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Sponsor: Pfizer, Inc.

Investigational Product: Tanezumab

Clinical Study Report Synopsis: Protocol A4091059

Protocol Title: A Phase 3, Randomized, Double Blind, Placebo and Active-Controlled, Multicenter, Parallel-Group Study of the Analgesic Efficacy and Safety of Tanezumab in Adult Subjects With Chronic Low Back Pain

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

Study Center(s): A total of 191 sites randomized patients in this study. The study was conducted at 245 sites in the United States (US), Canada, France, Spain, Sweden, Denmark, Hungary, Japan, and the Republic of Korea. Two patients were screened in Denmark; however, none were randomized.

Publications Based on the Study: None

Study Initiation and Completion Dates:

Study Initiation Date: 18 August 2015

Primary Completion Date: 17 October 2017

Study Completion Date: 20 December 2018

Report Date: 26 July 2019

Previous Report Date(s): Not applicable.

Phase of Development: Phase 3

Study Objective(s):

Primary Objective

- Demonstrate superior analgesic efficacy of tanezumab 10 mg and 5 mg administered subcutaneously (SC) every 8 weeks compared to placebo at Week 16.

Secondary Objectives

- Evaluate the long-term safety of tanezumab 10 mg and 5 mg SC administered every 8 weeks (7 administrations);

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- Estimate the long-term analgesic efficacy of tanezumab 10 mg and 5 mg SC administered every 8 weeks (7 administrations) up to Week 56;

- Compare the analgesic efficacy of tanezumab 10 mg SC administered every 8 weeks relative to an active comparator (oral tramadol prolonged release [PR]) at Week 16.

METHODS

Study Design:

This was a randomized, double-blind, placebo- and active-controlled, multicenter, parallel-group Phase 3 study of the efficacy and safety of tanezumab when administered SC for up to 56 weeks in patients with chronic low back pain (CLBP). Approximately 1800 patients were planned to be randomized in a 2:2:2:3 ratio to one of four treatment groups:

- Placebo administered SC at an 8-week interval plus placebo matching tramadol PR up to Week 16 (approximately 400 patients). At the Week 16 visit, patients in this group who met the efficacy responder criteria were switched in a blinded fashion in a 1:1 ratio to either tanezumab 5 mg or 10 mg administered SC at an 8-week interval plus placebo matching tramadol PR to Week 56;

- Tanezumab 5 mg SC administered at an 8-week interval plus placebo matching tramadol PR to Week 56 (approximately 400 patients);

- Tanezumab 10 mg SC administered at an 8-week interval plus placebo matching tramadol PR to Week 56 (approximately 400 patients);

- Oral tramadol PR plus placebo administered SC at an 8-week interval to Week 56 (approximately 600 patients).

The total study duration consisted of three periods: Screening (up to a maximum of 37 days, including a Washout Period [2-32 days] and an Initial Pain Assessment Period [IPAP], five days prior to randomization/baseline), a Double-blind Treatment Period (including the 16-week Primary Efficacy Phase and a 40-Week Long Term Safety and Efficacy Phase), and a Follow-up Period (24 weeks). The post-randomization study duration (ie, Double-blind Treatment Period and Follow-up Period) was approximately 80 weeks.

Patients who underwent total knee, hip, or shoulder joint replacement surgery during the study (ie, during the Treatment Period or the Follow-up Period) were discontinued from study treatment and were followed for 24 weeks after the procedure as part of a substudy, provided the patient met protocol criteria and provided consent. Patients who had other types of joint replacement surgery or arthroplasty during the study were discontinued from treatment and completed the Safety Follow-up Period.

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After obtaining informed consent at Screening, the Investigator evaluated the patient based on the Screening inclusion/exclusion criteria. The Screening Period included the discontinuation and washout of all prohibited pain medications, X-rays to confirm the patient's radiographic eligibility for the study, and the IPAP. Patients who did not require a washout of prohibited pain medications could have started the IPAP the day after X-ray confirmation of radiographic eligibility was received from the Central Reader.

Patients who met eligibility criteria at the Screening visit were instructed in the completion of an electronic diary that utilized Interactive Response Technology (IRT). Patients recorded Low Back Pain Intensity (LBPI) scores, joint pain scores, non-steroidal anti-inflammatory drug (NSAID) and rescue medication usage via the IRT. During the Screening Period, all patients underwent X-rays of the hips, knees, and shoulders. Other major joints exhibiting signs or symptoms suggestive of osteoarthritis (OA) were also imaged. At Screening, patients also provided a pain score (scored with an 11-point numerical rating scale [NRS]) for knees, hips, and shoulders, and any other major joint for which a radiograph was obtained.

Patients who were eligible at the Randomization/Baseline Visit (Day 1) were randomized to one of the four treatment groups.

Administration of SC study medication (placebo, tanezumab 5 mg, or tanezumab 10 mg) occurred at Baseline and Week 8. Assuming a sufficient treatment response was demonstrated at Week 16, additional administration of SC study medication occurred at Weeks 16, 24, 32, 40, and 48. Patients were observed for adverse events including signs and symptoms of hypersensitivity in the clinic for a minimum of one hour after each administration of SC study medication.

At the Week 16 visit, patients must have had at least a 30% reduction in average LBPI (aLBPI) score relative to Baseline and at least a 15% reduction in aLBPI score relative to Baseline at any week from Week 1 to Week 15 in order to continue study treatment to Week 32. At the Week 32 visit, patients must have had at least a 30% reduction in aLBPI score relative to Baseline in order to continue study treatment to Week 56. Patients who did not meet these response criteria were discontinued from the Double-blind Treatment Period and entered the Early Termination Follow-up Period.

Each treatment group received tramadol PR or matching placebo tablets to maintain blinding of the active oral study medication. Patients randomized to tramadol PR at Baseline were started on a tramadol PR dose of 100 mg once a day (QD). During the first four weeks of the Double-blind Treatment Period (Baseline to Week 4), the tramadol PR dose could be adjusted as necessary every five to seven days by 100 mg increments depending on pain relief or tolerability, up to a maximum dose of tramadol PR 300 mg QD. In order to maintain the blind, patients receiving matching placebo were also allowed to titrate their dose. Patients were contacted by telephone at Weeks 1 and 3 to evaluate pain relief and tolerability of the oral study medication and to receive counsel regarding dose adjustment, and a clinic visit occurred at Week 2. After the Week 4 visit, the dose of tramadol PR (or matching

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placebo) was held constant until the Week 56 visit. Note: For patients participating in Europe, following the completion of the Week 16 visit through the Week 56 visit, the dose of tramadol PR or oral placebo could be decreased to a minimum of 100 mg per day, if clinically indicated. If the dose of tramadol PR or oral placebo was reduced, it could later be re-escalated for reasons of inadequate pain control to a maximum of the previous individually titrated dose.

Oral study medication and rescue medication were dispensed at every clinic visit beginning at Baseline and concluding with the Week 48 visit. Oral tramadol PR or matching placebo was self-administered by patients on a daily basis from Baseline through Week 56.

At the Week 16 visit, presuming a treatment response was demonstrated, patients randomized to the placebo treatment arm were switched in a blinded manner to tanezumab SC treatment. These patients were switched in a 1:1 ratio to tanezumab 5 mg or tanezumab 10 mg SC plus matching placebo and received the first administration of SC tanezumab at Week 16.

The Primary Efficacy Phase comprised the time from Baseline to Week 16. The primary efficacy endpoint, aLBPI score, was collected daily via IRT from Baseline to Week 16. Rescue medication use was recorded daily and NSAID use and joint pain assessments were recorded once a week via the IRT. Secondary efficacy and safety assessments were collected at Weeks 2, 4, 8, and 16. During the Primary Efficacy Phase, all concomitant medications for the treatment of CLBP were prohibited with the exception of rescue medication (acetaminophen/paracetamol) and study medication. During the Primary Efficacy Phase, patients were permitted to continue with stable non-pharmacologic treatments (eg, massage, physical therapy) for CLBP, but were prohibited from beginning new non-pharmacological treatments until after Week 16.

The Long Term Safety and Efficacy Phase began after the Week 16 visit and continued until Week 56. The aLBPI score, rescue medication use, NSAID use, and joint pain assessments were collected once a week via IRT, and safety and secondary efficacy assessments were collected at study visits at Weeks 24, 32, 40, 48, and 56. In addition, patients were contacted by telephone at Weeks 20, 28, 36, 44, and 52 to assess compliance and collect adverse events, concomitant drug, and concomitant non-drug information. Starting at Week 16, at the discretion of the Investigator, patients could have started certain permitted medications and non-pharmacological therapies for the treatment of low back pain. X-rays of the hips, knees, and shoulders, as well as any additional joint that was imaged at Screening or identified as at risk during the study, were obtained for all patients at Weeks 24 and 56 and sent to the Central Reader for review. Confirmation by the Central Reader of the continuing radiographic eligibility of the patient must have been received at Week 24 prior to administration of the Week 24 SC study medication.

Patients who completed the Week 56 visit were considered to have completed the Double-blind Treatment Period and entered the 24-week Safety Follow-up period. Patients who completed the Double-blind Treatment period and entered the 24-week Safety Follow-up Period and completed the Week 80 visit were considered to have completed the

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study. Patients who discontinued study treatment prior to completing the Week 56 visit were not considered to have completed the Double-blind Treatment Period. Patients who did not complete the Double-blind Treatment Period but who entered and completed the 24-week Early-termination Follow-up Period were considered to have completed the study while those patients who did not complete the 24-week Early-termination Follow-up Period were not considered to have completed the study.

With the completion of the Week 56 visit, patients began the 24-week Follow-up Period and were asked to return to the clinic for two additional study visits.

At Week 64 or up to 16 weeks after the last dose of SC study medication, efficacy assessments, adverse event, and concomitant medication information was collected and standard of care medication was initiated if determined appropriate by the Investigator. Between the clinic visits in the Follow-up Period, patients were contacted by telephone at Weeks 60, 68, 72, and 76 to collect adverse event, concomitant drug, and concomitant non-drug information. The aLBPI score was collected once a week (using a 24-hour recall period) through the Week 64 visit via IRT. Patients continued to report new or increased joint pain, acetaminophen, and NSAID use on a weekly basis via IRT through Week 80. As in the Double-blind Treatment Period, patients with severe, persistent joint pain had more detailed evaluations to investigate the pain. At the end of the 24-week Follow-up Period, patients returned for a final study visit at Week 80 (End of Study). At that visit, all End of Study procedures were completed including X-rays of the hips, knees, and shoulders, as well as any additional joint that was imaged at Screening or identified as at risk during the study. The window for the Week 80 X-rays was ±30 days of the nominal time of the visit but was to be obtained as close as possible to the Week 80 visit, and preferably no more than 14 days after the Week 80 visit.

Patients who discontinued treatment prior to Week 56, whether at their request or at the decision of the Investigator, were required to undergo 24 weeks of follow-up (Early Termination Follow-up Period). The 24 weeks of follow-up were obtained through three clinic visits and monthly phone calls to yield 24 weeks of post-treatment follow-up. In addition, patients were asked about the presence and severity of joint pain (hips, knees, and shoulders), rescue medication use, and NSAID use once per week via IRT through the end of the Early Termination Follow-up Period.

X-rays of the hips, knees, and shoulders (and any other major joint imaged at Screening or identified as at risk during the study) were performed as soon as possible after the decision to withdraw from the study was made, provided at least 30 days had passed since the previous X-rays were taken. The remainder of efficacy and safety assessments were performed at the first scheduled visit, which was eight weeks following the last dose of study medication.

Two additional clinic visits were also scheduled. The second visit occurred at Week 64 or up to approximately 16 weeks after the patient's last dose of SC study medication to collect safety and efficacy data. Once this visit and final efficacy assessments were conducted,

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standard of care treatment was offered to patients for the remaining eight weeks of the Early Termination Follow-up Period.

