Supplemental Table 1. Studies included in the pooled analyses.

Study number (clinical trial registration; date of registration)	Pooled analyses	Treatment duration	Treatments*	Inclusion Criteria	Exclusion Criteria
A4091011 (NCT00733902; August 11, 2008)	Efficacy Safety	24 weeks	Tanezumab 2.5 mg IV Tanezumab 5 mg IV Tanezumab 10 mg IV Placebo IV	Diagnosis of OA of the knee according to ACR criteria and X-ray confirmation taken within the previous 12 months with KL X-ray grade >2, and ≥1 of the following: unwillingness or inability to take non-opiate pain medications, inadequate pain relief from non-opiate pain medications, or candidacy for invasive interventions such as intra-articular injections, knee arthroplasty, or knee replacement surgery; WOMAC† Pain subscale score in the index knee ≥4 at screening and ≥5 at baseline and, in pts who washed out of regularly taken pain medications after	Pregnant or intended to become pregnant during the study; had BMI >39 kg/m^2; pain syndromes that could confound assessment of pain from OA (eg, fibromyalgia, systemic lupus erythematosus, or others); or significant cardiac, neurologic, or psychological conditions

				screening, an increase ≥1 from screening to baseline; WOMAC Physical Function subscale score ≥4 at baseline; PGA of OA‡ of ‘‘fair,’’ ‘‘poor,’’ or ‘‘very poor,’’ at baseline	
A4091014 (NCT00744471; August 29, 2008)	Efficacy Safety	24 weeks	Tanezumab 2.5 mg IV Tanezumab 5 mg IV Tanezumab 10 mg IV Placebo IV	OA of the hip; ≥1 of the following: unwillingness or inability to take non-opiate pain medications, inadequate pain relief from non-opiate pain medications, or candidacy for invasive interventions such as intraarticular injections or hip surgery such as total joint replacement; WOMAC pain subscale score of 4 at screening and 5 at baseline, and an increase of 1 from screening to baseline if they had been regularly taking pain medications prior to screening and were required to wash out prior to baseline; WOMAC physical function subscale score of 4 at baseline was required for	Pregnant or intended to become pregnant during the study; had BMI >39 kg/m^2; moderate to severe pain other than that related to OA; any condition that could confound OA pain assessment; or significant cardiac, neurologic, or psychiatric conditions

				the hip being studied (ie, the index hip); PGA of OA disease activity as “fair,” “poor,” or “very poor” at baseline was also required	
A4091015 (NCT00830063; January 23, 2009)	Efficacy Safety	16 weeks	Tanezumab 5 mg IV Tanezumab 10 mg IV Naproxen 500 mg BID PO Placebo matching active PO and IV	Aged ≥18 years, BMI ≤39 kg/m^2 and diagnosis of knee OA based on the ACR criteria and radiographic confirmation (KL grade ≥2). At screening, eligible pts reported WOMAC Pain score ≥4 in the index joint, with or without analgesic medication. At baseline, pts had to report WOMAC Pain score ≥5 with an increase ≥1 point from screening if they had regularly taken medications (≥4 days.wk) during the month prior to screening; WOMAC Physical Function score ≥4; and a response of fair, poor, or very poor on PGA of OA to be randomized	Key exclusion criteria were similar to studies A4091011 and A4091014, but also included a history of naproxen intolerance, or existence of a medical condition or the use of concomitant medication for which naproxen is contraindicated

A4091017 (NCT00864097; March 17, 2009)	Safety	24 weeks	Tanezumab 2.5 mg IV + diclofenac SR 75 mg BID PO Tanezumab 5 mg IV + diclofenac SR 75 mg BID PO Tanezumab 10 mg IV + diclofenac SR 75 mg BID PO Diclofenac SR 75 mg BID PO + placebo IV	≥18 years old, BMI ≤39 kg/m^2 and a diagnosis of knee or hip OA based on ACR criteria for OA with radiographic confirmation (KL grade ≥2). Pts had to take a current stable oral regimen of diclofenac 150 mg/day ≥5 days per week during the 30 days before screening, tolerate the diclofenac daily regimen, and experience some benefit from this regimen but require additional pain relief. At screening, pts had to report moderate to severe pain despite diclofenac use, defined as a score of ≥4 on the WOMAC Pain subscale. Pts initiated diclofenac SR 75 mg BID at screening and must be at least 70% compliant the final 14 days prior to baseline. In addition, pts had to report a score ≥4 on WOMAC Pain and Physical Function subscales and a	Pain syndromes or index joint conditions that could confound OA pain assessment; history of significant trauma or surgery to the index joint within the previous year or planned surgical procedure during the study; largely or wholly incapacitated; significant cardiac, neurologic or psychiatric conditions; oral, intramuscular or intra-articular corticosteroids within 30 days, 30 days or 12 weeks, respectively; previous exposure to exogenous NGF or an anti-NGF antibody; history of reaction to a monoclonal antibody or IgG fusion protein; or use of biologics within 3 months of the initial pain assessment period

