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GENERIC DRUG NAME / COMPOUND NUMBER: Tanezumab / PF-04383119

PROTOCOL NO.: A4091017

PROTOCOL TITLE: A Phase 3, Randomized, Double Blind, Controlled, Multi-Center Study of the Analgesic Efficacy and Safety of Tanezumab Added on to Diclofenac SR in Patients With Osteoarthritis of the Knee or Hip

Study Centers: A total of 61 centers took part in the study, including 14 centers in the Ukraine, 10 centers in Germany, 8 centers each in Romania and the Russian Federation, 6 centers in Spain, 5 centers each in Austria and Poland, 3 centers in Sweden, and 1 center each in France and the United Kingdom (UK).

Study Initiation and Final Completion Dates: 11 August 2009 to 24 November 2010. The study was terminated prematurely following a United States Food and Drug Administration clinical hold for tanezumab osteoarthritis (OA) clinical studies which halted dosing and enrollment of subjects on 23 June 2010 due to potential safety issues.

Phase of Development: Phase 3

Study Objectives:

Primary Objective: Demonstrate superior efficacy of tanezumab 10 mg, 5 mg, and 2.5 mg administered intravenously (IV) every 8 weeks in combination with oral diclofenac slow release (SR) 75 mg twice daily (BID) versus (vs) placebo administered IV every 8 weeks in combination with oral diclofenac SR 75 mg BID at Week 16.

Secondary Objective: Evaluate safety of tanezumab 10 mg, 5 mg, and 2.5 mg administered IV every 8 weeks in combination with oral diclofenac SR 75 mg BID up to Week 32.

METHODS

Study Design: This was a randomized, double-blind, multicenter, placebo-controlled, parallel-group Phase 3 study of tanezumab in combination with diclofenac SR 75 mg BID in subjects that tolerated diclofenac 150 mg/day but required additional pain relief.

Treatment groups were:

- Three (3) IV doses of tanezumab 10 mg at 8 week intervals in addition to diclofenac SR 75 mg BID;

- Three (3) IV doses of tanezumab 5 mg at 8 week intervals in addition to diclofenac SR 75 mg BID;
- Three (3) IV doses of tanezumab 2.5 mg at 8 week intervals in addition to diclofenac SR 75 mg BID; and
- Three (3) IV doses of placebo (to match tanezumab) at 8 week intervals in addition to diclofenac SR 75 mg BID.

Due to reports of osteonecrosis after tanezumab treatment in OA studies, further dosing with both IV and oral study drugs were stopped in OA studies after 23 June 2010; the study was terminated prematurely.

The schedule of activities is presented in Table 1.

Table 1. Schedule of Activities

Study Activities	Screen[a]	Washout[b]	Initial Pain Assessment Period	Treatment[c,d,e]							End-of-Study/Early Termination
				Baseline[f]	Week 2	Week 4	Week 8	Week 12	Week 16[c]	Week 24[d]	Week 32[e]
	Day -30 to Day -1	Day -30 to Day -3	Day -3 to Day -1	Day 1	Day 15 (±3 Days)	Day 29 (±3 Days)	Day 57 (±5 Days)	Day 85 (±5 Days)	Day 113 (±5 Days)	Day 169 (±5 Days)	Day 225 (±5 Days)
Informed consent	X										
Inclusion/exclusion criteria (x-ray if needed)	X			X							
General medical history	X										
Primary diagnosis/demographics	X										
Physical examination	X										X
Radiographic assessment of hips (bilateral x-ray)											X[g]
Assessment of depression by medical history or PHQ-9 (subject worksheet)[h]	X										
Neurologic exam/[i] neuropathy impairment score	X			X	X	X	X	X	X	X	X
Vital signs (T, BP, HR, RR)	X			X[j]	X	X	X[j]	X	X[j]	X	X
Weight/height/BMI/smoking status/ female hormonal status/alcohol use	X										
Laboratory											
Hematology	X			X		X	X		X	X	X
Blood chemistry	X			X		X	X		X	X	X
Serum and plasma retention samples				X							
Urinalysis	X			X		X	X		X	X	X
Pregnancy test[k]	X			X			X		X	X	X
Serum FSH test[l]	X										
Hemoglobin A1c	X			X			X		X	X	X
Hep screen (Hep B & Hep C)	X										
HIV test	X										
Urine toxicology screen	X										
Serum anti-drug antibody				X			X		X	X	X
Plasma pharmacokinetic samples				X[j]		X	X[j]		X[j]	X	X
De-identified genetic sampling				X							
12-Lead electrocardiogram	X			X[j]		X	X		X	X	X
Discontinue current pain medication[b]		X									
Randomization				X							

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Trial treatments:											
Inject IV study medication				X			X		X		
Dispense oral study medication for screening period	X										
Dispense oral study medication (diclofenac SR 75 mg)				X		X	X	X	X	X	
Subject daily assessments (IVRS)											
Numeric pain scale rating			X----------								----------X
Rescue medication use		X----------									----------X
Subject reported assessments at study visits											
WOMAC pain subscale[m]	X			X	X	X	X	X	X	X	X
WOMAC physical function and stiffness subscales[m]				X	X	X	X	X	X	X	X
Patient Global Assessment of osteoarthritis[m]				X	X	X	X	X	X	X	X
SF-36 health survey[m]				X				X		X	X
EQ-5D[m]				X						X	X
Other assessments completed at study visits											
Adverse event assessment[n]				X[j]	X	X	X[j]	X	X[j]	X	X
Concomitant medication[n]	X			X	X	X	X	X	X	X	X
Review subject compliance with daily assessments	X			X	X	X	X	X	X	X	X
Diclofenac SR return/compliance				X		X	X	X	X	X	X
Dispense rescue medication	X			X		X	X	X	X	X	
Rescue medication return/compliance[o]				X	X	X	X	X	X	X	X

AE = adverse event, BID = twice a daily, BP = blood pressure; BMI = body mass index; EQ-5D = EuroQol 5D Health State Profile; FSH = follicle stimulating hormone; Hep = hepatitis; HR = heart rate; IEC = Independent Ethics Committee; IRB = Institutional Review Board; IV = intravenous; IVRS = Interactive voice response system; PHQ-9 = Patient Health Questionnaire; RR = respiratory rate; SR = sustained release; SF-36 = medical outcomes study short form-36; T = temperature; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

a. The screening period began up to 30 days prior to Randomization and lasted 14-30 days, allowing for a minimum 2 day washout for prohibited non-study medications (ie,

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other than diclofenac SR 75 mg BID) and a minimum 14 consecutive day diclofenac SR 75 mg BID run-in prior to entering the initial pain assessment period. These activities occurred in tandem. Subjects that did not require washout began the initial pain assessment period during the last 3 days of the 14 day diclofenac SR run-in period.

b. All analgesic medications (excluding study supplied diclofenac SR 75 mg BID) in use were discontinued and the washout was a minimum of 48 hours prior to the start of the initial pain assessment period (the 3 days prior to Randomization/Baseline) or ≥5 half-lives of the particular analgesic, whichever was greater.
c. Subjects who received their last dose of IV study medication at Baseline did not receive further doses of IV study medication. Subjects were to return at Week 16 for their Final Clinic Visit (End of Study/Early Termination). At the Week 16 Visit end of study/early termination procedures were performed.
d. Subjects who received their last dose of IV study medication at Week 8 did not receive further doses of IV study medication. Subjects were to return at Week 24 for their Final Clinic Visit (End of Study/Early Termination). At the Week 24 Visit end of study/early termination procedures were performed.
e. Subjects who received their last dose of IV study medication at Week 16, were to return at Week 32 for their Final Clinic Visit (End of Study/Early Termination).
f. All study activities at Baseline (Randomization/Day 1) were performed prior to dosing with study medication, unless otherwise noted.
g. Bilateral x-rays of the hips were obtained at End of Study/Early Termination Visit.
h. Use of the PHQ-9 at Screening was optional and might have been used by the Investigator to help determine if active severe major depression was present at Screening. Subjects with a hospital admission for depression or suicide attempt within 5 years of Screening, or active severe major depression (determined from medical history or a score >15 on questions 1-9 of the PHQ-9) at Screening were excluded from further participation in the study.
i. Subjects were referred to a neurologist for a full neurologic examination if they experienced an AE suggestive of new or worsening peripheral neuropathy, or if AEs of altered peripheral sensation (eg, dysesthesia, paresthesia, allodynia, hyperesthesia or hypoesthesia) were reported. Subjects with pain in the extremities (eg, fingers, hands, feet, soles of feet) that was suggestive of neuropathic pain, such as pain described as burning, shooting electric or tingling, were also referred to a neurologist for a full neurologic examination. Identification of a new or worsened clinically significant finding on the neurologic examination were reported as an AE and the subject was referred to a neurologist.
j. Review AEs occurring after signing informed consent (ie, pretreatment AEs), immediately prior to IV-dosing, and 1 hour post-IV-dose at dosing visits. ECGs were obtained at pre-IV-dose at IV dosing visits and 1 hour post-IV-dose at the Baseline (Randomization/Day 1) Visit. Pharmacokinetic samples and vital signs (T, RR, BP, and HR) were to be obtained pre-IV-dose and 1 hour post-IV-dose (BP and HR only) at all IV-dosing visits.
k. For females of childbearing potential: serum pregnancy test at Screening; urine pregnancy tests at Baseline (Randomization/Day 1) prior to initial IV-dosing, and at Week 8, 16 and 24 Visits; serum pregnancy test at Week 32 (end-of-study or early termination). Pregnancy tests were repeated as per request of IRB/ECs or if required by local regulations.
l. Female subjects of non-child bearing potential who did not had a hysterectomy or bilateral oophorectomy were required to have serum FSH testing at Screening.
m. The WOMAC subscales, Patient Global Assessment of Osteoarthritis, SF-36, and EQ-5D were administered using subject worksheets.
n. Subjects who experienced increased joint pain of a severe and persistent nature were not to continue to receive study medication. These subjects were followed for study-specified safety evaluations for at least 16 weeks after their last dose of IV study medication. These evaluations took place in the clinic for these subjects provided they agreed. Subjects who did not agree to continue with study-specified safety evaluations at clinic visits were followed as per the defined visit time-points for at least 16 weeks after their last dose of IV study medication. These Follow-up Visits were conducted by telephone to determine if the subject experienced any serious AEs or joint replacement surgeries since their previous (in-person at the site or telephone) visit and used any concomitant corticosteroid medication since their previous (in-person at the site or telephone) visit. Subjects reporting joint replacement during a telephone Follow-up Visit were requested to return to the clinic for examination and/or for collection of diagnostic information. Subjects were reminded about study contraceptive requirements (if applicable).

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o. Rescue medication was discontinued 48 hours prior to any study visit.

Number of Subjects (Planned and Analyzed): Approximately 600 subjects (150 subjects per treatment group) were planned to be randomized and 607 subjects were randomized; 59 in Austria, 1 in France and UK, 62 in Germany, 63 each in Poland and Russia, 116 in Romania, 68 in Spain, 9 in Sweden, and 165 in Ukraine.

However, 3 subjects (2 subjects in the placebo plus diclofenac treatment group and 1 subject in the tanezumab 5 mg plus diclofenac treatment group) did not receive any IV study medication. Thus 604 subjects were treated with IV study medication: 152 subjects were treated with placebo plus diclofenac; 157, 150, and 145 subjects were treated with tanezumab 2.5 mg plus diclofenac, tanezumab 5 mg plus diclofenac, and tanezumab 10 mg plus diclofenac, respectively.

Diagnosis and Main Criteria for Inclusion: The study included subjects with OA of the knee or hip according to American College of Rheumatology criteria with Kellgren-Lawrence x-ray grade ≥2; subjects who were experiencing some benefit from their current stable dose regimen of oral diclofenac 150 mg/day and were tolerating their diclofenac regimen; pain and function levels as required by the study at Screening and Baseline; who were willing to discontinue all non-study pain medications throughout the study except as permitted per study; who were willing and able to comply with lifestyle guidelines, scheduled visits, treatment plan, laboratory tests and other study procedures.

Exclusion Criteria: Pregnant women, subjects with body mass index >39; history of other disease that may involve index knee or hip including inflammatory joint diseases, crystalline disease (gout or pseudogout), endocrinopathies, metabolic joint diseases, lupus erythematosus, rheumatoid arthritis, joint infections, neuropathic disorders, avascular necrosis, Paget's disease or tumors; Fibromyalgia, regional pain caused by lumbar or cervical compression with radiculopathy or other moderate to severe pain that may confound assessments or self-evaluation of the pain associated with OA; signs and symptoms of clinically significant cardiac disease within 6 months prior to screening.

Study Treatment: Tanezumab (10 mg/mL, 5 mg/mL, and 2.5 mg/mL concentrations) and matching placebo were provided as blinded supplies. Tanezumab or corresponding placebo was to be administered by an IV infusion over 5 minutes without infusion pump (slow IV push) with a 5 mL flush of sodium chloride for injection at Baseline, Week 8, and Week 16. Diclofenac SR 75 mg was supplied as an oral tablet (open label). Diclofenac SR 75 mg was to be self-administered by the subject orally twice a day (morning and evening) from Screening to Week 32.

Efficacy and Pharmacokinetic Endpoints: The 3 co-primary efficacy endpoints were change from Baseline to Week 16 in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain subscale, the WOMAC Physical Function subscale, and the Patient Global Assessment (PGA) of OA.

The key secondary efficacy endpoint was Outcome Measures in Rheumatology Clinical Trials - Osteoarthritis Research Society International (OMERACT-OARSI) responder index at Week 16. Other secondary efficacy endpoints included change from Baseline to Weeks 2, 4, 8, 12, and 24 for WOMAC Pain subscale; WOMAC Physical Function subscale; and PGA

of OA; change from Baseline to Weeks 2, 4, 8, 12, 16, and 24 for treatment response: reduction in the WOMAC Pain subscale of ≥30%, ≥50%, ≥70% and ≥90%; treatment response: improvement of ≥2 points in PGA of OA; WOMAC Stiffness subscale; WOMAC Average score; WOMAC Pain subscale item: Pain When Walking on a Flat Surface; and WOMAC Pain subscale item: Pain When Going Up or Downstairs; OMERACT-OARSI responder index at Weeks 2, 4, 8, 12, and 24; cumulative distribution of percent change from Baseline in the WOMAC Pain subscale score to Week 16 and 24; average pain score in the index knee or hip change from Baseline to Weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24; Medical Outcomes Study Short Form 36 (SF-36) Health Survey change from Baseline to Weeks 12 and 24 (8 domains plus Physical Component Summary and Mental Component Summary); EuroQol 5D (EQ-5D) Health State Utility (ie Index Score) and Five Items (mobility; self-care; usual activities; pain/discomfort; anxiety/depression); time to discontinuation due to lack of efficacy up to Week 16 and 24; and incidence of discontinuation due to lack of efficacy; usage of rescue medication: incidence of subjects who used rescue medication during Weeks 2, 4, 8, 12, 16 and 24; number of days of rescue medication use per week during Weeks 2, 4, 8, 12, 16 and 24; amount (mg) of rescue medication taken per week during Weeks 2, 4, 8, 12, 16 and 24.

Pharmacokinetic Evaluations: Blood samples for pharmacokinetic (PK) analysis of tanezumab were collected prior to and 1 hour after study drug administration at the dosing visits (Baseline, Weeks 8 and 16) and at Weeks 4, 24, and 32 (or at End of Study/Early Termination).

Safety Evaluations: Adverse events (AEs), concomitant medications, laboratory safety tests, physical and neurological examinations (neuropathy impairment score), vital signs, electrocardiogram (ECG), and the anti-drug antibody (ADA) test.

Statistical Methods: The intent-to-treat (ITT) analysis set was defined as all randomized subjects who received at least 1 dose of IV study medication (either tanezumab or matching placebo). Any subject who received diclofenac and not IV study medication were excluded from this ITT analysis set. This analysis set was used for all presentation of safety data.

