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Sponsor: Pfizer, Inc.

Investigational Product: Tanezumab

Clinical Study Report Synopsis: Protocol A4091058

Protocol Title: A Phase 3 Randomized, Double-Blind, Active-Controlled, Multicenter Study of the Long-Term Safety and Efficacy of Subcutaneous Administration of Tanezumab in Subjects With Osteoarthritis of the Hip or Knee

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

Study Center(s): A total of 307 sites randomized at least one patient in this study. The study was conducted at sites in Australia, Brazil, Bulgaria, Colombia, Croatia, Japan, Lithuania, Mexico, New Zealand, Peru, Philippines, Republic of Korea, Russian Federation, Serbia, Slovakia, Taiwan, Ukraine, and the United States (US).

Publications Based on the Study: None

Study Initiation and Completion Dates:

Study Initiation Date: 21 July 2015

Primary Completion Date: 05 October 2018

Study Completion Date: 27 February 2019

Report Date: 06 November 2019

Previous Report Date(s): 05 September 2019

Phase of Development: Phase 3

Study Objective(s)

Primary Objectives

- Characterize the long-term risk of joint safety events in patients with osteoarthritis (OA) of the knee or hip who receive tanezumab 2.5 mg or tanezumab 5 mg subcutaneous (SC) versus non-steroidal anti-inflammatory drug (NSAID) treatment (naproxen 500 mg twice daily [BID], celecoxib 100 mg BID, or diclofenac extended release [ER] 75 mg BID) over the course of 56 weeks of treatment using a composite endpoint (includes adjudication outcomes of rapidly progressive OA type 1 or type 2, subchondral insufficiency fracture, primary osteonecrosis, or pathological fracture).

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- Demonstrate superior efficacy of tanezumab 2.5 mg and tanezumab 5 mg SC versus NSAID treatment (naproxen 500 mg BID, celecoxib 100 mg BID, or diclofenac ER 75 mg BID) at Week 16.

Secondary Objectives

- Characterize the long-term joint safety risk using a composite endpoint (includes adjudication outcomes of rapidly progressive OA (type 2 only), subchondral insufficiency fracture, primary osteonecrosis, or pathological fracture).

- Characterize the long-term risk of the following individual adjudication outcomes occurring: rapidly progressive OA (type 1 only), rapidly progressive OA (type 2 only), rapidly progressive OA (type 1 or type 2 combined), subchondral insufficiency fracture, primary osteonecrosis, and pathological fracture.

- Characterize the long-term risk of all cause total joint replacements (TJRs) (patients who undergo TJR plus patients who have an adjudicated outcome of rapidly progressive OA type 1 or type 2, subchondral insufficiency fracture, primary osteonecrosis, or pathological fracture whether they undergo TJR or not) occurring.

- Characterize joint space width changes in patients with Kellgren-Lawrence (KL) Grade 2 or 3 OA of the index knee or index hip.

- Demonstrate superior efficacy of tanezumab 5 mg and tanezumab 2.5 mg SC versus each separate NSAID treatment group (naproxen 500 mg BID, celecoxib 100 mg BID and diclofenac ER 75 mg BID) at Week 16.

- Demonstrate the efficacy of tanezumab 2.5 mg and tanezumab 5 mg SC versus NSAID (combined) treatment at all time points to Week 56.

- Evaluate the long-term safety of tanezumab 2.5 mg and tanezumab 5 mg SC.

- Explore relationships between adjudicated outcomes of rapidly progressive OA (type 1 or type 2), subchondral insufficiency fracture, primary osteonecrosis, or pathological fracture and variables that may be associated with these orthopedic risks.

- Characterize changes in physical activity level.

METHODS

Study Design

This was a randomized, double-blind, active-controlled, multicenter, parallel-group Phase 3 study of the safety and efficacy of tanezumab when administered by SC injection for 56 weeks compared to NSAIDs in patients with OA of the knee or hip.

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Approximately 3000 patients were randomized to one of three treatment groups in a 1:1:1 ratio (N=1000/treatment group):

1. SC placebo (to match tanezumab) once every eight weeks (a total of seven administrations) plus NSAID administered orally (PO) (naproxen 500 mg BID PO, celecoxib 100 mg BID PO, or diclofenac ER 75 mg BID PO) through Week 56.

2. Tanezumab 2.5 mg SC once every eight weeks (a total of seven administrations) plus placebo BID PO (to match naproxen, celecoxib or diclofenac ER) through Week 56.

3. Tanezumab 5 mg SC once every eight weeks (a total of seven administrations) plus placebo BID PO (to match naproxen, celecoxib or diclofenac ER) through Week 56.

Note: Treatment groups specific to Japan were as follows:

1. SC placebo (to match tanezumab) once every eight weeks (a total of seven administrations) plus celecoxib 100 mg BID administered PO through Week 56.

2. Tanezumab 2.5 mg SC once every eight weeks (a total of seven administrations) plus placebo BID PO to match celecoxib through Week 56.

3. Tanezumab 5 mg SC once every eigh weeks (a total of seven administrations) plus placebo BID PO to match celecoxib through Week 56.

Randomization was stratified by index joint, most severe KL grade of any knee or hip joint, and NSAID treatment administered during Screening.

The total study duration (post-randomization) was approximately 80 weeks and consisted of a Screening Period (maximum of 37 days), a Double-blind Treatment Period (56 Weeks), and a Safety Follow-up Period (24 Weeks).

Eligible patients must have been receiving a stable dosing regimen of oral NSAID therapy, be tolerating their NSAID regimen, and be taking their NSAID regularly (at least five days per week) for 30 days prior to Screening.

The Screening Period was a minimum of two to three weeks (14 to 21 days) duration to ensure patients were on a stable regimen of study-supplied NSAID for at least two to three weeks prior to randomization. Patients taking celecoxib, naproxen, or diclofenac prior to Screening were provided with the same NSAID for the remainder of the Screening Period. Patients taking other NSAIDs prior to Screening were assigned to celecoxib, naproxen, or diclofenac ER at the discretion of the Investigator for at least the final three weeks prior to Baseline.

On Day 1, patients were administered an SC injection of tanezumab 2.5 mg, tanezumab 5 mg, or placebo. Patients took their first oral dose of NSAID or matching placebo in the evening on Day 1. Additional administrations of SC study medication occurred every eight

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weeks through Week 48. Oral study medication (NSAID or placebo) was self-administered by the patients BID through Week 56. During the Treatment Period, clinic visits occurred at Weeks 2 and 4 and then every eight weeks from Week 8 to Week 56 and patients were contacted by telephone every eight weeks between Weeks 12 and 60.

Up to Week 16, patients were allowed to use limited acetaminophen/paracetamol rescue medication up to 3000 mg per day up to three days per week and abstained from using analgesics for OA. After Week 16, rescue medication was permitted daily up to 3000 mg per day.

At Week 16, patients had to meet the following criteria in order to continue receiving SC study medication:

- A 30% or greater reduction in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain subscale relative to Baseline in the index joint

- A 15% or greater reduction in WOMAC Pain subscale from Baseline at either Week 2, 4, or 8

Patients who did not meet these response criteria were discontinued from the Treatment Period and entered into the 24-week Early Termination Follow-up Period.

Patients who completed the Double-blind Treatment Period at Week 56 entered the 24-week Safety Follow-up Period and returned for two additional study visits at Weeks 64 and Week 80 (End of Study). At Week 60 and between Weeks 64 and 80, patients were contacted by site staff at approximately monthly intervals to collect adverse event, concomitant medication, and concomitant non-drug data.

Concomitant medication and rescue medication restrictions were maintained during the Safety Follow-up period until the last efficacy assessments were collected at the Week 64 visit.

Patients who were discontinued from treatment prior to Week 56 for any reason were required to participate in 24 weeks of follow-up, which included three clinic visits and monthly phone calls. Patients also continued to use interactive response technology (IRT) for weekly collection of pain scores for index joints (and non-index joints, when applicable), rescue medication use, and concomitant medication use. Radiographs and magnetic resonance imaging (MRI; when applicable) of all major joints imaged at Screening were performed as soon as possible after withdrawal from study treatment.

Concomitant medication and rescue medication restrictions (daily up to 3000 mg per day) were maintained during the Early Termination Follow-up period until the last efficacy assessments were collected at the Early Termination Visit 2.

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Patients who underwent or planned to undergo TJR or other arthroplasty procedure during the study were discontinued from study treatment. In addition, patients who underwent total knee, hip, or shoulder joint replacement surgery during the study (Treatment Period or Follow-up Period) were followed for 24 weeks after the procedure as part of a separate protocol (Study A4091064), provided the patient consented.

Diagnosis and Main Criteria for Inclusion

- Male or female of any race, ≥18 years of age; who provided informed consent.
- A diagnosis of OA of the index hip or knee based on American College of Rheumatology criteria with X-ray confirmation (a KL X-ray Grade of ≥2 as diagnosed by the Central Reader).
- Documented history indicating that acetaminophen therapy had not provided sufficient pain relief.
- Was receiving a stable dose regimen of oral NSAID therapy, was tolerating this NSAID and taking this medication regularly (defined as an average of at least 5 days per week during the 30 day period prior to the Screening visit):
- Maintained a stabilized dose regimen of either naproxen 500 mg BID, celecoxib 100 mg BID or diclofenac ER 75 mg BID (provided at Screening) with a minimum compliance of 70% (ie, 5 of 7 days per week) for the final 2 or 3 weeks of the Screening period directly prior to the Baseline (Day 1) visit.
- Documented history indicating that tramadol treatment had not provided adequate pain relief or patient was unable to take tramadol due to contraindication or inability to tolerate, or that opioid treatment had not provided adequate pain relief or patient was unwilling to take opioids or unable to take opioids due to contraindication or inability to tolerate.
- WOMAC Pain Subscale numerical rating scale (NRS) ≥5 in the index knee or hip at Screening.
- Patients were willing to discontinue all non-study pain medications for OA and not use prohibited pain medications throughout the duration of the study except as permitted per protocol.

Diagnosis and Main Criteria for Exclusion

- Body Mass Index (BMI) of >39 kg/m^2. For patients requiring dual energy X-ray absorptiometry (DXA) scan body weight ≥300 lbs was exclusionary.
- History of other disease that may have involved the index joint including inflammatory joint disease such as rheumatoid arthritis, seronegative spondyloarthropathy

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(eg, ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease related arthropathy), crystalline disease (eg, gout or pseudogout), endocrinopathies, metabolic joint diseases, lupus erythematosus, joint infections, Paget's disease, or tumors.

- Radiographic evidence of any of the following conditions in any screening radiograph as determined by the central radiology reviewer and as defined in the tanezumab program imaging atlas: excessive malalignment of the knee, severe chondrocalcinosis; other arthropathies (eg, rheumatoid arthritis), systemic metabolic bone disease (eg, pseudogout, Paget's disease, metastatic calcifications), large cystic lesions, primary or metastatic tumor lesions, stress or traumatic fracture.