				response of fair, poor or very poor on PGA of OA at baseline	
A4091018 (NCT00863304; March 13, 2009)	Efficacy Safety	16 weeks	Tanezumab 5 mg IV Tanezumab 10 mg IV Naproxen 500 mg BID PO Placebo matching active PO and IV	Aged ≥18 years, BMI ≤39 kg/m^2 and diagnosis of hip or knee OA based on the ACR criteria and radiographic confirmation (KL grade ≥2). At screening, eligible pts reported WOMAC Pain score ≥4 in the index joint, with or without analgesic medication. At baseline, had to report WOMAC Pain score ≥5 with an increase ≥1 point from screening if they had regularly taken medications (≥4 days/wk) during the month prior to screening; WOMAC Physical Function score ≥4; and a response of fair, poor, or very poor on PGA of OA	Key exclusion criteria were similar to studies A4091011 and A4091014, but also included a history of naproxen intolerance, or existence of a medical condition or the use of concomitant medication for which naproxen is contraindicated
A4091025 (NCT00809354; December 16, 2008)	Safety	56 weeks	NSAID (celecoxib 100 mg PO BID or naproxen 500 mg PO BID) + placebo IV	≥18 years old, diagnosis of knee or hip OA based on ACR criteria with radiographic confirmation (KL grade ≥2), BMI ≤39 kg/m^2, taking stable oral NSAID	Similar to other tanezumab trials but also included any abnormality that would preclude continued NSAID therapy, including country-specific restrictive

			Tanezumab 5 mg IV + placebo PO Tanezumab 5 mg IV +NSAID (celecoxib 100 mg PO BID or naproxen 500 mg PO BID) Tanezumab 10 mg IV +placebo PO Tanezumab 10 mg IV +NSAID (celecoxib 100 mg PO BID or naproxen 500 mg PO BID)	(naproxen [500–1000 mg/day] or celecoxib [200 mg/day]) for their OA pain for a minimum of 30 days prior to screening, and experiencing at least some analgesic benefit from the NSAID in the opinion of the investigator. Pts were required to report WOMAC Pain score ≥4 at screening. To be eligible for randomization, required to report WOMAC Pain score ≥4; WOMAC Physical Function score ≥4; overall condition of fair, poor or very poor on the PGA of OA at baseline; and have at least 70% compliance with study-supplied oral NSAID treatment over at least 14 days directly prior to baseline. Since pts were required to continue stable oral NSAID use prior to randomization, they were not required to report a worsening WOMAC Pain score (ie, no “flare”).	exclusion criteria for naproxen or celecoxib use in pts with cardiac disease

A4091026 (NCT00863772; March 17, 2009)	Safety	24 weeks	Tanezumab 5 mg IV Tanezumab 10 mg IV Placebo IV	≥18 years with diagnosis of knee or hip OA based on ACR criteria; WOMAC Pain subscale score ≥4 for the index joint at screening and baseline; and PGA of OA of fair, poor, or very poor at baseline	Signs of baseline peripheral neuropathy based on pre-specified NC and heart rate deep breathing parameters; abnormal baseline neurologic examination; pregnancy; BMI >39 kg/m^2; other moderate to severe pain that could confound assessments of OA pain; significant heart disease, cancer, neurologic or psychiatric disease; or clinically significant systemic disease that could confound interpretation of NC tests, autonomic testing, or skin biopsy assessments
A4091027 (NCT01089725; March 11, 2010)	Safety	16 weeks	Tanezumab 2.5 mg SC Tanezumab 5 mg SC Tanezumab 10 mg SC Tanezumab 10 mg IV Placebo IV and SC	≥18 years old with diagnosis of OA of the knee based on ACR criteria and radiographic confirmation (KL X-ray grade ≥2); and WOMAC Pain score in the index knee at screening ≥4 and ≥5 at baseline. Pts regularly taking pain medications (≥4 days/wk) during the month prior to screening had to have an	Pregnancy, nursing, or intent to become pregnant during the study; BMI >39 kg/m^2; history of joint disease or recent trauma to the index knee; significant incapacitation, fibromyalgia, or regional pain caused by lumbosacral radiculopathy; significant cardiac, neurologic, or psychiatric conditions; planned surgery during the

