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Sponsor: Pfizer Inc

Investigational Product: Tanezumab

Clinical Study Report Synopsis: Protocol A4091057

Protocol Title: A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of the Analgesic Efficacy and Safety of the 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 104 sites randomized patients in this study. The study was conducted at sites in Austria, Bulgaria, Finland, France, Germany, Hungary, Italy, Japan, Poland, Portugal, Romania, Slovakia, Spain, Sweden, and the United Kingdom.

Publications Based on the Study: None

Study Initiation and Completion Dates:

Study Initiation Date: 02 March 2016

Primary Completion Date: 08 June 2018

Study Completion Date: 14 November 2018

Report Date: 27 June 2019

Previous Report Date(s): 13 May 2019

Phase of Development: Phase 3

Study Objective(s)

Primary Objective

- Demonstrate superior efficacy of tanezumab 5 mg and tanezumab 2.5 mg administered subcutaneously (SC) every 8 weeks versus placebo at Week 24.

Secondary Objective

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

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METHODS

Study Design

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter Phase 3 study of the efficacy and safety of tanezumab when administered by SC injection over 24 weeks, compared to placebo, in patients with osteoarthritis (OA) of the knee or hip. Eight hundred ten (810) patients were planned to be randomized to one of three treatment groups in a planned 1:1:1 ratio (ie, 270/group). Patients were to receive up to three 1 mL SC injections of study medication in the abdomen or anterior aspect of the thigh at 8-week intervals.

- Tanezumab 2.5 mg;
- Tanezumab 5 mg;
- Placebo to match tanezumab.

The randomization was stratified by index joint (hip or knee), and most severe Kellgren-Lawrence (KL) grade (of any knee or hip joint) at study entry.

The study was designed with a total (post-Randomization) duration of 48 weeks and consisted of three periods: Screening (up to 37 days), Double-Blind Treatment Period (24 weeks), and Safety Follow-up Period (24 weeks). The Screening Period (beginning up to 37 days prior to Randomization) included a Washout Period (lasting a minimum of two days for all prohibited pain medications), if required, and an Initial Pain Assessment Period (IPAP) (7 days prior to Randomization/Baseline).

All patients signed an informed consent document and were assessed for eligibility prior to randomization. In addition, the Screening Period included the discontinuation and washout of all prohibited pain medications for at least five times the elimination half-life. The IPAP began 7 days prior to the Baseline (Day 1) Randomization Visit, and patients must have completed at least three diary entries during the IPAP; all diary entries were used to determine the Baseline value for the average pain score in the index joint. Patients experiencing pain during the Washout Period could take acetaminophen as needed up to 4000 mg per day, or as permitted by local or national labelling, but must have discontinued rescue medication for at least 24 hours prior to the Baseline (Randomization) Visit.

Prior to the beginning of the IPAP, patients were provided with an electronic diary (eDiary) to record, via Interactive Response Technology (IRT), index joint pain scores and rescue medication use daily from the IPAP to the end of the Treatment Period (Week 24), and then weekly to Week 48, index and non-index joint pain scores from IPAP to Week 48, and non-steroidal anti-inflammatory drug (NSAID) use weekly from Baseline to Week 48.

On Day 1, eligible patients were randomized and received their first dose of blinded study medication (tanezumab 2.5 mg, tanezumab 5 mg, or placebo) via SC injection, the second dose was administered at Week 8 (Day 57±7 days), and the third dose at Week 16 (Day

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113±7 days). Patients had additional in-clinic visits at Week 2 (Day 15±3 days), Week 4 (Day 29±3 days), Week 12 (Day 85±7 days), and Week 24 (Day 169±7 days); they were contacted by phone at Week 20 (Day 141±7 days). Patients could take rescue medication up to five days per week during the Treatment Patients were to discontinue rescue medication within 24 hours of any scheduled visit at which efficacy assessments were collected.

The Week 24 Visit marked both the end of the Treatment Period and the beginning of the 24-Week Safety Follow-up Period. After Week 24, patients could take rescue medication daily but were required to abstain from taking rescue medication within 24 hours prior to the Week 24 Visit. The Safety Follow-up Period included in-clinic visits at Week 32 (Day 225±7 days, when last efficacy assessments were obtained; standard of care treatment could be initiated following this visit), and Week 48 (Day 337±7 days, the End of Study Visit), and four telephone contacts (Week 28 [Day 197±7 days], Week 36 [Day 253±7 days], Week 40 [Day 281±7 days], and Week 44 [Day 309±7 days]) between site staff and enrolled patients. The patients completed the Safety Follow-up and the Study at Week 48.

Patients who left the study prior to completing the Week 24 Visit were not considered to have completed the Double-blind Treatment Period. Patients who discontinued from treatment prior to Week 24, either at their request or at the decision of the Investigator, were required to undergo 24 weeks of follow-up (referred to as Early Termination Follow-up).

The 24-week Early Termination Safety Follow-up was obtained through three clinic visits, beginning eight weeks after the last dose was administered (Early Termination Visit 1). Early Termination Visit 2 occurred 16 weeks after the last dose administered and Early Termination Visit 3 took place 24 weeks after the last dose. Telephone contact was made with the patient approximately 12 and 20 weeks after the last dose of study medication Patients who completed 24 weeks of Early Termination Follow-up were considered to have completed the Safety Follow-up and the Study.

Diagnosis and Main Criteria for Inclusion

- Male or female of any race, ≥18 years of age; willing and able to provide informed consent.

- A diagnosis of OA of the hip or knee in the index joint based on American College of Rheumatology (ACR) criteria with X-ray confirmation (a Kellgren-Lawrence [KL] X-ray grade of ≥2 as diagnosed by the Central Reader).

- Documented history indicating that acetaminophen therapy had not provided sufficient pain relief, that oral NSAID therapy had not provided adequate pain relief, or that the patient was unable to take NSAIDs due to contraindication or inability to tolerate.

- Documented history indicating that tramadol treatment had not provided adequate pain relief or patient was unable to take tramadol due to contraindication or inability

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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.

- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain Subscale numerical rating scale (NRS) ≥5 in the index joint at Screening.

- Patients were willing to discontinue all pain medications for OA except rescue medication (acetaminophen/paracetamol) 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 >39 kg/m^2.

- History of other disease that involved the index joint, including inflammatory joint disease, such as rheumatoid arthritis, seronegative spondyloarthropathy (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 osteoarthritis, 2) Atrophic or Hypotrophic osteoarthritis, 3) Subchondral insufficiency fractures, 4) Spontaneous osteonecrosis of the knee, 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 osteoarthritis. Patients with a present (current) history of sciatica were not eligible for participation. Patients with a past

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history of sciatica who were asymptomatic for at least one year and who had no evidence of radiculopathy or sciatic neuropathy on thorough neurologic examination were eligible for participation.

- Patients with 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 acetaminophen/paracetamol[1] or any of its excipients or existence of a medical condition or use of concomitant medication for which the use of acetaminophen was contraindicated (refer to product labeling).
- Signs and symptoms of clinically significant cardiac disease.
- Diagnosis of a transient ischemic attack in the six months prior to Screening, diagnosis of stroke with residual deficits (eg, aphasia, substantial motor or sensory deficits), that 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 (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 abstained from taking rescue medication (paracetamol) within the 24 hours that preceded dosing.
- WOMAC Pain subscale NRS ≥5 in the index knee or index hip at Baseline.
- WOMAC Physical Function subscale NRS ≥5 in the index knee or index hip at Baseline.

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

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- Patient's Global Assessment of Osteoarthritis (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.

- Radiographic eligibility must have been confirmed by the Central Reader.

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 tanezumab PFS contained a sufficient amount of tanezumab to provide the intended dose.

Each PFS was packed in an individual carton and had a unique container number.

Identity of Investigational Product

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	15-002256	2.5 mg/mL	Prefilled syringe
PF-04383119 solution for injection, 5 mg/mL	L50447	15-002258	5.0 mg/mL	Prefilled syringe
Placebo for PF-04383119 solution for injection	L39168	15-002262	0.0 mg/mL	Prefilled syringe

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 (Day 1 and Weeks 8 and 16).

Primary Efficacy Evaluation

The three co-primary efficacy endpoints were the change from Baseline to Week 24 in the WOMAC Pain Subscale (NRS 0-10, with a lower score indicating less pain), in the WOMAC Physical Function Subscale (NRS 0-10, with a lower score indicating better physical function), and in the PGA-OA (5-point Likert scale from Very Good [1] to Very Poor [5]).