- Radiographic evidence of any of the following conditions as determined by the central radiology reviewer and as defined in the tanezumab program imaging atlas at Screening: 1) rapidly progressive OA, 2) atrophic or hypotrophic OA, 3) subchondral insufficiency fractures, 4) spontaneous osteonecrosis of the knee (SPONK), 5) osteonecrosis, or 6) pathologic fracture.

- A history of osteonecrosis or osteoporotic fracture (ie, a patient with a history of osteoporosis and a minimally traumatic or atraumatic fracture).

- History of significant trauma or surgery to a knee, hip or shoulder within the previous year.

- Fibromyalgia, regional pain caused by lumbar or cervical compression with radiculopathy, or other moderate to severe pain that may confound assessments or self-evaluation of the pain associated with OA. Patients with a present (current) history of sciatica were not eligible for participation. Patients with a past history of sciatica who had been asymptomatic for at least one year and who had no evidence of radiculopathy or sciatic neuropathy on thorough neurologic examination were eligible for participation.

- A past history of carpal tunnel syndrome (CTS) with signs or symptoms of CTS in the one year prior to Screening.

- History of intolerance or hypersensitivity to the relevant oral NSAID (naproxen, celecoxib or diclofenac) the patient could have been randomized to receive or any of its excipients or existence of a medical condition or use of concomitant medication for which the use of this NSAID was contraindicated (refer to product labeling).

- History of intolerance or hypersensitivity to acetaminophen (paracetamol[1]) or any of its excipients or existence of a medical condition or use of concomitant medication for which the use of paracetamol was contraindicated (refer to product labeling).

[1] Acetaminophen/paracetamol will be referred to as paracetamol going forward.

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- Signs and symptoms of clinically significant cardiac disease.
- Diagnosis of a transient ischemic attack in the 6 months prior to Screening, diagnosis of stroke with residual deficits (eg, aphasia, substantial motor or sensory deficits), that would have precluded completion of required study activities.
- History, diagnosis, or signs and symptoms of clinically significant neurological disease.
- Previous exposure to exogenous nerve growth factor (NGF) or to an anti-NGF antibody.
- History of allergic or anaphylactic reaction to a therapeutic or diagnostic monoclonal antibody or immunoglobulin G (IgG)-fusion protein.
- Patients who had evidence of orthostatic hypotension based upon replicate orthostatic blood pressure measurements.

Randomization Criteria

- Patient must have completed appropriate washout of analgesics.
- Patient must have made at least three pain diary entries in the seven days prior to the Baseline (Day 1) visit.
- Patient must have maintained a stabilized dose regimen of either naproxen 500 mg BID, celecoxib 100 mg BID or diclofenac ER 75 mg BID (depending on the patient's pre-study NSAID) with a minimum compliance of 70% (ie, 5 of 7 days per week) for at least the final 2 or 3 weeks of the Screening period directly prior to the Baseline (Day 1) visit.

  NOTE: In Japan, all patients maintained a stabilized dose regimen of celecoxib as defined above.
- Patient must have abstained from taking rescue medication (paracetamol) within the 24 hours that preceded dosing.
- WOMAC Pain and Physical Function subscales NRS ≥5 in the index knee or index hip at Baseline.
- Patient's Global Assessment of OA (PGA-OA) must have been "fair," "poor," or "very poor" at Baseline.
- Review of the electrocardiogram (ECG) and laboratory results and confirmation that there were no clinically significant or exclusionary findings.
- Patient must have had required Baseline X-rays, MRI and DXA (if appropriate) scan(s) obtained.

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- The index joint should have been the most painful joint with a qualifying WOMAC Pain score and KL grade as confirmed by the Central Reader.

- In Japan, confirmation that female patients were not of childbearing potential.

STUDY TREATMENT

Tanezumab 2.5 mg, tanezumab 5 mg, and placebo for tanezumab were presented as a sterile solution for SC administration, in a glass pre-filled syringe (PFS) (Table S1). Each PFS contained a sufficient amount of sterile solution to provide the intended dose. Each PFS was packaged in an individual carton and had a unique container number.

Celecoxib was provided as oral capsules containing 100 mg of active celecoxib. Placebo for celecoxib was provided as oral capsules matching those used for celecoxib 100 mg capsules. Celecoxib 100 mg and matching placebo were packaged in high-density polyethylene (HDPE) bottles with child resistant closures.

Naproxen was provided as oral tablets containing 500 mg of active naproxen. Placebo for naproxen was provided as oral tablets matching those used for naproxen 500 mg tablets. Naproxen 500 mg and matching placebo were packaged in HDPE bottles with child resistant closures.

Diclofenac was provided as oral extended release capsules containing 75 mg of active diclofenac sodium. Placebo to match diclofenac was provided as oral capsules matching those used for diclofenac 75 mg ER active. Diclofenac 75 mg ER and matching placebo were packaged in HDPE bottles with child resistant closures.

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Table S1. Investigational Product Description

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/Potency	Dosage Form
PF-04383119 Solution for Injection, 2.5 mg/mL	L47506 M76804 S73087	15-002256, 15-002257 16-000830 17-001777	2.5 mg/mL	Pre-filled Syringe
PF-04383119 Solution for Injection, 5 mg/mL	L50447 M76807 S73916	15-002258, 15-002259 16-000831 17-001780	5 mg/mL	Pre-filled Syringe
Placebo for PF-04383119 Solution for Injection	L39168 S64269	15-002262, 15-002263 17-001779	0 mg/ml	Pre-filled Syringe
Celecoxib 100 mg Hard Gel Capsule	H04083 T0173V T0942VA	13-111559 12-004951 12-004950	100 mg	Capsule
Placebo for 100/200 mg Celecoxib Capsule	H04007 H04009 T0992V	13-111563 13-111564 12-004954	0 mg	Capsule
Naproxen 500 mg Tablet	HA00414 HF26915	14-001172 15-005106	500 mg	Tablet
Placebo for Naproxen 500 mg Tablet	B12222 B14010 B15118	12-004534 14-001197 15-004765	0 mg	Tablet
Diclofenac Sodium 75mg Extended Release Size AA Gray Capsule	8234.14 8234.17 8234.22 8234.25	14-005994 15-005386 16-004894 16-004895	75 mg	Capsule
Size AA Gray Placebo Capsule	8234.19 8234.2	15-006769 12-005114	0 mg	Capsule

EFFICACY EVALUATIONS

Questionnaires for primary and secondary efficacy parameters were completed by the patients at the site via IRT (electronic tablets), or at home via electronic diaries. Questionnaires at the site were completed prior to dosing on dosing days.

Primary Efficacy Evaluation

The three co-primary efficacy endpoints were change from Baseline to Week 16 in the WOMAC Pain subscale, change from Baseline to Week 16 in the WOMAC Physical Function subscale, and change from Baseline to Week 16 in the PGA-OA. The Japanese-specific co-primary efficacy endpoints were change from Baseline to Week 16 in the WOMAC Pain subscale and change from Baseline to Week 16 in the WOMAC Physical Function subscale.

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Secondary Efficacy Evaluation

The key secondary endpoint was patients with ≥50% reduction from Baseline in the WOMAC Pain at Week 16. Additional secondary endpoints included change from Baseline to Weeks 2, 4, 8, 16 (PGA-OA, Japan only), 24, 32, 40, 48, 56 and 64 in the WOMAC Pain subscale, WOMAC Physical Function subscale, and PGA-OA. Time points for the evaluation of other secondary endpoints were Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, and 64 unless stated otherwise: Outcome Measures in Rheumatology – Osteoarthritis Research Society Initiative (OMERACT-OARSI) responder index; treatment response defined as a reduction in the WOMAC Pain subscale of ≥30%, ≥50%, ≥70% or ≥90%; cumulative distribution of percent change from Baseline in the WOMAC Pain subscale score to Week 16, 24, and 56 (endpoint for summary only); treatment Response defined as reduction in the WOMAC Physical Function subscale of ≥30%, ≥50%, ≥70% or ≥90%; cumulative distribution of percent change from Baseline in the WOMAC Physical Function subscale score to Week 16, 24, and 56 (endpoint for summary only); treatment response defined as improvement of ≥2 points in the PGA-OA; change from Baseline in average pain score in the index joint (Weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 32, 40, 48, 56 and 64); change from Baseline in the WOMAC Stiffness Subscale; change from Baseline in the WOMAC Average; change from Baseline in the WOMAC Pain Subscale item: Pain When Walking on a Flat Surface; change from Baseline in the WOMAC Pain Subscale item: Pain When Going Up or Down Stairs; and incidence and time to discontinuation due to lack of efficacy.

Secondary patient-reported outcome endpoints included Work Productivity and Activity Impairment Questionnaire for Osteoarthritis (WPAI:OA) impairment scores change from Baseline to Weeks 16, 24, 56, and 64; EuroQol-5 Dimension-5 Level (EQ-5D-5L™) dimensions and overall health utility score at Baseline and Weeks 8, 16, 24, 40, 56, and 64; Treatment Satisfaction Questionnaire Medicine v.II (TSQM v.II) satisfaction with effectiveness, side effects and convenience, and overall satisfaction at Weeks 16 and 56; Patient Reported Treatment Impact Assessment-Modified (mPRTI) at Weeks 16 and 56; and Health Care Resource Utilization at Baseline and Weeks 64 and 80.

Rescue medication was measured by the incidence and number of days patients used rescue medication (Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, and 64) and the amount taken (Weeks 2, 4, 8, and 16) during the study.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and/or Other Evaluations:

Pharmacokinetic Evaluations

Tanezumab concentrations were measured to support the development of an SC administration population PK model that allows for the prediction of the tanezumab concentration over time in individuals. In addition, tanezumab concentrations were measured to inform the immunogenicity profile of tanezumab.

Pharmacodynamic Evaluations

Blood samples were collected for the assessment of NGF for PD analyses.

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Synovial fluid samples for the assessment of tanezumab and NGF could be collected when an Investigator performed arthrocentesis for a patient and the appropriate informed consent was obtained.

Biomarkers

Blood and urine samples for the assessment of biomarkers were collected for all patients. For patients that had activity level monitoring via accelerometry, additional biomarker samples were collected. Serum and urine biomarker assessments will be presented in a supplementary report. Additional exploratory analyses of biomarker concentrations in synovial fluid may be conducted for patients who had arthrocentesis performed during the study and who provided consent for analysis of synovial fluid samples.

SAFETY EVALUATIONS

Primary Safety Evaluation

The primary safety endpoint was the incidence of a predefined composite endpoint consisting of adjudication outcomes of rapidly progressive OA (type 1 or type 2), subchondral insufficiency fracture, primary osteonecrosis, or pathological fracture (primary composite endpoint).