The third and final clinic visit occurred approximately 24 weeks following the last dose of SC study medication. At this visit, repeated X-rays of the hips, knees, and shoulders (and any other major joint imaged at Screening or identified as at risk during the study) were performed, provided at least 30 days had elapsed since the previous set of X-rays were taken. The window for obtaining end of study X-rays was 30 days before or 14 days after the nominal time of the visit.

Telephone contact was made with patients who withdrew early from treatment at approximately 12 and 20 weeks following the last dose of SC study medication.

If a patient refused to complete the Early Termination Follow-up Period, or chose to discontinue during that time, a complete early termination visit was performed.

Diagnosis and Main Criteria for Inclusion

- Male or female of any race, ≥18 years of age; willing and able to provide informed consent.
- Presented with duration of CLBP of ≥3 months.
- Primary location of low back pain must have been between the 12th thoracic vertebra and the lower gluteal folds, with or without radiation into the posterior thigh, classified as Category 1 or 2 according to the classification of the Quebec Task Force in Spinal Disorders.
- Documented history of previous inadequate treatment response (ie, the agent did not provide sufficient pain relief while on the maximum tolerated dose of the therapy or the patient was unable to take the agent due to contraindication or inability to tolerate) to at least three different categories of agents commonly and generally considered effective for the treatment of CLBP. If a patient had been treated with two or more agents simultaneously but continued to have inadequate pain relief, the pain was considered unresponsive to all of the agents taken.
- LBPI score of ≥5 at Screening.
- Completed at least four daily pain diaries during the five days prior to the day of Randomization, with an aLBPI score of ≥5.
- Patient's Global Assessment (PGA) of Low Back Pain must have been "fair," "poor," or "very poor" at Baseline.

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- Patients must have been willing to discontinue all pain medications for CLBP except rescue medication and study medication 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 of ≥45 kg/m^2.

- Diagnosis of OA of the knee or hip as defined by the American College of Rheumatology (ACR) combined clinical and radiographic criteria; radiographic criteria were assessed by the Central Reader.

    - Patients who had Kellgren Lawrence (KL) grade ≥2 radiographic evidence of hip OA were excluded;

    - Patients who had KL grade ≥3 radiographic evidence of knee OA were excluded;

    - Patients who had KL grade ≤2 radiographic evidence of knee OA but who did not meet ACR criteria and did not have pain associated with their knee OA were allowed.

- Patients with symptoms and radiologic findings (ie, joint space narrowing, osteophytes) consistent with OA in the shoulder.

- History of lumbosacral radiculopathy within the past two years, history of spinal stenosis associated with neurological impairment, or history of neurogenic claudication.

- Back pain due to recent major trauma (eg, vertebral fracture, post-traumatic spondylolisthesis). Patients with trauma occurring >6 months prior to Screening were eligible to be considered for entry into the study.

- Fibromyalgia, back pain due to a visceral disorder (eg, endometriosis), or other moderate to severe pain that may confound assessments or self-evaluation of the pain associated with CLBP.

- History of disease that may involve the spine, including inflammatory joint diseases such as seronegative spondyloarthropathy (eg, ankylosing spondylitis), rheumatoid arthritis (RA), infections, or tumors of the spinal cord, or Paget's disease of the spine, pelvis, or femur.

- 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, RA), systemic metabolic bone disease (eg, pseudogout, Paget's disease, metastatic calcifications); large cystic lesions, primary or metastatic tumor lesions; or stress or traumatic fracture.

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- Patients with radiographic evidence of any one 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 5) osteonecrosis 6) pathologic fracture.

- Patients with 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.

- Subjects 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) or any of its excipients or existence of a medical condition or use of concomitant medication for which the use of acetaminophen is contraindicated (refer to product labeling).

- History of intolerance or hypersensitivity to tramadol or any of its excipients or existence of a medical condition or use of concomitant medication for which the use of tramadol is contraindicated (refer to product labeling).

- History of allergic or anaphylactic reaction to a therapeutic or diagnostic monoclonal antibody or immunoglobulin G-fusion protein.

- Signs and symptoms of clinically significant cardiac disease.

- Patients who had evidence of orthostatic hypotension (OH) based upon replicate orthostatic blood pressure (BP) measurements.

- 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 would preclude completion of required study activities.

- History, diagnosis, or signs and symptoms of clinically significant neurological disease.

- History, diagnosis, signs or symptoms of any clinically significant psychiatric disorder.

Randomization Criteria

- Patient must have completed appropriate washout of analgesics.

- Patient must have entered at least four LBPI scores on the daily pain diary in the five days prior to the Baseline (Day 1) visit.

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- Patient must have abstained from taking rescue medication (acetaminophen/paracetamol) within the 24 hours that preceded dosing.
- Patients must have met the Baseline LBPI score and PGA of Low Back Pain Baseline requirements.
- Review of the electrocardiogram (ECG) and laboratory results and confirmation that there were no clinically significant or exclusionary findings.
- Radiographic eligibility must have been confirmed by the Central Reader.

STUDY TREATMENT

Tanezumab 5 mg, tanezumab 10 mg, and placebo for tanezumab were each 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 of drug at a concentration of 5 mg/mL or 10 mg/mL.

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

Tramadol PR was provided as a tablet containing tramadol 100 mg, tramadol 200 mg, and tramadol 300 mg with a PR formulation. The bottles used for the titration period contained 60 tablets of tramadol 100 mg. The bottles for the treatment period contained 72 tablets of tramadol 100 mg, 200 mg, or 300 mg. Each bottle had a unique container number.

The placebo for tramadol PR was provided as tablets manufactured by a Pfizer designee to match the active tramadol PR 100 mg, tramadol PR 200 mg, and tramadol PR 300 mg, respectively. The bottles used for the titration period contained 60 tablets of placebo for tramadol 100 mg. The bottles for the treatment period contained 72 tablets of placebo for tramadol 100 mg, 200 mg, or 300 mg. Each bottle had a unique container number.

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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, 5 mg/mL	M76807	16-000831	5 mg/mL	Pre-filled Syringe
	L50447	15-002258		
		15-002259		
PF-04383119 Solution for Injection, 10 mg/mL	N09941	16-001924	10 mg/mL	Pre-filled Syringe
	L52539	15-002260		
		15-002261		
Placebo for PF-04383119 Solution for Injection	L39168	15-002262	0 mg/mL	Pre-filled Syringe
		15-002263		
Tramadol HCl PR, 100 mg	139705B	14-001196	100 mg	Tablet
	143759A	15-002127		
	147888A	15-004884		
	149290B	16-000960		
	145700A	15-003171		
Tramadol HCl PR, 200 mg	141648G	15-002128	200 mg	Tablet
	135509E	14-001049		
	148661A	15-004885		
	157289A	16-000961		
Tramadol HCl PR, 300 mg	135510E	14-000059	300 mg	Tablet
	141632D	15-002129		
	146699D	15-004886		
	152517Z	16-000962		
	169615A	17-001613		
Placebo for Tramadol HCl PR 100 mg	B13143	13-110345	0 mg	Tablet
	B12291	12-005704		
	B15115	15-004149		
	B16005	16-000640		
Placebo for Tramadol HCl PR 200 mg	B12292	12-005705	0 mg	Tablet
	B13144	13-110346		
	B15116	15-004150		
	B16006	16-000664		
Placebo for Tramadol HCl PR 300 mg	B12293	12-005830	0 mg	Tablet
	B13145	13-110574		
	B15117	15-004151		
	B16007	16-000665		
	B17029	17-001433		

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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 primary efficacy endpoint was the change from Baseline to Week 16 in the daily aLBPI score as measured by an 11-point numerical rating scale (NRS) for tanezumab versus placebo.

Key Secondary Efficacy Evaluation

The key secondary efficacy endpoints were the change from Baseline to Week 16 in the Roland Morris Disability Questionnaire (RMDQ) for tanezumab versus placebo, the response as defined by a ≥50% reduction from Baseline in daily aLBPI score derived from the patient diary at Week 16 for tanezumab versus placebo, and the change from Baseline to Week 2 in aLBPI score for tanezumab versus placebo.

Secondary Efficacy Evaluation

Secondary efficacy endpoints included change from Baseline to Weeks 2, 4, 8, 12, 24, 32, 40, 48, 56, and 64 in aLBPI score; change from Baseline to Weeks 2, 4, 8, 16 (for tanezumab vs tramadol) 24, 32, 40, 48, 56, 64 and 80 in RMDQ total score; change from Baseline to Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, and 64 in PGA of Low Back Pain; cumulative distribution of percent change from Baseline in aLBPI score to Weeks 16, 24, and 56 (endpoint for summary only); response as defined by a ≥30%, ≥50%, ≥70% and a ≥90% reduction from Baseline in daily aLBPI score derived from the patient diary at Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, 56, and 64; response as defined by a ≥30%, ≥50%, ≥70% and a ≥90% reduction from Baseline in the RMDQ score at Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, 64 and 80; cumulative distribution of percent change from Baseline in RMDQ score to Weeks 16, 24, and 56 (endpoint for summary only); CLBP Responder Index analysis (composite endpoint of aLBPI score, PGA of Low Back Pain, and RMDQ total score at Weeks 2, 4, 8 16, 24, 32, 40, 48 and 56); improvement of ≥2 points in PGA of Low Back Pain at Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, and 64; and incidence of and time to discontinuation due to lack of efficacy.

Secondary patient-reported outcome endpoints included change from Baseline to Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, and 64 in the Brief Pain Inventory short form (BPI-sf) scores; Work Productivity and Activity Impairment Questionnaire:Low Back Pain (WPAI:LBP) scores change from Baseline to Weeks 16, 56, and 64; Euro Quality of Life-5 Dimension-5 Level (EQ-5D-5L) dimensions and overall health utility score at Baseline, Weeks 8, 16, 24, 40, 56, and 64; Treatment Satisfaction Questionnaire for Medication v.II (TSQM) score 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.

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Rescue medication was measured by the incidence and number of days of usage during Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, 56 and Week 64 and the amount taken (mg) during Weeks 2, 4, 8, 12 and 16.

Pharmacokinetic and Pharmacodynamic Evaluations:

Pharmacokinetic Evaluations

Tanezumab concentrations were measured to support the development of an SC administration population pharmacokinetic (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.

Pharmacokinetic Sampling

Blood samples for the assessment of the PK of tanezumab were collected at Baseline (Day 1; predose) and at Weeks 2 and 4 (in approximately 30% of patients randomized at selected sites), Week 8 (predose), Week 16 (predose), Week 32 (predose), Week 48 (predose), Week 56, and Week 64.

Pharmacodynamic Evaluations

Blood samples were collected for the assessment of soluble p75, total nerve growth factor (NGF), and proNGF. In addition, blood and urine samples were collected for the assessment of biomarkers.

Pharmacodynamic Sampling

Blood samples for the assessment of NGF (total NGF and proNGF) and soluble p75 were collected at Baseline (Day 1; predose), at Weeks 2 and 4 (in approximately 30% of patients randomized at selected sites), Week 8 (predose), Week 48 (predose), and at Weeks 56 and 64 (or at Early Termination). Blood and urine samples for the assessment of biomarkers were collected at Baseline (Day 1; predose).

SAFETY EVALUATIONS

Safety evaluations for this study included assessment of adverse events, safety laboratory testing (chemistry and hematology), sitting vital signs, 12-lead ECG, orthostatic (supine/standing) BP, Survey of Autonomic Symptoms (SAS) scores, joint safety adjudication outcomes, total joint replacements (TJRs), neurologic examination (using the Neuropathy Impairment Score [NIS]), anti-drug antibodies (ADA), and physical examinations.

Safety Assessments

Adverse events, including serious adverse events (SAEs) and deaths, were collected throughout the study. A general physical examination was performed at Screening and at Week 56 or at Early Termination. Blood samples for clinical laboratory testing were collected at Screening, Baseline, Week 16, and Week 64 (or at Early Termination Visit 2).

