, significant adverse events, and concerns that chronic use may impair bone metabolism and increase fracture risk.7 Thus, a need remains for novel, safe, and effective treatments for the management of metastatic bone pain.

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Tanezumab, a monoclonal antibody against nerve growth factor (NGF), improves pain and function in chronic pain conditions such as osteoarthritis and chronic low-back pain.\textsuperscript{8-14} In a phase II study in subjects with cancer pain due to bone metastasis receiving background opioid therapy, a single intravenous dose of tanezumab 10 mg improved daily average pain intensity from baseline to week 6.\textsuperscript{15} Though the magnitude of improvement was numerically greater with tanezumab than with placebo, the difference was not statistically significant.\textsuperscript{15} However, preliminary evidence of efficacy was evident in posthoc subgroup analyses of subjects with higher (>5 out of 10) baseline pain scores and lower total daily opioid use (≤60.5 mg/day morphine-equivalent dose).

Here, we report findings from a phase III trial assessing the efficacy and safety of subcutaneous tanezumab in subjects with cancer pain predominantly due to bone metastasis receiving background opioid therapy.

Methods
Design
This phase III, randomized, double-blind, placebo-controlled trial (24-week treatment/24-week safety follow-up) was conducted in 15 countries (Europe, Latin America, and Asia-Pacific) from October 2015 to June 2021 (NCT02609828).

Subjects
Key inclusion criteria included: age ≥18 years; body weight ≥40 kg; diagnosis of cancer metastasized to bone (confirmed by imaging within 120 days of screening) or of multiple myeloma; average pain score ≥5 (on a scale from 0-10) at the index bone metastasis cancer pain site (defined as the most painful bone metastasis site); Patient’s Global Assessment of Cancer Pain (PGA-CP) score of “fair,” “poor,” or “very poor” (on a 5-point scale from “very good” to “very poor”); and Eastern Cooperative Oncology Group (ECOG) Performance Status Score of 0, 1, or 2 (on a scale from 0 = fully active to 5 = dead).

Key exclusion criteria included: pain unrelated to bone metastasis; systemic treatment for the primary malignancy, or bone metastasis initiated within 30 days prior to baseline; radiopharmaceutical or radiotherapy-based treatment of bone metastasis within 30 days prior to baseline; initiation or unstable dosing of adjuvant analgesics within 30 days prior to baseline; or diagnosis of osteoarthritis (knee or hip) as defined by American College of Rheumatology clinical and radiographic criteria.

Randomization
Initially, subjects were randomized (using a computer-generated randomization code) in a double-blind 1:1:1 manner to placebo, tanezumab 10 mg, or tanezumab 20 mg. The protocol was later amended to discontinue the tanezumab 10 mg group (Supplementary Text 1). Newly enrolled subjects were randomized in a 1:1 manner to placebo or tanezumab 20 mg (Fig. 1). Subjects receiving tanezumab 10 mg at the time of amendment implementation were administered tanezumab 20 mg for all remaining doses. Randomization was stratified by tumor aggressiveness (ECOG performance status score ≤1 corresponds to less aggressive, a score ≥2 corresponds to more aggressive) and the presence/absence of concomitant anticancer treatment.

Procedures
All subjects received optimized background opioid therapy during the study (Supplementary Text 2). Subjects were discontinued from study treatment (up to week 8) if the average total daily dose of opioids between clinic visits exceeded the baseline total daily morphine-equivalent opioid dose by >10%. Tanezumab or matching placebo was administered every 8 weeks for 24 weeks (3 total doses) via subcutaneous injection (pre-filled syringe of 1 mL volume) into the abdomen or anterior thigh.

Analgesics other than background opioids were prohibited from baseline to week 8 (unless stable dosing was initiated ≥30 days prior to baseline). Nonsteroidal anti-inflammatory drugs (NSAIDs) were prohibited through week 32, except for occasional use (<36 days total from baseline to week 32 and <10 days during an 8-week dosing interval) for self-limited conditions unrelated to cancer pain. Intra-articular corticosteroids were prohibited from 30 days prior to baseline through week 32. Monoclonal antibodies, hormonal therapy,
chemotherapy, and small-molecule inhibitors for the under-
lying cancer were allowed if stable dosing was ongoing ≥30
days prior to standard. Basis of care (except NSAIDs and
intra-articular corticosteroids) could be used after Week 8.
Subjects used an electronic diary (daily through week 8 and
then weekly to week 24) to assess average and worst pain
over the previous 24 h (on a numeric rating scale from 0 = no
pain to 10 = worst possible pain) at the index bone meta-
sasis cancer pain site. The PGA-CP (overall disease status)
was completed at baseline and weeks 2, 4, 8, 16, and 24. Scores
ranged from 1 = “very good” to 5 = “very poor.” Subjects used
the electronic diary to record opioid use (daily up to week 8
and then weekly through week 24).

