Supplementary Text

1. Key exclusion criteria for the studies were as follows: history of other disease involving index joint; trauma or surgery to index joint within previous year; planned surgical procedure during study; fibromyalgia; pain caused by lumbar or cervical compression with radiculopathy; other pain that may confound osteoarthritis pain assessments; clinically significant cardiac disease; transient ischemic attack in previous six months or stroke with residual effects that would preclude required study activity completion; clinically significant neurological disease or psychiatric disorder; history of acetaminophen or naproxen intolerance, or existence of medical condition or use of concomitant medication for which acetaminophen or naproxen is contraindicated; intra-articular hyaluronic acid injection of index joint within thirty days of initial pain assessment period; and intra-articular corticosteroid injection of index joint within twelve weeks or any other joint within thirty days of initial pain assessment period.

2. Medications used to relieve the pain of OA such as opioids, topical analgesics, NSAIDs, capsaicin products, oral/injectable corticosteroids, analgesic patches (eg, fentanyl), and viscosupplementation (e.g., hyaluronan) were prohibited during the study and required a washout period before the initial pain assessment period of >2 days or 5 half-lives, whichever was greater. Subjects were also not to use aspirin at doses >325 mg/day or lithium during the study.

3. Sample size was calculated using treatment differences for WOMAC Pain and Physical Function (PGA) of ≥1.0 (0.4), 1.1 (0.44), and 1.2 (0.48) for contrasts of tanezumab versus naproxen, tanezumab 5 mg versus placebo, and tanezumab 10 mg versus placebo, respectively.

Assumed standard deviations were 2.5 for WOMAC and 1.0 for PGA, with assumed correlations of 0.35 between PGA and WOMAC and 0.90 between WOMAC subscales[13].

4. In Study 1015, thirteen tanezumab-treated subjects reported serious adverse events: cancer (breast, thyroid, and prostate), uriteric calculus, complete atrioventricular block, hypertension, and OA in the tanezumab 5 mg group; breast cancer (2 subjects), pneumonia, chronic obstructive pulmonary disease, vertebral fracture, vertigo, pancreatitis, hemorrhagic stroke, and cellulitis in the tanezumab 10 mg group. In the naproxen group, five subjects reported serious adverse events: diverticulitis, metastatic neoplasm, chronic obstructive pulmonary disease, malignant neoplasm, muscular weakness, hypoesthesia, atrial fibrillation, constipation, and chest pain.

5. In Study 1018, seven tanezumab-treated subjects reported serious adverse events: pneumonia, hip fracture, mental status change, urinary tract infection, chronic obstructive pulmonary disease, drug exposure during pregnancy, and spontaneous abortion in the tanezumab 5 mg group; ischemic stroke, pelvic fracture, ischemic colitis, and hyperesthesia in the tanezumab 10 mg group. Nine subjects reported serious adverse events in the naproxen group: small intestine ulcer, hip fracture, sarcoidosis, breast cellulitis, respiratory tract infection, anemia, gastrointestinal hemorrhage, myocardial infarction, and OA.

6. For those adverse events of abnormal peripheral sensation in which the location was reported, the frequency of arm/hand involvement was quite similar to the frequency of leg/foot involvement. Bilateral involvement of the extremities was more commonly reported than unilateral involvement. Involvement of the head or trunk was much less frequent. In both studies,

all adverse events of abnormal peripheral sensation across all treatment groups were either mild or moderate in intensity except for one adverse event of burning sensation rated as severe intensity in a patient treated with tanezumab 10 mg in Study 1018.

In Study A4091015, adverse events of abnormal peripheral sensation were ongoing at the end of the study in 10 patients in the tanezumab 5 mg treatment group, 16 patients in the tanezumab 10 mg treatment group, and in 7 patients in the naproxen treatment group. Median durations of adverse events still ongoing at end of study were similar across the active treatment groups.