The per-protocol analysis set (PPAS) was the secondary efficacy analysis set. It was defined as all subjects in the ITT analysis set who were not major study deviators (which would potentially affect efficacy).

Primary Efficacy Analyses: The co-primary efficacy endpoints were analyzed using an analysis of covariance (ANCOVA) model, with model terms for baseline score, index joint, and treatment group as a factor and study site as a random effect. The primary efficacy endpoints were summarized using last observation carried forward (LOCF) imputation analysis and, in addition, baseline observation carried forward (BOCF) imputation analysis and observed data.

The 3 treatment contrasts (each tanezumab plus diclofenac group vs placebo plus diclofenac) were tested in a step-down manner from tanezumab 10 mg plus diclofenac vs placebo plus diclofenac, to tanezumab 5 mg plus diclofenac vs placebo plus diclofenac, and then to tanezumab 2.5 mg plus diclofenac vs placebo plus diclofenac. The test for a lower dose

group was conditional on statistical significance ($p \leq 0.05$) being achieved for the previous comparison. The step-down testing strategy maintained the Type I error to ≤5% within each of the co-primary efficacy endpoints and to <5% for all 3 co-primary efficacy endpoints.

Additional analysis models for the 3 co-primary endpoints were used to examine the interaction of a range of effects with treatment group using data up to Week 16. These effects included Baseline score, index joint, country, and study site. An additional (main effects ANCOVA) analysis for each of the co-primary efficacy endpoints used a PPAS which excluded subjects who were major study deviators.

Secondary Efficacy Analyses: Secondary efficacy data (except for Average Pain) were summarized using BOCF and LOCF only. Average pain in the index hip/knee was summarized using observed data, BOCF, and LOCF.

All individual plasma tanezumab concentrations were listed and sorted by subject number, tanezumab dose group, and nominal time postdose. Descriptive summaries of the plasma tanezumab concentrations were generated.

Standard safety reporting tables summarized and listed the safety data; nonstandard safety tables were also included.

RESULTS

Subject Disposition and Demography: Among the 846 subjects screened, 607 subjects were randomized; however, 3 subjects (2 subjects assigned to placebo plus diclofenac and 1 subject assigned to tanezumab 5 mg plus diclofenac treatment) did not receive any IV study medication (Table 2).

Table 2. Subject Disposition

Number (%) of Subjects[a]	Placebo + Diclofenac	Tanezumab		
		2.5 mg + Diclofenac	5 mg + Diclofenac	10 mg + Diclofenac
Screened, N=846				
Assigned to study drug	154	157	151	145
Randomized but not treated	2	0	1	0
Randomized and treated[b]	152	157	150	145
Completed study	15 (9.7)	20 (12.7)	19 (12.6)	20 (13.8)
Discontinued study	137 (89.0)	137 (87.3)	131 (86.8)	125 (86.2)

IV = intravenous; N = number of subjects.
a. Percentages were based on the number of subjects randomized.
b. Treated: Treated with IV study medication (either tanezumab or matching placebo).

Discontinuations from the study for the ITT population are presented in Table 3.

Table 3. Discontinuations From Study

Category	Number (%)[a] of Subjects			
	Placebo + Diclofenac N=152	Tanezumab		
		2.5 mg + Diclofenac N=157	5 mg + Diclofenac N=150	10 mg + Diclofenac N=145
Subject died	0	1 (0.6)[b]	0	0
Adverse event	6 (3.9)	8 (5.1)	11 (7.3)	9 (6.2)
Did not meet entrance criteria	0	0	0	0
Insufficient clinical response	9 (5.9)	3 (1.9)	7 (4.7)	2 (1.4)
Lost to follow-up	0	1 (0.6)	0	1 (0.7)
Subject no longer willing to participate in the study	15 (9.9)	11 (7.0)	11 (7.3)	12 (8.3)
Protocol violation	2 (1.3)	1 (0.6)	0	1 (0.7)
Study terminated by Sponsor	105 (69.1)	112 (71.3)	102 (68.0)	99 (68.3)
Withdrawn due to pregnancy	0	0	0	0
Other reasons	0	0	0	1 (0.7)
Total	137 (90.1)	137 (87.3)	131 (87.3)	125 (86.2)

ITT = intent-to-treat; N = number of subjects in each treatment group.
a. Percentages were based on the total number of subjects in each treatment group (ITT).
b. One (1) subject died after having withdrawn due to an adverse event.

The status of subjects at the time the clinical hold went into effect on 23 June 2010 is presented in Table 4.

Table 4. Subject Status at Time of Clinical Hold

	Number (%) of Subjects			
	Placebo + Diclofenac N=152	Tanezumab		
		2.5 mg + Diclofenac N=157	5 mg + Diclofenac N=150	10 mg + Diclofenac N=145
Last study visit completed prior to hold[a]				
Week 8	4 (2.6)	2 (1.3)	1 (<1.0)	3 (2.1)
Week 12	26 (17.1)	25 (15.9)	20 (13.3)	20 (13.8)
Week 16	61 (40.1)	61 (38.9)	63 (42.0)	61 (42.1)
Week 24	29 (19.1)	37 (23.6)	34 (22.7)	27 (18.6)
Total ongoing at time of clinical hold[b]	120 (78.9)	125 (79.6)	118 (78.7)	111 (76.6)
Total discontinued prior to hold[b]	27 (17.8)	20 (12.7)	23 (15.3)	22 (15.2)
Total completed prior to hold[b]	5 (3.3)	12 (7.6)	9 (6.0)	12 (8.3)

N = number of subjects in each treatment group; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
a. Last visit completed prior to clinical hold based on WOMAC data available prior to 23 June 2010.
b. Total subjects ongoing at time of clinical hold were subjects without a status of discontinued or completed on 23 June 2010.

The number of subjects included in the analyses and the subject evaluation groups is presented in Table 5.

Table 5. Number of Subjects (%) Included in the Analyses

Category	Placebo +	Tanezumab

	Diclofenac	2.5 mg + Diclofenac	5 mg + Diclofenac	10 mg + Diclofenac
Randomized to study drug	154	157	151	145
Randomized and treated (ITT population)[a]	152	157	150	145
Analyzed for safety, n (%)[b]				
Adverse events	152 (98.7)	157 (100.0)	150 (99.3)	145 (100.0)
Laboratory data[c]	148 (96.1)	155 (98.7)	147 (97.4)	143 (98.6)

ITT = intent-to-treat; IV = intravenous; n = number of subjects analyzed.
a. Treated: Treated with IV study medication (either tanezumab or matching placebo).
b. Percentages were based on the number of subjects randomized.
c. Included all subjects with a Baseline and ≥1 postbaseline laboratory assessment. The number of subjects with laboratory data was lower than the number treated due to missing samples.

Demographic characteristics and Baseline characteristics are presented in Table 6 and Table 7, respectively.

Table 6. Demographic Characteristics (ITT)

	Number (%) of Subjects			
	Placebo + Diclofenac N=152	Tanezumab		
		2.5 mg + Diclofenac N=157	5 mg + Diclofenac N=150	10 mg + Diclofenac N=145
Gender				
Male	34 (22.4)	36 (22.9)	40 (26.7)	25 (17.2)
Female	118 (77.6)	121 (77.1)	110 (73.3)	120 (82.8)
Age (years)				
18-44	4 (2.6)	6 (3.8)	4 (2.7)	1 (0.7)
45-64	84 (55.3)	86 (54.8)	88 (58.7)	78 (53.8)
≥65	64 (42.1)	65 (41.4)	58 (38.7)	66 (45.5)
Mean (SD)	62.3 (9.4)	62.1 (9.7)	62.2 (9.2)	63.1 (9.1)
Range	39-86	35-84	41-80	43-85
Race				
White	152 (100)	157 (100)	150 (100)	144 (99.3)
Asian	0	0	0	1 (0.7)
Weight (kg)				
Mean (SD)	81.6 (14.6)	80.2 (12.4)	83.4 (13.8)	81.6 (13.0)
Range	52.6-126.6	51.0-116.6	47.0-126.0	45.0-120.0
Body mass index (kg/m^2)				
Mean (SD)	30.8 (4.6)	30.3 (4.0)	30.7 (4.5)	30.8 (4.4)
Range	19.5-38.9	19.3-39.0	21.3-39.0	20.2-38.8

ITT = intent-to-treat; N = number of subjects in each treatment group; SD = standard deviation.

Table 7. Baseline Characteristics (ITT)

Number (%)[a] of Subjects	Placebo + Diclofenac N=152	Tanezumab 2.5 mg + Diclofenac N=157	Tanezumab 5 mg + Diclofenac N=150	Tanezumab 10 mg + Diclofenac N=145
Duration since diagnosis of OA of the index joint (years)[b]				
Mean	6.1	6.1	6.7	6.6
Range	0.1-29.8	0.0-40.1	0.2-29.9	0.1-30.0
Index joint				
Knee	121 (79.6)	121 (77.1)	115 (76.7)	117 (80.7)
Hip	31 (20.4)	36 (22.9)	35 (23.3)	28 (19.3)
Kellgren-Lawrence x-ray grade[c]				
Grade 2	68 (44.7)	77 (49.0)	64 (42.7)	73 (50.3)
Grade 3	68 (44.7)	68 (43.3)	71 (47.3)	62 (42.8)
Grade 4	16 (10.5)	12 (7.6)	15 (10.0)	10 (6.9)
Kellgren-Lawrence x-ray grade for knee[c]				
Grade 2	54 (44.6)	60 (49.6)	48 (41.7)	59 (50.4)
Grade 3	54 (44.6)	54 (44.6)	57 (49.6)	51 (43.6)
Grade 4	13 (10.7)	7 (5.8)	10 (8.7)	7 (6.0)
Kellgren-Lawrence x-ray grade for hip[c]				
Grade 2	14 (45.2)	17 (47.2)	16 (45.7)	14 (50.0)
Grade 3	14 (45.2)	14 (38.9)	14 (40.0)	11 (39.3)
Grade 4	3 (9.7)	5 (13.9)	5 (14.3)	3 (10.7)
WOMAC Pain subscale score at Screening (0 to 10 NRS)[d]				
n	152	157	150	145
Mean (SD)	6.16 (1.28)	6.08 (1.39)	6.08 (1.39)	6.26 (1.32)
Min, max	3.20, 9.60	2.80, 9.40	1.40, 9.60	4.00, 9.40
WOMAC Pain subscale score at Baseline (0 to 10 NRS)[d]				
n	152	156	150	145
Mean (SD)	6.06 (1.23)	5.78 (1.36)	5.76 (1.32)	5.87 (1.30)
Min, max	4.00, 9.60	1.80, 9.40	1.20, 9.60	3.20, 9.60
WOMAC Physical Function subscale score at Baseline (0 to 10 NRS)[d]				
n	152	156	150	145
Mean (SD)	6.24 (1.45)	5.86 (1.51)	5.90 (1.22)	5.91 (1.36)
Min, max	2.76, 9.53	0.65, 9.71	1.47, 8.82	1.71, 9.59
WOMAC Stiffness subscale score at Baseline (0 to 10 NRS)[d]				
n	152	156	150	145
Mean (SD)	5.84 (1.78)	5.61 (1.85)	5.51 (1.52)	5.60 (1.78)
Min, max	0.00, 10.00	0.50, 10.00	0.50, 9.00	1.50, 10.00
Average pain in the index knee at Baseline (0 to 10 NRS)[d]				
n	142	150	141	134
Mean (SD)	6.31 (1.39)	6.29 (1.30)	6.38 (1.48)	6.34 (1.31)
Min, max	0.00, 9.33	1.67, 9.00	1.00, 10.00	0.50, 9.33
PGA of OA at Baseline (5-point Likert scale)[e]				
Total	152	157	150	145
Good	2 (1.3)	0	0	2 (1.4)
Fair	92 (60.5)	114 (72.6)	91 (60.7)	91 (62.8)
Poor	54 (35.5)	41 (26.1)	54 (36.0)	49 (33.8)
Very poor	4 (2.6)	1 (<1.0)	5 (3.3)	3 (2.1)
Missing	0	1 (<1.0)	0	0

Table 7. Baseline Characteristics (ITT)

ITT = intent-to-treat; max = maximum; min = minimum; N = number of subjects in each treatment group; n = number of subjects with data available; NRS = numeric rating scale; OA = osteoarthritis; PGA = Patient Global Assessment; SD = standard deviation; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

a. Percentages were based on the total number of subjects in each treatment group (ITT).
b. Duration from first diagnosis to Day 1 of the study.
c. No subject had a Kellgren-Lawrence Grade of 0 or 1 at Baseline.
d. Collected via daily subject diary during the Initial Pain Assessment Period.
e. No subject had a PGA of OA score of 'very good' at Baseline.

Efficacy and Pharmacokinetic Results:

Efficacy Results: The changes from Baseline to Week 16 for the 3 co-primary endpoints using LOCF imputation of missing data are presented in Table 8.

Table 8. Summary of Co-Primary Efficacy Endpoints, Change From Baseline to Week 16 (ITT, LOCF)

Primary Efficacy Endpoint	Placebo + Diclofenac N=152	Tanezumab 2.5 mg + Diclofenac N=157[a]	Tanezumab 5 mg + Diclofenac N=150	Tanezumab 10 mg + Diclofenac N=145
WOMAC Pain Subscale[b], Baseline and Change From Baseline to Week 16 (0 to 10 NRS)				
Baseline Mean (SD)	6.06 (1.23)	5.78 (1.36)	5.76 (1.32)	5.87 (1.30)
Change from Baseline LS mean (SE)*	-1.68 (0.19)	-2.09 (0.18)	-2.19 (0.19)	-2.25 (0.19)
95% CI for LS mean	-2.04, -1.31	-2.45, -1.73	-2.56, -1.83	-2.62, -1.88
Comparison vs placebo + diclofenac				
Change from Baseline LS mean (SE)		-0.42 (0.20)	-0.52 (0.20)	-0.57 (0.20)
95% CI for LS mean		-0.81, -0.02	-0.91, -0.12	-0.97, -0.17
p-Value†		0.039	0.011	0.005
WOMAC Physical Function Subscale[b], Baseline and Change From Baseline to Week 16 (0 to 10 NRS)				
Baseline mean (SD)	6.24 (1.45)	5.86 (1.51)	5.90 (1.22)	5.91 (1.36)
Change from Baseline LS mean (SE)*	-1.53 (0.19)	-2.05 (0.18)	-2.16 (0.19)	-2.23 (0.19)
95% CI for LS mean	-1.90, -1.17	-2.41, -1.69	-2.53, -1.80	-2.61, -1.86
Comparison vs placebo + diclofenac				
Change from Baseline LS mean (SE)		-0.51 (0.20)	-0.63 (0.20)	-0.70 (0.20)
95% CI		-0.91, -0.12	-1.03, -0.23	-1.10, -0.30
p-Value†		0.010	0.002	<0.001
PGA of OA[c], Baseline and Change From Baseline to Week 16 (5-Point Likert Scale)				
Baseline mean (SD)	3.39 (0.57)	3.28 (0.46)	3.43 (0.56)	3.37 (0.55)
Change from Baseline LS mean (SE)*	-0.34 (0.07)	-0.52 (0.07)	-0.52 (0.07)	-0.58 (0.07)
95% CI for LS mean	-0.48, -0.21	-0.65, -0.38	-0.65, -0.39	-0.72, -0.45
Comparison vs placebo + diclofenac				
Change from Baseline LS mean (SE)		-0.17 (0.08)	-0.18 (0.08)	-0.24 (0.08)
95% CI		-0.32, -0.03	-0.33, -0.03	-0.40, -0.09
p-Value†		0.022	0.020	0.002

*LS means were estimated from the corresponding ANCOVA model. The ANCOVA model included treatment as main effect, baseline value and index joint as covariates and study site as random effect.
†p-Value was based on ANCOVA from pairwise comparisons.
ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent-to-treat; LOCF = last observation carried forward; LS = least squares; N = number of subjects in each treatment group; NRS = numeric rating scale; OA = osteoarthritis; PGA of OA = Patient Global Assessment of Osteoarthritis; SD = standard deviation; SE = standard error; vs = versus; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

a. One (1) subject had missing baseline data for all efficacy parameters and is thus not included in any efficacy evaluations.
b. WOMAC subscale scores ranged from 0 to 10, where 0 was the best response. A change from Baseline of <0 was an improvement.
c. PGA of OA was assessed with a 5-point Likert scale. A change from Baseline of <0 was an improvement.

