FDA Briefing Document

Joint Meeting of Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee

BLA 761130

Tanezumab

March 24–25, 2021

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. The Biologics License Application (BLA) 761130 for tanezumab subcutaneous injection, submitted by Pfizer Inc., for the proposed indication of relief of pain of moderate to severe osteoarthritis (OA) in adult patients for whom use of other analgesics is ineffective or not appropriate, has been brought to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

I. Briefing Memorandum to the Committee

MEMORANDUM

DATE: February 25, 2021

FROM: Division of Anesthesia, Addiction Medicine and Pain Medicine (DAAP) and Office of Neuroscience (ON). Office of New Drugs, CDER, FDA

TO: Members and Invited Guests of the Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee

SUBJECT: Briefing Memo Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee for Biologics License Application (BLA) 761130 for tanezumab subcutaneous injection, submitted by Pfizer Inc., for the proposed indication of relief of signs and symptoms of moderate to severe osteoarthritis (OA) in adult patients for whom use of other analgesics is ineffective or not appropriate

The Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee and invited guests will be meeting on March 24 and March 25, 2021, to discuss Biologics License Application (BLA) 761130 for tanezumab subcutaneous injection, submitted by Pfizer Inc., for the proposed indication of relief of signs and symptoms of moderate to severe osteoarthritis (OA) in adult patients for whom use of other analgesics is ineffective or not appropriate. The Applicant seeks approval for the 2.5 mg tanezumab dose, the lowest dose studied in the OA population, administered subcutaneously every 8 weeks by a certified healthcare professional in a healthcare setting, in accordance with a Risk Evaluation and Mitigation Strategy (REMS) program proposed by the Applicant.

Osteoarthritis is a very common progressive degenerative joint disease that most often affects middle-age to elderly people. It is characterized by loss of cartilage, bony changes of the joints, deterioration of tendons and ligaments, and various degrees of inflammation (synovitis). The cardinal symptom of OA is pain in the affected joint. Approved therapies for the treatment of OA provide pain relief, with some anticipated improvement in patient function. Most often, the approach to treatment is multimodal, and includes non-pharmacologic (e.g., weight loss, exercise, physical therapy, acupuncture) and pharmacologic therapies. If patients do not reach acceptable long-term pain control with existing non-invasive therapeutic options, arthroscopic repair or total joint replacement (TJR) surgery represent alternative treatment options.

Tanezumab is an immunoglobulin G Type 2 (IgG2) monoclonal antibody that selectively binds to nerve growth factor (NGF). NGF is upregulated in response to injury and inflammatory conditions and, based on preclinical data, plays a role in pain signaling by inducing peripheral and central sensitization. Tanezumab potentially reduces sensitization and pain by inhibiting the interaction of NGF with the tropomyosin receptor kinase A (TrkA). TrkA receptors are expressed by peptidergic nociceptors.

The development program for tanezumab spans over more than 15 years. The investigational new drug application (IND) for tanezumab was submitted in April 2004 and was initially structured to demonstrate efficacy in a variety of painful conditions, to support a broad chronic pain indication. In total, the Applicant conducted 41 clinical studies, 38 interventional trials, and 3 observational studies, enrolling close to 18,000 subjects, with approximately 13,000 exposed to at least one dose of tanezumab. FDA had extensive interaction with the Applicant during the tanezumab development program, with at least 43 formal meetings of various types with the Applicant (e.g., guidance meetings, meetings discussing responses to clinical hold, and BLA-related meetings).[1]

The goals of the tanezumab development program were to demonstrate efficacy of tanezumab as monotherapy and/or as add-on therapy to non-steroidal anti-inflammatory drugs (NSAIDs). Of the 41 clinical studies, 20 were conducted in the OA population, 5 in patients with chronic low back pain (CLBP), 11 in other painful conditions, and 2 in healthy volunteers. In addition, the Applicant conducted three observational studies (two in infants exposed to tanezumab in-utero and one in OA patients).

The review team has concluded that the tanezumab development program provides substantial evidence of effectiveness. However, the treatment effect size is modest, and there is no convincing evidence of a superior efficacy of tanezumab over NSAIDs.

As described in the clinical review below, two serious toxicities caused by tanezumab have been identified during the development program: joint destruction (described as Rapidly Progressing Osteoarthritis [RPOA]), and neuropathy.

In April 2010, FDA became aware of a potential safety signal based on reports of unusual and unexpected joint-related adverse events in tanezumab-treated patients with osteoarthritis in ongoing and completed Phase 2 and 3 trials being conducted in support of the OA indication. Studies were place on clinical hold, and an Advisory Committee Meeting (ACM) was convened in March 2012,[2],[3] to discuss the joint-related safety signal and its implications for the development program. Following the ACM and extensive discussions with FDA, studies in patients with OA were allowed to resume, with risk mitigation measures designed to minimize the deleterious effect of tanezumab on joints. The Applicant also created and maintained an independent, blinded Adjudication Committee comprised of a musculoskeletal radiologist, a rheumatologist, an orthopedic surgeon, and a pathologist. The objective of the Adjudication Committee was to conduct retrospective case ascertainment for reporting purposes.

As described in the FDA review below, the Applicant defined five radiographic diagnoses that would represent a Composite Joint Safety Endpoint (CJSE):

- RPOA Type 1: Defined as a decrease in joint space width (JSW) ≥ 2 mm in one year with no structural changes (but not applied to joints with baseline joint space of less than 2 mm).
- RPOA Type 2: Defined as loss/destruction/collapse of bone

[1] For details of the regulatory history, refer to the Appendices of this document.

[2] https://wayback.archive-it.org/7993/20170404145618

[3] https://www.fda.gov/AdvisoryCommittees/Calendar/ucm286556.htm

- Subchondral Insufficiency fracture (SIF): Defined as focal bone defect/radiolucency/subchondral cortex
- Osteonecrosis (ON): Defined as infarcted bone
- Pathologic fracture: Not formally defined

The studies conducted by the Applicant after these measures were introduced (described in the review below as "post-2015" studies) are the most relevant to evaluate the risk/benefit of tanezumab and the effectiveness of the risk mitigation approaches proposed by the Applicant, and are the focus of the FDA review included in this briefing package; these include Study 1056 and Study 1057 (both placebo-controlled), and Study 1058 (active-controlled [NSAID]).

Compared to NSAIDs, the risk for developing a CJSE is 2.4 (95% CI: [1.0, 3.8]) excessive events per 100 PY (NNH=43 per year) with tanezumab 2.5 mg, and 5.8 (95% CI: [4.0, 7.6]) excessive events per 100 PY (NNH=17 per year) with tanezumab 5 mg. Compared to placebo, the risk for developing a CJSE is 2.4 (95% CI: [1.0, 4.4]) excessive events per 100 PY (NNH=41 per year) with tanezumab 2.5 mg, 0.6 (95% CI: [-0.5, 3.4]) excessive events per 100 PY (NNH=162 per year) with tanezumab 2.5/5 mg, and 4.6 (95% CI: [2.4, 8.0]) excessive events per 100 PY (NNH=22 per year). The trajectory of incidence of joint events in patients with more than one year of treatment is unknown. Most of the joint safety events were detected towards the end of the treatment and during the follow-up period after the cessation of treatment. As there is no evidence that the risk plateaus, it is unknown whether the rates and risk will accelerate or plateau with continued dosing past one year.

Tanezumab is also associated with an elevated risk of requiring a total joint replacement, as observed in two of the three post-2015 clinical studies, with evidence of dose response. FDA analyses show hazard ratios for total joint replacement of approximately 2 for the 2.5 mg tanezumab dose in Studies 1056 and 1058, and hazard ratios over 3 for doses above 2.5 mg. Study 1057 did not show an increase rate of TJR in tanezumab-treated patients. The FDA review did not identify any factors that appear to predict patients more likely to develop CJSE. FDA also found no strong evidence to suggest that patients with less advanced disease at baseline may be at lower risk of treatment-related CJSE.

There is also evidence that tanezumab can target healthy joints. Of the 33 CJSE that occurred in joints with baseline radiographically healthy joints, 31 were in tanezumab-treated patients, and only two in naproxen-treated patients. All events of advanced destruction (RPOA2 and ON) that developed in healthy joints (n=6) were in patients treated with tanezumab.

Moreover, there is evidence that the risk for developing joint destruction is 2- to 3-fold higher if NSAIDs and tanezumab are used concomitantly.

The Applicant has proposed to market tanezumab under a Risk Evaluation and Mitigation Strategy (REMS). The REMS includes elements to assure safe use (ETASU), implementation system, and a timetable for submission of assessment reports. The ETASU include healthcare setting certification, pharmacy certification, patient enrollment, patient monitoring that includes bilateral X-rays of the knees and hips at baseline and then yearly thereafter, as well as monitoring each patient for pain of RPOA.

The review team has concerns that the Applicant's proposed REMS is not sufficient to mitigate the risk of RPOA and would not ensure that the benefits of tanezumab outweigh the risks of RPOA. The REMS is based on a premise that the proposed program would be able to affect the development and/or progression of RPOA in patients taking tanezumab. However, in spite of the

risk mitigation strategies in clinical studies, the risk of developing RPOA remained concerning, as a large number of patients with RPOA required total joint replacements (TJR); 15% of patients progressed to total joint replacement (TJR) following RPOA1, and 60% of patients with RPOA2 progressed to TJR. Stopping drug after patients develop RPOA2 does not appear to be effective in preventing further damage to the joints. In addition, the required precision and consistency of the medical imaging and interpretation do not appear feasible in practice.

Tanezumab also can cause abnormal peripheral sensation characterized as (predominantly) mild, self-limited mononeuropathy, with the most common manifestation being carpal tunnel syndrome.

No final decision has been made for this application, however, and the entire review team greatly looks forward to the insights that you can provide at the Advisory Committee meeting.

II. Draft Points To Consider

FOOD AND DRUG ADMINISTRATION (FDA)

Center for Drug Evaluation and Research (CDER)

Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee Meeting

DRAFT POINTS TO CONSIDER

March 24 and March 25, 2021

1. Consider whether the Applicant has adequately characterized the risk of joint-related adverse reactions that may be caused by tanezumab, including:

    - Characterization of the risk of destructive arthropathy over time
    - Evaluation of long-term prognosis and outcome in patients who develop a joint-related adverse reaction and discontinue tanezumab

2. Consider the risk mitigation strategies used in the post-2015 studies with tanezumab:

    - Were these strategies effective in mitigating the risk of destructive arthropathy?
    - Can these strategies be implemented in a real-world setting as part of a REMS?
    - Are there additional risk mitigation components that could be added to reduce the incidence of structural joint damage?

III. Clinical Review

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Glossary

AC	Adjudication Committee
ACM	Advisory Committee Meeting
ACR	American College of Rheumatology
AE	adverse event
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
APAP	acetaminophen
APS	abnormal peripheral sensation
APTC	Antiplatelet Trialists' Collaboration
BID	twice daily
BLA	biologics license application
BWS	best-worst scaling
CI	confidence interval
CJSE	composite joint safety endpoint
CLBP	chronic low back pain
C_{max}	maximum plasma concentration
CPK	creatine kinase
CR	Central Reader
CV	cardiovascular
DAAP	Division of Anesthesiology, Addiction Medicine, and Pain Medicine
DCE	discrete choice experiments
DCN	Division of Cardiology and Nephrology
DIRM	Division of Imaging and Radiation Medicine
ECG	electrocardiogram
ETASU	elements to assure safe use
FDA	Food and Drug Administration
GI	gastrointestinal
HCS	healthcare setting
HTA	Health Technology Assessment Report
IENF	intraepidermal nerve fiber
IENFD	intraepidermal nerve fiber density
IV	intravenous
IgG2	immunoglobulin G2
ITT	intent-to-treat
IV	intravenous
JSW	joint space width
KHS	knee, hip, and shoulder
KL	Kellgren-Lawrence
MACE	major adverse cardiovascular event
MAR	maximum acceptable risk
MCB	median changes from baseline
MRI	magnetic resonance imaging

NGF	nerve growth factor
NSAID	non-steroidal anti-inflammatory drug
OA	osteoarthritis
ON	osteonecrosis
PC	placebo-controlled
PPI	patient package insert
PT	preferred term
QD	once daily
RCT	randomized controlled trial
RD	risk difference
REMS	risk evaluation and mitigation strategy
RPOA	rapidly progressive osteoarthritis
RPOA1	rapidly progressive osteoarthritis Type 1
RPOA2	rapidly progressive osteoarthritis Type 2
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SIF	subchondral insufficiency fracture
SOC	system organ class
TAN	tanezumab
TEAE	treatment-emergent adverse event
TJR	total joint replacement
T_{max}	time to maximum concentration
TQT	thorough QT
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

1. Key Review Questions

To orient the reader of this review, the following table was constructed to allow cross reference to how key questions are addressed in certain subsections of the review. General questions are in plain font, efficacy questions are in italics, and safety questions are in bold.

Table 1. Key Questions

Key Question(s)	***Subsection in Document***	***High-Level Conclusion(s)***
Why did the review team focus on the "post-2015" studies?	3.2	The entire clinical development program comprises 41 studies. Three studies (1056, 1057, and 1058) are emphasized because they tested the treatment regimen proposed for marketing, in a relevant patient population, with implementation of the risk mitigation measures proposed for real-world use.
Do the patient preference data submitted inform the benefit-risk assessment?	4.8	There are methodological issues with the patient preference information submitted that render it uninformative for regulatory decision making.
Has tanezumab met the statutory requirement for substantial evidence of effectiveness?	3.2.1 and 3.3.1	Two adequate and well-controlled studies demonstrate that tanezumab 2.5 mg is superior to placebo for osteoarthritis (OA) pain.
How does tanezumab compare to NSAIDs for efficacy?	3.2.1 and 3.3.1	Tanezumab 2.5 mg is not superior to prescription-strength naproxen, celecoxib, or diclofenac in patients who had demonstrably failed prior Rx-strength NSAIDs.
Had the "post-2015" patients studied exhausted all other treatment options?	3.2	This is unclear and poorly documented for Studies 1056 and 1057. Data around the reasons for screen failures imply that screening for treatment failure was not diligent. Treatment failure/contraindication/intolerance to other symptomatic OA treatments was based upon patient history and investigator judgment. The run-in period and randomization criteria in Study 1058 assured that those patients did not report a response to open-label, Rx-strength NSAIDs. However, a post-hoc analysis of baseline characteristics and pain assessments at the time of screening (while on baseline analgesics) and at "baseline" (after analgesic washout) showed that the analgesics (acetaminophen, NSAID, opioid, or a combination) were not, on average, producing meaningful analgesia. Thus, we conclude that, while documentation was poor, patients likely had failed, not tolerated, had a contraindication to, or were not willing to take (opioids only) those therapies.
Has the Applicant identified the lowest effective dose?	3.3.3	Given the mixed results and small treatment effect size at 2.5 mg, this would appear to be the minimally effective dose.

Key Question(s)	*Subsection in Document*	*High-Level Conclusion(s)*
Why was Study 1058 negative, and what are the implications for the efficacy of tanezumab?	3.2.1	Beyond placebo effect, it is unclear why, after failing NSAIDs in the run-in to the study, patients randomized to NSAID + placebo experienced the large decrease in pain intensity observed.
Do subgroup analyses identify any predictors for better efficacy?	3.3.2	No patient-level predictors for efficacy were identified.
What is the risk of a composite joint safety event (CJSE) of tanezumab (TAN) vs. placebo and NSAID? Is the risk dose-dependent?	4.7.2	Risk analysis of CJSE in data from Studies 1056/1057 showed 0, 2.4, 0.6, and 4.6 events per 100PY for placebo, TAN 2.5, TAN2/5/5, and TAN 5, respectively. The risk difference (RD) for TAN 2.5 vs. placebo was 2.4 additional events per 100PYR. Risk analysis of CJSE for Study 1058 showed a RD of 2.4 additional events (1.0, 3.8) per 100 PY for TAN 2.5 vs. NSAID and hazard ratios of 2.6 and 5.0 for TAN 2.5 and TAN 5.0, respectively. The risk of CJSE is dose-dependent.
Does the process of tanezumab-associated joint destruction occur in healthy joints.	4.7.2	Cases of CJSE were identified in radiographically healthy (Kellgren-Lawrence) Grade 0-1 joints, non-index joints, and joints less commonly affected with OA (shoulder).
Is the risk of CJSE dependent on the number of doses administered?	9.11	The available data do not inform this question for several reasons, including the exclusion of ~20% of the study population after two doses for non-response (Study 1058) and the low frequency of imaging surveillance.
Why is there a discrepancy between the number of CJSE between the Central Reader (CR) and Adjudication Committee (AC)?	9.11	The Applicant asserts that the purpose of the CR and AC was different. The CR was for risk mitigation and to stop dosing in patients who showed objective joint damage. The AC was for case ascertainment.
Given the program definitions for specific CJSE classifications, was it appropriate for the AC to use non-radiographic information to adjudicate cases?	9.11	Given that the proportions of joint events are similar between the CR and AC, whether or not the Adjudication Committee used other criteria does not affect the conclusions.
What are the risk factors for rapidly progressive osteoarthritis (RPOA)?	4.7.2	While the Applicant states that more severe OA at baseline (based on Kellgren-Lawrence scoring) portends a higher risk of RPOA, our analysis did not confirm this.

Key Question(s)	*Subsection in Document*	*High-Level Conclusion(s)*
What is the trajectory of joint events when TAN is dosed >1 year?	4.7.2	KM curves for Studies 1056/1057 show no plateau in risk for CJSE risk for TAN 5. The KM curve for TAN 2.5 appears to continue to rise at the last timepoint with a reasonable sample size (>200 pts/arm at 0.8 years). KM curve for Study 1058 also shows continued rise at the last valid timepoint (~400 pts/arm at 1.4 years) for TAN 5. The curve for TAN 2.5 appears to be slowly rising as well. Our interpretation of the available data are that the risk of CJSE continues to rise in patients treated with TAN in a dose-dependent manner. Whether the rates and risk will accelerate with continued dosing past one year is unknown.
Does the risk of joint destruction persist after Rapidly Progressive Osteoarthritis Type 1 (RPOA1) and drug discontinuation? Did any RPOA1 joints go on to TJR after TAN was discontinued? Did any Rapidly Progressive Osteoarthritis Type 2 (RPOA2) joints go on to Total Joint Replacement (TJR) after TAN was discontinued?	9.11	This question cannot be answered with the available data. Reporting was based on the most severe classification following AC adjudication. In addition, follow-up imaging following RPOA1 determination was poor (only 66% had a f/u study at any time after RPOA1). 15% of patients progressed to total joint replacement (TJR) following RPOA1; 60% of patients with RPOA2 progressed to TJR. Thus, stopping TAN after RPOA2 does not appear to stop the progression of the joint damage.
Is it safe to use NSAIDs with TAN chronically?	4.7.5	No. Study 1025 clearly showed excess risk of joint destruction when TAN was co-administered with NSAIDs (Table 29.). The post-randomization subgroup analysis in the submission showed no difference in joint safety for patients who used prn NSAIDs. However, because this subgroup is based on post-randomization characteristics, a relationship between prn NSAIDs and joint events cannot be ruled out.
Are annual knee and hip radiographs sufficient surveillance? What is the sensitivity and specificity of x-ray for RPOA?	9.11	This question cannot be answered due to the absence of data to demonstrate the usefulness of the surveillance and stopping rules employed in the post-2015 trials. The data are insufficient to evaluate the sensitivity and specificity of MRI vs. plain radiographs due to paucity of corresponding MRI data in actual CJSE cases (while more patients underwent both X-rays and MRI, only 188/2996 patients in Study 1058 and 35/1545 in studies 1056 and 1057 combined had both imaging modalities assessed). Regardless, 95% of patients had equivocal X-rays, but had possible/ probable RPOA, SIF, or ON the MRI. This suggests that MRI is a superior technique to make a diagnosis in these patients.
Does TAN exposure result in worse TJR surgical outcomes?	9.11	The available data (Study 1064) are inadequate to draw a conclusion.
What is the risk of undergoing a TJR after tanezumab treatment vs. comparators?	4.7.1	Approximately double for TAN 2.5 mg.

Key Question(s)	*Subsection in Document*	*High-Level Conclusion(s)*
Is there biologic plausibility for CV toxicity?		No.
Does TAN have a signal for CV morbidity/mortality?	4.6.3 and 9.5	The BLA submission showed an imbalance in CV deaths. Reanalysis of cardiovascular serious adverse event data using the APTC definition for MACE shows no signal. The rates of MACE appear similar between the TAN and NSAID groups. Because patients at high risk for a cardiovascular event were largely excluded from the tanezumab studies, the real-world risks are unclear.
Does tanezumab offer a treatment option for patients with renal insufficiency?	9.6	The available data do not indicate whether tanezumab is different from either placebo or NSAIDs regarding renal adverse events or changes in laboratory parameters related to renal function. Given that the available data do not separate placebo from NSAID treatment, it is unclear whether the tanezumab program can address this question.
What is the risk of developing symptoms of abnormal peripheral sensation (APS) associated with TAN?	4.7.3	The data show a risk two times higher with tanezumab compared to placebo or NSAIDs. The risk is dose-dependent (frequency of APS with tanezumab ranges from 5 to 18%). No difference is observed after cessation of treatment. For the tanezumab 2.5 mg dose, the frequency is 4.8% vs. 2% in placebo (PC, 2-3 dose studies) and 5.9% vs. 4.2% in NSAIDs (AC, 7-dose studies).
What is the outcome of the APS events?	9.9	>70% of the events were mild, and events rarely led to discontinuations (<5%; primarily with higher doses). More than half resolved while treatment was still ongoing, but some persisted beyond 300 days. For TAN 2.5 mg, unresolved events were reported in 17% vs. 8% in placebo (PC, 2-3 dose studies), and 25% vs. 14% in NSAIDs (AC, 7-dose studies).
Do the safety data in patients with chronic low back pain change the assessment of the safety profile for tanezumab?	9.13	No. The adverse event pattern in patients with low back pain appears similar to that in OA.

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; CJSE, composite joint safety event; tanezumab, TAN; Rx, prescription; KM, Kaplan Meier; CV, cardiovascular; MACE, Major adverse cardiovascular events; PC, placebo-controlled; AC, active-controlled; MRI, Magnetic resonance imaging; PYR, patient years; SIF, Subchondral insufficiency fracture

A complete list of the studies submitted by "pre-2015" or "post-2015," patient population/ healthy volunteer, route of administration, and noninterventional/observational/interventional appears in Appendix 6.1

The general organization of each subsection will be a block of prose describing our assessment of the data and conclusions followed by selected data presentations where necessary. Additional data presentations can be found in the corresponding Appendix.

2. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Clinical pharmacology data are comprised of data from 18 clinical studies in patients with OA, 4 studies in patients with CLBP, 2 studies in healthy volunteers, and 1 study in patients undergoing bunionectomy, via the IV or SC route of administration of varied doses of tanezumab. Pharmacologic properties of tanezumab that are relevant to the interpretation of benefit and risk are summarized in the table below. Tanezumab is a therapeutic protein, a humanized Immunoglobulin G2 (IgG2) mAb directed against human NGF. In vitro studies typically done for small molecules, such as protein binding, metabolism, drug-drug interaction studies, were not conducted for tanezumab. At this time, correlation of in vitro data or animal data, with regard to therapeutic protein drug interactions, to humans is limited.

Table 2. Summary of Clinical Pharmacology Findings

Characteristic	Drug Information
	Pharmacologic Activity
Drug Product Description	Tanezumab (also referred to as PF-04383119 or RN624) is a humanized IgG2 mAb directed against human nerve growth factor (NGF).
Mechanism of action	NGF inhibition is hypothesized to play a role in pain secondary to inflammation or injury. Tanezumab is hypothesized to act peripherally to reduce sensitization and pain by inhibiting the interaction of NGF with the trkA receptors located on the peripheral terminals of peptidergic unmyelinated C-fibers and Aδ fibers.
Active moieties	Tanezumab
QT prolongation	Tanezumab is a monoclonal antibody which has a low likelihood of direct ion channel interactions. Potential for pro-arrhythmic risk is not suggested by mechanistic considerations or data from clinical or non-clinical studies. Therefore, a TQT study is not necessary for this product.
	General Information
Bioanalysis	An adequately validated ELISA sandwich method was used to quantify plasma tanezumab from clinical trials 1056, 1057, 1058, and 1059 that employed tanezumab 2.5 mg subcutaneous dose. This ELISA method used a mouse affinity purified anti-id Mab specific against tanezumab, followed by mouse anti-human IgG conjugate for chemiluminescence detection.
Healthy subjects versus patients	Plasma levels of tanezumab were not significantly different between healthy volunteers and osteoarthritis patients.

<table>
<tr><th>Characteristic</th><th>Drug Information</th></tr>
<tr><td>Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)</td><td>Table: PK Parameters of tanezumab 2.5 mg across studies 1027, 1056, 1057 and 1058, summarized by dose, based on the final population PK model (Empirical Bayesian Estimates (EBEs)).
<table>
<tr><th>Parameter</th><th>2.5 mg
Mean (SD)</th></tr>
<tr><td>Number of patients</td><td>1792</td></tr>
<tr><td>Cmax (ng/mL)</td><td>226 (48.6)</td></tr>
<tr><td>Cmax,ss (ng/mL)</td><td>275 (67.6)</td></tr>
<tr><td>tmax (day)</td><td>10.4 (1.86)</td></tr>
<tr><td>tmax,ss (day)</td><td>9.31 (1.26)</td></tr>
<tr><td>AUCinf (ng.day/mL)</td><td>9000 (2500)</td></tr>
<tr><td>AUCtau,ss (ng.day/mL)</td><td>9640 (2830)</td></tr>
<tr><td>t1/2,eff (day)</td><td>22.3 (3.89)</td></tr>
<tr><td>Cmin (ng/mL)</td><td>53.2 (22.3)</td></tr>
<tr><td>Cmin,ss (ng/mL)</td><td>65.1 (31.8)</td></tr>
<tr><td>RCmax</td><td>1.21 (0.0793)</td></tr>
<tr><td>RAUC</td><td>1.22 (0.0803)</td></tr>
</table></td></tr>
<tr><td>Range of effective dose(s) or exposure</td><td>Tanezumab 2.5 mg dose is proposed as lowest effective dose.</td></tr>
<tr><td>Maximally Tolerated Dose or Exposure</td><td>Clinical trials evaluated 2.5 – 10 mg of tanezumab.</td></tr>
<tr><td>Dose proportionality</td><td>Tanezumab PK have a small degree of nonlinearity that decreases with increase in dose. This resulted in an additional increase in $C_{max,ss}$, $C_{avg,ss}$, and $C_{min,ss}$ approximately 5%, 8%, and 19.6%, respectively, on doubling the SC dose from 2.5 mg to 5 mg.</td></tr>
<tr><td>Accumulation</td><td>1.2-fold</td></tr>
<tr><td>Time to achieve steady-state</td><td>Steady-state is expected to be achieved after second dose following subcutaneous administration every eight weeks.</td></tr>
<tr><td>Bridge between to-be marketed and clinical trial formulations</td><td>Tanezumab 2.5 mg in a pre-filled syringe was evaluated following subcutaneous administration in the pivotal clinical trials.</td></tr>
<tr><td></td><td>Absorption</td></tr>
<tr><td>Bioavailability</td><td>Subcutaneous administration of tanezumab has a bioavailability in the range of 62 -76% in different clinical studies.</td></tr>
<tr><td>T_{max}</td><td>10 days</td></tr>
<tr><td>Food effect (Fed/fasted) Geometric least square mean and 90% CI</td><td>Not applicable considering subcutaneous route of administration.</td></tr>
<tr><td></td><td>Distribution</td></tr>
<tr><td>Volume of distribution</td><td>4.37 L</td></tr>
<tr><td>Drug as substrate of transporters</td><td>Not Evaluated</td></tr>
<tr><td></td><td>Elimination</td></tr>
<tr><td>Clearance</td><td>0.133 L/day</td></tr>
<tr><td>Half-life</td><td>Mean effective half-life of tanezumab was approximately 22 days.</td></tr>
</table>

Characteristic	Drug Information
Metabolic pathway(s)	Tanezumab-alpb is expected to be metabolized by catabolic pathways into small peptides and amino acids by proteolytic enzymes widely distributed in the body.
Include, if not redundant with other information provided in the table.	**Intrinsic Factors and Specific Populations**
Body weight	Increase in body weight resulted in lower exposure of tanezumab However, tanezumab 2.5 mg is proposed as the lowest effective dose.
Age	No clinically relevant impact on the PK of tanezumab
Renal impairment	Renal impairment study was not conducted. Tanezumab, a monoclonal antibody, is not expected to be significantly cleared by renal route. Population PK data do not show clinically relevant impact of creatinine clearance on tanezumab PK.
Hepatic impairment	Hepatic impairment study was not conducted. Tanezumab is expected to be metabolized by proteolytic enzymes widely distributed in the body and therefore hepatic impairment is not expected to play a major role in its clearance.
Site of Injection	Effect of site of injection (thigh vs. abdomen) was investigated and not found to significantly impact tanezumab PK.
	Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism	In vitro and in vivo metabolic drug interaction studies with tanezumab were not conducted.
Inhibition/induction of transporter systems	In vitro and in vivo transporter drug interaction studies with tanezumab were not conducted.
	Immunogenicity (for Biologics)
Bioanalysis	Validated antidrug antibody (ADA) assay supported the Applicant's post-2015 clinical trials 1056, 1057, 1058, and 1059 which are the trials on which the immunogenicity assessment is primarily based. The measurement of ADA to tanezumab utilized an upfront acid treatment (UFAT) affinity capture elution method with electrochemiluminescent (ECL) detection. The Angiotensin-converting enzyme (ACE) technique along with the ADA was used in the assay sensitivity and drug tolerance to minimize Nerve Growth Factor (NGF) interference.
Incidence	The overall incidence of patients producing ADA to tanezumab following 2.5 mg SC dose of tanezumab administered every 8 weeks for 48 weeks is less than 10%. PK data of 657 ADA negative and 62 ADA positive subjects dosed with tanezumab 2.5 mg subcutaneous dose in different clinical trials were compared.
Clinical impact	No clinically relevant change on the PK of tanezumab-alpb was observed in ADA positive subjects as compared to ADA-negative subjects.

Abbreviations: TQT study, thorough QT/QTc study; ELISA, enzyme-linked immunosorbent assay; PK, pharmacokinetics

3. Assessment of Effectiveness

3.1. Dose and Dose Responsiveness

The Applicant has explored administration of tanezumab by both intravenous (IV) and subcutaneous (SC) routes, and has tested single doses up to 100 mg in humans. As described in this review, serious toxicities related to tanezumab have been identified, and have restricted the patients eligible for enrollment into clinical trials, the doses studied, and the route of administration (tanezumab has an absolute bioavailability of 62% to 76% when administered SC) in clinical trials. As information about the arthropathy and neuropathy risks continued to accumulate, the route of administration changed from IV to SC, and doses investigated in clinical trials shrank from as high as 200 mcg/kg IV to the proposed dose for marketing of 2.5 mg SC.

As described in this section, the modest efficacy effects at 2.5 mg SC every 8 weeks likely represents the minimal effective dose.

3.2. Clinical Trials Intended to Demonstrate Efficacy

Focus on Post-2015 OA Studies

Tanezumab was studied over a decade and a half, in various patient populations, at doses substantially higher than the 2.5 mg Q8 weeks currently proposed for marketing, via IV and SC routes, and both with and without risk mitigation measures designed to manage the risk of joint destruction. The dose, route of administration, permitted concomitant medications (avoid NSAIDs), and patient population continued to constrict due lack of efficacy in some patient populations and the accumulating evidence indicating a dose-related risk of potentially devastating arthropathy with tanezumab treatment. The evolution of identification of a patient population in which the benefits might outweigh the risks has resulted in the narrow, restricted indication currently sought.

Due to the heterogeneity of the other 38 studies and the direct relevance of the post-2015 OA studies to the regulatory decision to be made, the review team has focused on three adequate and well-controlled studies that share the characteristics of including the dose of 2.5 mg Q8W, subcutaneous route of administration, purportedly restricted osteoarthritis population, and including risk mitigation measures proposed for marketing (the post-2015 studies used more risk mitigation measures than those proposed in the Risk Evaluation and Mitigation Strategies [REMS]). Those clinical trials are Studies 1056 and 1057, 16- and 24-week placebo-controlled designs, and Study 1058, a 1-year active-controlled design.

Discussion of Proposed Indication

Pfizer seeks an indication of "Relief of signs and symptoms of moderate to severe osteoarthritis in adult patients for whom the use of other analgesics is ineffective or not appropriate." This represents a novel indication with regard to both the qualifier of "moderate to severe" and the exact wording of the allusion to treatment of the allusion to failure with prior analgesics.

With regard to the "signs and symptoms" portion of the proposed indication, the Division has previously granted the "signs and symptoms of osteoarthritis (OA)" indication based on a demonstration of efficacy on three co-primary endpoints: the Western Ontario and McMaster Universities Index (WOMAC) pain subscale, WOMAC function subscale, and a patient global assessment. The acceptability of this indication is undergoing further consideration within the Division, as the endpoints supporting it do not include any assessments of clinical signs related to OA, and the symptoms evaluated are primarily related to pain. Therefore, the Division is endorsing an approach whereby products intended to treat symptomatic OA are assessed for a "treatment of pain of OA" indication, where pain is the primary outcome of interest and primary efficacy endpoint. The additional function and patient global measures could be assessed as secondary outcomes, and could be included in the clinical studies section of the labeling, provided appropriate pre-specified statistical analyses have been performed. Thus, at this time, the "signs and…" portion of the proposed indication will not be entertained.

The Applicant seeks approval for the indication of "Relief of signs and symptoms of moderate to severe OA." Given the risks of tanezumab, if approved, the drug would represent third or fourth line therapy. Thus, allusions to the severity of the OA and this modifier are irrelevant because patients would have to have severe disease to be candidates for tanezumab therapy. The last part of the proposed indication (for whom the use of other analgesics is ineffective or not appropriate) is discussed below.

Patients Studied in Osteoarthritis Clinical Trials

The nominal selection criteria for the post-2015 studies was to be limited to patients who had exhausted all other treatment options. Pfizer defined this as a documented history that previous treatment with acetaminophen, NSAIDs (except for Study 1058), and either tramadol or opioids had not provided adequate pain relief, or that they could not be taken due to a contraindication, inability to tolerate, and for opioids only, they were unwilling to take. With the exception of one study (Study 1058), whether or not patients had treatment failures was largely based upon what patients told investigators at the time of screening.

Evidence to Support the Proposed Patient Population

In all three protocols, the required level of evidence necessary to document treatment "failure" was based on the Investigator's judgement. The guidance specified that Investigators should utilize any available medical records they may have had access to, prescription medication records, information provided by referring physicians and/or patient recall. There was no standardized script to obtain medication and OA treatment histories, recall time was unlimited, and the electronic, study-specific, pre-screening questionnaire was optional. In Studies 1056 and 1057 all patients had used and reported inadequate pain relief with acetaminophen and NSAIDs, and in these studies, approximately one third of the patients (35.5% in 1056 and 30.7% in 1057) were not using any medication at Screening.

In all 3 studies, significantly fewer patients took opioids or tramadol and, in patients who used opioids, the most common reason for discontinuation was "unwilling to take" rather than "inadequate pain relief." The screen failure rate for this criterion was significantly lower (1.2% in 1056, 1.1% in 1057, and 3.4% in 1058) than for other "hard" criteria such as American College of Rheumatology (ACR) Kellgren-Lawrence (KL) grade ≥2 and WOMAC Pain score ≥5.

Brief description of studies informing efficacy of tanezumab 2.5 mg SC in OA follows (detailed descriptions are in Section IV.8 of this document.

Design, Treatment Groups, Endpoints

Studies 1056 and 1057 were multicenter, randomized, placebo-controlled, double-blind, parallel-group, studies of tanezumab administered by SC injection every 8 weeks compared to placebo in patients with OA of the hip or knee. The studies consisted of three periods: screening (up to 37 days), treatment, and a safety follow-up period (24 weeks). Patients were stratified by the index joint and the most severe KL score of the hip or knee into three treatment groups. In Study 1056, the treatment period was 16 weeks, and the tanezumab dose groups were 2.5 mg, and 2.5 mg titrated up to 5 mg. In Study 1057, the treatment period was 24 weeks, and the tanezumab dose groups were 2.5 mg and 5 mg. There were three co-primary efficacy endpoints in both studies: change from baseline to Week 16 or 24 for WOMAC pain, WOMAC function, or Patient Global Assessment of Osteoarthritis. Study 1056 was conducted in the US, Canada and Puerto Rico, Study 1057 in Europe, Asia and the UK, and Study 1058 in the US, South America, Europe, Asia, Australia, and New Zealand.

Study 1058 was a multicenter, randomized, double-blind, double-dummy, active-controlled, parallel-group Phase 3 study of the long-term safety and efficacy of SC tanezumab in subjects with OA of the hip or knee. The primary objectives were to characterize the long-term risk of joint safety events in patients who receive SC tanezumab 2.5 mg or 5 mg versus NSAID treatment (naproxen 500 mg twice daily (BID), celecoxib 100 mg BID or diclofenac ER 75 mg BID) over 56 weeks, using a composite endpoint (RPOA type 1 or 2, Subchondral insufficiency fracture (SIF), ON, or pathological fracture), and to demonstrate superior efficacy of SC tanezumab 2.5 mg and 5 mg versus NSAID treatment at week 16 using the same 3 co-primary endpoints as in 1056 and 1057. The long duration of this study necessitated the use of an active control group that would provide some pain relief. The inclusion of an active comparator treatment group allowed for tanezumab to be benchmarked against commonly used NSAIDs for the treatment of OA. The population enrolled was similar to that in Study 1056 and 1057, except that subjects had to have been on a stable dose of oral NSAID therapy and tolerating it for a 30 day period prior to screening. From the final 2 or 3 weeks of the screening period to the baseline visit, they had to have maintained a stabilized dose of either naproxen 500 mg BID, celecoxib 100 mg BID or diclofenac ER 75 mg BID (provided at screening). Subjects who had been on naproxen, celecoxib, or diclofenac prior to Screening were maintained on the same NSAID if randomized to that treatment arm. The total duration (post randomization) was 80 weeks, consisting of 3 periods: a screening period (up to a maximum of 37 days), which included a wash out period and initial pain assessment, a double-blind treatment period (56 weeks), and a safety follow-up period (24 weeks).

As part of measures taken to minimize the risk and to protect subject safety in the long- term Study 1058, the reduction of pain from baseline was calculated at Week 16 of the double-blind treatment period, and only patients who met pre-defined response criteria were continued. If there was not a ≥30% reduction in WOMAC pain at week 16 and a ≥15% reduction at either week 2, 4, or 8, subjects were discontinued and entered the 24-week Early Termination Follow-up period. A total of 651 (22%) of subjects met protocol specified pain criteria for discontinuation at week 16; the proportion of patients meeting those criteria was similar across all treatment groups.

Eligibility Criteria

Studies 1056 and 1057 planned to enroll patients with the following key characteristics.

- Adults with OA of the hip or knee based on ACR criteria, confirmed with a plain film showing a Kellgren-Lawrence (KL) grade ≥ 2.
- Patients were to have a **documented history** [emphasis added by the Food and Drug Administration (FDA) review team] that treatment with acetaminophen (APAP), NSAIDs, and either tramadol or opioid had not provided adequate pain relief, was contraindicated, was not tolerated, or the patient was unwilling to take (for opioids only).
- WOMAC Pain Subscale NRS≥5 in the index knee or hip at Screening
- Patients with index joint pain due to causes other than OA (i.e. inflammatory joint disease), radiographic evidence of adverse events of special interest such as rapidly progressive osteoarthritis (RPOA), ON, etc., considered unfit for surgery (American Society of Anesthesiologists Grade >3), with clinically significant cardiac, psychiatric or neurologic disease were to be excluded.

The selection criteria for the one-year active-controlled study (Study 1058) were similar to the placebo-controlled studies except that patients in Study 1058 had to be receiving a stable dose regimen of an oral NSAID for at least 30 days prior to the Screening visit (in addition to a WOMAC Pain subscale ≥ 5 at Screening and Baseline. In addition, from the final 2 or 3 weeks of the Screening period to the Baseline visit patients eligible for randomization had to have maintained a stabilized dose of prescription strength naproxen, celecoxib, or diclofenac.

Prohibited Medications

The prohibited medications were all analgesics other than APAP. Stable doses of compounds such as glucosamine sulfate or chondroitin sulfate, and other herbal and homeopathic remedies were permitted provided that patients had been on stable doses for 30 days prior to the start of study drug. Short-term use of analgesics for acute pain/injury/surgical pain were allowed. The rescue drug was APAP to a maximum of either 3 or 4 grams/day.

Statistical Analysis Plan

Study 1056

- The sample size was calculated for 90% power over all three endpoints, resulting in a sample size of 690 patients. The sample size calculation was based on an assumed treatment difference of -1.0 for WOMAC pain and function.
- The primary efficacy population was defined as all randomized who received SC study drug.
- The three co-primary endpoints for Study 1056 were WOMAC pain, WOMAC function, and a patient global assessment at Week 16. Those were to be analyzed using an ANCOVA model. There was to be a step-down testing strategy to assess the higher dose (tanezumab 2.5/5 mg) vs. placebo before moving down to tanezumab 2.5 mg vs. placebo. Success was defined as statistically significant differences for all three endpoints.
- Generally, multiple imputation was to be used for missing data.

Study 1057

From the clinical perspective, the analysis of Study 1057 was similar to that of Study 1056 except:

- The sample size of 270/group was estimated to provide 80% power.
- Given that this study used three doses, dosed every 8 weeks, the primary outcome was tested at Week 24.

Study 1058

- It is important to note that Study 1058 was designed as a superiority study. Expected attrition over a one-year period and the superiority objective justified the large sample size (~1000/arm). The power calculation anticipated 95% power to detect superiority of each tanezumab arm versus the NSAID arm. The sample size for the three NSAID cohorts planned for comparisons between each tanezumab arm and each NSAID cohort separately.
- The intent-to-treat (ITT) population (primary analysis population) was acceptable being all randomized who received SC study drug.
- Given that one of the primary objectives was safety (incidence of joint events), the primary safety analysis focused on the events, patient and patient-years of exposure and calculation of risk ratio and 95% confidence intervals. Conventional safety event data presentations such as Kaplan-Meier estimates were to be generated.
- The efficacy analysis was similar to those of Studies 1056/7 with the primary analysis occurring at Week 16.

3.2.1. Results of Analyses, Post-2015 Studies

Baseline Demographics

All three post-2015 OA studies enrolled a typical osteoarthritis clinical trial population. The mean age was 60-65 years, and there was a female and Caucasian predominance (~65% and ~75%, respectively). The baseline demographics were similar between the studies. Table 60, in Appendix 7 shows key baseline characteristics by study.

Disposition

Studies 1056 (16 weeks) and 1057 (24 weeks) had high (>85%) completion rates. The most common reasons for early dropout were withdrawal by patient and lack of therapeutic response. Dropouts for adverse events comprised only 1% and 2.4% of the early discontinuations in Studies 1056 and 1057, respectively.

Study 1058, a one-year study, had a lower rate of completers (44%). The most common reasons for early discontinuation was a lack of therapeutic response after two doses of study drug (22%), followed by “other” (9.5%), adverse event (7.9%), and insufficient clinical response (7.1%). Study 1058 patients who failed to experience pain relief after two doses of study drug were discontinued as a risk mitigation measure under the reasonable assumption that longer exposure to tanezumab increases the risk of toxicity. The proportion of patients who failed to respond to

the first two doses of drug were similar (range 20.7% to 22.1%) across all three treatment arms. Table 3 summarizes discontinuations in Study 1058.

Table 3. Patient Disposition Study 1058

	Tanezumab 2.5 mg (N=1002)	Tanezumab 5 mg (N=998)	NSAID (N=996)	Total (N=2996)
Number (%) of Subjects	n (%)	n (%)	n (%)	n (%)
Disposition Phase: Treatment[1]				
Completed	447 (44.6)	419 (42.0)	446 (44.8)	1312 (43.8)
Discontinued	555 (55.4)	579 (58.0)	550 (55.2)	1684 (56.2)
Adverse Event	74 (7.4)	104 (10.4)	58 (5.8)	236 (7.9)
Death	2 (0.2)	3 (0.3)	0	5 (0.2)
Lost to Follow-Up	14 (1.4)	11 (1.1)	11 (1.1)	36 (1.2)
Withdrawal By Subject	63 (6.3)	62 (6.2)	55 (5.5)	180 (6.0)
Insufficient Clinical Response	60 (6.0)	63 (6.3)	91 (9.1)	214 (7.1)
Protocol Violation	18 (1.8)	31 (3.1)	27 (2.7)	76 (2.5)
Other	100 (10.0)	98 (9.8)	88 (8.8)	286 (9.5)
Patient Meets Protocol Specified Pain Criteria For Discontinuation	224 (22.4)	207 (20.7)	220 (22.1)	651 (21.7)
Disposition Phase: Study[2]				
Completed	741 (74.0)	729 (73.0)	757 (76.0)	2227 (74.3)
Discontinued	261 (26.0)	269 (27.0)	239 (24.0)	769 (25.7)
Adverse Event	23 (2.3)	22 (2.2)	8 (0.8)	53 (1.8)
Death	4 (0.4)	4 (0.4)	0	8 (0.3)
Lost to Follow-Up	25 (2.5)	21 (2.1)	31 (3.1)	77 (2.6)
Withdrawal By Subject	97 (9.7)	104 (10.4)	100 (10.0)	301 (10.0)
Insufficient Clinical Response	19 (1.9)	21 (2.1)	22 (2.2)	62 (2.1)
Protocol Violation	4 (0.4)	6 (0.6)	4 (0.4)	14 (0.5)
Other	89 (8.9)	91 (9.1)	74 (7.4)	254 (8.5)

Source: BLA 761130 Study 1058 CSR Table 14.1.1.2
Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drug

Efficacy Results

Studies 1056 and 1057

As shown in Table 4 and Table 5, tanezumab 2.5 mg was statistically superior for all three co-primary endpoints in Study 1056 and for WOMAC pain and WOMAC function in Study 1057. The treatment effect size for WOMAC pain was 0.60 and 0.46 for Studies 1056 and 1057, respectively. Compared to most systemic analgesics in OA studies, this represents a modest effect size versus placebo.