Secondary Efficacy Evaluation

Patients with ≥50% reduction from Baseline in WOMAC Pain at Week 24, change from Baseline to Week 2 in the WOMAC Pain subscale, and change from Baseline to Week 1 in

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average pain score in the index knee or hip were key secondary endpoints. Additional secondary endpoints included the change from Baseline to Weeks 2, 4, 8, 12, 16, and 32 in the WOMAC Pain Subscale, the WOMAC Physical Function Subscale, and the PGA-OA. Time points for the evaluation of other secondary endpoints were Weeks 2, 4, 8, 12, 16, 24, and 32, unless stated otherwise: Outcomes Measures in Arthritis Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) responder index; treatment response defined as a reduction from Baseline in the WOMAC Pain Subscale of ≥30%, ≥50%, ≥70%, or ≥90%; cumulative distribution of percent change in the WOMAC Pain Subscale score to Weeks 16 and 24 (endpoint for summary only); treatment response defined as a reduction from Baseline in the WOMAC Physical Function Subscale of ≥30%, ≥50%, ≥70%, or ≥90%; cumulative distribution of percent change in the WOMAC Physical Function Subscale score to Weeks 16 and 24 (endpoint for summary only); treatment response defined as an improvement of ≥2 points in PGA-OA; WOMAC Stiffness Subscale change from Baseline (0-10 NRS with a lower score indicating less stiffness); WOMAC Average Score (the mean of the three WOMAC subscale scores of Pain, Physical Function and Stiffness) change from Baseline; WOMAC Pain Subscale item: pain when walking on a flat surface, WOMAC Pain Subscale item: pain when going up or down stairs; and incidence and time to discontinuation due to lack of efficacy; average pain score in the index joint change from Baseline (Weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 28, and 32).

Secondary patient-reported outcome endpoints included Work Productivity and Activity Impairment Questionnaire for Osteoarthritis (WPAI:OA) impairment scores change from Baseline to Weeks 8, 16, and 24; EuroQol-5 Dimension-5 Level™ dimensions and overall health utility score at Baseline, Weeks 8, 16, and 24; Patient Reported Treatment Impact Assessment-Modified (mPRTI) at Weeks 16 and 24; and Health Care Resource Utilization at Baseline, and Weeks 32 and 48.

Rescue medication was measured by the incidence and number of days of patients using rescue medication (Weeks 2, 4, 8, 12, 16, 24, and 32) and the amount (mg) of rescue medication taken (Weeks 2, 4, 8, 12, 16, and 24) during the study.

Pharmacokinetic and Pharmacodynamic Evaluations

Pharmacokinetic Evaluations

Tanezumab concentrations were measured to support the development of an updated SC population pharmacokinetic (PK) model to allow the prediction of the tanezumab concentration over time in individuals. In addition, tanezumab concentrations were measured to inform the immunogenicity profile of tanezumab.

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Pharmacokinetic Sampling

Blood samples for the assessment of the PK of tanezumab were collected pre-dose at Baseline (Day 1, predose), Weeks 8 (predose), 16 (predose), 24, 32 and 48, or at Early Termination Visits 1 and 2.

Pharmacodynamic Evaluations

Blood samples were collected for the assessment of biomarkers, soluble p75, total NGF, and proNGF. In addition, urine samples were collected for the assessment of biomarkers.

Pharmacodynamic Sampling

Blood and urine samples for the assessment of biomarkers were collected at Baseline (Day 1; predose) and Week 8 (predose). Blood samples for the assessment of soluble p75 concentrations were collected at Baseline (Day 1; predose) and Week 8 (predose), Week 24, and Week 32, or at Early Termination. Blood samples for the assessment of NGF (total NGF and proNGF) were collected at Baseline (Day 1; predose) and Week 8 (predose), Week 24, Week 32, and Week 48, or at Early Termination.

SAFETY EVALUATIONS

Safety was evaluated in all patients who received at least one dose of investigational product, through the patient's last visit. Tanezumab safety was reviewed at two levels; blinded data reviews by the Sponsor and unblinded reviews by the External Safety Monitoring Committee (E-SMC). The E-SMC reviewed unblinded safety data including adverse events, serious adverse events (SAEs), joint safety adjudication outcomes, total joint replacements (TJRs), neurologic examination, vital signs data, and clinical laboratory data on a regular basis throughout the course of this study.

Safety Assessments

Except for adverse events which were collected at any time, all assessments were collected prior to dosing at dosing visits.

Adverse events, including serious adverse events and deaths, were collected throughout the study. A general physical examination was performed at Screening and at Week 24 or at Early Termination. Blood and urine samples for clinical laboratory testing were collected at Screening, Baseline, Week 16, and Week 32, or at Early Termination Visit 2. For women of child-bearing potential, serum pregnancy tests were conducted at Screening, Week 24 and Week 32, or at Early Termination Visits 1 and 2. Urine pregnancy tests were conducted prior to dosing at the Day 1 and Week 8 and Week 16 visits, prior to dosing. Sitting vital signs were obtained at all study visits; at each visit, vital signs were collected after the patient had been in a sitting position for at least five minutes.

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Neurological

Supine/Standing blood pressure (BP) measurements were done at all study visits to assess the patient for possible Orthostatic hypotension. An adverse event of Orthostatic hypotension was reported for all patients meeting criteria for Orthostatic hypotension at a visit. If the patient was symptomatic but with no apparent medical cause, a neurological consult was obtained. If the patient was asymptomatic or there was an apparent cause that could be addressed (eg, dehydration), a repeat assessment was done one to four weeks later. If Orthostatic hypotension was still present at time of the repeat assessment, a consult was obtained. Dosing could not resume until presence of sympathetic autonomic neuropathy was ruled out by the consulting cardiologist or neurologist.

Twelve-lead ECGs were performed at Screening, Week 24, and Week 48, or at Early Termination. An adverse event was reported for patients meeting protocol-defined criteria for bradycardia on a post-Baseline ECG (heart rate of ≤45 beats per minute [BPM]), or heart rate decrease from Screening of ≥25% with resulting heart rate <60 BPM, and patients were referred for consult with a cardiologist or neurologist to evaluate the patients for the possible presence of sympathetic autonomic neuropathy.

Consults were also obtained to rule out sympathetic autonomic neuropathy for patients with adverse event reports of Syncope, Anhidrosis, or Hypohydrosis.

Neurological examinations were performed at all study visits and the investigator completed the Neuropathy Impairment Score (NIS) at these time points based on the neurological examination. Neurologic examination assessed strength of groups of muscles of the head and neck, upper limbs and lower limbs, deep tendon reflexes, and sensation (tactile, vibration, joint position sense, and pinprick) of index fingers and great toes to complete the NIS. The neurological examinations were performed in a controlled and consistent manner by the same trained examiner when possible. The examiner was an MD or DO. The Survey of Autonomic Symptoms (SAS) was completed by the patient at Screening, Week 24, and at Week 48, or at Early Termination.

A neurological consultation was obtained if an adverse event suggestive of new or worsening peripheral neuropathy or an adverse event of abnormal peripheral sensation (eg, Allodynia, Burning sensation, Carpal tunnel syndrome, Dysesthesia, Hyperesthesia, Hyperpathia, Hypoesthesia, Neuralgia, Neuritis, Neuropathy peripheral, Pallanesthesia, Paresthesia, Peripheral sensory neuropathy, Sensory disturbance, Sensory loss, Sciatica, Tarsal tunnel syndrome) was reported as an SAE, resulted in the patient being withdrawn from the study, was ongoing at the end of the patient's participation in the study, or was of severe intensity. Consults were also obtained if new or worsened clinically significant abnormalities on the neurologic exam were reported as adverse events met criteria listed above, or if a reported non-neuropathic neurological event (eg, stroke, seizure) was considered medically important by the investigator.

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Musculoskeletal and Joint-Related

The investigator conducted a thorough musculoskeletal physical examination of all major joints at all study visits (Screening, Baseline [Day 1] and at Weeks 2, 4, 8, 12, 16, 24, 32, and 48; or at Early Termination if the patient discontinued early). The musculoskeletal physical exam evaluated the joints for swelling, redness, tenderness, deformity, osteophytes or nodes, crepitus and pain on motion, and was documented on the case report form. The investigator collected patient-reported information on any current joint symptoms including pain, stiffness, and swelling. Any clinically significant change in symptoms or the examination was reported as an adverse event.