Bone and Joint Safety

Bone and joint safety endpoints included the incidence of a predefined composite endpoint consisting of adjudication outcomes of rapidly progressive OA (type 2 only), subchondral insufficiency fracture, primary osteonecrosis, or pathological fracture; the incidence of individual adjudication outcomes of rapidly progressive OA (type 1 only), rapidly progressive OA (type 2 only), rapidly progressive OA (type 1 or type 2 combined), subchondral insufficiency fracture, primary osteonecrosis, and pathological fracture; and the incidence of all cause TJRs (patients who underwent TJR plus patients who had an adjudicated outcome of rapidly progressive OA type 1 or type 2, subchondral insufficiency fracture, primary osteonecrosis, or pathological fracture whether or not they underwent TJR).

Radiographic

Radiographic endpoints included the change from Baseline to Week 56 and Week 80 in Medial or Lateral Minimum Joint Space Width of the index knee (for patients with KL Grade 2 or 3 medial or lateral OA of the index knee); change from Baseline to Week 56 and Week 80 in Minimum Joint Space Width of the index hip (for patients with KL Grade 2 or 3 OA of the index hip); the incidence of patients with progression of OA in the index knee according to Bland and Altman method at Week 56 and Week 80 (separately) (for patients with KL Grade 2 or 3 medial or lateral OA of the index knee); and the incidence of patients with progression of OA in the index hip according to Bland and Altman method, at Week 56 and Week 80 (separately) (for patients with KL Grade 2 or 3 OA of the index hip).

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Activity Level Monitoring

Activity level monitoring endpoints were change from Baseline to Weeks 4, 8, 16, 24, 56 and 80 in the Lower Extremity Activity Scale (all patients); change from Baseline to Weeks 16 and 56 in average daily minutes of physical activity (a subset of patients); change from Baseline to Weeks 16 and 56 in average daily physical activity counts (a subset of patients); change from Baseline to Weeks 16 and 56 in average daily minutes of moderate to vigorous physical activity (a subset of patients); change from Baseline to Weeks 16 and 56 in average daily minutes of bouted (sustained) moderate to vigorous physical activity (a subset of patients); and change from Baseline to Weeks 16 and 56 in average daily step count (a subset of patients).

General Safety

Safety evaluations included adverse events, standard safety assessments (safety laboratory testing [chemistry, hematology], sitting vital signs, ECG [12-lead]), orthostatic (supine/standing) blood pressure assessments, Survey of Autonomic Symptom scores, neurologic exam (Neuropathy Impairment Score [NIS]), Anti-drug antibody (ADA) assessments, general physical examination, and musculoskeletal history and physical examination.

STATISTICAL METHODS

A sample size of approximately 1000 patients for each of the treatment groups of NSAID, tanezumab 2.5 mg, and tanezumab 5 mg were used in this study. This sample size allowed for a high probability of observing patients with any component of the composite endpoint where the event rate over this study was very small. If the event rate were 0.25%, then there would be a >90% probability of observing at least one patient with an event in any single treatment group. In addition, the sample size allowed for good precision to estimate the incidence rate for each treatment group in order to estimate an upper bound for the true incidence rate.

Analysis of Co-Primary Efficacy Endpoints

The primary efficacy population was the Intent-to-Treat (ITT) population, defined as all randomized patients who received SC investigational product (either tanezumab or matching placebo). The primary efficacy analysis used multiple imputation methods for missing data at Week 16. All treatment comparisons used the two-sided 5% significance level.

The co-primary efficacy endpoints were analyzed using an analysis of covariance (ANCOVA) model, with terms of Baseline score, Baseline diary average pain, index joint (knee or hip), highest KL grade (2, 3 or 4), NSAID cohort, treatment group, and study site as a random effect. The assessment of significance for SC tanezumab versus NSAID treatment contrasts of the primary and key secondary efficacy parameters used a graphical multiple testing (gate-keeping) approach to control the family-wise type I error rate at 5% (two-sided).

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Efficacy data collected during the post-treatment Safety Follow-up Period were generally considered off-treatment and excluded from analysis.

Analysis of Secondary Efficacy Endpoints

The secondary endpoint of patients with ≥50% reduction from Baseline in the WOMAC Pain at Week 16 was identified as a key secondary endpoint and was included in the graphical multiple testing strategy.

All secondary efficacy analyses used the ITT analysis set. Unless otherwise stated, efficacy data was summarized up to Week 64, and analyzed up to Week 56. Only observed data were presented at Week 64, ie, no imputation was used past Week 56.

The ANCOVA model for the co-primary endpoints was used in the analysis of WOMAC Pain, WOMAC Physical Function, PGA-OA, WOMAC Stiffness subscale, WOMAC Average score, WOMAC Pain item "Pain When Walking on a Flat Surface," WOMAC Pain item "Pain When Going Up or Down Stairs," and the Average Pain in the index joint from the diary.

The response endpoints of OMERACT, improvement in PGA ≥2 and WOMAC Pain and Physical Function ≥30%, ≥50%, ≥70% and ≥90% improvements as well as the incidence of rescue medication use and incidence of treatment discontinuation due to lack of efficacy were analyzed using logistic regression.

The time to treatment discontinuation due to lack of efficacy used the log-rank test.

The number of days and amount of rescue medication endpoints were analyzed using the negative binomial model.

Analysis of Pharmacokinetic and Pharmacodynamic Parameters

PK analyses included a listing of all plasma tanezumab concentrations sorted by patient, active treatment group, and actual and nominal time post-dose, a descriptive summary of the plasma tanezumab concentrations based on nominal time post-dose for each treatment group, boxplots of plasma tanezumab concentrations at the nominal times for the tanezumab treatment groups, and a listing of available synovial fluid tanezumab concentrations at the time of the arthrocentesis only sorted by patient, treatment group, and actual collection date and time. Samples were analyzed using a validated analytical method in compliance with Sponsor standard operating procedures.

Analysis of Joint Safety Endpoints

The primary joint safety endpoint is shown by number of patients treated and patient years of exposure (treatment plus follow-up periods) for individual treatment groups and differences between tanezumab treatment groups and the NSAID treatment group. The risk ratio and risk difference with 95% confidence interval (CI) was calculated for the comparisons of each tanezumab treatment group versus NSAID, as well as significance tests for each comparison.

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The time to each event was summarized and Kaplan-Meier estimates of the time to event were produced, together with an analysis of each tanezumab treatment group versus NSAID using the log-rank test.

The primary analysis of the primary joint safety endpoint was the analysis of the exposure-adjusted risk difference. The analyses of the exposure-adjusted risk ratio and risk difference and ratio based on percentage of patients with the event were secondary analyses.

The summary and analysis of the secondary joint safety endpoints followed the same method described above for the primary joint safety endpoint.

RESULTS

Subject Disposition and Demography

A total of 17,730 patients were screened for the study, of which 14,496 failed Screening and 213 were screened but not randomized (Table S2). In total, 3021 patients were randomized: 1008 in the tanezumab 2.5 mg treatment group, 1005 in the tanezumab 5 mg treatment group, and 1008 in the NSAID treatment group. The ITT population was comprised of 2996 patients that were randomized and treated with SC study medication. The Safety Population in this study is the same as the ITT population. Six patients in the tanezumab 2.5 mg treatment group, seven patients in the tanezumab 5 mg treatment group, and 12 patients in the NSAID treatment group were randomized and not treated.

Overall, 2227 (74.3%) patients completed the study. A total of 1312 (43.8%) patients completed the Treatment Period, and of those, 1222 (93.1%) patients completed the Safety Follow-up period. Of the 1684 (56.2%) patients who discontinued from the Treatment Period, 1005 (59.7%) completed the Safety Follow-up Period.

Table S2. Subject Evaluation Groups

	Tanezumab 2.5 mg (N=1008) n (%)	Tanezumab 5 mg (N=1005) n (%)	NSAID (N=1008) n (%)	Total (N=3021) n (%)
Screened: 17730 Screen Failure: 14496 Other Screened but not Randomized: 213				
Randomized	1008 (100.0)	1005 (100.0)	1008 (100.0)	3021 (100.0)
Treated	1002 (99.4)	998 (99.3)	996 (98.8)	2996 (99.2)
Not Treated	6 (0.6)	7 (0.7)	12 (1.2)	25 (0.8)
Safety Population	1002 (99.4)	998 (99.3)	996 (98.8)	2996 (99.2)
ITT Population	1002 (99.4)	998 (99.3)	996 (98.8)	2996 (99.2)
Per-Protocol Population	896 (88.9)	876 (87.2)	885 (87.8)	2657 (88.0)
Number of subjects[1]				

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Table S2. Subject Evaluation Groups

	Tanezumab 2.5 mg (N=1008) n (%)	Tanezumab 5 mg (N=1005) n (%)	NSAID (N=1008) n (%)	Total (N=3021) n (%)
Completed Treatment Phase	447 (44.6)	419 (42.0)	446 (44.8)	1312 (43.8)
Completed Safety Follow-Up	422 (42.1)	386 (38.7)	414 (41.6)	1222 (40.8)
Discontinued Safety Follow-Up	24 (2.4)	28 (2.8)	28 (2.8)	80 (2.7)
Did not enter Safety Follow-Up	1 (0.1)	5 (0.5)	4 (0.4)	10 (0.3)
Discontinued Treatment Phase	555 (55.4)	579 (58.0)	550 (55.2)	1684 (56.2)
Completed Safety Follow-Up	319 (31.8)	343 (34.4)	343 (34.4)	1005 (33.5)
Discontinued Safety Follow-Up	115 (11.5)	128 (12.8)	102 (10.2)	345 (11.5)
Did not enter Safety Follow-Up	121 (12.1)	108 (10.8)	105 (10.5)	334 (11.1)
Completed study	741 (74.0)	729 (73.0)	757 (76.0)	2227 (74.3)
Discontinued study	261 (26.0)	269 (27.0)	239 (24.0)	769 (25.7)
Rollover to Study A4091064	30 (3.0)	42 (4.2)	17 (1.7)	89 (3.0)

N is Number of Subjects Randomized. Percentages are based on the number of subjects Randomized.
[1]Subjects in Safety Population. Percentages are based on the number of subjects in Safety Population.
Treatment Period is planned for 56 weeks and Safety Follow-Up period is planned for 24 weeks.
Safety population consists of all subjects treated with SC study medication. ITT population consists of all randomized subjects who received at least one SC dose.
"Other Screened but not Randomized" displays subjects who were screened but not randomized for a reason not related to a specific eligibility criterion.
Rollover to Study A4091064 includes the subjects who intended to rollover at the time of discontinuation from 1058.
PFIZER CONFIDENTIAL SDTM Creation: 03APR2019 (02:27) Source Data: Listing 16.2.1.1 Output File: ./nda1/A4091058_IM_Safety/adsl_s002i Date of Generation: 09MAY2019 (16:44)
Table 14.1.1.1.i is for Pfizer internal use.