				increase ≥1 point in WOMAC Pain score between screening and baseline. Pts had WOMAC Physical Function score ≥4 in index knee; PGA of OA of “fair,” “poor,” or “very poor” at baseline; and ≥1 of the following: unwilling or unable to take non-opiate pain medications (eg, NSAIDs); inadequate pain relief with non-opiate pain medications; or candidates for or seeking invasive interventions (intra-articular injections, knee arthroplasty, or knee replacement surgery)	study; or previous exposure to exogenous NGF or NGF antibody
A4091030 (NCT00985621; September 25, 2009)	Safety	16 weeks	Tanezumab 5 mg IV Tanezumab 10 mg IV Oxycodone CR 10 - 40 mg PO BID Placebo matching active PO and IV	OA of the hip or knee with KL grade ≥2; WOMAC Pain score ≥4 at screening; WOMAC Pain score ≥5 at baseline and an increase of ≥1 following washout of prior analgesic treatment; WOMAC Physical Function score ≥4; PGA of OA of fair, poor, or very poor at baseline; and regular use of analgesics other than	Pregnancy, nursing, or intent to become pregnant during the study; BMI >39 kg/m^2; history of joint disease or recent trauma to the index joint; significant incapacitation, fibromyalgia or regional pain caused by lumbosacral radiculopathy; significant cardiac, neurologic, or psychiatric conditions; planned surgery during the

				acetaminophen for OA pain. In addition, eligible patients had to use non-opioids or opioids up to 90 mg/day in morphine equivalents, but this therapy had not provided adequate pain relief, had not been tolerated, or pt was a candidate for invasive intervention such as total hip or knee replacement	study; opioid abuse or illicit drug use; previous exposure to exogenous NGF or NGF antibody; exposure to opioids in doses exceeding 90 mg/day in morphine equivalents (ie, oxycodone >60 mg/day) within 30 days prior to screening; history of allergic or anaphylactic reaction to a monoclonal antibody or IgG type-fusion protein; history of intolerance or hypersensitivity to acetaminophen or oxycodone; an existing medical condition for which the use of oxycodone was contraindicated; corticosteroids or intraarticular hyaluronic acid injection to the index hip or index knee within 30 days prior to the initial pain assessment period (the 5 days before randomization); and any other condition, which, in the opinion of the investigator, would put the pt at increased

					safety risk or would otherwise make the pt unsuitable for the study

*Tanezumab/placebo was administered via IV or SC injection every 8 weeks.

† WOMAC is assessed on an 11-point numeric rating scale (greater scores represent greater pain intensity/worsening physical function)

‡ PGA of OA is assessed on a 5-point scale (1 = very good, 5 = very poor)

ACR, American College of Rheumatology; BID, twice a day; BMI, body mass index; CR, controlled release; Ig, immunoglobulin; IV, intravenous; KL, Kellgren-Lawrence; NC, nerve conduction; NGF, nerve growth factor; NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; PGA, Patient's Global Assessment; PO, oral; pt, patient; SC, subcutaneous; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table S2 Baseline demographics for four phase III OA studies pooled for analysis of efficacy

