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Characterization of adverse joint outcomes in patients with osteoarthritis treated with subcutaneous tanezumab

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SUMMARY

Objective: Due to the risk of rapidly progressive osteoarthritis (RPOA), the phase III studies of subcutaneous (SC) tanezumab in patients with moderate to severe hip or knee osteoarthritis (OA) included comprehensive joint safety surveillance. This pooled analysis summarizes these findings.
Method: Joint safety events in the phase III studies of SC tanezumab (2 placebo- and 1- nonsteroidal anti-inflammatory drug [NSAID]-controlled) were adjudicated by a blinded external committee. Outcomes of RPOA1 and RPOA2, primary osteonecrosis, subchondral insufficiency fracture, and pathological fracture comprised the composite joint safety endpoint (CJSE). Potential patient- and joint-level risk factors for CJSE, RPOA, and total joint replacement (TJR) were explored.
Results: Overall, 145/4541 patients (3.2%) had an adjudicated CJSE (0% placebo; 3.2% tanezumab 2.5 mg; 6.2% tanezumab 5 mg; 1.5% NSAID). There was a dose-dependent risk of adjudicated CJSE, RPOA1, and TJR with tanezumab vs NSAID. Patient-level cross-tabulation found associations between adjudicated RPOA with more severe radiographic/symptomatic (joint pain, swelling, and physical limitation) OA. Risk of adjudicated RPOA1 was highest in patients with Kellgren-Lawrence (KL) grade 2 or 3 OA at baseline. Risk of adjudicated RPOA2 or TJR was highest in patients with KL grade 4 joints at baseline. A higher proportion of joints with adjudicated RPOA2 had a TJR (14/26) than those with adjudicated RPOA1 (16/106).
Conclusion: In placebo- and NSAID controlled studies of SC tanezumab for OA, adjudicated CJSE, RPOA, and TJR most commonly occurred in patients treated with tanezumab and with more severe radiographic or symptomatic OA. NCT02697773; NCT02709486; NCT02528188

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Introduction

Nerve growth factor (NGF) inhibitors have entered clinical development for a number of pain conditions.[1] Initial phase II and III studies of NGF inhibitors identified an increased risk of serious joint safety events.[2,3] During a class-wide clinical hold, patients with reported osteonecrosis or who had undergone total joint replacement (TJR) during phase II and III trials were retrospectively reviewed by an external adjudication committee. They identified rapidly progressive osteoarthritis (RPOA) as a potential safety signal for this drug class, particularly in patients with osteoarthritis (OA).[2,3] In these analyses, the risk of RPOA appeared to be dose-related and higher in patients who took concomitant nonsteroidal anti-inflammatory drugs (NSAIDs).[2,3]

Tanezumab is an antibody targeted against NGF.[4–8] Acknowledging the risk of RPOA, phase III clinical trials of subcutaneous (SC) tanezumab conducted after the clinical hold utilized rigorous and comprehensive screening. This included scheduled radiographic assessment of all knees, hips, and shoulders. This aimed to exclude patients with RPOA, or with pre-specified risk factors for RPOA.[4–6,9] Efficacy studies were placebo-controlled, whereas another was a long-term, NSAID-controlled safety study.[4–6] Together, these studies involved over 480 sites worldwide and included 4541 patients with moderate to severe hip or knee OA, for whom other standard of care analgesics had been inadequate, intolerable, or contraindicated.[4–6] Findings from these studies showed the dose-dependent efficacy of tanezumab to be superior to placebo and comparable to NSAID treatment.[4–6] All possible or probable joint safety events and cases of TJR identified during the studies were adjudicated by an external blinded adjudication committee.[4–6] This analysis summarizes these joint safety surveillance data and explores the potential for associations between adjudicated joint safety outcomes and various patient- or joint-level characteristics.

Methods

Studies

Data were pooled from 3, international, randomized, double-blind, phase III trials of SC tanezumab. Study 1 (ClinicalTrials.gov: NCT02697773) included 696 patients administered placebo, tanezumab 2.5 mg, or tanezumab 2.5 mg then 5 mg over a 16-week treatment period (SC injections at baseline and week 8).[5] Study 2 (NCT02709486) included 849 patients administered placebo, tanezumab 2.5 mg, or 5 mg over a 24-week treatment period (SC injections at baseline and weeks 8 and 16).[6] Study 3 (NCT02528188) included 2996 patients administered tanezumab 2.5 mg or 5 mg, or oral NSAID (twice-daily naproxen 500 mg, celecoxib 100 mg, or diclofenac extended release 75 mg) over a 56-week treatment period (SC injections at baseline and every 8 weeks up to week 48).[4] Patients in study 3 were required to be tolerating a stable dosage of NSAID before enrollment and could not continue past week 16 unless efficacy was demonstrated. All studies included a 24-week post-treatment safety follow-up period.

The trials enrolled patients with moderate to severe OA pain who had experienced an inadequate response to, a contraindication to, or an inability to tolerate multiple standard of care analgesics.[4–6] Key inclusion criteria included radiographically determined Kellgren-Lawrence (KL) grade ≥2 OA in a hip or knee, moderate to severe pain and physical disability in the index hip or knee, and a patient's global assessment of OA of "fair" or poorer (on a scale from 1 = very good to 5 = very poor). All patients were required to have 1) a history of insufficient pain relief from acetaminophen; 2) a history of insufficient pain relief from, intolerance, or contraindication to NSAIDs (study 3 instead required a stable NSAID dosage); and 3) a history of inadequate pain relief from, intolerance, or contraindication to either tramadol or opioid analgesics (or unwillingness to take opioids). The index joint was the most painful hip or knee joint at baseline with a qualifying pain score and KL grade.

Enrolled patients were prohibited from using all other analgesics for OA pain until 16 weeks after the last SC treatment dose. Exceptions were rescue acetaminophen and limited or occasional use for self-limiting conditions other than OA (not NSAIDs or cyclooxygenase-2 inhibitors in study 3). Standard of care treatment could begin 16 weeks after the last SC treatment dose.

Patients had baseline radiographs taken of all knees, hips, and shoulders to exclude those with pre-existing RPOA, risk factors for RPOA, joint conditions, or other conditions that might interfere with study participation or assessments. Exclusionary joint conditions included severe malalignment of the knee based on anatomical axis (≥10° varus or valgus on the anterior–posterior view),[10] severe chondrocalcinosis, other arthropathies (e.g., rheumatoid arthritis), systemic metabolic bone disease (e.g., Paget disease), large cystic lesions, primary or metastatic tumor lesions, stress or traumatic fractures, atrophic OA (definite joint space narrowing without relevant osteophyte formation and absence of erosions or other radiographic signs of inflammatory arthritis),[10] subchondral insufficiency fractures, osteonecrosis, and pathologic fractures. Patients with significant trauma or surgery in a knee, hip, or shoulder in the year prior to screening, and those who planned to receive a TJR during the trial period were also ineligible.

These studies were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. The studies were approved by the institutional review board or independent ethics committee at each study center. All patients provided written informed consent before participating.

Joint imaging

Scheduled radiographs of each patient's knees, hips (index and non-index), and shoulders were obtained at screening (all studies), the end of follow-up or early termination (all studies), at the end of treatment (studies 2 and 3 only), and after 24 weeks of treatment (study 3). During treatment and follow-up periods, blinded Central Readers reviewed radiographs to identify possible or probable joint conditions to be evaluated by the blinded external adjudication committee. Magnetic resonance imaging (MRI) was not routinely performed in studies 1 and 2 but could be requested to evaluate suspected joint pathology occurring after enrollment. In study 3, knee and hip MRI was performed at screening but not used for the assessment of exclusion criteria. For patients with a knee or hip with KL grade 3 or 4 OA at screening, additional joint-specific MRI was performed at week 24, at the end of treatment, and at the end of follow-up (or at early termination). Further MRI could be requested to aid diagnosis of suspected joint pathology.

Radiographs were acquired by trained imaging technologists following program-specific guidance. Change in computer-assisted minimal joint space width measurement in knees and hips was assessed between sets to determine the presence of RPOA type 1 (RPOA1; minimum measurement of 1 pixel/~0.2 mm). Previous image sets were available for comparison.