Table 4. Summary of Co-Primary Efficacy Endpoint Change From Baseline to Week 16 Study 1056 (ITT, Multiple Imputation)

Change from Baseline to Week 16:		Placebo N=232	Tanezumab 2.5 mg N=231	Tanezumab 2.5/5 mg N=233
WOMAC Pain Subscale	LSMean (SE)	-2.6 (0.23)	-3.2 (0.23)	-3.4 (0.22)
	Diff. from placebo		-0.6	-0.7
0-10 scale	(95% CI) on diff.		(-1.1, -0.1)	(-1.2, -0.3)
	p-value		0.013	0.002
WOMAC Physical Function Subscale	LSMean (SE)	-2.6 (0.22)	-3.2 (0.22)	-3.5 (0.22)
	Diff. from placebo		-0.7	-0.9
0-10 scale	(95% CI) on diff.		(-1.1, -0.2)	(-1.4, -0.4)
	p-value		0.007	<0.001
Patient Global Assessment (PGA)	LSMean (SE)	-0.65 (0.08)	-0.87 (0.08)	-0.90 (0.08)
	Diff. from placebo		-0.22	-0.25
5-level Likert scale	(95% CI) on diff.		(-0.4, -0.1)	(-0.4, -0.1)
	p-value		0.011	0.004

Source: Statistical Review
Abbreviations: ITT, intent-to-treat; SE, Standard Error; CI, confidence interval; diff, different
Multiple imputation was applied for missing data, with imputation dependent on reason for missing data.
Six Randomization strata were defined by index joint (hip/knee) and Max K-L score (2; 3; or 4)
LSMeans and comparisons generated from ANCOVA model with terms for treatment, strata, baseline value, baseline average daily pain in index joint, and site.
Negative values indicate improvement

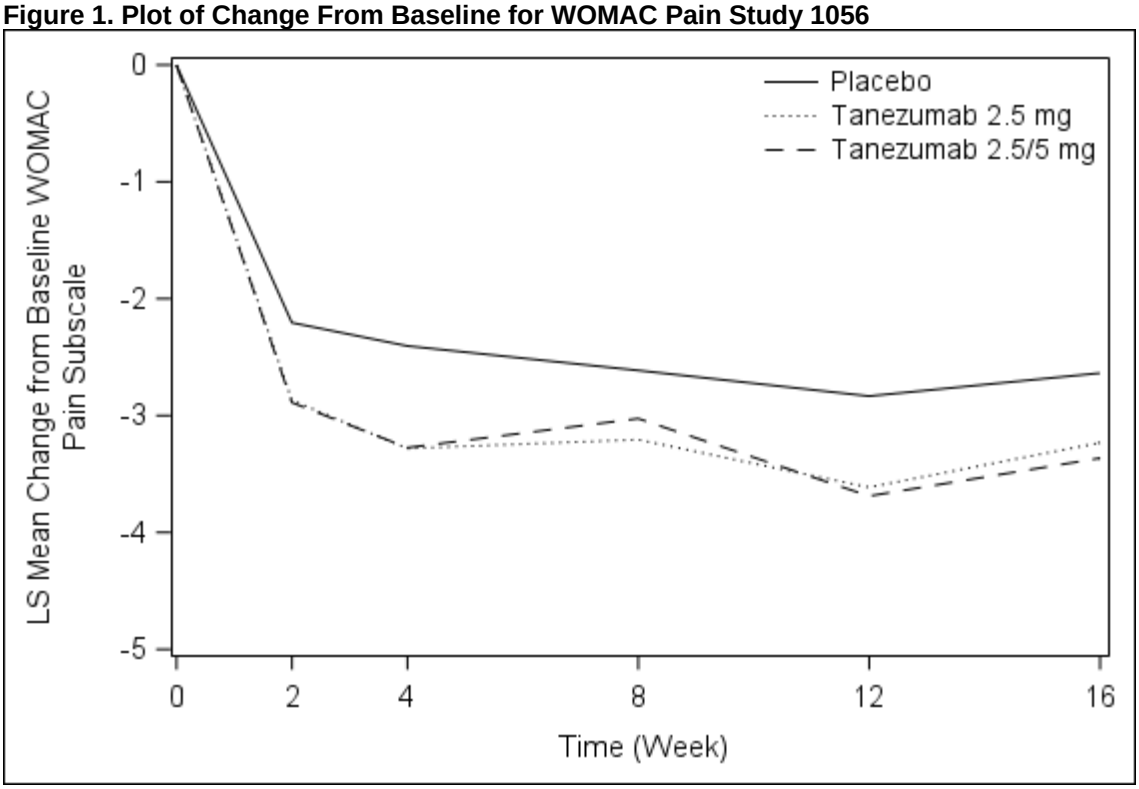
Table 5. Summary of Co-Primary Efficacy Endpoints-Analysis of Change From Baseline to Week 24 Study 1057 (ITT, Multiple Imputation)

Change from Baseline to Week 24:		Placebo N=282	Tanezumab 2.5 mg N=283	Tanezumab 5 mg N=284
WOMAC Pain Subscale **0-10 scale**	LSMean (SE) Diff. from placebo (95% CI) on diff. p-value	-2.2 (0.17)	-2.7 (0.17) -0.5 (-0.8, -0.1) 0.009	-2.9 (0.17) -0.6 (-1.0, -0.3) <0.001
WOMAC Physical Function Subscale **0-10 scale**	LSMean (SE) Diff. from placebo (95% CI) on diff. p-value	-2.1 (0.17)	-2.7 (0.17) -0.6 (-0.9, -0.2) <0.001	-2.8 (0.17) -0.7 (-1.1, -0.4) <0.001
Patient Global Assessment (PGA) **5-level Likert scale**	LSMean (SE) Diff. from placebo (95% CI) on diff. p-value	-0.72 (0.06)	-0.82 (0.06) -0.11 (-0.24, +0.02) 0.109	-0.9 (0.06) -0.19 (-0.32, -0.06) 0.005

Source: Statistical Review
Abbreviations: ITT, intent-to-treat; SE, Standard Error; CI, confidence interval; diff, different
Multiple imputation was applied for missing data, with imputation dependent on reason for missing data.
Six Randomization strata were defined by index joint (hip/knee) and Max K-L score (2; 3; or 4)
LSMeans and comparisons generated from ANCOVA model with terms for treatment, strata, baseline value, baseline average daily pain in index joint, and site.
Negative values indicate improvement

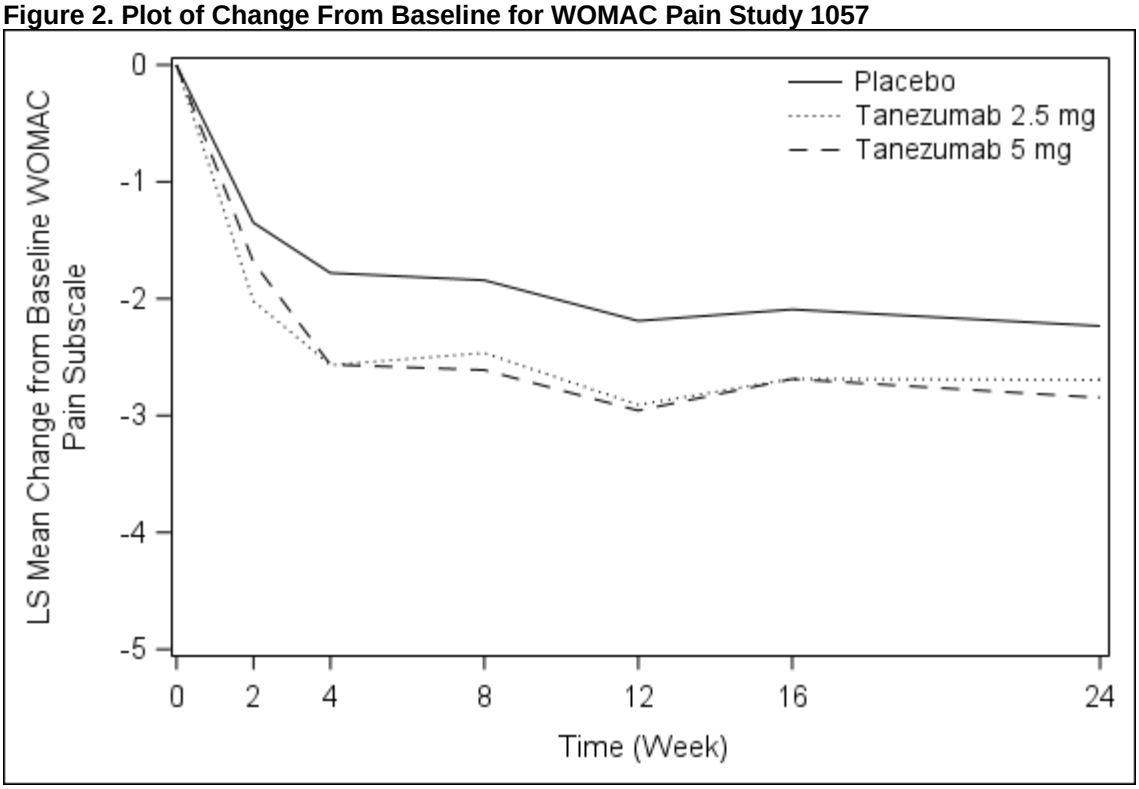
The secondary endpoints, such as differences in the outcome measures at other timepoints, and use of rescue, largely supported the primary results. Starting at Week 2 in both studies, there was a consistent pattern of increased efficacy for patients in both tanezumab treatment groups, compared to those in the placebo treatment group. The improvement in each of the tanezumab treatment groups versus placebo was similar and statistically significant. Data presentations for change in WOMAC pain over time are shown below in Figure 1 and Figure 2. Other secondary endpoints for 1056 and 1057 included patients with ≥50% reduction from Baseline in WOMAC Pain at Week 16 and 24, respectively. Overall, at Week 16 of double-blind therapy in Study 1056, both tanezumab treatment groups had significantly higher percentages of ≥50 % responders than the placebo group: placebo treatment group 37.9%, tanezumab 2.5 mg 54.5%, and tanezumab 2.5/5 mg 57.1%. The corresponding reduction in WOMAC Pain (at Week 24) for Study 1057 was 33.8%, 45.4% and 47.9% for placebo, tanezumab 2.5 mg, and tanezumab 5 mg.

Figure 1. Plot of Change From Baseline for WOMAC Pain Study 1056



Source: Generated by the statistical team based on BLA 761130 CSR 1056 Figure 3, page 123

Figure 2. Plot of Change From Baseline for WOMAC Pain Study 1057



Source: Generated by the statistical team based on BLA 761130 CSR 1057 Figure 4, page 131

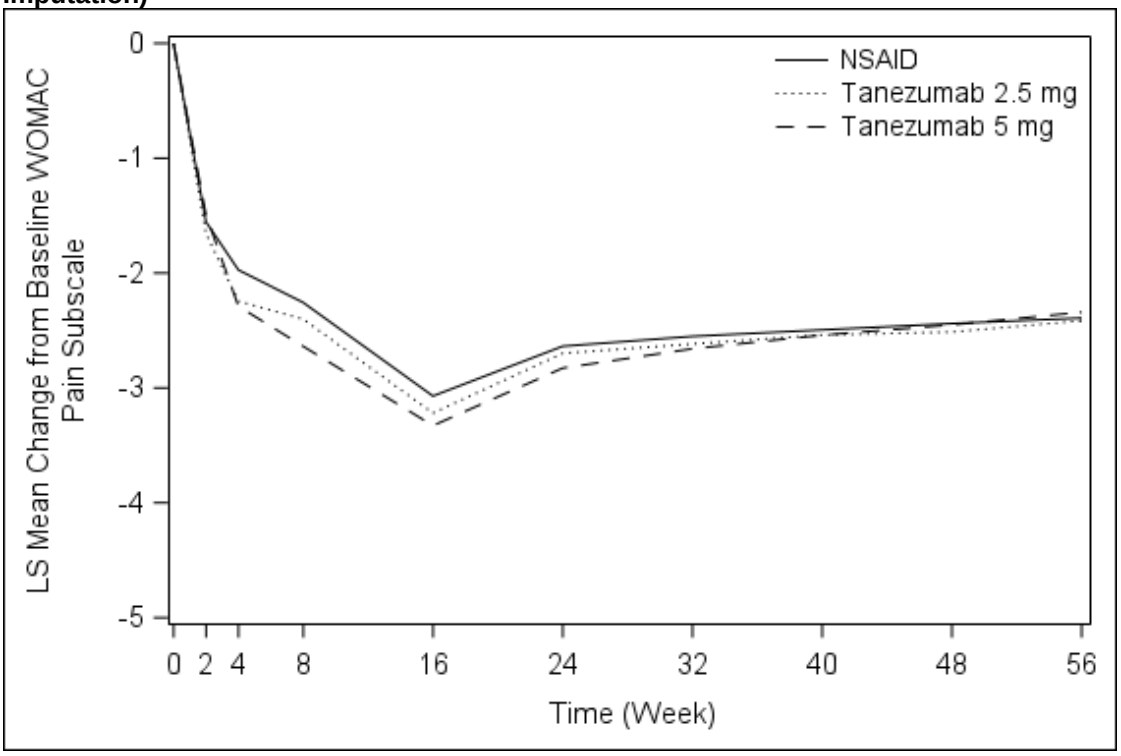
There was no meaningful difference in use of rescue medication between patients on placebo and those treated with tanezumab. Overall, over 16 weeks of double-blind therapy in Study 1056, rescue was used by 86.2%. 84.8%, and 85.4% of patients treated with placebo, tanezumab 2.5 mg and tanezumab 2.5/5 mg, respectively. The corresponding rescue use (at Week 24) for Study 1057 was 86.2%, 80.6%, and 83.1% for placebo, tanezumab 2.5 mg, and tanezumab 5 mg.

Study 1058

It is important to remember the design of Study 1058 when assessing the efficacy results. Patients were screened, underwent analgesic washout, and entered an open-label trial of prescription-strength naproxen, celecoxib, or diclofenac. Patients had to fail that run-in by reporting pain intensity ≥5 out of 10 to be randomized. Patients were randomized to one of three groups (double-blind/double-dummy): tanezumab 2.5 mg/placebo, tanezumab 5 mg/placebo, or NSAID/placebo. Hypothetically, if tanezumab is effective in NSAID non-responders, the pain should change minimally in patients who remain on NSAID and should decrease in patients switched to tanezumab.

However, that is not what was observed. All three groups had an average pain score of ~7 out of 10 at screening and after the open-label NSAID run-in. Figure 3 is post-randomization change in WOMAC pain subscore versus time for all three treatment groups. All three treatments resulted in a rapid decrease in reported pain, followed by a long plateau in the range of 2.5 to 3 points lower than the pre-randomization score. There are no known baseline characteristic or study conduct reasons to explain the lack of difference seen between the trial arms.

Figure 3. Change From Baseline for WOMAC Pain Subscale up to Week 56 (ITT, Multiple Imputation)



Source: Generated by the statistical team based on BLA 761130 CSR 1058 Figure 14.2.1.1.3 page 375
Abbreviations: LS- least squares; ITT-intent-to-treat

The lack of separation among the three treatment groups is reflected in the tabular summary and statistical analysis of the co-primary efficacy endpoints are presented in Table 6. Treatment with tanezumab 2.5 mg failed to meet any of the co-primary endpoints at Week 16. Tanezumab 5 mg showed a significant difference for two of the three co-primary endpoints versus NSAID. Hypothesis testing showed a p=0.015 for WOMAC Pain, and p=0.003 for WOMAC Physical Function, while the third endpoint (PGA-OA) had a not significant p-value (p=0.34). Due to the non-significant results of tanezumab 5 mg versus NSAID, further testing of the key secondary endpoints of proportion of patients with ≥ 50% reduction from Baseline in WOMAC Pain at Week 16 was not performed.

Table 6. Study 1058 Co-Primary Efficacy Endpoints: Analysis of Change From Baseline to Week 16 (ITT, Multiple Imputation)

Change from Baseline to Week 16:		Tanezumab 2.5 mg N=1002	Tanezumab 5 mg N=998	NSAIDS N=996
WOMAC Pain Subscale	LSMean (SE)	-3.2 (0.11)	-3.3 (0.11)	-3.1 (0.11)
	Diff. from NSAID	-0.2	-0.3	
0-10 scale	(95% CI) on diff.	(-0.4, +0.1)	(-0.5, -0.1)	
	p-value	0.16	0.015	
WOMAC Physical Function Subscale	LSMean (SE)	-3.3 (0.11)	-3.4 (0.11)	-3.1 (0.11)
	Diff. from placebo	-0.2	-0.3	
0-10 scale	(95% CI) on diff.	(-0.4, +0.02)	(-0.5, -0.1)	
	p-value	0.07	0.003	
Patient Global Assessment (PGA)	LSMean (SE)	-0.96 (0.04)	-0.97 (0.04)	-0.94 (0.04)
	Diff. from placebo	-0.02	-0.04	
5-level Likert scale	(95% CI) on diff.	(-0.1, +0.1)	(-0.1, +0.04)	
	p-value	0.63	0.34	

Source: Statistical Review
Abbreviations: ITT, intent-to-treat; SE, Standard Error; CI, confidence interval; diff, different; NSAIDs, nonsteroidal anti-inflammatory drugs
Multiple imputation was applied for missing data, with imputation dependent on reason for missing data.
Eighteen Randomization strata were defined by index joint (hip/knee); Max K-L score (2; 3; or 4); and NSAID cohort (Celecoxib;Naproxen;Diclofenac)
LSMeans and comparisons generated from ANCOVA model with terms for treatment, strata, baseline value, baseline average daily pain in index joint, and site.
Negative values indicate improvement.

3.3. Key Review Issues Relevant to Evaluation of Benefit

3.3.1. Has the Applicant Demonstrated a Clinically Meaningful Benefit?

The Applicant has met the statutory requirement for a finding of effectiveness against a control, in this case, placebo. However, the treatment effect size is modest. There is no convincing evidence of a superior efficacy of tanezumab over NSAIDs.

During the review cycle, the Applicant submitted a "Health Technology Assessment [HTA] Report" titled "Comparative safety and efficacy profile of tanezumab for knee and hip osteoarthritis." The report was prepared by the Center for Treatment Comparison and Integrative Analysis at Tufts Medical Center. The objective of this project was to assess the efficacy and safety of tanezumab compared to oral opioids and oral NSAIDs. The manuscript states that the HTA was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and Cochrane standards. Briefly, the authors used data for five randomized, controlled trials (RCT) of tanezumab, and identified pertinent journal articles of RCTs where placebo, oral opioids, and/or oral NSAIDs were studied in patients with knee or hip OA. The five tanezumab RCTs were Studies 1011, 1014, 1056, 1057, and 1058, described in other sections of this document. The authors used a meta-analysis to address 11 questions. The critical questions were to assess:

- Short-term safety and efficacy of tanezumab compared to placebo
- Short-term safety and efficacy of tanezumab compared to NSAIDs
- Long-term safety and efficacy of tanezumab compared to placebo
- Long-term safety and efficacy of tanezumab compared to NSAIDs

Other research questions addressed were permutations of these questions, such as short-term effects of tanezumab vs. opioids, or long-term effects of NSAIDs vs. placebo. There were no studies of tanezumab vs. opioids in patients with OA identified.

The report indicates that the authors included 5, 72, and 18 RCTs for tanezumab, NSAIDs, and opioids, respectively. The overall uncertainty with tanezumab is much higher than with NSAIDs and opioids due to the limited available data for tanezumab, evidenced by the small number of available studies included in the meta-analyses for the tanezumab comparisons. The report authors drew the following conclusions:

- Tanezumab, NSAIDs, and opioids result in small to moderate improvements in pain and function.
- Drug-specific adverse events may result in treatment discontinuation, and those include cardiovascular (CV) or gastrointestinal (GI) serious adverse events (SAEs).
- "In the long-term, use of tanezumab resulted in moderate improvements in pain and function, and demonstrated a safety profile comparable to NSAIDs and opioids."

The Clinical and Statistical review teams assessed the Tufts Medical Center HTA. The conclusions of the team follow:

- The report provides little information about tanezumab that is not discernable from a thorough review of the data submitted in the Biologics License Application (BLA). The comparisons to tanezumab in the report focused on Studies 1056, 1057, and 1058, which all have been thoroughly reviewed by FDA.

The inclusion of Studies 1011 and 1014 into the "short-term" placebo-controlled pool for an analysis of joint safety is inappropriate. These two pre-2015 studies lacked the joint safety risk mitigation measures, and the composite joint safety endpoints (CJSEs) were likely under-detected and under-reported.

- Limitations include:
  - The HTA authors only had access to study-level summary data, not patient-level data.
  - It is unclear why the authors classified Studies 1056 and 1057 as both short-term and long-term studies.
  - The comparison between tanezumab and NSAIDs in the report is based on a single trial, Study 1058, which is discussed extensively in the AC background package. No other trial has been conducted to compare tanezumab to NSAIDs.
  - The authors calculated and reported risk differences of adverse events (risk is defined as the number of events divided by number of subjects) across trials of different durations. We believe this approach is inadequate and potentially biased because it does not adjust for differential trial duration. It would have been more appropriate to calculate an Incidence Rate Difference standardized by time of exposure or time of follow-up that considers the different duration across trials.
- We do not agree with a conclusion that tanezumab has a safety profile comparable to NSAIDs and opioids for the following reasons:
  - There are no trials that compare tanezumab directly to opioids.
  - Based on the data from Study 1058, tanezumab has an increased risk of CJSE and TJR relative to NSAIDs.
  - Study 1058 observed few adverse CV events. The available data are not sufficient to compare the CV risk of tanezumab and NSAIDs.
  - Studies 1056, 1057, and 1058 excluded patients with significant CV disease. The CV risk of tanezumab relative to NSAIDs in patients with a history of CV disease is unknown.

The HTA concluded that the treatment effect size observed in studies of tanezumab, NSAIDs, and opioids in patients with OA were similar. Another source of context for the treatment effect size observed in the tanezumab program is a comparison to historical data from other registrational studies in patients with OA. Cross-study comparisons must be interpreted with caution due to differences in selection criteria, clinical practices at the time of study conduct, etc. However, studies are nearly always of a randomized, double-blind, placebo- and/or active-controlled, parallel-group design. Studies that used the same primary efficacy variable across all studies could be identified and that metric compared.

We reviewed labeling and publicly available data for drugs approved for knee or hip OA where the primary endpoint reported was the change from baseline in the WOMAC pain subscale. Many studies were excluded because the change from baseline in WOMAC pain was not

reported. As shown in Table 7, tanezumab consistently had the smallest treatment effect size of the approved products identified above.

Table 7. Summary of Registrational Studies in OA With a Primary Endpoint of Change in WOMAC Pain

Product	Description	Active Δ from baseline in WOMAC pain	Placebo Δ from baseline in WOMAC pain	Difference (treatment effect size)
Tanezumab 1056	α-NGF injection	-3.23	-2.64	0.59 (0-10 scale)
Tanezumab 1057	α-NGF injection	-2.70	-2.24	0.46 (0-10 scale)
Tanezumab 1058	α-NGF injection	-3.22	-3.07**	0.15 (0-10 scale)
Zilretta	Triamcinolone injection	-3.12	-2.14	0.98 (0-10 scale)
Vivlodex	Meloxicam capsules	-34 to -36	-25.68	8-10 (100-point scale)
Zorvolex	Diclofenac capsules	-42 to -47	-33.9	11.6(100-point scale)
Pennsaid*	Topical diclofenac	-4.5	-3.6	0.9 (0-10 scale)

Abbreviations: WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; NSAID, nonsteroidal anti-inflammatory drug
*4-week study
**The comparator was NSAID for this study

3.3.2. Has the Applicant identified Predictors for larger Treatment Effect Size?

The Applicant did not conduct subgroup analyses for efficacy. Responder analyses (based on percentage decrease in pain from baseline or OMERACT-OARSI [improvement ≥50% and ≥2 points on the WOMAC pain or function OR the patient experienced ≥20% improvement and ≥1 point on two of the three outcome measures {WOMAC pain, WOMAC function, patient global}]) did not suggest that a substantial proportion of patients treated with tanezumab were "super-responders." However, because a continuous responder analysis was not conducted, the numbers of patients who experience large reductions in pain (e.g., 80 or 90%) are not known.

Our statistical team conducted a subgroup analysis for efficacy by US vs. ex-US, age, race, sex, index joint (knee vs. hip), and baseline K-L score for Studies 1056, 1057, and 1058. Forest plots are located in Appendix 7. Our subgroup analysis did not identify any demographic characteristic associated with a higher or lower effect size.

3.3.3. Given the Dose-Related Risks of Tanezumab, Has the Applicant Identified the Lowest Effective Dose?

The Applicant has not tested below the dose of 2.5 mg SC Q8W proposed for marketing. However, given the small effect size at 2.5 mg, it is likely that 2.5 mg represents the minimal effective dose for this patient population.

4. Risk and Risk Management

4.1. Potential Risks or Safety Concerns Based on Nonclinical Data

As part of the tanezumab development program, a standard nonclinical development program was conducted in accordance with International Conference on Harmonisation guidance for industry: S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. Rats and monkeys were selected as relevant nonclinical species for the evaluation of the nonclinical safety profile of tanezumab. Nonclinical toxicology studies evaluating the safety profile of tanezumab included repeat-dose toxicology studies in rats and monkeys, a cardiovascular safety pharmacology study in monkeys (since Central Nervous System and respiratory assessments were incorporated into the other studies), and reproductive and developmental toxicity studies in rats and monkeys. Notable findings in nonclinical studies consisted of neuronal atrophy in the peripheral ganglia of the sympathetic nervous system. Thus far, manifestations of sympathetic ganglion atrophy (observed in toxicology studies) has not been observed in humans, although that might be due to limited ability to detect this risk clinically. In addition, post-birth mortalities and stillbirths were observed in monkey pre- and post-natal developmental studies.

4.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Joint destruction and neurosensory symptoms are adverse effects that have been observed with other anti-NGF agents. These effects are believed to be class-related. The joint safety signal associated with anti-NGFs was discussed at an Arthritis Advisory Committee meeting held in March 2012. The Committee opined that the anti-NGF class could continue in clinical development with adequate risk mitigation measures. Tanezumab (Pfizer) and fasinumab (Regeneron) have continued development. One sponsor decided to terminate their anti-NGF program following the Advisory Committee meeting.

4.3. Potential Safety Concerns Identified Through Postmarket Experience

No anti-NGF drug or biologic products are approved anywhere in the world.

4.4. FDA Approach to the Safety Review

Overall Strategy

The safety review was conducted with emphasis on the major safety findings (deaths, SAEs, and adverse events leading to discontinuations [AEDC]) and the adverse events of special interest,

specifically total joint replacement surgery, joint destruction (Composite Joint Safety Events [CJSE]), and neurosensory effects. Given that the following sections had no notable findings, the review of common AEs, immunogenicity, laboratory data, vital signs, and ECGs was completed but are not emphasized in this document.

Pooling Strategy

The pooling strategy will evaluate the safety of tanezumab separately in patients with OA and chronic low back pain (CLBP), and where appropriate, combine these two conditions. The safety findings for studies in other chronic pain conditions and healthy volunteer studies will be summarized separately.

Studies included in the OA study pools, including all pertinent study design details (e.g., where conducted, study population, randomized patients, treatment groups, tanezumab doses, comparators, randomization ratio, duration of treatment, duration of follow up, and effect of the clinical hold on the enrollment and duration of study) are described in Table 37 and Table 38.

For general safety, study pools of placebo-controlled, active-controlled, and uncontrolled studies were used. In earlier clinical studies, tanezumab had also been administered via the IV route. The bioavailability of subcutaneous (SC) tanezumab is 62% to 72% of the IV tanezumab and the plasma levels with SC are comparable to IV administration from Week 4 onward. Because the intended route of tanezumab administration is SC, randomized, controlled studies with SC tanezumab will be considered the primary pool for the analyses of tanezumab safety (pre-2015 Study 1027 and post-2015 studies 1056, 1057, and 1058). Studies in which tanezumab was administered via the IV route will be evaluated to provide additional information for the safety conclusions. Pooling irrespective of the route of administration (IV or SC) will be considered appropriate for analysis of infrequently occurring events.

The safety of tanezumab will be evaluated separately for the treatment and the follow-up period to assess the safety of tanezumab after the conclusion of treatment. As an increased incidence of joint-related events was noted late in the treatment period and during the follow-up period in the pre-2015 studies, the 8-week duration of follow-up instituted in the pre-2015 studies was determined to be insufficient to characterize what happens with the risk of joint destruction after tanezumab is discontinued. Therefore, the duration of follow-up was extended to 24 weeks in the clinical studies conducted after 2015. The data from the post-2015 SC controlled studies will be regarded as the primary source for the assessment of safety after the conclusion of treatment.

4.5. Adequacy of Clinical Safety Database

A substantial number of patients and healthy volunteers (13,266) have been dosed with tanezumab in 38 interventional clinical studies. At least 56 weeks of any tanezumab dose was received by 1785 patients, and at least 80 weeks by 93 patients in Phase 3 OA studies. At least 56 weeks of 2.5 mg SC tanezumab dose was received by 374 patients and at least 64 weeks by eight patients enrolled in Phase 3 OA studies.

The size of the clinical safety database is adequate to assess the safety of tanezumab for the intended use to treat OA pain, although, as described above, there are little data in patients dosed for more than 56 weeks. This is important because, as will be discussed in Sections 4.7.1 and 4.7.2, there is a substantial latency for the joint events, and the time-to-event curves (Kaplan-Meier [KM]) do not suggest that risk of joint destruction plateaus after one year. Summary statistics for exposure appear in Table 8 and Table 9 below.

Table 8. Duration of Exposure, Safety Population, Placebo-Controlled Studies 1027*, 1056, 1057

Variable	Placebo N=586 n (%)	Tanezumab 2.5 mg N=602 n (%)	Tanezumab 2.5/5 mg N=219 n (%)	Tanezumab 5 mg N=347 n (%)	Tanezumab 10 mg N=170 n (%)
Duration of treatment (weeks)					
Mean (SD)	18.1 (6.2)	18.6 (5.8)	16.2 (1.6)	21.3 (5.9)	11.5 (3)
Median (min, max)	16.4 (0.1, 26.1)	17.1 (0.3, 36)	16.1 (7.4, 24.1)	24.1 (1.1, 33.3)	12.1 (1.1, 16.3)
Subjects treated, by duration, n (%)					
<16 weeks	162 (27.6)	157 (26.1)	40 (18.3)	69 (19.9)	159 (93.5)
>=16 weeks	424 (72.4)	445 (73.9)	179 (81.7)	278 (80.1)	11 (6.5)

Source: adex.xpt; Software: Python
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; SD, standard deviation
14 subjects who were randomized to tanezumab 2.5/5 in Trial 1056 but only received the first dose of tanezumab 2.5 were summarized and analyzed as tanezumab 2.5.
*Study 1027 was a pre-2015 randomized, double-blind, placebo-controlled safety and efficacy study that included the regimen of tanezumab 2.5 mg SC Q 8 weeks

Table 9. Duration of Exposure, Safety Population, Study 1058

Variable	NSAID N=996 n (%)	Tanezumab 2.5 mg N=1002 n (%)	Tanezumab 5 mg N=998 n (%)
Duration of treatment (days)			
Mean (SD)	372.5 (185.3)	374.8 (184.6)	370.9 (178.2)
Median (min, max)	348.5 (1, 654)	386 (1, 795)	342.5 (1, 719)
Subjects treated, by duration, n (%)			
<365 days	501 (50.3)	492 (49.1)	512 (51.3)
≥365 days	495 (49.7)	510 (50.9)	486 (48.7)

Source: adex.xpt; Software: Python
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; SD, standard deviation

4.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

4.6.1. Overall Adverse Event Summary

Summary of Findings

The safety profile of tanezumab is consistent across the OA and CLBP studies, with a dose-dependent increase in the frequency of several specific types of adverse events (AEs) when compared to either the placebo or NSAID treatment groups, including joint-related, neurosensory, and peripheral edema AEs.

- The overall frequency of treatment-emergent adverse events (TEAEs), severe AEs, serious adverse events (SAEs), and discontinuation from treatment due to AEs with tanezumab was generally higher compared to placebo and NSAID treatments, but the differences were small.
- Tanezumab was associated with an increased risk of developing joint-related, neurosensory, and peripheral edema AEs. The risk of developing a joint-related AE with tanezumab continued to exist after drug discontinuation.
- A higher frequency of joint-related SAEs was observed in tanezumab versus placebo and NSAIDs treatment groups during the follow-up period.
- Joint and neurosensory AEs and SAEs were the most commonly reported events leading to treatment discontinuation with tanezumab.
- The data suggest that tanezumab has some advantage compared to NSAIDs in the GI system. While GI bleeds were infrequently reported, more GI bleeds were reported in the NSAID treatment arms than in the tanezumab treatment arms. However, no difference was noted for cardiovascular and renal safety outcomes.
- More patients from the tanezumab treatment groups than from the control groups died during the OA and CLBP studies, but no dose response was observed. The imbalance was driven by CV death, but a MACE analysis did not show a CV signal with tanezumab. However, the available data do not suggest that the CV risks of tanezumab is lower than that of NSAIDs.
- No concerning patterns were observed with regard to vital signs, laboratory abnormalities, and electrocardiogram (ECG) recordings.
- Safety data from CLBP studies were consistent with the findings in the OA population.

Methodology and Section Outline

Per routine, major safety findings (deaths, non-fatal serious adverse events (SAEs), and adverse events leading to discontinuation) were reviewed along with common adverse events, the majority of which were non-serious. Pooled data for both the most pertinent placebo-controlled (PC) studies (1027, 1056, and 1057) and Study 1058 (NSAID-controlled) were assessed to provide contextual information.

This section (General Safety) will contain the following topics in the order specified below:

- Overall adverse event summary
- Deaths

- SAEs
- AEs leading to discontinuation
- Common AEs
- Laboratory findings

Presentation of each topic will include data for the PC studies, followed by Study 1058, followed by a short description of other studies in OA and CLBP.

4.6.2. Overall Treatment-Emergent Adverse Event Summary

Summary statistics for general safety appear in Table 10 and Table 11 below. No clear dose-related effects are observed in this coarse categorization.

Table 10. Overview of Adverse Events, Safety Population, Placebo-Controlled Studies 1027, 1056, 1057

Event Category	Placebo N=586 n (%)	Tanezumab 2.5 mg N=602 n (%)	Tanezumab 2.5/5 mg N=219 n (%)	Tanezumab 5 mg N=347 n (%)	Tanezumab 10 mg N=170 n (%)
Any AE	357 (60.9)	378 (62.8)	130 (59.4)	221 (63.7)	80 (47.1)
Moderate or severe AEs	182 (31.1)	197 (32.7)	66 (30.1)	117 (33.7)	37 (21.8)
Any SAE	21 (3.6)	32 (5.3)	8 (3.7)	23 (6.6)	1 (0.6)
SAE with fatal outcome	0	0	0	0	0
AE leading to discontinuation of study drug	12 (2.0)	8 (1.3)	1 (0.5)	4 (1.2)	1 (0.6)
AE leading to dose modification of study drug	1 (0.2)	1 (0.2)	1 (0.5)	1 (0.3)	0
AE leading to interruption of study drug	1 (0.2)	1 (0.2)	1 (0.5)	1 (0.3)	0
AE leading to reduction of study drug	0	0	0	0	0
AE leading to delay of study drug	0	0	0	0	0

Source: FDA Clinical Data Scientist; adae.xpt; Software: Python
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event
Treatment-emergent adverse events defined as the event occurs for the first time during the effective duration of treatment and was not seen prior to the start of treatment (for example, during the baseline or run-in period) or the event was seen prior to the start of treatment but increased in severity during treatment.
The observation period was defined as the period from treatment start date up to the end of the follow-up date of the study.
14 subjects who were randomized to tanezumab 2.5/5 in Trial 1056 but only received the first dose of tanezumab 2.5 were summarized and analyzed as tanezumab 2.5.
Grading Scale: mild, moderate and severe.

Table 11. Overview of Adverse Events, Safety Population, Trial 1058

Event Category	NSAID N=996 n (%)	Tanezumab 2.5 mg N=1002 n (%)	Tanezumab 5 mg N=998 n (%)
Any AE	663 (66.6)	679 (67.8)	742 (74.3)
Moderate or severe AEs	358 (35.9)	380 (37.9)	455 (45.6)
Any SAE	62 (6.2)	78 (7.8)	105 (10.5)
SAE with fatal outcome	0	0	0
AE leading to discontinuation of study drug	58 (5.8)	74 (7.4)	103 (10.3)
AE leading to dose modification of study drug	25 (2.5)	17 (1.7)	22 (2.2)
AE leading to interruption of study drug	25 (2.5)	17 (1.7)	22 (2.2)
AE leading to reduction of study drug	0	0	0
AE leading to delay of study drug	0	0	0

Source: FDA Clinical Data Scientist; adae.xpt; Software: Python
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event
Treatment-emergent adverse events defined as the event occurs for the first time during the effective duration of treatment and was not seen prior to the start of treatment (for example, during the baseline or run-in period) or the event was seen prior to the start of treatment but increased in severity during treatment.
The observation period was defined as the period from treatment start date up to the end of the follow-up date of the study.
Grading Scale: mild, moderate and severe.

4.6.3. Deaths

A total of 62 patients died across all studies conducted with tanezumab. Considering the size of the safety database (N=17,779), the number of deaths that occurred in tanezumab clinical studies appears to be low. A total of 40 patients died while participating in OA and CLBP studies, 21 patients died in cancer pain studies (1003 and 1029), and one patient died in a post-herpetic neuralgia study.

Thirty-four (34) deaths occurred in controlled OA and CLBP studies, including 27 patients in OA studies and 7 patients in CLBP studies. This imbalance is not unexpected, given the larger number of subjects enrolled, and the total amount of follow-up time in the OA studies (N=12032; patient-years=8072) compared to the CLBP (N=3172; patient-years=1815) controlled studies.

In addition to the 34 deaths observed in the 14 controlled studies, six deaths occurred in 4 open-label extension studies (1016, 1032, 1039, 1040), including 3 patients in OA studies and 3 patients in CLBP studies.

A summary for the 34 deaths that occurred in controlled OA and CLBP studies appears in Table 12 below.

Table 12. Deaths up to End of Study and Post Study: OA + CLBP Controlled Pre- and Post-2015 Studies

Treatment Arm Sample Size Total Observation Time (patient-years)	Tan only N=8527 PY=5778	Tan + NSAID N=1530 PY=1083	Placebo N=2181 PY=927	NSAIDs N=2399 PY=1712	Oxy N=158 PY=46	Tramadol N=602 PY=531
Number (%) of subjects	24 (0.3)	5 (0.3)	3 (0.1)	1 (0.04)	0	1 (0.2)
Incidence rate *(per 1000 patient-years)*	4.2	4.6	3.2	0.6	0	1.9
Cause of death:	11	1	1	1		
Cardiovascular	3	2	1			
Malignancy	2					1
Infection	3					
Overdose/toxicity	5	2	1			
Other						

Source: Medical reviewer Anjelina Pokrovnichka based on analyses provided by the FDA safety statistical review team
Abbreviations: OA, osteoarthritis; CLBP, Chronic Low Back Pain; N, number of subjects in treatment arm; PY, patient-years
Studies included: 14 pre- and post- 2015 randomized, controlled OA and CLBP clinical studies: 1011, 1014, 1015, 1017, 1018, 1025, 1026, 1027, 1030, 1056, 1057, 1058, 1012, 1059 (for study description, refer to Section IV.6.1)
Observation time defined as:
a) If subject experienced the event: Time from first IV/SC dose to the date of death.
b) If the subject did not experience the event: Time from first IV/SC dose to the end of study.

From the 34 patients who died in the controlled OA and CLBP studies, 24 patients received tanezumab monotherapy. However, a dose-response was not observed.

Because the most common cause of death was Cardiovascular, an analysis of major adverse cardiovascular events (MACE) was performed. The event numbers were considered too low to conclude that tanezumab has greater CV risk than NSAIDs. However, the available data did not suggest that the CV risk of tanezumab is lower than NSAIDs either. Details about the MACE analysis, and a Division of Cardiology and Nephrology (DCN) consult, are presented in Appendix 9.5.

4.6.4. Serious Adverse Events

The overall frequency of serious adverse events (SAEs) in the OA studies was low and not notably different in the tanezumab treatment groups compared to the placebo or NSAID groups during the treatment period, except for higher rates with tanezumab 5 mg in Study 1058 (1 year of treatment, NSAIDs-controlled, post-2015 study). There was no discernible pattern with regard to the type of SAEs, with the exception of joint-related SAEs, such as arthralgia, OA and RPOA, which occurred at a higher frequency in the tanezumab treatment groups versus comparators. During the follow-up period, joint safety events were also reported at a higher frequency in tanezumab versus comparator treatment groups, leading to a higher overall frequency of SAEs with tanezumab.

Tanezumab may provide some mitigation of NSAID-related GI toxicity. More GI bleeds, although small in number, were observed in the NSAID treatment arms than in the tanezumab treatment arms. However, no difference was noted for cardiovascular and renal safety outcomes (discussed in detail in Section 9.5 and 9.6).

Summary statistics for SAEs appear in Table 13 and Table 14 below.

Table 13. Frequency of Select Treatment-Emergent SAEs – OA Placebo-Controlled SC+IV Studies (1011, 1014, 1015, 1018, 1026, 1027, 1030, 1056, 1057)

During Treatment Period (Select SAEs)					
Number of evaluable subjects	Placebo N=1543	Tan 2.5 mg N=929	Tan 2.5/5 mg N=219	Tan 5 mg N=1324	Tan 10 mg N=1142
n (%) of subjects by PT					
With any SAE	29 (1.9)	21 (2.3)	3 (1.4)	29 (2.2)	53 (2.1)
OA	4 (0.3)	3 (0.3)	0	3 (0.2)	0
Arthralgia	0	0	1 (0.5)	2 (0.2)	1 (0.1)
ON	0	0	0	0	2 (0.2)
…	…	…			
During Follow-up Period (Select SAEs)					
Subjects evaluable for AEs	Placebo N=787	Tan 2.5 mg N=611	Tan 2.5/5 mg N=215	Tan 5 mg N=590	Tan 10 mg N=432
n (%) of subjects by PT			n (%)		
With any SAE	15 (1.9)	21 (3.4)	8 (3.7)	18 (3.1)	3 (0.7)
OA	1 (0.1)	4 (0.7)	2 (0.9)	4 (0.7)	0
Arthralgia	0	1 (0.2)	0	1 (0.2)	0
RPOA	0	0	0	3 (0.5)	0
ON	0	0	0	0	2 (0.5)
…					

Source: Created by Anjelina Pokrovnichka using data from Applicant's tables 1.7.2.16.a from ISS Appendix Tables 2 – general safety and 1.7.2.18.a from BLA amendment submitted on May 12, 2020, page 2352

Abbreviations: OA, osteoarthritis; ON, osteonecrosis; RPOA, rapidly progressing osteoarthritis; PT, preferred term; SAE, serious adverse event; Tan, tanezumab, SC+IV, subcutaneous +intravenous

Table 14. Frequency of Select Treatment-Emergent SAEs–OA Active-Controlled SC Study 1058

During treatment period			
Number of evaluable subjects	NSAID (N=996)	Tan 2.5 mg (N=1002)	Tan 5 mg (N=998)
n (%) of subjects by PT			
With any SAE	46 (4.6)	51 (5.1)	80 (8.0)
OA	4 (0.4)	9 (0.9)	17 (1.7)
Arthralgia	0	4 (0.4)	9 (0.9)
RPOA	0	3 (0.3)	11 (1.1)
SIF	2 (0.2)	1 (0.1)	4 (0.4)
ON	0	0	2 (0.2)
Gastric ulcer hemorrhage	1 (0.1)	0	0
GI hemorrhage	2 (0.2)	0	0
Acute kidney injury	0	0	2 (0.2)
…			
During follow-up period			
Number of evaluable subjects	NSAID (N=887)	Tan 2.5 mg (N=880)	Tan 5 mg (N=885)
n (%) of subjects by PT			
With Any SAE	19 (2.1)	33 (3.8)	32 (3.6)
OA	0	4 (0.5)	9 (1.0)
Arthralgia	0	2 (0.2)	4 (0.5)
RPOA	0	3 (0.3)	1 (0.1)
SIF	0	1 (0.1)	1 (0.1)
Acute kidney injury	0	1 (0.1)	0
…			

Source: Created by Anjelina Pokrovnichka using data from Applicant's Table 1.7.2.16.m from ISS Appendix Tables 1-General safety and Table 14.3.2.4.1.2 from 1058 study report body
Abbreviations: OA, osteoarthritis; ON, osteonecrosis; GI, gastrointestinal; NSAID, non-steroidal anti-inflammatory drug; PT, preferred term; RPOA, rapidly progressing osteoarthritis; SAE, serious adverse event; SIF, subchondral insufficiency fracture; Tan, tanezumab, SC, subcutaneous

4.6.5. Dropouts and/or Discontinuations Due to Adverse Events

A higher frequency and a dose-effect for treatment discontinuations due to AEs was observed for tanezumab in the active-controlled, but not in the placebo-controlled OA studies (IV.9.3). A plausible explanation for this finding is that the active-controlled studies had a longer duration of treatment (56 weeks, 7 doses of tanezumab) compared to the placebo-controlled studies (16-24 weeks, 2-3 doses of tanezumab). The imbalance was driven by an increased number of discontinuations due to joint-related (arthralgia, joint swelling, OA, and RPOA) and neurosensory (hypoesthesia, paresthesia, and carpal tunnel syndrome) adverse events. Discontinuations due to GI events were higher in patients who received NSAIDs than in patients who received tanezumab. The findings from studies with IV tanezumab administration were consistent with the findings from studies with SC tanezumab administration.

Summary statistics for AE leading to discontinuation of treatment in the active-controlled, SC post-2015 Study 1058 appear in Table 15.

Table 15. Adverse Events Leading to Discontinuation of Treatment (Study 1058)

Preferred Term	NSAID N=996 n (%)	Tanezumab 2.5 mg N=1002 n (%)	Tanezumab 5 mg N=998 n (%)
Any AE leading to discontinuation	58 (5.8)	74 (7.4)	103 (10.3)
Arthralgia	5 (0.5)	6 (0.6)	10 (1.0)
Osteoarthritis	4 (0.4)	11 (1.1)	19 (1.9)
Subchondral insufficiency fracture	4 (0.4)	3 (0.3)	7 (0.7)
Rapidly progressive osteoarthritis	3 (0.3)	12 (1.2)	17 (1.7)
Carpal tunnel syndrome	3 (0.3)	2 (0.2)	7 (0.7)
Acute myocardial infarction	2 (0.2)	1 (0.1)	1 (0.1)
Gastritis	2 (0.2)	0	0
Gastrointestinal hemorrhage	2 (0.2)	0	0
Gastroesophageal reflux disease	2 (0.2)	0	0
Hypoesthesia	1 (0.1)	1 (0.1)	2 (0.2)
Edema peripheral	1 (0.1)	1 (0.1)	0
Paresthesia	1 (0.1)	0	5 (0.5)
Gastric ulcer hemorrhage	1 (0.1)	0	0
Joint swelling	0	2 (0.2)	3 (0.3)
Peripheral swelling	0	2 (0.2)	1 (0.1)
Dysesthesia	0	0	2 (0.2)

Data Source: adae.xpt; Software: Python; Qunshu Zhang, FDA Clinical data scientist
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event; NSAIDs, nonsteroidal anti-inflammatory drugs
Treatment-emergent adverse events defined as the event occurs for the first time during the effective duration of treatment and was not seen prior to the start of treatment (for example, during the baseline or run-in period) or the event was seen prior to the start of treatment but increased in severity during treatment.
The observation period was defined as the treatment period.

4.6.6. Treatment-Emergent Adverse Events

Although the overall frequency of AEs was relatively similar between the treatment groups, there was a dose-dependent increase in joint-related, neurosensory, and peripheral edema AEs in the tanezumab treatment groups compared to the placebo and NSAID treatment groups. The frequency of joint-related AEs was higher in patients treated with tanezumab, as observed both during the treatment period, and during the safety follow-up period after the treatment was completed. This indicates that the deleterious effect on the joints continues to evolve even after study drug discontinuation. In contrast to the joint events, the frequency of neurosensory events was higher with tanezumab compared to placebo and NSAIDs during treatment, but not notably different after the cessation of treatment.

The joint safety events were most often reported as AEs of RPOA, arthralgia, joint swelling, or OA, and the neurosensory events as paresthesia, hypoesthesia, and carpal tunnel syndrome.

Tables for common TEAEs ≥1% and where the incidence in tanezumab was greater than the comparator are summarized in Table 16 and Table 17.

Table 16. Treatment-Emergent Adverse Events in Placebo-Controlled OA Studies With SC Tanezumab Administration (1027, 1056, and 1057)

Preferred Term	Placebo N=586 n (%)	Tan_2.5 mg N=602 n (%)	Tan_2_5 mg N=219 n (%)	Tan_5 mg N=347 n (%)	Tan_10 mg N=170 n (%)
Any treatment-related AE	83 (14.2)	103 (17.1)	31 (14.2)	64 (18.4)	33 (19.4)
Arthralgia	15 (2.6)	16 (2.7)	6 (2.7)	11 (3.2)	1 (0.6)
Headache	7 (1.2)	10 (1.7)	1 (0.5)	5 (1.4)	2 (1.2)
Pain in extremity	6 (1)	7 (1.2)	1 (0.5)	1 (0.3)	2 (1.2)
Paresthesia	5 (0.9)	13 (2.2)	2 (0.9)	7 (2)	10 (5.9)
Hypoesthesia	3 (0.5)	7 (1.2)	2 (0.9)	3 (0.9)	4 (2.4)
Dizziness	3 (0.5)	3 (0.5)	2 (0.9)	3 (0.9)	3 (1.8)
Fatigue	3 (0.5)	1 (0.2)	0 (0)	0 (0)	2 (1.2)
Muscle spasms	2 (0.3)	1 (0.2)	1 (0.5)	0 (0)	2 (1.2)
Myalgia	1 (0.2)	3 (0.5)	2 (0.9)	2 (0.6)	2 (1.2)
Joint swelling	1 (0.2)	1 (0.2)	1 (0.5)	5 (1.4)	2 (1.2)
Burning sensation	1 (0.2)	1 (0.2)	0 (0)	1 (0.3)	2 (1.2)
Rapidly progressive osteoarthritis	0 (0)	2 (0.3)	1 (0.5)	7 (2)	0 (0)
Injection site reaction	0 (0)	2 (0.3)	0 (0)	1 (0.3)	2 (1.2)

Source: Qunshu Zhang, PhD, FDA Clinical Data Scientist; adae.xpt datasets from Placebo-Controlled Trials A4091027, A4091056, A4091057

Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event; OA, osteoarthritis, SC, subcutaneous, Tan, tanezumab

The observation period was defined as the period from treatment start date up to the end of the follow-up date of the study.

14 subjects who were randomized to tanezumab 2.5/5 in Trial 1056 but only received the first dose of tanezumab 2.5 were summarized and analyzed as tanezumab 2.5.

Table 17. Treatment-Emergent Adverse Events in Active-Controlled OA Study With SC Tanezumab Administration (Study 1058)

Preferred Term	NSAID N=996 n (%)	Tan_2.5 mg N=1002 n (%)	Tan_5 mg N=998 n (%)
Any treatment-related AE	177 (17.8)	189 (18.9)	249 (24.9)
Arthralgia	32 (3.2)	27 (2.7)	49 (4.9)
Paresthesia	8 (0.8)	12 (1.2)	14 (1.4)
Musculoskeletal pain	8 (0.8)	1 (0.1)	10 (1)
Edema peripheral	7 (0.7)	9 (0.9)	12 (1.2)
Hypoesthesia	6 (0.6)	15 (1.5)	12 (1.2)
Rapidly progressive osteoarthritis	5 (0.5)	19 (1.9)	32 (3.2)
Osteoarthritis	3 (0.3)	15 (1.5)	23 (2.3)
Headache	3 (0.3)	11 (1.1)	8 (0.8)
Carpal tunnel syndrome	2 (0.2)	4 (0.4)	12 (1.2)

Source: Qunshu Zhang, PhD, FDA Clinical Data Scientist; adae.xpt dataset from trial A4091058

Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event; OA, osteoarthritis, SC, subcutaneous, Tan, tanezumab

The observation period was defined as the period from treatment start date up to the end of the follow-up date of the study.