Outcomes
The primary endpoint was change in daily average pain in
the index bone metastasis cancer pain site from baseline to
week 8. Secondary endpoints included: change in daily aver-
age pain in the index bone metastasis cancer pain site from
baseline to weeks 1, 2, 4, 6, 12, 16, and 24; change in daily
worst pain in the index bone metastasis cancer pain site from
baseline to weeks 1, 2, 4, 6, 8, 12, 16, and 24; proportion of
subjects with ≥30%, ≥50%, ≥70%, and ≥90% reduction
(from baseline) in daily average and worst pain intensity in
the index bone metastasis cancer pain site at weeks 1, 2, 4, 6,
8, 12, 16, and 24; change in PGA-CP scores from baseline to
weeks 2, 4, 8, 16, and 24; percent change in average daily opio-
id consumption (in mg of morphine equivalent doses) from
baseline to weeks 1, 2, 4, 6, 8, 12, 16, and 24; and number of
doses of rescue medication at weeks 1, 2, 4, 6, 8, 12, 16,
and 24. Due to space constraints, results for most secondary
endpoints are only presented for weeks 8 (primary endpoint)
and 24 (end of treatment). Additional results can be found on
clinicaltrials.gov (NCT02609828).
Safety assessments included treatment-emergent adverse
events (TEAEs), physical examinations, laboratory tests, vital
signs, orthostatic blood pressure assessments, and 12-lead
electrocardiograms. TEAEs were coded using Medical
Dictionary for Regulatory Activities version 24.0, with severity
and causality assessed by investigators. Subjects received
radiographs of the shoulders, knees, and hips at screening,
week 16 (Japan only), week 24, week 48 (or early termina-
tion), and any time a joint was at risk for a joint safety event
(eg, increased severe persistent pain) was identified. A central
reader reviewed radiographs for study eligibility and identi-
fication of possible or probable joint safety events that could warrant further evaluation or referral to an orthopedic sur-
gon. All possible or probable joint safety events, including
total joint replacement, were adjudicated by a blinded exter-
nal adjudication committee of experts. Events adjudicated as
rapidly progressive osteoarthritis (RPOA) type 1 or 2, pri-
mary osteonecrosis, subchondral insufficiency fracture, or
pathologic fracture were included in a composite joint safety
endpoint.

Statistical Analysis
The primary endpoint was a change from baseline to week
8 in average daily pain intensity in the index bone meta-
sasis cancer pain site. Based on a previous study, the assumed
within-group SD for a change from baseline in average pain
score was 2.0.19 The targeted mean treatment difference for
tanezumab 20 mg + opioids vs. placebo + opioids was −1.0. A
group sequential design with a single interim analysis to assess
futility and efficacy after ≥50% of subjects had completed or
discontinued prior to week 8 was used. Accounting for this
interim analysis, a sample size of approximately 72 subjects
per group provides 80%-85% power to detect statisti-
cal significance (with an overall 2-sided 5% significance level)
for the targeted treatment difference. Based on the number of
subjects included in the interim and final analyses, and using
the Lan DeMets alpha spending function with the O’Brien
Fleming style boundary (implemented in EAST version 6.5),
the alpha-level used for a 2-sided test of the primary endpoint,
in the final analysis, was 0.0478.

The primary endpoint was analyzed using an analysis of
covariance (ANCOVA) model including treatment, region,
and randomization stratification variables as fixed effects,
and baseline average pain intensity at the index bone meta-
sasis cancer pain site and baseline opioid dose as covariates.
Secondary endpoints of change from baseline in average pain,
worst pain, PGA-CP score, and opioid consumption were
analyzed using an ANCOVA model including treatment,
region, and stratification variables used at randomization as
fixed effects, and baseline average pain intensity at the index
bone metastasis cancer pain site, respective baseline score,
and baseline opioid dose as covariates. Proportions of sub-
jects achieving ≥30%, ≥50%, ≥70%, and ≥90% improvement
in average and worst pain were analyzed using a logistic
regression model including baseline average pain intensity
(and worst pain intensity for worst pain analyses) at the index
bone metastasis cancer pain site, treatment, and randomiza-
tion stratification variables. The number of rescue opioid
doses was analyzed using a negative binomial model includ-
ing the total number of doses during the week as the response
variable, and the log of the number of days under observa-
tion as the offset variable. Independent variables included
treatment, region, baseline average pain intensity at the index
cancer pain site, baseline opioid consumption, and stratifica-
tion variables used at randomization. TEAEs, and joint safety
events were summarized descriptively.