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For female patients of childbearing potential, serum pregnancy tests were conducted at Screening, Weeks 56 and 64, or at Early Termination Visits 1 and 2. Urine pregnancy tests were performed at Baseline (Day 1, predose), and predose at Weeks 8, 16, 24, 32, 40, and 48. Vital signs (including systolic and diastolic BP and pulse rate) were collected and recorded at Screening, Baseline, prior to SC dosing at Weeks 2, 4, 8, 16, 24, 32, 40, 48, and at Weeks 56, 64, and 80, or Early Termination. Vital signs were collected after the patient had been sitting for at least 5 minutes. In addition to sitting vital sign measurements, orthostatic BP measurements were obtained using a standard manual sphygmomanometer at Screening, Baseline and at Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, 64 and 80 or at Early Termination. A 12-lead ECG was performed at Screening; Weeks 16, 56, and 80; and at Early Termination Visits 1 and 3 for determination of ECG-related eligibility and safety monitoring.

Neurological

An adverse event of OH was reported for all patients meeting criteria for OH at a visit. If no apparent medical cause was identified at the time the OH criteria were met and the patient was symptomatic, the patient was further evaluated for the presence of sympathetic autonomic neuropathy by a cardiologist or neurologist as soon as possible. If an apparent medical cause was identified at the time the OH criteria were met or if the patient was asymptomatic, the patient had a repeat assessment of OH performed at least one week, but not more than four weeks, later. If confirmed OH was present at the follow-up visit, the patient was further evaluated for the presence of sympathetic autonomic neuropathy by a cardiologist or neurologist as soon as possible.

Patients reporting adverse events of any seriousness or severity with preferred terms of Bradycardia, Syncope, OH, Anhidrosis, or Hypohidrosis were further evaluated for the presence of sympathetic autonomic neuropathy by a cardiologist or neurologist as soon as possible.

Neurological examinations were performed at Screening, Baseline, and Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, 64 and 80 (or at Early Termination) and the NIS was completed at these time points based on this 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 SAS was completed by the patient at Screening, prior to SC dosing at Week 24, and at Weeks 56 and 80 (or at Early Termination Visits 1 and 3).

A neurological evaluation was performed by a consulting neurologist if an adverse event suggestive of new or worsening peripheral neuropathy or an adverse event of abnormal peripheral sensation 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. Neurological evaluations were also obtained if a new or worsened clinically significant abnormality on the neurologic exam was reported as an adverse event and met

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criteria listed above, or if a reported non-neuropathic neurological adverse event (eg, stroke, seizure) was considered medically important by the investigator.

Musculoskeletal and Joint-Related

Each patient underwent a musculoskeletal physical examination at Screening, Baseline, Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, 64, and 80 (or Early Termination). A thorough musculoskeletal history was collected at Screening wherein the Investigator inquired about current and past history of OA, ligament tear or rupture, joint surgeries (including arthroscopic procedures), fractures, gout, osteoporosis or osteopenia, join injuries, or other conditions. At each subsequent visit, the Investigator conducted a thorough musculoskeletal physical examination of all major joints. This examination evaluated the joints for swelling, redness, tenderness, deformity, osteophytes or nodes, crepitus, and pain on motion. Findings were documented on the appropriate case report form. Information was also collected on any patient-reported joint symptoms including pain, stiffness, and swelling. Any clinically significant change in symptoms or the examination was reported as an adverse event.

Radiographic assessments (X-rays) of the hips, knees and shoulders were obtained at Screening, Weeks 24, 56 and 80 (or at Early Termination Visit 1 and 3).

A central radiology reader reviewed the radiology images for assessment of eligibility. During the study, the Central Reader reviewed radiology images for continued radiologic eligibility and 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 fracture, 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 ADA (anti-tanezumab antibodies) were collected at Baseline (Day 1; predose) and Weeks 8 (predose), 16 (predose), 32 (predose), 48 (predose), 56, 64, and 80. If patients terminated prior to Week 56, ADA was determined at approximately 8, 16, and 24 weeks after the last SC dose was administered (or at Early Termination).

Adverse Event Reporting

For SAEs, the active reporting period to Pfizer 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

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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 minimum sample size of approximately 400 patients per treatment group was needed to provide at least 80% power to achieve statistical significance (at the 5% 2-sided level) both for comparisons of tanezumab 10 mg and 5 mg versus placebo, as well as the comparison of tanezumab 10 mg versus the active comparator in the primary endpoint. Since placebo patients who reached Week 16 response criteria were switched to tanezumab treatment only, in order to balance patient exposure during the safety phase of the trial (post-Week 16), the number of patients randomized at Baseline to the active comparator group was increased to approximately 600. The total sample size was therefore planned to be approximately 1800 patients.

Analysis of the Primary Endpoint

The primary efficacy endpoint was change from Baseline to Week 16 in aLBPI score for the comparison of tanezumab versus placebo in the Intent-to-Treat (ITT) analysis set, which consisted of all randomized patients who received at least one dose of SC study medication (either tanezumab or placebo SC). The analysis for the primary endpoint used analysis of covariance (ANCOVA) with covariates of Baseline aLBPI score, treatment group, and study site as a random effect. Testing of the primary endpoint followed the graphical approach of gate-keeping strategy. This approach controls the family-wise type I error rate of 5% (two-sided).

Analysis of Key Secondary Endpoints

The analysis of the key secondary endpoint of change from Baseline to Week 16 in RMDQ for tanezumab versus placebo used the ANCOVA model described for the primary endpoint analysis with covariates of Baseline RMDQ score, Baseline aLBPI score, treatment group, and study site as a random variable.

The analysis of response as defined by a ≥50% reduction from Baseline in daily aLBPI score at Week 16 for tanezumab versus placebo used logistic regression with Baseline aLBPI score as a covariate.

The analysis of the change from Baseline to Week 2 in the daily aLBPI score for tanezumab versus placebo used the ANCOVA model described for the primary efficacy analysis with covariates of Baseline aLBPI score, treatment, and study site as a random effect.

Analysis of Secondary Endpoints

Secondary endpoints examined the change from Baseline to additional timepoints prior to Week 16 in LBPI score (ie, Weeks 2, 4, 8 and 12), using the multiple imputation for missing data procedure and analysis described above for the comparisons of tanezumab versus placebo and tramadol. The same analyses were undertaken for the change from Baseline to

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Weeks 24, 32, 40, 48, and 56 in aLBPI for the comparisons of tanezumab versus tramadol only.

Other secondary endpoints included the RMDQ total score, the PGA of Low Back Pain, and the 7 BPI-sf measures. The analysis of these endpoints, as change from Baseline to Weeks 2, 4, 8, and 16 (for tanezumab versus placebo and tramadol comparisons) and to Weeks 24, 32, 40, 48, and 56 (for tanezumab versus tramadol comparisons) used the same ANCOVA analysis as for the primary endpoint.

Patient response endpoints of improvement in the aLBPI score and the RMDQ score of ≥30, 50, 70 and 90%, improvement in the PGA of Low Back Pain ≥2 points and the CLBP Responder Index were analyzed at Weeks 2, 4, 8, 12 (aLBPI response only) and 16 (for tanezumab versus placebo and tramadol comparisons) and to Weeks 24, 32, 40, 48 and 56 (for tanezumab versus tramadol comparisons) using logistic regression for binary data. The model for the analysis of the responders based on aLBPI score and CLBP Responder Index included model terms for Baseline aLBPI score and treatment group. The model for the analysis of the PGA of Low Back Pain responders included the Baseline PGA score, Baseline aLBPI score and treatment group. These analyses were performed using a mixed baseline observation carried forward (BOCF)/last observation carried forward (LOCF) imputation approach. In this analysis BOCF imputation (ie, a patient would be a non-responder) was used for missing data due to discontinuation for reasons of lack of efficacy, adverse event, or death up to the timepoint of interest, and LOCF imputation was used for missing data for any other reason.

Analysis of Pharmacokinetic Data

Pharmacokinetic data was reported as follows:

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

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

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

RESULTS

Patient Disposition and Demography:

Of 6518 patients screened for the study, 1832 patients were randomized.

The majority of patients completed treatment up to Week 16 (77.8%). At the Week 16 visit, patients treated with placebo who met the Week 16 efficacy response criteria were eligible to continue in treatment and were switched to either tanezumab 5 mg or tanezumab 10 mg

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treatment for the remainder of the study. Of the 407 patients in the placebo treatment group, 99 patients were randomized at Week 16 to receive tanezumab 5 mg, and 95 patients were randomized at Week 16 to receive tanezumab 10 mg (Table S2).

Of the 1832 patients who were randomized, a total of 631 patients (34.4%) completed the Treatment Period (ie, up to Week 56) and of those, most (586 patients [92.9%]) completed the Safety Follow-up Period (Table S2). Of those who discontinued from the Treatment Period (1194 patients [65.2%]), fewer than half completed the Safety Follow-up Period (595 patients [49.8%]).

Overall, the proportion of patients who completed the Treatment Period was greater for patients treated with tanezumab (34.4% and 39.0% for tanezumab 5 mg and 10 mg, respectively) than for patients who started with placebo treatment (30.5% and 31.4% for the placebo → tanezumab 5 mg and placebo → tanezumab 10 mg treatment groups, respectively; Table S2). In general, the proportion of patients who completed the Treatment Period was similar in the placebo treatment groups, the tanezumab 5 mg treatment group, and the tramadol PR treatment group, ranging from 30.5% to 34.4%. The incidence of patients completing the Treatment Period in the tanezumab 10 mg treatment group (39.0%) was higher than in the other treatment groups (Table S2).

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Table S2. Subject Disposition

	Placebo -> Tanezumab 5 mg (N=203) n (%)	Placebo -> Tanezumab 10 mg (N=204) n (%)	Tanezumab 5 mg (N=407) n (%)	Tanezumab 10 mg (N=408) n (%)	Tramadol (N=610) n (%)	Total (N=1832) n (%)
Screened: 6518 Screen Failure: 4557 Other Screened but not Randomized: 129						
Randomized	203 (100.0)	204 (100.0)	407 (100.0)	408 (100.0)	610 (100.0)	1832 (100.0)
Treated	202 (99.5)	204 (100.0)	407 (100.0)	407 (99.8)	605 (99.2)	1825 (99.6)
Not Treated	1 (0.5)	0	0	1 (0.2)	5 (0.8)	7 (0.4)
Treated at Week 16	99 (48.8)	95 (46.6)	236 (58.0)	242 (59.3)	307 (50.3)	979 (53.4)
ITT Population	202 (99.5)	204 (100.0)	407 (100.0)	407 (99.8)	605 (99.2)	1825 (99.6)
Per-Protocol Population	148 (72.9)	170 (83.3)	335 (82.3)	327 (80.1)	492 (80.7)	1472 (80.3)
Safety Population	205 (101.0)	204 (100.0)	407 (100.0)	407 (99.8)	602 (98.7)	1825 (99.6)
Completed study	130 (64.0)	134 (65.7)	267 (65.6)	271 (66.4)	379 (62.1)	1181 (64.5)
Discontinued study	75 (36.9)	70 (34.3)	140 (34.4)	136 (33.3)	223 (36.6)	644 (35.2)
Number of subjects[1]						
Completed Treatment Phase	62 (30.5)	64 (31.4)	140 (34.4)	159 (39.0)	206 (33.8)	631 (34.4)
Completed Safety Follow-Up	61 (30.0)	57 (27.9)	132 (32.4)	145 (35.5)	191 (31.3)	586 (32.0)
Discontinued Safety Follow-Up	1 (0.5)	7 (3.4)	8 (2.0)	13 (3.2)	12 (2.0)	41 (2.2)
Did not enter Safety Follow-Up	0	0	0	1 (0.2)	3 (0.5)	4 (0.2)
Discontinued Treatment Phase	143 (70.4)	140 (68.6)	267 (65.6)	248 (60.8)	396 (64.9)	1194 (65.2)
Completed Safety Follow-Up	69 (34.0)	77 (37.7)	135 (33.2)	126 (30.9)	188 (30.8)	595 (32.5)
Discontinued Safety Follow-Up	43 (21.2)	32 (15.7)	76 (18.7)	59 (14.5)	133 (21.8)	343 (18.7)
Did not enter Safety Follow-Up	31 (15.3)	31 (15.2)	56 (13.8)	63 (15.4)	75 (12.3)	256 (14.0)