4.6.7. Laboratory Findings

The nonclinical program had identified no monitorable target organs and the pre-2015 studies showed no concerning patterns with regard to laboratory investigations. Blood for hematology and chemistry testing were collected and analyzed at screening, day of randomization, and end-of-treatment in Study 1056. Sampling was slightly more frequent in Studies 1057, occurring at screening, baseline, Week 16, and 16 weeks after the last dose.

Laboratory data presentations consisted of tables showing 1. Numbers and percentages of patients who experienced test values that met a certain threshold (e.g., hemoglobin <0.8x the lower limit of normal) by whether the baseline value was abnormal and 2. Median baseline values and change from baseline to last observation for each analyte. No shift tables were submitted. Different pooling strategies were used (placebo versus active-controlled and OA versus CLBP).

Review of the tables of median changes from baseline (MCB) shows possible small effects on alkaline phosphatase (ALP) and creatine kinase (CPK). For example, for ALP, the MCB was 0 for both placebo and NSAID and 4 or 6, 4.5 or 8, and 5 or 10 for the 2.5, 5, and 10 mg dose of tanezumab, respectively. Examples of CPK changes were MCB of 3/6/6 for tanezumab 2.5/5/10 and 4/12 for tanezumab 5/10. However, MCB for NSAID were 9.5 and 10. Some groups may have different values because of pooling differences (placebo vs. active-controlled studies). The trends observed in the analyses of central tendencies were not reflected in the tables of clinically significant lab abnormalities where the number of patients meeting threshold were generally 0-2 with no patterns.

The routine lab surveillance shows no worrisome signals. The clinical significance of the minor trends in ALP and CPK is unknown. Given the nephrotoxicity of NSAIDs, whether or not tanezumab could be a viable alternative for patients with renal insufficiency/failure was assessed. As discussed in Appendix 9.6, the available data and analyses do not differentiate between tanezumab, placebo, and NSAID for renal risk. Because placebo and NSAID did not appear different, no conclusion can be made regarding the effects of tanezumab on renal function.

4.7. Key Review Issues Relevant to Evaluation of Risk

The FDA background document for the March 2012 Advisory Committee Meeting (ACM) states, “In April, [sic] 2010, the Division became aware of a potential safety signal based on reports of unusual and unexpected joint-related adverse events in tanezumab-treated patients with osteoarthritis in ongoing and completed Phase 2 and 3 trials being conducted in support of the OA indication.” FDA followed-up on this signal with all three sponsors that were developing an anti-NGF agent at that time. In June 2010, tanezumab was placed on clinical hold and, pursuant to a pathologically verified case of “avascular necrosis” in another agent, all anti-NGF programs were eventually placed on hold. At the ACM, both industry and FDA presented the available data related to joint destruction and neurosensory symptoms and experts made presentations.

The ACM minutes indicate the following:

- Rapidly Progressing [sic] Osteoarthritis (RPOA) has been identified as a safety signal for tanezumab.
- It was not clear whether osteonecrosis was a safety signal.
- RPOA2 is a relatively distinct finding in the tanezumab studies.
- There is a need for newer classes of analgesics. However, it was not clear whether the risk-benefit profile of tanezumab monotherapy in the treatment of OA is favorable compared to placebo, NSAIDS, or extended-release oxycodone.
- The risk-benefit profile of tanezumab/NSAID combination therapy is unfavorable compared to NSAID or tanezumab monotherapy.
- Further clinical development of anti-NGF products could be acceptable in patient populations with pain disorders in which currently available therapies are inadequate, unless a patient is at high risk for joint destruction. The panel noted that further studies are needed to elucidate which patient populations would benefit from this drug and the pathology behind the events.
- Extensive imaging monitoring of all major joints (hips, knees, and shoulders) at baseline, through the duration of the trials, and during at least 6 months of follow up post-trials should be considered. The panel also recommended the use of Magnetic resonance imaging (MRI) at baseline and during follow-up to collect data on bone, cartilage, and tendons along with bone mineral density and biochemical bone markers.
- The panel recommended the use of a central lab to review the radiology and pathology data.
- Additional non-clinical studies should be conducted to provide additional insight into possible etiologies for the bone and joint AEs.

Additional information on this ACM can be found at https://wayback.archive-it.org/7993/20170403223728/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/ucm286552.htm

Joint Safety Risk Mitigation Measures Initiated in Post-2015 Studies

Following the clinical hold and 2012 ACM, the Applicant terminated the ongoing studies and redesigned the tanezumab program to include measures that were thought to either mitigate the risk of joint destruction or to better define the risk of joint destruction. For the sake of brevity, these features will be referenced collectively as "risk mitigation measures" throughout the remainder of this document.

- Dose was limited to 5 mg SC Q8 weeks.
- Eligible patients were required to have had inadequate therapeutic response, been unable to tolerate, have contraindication to, or be unwilling to use (opioids) other analgesic classes.
- The follow-up period off drug was extended from 8 weeks in the pre-2015 studies to 24 weeks in the post-2015 studies.
- Imaging surveillance was added as follows:
  - Placebo-controlled studies (1056 and 1057)
    - Plain radiographs of knee, hip, and shoulder (KHS) at screening and end-of-study. Study 1057 included films at end-of-treatment as well.

- ― Active-controlled study (1058)
    - Plain radiographs of KHS and MRI of hip and knees at screening.
    - Plain radiographs of KHS at Week 24, 56 (end-of-treatment), and 80 (end-of-study).
    - Surveillance MRI at Weeks 24, 56, and 80 for hip and knees with KL 3 or 4 at baseline.

- Blinded Central Reader/radiologist (CR) to read imaging studies. Radiographs were to be taken using standardized technique.
    - ― Study drug was stopped for Rapidly Progressive Osteoarthritis Type 1 (RPOA1) or a more severe change. Definitions of the radiographic findings will be described in the next section (Categorization of Tanezumab-Related Joint Adverse Events).
- NSAID use was limited.
- In Study 1058, patients who failed to respond to the first two doses of study drug were discontinued because the continued risk was not balanced by any efficacy.

Pfizer also created and maintained an independent, blinded Adjudication Committee (AC) comprised of musculoskeletal radiologist, a rheumatologist, an orthopedic surgeon, and a pathologist. However, the AC did not subserve a risk mitigation function because drug was stopped on the basis of the CR's reading alone. The objective of the AC was to conduct retrospective case ascertainment for reporting purposes.

Categorization of Tanezumab-Related Joint Adverse Events

The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) consulted August (Alex) Hofling, MD, PhD, from the Division of Imaging and Radiation Medicine (DIRM), regarding radiological aspects of the safety and risk management for tanezumab. His responses are added to the pertinent subsections of this document.

It is important to understand that RPOA was a rarely described clinical entity prior to its emergence as an anti-NGF-related risk and the 2012 ACM. A search of PubMed conducted on August 15, 2020, for "rapidly progressive osteoarthritis" displayed by year of publication resulted in only one citation from before 2012: Walker EA, Davis D, Mosher TJ. Rapidly progressive osteoarthritis: biomechanical considerations. Magn Reson Imaging Clin N Am. 2011;19(2):283-294[4]. Because of this, developers of the anti-NGF agents have largely invented the terminology and definitions used for this phenomenon.

Pfizer defined the following five radiographic diagnoses that would represent a Composite Joint Safety Endpoint (CJSE):

- RPOA Type 1: Defined as a decrease in joint space width (JSW) ≥ 2 mm in one year with no structural changes.

The Applicant liberalized the definition of RPOA1 from ≥ 1 mm, which was used in the pre-2015 studies.

[4] https://pubmed ncbi nlm.nih.gov/21665091/

In a response to IR, we learned that "RPOA1" was not applied to joints with baseline joint space of less than 2 mm. Cases that progressed to complete joint space loss without evident bone destruction were not captured as either RPOA1 nor RPOA2 events.

- RPOA Type 2: Defined as loss/destruction/collapse of bone
- Subchondral Insufficiency fracture (SIF): Defined as focal bone defect/radiolucency/subchondral cortex
- Osteonecrosis (ON): Defined as infarcted bone
- Pathologic fracture: not formally defined

The Adjudication Committee could also categorize a case as 1. Normal Progression, 2. Not Enough Information to Distinguish Between Normal Progression and Rapid Progression, 3. Other, or 4. Not information to specify a diagnosis. None of these latter categories would represent an adjudicated CJSE.

We asked Dr. Hofling (DIRM), "Regardless of whether you agree with the criteria used, do you agree with our conclusion that a CJSE is purely a radiographic diagnosis and the other factors used by the Adjudication Committee are not really consistent with Pfizer's definition?" Dr. Hofling responded:

The definition for RPAO1 appears to be based entirely on imaging criteria. While clinical information might contribute to the criteria for RPAO2, SIF, and ON, it seems that for practical purposes, these diagnoses also typically depend on imaging findings. Theoretically, the additional clinical information available to the Adjudication Committee might have overturned imaging results in certain cases. For example, an appropriate history of acute trauma or unexpected findings on surgery and pathology reports might lead to a diagnosis that differs from that of imaging. However, it seems that such cases would be relatively uncommon. If possible, it would be useful to evaluate the rationale by which the Adjudication Committee overturned the majority of SIF and ON called by central readers in the post-2015 trials and to assess the alternate diagnoses assigned in these cases, if any.

The most minor joint event that would comprise a CJSE is RPOA1. However, given the literature on JSW loss in OA, a case of RPOA1 would appear to represent a significant finding. The estimates of JSW narrowing in patients with OA cited in the literature are variable, but considerably below 2 mm/year. For instance, in a meta-analysis, including 27 studies published between January 1985 and October 2006, the estimated mean rate of joint space narrowing was 0.13 ± 0.15 mm/year, with a range from - 0.10 mm to 0.70 mm/year.[5] Similar estimates were found (0.13 ± 0.36 mm/year) in the placebo group from a 2-year long randomized, controlled study for a product developed as an OA disease modifying therapy.[6] It was prudent that Pfizer stopped the administration of the study drug following a case of RPOA1 or higher, although it is unclear whether the threshold should have been set lower.

[5] Emrani PS, et al., *Joint Space Narrowing and Kellgren-Lawrence Progression in Knee Osteoarthritis: An Analytic Literature Synthesis,* Osteoarthritis Cartilage. 2008 August;16(8): 873–882

[6] Hellio Le Graverand MP, et al., *Considerations When Designing a Disease-Modifying Osteoarthritis Drug (DMOAD) Trial Using Radiography*, Semin Arthritis Rheum. 2013 Aug;43(1):1-8.

Due to the substantial latency for the joint events and the fact that the follow-up of patients with joint event was limited to the duration of the study, the evolution of the destructive process after study drug is discontinued could not be characterized.

4.7.1. Tanezumab Is Associated With an Elevated Risk of Requiring a Total Joint Replacement

Issue/Background

As will be discussed in Section 9.11 below, we believe that even the lowest categorization of CJSE (RPOA1) represents significant joint damage and might herald a joint replacement sooner than later. However, for the most part, RPOA1 is asymptomatic. While the long-term consequence of RPOA1 would be expected to be significant, no good data currently exist to make a definitive prediction regarding outcomes. Thus, the importance of total joint replacements (TJRs) becomes paramount in understanding the risks of tanezumab therapy. If a patient on tanezumab is at higher risk of TJR than a patient who is not, that represents an unequivocally bad outcome because it indicates that the joint destruction has progressed, and patients become exposed to the morbidity and risks of major surgery.

Assessment

Summary statistics regarding the incidence and hazard ratios for TJR for Studies 1056, 57, and 58 are included here. Our analyses show hazard ratios of approximately 2 for the 2.5 mg dose in Studies 1056 and 1058. Study 1057 did not show an imbalance in TJRs and is discussed following the data presentations for this subsection.

Table 18. All-Cause TJRs in Trial 1056

	Placebo	Tan 2.5	Tan 2.5/5
N	232	245	219
Observed PY	161.20	170.65	161.43
# of Subjects with TJR(IR*/100 PY)	4 (2.48)	9 (5.27)	15 (9.29)
RD / 100 PY [95% CI] †	-	2.8 [-1.3, 6.9]	6.8 [1.7, 11.9]
NNH / year [95% CI]	-	35 [14, -74]	15 [8, 57]
HR [95% CI]^	-	2.1 [0.6, 6.7]	3.6 [1.2, 10.9]

Source: FDA reviewer using adadj.xpt from the ISS-joint-safety-analysis pool
Abbreviations: PY, Person Years; IR, Incidence Rate; RD, Risk Difference; NNH, Number Needed to Harm; HR, Hazard Ratio; CI, Confidence Interval (nominal), TJRs, total joint replacements; Tan, tanezumab
* IR was calculated by dividing the total number of subjects with any TJR by the total observation time, defined as time to first TJR, or time to end of the study, whichever was earlier.
† The 95% confidence intervals are calculated assuming normality of the proportions.
^ Calculated using a Cox proportional hazards model with actual treatment as the only covariate. For subjects with multiple TJRs, only the first TJR was used for analysis. Subjects with no TJR during study were censored at the end of the study.
Note: 14 subjects who were randomized to Tan 2.5/5 in Trial 1056 but only received the first dose of Tan 2.5 were summarized and analyzed as Tan 2.5.

Table 19. All-Cause TJRs in Trial 1057

	Placebo	Tan 2.5	Tan 5
N	282	283	284
Observed PY	233.43	244.43	239.98
# of Subjects with TJR(IR*/100 PY)	21 (9.00)	25 (10.22)	20 (8.33)
RD / 100 PY [95% CI] †	-	1.2 [-4.1, 6.5]	-0.7 [-5.8, 4.4]
NNH / year [95% CI]	-	81 [15, -25]	-147 [23, -17]
HR [95% CI]^	-	1.1 [0.6, 2.0]	1.0 [0.5, 1.8]

Source: FDA reviewer using adadj.xpt from the ISS-joint-safety-analysis pool
Abbreviations: PY, Person Years; IR, Incidence Rate; RD, Risk Difference; NNH, Number Needed to Harm; HR, Hazard Ratio; CI, Confidence Interval (nominal), TJRs, total joint replacements; Tan, tanezumab
* IR was calculated by dividing the total number of subjects with any TJR by the total observation time, defined as time to first TJR, or time to end of the study, whichever was earlier.
† The 95% confidence intervals are calculated assuming normality of the proportions.
^ Calculated using a Cox proportional hazards model with actual treatment as the only covariate. For subjects with multiple TJRs, only the first TJR was used for analysis. Subjects with no TJR during study were censored at the end of the study.

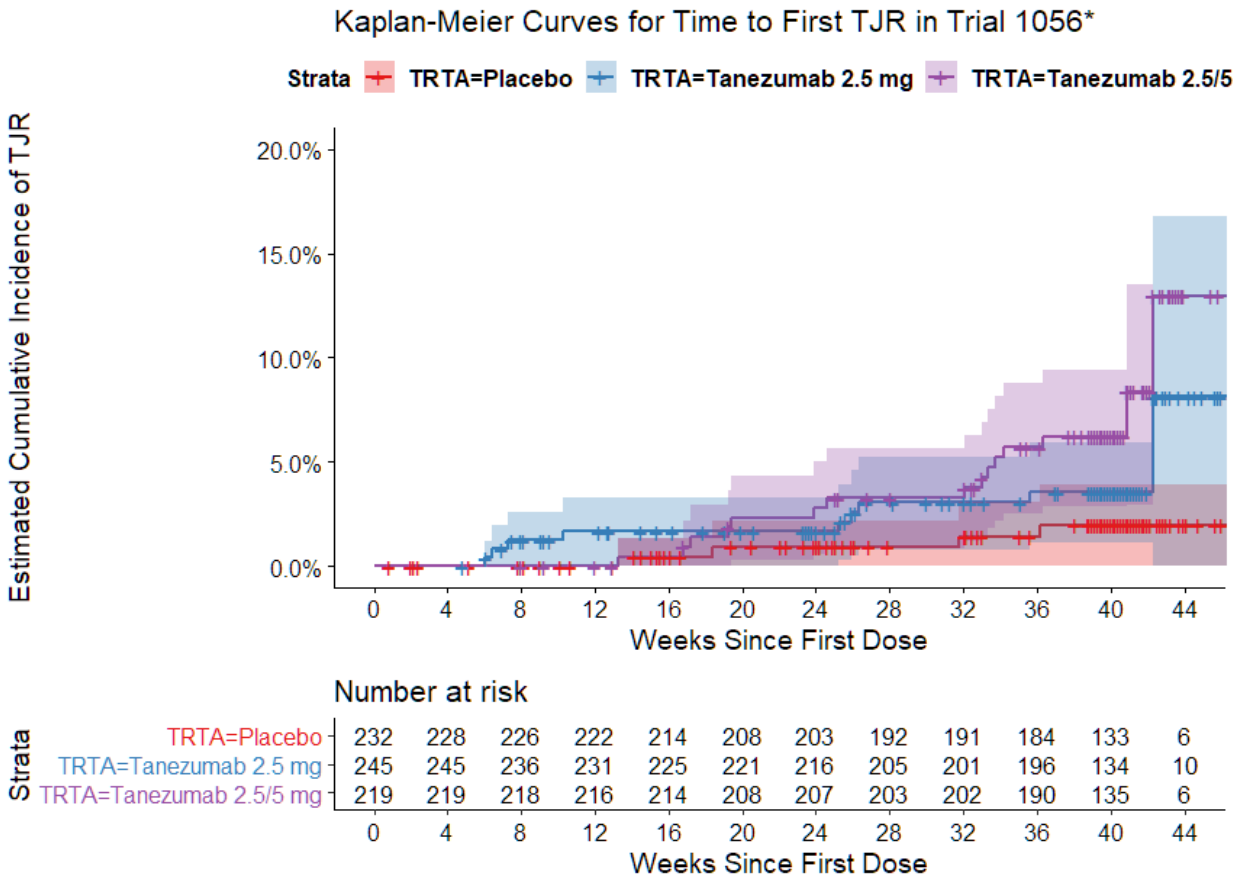
Table 20. All-Cause TJRs in Trial 1058

	NSAID	Tan 2.5	Tan 5
N	996	1002	998
Observed PY	1011.89	1022.84	1004.12
# of Subjects with TJR (IR*/100 PY)	26 (2.57)	56 (5.47)	82 (8.17)
RD/100 PY [95% CI]†	-	2.9 [1.2, 4.6]	5.6 [3.6, 7.6]
NNH/year [95% CI]	-	34 [22, 83]	18 [13, 27]
HR [95% CI]^	-	2.1 [1.3, 3.3]	3.2 [2.1, 5.0]

Source: FDA reviewer using adadj.xpt in the ISS-joint-safety-analysis pool
Abbreviations: PY, Person Years; IR, Incidence Rate; RD, Risk Difference; NNH, Number Needed to Harm; HR, Hazard Ratio; CI, Confidence Interval (nominal), TJRs, total joint replacements; Tan, tanezumab
* IR was calculated by dividing the total number of subjects with any TJR by the total observation time, defined as time to first TJR, or time to end of the study, whichever was earlier.
† The 95% confidence intervals are calculated assuming normality of the proportions.
^ Calculated using a Cox proportional hazards model with actual treatment as the only covariate. For subjects with multiple TJRs, only the first TJR was used for analysis. Subjects with no TJR during study were censored at the end of the study.

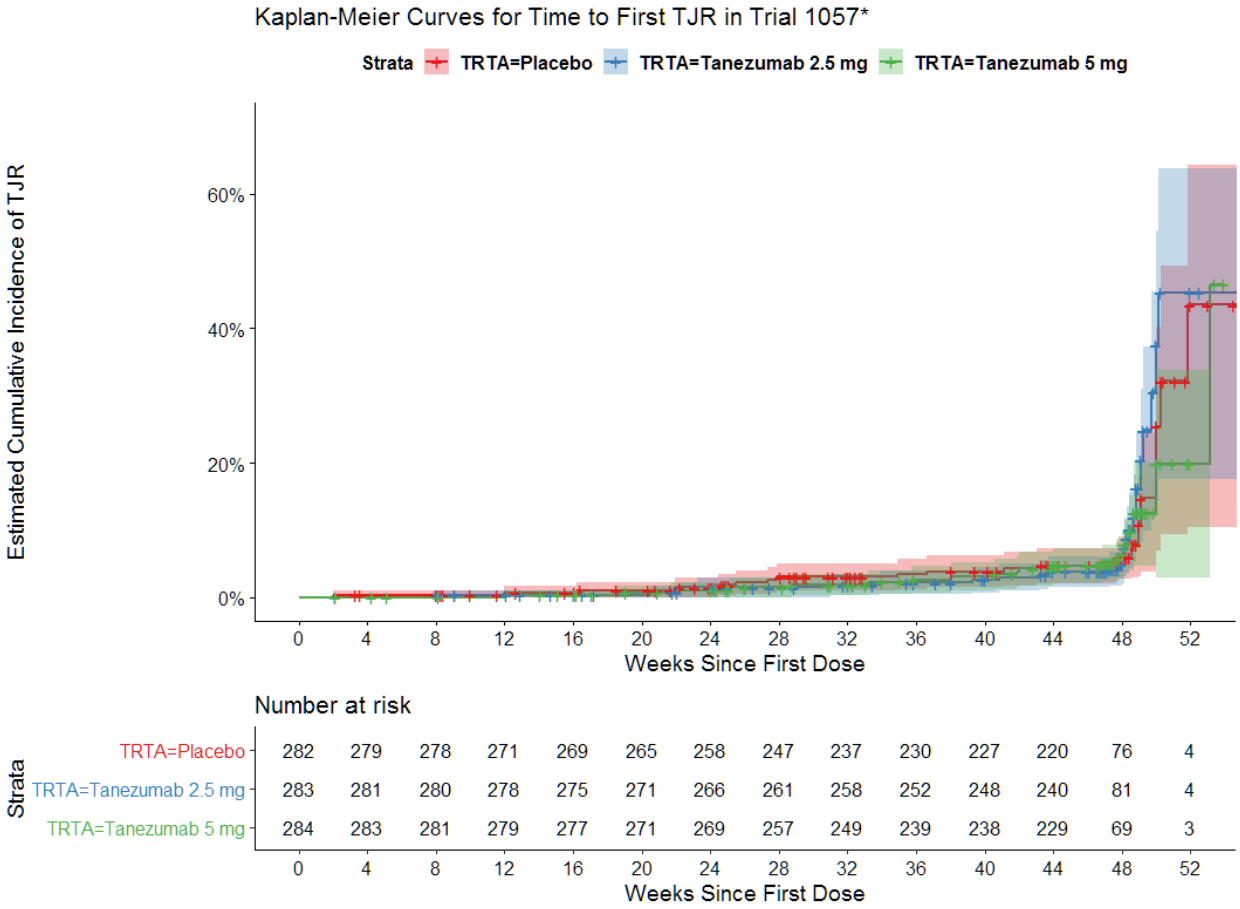
Time-to-event curves for the three post-2015 studies follow. These Kaplan-Meier curves include 95% confidence bands (shaded area of corresponding color to the line representing the events observed). Complimentary to the tabular data, the curves for Studies 1056 and 1058 show clear separation between the tanezumab arms and the controls. Another key finding from the Kaplan-Meier analyses is the latency to separation of the curves. Recalling that the duration of treatment was 16 and 56 weeks for Studies 1056 and 1058, respectively, the curves generally diverge after cessation of therapy. This finding impacts our assessment of the adequacy of long-term safety data.

Figure 4. Estimated Cumulative Probability of TJR Over Time in Trial 1056



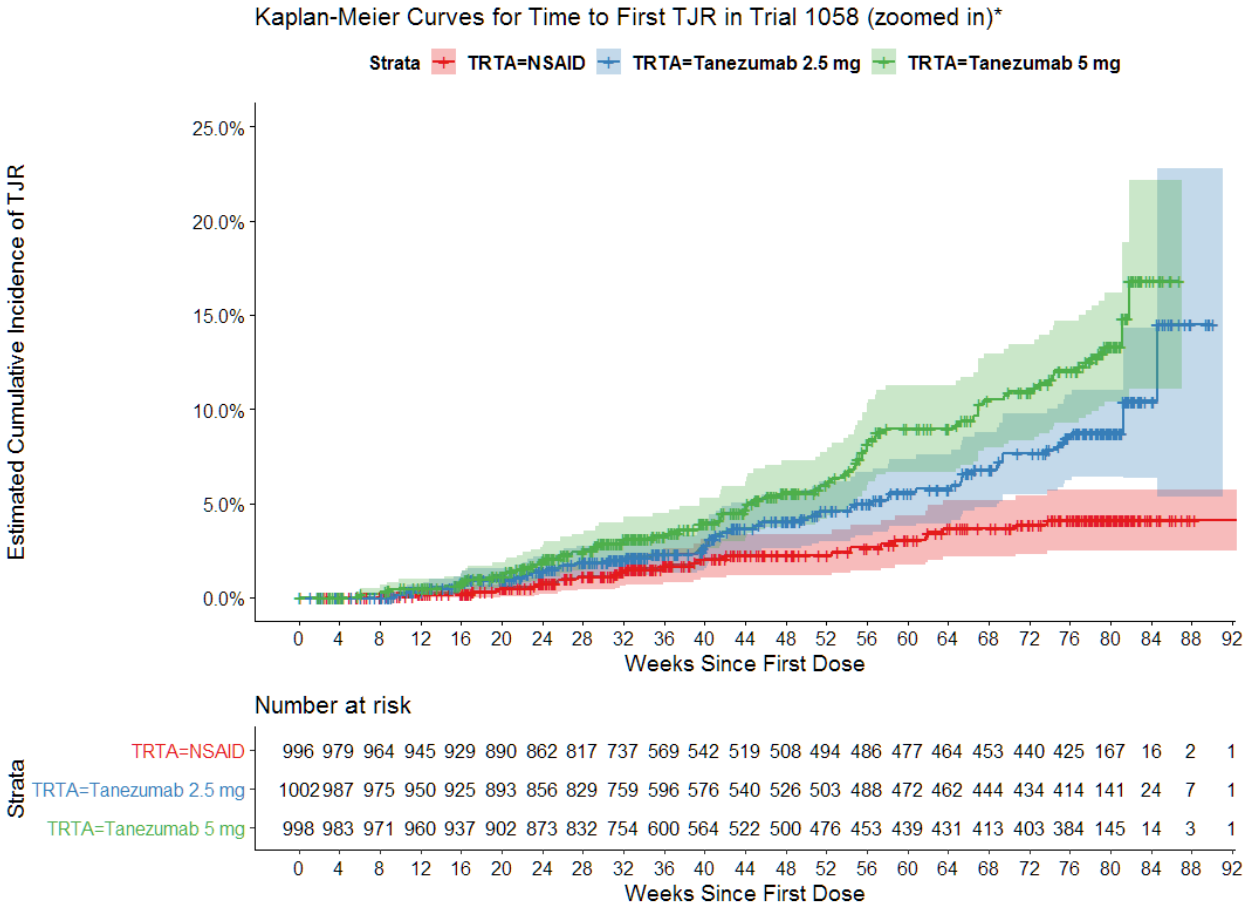
Source: FDA reviewer using the integrated datasets for Joint Safety Analysis adadj.xpt.
* Note: Data after 0.848 year (~44 weeks) are not shown in the K-M plot. At Year 0.848 (~Week 44), there were 22 subjects remaining in the risk set (6 for placebo, 10 for tanezumab 2.5 mg and 6 for tanezumab 2.5/5 mg), and 0 additional TJR events were observed after Year 0.85. Trial 1056 was designed to have a 16-week treatment period followed by a 24-week safety follow-up period (for a total of 40-week, or 0.77-year study duration).

Figure 5. Estimated Cumulative Probability of TJR Over Time in Trial 1057



Source: FDA reviewer using the integrated datasets for Joint Safety Analysis adadj.xpt.
* Note: Data after 1 year (52 weeks) are not shown in the K-M plot. At 1 year, there were 11 subjects remaining in the risk set (4 for placebo, 4 for tanezumab 2.5 mg and 3 for tanezumab 5 mg), and 2 additional TJR events were observed (1 for tanezumab 2.5 mg and 1 for tanezumab 5 mg) after 1 year. Trial 1057 was designed to have a 24-week treatment period followed by a 24-week safety follow-up period (for a total of 48-week, or 0.92-year study duration).

Figure 6. Estimated Cumulative Probability of TJR Over Time in Trial 1058



Source: FDA reviewer using the integrated datasets for Joint Safety Analysis adadj.xpt.
* Note: Data after 1.69 year (~88 weeks) are not shown in the K-M plot. At Year 1.69, there were 12 subjects remaining in the risk set (2 for NSAID, 7 for tanezumab 2.5 mg and 3 for tanezumab 5 mg), and 2 additional TJR events were observed (1 for tanezumab 2.5 mg and 1 for tanezumab 5 mg) after Year 1.69. Trial 1058 was designed to have a 56-week treatment period followed by a 24-week safety follow-up period (for a total of 80-week, or 1.54-year study duration). The zoomed-in version of the TJR K-M plot for Trial 1058 shows only 0%-25% on the y-axis since confidence bands become very wide towards the tails of the K-M plot with a small number of subjects remaining at risk.

It is unclear why the TJR data from Study 1057 differs from the other two studies in that it does not show an imbalance in TJRs. In Study 1057, the patient population was somewhat older, with more severe baseline disease (KL grade). However, these demographic differences do not explain why the rate of TJR was high in placebo and the rate in the 5 mg dose was not higher than the 2.5 mg dose. We note that a single site in Hungary reported more than 50% of the TJRs in Study 1057. It is possible that the criteria to take a patient to TJR were different at that site than at the other sites. The Agency had planned an inspection of that site to further investigate. However, unfortunately, due to the COVID-19 pandemic, it has not been feasible to travel to Hungary.

It is possible that TJR events have a medium to long latency that was not fully characterized in Studies 1056 and 1057.

Key Conclusions

- Tanezumab was associated with a 2- to 3-fold risk of TJR surgery in comparison to placebo in Study 1056. This signal was not replicated in Study 1057.
- Tanezumab is associated with a 2- to 3-fold risk of TJR surgery in comparison to NSAIDs. The risk increases with higher doses of tanezumab.
- The risk difference of TJR between the tanezumab and NSAID was most appreciable towards the end of the 1-year long treatment period and during the extended, 6-month, follow-up period in Study 1058. In this study, tanezumab 5 mg was associated with TJR of healthy joints with baseline KL Grade of 0 or 1.
- The trajectory of the risk for TJR in patients treated for over 1 year is unclear due to limited numbers of patients exposed.
- TJR surgeries occurred earlier in patients treated with tanezumab than patients treated with NSAIDs.
- Data from the CLBP studies support the above conclusions.

4.7.2. Tanezumab Is Associated With a Risk of Joint Destruction/Safety Events

Our review focused on establishing the relative incidence/risk between treatment groups, latency to and trajectory of detection of a CJSE, whether there are risk factors for a CJSE, and outcomes in patients who discontinued drug for a CJSE. Other issues and questions of less importance were interrogated and are discussed in Appendix 9.11, 9.12, and 9.14.

Data presentations informing overall numbers, categorization, and relative risk follow in Table 21 and Table 22. The key conclusions from the tabular data for CJSE are that tanezumab 2.5 mg is associated with a 2.6-fold risk of CJSE relative to NSAIDs at the 2.5 mg dose, and time-to-event curves are equivocal with regard to whether risk plateaus or continues to rise following one year of treatment. The most common form of CJSE observed was RPOA1.

Table 21. Primary Analysis of CJSE (Studies 1056 and 1057 Combined)

	Placebo	Tan 2.5	Tan 2.5/5	Tan 5
N	514	528	219	284
Observed PY	396.1	414.8	162.4	240.0
# of Subjects with CJSE (IR*/100 PY)	0 (0)	10 (2.4)	1 (0.6)	11 (4.6)
RD / 100 PY [95% CI] †	-	2.4 [1.0, 4.4]	0.6 [-0.5, 3.4]	4.6 [2.4, 8.0]
NNH / year [95% CI]	-	41 [23, 105]	162 [29, -213]	22 [12, 42]
HR [95% CI]^	-	N/A	N/A	N/A

Source: FDA reviewer using adadj.xpt in the ISS-joint-safety-analysis pool
Abbreviations: PY, Person Years; IR, Incidence Rate; RD, Risk Difference; NNH, Number Needed to Harm; HR, Hazard Ratio; CI, Confidence Interval (nominal), TJRs, total joint replacements; Tan, tanezumab
* IR was calculated by dividing the total number of subjects with any CJSE by the total observation time, defined as time to first CJSE, or time to end of the study, whichever was earlier.
† The 95% CIs for the RD are calculated using Wilson's (score) method.
^ HR was not calculated because there were 0 CJSE in the Placebo arm. Therefore, the HR estimate would be comparing tanezumab to placebo is undefined.
Note: Analyzed using actual treatment received (variable *TRTA*), using events under observation (*ANATYPE* == 'OBSTIME') and analysis flag for CJSE (*ANL06FL* == 'Y'). 14 subjects who were randomized to Tan 2.5/5 in Trial 1056 but only received the first dose of Tan 2.5 were summarized and analyzed as Tan 2.5.

Table 22. Primary Analysis of CJSE (Trial 1058)

	NSAID	Tan 2.5	Tan 5
N	996	1002	998
Observed PY	1010.9	1017.1	993.0
# of Subjects with CJSE (IR*/100 PY)	15 (1.5)	39 (3.8)	72 (7.3)
RD/100 PY [95% CI]†	-	2.4 [1.0, 3.8]	5.8 [4.0, 7.6]
NNH/year [95% CI]	-	43 [26, 104]	17 [13, 25]
HR [95% CI]^	-	2.6 [1.4, 4.7]	5.0 [2.9, 8.8]

Source: FDA reviewer using adadj.xpt in the ISS-joint-safety-analysis pool
Abbreviations: PY, Person Years; IR, Incidence Rate; RD, Risk Difference; NNH, Number Needed to Harm; HR, Hazard Ratio; CI, Confidence Interval (nominal), TJRs, total joint replacements; Tan, tanezumab
* IR was calculated by dividing the total number of subjects with any CJSE by the total observation time, defined as time to first CJSE, or time to end of the study, whichever was earlier.
† The 95% CIs for the RD are calculated using Wilson's (score) method.
^ The HR and 95% CIs are calculated using a Cox proportional hazards model with actual treatment as the only covariate. For subjects with multiple CJSEs, only the first CJSE was used for analysis. Subjects with no CJSE during study were censored at the end of the study.
Note: Analyzed using actual treatment received (variable *TRTA*), using events under observation (*ANATYPE* == 'OBSTIME') and analysis flag for CJSE (*ANL06FL* == 'Y').

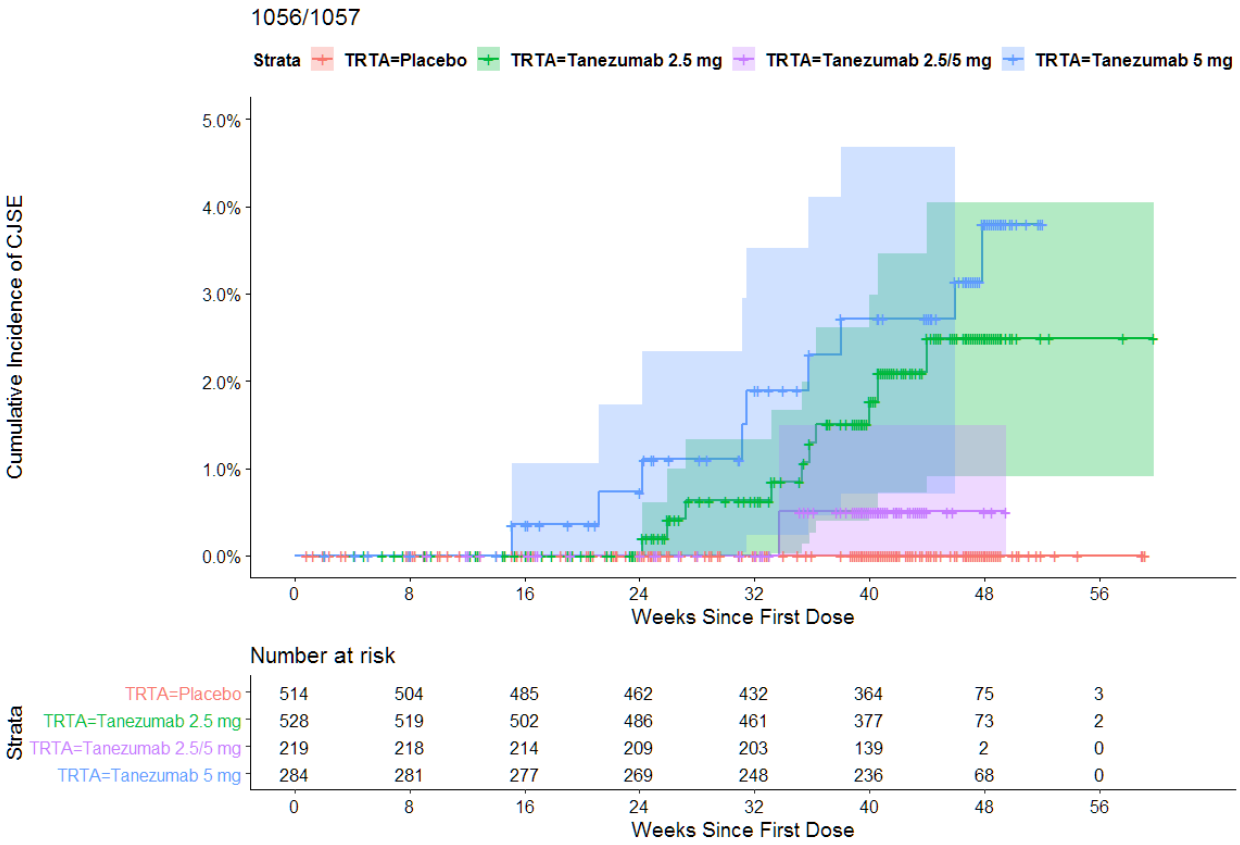
Table 23. Adjudicated Joint Safety Outcomes Included in Primary Composite Endpoint – Subject - Level (Post-2015 Studies 1056, 1057, 1058)

	Placebo N=514	Tan 2.5 mg N=1530	Tan 2.5/5 mg N=219	Tan 5 mg N=1282	NSAID N=996
			n (%)		
Primary CJSE (incidence rate per 100 PY)	0	49 (3.4)	1 (0.6)	83 (6.7)	15 (1.5)
RPOA1	0	35	1	57	10
RPOA2	0	6	0	17	1
SIF	0	7	0	7	4
ON	0	1	0	2	0
Pathologic fracture	0	0	0	0	0

Source: Prepared by clinical reviewer Anjelina Pokrovnichka using data displayed in Table 46 from ISS, page 193
Abbreviations: AC, Adjudication Committee; CJSE, Composite Joint Safety Endpoint; Tan, tanezumab; NSAID, non-steroidal anti-inflammatory drug; ON, osteonecrosis; SIF, subchondral insufficiency fracture; RPOA, rapidly progressing osteoarthritis; PY, Person Years; N, number of subjects in treatment arm; n, number of subjects with given treatment duration
Includes only select adjudication category outcomes, those that were included in the primary CJSE endpoint
Includes the three RPOA1 events in the tanezumab 5 mg dose group that occurred after the 26-weeks end of treatment follow-up period

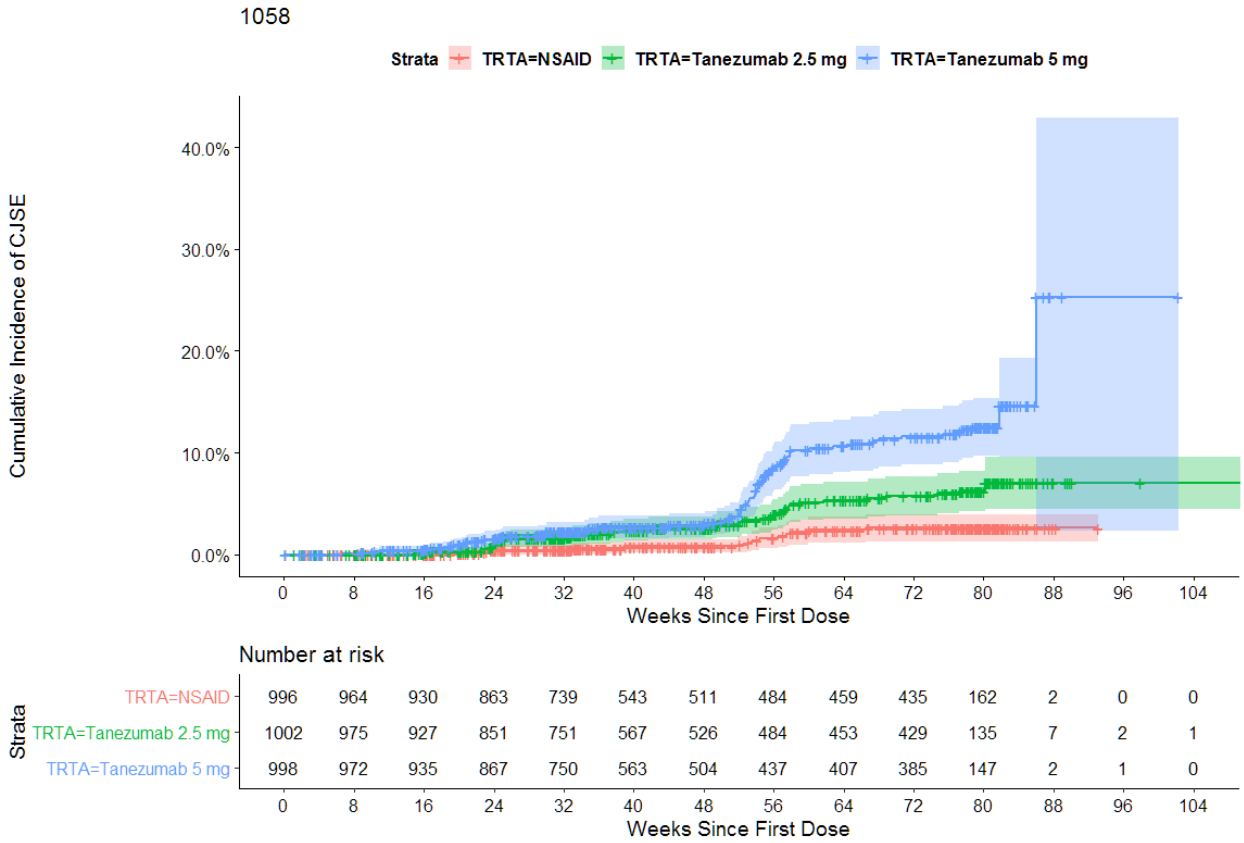
As for the TJRs, Kaplan-Meier curves showing the trajectory of CJSE were generated (Figure 7 and Figure 8). Given the loss of patients at risk toward the end of the observation period and the fact that the curves neither plateau nor do they show steep rise at the end of the treatment period, the trajectory of risk is unclear.

Figure 7. Kaplan-Meier Curves of CJSE With 95% Confidence Bands, Zoomed With Truncation* at 5% (Trials 1056/1057)



Source: FDA reviewer using adadj.xpt in the ISS-joint-safety-analysis pool
* This truncated graph excluded 2 CJSE events that occurred at Week 53.2 and Week 52.4, respectively, both in the tanezumab 5 mg arm in Study 1057.

Figure 8. Kaplan-Meier Curves of CJSE With 95% Confidence Bands (Trial 1058)



Source: FDA reviewer using adadj.xpt in the ISS-joint-safety-analysis pool

Risk Factor Analyses

Subgroup analyses to attempt to identify patients at particular risk for CJSE follow (Table 24 and Table 25). We did not identify any factors that appear to predict patients more likely to develop CJSE.

Table 24. Subgroup Analysis of CJSE (Studies 1056, 1057)

	Placebo	Tanezumab	Risk Difference* (IR/100PY) [95% CI]
All	0/514 ()	22/1031 (2.7)	2.7 [1.6, 3.8]
Gender			
Female	0/353 (0)	17/687 (2.5)	3.1 [1.6, 4.5]
Male	0/161 (0)	5/344 (1.9)	1.9 [0.2, 3.5]
Race			
Asian	0/47 (0)	1/85 (1.9)	1.9 [0.2,3.5]
Black or African	0/60 (0)	1/93 (1.9)	1.9 [0.2, 3.5]
American	0/403 (0)	20/841 (3.0)	3.0 [1.7, 4.3]
White	0/4	0/12	0
(Missing)			
Age			
<= 65	0/314 (0)	11/590 (2.4)	2.4 [1.0, 3.8]
> 65	0/200 (0)	11/441 (3.1)	3.1 [1.3, 4.9]
Region			
Europe	0/248 (0)	15/495 (3.6)	3.6 [1.8, 5.3]
Japan	0/34 (0)	1/72 (1.6)	1.6 [-1.5, 4.6]
North America	0/232 (0)	6/464 (1.8)	1.8 [0.4, 3.2]
Max KL Grade at Screening‡			
2	0/86 (0)	3/185 (2.1)	2.1 [-0.2, 4.4]
3	0/242 (0)	11/457 (3.0)	3.0 [1.3, 4.8]
4	0/514 (0)	8/389 (2.6)	2.6 [0.8, 4.4]
WOMAC Pain Subscale at Baseline			
< 7	0/267 (0)	9/545 (2.0)	2.0 [0.7, 3.3]
≥ 7	0/246 (0)	13/485 (3.5)	3.5 [1.6, 5.3]
(Missing)	0/1 (0)	0/1 (0)	0

Source: FDA reviewer

Abbreviations: CJSE, Composite Joint Safety Endpoint; IR, Incidence Rate; PY, Person Years; CI, Confidence Interval (nominal); KL grade, Kellgren-Lawrence grade; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

* The 95% CIs for the difference of proportions are calculated using Wilson's (score) method.

‡ The Max KL Grade at Screening is based on the *MAXKLGRD* variable in the integrated dataset adsl.xpt in the ISS Joint Safety Pool provided by the Applicant, representing the max KL grade of any joints.

Table 25. Subgroup Analysis of CJSE (Study 1058)

	NSAID	Tanezumab	Risk Difference* (IR / 100 PY) [95% CI]
All	15/996 (1.5)	111/2000 (5.5)	4.0 [2.8, 5.3]
Gender			
Female	9/662 (1.4)	75/1291 (5.8)	4.4 [2.9, 6.0]
Male	6/334 (1.8)	36/709 (5.1)	3.3 [1.1, 5.4]
Race			
Asian	1/99 (1.0)	16/205 (7.7)	6.6 [2.5, 10.8]
Black or African	4/186 (2.3)	16/328 (5.4)	3.2 [-0.2, 6.5]
American	10/680 (1.4)	75/1417 (5.1)	3.7 [2.3, 5.1]
White	0/31 (0)	4/50 (8.5)	8.5 [0.5, 16.4]
(Missing)			
Age			
<= 65	12/715 (1.7)	77/1383 (5.7)	4.0 [2.5, 5.6]
> 65	3/281 (1.0)	34/617 (5.1)	4.1 [2.1, 6.2]
Region			
Europe	0/14 (0)	0/18 (0)	0
Japan	0/67 (0)	9/133 (6.2)	6.2 [2.3, 10.2]
North America	14/769 (1.9)	73/1581 (4.7)	2.9 [1.4, 4.3]
Rest of World	1/146 (0.6)	29/268 (9.69)	9.1 [5.5, 12.6]
Max KL Grade at Screening‡			
1	0/0 (0)	0/1 (0)	0
2	2/239 (0.8)	19/472 (3.9)	3.1 [1.0, 5.1]
3	11/503 (2.2)	71/1039 (6.8)	4.7 [2.7, 6.7]
4	2/254 (0.8)	21/489 (4.4)	3.6 [1.5, 5.7]
WOMAC Pain Subscale at Baseline			
< 7	6/485 (1.2)	47/955 (4.8)	3.6 [2.0, 5.2]
≥ 7	9/510 (1.8)	64/1040 (6.3)	4.5 [2.6, 6.4]
(Missing)	0/2 (0)	0/5 (0)	0

Source: FDA reviewer
Abbreviations: CJSE, Composite Joint Safety Endpoint; IR, Incidence Rate; PY, Person Years; CI, Confidence Interval (nominal); KL grade, Kellgren-Lawrence grade; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index
* The 95% CIs for the difference of proportions are calculated using normal approximation.
‡ Note: The Max KL Grade at Screening is based on the *MAXKLGRD* variable in the integrated dataset adsl.xpt in the ISS Joint Safety Pool provided by the Applicant, representing the max KL grade of any joints.

Comment About Applicant's Assessment of Subgroup Analyses for CJSE

In the Integrated Summary of Safety for Studies 1056, 1057, and 1058, the Applicant posited that subjects with less severe disease at baseline may be less likely to experience treatment-emergent CJSE. This hypothesis appears to be based on the baseline WOMAC Pain subscale: subjects with worse baseline WOMAC (≥ 7) experienced more CJSE events than subjects with lower baseline WOMAC scores (<7). However, the difference was numerically small, and subjects with baseline WOMAC <7 still observed significantly more CJSE in the tanezumab arms than on placebo (studies 1056 and 1057) or NSAIDs (1058). This pattern was not replicated based on a

different measure of severity, the maximum KL grade at screening. In Study 1058, the incidence of CJSE in subjects with KL Grade 2 of any joint at baseline (0.8% in the NSAIDs treatment group and 4% in the tanezumab treatment group) was similar to patients with KL Grade 4 (0.8% in the NSAIDs treatment group and 4.3% in the tanezumab treatment group). Patients with KL Grade 3 at baseline observed a higher incidence of CJSE than patients with either KL Grade 2 or 4 (2.2% in the NSAIDs treatment group and 6.8% in the tanezumab treatment group) (Table 25). In summary, we found no strong evidence to suggest that patients with less advanced disease at baseline may be at lower risk of treatment-related CJSE.

