Postoperative Outcome of Patients Who Underwent Total Joint Replacement During the Tanezumab Phase 3 Osteoarthritis Development Program: A 24-Week Observational Study

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ABSTRACT

Introduction: This prospective cohort study (ClinicalTrials.gov identifier: NCT02674386) evaluated the postoperative outcomes of patients who had undergone total joint replacement (TJR) while participating in one of three tanezumab (a nerve growth factor inhibitor) randomized phase 3 osteoarthritis (OA) studies.

Materials and Methods: Eligible patients were those who underwent TJR (knee, hip, or shoulder) at any time during any of three tanezumab randomized phase 3 OA studies. Consenting patients were followed for 24 weeks post-surgery. Patients undergoing sub-total arthroplasty procedures were not eligible; there were no further protocol-defined exclusion criteria. Outcomes assessed in relation to joint adjudication outcome and prior tanezumab treatment included: 1) surgeon's assessment of procedural difficulty (uneventful, minor complications, major complications) at the time of the TJR; 2) postsurgical complications (clinically significant events attributable to the TJR, derived from adverse events) up to week 24; and 3) additional/corrective procedures (procedures or investigations related to the TJR) up to week 24.

Results: The 150 patients had received placebo (n=20), tanezumab 2.5mg (n=52), tanezumab 2.5mg titrated to 5mg (tanezumab 2.5/5mg, n=8), tanezumab 5mg (n=53), or a nonsteroidal anti-inflammatory drug (n=17) in the parent studies. The 150 patients were adjudicated to have primary osteonecrosis (n=1), rapidly progressive OA (RPOA) type 2 (n=8), RPOA type 1 (n=3), other joint outcome (n=6), normal progression of OA (NPOA) (n=130), or insufficient information to determine RPOA versus NPOA (n=2). Surgeon's assessment of procedural difficulty was uneventful for 95.1% (116/122) of patients. Through the 24-week study, there were no postsurgical complications for 96.0% (144/150) of patients; the 6 patients who had complications were all adjudicated as NPOA (tanezumab 2.5mg, n=2; tanezumab 5mg, n=4). There were no additional/corrective procedures for 93.3% (140/150) of patients.

Conclusion: Procedural difficulty of minor complications during surgery, postsurgical complications, and additional/corrective procedures were infrequent, although more common with tanezumab 5mg, typically occurring in patients adjudicated as NPOA. Adjudication outcome (RPOA/primary osteonecrosis vs. NPOA) was not associated with postoperative outcome.

INTRODUCTION

Tanezumab, a monoclonal antibody against nerve growth factor, is in development for osteoarthritis (OA) treatment. Cases of rapidly progressive OA (RPOA) in phase 3 clinical studies[1] resulted in a partial hold by the United States Food and Drug Administration in 2010. There are two types of RPOA: 1) a significant loss of joint space width ≥2mm within approximately one year, without gross structural failure (RPOA type 1); and 2) abnormal bone loss or destruction, including limited or total collapse of at least one subchondral surface, that is not normally present in conventional end-stage OA (RPOA type 2).[2] Following investigations, the partial hold was lifted and in the subsequent phase 3 OA program (after 2015), tanezumab was administered subcutaneously at lower doses in patients for whom standard analgesics had proved ineffective or unsuitable and who had no radiographic evidence of specified bone/joint conditions (e.g., RPOA, atrophic or hypotrophic OA, subchondral insufficiency fracture, spontaneous osteonecrosis of the knee, osteonecrosis, or pathologic fracture), and who had no contraindication to, and were willing to undergo, total joint replacement (TJR) if needed.

The TJR data from the completed studies prior to the clinical hold did not suggest different postoperative outcomes in patients treated with or without tanezumab, although long-term data were limited and based on retrospective analyses.[3] As part of the risk characterization process in the post-2015 studies, postoperative outcomes over a 24-week period after TJR were to be assessed prospectively.

The aim of the current 24-week observational study was to prospectively evaluate the surgical and postoperative outcomes in patients who had undergone TJR, while participating in any of three tanezumab phase 3 OA post-2015 studies,[4-6] and to assess any association with adjudication outcome or prior tanezumab treatment. More specifically, outcomes assessed included: 1) procedural difficulty, 2) postsurgical complications, and 3) additional/corrective procedures.

MATERIALS AND METHODS

Study design

This prospective, multicenter, phase 3 cohort study (ClinicalTrials.gov identifier: NCT02674386) enrolled consenting patients undergoing TJR during participation in any of three parent studies in the tanezumab OA phase 3 program and followed them from their TJR surgery (designated day 0 in the current study) for 24 weeks. The parent studies were all randomized controlled trials with double-blind treatment periods, during which tanezumab was administered subcutaneously every eight weeks, followed by an additional 24-week safety follow-up period. The first study had a 16-week treatment period and up to two doses of placebo or tanezumab 2.5mg or one dose of tanezumab 2.5mg and one dose of tanezumab 5mg (tanezumab 2.5/5mg) (NCT02697773).[4] The second study had a 24-week treatment period and up to three doses of placebo, tanezumab 2.5mg, or tanezumab 5mg (NCT02709486).[5] The third study had a 56-week treatment period and up to seven doses of tanezumab 2.5mg or tanezumab 5mg, or twice-daily oral nonsteroidal anti-inflammatory drug (NSAID) (NCT02528188).[6] Every effort was made to enroll all patients who underwent a qualifying TJR in the three parent studies.

The current study was conducted between August 23, 2016 and July 15, 2019. All patients, investigators, study coordinators, clinical site staff, orthopaedic surgeons, clinical research associates, and the sponsor's staff directly involved with the study and its designees were blinded to treatment assignment in the parent study. All patients provided written informed consent. The study was approved by an Institutional Review Board or Independent Ethics Committee at each investigational site and was conducted in compliance with the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice Guidelines.[7]

Patients

Eligible patients were those who had been randomized and treated in one of the three tanezumab studies (NCT02697773, NCT02709486, or NCT02528188) and had undergone or planned to have a TJR of a knee, hip, or shoulder at any time during the parent study (either during the treatment or safety follow-up periods), which they must have completed or have been withdrawn from. Patients undergoing sub-total arthroplasty procedures (e.g., hemi-arthroplasty) were not eligible for the study; additional procedures (e.g., revision of a previously replaced joint in addition to a new TJR) were permitted once a patient was enrolled. There were no further protocol-defined exclusion criteria.