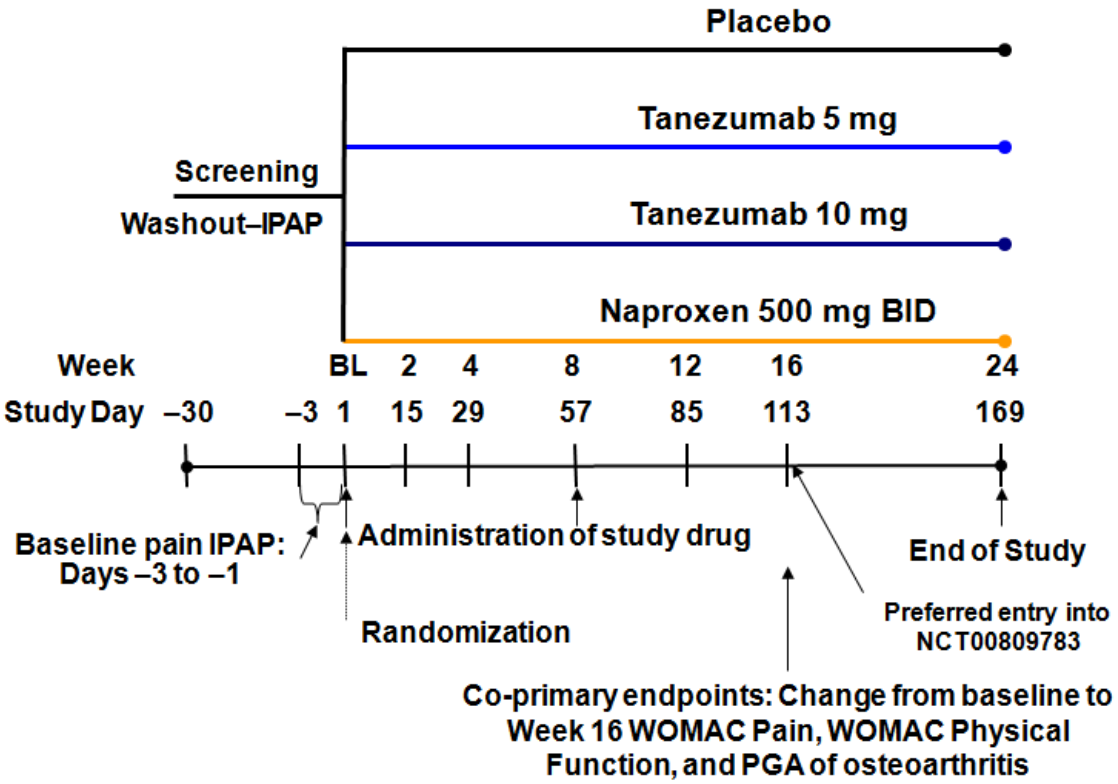
In Study A4091018, adverse events of abnormal peripheral sensation were ongoing at the end of the study in 1 patient in the placebo treatment group, 10 patients in the tanezumab 5 mg treatment group, 2 patients in the tanezumab 10 mg treatment group, and in 4 patients in the naproxen treatment group. Median durations of adverse events still ongoing at end of study were similar across the active treatment groups.

Paresthesia and hypoesthesia were most commonly reported adverse events of abnormal peripheral sensation. Investigator-reported terms that coded to the preferred term paresthesia included “pins and needles sensation”, “tingling”, “tingling sensation” or “paresthesia”. Investigator-reported terms that coded to the preferred term hypoesthesia included “numbness”, “numb sensation” and “hypoesthesia”.

7. Improvements observed with tanezumab were clinically meaningful as judged by several different methods of assessment, including the magnitude of mean improvement observed, analysis of WOMAC Pain 30% and 50% response rates (Rowbotham MC. Pain 2001;94:131-2; Salaffi et al. Eur J Pain 2004;8:283-91; Farrar et al. Pain 2000;88:287–94) and response rates

determined by Minimally Clinical Important Improvement (MCII) or Patient Acceptable Symptom Score (PASS) (Supplemental Figure 2; Supplemental Table 2). On the basis of these definitions, a greater proportion of patients treated with tanezumab experienced clinically meaning improvement in pain vs placebo and in some comparisons versus naproxen.