The primary and many secondary endpoints used a mul-
tiple imputation approach to missing data, with imputa-
tion method dependent on the reasons for missing data (See
Supplementary Text 3 for details). Analysis of opioid con-
sumption used a last observation carried forward (LOCF)
approach. Analysis of 30%/50%/70%/90% pain responders
used a mixed LOCF/baseline observation carried forward
(BOCF) approach. In this mixed approach, a BOCF impu-
tation used a last observation carried forward (LOCF)
approach. Analysis of opioid consumption used a logistic
regression model including baseline average pain intensity
(and worst pain intensity for worst pain analyses) at the index
bone metastasis cancer pain site, treatment, and randomiza-
tion stratification variables. The number of rescue opioid
doses was analyzed using a negative binomial model includ-
ing the total number of doses during the week as the response
variable, and the log of the number of days under observa-
tion as the offset variable. Independent variables included
treatment, region, baseline average pain intensity at the index
cancer pain site, baseline opioid consumption, and stratifica-
tion variables used at randomization. TEAEs, and joint safety
events were summarized descriptively.

Subject disposition, demographics, and safety assessments
used the safety population, which included all randomized
subjects who received ≥1 dose of placebo or tanezumab (10,
10/20, or 20 mg). Efficacy analyses used the modified intent-to-
treat population, which consisted of all randomized subjects
who received ≥1 dose of placebo or tanezumab 20 mg.

Results
Overall, 325 subjects were screened, 156 were randomized,
and 155 received ≥1 dose of study medication (Fig. 2). Overall,
69.9% (placebo) and 75.0% (tanezumab 20 mg) of subjects
completed at least 8 weeks of treatment, 49.3% (placebo) and

19. The targeted mean treatment difference for
tanezumab 20 mg + opioids vs. placebo + opioids was −1.0. A
group sequential design with a single interim analysis to assess
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50.0% (tanezumab 20 mg) completed the 24-week treatment period, and 42.5% (placebo) and 40.3% (tanezumab 20 mg) completed the full 48-week study period. Adverse events (placebo = 16.4%; tanezumab 20 mg = 12.5%) and death (placebo = 13.7%; tanezumab 20 mg = 15.3%) were the most common reasons for treatment discontinuation. There were more males in the tanezumab 20 mg group (63.9%) than in the placebo group (46.6%); other demographics and clinical characteristics were similar between these 2 groups (Table 1).

Tanezumab 20 mg met the primary endpoint by demonstrating greater improvement in daily average pain intensity at the index cancer pain site compared with placebo at week 8. Improvements in worst pain intensity at the index cancer pain site were also observed with tanezumab 20 mg compared with placebo at weeks 2, 4, and 6; significant differences between the 2 groups were not evident at or beyond week 8 (Fig. 3B). At week 8, the proportion of subjects achieving ≥50% improvement in average pain (placebo = 12.3%; tanezumab 20 mg = 25.4%) and in worst pain (placebo = 9.6%; tanezumab 20 mg = 22.5%) was greater with tanezumab 20 mg (average pain OR [95% CI] = 2.55 [1.04, 6.22], P = .0405; worst pain OR [95% CI] = 2.69 [1.02, 7.12], P = .0457) than with placebo (Table 2).

Figure 2. Subject disposition. mITT, modified intent-to-treat; SC, subcutaneous. *Other screened but not randomized indicates subjects who were screened but not randomized for a reason not related to a specific eligibility criterion. The study protocol initially included 3 treatment arms (SC placebo, SC tanezumab 10 mg, and SC tanezumab 20 mg). After initiation of the study, the protocol was amended to discontinue the tanezumab 10 mg dose arm. Nine subjects received tanezumab 10 mg and either completed the treatment phase or discontinued the treatment phase prior to implementation of the amendment; these subjects are in the tanezumab 10 mg group in the figure above. One subject received tanezumab 10 mg and was in the treatment phase at the time of implementation of the amendment; this subject was administered 20 mg of all remaining doses and is included in the tanezumab 10/20 mg group in the figure above. *Includes all subjects treated with placebo or tanezumab (including the tanezumab 10 mg and tanezumab 10/20 mg groups). The mITT was the primary efficacy analysis set and includes all subjects randomized to either placebo or tanezumab 20 mg who received at least 1 dose of SC study medication (excludes the tanezumab 10 mg and tanezumab 10/20 mg groups).
groups, respectively, at baseline. Mean use was 170-190 mg in both groups through week 16, and there were no differences between groups (based on percent change from baseline) at any point during the study (Supplementary Table S1).

Compared with placebo, the LS mean average daily number of doses of rescue medication for the tanezumab 20 mg group was significantly lower at week 4 \((P = .0211)\) and numerically (but not statistically significant) lower at weeks 1, 2, 6, 8, 12, 16, and 24 (Supplementary Table S2).