Procedures

There were no protocol-defined medications and no medications were specifically prohibited, although patients entering this study within 16 weeks of their last dose of study medication in the parent study were advised to avoid chronic NSAID use until at least 16 weeks had elapsed.

Surgeons were asked to obtain pathology specimens from the TJR to provide histological information for a blinded external adjudication committee comprised of external experts in orthopaedic surgery, rheumatology, orthopaedic pathology, or radiology with expertise in patients who had end-stage OA and osteonecrosis. The adjudication committee utilized the central pathologist's analysis of specimens (where available), as well as clinical study data and magnetic resonance and/or radiographic images, to determine an adjudicated diagnosis of primary osteonecrosis, RPOA type 1, RPOA type 2, subchondral insufficiency fracture, pathologic fracture, other joint outcome, normal progression of OA (NPOA), or there was insufficient information to distinguish between RPOA and NPOA or to specify a diagnosis. RPOA type 1 was defined as a significant loss of joint space width ≥2mm (predicated on optimal joint positioning) within approximately one year, without gross structural failure; RPOA type 2 was abnormal bone loss or destruction, including limited or total collapse of at least one subchondral surface, that is not normally present in conventional end-stage OA.[2]

At the time of the TJR, surgeons were asked to complete an assessment of procedural difficulty, based on the question: "Taking into consideration the subject's medical history and physical condition prior to surgery would you classify the operative procedure as uneventful, minor complications, or major complications?" Further details were requested in an open-ended manner if the category of minor or major complications was chosen.

Details of any additional/corrective procedures related to the TJR were obtained from patients during telephone contacts at weeks 12 and 24. Patients were asked to respond yes or no to the question: "Have you been told by your orthopaedic surgeon that additional or corrective procedures (for example a revision or implant replacement) are necessary for your total joint replacement?" If they answered yes, further details were obtained from the patient and also the surgeon if necessary. All reported concomitant non-drug treatments were reviewed to identify those attributable to the TJR.

During all telephone contacts (every four weeks from week 4 through week 24), patients were asked about adverse events (AEs). Postsurgical complications were those clinically important events, derived from AEs, that were attributable to the TJR (e.g., periprosthetic joint infection/wound infection, periprosthetic fracture, pulmonary embolism, sepsis/septicemia/shock).

Patients completed internet-based questionnaires at prespecified time points, assessing satisfaction, pain, and function. The self-administered patients satisfaction scale[8] was used to determine overall satisfaction with the result of surgery and consisted of four questions. "How satisfied are you with:

1. the results of your surgery?
2. the results of your surgery for improving your pain?
3. the results of surgery for improving your ability to do home or yard work?
4. the results of surgery for improving your ability to do recreational activities?"

Responses were scored on 4-point Likert scales (very satisfied, somewhat satisfied, somewhat dissatisfied, very dissatisfied). Average pain in the joint to be replaced (before surgery) and in the replaced joint was assessed using an 11-point numeric rating scale (NRS; zero = no pain, 10 = worst possible pain) based on "Select the number that best describes your average pain in the (joint to be replaced or replaced joint) in the past 24 hours."[9] Pain and functional status were assessed with Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC*)[10] Pain, Physical Function, and Stiffness subscales (11-point NRS) for patients who had hip or knee

Table I
Patient disposition

	Placebo	Tanezumab 2.5mg	Tanezumab 2.5/5mg	Tanezumab 5mg	NSAID	Total
Parent studies						
Patients randomized	515	1523	233	1289	1008	4568
Patients treated	514	1516	233	1282	996	4541
Patients with TJR[a,b]	25 (4.9)	89 (5.8)	16 (6.9)	102 (7.9)	26 (2.6)	258 (5.6)
Number of TJR events[b]	28	96	19	118	28	289
This study						
Patients enrolled[c]	20	53	8	56	17	154
Number of TJR events enrolled[d]	22	55	10	63	19	169
Patients eligible for analysis	20	52	8	53	17	150
Completed study	20	51	7	49	16	143
Discontinued study[e]	0	1	1	4	1	7

Data are n (%).
[a] The denominator is the number of patients randomized in the parent study.
[b] In parent study or in this study.
[c] Four enrolled patients were not eligible for analysis because their joint replacement was partial (n=2) or they withdrew before the TJR (n=2).
[d] Includes all initial and subsequent TJR events occurring within this study for which the patient consented to be followed.
[e] Due to withdrawal by the patient (n=4), lost to follow up (n=2), or other reasons (n=1).
NSAID, nonsteroidal anti-inflammatory drug; TJR, total joint replacement.