Secondary efficacy analyses of the WOMAC Pain subscale, WOMAC Physical Function subscale, and the PGA of OA included analysis for the change from Baseline to Weeks 2, 4, 8, 12, and 24 Table 9, Table 10, and Table 11, respectively.

Table 9. Summary of Analysis of Change From Baseline for the WOMAC Pain Subscale by Week (ITT, LOCF)

	Placebo IV + Diclofenac (N=152)	Tanezumab 2.5 mg + Diclofenac (N=157)	Tanezumab 5 mg + Diclofenac (N=150)	Tanezumab 10 mg + Diclofenac (N=145)
Week 2 (LOCF)				
LS mean (SE)[a]	-1.33 (0.14)	-1.32 (0.14)	-1.31 (0.14)	-0.94 (0.15)
95% CI for LS mean	(-1.61, -1.05)	(-1.60, -1.04)	(-1.59, -1.03)	(-1.23, -0.65)
Versus placebo IV + diclofenac				
LS mean difference (SE)		0.01 (0.17)	0.02 (0.17)	0.39 (0.17)
95% CI for LS mean difference		(-0.32, 0.34)	(-0.31, 0.35)	(0.06, 0.72)
p-Value[b]		0.957	0.899	0.022
Week 4 (LOCF)				
LS mean (SE)[a]	-1.48 (0.15)	-1.83 (0.15)	-2.17 (0.15)	-1.96 (0.16)
95% CI for LS mean	(-1.78, -1.18)	(-2.13, -1.53)	(-2.48, -1.87)	(-2.27, -1.65)
Versus placebo IV + diclofenac				
LS Mean difference (SE)		-0.35 (0.18)	-0.69 (0.18)	-0.48 (0.18)
95% CI for LS mean difference		(-0.70, 0.00)	(-1.05, -0.34)	(-0.84, -0.13)
p-Value[b]		0.052	<.001	0.008
Week 8 (LOCF)				
LS mean (SE)[a]	-1.54 (0.17)	-1.89 (0.17)	-2.23 (0.17)	-2.29 (0.17)
95% CI for LS mean	(-1.87, -1.21)	(-2.22, -1.57)	(-2.56, -1.89)	(-2.63, -1.95)
Versus placebo IV + diclofenac				
LS mean difference (SE)		-0.35 (0.19)	-0.69 (0.19)	-0.75 (0.19)
95% CI for LS mean difference		(-0.72, 0.01)	(-1.05, -0.32)	(-1.12, -0.38)
p-Value[b]		0.058	<.001	<.001
Week 12 (LOCF)				
LS mean (SE)[a]	-1.71 (0.18)	-2.24 (0.18)	-2.51 (0.18)	-2.38 (0.18)
95% CI for LS mean	(-2.06, -1.36)	(-2.59, -1.89)	(-2.86, -2.16)	(-2.74, -2.02)
Versus placebo IV + diclofenac				
LS Mean difference (SE)		-0.53 (0.19)	-0.80 (0.20)	-0.66 (0.20)
95% CI for LS mean difference		(-0.91, -0.15)	(-1.18, -0.41)	(-1.05, -0.28)
p-Value[b]		0.007	<.001	<.001
Week 16 (LOCF)				
LS mean (SE)[a]	-1.68 (0.19)	-2.09 (0.18)	-2.19 (0.19)	-2.25 (0.19)
95% CI for LS mean	(-2.04, -1.31)	(-2.45, -1.73)	(-2.56, -1.83)	(-2.62, -1.88)
Versus placebo IV + diclofenac				
LS mean difference (SE)		-0.42 (0.20)	-0.52 (0.20)	-0.57 (0.20)
95% CI for LS mean difference		(-0.81, -0.02)	(-0.91, -0.12)	(-0.97, -0.17)
p-Value[b]		0.039	0.011	0.005
Week 24 (LOCF)				
LS mean (SE)[a]	-1.61 (0.20)	-2.04 (0.20)	-2.17 (0.20)	-2.05 (0.20)
95% CI for LS mean	(-2.01, -1.22)	(-2.43, -1.66)	(-2.57, -1.78)	(-2.45, -1.65)
Versus placebo IV + diclofenac				
LS mean difference (SE)		-0.43 (0.22)	-0.56 (0.22)	-0.44 (0.22)
95% CI for LS Mean difference		(-0.85, 0.00)	(-0.99, -0.13)	(-0.87, -0.00)
p-Value[b]		0.051	0.011	0.048

Table 9. Summary of Analysis of Change From Baseline for the WOMAC Pain Subscale by Week (ITT, LOCF)

A change from Baseline <0 is an improvement.
ANCOVA model included treatment as main effect, baseline value and index joint as covariates, and study site as a random effect.
ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent-to-treat; IV = intravenous; LOCF = last observation carried forward; LS = least squares; N = number of subjects in each treatment group; SE = standard error; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
a. LS means were estimated from the corresponding ANCOVA model.
b. The p-value was based on ANCOVA from pairwise comparisons.

Table 10. Summary of Analysis of Change From Baseline for the WOMAC Physical Function Subscale by Week (ITT, LOCF)

	Placebo IV + Diclofenac (N=152)	Tanezumab		
		2.5 mg + Diclofenac (N=157)	5 mg + Diclofenac (N=150)	10 mg + Diclofenac (N=145)
Week 2 (LOCF)				
LS mean (SE)[a]	-1.29 (0.14)	-1.25 (0.14)	-1.35 (0.14)	-1.12 (0.15)
95% CI for LS mean	(-1.57, -1.01)	(-1.52, -0.97)	(-1.63, -1.07)	(-1.41, -0.83)
Versus placebo IV + diclofenac				
LS mean difference (SE)		0.05 (0.15)	-0.06 (0.16)	0.17 (0.16)
95% CI for LS mean difference		(-0.25, 0.35)	(-0.36, 0.25)	(-0.13, 0.48)
p-Value[b]		0.754	0.706	0.266
Week 4 (LOCF)				
LS mean (SE)[a]	-1.42 (0.16)	-1.65 (0.16)	-2.14 (0.16)	-1.85 (0.17)
95% CI for LS mean	(-1.74, -1.10)	(-1.97, -1.34)	(-2.46, -1.82)	(-2.17, -1.52)
Versus placebo IV + diclofenac				
LS mean difference (SE)		-0.23 (0.18)	-0.72 (0.18)	-0.43 (0.18)
95% CI for LS mean difference		(-0.58, 0.12)	(-1.07, -0.36)	(-0.78, -0.07)
p-Value[b]		0.195	<.001	0.019
Week 8 (LOCF)				
LS mean (SE)[a]	-1.46 (0.17)	-1.74 (0.17)	-2.20 (0.17)	-2.08 (0.18)
95% CI for LS mean	(-1.80, -1.12)	(-2.08, -1.41)	(-2.53, -1.86)	(-2.42, -1.73)
Versus placebo IV + diclofenac				
LS mean difference (SE)		-0.28 (0.18)	-0.73 (0.19)	-0.62 (0.19)
95% CI for LS mean difference		(-0.64, 0.08)	(-1.10, -0.37)	(-0.98, -0.25)
p-Value[b]		0.126	<.001	0.001
Week 12 (LOCF)				
LS mean (SE)[a]	-1.60 (0.18)	-2.13 (0.17)	-2.43 (0.18)	-2.24 (0.18)
95% CI for LS mean	(-1.95, -1.25)	(-2.47, -1.78)	(-2.78, -2.08)	(-2.60, -1.88)
Versus placebo IV + diclofenac				
LS mean difference (SE)		-0.52 (0.19)	-0.82 (0.19)	-0.64 (0.20)
95% CI for LS mean difference		(-0.90, -0.15)	(-1.21, -0.44)	(-1.02, -0.25)
p-Value[b]		0.007	<.001	0.001
Week 16 (LOCF)				
LS mean (SE)[a]	-1.53 (0.19)	-2.05 (0.18)	-2.16 (0.19)	-2.23 (0.19)
95% CI for LS mean	(-1.90, -1.17)	(-2.41, -1.69)	(-2.53, -1.80)	(-2.61, -1.86)
Versus placebo IV + diclofenac				
LS mean difference (SE)		-0.51 (0.20)	-0.63 (0.20)	-0.70 (0.20)
95% CI for LS mean difference		(-0.91, -0.12)	(-1.03, -0.23)	(-1.10, -0.30)
p-Value[b]		0.010	0.002	<.001
Week 24 (LOCF)				
LS mean (SE)[a]	-1.46 (0.20)	-1.91 (0.20)	-2.08 (0.20)	-1.95 (0.21)
95% CI for LS mean	(-1.86, -1.07)	(-2.30, -1.52)	(-2.47, -1.68)	(-2.35, -1.54)
Versus placebo IV + diclofenac				
LS mean difference (SE)		-0.44 (0.22)	-0.61 (0.22)	-0.48 (0.22)
95% CI for LS mean difference		(-0.87, -0.02)	(-1.04, -0.19)	(-0.92, -0.05)

Table 10. Summary of Analysis of Change From Baseline for the WOMAC Physical Function Subscale by Week (ITT, LOCF)

	Placebo IV + Diclofenac (N=152)	Tanezumab		
		2.5 mg + Diclofenac (N=157)	5 mg + Diclofenac (N=150)	10 mg + Diclofenac (N=145)
p-Value[b]		0.041	0.005	0.028

A change from Baseline <0 was an improvement.
ANCOVA model included treatment as main effect, baseline value and index joint as covariates, and study site as a random effect.
ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent-to-treat; IV = intravenous, LOCF = last observation carried forward; LS = least squares; N = number of subjects in each treatment group; SE = standard error; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
a. LS means were estimated from the corresponding ANCOVA model.
b. The p-value was based on ANCOVA from pairwise comparisons.

Table 11. Summary of Analysis of the Change From Baseline for the Patient Global Assessment of Osteoarthritis by Week (ITT, LOCF)

	Placebo IV + Diclofenac (N=152)	Tanezumab 2.5 mg + Diclofenac (N=157)	Tanezumab 5 mg + Diclofenac (N=150)	Tanezumab 10 mg + Diclofenac (N=145)
Week 2 (LOCF)				
LS mean (SE)[a]	-0.38 (0.06)	-0.47 (0.06)	-0.40 (0.06)	-0.33 (0.06)
95% CI for LS mean	(-0.51, -0.26)	(-0.59, -0.34)	(-0.53, -0.28)	(-0.46, -0.20)
Versus placebo IV + diclofenac				
LS mean difference (SE)		-0.09 (0.07)	-0.02 (0.07)	0.05 (0.07)
95% CI for LS mean difference		(-0.22, 0.05)	(-0.15, 0.11)	(-0.08, 0.18)
p-Value[b]		0.200	0.754	0.449
Week 4 (LOCF)				
LS mean (SE)[a]	-0.39 (0.06)	-0.52 (0.06)	-0.61 (0.06)	-0.55 (0.06)
95% CI for LS mean	(-0.52, -0.27)	(-0.65, -0.40)	(-0.74, -0.49)	(-0.68, -0.42)
Versus placebo IV + diclofenac				
LS mean difference (SE)		-0.13 (0.07)	-0.22 (0.07)	-0.16 (0.07)
95% CI for LS mean difference		(-0.27, 0.01)	(-0.36, -0.08)	(-0.30, -0.02)
p-Value[b]		0.062	0.002	0.026
Week 8 (LOCF)				
LS mean (SE)[a]	-0.32 (0.07)	-0.48 (0.07)	-0.65 (0.07)	-0.62 (0.07)
95% CI for LS mean	(-0.45, -0.18)	(-0.61, -0.34)	(-0.78, -0.51)	(-0.76, -0.49)
Versus placebo IV + diclofenac				
LS mean difference (SE)		-0.16 (0.07)	-0.33 (0.07)	-0.31 (0.08)
95% CI for LS mean difference		(-0.31, -0.01)	(-0.48, -0.19)	(-0.45, -0.16)
p-Value[b]		0.032	<.001	<.001
Week 12 (LOCF)				
LS mean (SE)[a]	-0.43 (0.07)	-0.58 (0.07)	-0.65 (0.07)	-0.61 (0.07)
95% CI for LS mean	(-0.56, -0.29)	(-0.72, -0.45)	(-0.78, -0.51)	(-0.75, -0.47)
Versus placebo IV + diclofenac				
LS mean difference (SE)		-0.15 (0.07)	-0.22 (0.07)	-0.18 (0.08)
95% CI for LS mean difference		(-0.30, -0.01)	(-0.37, -0.07)	(-0.33, -0.03)
p-Value[b]		0.038	0.003	0.016
Week 16 (LOCF)				
LS mean (SE)[a]	-0.34 (0.07)	-0.52 (0.07)	-0.52 (0.07)	-0.58 (0.07)
95% CI for LS mean	(-0.48, -0.21)	(-0.65, -0.38)	(-0.65, -0.39)	(-0.72, -0.45)
Versus placebo IV + diclofenac				
LS mean difference (SE)		-0.17 (0.08)	-0.18 (0.08)	-0.24 (0.08)
95% CI for LS mean difference		(-0.32, -0.03)	(-0.33, -0.03)	(-0.40, -0.09)
p-Value[b]		0.022	0.020	0.002
Week 24 (LOCF)				
LS mean (SE)[a]	-0.39 (0.07)	-0.48 (0.07)	-0.48 (0.07)	-0.51 (0.07)
95% CI for LS mean	(-0.53, -0.25)	(-0.62, -0.34)	(-0.62, -0.34)	(-0.66, -0.37)
Versus placebo IV + diclofenac				
LS mean difference (SE)		-0.09 (0.08)	-0.09 (0.08)	-0.13 (0.08)
95% CI for LS mean difference		(-0.25, 0.07)	(-0.25, 0.07)	(-0.28, 0.03)
p-Value[b]		0.271	0.261	0.124

Table 11. Summary of Analysis of the Change From Baseline for the Patient Global Assessment of Osteoarthritis by Week (ITT, LOCF)

A change from Baseline <0 was an improvement.
ANCOVA model included treatment as main effect, baseline value and index joint as covariates, and study site as a random effect.
ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent-to-treat; IV = intravenous, LOCF = last observation carried forward; LS = least squares; N = number of subjects in each treatment group; SE = standard error.
a. LS means were estimated from the corresponding ANCOVA model.
b. The p-value was based on ANCOVA from pairwise comparisons.

The changes from Baseline to Week 16 for the WOMAC Stiffness subscale and other secondary endpoints are presented in Table 12.