Screening and on-study images were read independently by 1 of 5 Central Readers who were expert musculoskeletal radiologists (9–21 years' experience) and blinded to treatment.[9] A program-specific imaging atlas was developed as an agreed reference point, and all readers undertook extensive calibration training to ensure alignment.[10–12] During active screening, readers achieved moderate

to substantial agreement on eligibility and substantial agreement on KL grading.[13–15]

Blinded external adjudication

Program-level blinded adjudication of all possible or probable joint safety events (Central Reader or investigator reported) and TJRs that took place during the 3 studies. The observation period for each patient was from baseline up to the end of the safety follow-up period, or 26 weeks after the end of the treatment period, whichever was later. Patients considered to have possible or probable joint safety events and those who had or planned to have TJR surgery were immediately discontinued from treatment and entered the safety follow-up period. Patients undergoing TJR in the 3 studies were eligible to join a 24-week observational follow-on study.[16] The outcome of TJR surgeries was uneventful for 95% of patients, and adjudicated joint safety outcomes showed no relationship to post-operative outcomes.[16]

The external adjudication committee consisted of experts in musculoskeletal radiology, orthopedic surgery, bone and joint pathology, and rheumatology. Each committee member was blinded to treatment and provided with a case summary, all available images of all joints, and all available source documentation for each patient. This included (but was not limited to) investigator-assessed progress, orthopedic consult, operative, radiology, MRI, and pathology reports. This information was reviewed independently by each adjudication committee member, who provided an adjudication classification based on the radiographical definitions of each joint condition in the context of the available clinical information. If consensus was reached i.e., agreement by 4/5 or 4/4 members, the classification was considered final. If consensus was not achieved, the case was reviewed again at a subsequent meeting in which consensus was determined by agreement among 3/4 members.

Possible adjudication outcomes were radiographically defined: RPOA1 (decrease in joint space width ≥2 mm [predicated on optimal joint positioning] within approximately 1 year, without gross structural failure),[17] RPOA type 2 (RPOA2; abnormal bone loss or destruction, including limited or total collapse of ≥1 subchondral surface that is not normally present in conventional end-stage OA),[3] primary osteonecrosis (or avascular necrosis; focal circumscribed or extended region of infarcted bone), subchondral insufficiency fracture (focal bone defect, or loss of sphericity of the articular surface and/or focal radiolucency in the subchondral trabecular bone, with or without adjacent cortical defect), pathological fracture (not including osteoporotic fractures), normal progression of OA (followed a normal course for OA progression and did not meet the criteria for any of the joint safety outcomes or have another diagnosis), not enough information to determine rapid vs normal progression of OA, and other (includes post-traumatic/post-procedure events and pre-existing conditions). Where a patient had more than one joint with an adjudicated outcome, the primary outcome for that patient was determined according to the following hierarchy: primary osteonecrosis; RPOA2; subchondral insufficiency fracture; pathological fracture; RPOA1; not enough information to determine rapid vs normal progression of OA; other; normal progression of OA. Outcomes of RPOA, osteonecrosis, subchondral insufficiency fracture, and pathological fracture were included in the adjudicated composite joint safety endpoint (CJSE).

Analysis

Pooled patient demographics, clinical and joint characteristics at baseline, and incidence of adjudicated joint safety endpoints and TJR are summarized for each treatment group. The titration treatment group i.e., tanezumab 2.5 mg followed by 5 mg from Study 1 comprised fewer patients relative to the other treatment groups, and were not receiving a stable dosage, so this group is not generally included in later analyses. Incidence and risk differences (95% confidence interval) for adjudicated joint safety outcomes are calculated for all treatments using exact methods, and on a patient-level. As patients have 2 knees and 2 hips, they could have met the criteria to be included in multiple subgroups. The absolute risk difference is referred to as the 'additional risk' in the text. Incidence over time is presented for study 3 data only, as this had the longest duration of observation. Potential associations between various patient- or joint-specific factors and the occurrence of adjudicated CJSE, RPOA, and TJRs were explored descriptively through qualitative assessment of cross-tabulation. These were assessed for suggestive visual trends only, and no statistical analyses were planned.

Results

Pooled patient population

In the 3 studies, which took place between July 2015 and February 2019, 4541 patients were treated in North America, Europe, South America, and Asia-Pacific regions. Across treatment groups, most patients were women (64–69%), White (68–78%), and had an index joint that was a knee (84–86%). Most index joints had a radiographically determined KL grade of 3 (43–48%) or 4 (23–33%) at baseline (Table I). More than 50% of patients in each treatment group had 2 joints with KL grade ≥2 OA (> 20% had 3 or 4; Table 1).

Adjudicated joint safety endpoints

Overall, 523 joints were reviewed by the adjudication committee. Of these, 0/28 joints reviewed from placebo-treated patients, 50/173 of those from tanezumab 2.5 mg treated patients, 1/19 from tanezumab 2.5 mg then 5 mg treated patients, 87/246 from tanezumab 5 mg treated patients, and 16/57 from NSAID-treated patients had an adjudicated CJSE. Of the 451 patients reviewed by the adjudication committee, CJSE was adjudicated in 145 (32.2%), representing 3.2% of those treated; 9 patients had adjudicated CJSE in 2 or more joints (1 in tanezumab 2.5 mg, 7 in tanezumab 5 mg, and 1 in NSAID groups; Fig. 1). The most commonly adjudicated condition comprising the CJSE was RPOA. This included a primary adjudication (by hierarchy) of RPOA1 for 100 patients (2.2% of those treated) and RPOA2 for 24 (0.5%; Fig. 1 and Supplemental Table 1). Subchondral insufficiency fracture and osteonecrosis were the primary adjudication outcomes for 0.4% and 0.07% of all treated patients, respectively. Most adjudicated patients had a primary adjudication of normal progression of OA (259 [57.4%]; Fig. 1 and Supplemental Table 1).

There were no adjudicated CJSEs in placebo-treated patients. Risk difference analyses showed that patients treated with tanezumab 2.5 mg and 5 mg, but particularly 5 mg, were at higher risk of an adjudicated CJSE, RPOA1, or RPOA2 outcome compared with those treated with placebo or NSAID (risk difference: 0.2–5.6%; Fig. 2 and Supplemental Table 2). Significantly higher risk of CJSE was observed in the tanezumab 5 mg group vs placebo (risk difference: 3.2% [95% confidence interval: 0.56%, 7.18%]) and NSAID (5.6% [3.55%, 8.14%]); and for RPOA1 (3.8% [1.99%, 6.12%]) and RPOA2 (1.3% [0.17%, 2.97%]) vs NSAID. Significantly higher risks of CJSE (2.4% [0.58%, 4.68%]) and RPOA1 (1.8% [0.16%, 3.92%]) were observed in the tanezumab 2.5 mg group vs NSAID. The risk of adjudicated osteonecrosis and subchondral insufficiency fracture were not significantly different across treatment groups. For patients with adjudicated outcomes, the primary affected joint was the index joint for 57% in the tanezumab 2.5 mg, 31% in the tanezumab 5 mg, and 60% in the NSAID groups.

