CLINICAL STUDY REPORT SYNOPSIS

Investigational Product: Tanezumab

Clinical Study Report Synopsis: Protocol A4091061

Protocol Title: A Phase 3 Randomized, Double-blind, Placebo-controlled, Multicenter Study of the Analgesic Efficacy and Safety of the Subcutaneous Administration of Tanezumab (PF-04383119) in Subjects With Cancer Pain Predominantly Due to Bone Metastasis Receiving Background Opioid Therapy

Investigators: Refer to Appendix 16.1.4.1 for a list of Investigators involved in this study.

Study Center(s): A total of 48 sites in Argentina, Australia, Austria, Brazil, Chile, China, Czech Republic, Hungary, Japan, Republic of Korea, Poland, Romania, Slovakia, Spain, and United Kingdom randomized subjects in this study. Refer to Appendix 16.1.4.1 for a list of sites involved in this study.

Publications Based on the Study: Fallon M, Sopata M, Dragon E, Brown MT, Viktrup L, West CR, Hamlett K, Bao W, Agyemang A. LBA62 Efficacy and safety of tanezumab in subjects with cancer pain predominantly due to bone metastasis receiving background opioid therapy. Annals of Oncology. 2021 Sep 1;32:S1339.

Study Initiation Date: 28 October 2015 (First Subject First Visit)

Primary Completion Date: 17 September 2020

Study Completion Date: 25 June 2021 (Last Subject Last Visit)

Report Date: 21 October 2021

Previous Report Date(s): Not applicable

Phase of Development: Phase 3

Study Objectives and Endpoints:

Table S1. Study Objectives

Type	Objective
Primary	
Efficacy	Demonstrate superior analgesic efficacy of tanezumab 20 mg subcutaneous (SC) versus matching placebo SC at Week 8 in subjects, with cancer pain predominantly due to bone metastasis, receiving background opioid therapy
Secondary	
Safety	Evaluate the safety of tanezumab 20 mg SC versus matching placebo SC in subjects, with cancer pain predominantly due to bone metastasis, receiving background opioid therapy.

CLINICAL STUDY REPORT SYNOPSIS

Table S2. Study Endpoints

Type	Endpoints
Primary	
Efficacy	Change from Baseline to Week 8 in the daily average pain intensity in the index bone metastasis cancer pain site.
Secondary	
Efficacy	• Change from Baseline to Weeks 1, 2, 4, 6, 12, 16 and 24 in the daily average pain intensity Numerical Rating Scale (NRS) score in the index bone metastasis cancer pain site. • Change from Baseline to Weeks 1, 2, 4, 6, 8, 12, 16 and 24 in the daily worst pain intensity NRS score in the index bone metastasis cancer pain site. • Change from Baseline to Weeks 1, 2, 4, 6, 8, 12, 16 and 24 in the weekly average pain intensity NRS score in non-index cancer pain sites. • Change from Baseline to Weeks 1, 2, 4, 6, 8, 12, 16 and 24 in the weekly worst pain intensity NRS score in non-index cancer pain sites. • Change from Baseline to Weeks 1, 2, 4, 6, 8, 12, 16 and 24 in the daily average pain intensity NRS score in the non-index visceral cancer pain sites. • Change from Baseline to Weeks 1, 2, 4, 6, 8, 12, 16 and 24 in the daily worst pain intensity NRS score in the non-index visceral cancer pain site. • Change from Baseline to Weeks 2, 4, 8, 16 and 24 in the Brief Pain Inventory Short Form (BPI-sf) average pain scores obtained at study visits. • Change from Baseline to Weeks 2, 4, 8, 16 and 24 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 and daily worst pain intensity NRS score in the index bone metastasis cancer pain site at Weeks 1, 2, 4, 6, 8, 12, 16 and 24. • Change from Baseline in Patient's Global Assessment (PGA) of Cancer Pain at Weeks 2, 4, 8, 16 and 24. • Response defined as an improvement of ≥2 points in PGA of Cancer Pain at Weeks 2, 4, 8, 16 and 24. • Change from Baseline to Weeks 2, 4, 8, 16 and 24 in the BPI Pain Interference with Function Composite Score and individual pain interference item scores obtained at study visits. • Euro Quality of Life-5 Dimension-5 Level (EQ-5D-5L™) dimensions and overall health utility score at Baseline and Weeks 8, 16 and 24. • Average daily total opioid consumption (in mg of morphine equivalent doses) at Weeks 1, 2, 4, 6, 8, 12, 16 and 24. • Average number of doses of rescue medication required per week at Weeks 1, 2, 4, 6, 8, 12, 16 and 24. • Change from Baseline in the weekly Opioid Related Symptom Distress Scale (OR-SDS) at Weeks 2, 4, 8, 16, and 24.
Safety	• Adverse events. • Standard safety assessments (safety laboratory testing [chemistry, hematology], sitting vital signs, 12-lead electrocardiogram (ECG). • Orthostatic (supine/standing) blood pressure assessment. • Weight measurements. • Physical examinations. • Joint safety adjudication outcomes. • Total joint replacements (TJRs). • Neurologic examination (Neuropathy Impairment Score [NIS]). • Survey of Autonomic Symptom (SAS) scores. • Anti-drug antibody (ADA) assessments.

CLINICAL STUDY REPORT SYNOPSIS

Table S2. Study Endpoints

Type	Endpoints
Tertiary Endpoints	
[redacted]	[redacted]

METHODS

Study Design: This was a randomized, double-blind, placebo-controlled, multicenter, parallel group, Phase 3 study in subjects with cancer pain predominantly due to bone metastasis receiving background opioid therapy.

The protocol was initially designed to include three treatment groups (tanezumab 20 mg SC, tanezumab 10 mg SC, and placebo), and was amended after study start to discontinue the tanezumab 10 mg dose arm.

Following implementation of Protocol Amendment 3, subjects were randomized in a 1:1 ratio to one of two treatment arms: tanezumab 20 mg SC or matching placebo SC, each administered in addition to background opioids. Subjects who had been randomized to the 10 mg dose treatment arm and who were in the Double-Blind Treatment Period at the time of after implementation of Protocol Amendment 3 were administered 20 mg for any remaining doses.