X-rays of shoulders, hips and knees (and other major joints considered at risk) were collected at Screening, Week 24, and Week 48, or if patient discontinued, at Early Termination Visit 1 and Early Termination Visit 3. Screening X-rays were reviewed by a Central Reader for determination of eligibility. After randomization, the Central Reader reviewed radiology images for diagnosis of joint conditions that would warrant further evaluation by the Adjudication Committee. For patients who were identified with a possible or probable joint event (ie, Rapidly progressive OA, Subchondral insufficiency fractures, Primary osteonecrosis, or Pathological fracture) and patients undergoing TJR for any reason, all images and other source documentation were provided to the blinded Tanezumab Adjudication Committee for review and adjudication of the event. The Adjudication Committee's assessment of the event represented the final classification of the event.

Immunogenicity

Blood samples for the assessment of anti-drug antibodies (ADA [anti-tanezumab antibodies]) were collected at Baseline (Day 1; pre-dose) and Weeks 8 (predose), 16 (predose), 24, 32, and 48, or at Early Termination.

Adverse Event Reporting

For SAEs, the active reporting period to the Sponsor or its designated representative began from the time that the patient provided informed consent, which was obtained prior to the patient's participation in the study (ie, prior to undergoing any study-related procedure and/or receiving study medication) through the end of the Safety Follow-up Period or through and including 112 calendar days after the patient's last administration of the SC study medication, if the patient refused the protocol-defined Follow-up Period.

Statistical Methods

A sample size of 270 patients per treatment group was needed to provide approximately 80% power to achieve statistical significance (at the 5% two-sided level) for the two comparisons of tanezumab 2.5 and tanezumab 5 mg SC versus placebo, over all three co-primary endpoints. The total sample size was planned to be approximately 810 patients.

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Analysis of the Co-Primary Endpoints

The primary efficacy population was the Intent-to-Treat (ITT) population, defined as all randomized patients who received SC study medication (either tanezumab or placebo). The primary analysis used multiple imputation methods for missing data at Week 24. Details of the multiple imputation procedure are given below. 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 model terms for Baseline score, Baseline diary average pain, index joint (knee or hip), highest KL grade, treatment group, and study site as a random effect. The assessment of significance for the tanezumab SC versus placebo treatment contrasts used a step-down testing strategy within each of the co-primary efficacy endpoints defined as first testing tanezumab 5 mg versus placebo, and if significant ($p \leq 0.05$), then testing tanezumab 2.5 mg versus placebo. Finally, a tanezumab treatment group was declared as superior to placebo if the corresponding treatment contrast was significant over all three co-primary endpoints. This testing procedure maintained the Type I error to ≤5% within each of the co-primary efficacy endpoints, and to <5% for all three co-primary efficacy endpoints.

Analysis of Secondary Endpoints

The secondary endpoints of patients with ≥50% reduction from Baseline in WOMAC Pain at Week 24, change from Baseline to Week 2 in the WOMAC Pain Subscale, and average pain score in the index knee or hip change from Baseline to Week 1 were identified as key secondary endpoints.

All endpoints up to Week 32 were summarized (where available) and endpoints up to Week 24 were analyzed. Efficacy data at Week 32 was planned to be off-treatment; all available data in the Week 32 window was used in summaries.

The analysis of secondary endpoints used the same ANCOVA analysis described for the co-primary endpoints, with multiple imputation for missing data.

Patient response endpoints were analyzed using logistic regression for binary data, with model terms for Baseline scores, Baseline diary average pain, index joint, KL grade, and treatment group. Imputation for missing data used both last observation carried forward (LOCF) and Baseline observation carried forward (BOCF), where imputation with BOCF led to the patient being assessed as a non-responder for the response endpoint at a particular time point. In addition, to closely match the primary imputation analysis, a mixed BOCF/LOCF imputation for response endpoints was used. In this analysis, BOCF imputation (ie, a patient was a non-responder) was used for missing data due to discontinuation for reasons of lack of efficacy, adverse event, or death up to the time point of interest, and LOCF imputation was used for missing data for any other reason.

Analysis of Pharmacokinetic Data

The following reporting of PK data was done:

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- A listing of all plasma tanezumab concentrations sorted by patient, active treatment group and nominal time post-dose. The listing of concentrations also includes the actual times post dose.

- A descriptive summary of the plasma tanezumab concentrations based on nominal time post-dose for each treatment group.

- Creation of boxplots of tanezumab plasma trough concentrations at the nominal times for the tanezumab treatment groups.

Samples were analyzed using a validated analytical method in compliance with Sponsor standard operating procedures.

RESULTS

Subject Disposition and Demography

A total of 2145 patients were screened for the study, of which 1248 failed Screening, and 48 were screened but not randomized; these patients were not randomized primarily because enrollment for the study had closed. Eight hundred and forty-nine (849) patients were enrolled into the study and randomized, 282 in the placebo treatment group, 283 in the tanezumab 2.5 mg treatment group and 284 in the tanezumab 5 mg treatment group (Table S2). All randomized patients received at least one dose of study medication. By definition, these 849 patients comprise the ITT population; in this study, the Safety Population is the same as the ITT population because there were no patients taking study medication other than as randomized.

A total of 750 (88.3%) patients completed the Treatment Period of the study: 257 (90.8%) patients in the tanezumab 2.5 mg treatment group, 255 (89.8%) patients in the tanezumab 5 mg treatment group and 238 (84.4%) patients in the placebo treatment group, and 726 (85.5%) patients completed the study per protocol, 249 (88.0%) patients in the tanezumab 2.5 mg treatment group, 239 (84.2%) patients in the tanezumab 5 mg treatment group and 238 (84.4%) patients in the placebo treatment group.

Table S2. Subject Evaluation Groups

	Placebo (N=282)	Tanezumab 2.5 mg (N=283)	Tanezumab 5 mg (N=284)	Total (N=849)
	n (%)	n (%)	n (%)	n (%)
Screened: 2145 Screen Failure: 1248 Other screened but not randomized: 48				
Randomized	282 (100.0)	283 (100.0)	284 (100.0)	849 (100.0)

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Table S2. Subject Evaluation Groups

	Placebo (N=282) n (%)	Tanezumab 2.5 mg (N=283) n (%)	Tanezumab 5 mg (N=284) n (%)	Total (N=849) n (%)
Treated	282 (100.0)	283 (100.0)	284 (100.0)	849 (100.0)
Not treated	0	0	0	0
Safety population	282 (100.0)	283 (100.0)	284 (100.0)	849 (100.0)
ITT population	282 (100.0)	283 (100.0)	284 (100.0)	849 (100.0)
Per-Protocol population	200 (70.9)	209 (73.9)	210 (73.9)	619 (72.9)
Number of subjects[1]				
Completed Treatment Phase	238 (84.4)	257 (90.8)	255 (89.8)	750 (88.3)
Completed Safety Follow-up	222 (78.7)	243 (85.9)	231 (81.3)	696 (82.0)
Discontinued Safety Follow-up	15 (5.3)	14 (4.9)	22 (7.7)	51 (6.0)
Did not enter Safety Follow-up	1 (0.4)	0	2 (0.7)	3 (0.4)
Discontinued Treatment Phase	44 (15.6)	26 (9.2)	29 (10.2)	99 (11.7)
Completed Safety Follow-up	16 (5.7)	6 (2.1)	8 (2.8)	30 (3.5)
Discontinued Safety Follow-up	12 (4.3)	5 (1.8)	5 (1.8)	22 (2.6)
Did not enter Safety Follow-up	16 (5.7)	15 (5.3)	16 (5.6)	47 (5.5)
Completed study	238 (84.4)	249 (88.0)	239 (84.2)	726 (85.5)
Discontinued study	44 (15.6)	34 (12.0)	45 (15.8)	123 (14.5)
Rollover to Study A4091064	17 (6.0)	17 (6.0)	14 (4.9)	48 (5.7)

N is Number of Subjects Randomized. Percentages were based on the number of subjects Randomized.
[1]Subjects in Safety Population. Percentages were based on the number of subjects in Safety Population.
Treatment Period was planned for 24 weeks and Safety Follow-Up period was planned for 24 weeks.
Safety population consisted of all subjects treated with SC study medication. ITT population consisted of all randomized subjects who received at least one dose.
'Other Screened but not Randomized displays subjects who were screened but not randomized for a reason not related to a specific eligibility criterion.
PFIZER CONFIDENTIAL SDTM Creation: 26DEC2018 (05:14) Source Data: Listing 16.2.1.1 Output File: ./nda1/A4091057/adsl_s002i Date of Generation: 22JAN2019 (20:27)
Table 14.1.1.1.i is for Pfizer internal use.