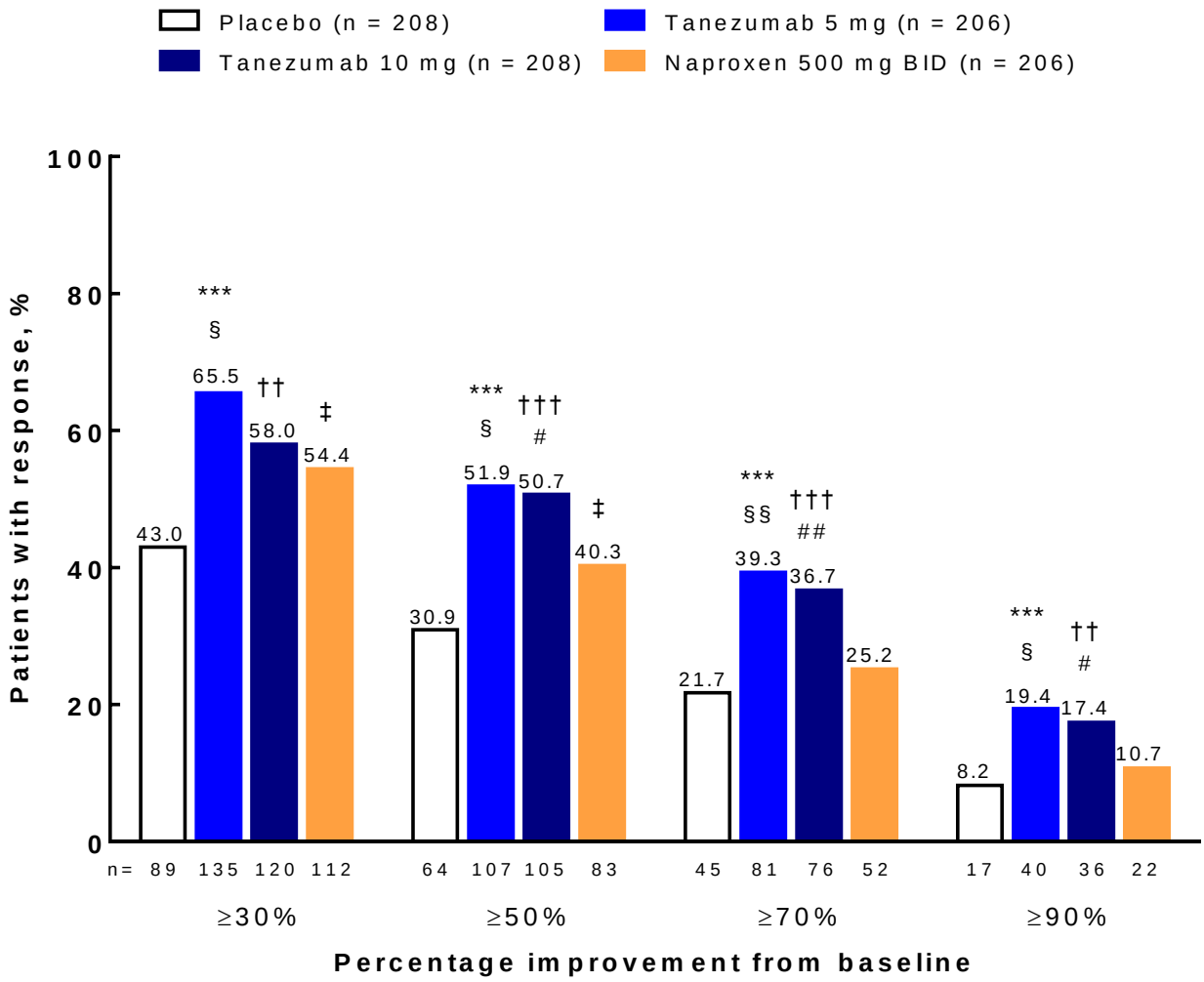
Supplementary Figure 1. Study design.