The study consisted of three periods: Pre-Treatment (up to 37 days), Double-Blind Treatment (24 weeks) and 6-month Safety Follow Up (24 weeks). The Pre-Treatment Period included a Screening Period (lasting up to 32 days) with washout of prohibited study medication and stabilization of background opioid regimen prior to a 5-day Baseline Assessment Period. Confirmation of radiographic eligibility by a central radiologist based on protocol-defined x-rays took place during the Pre-Treatment Period.

Diagnosis and Main Criteria for Inclusion: The population selected for this study consisted of male or female subjects, ≥18 years of age, with moderate to severe cancer pain predominantly due to bone metastasis who had inadequate pain relief with opioids and who were seeking effective treatment options. Subjects were expected to require daily opioid medication throughout the course of the study. Subjects with a diagnosis of osteoarthritis of the knee or hip as defined by the American College of Rheumatology combined clinical and radiographic criteria or with symptoms and radiographic findings consistent with osteoarthritis in the shoulder were excluded from participation.

CLINICAL STUDY REPORT SYNOPSIS

Study Treatment: Following implementation of Protocol Amendment 3, subjects were randomized in a 1:1 ratio to one of two treatment arms:

- Matching placebo for tanezumab SC once every 8 weeks × 3 administrations
- Tanezumab 20 mg SC once every 8 weeks × 3 administrations

Subjects randomized to the 10 mg dose treatment arm who were in the Double-Blind Treatment Period after implementation of Protocol Amendment 3 were administered 20 mg for any remaining doses.

Table S3. Investigational Product Description

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/Potency	Dosage Form
PF-04383119 Solution for Injection, 10 mg/mL	L52539	15-002260	10 mg/mL	Pre-filled Syringe
PF-04383119 Solution for Injection, 20 mg/mL	L60630	15-002264	20 mg/mL	Pre-filled Syringe
	N09943	16-001925		
	N54466	17-001819		
	W39819	18-001603		
Placebo for PF-04383119 Solution for Injection	L39168	15-002262	0 mg/mL	Pre-filled Syringe
	S64269	17-001779		

Efficacy Evaluations:

Average pain and worst pain in the index bone metastasis cancer pain site and non-index cancer pain sites were assessed by the subject at approximately the same time each day (or each week) with an 11-point NRS ranging from 0 (no pain) to 10 (worst possible pain) captured through Interactive Response Technology (IRT; subject diary). The subjects described their pain in the painful site during the past 24 hours by choosing the appropriate number from 0 to 10.

Average pain and worst pain in the index bone metastasis cancer pain site was assessed by the subject at Screening and daily during the Pre-Treatment Period to the Week 8 Visit, and

CLINICAL STUDY REPORT SYNOPSIS

then assessed weekly using a 24-hour recall period beginning after the Week 8 visit through Week 24 (and weekly during the Early Termination Follow-Up Period).

Assessment of pain in non-index site(s) of cancer pain was performed weekly during the Pre-Treatment Period to the Week 24 Visit (and weekly during the Early Termination Follow-Up Period up to the visit that occurred 16 weeks after the last dose of SC study medication was administered).

Background opioid medication use was collected in the IRT and in the case report form if dual concomitant opioids were used. The subject recorded dosing information pertinent to his/her around-the-clock (ATC) opioid medication and rescue opioid medication for the past 24 hours. Background opioid medication use was assessed daily via IRT during the Pre-Treatment Period to the Week 8 Visit and then was assessed weekly using a 24-hour recall period beginning after the Week 8 Visit through Week 24 Visit.

The BPI-sf is a self-administered questionnaire used to assess the severity of pain and the impact of pain on daily functions during a 24-hour period prior to evaluation. The BPI-sf was completed by the subjects via IRT during clinic visits at Baseline (Day 1, Pre-randomization),Weeks 2, 4, 8, 16, and 24, and Early Termination Visit 1.

The OR-SDS is a self-administered questionnaire that assesses frequency, severity, and level of bother of opioid associated adverse effects. The OR-SDS was completed by the subject via IRT during clinic visits (prior to SC dosing at dosing visits) at Baseline (Day 1, Pre-randomization),Weeks 2, 4, 8, 16, and 24, and Early Termination Visit 1.

The PGA of Cancer Pain is a global evaluation that utilizes a 5-point Likert scale with a score of 1 being the best (Very Good) and a score of 5 being the worst (Very Poor). It is intended to provide a qualitative measurement of the subject's impression of disease activity. The PGA of Cancer Pain was completed by the subjects via IRT during clinic visits at Baseline (Day 1, Pre-randomization),Weeks 2, 4, 8, 16, and 24, and Early Termination Visit 1.

The EQ-5D-5L is a subject completed questionnaire designed to assess the subject's current health and translate that score into an index value or utility score. Health status is described in terms of five dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. The responses record five levels of severity (no problems, slight problems, moderate problems, severe problems, extreme problems) within a particular EQ-5D dimension. There are two components to the EQ-5D-5L: a Health State Profile and a visual analog scale (VAS) item. The 5-item Health State Profile was assessed to calculate a single index value. The EQ-5D-5L was completed by the subjects via IRT during clinic visits at Baseline (Day 1, Pre-randomization),Weeks 8, 16, and 24, and Early Termination Visit 1.

CLINICAL STUDY REPORT SYNOPSIS

[redacted]

Safety Evaluations

Safety evaluations for this study included assessment of adverse events, safety laboratory testing (chemistry and hematology), sitting vital signs, 12-lead ECG, orthostatic (supine/standing) blood pressure assessment, weight measurements, physical examinations, joint safety adjudication outcomes, TJRs, neurologic examination (using the NIS), SAS scores, and ADA assessments.

Statistical Methods:

Analysis of the Primary Endpoint: The primary efficacy endpoint was analyzed using an analysis of covariance (ANCOVA) model, with model terms for Baseline score, the stratification variables, Baseline opioid use (ie, morphine equivalent amount in mg), region and treatment group. The stratification variables were (i) tumor aggressiveness (assessed by Eastern Cooperative Group [ECOG] performance status) and (ii) presence/absence of concomitant anticancer treatment (eg, chemotherapy or hormonal therapy or anti-hormonal therapy). The model was used to test the null hypothesis that the difference in tanezumab 20 mg and placebo treatment is zero versus the alternative that the difference is not zero.