	Placebo	Tanezumab 2.5 mg	Tanezumab 5 mg	Tanezumab 10 mg	Naproxen 500mg BID
Overall	n=744	n=327	n=743	n=748	n=417
Female, n (%)	478 (64.2)	195 (59.6)	449 (60.4)	450 (60.2)	265 (63.5)
Age, years, mean ± SD	61.2 ± 10.0	61.6 ± 10.1	61.1 ± 10.5	61.1 ± 10.6	60.8 ± 10.2
BMI, kg/m^2, mean ± SD	30.6 ± 4.8	30.2 ± 5.2	30.4 ± 4.9	30.3 ± 5.1	30.8± 4.7
Race, n (%)					
White	636 (85.5)	282 (86.2)	643 (86.5)	633 (84.6)	352 (84.4)
Black	83 (11.2)	37 (11.3)	88 (11.8)	86 (11.5)	54 (12.9)
Asian	9 (1.2)	3 (0.9)	4 (0.5)	10 (1.3)	7 (1.7)
Other	16 (2.2)	5 (1.5)	8 (1.1)	19 (2.5)	4 (1.0)
Diabetes‡	n= 88	n= 50	n= 90	n= 75	n= 60
Female, n (%)	49 (55.7)	28 (56.0)	49 (54.4)	46 (61.3)	28 (46.7)
Age, years, mean ± SD	63.6 ± 10.3	64.3 ± 7.8	65.5 ± 8.4	62.2 ± 9.5	62.5 ± 8.7
BMI, kg/m^2, mean ± SD	32.5 ± 3.8	32.6 ± 4.6	32.7 ± 4.3	32.5 ± 4.6	32.0 ± 4.4
Race, n (%)					
White	73 (83.0)	41 (82.0)	79 (87.8)	65 (86.7)	51 (85.0)
Black	12 (13.6)	6 (12.0)	9 (10.0)	8 (10.7)	7 (11.7)
Asian	1 (1.1)	2 (4.0)	0	1 (1.3)	1 (1.7)
Other	2 (2.3)	1 (2.0)	2 (2.2)	1 (1.3)	1 (1.7)
No diabetes	n= 656	n= 277	n= 653	n= 673	n= 357
Female, n (%)	429 (65.4)	167 (60.3)	400 (61.3)	404 (60.0)	237 (66.4)
Age, years, mean ± SD	60.9 ± 10.0	61.1 ± 10.4	60.5 ± 10.6	61.0 ± 10.7	60.5 ± 10.5
BMI, kg/m^2, mean ± SD	30.3 ± 4.8	29.8 ± 5.2	30.1 ± 4.8	30.0 ± 5.1	30.6 ± 4.7
Race, n (%)					
White	563 (85.8)	241 (87.0)	564 (86.4)	568 (84.4)	301 (84.3)
Black	71 (10.8)	31 (11.2)	79 (12.1)	78 (11.6)	47 (13.2)
Asian	8 (1.2)	1 (0.4)	4 (0.6)	9 (1.3)	6 (1.7)
Other	14 (2.1)	4 (1.4)	6 (0.9)	18 (2.7)	3 (0.8)

Severe OA symptoms at baseline[§]	n= 192	n= 88	n= 179	n= 170	n= 113
Female, n (%)	134 (69.8)	56 (63.6)	129 (72.1)	112 (65.9)	80 (70.8)
Age, years, mean ± SD	61.0 ± 9.5	60.9 ± 10.9	59.2 ± 10.2	60.1 ± 10.0	60.4 ± 10.5
BMI, kg/m^2, mean ± SD	31.7 ± 4.5	31.7 ± 4.7	31.4 ± 4.9	31.1 ± 5.0	31.4 ± 4.9
Race, n (%)					
White	154 (80.2)	77 (87.5)	149 (83.2)	131 (77.1)	92 (81.4)
Black	26 (13.5)	11 (12.5)	26 (14.5)	30 (17.6)	18 (15.9)
Asian	1 (0.5)	0	1 (0.6)	1 (0.6)	1 (0.9)
Other	11 (5.7)	0	3 (1.7)	8 (4.7)	2 (1.8)
Less severe OA symptoms at baseline	n= 192	n= 88	n= 179	n= 170	n= 113
Female, n (%)	134 (69.8)	56 (63.6)	129 (72.1)	112 (65.9)	80 (70.8)
Age, years, mean ± SD	61.0 ± 9.5	60.9 ± 10.9	59.2 ± 10.2	60.1 ± 10.0	60.4 ± 10.5
BMI, kg/m^2, mean ± SD	30.0 ± 4.8	31.7 ± 4.7	31.4 ± 4.9	31.1 ± 5.0	31.4 ± 4.9
Race, n (%)					
White	154 (80.2)	77 (87.5)	149 (83.2)	131 (77.1)	92 (81.4)
Black	26 (13.5)	11 (12.5)	26 (14.5)	30 (17.6)	18 (15.9)
Asian	1 (0.5)	0	1 (0.6)	1 (0.6)	1 (0.9)
Other	11 (5.7)	0	3 (1.7)	8 (4.7)	2 (1.8)
Aged ≥65 years	n= 275	n= 124	n= 269	n= 268	n= 151
Female, n (%)	175 (63.6)	73 (58.9)	159 (59.1)	169 (63.1)	107 (70.9)
Age, years, mean ± SD	71.5 ± 5.5	71.6 ± 5.2	71.8 ± 5.4	72.3 ± 5.8	71.5 ± 5.4
BMI, kg/m^2, mean ± SD	29.9 ± 4.6	30.1 ± 4.8	29.8 ± 4.8	29.4 ± 4.9	30.1 ± 4.5
Race, n (%)					
White	246 (89.5)	112 (90.3)	242 (90.0)	238 (88.8)	136 (90.1)
Black	25 (9.1)	11 (8.9)	23 (8.6)	23 (8.6)	13 (8.6)
Asian	2 (0.7)	0	1 (0.4)	2 (0.7)	2 (1.3)
Other	2 (0.7)	1 (0.8)	3 (1.1)	5 (1.9)	0
Aged <65 years	n= 469	n= 203	n= 474	n= 480	n= 266
Female, n (%)	303 (64.6)	122 (60.1)	290 (61.2)	281 (58.5)	155 (58.3)