The most frequent reasons for discontinuation from the Treatment Period across treatment groups were “Withdrawal by subject”, followed by “Insufficient clinical response” and “Adverse event”. The incidence of patients discontinuing from treatment due to insufficient clinical response was lower in tanezumab-treated patients compared to those receiving placebo: placebo (18 [6.4%]), tanezumab 2.5 mg (2 [0.7%]), and tanezumab 5 mg (3 [1.1%]). A similar trend for discontinuation due to Insufficient clinical response was observed in discontinuations from the Study overall: 3 (1.1%) in both tanezumab treatment groups and

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7 (2.5%) in the placebo treatment group; in the Safety Follow-up period, "Insufficient clinical response" applied to the response to any analgesic being taken for OA pain. Few patients discontinued from treatment or study due to adverse events and no dose-response was observed.

Forty-eight (48 [5.7%]) patients, 17 (6.0%) in the placebo, 17 (6.0%) in the tanezumab 2.5 mg, and 14 (4.9%) in the tanezumab 5 mg treatment groups who had joint replacements during the course of the study planned to roll over into Study A4091064 (Table S2) at time of discontinuation from Study A4091057.

Across the 3 treatment groups, the mean age of patients was 64.2 to 65.2 years (range 26 to 89 years); 68.0% to 70.0% of the patients were female; and 86.6% to 87.6% were white (3.5% to 6.7% Hispanic or Latino). The tanezumab 5 mg treatment group had fewer patients in the 45-64 age range (103 [36.3%]) versus the tanezumab 2.5 mg (136 [48.1%]) treatment group and placebo (132 [46.8%]) treatment group, and a higher proportion of patients over 65: tanezumab 5 mg treatment group (169 [59.5%]), tanezumab 2.5 mg treatment group (145 [51.2%]), placebo treatment group (144 [51.1%]). Patients 75 years or older represented 12.7%-16.5% of the study population across treatment groups.

Insufficient pain relief to paracetamol was an entry requirement for the study and was reported by 100% of patients. Inadequate pain relief was the primary reason for treatment failure with paracetamol, NSAIDs, opioids, and tramadol. Approximately 16% of patients across treatment groups were unwilling to take opioids.

The mean time from the first diagnosis of OA was similar across treatment groups, ranging from 6.7 years for patients in the tanezumab 2.5 mg treatment group to 8.2 years in the placebo treatment group. The mean time from the index joint OA diagnosis ranged from 6.0 years for patients in the tanezumab 2.5 mg treatment group to 7.4 years in the placebo treatment group.

The majority of patients (82.7%-83.3% across treatment groups) had the knee as the index joint. The overall radiographic severity of OA was similar across treatment groups, with similar proportions of patients reporting KL grades of 2, 3, or 4 for the index joint; KL grade 3 was reported most frequently for the index joint (42.6%-46.3% across treatment groups). The percentage of patients with a KL grade of 4 for the index joint was 35.5%-37.0% across treatment groups; KL grade 4 was reported by 19.1-27.1% of patients with the hip and 38.5%-39.0% of patients with the knee as the index joint. A majority of patients (56.7%-59.0% across treatment groups) reported two joints with KL grade $\geq$2.

The mean WOMAC Pain scores at Screening and Baseline were consistent across treatment groups, ranging from 6.49 to 6.54 at Screening and from 6.59 to 6.70 at Baseline. The mean WOMAC Physical Function score at Baseline ranged from 6.67 to 6.77 across treatment groups. All patients had a PGA-OA at Baseline of Fair, Poor, or Very poor, with the majority of patients (46.8% to 51.6%) reporting PGA-OA scores of Fair at Baseline. The

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percentage of patients who reported a PGA-OA of Very poor ranged from 6.0% in the tanezumab 5 mg treatment group to 7.4% in the tanezumab 2.5 mg treatment group.

Efficacy Results

The primary objective of the study was met for the 5 mg dose of tanezumab, but not for the 2.5 mg dose, applying the gate-keeping strategy.

For patients in the tanezumab 5 mg treatment group, significant[2] changes from Baseline were observed for all three co-primary endpoints (WOMAC Pain and Physical Function Subscales and PGA-OA) at Week 24 compared to those in the placebo treatment group. For patients in the tanezumab 2.5 mg treatment group, significant changes from Baseline were observed for two of three co-primary endpoints (WOMAC Pain and Physical Function Subscales) at Week 24, compared to those in the placebo treatment group. However, the changes in the PGA-OA were not significant, and no further testing was performed.

> Outside of the framework of the gate-keeping strategy, focusing on nominal (unadjusted) p-values, the tanezumab 5 mg treatment group showed improvement from Baseline in each co-primary efficacy endpoint (WOMAC Pain and Physical Function Subscales and PGA-OA) compared to the placebo treatment group from the first measurement obtained at Week 2 through Week 16 (unadjusted p-values ≤ 0.05), and including Week 24. Compared to the placebo treatment group, the tanezumab 2.5 mg treatment group showed improvement from Baseline in the WOMAC Pain and Physical Function Subscales from the first measurement obtained at Week 2 through Week 16 (unadjusted p-values ≤ 0.05) and including Week 24. Improvement from Baseline in the PGA-OA was also observed at Weeks 2 through 16.

The results for all key secondary efficacy endpoints (Patients with 50% reduction from Baseline in WOMAC Pain at Week 24; Change from Baseline to Week 2 in the WOMAC Pain Subscale; Change from Baseline to Week 1 in the average pain in the index joint) were deemed not significant due to the testing strategy, although both the tanezumab 5 mg treatment group and the tanezumab 2.5 mg treatment group had favorable observed percentages of patients compared to placebo for all key secondary efficacy endpoints (unadjusted p-values ≤ 0.05).

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

Table S3 summarizes the change from Baseline to Week 24 in the three co-primary endpoints. For the WOMAC Pain Subscale and the WOMAC Physical Function Subscale, the step-down testing procedure showed significant improvement in efficacy for treatment

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

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with tanezumab 5 mg and tanezumab 2.5 mg versus placebo at Week 24. In the PGA-OA, the tanezumab 5 mg treatment group was superior to placebo treatment ($p \leq 0.05$) but the tanezumab 2.5 mg treatment group was not ($p=0.1092$).

Table S3. Summary of Co-Primary Efficacy Endpoints - Analysis of Change from Baseline to Week 24 (ITT, Multiple Imputation)

		Placebo (N=282)	Tanezumab 2.5 mg (N=283)	Tanezumab 5 mg (N=284)
WOMAC Pain Subscale	LS Mean (SE)	-2.24 (0.17)	-2.70 (0.17)	-2.85 (0.17)
	95% CI for LS Mean	(-2.58,-1.90)	(-3.03,-2.37)	(-3.19,-2.52)
	Versus Placebo			
	LS Mean Difference (SE)		-0.46 (0.18)	-0.62 (0.18)
	95% CI for LS Mean Difference		(-0.81,-0.12)	(-0.97,-0.26)
	p-value		0.0088	0.0006
WOMAC Physical Function Subscale	LS Mean (SE)	-2.11 (0.17)	-2.70 (0.17)	-2.82 (0.17)
	95% CI for LS Mean	(-2.45,-1.77)	(-3.03,-2.37)	(-3.15,-2.49)
	Versus Placebo			
	LS Mean Difference (SE)		-0.59 (0.18)	-0.71 (0.17)
	95% CI for LS Mean Difference		(-0.93,-0.24)	(-1.05,-0.36)
	p-value		0.0008	<.0001
Patient Global Assessment of Osteoarthritis	LS Mean (SE)	-0.72 (0.06)	-0.82 (0.06)	-0.90 (0.06)
	95% CI for LS Mean	(-0.84,-0.59)	(-0.94,-0.70)	(-1.02,-0.78)
	Versus Placebo			
	LS Mean Difference (SE)		-0.11 (0.07)	-0.19 (0.07)
	95% CI for LS Mean Difference		(-0.24,0.02)	(-0.32,-0.06)
	p-value		0.1092	0.0051

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 and highest Kellgren-Lawrence grade) as fixed effects, Baseline Patient Global Assessment of Osteoarthritis 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: 02JAN2019 (14:20) Source Data: Listing 16.2.6.1 Output File: ./nda1/A4091057/adwn_sg_infr_chg_ancova_mi Date of Generation: 06JUN2019 (10:41)
Table 14.2.1.3.1.i is for Pfizer internal use.