The incidence of discontinuation from treatment was higher in the tanezumab 5 mg treatment group (58.0%) compared with the tanezumab 2.5 mg and NSAID treatment groups (55.4% and 55.2%, respectively). The most frequent reasons for discontinuation from treatment across treatment groups were “Patient meets protocol-specified pain criteria for discontinuation” (21.7%), “Other” (9.5%), “Adverse event” (7.9%), and “Insufficient clinical response” (7.1%). The incidence of treatment discontinuation due to “Patient meets protocol-specified pain criteria for discontinuation” was similar across treatment groups. The incidence of treatment discontinuation due to “Insufficient clinical response” was higher in patients who received NSAID (9.1%) compared with patients who received tanezumab (6.0% and 6.3% in the tanezumab 2.5 mg and 5 mg treatment groups, respectively). The proportion of patients who discontinued treatment due to adverse events was highest in the tanezumab 5 mg treatment group (10.4%).

The most frequent reasons for discontinuation from study were “Withdrawal by subject” (10%) and “Other” (8.5%). The proportion of patients who discontinued from study due to adverse events was higher in patients receiving tanezumab (2.3% and 2.2% in the tanezumab

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2.5 mg and 5 mg treatment groups, respectively) compared with patients receiving NSAID (0.8%).

A total of 89 of the 164 patients (54.3%) who had at least one TJR during the study intended to roll over into Study A4091064 at the time of discontinuation from Study A4091058 (Table S2).

Demographic characteristics were similar across treatment groups. More patients were female (63.6% to 66.5%) than male (33.5% to 36.4%) and most patients were white (68.3% to 71.3%). The mean age of patients was 60.3 to 61.2 years (range 28 to 90 years), and most patients were in the 45-64 years age range. Across treatment groups, patients 65 years or older represented 32.1% to 36.2% of the study population and those 75 years or older represented 5.5% to 8.0% of the study population.

Insufficient pain relief to paracetamol was an entry requirement and was reported by all patients with the exception of one patient in the NSAID treatment group. Inadequate pain relief was the primary reason for treatment failure with paracetamol and tramadol, and unwilling to take was the primary reason for treatment failure with opioids.

The mean time from the first diagnosis of OA was similar across treatment groups, ranging from 8.5 years for patients in the tanezumab 5 mg treatment group to 9.1 years for patients in the NSAID treatment group. The mean time from the index joint OA diagnosis ranged from 7.9 years for patients in the tanezumab 5 mg treatment group to 8.1 years for patients in the NSAID treatment group.

The majority of patients (84.9% to 85.5%) had the knee as the index joint. The overall radiographic severity of OA was similar across treatment groups, with KL grade 3 reported most frequently for the index joint (47.4% to 47.8%). Across treatment groups, the percentage of patients with a KL grade of 4 for the index joint was 21.5% to 22.7%. Most patients (53.7% to 56.2) reported two joints with KL grade ≥2. The WOMAC Pain subscale scores at Screening and the WOMAC Pain subscale, WOMAC Physical Function subscale, and PGA-OA scores at Baseline were similar across treatment groups.

Most patients were enrolled in the naproxen NSAID cohort (48.3% to 48.4%), followed by celecoxib (32.2% to 32.6%), then diclofenac (19.1% to 19.4%).

Efficacy Results

For tanezumab 5 mg treatment, two co-primary endpoints achieved significant[2] improvement over NSAID at Week 16 (WOMAC Pain, WOMAC Physical Function) while the third co-primary endpoint (PGA-OA) did not achieve significant improvement over NSAID at

[2] "Significant" is used here and following to mean statistically significant ($p \leq 0.05$).

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Week 16. Treatment with tanezumab 2.5 mg did not meet any of the co-primary efficacy endpoints at Week 16.

Outside of the framework of the gate-keeping procedure, focusing on nominal (unadjusted) p-values, both tanezumab treatment groups showed significant improvement from Baseline in the WOMAC Pain subscale, WOMAC Physical Function subscale, and the PGA-OA compared with NSAID treatment at Week 4, and tanezumab 5 mg treatment showed significant improvement compared with NSAID at Week 8. The tanezumab 2.5 mg treatment group showed significant improvement compared with NSAID in the WOMAC Physical Function subscale at Week 2.

Due to the non-significant results of tanezumab 5 mg treatment compared with NSAID treatment for PGA-OA at Week 16, further hypothesis testing of the key secondary endpoint (patients with ≥50% reduction from Baseline in WOMAC Pain at Week 16) could not be performed, and tanezumab treatment was concluded to be not significantly better than NSAID treatment due to the testing strategy.

The results of the co-primary efficacy endpoints and key secondary efficacy endpoint were evaluated considering the gate-keeping approach. All other efficacy endpoints were evaluated without considering multiplicity, focusing on unadjusted p-values.

Primary Efficacy Analysis

For the WOMAC Pain subscale and the WOMAC Physical Function subscale, the gate-keeping procedure showed significant improvement in efficacy for treatment with tanezumab 5 mg versus NSAID at Week 16 (p=0.0.0148 for WOMAC Pain and p=0.0030 for WOMAC Physical Function; Table S3). Treatment with 2.5 mg tanezumab did not result in significant improvement versus NSAID in the WOMAC Pain and Physical function subscales (p=0.1597 and p=0.0691, respectively). The PGA-OA did not achieve significant improvement versus NSAID (p=0.6332 and p=0.3431 for the tanezumab 2.5 and 5 mg treatment groups, respectively).

Table S3. Summary of Co-Primary Efficacy Endpoints - Analysis of Change from Baseline to Week 16 (ITT, Multiple Imputation)

		Tanezumab 2.5 mg (N=1002)	Tanezumab 5 mg (N=998)	NSAID (N=996)
WOMAC Pain Subscale	LS Mean (SE)	-3.22 (0.11)	-3.33 (0.11)	-3.07 (0.11)
	95% CI for LS Mean	(-3.43, -3.01)	(-3.54, -3.12)	(-3.29, -2.86)
	Versus NSAID			
	LS Mean Difference (SE)	-0.15 (0.11)	-0.26 (0.11)	
	95% CI for LS Mean Difference	(-0.36, 0.06)	(-0.46, -0.05)	

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Table S3. Summary of Co-Primary Efficacy Endpoints - Analysis of Change from Baseline to Week 16 (ITT, Multiple Imputation)

		Tanezumab 2.5 mg (N=1002)	Tanezumab 5 mg (N=998)	NSAID (N=996)
	p-value	0.1597	0.0148	
WOMAC Physical Funcation Subscale	LS Mean (SE)	-3.27 (0.11)	-3.39 (0.11)	-3.08 (0.11)
	95% CI for LS Mean	(-3.48, -3.05)	(-3.60, -3.17)	(-3.29, -2.86)
	Versus NSAID			
	LS Mean Difference (SE)	-0.19 (0.11)	-0.31 (0.10)	
	95% CI for LS Mean Difference	(-0.40, 0.02)	(-0.52, -0.11)	
	p-value	0.0691	0.0030	
Patient Global Assessment of Osteoarthritis	LS Mean (SE)	-0.96 (0.04)	-0.97 (0.04)	-0.94 (0.04)
	95% CI for LS Mean	(-1.03, -0.88)	(-1.05, -0.90)	(-1.01, -0.86)
	Versus NSAID			
	LS Mean Difference (SE)	-0.02 (0.04)	-0.04 (0.04)	
	95% CI for LS Mean Difference	(-0.09, 0.06)	(-0.11, 0.04)	
	p-value	0.6332	0.3431	

A change from Baseline < 0 is an improvement.
Multiple imputation method was applied for missing data, with imputation dependent on reason for missing data.
ANCOVA model for imputed datasets included treatment, randomization stratification variables (index joint, highest Kellgren-Lawrence grade, and NSAID) as fixed effects, Baseline value and Baseline diary average pain as covariates, and study site as a random effect.
Results were taken from a combined analysis of the individual imputed dataset ANCOVA results.
PFIZER CONFIDENTIAL SDTM Creation: 07APR2019 (22:38) Source Data: Listing 16.2.6.1 Output File: ./nda1/A4091058_IM_Efficacy/adwn_sg_infr_chg_ancova_mi Date of Generation: 08JUL2019 (11:32)
Table 14.2.1.3.1.i is for Pfizer internal use.

Secondary Efficacy Analysis

Key Secondary Efficacy Endpoint

Patients with ≥50% reduction from Baseline in WOMAC Pain at Week 16: Due to the non-significant results of tanezumab 5 mg versus NSAID treatment for the PGA-OA, under the specified testing procedure, further hypothesis testing of the key secondary endpoint could not be performed and tanezumab treatment was concluded to be not significantly better than NSAID treatment. However, both tanezumab treatment groups had numerically higher percentages of ≥50% responders than the NSAID treatment group at Week 16: tanezumab 2.5 mg treatment group, 54.9%; tanezumab 5 mg treatment group, 56.5% (unadjusted p≤0.05); NSAID treatment group, 51.5%.

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- There was a consistent improvement from Baseline in **WOMAC Pain subscale** scores across treatment groups beginning at Week 2 and persisting through Week 16. The reduction from Baseline was significantly greater with tanezumab 2.5 mg and tanezumab 5 mg treatment compared with NSAID treatment at Week 4 and was significantly greater with tanezumab 5 mg treatment compared with NSAID at Weeks 8 and 16.

- Across treatment groups, there was an improvement from Baseline in **WOMAC Physical Function subscale** scores from Week 2 to Week 16. Compared with NSAID, there was a significantly greater reduction from Baseline at Week 2 with tanezumab 2.5 mg treatment. At Week 4, both tanezumab treatment groups showed a significantly greater reduction from Baseline compared with the NSAID treatment group. There was a significantly greater reduction from Baseline with tanezumab 5 mg treatment compared with NSAID at Weeks 8 and 16.

- An improvement in **PGA-OA** score was observed across treatment groups beginning at Week 2 through Week 16. At Week 4, the reduction from Baseline was significantly greater in both tanezumab treatment groups compared with the NSAID treatment group. At Week 8, the tanezumab 5 mg treatment group showed a significantly greater reduction from Baseline compared with the NSAID treatment group.

- The proportion of responders on the **OMERACT-OARSI** responder index was significantly greater for patients in both tanezumab treatment groups compared with the NSAID treatment group at Week 4. At Week 8, the proportion of responders was significantly greater for patients in the tanezumab 5 mg treatment group compared with the NSAID treatment group.

- **Reduction in the WOMAC Pain subscale of ≥30%, ≥50%, ≥70%, and ≥90%:** A significantly greater proportion of patients in both tanezumab treatment groups than in the NSAID treatment group responded at the 30% and 50% levels at Week 4. Additionally, a significantly greater proportion of patients in the tanezumab 5 mg treatment group compared with the NSAID treatment group responded at the 70% and 90% levels at Weeks 4 and 16, at the 30%, 50%, 70%, and 90% level at Week 8, and at the 70% level at Week 24. The unadjusted p-value for tanezumab 5 mg treatment compared with NSAID treatment was ≤0.05 at Week 16 at the 50% response level, although this (the key secondary endpoint) could not be concluded as significantly different, due to the testing procedure.