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Table S2. Subject Disposition

	Placebo -> Tanezumab 5 mg (N=203) n (%)	Placebo -> Tanezumab 10 mg (N=204) n (%)	Tanezumab 5 mg (N=407) n (%)	Tanezumab 10 mg (N=408) n (%)	Tramadol (N=610) n (%)	Total (N=1832) n (%)
Entered into Sub-Study	0	3 (1.5)	0	1 (0.2)	0	4 (0.2)
Rollover to Study A4091064	0	0	0	0	0	0

N is Number of Subjects Randomized. Percentages are based on the number of subjects Randomized.
[1]Subjects in Safety Population.
Not treated is subjects who received no SC study medication.
Safety population consists of all subjects treated with Tanezumab or Placebo SC. ITT population consists of all randomized subjects who received at least one dose of Tanezumab or Placebo SC.
"Other Screened but not Randomized" displays subjects who were screened but not randomized for a reason not related to a specific eligibility criterion.
One (1) subject randomized to Placebo, 1 subject randomized to Tanezumab 10 mg, and 5 subjects randomized to Tramadol were not treated because the subjects were discovered violating inclusion/exclusion criteria after randomization.
Three (3) subjects who were randomized to Tramadol but did not receive Tramadol.
PFIZER CONFIDENTIAL SDTM Creation: 26JAN2019 (01:16) Source Data: Listing 16.2.1.1 Output File: ./nda1/A4091059/adsl_s002_chk_i Date of Generation: 20FEB2019 (18:31)
Table 14.1.1.1.2.i is for Pfizer internal use.

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The proportion of patients who discontinued treatment up to Week 16 was lower in the tanezumab 10 mg treatment group (17.0%) than all other treatment groups (22.0% to 25.7%). The proportion of patients who discontinued treatment during the Treatment Period (ie, up to Week 56) was lower in the tanezumab 10 mg treatment group (60.9%) than all other treatment groups (65.6% to 69.8%).

The most frequent reasons for discontinuation from treatment across treatment groups were "Patient meets protocol-specified pain criteria for discontinuation" (16.0% to 19.6%), "Other" (12.1% to 17.0%), and "Insufficient clinical response" (10.1% to 20.1%). The incidence of treatment discontinuation due to "Insufficient clinical response" and "Patient meets protocol-specified pain criteria for discontinuation" was highest in patients who received placebo up to Week 16 (12.2% and 20.1% due to "Insufficient clinical response" for the placebo → tanezumab 5 mg and placebo → tanezumab 10 mg treatment groups, respectively, and 19.5% and 19.6% due to "Patient meets protocol-specified pain criteria for discontinuation" for the placebo → tanezumab 5 mg and placebo → tanezumab 10 mg treatment groups, respectively). The incidence of patients discontinuing from treatment due to adverse events was highest with tramadol PR treatment (11.0%).

The most frequent reasons for discontinuation from the study were "Withdrawal by subject" and "Other". There were no apparent treatment- or dose-related trends in discontinuation from the study.

Demographic characteristics were similar across the treatment groups. Across treatment groups, there were more female patients than male patients. The majority of patients in all treatment groups were white, with the mean age ranging from 48.4 to 49.1 years. Mean age and range were similar across gender and treatment groups which were overall balanced within each age category. Overall racial groups were well balanced across the treatment groups, with slightly fewer Asian patients in the tanezumab 10 mg treatment group (6.9%) compared with the other groups (9.3% to 10.8%).

Inadequate pain relief was the primary reason for treatment failure with acetaminophen or low-dose NSAIDs, prescription NSAIDs or coxibs, and opioids. Intolerability was also reported as a reason for treatment failure by substantial numbers of patients for opioids (>18% of patients across treatment groups).

With the exception of one patient, all patients had data regarding the duration of the primary diagnosis of low back pain at baseline. The mean duration since first diagnosis of CLBP was similar across the treatment groups.

In general, Baseline disease characteristics such as aLBPI score, RMDQ score, PGA of Low Back Pain, and BPI-sf scores were similar across the treatment groups. The mean aLBPI at Baseline was greater than seven in all treatment groups. The Quebec Task Force Classification was similar across treatment groups, with the majority of patients in Quebec Task Force Category 1 (pain without radiation) at Baseline.

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The majority of patients did not have a neuropathic component (painDetect score ≤12) of their CLBP per the painDetect questionnaire. The proportion of patients in the 13 to 18 category (neuropathic component uncertain) was similar across the treatment groups at Baseline. The tanezumab 10 mg treatment group had a higher proportion of patients in the ≤12 category and a lower proportion of patients in the ≥19 category (neuropathic component is likely) compared to the other treatment groups, while the placebo treatment group had a lower proportion of patients in the ≤12 category and a higher proportion of patients in the ≥19 category compared to the other treatment groups.

Approximately one third of patients were assessed as having pain due to degenerative disc disease, and approximately one third of patients were assessed as having pain due to injury/muscular strain. Approximately 25% of patients were assessed as having CLBP due to degenerative joint disease/OA. The remainder (9.3% to 15.5%) was in the other category (unknown or multiple causes).

Efficacy Results

The primary objective of the study was met for tanezumab 10 mg, applying the gate-keeping strategy. Tanezumab 10 mg treatment resulted in significant improvement (reduction) compared to placebo treatment in the primary efficacy endpoint, change from Baseline to Week 16 in the aLBPI score. Further hypothesis testing for the key secondary endpoints was performed for tanezumab 10 mg versus placebo.

Treatment with tanezumab 10 mg resulted in significant improvements in all three key secondary efficacy endpoints compared to placebo (change from Baseline to Week 16 in RMDQ score, the proportion of patients with a ≥50% reduction in aLBPI score from Baseline to Week 16, change from Baseline to Week 2 in aLBPI score), applying the gate-keeping strategy.

Focusing on nominal (unadjusted) p-values, tanezumab 10 mg treatment resulted in significant improvement from Baseline in the aLBPI score compared to placebo treatment at Week 1 through Week 12 (p-values <0.05, with no multiplicity correction). Tanezumab 10 mg treatment resulted in significant improvement from Baseline in the RMDQ score compared to placebo treatment at Weeks 2, 4, and 8 (p-values <0.05, with no multiplicity correction).

The primary objective of the study was not met for tanezumab 5 mg, applying the gate-keeping strategy. For tanezumab 5 mg, no significant improvement in aLBPI score was demonstrated compared to placebo treatment at Week 16. As the primary objective for tanezumab 5 mg was not met, further hypothesis testing for the key secondary endpoints could not be performed for tanezumab 5 mg versus placebo.

Outside the framework of the gate-keeping strategy, treatment with tanezumab 5 mg resulted in numerical improvement in RMDQ score at Week 16 (p=0.0035), the proportion of patients

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with a ≥50% reduction in aLBPI score at Week 16 (p=0.0846), and aLBPI score at Week 2 (p=0.0015).

Focusing on nominal (unadjusted) p-values, tanezumab 5 mg treatment resulted in significant improvement from Baseline in the aLBPI score compared to placebo treatment at Week 1 through Week 12 (p-values <0.05, with no multiplicity correction). Tanezumab 5 mg treatment resulted in significant improvement from Baseline in the RMDQ score compared to placebo treatment at Weeks 2, 4, and 8 (p-values <0.05, with no multiplicity correction).

Treatment with tramadol PR did not result in significant improvements in any of the primary or key secondary efficacy endpoints compared to placebo (p-values ≥0.05, with no multiplicity correction).

Primary Efficacy Analysis

The primary efficacy endpoint was the change from Baseline in the aLBPI score at Week 16 for tanezumab versus placebo. The testing of significance for this endpoint used a gate-keeping strategy, with a multiple imputation method for missing data.

Using the gate-keeping strategy, treatment with tanezumab 10 mg resulted in significant improvement (reduction) in the aLBPI score from Baseline compared to placebo treatment and met the primary objective of the study (Table S3). Tanezumab 5 mg resulted in numerical improvement compared to placebo treatment; however, the treatment difference did not reach significance. The improvement with tramadol PR was modest, and the treatment difference compared to placebo was not significant. The incremental improvements from Baseline to Week 16 for tanezumab 10 mg and tanezumab 5 mg treatments compared to tramadol PR were modest and not significant.

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Table S3. Analysis of Primary Efficacy Endpoint - Change from Baseline to Week 16 (Intent-to-Treat, Multiple Imputation)

	Placebo (N=406)	Tanezumab 5 mg (N=407)	Tanezumab 10 mg (N=407)	Tramadol (N=605)
LS Mean (SE)	-2.68 (0.15)	-2.98 (0.14)	-3.08 (0.14)	-2.81 (0.12)
95% CI for LS Mean	(-2.97,-2.40)	(-3.26,-2.70)	(-3.36,-2.81)	(-3.04,-2.57)
Versus Placebo				
LS Mean Difference (SE)		-0.30 (0.19)	-0.40 (0.18)	-0.12 (0.17)
95% CI for LS Mean Difference		(-0.66,0.07)	(-0.76,-0.04)	(-0.46,0.21)
p-value		0.1117	0.0281	0.4620
Versus Tramadol				
LS Mean Difference (SE)		-0.17 (0.17)	-0.28 (0.17)	
95% CI for LS Mean Difference		(-0.50,0.16)	(-0.60,0.05)	
p-value		0.3118	0.0958	

A change from baseline < 0 is an improvement.
Multiple imputation method is applied for missing data, with imputation dependent on reason for missing data.
ANCOVA model for imputed datasets includes treatment as a fixed effect, and baseline average LBPI as a covariate, and study site as a random effect.
Results are taken from a combined analysis of the individual imputed dataset ANCOVA results.
PFIZER CONFIDENTIAL SDTM Creation: 29JAN2019 (12:20) Source Data: Listing 16.2.6.1 Output File: ./nda1/A4091059/adnr_infr_chg_ancova_mi_p1_i Date of Generation: 08JUL2019 (15:26)
Table 14.2.1.3.1.i is for Pfizer internal use.

Key Secondary Efficacy Analysis

- **Change from Baseline to Week 16 in the RMDQ score:** Tanezumab 10 mg treatment resulted in a significant improvement compared to placebo treatment. As the primary objective (tanezumab superiority compared to placebo for aLBPI score) was not met for tanezumab 5 mg, per the gate-keeping strategy, further hypothesis testing for the key secondary endpoints could not be performed for tanezumab 5 mg versus placebo. Tanezumab 5 mg treatment resulted in a numerical improvement in RMDQ score compared to placebo treatment (p=0.0035; with no multiplicity correction). Both tanezumab treatments resulted in significant improvements compared to tramadol PR treatment (with no multiplicity correction). No significant improvement was observed for treatment with tramadol PR versus placebo treatment (with no multiplicity correction).

- **Proportion of Patients with ≥50% Reduction in Average LBPI Score from Baseline to Week 16:** Treatment with tanezumab 10 mg was associated with a significant increase in the proportion of patients with a 50% or greater reduction from Baseline in aLBPI score compared with placebo treatment at Week 16 (p=0.0101). As the primary objective (superiority of tanezumab compared to placebo for aLBPI score) was not met for tanezumab 5 mg, per the gate-keeping strategy, further hypothesis testing for key

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secondary endpoints could not be performed for tanezumab 5 mg versus placebo. Tanezumab 5 mg resulted in a numerical improvement in the proportion of patients with a 50% or greater reduction from Baseline in aLBPI score compared to placebo treatment at Week 16 (p=0.0846, with no multiplicity correction). No significant difference was observed for either tanezumab treatment versus tramadol PR or for tramadol PR versus placebo.