Table 12. Summary of WOMAC Secondary Efficacy Endpoints, Change From Baseline to Week 16 (ITT, LOCF)

Secondary Efficacy Endpoint	Placebo + Diclofenac N=152	Tanezumab 2.5 mg + Diclofenac N=157[a]	Tanezumab 5 mg + Diclofenac N=150	Tanezumab 10 mg + Diclofenac N=145
WOMAC Stiffness Subscale[b] Baseline and Change From Baseline to Week 16 (0 to 10 NRS)				
Baseline mean (SD)	5.84 (1.78)	5.61 (1.85)	5.51 (1.52)	5.60 (1.78)
Change from Baseline LS mean (SE)*	-1.51 (0.20)	-2.19 (0.20)	-2.13 (0.20)	-2.44 (0.21)
95% CI for LS mean	-1.91, -1.12	-2.58, -1.80	-2.53, -1.74	-2.84, -2.04
Comparison vs placebo + diclofenac				
Change from Baseline LS mean difference (SE)		-0.68 (0.21)	-0.62 (0.22)	-0.93 (0.22)
95% CI for LS mean difference		-1.10, -0.26	-1.04, -0.19	-1.36, -0.50
p-Value†		0.002	0.004	<0.001
WOMAC Average Score[b] Baseline and Change From Baseline to Week 16 (0 to 10 NRS)				
Baseline mean (SD)	6.05 (1.31)	5.75 (1.43)	5.72 (1.19)	5.80 (1.32)
Change from Baseline LS mean (SE)*	-1.58 (0.18)	-2.11 (0.18)	-2.16 (0.18)	-2.31 (0.19)
95% CI for LS mean	-1.94, -1.22	-2.47, -1.76	-2.52, -1.80	-2.67, -1.94
Comparison vs placebo + diclofenac				
Change from Baseline LS mean difference (SE)		-0.53 (0.19)	-0.57 (0.20)	-0.72 (0.20)
95% CI for LS mean difference		-0.91, -0.15	-0.96, -0.19	-1.11, -0.33
p-Value†		0.007	0.004	<0.001
WOMAC Pain Subscale[b] Item When Walking on a Flat Surface, Baseline and Change From Baseline to Week 16 (0 to 10 NRS)				
Baseline mean (SD)	6.12 (1.67)	5.91 (1.74)	5.81 (1.54)	5.99 (1.71)
Change from Baseline LS mean (SE)*	-1.73 (0.20)	-2.06 (0.20)	-2.05 (0.20)	-2.17 (0.21)
95% CI for LS mean	-2.13, -1.33	-2.45, -1.66	-2.45, -1.65	-2.58, -1.76
Comparison vs placebo + diclofenac				
Change from Baseline LS mean difference (SE)		-0.32 (0.22)	-0.31 (0.23)	-0.44 (0.23)
95% CI for LS mean difference		-0.77, 0.12	-0.76, 0.13	-0.89, 0.01
p-Value†		0.149	0.166	0.055
WOMAC Pain Subscale[b] Item When Going up or Down Stairs, Baseline and Change From Baseline to Week 16 (0 to 10 NRS)				
Baseline mean (SD)	7.24 (1.57)	7.04 (1.65)	7.05 (1.63)	7.06 (1.62)
Change from Baseline LS mean (SE)*	-1.85 (0.21)	-2.50 (0.20)	-2.46 (0.21)	-2.71 (0.21)
95% CI for LS mean	-2.25, -1.44	-2.90, -2.10	-2.87, -2.06	-3.13, -2.29
Comparison vs placebo + diclofenac				
Change from Baseline LS mean difference (SE)		-0.65 (0.23)	-0.62 (0.24)	-0.86 (0.24)
95% CI for LS mean difference		-1.11, -0.19	-1.08, -0.15	-1.33, -0.40
p-Value†		0.005	0.009	<0.001

* LS means were estimated from the corresponding ANCOVA model. The ANCOVA model included treatment as main effect, baseline value and index joint as covariate, and study site as random effect.
† p-Value was based on ANCOVA from pairwise comparisons.
ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent-to-treat; LOCF = last observation carried forward; LS = least squares; N = number of subjects in each treatment group; NRS = numeric rating scale; SD = standard deviation; SE = standard error; vs = versus; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

a. One (1) subject had missing baseline data for all efficacy parameters and was thus not included in any efficacy evaluation.
b. WOMAC subscale scores ranged from 0 to 10, where 0 was the best response. A change from Baseline <0 was an improvement.

OMERACT-OARSI responses with all 3 doses of tanezumab plus diclofenac from Baseline to Weeks 16 and 24 in comparison with placebo plus diclofenac treatment are presented in Table 13.

Table 13. Summary of Analysis of OMERACT-OARSI Response[a] From Baseline to Week 16 and Week 24, Comparison With Placebo (ITT, LOCF)

Secondary Efficacy Endpoint	Placebo + Diclofenac N=152	Tanezumab		
		2.5 mg + Diclofenac N=157[b]	5 mg + Diclofenac N=150	10 mg + Diclofenac N=145
OMERACT-OARSI response from Baseline to Week 16				
Yes, n (%)	88 (57.9)	104 (66.7)	100 (66.7)	105 (72.4)
No, n (%)	64 (42.1)	52 (33.3)	50 (33.3)	40 (27.6)
vs placebo + diclofenac				
Odds ratio		1.52	1.52	1.95
95% CI for odds ratio		0.95, 2.42	0.95, 2.44	1.19, 3.17
p-Value*		0.080	0.081	0.008
Week 24				
Yes, n (%)	84 (55.3)	102 (65.4)	97 (64.7)	98 (67.6)
No, n (%)	68 (44.7)	54 (34.6)	53 (35.3)	47 (32.4)
vs placebo + diclofenac				
Odds ratio		1.64	1.59	1.75
95% CI for odds ratio		1.03, 2.61	0.99, 2.55	1.08, 2.82
p-Value*		0.039	0.053	0.022

* Odds ratio, 95% CI, and p-value were based on a logistic regression model (with treatment as main effect, and baseline WOMAC Pain score and index joint as covariates) from pairwise comparisons vs placebo.
CI = confidence interval; ITT = intent-to-treat; LOCF = last observation carried forward; N = number of subjects in each treatment group; n = number of subjects with/without a response; OA = osteoarthritis; OARSI = Osteoarthritis Research Society International; OMERACT = Outcome Measures in Rheumatology Clinical Trials; PGA = Patient Global Assessment; vs = versus; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

a. OMERACT response criteria were as follows: The change (improvement) from Baseline to Week 16 was ≥50% (percentage change) and ≥2 (absolute change) in either the WOMAC Pain or Physical Function subscales, or at least 2 of the following 3 were true: 1. The change (improvement) from Baseline to Week 16 was ≥20% (percentage change) and ≥1 (absolute change) in the WOMAC Pain subscale; 2. The change (improvement) from Baseline to Week 16 was ≥20% (percentage change) and ≥1 (absolute change) in the WOMAC Physical Function subscale; 3. The change (improvement) from Baseline to Week 16 was ≥20% (percentage change) and ≥1 (absolute change) in the PGA of OA (note: from the 5-point Likert scale, any change of ≥1 was also a change of ≥20%).
b. One (1) subject had missing baseline data for all efficacy parameters and was thus not included in any efficacy evaluation. Percentages were based on 156 subjects in this group.

The analysis of WOMAC Pain subscale treatment response for change from Baseline to Week 16 and Week 24 using LOCF imputation for missing data (ie, where a subject with missing data is counted as a nonresponder) are presented in Table 14.

Table 14. WOMAC Pain Subscale Reduction: ≥30%, ≥50%, ≥70%, and ≥90% Improvement From Baseline to Week 16 and Week 24, Comparison With Placebo (ITT, LOCF)

Secondary Efficacy Endpoint	Placebo + Diclofenac N=152	Tanezumab		
		2.5 mg + Diclofenac N=157[a]	5 mg + Diclofenac N=150	10 mg + Diclofenac N=145
Reduction ≥30% from Baseline to:				
Week 16				
Odds ratio		1.25	1.66	2.01
95% CI		0.79, 1.96	1.05, 2.64	1.25, 3.21
p-Value*		0.336	0.031	0.004
Week 24				
Odds ratio		1.58	1.66	1.61
95% CI		1.01, 2.49	1.05, 2.62	1.02, 2.56
p-Value*		0.048	0.032	0.043
Reduction ≥50% from Baseline to:				
Week 16				
Odds ratio		1.26	1.50	2.15
95% CI		0.78, 2.03	0.93, 2.42	1.33, 3.45
p-Value*		0.343	0.095	0.002
Week 24				
Odds ratio		1.57	1.68	1.82
95% CI		0.97, 2.54	1.04, 2.72	1.12, 2.96
p-Value*		0.064	0.036	0.015
Reduction ≥70% from Baseline to:				
Week 16				
Odds ratio		1.32	1.57	1.53
95% CI		0.70, 2.47	0.84, 2.92	0.82, 2.87
p-Value*		0.393	0.154	0.185
Week 24				
Odds ratio		1.52	1.95	1.84
95% CI		0.81, 2.85	1.05, 3.61	0.99, 3.45
p-Value*		0.196	0.035	0.055
Reduction ≥90% from Baseline to:				
Week 16				
Odds ratio		2.77	3.23	3.48
95% CI		0.73, 10.52	0.87, 12.07	0.93, 12.95
p-Value*		0.134	0.081	0.063
Week 24				
Odds ratio		1.95	1.86	2.05
95% CI		0.72, 5.33	0.67, 5.14	0.74, 5.66
p-Value*		0.192	0.233	0.164

* Odds ratio, 95% CI, and p-value were based on logistic regression model (with treatment as a main effect, baseline WOMAC Pain score and index joint as covariates) from pairwise comparisons versus placebo plus diclofenac.

CI = confidence interval; ITT = intent-to-treat; LOCF = last observation carried forward; N = number of subjects in each treatment group; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

a. One (1) subject had missing baseline data for all efficacy parameters and was thus not included in any efficacy evaluation.

The proportion of subjects who experienced a reduction (improvement) in pain on the WOMAC Pain subscale of ≥30, ≥50, ≥70, and ≥90% from Baseline to Weeks 2, 4, 8, 12, 16, and 24 is summarized in Table 15.

Table 15. WOMAC Pain Subscale Reduction: ≥30%, ≥50%, ≥70%, and ≥90% Improvement From Baseline to Weeks 2, 4, 8, 12, 16, and 24 (ITT, LOCF)

Secondary Efficacy Endpoint	Response, n (%)			
	Placebo + Diclofenac N=152	Tanezumab		
		2.5 mg + Diclofenac N=157[a]	5 mg + Diclofenac N=150	10 mg + Diclofenac N=145
Reduction ≥30% from Baseline at:				
Week 2	46 (30.3)	45 (28.8)	48 (32.0)	35 (24.1)
Week 4	64 (42.1)	81 (51.9)	86 (57.3)*	73 (50.3)
Week 8	66 (43.4)	81 (51.9)	86 (57.3)*	92 (63.4)†
Week 12	74 (48.7)	89 (57.1)	96 (64.0)*	92 (63.4)*
Week 16	76 (50.0)	85 (54.5)	92 (61.3)*	96 (66.2)*
Week 24	73 (48.0)	91 (58.3)*	89 (59.3)*	86 (59.3)*
Reduction ≥50% from Baseline at:				
Week 2	21 (13.8)	25 (16.0)	25 (16.7)	13 (9.0)
Week 4	26 (17.1)	42 (26.9)	51 (34.0)*	44 (30.3)*
Week 8	38 (25.0)	43 (27.6)	57 (38.0)*	56 (38.6)*
Week 12	41 (27.0)	57 (36.5)	70 (46.7)†	62 (42.8)*
Week 16	47 (30.9)	56 (35.9)	60 (40.0)	71 (49.0)*
Week 24	43 (28.3)	60 (38.5)	60 (40.0)*	61 (42.1)*
Reduction ≥70% from Baseline at:				
Week 2	7 (4.6)	10 (6.4)	11 (7.3)	4 (2.8)
Week 4	9 (5.9)	16 (10.3)	19 (12.7)	17 (11.7)
Week 8	6 (3.9)	15 (9.6)	26 (17.3)†	28 (19.3)†
Week 12	11 (7.2)	26 (16.7)*	36 (24.0)†	36 (24.8)†
Week 16	20 (13.2)	27 (17.3)	30 (20.0)	28 (19.3)
Week 24	19 (12.5)	29 (18.6)	34 (22.7)*	31 (21.4)
Reduction ≥90% from Baseline at:				
Week 2	3 (2.0)	2 (1.3)	2 (1.3)	1 (<1.0)
Week 4	3 (2.0)	3 (1.9)	9 (6.0)	3 (2.1)
Week 8	3 (2.0)	8 (5.1)	7 (4.7)	9 (6.2)
Week 12	3 (2.0)	10 (6.4)	13 (8.7)*	7 (4.8)
Week 16	3 (2.0)	9 (5.8)	10 (6.7)	10 (6.9)
Week 24	6 (3.9)	13 (8.3)	12 (8.0)	12 (8.3)

* Statistically significant ($p \leq 0.05$) decrease from Baseline compared with placebo plus diclofenac.
† Statistically significant ($p \leq 0.001$) decrease from Baseline compared with placebo plus diclofenac.
The p-value was based on pairwise comparisons from logistic regression versus placebo plus diclofenac.
ITT = intent-to-treat; LOCF = last observation carried forward; N = number of subjects in each treatment group; n = number of subjects with indicated response; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
a. One (1) subject had missing baseline data for all efficacy parameters and was thus not included in any efficacy evaluation. Percentages were based on 156 subjects in this group.

The change from Baseline at Week 12 and Week 24 for all SF-36 dimensions for the ITT population is presented in Table 16.

Table 16. Summary of Change From Baseline to Week 12 and Week 24 in Selected SF-36 Dimensions (ITT, LOCF)

SF-36 Dimension[a]	Placebo + Diclofenac N=152	Tanezumab		
		2.5 mg + Diclofenac N=157[b]	5 mg + Diclofenac N=150	10 mg + Diclofenac N=145
Physical Function				
Mean Baseline (SD)	33.51 (18.98)	36.22 (18.90)	34.70 (16.56)	36.52 (18.46)
Week 12 change from Baseline				
LS mean (SE)*	7.53 (1.81)	12.23 (1.78)	13.53 (1.81)	11.34 (1.86)
95% CI for LS mean	3.97, 11.09	8.74, 15.72	9.98, 17.08	7.69, 15.00
Versus placebo + diclofenac				
LS mean difference (SE)		4.70 (2.23)	6.00 (2.24)	3.81 (2.27)
95% CI for LS mean difference		0.32, 9.07	1.59, 10.41	-0.64, 8.26
p-Value†		0.035	0.008	0.093
Week 24 change from Baseline				
LS mean (SE)*	6.42 (1.99)	10.21 (1.96)	11.31 (1.99)	10.06 (2.04)
95% CI for LS mean	2.50, 10.34	6.36, 14.06	7.40, 15.22	6.05, 14.08
Versus placebo + diclofenac				
LS mean difference (SE)		3.79 (2.24)	4.89 (2.26)	3.64 (2.28)
95% CI for LS mean difference		-0.62, 8.20	0.45, 9.33	-0.85, 8.13
p-Value†		0.092	0.031	0.111
Role Physical				
n	152	156	150	145
Mean Baseline (SD)	46.67 (21.79)	47.44 (20.65)	48.50 (22.21)	47.46 (22.31)
Week 12 change from Baseline				
LS mean (SE)*	7.79 (1.98)	9.30 (1.94)	8.74 (1.97)	9.07 (2.02)
95% CI for LS mean	3.91, 11.67	5.50, 13.11	4.86, 12.61	5.10, 13.05
Versus placebo + diclofenac				
LS mean difference (SE)		1.52 (2.33)	0.95 (2.36)	1.28 (2.38)
95% CI for LS mean difference		-3.07, 6.10	-3.68, 5.57	-3.38, 5.95
p-Value†		0.516	0.688	0.589
Week 24 change from Baseline				
LS mean (SE)*	5.50 (2.14)	8.99 (2.10)	8.16 (2.13)	6.63 (2.18)
95% CI for LS mean	1.30, 9.69	4.87, 13.11	3.97, 12.35	2.34, 10.92
Versus placebo + diclofenac				
LS mean difference (SE)		3.49 (2.39)	2.66 (2.41)	1.13 (2.43)
95% CI for LS mean difference		-1.21, 8.19	-2.08, 7.40	-3.65, 5.91
p-Value†		0.145	0.270	0.642
Bodily Pain				
Mean Baseline (SD)	32.99 (13.77)	35.66 (12.43)	33.95 (14.15)	35.06 (13.47)
Week 12 change from Baseline				
LS mean (SE)*	8.22 (1.77)	13.57 (1.74)	15.18 (1.77)	13.44 (1.82)
95% CI for LS mean	4.74, 11.70	10.15, 16.98	11.71, 18.64	9.87, 17.00
Versus placebo + diclofenac				
LS mean difference (SE)		5.35 (2.12)	6.95 (2.14)	5.22 (2.16)
95% CI for LS mean difference		1.17, 9.52	2.75, 11.16	0.98, 9.46
p-Value†		0.012	0.001	0.016