The primary analysis of the primary endpoint used multiple imputation for missing data, to account for uncertainty around the unobserved subject response, where the method for imputation was dependent on the reason for missing data. In the final primary efficacy analysis, the alpha was adjusted to alpha = 0.0478 because an interim analysis was conducted.

Analysis of Secondary Endpoints: The change from Baseline for the daily average and worst pain intensity in the bone metastasis index cancer pain site were summarized for each week from 1 to 24. The change from Baseline to Days 1, 2, 3, 4, 5, 6, and 7, and to Weeks 1, 2, 4, 6, 8 (Worst Pain), 12, 16, and 24 were analyzed using ANCOVA as described for the primary endpoint analysis, using multiple imputation.

A secondary analysis for the change from Baseline in the daily average pain scores used a repeated measure mixed effects model, on the available data over Weeks 1 to 24. Additional secondary analysis for the change from Baseline to Week 8 and 16 in the daily average pain used single imputation Last Observation Carried Forward (LOCF) and Baseline Observation Carried Forward (BOCF) for missing data.

CLINICAL STUDY REPORT SYNOPSIS

The mean of the subject's average and worst pain in the non-index cancer sites, over all non-index sites (for up to 2 sites per subject) was calculated for Baseline and for each week, and for the change from Baseline. The change from Baseline to Weeks 1, 2, 4, 6, 8, 12, 16, and 24 in average and worst pain in the non-index cancer pain sites was analyzed using ANCOVA as described for the primary endpoint analysis, using multiple imputation. For non-index visceral cancer sites, the ANCOVA was not conducted because the number of available subjects was <10.

The change from Baseline to Weeks 2, 4, 8, 16, and 24 in the BPI average and worst pain scores and BPI pain interference with function (composite and individual items) were summarized and analyzed using the ANCOVA main effects model as described for the primary endpoint analysis, with multiple imputation.

The change from Baseline to Weeks 2, 4, 8, 16 and 24 in the PGA of Cancer Pain was summarized by treatment group and analyzed using ANCOVA as described above with multiple imputation. A second analysis of this parameter used Cochran-Mantel-Haenszel test for the change from Baseline to Weeks 2, 4, 8, 16, and 24. This analysis provided a sensitivity analysis for the ANCOVA analysis of the PGA. The missing data imputation used for this analysis was mixed BOCF/LOCF.

Average daily opioid consumption (mg of morphine equivalent dosage) and average number of doses of rescue opioid consumption per week were summarized for each week up to Week 24. Percent change from Baseline in average daily opioid consumption was analyzed using ANCOVA on the rank scores with treatment and the stratification variables as factors. Missing data were imputed using LOCF. The average number of doses of rescue opioid consumption per week was analyzed using a negative binomial model taking into account Baseline daily average pain and Baseline opioid use.

The response endpoint for daily worst and average pain in the index site (defined by a ≥30%, ≥50%, ≥70% and ≥90% change from Baseline to Weeks 1, 2, 4, 6, 8, 12, 16, and 24) was summarized and analyzed using logistic regression for binary data, with model terms for Baseline average/worst pain subscale score, stratification variables, and treatment group. Imputation for missing data used LOCF, BOCF, and mixed BOCF/LOCF imputation.

The response parameter of an improvement of ≥2 points in the PGA of Cancer Pain was analyzed as described for the daily average and worst pain response parameters using mixed BOCF/LOCF (using the covariates of Baseline PGA of Cancer Pain and Baseline daily average pain).

A table showing number and percentage of subjects summarized the response for each dimension (item) of the EQ-5D-5L at Baseline and Weeks 8, 16 and 24. These summary tables was shown by treatment group. In addition, for each treatment and each time point assessed, descriptive statistics (mean, standard deviation, median, number of subjects) characterized the five-item health status profile on the EQ-5D-5L in terms of the health utility score and the EQ-VAS (EuroQol Visual Analogue Scale).

CLINICAL STUDY REPORT SYNOPSIS

[redacted]

Safety Analyses: Adverse events, serious adverse events (SAEs), concomitant medications, laboratory safety tests, physical examinations, SAS, vital signs, and ECGs were summarized descriptively.

The following assessments of ADA data were presented:

- A listing of individual serum ADA results sorted by treatment group, subject identification and planned visit.
- The proportion of subjects who tested positive and negative was summarized by treatment group and planned visit. The summary will also include the proportion of subjects who tested positive and negative overall in the study.
- Subjects who developed anti-tanezumab antibodies after treatment were evaluated for the presence of anti-tanezumab neutralizing antibodies, and individual results were listed.
- Individual subjects with positive ADA results were evaluated for potential ADA impact on the individual's [redacted], efficacy and safety profile.

In addition, the following safety analyses were also presented:

- Summary of number of days of non-steroidal anti-inflammatory drug (NSAID) use per dosing interval (eg, Day 1 to Week 8, Week 8 to Week 16, Week 16 to Week 24) and for the first 8-week interval in the Safety Follow-Up Period. This showed the number and percentage of subjects in an interval who exceeded the limit of 10 days of NSAID use. Also, a summary of the overall number of days of NSAID use from Day 1 to Week 32 was shown, as well as the number and percentage of subjects who exceeded the limit of 36 days of NSAID use during this interval.
- Change from Baseline to each Post Baseline visit in the NIS, and to both the Last and Worst change from Baseline (over all post Baseline visits) were summarized and analyzed using Cochran Mantel Haenszel test (last change from Baseline was not

CLINICAL STUDY REPORT SYNOPSIS

analyzed). The NIS data, the neurological consultation data and the conclusion from neurological examination data were reported.

- The incidence of subjects with any of the joint safety adjudication outcomes of rapidly progressive osteoarthritis (type 1 and type 2), subchondral insufficiency fracture, primary osteonecrosis, or pathological fracture, and for occurrence of TJR was shown by number of subjects treated and subject years of exposure (treatment plus Follow-Up Periods), for individual treatment groups.