Table II
Demographics and background characteristics

	Placebo (n=20)	Tanezumab 2.5mg (n=52)	Tanezumab 2.5/5mg (n=8)	Tanezumab 5mg (n=53)	NSAID (n=17)	Total (n=150)
Gender, male/female/unspecified[a]	6/13/1	26/25/1	2/6/0	22/31/0	4/13/0	60/88/2
Race, white/black or African American/Asian/unspecified[a]	17/0/2/1	48/1/2/1	7/1/0/0	45/4/4/0	14/3/0/0	131/9/8/2
Age						
<65 years	9 (45.0)	23 (44.2)	3 (37.5)	29 (54.7)	9 (52.9)	73 (48.7)
≥65 years	10 (50.0)	28 (53.8)	5 (62.5)	24 (45.3)	8 (47.1)	75 (50.0)
Unspecified[a]	1 (5.0)	1 (1.9)	0	0	0	2 (1.3)
Mean (SD)	65.3 (8.8)	65.0 (7.1)	67.5 (8.2)	63.7 (9.1)	62.9 (9.1)	64.5 (8.3)
Body mass index, kg/m^2						
Mean (SD)[a,b]	30.5 (5.6)	31.2 (4.5)	33.3 (4.7)	31.1 (4.8)	30.5 (4.6)	31.1 (4.8)
Number of TJRs	22	55	10	63	19	169
Knee	12 (54.5)	36 (65.5)	4 (40.0)	37 (58.7)	10 (52.6)	99 (58.6)
Hip	10 (45.5)	19 (34.5)	6 (60.0)	26 (41.3)	8 (42.1)	69 (40.8)
Shoulder	0	0	0	0	1 (5.3)	1 (0.6)
Kellgren–Lawrence grade 0/1/2/3/4[c]	0/1/1/14/6	0/0/1/23/31	0/0/1/5/4	2/2/3/34/22	0/0/2/11/4	2/3/8/87/67
Time from randomization in parent study to the date of first TJR surgery, days, mean (SD)	256.80 (100.14)	291.21 (134.72)	179.75 (71.63)	324.49 (141.78)	345.53 (149.02)	298.59 (136.50)

Data are n (%) or n/n unless otherwise specified, for the population eligible for analysis.
[a] Some patients did not consent to the use of demography data.
[b] Sample size n=148.
[c] At baseline in the parent study. Some data missing (n=1) or not available for shoulder (n=1), both in the NSAID group.
NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; TJR, total joint replacement.

Table III
Adjudication outcome

	Placebo (n=20)	Tanezumab 2.5mg (n=52)	Tanezumab 2.5/5mg (n=8)	Tanezumab 5mg (n=53)	NSAID (n=17)	Total (n=150)
Patients with composite adjudicated joint safety endpoint[a]	0	0	0	10 (18.9)	2 (11.8)	12 (8.0)
RPOA type 1	0	0	0	2 (3.8)	1 (5.9)	3 (2.0)
RPOA type 2	0	0	0	7 (13.2)	1 (5.9)	8 (5.3)
Primary osteonecrosis	0	0	0	1 (1.9)	0	1 (0.7)
Pathologic fracture	0	0	0	0	0	0
Subchondral insufficiency fracture	0	0	0	0	0	0
Insufficient information to determine rapid vs. normal progression of OA	0	2 (3.8)	0	0	0	2 (1.3)
Normal progression of OA[b]	18 (90.0)	49 (94.2)	8 (100.0)	40 (75.5)	15 (88.2)	130 (86.7)
Other joint outcome[c]	2 (10.0)	1 (1.9)	0	3 (5.7)	0	6 (4.0)

Data are n (%). These are patient-level data, with n representing the number of patients in the population eligible for analysis. The primary outcome for each patient is shown, according to the following hierarchy: primary osteonecrosis, RPOA type 2, subchondral insufficiency fracture, pathologic fracture, RPOA type 1, insufficient information to determine rapid versus normal progression of OA, other joint outcome, normal progression of OA.
[a] The composite adjudicated joint safety endpoint includes any patient with an adjudicated outcome of primary osteonecrosis, RPOA type 1 or type 2, subchondral insufficiency fracture, or pathologic fracture.
[b] Indicates patient had no outcomes included in the composite adjudicated joint safety endpoint or other category.
[c] Preexisting inflammatory arthritis (n=1), fracture through an osteonecrotic lesion (n=1), preexisting osteonecrosis (n=2), post-traumatic subchondral fracture (n=1), posttraumatic meniscus tear (n=1).
NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; RPOA, rapidly progressive osteoarthritis.

Table IV
Patients with minor complications during surgery (surgeon's assessment of procedural difficulty)

Patient	Prior Treatment	Adjudicated Outcome	TJR	Surgeon's Description of Minor Complications
1	Tanezumab 2.5mg	NPOA	Hip	Some difficulty removing head due to attached ligamentum; used clamp to remove head
2	Tanezumab 5mg	NPOA	Knee	Bone severely discolored and abnormal looking
3	Tanezumab 5mg	NPOA	Knee	Severe osteosclerosis, fibrosis of soft tissue, stiff knee
4	Tanezumab 5mg	NPOA	Hip	Osteosclerosis of the femoral head was strong, and it was impossible to use the drill for osteotomy
5	Tanezumab 5mg	RPOA type 2	Hip	Significant stenosis of the capsule and surrounding articular tissue, muscles are shortened. Larger acetabular subchondral geodes with significantly present pseudomembrane
6	Tanezumab 5mg	RPOA type 2	Hip	The surgical procedure was somewhat complicated by the accumulation of synovial fluid spreading to the front of the hip joint

NPOA, normal progression of osteoarthritis; RPOA, rapidly progressive osteoarthritis; TJR, total joint replacement.

TJR, or the Shoulder Pain and Disability Index (SPADI; pain and function dimensions)[11] for patients who had shoulder TJR.

Statistical methods

All endpoints were prespecified, including surgeon's assessment of procedural difficulty (at the time of TJR), postsurgical complications (up to week 24), additional/corrective procedures (up to week 24), patient satisfaction (at week 24), and changes in WOMAC subscales and average pain in the joint (at week 24). Baseline scores (average pain in the joint and WOMAC subscales) were obtained at variable time intervals during this study before TJR surgery, or from the last observation in the parent study, if available, if a baseline score was missing. Observed data are presented descriptively without imputation for missing data.