- **Reduction in the WOMAC Physical Function Subscale of ≥30%, ≥50%, ≥70%, and ≥90%:** A significantly greater proportion of patients in both tanezumab treatment groups than in the NSAID treatment group responded at the 70% level at Week 2, at the 30%, 50%, 70%, and 90% levels at Week 4, and at the 50% and 70% levels at Week 8. A significantly greater proportion of patients in the tanezumab 2.5 mg treatment group responded at the 50% level at Week 2; in the tanezumab 5 mg treatment group there was a significantly greater proportion of responders compared with the NSAID treatment

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group at the 50% level at Week 16, at the 70% level at Weeks 16 and 24, and at the 90% level at Weeks 2, 8, 16, 24, 32, and 40.

- From Weeks 2 to 16, a greater proportion of tanezumab-treated patients tended to have a **≥2 point reduction in the PGA-OA** compared with NSAID-treated patients. The difference was significant for both tanezumab treatment groups at Week 4 and for the tanezumab 5 mg treatment group at Weeks 2 and 8.

- Patients in the study reported pain in the index joint using an eDiary daily from Day 1 to Week 16 and then weekly from Week 16 to End of Study. **Pain scores in the index joint** were significantly improved in both tanezumab treatment groups compared with the NSAID treatment group from Week 4 to 20. A significantly greater reduction from Baseline compared with NSAID treatment was also observed for the tanezumab 2.5 mg treatment group at Week 3 and the tanezumab 5 mg treatment group at Week 24.

- Treatment with tanezumab 2.5 mg resulted in significant improvement compared with NSAID at Week 16 in the **WOMAC Stiffness subscale**. Treatment with tanezumab 5 mg resulted in significant improvement compared with NSAID at Week 16 in reduction in the **WOMAC Stiffness subscale**, **WOMAC Average Score** (the mean of the WOMAC Subscale Scores of Pain, Physical Function, and Stiffness), and **WOMAC Pain subscale item: Pain When Going Up or Down Stai**rs.

- Patients in the NSAID treatment group showed a significantly greater improvement in the **WPAI:OA** item of reported percent activity impairment score compared with tanezumab-treated patients at Week 56. No additional significant differences were observed with tanezumab treatment compared to NSAID treatment for percent work time missed, percent impairment while working, or percent overall work impairment at Weeks 16, 24, or 56.

- The mean **EuroQol-5 Dimension-5 Level** index values were similar across treatment groups at all time points evaluated.

- A significant improvement in **TSQM satisfaction with effectiveness score** was observed with tanezumab 2.5 mg and tanezumab 5 mg treatments at Week 16 compared with NSAID treatment. A significant improvement in **TSQM satisfaction with convenience score** was observed with tanezumab 2.5 mg and tanezumab 5 mg treatments at Week 16 compared with NSAID treatment. A significant improvement in **TSQM global satisfaction score** was observed with tanezumab 2.5 mg and tanezumab 5 mg treatments at Week 16 compared with NSAID treatment.

- In the **mPRTI** assessment, at Week 16, significantly more patients in the tanezumab treatment groups than in the NSAID treatment group reported that they would be willing to use the same drug that they received in the study for their OA pain in the future. Additionally, significantly more patients in the tanezumab 5 mg treatment group than in the NSAID treatment group reported that they preferred the drug that they received in the

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study to their most recent treatment before entering the study. At Week 56, significantly more patients in the tanezumab 2.5 mg treatment group than in the NSAID treatment group reported that they would be willing to use the same drug that they received in the study for their OA pain in the future.

- The proportion of patients that **discontinued due to insufficient clinical response** was significantly higher in the NSAID treatment group compared with both tanezumab treatment groups. NSAID-treated patients tended to discontinue sooner due to insufficient clinical response than tanezumab-treated patients, and there was a significant difference in time to discontinuation due to insufficient clinical response between both tanezumab treatment groups and the NSAID treatment group.

- There was no significant difference in the **incidence of rescue medication use** for either tanezumab treatment group compared with the NSAID treatment group at any time point. From Week 4 to Week 32, the proportion of patients that did not take rescue medication tended to be higher in the tanezumab 5 mg treatment group compared with the tanezumab 2.5 mg and NSAID treatment groups.

- From Week 1 to Week 9, the mean **amount of rescue medication used** on a weekly basis was lower in the tanezumab 5 mg treatment group compared with the tanezumab 2.5 mg and NSAID treatment groups. The mean amount of rescue medication used was lower in both tanezumab treatment groups compared with the NSAID treatment group from Week 10 to Week 16. The amount of rescue medication used was significantly lower in the tanezumab 5 mg treatment group compared with the NSAID treatment group at Weeks 4 and 8.

Pharmacokinetic Results

At Weeks 8, 16, 32, 48, and 56, the mean tanezumab plasma concentrations were higher for the 5 mg dose group relative to the 2.5 mg dose group by a proportion approximately similar to the increase in dose. By Week 64, at 16 weeks after the last dose, the mean tanezumab plasma concentrations were low, consistent with complete elimination from the body over five half-lives post seventh injection and were similar for the two tanezumab treatment groups.

Pharmacodynamic Results

Mean serum total NGF concentrations were comparable at Baseline across treatment groups. From Weeks 8 through 56, mean serum total NGF concentrations were higher in the tanezumab 5 mg treatment group than in the tanezumab 2.5 mg treatment group by a proportion approximately similar to the increase in dose. Beginning at Week 64, mean serum total NGF concentrations began to decline in both the tanezumab 2.5 mg and tanezumab 5 mg treatment groups. Mean serum proNGF concentrations were comparable across treatment groups at all nominal sampling times. Mean and median serum soluble p75 concentrations were comparable at all time points for all treatment groups.

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Safety Results

Adverse Events

During the Treatment Period, adverse events were reported for a greater proportion of patients in the tanezumab 5 mg treatment group (67.1%) than in the tanezumab 2.5 mg treatment group (62.8%) (Table S4). The proportion of patients with adverse events was lowest in the NSAID treatment group (60.3%). Serious adverse events (SAEs) were reported for the greatest proportion of patients in the tanezumab 5 mg treatment group (8.0%) followed by the tanezumab 2.5 mg treatment group (5.1%) and the NSAID treatment group (4.6%). The incidence of treatment discontinuation due to an adverse event was highest in the tanezumab 5 mg treatment group (8.8%).

Table S4. Treatment-Emergent Adverse Events During the Treatment Period (All Causalities) - Safety Population

Number (%) of subjects	Tanezumab 2.5 mg n (%)	Tanezumab 5 mg n (%)	NSAID n (%)
Subjects evaluable for adverse events	1002	998	996
Number of adverse events	1723	2031	1498
Subjects with adverse events	629 (62.8)	670 (67.1)	601 (60.3)
Subjects with serious adverse events	51 (5.1)	80 (8.0)	46 (4.6)
Subjects with severe adverse events	45 (4.5)	68 (6.8)	45 (4.5)
Subjects discontinued from study due to adverse events (a)	23 (2.3)	20 (2.0)	7 (0.7)
Subjects discontinued study drug due to AE and continued Study (b)	53 (5.3)	88 (8.8)	52 (5.2)
Subjects with dose reduced or temporary discontinuation due to adverse events	17 (1.7)	22 (2.2)	22 (2.2)

Includes treatment-emergent events that begin up to the week 56 (end of treatment) visit date for subjects who completed the treatment period or up to the withdrawal
from treatment date for subjects who withdrew early from the treatment period.
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
Study.
MedDRA v21.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 04APR2019 (07:24) Source Data: Listing 16.2.7.1 Output File: ./nda1/A4091058_IM_Safety/adae_s020_i Date of Generation: 09MAY2019 (19:17)
Table 14.3.1.2.1.1.i is for Pfizer internal use.

The incidence of adverse events reported during the Safety Follow-up Period was higher in the tanezumab 5 mg treatment group (41.5%) than in the tanezumab 2.5 mg (33.5%) and NSAID (30.9%) treatment groups (Table S5). SAEs were reported for a greater proportion of patients in the tanezumab treatment groups (tanezumab 2.5 mg, 3.8%; tanezumab 5 mg, 3.6%) than in the NSAID treatment group (2.1%). One patient in the tanezumab 5 mg

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treatment group and one patient in the NSAID treatment group discontinued the study due to an adverse event during the Safety Follow-up Period.

Table S5. Treatment-Emergent Adverse Events During the Safety Follow-up Period (All Causalities) - Safety Population

Number (%) of Subjects	Tanezumab 2.5 mg n (%)	Tanezumab 5 mg n (%)	NSAID n (%)
Subjects evaluable for adverse events	880	885	887
Number of adverse events	580	688	501
Subjects with adverse events	295 (33.5)	367 (41.5)	274 (30.9)
Subjects with serious adverse events	33 (3.8)	32 (3.6)	19 (2.1)
Subjects with severe adverse events	26 (3.0)	27 (3.1)	23 (2.6)
Subjects discontinued from study due to adverse events (a)	0	1 (0.1)	1 (0.1)
Subjects discontinued study drug due to AE and continued Study (b)	0	0	0
Subjects with dose reduced or temporary discontinuation due to adverse events	0	0	3 (0.3)

Includes treatment-emergent events that began after the Week 56 (End of Treatment) visit date for subjects who completed the Treatment Period or after the withdrawal from treatment date for subjects who withdrew early from the Treatment Period.
Except for the number of adverse events subjects were counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
(a) Subjects who had an AE record that indicates that the AE caused the subject to be discontinued from the study.
(b) Subjects who had 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 Study.
MedDRA v21.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 04APR2019 (07:24) Source Data: Listing 16.2.7.1 Output File: ./nda1/A4091058_IM_Safety/adae_s020_fup_i Date of Generation: 23MAY2019 (10:59)
Table 14.3.1.2.1.2.i is for Pfizer internal use.

Adverse events occurring at a greater frequency (≥1% difference between treatment groups) in the tanezumab treatment groups versus the NSAID treatment group included Arthralgia, Nasopharyngitis, Osteoarthritis, Joint swelling, Headache, Rapidly progressive osteoarthritis, and Carpal tunnel syndrome (Table S6). Adverse events occurring at a greater frequency (≥1% difference between treatment groups) in the tanezumab 5 mg treatment group versus the tanezumab 2.5 mg and NSAID treatment groups included Arthralgia, Nasopharyngitis, Back pain, Osteoarthritis, Oedema peripheral, Rapidly progressive osteoarthritis, Paraesthesia, Carpal tunnel syndrome, Cough, and Joint effusion. Adverse events of Fall were reported at a higher frequency (≥1% difference between treatment groups) in the tanezumab 2.5 mg treatment group than in the tanezumab 5 mg and NSAID treatment groups. Bronchitis and Hypoaesthesia were reported at a higher frequency (≥1% difference between treatment groups) in the tanezumab 5 mg treatment group than in the NSAID treatment group. Upper respiratory tract infection was reported at a higher frequency (≥1%

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difference between treatment groups) in the NSAID and tanezumab 2.5 mg treatment groups than in the tanezumab 5 mg treatment group.