RESULTS

Subject Disposition and Demography:

A total of 325 subjects were screened for the study, of which 156 subjects were randomized; 155 subjects were treated, and one subject randomized to placebo was not treated. Of the randomized subjects, 74 subjects were randomized to Placebo group, 10 subjects were randomized to tanezumab 10 mg treatment group, and 72 subjects were randomized to tanezumab 20 mg treatment group. One subject who was randomized to the tanezumab 10 mg treatment group later received tanezumab 20 mg for any remaining doses (tanezumab 10/20 treatment group) after the implementation of Protocol Amendment 3.

A total of 77 subjects (49.7%) completed the Treatment Period: (ie, up to Week 24) and of those, 62 subjects (40.0%) completed the Safety Follow up Period. Of those who discontinued from the Treatment Period (78 subjects [50.3%]), few completed the Safety Follow-up Period (3 subjects [1.9%]). The proportion of subjects who completed the Treatment Period was comparable for the tanezumab 20 mg (36 subjects [50.0%]) and placebo treatment groups (36 subjects [49.3%]).

One subject who had a TJR agreed to participate in the substudy.

Two subjects discontinued treatment and from the study due to travel restrictions related to the Coronavirus Disease 2019 (COVID-19) pandemic.

Overall, demographic characteristics were balanced across tanezumab 20 mg and placebo treatment groups except for gender and some age categories. There were more male subjects (46 subjects [63.9%] vs 34 subjects [46.6%]) in tanezumab 20 mg treatment group compared with the placebo treatment group. The mean age was similar in the tanezumab 20 mg and placebo treatment groups. However, the proportion of subjects in the 45 to 64 years age group was lower in the tanezumab 20 mg treatment group than the placebo treatment group (45.8% vs 60.3%) and the proportion of subjects in the ≥65 years age group was higher in the tanezumab 20 mg treatment group than in the placebo treatment group (50.0% vs 26.0%).

Overall, racial groups were well balanced in the placebo and tanezumab 20 mg treatment groups**.**

CLINICAL STUDY REPORT SYNOPSIS

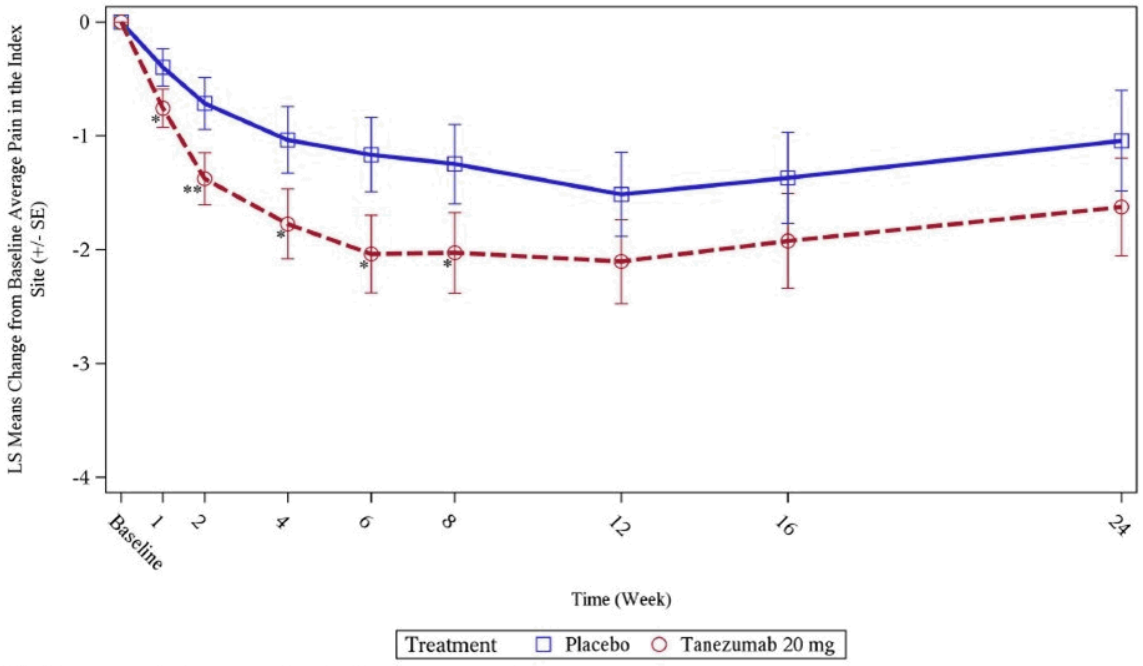
Efficacy Results:

Primary Endpoint Results

Treatment with tanezumab 20 mg resulted in significant improvement from Baseline to Week 8 in the daily average pain intensity at the index cancer pain site compared with placebo treatment and met the primary objective of the study (p=0.0381 at an adjusted $\alpha = 0.0478$ in a two-sided test, Figure S1).

Results of a sensitivity analysis of the primary endpoint that repeated the primary analysis using data prior to the COVID-19 pandemic (least squares [LS] mean difference: -0.55) were directionally consistent with the primary analysis (LS mean difference: -0.78); however, the results were not significant (p=0.1870).

Figure S1. Change From Baseline for Daily Average Pain Intensity at the Index Cancer Pain Site Up to Week 8 (Intent-to-Treat [ITT] Population, Multiple Imputation)



The index cancer pain site corresponds to the site of bone metastasis.
* denotes p-value <= 0.05, ** denotes p-value <= 0.01.
p-value = 0.0381 for the primary endpoint at Week 8, which is significant at alpha=0.0478 in a two-sided test.
PFIZER CONFIDENTIAL SDTM Creation: 13JUL2021 (10:42) Source Data: adnrmi Table Generation: 30JUL2021 (20:36)Output File: . /nda1/A4091061/plot_adnrmi24_desc

Secondary Endpoint Results

- **Change from Baseline in the Daily Average Pain Intensity in the Index Bone Metastasis Cancer Site:** Tanezumab 20 mg treatment resulted in significant improvement from Baseline in the daily average pain intensity at the index cancer pain site compared with placebo at Weeks 1, 2, 4, and 6. From Weeks 12 to 24, tanezumab 20

CLINICAL STUDY REPORT SYNOPSIS

mg treatment resulted in a numerical reduction from Baseline in the daily average pain intensity at the index cancer pain site compared with placebo, but the difference was not significant at any of these time points. Treatment differences from Weeks 12 to 24 were directionally consistent with the treatment difference at Week 8, but lower in magnitude. At Week 8, there were 58 and 62 subjects in the placebo and tanezumab 20 mg treatment groups, respectively. At Week 24, there were 38 and 41 subjects in the placebo and tanezumab 20 mg treatment groups, respectively.