In the longest study (study 3; 56-week treatment period and 24-week follow-up), increases in CJSE and RPOA adjudications were

	Placebo (n = 514)	Tanezumab 2.5 mg (n = 1530)	Tanezumab 2.5/5 mg (n = 219)	Tanezumab 5 mg (n = 1282)	NSAID (n = 996)
Female, n (%)	353 (68.7)	992 (64.8)	139 (63.5)	847 (66.1)	662 (66.5)
Age, mean (SD)	62.5 (9.8)	61.3 (9.3)	61.3 (9.1)	62.1 (9.8)	60.3 (9.5)
Race, n (%)					
White	403 (78.4)	1139 (74.4)	159 (72.6)	960 (74.9)	680 (68.3)
Black or African American	60 (11.7)	211 (13.8)	48 (21.9)	162 (12.6)	186 (18.7)
Asian	47 (9.1)	153 (10.0)	8 (3.7)	129 (10.1)	99 (9.9)
Other	4 (0.8)	27 (1.8)	4 (1.8)	31 (2.4)	31 (3.1)
Ethnicity, n (%)					
Hispanic or Latino	55 (10.7)	248 (16.2)	35 (16.0)	189 (14.7)	192 (19.3)
Not Hispanic or Latino	459 (89.3)	1282 (83.8)	184 (84.0)	1093 (85.3)	804 (80.7)
Region, n (%)					
North America	232 (45.1)	1041 (68.0)	219 (100.0)	785 (61.2)	769 (77.2)
Europe	248 (48.2)	252 (16.5)	0	261 (20.4)	14 (1.4)
Japan	34 (6.6).	112 (7.3)	0	93 (7.3)	67 (6.7)
Rest of the World*	0	125 (8.2)	0	143 (11.2)	146 (14.7)
Index joint (assessed for efficacy), n (%)					
Knee	434 (84.4)	1291 (84.4)	189 (86.3)	1086 (84.7)	852 (85.5)
Hip	80 (15.6)	239 (15.6)	30 (13.7)	196 (15.3)	144 (14.5)
Shoulder OA at baseline[a]	20 (3.9)	107 (7.0)	15 (6.8)	82 (6.4)	55 (5.5)
KL grade of the index joint (assessed for efficacy)[b,c]**, n (%)**					
0	0	2 (0.1)	0	4 (0.3)	1 (0.1)
1	0	3 (0.2)	0	2 (0.2)	3 (0.3)
2	124 (24.1)	410 (26.8)	56 (25.6)	361 (28.2)	291 (29.2)
3	221 (43.0)	714 (46.7)	98 (44.7)	595 (46.4)	476 (47.8)
4	169 (32.9)	401 (26.2)	64 (29.2)	320 (25.0)	225 (22.6)
Maximum KL grade in any joint[c]**, n (%)**					
0	0	0	0	0	0
1	0	1 (0.1)	0	0	0
2	86 (16.7)	329 (21.5)	48 (21.9)	280 (21.8)	239 (24.0)
3	242 (47.1)	752 (49.2)	99 (45.2)	645 (50.3)	503 (50.5)
4	186 (36.2)	448 (29.3)	72 (32.9)	357 (27.8)	254 (25.5)
Number of joints with a KL grade ≥2[c]**, n (%)**					
0	0	1 (0.1)	0	0	0
1	101 (19.6)	358 (23.4)	45 (20.5)	262 (20.4)	219 (22.0)
2	278 (54.1)	824 (53.9)	116 (53.0)	722 (56.3)	560 (56.2)
3	87 (16.9)	202 (13.2)	34 (15.5)	186 (14.5)	124 (12.4)
4	48 (9.3)	145 (9.5)	24 (11.0)	112 (8.7)	93 (9.3)

KL = Kellgren-Lawrence; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; SD = standard deviation; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

* Rest of World includes South America, Africa, Australia, and Asia Pacific (excluding Japan).

[a] Based on the investigator's assessment of musculoskeletal history.

[b] Index joint was the most painful hip or knee at screening with a qualifying WOMAC (© 1996 Nicholas Bellamy. WOMAC® is a registered trademark of Nicholas Bellamy [CDN, EU, USA]) Pain score and KL grade as confirmed by the Central Reader.

[c] KL grading is not applicable to shoulders.

Table I

Osteoarthritis and Cartilage

Patient demographics, clinical and joint characteristics at baseline.

often observed around (± 4 weeks) scheduled imaging timepoints in all treatment groups, particularly at week 56 (Fig. 3). The period after week 24 imaging, up to and including week 56 imaging, was the study period generally associated with the highest risk for tanezumab- vs NSAID-treated patients (Fig. 4). Assessments for RPOA2 were limited by the low number of adjudicated cases. Analysis of joint space narrowing in knees with RPOA1 indicated potential stabilization after the end of tanezumab treatment (Supplemental Fig. 1). Contralateral knees showed minimal narrowing through 80 weeks (Supplemental Fig. 1).

Associations between RPOA and joint characteristics

Adjudicated RPOA1 was observed most often in knees and was usually not associated with TJR surgery (16/106; Supplemental Table 3). The incidence of RPOA1 was highest among patients with KL grade 2 or 3 OA at baseline (0–3.5% of patients for knees and 0–1.2% of patients for hips, across treatments; Supplemental Table 4); however, there was minimal association between the additional risk with tanezumab vs NSAID and baseline KL grade (Fig. 5). Among all patients, the additional risk of knee RPOA1 was 1.0% with tanezumab 2.5 mg and 2.7% with tanezumab 5 mg, both vs NSAID (in hips was 0.2% and 0.3%, respectively).

Adjudicated RPOA2 was often associated with knees and hips that underwent TJR surgery (14/26; Supplemental Table 3). The incidence of RPOA2 was highest among patients with KL grade 4 OA at baseline (0–0.9% of patients for knees and 0–5.0% of patients for hips, across treatments; Supplemental Table 4). The additional risk associated with tanezumab was highest for patients with joints with KL grade 4 OA at baseline, particularly hips (5.0% for 2.5 mg vs NSAID and 3.4% for 5 mg vs NSAID). Among all patients, the additional risk of knee RPOA2 was 0.2% for tanezumab 2.5 mg and 0.5%

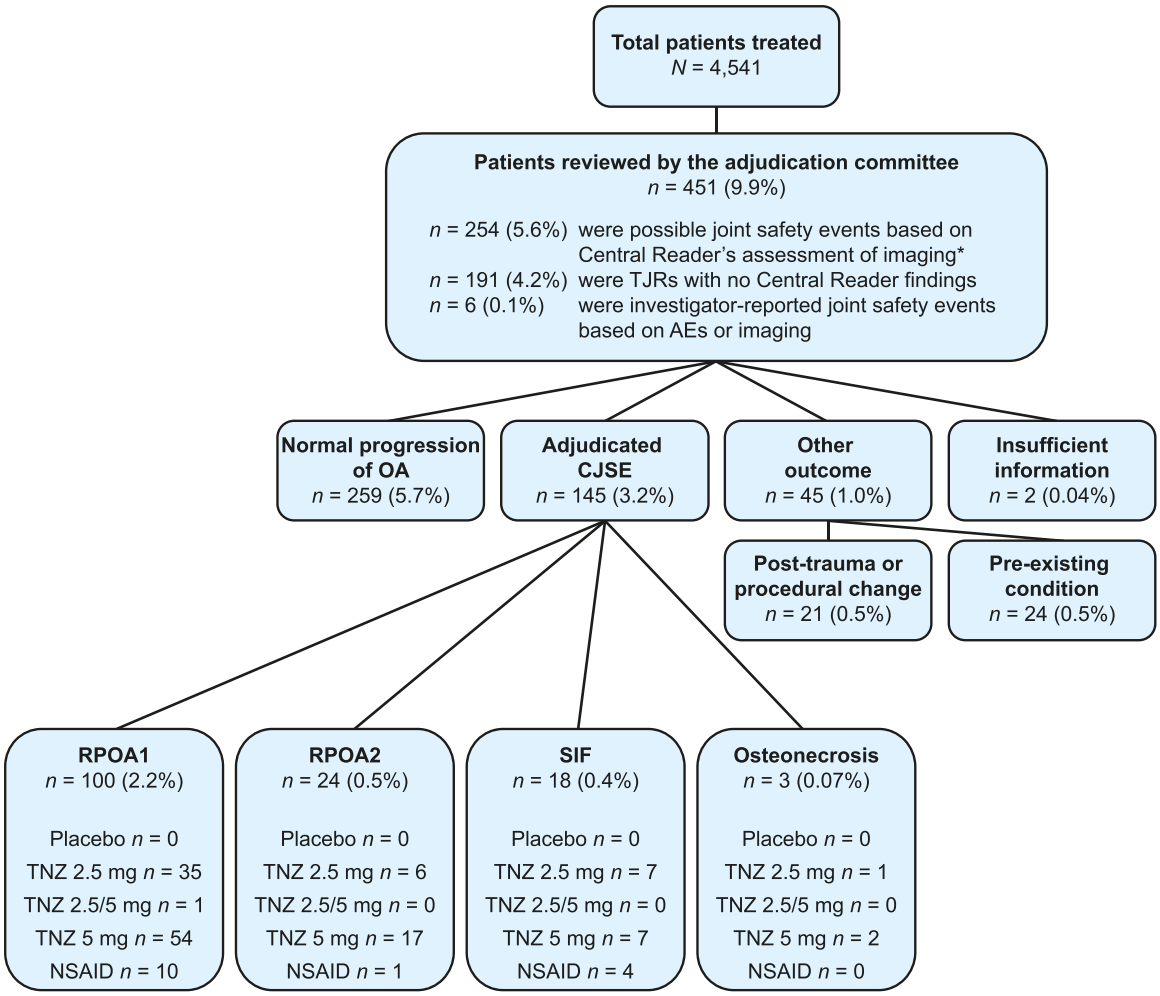

Fig. 1 Osteoarthritis and Cartilage

Outcome of adjudicated joint safety endpoints. *RPOA1 or RPOA2, primary osteonecrosis, subchondral insufficiency fracture, or pathologic fracture based on a program-level imaging atlas. There were no adjudicated joint safety events of pathological fracture. Adjudicated events up to the end of the follow-up period or 26 weeks after the end of the treatment period, whichever was later. AE = adverse event; CJSE = composite joint safety endpoint; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; RPOA = rapidly progressive osteoarthritis; SIF = subchondral insufficiency fracture; TJR = total joint replacement; TNZ = tanezumab.

for tanezumab 5 mg, both vs NSAID (in hips was 0.2% and 0.8%, respectively; Fig. 5).