Table V
Patients with postsurgical complications and additional/corrective procedures up to week 24

Patient	Prior Treatment	Adjudicated Outcome	TJR	Postsurgical Complications[a,b]	Additional/Corrective Procedure(s)[b]	Notes on Additional Procedures
1[c]	Tanezumab 2.5mg	NPOA	Hip	Hematoma; right femur periprosthetic fracture; and right hip infection secondary to complications from right hip surgery	Central venous catheter removal; central line placement; fracture treatment; hematoma evacuation; surgery	
2	Tanezumab 2.5mg	NPOA	Hip	Infection at incision site left hip	None	
3	Tanezumab 5mg	NPOA	Hip	Luxation of prosthesis joint	Medical device repositioning	
4	Tanezumab 5mg	NPOA	Knee	Anemia	Joint fluid drainage	
5	Tanezumab 5mg	NPOA	Hip	Periprosthetic infection right hip; and right hip dislocation	Joint debridement	
6	Tanezumab 5mg	NPOA	Hip	Anemia	None	
7	Tanezumab 2.5mg	NPOA	Hip	None	Ultrasound scan[d]	Reason: DVT (this was reported as an AE, not classified as a postsurgical complication)
8	Tanezumab 2.5mg	NPOA	Knee	None	Joint debridement; joint manipulation	Reason: stiff right total knee arthroplasty (stiff right knee was reported as an AE, not classified as postsurgical complication)
9[c]	Tanezumab 5mg	NPOA	Knee	None	Venous Doppler[d]	Reason: rule out DVT (no DVT was reported as an AE)
10	Tanezumab 5mg	RPOA type 2	Knee	None	Tendon repair	Reason: fall, torn right patellar tendon (this patient had a right knee TJR and had a fall on day 10 post-surgery; fall and torn right patellar tendon were reported as AEs, not classified as postsurgical complications)
11	Tanezumab 5mg	NPOA	Hip	None	CT scan; hip X-ray[d]	Reason: pain associated with prosthesis left hip (pain associated with prosthesis insertion was reported as an AE, not classified as postsurgical complication)
12[c]	NSAID	NPOA	Hip	None	Venous Doppler[d]	Reason: rule out DVT (right leg swelling was reported as an AE, not classified as postsurgical complication)

[a] Clinically significant events derived from AEs up to week 24 that were attributable to the TJR.
[b] Preferred term.
[c] There was no surgeon's assessment of procedural difficulty for this patient.
[d] Diagnostic procedure.
AE, adverse event; CT, computed tomography; DVT, deep vein thrombosis; NPOA, normal progression of osteoarthritis; NSAID, nonsteroidal anti-inflammatory drug; RPOA, rapidly progressive osteoarthritis; TJR, total joint replacement.

Table VI
Patients' overall satisfaction with surgery as assessed by the self-administered patient satisfaction scale at week 24

	Placebo (n=19)	Tanezumab 2.5mg (n=46)	Tanezumab 2.5/5mg (n=7)	Tanezumab 5mg (n=46)	NSAID (n=13)
Satisfaction with the result of surgery					
Very satisfied	16 (84.2)	38 (82.6)	6 (85.7)	35 (76.1)	10 (76.9)
Somewhat satisfied	2 (10.5)	4 (8.7)	1 (14.3)	9 (19.6)	2 (15.4)
Somewhat dissatisfied[a]	0	1 (2.2)	0	2 (4.3)	0
Very dissatisfied[a]	1 (5.3)	3 (6.5)	0	0	1 (7.7)
Results of surgery for relieving pain					
Very satisfied	13 (68.4)	40 (87.0)	5 (71.4)	39 (84.8)	10 (76.9)
Somewhat satisfied	5 (26.3)	2 (4.3)	2 (28.6)	5 (10.9)	2 (15.4)
Somewhat dissatisfied	1 (5.3)	2 (4.3)	0	0	1 (7.7)
Very dissatisfied	0	2 (4.3)	0	2 (4.3)	0
Improving ability to do home or yard work					
Very satisfied	14 (73.7)	35 (76.1)	5 (71.4)	34 (73.9)	7 (53.8)
Somewhat satisfied	4 (21.1)	5 (10.9)	2 (28.6)	8 (17.4)	5 (38.5)
Somewhat dissatisfied	1 (5.3)	2 (4.3)	0	3 (6.5)	1 (7.7)
Very dissatisfied	0	4 (8.7)	0	1 (2.2)	0
Improving ability to do recreational activities					
Very satisfied	15 (78.9)	29 (63.0)	4 (57.1)	29 (63.0)	8 (61.5)
Somewhat satisfied	3 (15.8)	11 (23.9)	3 (42.9)	14 (30.4)	4 (30.8)
Somewhat dissatisfied	1 (5.3)	4 (8.7)	0	1 (2.2)	1 (7.7)
Very dissatisfied	0	2 (4.3)	0	2 (4.3)	0
Scale score					
Mean (SD)	92.43 (14.52)	90.08 (18.71)	92.86 (9.83)	91,44 (14.03)	89.42 (16.61)

Data are n (%), unless otherwise specified, in the population eligible for analysis and responding to the questionnaire at week 24. These data are patient-level, with n representing patients rather than TJRs. Each patient counted once for the total, based on worst satisfaction assessment. The response categories were "very satisfied" (100 points), "somewhat satisfied" (75 points), "somewhat dissatisfied" (50 points), and "very dissatisfied" (25 points), and the scale score was the unweighted mean of the scores from the individual items.
[a] For details of these patients, see Table VII.
NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; TJR, total joint replacement.

RESULTS

Study population

Of the 4,541 patients randomized and treated in the three parent studies, 258 had one or more TJRs and, of these, 59.7% (154/258) of patients consented and were enrolled: four were not eligible for analysis, leaving a total of 150 evaluable patients (Table I). These 150 patients had 154 initial TJRs and 14 of these patients had 15 subsequent new TJRs. The evaluable population was, therefore, 150 patients who had 169 TJRs. Of the 169 TJRs, 58.6% (99/169) were knees, 40.8% (69/169) were hips, and one was a shoulder; 92.2% (154/167) of joints assessed were determined to be Kellgren–Lawrence[12] grade 3 or 4 at baseline in the parent study (Table II). The number of days (mean) from the date of randomization in the parent study to the date of the first TJR surgery in the current study was 180 to 346 days across the groups (Table II). During the parent studies, the patients had received placebo (n=20), tanezumab 2.5mg (n=52), tanezumab 2.5/5mg (n=8), tanezumab 5mg (n=53), or NSAID (n=17).