The incidence of TEAEs during the 24-week treatment period was 68.5% for placebo, 88.9% for tanezumab 10 mg, 100.0% for tanezumab 10/20 mg, and 73.6% for tanezumab 20 mg (Table 3, upper panel). The incidence of serious and severe TEAEs was lower with placebo (serious = 30.1%; severe = 32.9%) than with tanezumab 20 mg (serious = 40.3%, severe = 41.7%), although treatment discontinuations due to TEAEs were higher with placebo (6.8%) than with tanezumab 20 mg (5.6%). A summary of TEAEs during safety follow-up and up to end of study is shown in Supplementary Table S3. Anemia, arthralgia, decreased appetite, progression of prostate cancer, peripheral edema, and pain were the most common TEAEs in the tanezumab 20 mg group (Table 3 middle panel). Of these, decreased appetite, peripheral edema, and pain occurred more frequently (>1% difference) in the tanezumab 20 mg group than in the placebo group. Neurological TEAEs of abnormal peripheral sensation were more frequent with tanezumab 20 mg (9.7%) than with placebo (5.5%). The only TEAEs of abnormal peripheral sensation reported in ≥2% of subjects in any group were paresthesia (placebo = 0%; tanezumab 20 mg = 2.8%) and neuralgia (placebo = 2.7%, tanezumab 20 mg = 1.4%). A total of 46 deaths were reported during the study (placebo = 23, tanezumab 10 mg = 1, tanezumab 10/20 mg = 1, tanezumab 20 mg = 21); none were considered treatment-related by investigators.

Four subjects had 5 events (1 subject had 2 events) that met criteria for evaluation by the joint safety adjudication committee (Table 3 lower panel). Two subjects in the tanezumab

### Table 1. Subject demographic and baseline characteristics.

<table>
<thead>
<tr>
<th>Demographic/characteristic</th>
<th>SC placebo (N = 73)</th>
<th>SC tanezumab 10 mg (N = 9)</th>
<th>SC tanezumab 10/20 mg (N = 1)</th>
<th>SC tanezumab 20 mg (N = 72)</th>
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</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD); [range]</td>
<td>58.0 (11.1); [30-82]</td>
<td>61.6 (9.9); [44-73]</td>
<td>58.0 (--); [58-58]</td>
<td>63.5 (10.1); [36-86]</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>34 (46.6)</td>
<td>5 (55.6)</td>
<td>1 (100-0)</td>
<td>46 (63.9)</td>
</tr>
<tr>
<td>Female</td>
<td>39 (53.4)</td>
<td>4 (44.4)</td>
<td>0</td>
<td>26 (36.1)</td>
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<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>56 (76.7)</td>
<td>6 (66.7)</td>
<td>1 (100.0)</td>
<td>55 (76.4)</td>
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<tr>
<td>Black or African American</td>
<td>1 (1.4)</td>
<td>0</td>
<td>0</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Asian</td>
<td>16 (21.9)</td>
<td>3 (33.3)</td>
<td>0</td>
<td>16 (22.2)</td>
</tr>
<tr>
<td>Ongoing anticancer treatment, n (%)</td>
<td>44 (60.3)</td>
<td>8 (88.9)</td>
<td>1 (100.0)</td>
<td>48 (66.7)</td>
</tr>
<tr>
<td>PGA-CP score at baseline, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Very good</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1.4)</td>
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<tr>
<td>Good</td>
<td>0</td>
<td>2 (22.2)</td>
<td>0</td>
<td>2 (2.8)</td>
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<tr>
<td>Fair</td>
<td>42 (57.5)</td>
<td>4 (44.4)</td>
<td>1 (100.0)</td>
<td>41 (57.7)</td>
</tr>
<tr>
<td>Poor</td>
<td>31 (42.5)</td>
<td>3 (33.3)</td>
<td>0</td>
<td>24 (33.8)</td>
</tr>
<tr>
<td>Very poor</td>
<td>0</td>
<td></td>
<td>0</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>Daily average pain score in index bone metastasis cancer pain site at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>6.34 (1.16)</td>
<td>5.84 (1.07)</td>
<td>7.20 (--</td>
<td>6.19 (1.47)</td>
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<tr>
<td>Median; [range]</td>
<td>6.0; [4.3-10.0]</td>
<td>5.8; [4.6-7.8]</td>
<td>7.2; [7.2-7.2]</td>
<td>6.0; [0-10.0]</td>
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<tr>
<td>ECOG performance status score at screening, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Less aggressive</td>
<td>60 (82.2)</td>
<td>8 (88.9)</td>
<td>1 (100.0)</td>
<td>54 (75.0)</td>
</tr>
<tr>
<td>More aggressive</td>
<td>13 (17.8)</td>
<td>1 (11.1)</td>
<td>0</td>
<td>18 (25.0)</td>
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<tr>
<td>Duration since cancer diagnosis, years</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean; [range]</td>
<td>4.2; [0.4-17.5]</td>
<td>5.8; [1.4-14.4]</td>
<td>1.9; [1.9-1.9]</td>
<td>4.6; [0.2-20.9]</td>
</tr>
<tr>
<td>Duration since bone metastasis diagnosis, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean; [range]</td>
<td>2.0; [0.1-12.0]</td>
<td>1.8; [0.1-4.0]</td>
<td>1.9; [1.9-1.9]</td>
<td>2.2; [0.1-20.9]</td>
</tr>
<tr>
<td>Primary cancer type, n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Breast carcinoma</td>
<td>31 (42.5)</td>
<td>6 (66.7)</td>
<td>0</td>
<td>21 (29.2)</td>
</tr>
<tr>
<td>Prostate carcinoma</td>
<td>15 (20.5)</td>
<td>3 (33.3)</td>
<td>1 (100.0)</td>
<td>26 (36.1)</td>
</tr>
<tr>
<td>Lung carcinoma</td>
<td>13 (17.8)</td>
<td>0</td>
<td>0</td>
<td>9 (12.5)</td>
</tr>
</tbody>
</table>