Furthermore, it is important to note that 33 of the adjudicated CJSE occurred in radiographically healthy joints. No CJSE in KLG 0/1 joints occurred in Study 1056. Four CJSE in KLG 0/1 joints occurred in Study 1057, two in patients who received tanezumab 2.5 mg and two in patients who received tanezumab 5 mg. Twenty-nine CJSE in KLG 0/1 joints occurred in Study 1058, two in patients who received naproxen, eight in patients who received tanezumab 2.5 mg, and 19 in patients who received tanezumab 5 mg.

Table 26 shows a clear, dose-dependent imbalance in CJSE in KL 0-1 joints in Study 1058.

Table 26. CJSE in Joints With Baseline KLG 0/1 (Study 1058)

	NSAIDs (N=996)	Tan 2.5 mg (N=1002)	Tan 5 mg (N=998)
CJSE in any joint, n (%)	15 (1.5)	39 (3.9)	72 (7.2)
CJSE in KLG 0/1 joint, n (%)	2 (0.2)	8 (0.8)	19 (1.9)
RPOA1	1	9	14
RPOA2			3
SIF	1		2
ON		1	2

Source: Created by clinical reviewer Anjelina Pokrovnichka using data provided in response to information request submitted on May 13, 2020
Abbreviations: CJSE, Composite Joint Safety Endpoint; KLG, Kellgren-Lawrence grade; NSAIDs, nonsteroidal anti-inflammatory drugs; Tan, tanezumab; RPOA, rapidly progressing osteoarthritis; SIF, subchondral insufficiency fracture; ON, osteonecrosis

Key Conclusions: CJSE Risk

For the purposes of brevity, for conclusions not supported in preceding data presentations, a brief description of the data informing the decision follow the conclusion. Again, further detail and an assessment of lower priority issues related to joint destruction are contained in Appendix 9.11.

- Compared to NSAIDs, the risk for developing a CJSE is 2.4 (95% CI: [1.0, 3.8]) excessive events per 100 PY (NNH=43 per year) with tanezumab 2.5 mg, and 5.8 (95% CI: [4.0, 7.6]) excessive events per 100 PY (NNH=17 per year) with tanezumab 5 mg.
- Compared to placebo, the risk for developing a CJSE is 2.4 (95% CI: [1.0, 4.4]) excessive events per 100 PY (NNH=41 per year) with tanezumab 2.5 mg, 0.6 (95% CI: [-0.5, 3.4]) excessive events per 100 PY (NNH=162 per year) with tanezumab 2.5/5 mg, and 4.6 (95% CI: [2.4, 8.0]) excessive events per 100 PY (NNH=22 per year).
- The time-to-event analysis also shows a higher relative risk of CJSE with tanezumab compared to NSAIDs: the estimated hazard ratios are 2.6 (95% CI: [1.4, 4.7]) and 5.0 (95% CI: [2.9, 8.8]) with tanezumab 2.5 mg and 5 mg, respectively. As there was no CJSE in the placebo group, the hazard ratios relative to placebo were not estimable.

- The trajectory of incidence of joint events in patients with more than one year of treatment is unknown. Most of the joint safety events were detected towards the end of the treatment and during the follow-up period after the cessation of treatment. As there was no evidence that the risk plateaus, it is unknown whether the rates and risk will accelerate or plateau with continued dosing past one year.
- RPOA1was the most common type of adjudicated event across the NSAIDs and tanezumab treatment groups (67% to 71% of all adjudicated events). The incidence of RPOA1 was two to four times higher in patients treated with tanezumab compared to patients treated with NSAIDs.
- Processes that present with bone destruction/collapse, such as osteonecrosis (ON) and RPOA2, occurred exclusively in patients treated with tanezumab.
- Tanezumab can target healthy joints. Of the 33 CJSE that occurred in joints with baseline KL Grade scores of 0 or 1, 31 were in tanezumab-treated patients and only two in naproxen-treated patients. All events of advanced destruction (RPOA2 and ON) that developed in healthy joints (n=6) were in patients treated with tanezumab.
- No risk factors for CJSE were identified.
- Data from pre-2015 studies demonstrate that the risk for developing joint destruction is 2- to 3-fold higher if NSAIDs and tanezumab are used concomitantly.
- Data from the pre-2015 OA and CLBP studies support the above conclusions.

4.7.3. Tanezumab Is Associated With a Risk of Abnormal Peripheral Sensation

Given the function of NGF in the body, some sort of an effect upon nerve function was anticipated. At the time of the 2012 Advisory Committee Meeting, this signal had been identified as a class effect for the anti-NGF agents, and available data were presented.

Abnormal peripheral sensation was an identified risk early in development and was designated as an adverse event of special interest. Thus, the submission contains appropriate summary statistics to characterize this risk. In all Phase 3 tanezumab studies, peripheral neurological safety was monitored and evaluated through assessment of AEs, neurological examinations by investigators with a Neuropathy Impairment Score collected at baseline and each clinic visit, and by referring patients for neurological consultation if they met pre-specified criteria. In post-2015 studies, neurologic consultation was required if the AEs or neurologic examination changes were reported as 1) a SAE or 2) an AE which has resulted in the patient being withdrawn from the study, or 3) an AE ongoing at the end of the patient's participation in the study, or 4) an AE of severe intensity (for pre-2015 studies, refer to Appendix 9.9). Study 1026 was a randomized, double-blind, placebo-controlled neurological safety study that also included nerve conduction velocity testing.

Summary data show that tanezumab is associated with an imbalance in AEs related to abnormal peripheral sensation. The most common events were hypoesthesia, paresthesia, and carpal tunnel syndrome. Neuropathy Impairment Scores showed that patients were similar at baseline across treatment groups. Most of the AEs of APS were mild-to-moderate in severity (>70% mild and <3.8% severe). For most of the patients, the APS events resolved.

Table 27. Frequency of TEAEs of Abnormal Peripheral Sensation During the Treatment Period in Placebo-Controlled OA Studies

	SC study pool			
	Placebo N=586	Tan 2.5 mg N=602	Tan 5 mg N=347	Tan 10 mg N=86
Subjects (%) with APS events	12 (2.0%)	29 (4.8%)	20 (5.8%)	11 (12.8%)
	IV study pool			
	Placebo N=1029	Tan 2.5 mg N=327	Tan 5 mg N=977	Tan 10 mg N=1056
Subjects (%) with APS events	33 (3.2%)	30 (9.2%)	85 (8.7%)	132 (12.5%)

Source: Prepared by Anjelina Pokrovnichka using data from Applicant's Table 4.1.1.c and Table 4.1.1.b, from Appendix Tables 2 – Neurological Safety
Abbreviations: TEAEs, treatment-emergent adverse events; OA, osteoarthritis; Tan, tanezumab; APS, abnormal peripheral sensation; SC, subcutaneous; IV, intravenous
SC placebo-controlled pool includes: 1027, 1056, and 1057 studies
IV placebo-controlled pool includes: 1011, 1014, 1015, 1018, 1026, 1027, 1030 studies
Excludes events of sciatica.

Table 28. Frequency of TEAEs of Abnormal Peripheral Sensation During the Treatment Period in Active-Controlled OA Studies

	SC study pool			
	NSAIDs N=996	Tan 2.5 mg **N=1002**	Tan 5 mg **N=998**	
Subjects (%) with APS events	42 (4.2%)	**59 (5.9%)**	85 (8.5%)	**-**
	IV study pool			
	NSAIDs N=691		Tan 5 mg N=541	Tan 10 mg N=542
Subjects (%) with APS events	48 (6.9%)	-	77 (14.2%)	95 (17.5%)

Source: Prepared by Anjelina Pokrovnichka using data from Applicant's Table 4.1.1.m and Table 4.1.1.l, from Appendix Tables 2 – Neurological Safety
Abbreviations: TEAEs, treatment-emergent adverse events; OA, osteoarthritis; Tan, tanezumab; APS, abnormal peripheral sensation; SC, subcutaneous; IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs
SC active-controlled pool includes: 1058 study
IV active-controlled pool includes: 1017 and 1025 studies
Excludes events of sciatica.

Congruent with the AE data, patients treated with tanezumab required neurology consultation more often than comparator groups. The most common diagnoses were mononeuropathy (carpal tunnel syndrome) followed by polyneuropathy.

Study 1026 was terminated early due to the clinical hold although >70 patients per group were dosed. No meaningful differences in sensory-motor nerve conduction were observed.

Key Conclusion

Tanezumab carries a risk of abnormal peripheral sensation characterized as (predominantly) mild, self-limited mononeuropathy, with the most common manifestation being carpal tunnel syndrome. Data from the pre-2015 OA and CLBP studies support this conclusion.

4.7.4. The Risk Mitigation Measures Proposed Are Likely Unfeasible and No Data Exist to Support the Effectiveness of Risk Mitigation Measures Proposed

The Applicant has proposed to market tanezumab under a Risk Evaluation and Mitigation Strategy (REMS) that includes elements to assure safe use (ETASU) that would include restricted distribution. The proposed clinical risk mitigation measures include 1. Patient counseling on the risk of joint destruction and to avoid the use of NSAIDs, 2. Bilateral X-rays of knees and hips within two months of the first dose, 3. Conduct of bilateral X-rays of knees and hips annually, 4. Monitoring the patient for pain of rapidly progressive OA, and 5. Unenrolling the patient from the REMS if they develop RPOA. The review team assessed whether or not these risk mitigation strategies under the proposed REMS or any additional risk mitigation strategies would likely mitigate the risks of joint destruction to result a favorable benefit-risk relationship.

The tanezumab development program potentially contains a natural experiment (there is a set of studies with risk mitigation measures and a set without) to inform the degree of risk mitigation achieved. The pre-2015 studies were designed and conducted prior to the identification of the joint safety signal. Thus, they largely contain standard clinical trial risk mitigation measures. Following the 2012 Advisory Committee meeting, substantial risk mitigation measures were added to studies, as described in Section 4.7. Thus, on face, a comparison of the rates of CJSE and TJR could be conducted to assess whether the post-2015 conditions had their desired effect.

After careful consideration, it is not possible to compare the two sets of data to assess the effectiveness of the risk mitigation measures for the following reasons:

- In general, the pre-2015 studies used higher doses and included the IV route, which resulted in higher tanezumab exposures. This would tend to bias the assessment towards concluding that the risk mitigation measures are effective.
- The definition of RPOA1 changed, and the Applicant introduced the blinded Central Reader and blinded Adjudication Committee. Because the threshold of decrease in JSW increased from 1mm to 2mm, this biases against detecting a joint event.
- Surveillance for joint events was higher in the latter studies, favoring detection of more events.
- Excepting pre-2015 Study 1025, patients were treated for longer durations in the post-2015 studies, increasing the likelihood of experiencing an event.
- As shown in Section 9 under discussion of joint safety, there is substantial latency to a joint event, and joint events can occur long after drug discontinuation. The follow-up in the pre-2015 studies was only 8 weeks, compared to 24 weeks in the post-2015 studies. This increases the likelihood of detecting a joint event.

The plain radiography surveillance scheme is unlikely to be feasible. As noted in Appendix 9.11 of this review, there were a substantial number of disagreements between experts recruited by Pfizer to assess surveillance radiographs. Those radiographs were performed and interpreted under optimal conditions. Under real-world conditions, measuring JSW and comparing to the prior study and detecting changes in the range of fractions of millimeters does not appear feasible.

Dr. Hofling (DIRM) concurred regarding the feasibility of the proposed surveillance scheme. He wrote:

Reliable monitoring of joint space narrowing on radiographs, particularly in any quantitative fashion, will likely be very challenging in practice. Although patient positioning and radiographic techniques are standardized to a degree, even qualitative comparison of serial radiographs is often limited by variability in these technical factors. Availability of the prior imaging studies required for comparison often also presents a challenge since patients frequently use different imaging practices over time. Furthermore, variability in image interpretation factors such as measurement technique will likely limit consistent monitoring among a large population of radiologists with heterogeneous training background and practice experience.

Key Conclusions

The available data do not inform whether the risk mitigation measures used in the post-2015 studies and those proposed in the REMS reduce the risk of joint destruction. As described in Appendix 9.11, while discontinuing drug after RPOA1 might arrest the destructive process, there are inadequate data to inform whether that assumption is true. The entire risk management scheme assumes that detection of RPOA1 and discontinuing drug substantially affects outcome.

Next, the required precision and consistency of the medical imaging and interpretation is not feasible in practice. Thus, there is no reason to believe that a tanezumab REMS will affect the benefit-risk relationship.

Last, as discussed in Appendix 9.11, MRI likely represents a superior imaging modality, although the feasibility of surveillance MRI to safely administer tanezumab may also be unfeasible in practice. Dr. Hofling wrote:

Because most MRIs were unread in Study 1058, the performance of radiographs as a screening tool cannot be accurately estimated. From a practical perspective, radiographs are almost certain to be less sensitive than MRI for the imaging findings associated with the CJSE, particularly for the hallmark cartilage loss of RPAO1. Given the additional reliability concerns noted…it seems unlikely that radiographs would act as an adequate screening test, particularly for early disease that clinically may matter most. While MRI surveillance would be superior to radiographs, it would be hindered by practicality… Annual MRIs are performed in practice in some clinical contexts including surveillance and follow up of certain cancers. For example, some guidelines recommend annual breast MRI to supplement mammographic screening of certain patients who are considered at high risk. The feasibility of annual MRI becomes more questionable when multiple anatomic areas must be evaluated, as is likely the case with patients on tanezumab. While new scanners and techniques are being developed to allow more rapid MRI surveys over extended fields of view, such technology is not widely available in practice. While abbreviated exams with limited screening sequences might be considered, it seems unlikely that they would allow accurate detection of only millimeters of cartilage loss. Thus, MRI of the shoulders, hips, and knees bilaterally would typically require six independent studies with distinct fields of view that would in total require several hours of scan time. It is very likely that multiple MRI visits would be required to accommodate patient intolerance of long scanning times. Both cost and patient inconvenience seem to be significant factors that would limit the practicality of such an approach. Considering that adequate screening of patients on tanezumab

may actually require MRI more frequently than once a year, these concerns are compounded further.

4.7.5. The risk of CJSE When Tanezumab Is Administered With Chronic NSAID Therapy Is Unacceptably High – Labeling Implications

The pre-2015 data (specifically Study 1025) showed that the rates of joint safety events were roughly doubled when tanezumab was co-administered with NSAIDs.

As will be shown in the assessment below, because of the utility of NSAIDs in the management of OA pain, this drug interaction is important to understand for labeling.

Table 29 shows the incidence of certain joint safety events in Study 1025, a pre-2015 study. Study 1025 was a randomized, double-blind, double-dummy, placebo- and active-controlled, 5-arm study in patients with OA. The study compared the following groups: tanezumab 5 mg, tanezumab 10 mg, tanezumab 5 mg + NSAID, tanezumab 10 mg +NSAID, and NSAID alone in patients with hip or knee OA. Pursuant to the clinical hold, the study was terminated prematurely, although all patients had completed dosing at the time of the clinical hold.

Table 29. Incidence of All-Cause TJR and Adjudicated on and RPOA Events in Study 1025

		Tanezumab monotherapy		Tanezumab+NSAIDs	
	NSAIDs	5 mg	10 mg	5 mg+NSAIDs	10 mg +NSAIDs
N	539	541	542	536	542
Total exposure (PYs)	416	426	415	423	416
All-cause TJR, n (%)	25 (4.6)	24 (4.4)	19 (3.5)	40 (7.5)	42 (7.8)
All-cause TJR, events /100 PY	6.0	5.6	4.6	9.5	10.1
ON, n (%)	0	0	1 (0.2)	0	0
ON, events/100 PY	0	0	0.24	0	0
RPOA 1 and 2, n (%)	1 (0.2)	4 (0.7)	7 (1.3)	9 (1.7)	13 (2.4)
RPOA 1 and 2, events/100 PY	0.24	0.94	1.7	2.1	3.1

Source: Created by Anjelina Pokrovnichka using data from Applicant's Table 94 and Table 95 from Study 1025 report body, page 283 and page 285

Abbreviations: TJR, total joint replacements; RPOA, rapidly progressing osteoarthritis; NSAIDs, nonsteroidal anti-inflammatory drugs; PYs, Person Years; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; ON, osteonecrosis

Note: This study was affected by the clinical hold. It had complete enrollment but incomplete duration. However, about 60% of the enrolled patients received 5 to 7 doses of study medication.

Because of these findings, the post-2015 studies heavily restricted NSAID use. In the BLA submission, the Applicant conducted exploratory analyses of the post-2015 studies to assess whether the small amount of NSAID use permitted affected the incidence of CJSE. Pfizer concluded that NSAID use of any duration had no effect on CJSE.

Conclusions

The findings from the Applicant's post-hoc analyses in the post-2015 studies are difficult to interpret. It is challenging to determine whether post-randomization NSAID use was associated with an increase (or decrease) in the risk of joint safety events. Because NSAID use was not a randomized treatment strategy, it is possible that subjects who required or elected to use NSAIDs during these studies experienced different symptoms and had a different risk profile than subjects who did not use NSAIDs. Therefore, analyses based on post-baseline characteristics should be interpreted as hypothesis generating only.

4.7.6. There Is a Substantial Number of Questions Left Unanswered by the Data Currently Available

Referring back to Table 1 (Questions and Answers) in the Introduction, our review of tanezumab raised a large number of questions, only some of which the available data answer. Questions considered open include:

- Were the patients enrolled in Studies 1056, 1057, and 1058 "treatment-resistant"?
- Given the safety profile of tanezumab, what patients are particularly likely to benefit from tanezumab therapy?
- Similarly, what patients are particularly susceptible to tanezumab-related joint destruction?
- What is the trajectory of joint events when tanezumab is dosed for longer than one year?
- What happens to patients after they develop RPOA1 and drug is stopped? Does the process stop? Reverse?

Dr. Hofling (DIRM) raised a similar question in his consult response. He wrote:

A critical question is whether cessation of tanezumab at the time of a concerning imaging abnormality, regardless of the modality, would halt drug-related progression of joint pathology. It seems that the available data leave this question largely unanswered. While reliable detection of concerning findings through imaging surveillance faces considerable challenges, it's unclear if such surveillance, even if successful, would mitigate the risks of tanezumab. In other words, once concerning imaging findings are present, it may already be too late to avert more serious joint pathology.

- Given that the literature suggests more surgical complications following total joint arthroplasty due to RPOA, does antecedent tanezumab predict worse TJR outcomes if TJR becomes necessary?
- Did the risk mitigation measures used, particularly imaging, improve outcomes?
- Is the proposed surveillance strategy likely to be adequate or feasible?
- How do patients consider the risks and benefits of treatment with tanezumab? See Section 4.8, immediately below.

4.8. Submitted Patient Preference Information Could Not Inform Regulatory Benefit-risk Assessment for Tanezumab

Background

The Applicant submitted a patient preference information (PPI) study and a quantitative benefit-risk analysis. The PPI study was a survey designed to estimate the relative importance of the benefits compared to the risks of tanezumab in comparison to alternative analgesics for the proposed indicated patient population. The study focused on estimating the maximum chance of severe joint problems leading to TJR that the survey respondents are willing to accept in exchange for improvements in symptom control. Of note, the PPI quantified the acceptability of tradeoffs between increments or decrements in individual outcomes, e.g., elevated 0.2% additional risk each year of heart attack from 0% against improvement from "poor" to "fair" in symptom control, not the tradeoffs between individual treatment profiles. The latter, however, could be inferred from the estimates of the former.

Stated Preference Methods

This complex PPI study (5.3.5.4 A9001505 Non-Interventional Final Study) used two different methods, discrete choice experiments (DCE) and best-worst scaling (BWS) to elicit quantitative benefit-risk tradeoff preferences among patients. Both methods belong to the same type of method called stated preference methods, which assume that the value of a drug to a patient is driven by the values of the drug's outcomes (e.g., benefits and risks) to the patient. In other words, these methods first breakdown a drug into its benefits and risks and then calculate the value of the drug to a patient by summing up how much the patient values the drug's individual benefits and risks. Further, these methods can use the same scale to measure the values of the drug's benefits and risks to the patient. For example, values of both benefits and risks can be measured in the same scale of how much additional risk of heart attack that patient is willing to tolerate in exchange for an increment in a benefit or a decrement in a risk. By including multiple drugs' benefits and risks in the same study, these methods can convert a complex choice problem of weighing the tradeoffs between benefits and risks of multiple drugs into a matter of comparing the values of these drugs' benefits and risks on the same scale.

To supplement a medical product's well-defined and reliable outcome measurements generated by clinical trials, PPI methods can be used to quantitatively measure the relative values of these outcomes to patients, the end-users of these products. These methods often characterize a medical product in terms of its benefit-risk profile, or a set of outcomes called *attributes* (e.g., benefits, harms, uncertainties, and treatment burdens on patients). Each attribute has a set of *levels* (e.g., 30% pain relief from baseline or injection every 4 weeks). If multiple products share the same benefit-risk profile, then patients would be indifferent between them. Therefore, a complex choice problem of comparing the benefit-risk outcomes of different treatment options can be broken down into smaller components of attributes or attribute levels.

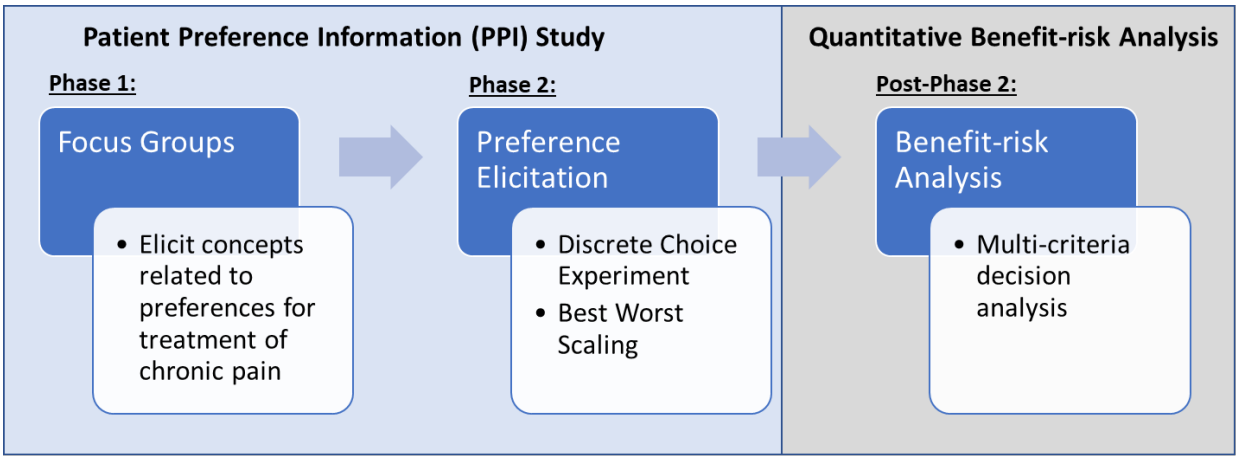
PPI methods allow for the estimation of *preference weight* (PW) which is an unit-free numeric value that represents the relative importance of these individual components (i.e., attribute levels).

Aggregating the PWs of each treatment option based on the option's own profile of attribute levels allow us to predict which option respondents would prefer the most (i.e. the option with the highest aggregated PWs) and to quantify the relative importance of individual components behind respondents' choices. Further details on the interpretation of the PWs are included in the section Data Analysis section.

Overall Schematic for PPI Study in BLA 761130

Figure 9 shows the overall schematic of the PPI study conducted by the Applicant, followed by their quantitative benefit-risk analysis (qBRA). The PPI study comprised two phases. In Phase 1 ("Focus Groups"), the Applicant conducted focus groups to collect qualitative information on concepts relevant to treatment preferences in chronic pain. In Phase 2 ("Preference Elicitation"), the Applicant used two stated preference methods, DCE, and Best-Worst Scaling (BWS), to quantify the preferences for specific benefits and risks of OA treatment, and to quantify the trade-offs between benefits and risks that the study respondents were willing to make. Results from the PPI study were used as input parameters to a subsequent qBRA using a method called multi-criteria decision analysis. As a result, the results and interpretations from the qBRA are highly dependent on the results of the PPI study.

Figure 9. Overall Schematic



The submission included data not relevant to the proposed indication, and thus the review focused on the relevant parts only, including:

- US study results only, i.e. exclusive of results from UK
- Data from respondents who self-reported presence of OA or OA and CLBP i.e., exclusive of any data of respondents who self-reported presence of CLBP only (data submitted on June 25, 2020 information request)
- Marginal rates of substitutions between benefit, risks, and administration mode and frequency, i.e., exclusive of analyses involving monthly out-of-pocket cost

In general, the PPI study and the subsequent qBRA followed good research practices in their design and conduct. However, the applicability of the qBRA conclusions is dependent on the results of

the PPI Study. We identified several key deficiencies in the PPI study, and that rendered the subsequent qBRA inapplicable for the Agency's consideration. Therefore, the review here focuses on the PPI study only.

4.8.1. Study Design

Phase 1: Focus Groups

Four focus groups (6 – 8 participants each) were conducted to select attributes of treatments for moderate-to-severe OA and CLBP. The recruited focus group participants were adults who self-reported as having OA or CLBP and met the following inclusion and exclusion criteria:

- Have a self-reported physician diagnosis of hip or knee OA and/or CLBP
- Aged 18 years or older
- Self-report moderate-to-severe chronic pain in the hip, knee, and/or low back for ≥ 3 months
- Self-report an average pain intensity of 5 or higher on a 0-to-10 NRS over the past week
- Self-report previous use of three or more pain medication classes for their OA or CLBP
- Be able to read and understand English to provide informed consent
- Without neuropathic pain, radiculopathy/sciatica, fibromyalgia, rheumatoid arthritis, spinal stenosis, spondyloarthropathy, myopathy, major depressive disorder, and Alzheimer's disease

The following subgroups were targeted for the four focus groups:

- Three groups (up to 24 patients in total) must have tried or still be taking an opioid (as one of the 3 pain medication classes) in the past 2 years.
  - Each group targeted a mix of participants who had taken immediate or extended release (ER) opioids.
- One group, including both participants with OA and CLBP, required all participants to be opioid naïve (i.e., not currently on and had never taken an opioid pain medication).
- Target a minimum of 4 chronic users of NSAIDs.

Six categories of treatment attributes were identified by the Applicant as being particularly important to participants in the focus groups. These were (1) efficacy, (2) side effects (both opioid and nonopioid), (3) out-of-pocket cost or insurance coverage of the medication, (4) risk of addiction/dependence, (5) frequency of administration, and (6) mode of administration. These were used to develop the attributes for the DCE.

Phase 2: Preference Elicitation

The Applicant assessed preferences using two preference elicitation methods, DCE and BWS, to measure how respondents weighed the benefits and risks of tanezumab against alternative analgesics. An online survey that included eight DCE questions, ten BWS questions, demographic questions and the Multidimensional Health Locus of Control Scale – Form C was implemented.

The survey instrument was pretested among 15 participants via face-to-face interviews before finalization and implementation.

Figure 10 and Figure 11 show examples of the DCE and BWS questions used in the online survey.

4.8.2. Discrete Choice Experiment (DCE)

The DCE is a common approach used in healthcare research to elicit preferences for treatment characteristics (i.e., attributes) and the willingness to accept trade-offs among these attributes. Figure 10 shows an example of DCE formatted "choice question," which is a pairwise comparison in this study. Respondents were presented with a series of eight "choice questions" and they chose a preferred alternative among the presented pair of benefit-risk profiles of hypothetical treatments. These treatment profiles were characterized by a set of attributes (e.g., benefit– "symptom control" and risk– "risk of physical dependence") with levels (i.e. different values an attribute can take, say "good" or "very good" of the attribute Symptom Control) that varied by a prespecified experimental design. The experimental design was constructed using a D-optimal algorithm that determines the combination of levels used to define each profile, the set of profiles in each choice question, and the full set of choice questions in the DCE.

Figure 10. Example of Discrete Choice Experiment Question

Medicine Feature	Medicine A	Medicine B
Symptom control: Symptom control while you are taking the medicine	**GOOD** mild symptoms; no limitations on normal activities	**VERY GOOD** no symptoms; no limitations on normal activities
Additional risk of severe joint problems: Additional risk each year of having joint problems that are severe enough that you would need a total joint replacement while you are taking the medicine or within 6 months of stopping the medicine	 40 people out of 1,000 (4%)	 5 people out of 1,000 (0.5%)
Additional risk of heart attack: Additional risk each year of having a heart attack while you are taking the medicine	 5 people out of 1,000 (0.5%)	 No additional risk (0%)
Risk of physical dependence: Risk each year of becoming physically dependent on the medicine	 250 out of 1,000 people (25%)	 50 people out of 1,000 (5%)
How you take the medicine	 Oral pills once a day	 Injection every 8 weeks (about every 2 months)
Cost: Personal cost of the medicine to you every month	$0 every month	$30 every month
Which medicine would you choose if these were the only two medicines available?	☐	☐

Source: 5.3.5.4 A9001505 Non-Interventional Final Study Report Appendix 10 Survey Instrument Figure A4-1

Table 30 presents the attributes, attribute label (i.e. patient-friendly description of the attributes in the DCE choice questions) and the attribute levels of the DCE survey instrument.

Table 30. Attributes and Levels Included in the Discrete-Choice Experiment

Attribute	Patient-facing attribute label	Patient-facing attribute levels
Symptom control (patient global assessment)	Symptom control: Symptom control while you are taking the medicine	Very good (no symptoms; no limitations on normal activities)
		Good (mild symptoms; no limitations no normal activities)
		Fair (moderate symptoms; limitations on some normal activities)
		Poor (severe symptoms; unable to carry out most normal activities)
Incremental treatment-related risk of severe rapidly progressive joint problems requiring total joint replacement	Additional risk of severe joint problems: Additional risk each year of having joint problems that are severe enough that you would need a total joint replacement while you are taking the medicine or within 6 months of stopping the medicine	No additional risk (0%)
		5 people out of 1,000 (0.5%)
		40 people out of 1,000 (4%)
Risk of heart attack	Additional risk of heart attack: Additional risk each year of a heart attack while you are taking the medicine	No additional risk (0%)
		2 people out of 1,000 (0.2%)
		5 people out of 1,000 (0.5%)
Risk of physical dependence	Risk of physical dependence: Risk each year of becoming physically dependent on the medicine	No risk (0%)
		50 people out of 1,000 (5%)
		250 people out of 1,000 (25%)
Mode and frequency of administration	How you take the medicine	Oral pills 2 or more times a day
		Oral pills once a day
		Injection every 4 weeks
		Injection every 8 weeks

Source: 5.3.5.4 A9001505 Final Study Report §8.1.2 p.29 Table 3
Note: This table excludes monthly personal out of pocket cost, which is irrelevant in this regulatory context.

The Applicant stated that these attributes and levels were selected "based on observations from the qualitative interviews, knowledge of the tanezumab clinical development program, and an understanding of the characteristics of NSAID and opioid treatments for OA pain and CLBP." Of note, the attributes did not include NSAID's major side effect of gastrointestinal risks, which was studied in the Best-Worst Scaling format.

4.8.3. Best-Worst Scaling (BWS)

Given sample size limitations, a DCE can only accommodate a number of attributes that are cognitively feasible for an average respondent to consider simultaneously. The Applicant included the six primary attributes in the DCE. However, other relevant risks could not be captured in the DCE because of the limit on the number of attributes. To capture the other relevant risks, the Applicant used the case 1 BWS method to elicit the relative importance of these risks. The DCE method can elicit a higher 'resolution' of preference data, yielding an estimate of preference weight for an attribute level, while the case 1 BWS method can elicit the difference between the lowest and the highest levels in preference weight for each attribute as a whole.

For this BWS, the Applicant selected 10 risk attributes called *items*, "based on existing, publicly available clinical data" and these 10 items are as follows:

1. 10% (100 out of 1,000) risk of moderate-to-severe constipation while taking a medicine
2. 10% (100 out of 1,000) risk of feeling foggy and drowsy while taking a medicine
3. 1% (10 out of 1,000) risk of having a bleeding stomach ulcer when first starting a medicine
4. 10% (100 out of 1,000) risk of mild-to-moderate nausea and vomiting while taking a medicine
5. 0.5% (5 out of 1,000) risk each year of having a heart attack because of a medicine
6. 4% (40 out of 1,000) risk each year of severe joint problems because of a medicine
7. 25% (250 out of 1,000) risk each year of becoming physically dependent on a prescription pain medicine
8. 6% (60 out of 1,000) risk of having a tingling or burning sensation in the fingers or toes while taking a medicine
9. 5% (50 out of 1,000) risk of mild-to-moderate swelling in the ankles and feet while taking a medicine
10. 0.6% (6 out of 1,000) risk each year of having a moderate stroke because of a medicine

Figure 11. Example of Best Worst Scaling Question

This is the MOST important risk to avoid **(Check only ONE)**	**Side-Effect Risk**	**This is the LEAST important risk to avoid** **(Check only ONE)**
☐	**0.5% (5 out of 1,000) risk each year of having a heart attack** because of a medicine	☐
☐	**10% (100 out of 1,000) risk of mild-to-moderate nausea and vomiting** while taking a medicine	☐
☐	**10% (100 out of 1,000) risk of moderate-to-severe constipation** while taking a medicine	☐

Source: 5.3.5.4 A9001505 Non-Interventional Final Study Report Appendix 10 Survey Instrument Figure A5-1

Figure 11 shows an example of a BWS question. In each question, a subset of three out of the ten items were shown, and respondents picked the most and least important risks. The particular combination of items shown in each question followed a prespecified experimental design. Unlike aforementioned DCE questions, in this case 1 BWS approach, each item has a fixed level which does not vary across questions, e.g., 0.5% risk each year of having a heart attack because of a medicine. The only thing that varies across questions is the 3 items shown in each question. This approach is appropriate when the objective is the relative desirability of discrete options and not to examine trade-offs among the multiple levels of attributes.

Three of the items included in the BWS also corresponded to the DCE and these serve as linking attributes to allow for comparison of results obtained by both methods. The three linking attributes

are: 4% risk of severe joint problems, 25% risk of physical dependence and 0.5% risk of heart attack.

4.8.4. Survey Instrument Pretest

The Applicant conducted 15 face-to-face interviews with participants who had a self-reported physician diagnosis of hip or knee OA and/or CLBP. Key inclusion and exclusion criteria were as followed: (1) age 18 years or older; (2) had a self-reported physician diagnosis of hip or knee OA only, CLBP only, or concurrent OA and CLBP diagnosed at least 3 months ago; (3) had self-reported moderate-to-severe pain in the hip, knee, or lower back, defined as a self-assessed pain score of 4 or greater on average in the past week on an 11-point numeric rating scale ranging from 0 (no pain) to 10 (worst possible pain); (4) had taken or tried three or more classes of pain treatment in the past 2 years or had taken or tried two prior classes of pain treatment, either excluding NSAIDs due to NSAID contraindication or excluding opioids due to the respondent's unwillingness to take opioids, or had one prior class of pain treatment excluding NSAIDs due to NSAID contraindication and excluding opioids due to the respondents' unwillingness to take opioids

During the pretest, participants were cognitively debriefed on the on the draft survey instrument. Cognitive debriefing allows participants who represent the final study population to review the survey and are asked if they understand what the survey is asking and if any topics are missing from the survey. For this PPI study, interviewers asked the participants to think aloud while they completed the draft survey instrument. With the first 5 participants on the first day, the interviewers explored their general reactions to the draft survey instrument and then revised the survey instrument accordingly. The Applicant repeated the process with the remaining 10 participants to ensure that the survey instrument was performing as intended. Based on the results from the pretest, the minimum pain rating requirement of the final PPI study ("moderate-to-severe pain on average in the past week") was changed from a pain score of 4 or greater to pain score of 5 or greater on an 11-point numeric pain scale ranging from 0 (no pain) to 10 (worst possible pain).

4.8.5. Sample Size for PPI Study

The original sample size was a total of 450 respondents, with 150 respondents for each subgroup (OA only, CLBP only, concurrent OA and CLBP). However, the final online survey instrument was administered to 602 respondents in the US. 152 additional respondents were recruited to compensate for a randomization assignment error: the versions of the survey that included the wide range of cost levels for the scope test in the DCE were not assigned to respondents. Of the 602 respondents, 202 self-reported with CLBP only and were excluded from this review as it does not reflect the proposed indication population. This yielded the final study sample of 400 respondents (201 with OA only, and 199 with OA and CLBP) for the DCE.

4.8.6. Experimental Design

The Applicant used a D-optimal algorithm to construct a fractional factorial experimental design for estimation of main effects in a random parameter logit model for the DCE. This experimental design determines the combination of levels used to define each profile, the set of profiles in each DCE choice question, and the full set of choice questions in the DCE. There is a limit to the number of choice questions each respondent can reasonably answer before becoming fatigued. Therefore, the experimental design was split into a number of blocks of questions. Respondents were randomly assigned to a block of 8 questions with 2 stratification factors: condition (OA, CLBP, or concurrent OA and CLBP) and opioid experience (yes or no).

For the BWS formatted questions, the Applicant used 9 blocks of 10 questions, where each question comprised 3 risk items. Respondent were randomly assigned to one of these 9 blocks with 2 stratification factors: condition (OA, CLBP, or concurrent OA and CLBP) and opioid experience (yes or no).

4.8.7. Study Sample

Key inclusion and exclusion criteria for the full study follows:

- Have a self-reported physician diagnosis of hip or knee OA only, CLBP only, or concurrent OA and CLBP received at least 3 months ago.
- Have self-reported moderate-to-severe pain in the hip or knee, and/or lower back, defined as a pain score 5 or greater on average in the past week on an 11-point numeric rating scale ranging from 0 (no pain) to 10 (worst possible pain). For respondents with concurrent OA pain and CLBP, a self-assessed pain rating of 5 or greater was required for only OA pain or CLBP pain.
- Have taken or tried three or more classes of pain treatment in the past 2 years; or two prior classes of pain treatment, either excluding NSAIDs due to NSAID contraindication or excluding opioids due to the respondent’ s unwillingness to take opioids; or one prior class of pain treatment excluding NSAIDs due to NSAID contraindication and excluding opioids due to the respondents’ unwillingness to take opioids.
- Without a self-reported diagnosis of Alzheimer’s disease, axial spondyloarthritis, fibromyalgia, major depressive disorder, migraine headaches, myopathy, neuropathic pain, psoriatic arthritis, radiculopathy or sciatica, rheumatoid arthritis, spinal stenosis, or spondyloarthropathy or if they had experienced pain as a result of having had surgery in the past 3 months.

4.8.8. Data Analysis

4.8.8.1. Discrete Choice Experiment

Random parameter logit (RPL) models were used to analyze the responses to the DCE questions. The RPL estimates a preference weight (PW) is for each attribute level in the DCE.

The following RPL main-effect model was used to analyze the DCE data:

$V = \beta_{EFF1} \times EFF1 + \beta_{EFF2} \times EFF2 + \beta_{EFF3} \times EFF3 + \beta_{JOINT1} \times JOINT1 + \beta_{JOINT2} \times JOINT2 + \beta_{HEART1} \times HEART1 + \beta_{HEART2} \times HEART2 + \beta_{ADD1} \times ADD1 + \beta_{ADD2} \times ADD2 + \beta_{MODE1} \times MODE1 + \beta_{MODE2} \times MODE2 + \beta_{MODE3} \times MODE3 + \beta_{Cost} \times COST*\ln(income)$, where V denotes the indirect utility, EFF1/2/3 denotes the effect-coded variables for various levels of symptom control attribute, JOINT1/2 denotes the effect-coded variables for various the risk levels of developing severe joint problems, HEART1/2 denotes the effect-coded variables for various the risk levels of heart attack, ADD1/2 denotes the effect-coded variables for various the risk levels of developing physical dependence on opioid, MODE1/2/3 the effect-coded variables for various denotes various modes of administration (frequency and route), and COST denotes various levels of out-of-pocket costs. The *preference weight* of an attribute level is the log odds of its corresponding β (e.g., log odds of β_{EFF1} is the *preference weight* of the attribute level EFF1).

The PW of an attribute level can also be interpreted as a unit-less scale that measures the relative value of the attribute level to other attribute levels of the study. The greater the PW of an attribute level is, the more appealing the level is to the respondents. In other words, respondents would be more likely to choose an option with that level than another option with a level with a lower PW.

The magnitude of change in PWs between attribute levels also represents the relative impact of level changes on preferences. This means that if the change in PWs between poor and fair symptom control is greater than the change between good and very good symptom control, it implies that respondents are more likely to prefer a treatment that can improve symptoms from poor to fair, compared to a treatment that improves symptoms from good to very good. Similarly, if the change in PWs from no risk of TJR to 4% risk of TJR is greater than the change in PWs from no risk of heart-attack to 0.5% risk of heart attack, it means that respondents are more likely to prefer a 4% reduction in risk of TJR over a reduction of 0.5% risk of heart attack.

Maximum acceptable risk (MAR) for a given amount of benefit improvement were computed. This is done by calculating the increase in PW for a given change in one attribute that could be offset by the reduction in PW from a change in in another attribute. The MAR represents the risks that respondents in the study sample were willing to tolerate in return for an improvement in benefit. Specifically, the Applicant presented their estimated MAR of treatment-related severe rapidly progressive joint problems requiring TJR, heart attack and physical dependency that respondents were willing to tolerate in return for different improvements in symptom control (e.g., Poor → Fair, Fair → Good, etc.), and mode and frequency of administration (e.g., Injection every 4 weeks → Oral Pills 2 or more times a day)

4.8.8.2. Best-Worst Scaling

The Applicant also used a RPL model to analyze the BWS data. The Applicant used a probability-based rescaling procedure to transform the estimated coefficients into relative importance weights of the attributes: The estimated coefficient of each item was divided by the estimated coefficient of one fixed reference item multiplied by 10. Thus, the reference item has a scaled relative importance weight of 10, and the scaled relative importance of the other items in the study are measured with respect to this reference item. These relative importance weights allow for a ranking of the respondents' preferences for the 10 risk items included in the BWS, where the reference item is deemed the most important with the highest weight of 10.

4.8.8.3. Subgroup Analysis

The Applicant conducted a subgroup analysis by estimating interaction models for mutually exclusive pairs of subgroups in the study sample and testing for systematic differences in preferences between each subgroup pair. A chi-square test of the joint significance of the interaction terms indicated whether preferences between the groups were systematically different. The analysis included the key subgroups indicated in Table 31.

Table 31. Subgroup Analysis

Subgroup Pair	Subgroup Description
Opioid experience in the last 2 years	Respondents with opioid experience
	Respondents without opioid experience
Age (younger and older than median age)	Younger than median age
	Median age or older
Time living with chronic pain (for more time and less time than the median)a	Respondents living with chronic pain for 5 years or more
	Respondents living with chronic pain for less than 5 years
Baseline pain in the past week as self-assessed on an 11-point numeric pain scale	Respondents with moderate baseline pain (ranked 5- 6)
	Respondents with severe baseline pain (ranked 7-10)
Correct answers in the comprehension questionsb	Respondents who provided incorrect responses to fewer than three comprehension questions
	Respondents who provided incorrect responses to three or more comprehension questions
Prior experience with joint replacement	Respondents who had prior joint replacement
	Respondents who did not have prior joint replacement

[a]Twelve respondents did not answer the question on time living with chronic pain and were excluded from this subgroup analysis.
[b]Seven comprehension questions were used to evaluate each respondent's understanding of the presented choice questions.
Adapted from: 5.3.5.4 A9001505 Final Study Report §9.5 p.62 Table 12.

4.8.9. Main Results From Preference Elicitation

Figure 12 summarizes the respondent disposition. 316,214 emails were sent to panel panels and 601 eligible respondents completed the survey. After excluding 202 with CLBP only, there were 400 respondents who had OA only or OA and CLBP.

Figure 12. Disposition of Study Respondents From Initial Email Invitation to Survey Completion

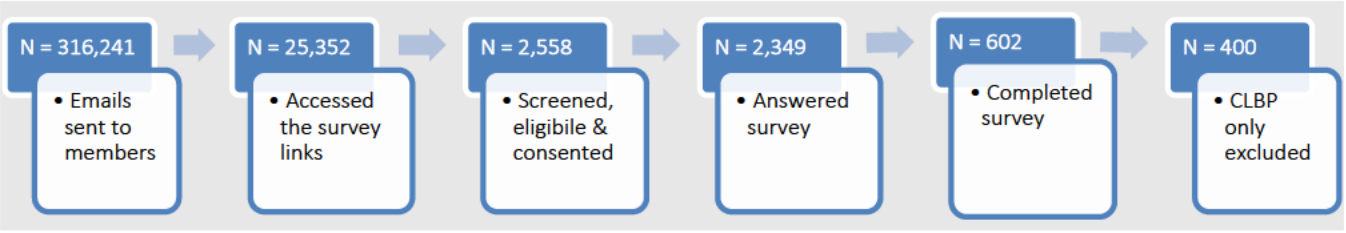


Table 32 presents the key demographics and characteristics of the study sample relevant for this application.

Table 32. Demographics of the U.S. PPI Study Respondents

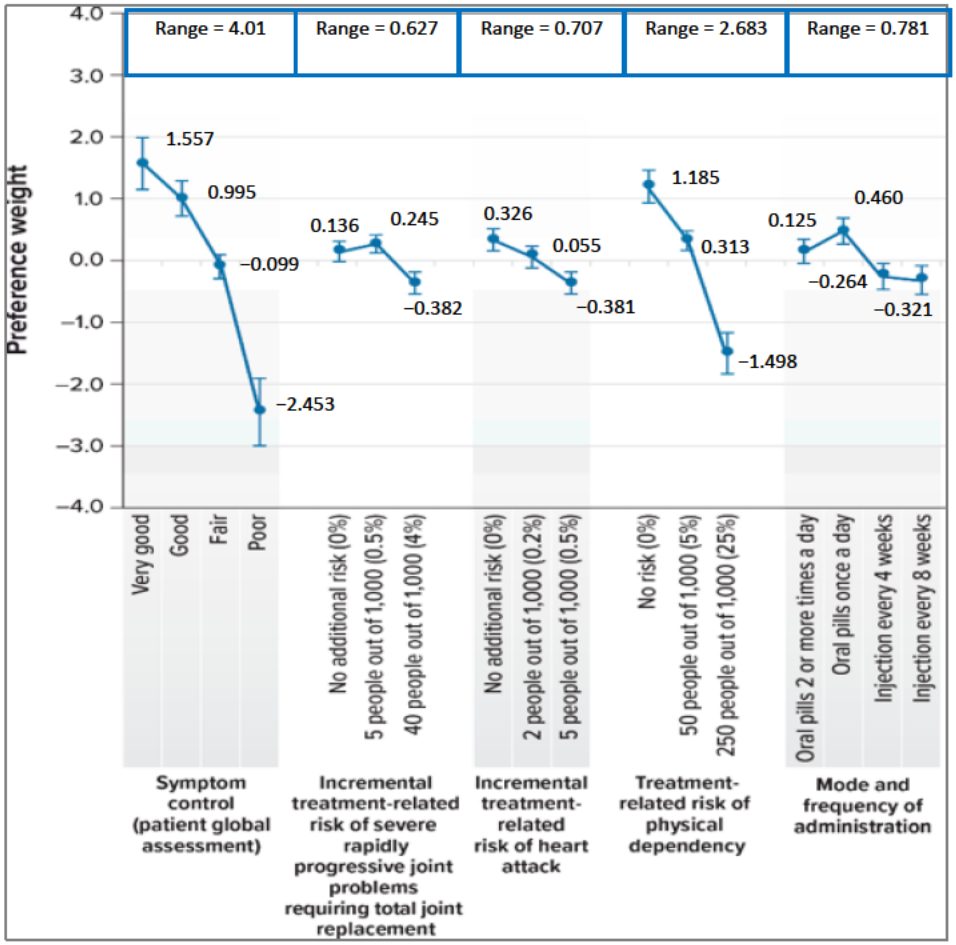
Question	Respondents with OA only (n = 201)	Respondents with OA and CLBP (n = 199)	All respondents[†] (n = 400)
B1. What is your gender?			
Male	70 (34.8%)	66 (33.2%)	136 (34.0 %)
Female	131 (65.2%)	133 (66.8%)	264 (66.0%)
S1. Age (in years)			
Mean (SD)	65.7 (8.7)	65.2 (9.5)	65.5 (9.1)
Median	66	66	66
Min, max	21, 87	25, 90	21, 90
B3. Which of the following describes your ethnic group? (Check all that apply)			
White	189 (94.0%)	189 (95.0%)	378 (94.5%)
Hispanic or Latino	6 (3.0%)	2 (1.0%)	8 (2.0%)
Black or African American	5 (2.5%)	10 (5.0%)	15 (3.8%)
Native American or American Indian	6 (3.0%)	2 (1.0%)	8 (2.0%)
Asian/Pacific Islander	3 (1.5%)	1 (0.5%)	4 (1.0%)
Other	2 (1.0%)	0	2 (0.5%)
B4. What is the highest level of education you have completed? (Check only one answer)			
Some high school	3 (1.5%)	0	3 (0.8%)
High school or equivalent (e.g., GED)	27 (13.4%)	32 (16.1%)	59 (14.8%)
Some college but no degree	43 (21.4%)	49 (24.6%)	92 (23.0%)
Technical school	7 (3.5%)	13 (6.5%)	20 (5.0%)
Associate degree (2-yr college degree)	26 (12.9%)	24 (12.1%)	50 (12.5%)
4-year college degree (e.g., BA, BS)	52 (25.9%)	42 (21.1%)	94 (23.5%)
Some graduate school but no degree	13 (6.5%)	5 (2.5%)	18 (4.5%)
Graduate or professional degree	30 (14.9%)	34 (17.1%)	64 (16.0%)
S3. Have you been diagnosed by a doctor with any of the following conditions? (*check all that apply*)			
CLBP	—	199 (100%)	199
OA in your knee(s) or hip(s)	201 (100%)	199 (100%)	400 (100%)
S7. [if OA is selected in S3] How would you rate the level of your pain caused by your OA in your knee(s) or hip(s) on average over the past week on a scale from 0 (no pain) to 10 (worst pain you can imagine)? [‡]			
Minimum pain level	5	0	0
Mean pain level (SD)	6.6 (1.2)	6.1 (1.8)	6.4 (1.5)
Median pain level	7	7	7
Maximum pain level	10	10	10

Question	Respondents with OA only (n = 201)	Respondents with OA and CLBP (n = 199)	All respondents† (n = 400)
Respondent eligibility based on classes of pain treatment, selected 2 or at least 3 current or prior medications in (Questions S9, S10, S11)			
≥3 current or prior medications	173 (86.1%)	162 (81.4%)	335 (83.8%)
2 current or prior medications; could not take *NSAIDs*	16 (8.0%)	13 (6.5%)	29 (7.3%)
2 current or prior medications; could not take or would never consider taking *opioids*	9 (4.5%)	17 (8.5%)	26 (6.5%)
2 current or prior medications; could not take *NSAIDs*; could not take or would never consider taking opioids	1 (0.5%)	2 (1.0%)	3 (0.8%)
1 current or prior medication; could not take *NSAIDs*; could not take or would never consider taking opioids	2 (1.0%)	5 (2.5%)	7 (1.8%)

Adapted from 5.3.5.4 A9001505 Study Report p.47 Tables 4 and 5.
Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; OA, osteoarthritis; CLBP, chronic low back pain; GED, General Educational Development; BA, Bachelor of Arts; BS, Bachelor of Science
Note: The percentage totals may not sum exactly to 100% because of rounding.
† Exclusive of respondents with CLBP only.
‡ Respondents with OA and CLBP were eligible for the survey if their average pain level in the past week for OA or CLBP was ≥ 5 on an 11-point numeric pain scale ranging from 0 (no pain) to 10 (worst poss ble pain). Thus, the minimum pain level for OA shown for respondents with both OA and CLBP for questions S7 and S8 may be < 5 based on the eligibility criteria. The minimum pain level selected by respondents with OA and CLBP is also reflected in the full sample summary results.
Adapted from IR 20-06-05 Additional Discrete Choice Analysis Excluding Respondents with Chronic Low Back Pain Only Figure 5 Preference Weights Relating to Monthly Out-of-Pocket Costs were Excluded from the Figure.