- **Change from Baseline in the Daily Worst Pain Intensity in the Index Bone Metastasis Cancer Site:** Tanezumab 20 mg treatment resulted in significant improvement from Baseline in the daily worst pain intensity at the index cancer pain site compared with placebo at Weeks 2, 4, and 6. From Weeks 8 to 24, tanezumab 20 mg treatment resulted in numerical reduction from Baseline in the daily worst pain intensity at the index cancer pain site compared with placebo, but the difference was not significant at any of these time points.

- **Change from Baseline in the Weekly Average Pain Intensity in Non-index Cancer Pain Sites:** Non-index cancer pain sites selected by the subject were pain confirmed by the Investigator to be due to cancer or cancer treatment, and the pain was judged by the Investigator to be somatic, neuropathic, or visceral in nature. One subject reported non-index visceral cancer pain. Tanezumab 20 mg treatment resulted in numerical reduction from Baseline in the weekly average pain intensity in non-index cancer pain sites compared with placebo at Weeks 1 through 24, but the treatment difference was not significant at any time point. At Weeks 8 and 24, treatment differences in the non-index cancer pain sites were directionally consistent with those in the index cancer pain site. For subjects with a Baseline score ≥5, tanezumab 20 mg treatment resulted in numerical reduction from Baseline in the weekly average pain intensity in non-index cancer pain sites compared with placebo at Weeks 1 through 24, but the treatment difference was not significant at any time point.

- **Change from Baseline in the Weekly Worst Pain Intensity in Non-index Cancer Pain Sites:** Tanezumab 20 mg treatment resulted in significant improvement from Baseline in the weekly worst pain intensity at the non-index cancer pain sites compared with placebo at Weeks 2, 4, and 16 ($p \leq 0.0410$). At Weeks 1, 6, 8, 12, and 24, tanezumab 20 mg treatment resulted in numerical reduction from Baseline in weekly worst pain intensity at the non-index cancer pain sites compared with placebo, but the treatment difference was not significant at any of these time points. For subjects with a Baseline score ≥5, tanezumab 20 mg treatment resulted in significant improvement from Baseline in the weekly worst pain intensity at the non-index cancer pain sites compared with placebo at Weeks 2, 4, 12, 16, and 24 ($p \leq 0.0460$).

- **Change from Baseline in the Brief Pain Inventory – Short Form (BPI-sf):** For both the change from Baseline in BPI-sf average and worst pain scores, there was an improvement (reduction) from Baseline in the tanezumab 20 mg treatment group

CLINICAL STUDY REPORT SYNOPSIS

compared with the placebo treatment group at all time points. Tanezumab 20 mg treatment resulted in significant improvement in the average pain BPI-sf score compared with placebo at Weeks 4 and 8 (p=0.0244 and p=0.0401, respectively) and in the worst pain BPI-sf score compared with placebo at Weeks 4 and 24 (p=0.0355 and p=0.0438, respectively). Tanezumab 20 mg treatment resulted in significant improvement from Baseline in the BPI-sf pain interference index compared with placebo at Week 8 (p=0.0462). At Weeks 2, 4, 6, 16, and 24, tanezumab 20 mg treatment resulted in numerical reduction from Baseline in the BPI-sf pain interference index compared with placebo, but the difference was not significant at any of these time points. Tanezumab 20 mg treatment resulted in significant improvement compared with placebo for the BPI-sf individual scores of pain interference with general activity at Week 8 (p=0.0145) and pain interference with sleep at Week 4 (p=0.0450); numerical reduction was observed at all other time points. Tanezumab 20 mg treatment resulted in numerical reduction for all other BPI-sf individual scores (walking ability, normal work, mood, relations with other people, and enjoyment of life) compared with placebo at all time points, except for relations with other people at Week 2 (LS mean difference [SE]: 0.18 [0.40]).

- **Percent Reduction From Baseline in Daily Average and Worst Pain Intensity in the Index Bone Metastasis Cancer Pain Site:** Tanezumab 20 mg treatment was associated with a numerical increase in the proportion of responders in daily average and worst pain intensity at the index cancer pain site at all levels (≥30%, ≥50%, ≥70%, and ≥90%) at all weeks compared with placebo (except Week 1, ≥90%). Tanezumab 20 mg treatment was associated with a significant increase in the proportion of responders in daily average and worst pain intensity pain intensity in the index cancer pain site compared with placebo for the ≥50% response level at Week 8 (p=0.0405 and p=0.0457, respectively). Tanezumab 20 mg treatment was also associated with a significant increase in the proportion of responders in daily average pain intensity in the index cancer pain site compared with placebo for the ≥50% response level at Weeks 2, 4, and 6 and for the ≥70% response level at Weeks 4 and 6. Additionally, tanezumab 20 mg treatment was associated with a significant increase in the proportion of responders in daily worst pain intensity in the index cancer pain site compared with placebo for the ≥50% response level at Weeks 4 and 6 and for the ≥30% response level at Weeks 6, 16, and 24.

- **Change from Baseline in PGA of Cancer Pain:** Tanezumab 20 mg treatment resulted in significant improvement from Baseline in PGA of Cancer Pain compared with placebo at Week 4 (p=0.0402), using multiple imputation. At Weeks 2, 6, 8, 16, and 24, tanezumab 20 mg treatment resulted in numerical reduction from Baseline in PGA of Cancer Pain compared with placebo, but the treatment difference was not significant at any of these time points.

- **Improvement of at least Two Points in PGA of Cancer Pain:** Treatment with tanezumab 20 mg was associated with a numerical increase in the proportion of subjects reporting a ≥2-point reduction from Baseline in PGA of Cancer Pain compared with

CLINICAL STUDY REPORT SYNOPSIS

placebo treatment at Weeks 4 through 24, but the difference was not significant at any time point.