- **Change from Baseline to Week 2 in Average LBPI Score:** Tanezumab 10 mg treatment resulted in a significant improvement compared to placebo treatment, which demonstrated an early onset of effect by tanezumab 10 mg at Week 2. As the primary objective (superiority of tanezumab compared to placebo for aLBPI score) was not met for tanezumab 5 mg, per the gate-keeping strategy, further hypothesis testing for key secondary endpoints could not be performed for tanezumab 5 mg versus placebo. Tanezumab 5 mg resulted in a numerical improvement in aLBPI score at Week 2 compared to placebo (p=0.0015; with no multiplicity correction). Treatment with tanezumab 10 mg resulted in a significant improvement compared to tramadol PR treatment at Week 2 (with no multiplicity correction). No significant difference was observed for tramadol PR treatment versus placebo treatment.

Secondary Efficacy Analysis

- Tanezumab 5 mg and 10 mg treatments resulted in significant improvement in the **aLBPI score from Baseline** compared to placebo treatment at Weeks 1, 2, 4, 8 and 12. Tramadol PR treatment resulted in significant improvement in aLBPI score compared to placebo treatment at Weeks 1 and 8. From Weeks 24 to 56, tanezumab 10 mg treatment resulted in a numerical reduction in aLBPI score from Baseline compared to tramadol PR treatment, but the difference was not significant at any of the time points. The reduction in aLBPI score from Baseline for tanezumab 5 mg treatment was similar to tanezumab 10 mg treatment from Weeks 24 to 56, and treatment differences compared to tramadol PR treatment were not significant.

- Tanezumab 5 and 10 mg treatments resulted in significant improvement (reduction) in **RMDQ score** compared to placebo treatment at Weeks 2, 4, and 8. Significant reductions in RMDQ score versus tramadol PR treatment were observed for tanezumab 10 mg at Weeks 2, 4, and 8 and for tanezumab 5 mg at Weeks 4 and 8. From Week 24 to Week 56, treatment with tanezumab 10 mg resulted in numerical improvement in RMDQ score compared to tramadol PR, but the differences were not significant, except at Week 24. Treatment with tanezumab 5 mg also resulted in numerical reductions in RMDQ score compared to tramadol PR treatment; however, the reductions were smaller than those observed for tanezumab 10 mg treatment. No significant differences were observed compared to tramadol PR treatment at Week 56.

- Tanezumab 10 mg treatment resulted in significant improvement in **PGA score** compared to placebo at Week 16 and all interim time points (Weeks 2, 4, and 8). For tanezumab 5 mg treatment, significant improvements compared to placebo were detected

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at Weeks 4 and 8. For the tramadol PR treatment group, there were no significant differences compared to placebo treatment at any time point assessed. For the comparison to the tramadol PR, tanezumab 10 mg treatment resulted in significant improvement in PGA score at Week 16 and all interim time points (Weeks 2, 4, and 8). For the tanezumab 5 mg treatment group, significant improvements compared to tramadol PR were detected at Weeks 4 and 16. From Week 24 to Week 56, no significant differences in PGA score were observed for either tanezumab treatment compared to tramadol PR.

- Analysis of the **CLBP Responder Index** showed higher proportions of responders in the tanezumab treatment groups than in the placebo and tramadol PR treatment groups at each week analyzed. Treatment differences with tanezumab 5 mg and 10 mg versus placebo were significant at Weeks 2, 4, 8, and 16 ($p<0.0001$ to $p=0.0179$). The treatment differences with tramadol PR versus placebo were significant at Weeks 2, 4, and 8 ($p=0.0033$ to $p=0.0300$). Treatment differences with tanezumab 10 mg versus tramadol PR were significant at Weeks 2, 4, 8, and 16 ($p=0.0005$ to $p=0.0100$). The treatment differences with tanezumab 5 mg versus tramadol PR were significant at Weeks 4, 16, and 24 ($p=0.0179$ to $p=0.0296$).

- **Reduction in the Average LBPI Score of ≥30%, ≥50%, ≥70%, and ≥90%:** Overall, tanezumab 5 and 10 mg treatments were associated with numerical increases in the proportion of responders in aLBPI score at all levels at all weeks compared to placebo (except Week 1, ≥70%), and the proportions of responders at these doses were comparable or greater than those for the tramadol PR treatment groups.

- **Reduction in the RMDQ Score of ≥30%, ≥50%, ≥70%, and ≥90%:** Overall, tanezumab 5 mg and 10 mg treatments were associated with numerical increases in the proportion of responders in RMDQ score at all levels at all weeks compared to placebo treatment, and the proportions of responders at these doses were comparable or greater than those for tramadol PR treatment.

- Treatment with tanezumab 10 mg was associated with a significant increase in the proportion of patients reporting a **≥2 point reduction from Baseline in PGA score** compared to placebo treatment at Weeks 2, 4, 8, and 16. Significant differences were observed for tanezumab 5 mg treatment compared to placebo treatment at Weeks 4 and 8. Significant differences compared to tramadol PR treatment were observed with tanezumab 10 mg treatment at Weeks 2, 4, and 16 and with tanezumab 5 mg treatment at Weeks 4, 16, 24, 32, and 40. No significant difference compared to placebo treatment was observed with tramadol PR treatment.

- For both the **change from Baseline in BPI-sf** worst and average pain scores, there was an improvement (reduction) from Baseline in all treatment groups at all weeks. For the BPI-sf pain interference index, there was a numerical improvement in all treatment groups at Week 16. Tanezumab 5 mg and 10 mg treatments resulted in significant

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improvements in the pain interference index compared to placebo treatment at Weeks 2, 4, 8, and 16. Significant improvements in the BPI-sf pain interference index compared to tramadol PR treatment were observed with tanezumab 5 mg treatment at Weeks 2 and 4 (p=0.0160 and p=0.0209) and with tanezumab 10 mg treatment at Weeks 2, 4, 8, and 16 (p=0.0003 to p=0.0121). Treatment with tramadol PR was not statistically different from placebo treatment at any week analyzed. Tanezumab 5 mg and 10 mg treatments resulted in numerical improvements in BPI-sf pain interference index compared to tramadol PR treatment, but the differences were not significant at any week beyond Week 16.

- At Weeks 16 and 56, decreases from Baseline were observed for all **WPAI:LBP measures**, across all treatment groups. No significant differences were observed for the change from Baseline in percent work time missed between tanezumab treatment groups and the placebo or tramadol PR treatment groups. Significant improvements in percent impairment while working and percent overall work impairment were observed at Week 16 for the tanezumab 10 mg treatment group compared to placebo (p=0.0477 and p=0.0289, respectively); no significant differences were observed for the tanezumab 5 mg treatment group compared to placebo or the tanezumab treatment groups compared to tramadol PR. A significant improvement in activity impairment was observed for the tanezumab 5 mg and 10 mg treatment groups compared to placebo (p=0.0157 and p=0.0159, respectively) at Week 16. No significant treatment difference was observed for the tanezumab treatments compared to tramadol PR at Week 16 or Week 56.

- During the first 16 weeks, a significantly larger proportion of patients treated with placebo (14.0%) discontinued due to insufficient clinical response than patients treated with tanezumab 5 mg (7.4%), tanezumab 10 mg (8.6%), or tramadol PR (8.3%). During the Treatment Period (ie, up to Week 56), the proportion of patients who discontinued treatment due to insufficient clinical response was highest in the treatment groups that began the study on placebo and switched to tanezumab at Week 16 (12.4% and 20.1% for the placebo $\rightarrow$ tanezumab 5 mg and placebo $\rightarrow$ tanezumab 10 mg treatment groups, respectively), followed by the tanezumab 10 mg (11.3%), tramadol PR (10.7%), and tanezumab 5 mg treatment groups (10.1%). There was no significant difference in the incidence of treatment discontinuation due to insufficient clinical response for the tanezumab treatment groups compared with the tramadol PR treatment group.

- The mean **number of days of rescue medication use** per week at Week 16 was similar across the treatment groups, ranging from 0.7 to 0.9 days. There was no significant difference in the number of days of rescue medication use per week at Week 16 for the tanezumab treatment groups versus placebo or tramadol PR treatment groups. There was no significant difference in the number of days of rescue medication use per week at Week 56 for the tanezumab treatment groups versus the tramadol PR treatment group.

- The **incidence of rescue medication use** per week was highest at Baseline (during the five days prior to the start of treatment; 71.7% to 76.2%) and decreased in all treatment groups up to Week 16 (29.0% to 31.4%). Overall, the incidence of rescue medication use

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by week was similar across treatment groups. No significant differences in the incidence of rescue medication use were observed at any time point between the tanezumab treatment groups and the placebo or tramadol PR treatment groups.

- The mean **amount of rescue medication used** by patients at Week 16 was similar across the treatment groups, ranging from 829 to 944 mg. There was no significant difference in the amount of rescue medication used at Week 16 for tanezumab treatment groups versus placebo or tramadol PR treatment groups.

- In general, patients in all treatment groups expressed improvement in each **TSQM** endpoint between Week 16 and Week 56.

- Treatment with tanezumab 5 mg and 10 mg resulted in significant improvements in **mPRTI** (preference for the study drug received to previous treatment) at Week 16 compared to placebo treatment (p=0.0333 and p=0.0244). Similarly, treatment with tanezumab 5 mg and 10 mg resulted in significant improvements in mPRTI (willingness to use the study drug received for low back pain) at Week 16 compared to placebo treatment (p=0.0045 and p=0.0099). No significant improvements in mPRTI were observed for tanezumab treatments versus tramadol PR treatment at Week 16 or Week 56.

Pharmacokinetic and Pharmacodynamic Results:

Pharmacokinetic Results

The mean tanezumab plasma concentrations were higher in the tanezumab 10 mg treatment group than the tanezumab 5 mg treatment group at all nominal sampling times (Week 2 to Week 56) by a proportion similar to the increase in dose. By Week 64, 16 weeks after the seventh dose of study medication, the mean tanezumab plasma concentrations were low, consistent with elimination of tanezumab from the body over five half-lives postdose. Tanezumab plasma concentrations in patients who were administered tanezumab after receiving placebo treatment for the first 16 weeks (placebo → tanezumab 5 mg and placebo → tanezumab 10 mg treatment groups) were similar to the tanezumab treatment groups wherein patients started and finished on tanezumab, with the exception of nominal sampling time Week 48. Plasma tanezumab concentrations at this nominal sampling time were lower in the placebo → tanezumab treatment groups in contrast to what was reported for patients starting on tanezumab. This is a consequence of the Week 48 nominal sampling time point occurring 16 weeks after the last dose for patients who first received tanezumab at Study Week 16, compared to eight weeks for those patients randomized to tanezumab for the duration of the trial.

Pharmacodynamic Results

Mean and median soluble p75 plasma trough concentrations were comparable at all time points for all treatment groups.

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Mean serum total NGF concentrations were comparable at Baseline across treatment groups and increased with tanezumab dosing. Mean total NGF trough concentrations were higher in the tanezumab 10 mg treatment group compared with the tanezumab 5 mg treatment group by approximately 28% at Week 8 (eight weeks after the first dose). Similarly, at Week 48, just prior to the seventh and last dose, mean total NGF trough concentrations were higher in the tanezumab 10 mg treatment group by approximately 37%. At Week 56, eight weeks after the last dose, mean total NGF trough concentrations were similar to the Week 48 observations with mean total NGF trough concentrations higher in the tanezumab 10 mg compared to the tanezumab 5 mg treatment group by approximately 42%. At Week 64, mean total NGF concentrations had declined in both the 10 mg and 5 mg tanezumab treatment groups and were approximately 53% and 32% of the Week 56 values, respectively.