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Secondary Efficacy Analysis

Key Secondary Efficacy Endpoints

Patients with ≥50% reduction from Baseline in WOMAC Pain at Week 24: Both tanezumab treatment groups had higher percentages of ≥50% responders at Week 24 than the placebo treatment group: placebo treatment group, 95 (33.8%); tanezumab 2.5 mg treatment group, 128 (45.4%), (unadjusted p=0.0022 versus placebo); tanezumab 5 mg treatment group 136 (47.9%), (unadjusted p=0.0004 versus placebo).

Change from Baseline to Week 2 in the WOMAC Pain Subscale: At Week 2, the change from Baseline for both tanezumab treatment groups compared to the placebo treatment group was favorable: tanezumab 2.5 mg treatment group (unadjusted p<0.0001), tanezumab 5 mg treatment group (unadjusted p=0.0149).

Change from Baseline to Week 1 in the Average Pain in the Index Joint: At Week 1, the change from Baseline for both tanezumab treatment groups compared to the placebo treatment group was favorable: tanezumab 2.5 mg treatment group (unadjusted p<0.0001), tanezumab 5 mg treatment group (unadjusted p=0.0009).

- There was a consistent pattern of increased efficacy on the change from Baseline in the **WOMAC Pain Subscale** for patients in both tanezumab treatment groups compared to those in the placebo treatment group starting at Week 2. The improvement in patients in each of the tanezumab treatment groups versus placebo was similar in magnitude between the tanezumab treatment groups and remained significant through Week 24.

- There was a consistent pattern of increased efficacy on the change from Baseline in the **WOMAC Physical Function Subscale** for patients in the tanezumab treatment groups compared to those in the placebo treatment group starting at Week 2. Comparisons to placebo were significant at all time points analyzed. The improvement in patients in each of the tanezumab treatment groups versus placebo was similar in magnitude between the tanezumab treatment groups and remained significant through Week 24.

- The change from Baseline on the **PGA-OA** was significantly different from placebo starting at Week 2, through Week 16 for patients in the tanezumab 2.5 mg treatment group, and through Week 24 for patients in the tanezumab 5 mg treatment group.

- The proportion of responders on the **OMERACT-OARSI** responder index was significantly greater for patients in both tanezumab treatment groups compared to the placebo treatment group at all weeks reported.

- **Reduction in the WOMAC Pain Subscale of ≥30%, ≥50%, ≥70%, and ≥90%:** A significantly greater proportion of patients in the tanezumab 2.5 mg treatment group than in the placebo treatment group responded at the 30% level and 50% level at all weeks from Week 2 through Week 24. A significantly greater proportion of patients in the tanezumab 5 mg treatment group than in the placebo treatment group responded at the

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30% from Week 2 to Week 24, at the 50% level at all weeks from Week 4 to 24, at the 70% and 90% levels at all weeks from Week 4 through Week 12, and at the 70% level at Week 16.

- **Reduction in the WOMAC Physical Function Subscale of ≥30%, ≥50%, ≥70%, and ≥90%:** A significantly greater proportion of patients in the tanezumab 2.5 mg treatment group than in the placebo treatment group responded at the 30% level at all weeks from Week 2 through Week 24, at the 50% level from Weeks 4 through 24, at the 70% level from Weeks 2 through 16, and at the 90% level from Weeks 8 through 24. A significantly greater proportion of patients in the tanezumab 5 mg treatment group than in the placebo treatment group responded at the 30% level at all weeks from Week 2 through Week 24, at the 50% level from Weeks 4 through 24, at the 70% level from Weeks 4 through 12, and at the 90% level from Weeks 4 through 24.

- A significantly greater proportion of patients in the tanezumab 2.5 mg treatment group showed a **≥2-point reduction in the PGA-OA** at Week 2 through Week 16 compared to patients in the placebo treatment group; for patients in the tanezumab 5 mg treatment group, the difference from patients in the placebo treatment group was significant at Week 4 through Week 24.

- Patients in the tanezumab treatment groups showed a statistically significant decrease in **pain in the index** joint, based on patient-reported eDiary data, starting one week after the first dose of study drug (starting on Day 2 for patients in the tanezumab 2.5 mg treatment group and on Day 4 in the tanezumab 5 mg treatment group) that was maintained through to Week 20 in the tanezumab 2.5 mg treatment group and through Week 24 in the tanezumab 5 mg treatment group.

- Starting at Week 2 and continuing through the Week 24 Visit, patients in the tanezumab treatment groups showed a significant improvement compared to placebo-treated patients in the **WOMAC Stiffness Subscale, WOMAC Average Score, WOMAC Pain Subscale Items: Pain when walking on a flat surface,** and **Pain when going up or down stairs**.

- In the components of the **WPAI:OA**, patients in the tanezumab 2.5 mg treatment group showed significant improvement over placebo-treated patients in reported percent impairment while working and overall work impairment at Week 16, and in percent activity impairment at Weeks 8 and 16. Patients in the tanezumab 5 mg treatment group showed significant improvement over placebo-treated patients in reported percent impairment while working and in reported percent overall work impairment at Weeks 8 and 16, and in reported percent activity impairment at Weeks 8, 16, and 24.

- For each of the dimensions of the **EuroQol-5 Dimension-5 Level** analyzed (Mobility, Self-care, Usual activities, Pain/Discomfort, Anxiety/Depression), as well as the Index

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Value, the mean values reported for patients in the placebo, tanezumab 2.5, and tanezumab 5 mg treatment groups were the same or similar at all time points evaluated.

- In the **mPTRI** assessment, patients in both tanezumab treatment groups reported significantly more frequently than those in the placebo treatment group that they were satisfied with the drug that they received in the study, that they preferred the drug that they received in the study to previous treatment, and that they would be willing to use the same drug that they received in the study for their OA pain.

- In general, the **Health Care Resource Utilization** was relatively low and the proportion of patients who visited a health care provider within the three months that preceded the Baseline Visit was higher than in the three months that preceded the Week 48 visit, ie, during the Safety Follow-up. Across treatment groups, primary care physician visits were the most frequently used resource within the three months that preceded the Baseline Visit (39-41% of patients). Rheumatologists (29-35% of patients), orthopedists (29-30% of patients), radiologists (12-16%), physical therapists (7-11%), pain specialists (4-8%) and other practitioners (5-7%) were other healthcare providers commonly consulted during that period.

- A small percentage of patients in any group **discontinued treatment due to lack of efficacy** (placebo, 18 [6.4%]; tanezumab 2.5 mg, 2 [<1.0%]; tanezumab 5 mg, 3 [1.1%]). Placebo-treated patients discontinued treatment sooner due to lack of efficacy than tanezumab-treated patients. There was a significant difference in the number of patients that discontinued and the time to discontinuation between the tanezumab treatment groups and the placebo treatment group.

- Overall up to Week 24, the **incidence of rescue medication** use by week was slightly larger in the placebo treatment group than the 2 active treatment groups (placebo [86.2%], tanezumab 2.5 mg [80.6%], tanezumab 5 mg [83.1%]); the frequency of use reported in tanezumab-treated patients was consistently lower than that reported by placebo-treated patients from Week 1 to Week 23. Significant differences from patients in the placebo treatment group were seen in patients in the tanezumab 2.5 mg treatment group at Weeks 2 to 16, and in the tanezumab 5 mg treatment group at Weeks 2, 4, 12, and 16.

- Only at Week 2 in the tanezumab 2.5 mg treatment group was the **amount of rescue medication** used by patients in either tanezumab treatment group significantly less than that used by those in the placebo treatment group. At all other weeks the differences between tanezumab and placebo-treated patients in the amount of rescues medication used per week failed to reach significance.

Pharmacokinetic Results

At Weeks 8, 16, and 24, the mean tanezumab plasma concentrations were higher in the tanezumab 5 mg treatment group than the tanezumab 2.5 mg treatment group by a proportion

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similar to the larger dose. By Week 32, 16 weeks after the third dose of study medication, the mean tanezumab plasma concentrations were low, consistent with complete elimination of tanezumab from the body over five half-lives post-injection and were similar for the two treatment groups.

Pharmacodynamic Results

Mean total NGF concentrations were comparable at Baseline across treatment groups. From Weeks 8 through 24, mean 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 32, mean total NGF concentrations began to decline in both the tanezumab 2.5 mg and tanezumab 5 mg treatment groups and were approaching the Baseline values by Week 48. Mean proNGF was comparable across treatment groups at all nominal sampling times. Mean and median soluble p75 serum trough concentrations were comparable at all time points for all treatment groups.