Pathology specimens were provided by the surgeon for 60.4% (102/169) of the TJRs. Based on the joint with the worst adjudicated outcome, the patients were adjudicated to have primary osteonecrosis (n=1), RPOA type 1 (n=3), RPOA type 2 (n=8), NPOA (n=130), other joint outcome (n=6), or there was insufficient information to determine RPOA versus NPOA (n=2) (Table III).

Surgeon's assessment of procedural difficulty

The surgeon's assessment of procedural difficulty was uneventful for 95.1% (116/122) of patients assessed, and none had ratings of major complications. There were six patients who had procedural difficulty of minor complications during surgery, including one in the tanezumab 2.5mg group (2.4%, 1/41) and five in the tanezumab 5mg group (11.4%, 5/44), of whom four were adjudicated as NPOA and two as RPOA type 2 (Table IV). None of these six patients who had procedural difficulty of minor complications during surgery had postsurgical complications or additional/corrective procedures related to their TJR.

Table VII
Patients dissatisfied with the result of surgery at week 24

Patient	Prior Treatment	Adjudicated Outcome	TJR	Patient Satisfaction With the Results of Surgery at Week 24[a]
1	Placebo	NPOA	Hip	Very dissatisfied
2	Tanezumab 2.5mg	NPOA	Knee	Very dissatisfied
3	Tanezumab 2.5mg	NPOA	Knee	Very dissatisfied
4	Tanezumab 2.5mg	NPOA	Knee	Somewhat dissatisfied
5	Tanezumab 2.5mg	NPOA	Knee	Very dissatisfied
6[b]	Tanezumab 5mg	NPOA	Knee	Somewhat dissatisfied
7	Tanezumab 5mg	Other[c]	Hip	Somewhat dissatisfied
8	NSAID	NPOA	Knee	Very dissatisfied

[a] Overall satisfaction with the result of surgery, at week 24, as assessed by the self-administered patient satisfaction scale, in response to: "How satisfied are you with the results of your surgery?"
[b] This patient also had a postsurgical complication (anemia) and underwent additional/corrective procedures (joint fluid drainage) (patient 4, Table V).
[c] Other joint outcome: posttraumatic subchondral fracture.
NPOA, normal progression of osteoarthritis; NSAID, nonsteroidal anti-inflammatory drug; RPOA, rapidly progressive osteoarthritis; TJR, total joint replacement.

Postsurgical complications

There were no postsurgical complications for 96.0% (144/150) of the patients. Complications occurred in six patients (4.0%, 6/150), of whom two were in the tanezumab 2.5mg group (3.8%, 2/52) and four in the tanezumab 5mg group (7.5%, 4/53). All patients who had postsurgical complications had TJRs adjudicated as NPOA, and four also had additional/corrective procedures (Table V). None of the patients who had a postsurgical complication had procedural difficulty of minor complications during surgery as assessed by the surgeon, although one patient's surgery was not assessed for procedural difficulty.

Additional/corrective procedures

There were no additional/corrective procedures for 93.3% (140/150) of patients. Six patients (4.0%, 6/150) underwent corrective procedures and four (2.7%, 4/150) had additional procedures that were diagnostic in nature (Table V). Of the 10 patients in total, nine had TJRs adjudicated as NPOA and one had a TJR adjudicated as RPOA type 2; three were in the tanezumab 2.5mg group, six in the tanezumab 5mg group, and one in the NSAID group. None of these 10 patients had procedural difficulty of minor complications as assessed by the surgeon, although three patients' surgeries were not assessed for procedural difficulty.

Self-administered patients satisfaction scale

A total of 93.9% (123/131) of patients with responses to the questionnaire were somewhat satisfied or very satisfied with the result of surgery at week 24 (Table VI), including nine with TJRs adjudicated as RPOA and one with osteonecrosis (two patients with TJRs adjudicated as RPOA did not provide a response at week 24). Eight patients (6.1%, 8/131) were somewhat dissatisfied or very dissatisfied with the result of surgery at week 24, one of whom had a postsurgical complication and an additional/corrective procedure (Table VII). None of the eight dissatisfied patients had procedural difficulty of minor complications as assessed by the surgeon, although one patient's surgery was not assessed for procedural difficulty.

Pain and functional status

By week 24, average pain in the joint (Fig. 1A and B) and WOMAC subscale (Fig. 2A–C) scores decreased from baseline across the groups to values suggesting mild levels of pain, stiffness, and difficulty in physical function, with hip TJRs having lower mean scores than knee TJRs. The patient who had a shoulder TJR reported reductions in average pain in the joint (from 9 at baseline to 0 at week 24) and total SPADI (from 89.88 at baseline and 0 at week 24) scores.

Safety

Tanezumab-treated patients experienced more AEs compared with placebo, and severe and serious AEs were experienced by patients in the tanezumab groups and the NSAID group, but not the placebo group (Table VIII). The most common AE was procedural pain, reported only by tanezumab-treated patients.

DISCUSSION

This 24-week observational study evaluating surgical and postoperative outcomes in 150 patients after TJR in the tanezumab OA development program showed that procedural difficulty, postsurgical complications, and additional/corrective procedures were infrequent. All occurred primarily in patients treated with tanezumab (mostly tanezumab 5mg) in the parent study. Most of the cases were adjudicated as NPOA, few patients were dissatisfied with the result of surgery, and the postsurgical complications themselves were minor.