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*N = 71 for the tanezumab 20 mg group.*

*Scores range from 0 to 10, with higher scores indicating greater severity.*

*ECOG performance status score ≤2.*

*Cancer types occurring in >10% in any treatment group.*

*Abbreviations: ECOG, Eastern Cooperative Oncology Group; PGA-CP, Patient’s Global Assessment of Cancer Pain (PGA-CP); SC, subcutaneous; SD, standard deviation.*
20 mg group had events included in the composite joint safety endpoint (pathologic fracture near the site of pre-existing bone metastasis). One of these subjects had a total joint replacement of the left hip 2 days after discontinuing the study due to a non-serious TEAE of pathologic fracture of left acetabulum; this subject had received prior radiotherapy of the left hemipelvis. The remaining adjudicated events (not included in the composite joint safety endpoint) were traumatic avulsion fracture of the ankle (placebo) and extra-articular pathologic fracture (tanezumab 10 mg). None of the events adjudicated by the committee were deemed related to study medication by investigators.

Three fracture-related events were reported that did not require adjudication committee review since they did not meet any of the review criteria (possible joint safety event based on study radiography, persistent increased joint pain, subject underwent total joint replacement). These events included 2 instances of lumbar spinal compression fracture at the site of pre-existing bone metastasis (placebo) and an extra-articular pathologic fracture of the left femur (tanezumab 20 mg treatment group). No events of RPOA, primary osteonecrosis, or subchondral insufficiency fracture occurred in the study.

There was no evidence of an effect of tanezumab on sympathetic nervous system function, vital signs, electrocardiogram measures, and clinical laboratory findings.

**Discussion**

Tanezumab 20 mg met the primary endpoint by demonstrating greater improvement in daily average pain intensity at the index bone metastasis cancer pain site at week 8 than placebo. Tanezumab 20 mg also demonstrated improvement over placebo in secondary measures of pain intensity at or before week 8. Despite improvements in pain intensity, no significant difference in global patient assessment of the impact of metastatic bone pain on daily activities or in background opioid use was observed between the tanezumab and placebo groups.

There was a lack of significant difference between the tanezumab and placebo groups for some endpoints at week 8 (eg, 30% responder rates), which may be due to a
NGF antibody therapy is capable of providing an analgesic observed in previous phase II studies and establishes that anti-hoc subgroup analyses and secondary efficacy endpoints, builds upon preliminary evidence of efficacy, based on post-cancer pain unrelated to bone metastasis.

But generalizing findings to subjects with less severe pain or pain relief with opioids, and therefore, care should be taken dominantly due to bone metastasis who have had inadequate enrolled subjects with moderate-to-severe cancer pain pre-weeks is a limitation of this study. Additionally, this study compared with placebo at week 8. In a phase II study of the anti-NGF antibody fulranumab, a single 9 mg intravenous dose failed to improve cancer-related pain at week 4 (primary endpoint), although improvements in secondary assessments of pain and function were observed. While cancer pain of all types and etiologies was assessed, the presence or absence of bone metastasis did not seem to impact the efficacy of fulranumab.

Overall, TEAEs reported in the trial were generally consistent with the known safety profile of tanezumab and the expected TEAE profile in subjects with cancer pain due to bone metastasis. More subjects reported TEAEs during the treatment period with tanezumab 20 mg (73.6%) than with placebo (68.5%). However, few patients had a severe (placebo = 1, tanezumab 20 mg = 2) or serious (n = 0 in both groups) TEAE during the treatment period that was consistent with the known safety profile of tanezumab and the expected TEAE profile in subjects with cancer pain due to bone metastasis.15

There were no differences between tanezumab 20 mg and placebo for most efficacy endpoints beyond week 8. However, the study was not designed to evaluate durability of efficacy beyond 8 weeks. For example, although there were no significant differences in the use of background opioids between groups at any time point, standard-of-care analgesia (except for NSAIDs and intra-articular corticosteroids) was allowed beyond 8 weeks. For example, though there were no significant differences in the use of background opioids between groups at any time point, standard-of-care analgesia (except for NSAIDs and intra-articular corticosteroids) was allowed after week 8 and could have masked the effects of study drug at later time points. Data on weekly use of standard of care analgesia, however, were not captured to support or refute this possibility.