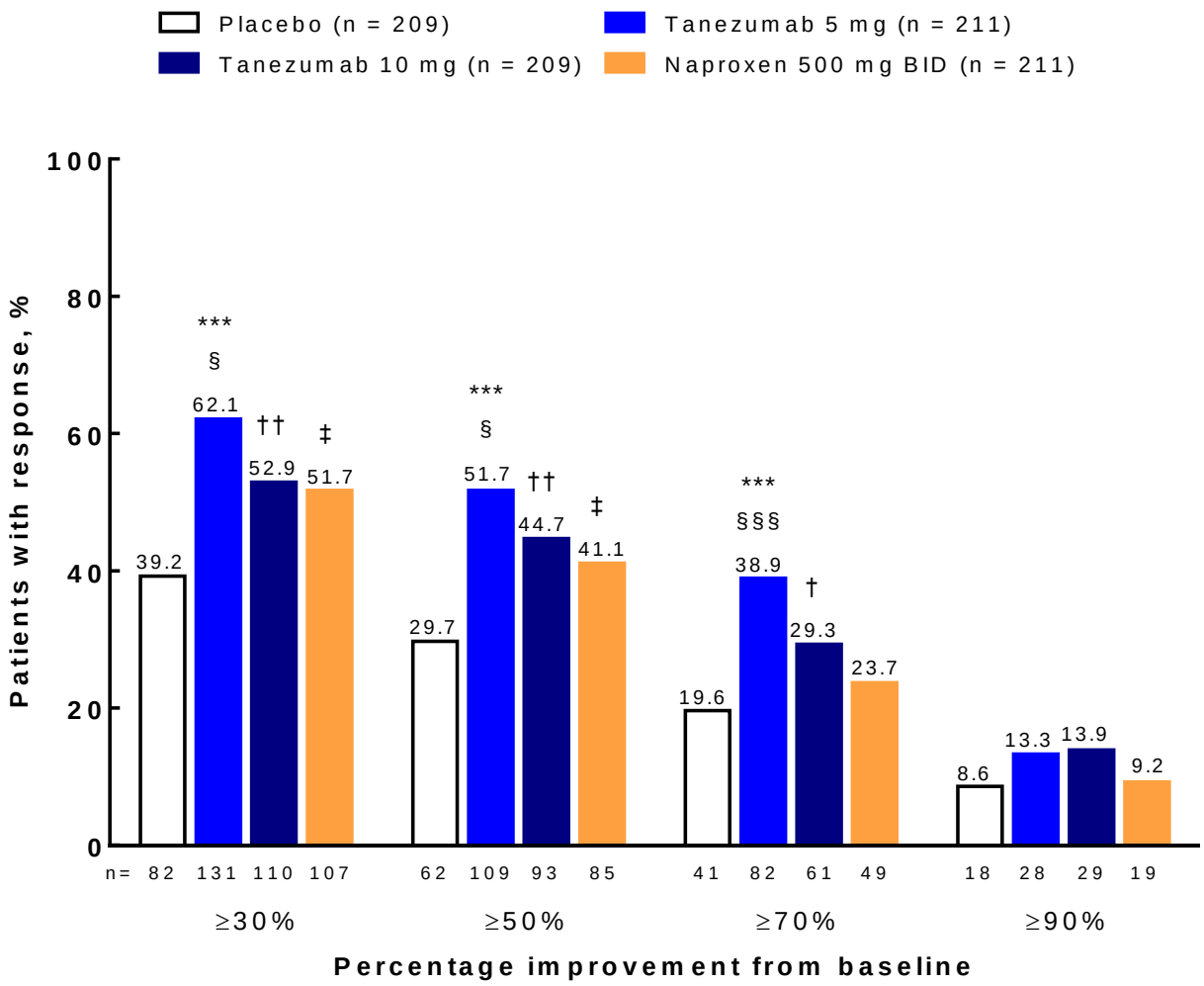
IPAP: Initial Pain Assessment Period; BL: baseline; WOMAC: Western Ontario McMaster Universities Osteoarthritis Index; PGA: Patient's Global Assessment; OA: osteoarthritis.