Age, years, mean ± SD	55.1 ± 6.5	55.5 ± 6.9	55.0 ± 7.2	54.9 ± 6.8	54.8 ± 6.9
BMI, kg/m^2, mean ± SD	30.9 ± 4.8	30.3 ± 5.5	30.7 ± 4.9	30.8 ± 5.1	31.2 ± 4.7
Race, n (%)					
White	390 (83.2)	170 (83.7)	401 (84.6)	395 (82.3)	216 (81.2)
Black	58 (12.4)	26 (12.8)	65 (13.7)	63 (13.1)	41 (15.4)
Asian	7 (1.5)	3 (1.5)	3 (0.6)	8 (1.7)	5 (1.9)
Other	14 (3.0)	4 (2.0)	5 (1.1)	14 (2.9)	4 (1.5)

‡ Patients who had medical history of diabetes mellitus, hyperglycemia, insulin-requiring type 2 diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, or with baseline hemoglobin A1c ≥6.5.

§ Patients with severe OA symptoms had a baseline WOMAC pain score ≥7 on 11-point numeric rating scale, WOMAC physical function score ≥7, and score of “poor” or “very poor” in the PGA of OA.

BMI, body mass index; NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; PGA, Patient’s Global Assessment; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

Supplemental text S1:

The patient was referred to a consulting neurologist for further evaluation if any of the following were reported:

- Any adverse event (AE) suggestive of new or worsening peripheral neuropathy* or any AE of abnormal peripheral sensation (eg, allodynia, axonal neuropathy, burning sensation, decreased vibratory sense, demyelinating polyneuropathy, dysesthesia, formication, hyperesthesia, hyperpathia, hypoesthesia, hypoesthesia facial, hypoesthesia oral, intercostal neuralgia, neuralgia, neuritis, neuropathy peripheral, paresthesia, paresthesia oral, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy, polyneuropathy chronic, sensory disturbance, sensory loss, and thermohypoesthesia).
- Pain in the extremities suggestive of neuropathic pain.
- New or worsened clinically significant abnormality on the neurologic examination.

*Though pre-existing neuropathy was an exclusionary criterion, there could be some cases in which a subject was considered not to have a peripheral neuropathy by the study investigator (who typically was a non-neurologist). If these subjects were randomized into a study and thereafter developed neurologic symptoms which required a neurology consultation, the neurologist's evaluation could indicate that the subject had a pre-existing neuropathy. In such cases, the patient would be considered to have worsened peripheral neuropathy.

Supplemental Text S2:

Standardized Medical Dictionary for Regulatory Activities (MedDRA) queries have not been developed to assess sympathetic nervous system function. Therefore, adverse events (AEs) described in conditions characterized by post-ganglionic sympathetic dysfunction were identified and designated as “decreased sympathetic function.” The identified AE terms were further categorized as those that may be indicative of cardiac-related decreased sympathetic function and those indicative of non–cardiac-related decreased sympathetic function.

Cardiac-related AEs included blood pressure orthostatic decreased, bradycardia, dizziness postural, heart rate decreased, orthostatic hypotension, presyncope, sinus bradycardia, and syncope. Non-cardiac-related AEs included anhidrosis, hypohidrosis, abdominal discomfort, diarrhea, early satiety, fecal incontinence, nausea, vomiting, ejaculation delay, ejaculation disorder, ejaculation failure, hypertonic bladder, micturition urgency, nocturia, urinary frequency, urinary hesitation, urinary incontinence, respiratory distress, and respiratory failure.