Six cases of RPOA were adjudicated in joints with no radiographic evidence of OA (KL grade 0) at baseline, and all of these were in patients administered tanezumab (4 of RPOA1, 2 in the 2.5 mg and 2 in the 5 mg group; 2 of RPOA2, both in the 5 mg group; Supplemental Table 3). There was generally a small additional risk of CJSE, RPOA, subchondral insufficiency fracture, osteonecrosis, and TJR associated with tanezumab in patients with joints that were KL grade 0 at baseline (risk difference: −0.1–0.7%; Fig. 6).

Few potential associations were identified in our exploratory cross-tabulation of various patient-level factors (detailed in Supplemental Table 5). and the incidence of adjudicated CJSE or RPOA outcomes. The incidence of adjudicated CJSE and both types of RPOA outcomes showed a possible association with adverse events of arthralgia or joint swelling (Supplemental Table 6). There were also possible associations between adjudicated CJSE and RPOA1 with a maximum KL grade in any joint at baseline of 3, and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC[1]) Pain and Physical Function scores at baseline of ≥7/10 (indicating more severe pain and physical limitation; Supplemental Table 6). Possible associations between the incidence of adjudicated RPOA2 outcomes and a maximum KL grade in any joint at baseline of 4 and a WOMAC pain score at baseline of ≥7/10 were also observed (Supplemental Table 6). No other associations with numerous other factors were suggested, including demographics, efficacy response, and concomitant medication.

TJRs

Overall, 248 patients had ≥1 TJRs during the observation period, for any reason (26 had 2 or more). The incidence of patients with a

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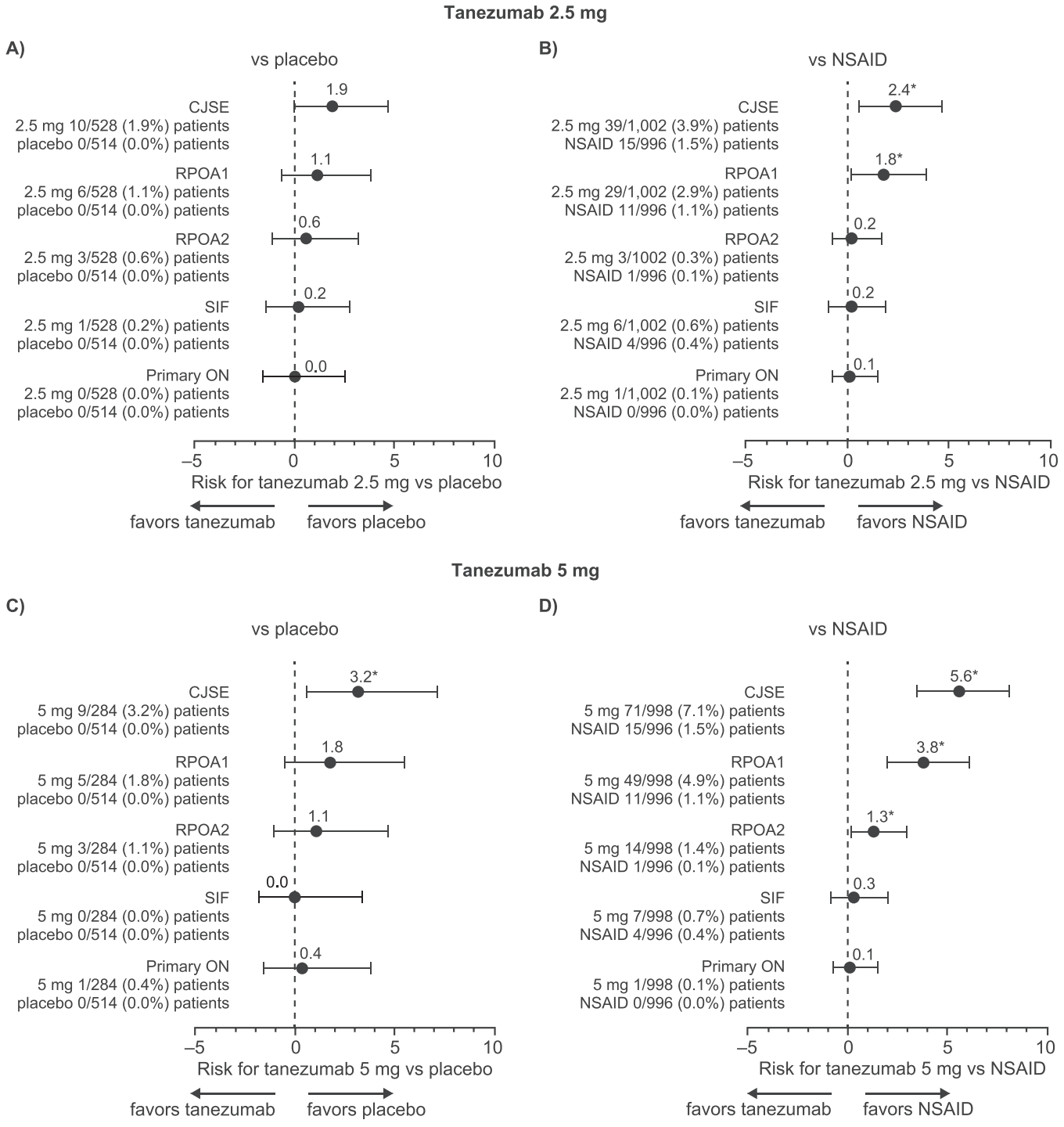

Fig. 2

Osteoarthritis and Cartilage

Risk differences for adjudicated joint safety outcomes for tanezumab 2.5 mg (A/B) and 5 mg (C/D) as compared with placebo or NSAID treatment. Shows risk difference with 95% confidence interval at the patient-level. Patients are included where ≥1 joint met the criteria. Comparisons with placebo from pooled studies 1 and 2; comparisons with NSAID from study 3. Adjudicated endpoints up to the end of the follow-up period or 26 weeks after the end of the treatment period, whichever was later. *$p \leq 0.05$. CJSE = composite joint safety endpoint; NSAID = nonsteroidal anti-inflammatory drug; ON = osteonecrosis; RPOA = rapidly progressive osteoarthritis; SIF = subchondral insufficiency fracture.