Mean proNGF was comparable across treatment groups at all nominal sampling times.

Safety Results

The incidence of adverse events reported up to Week 16 was higher in the tramadol PR treatment group (Table S4). The incidence of SAEs during this period was low across treatment groups, with fewer patients reporting SAEs in the placebo treatment group compared with the tanezumab and tramadol PR treatment groups. The incidence of treatment discontinuation due to an adverse event was low in all treatment groups, but highest in the tramadol PR treatment group (8.5%).

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Table S4. Treatment-Emergent Adverse Events Up to Week 16 (All Causalities) - Safety Population

Number (%) of Subjects	Placebo n (%)	Tanezumab 5 mg n (%)	Tanezumab 10 mg n (%)	Tramadol n (%)
Subjects evaluable for adverse events	409	407	407	602
Number of adverse events	407	366	394	812
Subjects with adverse events	189 (46.2)	191 (46.9)	211 (51.8)	339 (56.3)
Subjects with serious adverse events	4 (1.0)	6 (1.5)	7 (1.7)	10 (1.7)
Subjects with severe adverse events	16 (3.9)	8 (2.0)	9 (2.2)	16 (2.7)
Subjects discontinued study drug due to adverse event	16 (3.9)	18 (4.4)	19 (4.7)	51 (8.5)
Subjects discontinued from study due to adverse event (a)	4 (1.0)	4 (1.0)	4 (1.0)	12 (2.0)
Subjects discontinued study drug due to adverse event and continued Study (b)	13 (3.2)	14 (3.4)	16 (3.9)	40 (6.6)
Subjects with dose reduced or temporary discontinuation due to adverse events	10 (2.4)	10 (2.5)	12 (2.9)	45 (7.5)

Includes treatment-emergent events that begin up to the week 16 dosing visit date for subjects who completed the Week 16 dosing visit, or up to the withdrawal from treatment date for subjects who withdrew before the Week 16 dosing visit. Any events started on the Week 16 dosing date are not included.
For 2 subjects who missed the Week 16 dose, treatment-emergent events that begin up to the Week 24 dosing visit (exclusive) are included.
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 Adverse Event record that indicates that the Adverse Event caused the subject to be discontinued from the study
(b) Subjects who have an Adverse Event record that indicates that action taken with study treatment was drug withdrawn but Adverse Event did not cause the subject to be discontinued from study
MedDRA v21.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 26JAN2019 (01:55) Source Data: Listing 16.2.7.1 Output File: ./nda1/A4091059/adae_s020_tp1_i Date of Generation: 19FEB2019 (15:24)
Table 14.3.1.2.1.1.i is for Pfizer internal use.

The incidence of adverse events reported during the Treatment Period (ie, up to Week 56) was highest in the tramadol PR (65.4%) and tanezumab 10 mg (63.7%) groups and lowest in the tanezumab 5 mg treatment group (58.3%; Table S5). The incidence of SAEs during the Treatment Period was lowest in the tanezumab 5 mg treatment group (2.2%) and highest in the tanezumab 10 mg treatment group (4.6%). There were patients in all treatment groups who discontinued treatment during this period due to an adverse event, with the greatest incidence in the tramadol PR group (10.5%) and lowest in the tanezumab 5 mg treatment group (6.7%).

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

Number (%) of Subjects	Tanezumab 5 mg n (%)	Tanezumab 10 mg n (%)	Tramadol n (%)
Subjects evaluable for adverse events	506	502	602
Number of adverse events	815	894	1197
Subjects with adverse events	295 (58.3)	320 (63.7)	394 (65.4)
Subjects with serious adverse events	11 (2.2)	23 (4.6)	19 (3.2)
Subjects with severe adverse events	12 (2.4)	24 (4.8)	26 (4.3)
Subjects discontinued study drug due to adverse event	34 (6.7)	37 (7.4)	63 (10.5)
Subjects discontinued from study due to adverse event (a)	5 (1.0)	10 (2.0)	15 (2.5)
Subjects discontinued study drug due to adverse event and continued Study (b)	29 (5.7)	29 (5.8)	50 (8.3)
Subjects with dose reduced or temporary discontinuation due to adverse events	17 (3.4)	19 (3.8)	52 (8.6)

Includes treatment-emergent events that begin up to the week 56 visit 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 Adverse Event record that indicates that the Adverse Event caused the subject to be discontinued from the study
(b) Subjects who have an Adverse Event record that indicates that action taken with study treatment was drug withdrawn but Adverse Event did not cause the subject to be discontinued from study
Patients who were randomized to Tanezumab 5 mg (or 10 mg) and patients who were randomized to Placebo and received Tanezumab 5 mg (or 10 mg) at Week 16 are included in the Tanezumab 5 mg (or 10 mg) group.
MedDRA v21.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 26JAN2019 (01:55) Source Data: Listing 16.2.7.1 Output File: ./nda1/A4091059/adae_s020_tp3g_i Date of Generation: 21FEB2019 (14:09)
Table 14.3.1.2.1.3.i is for Pfizer internal use.

During the 24-week Safety Follow-up or Early Termination Follow-up Periods, a similar proportion of patients in the placebo, tanezumab 10 mg, and tramadol PR treatment groups reported adverse events (Table S6); a higher proportion of patients reported adverse events in the tanezumab 5 mg treatment group (33.5%). The incidence of SAEs during this period was low, ranging from 1.1% to 3.7% across all treatment groups.

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Table S6. Treatment-Emergent Adverse Events During the Safety Follow-up Period and the Early Termination Follow-up Period (All Causalities) - Safety Population

Number (%) of Subjects	Placebo n (%)	Tanezumab 5 mg n (%)	Tanezumab 10 mg n (%)	Tramadol n (%)
Subjects evaluable for adverse events	166	442	433	524
Number of adverse events	83	304	260	258
Subjects with adverse events	46 (27.7)	148 (33.5)	136 (31.4)	146 (27.9)
Subjects with serious adverse events	3 (1.8)	11 (2.5)	16 (3.7)	6 (1.1)
Subjects with severe adverse events	3 (1.8)	11 (2.5)	13 (3.0)	13 (2.5)
Subjects discontinued study drug due to adverse event	1 (0.6)	5 (1.1)	0	5 (1.0)
Subjects discontinued from study due to adverse event (a)	1 (0.6)	1 (0.2)	1 (0.2)	3 (0.6)
Subjects discontinued study drug due to adverse event and continued Study (b)	0	4 (0.9)	0	3 (0.6)
Subjects with dose reduced or temporary discontinuation due to adverse events	1 (0.6)	0	0	1 (0.2)

Includes treatment-emergent events that begin after the week 56 visit 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 are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
(a) Subjects who have an Adverse Event record that indicates that the Adverse Event caused the subject to be discontinued from the study
(b) Subjects who have an Adverse Event record that indicates that action taken with study treatment was drug withdrawn but Adverse Event did not cause the Subject to be discontinued from Study
Placebo group represents subjects who received only Placebo in the treatment period. Patients who were randomized to Placebo ->tanezumab 5 mg (or 10 mg) and received Tanezumab 5 mg (or 10 mg) at Week 16 are included in the Tanezumab 5 mg (or 10 mg) group.
MedDRA v21.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 26JAN2019 (01:55) Source Data: Listing 16.2.7.1 Output File: ./nda1/A4091059/adae_s020_fup_i Date of Generation: 19FEB2019 (15:47)
Table 14.3.1.2.1.4.i is for Pfizer internal use.

Treatment-emergent adverse events occurring at a greater frequency (≥1% difference between treatment groups) in the tanezumab 5 mg treatment group versus the placebo treatment group included Headache, Hypoaesthesia, and Pruritis (Table S7).
Treatment-emergent adverse events occurring at a greater frequency (≥1% difference between treatment groups) in the tanezumab 10 mg treatment group versus the placebo treatment group included Headache, Upper respiratory tract infection, Nasopharyngitis, Paraesthesia, and Hypoaesthesia.

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Table S7. Incidence of Treatment-Emergent Adverse Events Up to Week 16 in ⩾2% subjects by Descending Frequency (All Causalities) - Safety Population

Number of Subjects Evaluable for AEs Number (%) of Subjects: by Preferred Term	Placebo (N=409) n (%)	Tanezumab 5 mg (N=407) n (%)	Tanezumab 10 mg (N=407) n (%)	Tramadol (N=602) n (%)
Arthralgia	28 (6.8)	21 (5.2)	28 (6.9)	38 (6.3)
Headache	16 (3.9)	24 (5.9)	23 (5.7)	38 (6.3)
Upper respiratory tract infection	10 (2.4)	11 (2.7)	16 (3.9)	18 (3.0)
Nasopharyngitis	10 (2.4)	12 (2.9)	14 (3.4)	13 (2.2)
Paraesthesia	4 (1.0)	6 (1.5)	13 (3.2)	9 (1.5)
Musculoskeletal pain	15 (3.7)	6 (1.5)	10 (2.5)	19 (3.2)
Nausea	7 (1.7)	6 (1.5)	10 (2.5)	68 (11.3)
Back pain	14 (3.4)	15 (3.7)	9 (2.2)	15 (2.5)
Hypoaesthesia	3 (0.7)	8 (2.0)	8 (2.0)	5 (0.8)
Pain in extremity	8 (2.0)	5 (1.2)	8 (2.0)	7 (1.2)
Dizziness	5 (1.2)	6 (1.5)	7 (1.7)	31 (5.1)
Constipation	6 (1.5)	5 (1.2)	6 (1.5)	45 (7.5)
Fall	7 (1.7)	8 (2.0)	6 (1.5)	7 (1.2)
Neck pain	8 (2.0)	5 (1.2)	6 (1.5)	8 (1.3)
Dry mouth	6 (1.5)	3 (0.7)	5 (1.2)	17 (2.8)
Fatigue	3 (0.7)	3 (0.7)	5 (1.2)	16 (2.7)
Sinusitis	5 (1.2)	8 (2.0)	5 (1.2)	10 (1.7)
Somnolence	8 (2.0)	3 (0.7)	4 (1.0)	33 (5.5)
Pruritus	2 (0.5)	6 (1.5)	2 (0.5)	15 (2.5)
Vomiting	7 (1.7)	1 (0.2)	1 (0.2)	23 (3.8)

Includes treatment-emergent events that begin up to the week 16 dosing visit date for subjects who completed the Week 16 dosing visit, or up to the withdrawal from treatment date for subjects who withdrew before the Week 16 dosing visit. Any events started on the Week 16 dosing date are not included.
Subjects are only counted once per treatment per event.
Adverse events are shown by descending frequency by the highest tanezumab dose.
MedDRA v21.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 26JAN2019 (01:55) Source Data: Listing 16.2.7.1 Output File: ./nda1/A4091059_IMMU_CUTOFF/adae_s180_tp1_i Date of Generation: 08MAR2019 (11:21)
Table 14.3.1.2.2.6.i is for Pfizer internal use.

Arthralgia and Headache were the most commonly reported adverse events during the Treatment Period (ie, up to Week 56) in the tanezumab treatment groups and were reported at a similar frequency across both treatment groups. Nausea was the most commonly reported adverse event in the tramadol PR group (Table S8) and was reported less frequently in the tanezumab treatment groups. Treatment-emergent adverse events occurring at a greater

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frequency (≥1% difference between treatment groups) in the tanezumab 5 mg versus the tramadol PR treatment groups included Back pain, Hypoaesthesia, Bronchitis, Fall, Muscle spasms, and Contusion. Treatment-emergent adverse events occurring at a greater frequency (≥1% difference between treatment groups) in the tanezumab 10 mg treatment group versus the tramadol PR treatment group included Arthralgia, Upper respiratory tract infection, Paraesthesia, Pain in extremity, Hypoaesthesia, Bronchitis, Bradycardia, Muscle spasms, Toothache.