Table 16. Summary of Change From Baseline to Week 12 and Week 24 in Selected SF-36 Dimensions (ITT, LOCF)

SF-36 Dimension[a]	Placebo + Diclofenac N=152	Tanezumab 2.5 mg + Diclofenac N=157[b]	Tanezumab 5 mg + Diclofenac N=150	Tanezumab 10 mg + Diclofenac N=145
Week 24 change from Baseline				
LS mean (SE)*	7.68 (1.97)	12.95 (1.93)	12.33 (1.96)	11.37 (2.01)
95% CI for LS mean	3.82, 11.54	9.16, 16.73	8.48, 16.18	7.42, 15.33
Versus placebo + diclofenac				
LS mean difference (SE)		5.27 (2.30)	4.65 (2.31)	3.70 (2.34)
95% CI for LS mean difference		0.76, 9.78	0.11, 9.20	-0.89, 8.29
p-Value†		0.022	0.045	0.114
Vitality				
n	152	156	150	145
Mean Baseline (SD)	49.08 (17.73)	52.22 (16.82)	53.00 (17.89)	51.29 (18.21)
Week 12 change from Baseline				
LS mean (SE)*	3.71 (1.41)	5.60 (1.38)	5.55 (1.40)	6.40 (1.44)
95% CI for LS mean	0.94, 6.48	2.90, 8.31	2.79, 8.31	3.57, 9.23
Versus placebo + diclofenac				
LS mean difference (SE)		1.90 (1.69)	1.84 (1.71)	2.69 (1.72)
95% CI for LS mean difference		-1.42, 5.22	-1.51, 5.20	-0.69, 6.07
p-Value†		0.262	0.281	0.118
Week 24 change from Baseline				
LS mean (SE)*	0.96 (1.60)	3.44 (1.57)	4.24 (1.59)	3.56 (1.63)
95% CI for LS mean	-2.18, 4.09	0.37, 6.52	1.11, 7.37	0.35, 6.76
Versus placebo + diclofenac				
LS mean difference (SE)		2.48 (1.82)	3.28 (1.84)	2.60 (1.85)
95% CI for LS mean difference		-1.09, 6.06	-0.33, 6.89	-1.04, 6.23
p-Value†		0.173	0.074	0.161
Physical Component Summary				
Mean Baseline (SD)	-1.84 (0.67)	-1.76 (0.64)	-1.80 (0.61)	-1.76 (0.61)
Week 12 change from Baseline				
LS mean (SE)*	0.35 (0.07)	0.54 (0.07)	0.59 (0.07)	0.55 (0.07)
95% CI for LS mean	0.22, 0.49	0.41, 0.67	0.45, 0.72	0.41, 0.68
Versus placebo + diclofenac				
LS mean difference (SE)		0.18 (0.08)	0.23 (0.08)	0.20 (0.08)
95% CI for LS mean difference		0.03, 0.34	0.08, 0.39	0.04, 0.35
p-Value†		0.019	0.003	0.014
Week 24 change from Baseline				
LS mean (SE)*	0.28 (0.07)	0.46 (0.07)	0.49 (0.07)	0.43 (0.08)
95% CI for LS mean	0.14, 0.43	0.31, 0.60	0.34, 0.64	0.28, 0.58
Versus placebo + diclofenac				
LS mean difference (SE)		0.18 (0.08)	0.21 (0.08)	0.15 (0.08)
95% CI for LS mean difference		0.01, 0.34	0.04, 0.37	-0.02, 0.31
p-Value†		0.034	0.013	0.080

Table 16. Summary of Change From Baseline to Week 12 and Week 24 in Selected SF-36 Dimensions (ITT, LOCF)

SF-36 Dimension[a]	Placebo + Diclofenac N=152	Tanezumab		
		2.5 mg + Diclofenac N=157[b]	5 mg + Diclofenac N=150	10 mg + Diclofenac N=145

* LS means were estimated from the corresponding ANCOVA model. The ANCOVA model included treatment as main effect, baseline value and index joint as covariates, and study site as random effect.
† The p-value was based on ANCOVA from pairwise comparisons.
ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent-to-treat; LOCF = last observation carried forward; LS = least squares; N = number of subjects in each treatment group; n = number of evaluable subjects for specified criteria; SD = standard deviation; SE = standard error; SF-36 = Quality Metric's Short Form-36 Health Survey. .

a. SF-36 domain scores ranged from 0 to 100, where 100 was the best response. A change from Baseline >0 was an improvement.
b. One (1) subject had missing baseline data for all efficacy parameters and was thus not included in any efficacy evaluation.

The change from Baseline to Week 24 for the EQ-5D index score, as well as for the items mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, using LOCF imputation are presented in Table 17.

Table 17. Summary of Change From Baseline to Week 24 in the EQ-5D Index Score and Individual Health State Profile (ITT, LOCF)

EQ-5D Item	Placebo + Diclofenac N=152	Tanezumab		
		2.5 mg + Diclofenac N=157[a]	5 mg + Diclofenac N=150	10 mg + Diclofenac N=145
EQ-5D index score				
Baseline mean (SD)	0.45 (0.29)	0.48 (0.25)	0.47 (0.26)	0.47 (0.27)
Change from Baseline LS mean (SE)*	0.06 (0.02)	0.11 (0.02)	0.10 (0.02)	0.09 (0.02)
95% CI for LS mean	0.01, 0.10	0.07, 0.16	0.05, 0.14	0.04, 0.13
Comparison vs placebo + diclofenac				
Change from Baseline LS mean (SE)		0.06 (0.03)	0.04 (0.03)	0.03 (0.03)
95% CI for LS mean		0.01, 0.11	-0.01, 0.10	-0.02, 0.09
p-Value†		0.032	0.116	0.218
		Number (%) of Subjects		
Mobility				
Improved	21 (13.8)	25 (16.0)	30 (20.0)	25 (17.2)
No change	127 (83.6)	129 (82.7)	114 (76.0)	120 (82.8)
Worsened	4 (2.6)	2 (1.3)	6 (4.0)	0
Total	152 (100)	156 (100)	150 (100)	145 (100)
p-Value‡		0.436	0.266	0.204
Self-care				
Improved	19 (12.5)	33 (21.2)	32 (21.3)	30 (20.7)
No change	118 (77.6)	112 (71.8)	110 (73.3)	104 (71.7)
Worsened	15 (9.9)	11 (7.1)	8 (5.3)	11 (7.6)
Total	152 (100)	156 (100)	150 (100)	145 (100)
p-Value‡		0.042	0.018	0.067
Usual activities				
Improved	16 (10.5)	27 (17.3)	31 (20.7)	27 (18.6)
No change	125 (82.2)	125 (80.1)	106 (70.7)	111 (76.6)
Worsened	11 (7.2)	4 (2.6)	13 (8.7)	7 (4.8)
Total	152 (100)	156 (100)	150 (100)	145 (100)
p-Value‡		0.021	0.093	0.043
Pain/discomfort				
Improved	28 (18.4)	29 (18.6)	34 (22.7)	33 (22.8)
No change	116 (76.3)	125 (80.1)	109 (72.7)	105 (72.4)
Worsened	8 (5.3)	2 (1.3)	7 (4.7)	7 (4.8)
Total	152 (100)	156 (100)	150 (100)	145 (100)
p-Value‡		0.465	0.342	0.407
Anxiety/depression				
Improved	27 (17.8)	26 (16.7)	28 (18.7)	19 (13.1)
No change	106 (69.7)	111 (71.2)	109 (72.7)	107 (73.8)
Worsened	19 (12.5)	19 (12.2)	13 (8.7)	19 (13.1)
Total	152 (100)	156 (100)	150 (100)	145 (100)
p-Value‡		0.817	0.472	0.396

* LS means were estimated from the corresponding ANCOVA model. The ANCOVA model included treatment as main effect, baseline value and index joint as covariates, and study site as random effect.
† The p-value was based on ANCOVA from pairwise comparisons.
‡ The p-value was based on Cochran-Mantel-Haenszel Test stratified by index joint.
ANCOVA = analysis of covariance; CI = confidence interval; EQ-5D = EuroQol 5D; ITT = intent-to-treat; LOCF = last observation carried forward; LS = least squares; N = number of subjects in each treatment group; SD = standard deviation; SE = standard error; vs = versus.
a. One (1) subject had missing baseline data for all efficacy parameters and was thus not included in any efficacy evaluations. Percentages were based on 156 subjects in this group.

The statistical analysis of incidence of subjects who discontinued from the study due to lack of efficacy is presented for the ITT population in Table 18.

Table 18. Analysis of Subjects Who Discontinued From the Study due to Lack of Efficacy (ITT)

	Number (%) of Subjects			
	Placebo + Diclofenac N=152	Tanezumab		
		2.5 mg + Diclofenac N=157	5 mg + Diclofenac N=150	10 mg + Diclofenac N=145
Discontinued from study due to lack of efficacy				
Yes	9 (5.9)	3 (1.9)	7 (4.7)	2 (1.4)
No	143 (94.1)	154 (98.1)	143 (95.3)	143 (98.6)
Comparison vs placebo + diclofenac				
Odds ratio		0.31	0.78	0.22
CI for odds ratio		0.08, 1.17	0.28, 2.15	0.05, 1.05
p-Value*		0.083	0.627	0.057

* The p-value (odds ratio and 95% CI) was based on logistic regression model from pairwise comparisons versus placebo plus diclofenac. Logistic regression model included treatment as a main effect.
CI = confidence interval; ITT = intent-to-treat; N = number of subjects in each treatment group; vs = versus.

The time to study discontinuation due to lack of efficacy up to Week 16 (Day 113) and Week 24 (Day 169) is presented in Table 19.

Table 19. Summary of Analysis of Time to Discontinuation due to Lack of Efficacy up to Week 16 and Week 24 (ITT)

	Placebo + Diclofenac N=152	Tanezumab 2.5 mg + Diclofenac N=157	Tanezumab 5 mg + Diclofenac N=150	Tanezumab 10 mg + Diclofenac N=145
Time to discontinuation due to lack of efficacy up to				
Week 16				
Number of subjects withdrawn	4	3	5	1
Number of subjects censored	148	154	145	144
Discontinuation time (days)				
Time to discontinuation percentile (days)				
1st	35	59	33	–
2nd	61	–	51	–
3rd	–	–	95	–
4th	–	–	–	–
5th	–	–	–	–
Min, max	13, 85	43, 88	22, 95	32, 32
Comparison vs placebo + diclofenac				
p-Value*		0.634	0.727	0.204
Week 24				
Number of subjects withdrawn	9	3	6	2
Number of subjects censored	143	154	144	143
Discontinuation time (days)				
Time to discontinuation percentile (days)				
1st	35	59	33	120
2nd	61	–	51	–
3rd	117	–	95	–
4th	117	–	166	–
5th	158	–	–	–
Min, max	13, 168	43, 88	22, 166	32, 120
Comparison vs placebo + diclofenac				
p-Value*		0.071	0.479	0.044

* The p-value was based on the Wilcoxon Test.
Analysis was of time to discontinuation due to lack of efficacy up to Week 16 (Study Day 113) and Week 24 (Study Day 169). Censored observations included subject completed study, discontinuation for other reasons, and discontinuation due to lack of efficacy after the Week 16 (for up to Week 16 data) or the Week 24 (for Week 24 data) time point.
ITT = intent-to-treat; min = minimum; max = maximum; N = number of subjects in each treatment group; vs = versus.

The incidence of subjects who took rescue medication using LOCF imputation is presented in Table 20.

Table 20. Summary of Incidence of Taking Rescue Medication (ITT, LOCF)

	Number (%) of Subjects			
	Placebo + Diclofenac N=152	Tanezumab		
		2.5 mg + Diclofenac N=157	5 mg + Diclofenac N=150	10 mg + Diclofenac N=145
Incidence of taking rescue medication at:				
Week 2	57 (41.6)	64 (45.1)	57 (41.0)	67 (50.0)
Week 4	58 (41.1)	51 (34.7)	44 (31.7)	51 (37.8)
Week 8	46 (31.9)	47 (31.8)	45 (32.4)	44 (32.4)
Week 12	45 (31.3)	44 (29.7)	50 (36.0)	43 (31.4)
Week 16	37 (25.7)	36 (24.3)	38 (27.3)	35 (25.5)
Week 24	34 (23.6)	26 (17.6)	30 (21.6)	38 (27.7)

ITT = intent-to-treat; LOCF = last observation carried forward; N = number of subjects in each treatment group.

The number of days when rescue medication (acetaminophen) was taken (days/week) and the amount (mg) of rescue medication taken at Week 16 and Week 24 using LOCF imputation are Presented in Table 21.

Table 21. Summary of Analysis of the Rescue Medication Taken – Days per Week and Amount per Week (ITT, LOCF)

	Placebo + Diclofenac N=152	Tanezumab 2.5 mg + Diclofenac N=157	Tanezumab 5 mg + Diclofenac N=150	Tanezumab 10 mg + Diclofenac N=145
Number of days per week for subjects taking rescue medication[a]				
Week 16				
LS mean (SE)*	0.85 (0.20)	0.72 (0.16)	0.66 (0.16)	0.95 (0.22)
95% CI for LS mean	0.54, 1.34	0.46, 1.13	0.41, 1.04	0.60, 1.49
Comparison vs placebo + diclofenac				
LS mean ratio (SE)		0.85 (0.26)	0.77 (0.24)	1.11 (0.34)
95% CI for LS mean ratio		0.47, 1.53	0.42, 1.42	0.61, 2.03
p-Value†		0.586	0.402	0.724
Week 24				
LS mean (SE)*	0.68 (0.17)	0.46 (0.12)	0.56 (0.14)	1.02 (0.24)
95% CI for LS mean	0.42, 1.11	0.27, 0.77	0.35, 0.92	0.64, 1.63
Comparison vs placebo + diclofenac				
LS mean ratio (SE)		0.67 (0.22)	0.83 (0.28)	1.49 (0.49)
95% CI for LS mean ratio		0.35, 1.29	0.43, 1.60	0.78, 2.85
p-Value†		0.235	0.574	0.225
Amount (mg) total per week of rescue medication taken[b]				
Week 16				
LS mean (SE)*	751.6 (379.3)	795.1 (391.3)	762.8 (384.0)	842.5 (422.8)
95% CI for LS mean	279.5, 2021.0	303.0, 2086.2	284.4, 2045.8	315.1, 2252.7
Comparison vs placebo + diclofenac				
LS mean ratio (SE)		1.06 (0.69)	1.01 (0.68)	1.12 (0.75)
95% CI for LS mean ratio		0.29, 3.82	0.27, 3.77	0.30, 4.18
p-Value†		0.931	0.982	0.865
Week 24				
LS mean (SE)*	551.7 (303.3)	354.8 (207.9)	652.1 (353.5)	930.3 (496.5)
95% CI for LS mean	187.8, 1620.6	112.6, 1118.5	225.4, 1886.9	326.9, 2647.8
Comparison vs placebo + diclofenac				
LS mean ratio (SE)		0.64 (0.47)	1.18 (0.85)	1.69 (1.25)
95% CI for LS mean ratio		0.15, 2.67	0.29, 4.87	0.39, 7.21
p-Value†		0.543	0.817	0.481

* Negative binomial regression model with model terms for treatment as a main effect and baseline WOMAC pain score and index joint as a covariate. Results shown as estimated number of days of rescue medication used per week and estimated amount of rescue medication used per week, and ratio of estimated number of days of rescue medication per week and estimated amount of rescue medication, for comparisons vs placebo plus diclofenac.