- **EQ-5D-5L Dimensions and Overall Health Utility Score:** The mean EQ-5D-5L index values were similar for the placebo and tanezumab 20 mg treatment groups at all time points evaluated.

- **Opioid Consumption and Rescue Medication Use:** At Week 8, the percent change from Baseline for average daily opioid consumption (ATC and rescue medication in mg of morphine equivalent dose) was numerically similar between the tanezumab 20 mg and placebo treatment groups and not significant (p=0.8692). The mean average daily number of doses of rescue medication was significantly lower for the tanezumab 20 mg treatment group compared with placebo at Week 4 (p=0.0211) and numerically lower for the tanezumab 20 mg treatment group than the placebo treatment group at Weeks 1, 2, 6, 8, 12, 16, and 24, although analysis showed no significant differences between treatment groups (all p-values ≥0.0750).

- **Opioid-Related Symptom Distress Scale:** There were no significant differences in the change from Baseline in the frequency, severity, distress, or multi-domain average composite scores between the tanezumab 20 mg and placebo treatment groups at any week.

[redacted]

Safety Results:

All adverse events described in this report were treatment emergent (TE), unless otherwise specified.

CLINICAL STUDY REPORT SYNOPSIS

A higher proportion of subjects in the tanezumab 20 mg treatment group reported adverse events up to the end of the study compared with the placebo treatment group. The incidence of SAEs or severe adverse events during this period were higher in the tanezumab 20 mg treatment group compared with the placebo treatment group (Table S4). The incidence of treatment discontinuation due to an adverse event during this period was similar between the tanezumab 20 mg (4 subjects [5.6%]) and placebo (5 subjects [6.8%]) treatment groups.

Table S4. Treatment-Emergent Adverse Events Up To End of Study (All Causalities) - Safety Population

Number (%) of Subjects	Placebo n (%)	Tanezumab 10 mg n (%)	Tanezumab 10/20 mg n (%)	Tanezumab 20 mg n (%)
Subjects evaluable for adverse events	73	9	1	72
Number of adverse events	271	39	10	302
Subjects with adverse events	52 (71.2)	9 (100.0)	1 (100.0)	62 (86.1)
Subjects with serious adverse events	28 (38.4)	2 (22.2)	1 (100.0)	39 (54.2)
Subjects with severe adverse events	31 (42.5)	4 (44.4)	1 (100.0)	38 (52.8)
Subjects discontinued from study due to adverse events[a]	9 (12.3)	1 (11.1)	0	7 (9.7)
Subjects discontinued study drug due to AE and continue Study[b]	5 (6.8)	1 (11.1)	0	4 (5.6)
Subjects with dose reduced or temporary discontinuation due to adverse events	0	0	0	2 (2.8)

Includes treatment-emergent events that begin on or after the first dose date up to the end of the study.
Except for the Number of adverse events, subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
[a] Subjects who have an AE record that indicates that the AE caused the subject to be discontinued from the study.
[b] Subjects who have an AE record that indicates that action taken with study treatment was drug withdrawn but AE did not cause the subject to be discontinued from the study.
MedDRA v24.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 13JUL2021 (08:55) Source Data: adae Table Generation: 19JUL2021 (14:51)
Output File: ./nda1/A4091061/adae_s020_eos
Table 14.3.1.2.1.3 Tanezumab is for Pfizer internal use.

The incidence of adverse events reported during the Treatment Period was similar in the tanezumab 20 mg and placebo treatment groups. The incidence of SAEs or severe adverse events during the Treatment Period were higher in the tanezumab 20 mg treatment group compared with the placebo treatment group. The incidence of treatment discontinuation due to an adverse event during the Treatment Period was similar between the tanezumab 20 mg (4 subjects [5.6%]) and placebo (5 subjects [6.8%]) treatment groups.

CLINICAL STUDY REPORT SYNOPSIS

The most common adverse events occurring in the tanezumab 20 mg were Anemia, Arthralgia, Decreased appetite, Prostate cancer (verbatim term: Progression of prostate cancer), Peripheral edema, and Pain. The proportion of subjects reporting Peripheral edema was higher in the tanezumab 20 mg treatment group compared with the placebo group, as seen in previous tanezumab studies.

- The majority of adverse events reported during the Treatment Period were moderate to severe in severity in both the tanezumab 20 mg and placebo treatment groups.

- The overall incidence of treatment-related adverse events reported during this period was similar across the placebo and tanezumab 20 mg treatment groups in the placebo treatment group.

- The majority of treatment-related adverse events were mild in severity. The General Disorders and Administration Site Conditions system organ class (SOC) had the highest incidence of adverse events in the tanezumab 20 mg treatment group. The Gastrointestinal Disorders SOC and Skin and Subcutaneous Tissue Disorders SOC each had the highest incidence of adverse events in the placebo treatment group.

Up to the end of the study, the placebo treatment group had a larger proportion of subjects who discontinued from treatment and/or the study due to an adverse event (14 subjects [19.2%]) than the tanezumab 20 mg treatment group (11 subjects [15.3%]).

- Adverse events resulting in discontinuation from treatment and/or the study occurred most frequently in the Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps) SOC.

- The incidence of discontinuations from treatment and/or the study due to adverse events in the Neoplasms Benign, Malignant and Unspecified (Including Cysts And Polyps) SOC was higher in the placebo group (9 subjects [12.3%]) compared with the tanezumab 20 mg treatment group (6 subjects [8.3%]).

- Most adverse events resulting in discontinuation from treatment and/or the study were moderate to severe in severity.

Throughout the duration of the entire study, 2 subjects temporarily discontinued treatment due to an adverse event and both subjects were in the tanezumab 20 mg treatment group (2 subjects [2.8%]). The causality for both the adverse events was reported as "Not Related; Other Disease Under Study" and they were severe in severity.

CLINICAL STUDY REPORT SYNOPSIS

- **Deaths:** A total of 46 subjects died during the study. The cause of the death for the majority of subjects across the treatment groups was Neoplasm progression. None of the deaths were considered by the Investigator to be related to study treatment.