Table S8. Incidence of Treatment-Emergent Adverse Events During the Treatment Period in ⩾2% subjects by Descending Frequency (All Causalities) - Safety Population

Number of Subjects Evaluable for AEs	Tanezumab 5 mg (N=506)	Tanezumab 10 mg (N=502)	Tramadol (N=602)
Number (%) of Subjects: by Preferred Term	n (%)	n (%)	n (%)
Arthralgia	46 (9.1)	53 (10.6)	54 (9.0)
Headache	35 (6.9)	33 (6.6)	45 (7.5)
Nasopharyngitis	23 (4.5)	31 (6.2)	35 (5.8)
Upper respiratory tract infection	22 (4.3)	31 (6.2)	26 (4.3)
Musculoskeletal pain	18 (3.6)	24 (4.8)	29 (4.8)
Back pain	27 (5.3)	21 (4.2)	23 (3.8)
Paraesthesia	13 (2.6)	21 (4.2)	14 (2.3)
Pain in extremity	11 (2.2)	20 (4.0)	14 (2.3)
Hypoaesthesia	15 (3.0)	19 (3.8)	7 (1.2)
Nausea	11 (2.2)	15 (3.0)	75 (12.5)
Bronchitis	14 (2.8)	12 (2.4)	8 (1.3)
Fall	21 (4.2)	11 (2.2)	17 (2.8)
Bradycardia	5 (1.0)	10 (2.0)	4 (0.7)
Dizziness	11 (2.2)	10 (2.0)	41 (6.8)
Muscle spasms	12 (2.4)	10 (2.0)	5 (0.8)
Sinusitis	18 (3.6)	10 (2.0)	17 (2.8)
Toothache	8 (1.6)	10 (2.0)	4 (0.7)
Constipation	7 (1.4)	9 (1.8)	49 (8.1)
Diarrhoea	7 (1.4)	9 (1.8)	12 (2.0)
Influenza	10 (2.0)	9 (1.8)	13 (2.2)
Neck pain	7 (1.4)	8 (1.6)	12 (2.0)
Fatigue	4 (0.8)	7 (1.4)	18 (3.0)
Somnolence	4 (0.8)	7 (1.4)	33 (5.5)

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Table S8. Incidence of Treatment-Emergent Adverse Events During the Treatment Period in ⩾2% subjects by Descending Frequency (All Causalities) - Safety Population

Number of Subjects Evaluable for AEs	Tanezumab 5 mg (N=506)	Tanezumab 10 mg (N=502)	Tramadol (N=602)
Number (%) of Subjects: by Preferred Term	**n (%)**	**n (%)**	**n (%)**
Contusion	11 (2.2)	6 (1.2)	6 (1.0)
Dry mouth	5 (1.0)	6 (1.2)	19 (3.2)
Gastroenteritis	10 (2.0)	6 (1.2)	9 (1.5)
Vomiting	2 (0.4)	5 (1.0)	25 (4.2)
Pruritus	6 (1.2)	4 (0.8)	16 (2.7)

Includes treatment-emergent events that begin up to the week 56 visit for subjects who completed the treatment period or up to the withdrawal from treatment date for subjects who withdrew early from the treatment period.
Subjects are only counted once per treatment per event.
Adverse events are shown by descending frequency by the highest tanezumab dose.
Patients who were randomized to Tanezumab 5 mg (or 10 mg) and patients who were randomized to Placebo and received Tanezumab 5 mg (or 10 mg) at Week 16 are included in the Tanezumab 5 mg (or 10 mg) group.
MedDRA v21.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 26JAN2019 (01:55) Source Data: Listing 16.2.7.1 Output File: ./nda1/A4091059/adae_s180_tp3g_i Date of Generation: 19FEB2019 (16:20)
Table 14.3.1.2.2.8.i is for Pfizer internal use.

Arthralgia was the most frequently reported adverse event during the 24-week Safety Follow-up or the Early Termination Follow-up Periods across treatment groups, and it was reported with higher frequency in the tanezumab treatment groups than in the tramadol PR and placebo treatment groups (Table S9). Back pain, Musculoskeletal pain, and Nasopharyngitis were also reported with greater frequency in the tanezumab 5 mg treatment group than the other treatment groups.

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Table S9. Incidence of Treatment-Emergent Adverse Events During the Safety Follow-Up Period and the Early Termination Follow-Up Period in ⩾2% subjects by Descending Frequency (All Causalities) - Safety Population

Number of Subjects Evaluable for AEs	Placebo (N=166)	Tanezumab 5 mg (N=442)	Tanezumab 10 mg (N=433)	Tramadol (N=524)
Number (%) of Subjects: by Preferred Term	n (%)	n (%)	n (%)	n (%)
Arthralgia	6 (3.6)	27 (6.1)	27 (6.2)	15 (2.9)
Back pain	4 (2.4)	17 (3.8)	12 (2.8)	11 (2.1)
Musculoskeletal pain	3 (1.8)	19 (4.3)	5 (1.2)	3 (0.6)
Pain in extremity	0	9 (2.0)	5 (1.2)	1 (0.2)
Nasopharyngitis	3 (1.8)	10 (2.3)	3 (0.7)	5 (1.0)
Bronchitis	5 (3.0)	3 (0.7)	2 (0.5)	5 (1.0)

Includes treatment-emergent events that begin after the week 56 visit for subjects who completed the treatment period or after the withdrawal from treatment date for subjects who withdrew early from the treatment period
Subjects are only counted once per treatment per event.
Adverse events are shown by descending frequency by the highest tanezumab dose.
Placebo group represents subjects who received only Placebo in the treatment period. Patients who were randomized to Placebo ->tanezumab 5 mg (or 10 mg) and received Tanezumab 5 mg (or 10 mg) at Week 16 are included to in the Tanezumab 5 mg (or 10 mg) group.
MedDRA v21.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 26JAN2019 (01:55) Source Data: Listing 16.2.7.1 Output File: ./nda1/A4091059/adae_s180_fup_i Date of Generation: 19FEB2019 (16:21)
Table 14.3.1.2.2.9.i is for Pfizer internal use.

- **Treatment-Related Adverse Events:** Up to Week 16, the overall incidence of treatment-related adverse events was similar across the placebo and tanezumab treatment groups (15.9% in the placebo treatment group, 17.9% in the tanezumab 5 mg treatment group, and 19.7% in the tanezumab 10 mg treatment group) and higher in the tramadol PR treatment group (30.2%). Treatment-related adverse events occurring at a greater frequency (≥1% difference between treatment groups) in the tanezumab 10 mg versus the placebo treatment group included Fatigue, Arthralgia, Dizziness, Headache, and Paraesthesia. Arthralgia, Paraesthesia, Headache, and Nausea were the most commonly reported treatment-related adverse events during the Treatment Period (ie, up to Week 56) in the tanezumab treatment groups. Nausea, Constipation, and Dizziness were the most commonly reported treatment-related adverse events in the tramadol PR treatment group. Arthralgia was the only treatment-emergent adverse event occurring at a greater frequency (≥1% difference between treatment groups) in the tanezumab 5 mg treatment group versus the tramadol PR treatment group. Treatment-emergent adverse events occurring at a greater frequency (≥1% difference between treatment groups) in the tanezumab 10 mg treatment group versus the tramadol PR treatment group included Arthralgia and Paraesthesia.

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- **Severe Adverse Events:** Severe adverse events were infrequently reported during the Treatment Period (ie, up to Week 56) across treatment groups. The most commonly reported all-causality severe adverse events during the Treatment Period were Back pain (four patients [0.8%]) in the tanezumab 5 mg treatment group, Rapidly progressive OA (three patients [0.6%]) in the tanezumab 10 mg treatment group, and Dizziness (three patients [0.5%]) in the tramadol PR treatment group.

- **Injection Site Reactions:** Injection site reactions were infrequently reported across treatment groups during the Treatment Period (ie, up to Week 56). All injection site reactions were mild in severity except for one moderate adverse event of Injection site pain in a patient who received placebo SC in the tramadol PR treatment group. One patient who received tanezumab 5 mg had two adverse events, Injection site rash and Injection site reaction, which were both mild in severity. The patient permanently discontinued study treatment due to the adverse event of Injection site rash. No other injection site reaction resulted in permanent discontinuation.

- **Potential Hypersensitivity Adverse Events:** Overall, few potential hypersensitivity adverse events were reported during the study. All potential hypersensitivity adverse events were mild or moderate in severity, except for one adverse event of Drug hypersensitivity in a patient in the tramadol PR group which was severe and serious.

- **Tier 1 Adverse Events:** Up to Week 16, the overall incidence of Tier 1 adverse events (a pre-specified composite of adverse events of potential sympathetic dysfunction [Syncope, Bradycardia, OH, Anhidrosis, and Hypohidrosis] considered clinically important) was low and there was no significant difference in the frequencies of occurrence when comparing either of the tanezumab treatment groups or the tramadol PR treatment group to the placebo treatment group. During the entire Treatment Period (ie, up to Week 56), the overall incidence of this composite event was also low (nine patients [1.8%] in the tanezumab 5 mg treatment group, 12 patients [2.4%] in the tanezumab 10 mg treatment group, and nine patients [1.5%] in the tramadol PR treatment group). As observed up to Week 16, there were no significant differences in the frequency of occurrence of this composite event in either tanezumab treatment group versus the tramadol PR treatment group.

- **Tier 2 Adverse Events:** Tier 2 adverse events were defined as non-Tier 1 adverse events occurring in ≥3% of patients in any treatment group. Up to Week 16, Paraesthesia occurred more frequently (confidence interval [CI] did not include zero) in the tanezumab 10 mg treatment group than in the placebo treatment group. There were no differences in the frequency of occurrence of events in the tanezumab 5 mg treatment group versus the placebo treatment group. During the Treatment Period (ie, up to Week 56), Hypoaesthesia occurred more frequently (CI did not include zero) in the tanezumab 10 mg treatment group than in the tramadol PR treatment group.

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- **Deaths:** A total of seven patients died during the study; one patient following placebo treatment (Cardiac failure), three patients following tanezumab 5 mg treatment (Aneurysm, Aneurysm ruptured, and Myocardial infarction; Toxicity to various agents; and Influenza), two patients following tanezumab 10 mg treatment (Toxicity to various agents and Road traffic accident), and one patient following tramadol PR treatment (Aspiration and Pneumonia). None of the SAEs resulting in death were considered related to study treatment.

- **Serious Adverse Events:** Over the course of the entire study, a greater proportion of patients reported treatment emergent SAEs in the tanezumab 10 mg treatment group (37 patients [7.4%]) than in the placebo treatment group (seven patients [3.3%]), the tanezumab 5 mg treatment group (21 patients [4.2%]), or the tramadol PR group (25 patients [4.2%]). The incidence of SAEs up to Week 16 was similar across treatment groups. No single preferred term was reported by more than one patient in any treatment group. During the entire Treatment Period (ie, up to Week 56), the incidence of SAEs was higher in the tanezumab 10 mg treatment group (4.6%) than in the other treatment groups (3.2% in the tramadol PR treatment group and 2.2% in the tanezumab 5 mg treatment group). The system organ class, Musculoskeletal and connective tissue disorders, was the only system organ class with more (≥1% difference between groups) SAEs for the tanezumab 10 mg treatment group than the tramadol PR treatment group. In general, each SAE occurred in only one patient per treatment group, with the exception of Vertigo, which occurred in two patients in the tramadol PR treatment group and Rapidly progressive OA which occurred in four patients in the tanezumab 10 mg treatment group.