Figure 13 presents the PWs estimated for each of the attribute level in the DCE. Respondents preferred an improvement in symptom control from 'poor' to 'very good' the most as this has the largest magnitude in change of PW (change in PW = 1.557 - [-2.453] = 4.01). The second most preferred improvement is a reduction in treatment-related risk of physical dependence from 25% to no risk (change in PW = 2.683). MAR estimates are presented in Table 30. Based on the MAR analysis (Table 33), the Applicant concluded that respondents with moderate to severe OA pain were willing to accept a more than 4% additional risk of severe joint problems requiring TJR and more than 0.5% risk of heart attack for all the levels of symptom improvement from "poor."

Figure 13. Preference Weights of Respondents With OA or OA and CLBP (N = 400)



Based on the results, the Applicant concluded that "On average, respondents strongly preferred better symptom control and avoiding the treatment-related risk of physical dependence. Avoiding incremental annual treatment-related risks of heart attack and severe rapidly progressive joint problems requiring total joint replacement were much less important, both statistically and qualitatively, than either improving symptom control or avoiding the risk of physical dependence." (Excerpted verbatim from 5.3.5.4 A9001505 Non-Interventional Final Study Report §11.1).

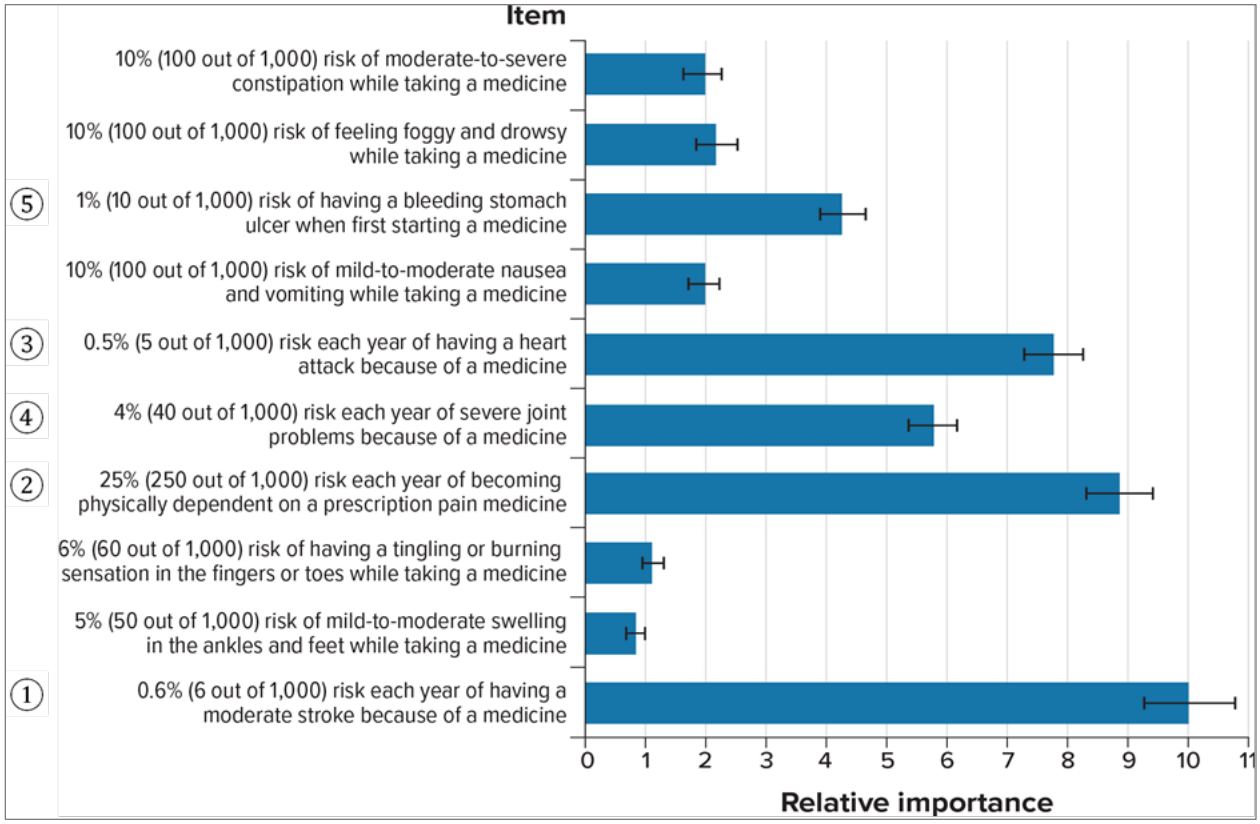
Table 33. Mean (95% Confidence Interval) Estimates of Maximum Acceptable Risk (MAR) (N = 400)

	Benefit Increment	Estimate (95% CI) of MAR in Exchange for a Given Benefit Increment		
Attribute (Benefit)	**Worse Level → Better Level**	**Incremental Risk of TJR**	**Risk of Heart Attack**	**Risk of Physical Dependence**
Symptom control (patient global assessment)	*Poor → Fair*	*> 4% (-)*	*> 0.5% (-)*	*21.38% (16.26, 26.5(*
	Poor → Good	> 4% (-)	> 0.5% (-)	> 25% (-)
	Poor → Very Good	> 4% (-)	> 0.5% (-)	> 25% (-)
Mode and frequency of administration	Oral Pills ≥ 2X per day → 1X per day	2.37% (0.66, 4.08)	0.24% (-0.02, 0.50)	1.93% (0.15, 3.71)
	Injection every 4 weeks → Oral Pills ≥ 2X per day	2.67% (0.56, 4.78)	0.28% (-0.02, 0.58)	2.23% (0.25, 4.22)
	Injection every 8 weeks → Oral Pills ≥ 2X per day	2.98% (0.79, 5.18)	0.32% (0.00, 0.64)	2.55% (0.42, 4.69)
	Injection every 4 weeks → Oral pills 1X a day	> 4% (-)	> 0.5% (-)	4.16 (1.91, 6.40)
	Injection every 8 weeks → Oral pills 1X a day	*> 4% (-)*	*> 0.5% (-)*	*4.48% (2.12, 6.85)*
	Injection every 8 weeks → Injection every 4 weeks	0.81% (-1.11, 2.74)	0.04% (-0.22, 0.30)	0.32% (-1.67, 2.31)

Adapted from: IR Response: Additional Discrete Choice Analysis Excluding Respondents with CLPB Only §3.3 Tables 13, 14, 15
Abbreviations: TJR, total joint replacements; CI, confidence intervals

Figure 14 presents the estimated scaled relative importance weight (SRIW) from the BWS. The BWS analysis identified "0.6% risk each year of having a moderate stroke because of a medicine" as the most important risk to the respondents and it was chosen to be the reference item with its importance weight set to 10. The estimates of the other items were rescaled relative to this reference item as explained in the Data Analysis section. Based on the BWS, the most important risks in descending order are: 0.6% increased annual risk of having a moderate stroke because of a medicine, 25% annual risk of becoming physically dependent on a prescription pain medicine, 0.5% increased annual risk of heart attack because of a medicine, 4% increased annual risk of severe joint problems because of a medicine, and 1% risk of having a bleeding stomach ulcer when first starting a medicine. The most important risk identified, "0.6% risk each year of having a moderate stroke because of a medicine," was not included in the DCE.

Figure 14. Estimates (95% Confidence Interval) of Scaled Relative Importance Weight by Item (N = 602)



Source: 5.3.5.4 A9001505 Non-Interventional US Final Study Report §9.7.1 p.79
Note: ①, ②, ③, ④, and ⑤ indicate the ranks of top five items in terms of their scaled relative importance weights.
Note: The BWS analysis included respondents with OA only, CLBP only or OA and CLBP, but the Agency did not request for a new analysis exclusive of the 202 respondents with CLBP only as the results were unl kely to address the key issues identified.

4.8.10. Key Issues

We disagree with the Applicant's conclusion that patients would view severe joint problems as much less important and were willing to accept increases in the annual risk of severe rapidly progressive joint problems requiring total joint replacement that exceeded those levels of risk believed to be associated with tanezumab (i.e. more than 4% annual incremental risk). The study survey respondents were members of online panels which differed from patients with physician-confirmed OA. Thus, the study conclusions regarding the formers' acceptability of TJR risk may not be generalizable to the latter. It is our opinion that the impact of severe joint problems on patients' daily lives was under-explained and the forced choice format of the DCE may have biased the preference parameter estimates.

Despite being the end-user of the study results, the Agency's input was not sought at critical stages of the PPI study e.g. study design, sample selection and finalization of attributes for the DCE. The Agency was informed of a completed PPI Study at time of the pre-BLA meeting. The Agency's input may have helped to circumvent some of the issues. The key issues pertinent to the review are presented below:

4.8.10.1. Study Sample Was Not Appropriate for Regulatory Decision

Enrollment of participants in the PPI study, were members of internet survey panels (Dynata) and self-reported of having moderate or severe OA pain. An online screening tool was used to screen potential eligible participants.

The screening tool included questions on the worst possible pain in the past week, and current and ever use of pain treatments in the past 2 years. Based on the screening tool respondents were eligible if they: that had a pain score of 5 or greater, have taken or tried three or more classes of pain treatment in the past 2 years; or two prior classes of pain treatment, either excluding NSAIDs due to NSAID contraindication or excluding opioids due to the respondent's unwillingness to take opioids; or one prior class of pain treatment excluding NSAIDs due to NSAID contraindication and excluding opioids due to the respondents' unwillingness to take opioids.

The study did not enroll patients with documentation of a physician-confirmed OA diagnosis. Additionally, Dynata's online panel is non-probability based, i.e., their panelists are not recruited using random sampling methods, e.g., random digit dialing and address-based sampling. Therefore, the PPI study's sample may not be as representative of the proposed indicated OA population.

Additionally, the eligibility screening questions may not have been optimal for inclusion of the proposed indicated OA population. First, potential participants of the PPI study were asked to rate their worst pain in the last week. A 11-point numeric rating scale (0-no pain to 10 worst possible pain) was used to assess a person's level of pain due to OA or CLBP. Inclusion in to the PPI study was a pain score of 5 or greater. However, in the case of respondents with both OA and CLBP, they would be included if their pain level due to either OA or CLBP was 5 or greater, meaning that some of them might not have OA pain that is 5 or more. Again, the study sample may not be representative of the proposed indicated population. Also, the recall period for which the study sample had to recall their past analgesic use (past 2 years) may not been appropriate for the study sample to reflect on. With this, the potential for an incorrect estimation of analgesic use again may not represent the proposed indication population.

4.8.10.2. Inadequate Description of Severe Joint Problems Requiring Total Joint Replacement

The Applicant included descriptions of each the attributes in the DCE survey prior to the choice questions. Risk of severe joint problems requiring TJR, the main risk associated with tanezumab, had the following description (Table 34).

Table 34. Descriptions Provided for Risk of Severe Joint Problems Requiring Total Joint Replacement

Attribute Name and Description in DCE Choice Questions	Detailed Attribute Description in Survey Prior to Choice Questions
Additional risk of severe joint problems: Additional risk each year of having joint problems that are severe enough that you would need a total joint replacement while you are taking the medicine or within 6 months of stopping the medicine	Everyone is likely to face some risk of having severe joint problems during their life. On average, 2 people out of 1,000 (0.2%) who have [OA] [CLBP] [OA and CLBP], but who do not take [OA] [CLBP] [OA and CLBP] medicine(s), will have joint problems that are severe enough that they will need a total joint replacement. However, some [OA] [CLBP] [OA and CLBP] medicines may increase the risk that you will have severe joint problems. These joint problems are painful and get bad so quickly that, if they occur, you would need to have a total joint replacement. This type of severe joint problem can occur in any of the major joints in your body while you are taking the medicine or within 6 months of stopping the medicine, even if you don't have pain or stiffness in that joint when you start taking the medicine.

Source: A9001505 Non-Interventional Final Study Report Appendix 10 Survey Instrument
Abbreviations: DCE, discrete-choice experiment; OA, osteoarthritis; CLBP, chronic low back pain

The focus group transcripts did not show that the moderator following up with participants when they spontaneously brought up the need for total joint replacement or having had a prior total joint replacement. Additionally, the need for total joint replacement was not a discussion point in the moderator guide. This was a missed opportunity to get patient input on how they viewed total joint replacement in terms of their OA and as a possible safety event. Had this been done, it would have better informed the PPI survey.

While good research practices of providing a description of the attributes was done, the description of severe joint problems does not include the consequence of requiring TJR. The impact of a TJR, such as the pain associated with the surgical procedure, the pain and reduction in joint function pre and post the rehabilitation period, and the uncertain level of function after rehabilitation were not listed in the description of the attribute. Understanding the potential complete impact of a TJR is directly related to how respondents weigh the importance of this risk. The inadequate description of the impact of the additional risk of joint problems requiring TJR may have led to an under-weighing of this risk attribute, leading to an overestimated MAR.

4.8.10.3. Missing Critical Attributes

The main benefit attribute in the DCE was symptom control and the attribute description in the survey included:

- Pain, tenderness, and stiffness in the affected joint(s)
- Loss of flexibility or limitations in the range of motion of the affected joint(s)
- A grating sensation when you use the affected joint(s)
- Bone spurs that may form around the affected joint(s) and feel like hard lumps

These benefit levels were defined based on the Patient Global Assessment – Osteoarthritis (PGA-OA), one of the three co-primary endpoints of the confirmatory clinical trials. However, benefit attribute in the preference study is characterized as "symptom control," which is a different question from the PGA-OA endpoint. The PGA-OA does not specify that it is about symptom control but captures how OA affected the patient in general.

Due to the multiple-domain nature of the PGA-OA (e.g., pain relief, improvements in functions and other daily activities) and the response options, it is challenging to distinguish which OA symptom domains resulted in changes in the PGA-OA score. Likewise, the levels of this symptom control attribute used in the DCE captures numerous changes at the same time.

Interpretation of changes in the levels of symptom control across patients may differ. It is unclear if a change from "poor" to "fair" in symptom control means the same amount of improvement to two patients as they can attribute the change to different combinations of changes in domains, e.g., pain and function. We cannot discern which of the listed symptoms are driving the change in the level of symptoms control. Without the other two co-primary endpoints, using the PGA-OA alone to define the benefit attribute lacks sufficient clarity qualitatively and quantitatively for regulatory considerations.

The Applicant explained their decision of excluding two of the three co-primary endpoints (pain and function) from the PPI study because "previous studies of patient and physician preferences for pain management [7,8] demonstrated that pain and function are nearly perfectly confounded and cannot be treated effectively as separate attributes in a DCE)." (Final Study Report – US, page 27) However, the cited literature was based on one physician [7] and one patient sample [8] in the UK. Additionally, both studies did not demonstrate empirically that patients were incapable to discern between these 2 domains. Based on a single patient sample, the argument is insufficient to justify such exclusion.

Additionally, the Agency provided key attributes to the Applicant in response to their pre-BLA meeting (Table 35). At that time, the PPI study was completed.

[7] Arden NK, Hauber AB, Mohamed AF, Johnson FR, Peloso PM, Watson DJ, et al. How do physicians weigh benefits and risks associated with treatments in patients with osteoarthritis in the United Kingdom? *J Rheumatol*. 2012;39(5):1056-63.

[8] Hauber AB, Arden NK, Mohamed AF, Johnson FR, Peloso PM, Watson DJ, et al. A discrete-choice experiment of United Kingdom patients' willingness to risk adverse events for improved function and pain control in osteoarthritis. *Osteoarthritis Cartilage*. 2013;221(2):289-97.

Table 35. Key Attributes Identified by the FDA in Response to the Pre-BLA Meeting

Benefits	Risks
Pain relief	Joint destruction
Function improvement	Neurosensory disturbance
Patient Global Assessment	Cardiovascular (CV) risks
	GI bleeding
	Addiction and dependence
	Overdose

4.8.10.4. Forced Choice Format of Survey Design

In the DCE survey, respondents had to choose one of the two presented options, i.e., their responses were forced choices and they could not "opt-out" or choose to stick with status quo, e.g., stay on the current treatments they received. However, in daily clinical practice, patients typically select their treatment options in an unforced manner, (i.e., they could decline both presented options if they prefer their status quo than the outcomes of both options). The preference weight and MAR estimand elicited under forced choice and unforced choice can be different. It is the Agency's opinion that PPI elicited under unforced choice is more informative as it reflects standard of care outside of the trial setting.

4.8.10.5. Unexplained Data Anomalies

Anomalies in the Applicant's results were observed. For example, the PW of an incremental increase of 0.5% in the risk of severe joint problems requiring total joint replacements (TJR) is nominally higher than the PW of zero risk (Figure 13), meaning that the respondents are nominally slightly more likely to choose a product with a 0.5% risk compared to a product with no risk of TJR. The p-value against the null hypothesis of these two levels having the same PWs was not rejected. However, this anomaly was consistently observed across different subgroup analyses, including those who gave at least 3 incorrect answers to the comprehension questions and those who did not.

The same anomaly was observed with the PW for injection every 4 weeks versus injection every 8 weeks, where respondents appeared nominally more likely to choose a product requiring more frequent injections i.e. injection every 4 weeks was preferred over injection every 8 weeks (Figure 13).

4.9. REMS Proposed by the Applicant

FDA can require applicants to develop and comply with a risk evaluation and mitigation strategies (REMS) for a drug if the Agency determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. A REMS is a required risk management plan that uses risk minimization strategies beyond the professional labeling. The elements of a REMS can include: Medication Guide or patient package insert, a communication plan for healthcare providers, certain packaging and safe disposal technologies for drugs that pose a serious risk of abuse or overdose, ETASU, and implementation system. ETASU are interventions or other actions healthcare professionals need to execute prior to prescribing or dispensing the drug to the patient and may include restricted distribution.

The Applicant submitted a proposed REMS to mitigate the risk of rapidly progressive osteoarthritis (RPOA). The REMS includes ETASU, implementation system, and a timetable for

submission of assessment reports. The ETASU include healthcare setting certification, pharmacy certification, patient enrollment, patient monitoring that includes bilateral X-rays of the knees and hips at baseline and then yearly thereafter as well as monitoring each patient for pain of symptoms of RPOA.

The proposed goal of the tanezumab REMS is to mitigate the increased risk of rapidly progressive osteoarthritis (OA) with tanezumab by:

- Ensuring healthcare providers are educated about the increased risk of rapidly progressive OA with tanezumab.
- Ensuring healthcare settings and pharmacies that dispense tanezumab are certified.
- Ensuring patients are counselled about the increased risk of rapidly progressive OA with tanezumab including:
  - The importance of avoiding nonsteroidal anti-inflammatory drugs (NSAIDs) while being treated with tanezumab and for 16 weeks after the last dose of tanezumab.
  - The signs and symptoms of rapidly progressive OA.

Ensuring certified healthcare settings that administer tanezumab adhere to the baseline and annual X-ray requirements for rapidly progressive OA as described in the Prescribing Information.

The Applicant is proposing that the healthcare setting (HCS) designates an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS. The authorized representative would be responsible for identifying and training staff involved in prescribing, dispensing, and administering tanezumab. HCS requirements include that patients would be counseled to avoid NSAID use while being treated and for 16 weeks after the last dose of tanezumab, assessed for patient risk factors of rapidly progressive OA by conducting bilateral X-rays of the knees and hips within two months before the first dose and, patients would be enrolled into the REMS program. The Applicant developed educational materials for patients and HCS. The HCS are to ensure that bilateral x-rays of the knees and hips are done for each patient annually thereafter. They would also ensure that every 12 months a *Patient Continuation Form* is submitted for each patient to indicate that the patient had the required X-rays and that the patient is authorized to continue treatment.

Pharmacies that dispense tanezumab must be certified. Pharmacies must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS. The pharmacy must verify that the healthcare setting is certified, the patient is enrolled and authorized to receive the tanezumab before dispensing each prescription.

4.10. REMS Considerations

The Agency has concerns that the Applicant's proposed REMS is not sufficient to mitigate the risk of RPOA. The REMS is based on a premise that the proposed program would be able to affect the development and/or progression of RPOA in patients taking tanezumab. However, in spite of the risk mitigation strategies described in 5.7, the risk of developing RPOA remained concerning as a large number of patients with RPOA required total joint replacements (TJR); 15% of patients progressed to total joint replacement (TJR) following RPOA1 and 60% of patients with RPOA2 progressed to TJR. Stopping drug after patients develop RPOA2 does not appear to be effective in preventing further damage to the joints.

There are several complicating factors in the studied and proposed risk mitigation strategies. One serious concern is that RPOA is not easily identified and followed by X-ray; the patient's position and subjectivity of the reader can affect the interpretation of the findings. Real world scenarios would not incorporate standardized or centralized processes as was done in the clinical development program. Clinical trials relied on specially trained radiologists, a model that may not be reproducible in current US healthcare system. Furthermore, substantial disagreements occurred between experts recruited by Pfizer to assess surveillance of radiographs which were performed and interpreted under optimal conditions. In addition, the effect of stopping drug when RPOA1 was detected and the trajectory of the risk beyond one year of treatment is unknown. Tanezumab would be indicated for chronic administration, and therefore patients would require monitoring with multiple X-rays for the duration of treatment. As stated in Sections 4.7.6 and 9.11, the risk to the joints may continue to exist after study drug is discontinued. Even more worrisome is that RPOA can occur in joints that are determined to be healthy prior to starting treatment with tanezumab. Patients may not be aware if their healthy joints, or arthritic joints, are undergoing these damaging changes as they may not experience reportable symptoms. Even if they do report them, or if the damage is found in imaging, discontinuing tanezumab may not alter the course of further joint destruction as discussed above. Overall, the Agency is concerned that the risk mitigation strategies applied to the post 2015 studies largely may not be able to be duplicated with a REMS.

4.11. Agency REMS Conclusions

The Agency is concerned that the proposed REMS will not ensure the benefits of tanezumab outweigh the risks of RPOA. Although the Applicant has proposed the REMS program described above which is consistent with the mitigation strategies implemented during the development program, there is no clear evidence to support that requiring and implementing the proposed elements will have an impact on preventing or the progression of RPOA. Furthermore, even if the mitigation strategies employed in the clinical trial demonstrated effectiveness, it is unclear that those strategies could be replicated in clinical practice.

IV. Appendices

Key interactions between the Agency and Applicant are summarized in tabular form following.

5. Summary of Regulatory History

Table 36. Summary of Regulatory History

Date	Activity	Key Outcome(s)
April 30, 2004	New IND 11680 submitted	Proposed Indication: for use in moderate to severe chronic pain states such as Osteoarthritis. IND was allowed to proceed.
April 22, 2008	End-of-Phase-2 clinical program	Due to concerns about immunogenicity, the Applicant was asked to conduct long-term, controlled trials to assess for decreasing efficacy with repeated tanezumab dosing, as well as safety. The Applicant was advised that the indication for the relief of SS of OA requires positive outcome from 2 AWC trials with the following co-primary endpoints: WOMAC pain, WOMAC function, and Patient Global. To explore the efficacy of tanezumab as analgesic across a variety of painful conditions for evaluation of efficacy after two doses, Week 16 primary efficacy assessment, is acceptable to support a chronic pain indication for tanezumab That comparative claims require replicated evidence of superiority over the same comparator To assess for the effect of immunogenicity on efficacy and safety in long-term trials
April 23, 2008	Type B, CMC End-of-Phase-2	Discussion on comparability analysis for two master cell banks
September 19, 2008	IND placed on partial clinical hold	The hold was due to insufficient information to evaluate stability of the drug substance and drug product. The partial hold was removed on October 29, 2008, after the Applicant adequately responded to the CMC deficiencies.
July 16, 2009	Type B meeting to discuss a chronic low back pain indication.	Division clarified that benefit: risk rationale should be acceptable for narrow indication like chronic low back pain (CLBP). Specific recommendations for neurologic safety monitoring program were discussed.
January 19, 2010	Guidance meeting to discuss Phase 3 program w/ addition of subcutaneous route	The Applicant proposed to add the subcutaneous route of administration to bridge the OA development program and agreed to provide comparability data to bridge the efficacy
June 23, 2010	Clinical Hold for Phase 2 and Phase 3 OA studies	Patients with OA were excluded from clinical trials for the other indications because, at this time, the joint safety risk was thought to be limited to arthritic joints. On December 2, 2010, Phase 2 protocols: patients with Diabetic Peripheral Neuropathy and Treatment of Moderate to Severe Pain Associated with Interstitial Cystitis/ Painful Bladder Syndrome were allowed to proceed.

Date	Activity	Key Outcome(s)
December 23, 2010	Protocols in patients with chronic pancreatitis, diabetic peripheral neuropathy and moderate to severe pain associated with Interstitial Cystitis/ Painful Bladder Syndrome were placed on hold.	Unexpected cases of joint destruction and rapidly progressing osteoarthritis (RPOA) were observed at a higher rate compared to that seen in general population. FDA imposed partial clinical hold; only the study in terminal cancer patients was allowed to continue. The Applicant was asked to submit rigorous, scientific data to support an alternative explanation for the high incidence of this unexpected adverse event in patients treated with anti-NGF antibody drugs.
December 5, 2011	Guidance meeting to discuss plans for upcoming Advisory Committee meeting	The discussion focused on the logistics and the division of presentation topics for the Advisory Committee.
March 12, 2012	Arthritis Advisory Committee meeting	The members of the committee opined that there was a role for the ongoing development of the class of anti-NGF agents in select populations with adequate monitoring and safety evaluations.
June 14, 2012	Meeting to discuss removal of the partial clinical hold	For OA patients, the tanezumab dose was limited to 5 mg. Histopathology should be collected. Imaging assessments should be standardized and performed by an expert central reader. The role of the adjudication Committee was to be to determine the final diagnosis.
August 28, 2012	Study A4091056 allowed to proceed.	The Applicant agreed to use the product at a maximum dose of 5 mg limited to patients who had failed other approved or standard of care therapies with the addition of strict safety precautions.
December 14, 2012	Partial clinical hold imposed.	Protocol A4091056 and Protocol A4091059 were placed on hold due adverse changes in the sympathetic nervous system found in animal studies using an Anti-NGF mAb.
April 24, 2013	Type A meeting	A new safety signal of sympathetic nervous system toxicity had been identified for the class of anti-NGF products in December of 2012. Therefore, Phase 3 protocols with OA pain and CLBP were placed on hold. The Applicant committed to conduct additional nonclinical primate study to support the safety of the proposed clinical dose. On July 19, 2013, the partial hold was removed.
August 28, 2013	Partial clinical hold	The Applicant was notified that the removal of hold in July was an error and the IND is still on partial hold.
November 27, 2013	EOP2 meeting for cancer pain	Discussion on Phase 3 study design in patients with pain due to bone metastases despite receiving treatment with opioids.
November 14, 2014	Written Responses Only Type C Guidance	Input on Study A4091061 provided. The Division expressed concern related to patient population selection, collection of safety data in an unblinded manner, and management of patients with adverse events. Applicant was advised to include stopping criteria for sympathetic and neurosensory adverse events and plan for management of patients with signs and symptoms suggestive of autonomic dysfunction.

Date	Activity	Key Outcome(s)
January 12, 2015	Type C Guidance	The Applicant updated the Division on non-clinical data related to the effects of tanezumab on the sympathetic nervous system. The Division stated that the adequacy of nonclinical data to support the removal of clinical hold can only be determined upon the review of the final study reports. The partial clinical hold was removed on March 20, 2015.
May 26, 2017	Fast Track Request on March 30, 2017	Fast Track was granted for the management of the signs and symptoms of OA and the management of CLBP.
May 26, 2017	Breakthrough Therapy Designation Request on March 30, 2017	Request for Breakthrough Therapy designation for the management of the signs and symptoms of OA was denied because the clinical evidence submitted did not indicate that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints.
October 2, 2017	WRO, Type C Guidance	Feedback provided on the abuse potential assessment for tanezumab. There was agreement that tanezumab has no relevant functional CNS activity. Thus, it was not anticipated that the Agency would seek scheduling tanezumab as a controlled substance. The abuse potential will be determined during the BLA review.
June 22, 2018	Initial PSP agreement	Agreement achieved for the iPSP for the treatment of osteoarthritis, chronic low back pain, and cancer pain due to bone metastases indications.
November 21, 2018	WRO, Type C	Discussed the acceptability of key CMC development strategies, nonclinical data package to support the BLA filing, and proposed biomarker analysis plan for tanezumab. There was overall agreement with the Applicant's proposal. The Applicant was asked to include a carcinogenicity assessment in the BLA.
March 20, 2019	Proprietary name	The proposed proprietary name, tanezumab was conditionally acceptable.
March 20, 2019	WRO	The Division agreed to the format, structure and content of the Biologics License Application (BLA) to support a substantive review.
June 6, 2019	Pre-BLA meeting	The Division recommended that the Applicant quantify the efficacy and risks of tanezumab in comparison to the active comparators used in tanezumab trials, provide a safety and efficacy comparison of tanezumab to available treatments for OA based on literature or other sources, quantify the benefit/risk relationship across the full timeframe for potential exposure, and evaluate if the risk-mitigation measures instituted in post-2015 studies improved the joint-safety outcome compared to pre-2015 studies. Adequacy of REMS to be determined at the time of BLA review
August 2, 2019	WRO	The Applicant sought comments on postmarketing study, agreement to hold Application orientation meeting, and plan to provide complete biomarker data listings for joint-safety events for A4091056 and A4091057

Date	Activity	Key Outcome(s)
September 11. 2019	Rolling Review request received August 30, 2019	Rolling Review Granted
December 18, 2019	Complete BLA 761130 received	For the treatment of chronic pain associated with OA in patients who have failed to respond to, or who are intolerant to available treatments, or those unwilling take an opioid medication. Total 39 clinical studies were conducted. The proposed regimen is administration of 2.5 mg of drug product subcutaneously every 8 weeks.
February 28, 2020	Filing Review Issued identified letter issued	The application was filed on February 16, 2020. In the 74 day letter, potential review issued was identified: Based on the preliminary review, in addition to the safety concerns identified with tanezumab during clinical development (e.g., destructive arthropathy), we note a higher incidence of cardiovascular deaths with tanezumab compared to NSAIDs. This issue will be further assessed during the review cycle, and additional information requests may be forthcoming.

Abbreviations: SS, signs and symptoms; OA, osteoarthritis; AWC, adequate and well-controlled; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; NSAIDs, nonsteroidal anti-inflammatory drugs; IND, investigational new drug; CMC, chemistry, manufacturing, and controls, CNS, central nervous system; EOP2, end-of-phase2; iPSP, inh bitory postsynaptic potential

6. Trial Design: Additional Information and Assessment

6.1. Tabular Listing of All Clinical Studies

The Applicant conducted 41 clinical studies, 38 of which were interventional and three were observational. The majority of the interventional studies were conducted in patients with OA (20 studies); the remaining studies were conducted in patients with CLBP (five studies), patients with other painful conditions (11 studies), and healthy volunteers (two studies).

The key features for all 41 clinical studies, including study design, tanezumab regimens, comparators, and duration of treatment and follow-up, are captured in the tables that follow.

Table 37. Clinical Studies in Osteoarthritis Conducted Prior to 2015

Study/ Index Joint/ Country	N (Total # of Subjects Randomized)	Study Design/ Key Features	Treatment Duration wks (# Doses) q8 wks[a]	Follow-up Duration (wks)	Tanezumab Doses[b] (# of Treated Subjects)	Comparators (# of Treated Subjects)
Phase 1/ 2 Studies with IV Tanezumab						
1006 K U.S.	Part 1: 42 2: 79	R, DB, PC Primary efficacy endpoint was change from baseline to Days 2 to 181: SPID for current index knee pain	8 (1)	16 and 38[c]	Part 1: 3 to 1000 µg/kg (30) (dose escalation) Part 2:100 to 300 µg/kg (53)	Part 1: PBO (12) Part 2: PBO (26)
1008 K U.S.	450	R, DB, PC Primary efficacy endpoints were the change from baseline averaged over the treatment period from Week 1 to 16 in: Daily walking pain on a flat surface in index knee Subject Global Assessment (SGA)	16 (2)	Up to 10 wks	10 µg/kg (74) 25 µg/kg (74) 50 µg/kg (74) 100 µg/kg (74) 200 µg/kg (74)	PBO (74)
1009 K U.S.	281	OL, extension to Study 1008 Efficacy endpoints were change from Baseline to Week 72 in: Overall pain intensity in the index knee WOMAC Pain, Physical Function, and Stiffness Subscales SF-36 subscales SGA	16 (2)	12	50 µg/kg (281)	None

Study/ Index Joint/ Country	N (Total # of Subjects Randomized)	Study Design/ Key Features	Treatment Duration wks (# Doses) q8 wks[a]	Follow-up Duration (wks)	Tanezumab Doses[b] (# of Treated Subjects)	Comparators (# of Treated Subjects)
1022 K Japan	83	R, DB, PC Efficacy endpoints were change from baseline to Week 8 in: VAS for index knee pain during walking in the past 24 hours VAS for index knee pain in the past 24 hours VAS for current index knee pain WOMAC Pain, stiffness, and physical function subscales	8 (1)	5 and 9[e]	10 µg/kg (15) 25 µg/kg (15) 50 µg/kg (15) 100 µg/kg (16) 200 µg/kg (6)	PBO (16)
Phase 3 Studies with IV Tanezumab						
1011 K U.S.	697	R, DB, PC Coprimary efficacy endpoints were change from baseline to Week 16 in: WOMAC Pain WOMAC Physical Function PGA of OA Key secondary efficacy endpoint: OMERACT-OARSI responder index at Week 16	24 (3) Doses received: 1 dose: 2.5 mg (13%), 5 mg (19%), 10 mg (17%) 2 doses: 2.5 mg (7%), 5 mg (5%), 10 mg (8%) 3 doses: 2.5 mg (80%), 5 mg (76%), 10 mg (75%)	8	2.5 mg (172) 5 mg (172) 10 mg (174)	PBO (172)

Study/ Index Joint/ Country	N (Total # of Subjects Randomized)	Study Design/ Key Features	Treatment Duration wks (# Doses) q8 wks[a]	Follow-up Duration (wks)	Tanezumab Doses[b] (# of Treated Subjects)	Comparators (# of Treated Subjects)
1014 H U.S.	627	R, DB, PC Co-primary efficacy endpoints were change from baseline to Week 16 in: WOMAC Pain WOMAC Physical Function PGA of OA Key secondary efficacy endpoint: OMERACT-OARSI responder index at Week 16	24 (3) Doses received: 1 dose: 2.5 mg (22%), 5 mg (14%), 10 mg (22%) 2 doses: 2.5 mg (11%), 5 mg (8%), 10 mg (10%) 3 doses: 2.5 mg (76%), 5 mg (77%), 10 mg (68%)	8	2.5 mg (155) 5 mg (154) 10 mg (157)	PBO (155)
1015 K U.S.	832	R, DB, DD, PC, AC Co-primary efficacy endpoints were change from baseline to Week 16 vs. PBO and active comparator in: WOMAC Pain WOMAC Physical Function PGA of OA Key secondary efficacy endpoint: OMERACT-OARSI responder index at Week 16	16 (2) Doses received: 1 dose: 5 mg (16%), 10 mg (25%) 2 doses: 5 mg (85%), 10 mg (75%)	8	5 mg (206) 10 mg (208)	PBO (208) NAP (206)

Study/ Index Joint/ Country	N (Total # of Subjects Randomized)	Study Design/ Key Features	Treatment Duration wks (# Doses) q8 wks[a]	Follow-up Duration (wks)	Tanezumab Doses[b] (# of Treated Subjects)	Comparators (# of Treated Subjects)
1016[f] K/H U.S.	2147	R, Dose-blinded, LT extension to 1011, 1014, 1015, 1018 Coprimary efficacy endpoints were change from baseline to Week 24 and 48 in: WOMAC Pain WOMAC Physical Function WOMAC Stiffness PGA of OA Efficacy was a secondary objective and no statistical analyses were performed.	104 (13) *Due to clinical hold, 10% completed 1 year of treatment* Median dose received: 4 (1-9) 1 dose: 8.4% 2 doses: 19% 3 doses: 21% 4 doses: 18% 5 doses: 14% 6 doses: 10% 7 doses: 7% 8 doses: 2% 9 doses: 0.6%	8	2.5 mg (522) 5 mg (832) 10 mg (788) StOC allowed	None
1017 [f] K/H Global	607	R, DB, add-on to DIC Coprimary efficacy endpoints were change from baseline to Week 16 in: WOMAC Pain WOMAC Physical Function PGA of OA Key secondary efficacy endpoint: OMERACT-OARSI responder index at Week 16	24 (3)	16	2.5 mg + DIC (157) 5 mg + DIC (150) 10 mg + DIC (145)	PBO + DIC (152)

Study/ Index Joint/ Country	N (Total # of Subjects Randomized)	Study Design/ Key Features	Treatment Duration wks (# Doses) q8 wks[a]	Follow-up Duration (wks)	Tanezumab Doses[b] (# of Treated Subjects)	Comparators (# of Treated Subjects)
1018 K/H U.S.	849	R, DB, DD, PC, AC Coprimary efficacy endpoints were change from baseline to Week 16: WOMAC Pain WOMAC Physical Function PGA of OA Key secondary efficacy endpoint: OMERACT-OARSI responder index at Week 16	16 (2) Doses received: 1 dose: 5 mg (19%), 10 mg (26%) 2 doses: 5 mg (81%), 10 mg (74%)	8	5 mg (211) 10 mg (209)	PBO (209) NAP (211)
1025[f] K/H Global	2720	R, DB, DD, AC Coprimary efficacy endpoints were change from baseline to Week 16 in: WOMAC Pain WOMAC Physical Function PGA of OA Key secondary efficacy endpoint: OMERACT-OARSI responder index at Week 16	56 (7) Doses received: 1 dose: ~11% 2 doses: ~6% 3 doses: ~8% 4 doses: ~15% 5 doses: ~28% 6 doses: ~15% 7 doses: ~16%	8	5 mg (541) 10 mg (542) 5 mg + NSAID (536) 10 mg + NSAID (542)	PBO + NSAID BID (NAP or CEL) (539)

Study/ Index Joint/ Country	N (Total # of Subjects Randomized)	Study Design/ Key Features	Treatment Duration wks (# Doses) q8 wks[a]	Follow-up Duration (wks)	Tanezumab Doses[b] (# of Treated Subjects)	Comparators (# of Treated Subjects)
1026 [h] K/H U.S.	220	R, DB, PC Neurological safety study assessments of nerve conduction velocity, heart rate deep breathing and IENFD at Week 24. Efficacy was a secondary objective. Efficacy endpoints included change from baseline to Week 8, 16 and 24 in: WOMAC Pain WOMAC Physical Function PGA of OA	24 (3)	8	5 mg (73) 10 mg (74)	PBO (72)
1030 [h] K/H Global	614	R, DB, DD, PC, AC Primary efficacy endpoint was change from baseline to Week 8 in: WOMAC Pain only, ANCOVA, LOCF	16 (2)	2	5 mg (161) 10 mg (150)	PBO (141) OXY CR (158)
1040 [h] K/H U.S.	21	R, DB, PC, LT extension to Study 1026 Neurological safety study: NC and IENFD at Week 24 Efficacy was a secondary objective. Efficacy endpoints included change from Baseline (from Study 1026) up to Week 80 in: WOMAC Pain WOMAC Physical Function PGA of OA	56 (7)	0	5 mg (7) 10 mg (4) StOC allowed	PBO (10) StOC allowed

Study/ Index Joint/ Country	N (Total # of Subjects Randomized)	Study Design/ Key Features	Treatment Duration wks (# Doses) q8 wks[a]	Follow-up Duration (wks)	Tanezumab Doses[b] (# of Treated Subjects)	Comparators (# of Treated Subjects)
Phase 3 Studies with SC Tanezumab						
1027 [h] K U.S.	385	R, DB, DD, PC 3 coprimary efficacy endpoints were change from baseline to Week 8 and 16 in: WOMAC Pain WOMAC Physical Function PGA of OA	16 (2)	8	2.5 mg (SC) (74) 5 mg (SC) (63) 10 mg (SC) (86) 10 mg (IV) (84)	PBO (72)
1032[h] K U.S.	1	R, Dose-blinded, LT extension to Study 1027 Assessment of efficacy was a secondary objective and included change from Baseline up to Week-64 in: WOMAC Pain WOMAC Physical Function PGA of OA	56 (7)	8	2.5 mg (1) 5 mg 10 mg StOC allowed	None

Study/ Index Joint/ Country	N (Total # of Subjects Randomized)	Study Design/ Key Features	Treatment Duration wks (# Doses) q8 wks[a]	Follow-up Duration (wks)	Tanezumab Doses[b] (# of Treated Subjects)	Comparators (# of Treated Subjects)
1043 [f] K/H U.S.	679	R, dose-blinded coprimary efficacy endpoints were change from baseline to Weeks 8 and 16: WOMAC Pain WOMAC Physical Function PGA of OA	56 (7) planned Doses received: Similar between groups with median 2 doses (1- 4) 1 dose: 18% 2 doses: 43% 3 doses: 29% 4 doses: 10%	8	2.5 mg (230) 5 mg (222) 10 mg (226) StOC allowed	None

Source: Clinical Reviewer Anjelina Pokrovnichka

Abbreviations: wks, weeks; R, randomized; DB, double-blind; PC, placebo-controlled; SPID, Sum of pain intensity difference; PBO, placebo; OL, open-label WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; DD, double-dummy; LTE, long-term extension study; MC, multi-center; N, number of subjects; IV, intravenous; SC, subcutaneous; PO, per oral; PC, placebo-controlled; PG, parallel group; SAD, single ascending dose; MAD, multiple ascending dose; TAN, tanezumab; NAP, naproxen; CEL, celecoxib; DIC, diclofenac; OXY, oxycodone; SR, slow-release; CR, controlled-release; ER, extended-release; NSAIDs, non-steroidal anti-inflammatory drugs; StOC, standard-of-care; H, hip; K, knee; OA, osteoarthritis; CLBP, chronic low back pain; NRS, numerical rating scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; PGA, Patient Global Assessment; OMERACT-OARSI, Outcome Measures in Rheumatology - Osteoarthritis Research Society International; SF, short form survey; SGA, subject global assessment; DPN, diabetic peripheral neuropathy; PHN, post-herpetic neuralgia; NCS, nerve conduction studies; IENFD, intra epidermal nerve f ber density; LOCF, last observation carried forward; ANCOVA, analyses of covariance; VAS, visual analogue scale

Doses for comparator drugs:

NSAID doses: NAP 500 mg BID, CEL 100 mg BID, Diclofenac ER 75 mg BID

Tramadol PR 100-300 mg QD

Oxycodone doses: Oxycodone CR 10 to 40 mg q 12 hours

a. Treatment duration and dosing scheme reflect tanezumab treatment duration and tanezumab dosing scheme.

b. Plus add-on therapy/Standard of Care where stated.

c. For Group I only, post-termination visit telephone safety follow-up calls were conducted on Days 91 and 181.

d. Tanezumab IV infusion was administered on Day 1 and Day 56 in an open label manner. Additional doses of tanezumab could be administered at investigator's discretion

at 8-week intervals from Day 56.

e. Patients received study drug on Day 1 and were observed for 24 hours after administration prior to discharge. Cohorts A, B and C were followed for 92 days, and Cohorts

D and E were followed for 120 days.

f. Terminated: Complete Enrollment, Incomplete Duration, Due to FDA partial clinical hold and global self-imposed hold in 2010.

g. A total of 827 patients (38.6%) received tanezumab for the first time in Study 1016, following treatment with PBO (1011, 1014, 1015, 1018) or NAP (1015, 1018).

h. Terminated: Incomplete Enrollment, Incomplete Duration, Due to FDA Partial Clinical Hold and global self-imposed hold in 2010.

i. Patients randomized to PBO in Study 1026 received PBO plus 'Standard of Care' in Study 1040.

j. Study 1027 used IV dosing for tanezumab 10 mg.

Table 38. Clinical Studies in Osteoarthritis Conducted After 2015

Study/ Index Joint/ Country	N (Total # of Subjects Randomized)	Study Design/Key Features	Treatment. Duration wks (# Doses) q8 wks[a]	Follow-up Duration (wks)	Tanezumab Doses[b] (# of Treated Subjects)	Comparators (# of Treated Subjects)
1056 K/H US/Canada	698	R, DB, PC Co-primary efficacy endpoints were change from baseline to Week 16 in: WOMAC Pain WOMAC Physical Function PGA of OA Key secondary efficacy endpoint: Patients with ≥50% reduction from Baseline in the WOMAC Pain Subscale at Week 16	16 (2) ~ 95% received 2 doses	24	2.5 mg SC (231) 2.5/ 5 mg SC (233) – forced titration	PBO (232)

Study/ Index Joint/ Country	N (Total # of Subjects Randomized)	Study Design/Key Features	Treatment. Duration wks (# Doses) q8 wks[a]	Follow-up Duration (wks)	Tanezumab Doses[b] (# of Treated Subjects)	Comparators (# of Treated Subjects)
1057 K/H EU/Japan	849	R, DB, PC Co-primary efficacy endpoints were change from baseline to Week 16 in: WOMAC Pain WOMAC Physical Function PGA of OA Key secondary efficacy endpoint: Patients with ≥50% reduction from Baseline in the WOMAC Pain Subscale at Week 24 Change from Baseline to Week 2 in the WOMAC Pain. Change from Baseline to Week 1 in average pain score in the index knee or hip joint	24 (3) ~ 93% received 3 doses	24	2.5 mg SC (283) 5 mg SC (284)	PBO (282)

Study/ Index Joint/ Country	N (Total # of Subjects Randomized)	Study Design/Key Features	Treatment. Duration wks (# Doses) q8 wks[a]	Follow-up Duration (wks)	Tanezumab Doses[b] (# of Treated Subjects)	Comparators (# of Treated Subjects)
1058 K/H Global	3021	R, DB, DD, AC The primary safety endpoint was incidence of a predefined composite endpoint consisting of adjudication outcomes of RPOA (type 1 or type 2), SIF, primary ON, or pathological fracture (primary composite endpoint) Co-primary efficacy endpoints were change from baseline to Week 16 in: WOMAC Pain WOMAC Physical Function PGA of OA Key secondary efficacy endpoint: Patients with ≥50% reduction from Baseline in the WOMAC Pain at Week 16	56 (7) Doses received: 1 dose: ~8% 2 doses: ~31% 3 doses: ~7% 4 doses: ~3% 5 doses: ~3% 6 doses: ~3% 7 doses: ~45%	24	2.5 mg SC (1002) 5 mg SC (998)	NSAIDs: NAP, CEL, DIC (996)

Source: Clinical Reviewer Anjelina Pokrovnichka
Abbreviations: R, randomized; DB, double-blind; PC, placebo-controlled, WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; PGA, Patient Global Assessment; OA, osteoarthritis; PBO, placebo; DD, double-dummy; AC, active-controlled; SC, subcutaneous; NSAIDs, nonsteroidal anti-inflammatory drugs; NAP, naproxen; CEL, celecoxib; DIC, diclofenac; RPOA, rapidly progressing osteoarthritis; SIF, subchondral insufficiency fracture; ON, osteonecrosis
a. Treatment duration and dosing scheme reflect tanezumab treatment duration and tanezumab dosing scheme.
b. Plus add-on therapy/Standard of Care where stated.