† The p-value was based on a negative binomial regression model from pairwise comparisons vs placebo plus diclofenac.

CI = confidence interval; ITT = intent-to-treat; LOCF = last observation carried forward; LS = least squares; N = number of subjects in each treatment group; SE = standard error; vs = versus; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

a. Data shown were number of days of rescue medication use in each week and range from 0 to 7.

b. Data shown were total dose of acetaminophen (in mg) for each week.

Pharmacokinetic Results: Descriptive summaries of tanezumab plasma concentrations by treatment using nominal PK sampling times and nominal dosing times are presented in Table 22.

Table 22. Descriptive Summary of Tanezumab Plasma Concentration by Treatment

Visit	Planned Time Postdose	N	NALQ	Mean	SD	CV (%)	Median	Minimum	Maximum
Tanezumab 2.5 mg + Diclofenac									
Day 1	0 h	154	16	85.90	786.94	916	0.0000	0.000	9660
	1 h	152	148	1034	624.96	60	982.5	0.000	7100
Week 4		139	134	180.4	75.658	42	175.0	0.000	450
Week 8	0 h	141	122	986.4	10654	1080	56.20	0.000	127000
	1 h	141	140	3442	15203	442	1047	0.000	125000
Week 16	0 h	131	114	504.9	4875.1	966	57.90	0.000	55900
	1 h	112	111	2035	6829.6	336	1028	0.000	56400
Week 24		101	85	65.02	60.117	92	52.20	0.000	421
Week 32		127	25	13.57	43.246	319	0.0000	0.000	359
Tanezumab 5 mg + Diclofenac									
Day 1	0 h	146	21	36.06	172.91	480	0.0000	0.000	1720
	1 h	145	143	2568	4286.0	167	1909	0.000	34300
Week 4		130	130	462.5	190.47	41	441.0	77.5	1670
Week 8	0 h	134	133	228.1	574.46	252	140.5	0.000	6480
	1 h	133	132	9035	55170	611	1963	0.000	581000
Week 16	0 h	123	122	477.8	2926.7	613	175.0	0.000	32600
	1 h	107	107	7880	33692	428	1925	73.3	275000
Week 24		94	92	177.8	100.34	56	162.5	0.000	547
Week 32		115	44	45.39	104.05	229	0.0000	0.000	563
Tanezumab 10 mg + Diclofenac									
Day 1	0 h	136	17	986.1	9773.0	991	0.0000	0.000	114000
	1 h	136	136	5104	10619	208	3883	31.8	122000
Week 4		130	130	995.5	650.49	65	973.0	92.5	7630
Week 8	0 h	123	122	3136	29603	944	400.0	0.000	329000
	1 h	124	124	17600	73739	419	4272	251	457000
Week 16	0 h	118	117	3796	32021	844	491.5	0.000	348000
	1 h	99	99	11370	35921	316	4204	460	217000
Week 24		87	86	464.0	231.95	50	446.0	0.000	1210
Week 32		115	87	112.8	196.20	174	41.80	0.000	1090

Summary statistics were calculated by setting concentration values below the lower limit of quantification to 0.
Nominal sampling times were used. For the pharmacokinetic assay, 12 ng/mL was the lower limit of quantification.
CV = coefficient of variance; N = number of observations (non-missing concentrations); NALQ = number of observations above lower limit of quantification; SD = standard deviation.

Safety Results: The incidence of AEs is summarized in Table 23.

Table 23. Incidence of Adverse Events (ITT)

	Number (%)[a] of Subjects			
	Placebo + Diclofenac N=152	**Tanezumab 2.5 mg + Diclofenac N=157**	**Tanezumab 5 mg + Diclofenac N=150**	**Tanezumab 10 mg + Diclofenac N=145**
All-causality AEs				
Number of AEs	142	158	137	172
Subjects with AEs	53 (34.9)	71 (45.2)	73 (48.7)	72 (49.7)
Subjects with serious AEs[b]	8 (5.3)	12 (7.6)	8 (5.3)	10 (6.9)
Subjects with severe AEs	8 (5.3)	11 (7.0)	10 (6.7)	13 (9.0)
Subjects discontinued due to AEs	6 (3.9)	8 (5.1)	11 (7.3)	9 (6.2)
Subjects with dose reduced or temporary discontinuation due to AEs	2 (1.3)	1 (0.6)	1 (0.7)	3 (2.1)
Treatment-related AEs				
Number of AEs	38	59	39	70
Subjects with AEs	19 (12.5)	28 (17.8)	30 (20.0)	44 (30.3)
Subjects with serious AEs[b]	0	4 (2.5)	2 (1.3)	5 (3.4)
Subjects with severe AEs	1 (0.7)	4 (2.5)	5 (3.3)	6 (4.1)
Subjects discontinued due to AEs	3 (2.0)	5 (3.2)	7 (4.7)	5 (3.4)
Subjects with dose reduced or temporary discontinuation due to AEs	1 (0.7)	1 (0.6)	0	2 (1.4)

Non-SAEs and SAEs were not separated out.
MedDRA (version 13.1) coding dictionary was applied. Table included data up to 9999 days after last dose of study drug. Except for the number of AEs, subjects were counted only once per treatment in each row.
AEs = adverse events; ITT = intent-to-treat; MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects with AEs, SAE = serious adverse event.
a. Percentages were based on the total number of subjects in each treatment group (ITT).
b. According to the Investigator's assessment.

The all causality treatment-emergent AEs (TEAEs) are presented in Table 24.

Table 24. Treatment-Emergent Adverse Events by Special Organ Class and Preferred Term (All Causalities)

System Organ Class MedDRA (v13.1) Preferred Term	Placebo IV + Diclofenac	Tanezumab 2.5 mg + Diclofenac	Tanezumab 5 mg + Diclofenac	Tanezumab 10 mg + Diclofenac
	n (%)	n (%)	n (%)	n (%)
Number (%) of subjects:				
Evaluable for adverse events	152	157	150	145
With adverse events	50 (32.9)	70 (44.6)	68 (45.3)	71 (49.0)
Blood and lymphatic system disorders	4 (2.6)	1 (0.6)	0	2 (1.4)
Anemia	1 (0.7)	0	0	2 (1.4)
Eosinophilia	1 (0.7)	0	0	0
Iron deficiency anemia	1 (0.7)	0	0	0
Leukocytosis	1 (0.7)	0	0	0
Leukopenia	0	1 (0.6)	0	0
Neutrophilia	1 (0.7)	0	0	0
Cardiac disorders	2 (1.3)	2 (1.3)	2 (1.3)	4 (2.8)
Aortic valve incompetence	0	1 (0.6)	0	0
Arrhythmia	0	0	1 (0.7)	0
Atrial fibrillation	2 (1.3)	1 (0.6)	0	0
Bundle branch block left	0	0	0	1 (0.7)
Bundle branch block right	0	0	1 (0.7)	1 (0.7)
Cardiovascular disorder	0	0	0	1 (0.7)
Ventricular extrasystoles	0	0	0	1 (0.7)
Ear and labyrinth disorders	1 (0.7)	4 (2.5)	0	1 (0.7)
Ear pain	1 (0.7)	2 (1.3)	0	0
Vertigo	0	2 (1.3)	0	1 (0.7)
Eye disorders	1 (0.7)	1 (0.6)	0	2 (1.4)
Amaurosis fugax	0	1 (0.6)	0	0
Conjunctivitis	0	0	0	1 (0.7)
Eye disorder	0	0	0	1 (0.7)
Eye haemorrhage	0	0	0	1 (0.7)
Glaucoma	1 (0.7)	0	0	0
Ocular hyperaemia	0	0	0	1 (0.7)
Gastrointestinal disorders	12 (7.9)	12 (7.6)	13 (8.7)	14 (9.7)
Abdominal pain	0	1 (0.6)	1 (0.7)	2 (1.4)
Abdominal pain lower	0	1 (0.6)	0	0
Abdominal pain upper	0	2 (1.3)	1 (0.7)	2 (1.4)
Colitis ulcerative	0	0	1 (0.7)	0
Diarrhoea	2 (1.3)	3 (1.9)	2 (1.3)	3 (2.1)
Duodenal ulcer	0	0	0	1 (0.7)
Duodenitis	0	1 (0.6)	0	0
Dyspepsia	0	0	1 (0.7)	1 (0.7)
Flatulence	0	0	0	1 (0.7)
Gastric ulcer	0	0	1 (0.7)	0
Gastritis	0	1 (0.6)	0	2 (1.4)
Haemorrhoidal haemorrhage	1 (0.7)	0	0	0
Hiatus hernia	0	0	0	1 (0.7)
Nausea	1 (0.7)	1 (0.6)	1 (0.7)	1 (0.7)
Oesophageal disorder	0	1 (0.6)	0	0
Toothache	9 (5.9)	3 (1.9)	6 (4.0)	1 (0.7)
Vomiting	0	0	1 (0.7)	0
General disorders and administration site conditions	2 (1.3)	5 (3.2)	7 (4.7)	8 (5.5)
Asthenia	1 (0.7)	1 (0.6)	0	0

Table 24. Treatment-Emergent Adverse Events by Special Organ Class and Preferred Term (All Causalities)

System Organ Class MedDRA (v13.1) Preferred Term	Placebo IV + Diclofenac	Tanezumab 2.5 mg + Diclofenac	Tanezumab 5 mg + Diclofenac	Tanezumab 10 mg + Diclofenac
	n (%)	n (%)	n (%)	n (%)
Catheter site pain	0	0	1 (0.7)	0
Catheter site swelling	0	0	1 (0.7)	0
Chest pain	0	1 (0.6)	1 (0.7)	1 (0.7)
Chills	0	0	1 (0.7)	0
Fatigue	0	1 (0.6)	0	0
Gait disturbance	0	1 (0.6)	0	0
Oedema peripheral	2 (1.3)	2 (1.3)	4 (2.7)	7 (4.8)
Hepatobiliary disorders	0	0	0	1 (0.7)
Cholelithiasis	0	0	0	1 (0.7)
Immune system disorders	3 (2.0)	0	1 (0.7)	1 (0.7)
Allergy to vaccine	1 (0.7)	0	0	0
Anaphylactic shock	0	0	1 (0.7)	0
Seasonal allergy	2 (1.3)	0	0	1 (0.7)
Infections and infestations	17 (11.2)	22 (14.0)	20 (13.3)	26 (17.9)
Acute tonsillitis	0	1 (0.6)	0	0
Bacteriuria	1 (0.7)	1 (0.6)	1 (0.7)	0
Breast abscess	0	0	1 (0.7)	0
Bronchitis	2 (1.3)	1 (0.6)	0	3 (2.1)
Cellulitis	0	1 (0.6)	0	0
Cystitis	1 (0.7)	2 (1.3)	0	0
Erysipelas	1 (0.7)	0	0	0
Febrile infection	0	0	0	1 (0.7)
Folliculitis	1 (0.7)	0	0	0
Gastric infection	0	0	0	1 (0.7)
Gastroenteritis	1 (0.7)	1 (0.6)	0	2 (1.4)
Helicobacter infection	0	0	0	1 (0.7)
Herpes zoster	0	0	0	1 (0.7)
Influenza	1 (0.7)	2 (1.3)	4 (2.7)	2 (1.4)
Nasopharyngitis	7 (4.6)	10 (6.4)	12 (8.0)	10 (6.9)
Onychomycosis	0	1 (0.6)	0	1 (0.7)
Oral herpes	1 (0.7)	1 (0.6)	0	0
Oral infection	0	1 (0.6)	0	0
Pneumonia	0	2 (1.3)	2 (1.3)	0
Respiratory tract infection	0	0	0	1 (0.7)
Respiratory tract infection viral	1 (0.7)	2 (1.3)	1 (0.7)	0
Rhinitis	0	0	0	1 (0.7)
Sinusitis	0	1 (0.6)	0	0
Tracheobronchitis	1 (0.7)	0	0	0
Upper respiratory tract infection	1 (0.7)	0	1 (0.7)	2 (1.4)
Urinary tract infection	2 (1.3)	2 (1.3)	1 (0.7)	1 (0.7)
Viral infection	0	0	1 (0.7)	0
Injury, poisoning and procedural complications	4 (2.6)	7 (4.5)	2 (1.3)	4 (2.8)
Contusion	1 (0.7)	1 (0.6)	0	0
Epicondylitis	1 (0.7)	0	0	0
Facial bones fracture	1 (0.7)	0	0	0
Fall	0	0	0	1 (0.7)
Foot fracture	0	0	0	1 (0.7)
Joint dislocation	0	1 (0.6)	0	0
Joint sprain	0	1 (0.6)	0	0

Table 24. Treatment-Emergent Adverse Events by Special Organ Class and Preferred Term (All Causalities)

System Organ Class MedDRA (v13.1) Preferred Term	Placebo IV + Diclofenac	Tanezumab 2.5 mg + Diclofenac	Tanezumab 5 mg + Diclofenac	Tanezumab 10 mg + Diclofenac
	n (%)	n (%)	n (%)	n (%)
Ligament injury	0	0	0	1 (0.7)
Lower limb fracture	0	1 (0.6)	0	0
Meniscus lesion	0	1 (0.6)	1 (0.7)	0
Muscle injury	0	1 (0.6)	0	0
Muscle rupture	0	1 (0.6)	1 (0.7)	0
Skin laceration	0	0	0	1 (0.7)
Tendon rupture	0	0	0	1 (0.7)
Thermal burn	1 (0.7)	0	0	0
Traumatic hematoma	0	1 (0.6)	0	0
Investigations	6 (3.9)	7 (4.5)	5 (3.3)	8 (5.5)
Alanine aminotransferase increased	0	1 (0.6)	0	2 (1.4)
Aspartate aminotransferase increased	0	0	0	1 (0.7)
Blood alkaline phosphatase increased	0	0	0	1 (0.7)
Blood creatine phosphokinase increased	1 (0.7)	1 (0.6)	2 (1.3)	1 (0.7)
Blood creatinine increased	0	0	0	1 (0.7)
Blood glucose increased	1 (0.7)	0	0	0
Blood pressure increased	1 (0.7)	1 (0.6)	0	0
Blood triglycerides increased	1 (0.7)	0	0	0
Blood urea increased	1 (0.7)	1 (0.6)	0	1 (0.7)
Body temperature increased	0	1 (0.6)	0	0
Electrocardiogram repolarization abnormality	0	0	0	1 (0.7)
Eosinophil count increased	1 (0.7)	0	0	0
Fibrin D dimer increased	0	0	0	1 (0.7)
Gamma-glutamyltransferase increased	3 (2.0)	1 (0.6)	2 (1.3)	1 (0.7)
QRS axis abnormal	1 (0.7)	0	0	0
Red blood cell sedimentation rate increased	0	1 (0.6)	0	0
Respiratory rate increased	0	0	1 (0.7)	0
Weight decreased	0	1 (0.6)	0	0
Weight increased	0	0	0	1 (0.7)
Metabolism and nutrition disorders	1 (0.7)	5 (3.2)	4 (2.7)	5 (3.4)
Decreased appetite	0	2 (1.3)	0	0
Dyslipidaemia	0	0	1 (0.7)	0
Glucose tolerance impaired	0	0	1 (0.7)	0
Hypercholesterolaemia	1 (0.7)	1 (0.6)	2 (1.3)	2 (1.4)
Hyperkalaemia	0	0	1 (0.7)	1 (0.7)
Hypertriglyceridaemia	0	1 (0.6)	0	1 (0.7)
Hypocalcaemia	0	0	0	1 (0.7)
Hypoglycaemia	0	1 (0.6)	0	0
Musculoskeletal and connective tissue disorders	15 (9.9)	22 (14.0)	21 (14.0)	23 (15.9)
Arthralgia	8 (5.3)	7 (4.5)	7 (4.7)	12 (8.3)
Arthritis	1 (0.7)	0	1 (0.7)	2 (1.4)
Arthropathy	0	0	0	1 (0.7)