Table S6. Incidence of Treatment-Emergent Adverse Events During the Treatment Period in >=2% of Subjects in Any Treatment Group (All Causalities) – Safety Population

Number of subjects evaluable for adverse events	Tanezumab 2.5 mg (N=1002)	Tanezumab 5 mg (N=998)	NSAID (N=996)
Number (%) of subjects: by Preferred Term	**n (%)**	**n (%)**	**n (%)**
With any adverse event	629 (62.8)	670 (67.1)	601 (60.3)
Arthralgia	133 (13.3)	165 (16.5)	117 (11.7)
Nasopharyngitis	57 (5.7)	67 (6.7)	40 (4.0)
Back pain	34 (3.4)	55 (5.5)	35 (3.5)
Osteoarthritis	39 (3.9)	54 (5.4)	23 (2.3)
Fall	65 (6.5)	53 (5.3)	46 (4.6)
Joint swelling	43 (4.3)	48 (4.8)	10 (1.0)
Headache	56 (5.6)	45 (4.5)	25 (2.5)
Upper respiratory tract infection	57 (5.7)	45 (4.5)	59 (5.9)
Oedema peripheral	19 (1.9)	43 (4.3)	17 (1.7)
Musculoskeletal pain	43 (4.3)	41 (4.1)	37 (3.7)
Rapidly progressive osteoarthritis	18 (1.8)	41 (4.1)	4 (0.4)
Pain in extremity	31 (3.1)	37 (3.7)	28 (2.8)
Paraesthesia	18 (1.8)	30 (3.0)	13 (1.3)
Bronchitis	22 (2.2)	28 (2.8)	13 (1.3)
Hypoaesthesia	27 (2.7)	28 (2.8)	18 (1.8)
Carpal tunnel syndrome	16 (1.6)	27 (2.7)	6 (0.6)
Cough	13 (1.3)	26 (2.6)	7 (0.7)
Influenza	20 (2.0)	21 (2.1)	26 (2.6)
Joint effusion	8 (0.8)	21 (2.1)	5 (0.5)
Muscle spasms	15 (1.5)	20 (2.0)	19 (1.9)
Urinary tract infection	12 (1.2)	20 (2.0)	15 (1.5)
Hypertension	16 (1.6)	11 (1.1)	25 (2.5)
Nausea	14 (1.4)	11 (1.1)	21 (2.1)

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Table S6. Incidence of Treatment-Emergent Adverse Events During the Treatment Period in >=2% of Subjects in Any Treatment Group (All Causalities) – Safety Population

Number of subjects evaluable for adverse events	Tanezumab 2.5 mg (N=1002)	Tanezumab 5 mg (N=998)	NSAID (N=996)
Number (%) of subjects: by Preferred Term	**n (%)**	**n (%)**	**n (%)**

Subjects are only counted once per treatment per event.
Adverse events are shown by descending frequency by the highest Tanezumab dose.
Includes treatment-emergent events that begin up to the Week 56 (end of treatment) visit date for subjects who completed the treatment period or up to the withdrawal from treatment date for subjects who withdrew early from the Treatment Period.
MedDRA v21.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 04APR2019 (07:24) Source Data: Listing 16.2.7.1 Output File: ./nda1/A4091058_IM_Safety/adae_s030_i Date of Generation: 05JUN2019 (16:57)
Table 14.3.1.2.3.i is for Pfizer internal use.

- **Treatment-Related Adverse Events**: Adverse events considered by the Investigator to be treatment-related were reported for a higher proportion of patients in the tanezumab 5 mg treatment group (20.8%) than in the tanezumab 2.5 mg treatment group (16.5%) and the NSAID treatment group (15.9%). Adverse events most frequently considered treatment-related by the Investigator (≥1% of patients) in the tanezumab 2.5 mg treatment group were Arthralgia, Hypoaesthesia, Paraesthesia, Rapidly progressive osteoarthritis, Headache, and Osteoarthritis. Adverse events most frequently considered treatment-related by the Investigator (≥1% of patients) in the tanezumab 5 mg treatment group were Arthralgia, Rapidly progressive osteoarthritis, Osteoarthritis, Paraesthesia, Hypoaesthesia, Oedema peripheral, and Carpal tunnel syndrome. Arthralgia was the only treatment-related adverse event reported in ≥1% of patients in the NSAID treatment group. Treatment-related Arthralgia was reported more frequently (≥1% difference between treatment groups) in the tanezumab 5 mg treatment group than in the tanezumab 2.5 mg and NSAID treatment groups. Treatment-related Osteoarthritis, Rapidly progressive osteoarthritis, and Carpal tunnel syndrome were reported more frequently (≥1% difference between treatment groups) in the tanezumab 5 mg treatment group than in the NSAID treatment group, and treatment-related Rapidly progressive osteoarthritis was reported more frequently reported (≥1% difference between treatment groups) in the tanezumab 5 mg treatment group than in the tanezumab 2.5 mg treatment group.

- **Severe Adverse Events**: During the Treatment Period, severe adverse events were reported for more patients in the tanezumab 5 mg treatment group (6.8%) than in the tanezumab 2.5 mg treatment group (4.5%) and the NSAID treatment group (4.5%). The most commonly reported (≥0.5% of patients in any treatment group) severe adverse events were Arthralgia, Osteoarthritis, and Rapidly progressive osteoarthritis.

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Osteoarthritis that was considered severe occurred more frequently (≥0.5% difference between treatment groups) in the tanezumab 5 mg treatment group than in the tanezumab 2.5 mg treatment group and the NSAID treatment group. Severe Rapidly progressive osteoarthritis was reported more frequently (≥0.5% difference between treatment groups) in the tanezumab 5 mg treatment group than in the NSAID treatment group.

- **Injection Site Reactions**: Injection site reactions were infrequently reported (0.5% across treatment groups) during the Treatment Period. All Injection site reactions were mild in severity, and none were serious.

- **Potential Hypersensitivity Adverse Events:** Few hypersensitivity adverse events were reported during the Treatment Period. The incidence of potential hypersensitivity adverse events was slightly greater in both tanezumab treatment groups (tanezumab 2.5 mg, 3.0%; tanezumab 5 mg, 3.1%) than in the NSAID treatment group (2.1%). These adverse events were mild or moderate in severity, except for one adverse event of Hypersensitivity in a patient in the tanezumab 5 mg treatment group that was serious and considered severe; this SAE was considered related to a concomitant drug treatment and had resolved within 24 hours.

- **Tier 1 Adverse Events:** Pre-specified adverse events of potential sympathetic dysfunction (Syncope, Bradycardia, orthostatic hypotension [OH], Anhidrosis, and Hypohidrosis) were considered clinically important and the overall pooled incidence of the events was classified as a Tier 1 adverse event in the Product's Safety Review Plan. The overall incidence of these events during the Treatment Period was low (tanezumab 2.5 mg, 1.8%; tanezumab 5 mg, 2.3%; NSAID, 2.9%). There was no significant difference between the frequencies of occurrence when comparing either of the tanezumab treatment groups to the NSAID treatment group.

- **Tier 2 Adverse Events:** Tier 2 adverse events were defined as adverse events occurring at ≥3% in any treatment group. The frequency of occurrence in each tanezumab treatment group is compared to the NSAID group with 95% confidence intervals provided to help gauge the precision of the estimates for risk difference. Joint swelling, Osteoarthritis, and Headache occurred more frequently (CI did not include zero) in the tanezumab 2.5 mg treatment group than in the NSAID treatment group. Oedema peripheral, Nasopharyngitis, Arthralgia, Joint swelling, Rapidly progressive osteoarthritis, Osteoarthritis, Back pain, Headache, and Paraesthesia occurred more frequently (CI did not include zero) in the tanezumab 5 mg treatment group than in the NSAID treatment group.

- **Deaths:** A total of 10 patients died during the study. Five deaths occurred during the Treatment Period (two patients in the tanezumab 2.5 mg treatment group [Myocardial infarction and Cardiac arrest] and three patients in the tanezumab 5 mg treatment group [Acute myocardial infarction and Myocardial rupture, Pulmonary embolism, and Myocardial infarction]) and three deaths occurred during the Safety Follow-up Period

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(two patients in the tanezumab 2.5 mg treatment group [Toxicity to various agents and Acute respiratory failure secondary to Lung adenocarcinoma] and one patient in the tanezumab 5 mg treatment group [Acute respiratory failure]). Two deaths occurred in patients who had discontinued from the study: one patient in the tanezumab 5 mg treatment group (Sudden death) and one patient in the NSAID treatment group (Cardio-respiratory arrest).

- **Serious Adverse Events:** During the Treatment Period, SAEs were reported for a greater proportion of patients in the tanezumab 5 mg treatment group (8.0%) than in the tanezumab 2.5 mg treatment group (5.1%) and the NSAID treatment group (4.6%). In the Musculoskeletal and connective tissue disorders system organ class, more (≥1% difference between treatment groups) SAEs were reported for patients in the tanezumab 5 mg treatment group (4.5%) than for patients in the tanezumab 2.5 mg treatment group (1.8%) and the NSAID treatment group (1.0%). SAEs of Osteoarthritis, Rapidly progressive osteoarthritis, and Arthralgia were reported more frequently (≥0.5% difference between treatment groups) in the tanezumab 5 mg treatment group than in the tanezumab 2.5 mg and NSAID treatment groups. All other individual preferred terms occurred in one or two patients per treatment group, with the exception of Acute myocardial infarction (three patients in the NSAID treatment group), Meniscus injury (three patients in the tanezumab 5 mg treatment group) and Subchondral insufficiency fracture (four patients in the tanezumab 5 mg treatment group).

Joint Safety Events of Special Interest

Primary Composite Joint Safety Outcome

Across treatment groups, 335 patients had joint safety events that met criteria for adjudication (Table S7). The highest number of patients with events requiring adjudication was in the tanezumab 5 mg treatment group, followed by the tanezumab 2.5 mg treatment group and the NSAID treatment group.

The incidence of the primary composite joint safety outcome was highest in the tanezumab 5 mg treatment group (7.1%), followed by the tanezumab 2.5 mg treatment group (3.8%) and the NSAID treatment group (1.5%). The risk difference versus NSAID was significantly greater for both tanezumab treatment groups (tanezumab 2.5 mg, $p=0.0156$; tanezumab 5 mg, $p<0.0001$).

The primary analysis of the primary composite joint safety outcome, observation time-adjusted rate of the primary composite joint safety outcome, was highest in the tanezumab 5 mg treatment group (71.5 events/1000 patient-years), followed by the tanezumab 2.5 mg treatment group (37.4 events/1000 patient-years) and the NSAID treatment group (14.8 events/1000 patient-years). The observation time-adjusted rate was significantly greater for both tanezumab treatment groups compared with the NSAID treatment group (rate difference versus NSAID: tanezumab 2.5 mg, $p=0.0017$; tanezumab 5 mg, $p<0.0001$).