Table 39. Clinical Studies in Chronic Low Back Pain Conducted Prior to 2015

Study/ Index Joint/ Country	N (Total # of Subjects Randomized)	Study Design/Key Features	Treatment. Duration wks (# Doses) q8 wks[a]	Follow-up Duration (wks)	Tanezumab Doses[b] (# of Treated Subjects)	Comparators (# of Treated Subjects)
Phase 1/2 Study with IV Tanezumab						
1004 US	220	R, DB, PC, AC Primary efficacy endpoint: Change from Baseline to Week 6 in the daily average LBPI as measured by an 11-point NRS.	12 (1)	4	200 µg/kg IV (88)	PBO (41) NAP (88)
Phase 2b/3 Studies with IV or SC Tanezumab						
1012 US	1359	R, DB, DD, AC, PC Primary efficacy endpoint: Change from Baseline to Week 16 in the daily average LBPI as measured by an 11-point NRS. Key Secondary efficacy endpoints: Change from Baseline to Week 16 in the RMDQ score Change from Baseline to Week 16 in the PGA of LBP score.	16 (2)	8	5 mg IV (232) 10 mg IV (295) 20 mg IV (295)	PBO (230) NAP (295)

Study/ Index Joint/ Country	N (Total # of Subjects Randomized)	Study Design/Key Features	Treatment. Duration wks (# Doses) q8 wks[a]	Follow-up Duration (wks)	Tanezumab Doses[b] (# of Treated Subjects)	Comparators (# of Treated Subjects)
1039[c] US	849[d]	R, Dose-blinded, LT extension to Study 1012 Efficacy endpoints assessed at various time points throughout the study (change from baseline of the parent study) included: BPI-sf pain and interference scores, RMDQ total score, PGA of LBP and discontinuation due to lack of efficacy.	56 (7) - 24 weeks IV followed by 32 weeks SC	8	10 mg (321) 20 mg (527) StOC allowed	None

Source: Clinical Reviewer Anjelina Pokrovnichka
Abbreviations: R, randomized; DB, double-blind; PC, placebo-controlled, WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; PGA, Patient Global Assessment; OA, osteoarthritis; PBO, placebo; DD, double-dummy; AC, active-controlled; PC, placebo-controlled; SC, subcutaneous; IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs; NAP, naproxen; CEL, celecoxib; DIC, diclofenac; RPOA, rapidly progressing osteoarthritis; SIF, subchondral insufficiency fracture; ON, osteonecrosis; LBP, lower back pain; NRS, numeric pain rating scale; RMDQ, Roland-Morris Disability Questionnaire; LT, long-term; StOC, standard-of-care; BPI-sf, Brief Pain Inventory - Short Form
a. Treatment duration and dosing scheme reflects tanezumab treatment duration and tanezumab dosing scheme.
b. Plus add-on therapy/Standard of Care where stated.
c. Terminated: Complete enrollment, Incomplete duration due to FDA partial clinical hold and global self-imposed hold in 2010.
d. A total of 341 patients (40.2%) received tanezumab for the first time in Study 1039, following treatment with placebo or naproxen in Study 1012.

Table 40. Clinical Studies in Chronic Low Back Pain Conducted After 2015

Study/ Index Joint/ Country	N (Total # of Subjects Randomized)	Study Design/Key Features	Treatment. Duration wks (# Doses) q8 wks[a]	Follow-up Duration (wks)	Tanezumab Doses (# of Treated Subjects)	Comparators (# of Treated Subjects)
1059 Global	1832	R, DB, DD, PC, AC Primary efficacy endpoint: Change from Baseline to Week 16 in the daily average LBPI score as measured by an 11-point NRS. Key secondary efficacy endpoints: Change from Baseline to Week 16 in the RMDQ for Tan vs. PBO Response as defined by a ≥50% reduction from Baseline in daily average LBPI score derived from the patient diary at Week 16 for Tan vs. PBO Change from Baseline to Week 2 in average LBPI score for Tan vs. PBO.	56 (7) *PBO (16 weeks), switched 1:1 into Tan 5 or 10 mg treatment group*	24	5 mg SC (407) 10 mg SC (407)	PBO (406) Tramadol (602)

Study/ Index Joint/ Country	N (Total # of Subjects Randomized)	Study Design/Key Features	Treatment. Duration wks (# Doses) q8 wks[a]	Follow-up Duration (wks)	Tanezumab Doses (# of Treated Subjects)	Comparators (# of Treated Subjects)
1063 Japan ongoing	277	R, DB, AC Primary safety endpoints included joint safety adjudication outcomes, TJRs, neurologic examination and ADA assessments. Secondary efficacy endpoints assessed at various time points throughout the study (change from baseline of the parent study) included: Average LBPI score, RMDQ score, and PGA of LBP score.	56 (7)	24	5 mg SC (92) 10 mg SC (93)	CEL (92)

Source: Clinical Reviewer Anjelina Pokrovnichka
Abbreviations: R, randomized; DB, double-blind; PC, placebo-controlled, DD, double-dummy; AC, active-controlled; SC, subcutaneous; PBO, placebo; LBP, lower back pain; NRS, numeric pain rating scale; RMDQ, Roland-Morris Disability Questionnaire; Tan, tanezumab
a. Treatment duration and dosing scheme reflects tanezumab treatment duration and tanezumab dosing scheme.

Table 41. Clinical Studies in Other Pain Conditions

Study/ Country or Region/ Population	N (Total # of Subjects Randomized)	Treatment Duration, wks (# Doses)[a]	Follow-up Duration (wks)	Tanezumab Doses[b]/Comparator Treatments (# of Treated Subjects)
Phase 2 Studies with Tanezumab IV or SC				
1003 Global Cancer pain	59	8 (1)	8	10 mg IV + Opioids (29) PBO + Opioids (30)
1005 US Post-herpetic neuralgia	99	8 (1)	8	50 µg/kg IV (33) 200 µg/kg IV (32) PBO (31)

Study/ Country or Region/ Population	N (Total # of Subjects Randomized)	Treatment Duration, wks (# Doses)[a]	Follow-up Duration (wks)	Tanezumab Doses[b]/Comparator Treatments (# of Treated Subjects)
1007 US Bunionectomy	50	8 (1)	~18[c]	10 µg/kg IV (8) 30 µg/kg IV (8) 100 µg/kg IV (8) 300 µg/kg IV (8) 1000 µg/kg IV (8) PBO (10)
1010 US Interstitial cystitis	65	8 (1)	8	200 µg/ kg IV (34) PBO (30)
1019 Global Chronic prostatitis	62	8 (1)	8	20 mg IV (30) PBO (32)
1023 US Endometriosis	48	8 (1)	8	15 mg IV (22) PBO (25)
1029 Global Cancer pain, OL extension to Study 1003	42	32 (4)	8	10 mg IV (41) q8wks
1031[d] US Peripheral diabetic neuropathy	73	16 (2)	8	20 mg SC (38) q8wks PBO (35)
1035[d] Global Interstitial cystitis/Painful bladder syndrome	205	16 (2)	8	1 mg SC (41) q8wks 2.5 mg SC (37) q8wks 10 mg SC (40) q8wks 20 mg SC (40) q8wks PBO (42)
1044[e] US Chronic pancreatitis	2	8 (1)	16	20 mg SC (0) PBO (2)
Phase 3 Study with Tanezumab SC				
1061[f] Cancer pain (ongoing)				

Source: Clinical Reviewer Anjelina Pokrovnichka

Abbreviations: wks, weeks; SC, subcutaneous; IV, intravenous; PBO, placebo; OL, open-label

a. Treatment duration and dosing scheme reflects tanezumab treatment duration and tanezumab dosing scheme.

b. Plus add-on therapy/Standard of Care where stated.

c. Subjects were admitted to the research unit for study drug administration, surgery, and postoperative observation (Day 1 to Day 4). Tanezumab was administered prior to surgery on Day 1; surgery was performed on Day 2, 12 ± 4 hours after administration of study drug.

d. Terminated: Incomplete Enrollment, Incomplete Duration, Due to FDA partial clinical hold and global self-imposed hold in 2010.

e. Study 1044 was affected by the partial clinical hold; enrollment could not be completed (only two patients were randomized, both to placebo). Safety data from Study 1044 are not included in the safety analysis of tanezumab.

f. Cancer pain Study 1061 is ongoing, currently an indication for cancer pain is not being sought and data are blinded hence not included in this submission. The columns have been left blank.

Table 42. Clinical Studies in Healthy Volunteers

Study/Country	Study Design/Key Features	N (Randomized)	Treatment Duration wks (# Doses)	Follow-up Duration (wks)	Tanezumab Doses/Comparator Treatments (# of Treated Subjects)
1013 US	PK and safety of a single dose SC or IV administration of TAN in healthy volunteers: An OL, non-randomized Phase 1 study Objectives: To assess the safety, tolerability and immunogenicity of TAN when administered SC or IV in healthy subjects including Japanese subjects To evaluate the PK of TAN when administered SC or IV in healthy subjects including Japanese subjects To perform exploratory analyses to characterize the time-course of total and bound NGF when administered SC or IV in healthy subjects, including Japanese subjects	76	16 (1)	16	SC 5 mg (20) 10 mg (19) 19 mg (18) IV 10 mg (19)

Study/Country	Study Design/Key Features	N (Randomized)	Treatment Duration wks (# Doses)	Follow-up Duration (wks)	Tanezumab Doses/Comparator Treatments (# of Treated Subjects)
1046 US	A Phase 1, randomized, DB (sponsor-open), PC study to examine the density of IENFD after a single SC administration of Tan in healthy volunteers Objectives: To assess the change in IENF density in skin biopsies from the proximal thigh and distal leg between baseline and post dose time points after a single SC injection of Tan 20 mg or PBO in healthy volunteers To compare the treatment effect between Tan 20 mg SC and PBO on the change in IENF density between baseline and post dose time points in skin biopsies from the proximal thigh and distal leg in healthy volunteers To assess the safety, tolerability, and immunogenicity of a single dose of Tan 20 mg SC in healthy volunteers To evaluate the PK of a single dose of Tan 20 mg SC administered in the proximal thigh in healthy volunteers	28	16 (1)	16[a]	20 mg (14) PBO (14)

Source: Clinical Reviewer Anjelina Pokrovnichka
Abbreviations: wks, weeks; DB, double-blind; PC, placebo-controlled; IENFD, intra epidermal nerve fiber density; SC, subcutaneous; Tan, tanezumab; PBO, placebo; PK, pharmacokinetics
a. If one or both biopsy sites indicated ≥50% decrease in IENF density at the Week 16 visit relative to the Baseline measurement, a repeat biopsy from that site was to be performed at the Week 24 visit. If, at the Week 24 visit, a ≥50% decrease in IENF density relative to the Baseline visit was observed, the subject was asked to follow-up at an appropriate time in the future (approximately 6 months) to perform additional biopsies.

Table 43. Observational Studies

Study/ Country	N	Route	Follow-up Duration	Study Design
1055 US	7	IV	15 Months	Multicenter, cohort study with enhanced surveillance to describe the outcomes related to the development of infants up to the age of 15 months who were potentially exposed to Tan or a comparator at conception or in utero in any Tan clinical study at investigational sites overseen by the Schulman and Associates IRB. The postnatal monitoring included assessments at birth (0-2 months), at ~ 8 months, and at ~ 15 months of age. This was an observational study of infants born to a parent who had participated in a Tan clinical study; no active or control study treatments were employed. The objectives of the study were: To evaluate the physical development, the neurological development (including the ANS), and the cognitive development of infants through the age of 15 months who were potentially exposed to Tan or comparator in utero due to either maternal or paternal participation in a Tan clinical study using neurological and physical examination, and using psychological assessment.
1064 Global	154	SC	24 Weeks[a]	Multicenter, long-term observational study to describe the post-operative outcome of patients from Tan Studies 1056, 1057, or 1058 (regardless of treatment group) who underwent a total knee, hip, or shoulder replacement during the treatment period or safety follow-up period of the study. Patients were followed for 24 weeks after the TJR surgery (treatment period or safety follow-up period). The primary objective of the study was: To describe the post-operative outcome of subjects who underwent a total knee, hip, or shoulder replacement while participating in Tan Study 1056, 1057 or 1058 (treatment period and safety follow-up period) Secondary objectives of the study were: To compare the post-operative outcome for Tan 2.5 and 5 mg vs. NSAID for subjects who underwent a total knee, hip, or shoulder replacement while participating in Tan Study 1058 To describe the post-operative outcome of subjects from the 1059, 1061 or 1063 studies who underwent a total knee, hip, or shoulder replacement

Study/ Country	N	Route	Follow-up Duration	Study Design
1065 Global ongoing	4	SC	36 Months	Multicenter, cohort study with enhanced physical and neurodevelopmental surveillance to characterize the outcomes related to the development of infants up to the age of 15 months, who were exposed to Tan, PBO or comparator via maternal exposure at conception or in utero in any Tan clinical study (Studies 1056, 1057, 1058, 1059, 1061, and 1063) at any investigational site. The postnatal monitoring included assessments at birth, (0-2 months), ~ 8 months and ~15 months of age up to a maximum of 36 months of age as needed. The objective of the study was: To examine post-natal neurologic and cognitive development of infants who were exposed to Tan or PBO or comparator in-utero during the Tan clinical program (through maternal participation in a Tan clinical study) within the following protocols: 1056, 1057, 1058, 1059, 1061 and 1063 The specific objective was: To evaluate physical development, neurological development (including the ANS) and cognitive development through the age of 15 months of infants (and possibly beyond until the infant is considered stable in the judgment of the pediatric neurologist, developmental psychologist or pediatrician) exposed to Tan, PBO or comparator in-utero due to maternal participation in a Tan clinical study. All observed or volunteered SAEs and non-serious neurological or neuro-developmental adverse events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported.

Source: Clinical Reviewer Anjelina Pokrovnichka
Abbreviations: IV, intravenous; SC, subcutaneous; Tan, tanezumab; ANS, autonomic nervous system; TJR, total joint replacement; NSAID, nonsteroidal anti-inflammatory drug; PBO, placebo; SAEs, serious adverse events
a.The study was designed with a total duration of patient follow-up of 24 weeks after the total joint replacement surgery

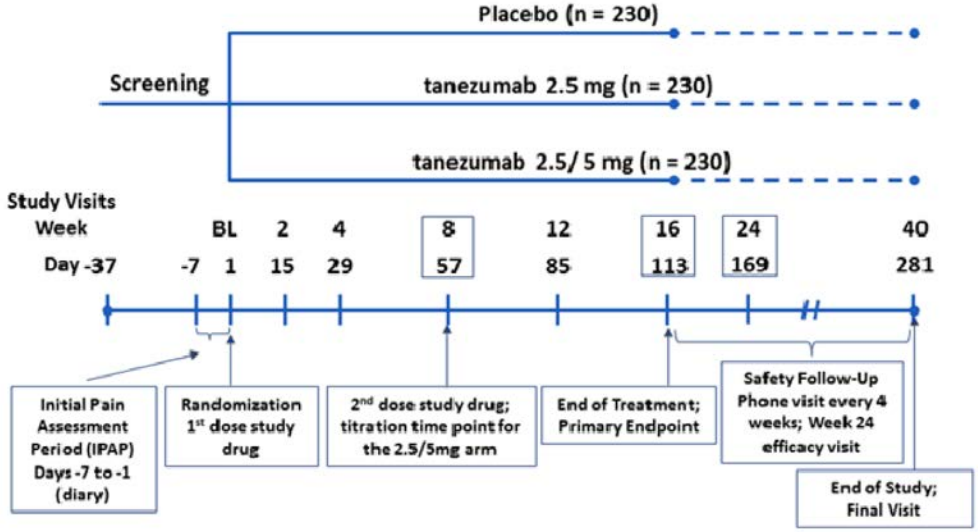
Table 44. Non-Interventional Studies

Study/Country	N	Study Objectives
1505 US, UK	The survey instrument was administered to 602 respondents in the US and 437 respondents in the UK	Patient preferences for OA pain and CLBP treatments in the US and UK The objective of the study was: To quantify US and UK pts' preferences for attributes of pharmaceutical treatments for moderate-to-severe musculoskeletal pain associated with OA and/or CLBP that are both relevant to pts and that differentiate Tan from alternative analgesics. Including NSAIDs, opioids, and other NGF-inhibitor products and to quantify both the relative importance of each of these treatment attributes to pts and the tradeoffs they are willing to make among these attributes. A secondary objective of this study was to explore heterogeneity in preferences for 9 prespecified subgroup pairs. An exploratory objective was to use latent class analysis to further explore preference heterogeneity in the sample.
1089 US	81909 No direct contact with patients	Non-Interventional retrospective cohort study. Incidence of opioid abuse, dependence and overdose in OA pts prescribed opioids in the US The objectives of the study were: To identify a cohort of pts diagnosed with OA who have used at least 2 specific analgesic medications in the past 24 months. Sub-divide the pts into cohorts of opioid new users and non-users of opioids (new users of the NSAID, DIC). Assess baseline characteristics of each cohort to show the extent that the OA cohorts are reflective of the Tan target population Estimate the incidence rates for a diagnosis of opioid abuse or dependence from any medical setting, opioid overdose recorded during a hospitalization or ED visit, opioid overdose that is linked with death occurring either during the ED or inpatient stay, or up to 30 days following discharge (i.e., a subset of all opioid overdoses above)

Source: Clinical Reviewer Anjelina Pokrovnichka
Abbreviations: OA; osteoarthritis; CLBP; chronic lower back pain; NGF, nerve growth factor; NSAID, nonsteroidal anti-inflammatory drug; DIC, diclofenac; ED, emergency department

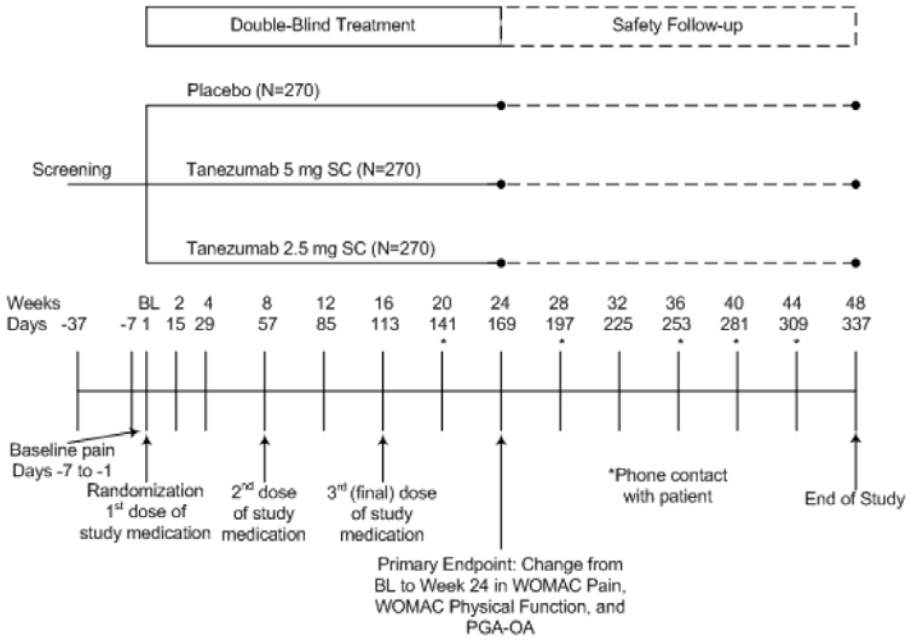
6.2. Nonsteroidal Anti-Inflammatory Drugs Study Schematic of Post-2015 OA Studies

Figure 15. Study 1056



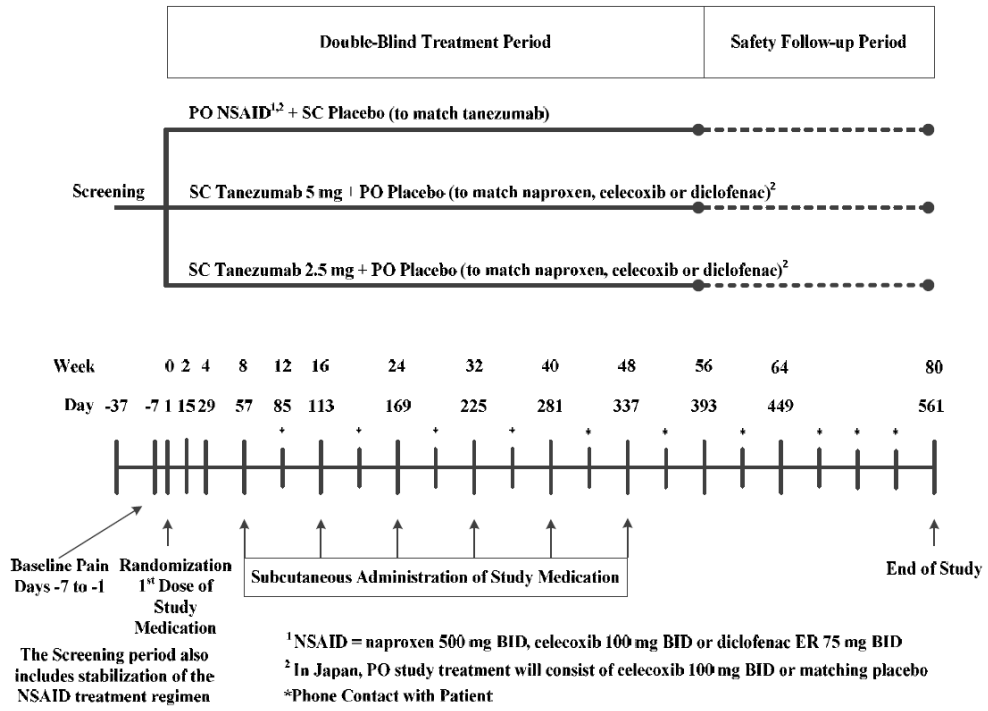
Source: Applicant's figure

Figure 16. Study 1057



Source: Applicant's figure

Figure 17. Study 1058



Source: Applicant's figure

6.3. OA Studies: Comparative Summary of Key Design Elements

Given the large number of studies, in lieu of a protocol synopsis for each study, an outline and discussion of the important differences between the studies will be provided in this section.

As explained in Section I, Briefing Memorandum to the Committee the identification of the joint destruction signal resulted in the dichotomization of the clinical studies into two eras, pre-2015 and post-2015. Most of the differences between the pre- and post-2015 studies were driven by the risk mitigation measures instituted in post-2015 studies (Section III.4.7) to minimize the deleterious effect of tanezumab on joints.

6.3.1. Study Design

There were a total of 16 Phase 3 OA studies. Twelve were of a randomized, controlled design; four were uncontrolled. The control arm, route of tanezumab administration, duration of treatment, dose, and whether tanezumab was administered as monotherapy or in combination with NSAIDs varied between studies.

Table 45 is a pictorial summary of the Phase 3 OA studies.

Table 45. Phase 3 OA Studies by Study Design Features

Study Type	Short-term	Long-term
Pre-2015 (13 studies)		
Controlled (9 studies) TAN mono	Placebo and Active **1011**[b] IV 24 wk **1014**[b] IV 24 wk **1026**[a] IV 24 wk **1027**[ab] **SC** 16 wk **1030**[a] IV 16 wk	
TAN+NSAID	Active **1017**[a] IV 16 wk	
TAN mono and TAN+NSAID		Active **1025**[a] IV **56 wk**
Uncontrolled (4 studies)		Uncontrolled **1016***[a] IV 104 wk **1032***[a] **SC** 56 wk **1043***[a] **SC** 56 wk
Post-2015 (3 studies)		
Controlled (3 studies) TAN mono	Placebo **1056**[b] SC 16 wk **1057**[b] SC 24 wk	Active **1058**[b] SC 56 wk

(Source: Clinical reviewer Anjelina Pokrovnichka)
Abbreviations: TAN, tanezumab; mono, monotherapy, NSAID, nonsteroidal anti-inflammatory drug
*Standard of care pain treatment allowed.
a. Enrollment and/or duration affected by the clinical hold.
b. Controlled studies in which 2.5 mg tanezumab dose was administered.

6.3.2. Study Treatments

Table 46 summarizes the dose and route of administration of study drugs administered in Phase 3 OA studies.

The switch in route of administration from IV to SC was not necessarily driven by the joint safety signal. The Applicant explored switching the route of administration to provide a more practical method to administer tanezumab via a parenteral route that can be easily operationalized in real world practice. Three out of the 13 Phase 3 pre-2015 OA studies were conducted with SC tanezumab (1027, 1032, and 1043) and in all post-2015 studies, tanezumab was administered via the SC route. We note that the absolute bioavailability of tanezumab administered SC is 62%-76%. To assess the effect of the change in route on efficacy, the Applicant conducted pharmacokinetic/pharmacokinetic modeling. Pfizer concluded that the difference in exposure would correlate to a difference of 0.1 to 0.2 points (treatment effect size was 0.5-0.6 out of 10 on the WOMAC scale). There was no prediction made on the effect of SC dosing on safety.

Table 46. Study Drugs Administered in Phase 3 OA Studies

Study drug	Study
Tanezumab 2.5 mg IV	1011, 1014, 1016*
Tanezumab 5 mg IV	1011, 1014, 1015, 1016*, 1018, 1025, 1026, 1030, 1040*
Tanezumab 10 mg IV	1011, 1014, 1015, 1016*, 1018, 1025, 1026, 1027, 1030, 1040*
Tanezumab 2.5 mg SC	1027, 1032*, 1043*, 1056, 1057, 1058
Tanezumab 5 mg SC	1027, 1056, 1057, 1058
Tanezumab 10 mg SC	1027, 1043*
Tanezumab 2.5 mg IV + NSAID	1017
Tanezumab 5 mg IV + NSAID	1017, 1025
Tanezumab 10 mg IV + NSAID	1017, 1025
Diclofenac ER 75 mg BID	1017
Naproxen 500 mg BID	1015, 1018, 1025, 1058
Celecoxib 100 mg BID	1025, 1058
Oxycodone CR 10-40 mg q 12h	1030
Placebo	1011, 1014, 1015, 1018, 1026, 1027, 1030, 1056, 1057

Source: Clinical reviewer Anjelina Pokrovnichka
Abbreviations: OA, osteoarthritis; IV, intravenous; SC, subcutaneous; BID, twice daily; NSAID, nonsteroidal anti-inflammatory drug
*In the uncontrolled studies (1016, 1032, 1040, and 1043), standard of care medications were allowed to be used.

6.3.3. Duration of Follow-Up Period

The follow up period did not start after the last dose of study drug but after the end of the treatment period, which is eight weeks after the last dose of study drug.

For joint-related adverse events, the risk of developing an event appears to persist long after treatment discontinuation. Thus, longer follow-up is important to accurately characterize the incidence rate of these events. As reflected in Table 47, for studies conducted after the lift of the clinical hold, the Applicant was required to extend the follow up period from eight to 24 weeks.

Table 47. Duration of Follow-up Period in OA and CLBP Studies

	Ph2 OA pre-2015	Ph3 OA pre-2015	Ph3 OA post-2015	CLBP pre-2015	CLBP post-2015
Duration of follow-up (wks)	5 to 32	8 Except in 1030: 2 wks	24	8	24

Source: Medical reviewer Anjelina Pokrovnichka
Abbreviations: OA, osteoarthritis; CLBP, chronic lower back pain; wks, weeks; Ph2, phase 2; Ph3, phase 3

6.3.4. Key Eligibility Criteria

OA Diagnosis

In the **Pre-2015 OA studies,** eligible patients were to have a diagnosis of knee and/or hip OA based on the ACR criteria with X-ray confirmation (KL grade of ≥2). It is important to note that in these studies, X-rays of the index joint taken within the last 12 months may have been used for confirmation. Imaging studies of other joints prior to enrollment were not required. The absence of recent baseline imaging in many cases compromises the interpretation of the joint events detected on study.

The **Post-2015 OA studies,** enrolled patients with a diagnosis of knee and/or hip OA based on the ACR criteria with X-ray confirmation (KL grade of ≥2 as diagnosed by the Central Reader). In these studies, X-rays of both knees, both hips, and both shoulders were obtained at Screening and evaluated by the Central Reader for study eligibility.

Response to Prior Pain Therapies

Table 48 provides a comparative description of the eligibility criteria for response to prior pain therapies in key efficacy studies.

Table 48. Eligibility Criteria for Response to Prior Pain Therapies in Key Efficacy OA Studies

	Placebo-Controlled Studies		Placebo- and Active-Controlled Studies	Active Controlled Studies	
Criteria	1011, 1014, 1027	1056, 1057	1015, 1018	1025	1058
Unsatisfactory prior therapies	Non-opiates inadequate/ unable/ unwilling *or* candidate for invasive intervention	**APAP** inadequate *and* **NSAID** inadequate/ unable, *and ≥1 of:* **TRA** inadequate/ unable *or* **Opioid** inadequate/ unable/ unwilling	None	None	APAP inadequate *and ≥1 of:* TRA inadequate/ unable *or* Opioid inadequate/ unable/ unwilling
Patient tolerating and experiencing some benefit from regular use of prior therapies but still requiring additional pain relief	None	None	None	**NAP** 500-1000 mg/day *or* **CEL** 200 mg/day	NSAIDs [a] with 70% compliance for the final 2 wks of screening

Source: Modified Applicant's Table 26, from 2.7.3 Summary of Clinical Safety, page 151
Abbreviations: OA, osteoarthritis; APAP, acetaminophen; NSAID, Non-steroidal anti-inflammatory drug; TRA, tramadol; naproxen; CEL, celecoxib
a. Naproxen [440 mg (sodium salt) or 500 mg to 1000 mg/day], Celecoxib (200 mg/day), Diclofenac (100 to 150 mg/day), Aceclofenac (200 mg/day), Loxoprofen (120 to 180 mg/day), Ibuprofen (1200 to 3200 mg/day), Meloxicam (5 to 15 mg/day), Nabumetone (1000 to 2000 mg/day), Sulindac (200 to 400 mg/day), Ketoprofen (200 mg/day).

The eligibility criteria pertaining to the response to prior therapies in the pre-2015 and the post-2015 OA studies do not appear to be substantially different. Both describe an OA population resistant to therapy. Nevertheless, adding a requirement for failed or not willing to use opioids in post-2015 studies, and baseline WOMAC Physical function score of ≥ 5 instead of ≥ 4, likely selects for a patient population with more severe OA in post-2015 studies.

Inadequate response or contraindication to non-opioids was a requirement in both, pre-2015 and post-2015 placebo-controlled studies. In post-2015 studies, inadequate response, contraindication, or unwillingness to take opioids was added. However, pre-2015 studies required subjects to be candidates for invasive intervention, which indirectly speaks for unresponsiveness to available noninvasive therapies, which, although not specified, may have included opioids.

Pain, Physical Function, and Patient Global

Table 49 summarizes the enrollment criteria for WOMAC pain, function, and global. Slightly higher scores were required in post-2015 (≥ 5) than pre-2015 studies (≥ 4) for baseline WOMAC pain in the active-controlled studies and WOMAC physical function in the placebo- and active-controlled studies.

Table 49. Eligibility Criteria for WOMAC Pain, Function and Patient Global – OA Controlled Studies

	Placebo-Controlled Studies		Placebo- and Active-Controlled Studies	Active-Controlled Studies	
Criteria	1011, 1014	1056, 1057	1015, 1018, 1027, 1030	1017, 1025, 1026	1058
WOMAC pain index joint at Screening	≥ 4	≥ 5	≥ 4	≥ 4	≥ 5
WOMAC pain at Baseline	≥ 5	≥ 5	≥ 5	≥ 4	≥ 5
An increase in WOMAC pain for patients taking pain medications (>4 day/week) before Screening.			≥ 1 point		
WOMAC Physical function at Baseline	≥ 4	≥ 5	≥ 4	≥ 4	≥ 5
PGA of OA at Baseline	"fair" "poor," or "very poor"				

Source: Medical reviewer Anjelina Pokrovnichka
Abbreviations: WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; OA, osteoarthritis; PGA, Patient Global Assessment; NRS, numerical rating scale

Joint-Related Medical History

As described in Table 50, the post-2015 studies excluded patients with predicted risk factors for RPOA. The extent data have exposed only one clear RPOA risk factor, concurrent, chronic NSAID administration.

Table 50. Eligibility Criteria for Joint-Related Medical History (OA and CLBP Studies)

Pre-2015 OA and CLBP	Post-2015 OA	Post-2015 CLBP
No prespecified criteria for excluding subjects at risk for developing joint destruction, except for: use of oral and/or intra-articular steroids, and h/o significant trauma to index joint	Excluded: Radiographic evidence of: excessive joint malalignment severe chondrocalcinosis other arthropathies metabolic bone disease large cystic lesions tumor lesions stress or traumatic fractures pathologic fracture RPOA atrophic or hypotrophic OA ON SIF History of: significant trauma to knee, hip, or shoulder within 1 year ON or osteoporotic fracture use of oral and/or intra-articular steroids	Same as for post-2015 OA studies plus excluding subjects with OA based on the following criteria: Excluded: KL Gr. ≥ 2 of hip OA and KL Gr. ≥3 of knee OA and radiologic findings and symptoms for OA of the shoulder Allowed: KL Gr. 2 knee OA but who do not meet ACR criteria and do not have pain associated with their knee OA Subjects entering the study with asymptomatic knee OA, KLG 2, who progress to KLG ≥3 at Week 24 were discontinued from treatment

Source: Medical reviewer Anjelina Pokrovnichka
Abbreviations: OA, osteoarthritis; CLBP, chronic lower back pain; ON, osteonecrosis ; SIF, Subchondral insufficiency fracture; KLG, Kellgren-Lawrence grade

Neurological Medical History

Table 51 summarizers the exclusion criteria for neurological conditions in pre- and post-2015 studies. Exclusion of patients with radiculopathy, carpal tunnel syndrome, and autonomic neuropathy were added in post-2015 studies.

Table 51. Exclusion Criteria for Neurological Conditions in OA and CLBP Studies

	Pre-2015 studies	Post-2015 studies
Central nervous system	TIA within 6 months and stroke with residual deficits that would have precluded completion of study activities.	TIA within 6 months and stroke with residual deficits that would have precluded completion of study activities.
Peripheral nervous system	Peripheral neuropathy Lab findings suggestive of diabetes: HgA1c ≥10%	Peripheral neuropathy Lab findings suggestive of diabetes: HgA1c ≥10% Regional pain caused by lumbar or cervical compression with radiculopathy, including present history of sciatica Patients with history of sciatica who were asymptomatic for at least one year and who had no evidence of radiculopathy or sciatic neuropathy on neuro exam were eligible to enroll History of CTS with signs or symptoms in the one year prior to Screening Autonomic neuropathy OH Total SAS impact score of >7

Source: Medical reviewer Anjelina Pokrovnichka
Abbreviations: TIA, Transient ischemic attack; HgA1c, glycosylated hemoglobin; CTS, carpal tunnel syndrome; OH, Orthostatic hypotension; SAS, Survey of Autonomic Symptoms

Cardiac Medical History

Throughout clinical development, patients a high risk for a cardiovascular adverse event were not deemed eligible to participate in tanezumab studies.

The following exclusion criteria for cardiovascular conditions were applied for studies conducted pre- and post-2015.

- Signs and symptoms of clinically significant cardiac disease including but not limited to:
  - Ischemic cardiac disease (e.g., unstable angina, myocardial infarction) in the past 6 months
  - Surgery or stent placement for coronary artery disease in the past 6 months
  - New York Heart Association Class III or IV congestive heart failure or known left ventricular dysfunction with ejection fraction ≤35%, cardiomyopathy, myocarditis in the past 6 months
  - Resting tachycardia (HR ≥120 bpm) or resting bradycardia (HR ≤45 bpm) on ECG
  - QTcF interval >500 mSec in the absence of confounding factors like bundle branch block or paced rhythm
  - Any other cardiovascular illness that in the opinion of the Investigator would render a patient unsuitable to participate in the study
  - Patients with a history of heart block that was controlled by a functioning cardiac pacemaker were eligible.
- Resting, sitting BP ≥160 mm Hg in systolic pressure or ≥100 mm Hg in diastolic pressure. If a patient was found to have untreated hypertension at Screening and treatment was initiated, assessment for study eligibility could be deferred until BP and antihypertensive medication were stable for at least one month. For patients with

previously diagnosed hypertension, antihypertensive medications must have been stable for at least one month prior to Screening.
- Replicated orthostatic BP measurements
- Renal medical history

Patients with abnormal kidney function, defined as creatinine exceeding 1.7 mg/dL (150 μmol/L) in men or 1.5 mg/dL (133 μmol/L) in women, were excluded from pre- and post-2015 studies.

6.3.5. Concomitant Therapies

Rescue

In all controlled OA (and CLBP) studies, the rescue medication was acetaminophen. The dose and duration allowed during the double-blind treatment period varied between studies from 3000 mg to 4000 mg per day for three or five days. Patients who had taken rescue more frequently and indicated that could not follow the protocol requirements because of insufficient pain relief were withdrawn from treatment due to lack of efficacy.

Use of NSAIDs

Pre-2015 Studies

In the placebo-controlled OA studies conducted prior to 2015, use of analgesics (including NSAIDs) other than the designated rescue was not allowed during the blinded treatment period. In the uncontrolled OA studies, NSAIDs could be used with no restrictions for duration of use. In two active-controlled studies, 1017 and 1025, safety and efficacy of tanezumab added to a NSAID was investigated.

Post-2015 Studies

In the post-2015 studies, the use of prescription or over-the-counter (OTC) NSAIDs were prohibited except on an occasional basis for self-limited conditions not related to OA. NSAID use was not to exceed a total of 10 days in every 8-week dosing interval, 30 days for 6 months, and 60 days for 1 year and they were not to be taken within 48 hours (or five half-lives, whichever was greater) of a study visit where efficacy assessments were being collected. Beginning at 16 weeks after the last dose of study medication, patients could use NSAIDs at their discretion.

Patients taking more than 10 days of NSAIDs per 8-week dosing interval were interviewed to determine the reason for use. Patients who indicated they were taking NSAIDs because of insufficient pain relief or those who continued to be non-compliant were withdrawn from study treatment.

Daily low dose aspirin (≤325 mg) for cardiovascular prophylaxis was permitted without restriction.

Concomitant Non-Pharmacologic Therapies

In both pre- and post-2015 OA studies, products containing glucosamine sulfate and chondroitin sulfate, or herbal and homeopathic remedies were not to be initiated during the study; however, patients who had taken a stable dose of these products for at least 30 days prior to randomization could continue their regimen. Patients were asked to maintain stable exercise program.

6.3.6. Joint Safety Monitoring

Pre-2015 studies did not include assessments focused on joint safety.

Post-2015 studies included the following pre-defined, prospective joint safety assessments:

- Musculoskeletal exam
  - At baseline and each follow-up visit, all major joints were examined and patient-reported information on joint symptoms was collected. Clinically significant change in symptoms or exam as determined by the investigator was reported as an AE.
- Evaluation for increased, severe, and persistent joint pain
  - Pain scores from the electronic diary were monitored to identify patients who had a pattern of severe pain over several days or a rapid increase in pain.
  - Patients with increased severe and persistent pain (score of 7-10 on a 11-point NRS for at least two weeks despite treatment) or patients with other clinically significant findings had X-rays of the joint(s) obtained and sent to the Central Reader. MRIs were not required but could be obtained if warranted. Patient were also referred to an orthopedic surgeon if needed.
- Imaging surveillance

Studies conducted after 2015 included the following imaging assessments:

- In all studies, X-rays of bilateral knees, hips, shoulders, and any other joint exhibiting signs and symptoms of OA were obtained at baseline and pre-specified time points during the study (Table 52).
- In all studies, "for cause" X-rays were obtained for joint(s) with increased severe or persistent pain or clinically significant findings on exam and assessed by the Central Reader for possible or probable joint safety event. "For-cause" MRIs could be acquired at the investigator's discretion or by Central Reader request (Table 53). An MRI requested for cause and received from the clinical site was assessed by the Central Reader if the lead study clinician approved the reading of the MRI. If an MRI was submitted by the site but did not seem to be submitted for cause, this MRI could not have been evaluated.
- In Study 1058 only, the following on-study MRI scans were obtained (Table 53):
  - Patients with confirmed X-ray eligibility also had an MRI of each hip and knee as part of the Screening.
  - Patients with KLG 3 or 4 in any knee or hip as determined by the Central Reader at the Screening X-ray, had a follow-up MRI of each hip and knee at Week 24, 56, and 80 (or Early Termination).

— However, although collected, the MRI scans were read under only the following two conditions:

  - When the interpretation of an X-ray indicated a possible joint safety finding and the MRI exam had to be read to complete the assessment.
  - When the central read of the MRI confirmed the presence of a joint safety finding and a subject was escalated for Adjudication Committee review, the MRI exams of all other joints were read in order to have a comprehensive assessment of the subject.

Table 52. Schedule of Radiographic Assessments in Post-2015 OA and CLBP Studies

Study	Population	Duration of treat.	X-ray							
			Screening	Week 24	Week 40	Week 48	Week 56	Week 80	Early Term. Visit 1*	Early Term. Visit 3 24 wks after last dose
1056	OA	16	X		X				X	X
1057	OA	24	X	X		X			X	X
1058	OA	56	X	X			X	X	X	X
1059	CLBP	56	X	X			X	X		
1063	CLBP	24	X	X					X	X
1063	CLBP	24	X	X					X	X

Source: Clinical reviewer Anjelina Pokrovnichka
Abbreviations: OA, osteoarthritis, CLBP, chronic lower back pain
*As soon as possible after determining that the treatment will be discontinued and provided that at least 30 days have passed since the last set of X-rays were collected.

Table 53. Schedule of MRI Assessments in Post-2015 OA and CLBP Studies

Study	Joint	MRI	
		Screening	Post-baseline
1056 (OA)	S/H/K	-	'For cause'
1057 (OA)	S/H/K	-	'For cause'
1058 (OA)	Shoulder	-	'For cause'
	Hip	Required[1]	Required[2] 'For cause'
	Knee	Required[1]	Required[2] 'For cause'
CLBP studies	S/H/K	-	'For cause'

Source: Clinical reviewer Anjelina Pokrovnichka
Abbreviations: CLBP, chronic low back pain; MRI, magnetic resonance imaging; OA, osteoarthritis; S/H/K, shoulder, hip, knee
[1] MRI of both knees and hips required in all subjects
[2] MRI of each hip and knee required at study visits (Week 24, 56, 80, or early termination) for subjects with any knee or hip with KLG 3 or 4 at screening
'For-cause MRI' could be acquired at the investigator's discretion or by central reader request.

6.3.7. Central Reader

Scheduled imaging assessments were required in all post-2015 studies and program-level central musculoskeletal (MSK) radiologists read all imaging. The Applicant termed the treatment-blinded MSK radiologists "Central Readers." The work scope of the Central Reader (CR) was to evaluate subjects for eligibility and to monitor joint safety via imaging during the study. The primary functions of the CR were to provide consistent reads of imaging studies and to make an initial diagnosis of a Joint Safety Event which triggered treatment discontinuation.

The criteria outlined in Table 54 were used by the CR for KLG scoring.

Table 54. Kellgren-Lawrence Grade Scoring Criteria

Grade	Definition
0	No abnormality detected; No features of OA
1	Doubtful changes; minute osteophyte of doubtful significance or equivocal diminution of joint space of doubtful significance
2	Minimal; definite osteophyte, with mild diminution of joint space
3	Moderate; definite diminution of joint space with at least a minimal osteophyte
4	Severe; joint space greatly impaired with sclerosis of subchondral bone

Source: Imaging charter provided by the Applicant
Abbreviation: OA, osteoarthritis

Historical radiographs of prospective subjects could be submitted and evaluated for the purposes of ruling out RPOA during the screening period. Imaging studies that were obtained outside the protocol-specified activities were also read by the CR. Available pain scores were presented during reading with the purpose of identifying changes in pain that were discordant with radiographic findings. In certain cases of discordant pain, and if not required per protocol, the CR could suggest an MRI for further investigation of the joint.

The following conditions were considered to possibly lead to an increased risk of a joint event and patients who were identified to have any of these conditions were not eligible for enrollment.

- SIF
- Atrophic/hypotrophic OA

- Excessive malalignment of the knee
- Osteonecrosis
- Chondrocalcinosis (severe)
- Other arthropathies, e.g., rheumatoid arthritis, pseudogout
- Systemic, metabolic bone disease, e.g., Paget's disease, metastatic calcifications
- Tumors, primary or metastatic
- Fractures (stress, traumatic, pathologic)
- Large cystic lesions

The process for identification of possible or probable RPOA1 events by the CR in post-2015 studies was originally based on the joint space width (JSW) measurement from X-rays. After the first possible or probable case of RPOA1 was identified based on radiographic JSW measurements, the Applicant became concerned that variability in JSW measurements due to sub-optimal/inconsistent positioning could occur despite efforts to train clinical sites to collect high quality X rays and quality control reviews at the Central Radiology vendor. Therefore, in August 2016, the process for identifying possible or probable RPOA1 events by the CR was modified. From that point forward, for patients with decreases in JSW ≥2 mm within approximately 1 year on X rays, MRI was performed and assessed by the CR before making a final classification for the event.

6.3.8. Adjudication Committee

Potential joint safety events were evaluated by a blinded Adjudication Committee (AC). The primary function of the AC was case ascertainment for reporting. The AC did not function as a risk mitigation in the tanezumab program. The difference in the adjudication process between the pre- and post-2015 studies is illustrated in Table 55.

Table 55. Joint Analysis and Adjudication in Pre-2015 and Post-2015 Studies

	Pre-2015	Post-2015
Assessment	Retrospective blinded	Predefined, prospective, blinded, including imaging, exam, review of AEs and pain intensity
Medical specialty of adjudication committee members	Orthopedic surgeons, rheumatologists, and pathologist	One each: Orthopedic surgeon, rheumatologist, radiologist, and pathologist
Cases reviewed	Patients with all-cause TJR Patients with reported ON regardless of whether they underwent TJR or not	Investigator-reported joint events based on AEs and/or imaging Possible or probable joint events identified by the CR's assessment of imaging TJR during treatment or 24-week safety f/u period
Adjudication categories	Primary ON Worsening OA a. RPOA (Type 1 or Type 2) b. Normal progression c. Not enough information to distinguish b/w the two Other (with Dx specified) Not enough information to distinguish b/w primary ON and worsening OA or specify another Dx.	Primary ON Worsening OA a. RPOA (Type 1 or Type 2) b. Normal progression c. Not enough information to distinguish b/w the two SIF Pathologic fracture. Other (with Dx specified) Not enough information to specify Dx.
Criteria for defining RPOA	RPOA1: Change of ≥1 mm in joint space narrowing in 1 year RPOA2: Abnormal loss/destruction of bone that is not normally present in conventional end-stage OA	RPOA1: Change of ≥2 mm in joint space narrowing in 1 year without gross structural failure RPOA2: Abnormal loss/destruction of bone including limited or total collapse of at least one subchondral surface that is not normally present in conventional end-stage OA
Final categorization of event	Four members required to provide final assessment for an event and three out of the four must agree on the categorization for the case to be closed	Four members required to provide final assessment for an event and three out of the four must agree on the categorization for the case to be closed

Source: Clinical reviewer Anjelina Pokrovnichka
Abbreviations: b/w, between; CR, central reader; Dx, diagnosis; RPOA, rapidly progressive osteoarthritis; OA, osteoarthritis; ON, osteonecrosis; SIF, subchondral insufficiency fracture; TJR, total joint replacement

Of note, the ability to identify RPOA1 events in pre-2015 studies was limited because few patients in these studies had serial radiographs allowing for measurement of joint space width over time.

Neurological safety monitoring in all tanezumab studies, peripheral neurological safety was monitored and evaluated through assessment of AEs, neurological examinations by investigators at each clinic visit, and by referring patients for neurological consultation if they met pre-specified criteria.

In pre-2015 studies, a neurologic consultation was required for any AE suggestive of new or worsening peripheral neuropathy or any AE of abnormal peripheral sensation or for a clinically significant change on a patients' neurologic examination. In post-2015 studies, neurologic

consultation was required if the AEs or neurologic examination changes were reported as 1) a SAE or 2) an AE which has resulted in the patient being withdrawn from the study, or 3) an AE ongoing at the end of the patient's participation in the study, or 4) an AE of severe intensity. As a result of the change in requirements for neurologic consultation, neurological consultation was requested for fewer patients in post-2015 studies compared to pre-2015 studies.