Supplementary Figure 2. Percentages subjects with ≥ 30%, ≥ 50%, ≥ 70%, and ≥ 90% improvement on the WOMAC Pain subscale at Week 16 for (A) Study 1015 and (B) Study 1018. Baseline observation carried forward imputation was applied for missing data.

A)



B)



*p < 0.05, **p ≤ 0.01, ***p ≤ 0.001 tanezumab 5 mg versus placebo. †p < 0.05, ††p ≤ 0.01, †††p ≤ 0.001 tanezumab 10 mg versus placebo. ‡p < 0.05, ‡‡p ≤ 0.01, ‡‡‡p ≤ 0.001 naproxen versus placebo. §p < 0.05, §§p ≤ 0.01, §§§p ≤ 0.001 tanezumab 5 mg versus naproxen. #p < 0.05, ##p ≤ 0.01, ###p ≤ 0.001 tanezumab 10 mg versus naproxen.

BID: twice daily; WOMAC: Western Ontario McMaster Universities Osteoarthritis Index.

Supplementary Table 1. Co-primary efficacy endpoints, change from baseline to Week 16.

	Study 1015				Study 1018			
	Placebo n = 208	**Tanezumab 5 mg* n = 206**	**Tanezumab 10 mg* n = 208**	**Naproxen 500 mg BID n = 206**	**Placebo n = 209**	**Tanezumab 5 mg* n = 211**	**Tanezumab 10 mg* n = 209**	**Naproxen 500 mg BID n = 211**
WOMAC Pain								
Baseline mean ± SD	7.20 ± 1.40	7.29 ± 1.46	7.23 ± 1.40	7.17 ± 1.35	7.41 ± 1.38	7.27 ± 1.38	7.37 ± 1.39	7.30 ± 1.41
LS mean change from baseline ± SE	-2.23 ± 0.20	-3.44 ± 0.20	-3.14 ± 0.20	-2.67 ± 0.20	-1.81 ± 0.22	-2.95 ± 0.22	-2.62 ± 0.22	-2.26 ± 0.22
95% CI for LS mean	[-2.62, -1.83]	[-3.84, -3.04]	[-3.54, -2.74]	[-3.07, -2.28]	[-2.25, -1.38]	[-3.39, -2.51]	[-3.06, -2.18]	[-2.70, -1.82]
Comparison vs placebo								
LS mean change from baseline ± SE		-1.21 ± 0.26	-0.91 ± 0.26	-0.45 ± 0.26		-1.13 ± 0.26	-0.80 ± 0.26	-0.45 ± 0.26
95% CI for LS mean		[-1.72, -0.70]	[-1.42, -0.40]	[-0.95, 0.06]		[-1.65, -0.62]	[-1.32, -0.29]	[-0.96, 0.07]
P-value		<0.001	<0.001	0.083		<0.001	0.002	0.090
Comparison vs naproxen								
LS mean change from baseline ±SE		-0.76 ± 0.26	-0.46 ± 0.26			-0.69 ± 0.26	-0.36 ± 0.26	
95% CI for LS mean		[-1.28, -0.25]	[-0.97, 0.04]			[-1.21, -0.17]	[-0.87, 0.16]	
P-value		0.003	0.073			0.009	0.175	
WOMAC Physical Function								
Baseline mean ±SD	6.82 ± 1.54	6.84 ± 1.71	6.82 ± 1.50	6.83 ± 1.57	7.04 ± 1.49	6.83 ± 1.56	7.09 ± 1.52	6.95 ± 1.64
LS mean change from baseline ±SE	-1.84 ± 0.19	-3.09 ± 0.19	-2.82 ± 0.19	-2.30 ± 0.19	-1.45 ± 0.21	-2.68 ± 0.21	-2.45 ± 0.21	-1.91 ± 0.21
95% CI for LS mean	[-2.21, -1.48]	[-3.47, -2.72]	[-3.19, -2.45]	[-2.67, -1.93]	[-1.86, -1.04]	[-3.10, -2.27]	[-2.86, -2.03]	[-2.33, -1.49]
Comparison vs placebo								
LS mean change from baseline ±SE		-1.25 ± 0.24	-0.97 ± 0.24	-0.46 ± 0.24		-1.23 ± 0.25	-0.99 ± 0.25	-0.46 ±0.25
95% CI for LS mean		[-1.72, -0.78]	[-1.44, -0.50]	[-0.92, 0.01]		[-1.71, -0.75]	[-1.48, -0.51]	[-0.94, 0.03]
P-value		<0.001	<0.001	0.056		<0.001	<0.001	0.067
Comparison vs naproxen								
LS mean change		-0.79 ± 0.24	-0.52 ± 0.24			-0.77 ± 0.25	-0.54 ± 0.25	