Safety Results

The incidence of adverse events during the Treatment Period and Safety Follow-up are summarized in Table S4 and Table S5, respectively. The incidence of adverse events in the Treatment Period and the Safety Follow-up do not add up to the total incidence to End of Study, as some patients had events that occurred in both time periods.

The overall incidence of adverse events was similar across treatment groups both during the Treatment Period (55.0%, 53.0%, and 57.0% of patients in the placebo, tanezumab 2.5 mg, and tanezumab 5 mg treatment groups, respectively); during the Safety Follow-up fewer patients in the placebo treatment group (35.1%) reported adverse events than those in the tanezumab 2.5 mg (44.4%), and tanezumab 5 mg treatment groups (43.6%).

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

Number (%) of subjects	Placebo n (%)	Tanezumab 2.5 mg n (%)	Tanezumab 5 mg n (%)
Subjects evaluable for adverse events	282	283	284
Number of adverse events	349	354	424
Subjects with adverse events	155 (55.0)	150 (53.0)	162 (57.0)
Subjects with medication error events	0	0	0
Subjects with serious adverse events	3 (1.1)	8 (2.8)	9 (3.2)
Subjects with severe adverse events	4 (1.4)	9 (3.2)	11 (3.9)
Subjects discontinued from study due to adverse events (a)	2 (0.7)	5 (1.8)	1 (0.4)
Subjects discontinued study drug due to AE and continued Study (b)	7 (2.5)	3 (1.1)	4 (1.4)

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

Number (%) of subjects	Placebo n (%)	Tanezumab 2.5 mg n (%)	Tanezumab 5 mg n (%)
Subjects with dose reduced or temporary discontinuation due to adverse events	0	0	0

Includes treatment-emergent events that began up to the Week 24 (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 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: 02JAN2019 (05:35) Source Data: Listing 16.2.7.1 Output File: ./nda1/A4091057/adae_s020_i Date of Generation: 22JAN2019 (20:51)
Table 14.3.1.2.1.1.i is for Pfizer internal use.

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

Number (%) of Subjects	Placebo n (%)	Tanezumab 2.5 mg n (%)	Tanezumab 5 mg n (%)
Subjects evaluable for adverse events	265	268	266
Number of adverse events	197	243	213
Subjects with adverse events	93 (35.1)	119 (44.4)	116 (43.6)
Subjects with medication error events	0	0	0
Subjects with serious adverse events	8 (3.0)	16 (6.0)	16 (6.0)
Subjects with severe adverse events	6 (2.3)	11 (4.1)	14 (5.3)
Subjects discontinued from study due to adverse events (a)	0	1 (0.4)	1 (0.4)
Subjects discontinued study drug due to AE and continued Study (b)	1 (0.4)	0	0
Subjects with dose reduced or temporary discontinuation due to adverse events	0	0	0

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

Number (%) of Subjects	Placebo n (%)	Tanezumab 2.5 mg n (%)	Tanezumab 5 mg n (%)

Includes treatment-emergent events that began after the Week 24 (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: 02JAN2019 (05:35) Source Data: Listing 16.2.7.1 Output File: ./nda1/A4091057/adae_s020_fup_i Date of Generation: 25JAN2019 (14:21)
Table 14.3.1.2.1.2.i is for Pfizer internal use.

Arthralgia was the most frequently observed adverse event during the Treatment Period with a reported frequency of 8.1% (tanezumab 5 mg treatment group) to 12.1% (placebo treatment group) (Table S6). Other adverse events reported in ≥2% of subjects in any treatment group included Nasopharyngitis (placebo [8.9%], tanezumab 2.5 mg [11.0%], tanezumab 5 mg [7.7%]) and Back pain (placebo [5.3%], tanezumab 2.5 mg [5.7%], tanezumab 5 mg [6.0%]), the frequency of which was comparable across treatment groups.

Although the number of reported events was small, the adverse events for which a dose-related increase in frequency was observed were OA, Joint swelling, and Hypoesthesia. Dizziness was observed more frequently in the tanezumab treatment groups than in the placebo treatment group; however, there was no dose-dependence.

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	Placebo (N=282)	Tanezumab 2.5 mg (N=283)	Tanezumab 5 mg (N=284)
Number (%) of subjects: by SYSTEM ORGAN CLASS and by Preferred Term	**n (%)**	**n (%)**	**n (%)**
With any adverse event	155 (55.0)	150 (53.0)	162 (57.0)
INFECTIONS AND INFESTATIONS	53 (18.8)	58 (20.5)	57 (20.1)

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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	Placebo (N=282)	Tanezumab 2.5 mg (N=283)	Tanezumab 5 mg (N=284)
Number (%) of subjects: by SYSTEM ORGAN CLASS and by Preferred Term	**n (%)**	**n (%)**	**n (%)**
Influenza	5 (1.8)	5 (1.8)	9 (3.2)
Nasopharyngitis	25 (8.9)	31 (11.0)	22 (7.7)
Upper respiratory tract infection	3 (1.1)	5 (1.8)	6 (2.1)
Urinary tract infection	4 (1.4)	6 (2.1)	2 (0.7)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	21 (7.4)	17 (6.0)	19 (6.7)
Fall	8 (2.8)	12 (4.2)	7 (2.5)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	67 (23.8)	69 (24.4)	74 (26.1)
Arthralgia	34 (12.1)	27 (9.5)	23 (8.1)
Back pain	15 (5.3)	16 (5.7)	17 (6.0)
Joint swelling	3 (1.1)	6 (2.1)	8 (2.8)
Musculoskeletal pain	7 (2.5)	6 (2.1)	7 (2.5)
Osteoarthritis	5 (1.8)	9 (3.2)	13 (4.6)
Pain in extremity	7 (2.5)	9 (3.2)	5 (1.8)
NERVOUS SYSTEM DISORDERS	28 (9.9)	37 (13.1)	35 (12.3)
Dizziness	2 (0.7)	7 (2.5)	6 (2.1)
Headache	18 (6.4)	15 (5.3)	14 (4.9)
Hypoaesthesia	2 (0.7)	4 (1.4)	6 (2.1)
Paraesthesia	5 (1.8)	5 (1.8)	12 (4.2)
VASCULAR DISORDERS	9 (3.2)	5 (1.8)	21 (7.4)
Hypertension	6 (2.1)	2 (0.7)	6 (2.1)

Subjects were only counted once per treatment per event.
Adverse events are shown by descending frequency by the highest tanezumab dose.
Includes treatment-emergent events that began up to the Week 24 (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.
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Table 14.3.1.2.2.1.i is for Pfizer internal use.

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- **Treatment-Related Adverse Events**: During the Treatment Period, 130 patients experienced 201 adverse events considered by the Investigator to be treatment-related. More treatment-related adverse events were reported in the tanezumab 5 mg treatment group (84 adverse events in 48 [16.9%] patients) than in the tanezumab 2.5 mg treatment group (59 adverse events in 42 [14.8%] patients) or placebo treatment group (58 adverse events in 40 [14.2%] patients). Most of the adverse events during the Treatment Period assessed as treatment-related were mild or moderate in severity; two patients experienced severe adverse events that were considered treatment-related during the treatment period.

- **Severe Adverse Events**: A total of 24 patients experienced severe adverse events during the Treatment Period: 4 (1.4%) in the placebo treatment group, 9 (3.2%) in the tanezumab 2.5 mg treatment group, and 11 (3.9%) in the tanezumab 5 mg treatment group. Nasopharyngitis and Cardio-respiratory arrest in the tanezumab 5 mg treatment group were fatal.

- **Injection Site Reactions**: Seven (7) injection site reactions were reported by six patients in total: one patient each in the placebo treatment group and the tanezumab 2.5 mg treatment group and four in the tanezumab 5 mg treatment group. Injection site reactions reported were Injection site erythema, Administration site pain, Injection site warmth, and Injection site reaction. All were mild in severity and resolved.

- **Potential Hypersensitivity Adverse Events:** Overall few hypersensitivity adverse events were reported during the study: 10 adverse events in 10 patients (3.5%) in the placebo treatment group, 3 adverse events in 3 patients (1.1%) in the tanezumab 2.5 mg treatment group, and 10 adverse events in 9 patients (3.2%) in the tanezumab 5 mg treatment group. Hypersensitivity adverse events reported were Rash, Rhinitis allergic, Eczema, Rash macular, Dermatitis allergic, Bronchospasm, Conjunctivitis allergic, Hypersensitivity, and Urticaria. These adverse events were mild or moderate in severity, and most had resolved prior to the end of the study.