- **Adverse Events of Abnormal Peripheral Sensation:** Adverse events of abnormal peripheral sensation occurring up to Week 16 at a greater frequency (≥1% difference between treatment groups) in the tanezumab 10 mg treatment group versus the placebo treatment group included Burning sensation, Carpal tunnel syndrome, Hypoaesthesia, and Paraesthesia. For tanezumab 5 mg, only Hypoaesthesia occurred at a greater frequency (≥1% difference between treatment groups) versus the placebo treatment group. The same adverse events occurred at a higher incidence (≥1% difference) in the tanezumab treatment groups versus the tramadol PR treatment group during the entire Treatment Period (ie, up to Week 56). All adverse events of abnormal peripheral sensation occurring up to Week 16 were mild or moderate in severity.

- **Peripheral Neurological Consultations:** More patients in the tanezumab 5 and 10 mg treatment groups had adverse events of abnormal peripheral sensation that met criteria for requiring a neurologic consult than the placebo and tramadol PR treatment groups. Clinical data, including consultation data when available, were reviewed by an external neurology expert for all patients who had at least one event requiring consult. The most frequent (occurring in ≥1% in any one treatment group) expert primary diagnoses were Mononeuropathy and Radiculopathy, and these occurred at a greater frequency in the tanezumab treatment groups versus the placebo and tramadol PR treatment groups.

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- **Adverse Events Potentially Indicative of Decreased Sympathetic Function:** The proportion of patients reporting adverse events potentially indicative of decreased sympathetic function up to Week 16 was similar across the placebo and tanezumab treatment groups and higher in the tramadol PR treatment group. This is due to the increased incidence of Nausea and Vomiting in the tramadol PR treatment group versus all other treatment groups. No individual adverse event potentially indicative of decreased sympathetic function occurred at a greater frequency (≥1%) in the tanezumab treatment groups relative to the placebo or tramadol PR treatment groups. Severe adverse events potentially indicative of decreased sympathetic function occurred in one patient (Presyncope) in the placebo treatment group and two patients (Nausea and Vomiting) in the tramadol PR treatment group. During the Treatment Period (ie, up to Week 56), the incidence of adverse events potentially indicative of decreased sympathetic function was similar in the tanezumab groups, and was highest in the tramadol PR treatment group, due to the increased incidence of Nausea and Vomiting. Bradycardia, in the tanezumab 10 mg treatment group, was the only adverse event potentially indicative of decreased sympathetic function reported at a greater frequency (≥1% difference) for a tanezumab treatment group versus the tramadol PR treatment group. As with events observed up to Week 16, few of these were considered severe and all were reported by patients in the tramadol PR treatment group: two patients (0.3%) reported Nausea, one patient (0.2%) reported Respiratory failure, and one patient (0.2%) reported Vomiting.

- **Consultations for Adverse Events Potentially Indicative of Decreased Sympathetic Function:** The only key adverse events meeting criteria for consultation were Bradycardia and Syncope, and each occurred with similar frequency across treatment groups. No patient was reported to have Anhidrosis or Hypohidrosis. 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:** The conclusion from the neurological examination for over 95% of patients in each treatment group 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.

- **Adjudication:** A total of 30 patients had 34 events that met criteria for adjudication. These included all TJRs, possible or probable joint safety events as identified on X-ray or magnetic resonance imaging by the Central Reader based on the tanezumab program imaging charter, and Investigator-reported joint safety events. The treatment group with the highest number of patients with events requiring adjudication was the tanezumab 10 mg treatment group (17 patients [3.4%]), followed by the tanezumab 5 mg treatment group (nine patients [1.8%]), and the tramadol PR treatment group (four patients [0.7%]). Four of the patients in the tanezumab 10 mg treatment group and two of the patients in

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the tanezumab 5 mg treatment group initially received placebo and were switched to active tanezumab treatment at Week 16; the events requiring adjudication occurred after Week 16 for all these patients, with the exception of one patient. No events requiring adjudication occurred in the placebo treatment group. Most of the joints adjudicated within each tanezumab treatment group were adjudicated as Rapidly progressive OA by the Adjudication Committee, and most of the joints adjudicated within the tramadol PR treatment group were Other joint outcome. Of the seven patients who had TJRs, two patients had an adjudication outcome of Rapidly progressive OA type 1, two patients had an adjudication outcome of Rapidly progressive OA type 2, and one patient had an adjudication outcome of Subchondral insufficiency fracture. For the remaining two patients who had a TJR, their adjudication outcome was Other (meniscal tear and trauma).

- **Total Joint Replacements:** A total of seven patients had one TJR during the study, all in the tanezumab 10 mg treatment group. No patient had more than one TJR during the study. Three of the seven patients had their TJR during the Treatment Period (ie, up to Week 56), two of whom initially received placebo treatment and were then switched to tanezumab 10 mg treatment at Week 16; both of these patients had their TJRs after receiving tanezumab treatment. Two patients had their TJR after completing the Treatment Period and after the Safety Follow-up Period, and two patients had their TJR during the Safety Follow-up Period after discontinuing the Treatment Period. All TJRs were associated with an adverse event (ie, not elective). One of the seven patients had a previous TJR (hip joint). All seven TJRs were adjudicated: five were adjudicated as composite joint endpoints and two were adjudicated as Other. Of the four knee TJRs, two were adjudicated as Rapidly progressive OA type 1, one was adjudicated as Subchondral insufficiency fracture, and one was adjudicated as Other (meniscal tear). The four patients who had a TJR in the knee during the study had radiographic evidence of OA on the Screening X-ray (with KL grade 1 [n=2] and KL grade 2 [n=2]). The hip TJR was adjudicated as Rapidly progressive OA type 2, and the patient had no evidence of OA (KL grade 0) in the hip on the Screening X-ray. One shoulder TJR was adjudicated as Rapidly progressive OA type 2, and the other shoulder TJR was adjudicated as Other (trauma). KL grade was not evaluated on shoulder X-rays, but neither patient who had a TJR in the shoulder had radiographic evidence of OA on the Screening shoulder X-rays.

- **Laboratory Parameters:** The incidence of patients with normal Baseline who had post-Baseline laboratory test abnormalities at any point during the study that met the pre-specified threshold for change from Baseline was low, affected no more than 14 patients within a treatment group, and was generally distributed evenly across treatment groups. Laboratory abnormalities considered clinically significant by the investigator post-Baseline were to be reported as adverse events. Laboratory abnormalities resulting in adverse events were reported at a low frequency of one to two patients per treatment group, with the exception of Blood creatine phosphokinase increased, which occurred in five patients in the tanezumab 5 mg treatment group. Three patients discontinued

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treatment due to adverse events related to laboratory abnormalities, two patients in the tanezumab 5 mg treatment group (Blood creatine phosphokinase increased and White blood cell count increased) and one patient in the tramadol PR treatment group (Gamma glutamyltransferase abnormal). None of these adverse events related to laboratory abnormalities were severe.

- **Vital Signs:** Categorical changes from Baseline to the last post-Baseline value in sitting BP during the Treatment Period (ie, up to Week 56) were generally similar across treatment groups for systolic and diastolic BP. The proportion of patients with a maximum increase from Baseline of greater than 10 to 20 mmHg in sitting systolic and diastolic BP was higher in the tanezumab and tramadol PR treatment groups than in the placebo treatment group. The proportion of patients with a decrease or no change in sitting systolic and diastolic BP was lower in the tanezumab and tramadol PR treatment groups than in the placebo treatment group. The proportion of patients with a maximum decrease from Baseline of -30 to less than -20 mmHg in sitting systolic BP was higher in the tanezumab treatment groups than in the placebo and tramadol PR treatment groups. The proportion of patients with a maximum decrease from Baseline of less than -20 mmHg in sitting diastolic BP was lower in the placebo treatment group than in all other treatment groups. The proportion of patients with a maximum decrease from Baseline of -20 to less than -10 mmHg in sitting systolic and diastolic BP was higher in the tanezumab 10 mg treatment group than in all other treatment groups. The proportion of patients with only an increase or no change in sitting systolic and diastolic BP was lower in the tanezumab treatment groups than in the placebo and tramadol PR treatment groups.

  Overall, the incidence of adverse events associated with vital signs was similar across treatment groups during the Treatment Period (ie, up to Week 56). Bradycardia was the most commonly reported adverse event associated with vital signs in the tanezumab groups and it was reported with greater frequency (≥1% difference between treatment groups) in the tanezumab 10 mg treatment group than the tanezumab 5 mg or the tramadol PR treatment groups. Hypertension was the most commonly reported adverse event associated with vital signs in the tramadol PR treatment group; however, Hypertension was infrequently reported in the tanezumab treatment groups.

- **ECG:** No patient had a QTcB (QTc corrected using Bazett's formula) or QTcF (QTcF corrected using Fridericia's formula) value ≥500 msec at any point during the study. The maximum changes in all ECG parameters up to Week 16 and up to the end of the study were similar across the treatment groups.

  ECG abnormalities considered by the Investigator to be clinically significant and any episode of a decrease in heart rate that met protocol criteria for Bradycardia on ECG were to be reported as adverse events. Overall, few ECG-related adverse events were observed during the Treatment Period (ie, up to Week 56). Bradycardia was reported in all treatment groups, with the highest incidence in the tanezumab 10 mg treatment group.

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

CONCLUSIONS

- Tanezumab 10 mg significantly improved pain and function at Week 16 versus placebo.
    - Treatment with tanezumab 10 mg met the primary objective (change from Baseline to Week 16 in the aLBPI score compared to placebo).
    - Treatment with tanezumab 10 mg resulted in significant improvements in all three key secondary efficacy endpoints compared to placebo (change from Baseline to Week 16 in RMDQ score, the proportion of patients with a ≥50% reduction in aLBPI score from Baseline to Week 16, change from Baseline to Week 2 in aLBPI score), applying the gate-keeping strategy.
- Tanezumab 5 mg did not significantly improve pain at Week 16 versus placebo as it did not meet the primary objective (change from Baseline to Week 16 in the aLBPI score compared to placebo). Therefore, further hypothesis testing for the three key secondary endpoints for tanezumab 5 mg could not be performed.
    - Outside the framework of the gate-keeping strategy, treatment with tanezumab 5 mg resulted in numerical improvement in the key secondary endpoints compared to placebo (change from Baseline to Week 16 in RMDQ score [p=0.0035], the proportion of patients with a ≥50% reduction in aLBPI score from Baseline to Week 16 [p=0.0846], change from Baseline to Week 2 in aLBPI score [p=0.0015]).
    - Focusing on nominal (unadjusted) p-values, tanezumab 5 mg treatment resulted in significant improvement from Baseline in the aLBPI score compared to placebo treatment at Week 1 through Week 12 (p-values <0.05, with no multiplicity correction). Tanezumab 5 mg treatment resulted in significant improvement from Baseline in the RMDQ score compared to placebo treatment at Weeks 2, 4, and 8 (p-values <0.05, with no multiplicity correction).
- Treatment with tramadol PR did not result in significant improvements in any of the primary or key secondary efficacy endpoints compared to placebo (p-values ≥0.05, with no multiplicity correction).

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- Reduction relative to Baseline in aLBPI score, RMDQ score, and PGA of Low Back Pain was maintained for tanezumab 5 mg and tanezumab 10 mg treatments over the 56-week Treatment Period.

- 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; the incidence of 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.

    - Based on blinded external neurologist's reviews of the peripheral neurologic adverse events including neurological consult data when available, 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.

- Treatment with tanezumab was associated with an increased incidence of adjudicated joint safety events. Tanezumab 5 mg treatment had a more favorable joint safety profile than tanezumab 10 mg treatment based on the frequency and severity of joint safety events observed.

    - Composite joint safety endpoints occurred in 13 patients (2.6%) in the tanezumab 10 mg treatment group, five patients (1.0%) in the tanezumab 5 mg treatment group, one patient (0.2%) in the tramadol PR treatment group, and no patients in the placebo treatment group. In five of 19 patients (26.3%), the composite joint safety event was associated with a TJR; all of these patients received tanezumab 10 mg. Two additional patients treated with tanezumab 10 mg had a TJR.

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