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There were 124 patients across treatment groups who had adjudication results included in the primary composite joint safety outcome; the most frequently observed outcome was Rapidly progressive OA type 1 (88 patients [71.0%]), followed by Rapidly progressive OA type 2 (18 patients [14.5%]) and Subchondral insufficiency fracture (17 patients [13.7%]). One patient in the tanezumab 5 mg treatment group had an outcome of Primary osteonecrosis. There were no events of Pathologic fracture observed in any treatment group.

One patient in the tanezumab 2.5 mg group had an Investigator-reported adverse event of suspected Osteonecrosis of the right hip that was not evaluated by the Adjudication Committee until after the study database had been locked. The Adjudication Committee's final evaluation of the event was "Osteonecrosis". This adjudicated event is not included in analyses of the primary or secondary composite joint safety outcomes or in the analysis of individual adjudication outcomes of primary osteonecrosis. No other joint safety analyses are affected by this case and the overall conclusions regarding joint safety are not impacted.

Table S7. Summary of Adjudicated Joint Safety Outcomes - Subject-Level, Primary Outcome - Safety Population

	Tanezumab 2.5 mg (N=1002)	Tanezumab 5 mg (N=998)	NSAID (N=996)
Subjects analyzed by the Adjudication Committee [n (%)]	115 (11.5%)	171 (17.1%)	49 (4.9%)
Primary Composite Joint Safety Endpoint (1) [n (%), {95% CI}]	38 (3.8%)	71 (7.1%)	15 (1.5%)
	[2.7%, 5.2%]	[5.6%, 8.9%]	[0.8%, 2.5%]
Secondary Composite Joint Safety Endpoint (2) [n (%), {95% CI}]	9 (0.9%)	22 (2.2%)	5 (0.5%)
	[0.4%, 1.7%]	[1.4%, 3.3%]	[0.2%, 1.2%]
Rapidly Progressive OA [n (%), {95% CI}]	32 (3.2%)	63 (6.3%)	11 (1.1%)
	[2.2%, 4.5%]	[4.9%, 8.0%]	[0.6%, 2.0%]
Rapidly Progressive OA type 1 [n (%), {95% CI}]	29 (2.9%)	49 (4.9%)	10 (1.0%)
	[1.9%, 4.1%]	[3.7%, 6.4%]	[0.5%, 1.8%]
Rapidly Progressive OA type 2 [n (%), {95% CI}]	3 (0.3%)	14 (1.4%)	1 (0.1%)
	[0.1%, 0.9%]	[0.8%, 2.3%]	[0.0%, 0.6%]
Primary Osteonecrosis [n (%), {95% CI}]	0	1 (0.1%)	0
	[0.0%, 0.4%]	[0.0%, 0.6%]	[0.0%, 0.4%]
Pathological Fracture [n (%), {95% CI}]	0	0	0
	[0.0%, 0.4%]	[0.0%, 0.4%]	[0.0%, 0.4%]
Subchondral Insufficiency Fracture [n (%), {95% CI}]	6 (0.6%)	7 (0.7%)	4 (0.4%)
	[0.2%, 1.3%]	[0.3%, 1.4%]	[0.1%, 1.0%]
Not Enough Info to Determine Rapid vs. Normal Progression of OA [n (%)]	2 (0.2%)	0	0
Normal Progression of OA [n (%)]	66 (6.6%)	79 (7.9%)	27 (2.7%)
Other Joint Outcome [n (%)]	9 (0.9%)	21 (2.1%)	7 (0.7%)

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Table S7. Summary of Adjudicated Joint Safety Outcomes - Subject-Level, Primary Outcome - Safety Population

	Tanezumab 2.5 mg (N=1002)	Tanezumab 5 mg (N=998)	NSAID (N=996)

(1) The primary composite joint safety endpoint includes any subject with an adjudicated outcome of primary osteonecrosis, rapidly progressive OA type 1 or type 2,subchondral insufficiency fracture, or pathological fracture.
(2) The secondary composite joint safety endpoint includes any subject with an adjudicated outcome of primary osteonecrosis, rapidly progressive OA type 2,subchondral insufficiency fracture, or pathological fracture.
Primary outcome for each subject is shown, according to the following hierarchy: primary osteonecrosis, rapidly progressive OA type 2, subchondral insufficiency fracture, pathological fracture, rapidly progressive OA type 1, not enough info to determine rapid vs. normal progression of OA, other, normal progression of OA.
Includes TJR or adjudicated event up to the end of the safety follow-up period or 26 weeks after the end of the treatment period, whichever is later.
PFIZER CONFIDENTIAL SDTM Creation: 15APR2019 (18:25) Source Data: Table 16.2.8.7 Output File: ./nda1/A4091058_IM_Efficacy/adadj_s0032_i Date of Generation: 05JUN2019 (17:40)
Table 14.5.1.2.2.1.i is for Pfizer internal use.

Secondary Joint Safety Analysis

- The **secondary composite joint safety outcome**, reported for 36 patients total, was more frequently observed in the tanezumab 5 mg treatment group (22 patients [2.2%]) compared with the tanezumab 2.5 mg and NSAID treatment groups (nine patients [0.9%] and five patients [0.5%], respectively). The risk difference was significantly greater for the tanezumab 5 mg treatment group compared with the NSAID treatment group (p=0.0238); there was no significant difference with tanezumab 2.5 mg treatment compared with NSAID treatment. The observation time-adjusted rate of the secondary composite joint safety outcome was highest in the tanezumab 5 mg treatment group (21.8 events/1000 patient-years), followed by the tanezumab 2.5 mg treatment group (8.8 events/1000 patient-years) and the NSAID treatment group (4.9 events/1000 patient-years). The observation time-adjusted rate was significantly greater in the tanezumab 5 mg treatment group compared with the NSAID treatment group (rate difference versus NSAID: p=0.0010); there was no significant difference with tanezumab 2.5 mg treatment compared with NSAID treatment.

- Rapidly progressive OA was the most common **individual adjudication outcome**, with 114 events observed in 107 patients. Of these, the majority of events were Rapidly progressive OA type 1, with 94 events reported for 89 patients across treatment groups. The incidence of the Rapidly progressive OA type 1 was highest in the tanezumab 5 mg treatment group (49 patients [4.9%]) followed by the tanezumab 2.5 mg treatment group (29 patients [2.9%]) and the NSAID treatment group (11 patients [1.1%]); the incidence was significantly greater for both tanezumab treatment groups compared with the NSAID treatment group. A total of seventeen events adjudicated to Subchondral insufficiency fracture (six in the tanezumab 2.5 mg treatment group, seven in the tanezumab 5 mg treatment group, and four in the NSAID treatment group) and one event for a patient in

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the tanezumab 5 mg treatment group adjudicated to Primary osteonecrosis. No events adjudicated to Pathological fracture.

In total, 172 patients had joint safety events adjudicated to Normal progression of OA and did not also have an event in the primary composite joint safety outcome. The incidence of these events was higher in the tanezumab treatment groups (66 patients [6.6%] and 79 patients [7.9%] in the tanezumab 2.5 and 5 mg treatment groups, respectively) than in the NSAID treatment group (27 patients [2.7%]). A total of 37 patients across treatment groups had 42 joint safety events adjudicated to Other joint outcome and did not also have an event included in the primary composite joint safety outcome, with a higher incidence in the tanezumab 5 mg treatment group (21 patients [2.1%]) compared with the tanezumab 2.5 mg and NSAID treatment groups (nine patients [0.9%] and seven patients [0.7%], respectively).

- **Total Joint Replacements:** A total of 159 patients across treatment groups had at least one TJR. The incidence of TJR was highest in the tanezumab 5 mg treatment group (8.0%), followed by the tanezumab 2.5 mg treatment group (5.3%) and the NSAID treatment group (2.6%); the incidence was significantly higher for both tanezumab treatment groups compared with NSAID. More patients had an adjudicated outcome that was a component of the primary composite joint safety outcome in the tanezumab 5 mg treatment group (20 patients [25.0%]) compared with the tanezumab 2.5 mg treatment group (four patients [7.5%]) and NSAID treatment group (four patients [15.4%]). The secondary composite joint safety outcome was also more frequently associated with a TJR for patients in the tanezumab 5 mg treatment group (13 patients [16.3%]) compared with the tanezumab 2.5 mg (one patient [1.9%]) and the NSAID (two patients [7.7%]) treatment groups. Rapidly progressive OA types 1 and 2 were both most frequently associated with a TJR in the tanezumab 5 mg treatment group. Three patients in the tanezumab 5 mg treatment group and one patient in the NSAID treatment group with a TJR had an adjudication outcome of Subchondral insufficiency fracture, and one patient in the tanezumab 5 mg treatment group with a TJR had an adjudication outcome of Primary osteonecrosis. Five patients had an adjudicated outcome of Other joint outcome.

- **Radiography:** In patients with Baseline KL grade 2 or 3, a significantly greater decrease in minimum joint space width (JSW) of the medial compartment of the index knee was observed in the tanezumab 5 mg treatment group compared with the NSAID treatment group at Weeks 56 and 80. There were no significant differences in JSW decrease of the index hip for either tanezumab treatment group compared with NSAID at Week 56 or Week 80, although the sample size evaluated was relatively small (approximately 5% of the total population).

  Using the Bland and Altman method, the proportion of patients with progression of OA in the index knee (medial compartment, KL Grade 2 or 3) was significantly greater in the tanezumab 5 mg treatment group compared with the NSAID treatment group at Weeks 56 and 80. There was no significant difference in the proportion of patients with

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progression of OA in the index hip when comparing tanezumab-treated patients with NSAID-treated patients at Weeks 56 and 80, although the proportion of patients in both tanezumab treatment groups who were considered to have progression of OA was numerically higher than in the NSAID treatment group at Week 80 and the sample size evaluated was relatively small (approximately 5% of the total population).

Other Safety Analysis

- **Adverse Events of Abnormal Peripheral Sensation**: The incidence of adverse events of abnormal peripheral sensation was highest in the tanezumab 5 mg treatment group (9.0%), followed by the tanezumab 2.5 mg treatment group (6.2%) and the NSAID treatment group (4.6%). Carpal tunnel syndrome occurred at a greater frequency (≥1% difference between treatment groups) in the tanezumab 5 mg treatment group than in the tanezumab 2.5 mg treatment group and the NSAID treatment group, and also occurred at a greater frequency in the tanezumab 2.5 mg treatment group than in the NSAID treatment group. Hypoaesthesia occurred at a greater frequency (≥1% difference between treatment groups) in the tanezumab 5 mg treatment group than in the NSAID treatment group, and Paraesthesia occurred at a greater frequency in the tanezumab 5 mg treatment group than in the tanezumab 2.5 mg and NSAID treatment groups. An SAE of Carpal tunnel syndrome was reported for one patient in the tanezumab 2.5 mg treatment group. Carpal tunnel syndrome was considered severe for one patient in the tanezumab 2.5 mg treatment group, two patients in the tanezumab 5 mg treatment group, and one patient in the NSAID treatment group. Across treatment groups, 12 patients had a total of 14 carpal tunnel release surgeries. Seven (four in the tanezumab 2.5 mg treatment group, two in the tanezumab 5 mg treatment group, and one in the NSAID treatment group) of these surgeries occurred within 16 weeks of the last dose of SC study medication. Sensory loss was considered severe for one patient in the tanezumab 5 mg treatment group. All other adverse events of abnormal peripheral sensation were mild or moderate in severity.