Table 24. Treatment-Emergent Adverse Events by Special Organ Class and Preferred Term (All Causalities)

System Organ Class MedDRA (v13.1) Preferred Term	Placebo IV + Diclofenac	Tanezumab 2.5 mg + Diclofenac	Tanezumab 5 mg + Diclofenac	Tanezumab 10 mg + Diclofenac
	n (%)	n (%)	n (%)	n (%)
Back pain	2 (1.3)	4 (2.5)	3 (2.0)	3 (2.1)
Bone pain	1 (0.7)	0	0	2 (1.4)
Bursitis	0	1 (0.6)	0	0
Enthesopathy	0	1 (0.6)	0	0
Joint stiffness	1 (0.7)	0	0	0
Joint swelling	1 (0.7)	1 (0.6)	2 (1.3)	2 (1.4)
Muscle spasms	0	0	1 (0.7)	2 (1.4)
Muscle tightness	0	0	1 (0.7)	0
Muscular weakness	1 (0.7)	0	0	2 (1.4)
Musculoskeletal pain	2 (1.3)	0	0	1 (0.7)
Musculoskeletal stiffness	1 (0.7)	0	0	0
Myalgia	1 (0.7)	1 (0.6)	3 (2.0)	1 (0.7)
Myofascial pain syndrome	0	0	1 (0.7)	0
Neck pain	0	1 (0.6)	0	0
Osteitis	1 (0.7)	0	0	0
Osteoarthritis	2 (1.3)	2 (1.3)	2 (1.3)	2 (1.4)
Osteoporotic fracture	0	1 (0.6)	0	0
Pain in extremity	3 (2.0)	2 (1.3)	1 (0.7)	3 (2.1)
Rotator cuff syndrome	2 (1.3)	0	0	0
Spinal column stenosis	0	1 (0.6)	0	0
Spinal disorder	1 (0.7)	0	0	0
Spinal osteoarthritis	0	1 (0.6)	0	0
Spondylolisthesis	0	0	0	1 (0.7)
Synovial cyst	0	0	0	1 (0.7)
Synovitis	0	0	2 (1.3)	0
Tendon disorder	0	0	1 (0.7)	0
Tenosynovitis	1 (0.7)	0	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	1 (0.7)	0
Lipoma	0	0	1 (0.7)	0
Nervous system disorders	15 (9.9)	20 (12.7)	18 (12.0)	20 (13.8)
Allodynia	0	1 (0.6)	0	0
Areflexia	0	0	0	1 (0.7)
Burning sensation	0	0	1 (0.7)	1 (0.7)
Carpal tunnel syndrome	1 (0.7)	2 (1.3)	1 (0.7)	1 (0.7)
Cervicobrachial syndrome	0	0	2 (1.3)	0
Dizziness	1 (0.7)	1 (0.6)	2 (1.3)	3 (2.1)
Dysaesthesia	1 (0.7)	0	0	0
Facial paresis	1 (0.7)	0	0	0
Headache	11 (7.2)	9 (5.7)	7 (4.7)	6 (4.1)
Hyperaesthesia	0	0	1 (0.7)	1 (0.7)
Hypoaesthesia	1 (0.7)	2 (1.3)	1 (0.7)	0
Hyporeflexia	1 (0.7)	1 (0.6)	0	0
Intercostal neuralgia	1 (0.7)	0	0	0
Neuralgia	0	0	1 (0.7)	0
Neuropathy peripheral	1 (0.7)	0	2 (1.3)	2 (1.4)
Paresthesia	0	4 (2.5)	0	2 (1.4)
Polyneuropathy	1 (0.7)	1 (0.6)	1 (0.7)	0
Radicular syndrome	0	3 (1.9)	1 (0.7)	0

Table 24. Treatment-Emergent Adverse Events by Special Organ Class and Preferred Term (All Causalities)

System Organ Class MedDRA (v13.1) Preferred Term	Placebo IV + Diclofenac	Tanezumab 2.5 mg + Diclofenac	Tanezumab 5 mg + Diclofenac	Tanezumab 10 mg + Diclofenac
	n (%)	n (%)	n (%)	n (%)
Radiculopathy	0	0	0	1 (0.7)
Restless legs syndrome	0	0	0	1 (0.7)
Sciatica	0	1 (0.6)	3 (2.0)	3 (2.1)
Psychiatric disorders	1 (0.7)	1 (0.6)	0	2 (1.4)
Anxiety	0	0	0	2 (1.4)
Nervousness	0	1 (0.6)	0	0
Sleep disorder	1 (0.7)	0	0	0
Renal and urinary disorders	2 (1.3)	2 (1.3)	1 (0.7)	1 (0.7)
Leukocyturia	0	1 (0.6)	1 (0.7)	0
Nephrolithiasis	1 (0.7)	0	0	0
Nocturia	1 (0.7)	0	0	0
Proteinuria	0	0	1 (0.7)	0
Renal colic	0	1 (0.6)	0	0
Renal failure	0	0	0	1 (0.7)
Reproductive system and breast disorders	1 (0.7)	1 (0.6)	1 (0.7)	0
Atrophic vulvovaginitis	0	0	1 (0.7)	0
Erectile dysfunction	0	1 (0.6)	0	0
Vaginal hemorrhage	1 (0.7)	0	0	0
Respiratory, thoracic and mediastinal disorders	0	3 (1.9)	2 (1.3)	2 (1.4)
Cough	0	1 (0.6)	1 (0.7)	1 (0.7)
Dysphonia	0	1 (0.6)	0	0
Respiratory distress	0	0	1 (0.7)	0
Rhinorrhoea	0	1 (0.6)	0	0
Sleep apnoea syndrome	0	0	0	1 (0.7)
Skin and subcutaneous tissue disorders	4 (2.6)	6 (3.8)	6 (4.0)	7 (4.8)
Acne	1 (0.7)	0	0	0
Alopecia	0	1 (0.6)	0	0
Dermatitis	0	0	1 (0.7)	1 (0.7)
Dry skin	0	0	0	1 (0.7)
Eczema	0	2 (1.3)	1 (0.7)	1 (0.7)
Erythema	1 (0.7)	0	0	0
Hyperhidrosis	0	3 (1.9)	1 (0.7)	0
Pruritus	0	0	1 (0.7)	2 (1.4)
Pruritus allergic	1 (0.7)	0	0	0
Psoriasis	0	0	0	1 (0.7)
Rash	0	1 (0.6)	1 (0.7)	1 (0.7)
Rash vesicular	0	0	1 (0.7)	0
Skin lesion	1 (0.7)	0	0	0
Swelling face	0	0	0	1 (0.7)
Surgical and medical procedures	1 (0.7)	0	0	0
Skin neoplasm excision	1 (0.7)	0	0	0
Vascular disorders	12 (7.9)	1 (0.6)	5 (3.3)	7 (4.8)
Hematoma	1 (0.7)	0	1 (0.7)	1 (0.7)
Hot flush	2 (1.3)	0	0	0
Hypertension	9 (5.9)	1 (0.6)	3 (2.0)	6 (4.1)
Hypertensive crisis	0	0	1 (0.7)	1 (0.7)
Thrombophlebitis	0	0	1 (0.7)	0

Table 24. Treatment-Emergent Adverse Events by Special Organ Class and Preferred Term (All Causalities)

System Organ Class MedDRA (v13.1) Preferred Term	Placebo IV + Diclofenac	Tanezumab 2.5 mg + Diclofenac	Tanezumab 5 mg + Diclofenac	Tanezumab 10 mg + Diclofenac
	n (%)	n (%)	n (%)	n (%)
Venous insufficiency	0	0	0	1 (0.7)

Subjects were only counted once per treatment for each row.
Included data up to 9999 days after last dose of study drug.
MedDRA (v13.1) coding dictionary applied.
IV = intravenous, MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with adverse events; v = version.

The incidence of TEAEs (treatment related) are presented in Table 25.

Table 25. Incidence of Treatment-Emergent Adverse Events (Treatment Related)

System Organ Class MedDRA (v13.1) Preferred Term	Placebo IV + Diclofenac	Tanezumab 2.5 mg + Diclofenac	Tanezumab 5 mg + Diclofenac	Tanezumab 10 mg + Diclofenac
	n (%)	n (%)	n (%)	n (%)
Number (%) of subjects				
Evaluable for AEs	152	157	150	145
With AEs	19 (12.5)	28 (17.8)	30 (20.0)	44 (30.3)
Discontinued due to AEs	3 (2.0)	5 (3.2)	7 (4.7)	5 (3.4)
Blood and lymphatic system disorders	2 (1.3)	0	0	1 (0.7)
Anaemia	1 (0.7)	0	0	1 (0.7)
Leukocytosis	1 (0.7)	0	0	0
Neutrophilia	1 (0.7)	0	0	0
Cardiac disorders	1 (0.7)	0	1 (0.7)	0
Atrial fibrillation	1 (0.7)	0	0	0
Bundle branch block right	0	0	1 (0.7)	0
Ear and labyrinth disorders	0	3 (1.9)	0	0
Ear pain	0	1 (0.6)	0	0
Vertigo	0	2 (1.3)	0	0
Gastrointestinal disorders	2 (1.3)	3 (1.9)	4 (2.7)	8 (5.5)
Abdominal pain	0	0	1 (0.7)	1 (0.7)
Abdominal pain upper	0	2 (1.3)	1 (0.7)	2 (1.4)
Diarrhoea	2 (1.3)	1 (0.6)	0	1 (0.7)
Duodenal ulcer	0	0	0	1 (0.7)
Dyspepsia	0	0	1 (0.7)	1 (0.7)
Gastric ulcer	0	0	1 (0.7)	0
Gastritis	0	0	0	1 (0.7)
Gastrointestinal hemorrhage	0	0	0	1 (0.7)
Nausea	1 (0.7)	0	0	1 (0.7)
General disorders and administration site conditions	1 (0.7)	4 (2.5)	2 (1.3)	5 (3.4)
Asthenia	0	1 (0.6)	0	0
Chest pain	0	1 (0.6)	0	0
Fatigue	0	1 (0.6)	0	0
Gait disturbance	0	1 (0.6)	0	0
Oedema peripheral	1 (0.7)	1 (0.6)	2 (1.3)	5 (3.4)
Infections and infestations	1 (0.7)	3 (1.9)	3 (2.0)	1 (0.7)
Bacteriuria	1 (0.7)	1 (0.6)	1 (0.7)	0
Breast abscess	0	0	1 (0.7)	0
Cellulitis	0	1 (0.6)	0	0
Nasopharyngitis	0	0	1 (0.7)	1 (0.7)
Onychomycosis	0	1 (0.6)	0	0
Osteomyelitis	0	1 (0.6)	0	0
Injury, poisoning and procedural complications	0	2 (1.3)	0	1 (0.7)
Foot fracture	0	0	0	1 (0.7)
Muscle injury	0	1 (0.6)	0	0
Muscle rupture	0	1 (0.6)	0	0
Investigations	4 (2.6)	3 (1.9)	2 (1.3)	6 (4.1)
Alanine aminotransferase increased	0	1 (0.6)	0	1 (0.7)
Aspartate aminotransferase increased	0	0	0	1 (0.7)
Blood alkaline phosphatase increased	0	0	0	1 (0.7)
Blood creatine phosphokinase increased	1 (0.7)	0	0	1 (0.7)
Blood creatinine increased	0	0	0	1 (0.7)
Blood glucose increased	1 (0.7)	0	0	0
Blood pressure increased	0	1 (0.6)	0	0

Table 25. Incidence of Treatment-Emergent Adverse Events (Treatment Related)

System Organ Class MedDRA (v13.1) Preferred Term	Placebo IV + Diclofenac	Tanezumab 2.5 mg + Diclofenac	Tanezumab 5 mg + Diclofenac	Tanezumab 10 mg + Diclofenac
	n (%)	n (%)	n (%)	n (%)
Blood triglycerides increased	1 (0.7)	0	0	0
Blood urea increased	1 (0.7)	0	0	1 (0.7)
Electrocardiogram repolarisation abnormality	0	0	0	1 (0.7)
Eosinophil count increased	1 (0.7)	0	0	0
Gamma-glutamyltransferase increased	2 (1.3)	0	1 (0.7)	1 (0.7)
Respiratory rate increased	0	0	1 (0.7)	0
Weight decreased	0	1 (0.6)	0	0
Weight increased	0	0	0	1 (0.7)
Metabolism and nutrition disorders	0	2 (1.3)	1 (0.7)	1 (0.7)
Decreased appetite	0	1 (0.6)	0	0
Hypercholesterolaemia	0	0	0	1 (0.7)
Hyperkalaemia	0	0	1 (0.7)	0
Hypertriglyceridaemia	0	1 (0.6)	0	0
Musculoskeletal and connective tissue disorders	6 (3.9)	12 (7.6)	12 (8.0)	16 (11.0)
Arthralgia	3 (2.0)	4 (2.5)	5 (3.3)	8 (5.5)
Arthritis	0	0	0	1 (0.7)
Back pain	0	2 (1.3)	0	0
Bone pain	1 (0.7)	0	0	0
Bursitis	0	1 (0.6)	0	0
Joint swelling	0	1 (0.6)	0	1 (0.7)
Muscle spasms	0	0	1 (0.7)	1 (0.7)
Muscular weakness	0	0	0	1 (0.7)
Myalgia	1 (0.7)	1 (0.6)	2 (1.3)	1 (0.7)
Myofascial pain syndrome	0	0	1 (0.7)	0
Osteoarthritis	1 (0.7)	0	1 (0.7)	1 (0.7)
Osteonecrosis	0	2 (1.3)	1 (0.7)	3 (2.1)
Pain in extremity	1 (0.7)	0	1 (0.7)	2 (1.4)
Pathological fracture	0	1 (0.6)	0	0
Spinal osteoarthritis	0	1 (0.6)	0	0
Nervous system disorders	6 (3.9)	11 (7.0)	7 (4.7)	13 (9.0)
Allodynia	0	1 (0.6)	0	0
Areflexia	0	0	0	1 (0.7)
Burning sensation	0	0	1 (0.7)	1 (0.7)
Carpal tunnel syndrome	0	1 (0.6)	0	1 (0.7)
Demyelinating polyneuropathy	0	1 (0.6)	0	0
Dizziness	0	1 (0.6)	0	2 (1.4)
Dysaesthesia	1 (0.7)	0	0	0
Facial paresis	1 (0.7)	0	0	0
Headache	3 (2.0)	4 (2.5)	3 (2.0)	2 (1.4)
Hyperaesthesia	0	0	1 (0.7)	1 (0.7)
Hypoaesthesia	0	1 (0.6)	1 (0.7)	0
Hyporeflexia	0	1 (0.6)	0	0
Intercostal neuralgia	1 (0.7)	0	0	0
Neuropathy peripheral	0	0	2 (1.3)	1 (0.7)
Paraesthesia	0	3 (1.9)	0	1 (0.7)
Polyneuropathy	0	1 (0.6)	1 (0.7)	0
Radicular syndrome	0	3 (1.9)	0	0
Radiculopathy	0	0	0	1 (0.7)
Restless legs syndrome	0	0	0	1 (0.7)
Sciatica	0	0	0	2 (1.4)

Table 25. Incidence of Treatment-Emergent Adverse Events (Treatment Related)

System Organ Class MedDRA (v13.1) Preferred Term	Placebo IV + Diclofenac	Tanezumab 2.5 mg + Diclofenac	Tanezumab 5 mg + Diclofenac	Tanezumab 10 mg + Diclofenac
	n (%)	n (%)	n (%)	n (%)
Psychiatric disorders	1 (0.7)	0	0	0
Sleep disorder	1 (0.7)	0	0	0
Renal and urinary disorders	1 (0.7)	1 (0.6)	1 (0.7)	0
Leukocyturia	0	1 (0.6)	1 (0.7)	0
Nocturia	1 (0.7)	0	0	0
Proteinuria	0	0	1 (0.7)	0
Reproductive system and breast disorders	0	1 (0.6)	0	0
Erectile dysfunction	0	1 (0.6)	0	0
Skin and subcutaneous tissue disorders	2 (1.3)	4 (2.5)	0	4 (2.8)
Alopecia	0	1 (0.6)	0	0
Eczema	0	1 (0.6)	0	1 (0.7)
Erythema	1 (0.7)	0	0	0
Hyperhidrosis	0	2 (1.3)	0	0
Pruritus	0	0	0	1 (0.7)
Pruritus allergic	1 (0.7)	0	0	0
Psoriasis	0	0	0	1 (0.7)
Rash	0	1 (0.6)	0	1 (0.7)
Swelling face	0	0	0	1 (0.7)
Vascular disorders	5 (3.3)	0	3 (2.0)	5 (3.4)
Hot flush	1 (0.7)	0	0	0
Hypertension	4 (2.6)	0	1 (0.7)	4 (2.8)
Hypertensive crisis	0	0	1 (0.7)	1 (0.7)
Thrombophlebitis	0	0	1 (0.7)	0

Non-SAEs and SAEs were not separated out.
Subjects were only counted once per treatment for each row.
Included data up to 9999 days after last dose of study drug.
MedDRA (v13.1) coding dictionary applied.
AEs = adverse events; IV = intravenous; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with adverse events; SAEs = serious adverse events; v = version.