- **Serious Adverse Events:** The incidence of SAEs up to end of study was higher in the tanezumab 20 mg treatment group (39 subjects [54.2%]) compared with the placebo treatment group (28 subjects [38.4%]). The majority of SAEs were in the Neoplasms Benign, Malignant and Unspecified (Including Cysts And Polyps) SOC. Prostate cancer (verbatim term: Progression of prostate cancer) was the most frequently reported SAE in the tanezumab 20 mg and placebo treatment groups. The majority of all reported SAEs were considered by the Investigator to be unrelated to study treatment.

- **Adverse Events Related to COVID-19:** No treatment-emergent COVID-19-related adverse events were reported. Across the treatment groups, 30 subjects were evaluable for adverse events in the time periods before and during the COVID-19 pandemic. The incidence of adverse events in the during-COVID-19 period was higher than in the period before COVID-19.

- **Peripheral Nervous System Adverse Events of Special Interest:** Adverse events of abnormal peripheral sensation were reported by 7 subjects (9.7%) in the tanezumab 20 mg treatment group and 4 subjects (5.5%) in the placebo treatment group. In tanezumab 20 mg treatment group, Paresthesia was most frequent (n=2; 2.8%) and the other adverse events were each reported in a single subject. All adverse events of abnormal peripheral sensation during the Treatment Period were mild to moderate in severity. Of the 6 subjects who met criteria for neurological consults, in the tanezumab 20 group, mononeuropathy and radiculopathy were each diagnosed by the blinded external neurologist in 1 subject and no subjects were diagnosed with polyneuropathy; in the placebo group 1 subject was diagnosed with a polyneuropathy.

- **Adverse Events Potentially Indicative of Decreased Sympathetic Function:** The proportion of subjects reporting adverse events potentially indicative of decreased sympathetic function during the Treatment Period was similar for the tanezumab 20 mg (12 subjects [16.7%]) and placebo treatment groups (9 subjects [12.3%]). The majority of these events in both tanezumab 20 mg and placebo treatment groups was due to nausea and vomiting which are sensitive but not specific for decreased sympathetic function.

- **Orthostatic Hypotension:** Two subjects had confirmed orthostatic hypotension (OH) during the Treatment Period, 1 subject each in the tanezumab 10 mg and tanezumab 20 mg treatment groups. No subjects in the tanezumab 10 mg or tanezumab 20 mg treatment groups had confirmed OH during the Safety Follow-up Period and no subjects in the

CLINICAL STUDY REPORT SYNOPSIS

placebo or tanezumab 10/20 mg treatment groups had a confirmed OH during the Treatment Period or Safety Follow-up Period based on the protocol specified criteria.

- **Sympathetic Function Consultations:** The only key adverse events meeting criteria for consultation were Bradycardia in the placebo treatment group and Syncope in the tanezumab 20 mg treatment group, and each occurred with similar frequency (1 subject each). No subject was reported to have Anhidrosis or Hypohidrosis. Sympathetic neuropathy was not confirmed for either subject as determined by the Investigator after a review of clinical data, including available consultation material. There were no apparent changes from Screening among SAS scores.

- **Adjudicated Joint Safety Outcomes:** A total of four subjects had five events (1 subject had 2 events) that met criteria for adjudication for the tanezumab 20 mg, tanezumab 10 mg, and placebo treatment groups. These included but were not limited to TJRs and possible or probable joint safety events as identified by the Central Reader. Two subjects in the tanezumab 20 mg and one subject each in the placebo and tanezumab 10 mg treatment groups had joint safety events that required adjudication; none were considered related to study treatment by the Investigators. There were two subjects with a composite joint safety endpoint (both Pathological fractures; left acetabulum and right hip respectively). Both subjects were in the tanezumab 20 mg treatment group. One had an associated TJR of the left hip 2 days after the subject discontinued the study due to the NSAE of pathologic fracture of left acetabulum (Pathological fracture of the left acetabulum). Both Pathological fractures occurred at a site of pre-existing bone metastasis and the subject with the fracture of the left acetabulum had received prior radiotherapy of the left hemipelvis. The subject who had TJR of the left hip had no evidence of osteoarthritis (OA) at Screening (Baseline Kellgren-Lawrence grade 0). No subject in any treatment group had a joint safety event adjudicated as Rapidly progressive OA, Primary osteonecrosis, or Subchondral insufficiency fracture. One subject each in the tanezumab 20 mg, tanezumab 10 mg, and in the placebo treatment groups, had joint safety events adjudicated as Other Joint Outcome: normal joint in the tanezumab 20 mg treatment group, extra-articular pathologic fracture in tanezumab 10 mg group, and traumatic avulsion fracture of the ankle in the placebo treatment group. The subject who had a normal joint in the right hip also had a pathological fracture at the left hip and it is described in the preceding paragraph.

- **Non-Adjudicated Fractures:** Lumbar spinal compression fracture at the site of pre-existing bone metastasis was reported in each of 2 subjects in the placebo treatment group. In addition, an extra-articular pathologic fracture of the left femur was reported in

CLINICAL STUDY REPORT SYNOPSIS

one subject in the tanezumab 20 mg treatment group and was considered not related to study medication but rather due to the disease under study.

- **Total Joint Replacements:** One subject in the tanezumab 20 mg group with a reported pathologic fracture of the left acetabulum on Study Day 31 had a TJR of the left hip 2 days after the subject discontinued the study due to the event.

- **Clinical Laboratory Evaluation:** The incidence of subjects with normal Baseline who had post-Baseline laboratory test abnormalities at any point during the study that met the pre-specified threshold for change from Baseline affected no more than eight subjects within a treatment group for any laboratory parameter, and was similar between tanezumab 20 mg and placebo treatment groups.

- **Vital Signs:** Categorical changes from Baseline to the last Post-Baseline value in sitting systolic and diastolic BP during the Treatment Period (ie, up to Week 24) were generally comparable in the tanezumab 20 mg and placebo treatment groups.

- **ECG:** None of the subjects had a QTc corrected using Bazett's formula (QTcB) or QTc corrected using Fridericia's formula (QTcF) value ≥500 msec at any point during the study. There was no apparent difference in the mean maximum changes from Baseline in any of the ECG parameters.