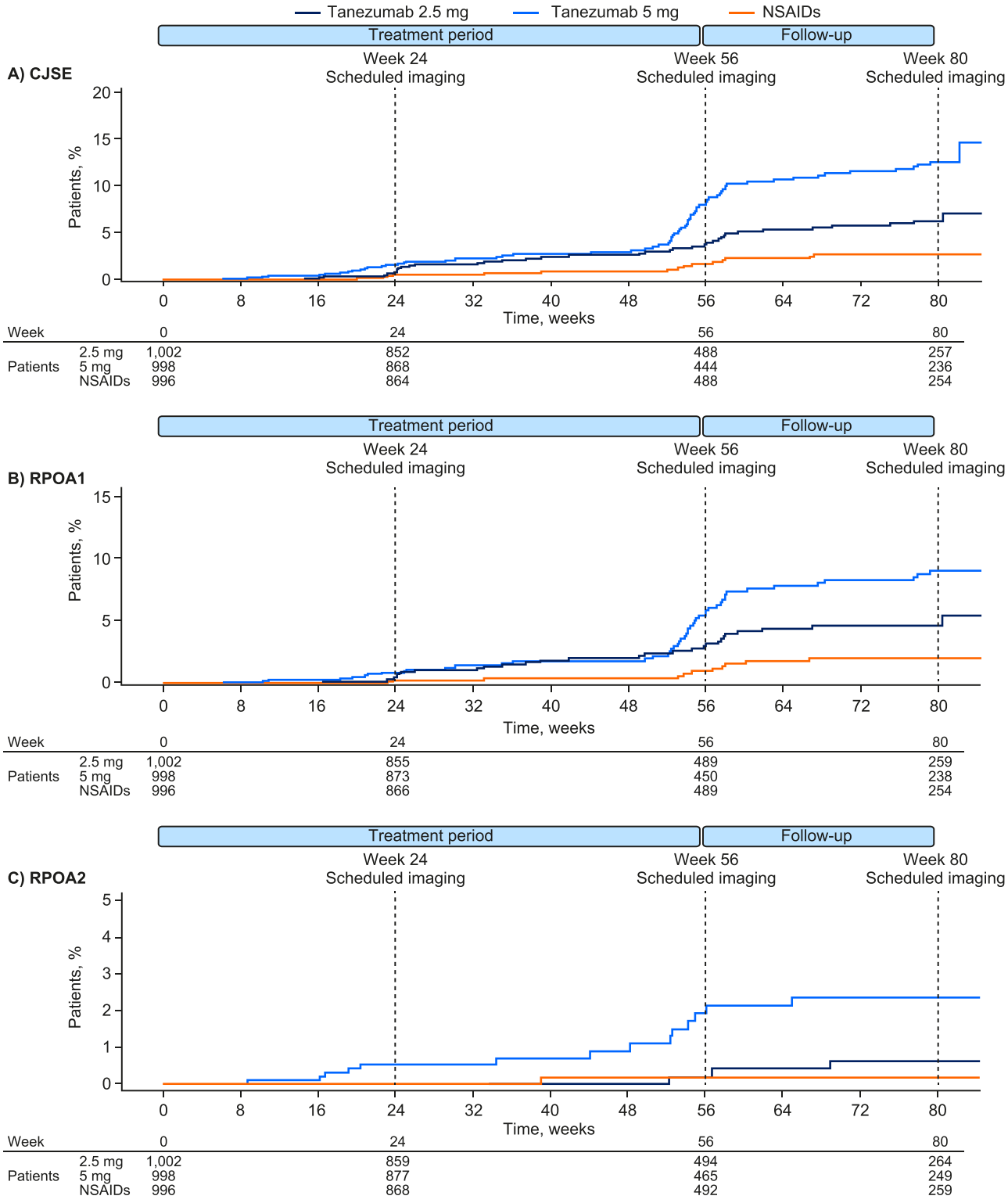

Fig. 3

Osteoarthritis and Cartilage

Incidence of adjudicated CJSE (A), RPOA1 (B), and RPOA2 (C) over time in a study with a 56-week treatment period (study 3). Data from study 3. Week 24 and week 56 imaging visits defined as study days 169 and 393, respectively, +/– 4 weeks. Adjudicated endpoints up to the end of the follow-up period or 26 weeks after the end of the treatment period, whichever was later. CJSE = composite joint safety endpoint; NSAID = nonsteroidal anti-inflammatory drug; RPOA = rapidly progressive osteoarthritis.

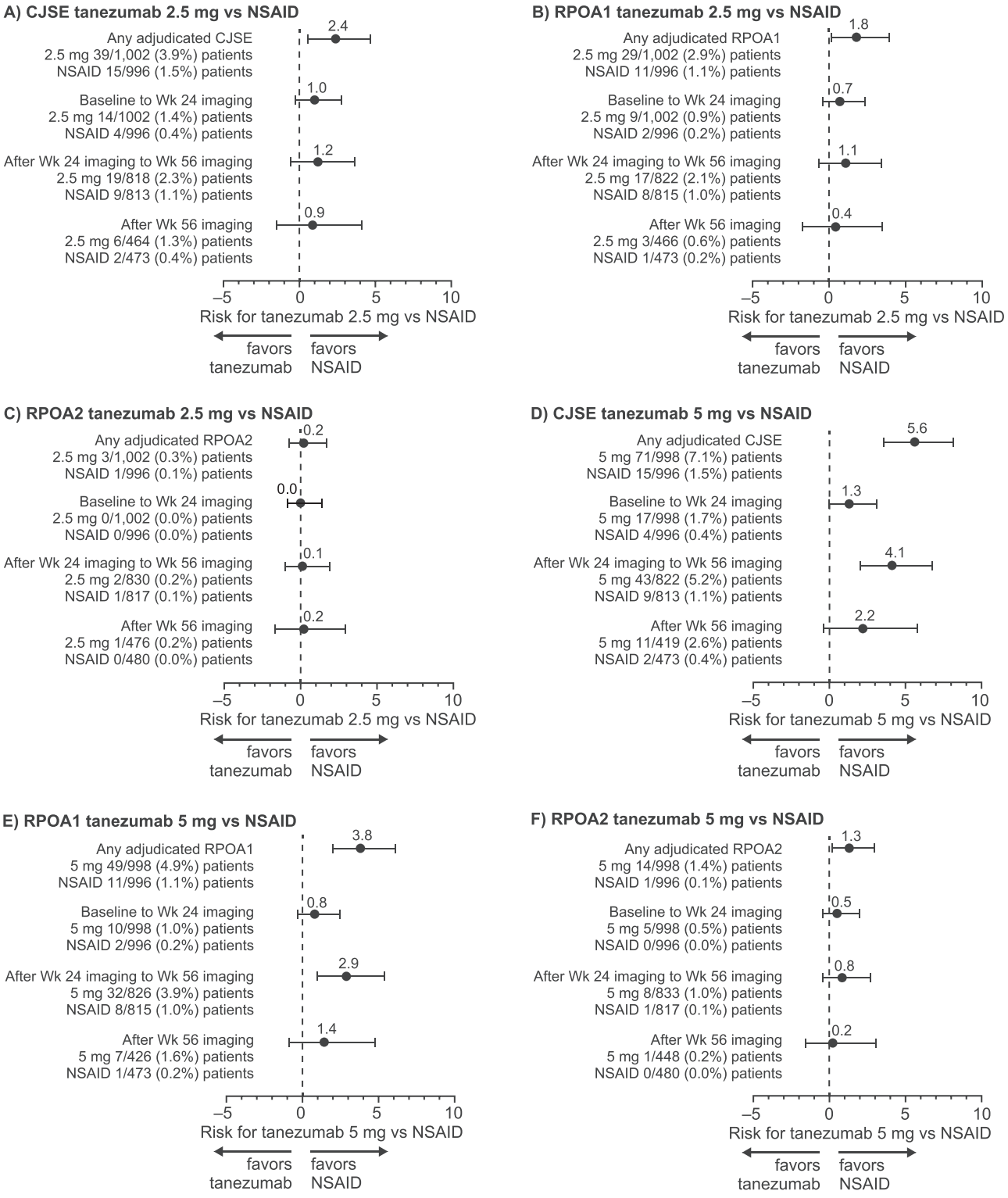

Fig. 4

Osteoarthritis and Cartilage

Risk of adjudicated CJSE, RPOA1, and RPOA2 for patients taking tanezumab 2.5 mg (A–C) and 5 mg (D–F) vs NSAID by study period in a study with 56 weeks of treatment (study 3). Shows risk difference with 95% confidence interval at the patient-level. Patients are included where ≥1 joint met the criteria. Data from study 3. Adjudicated endpoints up to the end of the follow-up period or 26 weeks after the end of the treatment period, whichever was later. CJSE = composite joint safety endpoint; NSAID = nonsteroidal anti-inflammatory drug; RPOA = rapidly progressive osteoarthritis; Wk = week.