6.3.9. Subject and Study Stopping Criteria

Subject-Level Stopping Criteria

For neurosensory Symptoms (Same in Pre- and Post-2015 Phase 3 Studies)

Transient, resolved dysesthesia/allodynia: Administer study drug as planned if the condition has resolved before the next scheduled dose.

Unresolved dysesthesia/allodynia: Withhold study drug for a maximum of 14 days beyond the planned dosing day to allow for resolution of the AE. If the dysesthesia/allodynia has not resolved within the 14-day period after the scheduled dosing date, the subject will not receive any additional doses.

For Orthostatic Hypotension and Sympathetic Function AEs (Only in Post-2015 Studies)

Orthostatic hypotension: Confirmed blood pressure changes meeting prespecified criteria (Table 56) and reported as an AE whether or not the subject had accompanying symptoms.

Table 56. Orthostatic Blood Pressure Changes

Mean Supine Systolic BP	Decrease in BP Defining Orthostatic Hypotension	Actions (for Both Criteria)
≤150 mm Hg	≥20 mm Hg systolic **or** ≥10 mm Hg diastolic	Repeat the sequence of measurements (supine and standing) up to two times. If either the 1- or 3-minute standing BP meets the orthostatic hypotension (OH) criteria, then that sequence is considered positive. If 2 of 2 or 2 of 3 sequences are positive, then OH is considered confirmed and reported as an AE.
or		
>150 mm Hg	≥30 mm Hg systolic **or** ≥15 mm Hg diastolic	

Source: Clinical reviewer Anjelina Pokrovnichka
Abbreviations: BP, blood pressure; OH, orthostatic hypertension

Subjects with confirmed orthostatic hypotension (OH) were evaluated to determine if a neurology or cardiology consult was needed and/or whether treatment with study drug may continue.

- If no apparent medical cause (e.g., dehydration, illness, medications) was identified, the dosing was suspended and subject further evaluated for the presence of sympathetic autonomic neuropathy by a cardiologist or neurologist. If absence of sympathetic neuropathy was confirmed and there were no symptoms of OH, bradycardia, syncope, anhidrosis, or hypohidrosis, dosing with study drug was continued, provided that no more than 12 weeks have elapsed since the last dose. If sympathetic neuropathy was

confirmed, treatment was discontinued, and patient entered early termination follow-up period.
- If an apparent medical cause was identified, the subject had a repeat assessment of OH performed at least 1 week later but not more than 4 weeks later. During this time, attempts were made to address the underlying medical cause of the OH.

Sympathetic function AEs:

- Subjects reporting AEs with preferred terms of bradycardia, syncope, OH, anhidrosis or hypohidrosis were further evaluated for the presence of sympathetic autonomic neuropathy by a cardiologist or neurologist.

Bradycardia was defined as follows:

- Significant bradycardia (heart rate of ≤45 beats per minute (BPM) on an ECG, exclusionary at Screening).
- Heart rate decrease from Screening of ≥25% with resulting heart rate <60 BPM

The dosing in these subjects was suspended until the absence of sympathetic autonomic neuropathy has been confirmed. Subjects who were deemed not to have a sympathetic autonomic neuropathy could continue the study provided no more than 12 weeks have elapsed since the last dose. Subjects found to have a sympathetic autonomic or were not found to have sympathetic autonomic neuropathy but were still symptomatic, discontinued treatment.

For Joint Events (Only in Post-2015 Studies)

- Patients with increased or severe joint pain (≥7 on 11 NRS) for at least 2 weeks despite treatment with analgesic medication underwent further evaluation by the investigator and additional imaging and/or orthopedic evaluation, if warranted, prior to continuing treatment.
- Subjects determined by the CR to have a possible or probable joint safety event were withdrawn from treatment and entered the Early Termination Follow-up period.

For Lack of Efficacy Response (Only in Long-Term Post-2015 Studies)

In order to continue receiving study medication beyond 16 weeks in Study 1058 and Study 1059, patients had to meet the following response criteria:

- ≥30% reduction in WOMAC Pain subscale relative to Baseline in the index joint
- ≥5% reduction in WOMAC Pain subscale from Baseline at either Week 2, 4, or 8

Study/Program Stopping

For Neuropathy and Sympathetic Events

- If a given prespecified serious adverse event was reported in three more subjects in any individual tanezumab treatment group than for control group subjects

For Joint-Events

For Studies 1056 and 1057 (2 or 3 doses)

The protocol (or treatment group) stopping rule was based on the assessment of the number of subjects with adjudicated events of interest (**RPOA2, SIF, ON, or pathological fracture)** during the study. Assuming the rate of adjudicated events in the placebo group was no more than 6 per 1000 patient-years, if adjudicated events of interest were reported in three or more subjects in any tanezumab treatment group than for the placebo treatment group, a treatment-group or protocol-based stopping rule was to be triggered. If the rate of events in the placebo treatment group was higher than 6 per 1000 patient-years, the appropriate threshold number of events for the stopping rule was to be reassessed. If the protocol-based stopping rule was triggered, the data monitoring committee was to formulate a recommendation whether it is safe to continue dosing in some or all treatment groups or whether the study should be terminated completely.

For Study 1058 and the long-term CLBP study

The protocol (or treatment group) stopping rule had three components: 1. The difference in the number of subjects with an adjudicated joint safety event, 2. The exposure-adjusted risk difference (RD), and 3. The exposure adjusted risk ratio (RR) between each tanezumab treatment group and the active comparator group. The exposure-adjusted RD was to be calculated as the difference in the ratios of the number of subjects with an adjudicated joint safety event divided by exposure (patient-years) between each tanezumab group and the comparator group. The exposure-adjusted RR was to be similarly calculated using the ratio of exposure adjusted event rates (number of subjects with an adjudicated joint safety event divided by exposure) for each tanezumab group relative to the comparator group. The exposure was to be calculated as the combined treatment and follow-up periods.

Rule triggered if: RD ≥0.008 (i.e., 8 or more events per 1000 patient-years of exposure), RR is ≥3, and the difference in the number of subjects with adjudicated joint safety events ≥4 for any tanezumab treatment group versus the comparator treatment group.

6.3.10. Phase 2 OA Studies and Studies in Other Painful Conditions

The Applicant conducted four Phase 2 OA studies in which tanezumab was administered IV and dosed on a µg/kg basis. Treatment included either single or two doses of tanezumab and the follow-up period ranged between 5 to 32 weeks. The eligibility criteria, safety monitoring, and stopping criteria in these studies had no particular risk mitigation measures because the joint safety signal emerged later in development. Because NGF is required for survival and growth of sympathetic and nociceptive neurons during certain stages of development, autonomic or sensory neuropathy was a theoretical concern in these early studies. Therefore, patients with peripheral neuropathies and/or findings on the neurological exam suggestive of neuropathies were not allowed to enroll in these studies. In addition, patient was discontinued from treatment for emerging dysesthesia and allodynia that have not resolved by the time of the next scheduled dosing.

The highest dose of tanezumab administered in the development program as a single dose, 1000 µg/kg (or 1 mg/kg), was given in two studies, the bunionectomy Study 1007 and the single

ascending dose Study 1006 in OA patients. In Study 1006, four females with average body weight (BW) 86.7 kg (range 68.5 to 94.3 kg) and two males with average BW 91.2 kg (range 78 to 104.3 kg) received 1 mg/kg tanezumab, corresponding to a fixed dose of tanezumab between 68.5 mg to 104 mg. In Study 1007, seven females with average BW 76.5 (range 69.5 to 83 kg) and one male with BW of 72 kg received 1 mg/kg, corresponding to a fixed dose of tanezumab between 69.5 mg and 83 mg. These two studies were conducted early in development and resulted in identification of the neurosensory safety signal. Tanezumab doses ≥100 µg/kg were clearly associated with the development of neurosensory symptoms.

6.4. CLBP Studies: Summary

Chronic Low back pain (CLBP) is not a proposed indication for the BLA application and the dose levels studied are higher than the proposed dose level for use of tanezumab in patients with OA. The safety review of the CLBP studies is not intended to be a detailed review. The CLBP review focused on general safety for the purpose of trying to identify new safety signals at high dose levels and on joint safety in order to determine the potential adverse effects of high dose of tanezumab on relatively healthy joints in the population not treated for OA.

The five CLBP studies are briefly summarized in Table 57 in terms of study design, treatment plan, and length of safety follow-up period. The eligibility criteria related to joint history and prior medications, the joint safety monitoring procedures including periodic radiographic assessment, the use of concomitant medication, and other design features for CLBP studies have been covered in detail by Dr. Anjelina Pokrovnichka together with her discussions about study design detail in OA studies in the review sections 15.1.

- Four of five CLBP studies were double-blind and controlled with both a placebo and active control in each of the three Studies 004, 012, and Part 1 of Study 059 and an active control alone in Study 063 and Part 2 of Study 059. Study 039 was an extension of Study 012 and had patients receiving placebo, tanezumab 5 mg, or naproxen in Study 012 assigned to tanezumab 10 or 20 mg dose in Study 039.
- Tanezumab was studied at three dose levels (5, 10, and 20 mg) in Study 012, two dose levels (10 and 20 mg) in Study 039, and two dose levels (5 and 10 mg) in Studies 059 and 063. Weight-based dosing at 200 µg/kg was studied in the single-dose Study 004.
- Tanezumab was administered by the IV route in Studies 004 and 012, by the SC route in Studies 059 and 063 and given as three IV doses followed by four SC doses in the extension Study 039.
- Short-term studies included studies of up to two tanezumab doses, a single tanezumab dose in Study 004 and two tanezumab doses in Study 012 and Part 1 of Study 059. Long-term studies included studies of seven tanezumab doses in 56 weeks, the combined Studies 012 and 039 and combined Part 1 and 2 of Study 059, and Study 063.
- The duration of the follow-up period was eight weeks in 2-dose studies, Part 1 of Study 059 and Study 012, 12 weeks in single-dose Study 004, and 24 weeks in 7-dose Studies 039, 059, and 063.

Table 57. Summary of CLBP Studies

	A4091004 (004)	A4091012 (012)	A4091039 (039) Extension of 012	A4091059 (059)	A4091063 (063)
Dates	7/5/07 to 9/2/08	6/15/09 to 2/1/11	8/20/09 to 6/22/11	8/18/15 to 10/17/17	5/26/16 to 6/11/19
Site	29 sites US	114 sites US	108 sites US	191 sites in US; multiple foreign sites	58 sites in Japan
Design	Double-blind 12-week	Double-blind 16-week	Partially blinded 56-week, including exposure in Study 012	Double-blind 56 weeks	Double-blind 56 weeks
Treatment group Tan injection	IV single dose Tan 200 µg/kg	IV 2 doses Tan 5 mg Tan 10 mg→ Tan 20 mg→	IV 3 doses →SC 4 doses Tan 10 mg Tan 20 mg	Part 1 SC 2 doses Part 2 SC 5 doses Tan 5 mg Tan 10 mg	SC 7 doses Tan 5 mg Tan 10 mg
PO active controls	Naproxen 500 mg bid for 12 weeks	Naproxen 500 mg bid for 16 weeks	No	Tramadol ER 100 mg qd up to 300 mg qd	Celecoxib 100 mg bid for 56 weeks
Placebo	Placebo	Placebo	(Placebo+Tan5+Nap500 from Study 012 reassigned at 1:2 ratio to Tan10 mg: Tan 20 mg)	Placebo for 16 weeks in Part 1 and in Part 2: assigned at 1:1 ratio to Tar 5 mg: Tan 10 mg	No
Follow-up	12 weeks	8 weeks	8 weeks	24 weeks	24 weeks

Source: Table created by Christina Fang using data from individual study protocols
Abbreviations: bid, twice daily; IV, intravenous; Nap, naproxen; PO, per oral; qd, once daily; SC, subcutaneous; Tan, tanezumab

7. Efficacy: Additional Information and Assessment

As stated in Section 6.2 of this review remains focused on the three post-2015 studies: 1056, 1057 and the long-term study 1058. Additional detail from the review of efficacy include:

Had Patients Exhausted Their Treatment Options at The Time of Screening in the Post-2015 Studies

Issue

A key risk mitigation measure was that the population to be exposed to tanezumab was defined as having a documented history that previous treatment with acetaminophen, oral NSAIDs (for Studies 1056 and 1057 not Study 1058) and either tramadol or opioids had not provided adequate pain relief, or that they could not be taken by patients due to contraindication, inability to tolerate, or unwillingness to take (for opioids only). It can be difficult to adequately document what therapies were tried and what the results were. Nonetheless, in Studies 1056 and 1057, minimal effort was made by the Applicant to demonstrate this very important factor. As noted

earlier, the Investigator largely relied on patient recall to address the selection criteria around treatment history.

There are some objective data that cast doubt on whether patients were actually treatment resistant. Table 58 summarizes the screen fail rates and reasons for the three key studies.

Table 58. Summary of Screen Fail Data by Reason

Reason	Study 1056	Study 1057	Study 1058
Total screen failed	2474	1248	14496
IC03 – OA per ACR KL≥2	501 (20.3%)	217 (17.4%)	2773 (19.1%)
IC05 – Pain ≥5	472 (19.1%)	169 (13.5%)	2162 (14.9%)
IC09 – Willing to comply with procedures	295 (11.9)	162 (13.0%)	1883 (13.0%)
EC04 – Severe X-ray findings	143 (5.8%)	112 (9.0%)	764 (5.3%)
EC05 – X-ray evidence of RPOA, SIF, ON, etc.	200 (8.1%)	207 (16.6%)	1124 (7.8%)
EC28 (30) – High score on survey of autonomic Sxs	299 (12.1%)	102 (8.2%)	1413 (9.7%)
IC04 – Documented evidence of treatment failure	29 (1.2%)	14 (1.1%)	487 (3.4%)

Source: Table produced by Robert Shibuya from tabular data in the CSRs for Studies 1056-8.
Abbreviations: ACR, American College of Rheumatology; EC, Exclusion Criterion; IC, Inclusion Criterion; KL, Kellgren-Lawrence; OA, osteoarthritis; ON, osteonecrosis; RPOA, rapidly progressive osteoarthritis; SIF, subchondral insufficiency fracture; Sxs, symptoms

The table shows that, compared to other selection criteria that resulted in screen failures, a very small number of patients screened failed due to the requirement for documented evidence of treatment failure. The smallest proportions of these screen failures came from Studies 1056 and 1057.

At the time of the Mid-Cycle Review, the clinical team was unsure whether patients had exhausted their treatment options and this concern was articulated to the Applicant. In response to this, the Applicant submitted some post-hoc analyses, summarized below.

The key data presentations involve 1. Screening data for analgesic use at screening and 2. Pain scores at screening and baseline. The key difference between screening and baseline is that patients found eligible at screening underwent analgesic washout in an initial pain assessment period.

Table 59 (Applicant's Table 2) summarizes the analgesic regimen at the time of screening.

Table 59. Applicant's Table 2

Table 2. Protocol-Qualifying Medication(s) Used During Screening Period and Duration of Use for Medications Used at Screening for Studies 1056 and 1057

	Study 1056 (N=696)			Study 1057 (N=849)		
	N (%)	Mean ± SD Duration (years)[a]	Mean ± SD Duration (years)[b]	N (%)	Mean ± SD Duration (years)[a]	Mean ± SD Duration (years)[b]
None	247 (35.5)			261 (30.7)		
Only acetaminophen	84 (12.1)	6.26 (5.60)	6.26 (5.60)	131 (15.4)	4.23 (4.93)	4.23 (4.93)
Only NSAIDs	131 (18.8)	5.16 (5.39)	5.16 (5.39)	99 (11.7)	2.49 (3.61)	2.49 (3.61)
Only opioids/tramadol	22 (3.2)	2.63 (3.13)	2.05 (2.54)	15 (1.8)	1.07 (1.09)	1.07 (1.09)
Only acetaminophen and NSAIDs	98 (14.1)	6.50 (6.16)	4.06 (4.60)	104 (12.2)	4.05 (5.46)	2.90 (4.56)
Only acetaminophen and opioids/tramadol	20 (2.9)	7.69 (6.65)	2.66 (2.55)	100 (11.8)	3.56 (4.88)	2.02 (2.63)
Only NSAIDs and opioids/tramadol	31 (4.5)	7.84 (10.07)	4.21 (4.89)	18 (2.1)	1.87 (1.70)	1.13 (1.74)
Acetaminophen, NSAIDs, and opioids/tramadol	63 (9.1)	6.29 (5.33)	2.13 (2.26)	121 (14.3)	2.45 (3.44)	1.88 (3.34)

a. If a patient was taking multiple medications at Screening, the medication with the longest duration was summarized.

b. If a patient was taking multiple medications at Screening, the medication summarized was selected by the following hierarchy (longest duration within selected class): opioid, tramadol, NSAID, acetaminophen.

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation

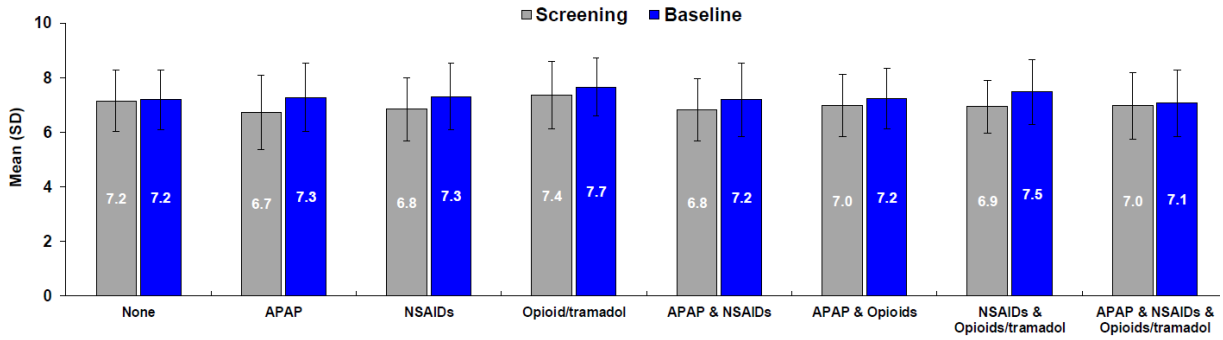
Row 1 (None) is interesting in that it represents perfectly rational behavior. If patients had tried APAP, NSAIDs, and opioids and failed, it makes sense not to take anything. This may be contradictory with human nature but can be construed as evidence that these patients had failed everything and had given up on pharmacologic therapy. The other 2/3 of patients were on monotherapy or some combination of APAP, NSAID, or opioid. This is not necessarily irrational therapy because some patients may report some pain relief albeit the overall effect is inadequate (the protocol required pain of at least 5/10 to qualify).

Figure 18 and

Figure 19 (Applicant's Figures 1 and 2) show pairs of mean pain scores at screening and baseline by screening analgesic regimen in Studies 1056 and 1057.

Figure 18. Applicant's Figure 1

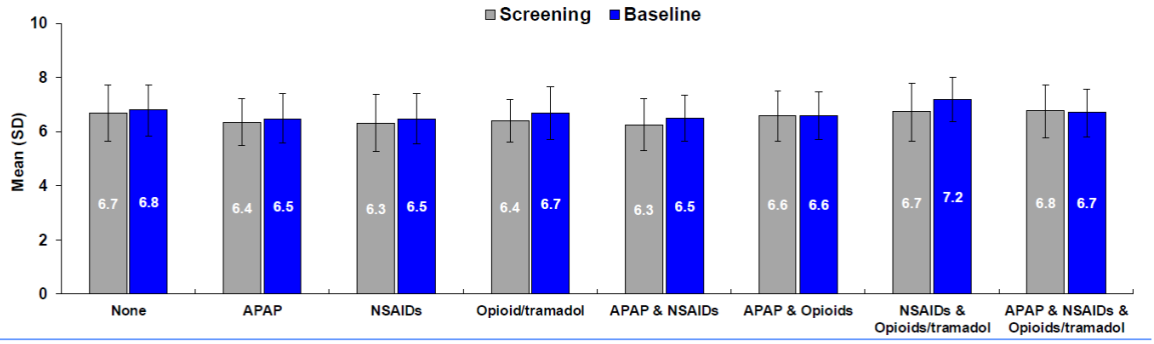
Figure 1. Study 1056 WOMAC Pain Subscale at Screening and Baseline Based on Medication Used During the Screening Period



N	247	84	131	22	98	20	31	63
Mean (SD) Days Scr to BL	26.69 (8.86)	24.11 (7.60)	27.25 (7.36)	24.77 (8.27)	27.00 (7.82)	24.45 (9.06)	25.00 (8.87)	25.37 (8.86)
% of total patients	35.5	12.1	18.8	3.2	14.1	2.9	4.5	9.1

Figure 19. Applicant's Figure 2

Figure 2. Study 1057 WOMAC Pain Subscale at Screening and Baseline Based on Medication Used During the Screening Period



N	253	130	99	15	104	100	18	120
Mean (SD) Days Scr to BL	27.24 (7.80)	30.18 (7.04)	27.27 (6.98)	22.20 (8.11)	29.15 (6.75)	28.74 (7.70)	25.44 (7.74)	28.62 (7.00)
% of total patients	29.8	15.3	11.7	1.8	12.2	11.8	2.1	14.1

These inferential data support the conclusion that patients were not deriving a clinically meaningful benefit from APAP, NSAIDs, or opioids. If the screening analgesics were conveying benefit, the blue (baseline) bar would be higher than the gray bar because the analgesics had been washed out and pain would return. While there is a consistent trend showing that, it is very small. A small proportion of patients may have been benefiting from their baseline regimen, but most patients would be unlikely to have derived a clinically meaningful benefit.

Conclusion

While the Applicant did not strictly meet the protocol-required "documented history" of treatment failure, the inferential data support that the patients likely had inadequate response to APAP, NSAIDs, or opioids.

Agency's Subgroup Analyses for Efficacy

As noted in Section 3.3.2, to fully assess the benefit-risk relationship for tanezumab, the review team conducted subgroup analyses for various baseline factors in an attempt to identify a subset of patients who appear to show greater benefit than the aggregate populations. No group of "super-responders" was identified. Forest plots of this analysis are below (Figure 20, Figure 21, and Figure 22).

Figure 20. Subgroup Analyses of Tanezumab 2.5 mg Versus Placebo on WOMAC Pain

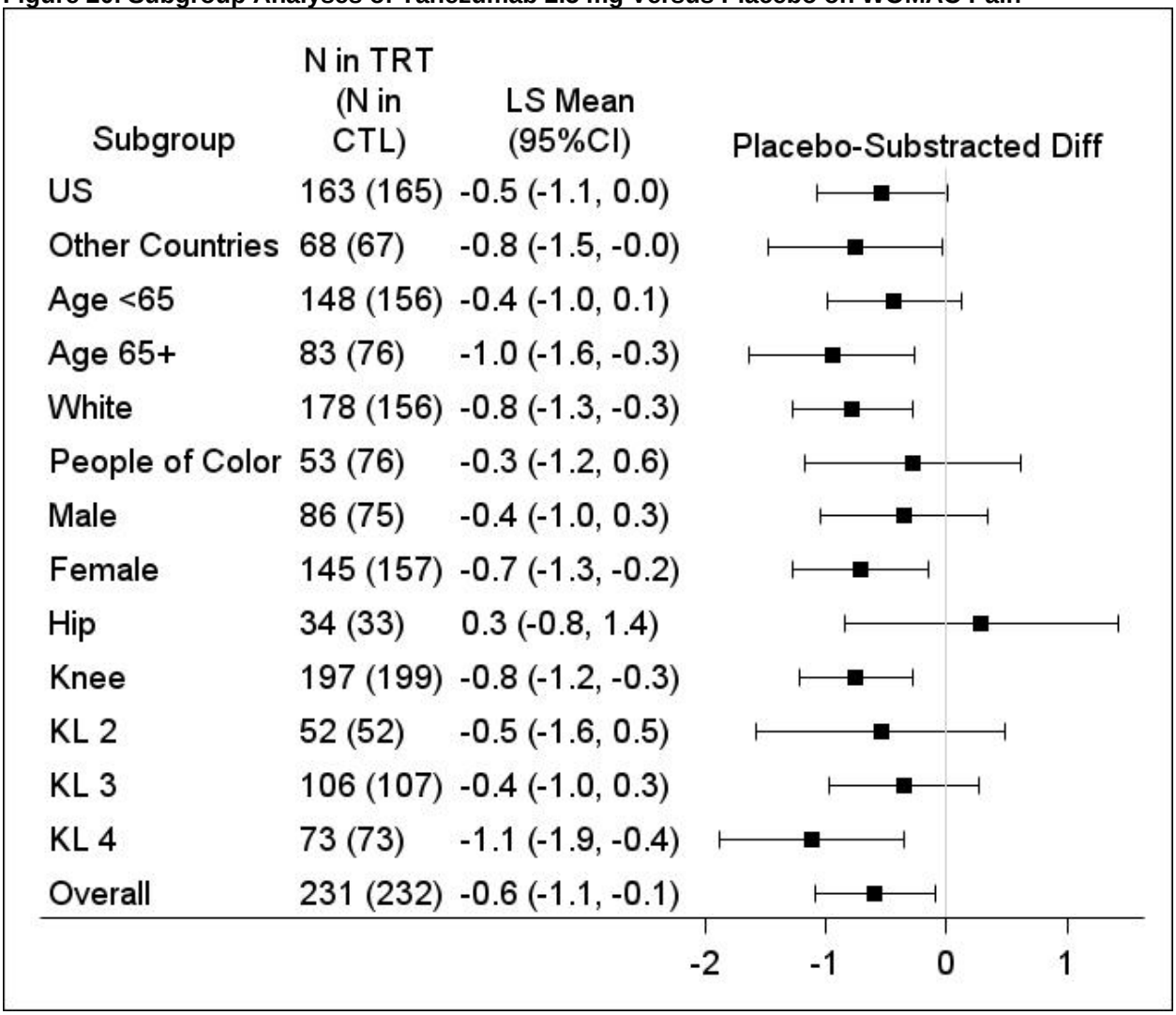


Figure 21. Subgroup Analyses of Tanezumab 2.5 mg Versus Placebo on WOMAC Pain

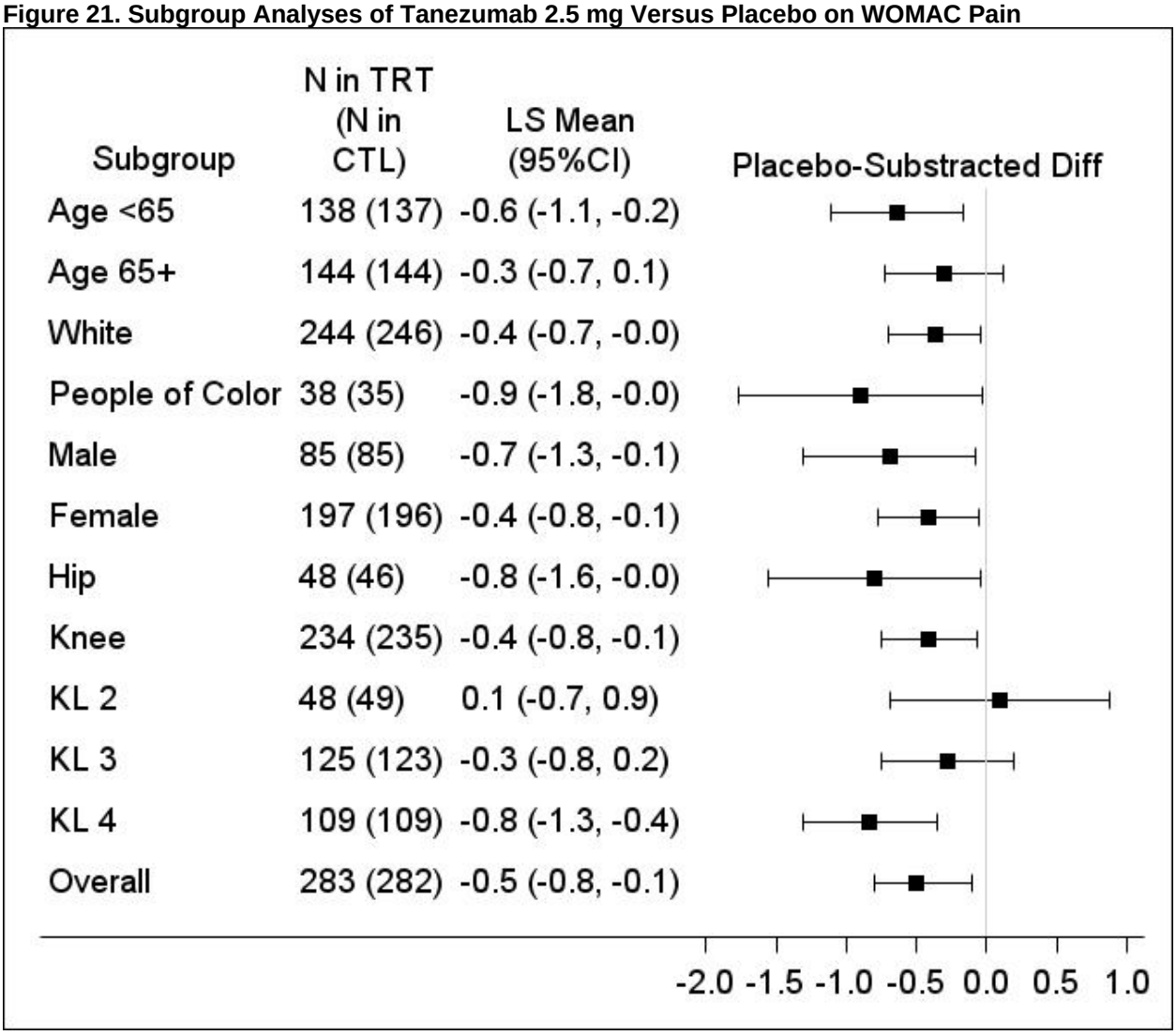
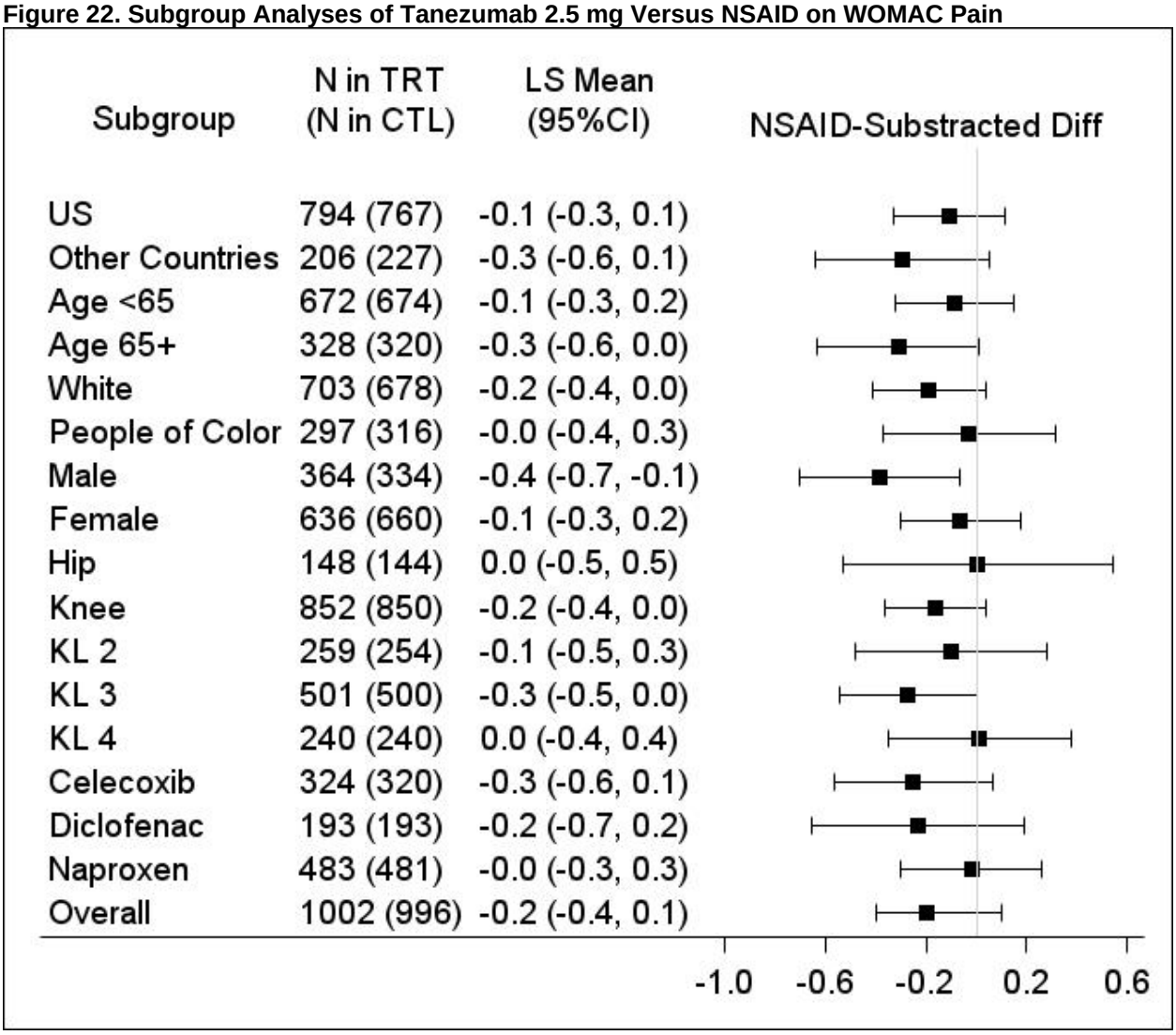


Figure 22. Subgroup Analyses of Tanezumab 2.5 mg Versus NSAID on WOMAC Pain



Baseline Demographics

The baseline demographics are summarized in Table 60.

Table 60. Baseline Demographic and OA Disease Characteristics (1056, 1057, and 1058)

	Study 1056 N=696	Study 1057 N=849	Study 1058 N=2996
Age (years)			
Mean	60	65	60
≥65	35%	**54%**	34%
≥75	8%	14%	7%
Gender			
Male	35%	31%	35%
Female	65%	69%	65%
Race			
White	73%	**87%**	70%
BMI			
Mean	31	30	31
WOMAC pain at baseline			
Mean (SD)	7	7	7
Index joint			
Knee	85%	83%	85%
Hip	15%	17%	15%
KLG of index joint			
0	0	2	5
1	1	0	7
2	26%	20%	30%
3	44%	44%	48%
4	30%	36%	22%
KLG index knee			
0	0	0	2
1	1	0	5
2	24%	18%	27%
3	44%	43%	48%
4	32%	**39%**	25%
KLG index hip			
0	0	2	3
1	0	0	2
2	43%	26%	43%
3	43%	51%	47%
4	14%	**23%**	10%
Max KLG of any knee or hip			
0	0	0	0
1	0	0	1
2	21%	15%	24%
3	47%	44%	51%
4	32%	**41%**	25%
Duration since index joint OA Dx			
Mean (years)	8	7	8
Duration since first OA Dx			
Mean (years)	9	8	9

Source: Medical reviewer Anjelina Pokrovnichka
Abbreviations: BMI, body mass index; DX, diagnosis; KLG, Kellgren-Lawrence grade; OA, osteoarthritis; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

Rescue Medication

In all 3 studies, patients were provided with rescue medication (acetaminophen/paracetamol). The maximum daily dose was 3000 mg per day up to 3 days per week in 1056, 4000 mg per day up to 5 days a week for 1057 and in 1058 it was 3000 mg per day up to 3 days per week up to the week 16 visit and daily thereafter. Rescue medication was required to be discontinued 24 hours prior to clinic visits where efficacy was being assessed. Patients who took rescue medication more frequently during the Treatment Period and indicated that they could not or would not follow the rescue medication protocol requirements because of insufficient pain relief were withdrawn from study treatment and entered the Early Termination Follow-up Period. Use of rescue medications was similar across treatment groups and are summarized in Table 61 to Table 63.

Table 61. Study 1056, Incidence of Taking Rescue Medication by Week (ITT)

	Placebo		Tanezumab			
	N = 232		2.5 mg N = 231		2.5/5 mg N = 233	
Any RM Use	N	n (%)	N	n (%)	N	n (%)
Baseline	230	172 (74.8%)	228	185 (81.1%)	232	180 (77.6%)
Week 1	232	161 (69.4%)	229	147 (64.2%)	232	155 (66.8%)
Week 2	228	157 (68.9%)	230	137 (59.6%)	227	135 (59.5%)
Week 3	229	138 (60.3%)	229	132 (57.6%)	229	121 (52.8%)
Week 4	226	139 (61.5%)	227	116 (51.1%)	226	103 (45.6%)
Week 5	226	129 (57.1%)	227	112 (49.3%)	229	117 (51.1%)
Week 6	223	134 (60.1%)	225	111 (49.3%)	227	121 (53.3%)
Week 7	223	115 (51.6%)	226	102 (45.1%)	228	111 (48.7%)
Week 8	220	108 (49.1%)	223	105 (47.1%)	228	114 (50.0%)
Week 9	221	102 (46.2%)	223	102 (45.7%)	222	95 (42.8%)
Week 10	220	106 (48.2%)	217	88 (40.6%)	216	96 (44.4%)
Week 11	216	97 (44.9%)	220	87 (39.5%)	216	87 (40.3%)
Week 12	212	94 (44.3%)	220	89 (40.5%)	219	84 (38.4%)
Week 13	199	78 (39.2%)	216	97 (44.9%)	211	89 (42.2%)
Week 14	198	74 (37.4%)	213	92 (43.2%)	207	80 (38.6%)
Week 15	196	81 (41.3%)	213	96 (45.1%)	206	82 (39.8%)
Week 16	194	81 (41.8%)	206	92 (44.7%)	204	84 (41.2%)
OVERALL (up to Week 16)	232	200 (86.2%)	231	196 (84.8%)	233	199 (85.4%)

Source: Study 1056 CSR Table 37, page 143
Abbreviations: ITT, intent to treat; RM, rescue medication

Table 62. Study 1057, Incidence of Taking Rescue Medication by Week (ITT)

		Placebo (N=282)		Tanezumab 2.5 mg (N=283)		Tanezumab 5 mg (N=284)	
		N	n(%)	N	n(%)	N	n(%)
Any RM Use	BASELINE	282	210 (74.5%)	283	203 (71.7%)	283	199 (70.3%)
	WEEK 1	282	196 (69.5%)	283	172 (60.8%)	282	183 (64.9%)
	WEEK 2	281	205 (73.0%)	280	150 (53.6%)	284	169 (59.5%)
	WEEK 3	278	188 (67.6%)	279	144 (51.6%)	281	161 (57.3%)
	WEEK 4	277	179 (64.6%)	276	131 (47.5%)	279	147 (52.7%)
	WEEK 5	277	168 (60.6%)	279	131 (47.0%)	280	146 (52.1%)
	WEEK 6	276	168 (60.9%)	277	139 (50.2%)	279	137 (49.1%)
	WEEK 7	276	169 (61.2%)	279	138 (49.5%)	278	142 (51.1%)
	WEEK 8	273	160 (58.6%)	277	130 (46.9%)	278	143 (51.4%)
	WEEK 9	268	155 (57.8%)	278	130 (46.8%)	277	130 (46.9%)
	WEEK 10	270	153 (56.7%)	278	125 (45.0%)	275	127 (46.2%)
	WEEK 11	268	147 (54.9%)	273	117 (42.9%)	274	118 (43.1%)
	WEEK 12	264	141 (53.4%)	270	116 (43.0%)	276	117 (42.4%)
	WEEK 13	259	128 (49.4%)	266	115 (43.2%)	273	117 (42.9%)
	WEEK 14	254	135 (53.1%)	271	123 (45.4%)	272	124 (45.6%)
	WEEK 15	256	137 (53.5%)	270	128 (47.4%)	271	126 (46.5%)
	WEEK 16	254	137 (53.9%)	263	118 (44.9%)	268	113 (42.2%)
	WEEK 17	249	126 (50.6%)	266	111 (41.7%)	268	98 (36.6%)
	WEEK 18	251	123 (49.0%)	263	105 (39.9%)	266	107 (40.2%)
	WEEK 19	248	124 (50.0%)	263	109 (41.4%)	266	112 (42.1%)
	WEEK 20	248	124 (50.0%)	258	108 (41.9%)	262	108 (41.2%)
	WEEK 21	234	109 (46.6%)	253	103 (40.7%)	258	98 (38.0%)
	WEEK 22	231	109 (47.2%)	252	107 (42.5%)	255	102 (40.0%)
	WEEK 23	232	114 (49.1%)	248	105 (42.3%)	254	104 (40.9%)
	WEEK 24	229	102 (44.5%)	244	106 (43.4%)	253	105 (41.5%)
	OVERALL (up to Week 24)	282	243 (86.2%)	283	228 (80.6%)	284	236 (83.1%)
	WEEK 28	244	137 (56.1%)	262	149 (56.9%)	258	147 (57.0%)
	WEEK 32	231	130 (56.3%)	251	158 (62.9%)	249	149 (59.8%)

Source: Study 1057 CSR Table 34, page 151
Abbreviations: ITT, intent to treat; RM, rescue medication

Table 63. Study 1058 Incidence of Taking Rescue Medication to Week 16 (ITT)

Visit			Tanezumab 2.5 mg (N=1002) N	Tanezumab 2.5 mg (N=1002) n(%)	Tanezumab 5 mg (N=998) N	Tanezumab 5 mg (N=998) n(%)	NSAID (N=996) N	NSAID (N=996) n(%)
Observed Data	Any RM Use	BASELINE	998	644 (64.5%)	996	660 (66.3%)	994	631 (63.5%)
		WEEK 1	994	595 (59.9%)	991	575 (58.0%)	991	543 (54.8%)
		WEEK 2	990	561 (56.7%)	983	540 (54.9%)	988	524 (53.0%)
		WEEK 3	985	520 (52.8%)	984	509 (51.7%)	979	492 (50.3%)
		WEEK 4	976	469 (48.1%)	969	422 (43.6%)	971	452 (46.5%)
		WEEK 5	975	429 (44.0%)	968	396 (40.9%)	969	435 (44.9%)
		WEEK 6	971	430 (44.3%)	955	384 (40.2%)	966	428 (44.3%)
		WEEK 7	963	428 (44.4%)	948	381 (40.2%)	956	403 (42.2%)
		WEEK 8	962	414 (43.0%)	945	360 (38.1%)	947	392 (41.4%)
		WEEK 9	956	383 (40.1%)	944	330 (35.0%)	951	378 (39.7%)
		WEEK 10	941	344 (36.6%)	936	321 (34.3%)	939	362 (38.6%)
		WEEK 11	925	328 (35.5%)	932	322 (34.5%)	925	348 (37.6%)
		WEEK 12	927	333 (35.9%)	929	305 (32.8%)	919	351 (38.2%)
		WEEK 13	900	309 (34.3%)	885	291 (32.9%)	882	304 (34.5%)
		WEEK 14	891	303 (34.0%)	881	296 (33.6%)	880	286 (32.5%)
		WEEK 15	888	322 (36.3%)	879	288 (32.8%)	872	289 (33.1%)
		WEEK 16	881	299 (33.9%)	874	280 (32.0%)	858	282 (32.9%)
		OVERALL (up to Week 16)	1000	797 (79.7%)	996	786 (78.9%)	996	779 (78.2%)
		WEEK 20	881	294 (33.4%)	866	303 (35.0%)	865	313 (36.2%)
		WEEK 24	622	175 (28.1%)	626	208 (33.2%)	591	174 (29.4%)
		WEEK 28	579	157 (27.1%)	587	187 (31.9%)	555	159 (28.6%)
		WEEK 32	536	154 (28.7%)	543	175 (32.2%)	525	149 (28.4%)
		WEEK 36	531	136 (25.6%)	527	171 (32.4%)	508	129 (25.4%)
		WEEK 40	513	154 (30.0%)	500	173 (34.6%)	489	131 (26.8%)
		WEEK 44	490	134 (27.3%)	482	161 (33.4%)	484	141 (29.1%)
		WEEK 48	473	133 (28.1%)	461	160 (34.7%)	464	124 (26.7%)
		WEEK 52	466	122 (26.2%)	456	164 (36.0%)	470	125 (26.6%)
		WEEK 56	451	122 (27.1%)	432	160 (37.0%)	448	122 (27.2%)
		OVERALL (up to Week 56)	1001	852 (85.1%)	996	855 (85.8%)	996	842 (84.5%)

Source: Study 1058 CSR Table 32, page 161
Abbreviations: ITT, intent to treat; RM, rescue medication

8. Study Conduct

The Applicant certified that all three studies were conducted in compliance with Good Clinical Practice guidelines and, where applicable, local country regulations. Unfortunately, due to the COVID-19 pandemic, clinical investigator inspections have been limited and no information on site inspections is currently available.

Regarding the domestic site inspections, the Office of Scientific Investigations emailed DAAP with the preliminary findings of site #1714 (b) (4) who participated in Study 1058. Specifically, the Office of Scientific Investigations reported subject charts reviewed where subjects did not meet randomization criteria or met exclusion criteria but were randomized and received IP and subjects who received the Week 24 SC IP prior to confirmation from the Central Reader. Given the scope of the findings of this site, per routine, our statistical team conducted a sensitivity analysis for the primary efficacy endpoint. Excluding site #1714 from this analysis did not change the results or conclusions about the efficacy of Study 1058. The site enrolled approximately 2% of the total patients in Study 1058. Table 64 shows the numbers and distribution of patients contributed by Site 1714.

Table 64. Sensitivity Analysis

	TANZ 2.5mg	TANZ 5mg	NSAID	TOTAL
Site 1714	20 2.0%	17 1.7%	22 2.2%	59 2.0%
Total (ITT)	1002	998	996	2996

Source: Statistical Review
Abbreviations: ITT, intent to treat; NSAID, nonsteroidal anti-inflammatory drug; TANZ, tanezumab

Given the fairly short duration of Study 1056 (16 weeks double-blind with 24 weeks follow-up off drug), there was a high rate of protocol violations. Deviations related to concomitant medications occurred in 31.3, 28.4, and 25.3% of patients randomized to placebo, tanezumab 2.5 mg, or tanezumab 2.5/5 mg, respectively. These violations primarily related to excessive NSAID use. That more NSAID use occurred in placebo would have biased the study in favor of placebo. Deviations related to selection criteria were 15% and similar across arms. The other common protocol violation pertained to procedures/tests had an incidence of 37-39% and were similar across treatment arms. While the overall rate of protocol violations seems high, there were no patterns that would suggest that the violations biased the study.

Table 65. Selected Protocol Violations, Study 1056

Category	Term	Tanezumab 2.5 mg (N=232)	Tanezumab 2.5 /5 mg (N=233)	Placebo (N=233)
Concomitant meds		66 (28.4%)	59 (25.3%)	73 (31.3%)
	Exceeded cumulative NSAID limit	5 (2.2%)	5 (2.1%)	10 (4.3%)
	Rescue medication/APAP more than 3 days/week >2 occasions	58 (25%)	54 (23.2%)	63 (27.0%)
	Rescue medication use within 24 hours of primary endpoint collection	1 (0.4%)	0	1(0.4%)
Inclusion/exclusion		33 (14.2%)	36 (15.5%)	34 (14.6%)
Procedure/tests		85 (36.6%)	91 (39.1%)	91 (39.1%)
Visit schedule		24 (10.3%)	34 (14.6%)	35 (15.0%)

Source: Table truncated from Table 14, CSR for Study 1056, p 96
Abbreviations: APAP, acetaminophen; NSAID, nonsteroidal anti-inflammatory drug

In Study 1057, protocol violations overall were balanced across treatment arms. The incidence of protocol deviations in selection criteria ranged from 25.1% to 33.3% which was much higher than Study 1056. There were no patterns in the protocol violation tables suggesting protocol noncompliance biased the study.

Table 66. Selected Protocol Violations, Study 1057

Category	Term	Tanezumab 2.5 mg (N=283)	Tanezumab 5 mg (N=284)	Placebo (N=282))
Concomitant meds		65 (23.0%)	73 (25.7%)	93 (33.0%)
	Exceeded cumulative NSAID limit	13 (4.6%)	14 (4.9%)	21 (7.4%)
	Rescue medication/APAP more than 3 days/week >2 occasions	52 (18.4%)	55 (19.4%)	73 (25.9%)
	Rescue medication use within 24 hours of primary endpoint collection	7 (2.5%)	3 (1.1%)	3(1.1%)
Inclusion/exclusion		71 (25.1%)	83 (29.2%)	94 (33.3%)
Procedure/tests		83 (31.1%)	91 (32.0%)	104 (36.9%)
Visit schedule		30 (10.6%)	31 (10.9%)	31 (11.0%)

Source: Table truncated from Table 14, CSR for Study 1057, p 97
Abbreviations: APAP, acetaminophen; NSAID, nonsteroidal anti-inflammatory drug

The overall rates of protocol violations in Study 1058 trended lower than Studies 1056 and 1057 which is unexpected given the complexity and duration of the study. Based on data submitted by the Applicant, protocol violations were balanced among the treatment groups. Pertinent protocol violations are summarized in Table 67.