There were no indications that adjudication outcome was associated with postoperative outcome, with procedural difficulty, postsurgical complications, additional/corrective procedures, and satisfaction being similar in patients with or without an adjudicated joint safety endpoint (e.g., RPOA/osteonecrosis vs. NPOA). Of 12 patients with TJRs adjudicated as osteonecrosis or RPOA, two

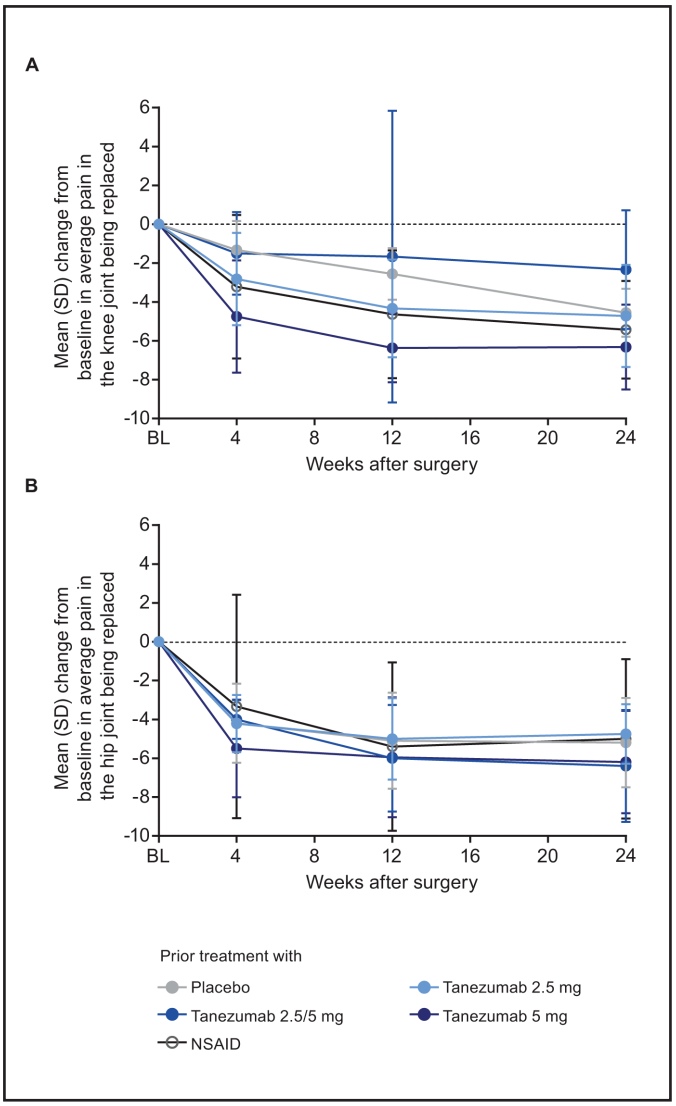

Figure 1. Change from baseline in average pain in the replaced joint for (A) knee TJRs and (B) hip TJRs.
These observed data are joint-level, with each TJR counted once, and n representing the number of TJRs rather than patients. A patient may have more than one TJR. Average pain score ranges from 0 (no pain) to 10 (worst pain), and a reduction from baseline is an improvement. Baseline scores were obtained at variable time intervals during this study before TJR surgery or were obtained from the last observation in the parent study, if available, if a baseline score was missing. Note that no specific medications (including analgesia) were prohibited during the current observational study, and analgesia was not restricted before the TJR. For knee TJR, baseline scores (mean ± SD) were: 6.00 ± 2.31 for placebo, 6.44 ± 2.16 for tanezumab 2.5mg, 5.33 ± 4.04 for tanezumab 2.5/5mg, 7.47 ± 1.80 for tanezumab 5mg, and 6.80 ± 2.20 for NSAID groups. The number of TJRs contributing to the dataset (at baseline/week 4/week 12/week 24): n=10/9/9/9 for placebo, n=36/33/33/32 for tanezumab 2.5mg, n=3/2/3/3 for tanezumab 2.5/5mg, n=32/28/30/28 for tanezumab 5mg, and n=10/9/8/7 for NSAID. For hip TJR, baseline scores (mean ± SD) were: 6.10 ± 2.13 for placebo, 6.37 ± 1.86 for tanezumab 2.5mg, 7.17 ± 2.56 for tanezumab 2.5/5mg, 7.09 ± 2.52 for tanezumab 5mg, and 5.86 ± 3.44 for NSAID groups. The number of TJRs contributing to the dataset (at baseline/week 4/week 12/week 24): n=10/10/10/10 for placebo, n=19/18/16/16 for tanezumab 2.5mg, n=6/3/5/5 for tanezumab 2.5/5mg, n=23/22/21/21 for tanezumab 5mg, and n=7/6/5/6 for NSAID.
BL, baseline; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; TJR, total joint replacement.