- **Tier 1 Adverse Events:** The overall incidence of Tier 1 adverse events (pre-specified adverse events of potential sympathetic dysfunction [Syncope, Bradycardia, Orthostatic hypotension, Anhidrosis, and Hypohidrosis] considered clinically important) was low: 2 (0.7%) in the placebo treatment group, 3 (1.1%) in the tanezumab 2.5 mg treatment group, and 8 (2.8%) in the tanezumab 5 mg treatment group. There was no significant difference between the frequencies of occurrence when comparing placebo to either of the tanezumab treatment group.

- **Tier 2 Adverse Events:** Tier 2 adverse events are defined as non-Tier 1 adverse events occurring in ≥3% of patients in any treatment group. The number of Tier 2 events overall was small and when comparing the incidence of adverse events in the placebo treatment group to either tanezumab treatment group, in all cases, the confidence interval (CI) included 0.

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- **Deaths:** There were three deaths during the study. Two, in patients in the tanezumab 5 mg treatment group (Nasopharyngitis, in an 82-year-old patient, with the cause of death reported as severe cold with probable influenza virus infection; Cardio-respiratory arrest, in a 77-year-old patient), occurred during the Treatment Period. The cause of death in each case was not considered by the Investigator to be related to study medication. One death (Cerebrovascular accident), in a 60-year-old patient in the tanezumab 2.5 mg treatment group, occurred in a patient who was lost to follow-up; this death was not confirmed by the family or the treating physician, but stated on a returned letter that was sent to the patient by the site.

- **Serious Adverse Events:** There were 15 SAEs in the placebo treatment group, 34 in the tanezumab 2.5 mg treatment group, and 42 in the tanezumab 5 mg treatment group. The majority of events had resolved at time of last contact; the exceptions were the following. In the tanezumab 2.5 mg treatment group, one patient was diagnosed with Diffuse B-cell lymphoma 202 days after last dose of study medication, and one patient was reported to have a Cerebrovascular accident, which was fatal, 55 days after last dose of study medication. In the tanezumab 5 mg treatment group, one patient was reported to have Cardio-pulmonary failure 204 days after last dose of study medication; one patient reported SAEs of Back pain and Condition aggravated (worsening of low back pain) 110 days after last dose of study medication; one patient was diagnosed with Parkinson's disease 351 days after last dose of study medication; and one patient had an adjudicated diagnosis of Osteonecrosis, 45 days after the last dose of study medication (study Day 106). There were two fatal SAEs: Nasopharyngitis (40 days after last dose of study medication) and Cardio-respiratory arrest (56 days after last dose of study medication).

- **Adverse Events of Abnormal Peripheral Sensation (Burning Sensation, Carpal tunnel syndrome, Decreased vibratory sense, Hypoesthesia, Neuralgia, Neuropathy peripheral, Paresthesia, Sciatica):** The incidence of adverse events related to abnormal peripheral sensation during the Treatment Period was low overall, but dose-dependent. Patients in the tanezumab 5 mg treatment group showed a higher incidence of Paresthesia and Hypoesthesia (12 [4.2%], 6 [2.1%]) than those in the tanezumab 2.5 mg treatment group (5 [1.8%], 4 [1.4%]) or placebo treatment group (5 [1.8%], 2 [0.7%]). All adverse events of abnormal peripheral sensation during the Treatment Period were mild or moderate in severity, and most had resolved at the time of last visit.

- **Peripheral Neurological Consultations:** More patients in the tanezumab 2.5 mg treatment group (12) had adverse events that met the criteria for requiring a neurologic consultation than in the tanezumab 5 mg treatment group (6) or placebo treatment group (4). Expert primary diagnoses for events that met criteria for consult after review of all clinical data available for the patients were as follows. Mononeuropathy (Carpal tunnel syndrome) was diagnosed in six patients: one patient in the placebo treatment group (preexisting); three patients in the tanezumab 2.5 mg treatment group (one pre-existing and two new onset); and two patients in the tanezumab 5 mg treatment group (one preexisting and one new onset). In all cases, the presentation was sensory. One

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patient had Carpal tunnel release surgery after the study was completed. The remaining three cases of Mononeuropathy had an expert diagnosis of Mononeuropathy (Other), two patients in the tanezumab 2.5 mg treatment group (presentation one sensory, one motor), and one patient in the tanezumab 5 mg treatment group (sensory presentation). The expert reviewer diagnosed Radiculopathy in eight patients, in all cases the presentation was sensory: one patient in the placebo treatment group (lumbosacral, new onset); five patients in the tanezumab 2.5 mg treatment group (all lumbosacral, new onset); and three cases in the tanezumab 5 mg treatment group (all lumbosacral; two preexisting, one new onset). One patient in the tanezumab 2.5 mg treatment group was diagnosed with a preexisting sensory polyneuropathy.

- **Adverse Events Potentially Indicative of Decreased Sympathetic Function:** The incidence of these events was similar across treatment groups. With one exception, all reported adverse events potentially indicative of decreased sympathetic function during the Treatment Period were mild or moderate in severity. One patient in the tanezumab 5 mg treatment group reported severe adverse events of diarrhea/vomiting of 2 days' duration due to food poisoning.

- **Consultations for Adverse Events Potentially Indicative of Decreased Sympathetic Function:** Nineteen (19) patients overall, 6 (2.1%) in the placebo treatment group, 5 (1.8%) in the tanezumab 2.5 mg treatment group, and 8 (2.8%) in the tanezumab 5 mg treatment group were reported to have at least one potential sympathetic event requiring a consultation. No confirmed cases of sympathetic neuropathy were present and there was no evidence of study medication effect on sympathetic function.

- **Neuropathy Impairment Score:** The conclusion from the neurological examinations at the last assessment for over 94% of patients was no new or worsened neurological examination abnormality. Less than 1% of patients in any treatment group had a new or worsened neurological exam abnormality that was considered clinically significant by the Investigator.

- **Total Joint Replacements:** Patients who opted to have TJR during the study were required to discontinue from treatment and enter the Safety Follow-up until the time the surgery became imminent, at which time the patients were to discontinue from study and enter observational Study A4091064, provided they consented to participate. Patients who informed the Investigator that they had had a TJR during participation in Study A4091057 were also eligible for Study A4091064. The number of TJRs was similar across treatment groups; a total of 61 patients had at least one TJR: 19 (6.7%) in the placebo treatment group, 22 (7.8%) in the tanezumab 2.5 mg treatment group, and 20 (7.0%) in the tanezumab 5 mg treatment group. Of the 61 patients who had or planned a TJR while participating in Study A4091057, 48 agreed to participate in Study A4091064 at the time of discontinuation from Study A4091057. The majority of the TJRs were adjudicated as normal progression of OA: 17/19 (89.5%) in the placebo treatment group, 20/22 (90.9%) in the tanezumab 2.5 mg treatment group, and

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16/20 (80.0%) in the tanezumab 5 mg treatment group. Four TJRs, 2 each in the tanezumab 2.5 mg treatment group and tanezumab 5 mg treatment group, contributed to the composite joint safety endpoint.

- **Adjudication:** A total of 84 events in 79 patients met criteria for adjudication and were reviewed by the Adjudication Committee. These included all TJRs, possible or probable joint safety events as identified on X-ray or magnetic resonance imaging (MRI) by the Central Reader based on the tanezumab program imaging charter, and Investigator-reported joint safety events. There were 22 events (19 patients) reviewed for the placebo treatment group, 27 events (27 patients) for the tanezumab 2.5 mg treatment group, and 35 events (33 patients) for the tanezumab 5 mg treatment group. Most of the adjudication events within each treatment group were adjudicated as normal progression of OA by the Adjudication Committee (18 of 22 events [81.8%] in the placebo treatment group, 22 of 27 events [81.5%] in the tanezumab 2.5 mg treatment group, and 21 of 35 events [60.0%] in the tanezumab 5 mg treatment group). One patient in the tanezumab 2.5 mg treatment group had an adjudicated diagnosis of Subchondral insufficiency fracture of the left (non-index) knee (Baseline KL grade=2); the adverse event was identified via imaging on study Day 233. One patient in the tanezumab 5 mg treatment group had an adjudicated diagnosis of Primary osteonecrosis in the left (non-index) hip (Baseline KL grade=0); the adverse event was identified via imaging on study Day 106. Outcomes of Rapidly progressive OA were assigned to four adjudicated cases in the tanezumab 2.5 mg treatment group, eight adjudicated cases in the tanezumab 5 mg treatment group, and none in the placebo treatment group. Additional information on cases of Rapidly progressive OA is provided in Table S7.