- **Peripheral Neurological Consultations:** More patients in the tanezumab 2.5 mg and 5 mg treatment groups had adverse events of abnormal peripheral sensation that met criteria for requiring a neurologic consult than in the NSAID treatment group. The most frequent expert primary diagnosis across treatment groups was Mononeuropathy, which occurred at a greater frequency in the tanezumab 5 mg treatment group than in the tanezumab 2.5 mg and NSAID treatment groups. Radiculopathy was diagnosed in more patients in the tanezumab 2.5 mg treatment group than in the tanezumab 5 mg treatment group and the NSAID treatment group. Polyneuropathy was diagnosed in tanezumab-treated patients only.

- **Adverse Events Potentially Indicative of Decreased Sympathetic Function:** The incidence of treatment emergent adverse events of interest that could be indicative of decreased sympathetic function during the Treatment Period was highest in the NSAID treatment group (7.3%), followed by the tanezumab 5 mg treatment group (6.8%) and the tanezumab 2.5 mg treatment group (6.1%). Nausea occurred at a greater frequency (≥1% difference between treatment groups) in the NSAID treatment group than in the

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tanezumab 5 mg treatment group. One patient in both the tanezumab 2.5 mg and NSAID treatment groups had an adverse event of syncope that was considered severe. Diarrhoea was considered severe for one patient in the tanezumab 5 mg treatment group and one patient in the NSAID treatment group. In the tanezumab 5 mg treatment group, severe adverse events of Nausea and Vomiting were reported for one patient each. All other adverse events potentially indicative of decreased sympathetic function were mild or moderate in severity.

A subset of these adverse events (Bradycardia, OH, Syncope, Anhidrosis, and Hypohidrosis) were considered signs or symptoms suggestive of sympathetic dysfunction. The incidence of these events was low across treatment groups. Bradycardia was reported at a higher incidence in the NSAID treatment group (1.6%) than in the tanezumab 2.5 mg and 5 mg treatment groups (0.7% and 0.9%, respectively). OH and Syncope occurred at similar, low frequencies across treatment groups. Hypohidrosis occurred in one patient in the tanezumab 5 mg treatment group and was mild in severity. No events of Anhidrosis were reported.

- **Consultations for Adverse Events Potentially Indicative of Decreased Sympathetic Function:** Patients with adverse events of Bradycardia and Syncope met criteria for consultation in all treatment groups. Patients with adverse events of OH met criteria for consultation in the tanezumab 5 mg and NSAID treatment groups. One patient in the tanezumab 5 mg treatment group had an adverse event of Hypohidrosis that met criteria for consult. No events of Anhidrosis were reported. Consults were obtained in the majority of patients who met criteria for a consult. Sympathetic neuropathy was not confirmed for any of the patients who had a consultation, as determined by the Investigator after a review of clinical data, including available consultation material.

- **Neuropathy Impairment Score:** For over 93% of patients across treatment groups, the conclusion from the neurological examinations at the last assessment was no new or worsened neurological examination abnormality. Less than 1% of patients in any treatment group had a new or worsened neurological examination abnormality that was considered by the Investigator to be clinically significant.

- **Laboratory Parameters:** The incidence of patients with normal Baseline who had post-Baseline laboratory test abnormalities that met the pre-specified threshold for change from Baseline was low, affected no more than 25 (approximately 3%) patients within a treatment group, and was generally evenly distributed across treatment groups. Laboratory abnormalities considered clinically significant by the Investigator post-Baseline were to be reported as adverse events. The incidence of adverse events associated with laboratory abnormalities during the Treatment Period was low and similar across treatment groups. All laboratory abnormalities reported as adverse events in the Treatment Period were reported in one or two patients each in any treatment group, with the exception of Blood creatinine phosphokinase increased (six patients and three patients in the tanezumab 2.5 mg and 5 mg treatment groups, respectively) and

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Gamma-glutamyltransferase increased (three patients in the NSAID treatment group). One patient in the tanezumab 2.5 mg treatment group had an adverse event of Blood creatinine increased, considered mild, that resulted in discontinuation. No laboratory abnormalities were considered severe.

- **Vital Signs:** Categorical changes from Baseline to the last post-Baseline value during the Treatment period in sitting systolic and diastolic blood pressure (BP) were generally similar across treatment groups. The proportion of patients with a maximum increase from Baseline of greater than zero and less than 10 mmHg in sitting systolic and diastolic BP was lower in the tanezumab 5 mg treatment group than in the tanezumab 2.5 mg and NSAID treatment groups. The proportion of patients with only a decrease or no change from Baseline in sitting systolic and diastolic BP was greater in the tanezumab treatment groups than in the NSAID treatment group. The proportion of patients with only an increase or no change from Baseline in sitting systolic and diastolic BP was lower in the tanezumab 5 mg treatment group than in the tanezumab 2.5 mg and NSAID treatment group.

  During the Treatment Period, the incidence of adverse events associated with vital signs was higher in the NSAID treatment group (5.3%) compared with the tanezumab 2.5 mg (3.9%) and tanezumab 5 mg (3.8%) treatment groups. Hypertension was the most frequently reported adverse event associated with vital signs and occurred most frequently in the NSAID treatment group (2.5%), followed by the tanezumab 2.5 mg treatment group (1.6%) and the tanezumab 5 mg treatment group (1.1%). Adverse events of Bradycardia occurred at a higher frequency in the NSAID treatment group (1.6%) than in the tanezumab 2.5 mg (0.7%) and tanezumab 5 mg (0.9%) treatment groups.

- **ECG:** One patient in the tanezumab 5 mg treatment group and one patient in the NSAID treatment group had a QTcB (QTc corrected using Bazett's formula) interval ≥500 msec. The maximum changes in all ECG parameters were similar across treatment groups.

  ECG abnormalities considered clinically significant by the Investigator and any episode of a decrease in heart rate that met protocol criteria for Bradycardia on ECG were to be reported as adverse events. Across treatment groups, few ECG-related adverse events were observed during the Treatment Period. The most frequently reported adverse event associated with ECG was Bradycardia, which was reported at a higher frequency in the NSAID treatment group (1.6%) than in the tanezumab 2.5 mg (0.7%) and tanezumab 5 mg (0.9%) treatment groups.

- **Immunogenicity:** Treatment-emergent (TE) ADA status (ie, TE ADA+ or TE ADA-) did not appear to influence the proportion of patients identified as responders (ie, patients with a change from Baseline in WOMAC Pain Subscale reduction of ≥30% at Week 16) in the tanezumab treatment groups. The overall percent incidence of adverse events and injection site reactions in the combined TE ADA+ tanezumab treatment group was

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

CONCLUSIONS

- The incidence of the primary composite joint safety outcome was significantly higher in both tanezumab treatment groups compared with the NSAID treatment group, primarily due to a higher rate of Rapidly progressive OA with tanezumab treatment. The observation time-adjusted rate of the primary composite joint safety outcome was significantly greater for both the tanezumab 2.5 mg (37.4 events/1000 patient-years; p=0.0017) and tanezumab 5 mg (71.5 events/1000 patient-years; p<0.0001) treatment groups compared with the NSAID treatment group (14.8 events/1000 patient-years).

- There were 124 patients total who had adjudication results included in the primary composite joint safety outcome; the most frequently observed individual outcome was Rapidly progressive OA type 1 (89 patients [71.8%]).

- The incidence and observation time-adjusted rate of TJR were significantly higher for both tanezumab treatment groups compared with the NSAID treatment group.

- In patients with Baseline KL grade 2 or 3, treatment with tanezumab 5 mg resulted in a significantly greater decrease in JSW of the medial compartment of the index knee and a significantly greater proportion of patients with progression of OA in the medial compartment of the index knee at Weeks 56 and 80; there were no significant differences when comparing tanezumab 2.5 mg treatment with NSAID treatment.

- Treatment with tanezumab was associated with an increased incidence of adjudicated joint safety events. Tanezumab 2.5 mg treatment had a more favorable joint safety profile than tanezumab 5 mg treatment based on the frequency and severity of joint safety events observed.

- The adverse event data were generally consistent with previous tanezumab studies and no new safety signals were identified.

- The adverse event data related to abnormal peripheral sensation were consistent with previous studies and the incidence of these events was more frequent in the tanezumab treatment groups. As in previous studies, Paraesthesia and Hypoaesthesia were the most commonly reported adverse events of abnormal peripheral sensation.

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

- The immunogenicity results do not provide any evidence that the presence of treatment-emergent ADA affects the safety or efficacy profile of tanezumab.

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- Treatment with tanezumab 5 mg met two co-primary efficacy endpoints (WOMAC Pain and Physical Function subscales) but not the third co-primary endpoint (PGA-OA) at Week 16, and so did not meet the overall primary objective. Further hypothesis testing of the key secondary endpoint could not be performed because the PGA-OA endpoint for tanezumab 5 mg was not met.

- Treatment with tanezumab 2.5 mg did not meet any of the co-primary efficacy endpoints at Week 16.

- The results for the key secondary efficacy endpoint were deemed not significant due to the testing strategy. Both tanezumab treatment groups had numerically higher percentages of ≥50% responders than the NSAID treatment group at Week 16 and the unadjusted p-value for tanezumab 5 mg compared with NSAID was ≤0.05.

- Both tanezumab treatment groups tended to have numerically higher percentages of responders than the NSAID treatment group at the 30%, 50%, 70%, and 90% levels in WOMAC Pain and Physical Function scores at Weeks 2, 4, 8, and 16. Most of these comparisons were significant (unadjusted p≤0.05) for the tanezumab 5 mg treatment group compared with the NSAID treatment group, while fewer were significant for the tanezumab 2.5 mg treatment group compared with the NSAID treatment group.

- Treatment with tanezumab 2.5 mg resulted in significant (unadjusted p≤0.05) improvement compared with NSAID at Week 16 in average pain score in the index joint and the WOMAC Stiffness subscale. Treatment with tanezumab 5 mg resulted in significant improvement (unadjusted p≤0.05) compared with NSAID at Week 16 in average pain score in the index joint, WOMAC Stiffness subscale, WOMAC Average Score, and WOMAC Pain subscale item: Pain When Going Up or Down Stairs.

- For all endpoints evaluated across the 56-week treatment duration, tanezumab treatment resulted in improved or similar efficacy compared with NSAID treatment.

- This study was primarily a long-term safety study and was not powered nor designed optimally to assess long-term efficacy (eg, large amount of imputed data due to planned discontinuation of non-responding subjects from treatment) for treatment group comparisons of efficacy after Week 16. Given these limitations, improvement in pain was maintained long-term across all treatment groups.