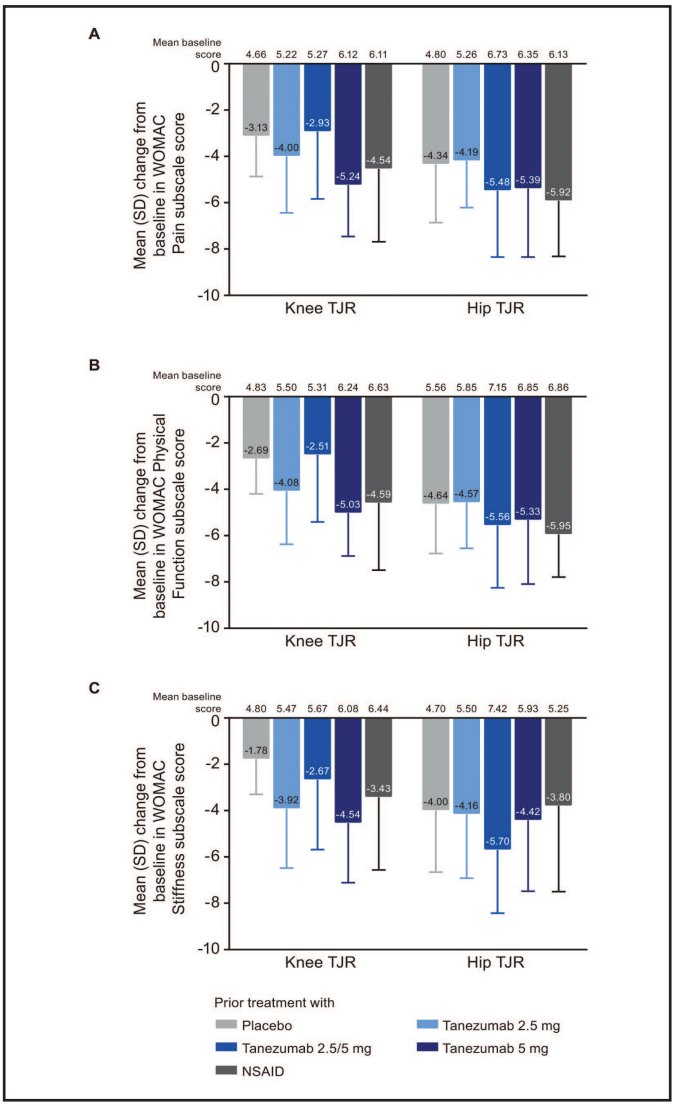

Figure 2. Change from baseline in (A) WOMAC Pain, (B) WOMAC Physical Function, and (C) WOMAC Stiffness subscales in the replaced joint at week 24 following TJR.
These observed data are joint-level, with n representing the number of TJRs rather than patients. A patient may have more than one TJR. Each WOMAC subscale is scored from 0 to 10, where 0 indicates no pain/difficulty/stiffness and 10 means extreme pain/difficulty/stiffness. A reduction from baseline is an improvement. Baseline scores were obtained at variable time intervals during this study before TJR surgery or were obtained from the last observation in the parent study, if available, if a baseline score was missing. Note that no specific medications (including analgesia) were prohibited during the current observational study, and analgesia was not restricted before the TJR. The number of knee TJRs contributing to the dataset (at baseline/week 24): n=10/9 for placebo, n=35/31 for tanezumab 2.5mg, n=3/3 for tanezumab 2.5/5mg, n=30/27 for tanezumab 5mg, and n=9/7 for NSAID. The number of hip TJRs contributing to the dataset (at baseline/week 24): n=10/10 for placebo, n=18/16 for tanezumab 2.5mg, n=6/5 for tanezumab 2.5/5mg, n=22/19 for tanezumab 5mg, and n=6/5 for NSAID.
NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; TJR, total joint replacement; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

had procedural difficulty of minor complications, none had postsurgical complications, one had an additional/corrective procedure, and 10 were satisfied with the result of surgery. The findings of a favorable postoperative outcome for patients who had RPOA are supported by a systematic review of outcomes following total hip arthroplasty that reported good mid-term (mean, five years) results with a 3% revision rate in patients who had rapidly progressive hip disease.[13]

Table VIII
Safety results for patients followed for 24 weeks after TJR

	Placebo (n=20)	Tanezumab 2.5mg (n=52)	Tanezumab 2.5/5mg (n=8)	Tanezumab 5mg (n=53)	NSAID (n=17)
Patients with ≥1 treatment-emergent AE	3 (15.0)	19 (36.5)	4 (50.0)	19 (35.8)	5 (29.4)
Preferred term[a]					
Procedural pain	0	3 (5.8)	0	6 (11.3)	0
Anemia[b]	0	1 (1.9)	0	2 (3.8)	0
Arthralgia	0	0	1 (12.5)	2 (3.8)	0
OA	0	4 (7.7)	0	2 (3.8)	2 (11.8)
Fall	0	2 (3.8)	0	1 (1.9)	0
Number of AE events	4	40	7	49	10
Patients with ≥1 serious AE[c]	0	5 (9.6)	3 (37.5)	7 (13.2)	2 (11.8)
Patients with ≥1 severe AE	0	3 (5.8)	2 (25.0)	3 (5.7)	2 (11.8)
Patients discontinuing study due to AE	0	0	0	0	0

Data are n (%) in the population eligible for analysis. Treatment-emergent AEs were those that started on or after the patient's first TJR in this study until their last day of the study, or AEs that were ongoing from the parent study with worsened severity on or after the patient's first TJR in this study.
[a] Preferred terms shown for all those AEs occurring in two or more patients in any treatment group.
[b] Patient records of hemoglobin level (anemia) were not systematically assessed to identify anemia.
[c] Coronary artery occlusion (n=1), diarrhea (n=1), enteritis (n=1), postprocedural infection (n=1), periprosthetic fracture (n=1), OA (n=1), deep vein thrombosis (n=1), and hematoma (n=1) in the tanezumab 2.5mg group. Ischemic colitis (n=1), hiatus hernia (n=1), viral gastroenteritis (n=1), and transitional cell carcinoma (n=1) in the tanezumab 2.5/5mg group. Cholecystitis (n=1), device-related infection (n=1), pneumonia (n=1), tendon rupture (n=1), OA (n=2), Parkinson's disease (n=1), device dislocation (n=1), and hallucination (n=1) in the tanezumab 5mg group. OA (n=2) in the NSAID group.
AE, adverse event; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; TJR, total joint replacement.

The endpoints encompassed both surgical and postsurgical time periods. The surgeon's assessment of procedural difficulty was a subjective outcome that was dependent on each surgeon's perspective, taking into consideration the patient's medical history and physical condition prior to surgery; in some cases though, this was not completed by the surgeon. Patient report during monthly telephone contacts formed the basis of the postsurgical complications and additional/corrective procedures endpoints, so these data could have been subject to recall bias. Procedural pain, which was reported as an AE, might be expected following surgery and would be affected by postoperative analgesia regimens, which were not standardized. Although literature-reported analyses of postsurgical complications were used to guide the development of the list of AEs that were deemed clinically significant and attributable to the TJR, it is not always possible to definitively attribute an individual AE to the TJR (e.g., periprosthetic fracture that occurs during, but is not evident at the time of surgery). Alternative classifications of postsurgical complications could be justified, but for this study, additional/corrective procedures were prespecified as a discrete endpoint.