The inability to evaluate durability of efficacy beyond 8 weeks is a limitation of this study. Additionally, this study enrolled subjects with moderate-to-severe cancer pain predominantly due to bone metastasis who have had inadequate pain relief with opioids and, therefore, care should be taken when generalizing findings to subjects with less severe pain or cancer pain unrelated to bone metastasis.

The efficacy of tanezumab 20 mg observed in this study builds upon preliminary evidence of efficacy, based on post-hoc subgroup analyses and secondary efficacy endpoints, observed in previous phase II studies and establishes that anti-NGF antibody therapy is capable of providing an analgesic benefit to some subjects with painful bone metastasis. In a phase II study of tanezumab in subjects with painful bone metastasis (of any severity) receiving background opioid treatment, a single 10 mg intravenous dose failed to meet the primary endpoint of change in daily average pain intensity at the index bone metastasis site at week 6 but posthoc subgroup analysis in patients with baseline pain scores >5 and opioid use ≤60.5 mg/day (morphine equivalents) resulted in statistically significant improvements in average pain compared with placebo at week 8. In a phase II study of the anti-NGF antibody fulranumab, a single 9 mg intravenous dose (as an adjuvant to opioids) failed to improve cancer-related pain at week 4 (primary endpoint), although improvements in secondary assessments of pain and function were observed.

While cancer pain of all types and etiologies was assessed, the presence or absence of bone metastasis did not seem to impact the efficacy of fulranumab. Overall, TEAEs reported in the trial were generally consistent with the known safety profile of tanezumab and the expected TEAE profile in subjects with cancer pain due to bone metastasis. More subjects reported TEAEs during the treatment period with tanezumab 20 mg (73.6%) than with placebo (68.5%). However, few patients had a severe (placebo = 1, tanezumab 20 mg = 2) or serious (n = 0 in both groups) TEAE during the treatment period that was considered related to treatment and the proportion of subjects discontinuing treatment due to TEAEs was similar across treatment groups. As in previous studies of tanezumab and other anti-NGF antibodies, TEAEs of abnormal peripheral sensation during the treatment period were more frequent with tanezumab 20 mg (9.7%) than with placebo (5.5%) in the current study. The only TEAE of abnormal peripheral

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**Table 2.** Proportion of subjects with ≥30%, ≥50%, ≥70%, and ≥90% improvement (from baseline) in daily average and worst pain intensity at the index bone metastasis cancer pain site at weeks 8 and 24

<table>
<thead>
<tr>
<th>Pain measure</th>
<th>Week 8</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SC placebo (N = 73)</td>
<td>SC tanezumab 20 mg (N = 72)</td>
</tr>
<tr>
<td>Average pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%) of subjects with ≥30% improvement</td>
<td>19 (26.0)</td>
<td>28 (39.4)</td>
</tr>
<tr>
<td>Odds ratio (95% CI) vs placebo; P value</td>
<td>—</td>
<td>1.71 (0.83, 3.52); 0.1471</td>
</tr>
<tr>
<td>Number (%) of subjects with ≥50% improvement</td>
<td>9 (12.3)</td>
<td>18 (25.4)</td>
</tr>
<tr>
<td>Odds ratio (95% CI) vs placebo; P value</td>
<td>—</td>
<td>2.55 (1.04, 6.22); 0.0405</td>
</tr>
<tr>
<td>Number (%) of subjects with ≥70% improvement</td>
<td>3 (4.1)</td>
<td>9 (12.7)</td>
</tr>
<tr>
<td>Odds ratio (95% CI) vs placebo; P value</td>
<td>—</td>
<td>3.21 (0.80, 12.83); 0.0993</td>
</tr>
<tr>
<td>Number (%) of subjects with ≥90% improvement</td>
<td>1 (1.4)</td>
<td>5 (7.0)</td>
</tr>
<tr>
<td>Odds ratio (95% CI) vs placebo; P value</td>
<td>—</td>
<td>4.71 (0.51, 43.64); 0.1726</td>
</tr>
<tr>
<td>Worst pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%) of subjects with ≥30% improvement</td>
<td>14 (19.2)</td>
<td>24 (33.8)</td>
</tr>
<tr>
<td>Odds ratio (95% CI) vs placebo; P value</td>
<td>—</td>
<td>2.15 (0.99, 4.67); 0.0527</td>
</tr>
<tr>
<td>Number (%) of subjects with ≥50% improvement</td>
<td>7 (9.6)</td>
<td>16 (22.5)</td>
</tr>
<tr>
<td>Odds ratio (95% CI) vs placebo; P value</td>
<td>—</td>
<td>2.69 (1.02, 7.12); 0.0457</td>
</tr>
<tr>
<td>Number (%) of subjects with ≥70% improvement</td>
<td>2 (2.7)</td>
<td>8 (11.3)</td>
</tr>
<tr>
<td>Odds ratio (95% CI) vs placebo; P value</td>
<td>—</td>
<td>3.91 (0.77, 19.76); 0.0994</td>
</tr>
<tr>
<td>Number (%) of subjects with ≥90% improvement</td>
<td>2 (2.7)</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Odds ratio (95% CI) vs placebo; P value</td>
<td>—</td>
<td>0.65 (0.07, 5.86); 0.6977</td>
</tr>
</tbody>
</table>

aScores range from 0 to 10, with higher scores indicating greater pain severity.