Table S7. Adjudicated Cases: Rapidly Progressive Osteoarthritis (RPOA)

Adjudicated diagnosis	Treatment Group	Affected Joint	Index Joint?	KL Grade of Affected Joint at Screening	AE Start Day (Study Day)	SAE?	TJR?
RPOA type 1	Tanezumab 2.5 mg	Right hip	Yes	3	225	No	Yes
		Left knee	No	1	248	No	No
		Right knee	No	0	191	No	No
	Tanezumab 5 mg	Right knee	Yes	2	170	No	No
		Left knee	Yes	2	336	No	No
		Left knee	Yes	2	221	No	No
		Right knee	No	2	323	No	No
		Right knee	No	3	267	No	Yes
RPOA type 2	Tanezumab 2.5 mg	Left hip	Yes	4	170	No	Yes
	Tanezumab 5 mg	Right hip	No	3	149	No	No
		Right hip	Yes	3			Yes
		Right hip	No	3	219	Yes	No

- **Laboratory Parameters:** The incidence of patients with normal Baseline who had post-Baseline laboratory test abnormalities that met pre-specified threshold for change from Baseline was low, affected no more than four patients within a treatment group, and

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was generally distributed across treatment groups, with the following exceptions. Eight (8 [3.1%]) patients in the placebo treatment group showed basophils/leukocytes (%) >1.2× upper limit of normal (ULN); triglycerides >1.3× ULN were seen in 4 (1.7%), 7 (2.8%), and 9 (3.5%) of patients in the placebo, tanezumab 2.5 mg, and tanezumab 5 mg treatment groups, respectively; and glucose >1.5× occurred in 3 (2.0%), 4 (2.6%), and 8 (5.1%) of patients in the placebo, tanezumab 2.5 mg, and tanezumab 5 mg treatment groups, respectively. Observations were similar for patients with an abnormal Baseline except for blood glucose for which values meeting the pre-specified threshold of >1.5× the upper limit of normal and >1.25× the Baseline value were seen for 9 patients in the placebo treatment group (9 of 115 [7.8%] patients with an abnormal glucose at Baseline), 16 patients in the tanezumab 2.5 mg treatment group (16 of 118 [13.6%] patients with an abnormal glucose at Baseline), and 12 in the tanezumab 5 mg treatment group (12 of 116 [10.3%] patients with an abnormal glucose at Baseline). Laboratory abnormalities considered clinically significant by the Investigator post-Baseline were to be reported as adverse events. All laboratory abnormalities reported as adverse events in the Treatment Period were reported in one patient each, with the exception of Blood creatinine phosphokinase increased, which was reported in 2 (0.7%) patients in the placebo treatment group and 4 (1.4%) patients in the tanezumab 2.5 mg treatment group.

- **Vital Signs:** A higher proportion of patients in the tanezumab 2.5 mg (23 [8.2%]) treatment group and tanezumab 5 mg (26 [9.3%]) treatment group than in the placebo treatment group (8 [2.9%]) showed a decrease in the sitting systolic BP measurement (change >-30 to -20), and a higher proportion of patients in the placebo treatment group (112 [40.0%]) than in the tanezumab 2.5 mg treatment group (94 [33.5%]) or tanezumab 5 mg treatment group (97 [34.5%]) showed a decrease in the sitting systolic BP measurement (change >-10 to 0); and more patients in the tanezumab 2.5 mg treatment group (142 [50.5%]) and tanezumab 5 mg treatment group (137 [48.8%]) than in the placebo treatment group (123 [43.9%]) showed a decrease in the sitting diastolic BP measurement (change >-10 to 0). A higher proportion of patients in the tanezumab 2.5 mg treatment group (120 [42.7%]) and tanezumab 5 mg treatment group (132 [47.0%]) than in the placebo treatment group (107 [38.2%]) showed an increase in the sitting systolic BP measurement (change >0 to 10), and a higher proportion of patients in the tanezumab 2.5 mg treatment group (82 [29.2%]) and tanezumab 5 mg treatment group (89 [31.7%]) than in the placebo treatment group (63 [22.5%]) showed only a decrease or no change in the sitting diastolic blood pressure measurement. A higher proportion of patients in the tanezumab 2.5 mg treatment group (39 [13.9%]) and tanezumab 5 mg treatment group (42 [14.9%]) than in the placebo treatment group (21 [7.5%]) showed a decrease in the sitting systolic BP measurement (change -30 to <-20), and a higher proportion of patients in the tanezumab 2.5 mg treatment group (14 [5.0%]) and tanezumab 5 mg treatment group (14 [5.0%]) then in the placebo treatment group (7 [2.5%]) showed a decrease in the sitting diastolic BP measurement (change <-20).

  Vital sign abnormalities during the Treatment Period that were considered clinically significant by the Investigator, and any confirmed episode of Orthostatic hypotension

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were to be reported as adverse events. All adverse events associated with vital signs, with the exception of Blood pressure fluctuation, Hypertension, and Orthostatic hypotension were reported in only one patient in any treatment group. In the placebo treatment group, two patients reported Blood pressure fluctuation and six patients reported Hypertension. In the tanezumab 2.5 mg treatment group, one patient reported Blood pressure fluctuation and two patients reported Hypertension. In the tanezumab 5 mg treatment group, six patients reported Hypertension. Three patients in the tanezumab 5 mg treatment group had an adverse event of Orthostatic hypotension, compared to none in each of the other treatment groups.

- **ECG:** There was no evidence of an effect of tanezumab on safety related to ECG measures. The maximum changes in all ECG parameters were similar across 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 24) 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 comparable to the corresponding TE ADA- combined tanezumab treatment group and there was no association between TE ADA+ and potential hypersensitivity reactions.

CONCLUSIONS

- Treatment with tanezumab 5 mg met all three co-primary endpoints (WOMAC Pain and Physical Function and PGA-OA) at Week 24.

- The tanezumab 2.5 mg treatment group met two co-primary endpoints (WOMAC Pain and Physical Function Subscales), but not the third co-primary endpoint (PGA-OA), and so did not meet the overall primary objective. Further hypothesis testing of the three key secondary endpoints for both tanezumab treatment groups could not be performed because significance for the PGA-OA was not met.

- The results for all key secondary efficacy endpoints (Patients with 50% reduction from Baseline in WOMAC Pain at Week 24; Change from Baseline to Week 2 in the WOMAC Pain Subscale; Change from Baseline to Week 1 in the average pain in the index joint) were deemed not significant due to the testing strategy, although both the tanezumab 5 mg treatment group and the tanezumab 2.5 mg treatment group had favorable observed percentages of patients compared to placebo for all key secondary efficacy endpoints (unadjusted p-values≤0.05).

- Of the remaining secondary endpoints 10 of 10 had unadjusted p≤0.05 at Week 24 for the tanezumab 5 mg treatment group and 7 of 10 had unadjusted p≤0.05 at Week 24 for the tanezumab 2.5 mg treatment group.

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- Collectively, the efficacy data across the primary and secondary endpoints indicate tanezumab 5 mg and 2.5 mg are efficacious in patients with moderate to severe OA. Moreover, the results for the Patient's Global Assessment of OA at Week 24 and the results for the secondary endpoints (unadjusted p-values) provide evidence that treatment with tanezumab 5 mg provides additional benefit above treatment with 2.5 mg.

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

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

    - Based on blinded external neurologist's reviews of peripheral neurologic consultation data, the most common diagnoses were Radiculopathy and Mononeuropathy (primarily Carpal tunnel syndrome) and overall, the results do not indicate that tanezumab treatment is associated with a peripheral polyneuropathy.

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

- A similar number of total joint replacements were reported in patients receiving placebo and tanezumab 2.5 or 5 mg; there was no difference across treatment groups for the incidence or observation-adjusted incidence.

- No placebo-treated patient had an adjudicated joint safety outcome included in the composite joint safety endpoint, whereas 14 tanezumab-treated patients had an outcome included in the composite joint safety endpoint. The tanezumab 5 mg treatment group had the highest incidence of Rapidly progressive OA type 1, Rapidly progressive OA type 2, and the only case of Primary osteonecrosis; the only Subchondral insufficiency fracture was observed in the tanezumab 2.5 mg treatment group.

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