We wanted to investigate whether outcomes in patients treated with tanezumab would be different than in those treated with placebo or a comparator, but the limitations of the study made it difficult to reach a definitive conclusion. This was a small study, and not a randomized controlled trial. It was not possible to control for all potential sources of bias in this observational study. Although every effort was made to enroll all qualifying TJRs, to a certain extent the participants were self-selected, and there were patients with a qualifying TJR who chose not to enter the study. Postoperative care and medications, including thrombosis prophylaxis, were provided at the discretion of each patient's healthcare provider and were not stipulated by the study protocol. The baseline pain and function data were collected at variable times in relation to the day of surgery, which could affect the magnitude of the changes from baseline. In addition, concomitant analgesia was not prohibited at any time during this study, including at baseline and following. Postoperative outcome comparisons between the groups should be considered with caution given the small sample sizes of the placebo, NSAID, and tanezumab 2.5mg/5mg groups. The three parent studies had similar designs in many respects, including key eligibility criteria and control of concomitant medication. However, the parent studies differed markedly in duration of treatment period (16 to 56 weeks) and other characteristics: tanezumab 2.5mg/5mg was administered only in NCT02697773, and NSAIDs were administered only in NCT02528188 (and these patients had not failed NSAID treatment, unlike the populations of the other two studies). However, there did not appear to be a substantial difference in outcomes between those treated with tanezumab and those treated with comparators. The three studies also differed in their geo-

graphical locations, and the impact of the various healthcare systems are not known. Although knee TJR and hip TJR were well represented in the current study, there was only one patient with a shoulder TJR.

CONCLUSION

Procedural difficulty of minor complications during surgery, postsurgical complications, and additional/corrective procedures were infrequent although more common with tanezumab 5mg, typically occurring in patients adjudicated as NPOA. Adjudication outcome (RPOA/primary osteonecrosis vs. NPOA) was not associated with postoperative outcome of patients undergoing TJR. STI

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DATA-SHARING STATEMENT

Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices 1) for indications that have been approved in the US and/or EU or 2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

AUTHORS' DISCLOSURES

The study was sponsored by Pfizer and Eli Lilly and Company. Pfizer is the manufacturer of tanezumab, which is being investigated for the treatment of patients with chronic pain. Manuscript authors from Pfizer contributed to the study design; data collection, management, and interpretation of data; and the preparation, review, and approval of the manuscript. Manuscript authors from Eli Lilly and Company contributed to the study design, interpretation of data, and the preparation, review, and approval of the manuscript.

Dr. Mont has received consulting fees from CyMedica, Flexion Therapeutics, Johnson & Johnson, Pfizer, Stryker, and Kolon-Tissue Gene; royalties from Stryker; holds stock or stock options in Peerwell, USMI, Mirror-AR, and Ceras Health; has received research support as principal investigator for Johnson & Johnson, National Institutes of Health (NIAMS and NICHD), Stryker, and Kolon-Tissue Gene; has received royalties, financial or material support from Medicus Works LLC, Up-to-Date, Wolters Kluwer Health – Lippincott Williams & Wilkins; is on the editorial/governing board of American Journal of Orthopaedics, Journal of Arthroplasty, Journal of Knee Surgery Orthopedics, and Surgical Techniques International; and is a member of the American Academy of Orthopaedic Surgeons.

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All authors meet the International Committee of Medical Journal Editors criteria for authorship, have given their approval for this version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Hochberg MC, Tive LA, Abramson SB, et al. When is osteonecrosis not osteonecrosis? Adjudication of reported serious adverse joint events in the tanezumab clinical development program. Arthritis Rheumatol 2016;68(2):382–91.
2. Miller CG, Guermazi A, Roemer F. The current status of imaging in anti-NGF clinical trials. Osteoarthritis Cartilage 2015;23(Suppl 1):S3–7.
3. Hochberg MC. Serious joint-related adverse events in randomized controlled trials of anti-nerve growth factor monoclonal antibodies. Osteoarthritis Cartilage 2015;23 (Suppl 1):S18–21.
4. Schnitzer TJ, Easton R, Pang S, et al. Efficacy and safety of tanezumab for the treatment of osteoarthritis pain in the hip or knee. A randomized clinical trial. JAMA 2019;322(1):37–48.
5. Berenbaum F, Blanco FJ, Guermazi A, et al. Subcutaneous tanezumab for osteoarthritis of the hip or knee: efficacy and safety results from a 24-week randomised phase 3 study with a 24-week follow-up period. Ann Rheum Dis 2020;79(6):800–10.
6. Hochberg MC, Carrino JA, Schnitzer TJ, et al. Long-term safety and efficacy of subcutaneous tanezumab versus nonsteroidal antiinflammatory drugs for hip or knee osteoarthritis: a randomized trial. Arthritis Rheumatol 2021. Epub ahead of print.
7. International Council for Harmonisation. Good clinical practice. ICH consensus guideline E6. Accessed 2020 Feb 6. https://www.ich.org/page/efficacy-guidelines.
8. Mahomed N, Gandhi R, Daltroy L, et al. The self-administered patient satisfaction scale for primary hip and knee arthroplasty. Arthritis 2011;2011:591253.
9. Hawker GA, Mian S, Kendzerska T, et al. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken) 2011;63(Suppl 11)S240–52.
10. Theiler R, Spielberger J, Bischoff HA, et al. Clinical evaluation of the WOMAC 3.0 OA Index in numeric rating scale format using a computerized touch screen version. Osteoarthritis Cartilage 2002;10(6):479–81.
11. Roach KE, Budiman-Mak E, Songsiridej N, et al. Development of a shoulder pain and disability index. Arthritis Care Res 1991;4(4):143–9.
12. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494–502.
13. Pivec R, Johnson AJ, Mont MA. Results of total hip arthroplasty in patients who have rapidly progressive hip disease: a systematic review of the literature. Expert Rev Med Devices 2012;9(3):257–62.