Abbreviations: CI, confidence interval; SC, subcutaneous.
sensation occurring in ≥2% of subjects in any group and at a higher raw incidence in the tanezumab 20 mg group than in the placebo group was paresthesia (placebo n = 0; tanezumab 20 mg n = 2 [1 mild, 1 moderate]).

Dose-dependent increases in joint safety events, particularly rapidly progressive osteoarthritis, have been observed in previous anti-NGF antibody trials, including those of tanezumab.20,21 Despite excluding subjects with a diagnosis of osteoarthritis, 2 subjects in the tanezumab 20 mg group had an event included in the composite joint safety endpoint. Both of these events were adjudicated as pathologic fractures (occurring near the site of pre-existing bone metastasis) and 1 subject had a total joint replacement after discontinuing the study. Additional fractures (not meeting requirements for review by the adjudication committee) were observed in the placebo (2 subjects with vertebral compression fracture at a site of pre-existing bone metastasis) and tanezumab 20 mg (extra-articular fracture) groups. Subjects with vertebral compression fractures are noteworthy, since, although each was reported to have a spinal compression fracture, the literature indicates that fractures developing in an area of bone pathology (including metastases from benign or malignant tumors) may be considered a pathologic fracture, and the definition of pathologic fracture includes compression fracture for spinal sites.22,23

Overall, our findings support a mechanism whereby NGF drives pain related to metastatic bone cancer (Fig. 4). Approximately 80% of sensory neurons innervating bone express tropomyosin receptor kinase A (TrkA).24 NGF is released at sites of inflammation or injury where it binds to, and forms a signaling complex with TrkA on peripheral terminals of nociceptors.8,9 NGF/TrkA signaling has short- and long-term effects on the activity and/or expression of pro-nociceptive ion channels, receptors, and peptides, which results in increased nociceptive signaling in the periphery (peripheral sensitization) and dorsal horn of the spinal cord (central sensitization) that presents as hyperalgesia.8,9 Sprouting of nerve fibers may also contribute to this hyperalgesia since, in animal models of bone cancer pain, NGF

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Table 3. Summary of TEAEs (during the treatment period) and adjudicated joint safety events (over the full study period).

<table>
<thead>
<tr>
<th>N (% ) subjects</th>
<th>SC placebo (N = 73)</th>
<th>SC tanezumab 10 mg (N = 9)</th>
<th>SC tanezumab 10/20 mg (N = 1)</th>
<th>SC tanezumab 20 mg (N = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAE</td>
<td>50 (68.5)</td>
<td>8 (88.9)</td>
<td>1 (100.0)</td>
<td>53 (73.6)</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>22 (30.1)</td>
<td>2 (22.2)</td>
<td>1 (100.0)</td>
<td>29 (40.3)</td>
</tr>
<tr>
<td>Severe TEAE</td>
<td>24 (32.9)</td>
<td>4 (44.4)</td>
<td>1 (100.0)</td>
<td>30 (41.7)</td>
</tr>
<tr>
<td>Discontinued study due to TEAE</td>
<td>7 (9.6)</td>
<td>1 (11.1)</td>
<td>0</td>
<td>5 (6.9)</td>
</tr>
<tr>
<td>Discontinued treatment due to TEAE</td>
<td>5 (6.8)</td>
<td>1 (11.1)</td>
<td>0</td>
<td>4 (5.6)</td>
</tr>
</tbody>
</table>

Common TEAEs

<table>
<thead>
<tr>
<th>Event</th>
<th>SC placebo (N = 73)</th>
<th>SC tanezumab 10 mg (N = 9)</th>
<th>SC tanezumab 10/20 mg (N = 1)</th>
<th>SC tanezumab 20 mg (N = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>9 (12.3)</td>
<td>1 (11.1)</td>
<td>1 (100.0)</td>
<td>6 (8.3)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>6 (8.2)</td>
<td>0</td>
<td>0</td>
<td>6 (8.3)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>2 (2.7)</td>
<td>0</td>
<td>1 (100.0)</td>
<td>6 (8.3)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>6 (8.2)</td>
<td>0</td>
<td>1 (100.0)</td>
<td>6 (8.3)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5 (6.9)</td>
</tr>
<tr>
<td>Pain</td>
<td>3 (4.1)</td>
<td>0</td>
<td>0</td>
<td>5 (6.9)</td>
</tr>
<tr>
<td>Atenia</td>
<td>3 (4.1)</td>
<td>0</td>
<td>1 (100.0)</td>
<td>4 (5.6)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>5 (6.8)</td>
<td>1 (11.1)</td>
<td>0</td>
<td>4 (5.6)</td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (4.1)</td>
<td>0</td>
<td>1 (100.0)</td>
<td>4 (5.6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (5.5)</td>
<td>1 (11.1)</td>
<td>1 (100.0)</td>
<td>4 (5.6)</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>0</td>
<td>1 (11.1)</td>
<td>0</td>
<td>4 (5.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (6.8)</td>
<td>0</td>
<td>0</td>
<td>4 (5.6)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3 (4.1)</td>
<td>0</td>
<td>0</td>
<td>4 (5.6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (6.8)</td>
<td>0</td>
<td>1 (100.0)</td>
<td>4 (5.6)</td>
</tr>
</tbody>
</table>