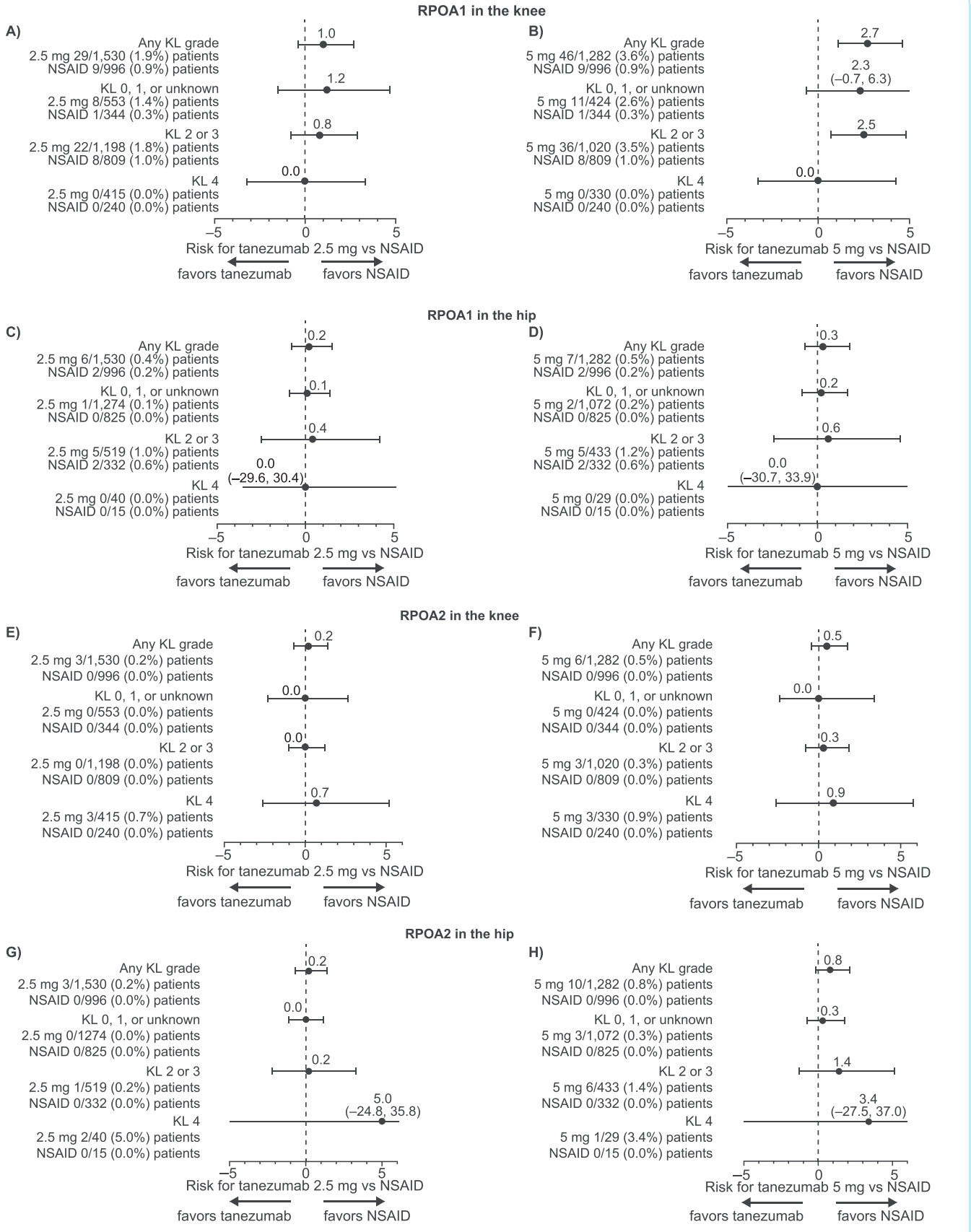

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Fig. 5 Osteoarthritis and Cartilage

Risk difference for RPOA1 (A–D) and RPOA2 (E–H) in patients treated with tanezumab 2.5 mg (A, C, E, G) or 5 mg (B, D, F, H) vs NSAID by KL grade and joint. Shows risk difference with 95% confidence interval at the patient-level. Patients are included in all subgroups where ≥1 joint met the criteria and could be in ≥1 KL category. All comparisons from pooled data from studies 1–3. Shows risk difference with 95% confidence interval. Adjudicated endpoints up to the end of the follow-up period or 26 weeks after the end of the treatment period, whichever was later. KL = Kellgren-Lawrence; NSAID = nonsteroidal anti-inflammatory drug; RPOA = rapidly progressive osteoarthritis.

TJR was 4.5% with placebo, 5.5% with tanezumab 2.5 mg, 7.8% with tanezumab 5 mg, and 2.6% with NSAID (Supplemental Table 7). Overall, 83.5% of patients with ≥1 TJR had an index joint replaced.

Across treatment groups, over 85% of joints undergoing TJR had KL grade 3 or 4 OA at baseline, but the highest incidences of TJR were seen in patients with joints with KL grade 4 OA at baseline, particularly hips (Fig. 7; Supplemental Table 8). The additional risk of knee TJR in patients with KL grade 3 OA at baseline was 0.9% with tanezumab 2.5 mg and 3.3% with tanezumab 5 mg, both vs NSAID (in hips was 1.0% and 7.7%, respectively; Fig. 7). The additional risk was higher in patients with KL grade 4 OA at baseline (knees vs NSAID: 2.5 mg: 4.7%; 5 mg: 3.6%; hips vs NSAID: 2.5 mg: 35.0%; 5 mg: 24.1%; Fig. 7). Additional risks were slightly lower vs placebo (Supplemental Table 8). Exploratory and descriptive cross-tabulation did not suggest any patient-level factors to be potentially associated with the incidence of TJR.

All TJRs were adjudicated for potential CJSE and have been included in the results. When looking at patients with TJR in isolation, across treatment groups, 73–93% had a primary adjudication of normal progression of OA (Supplemental Table 9). The incidence of CJSE, RPOA1, and RPOA2, were higher among treatment groups including only patients with TJRs than when including patients with and without TJRs.

Discussion

This integrated analysis shows dose-related increases in the risk of adjudicated CJSE, RPOA, and TJR outcomes in patients with moderate to severe OA treated with SC tanezumab. These findings build on the previous adjudication of joint safety events in patients treated with intravenous tanezumab, which found an increased risk of RPOA, particularly in patients taking concomitant NSAIDs.[2,3] Our analyses of joint- and patient-level factors suggest that the risk of adjudicated RPOA1 is highest in joints with KL grade 2 or 3 OA at baseline, and the risk of RPOA2 is highest in joints with KL grade 4 OA, particularly hips. Most cases of TJR had advanced OA at baseline (KL grade 3 or 4, but particularly KL grade 4 hips). Patient-level subgroup analyses explored potential associations between CJSE, RPOA1, and RPOA2 and more severe radiographic or symptomatic OA.

These clinical trials of SC tanezumab included a rigorous screening program to exclude patients with RPOA, or with potential risk factors for RPOA. Pre-existing RPOA2 or other risk factors were each identified in < 5% of radiographically screened patients and infrequently observed in more than one joint per patient.[18] Other exclusion criteria (such as strict NSAID restrictions) also aimed to limit the risk of RPOA. Nonetheless, 3.2% of treated patients had an adjudicated CJSE during these studies (2.7% RPOA).

Several potential forms of RPOA have been described in the literature, with variable clinical courses and diverse proposed etiologies.[19,20] Joints with OA naturally display individual rates of joint space narrowing, typically ≤ 0.2 mm a year and with very variable trajectories over longer terms.[21–24] Several causes of RPOA have been proposed with some analgesics including NSAIDs and intra-articular steroids implicated.[20,25–29] Definitions of RPOA in the 3 phase III trials of SC tanezumab matched those used in the previous adjudication.[2,3] The definition of RPOA1 is derived from that proposed by Lequesne and describes a scenario of rapid joint space narrowing (≥2mm a year) without gross structural failure.[17] A previous study that grouped knee joint space narrowing trajectories found patients displaying the most rapid progression (11/549 [2%]) to have a mean narrowing of 2.1 mm over 2 years.[21] The definition of RPOA2 describes a scenario of abnormal joint destruction (limited or total collapse of at least one subchondral surface).[19,20] Prior to the studies, the background incidence of RPOA1 and 2 were estimated by the study sponsor to be up to 3% and 0.2%, respectively, and these were comparable to our findings (2.2% and 0.5% across treatment groups).