from baseline ±SE								
95% CI for LS mean		[-1.26, -0.32]	[-0.99, -0.05]			[-1.26, -0.29]	[-1.03, -0.05]	
P-value		<0.001	0.030			0.002	0.031	
PGA of OA								
Baseline mean ±SD	3.42 ± 0.61	3.40 ± 0.58	3.39 ± 0.55	3.44 ± 0.61	3.46 ± 0.65	3.36 ± 0.56	3.40 ± 0.61	3.48 ± 0.61
LS mean change	-0.53 ± 0.07	-0.87 ± 0.07	-0.73 ± 0.07	-0.65 ± 0.07	-0.39 ± 0.07	-0.73 ± 0.07	-0.72 ± 0.07	-0.54 ± 0.07
from baseline ±SE								
95% CI for LS mean	[-0.66, -0.40]	[-1.00, -0.74]	[-0.86, -0.60]	[-0.78, -0.53]	[-0.53, -0.26]	[-0.86, -0.60]	[-0.85, -0.58]	[-0.67, -0.40]
Comparison vs placebo								
LS mean change		-0.34 ± 0.09	-0.20 ± 0.09	-0.12 ± 0.08		-0.34 ± 0.08	-0.32 ± 0.08	-0.14 ± 0.08
from baseline ±SE								
95% CI for LS mean		[-0.51, -0.17]	[-0.36, -0.03]	[-0.29, 0.04]		[-0.50, -0.18]	[-0.48, -0.16]	[-0.30, 0.02]
P-value		<0.001	0.021	0.145		<0.001	<0.001	0.078
Comparison vs naproxen								
LS mean change		-0.22 ± 0.09	-0.07 ± 0.08			-0.19 ± 0.08	-0.18 ± 0.08	
from baseline ±SE								
95% CI for LS mean		[-0.38, -0.05]	[-0.24, 0.09]			[-0.35, -0.03]	[-0.34, -0.02]	
P-value		0.012	0.391			0.019	0.029	

BID: twice daily; OA: osteoarthritis; PGA: Patient's Global Assessment; SE: standard error.

Supplementary Table 2. Summary of Minimally Clinical Important Improvement (MCII) or Patient Acceptable Symptom Score at Week 16**.**

MCII		Placebo	Tanezumab 5 mg	Tanezumab 10 mg	Naproxen
Study 1015	n/N (%)	42/202 (20.8%)	87/203 (42.9%)	79/202 (39.1%)	65/205 (31.7%)
	P-value vs placebo	-	<0.0001	<0.0001	0.0134
	P-value vs naproxen	-	0.0242	0.1215	-
Study 1018	n/N (%)	52/207 (25.1%)	85/206 (41.3%)	71/205 (34.6%)	64/207 (30.9%)
	P-value vs placebo	-	0.0006	0.0408	0.2286
	P-value vs naproxen	-	0.0316	0.4628	-
Studies 1015 & 1018 combined	n/N (%)	94/409 (23.0%)	172/409 (42.1%)	150/407 (36.9%)	129/412 (31.3%)
	P-value vs placebo	-	<0.0001	<0.0001	=0.0077
	P-value vs naproxen	-	0.0015	0.1048	-
PASS					
Study 1015	n/N (%)	31/207 (15.0%)	72/206 (35.0%)	63/204 (30.9%)	46/206 (22.3%)
	P-value vs placebo	-	<0.0001	0.0002	0.0589
	P-value vs naproxen	-	0.0063	0.0574	-
Study 1018	n/N (%)	38/209 (18.2%)	75/208 (36.1%)	56/207 (27.1%)	43/209 (20.5%)
	P-value vs placebo	-	<0.0001	0.0349	0.6208
	P-value vs naproxen	-	0.0005	0.1349	-
Studies 1015 & 1018 combined	n/N (%)	69/416 (16.5%)	147/414 (35.5%)	119/411 (29.0%)	89/415 (21.4%)
	P-value vs placebo	-	<0.0001	<0.0001	0.0776
	P-value vs naproxen	-	<0.0001	0.0131	-
BOCF analysis					