- **Neurological Examination (NIS):** At the last assessment, the conclusion from the neurological examination for over 75% of subjects in the tanezumab 20 mg and the placebo treatment groups was no new or worsened neurological examination abnormality. One subject (1.5%) in tanezumab 20 mg treatment group and no subjects in the tanezumab 10 mg, tanezumab 10/20 mg, or placebo treatment groups had a new or worsened neurological examination abnormality that was considered by the Investigator to be clinically significant at the last assessment.

- **Physical Examination:** There was no apparent difference in physical examination findings at Screening between the placebo and tanezumab 20 mg treatment groups.

- **Immunogenicity:** TE ADA status (ie, TE ADA+ or TE ADA-) did not appear to influence the proportion of subjects identified as responders (ie, Reduction of >=30% from Baseline to Week 8 in the daily average pain intensity in the index bone metastasis cancer pain site) in the tanezumab treatment groups. The overall percent incidence of adverse events in the combined TE ADA+ tanezumab treatment group was comparable to

CLINICAL STUDY REPORT SYNOPSIS

the corresponding TE ADA- combined tanezumab treatment group and there was no association between TE ADA+ and potential hypersensitivity reactions.

Conclusion(s):

Efficacy

- Tanezumab 20 mg significantly improved cancer pain predominantly due to bone metastasis at Week 8 versus placebo and met the primary objective of the study.
    - Treatment with tanezumab 20 mg resulted in significant improvement (reduction) from Baseline to Week 8 in the daily average pain intensity at the index cancer pain site compared with placebo treatment ($p=0.0381$ at $\alpha = 0.0478$ in a two-sided test).
- Results of secondary efficacy endpoint analyses supported the primary endpoint analysis:
    - Treatment with tanezumab 20 mg resulted in significant improvement from Baseline to Weeks 1, 2, 4, and 6 in the daily average pain intensity and to Weeks 2, 4, and 6 in the daily worst pain intensity at the index cancer pain site compared with placebo treatment.
    - Treatment with tanezumab 20 mg resulted in significant improvements at Weeks 2, 4, 6, and 8 in the secondary efficacy endpoint of percent reduction from Baseline in daily average pain intensity in the index cancer pain site (at the ≥50% response level). Significant improvements for tanezumab 20 mg at the ≥70% response level were also noted at Weeks 4 and 6.
    - Treatment with tanezumab 20 mg resulted in significant improvements at Weeks 4, 6, and 8 in the secondary efficacy endpoint of percent reduction from Baseline in daily worst pain intensity in the index cancer pain site (at the ≥50% response level).
    - Treatment with tanezumab 20 mg resulted in numerical improvement at Week 8 in the secondary efficacy endpoints of daily worst pain intensity at the index cancer pain site, weekly average and worst pain intensity at the non-index cancer pain sites, and PGA of Cancer Pain.
    - Numerical reduction relative to Baseline in daily average and worst pain intensity at the index cancer pain site, weekly average and worst pain intensity at the non-index cancer pain sites, and PGA of Cancer Pain was maintained for tanezumab 20 mg over the 24-week Treatment Period. The magnitude of the treatment difference for daily average pain intensity at the index cancer pain site from Weeks 12 to 24 and for PGA of Cancer Pain at Weeks 16 and 24 was lower than at Week 8; however, it should be noted that the study was not designed to determine treatment differences after Week 8.

CLINICAL STUDY REPORT SYNOPSIS

- Treatment with tanezumab 20 mg resulted in significant improvement from Baseline compared to placebo on the BPI-sf assessments of average pain (at Weeks 4 and 8), worst pain (at Weeks 4 and 24), pain interference index (at Week 8), interference with general activity (at Week 8), and interference with sleep interference (at Week 4).

- Treatment with tanezumab 20 mg resulted in no significant difference in opioid consumption and rescue medication use when compared with placebo except the mean average daily number of doses of rescue medication was significantly lower for the tanezumab 20 mg treatment group compared with placebo at Week 4 (p=0.0211). No apparent differences between tanezumab 20 mg and placebo were observed for OR-SDS.

Safety

- The safety findings in this study, including the adverse event profile in the tanezumab treatment groups, were generally consistent with those anticipated in subjects with cancer pain predominantly due to bone metastasis and/or the known safety profile of tanezumab. No new safety risks were identified.

- The incidence of adverse events of abnormal peripheral sensation was higher in the tanezumab treatment groups than in the placebo group, consistent with prior studies.

- There was no evidence of an effect of tanezumab on sympathetic nervous system function.

- There was no evidence of an effect of tanezumab on safety related to vital signs, ECG measures, safety labs, or other body systems.

- Adjudicated joint safety outcomes consisted of an intra-articular pathological fracture in 2 subjects (2.8%) in the tanezumab 20 mg treatment group, both of which occurred at a site of pre-existing bone metastasis. No subject in any treatment group had a joint safety event adjudicated as Rapidly Progressive OA, Primary Osteonecrosis, or Subchondral Insufficiency Fracture. Of the 2 subjects with Pathologic fractures in the tanezumab 20 mg treatment group, 1 subject had an associated TJR. The subject who had the TJR in the hip had no radiographic evidence of OA at Screening.

- A total of three subjects, one subject each in the tanezumab 20 mg, tanezumab 10 mg, and in placebo treatment groups, had joint safety events adjudicated as Other Joint Outcome: the outcomes were normal joint in the tanezumab 20 mg treatment group, extra-articular pathologic fracture in the tanezumab 10 mg group, and traumatic avulsion fracture of the ankle in the placebo treatment group.

CLINICAL STUDY REPORT SYNOPSIS

- Lumbar spinal compression fractures at the site of pre-existing bone metastasis which did not require adjudication committee review were reported in 2 subjects in the placebo group. An extra-articular pathologic fracture of the left femur which also did not require adjudication committee review was reported in one subject in the tanezumab 20 mg treatment group.

- COVID-19 did not appear to have an impact on the safety results of the study. There were no COVID-19-related adverse events, and the COVID-19 pandemic did not appear to impact timely reporting of adverse events or SAEs.

Immunogenicity

- The results suggest that the immunogenicity profile of tanezumab was minimal, as the incidence rate of TE ADA+ was low. The immunogenicity results do not provide any evidence that the presence of TE ADA affects the [redacted], safety, or efficacy profile of tanezumab.