As reported in the individual study publications and confirmed in this analysis, there is a dose-related increase in the risk of CJSE, RPOA, and TJR outcomes in patients with moderate to severe OA treated with SC tanezumab.[1–3] Although efficacy is numerically higher for tanezumab 5 mg than 2.5 mg, we found no consistent relationship between patient-level efficacy outcomes and the incidence of CJSE or RPOA.[4–6] Analyses from the long-term study show tanezumab 2.5 mg to be associated with an additional 1.8% risk of RPOA1 vs NSAID treatment. Although our longer-term analysis is limited by the 24-week follow-up period, the incidence of CJSE and RPOA appears to decline after the end of treatment, suggesting this additional risk may be attenuated. The increased incidence of RPOA seen with NGF inhibitors is currently unexplained. Speculative theories include a potential role (or combined roles) for analgesic arthropathy, an exacerbation of pre-existing poor bone integrity, and alteration of bone or cartilage repair.[7] These mechanisms are yet to be fully evaluated.

Our analyses also aimed to explore potential factors associated with adjudicated CJSE and RPOA outcomes identified in the phase III studies of SC tanezumab. These findings provide hypotheses requiring further investigation, particularly for RPOA2, where there were only a small number of adjudicated events. Previous findings in hips showed patients with a trajectory of rapid joint space loss (> 0.2 mm/year) to generally have a higher KL grade at baseline compared with those with slower joint space loss, and joints with a KL grade ≥2 to be associated with a somewhat faster decline in joint space width.[22] Separately, patients with the most rapid progression of knee OA (mean 2.1 mm/year) are more likely to be male and in a higher degree of pain than patients with stable joint space width.[21] Suggestions of more severe OA symptoms in those who later develop RPOA have been made in the literature, but not in all cases.[19,21,22,30] Our exploratory analyses broadly supported these previous findings. RPOA occurred most frequently in patients with knees and hips with more advanced radiographic OA at baseline, in patients with more pain and physical disability at baseline, and reporting symptoms of arthralgia and joint swelling during the studies. We found very small risks of adjudicated CJSE, RPOA, and TJR even in joints without radiographic evidence of OA at baseline. Together, evidence suggest more advanced and symptomatic OA is associated with increased risk of RPOA, and that this is limited to the affected joint. How tanezumab interacts with this process remains unclear.

On October 26, 2021, Pfizer Inc and Eli Lilly and Company announced discontinuation of the global clinical development program

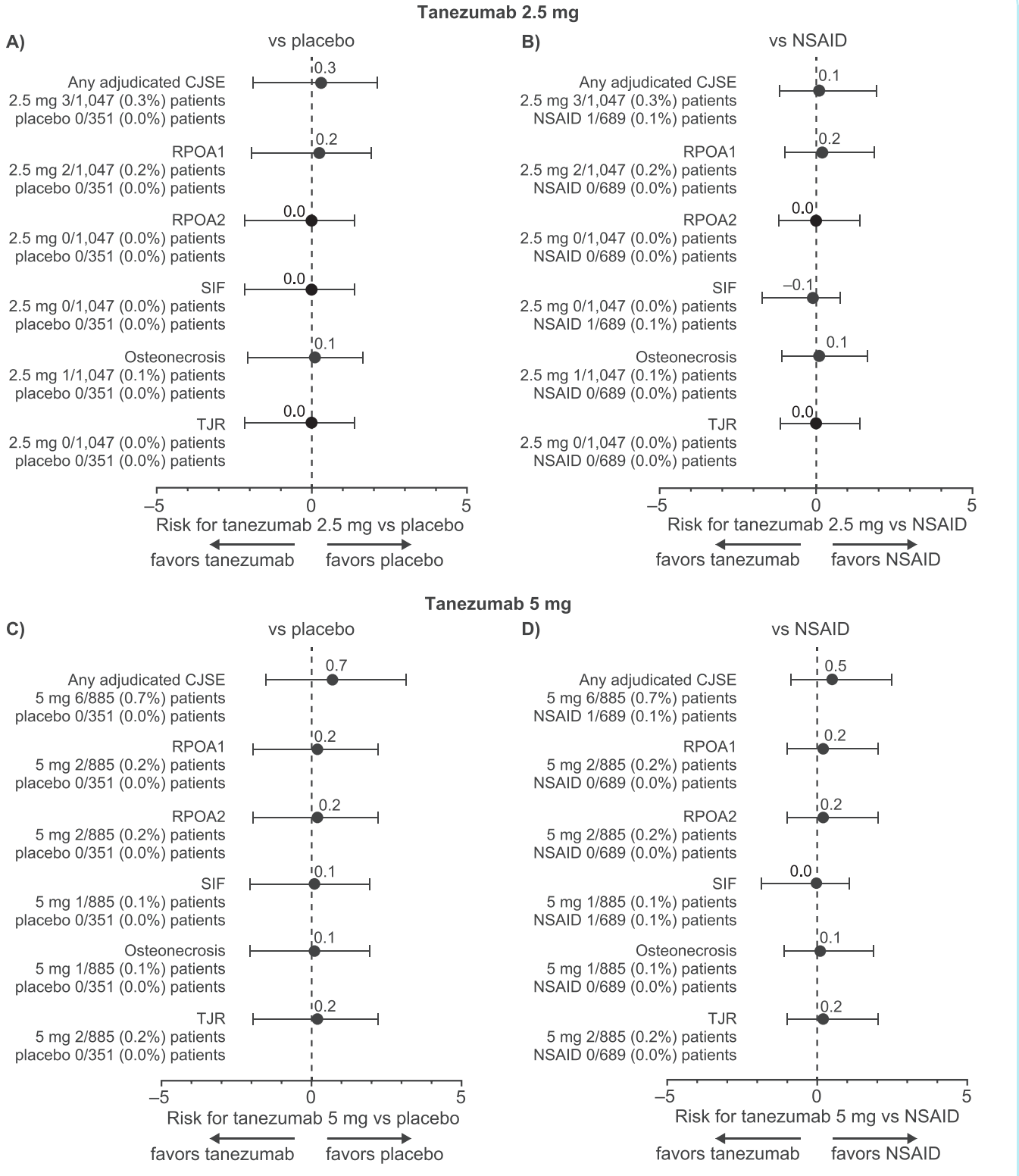

Fig. 6

Osteoarthritis and Cartilage

Risk of adjudicated CJSE and TJR for tanezumab 2.5 mg (A/B) or 5 mg (C/D) vs placebo or NSAID in patients with KL grade 0 joints at baseline. Shows risk difference with 95% confidence interval at the patient-level. Patients are included where ≥1 joint met the criteria and could have had ≥1 outcome. All comparisons from pooled data from studies 1–3. Adjudicated endpoints up to the end of the follow-up period or 26 weeks after the end of the treatment period, whichever is later. CJSE = composite joint safety endpoint; NSAID = nonsteroidal anti-inflammatory drug; RPOA = rapidly progressive osteoarthritis; SIF = subchondral insufficiency fracture; TJR = total joint replacement.