The all causality treatment-emergent serious AEs (SAEs) are presented in Table 26. The number of subjects reporting SAEs was similar across treatment groups. The majority of subjects had only 1 SAE. Four (4) subjects in the tanezumab 2.5 mg plus diclofenac treatment group and 1 subject in the tanezumab 5 mg plus diclofenac treatment group had more than 1 SAE. OA, (reported) osteonecrosis, ankle fracture, and foot fracture were the only SAEs that were reported in >1 subject; OA and (reported) osteonecrosis were reported in 6 subjects each, and ankle fracture and foot fracture in 2 subjects each.

The treatment-related SAE osteonecrosis was reported for 3 subjects in the tanezumab 10 mg plus diclofenac treatment group, 1 subject in the tanezumab 5 mg plus diclofenac treatment group, and 2 subjects in the tanezumab 2.5 mg plus diclofenac treatment group. Osteonecrosis was not reported in the placebo plus diclofenac treatment group. These events were reviewed by an external adjudication committee to confirm the diagnosis, and the committee did not confirm primary osteonecrosis in any of the 6 subjects. One (1) subject was considered to have rapidly progressing OA (type 2), 1 subject was considered to have an 'other' diagnosis of an old femoral neck fracture (and no OA) at Baseline, and 1 subject was considered to have an 'other' diagnosis of subchondral insufficiency fracture. For 3 subjects,

there was not enough information available for the adjudication committee to distinguish between primary osteonecrosis and worsening osteoarthritis or to specify another diagnosis.

Table 26. Treatment-Emergent Serious Adverse Events by Special Organ Class and Preferred Term (All Causalities)

System Organ Class MedDRA (v13.1) Preferred Term	Placebo IV + Diclofenac	Tanezumab 2.5 mg + Diclofenac	Tanezumab 5 mg + Diclofenac	Tanezumab 10 mg + Diclofenac
	n (%)	n (%)	n (%)	n (%)
Number (%) of subjects:				
Evaluable for adverse events	152	157	150	145
With adverse events	8 (5.3)	12 (7.6)	8 (5.3)	10 (6.9)
Cardiac disorders	1 (0.7)	0	1 (0.7)	1 (0.7)
Atrial fibrillation	0	0	1 (0.7)	0
Cardiac failure	0	0	0	1 (0.7)
Myocardial infarction	1 (0.7)	0	0	0
Ventricular extrasystoles	0	0	1 (0.7)	0
Congenital, familial and genetic disorders	1 (0.7)	0	0	0
Benign familial pemphigus	1 (0.7)	0	0	0
Gastrointestinal disorders	1 (0.7)	1 (0.6)	0	1 (0.7)
Abdominal hernia	1 (0.7)	0	0	0
Abdominal rigidity	0	1 (0.6)	0	0
Gastrointestinal haemorrhage	0	0	0	1 (0.7)
Large intestine perforation	0	1 (0.6)	0	0
Hepatobiliary disorders	0	1 (0.6)	0	0
Cholecystitis	0	1 (0.6)	0	0
Cholelithiasis	0	1 (0.6)	0	0
Infections and infestations	1 (0.7)	1 (0.6)	0	0
Bronchitis	1 (0.7)	0	0	0
Osteomyelitis	0	1 (0.6)	0	0
Injury, poisoning and procedural complications	0	3 (1.9)	2 (1.3)	1 (0.7)
Ankle fracture	0	1 (0.6)	0	1 (0.7)
Fall	0	1 (0.6)	0	0
Foot fracture	0	1 (0.6)	1 (0.7)	0
Spinal column injury	0	1 (0.6)	0	0
Spinal fracture	0	0	1 (0.7)	0
Metabolism and nutrition disorders	1 (0.7)	0	0	0
Hyperkalaemia	1 (0.7)	0	0	0
Musculoskeletal and connective tissue disorders	1 (0.7)	3 (1.9)	4 (2.7)	5 (3.4)
Osteoarthritis	1 (0.7)	1 (0.6)	3 (2.0)	1 (0.7)
Osteonecrosis	0	2 (1.3)	1 (0.7)	3 (2.1)
Pathological fracture	0	1 (0.6)	0	0
Synovial cyst	0	0	0	1 (0.7)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.7)	2 (1.3)	0	0
Brain neoplasm	1 (0.7)	0	0	0
Cholesteatoma	0	1 (0.6)	0	0
Metastases to bone	0	1 (0.6)	0	0
Nervous system disorders	0	1 (0.6)	0	1 (0.7)
Demyelinating polyneuropathy	0	1 (0.6)	0	0
Radiculopathy	0	0	0	1 (0.7)
Respiratory, thoracic and mediastinal disorders	0	0	1 (0.7)	0
Dyspnoea	0	0	1 (0.7)	0
Skin and subcutaneous tissue disorders	0	1 (0.6)	0	0
Angioedema	0	1 (0.6)	0	0
Vascular disorders	1 (0.7)	0	0	1 (0.7)
Hypertensive crisis	0	0	0	1 (0.7)
Thrombophlebitis	1 (0.7)	0	0	0

Table 26. Treatment-Emergent Serious Adverse Events by Special Organ Class and Preferred Term (All Causalities)

Subjects were only counted once per treatment for each row.
Included data up to 9999 days after last dose of study drug.
MedDRA (v13.1) coding dictionary applied.
IV = intravenous; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with serious adverse events; v = version.

AEs leading to discontinuation from the study are presented in Table 27.

Table 27. Adverse Events Leading to Discontinuation From the Study (ITT)

MedDRA Preferred Term	Number (%)[a] of Subjects			
	Placebo + Diclofenac N=152	Tanezumab		
		2.5 mg + Diclofenac N=157	5 mg + Diclofenac N=150	10 mg + Diclofenac N=145
Arthralgia	1 (0.7)	0	1 (0.7)[b]	2 (1.4)[c]
Bundle branch block left	0	0	0	1 (0.7)
Ventricular extrasystoles	0	0	0	1 (0.7)
Gastritis[b]	0	0	0	1 (0.7)
Gastrointestinal haemorrhage[b,d,e]	0	0	0	1 (0.7)
Oedema peripheral[b]	0	0	0	1 (0.7)
Arthritis	0	0	0	1 (0.7)
Restless legs syndrome[b]	0	0	0	1 (0.7)
Abdominal pain[b]	0	0	1 (0.7)	0
Gastric ulcer[b]	0	0	1 (0.7)	0
Spinal fracture[d]	0	0	1 (0.7)	0
Myalgia[b]	0	0	1 (0.7)	0
Osteoarthritis[d]	0	0	1 (0.7)	0
Osteonecrosis[b,d]	0	1 (0.6)	1 (0.7)	0
Synovitis	0	0	1 (0.7)	0
Cervicobrachial syndrome	0	0	1 (0.7)	0
Neuropathy peripheral[b]	0	0	1 (0.7)	0
Hypertension[b]	1 (0.7)	0	1 (0.7)	0
Atrial fibrillation[b]	1 (0.7)	0	0	0
Abdominal hernia[d]	1 (0.7)	0	0	0
Cholecystitis[d]	0	1 (0.6)	0	0
Cholelithiasis[d]	0	1 (0.6)	0	0
Ankle fracture[d]	0	1 (0.6)	0	0
Osteoporotic fracture	0	1 (0.6)	0	0
Pathological fracture[b,d]	0	1 (0.6)	0	0
Brain neoplasm[d]	1 (0.7)	0	0	0
Carpal tunnel syndrome[b,f]	0	1 (0.6)	0	0
Demyelinating polyneuropathy[b,d]	0	1 (0.6)	0	0
Facial paresis[b]	1 (0.7)	0	0	0
Headache[b]	0	1 (0.6)	0	0
Paraesthesia[b,f]	0	1 (0.6)	0	0
Radicular syndrome[b,f]	0	1 (0.6)	0	0

MedDRA (version 13.1) coding dictionary was applied. Subjects were only counted once per treatment for each row. Table included data up to 9999 days after last dose of study drug.
ITT = intent-to-treat; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in a treatment group.

a. Percentages were based on the total number of subjects in each treatment group (ITT).
b. Treatment related.
c. Treatment related in 1 subject.
d. Serious adverse event(s).
e. This subject also had duodenal ulcer that resulted in permanent discontinuation of study drug. Only gastrointestinal hemorrhage was noted as leading to discontinuation from study.
f. Carpal tunnel syndrome, paresthesia, and radicular syndrome occurred in the same subject.

The incidence of abnormal laboratory tests with normal baseline values was similar across all treatment groups. Among the most frequently reported laboratory abnormalities (≥3% in each treatment group) were increased urine leukocyte esterase, urine bilirubin, urine specific

gravity, urine nitrite, urine blood/hemoglobin, red blood cell distribution width, blood urea nitrogen, triglycerides, and decreased bicarbonate (venous).

Mean changes in vital signs from Baseline were small, and no trends towards relevant increases or decreases in mean vital sign values were observed over time.

One subject in the tanezumab 10 mg plus diclofenac treatment group had QTcF values exceeding 500 msec during the course of the study; 2 subjects in each of the tanezumab 5 mg and 2.5 mg plus diclofenac treatment groups and 1 subject in the tanezumab 10 mg plus diclofenac treatment group had QTcF increases from Baseline ≥60 msec.

Twelve serum samples from 6 different subjects (1 in the tanezumab 2.5 mg plus diclofenac treatment group, 3 in the tanezumab 5 mg plus diclofenac treatment group, and 2 in the tanezumab 10 mg plus diclofenac treatment group) tested positive for the presence of ADA. These antibodies were either preexisting (n =5) or developing (n =1). In all 12 samples, the level of antibody was relatively low. Of these, 3 samples (from 2 subjects) were confirmed as positive in the neutralizing anti-tanezumab assay. No apparent alteration in the tanezumab levels, efficacy profile, or the incidence and severity of AEs were noted for the 6 subjects who were ADA positive when compared to subjects who tested negative for ADA.

Deaths:

One death occurred during the treatment period of the study. A 62-year-old male who received 3 of 3 planned doses of tanezumab 2.5 mg and received diclofenac up to Day 194. On Study Day 215, the subject died as a result of an accident: he fell from a ladder at his summer cottage and experienced spinal column injury (Investigator term: trauma of cervical spine). The events fall and spinal column injury were not attributed to study treatment.

One death occurred in 1 subject in the tanezumab 2.5 mg plus diclofenac treatment group after the subject had withdrawn from the study. An 81-year-old female who experienced many AEs during the study, including the SAE of severe demyelinating polyneuropathy starting on Day 58. The subject had received 2 of 3 planned doses of tanezumab 2.5 mg and received diclofenac up to Day 107. The event was assessed as treatment related by the Investigator.

The subject prematurely discontinued the study due to the demyelinating polyneuropathy on Day 127 and died on Day 404. The subject also experienced other SAEs (large intestinal perforation and abdominal rigidity) of unknown cause on Day 385; the perforation was treated surgically and considered resolved with sequelae the following day. The rigidity remained ongoing, and the subject remained hospitalized. The subject developed severe pneumonia on Day 398, which remained unresolved until her death 6 days later. In the opinion of the Investigator, the death was attributed to demyelinating polyneuropathy.

Deaths which occurred during the study are presented in Table 28.

Table 28. Deaths (ITT)

Serial No.	Treatment Group	Sex/Age (Years)	Event With Fatal Outcome MedDRA Preferred Term	Event Start Day/Day of Death[a]	Causality
Tanezumab + Diclofenac					
1	2.5 mg	Male, 62	Fall Spinal column injury	215/215	Other – the subject had died as a result of an accident
2	2.5 mg	Female, 81	Demyelinating polyneuropathy[b]	58/404	Study drug

MedDRA (version 13.1) coding dictionary applied.
ITT = intent-to-treat; MedDRA = Medical Dictionary for Regulatory Activities; No. = number.
a. First day of study treatment = Day 1. Day of death day was calculated as the death date minus treatment period start date +1.
b. Subject had permanently discontinued the study due to this adverse event on Day 127.

CONCLUSIONS:

- Tanezumab 2.5 mg, 5 mg, and 10 mg in combination with diclofenac were efficacious in OA of the knee or the hip as demonstrated by significantly improved pain, physical function, and global assessments compared to placebo plus diclofenac treatment.

- Treatment with tanezumab 5 mg plus diclofenac and 10 mg plus diclofenac were associated with greater and more consistent efficacy responses than tanezumab 2.5 mg plus diclofenac treatment.

- The efficacy of tanezumab plus diclofenac was maintained throughout the study period.

- The efficacy of tanezumab plus diclofenac was clinically meaningful and consistently demonstrated across all measures of efficacy.

- Tanezumab was generally well tolerated in this study. The incidences of AEs and withdrawals due to AEs were higher with tanezumab plus diclofenac treatment than with placebo plus diclofenac treatment; the incidence of SAEs was generally similar across all treatment groups.

- Among the AEs of abnormal peripheral sensation, paresthesia was most commonly reported. Most AEs of peripheral sensation were mild to moderate in severity and infrequently led to withdrawal from treatment.

- Safety evaluations did not show progressive worsening of peripheral nerve damage leading to sensory polyneuropathy in subjects treated with tanezumab plus diclofenac. Clinically significant signs and symptoms or positive diagnostic tests of neurological abnormality were most often associated with evidence of focal mononeuropathy (eg, carpal tunnel syndrome) that was generally considered to be preexisting or possibly aggravated by tanezumab treatment.

- AEs of osteonecrosis were reported only in tanezumab plus diclofenac treatment groups. A blinded external adjudication committee did not confirm primary osteonecrosis in any of the events they reviewed for this study. The committee identified rapidly progressive OA in 2 subjects treated with tanezumab 10 mg plus diclofenac. The adjudication outcomes are similar to those of other studies in which tanezumab was studied in combination with a nonsteroidal anti-inflammatory drug for the treatment of OA.

- Tanezumab plus diclofenac treatment was not associated with meaningful changes to clinical laboratory values, vital signs, or ECG results as compared to placebo treatment, and there was no evidence in this study to suggest tanezumab plus diclofenac treatment impaired sympathetic nervous system activity.