Analyzed by the adjudication committee

<table>
<thead>
<tr>
<th>Event</th>
<th>SC placebo (N = 73)</th>
<th>SC tanezumab 10 mg (N = 9)</th>
<th>SC tanezumab 10/20 mg (N = 1)</th>
<th>SC tanezumab 20 mg (N = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event</td>
<td>1 (1.4%)</td>
<td>1 (11.1%)</td>
<td>0</td>
<td>2 (2.8%)</td>
</tr>
<tr>
<td>Included in the composite joint safety endpoint</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (2.8%)</td>
</tr>
<tr>
<td>Pathologic fracture</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (2.8%)</td>
</tr>
</tbody>
</table>

Other outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>SC placebo (N = 73)</th>
<th>SC tanezumab 10 mg (N = 9)</th>
<th>SC tanezumab 10/20 mg (N = 1)</th>
<th>SC tanezumab 20 mg (N = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traumatic avulsion fracture of the ankle</td>
<td>1 (1.4%)</td>
<td>0</td>
<td>0</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Extra-articular pathological fracture</td>
<td>0</td>
<td>1 (11.1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Normal joint</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1.4%)</td>
</tr>
</tbody>
</table>

Abbreviations: SC, subcutaneous; TEAE, treatment-emergent adverse event.
The study demonstrates the potential of anti-NGF therapies such as tanezumab to reduce pain caused by bone metastases. However, durability of efficacy beyond 8 weeks was not demonstrated, and adjudicated intra-articular pathologic fractures were only observed with tanezumab. On October 26, 2021, Pfizer Inc and Eli Lilly and Company announced discontinuation of the tanezumab global clinical development program (including cancer-related pain) as a result of the outcomes of regulatory reviews of tanezumab for the treatment of osteoarthritis pain by the U.S. Food and Drug Administration and European Medicines Agency. Previously, development of the anti-NGF antibodies fasinumab and fulranumab have been discontinued by Regeneron and Janssen, respectively, leaving the future of anti-NGF therapy for cancer-related pain in doubt unless other agents targeting the NGF-signaling pathway (with improved joint safety profiles) emerge in the future.

**Acknowledgments**

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**Funding**

The study was sponsored by Pfizer and Eli Lilly and Company.

**Conflict of Interest**

The study was sponsored by Pfizer and Eli Lilly and Company. Marie Fallon served as a study investigator for this trial and has served as an advisor to Pfizer, Eli Lilly and Company, and Fitabeo Therapeutics. Maciej Sopata served as a study investigator for this trial. Erika Dragon is a full-time employee of, and owns stock and/or options in, Pfizer. Mark T. Brown was a full-time employee of Pfizer at the time the study was conducted and owns stock in Pfizer. Lars Viktrup is a full-time employee of, and owns stock in, Eli Lilly & Company. Christine R. West is a full-time employee of, and own stock and/or options in, Pfizer. Weihang Bao is a full-time employee of, and own stock and/or options in, Pfizer. Alex Agyemang is a full-time employee of, and own stock and/or options in, Pfizer. The study was sponsored by Pfizer and Eli Lilly and Company. Pfizer Inc and Eli Lilly and Company contributed to the study design; Pfizer contributed to the management and collection of data. In their role as authors, employees of Pfizer and Eli Lilly were involved in the interpretation of data, preparation, review, and approval of the manuscript and the decision to submit for publication, along with their co-authors. The study sponsors approved the manuscript from an intellectual property perspective but had no right to veto the publication.

**Ethical Oversight**

The protocol was approved by an Institutional Review Board or Independent Ethics Committee for each participating...
investigational center (individual IRB’s for participating institutions were provided upon request). All subjects provided written informed consent. This study was conducted in compliance with ethical principles of the Declaration of Helsinki and all International Conference on Harmonization Good Clinical Practice Guidelines.

Author Contributions
Conception/design: M.T.B., L.V., C.R.W. Provision of study material or patients: M.F., M.S. Data analysis and interpretation: All authors. Manuscript writing and final approval of manuscript: All authors.

Data Availability
Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Supplementary Material
Supplementary material is available at The Oncologist online.

References