The definitions used for the determination of MCII and PASS were as follows:

	Minimum clinically Important Improvement (MCII)[1]		Patient Acceptable Symptom Score (PASS)[2]	
	Knee	Hip	Knee	Hip
Osteoarthritis Pain[3]	≤-1.99	≤-1.53	≤3.23	≤3.50
Patient Global Assessment[4]	≥1 category improvement	≥1 category improvement	Good or Very Good	Good or Very Good
WOMAC Physical Function subscale[5]	≤-0.91	≤-0.79	≤3.10	≤3.44

[1]Tubach F, Ravaud P, Baron G, Falissard B, Logeart I, Bellamy N, et al. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. Ann Rheum Dis 2005;64:29–33.
[2]Tubach F, Ravaud P, Baron G, Falissard B, Logeart I, Bellamy N, et al. Evaluation of clinically relevant states in patient reported outcomes in knee and hip osteoarthritis: the patient acceptable symptom state. Ann Rheum Dis 2005;64:34–37.
[3]Mean of Week 16 Daily Average Pain (0-10 NRS); adapted from 0-100 mm VAS.
[4]Discrete Likert scale (0-5) of Very Good; Good; Fair; Poor; Very Poor. 0-100 mm VAS scores categorized as 10/30/50/70/90 or 0/25/50/75/100 values for PASS would correspond to Good and Very Good. For MCII, an improvement of at least 18.3/15.2 is closest to an improvement of at least one-category on the 5-point scale.
[5]Mean of Week 16 WOMAC Physical Function Subscale (0-10 NRS); adapted from 0-100 VAS

Supplementary Table 3. Effect size for co-primary endpoints.

Effect Size (95%CI)	Comparison	Tanezumab 5 mg	Tanezumab 10 mg	Naproxen
Study 1015				
WOMAC Pain	vs placebo	-0.47 (-0.67, -0.27)	-0.35 (-0.55, -0.16)	-0.17 (-0.37, 0.02)
	vs naproxen	-0.30 (-0.49, -0.10)	-0.18 (-0.38, 0.02)	--
WOMAC Physical	vs placebo	-0.52 (-0.72, -0.33)	-0.41 (-0.61, -0.21)	-0.19 (-0.39, 0.00)
Function	vs naproxen	-0.33 (-0.53, -0.14)	-0.22 (-0.41, -0.02)	--
Patient's Global	vs placebo	-0.40 (-0.60, -0.20)	-0.23 (-0.43, -0.03)	-0.15 (-0.34, 0.05)
Assessment	vs naproxen	-0.25 (-0.45, -0.06)	-0.09 (-0.28, 0.11)	--
Study 1018				
WOMAC Pain	vs placebo	-0.43 (-0.63, -0.24)	-0.30 (-0.50, -0.11)	-0.17 (-0.37, 0.03)
	vs naproxen	-0.26 (-0.46, -0.07)	-0.14 (-0.33, 0.06)	--
WOMAC Physical	vs placebo	-0.49 (-0.69, -0.30)	-0.40 (-0.60, -0.20)	-0.18 (-0.38, 0.01)
Function	vs naproxen	-0.31 (-0.51, -0.12)	-0.22 (-0.41, -0.02)	--
Patient's Global	vs placebo	-0.41 (-0.61, -0.21)	-0.40 (-0.59, -0.20)	-0.18 (-0.37, 0.02)
Assessment	vs naproxen	-0.23 (-0.43, -0.04)	-0.22 (-0.42, -0.02)	--