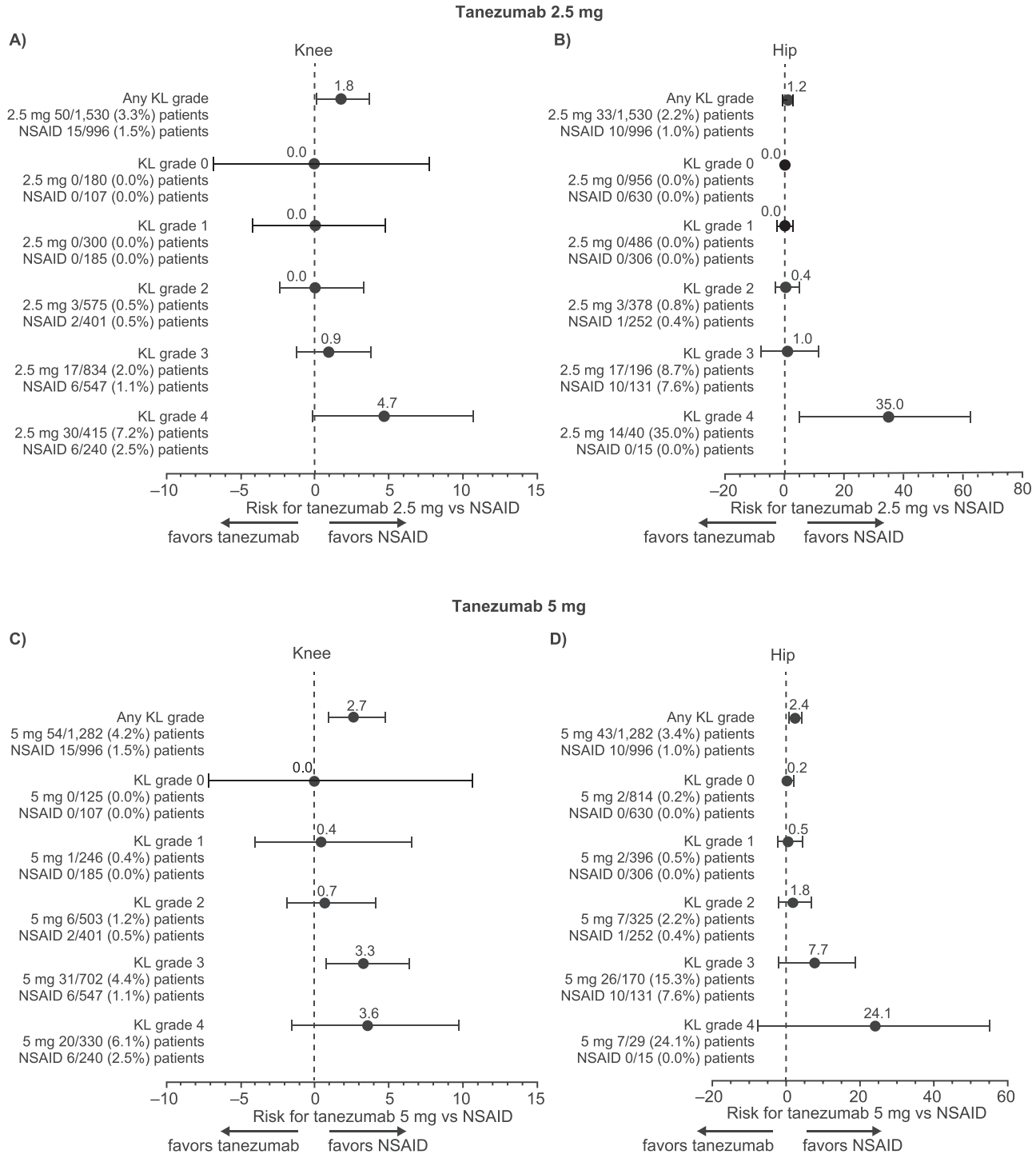

Fig. 7

Osteoarthritis and Cartilage

Risk difference for TJR with tanezumab 2.5 mg (A/B) or 5 mg (C/D) vs NSAID in hips and knees by KL grade. Shows risk difference with 95% confidence interval at the patient-level. Patients are included in all subgroups where ≥1 joint met the criteria and could be in ≥1 KL category. All comparisons from pooled data from studies 1–3. Shows risk difference with 95% confidence interval. TJRs up to the end of the follow-up period or 26 weeks after the end of the treatment period, whichever was later. KL = Kellgren-Lawrence; NSAID = nonsteroidal anti-inflammatory drug; TJR = total joint replacement.

as a result of the outcomes of regulatory reviews of tanezumab for the treatment of OA pain by the US Food and Drug Administration and European Medicines Agency.[31,32]

The main limitation of this analysis is the lack of longer-term follow-up data, including after treatment has finished. While study 3 provided data for up to 56 weeks of tanezumab and NSAID treatment and a further 24-week safety follow-up, placebo data are only available from studies 1 and 2, which had a maximum treatment duration of 16 or 24 weeks of treatment, respectively, and 24 weeks of follow-up. The trials were also designed to reduce the risk of RPOA and employed protocol procedures to specifically detect it. These features may not be easy to replicate in a real-world clinical setting, so we cannot rule out additional risk if used in the real-world, where restrictions are harder to implement. Lastly, RPOA was defined per program-specific definitions for these trials. Though we analysed incidence by KL grade at baseline, we acknowledge that adjudication of RPOA1 in joints that were KL grade 4 at baseline is unlikely using these definitions. Consistent definitions are not currently used in clinical practice, making research into the causes of RPOA challenging.

In conclusion, in placebo- and NSAID-controlled studies of SC tanezumab for the treatment of OA, the risk of adjudicated CJSE, RPOA, and TJR was higher in patients who received tanezumab than NSAID or placebo. These outcomes were most common in patients with more severe radiographic and symptomatic OA at baseline. Joints with no radiographically detectable signs of OA at baseline had a low, but not zero, risk of CJSE.

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Role of the funding source

Pfizer Inc. and Eli Lilly and Company contributed to the study design; Pfizer contributed to the management and collection of data. In their role as authors, employees of Pfizer and Eli Lilly were involved in the interpretation of data, preparation, review, and approval of the manuscript and the decision to submit for publication, along with their co-authors. The study sponsors approved the manuscript from an intellectual property perspective but had no right to veto the publication.

Author contributions

Conception and design: MB, AB, RF, GP, LV, CW, KV. Analysis and interpretation of the data: JC, TM, TS, AG, MH, PC, MB, AB, RF, GP, LV, CW and KV. Drafting of the article: JC, TM, TS, AG, MH, PC, MB, AB, RF, GP, LV, CW and KV. Critical revision of the article for important intellectual content: JC, TM, TS, AG, MH, PC, MB, AB, RF, GP, LV, CW and KV. Final approval of the article: JC, TM, TS, AG, MH, PC, MB, AB, RF, GP, LV, CW and KV. Provision of study materials or patients: N/A. Statistical expertise: GP. Obtaining of funding: N/A. Administrative, technical, or logistic support: N/A. Collection and assembly of data: JC, TM, TS, AG, MH, PC, MB, AB, RF, GP, LV, CW and KV.

Data availability

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Declaration of Competing Interest

John A. Carrino has received consulting fees from Covera Health, Globus, and Pfizer, and is on the medical advisory board of Image Analysis Group, Image Biopsy Lab and Carestream. Timothy E McAlindon has served on an advisory board for Pfizer, Samumed, Seikagaku, Flexion Therapeutics, Sanofi, Roche, Astellas, and Regeneron. Tom J. Schnitzer has received grants from Kolon TissueGene, Pfizer, Regeneron, Galapagos, Eli Lilly & Company, Paradigm, TLC, Ltd, Anika, Novartis; personal fees and non-financial support from Pfizer, Eli Lilly & Company, Regeneron, Aptinyx, Calibr, GSK, Astra-Zeneca, Genascence, Biosplice, Xalud, IBSA, IQVIA and Vertex. Ali Guermazi has received consulting fees from AstraZeneca, Merck Serono, Pfizer, Organogenesis, Novartis and TissueGene, and is a shareholder of Boston Imaging Core Lab LLC. Marc C Hochberg has received consulting fees from Bone Therapeutics, Bristol Myers Squibb, Eli Lilly, EMD Serono, Novartis Pharma AG, Pfizer, Regenosine, Samumed LLC, Theralogix LLC, TissueGene Inc., TLC Biopharmaceuticals, Inc., and Zynerba; is a member of the Data Safety Monitoring Committee for clinical trials conducted by Covance, Galapagos, ICON plc, IQVIA, and SunPharma; received royalties from Elsevier (Editor, Rheumatology 7e and Editor-in-Chief, Seminars in Arthritis and Rheumatism) and UpToDate™; and has stock ownership in BriOri Biotech and Theralogix LLC. Philip Conaghan has received consulting fees from AbbVie, AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, Galapagos, Genascence, GlaxoSmithKline, Janssen, Levicept, Novartis, Pfizer, Stryker and UCB. Mark T Brown, Aimee Burr, Robert J. Fountaine, Glenn C Pixton, Christine West and Kenneth M Verburg are employees of Pfizer and have stock/stock options. Lars Viktrup is an employee and stockholder of Eli Lilly and Company.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.joca.2023.08.010.

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