Table 67. Selected Protocol Violations, Study 1058

Category	Term	Tanezumab 2.5 mg (N=1008)	Tanezumab 5 mg (N=1005)	NSAID (N=1008)
Concomitant meds		294 (29.2%)	243 (24.2%)	268 (25.6%)
	Exceeded cumulative NSAID limit	53 (5.3%)	43 (4.3%)	42 (4.2%)
	Rescue medication/APAP more than 3 days/week >2 occasions	242 (24.0%)	199 (19.8%)	219 (21.7%)
	Rescue medication use within 24 hours of primary endpoint collection	2 (0.2%)	4 (0.4%)	5 (0.5%)
Discontinuation criteria		27 (2.7%)	35 (3.5%)	18 (1.8%)
	Prohibited meds without washout	3 (0.3%)	6 (0.6%)	4 (0.4%)
	Maintain stable NSAID dosing for at least final 2 weeks of screening	20 (2.0%)	20 (2.0%)	18 (1.8%)
Informed consent		7 (0.7%)	7 (0.7%)	5 (0.5%)
Investigational product		83 (8.2%)	68 (6.8%)	76 (7.5%)
	Compliance with oral study drug <70% or >120% between baseline and primary endpoint visit	52 (5.2%)	44 (4.4%)	50 (5.0%)
	Overall compliance with oral study drug <70% or >120%	17 (1.7%)	12 (1.2%)	18 (1.8%)
Visit schedule		181 (18.0%)	197 (19.6%)	189 (18.8%)

Source: Table from Robert Shibuya truncated from Table 11, CSR for Study 1058, p 107/5305
Abbreviations: APAP, acetaminophen; NSAID, nonsteroidal anti-inflammatory drug

9. Clinical Safety: Additional Information and Assessment

9.1. Deaths

Number of Deaths Per Study

The number of deaths by treatment group for each Phase 3 study is presented in Table 68 and Table 69.

Most of the deaths occurred in the studies of one-year duration. Ten deaths were reported in the OA Study 1058, seven in the CLBP Study 1059, and five in the OA Study 1025. This finding is expected given the longer observation time in these studies.

Table 68. Number of Deaths Per Study and Treatment Group in Controlled OA and CLBP Studies

Table of STUDYID by TRTA											
	TRTA(Actual Treatment)										
STUDYID(Study Identifier)	NSAID	Placebo	Tanezumab 10 mg	Tanezumab 10 mg + NSAID	Tanezumab 2.5 mg	Tanezumab 2.5 mg + NSAID	Tanezumab 2.5/5 mg	Tanezumab 5 mg	Tanezumab 5 mg + NSAID	Tramadol PR 100-300 mg QD	Total
A4091011	0	0	1	0	0	0	0	0	0	0	1
A4091014	0	1	1	0	0	0	0	1	0	0	3
A4091015	0	1	0	0	0	0	0	0	0	0	1
A4091017	0	0	0	0	0	2	0	0	0	0	2
A4091025	0	0	0	1	0	0	0	2	2	0	5
A4091056	0	0	0	0	0	0	2	0	0	0	2
A4091057	0	0	0	0	1	0	0	2	0	0	3
A4091058	1	0	0	0	4	0	0	5	0	0	10
A4091059	0	1	2	0	0	0	0	3	0	1	7
Total	1	3	4	1	5	2	2	13	2	1	34

Source: DB7 review team
Abbreviations: CLBP, chronic low back pain; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; QD, once daily
Note: No deaths were reported in post-2015 CLBP Japanese Study 1063

Table 69. Number of Deaths Per Study and Treatment Group in Uncontrolled OA and CLBP Studies

Table of STUDYID by TRTA				
STUDYID(Study Identifier)	TRTA(Actual Treatment)			
	Tanezumab 2.5 mg	Tanezumab 20 mg	Tanezumab 5 mg	Total
A4091016	1	0	2	3
A4091039	0	3	0	3
Total	1	3	2	6

Source: DB7 review team
Abbreviations: CLBP, chronic low back pain; OA, osteoarthritis
Note: No deaths were reported in studies 1032, 1040, and 1043).
Causes of death: Four cardiovascular, one malignancy, and one other.

Deaths in Study 1058

Most of the deaths (N=10) occurred in Study 1058. Table 70 presents the observation-time adjusted incidence rates for all-cause death in this study by treatment group.

Table 70. All-Cause Deaths in Study 1058

Parameter	NSAID N=996	Tanezumab 2.5 mg N=1002	Tanezumab 5 mg N=998
Total observation time (PY[1])	1016.1	1028.3	1013.6
Number of subjects with death (IR[2] per 1000 PY)	1 (0.98)	4 (3.89)	5 (4.93)

Source: DB7 using the addthexp.xpt dataset in the ISS-controlled pool submitted by the Applicant.
Abbreviations: IR, incidence rate; NSAID, nonsteroidal anti-inflammatory drug; PY, person-year
[1] PY (for all subjects) calculated from first dose to the date of all-cause death or study end date, whichever is earlier.
[2] IR, with the denominator calculated as the period from first dose until the date of all-cause death or study end date, whichever is earlier.

During Study 1058, nine patients treated with tanezumab versus one patient treated with NSAID died. Seven of the nine tanezumab deaths and the single NSAID death were due to cardiovascular (CV) causes. Review of the narratives provided indicate that most of the patients who died due to a CV event had underlying medical condition(s) including, hypertension, hyperlipidemia, diabetes, and coronary artery disease, or a combination of those, that may have

contributed to the death. Review of the general medical history and demographic characteristics of the patient population for Study 1058 revealed that risk factors for CV death, including medical conditions (CAD, hypertension, diabetes all types), age, smoking, obesity, were similar across treatment groups.

This finding is further discussed in Section 9.5.

9.2. Serious Adverse Events

Active-Controlled IV Studies 1017 and 1025

No new safety findings were observed in the active-controlled IV study pool. During the treatment period, in the OA active-controlled IV pool, the overall incidence of SAEs was similar between the NSAID and the tanezumab 5 mg and 10 mg treatment groups (6.7%, 7.2%, 7.9%, respectively) but higher in the tanezumab + NSAID groups (8% to 9.2%) with the exception of the tanezumab 2.5 mg + NSAID group (5.1%). The higher incidence of SAEs in these groups was primarily due to a higher incidence of OA and ON events. Otherwise, SAEs occurred across multiple system organ classes (SOCs) with no obvious pattern.

Uncontrolled Studies

Up to the end of the study, the overall incidence of SAEs were similar between the tanezumab 2.5 mg and 5 mg treatment groups and higher in the tanezumab 10 mg group (range 7.4% to 10.8%). The most frequently reported SAEs were in the Musculoskeletal and connective tissue disorders SOC (range 3.5 to 5.3%). In this SOC, AEs that were reported at a higher incidence in the tanezumab 10 mg treatment group included osteoarthritis and osteonecrosis.

9.3. Dropouts and/or Discontinuations

The discontinuations from treatment due to AEs in the placebo-controlled OA studies was similar between the placebo, tanezumab 2.5 mg, and tanezumab 5 mg treatment groups, although higher in the tanezumab 10 mg treatment group in studies where tanezumab was administered via the IV route (Table 71 and Table 72). The higher frequency of discontinuations in the tanezumab 10 mg IV treatment group was due to joint-related and neurosensory adverse events.

Table 71. Subjects With Adverse Events Who Discontinued Treatment—Placebo-Controlled SC OA Study Pool

Parameter	Placebo (N=586)	Tan 2.5 mg (N=602)	Tan 2.5/5 mg (N=219)	Tan 5 mg (N=347)	Tan 10 mg (N=86)
Subjects (%) with AE who discontinued treatment	13 (2.2%)	11 (1.8%)	1 (0.5%)	5 (1.4%)	0

Source: Created by Anjelina Pokrovnichka using data from Applicant's Tables 1.7.2.13.c from ISS Appendix Tables 1, page 13465
Abbreviations: AE, adverse event; OA, osteoarthritis; SC, subcutaneous; Tan, tanezumab
SC placebo-controlled pool includes Studies 1027, 1056, and 1057

Table 72. Subjects With Adverse Events Who Discontinued Treatment—Placebo-Controlled IV OA Study Pool

Parameter	Placebo (N=1029)	Tan 2.5 mg (N=327)	Tan 5 mg (N=977)	Tan 10 mg (N=1056)
Subjects (%) with AE who discontinued treatment	29 (2.8%)	11 (3.4%)	30 (3.1%)	56 (5.3%)

Source: Created by Anjelina Pokrovnichka using data from Applicant's Table 1.7.2.13.b from ISS Appendix Table 1, page 13453
Abbreviations: AE, adverse event; IV, intravenous; OA, osteoarthritis
IV placebo-controlled pool includes Studies 1011, 1014, 1015, 1018, 1026, 1027, and 1030
Naproxen and oxycodone arms are not presented

A dose-related imbalance was noted for treatment discontinuations due to AEs in the active-controlled OA studies in which tanezumab was administered for a longer duration. The imbalance was driven by discontinuations due to joint-related AEs in studies with SC tanezumab administration and joint-related and neurosensory AEs in studies with IV tanezumab administration. Discontinuations due to GI events were higher in patients who received NSAIDs than in patients who received tanezumab (Table 73).

Table 73. Subjects With Adverse Events Who Discontinued Treatment—Active-Controlled SC OA Study 1058

Parameter	NSAIDs (N=996)	Tan 2.5 mg (N=1002)	Tan 5 mg (N=998)
Subjects (%) with AE who discontinued treatment	59 (5.9%)	75 (7.5%)	105 (10.5%)

Source: Created by Anjelina Pokrovnichka using data from Applicant's Table 1.7.2.13.m from ISS Appendix Tables 1, page 13515.
Abbreviations: AE, adverse event; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; SC, subcutaneous

Table 74. Subjects With Adverse Events Who Discontinued Treatment—Active-Controlled IV OA Study Pool

Parameter	NSAIDs (N=691)	Tan 5 mg (N=541)	Tan 10 mg (N=542)
Subjects (%) with AE who discontinued treatment	54 (7.8%)	64 (11.8%)	84 (15.3%)

Source: Prepared by Anjelina Pokrovnichka using data from Applicant's Table 1.7.2.13.1 from ISS Appendix Table 1, page 13499
Abbreviations: AE, adverse event; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis
IV active-controlled pool includes Studies 1017 and 1025
Tanezumab+NSAID arms are not presented

Table 75. Subjects Who Discontinued Treatment Due to GI Disorder AE—Active-Controlled OA Studies

Active-Controlled SC (Study 1058)			
	NSAIDs (N=996)	Tan 2.5 mg (N=1002)	Tan 5 mg (N=998)
Subjects (%) with AE who discontinued treatment due to a GI disorder	16 (1.6%)	4 (0.4%)	1 (0.1%)
Active-Controlled IV (Pooled Study 1017 and Study 1025)			
	NSAIDs (N=691)	Tan 5 mg (N=541)	Tan 10 mg (N=542)
Subjects (%) with AE who discontinued treatment due to a GI disorder	4 (0.6)	2 (0.4)	2 (0.4)

Source: Created by Anjelina Pokrovnichka using data from Applicant's Table 1.7.2.13.m from ISS Appendix Table 1, page 13515 and Table 1.7.2.13.1 from ISS Appendix Table 1, page 13499
Abbreviations: AE, adverse event; GI, gastrointestinal; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; Tan, tanezumab
Tanezumab+NSAID arms are not presented

9.4. Treatment-Emergent Adverse Events

The AE profile of IV tanezumab was generally consistent with the safety profile of SC tanezumab. Tanezumab was associated with a dose-related increase in the frequency of AEs occurring primarily in three SOCs, Musculoskeletal and Connective Tissue disorders (arthralgia, joint swelling, OA, RPOA, referred to as joint safety events), Nervous System disorders (paresthesia, hypoesthesia, carpal tunnel syndrome, referred to as events of abnormal peripheral sensation), and General disorders (peripheral edema). The frequency of the abnormal peripheral sensation events was higher with the IV route when compared to the SC route of tanezumab administration. These events were rarely seen after the cessation of treatment (during the follow up period). In contrast to the neurosensory events, joint safety events were seen both during treatment and after cessation of treatment. Most of the AEs were of mild or moderate severity. Review of AEs of lower frequency did not reveal additional safety issues.

Adverse events coded as fracture were examined separately in Study 1058 and focused on fractures without documented trauma. Atraumatic fractures occurred more often in the tanezumab treatment groups, although dose response was not observed, 1 (0.1%) in NSAIDs, 9 (0.9%) in tanezumab 2.5 mg, and 5 (0.5%) in tanezumab 5 mg treatment group. However, the small numbers, preclude any definitive conclusions.

Summary statistics for the controlled OA studies are presented in Table 76, Table 77, Table 78, and Table 79.

Table 76. Incidence of Treatment-Emergent AEs During Treatment and Follow-up, All Causalities (Placebo-Controlled OA SC Studies 1027, 1056, and 1057)

During Treatment Period					
Subjects Evaluable for AEs	**Placebo N=586**	**Tan 2.5 mg N=602**	**Tan 2.5/5 mg N=219**	**Tan 5 mg N=347**	**Tan 10 mg N=86**
N (%) of subjects by PT			n (%)		
With any AE	303 (51.7)	315 (52.3)	103 (47.0)	190 (54.8)	34 (39.5)
Arthralgia	67 (11.4)	52 (8.6)	19 (8.7)	30 (8.6)	4 (4.7)
Osteoarthritis	10 (1.7)	13 (2.2)	1 (0.5)	13 (3.7)	0
Paresthesia	6 (1.0)	14 (2.3)	3 (1.4)	14 (4.0)	6 (7.0)
Hypoesthesia	5 (0.9)	11 (1.8)	3 (1.4)	8 (2.3)	5 (5.8)
Edema peripheral + peripheral swelling	6 (1.0)	10 (1.7)	8 (3.7)	11 (3.2)	2 (2.3)
Synovial cyst	2 (0.3)	3 (0.5)	1 (0.5)	3 (0.9)	2 (2.3)
Injection site reaction	3 (0.5)	2 (0.3)	0	1 (0.3)	4 (4.7)
During Follow-up Period (Select AEs)					
Subjects Evaluable for AEs	**Placebo N=545**	**Tan 2.5 mg N=564**	**Tan 2.5/5 mg N=215**	**Tan 5 mg N=322**	**Tan 10 mg N=80**
N (%) of subjects by PT			n (%)		
With any AE	182 (33.4)	216 (38.3)	86 (40.0)	123 (38.2)	9 (11.3)
Arthralgia	41 (7.5)	50 (8.9)	20 (9.3)	30 (9.3)	1 (1.3)
Osteoarthritis	9 (1.7)	12 (2.1)	4 (1.9)	11 (3.4)	1 91.3)
RPOA	0	7 (1.2)	1 (0.5)	8 (2.5)	0
Edema peripheral + peripheral swelling	1 (0.2)	1 (0.2)	1 (0.5)	5 (1.6)	2 (2.5)
Paresthesia	1 (0.2)	1 (0.2)	1 (0.5)	1 (0.3)	0
Hypoesthesia	3 (0.6)	5 (0.9)	2 (0.9)	1 (0.3)	1 (1.3)

Source: Prepared by Anjelina Pokrovnichka using data from Applicant's Table 1.7.2.8.c from ISS Appendix Table 1, page 12616 and Table 1.7.2.11.c from the BLA amendment submitted on May 12, 2020, page 176.
Abbreviations: AE, adverse event; OA, osteoarthritis; PT, preferred term; RPOA, rapidly progressing osteoarthritis; SC, subcutaneous; Tan, tanezumab
Includes AEs that occurred in ≥2% of patients and at a higher incidence in tanezumab treatments relative to placebo during treatment.

Table 77. Incidence of Treatment-Emergent AEs for Select PTs, All Causalities (Active-Controlled SC Study 1058)

During Treatment Period			
Subjects Evaluable for AEs	**NSAIDs N=996**	**Tan 2.5 mg N=1002**	**Tan 5 mg N=998**
Number (%) of subjects by PT		n (%)	
With any AEs	601 (60.3)	629 (62.8)	670 (67.1)
Arthralgia	117 (11.7)	133 (13.3)	165 (16.5)
Osteoarthritis	23 (2.3)	39 (3.9)	54 (5.4)
Joint swelling	10 (1.0)	43 (4.3)	48 (4.8)
Joint effusion	5 (0.5)	8 (0.8)	21 (2.1)
RPOA	4 (0.4)	18 (1.8)	41 (4.1)
Hypoesthesia	18 (1.8)	27 (2.7)	28 (2.8)
Paresthesia	13 (1.3)	18 (1.8)	30 (3.0)
Carpal tunnel syndrome	6 (0.6)	16 (1.6)	27 (2.7)
Edema peripheral	17 (1.7)	19 (1.9)	43 (4.3)

During Follow-up Period			
Subjects Evaluable for AEs	**NSAIDs N=887**	**Tan 2.5 mg N=880**	**Tan 5 mg N=885**
Number (%) of subjects by PT		n (%)	
With any AEs	270 (30.4)	287 (32.6)	356 (40.2)
Osteoarthritis	8 (0.9)	19 (2.2)	45 (5.1)
RPOA	6 (0.7)	16 (1.8)	19 (2.1)
Arthralgia	52 (5.9)	56 (6.4)	59 (6.7)
Joint swelling	5 (0.6)	4 (0.5)	7 (0.8)
Joint effusion	2 (0.2)	2 (0.2)	10 (1.1)
Musculoskeletal pain	11 (1.2)	14 (1.6)	24 (2.7)
Edema peripheral	2 (0.2)	2 (0.2)	2 (0.2)

Source: Prepared by Anjelina Pokrovnichka using data from Applicant's Table 1.7.2.8.m and Table 1.7.2.6.m from ISS Appendix Table 1, pages 12623 and 12125.
Abbreviations: AE, adverse event; PT, preferred term; RPOA, rapidly progressing osteoarthritis; SC, subcutaneous; Tan, tanezumab
Includes AEs that occurred in ≥2% of patients and higher in tanezumab treatments relative to placebo.

Table 78. Incidence of Treatment-Emergent AEs for Select PTs During the Treatment Period, All Causalities (Placebo-Controlled OA IV Studies 1011, 1014, 1015, 1018, 1026, 1027, and 1030)

Subjects Evaluable for AEs	**Placebo N=1029**	**Tan 2.**5 mg **N=327**	**Tan** 5 mg **N=977**	**Tan 1**0 mg **N=1056**	**NAP N=417**	**Oxy N=158**
N (%) of subjects by PT			n (%)			
With any AEs	447 (43.4)	190 (58.1)	488 (49.9)	557 (52.7)	213 (51.1)	95 (60.1)
Paresthesia	17 (1.7)	13 (4.0)	53 (5.4)	63 (6.0)	11 (2.6)	1 (0.6)
Hypoesthesia	9 (0.9)	13 (4.0)	28 (2.9)	26 (2.5)	10 (2.4)	2 (1.3)
Carpal tunnel	1 (0.1)	5 (1.5)	9 (0.9)	18 (1.7)	1 (0.2)	0
Burning sensation	1 (0.1)	0	6 (0.6)	17 (1.6)	3 (0.7)	0
Hyperesthesia	1 (0.1)	1 (0.3)	5 (0.5)	13 (1.2)	0	0
Arthralgia	35 (3.4)	17 (5.2)	45 (4.6)	75 (7.1)	15 (3.6)	2 (1.3)
Joint swelling	6 (0.6)	4 (1.2)	19 (1.9)	23 (2.2)	5 (1.2)	0
Pain in extremity	24 (2.3)	9 (2.8)	25 (2.6)	61 (5.8)	3 (0.7)	3 (1.9)
Edema peripheral	7 (0.7)	6 (1.8)	23 (2.4)	41 (3.9)	7 (1.7)	1 (0.6)
Blood CPK increased	5 (0.5)	8 (2.4)	16 (1.6)	15 91.4)	5 (1.2)	1 (0.6)

Source: Prepared by Anjelina Pokrovnichka using data from Applicant's Tables 1.7.2.8.b and 1.7.2.4.b from ISS Appendix Table 1, pages 12614 and 11278
Abbreviations: AE, adverse event; CPK, creatine phosphokinase; PT, preferred term; SC, subcutaneous; Tan, tanezumab
Includes AEs that occurred in ≥2% of patients in any treatment group and that occurred at a higher incidence (i.e., 95% CI excluded 0) in one of the tanezumab groups relative to the placebo group. Also includes events with a lower frequency that were reported more frequently in the tanezumab groups compared to the placebo groups.

Table 79. Incidence of Treatment-Emergent AEs (≥2%) During the Treatment Period, All Causalities (OA Active-Controlled IV Studies 1017, 1025)

Number of subjects evaluable for Adverse Events	Tanezumab 5 mg (N=541)	Tanezumab 10 mg (N=542)	Tanezumab 2.5 mg + NSAID (N=157)	Tanezumab 5 mg + NSAID (N=686)	Tanezumab 10 mg + NSAID (N=687)	NSAID (N=691)
Number (%) of subjects: by PT	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	401 (74.1)	395 (72.9)	69 (43.9)	459 (66.9)	469 (68.3)	411 (59.5)
Arthralgia	69 (12.8)	87 (16.1)	6 (3.8)	76 (11.1)	72 (10.5)	55 (8.0)
Paresthesia	34 (6.3)	39 (7.2)	4 (2.5)	48 (7.0)	62 (9.0)	16 (2.3)
Osteoarthritis	29 (5.4)	34 (6.3)	2 (1.3)	42 (6.1)	35 (5.1)	29 (4.2)
Hypoesthesia	25 (4.6)	29 (5.4)	2 (1.3)	36 (5.2)	36 (5.2)	14 (2.0)
Edema peripheral	24 (4.4)	20 (3.7)	2 (1.3)	35 (5.1)	38 (5.5)	9 (1.3)
Joint swelling	22 (4.1)	26 (4.8)	1 (0.6)	19 (2.8)	18 (2.6)	8 (1.2)
Peripheral swelling	9 (1.7)	6 (1.1)	0	8 (1.2)	19 (2.8)	5 (0.7)
Pain in extremity	19 (3.5)	35 (6.5)	2 (1.3)	22 (3.2)	30 (4.4)	20 (2.9)
Musculoskeletal pain	15 (2.8)	13 (2.4)	0	19 (2.8)	15 (2.2)	15 (2.2)
Carpal tunnel syndrome	9 (1.7)	22 (4.1)	2 (1.3)	11 (1.6)	11 (1.6)	5 (0.7)
Synovial cyst	7 (1.3)	11 (2.0)	0	6 (0.9)	9 (1.3)	2 (0.3)

Source: Modified version of Applicant's Table 35 from ISS, page 147
Abbreviations: AE, adverse event; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; PT, preferred term

Uncontrolled OA Studies

Up to end of study, the overall frequency of AEs was similar across the tanezumab dose groups (69% to 71%). The most frequently reported AEs were in the Musculoskeletal and Connective Tissue disorders SOC (>35%) and the Nervous System disorders SOC (>18%). AEs that showed a dose-relationship were paresthesia, OA, joint swelling, edema peripheral, and peripheral swelling. The majority of events were mild to moderate in severity.

CLBP Studies

Common treatment emergent AEs (TEAEs) are summarized in Table 80 and Table 81, one for short-term (up to two doses) and one for long-term (up to seven doses) studies. Common AEs are summarized by AEs with incidence rates of >2% in any tanezumab group in short-term studies (004, 012, and Part 1 of 059) and by AEs with incidence rates of >3% in any tanezumab group in long-term studies (Study 012 extended to 039, and Part 1 extended to Part 2 of Study 059, and Study 063).

Short-Term Studies

- In short-term studies, compared to placebo, tanezumab 5 mg (the lowest tanezumab dose studied in the CLBP population) demonstrated at least two times higher rates of paresthesia, and all tanezumab doses tested (5, 10, and 20 mg) had remarkably higher rates of paresthesia, hypoesthesia, peripheral edema, nausea, and nasopharyngitis.
- Dose-related increases in common AEs in patients treated with one or two doses of tanezumab at 5, 10, or 20 mg level were clearly shown in neurosensory AEs such as paresthesia, hyperesthesia, hypoesthesia, and dysesthesia, and musculoskeletal AEs such as arthralgia and pain in extremity, and peripheral edema.
- The highest rates of common individual AEs in short-term studies were reported as paresthesia (13%) and arthralgia (11%) in the tanezumab 20 mg group and were much higher than the AE rates in the tramadol and naproxen control groups.

Long-Term Studies

- In long-term studies of up to 56 weeks in duration, dose-related increases in common AEs were most noticeable in the areas of neurosensory AEs and peripheral edema. A trend of increase in common AEs at higher dose levels was also shown in terms of joint swellings, pain in extremity, and diarrhea.
- All tanezumab treatment groups had higher rates of arthralgia and joint swelling than the tramadol and celecoxib control groups.
- The highest rates of common individual AEs in long-term studies were again paresthesia (14%) and arthralgia (16%) in the tanezumab 20 mg group and were much higher than the AE rates in the active control groups.

The common AEs and dose-related increases in common AEs with tanezumab treatment were mainly neurosensory abnormalities and symptoms and signs indicating impact of tanezumab treatment on the joints. The findings are consistent with that from OA studies with no new safety signals identified.

Table 80. Common AEs (>2% in Any Tanezumab Group) in Short-Term CLBP Studies

Parameter	Treatment						
	Pla	Tan 5	Tan 10	Tan 20	Tan Total	Tramadol	Nap 500
Number of patients treated TEAEs, N (%)	680	639	702	295	1724	602	383
Gastrointestinal Disorders							
Diarrhea	15 (2.2)	11 (1.7)	15 (2.1)	8 (2.7)	36 (2.1)	9 (1.5)	5 (1.3)
Nausea	10 (1.5)	12 (1.9)	16 (2.3)	12 (4.1)	42 (2.4)	68 (11.3)	10 (2.6)
General Disorders and Administration Site Conditions							
Edema peripheral	3 (0.4)	5 (0.8)	11 (1.6)	10 (3.4)	27 (1.6)	1 (0.2)	3 (0.8)
Infections and Infestations							
Nasopharyngitis	13 (1.9)	16 (2.5)	24 (3.4)	13 (4.4)	55 (3.2)	13 (2.2)	15 (3.9)
Upper respiratory tract infection	22 (3.2)	21 (3.3)	26 (3.7)	1 (3.4)	61 (3.5)	18 (3.0)	16 (4.2)
Urinary tract infection	11 (1.6)	7 (1.1)	6 (0.9)	11 (3.7)	27 (1.6)	4 (0.7)	10 (2.6)
Musculoskeletal and Connective Tissue Disorders							
Arthralgia	32 (4.7)	30 (4.7)	54 (7.7)	31 (10.5)	128 (7.4)	38 (6.3)	10 (2.6)
Back pain	15 (2.2)	15 (2.3)	10 (1.4)	2 (0.7)	30 (1.7)	15 (2.5)	7 (1.8)
Muscle spasms	10 (1.5)	7 (1.1)	14 (2.0)	7 (2.4)	29 (1.7)	4 (0.7)	2 (0.5)
Pain in extremity	14 (2.1)	11 (1.7)	28 (4.0)	19 (6.4)	62 (3.6)	7 (1.2)	4 (1.0)
Nervous System Disorders							
Dysesthesia	2 (0.3)	2 (0.3)	4 (0.6)	8 (2.7)	16 (0.9)	1 (0.2)	1 (0.3)
Headache	33 (4.9)	37 (5.8)	30 (4.3)	13 (4.4)	90 (5.2)	38 (6.3)	16 (4.2)
Hyperesthesia	3 (0.4)	2 (0.3)	10 (1.4)	12 (4.1)	30 (1.7)	0	0
Hypoesthesia	10 (1.5)	13 (2.0)	17 (2.4)	10 (3.4)	40 (2.3)	5 (0.8)	8 (2.1)
Paresthesia	9 (1.3)	17 (2.7)	34 (4.8)	38 (12.9)	93 (5.4)	9 (1.5)	6 (1.6)
Study	004, 012, 059 Part 1	012, 059 Part 1	012, 059 Part 1	012		059 Part 1	004, 012

Sources: Table 13.6.2.3 on pages 367 to 374 in the report for Study 004; Table 13.6.2 on pages 574 to 589 in the report for Study 012; and Table 14.3.1.2.2.1 on pages 1583 to 1604 in the report for Study 059.
Abbreviations: Nap, naproxen; Pla, placebo; Tan, tanezumab; TEAE, treatment-emergent adverse event

Table 81. Common AEs (>3% in Any Tanezumab Group) in Long-Term CLBP Studies

Parameter	Treatment						
	Tan 5	Tan 10	Tan 20	Tan Total	Tramadol	Celecoxib	
Number of patients treated	N=598	N=1036	N=647	N=2281	N=602	N=92	
TEAEs, N (%)							
Gastrointestinal Disorders							
Diarrhea	10 (1.7)	26 (2.5)	26 (3.9)	62 (2.7)	14 (2.3)	3 (3.3)	
Nausea	18 (3.0)	27 (2.6)	20 (3.1)	65 (2.8)	78 (13.0)	1 (1.1)	
General Disorders and Administration Site Conditions							
Edema peripheral	2 (0.3)	20 (1.9)	25 (3.9)	47 (2.1)	5 (0.8)	0	
Infections and Infestations							
Nasopharyngitis	50 (8.4)	64 (6.2)	26 (4.0)	140 (6.1)	37 (6.1)	11 (12.0)	
Sinusitis	19 (3.2)	30 (2.9)	17 (2.6)	66 (2.9)	21 (3.5)	1 (1.1)	
Upper respiratory infection	26 (4.3)	54 (5.2)	35 (5.3)	115 (5.0)	30 (5.0)	0	
Urinary tract infection	8 (1.3)	19 (1.8)	24 (3.7)	51 (2.2)	8 (1.3)	1 (1.1)	
Injury, Poisoning, and Procedural Complications							
Contusion	20 (3.3)	22 (2.1)	9 (1.1)	51 (2.2)	6 (1.0)	3 (3.3)	
Fall	33 (5.5)	39 (3.8)	20 (3.1)	92 (4.0)	18 (3.0)	5 (5.4)	
Muscle strain	6 (1.0)	19 (1.8)	21 (3.2)	46 (2.0)	8 (1.3)	2 (2.2)	
Musculoskeletal and Connective Tissue Disorders							
Arthralgia	79 (13.2)	140 (13.5)	101 (15.6)	320 (14.0)	65 (10.8)	7 (7.6)	
Back pain	47 (7.9)	51 (4.9)	19 (2.9)	117 (5.1)	33 (5.5)	9 (9.8)	
Joint swelling	11 (1.8)	26 (2.5)	20 (3.1)	57 (2.5)	4 (0.7)	0	
Muscle spasms	15 (2.5)	27 (2.6)	22 (3.4)	64 (2.8)	7 (1.2)	0	
Musculoskeletal pain	39 (6.5)	45 (4.3)	27 (4.2)	111 (4.9)	31 (5.1)	4 (4.3)	
Myalgia	12 (2.0)	22 (2.1)	24 (3.7)	58 (2.5)	9 (1.5)	1 (1.1)	
Pain in extremity	26 (4.3)	56 (5.4)	56 (8.7)	138 (6.0)	15 (2.5)	4 (4.3)	
Nervous System Disorders							
Headache	42 (7.0)	57 (5.5)	39 (6.0)	138 (6.0)	50 (8.3)	4 (4.3)	
Hyperesthesia	0	15 (1.4)	24 (3.7)	39 (1.7)	0	0	
Hypoesthesia	22 (3.7)	56 (5.4)	52 (8.0)	130 (5.7)	10 (1.7)	5 (5.4)	
Paresthesia	13 (2.2)	74 (7.1)	91 (14.1)	178 (7.8)	15 (2.5)	0	
Study	059, 063	012→039, 059, 063	012→039		059	063	

Sources: Table 5 on pages 11 to 31 in the submission dated April 24, 2020 as a response to the Division's Information Request on AEs for the combined Study 012 and Study 039; Table 14.3.1.2.2.5 on pages 1680 to 1715 in the report for Study 059; and Table 14.3.1.2.2.3 on pages 449 to 460 in the report for Study 063.
Abbreviations: AE, adverse event; Pla, placebo; Tan, tanezumab; TEAE, treatment-emergent adverse event

9.5. MACE Analysis

Issue/Background

As noted in Section 9.1, a higher death rate was observed in the combined tanezumab monotherapy treatment group relative to the placebo group or the NSAID group in the OA controlled post-2015 studies. Although the number of deaths was low in all groups, the most frequently reported fatal events in all groups were related to cardiovascular (CV) disease. In light

of these findings, the Applicant conducted an exploratory analysis of SAEs related to major adverse cardiovascular events (MACE) to assess the CV safety of tanezumab.

DAAP consulted DCN to further assess the Applicant's MACE analyses. DCN provided initial comments to DAAP on the proposed MACE analyses and an information request (IR) was subsequently sent on March 5, 2020 requesting the Applicant to provide an appropriate operational definition of MACE and reconduct their MACE analyses accordingly. Additional requested analyses include performing searches for CV-related AEs and conducting Kaplan-Meier analyses for the MACE outcome. The Applicant's response to this IR was received on March 29 and reviewed by DCN. The major findings related to CV safety of tanezumab are summarized in the sections below.

Assessment

MACE Analysis

MACE was defined as a composite outcome including CV death, nonfatal stroke and nonfatal myocardial infarction (MI) based on the Antiplatelet Trialists' Collaboration (APTC) definition.[9] The Applicant further defined each component of MACE according to the published definitions developed by the Standardized Data Collection for Cardiovascular Trials Initiative (SCTI) and the US FDA.[10] As the tanezumab clinical studies did not have pre-specified analyses for MACE, non-fatal MI and non-fatal stroke events were assigned based on selection of the investigator-reported preferred terms (PTs) for serious adverse events (SAEs) that were consistent with the definition published by SCTI and US FDA. CV death was defined as any death resulting from an acute MI, sudden cardiac death, death due to heart failure (HF), death due to CV procedure, death due to CV hemorrhage, and death due to other CV causes (e.g., pulmonary embolism).

The MACE analyses were conducted for the various pools of patients and in each pool, analyses were conducted separately for the treatment period, up to end of study, and through the post-study period. The primary MACE analysis used the pool of all controlled studies in patients with OA + CLBP and including all MACE up to end of study (Table 82). This broader pool of patients with a longer follow-up time provides the most data to evaluate CV safety of tanezumab given the overall low numbers of CV events reported in the tanezumab clinical program.

The observation time-adjusted incidence rate for any MACE was low and similar in the placebo, all tanezumab monotherapy, and NSAID groups (4.3, 4.9, and 5.3 events per 1,000 patient years, respectively). While the incidence rates of MACE and non-fatal MI were numerically higher in the tanezumab 2.5 mg group (i.e., the only dose proposed for OA) than in the placebo group, the difference was small with a wide 95% CI including zero. With no observed dose-response in event rate across tanezumab groups and considerations about some underlying differences among treatment groups (e.g., long-term OA studies did not include a placebo group), the small

[9] Anonymous. Collaborative overview of randomized trials of antiplatelet therapy- I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients: Antiplatelet Trialists' Collaboration. BMJ 1994; 308 (6921): 81-106

[10] Hicks KA, Mahaffey KW, Mehran R, et al. Cardiovascular and stroke endpoint definitions for clinical trials. Circulation 2018; 137 (9):961-72.

differences among the groups may be incidental. The incidence rate of CV death and non-fatal stroke was also similar between the placebo and the tanezumab groups.

It is noted that a higher incidence rate of non-fatal MI (4.1 per 1,000 patient-years) and lower incidence rate of CV death (0.6 per 1,000 patient-years) were observed in the NSAID group than in the placebo and tanezumab groups. The Applicant indicated the uncharacteristically low incidence of CV death in patients receiving NSAIDs and used a published meta-analysis[11] to provide an external reference for the MACE event rate in OA patients treated with NSAIDs. To align with the MACE analysis utilized for tanezumab, the Applicant generated data from the publication[11] applied similar methods to define MACE, and attempted to match the patient population to that in the clinical studies for tanezumab.

Table 82 shows the expected event rate for MACE and its components in OA patients treated with NSAIDs based on the published studies. The overall MACE rate was 12 to 13 per 1,000 patient years and the CV death rate was 4.8 per 1,000 patient years for both celecoxib and NSAIDS. These event rates were considerably higher than were observed in tanezumab clinical studies; while the event rate for non-fatal MI was similar between data sources.

Table 82. Major Adverse Cardiovascular Events up to End of Study and Post-Study, OA + CLBP Controlled Studies

Number of Events/Observation Time (per 1,000 Subject-Years)	Placebo (N=2182)	Tanezumab 2.5 mg (N=1931)	All Tanezumab Monotherapy[2] (N=8527)	NSAID (N=2399)	Tanezumab 2.5 mg vs. Placebo RD (95% CI)	All Tanezumab Monotherapy vs. Placebo RD (95% CI)	Tanezumab 2.5 mg vs. NSAID RD (95% CI)	All Tanezumab Monotherapy vs. NSAID RD (95% CI
Any MACE	4/925.6 (4.3)	10/1598.9 (6.3)	28/5772.7 (4.9)	9/1708.8 (5.3)	1.9 [-3.8, 7.7]	0.5 [-4.1, 5.1]	1.0 [-4.2, 6.2]	-0.4 [-4.3, 3.5]
CV Death	2/926.8 (2.2)	3/1600.9 (1.9)	13/5776.7 (2.3)	1/1711.8 (0.6)	-0.3 [-4.0, 3.4]	0.1 [-3.1, 3.3]	1.3 [-1.1, 3.7]	1.7 [-0.0, 3.3]
Non-fatal MI	1/926.1 (1.1)	5/1599.6 (3.1)	6/5774.9 (1)	7/1708.7 (4.1)	2.0 [-1.4, 5.5]	-0.0 [-2.3, 2.2]	-1.0 [-5.1, 3.1]	-3.1 [-6.2, 0.1]
Non-fatal stroke[1]	1/926.3 (1.1)	2/1600.2 (1.2)	9/5773.7 (1.6)	1/1711.4 (0.6)	0.2 [-2.6, 2.9]	0.5 [-1.9, 2.8]	0.7 [-1.4, 2.7]	1.0 [-0.6, 2.5]

Source: Reviewer's table adapted from Table 2.4.z. in the Applicant's March 29 IR response
Abbreviations: CV, cardiovascular; MACE, major adverse cardiovascular event; MY, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug
[1] Excluding hemorrhage not likely to be stroke
[2] Includes tanezumab 2.5 mg, 5 mg, 10 mg and 20 mg

[11] White WB, West CR, Borer JS et al. Risk of cardiovascular events in patients receiving celecoxib: a meta-analysis of randomized clinical trials. Am J Cardiol 2007;99:91-8.

Table 83. Meta-Analysis of Serious Cardiovascular Events Defined by the APTC for Celecoxib and Non-Selective NSAIDs Among Patients With OA

Event	Celecoxib 200 mg N=7375 1666.3 Pt-yrs		Nonselective NSAIDs N=7350 1676.1 Pt-yrs	
	Events	Rate/1000 Pt-yrs	Events	Rate/1000 Pt-yrs
Non-adjudicated (investigator-reported events)				
APTC composite	20	12.0	22	13.1
CV deaths	8	4.8	8	4.8
Nonfatal MI	11	6.6	5	3.0
Nonfatal stoke	1	0.6	9	5.4

Source: Table 1 in the Applicant's March 29 IR response.
Abbreviations: APTC, Antiplatelet Trialists Collaboration; CV, cardiovascular; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; Pt, patient

Kaplan-Meier curves for the composite MACE show no reliable differences in the occurrence of events over time between the placebo and various tanezumab groups with most events occurring in the first 350 days. There were some later events (i.e., non-fatal MI) occurring in the treatment groups (i.e., tanezumab 2.5 mg and 5 mg and NSAID) included in the longer-term study. Kaplan-Meier curves for non-fatal MI revealed an earlier onset of events in the NSAID group than in the all tanezumab monotherapy group. There were no meaningful differences in the time to occurrence of non-fatal stroke or CV death across all groups.

Cardiovascular-Related Adverse Events

The time-adjusted incidence rate of CV-related AEs was not notably different across the treatment groups of tanezumab, NSAIDs and placebo, for the SMQs for cardiac arrythmia, cardiac failure (narrow), central nervous system vascular disorder, and ischemic heart disease (Table 84). There was a higher incidence of events noted for tanezumab groups for the cardiac failure SMQ (broad) but the differences were due to a dose-related increased in the incidence of edema peripheral and peripheral swelling; both events are considered adverse drug reactions for tanezumab. The incidence of cardiac failure SMQ (narrow) excluding edema-related events shows the similar results across treatment groups.

There was a numerically higher incidence of embolic and thrombotic SMQ AEs in the tanezumab groups than in the placebo or NSAID group. An assessment of PTs under embolic and thrombotic SMQ reveals that there was a dose-related trend in the incidence rate of deep vein thrombosis (DVT) in the tanezumab groups (1.9, 2.3, and 5.2 per 1,000 subject-years in the tanezumab 2.5, 5, and 10 mg groups, respectively) as compared to the placebo and NSAID groups (1.1 and 0 per 1,000 subject years, respectively). However, given the overall low rate of the DVT events, the association to tanezumab is uncertain. Of note, there are no similar findings from the preclinical studies.

Table 84. Selected CV-Related AEs Up to End of Study and Post

Number of Subjects (per 1000 Subject-Years)	Placebo (N=2182)	Tanezumab 2.5 mg (N=1931)	All Tanezumab Monotherapy (N=8527)	All Tanezumab +NSAID (N=1530)	NSAID (N=2399)
Cardiac arrhythmia AEs[1]	47 (51.5)	68 (43.1)	239 (41.9)	46 (43.3)	73 (43.4)
Cardiac failure AEs[2]	3 (3.2)	3 (1.9)	12 (2.1)	4 (3.7)	3 (1.8)
Central nervous system vascular disorder AEs[1]	4 (4.3)	9 (5.6)	27 (4.7)	10 (9.2)	8 (4.7)
Embolic/thrombotic AEs[1]	7 (7.6)	17 (10.6)	57 (9.9)	14 (13)	11 (6.4)
Ischemic heart disease AEs[1]	22 (23.9)	39(24.6)	139 (24.3)	38 (35.8)	41 (24.2)

Source: Reviewer's table, adapted from Table 3.2.z. in March 29 IR response.
Abbreviations: AE, adverse event; CV, cardiovascular; NSAID, nonsteroidal anti-inflammatory drug
[1] MedDRA SMQ broad
[2] MedDRA SMQ narrow

Conclusion

There are small differences among the groups for MACE and its components in the pooled analysis of all controlled clinical studies in patients with OA and CLBP, which could be a chance finding given the overall small number of events. The MACE event rate was generally similar (~4–5 per 1,000 patient-years) in the placebo, all tanezumab monotherapy, and NSAID groups. Within the limitations of the data, there is little evidence of cardiovascular risk attributable to tanezumab.

9.6. Renal Safety

Background

Given the known deleterious effects of NSAIDs on renal function, the question of whether tanezumab has any effects on the kidney has been raised. If tanezumab were conclusively less nephrotoxic than NSAIDs, tanezumab could be a treatment alternative in OA patients with renal insufficiency or failure.

Analysis

The tanezumab program was not specifically designed to assess renal safety. Pfizer subjected the available renal safety data to additional analyses including subgroup analyses of patients at higher risk of NSAID-nephropathy, assessment of kidney-related AEs, and assessment of laboratory abnormalities related to renal function including estimation of the glomerular filtration rate (eGRF). Analysis pools included placebo-controlled OA, active-controlled OA, and OA and CLBP combined. Renal function over time was also assessed. Representative key summary data are show in Table 85 and Table 86 below.

Table 85. Summary of Treatment-Emergent Renal Adverse Events and Renal Parameters During the Treatment Period (All Causalities) (Safety: OA Placebo-Controlled Studies 1011, 1014, 1015, 1018, 1026, 1027, 1030, 1056, and 1057) [Number (%)]

Parameter	Placebo (N=1543)	Tanezumab 2.5 (N=929)	NSAID (N=417)	Tanezumab 5 (N=1324)
Any renal AE	5 (0.3%)	3 (0.3%)	3 (0.7%)	1 (0.1%)
Renal SAE	1 (0.1%)	0	0	0
Serum Cr worsening from baseline ≥25%	54 (4.4%)	45 (6.7%)	24 (5.9%)	80 (6.3%)
Sustained serum Cr worsening from baseline ≥25%	7 (0.6%)	14 (2.1%)	2 (0.5%)	14 (1.1%)
Serum Cr worsening from baseline ≥50%	12 (1.0%)	7 (1.0%)	5 (1.2%)	13 (1.0%)
Sustained serum Cr worsening from baseline ≥50%	1 (0.1%)	1 (0.1%)	2 (0.5%)	3 0.2(%)
Serum Cr worsening from baseline ≥100%	4 (0.3%)	1 (0.1%)	1 (0.2%)	5 (0.4%)
Sustained serum Cr worsening from baseline ≥100%	0	0	0	0
eGFR worsening from baseline ≥25%	37 (3.0%)	32 (4.7%)	16 (3.9%)	46 (3.6%)
Sustained eGFR worsening from baseline ≥25%	3 (0.2%)	7 (1.0%)	1 (0.2%)	12 (0.9%)
eGFR worsening from baseline ≥50%	4 (0.3%)	3 (0.4%)	1 (0.2%)	5 (0.4%)
Sustained eGFR worsening from baseline ≥50%	1 (0.1%)	0	0	0

Source: Robert Shibuya truncation from Table 79, ISS
Abbreviations: Cr, creatinine; eGFR, estimated glomerular filtration rate; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; SAE, severe adverse event

Table 86. Incidence of Treatment-Emergent Renal Adverse Events During the Treatment Period (All Causalities) (Safety: OA Placebo-Controlled Studies 1011, 1014, 1015, 1018, 1026, 1027, 1030, 1056, and 1057) [Number (%)]

Parameter	Placebo (N=1543)	Tanezumab 2.5 (N=929)	NSAID (N=417)	Tanezumab 5 (N=1324)
Any renal AE	5 (0.3%)	3 (0.3%)	3 (0.7%)	1 (0.1%)
Acute renal failure (SMQ broad)	4 (0.3%)	3 (0.4%)	3 (0.7%)	1 (0.1%)
Acute renal failure (SMQ broad) Blood urea increased	1 (0.1%)	2 (0.2%)	0	1 (0.1%)
Acute renal failure (SMQ broad) Blood creatinine increased	4 (0.3%)	1 (0.1%)	0	0
Acute renal failure (SMQ broad) Proteinuria	0	1 (0.1%)	2 (0.5%)	0
Acute renal failure (SMQ broad) Protein urine present	0	0	1 (0.2%)	0
Acute renal failure (SMQ narrow) Acute kidney injury	1 (0.1%)	0	0	0

Source: Robert Shibuya truncation from Table 80, ISS
Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; SMQ, Standardized MedDRA Query

Conclusions

The available data show low rates of renal AEs and a low rate of divergence from normal renal labs and decreases in eGFR overall. Based on the available data, tanezumab 2.5 mg does not appear different from placebo or NSAIDs. Importantly, in the available data, placebo does not appear different from NSAIDs. Given that we know that there is a signal for renal safety for NSAIDs (vs. placebo), the available data and analyses likely lack the power to detect a difference. No conclusion can be drawn regarding the nephrotoxicity of tanezumab compared to NSAIDs. The Division of Cardiology and Nephrology was consulted on this issue and agrees with the conclusions.

9.7. Potential Hypersensitivity Events

The data described in this section are based on analyses performed by the Applicant.

Background

For the hypersensitivity analyses, the Applicant selected preferred terms related to hypersensitivity from the following three Standard Medical Dictionary for Regulatory Activities Query (SMQ):

- Anaphylactic reaction (narrow)
- Angioedema (narrow)
- Hypersensitivity (narrow)
    - Terms related to injection site reactions or infusion site reactions were removed because they were analyzed separately

Additionally, relevant SOCs, including Immune system disorders and Skin and subcutaneous tissue disorders or related PTs (not captured in the above three SMQs) were reviewed by the Applicant for potential events.

Analysis

In the analysis of the SMQs (narrow) for anaphylactic reaction, angioedema, and hypersensitivity in the placebo-controlled post-2015 study pool no notable differences were observed between the placebo, tanezumab 2.5 mg, and tanezumab 5 mg treatment groups. The most common AE was rash. All events were classified as mild to moderate in severity. None met the criteria for a SAE.

In the active-controlled study (Study 1058), the overall frequency of potential hypersensitivity events during treatment was higher in the tanezumab treatment groups (3%) than in the NSAID group (2.2%). The most frequently reported event was rash (1.2% to 1.5% in the tanezumab treatment groups and 0.6% in the NSAIDs treatment group) and this was the event driving the difference in the overall frequency. There was a single event of swollen face and tongue of mild intensity in tanezumab-treated patient.

Review of the PTs within the Immune system and Skin and subcutaneous tissue disorders SOCs revealed the overall frequency of pruritus to be low and similar between the treatment groups, 0.5% for tanezumab and 0.6% for the NSAIDs.

No events were reported under the Anaphylactic reaction SMQ (narrow) search.

Conclusion

Tanezumab 2.5 mg SC administered every eight weeks, is not associated with an increased risk for concerning potential hypersensitivity events.

This conclusion was drawn based on the following findings:

- There were no events within the Anaphylactic reaction SMQ narrow search in any tanezumab treatment group across the study pools.
- The most frequently reported potential hypersensitivity event after SC tanezumab administration was rash. The frequency of "any rash" at the tanezumab 2.5 mg dose in the placebo-controlled pools was <1% and was similar to placebo. In the active-controlled pool, the overall frequency of 'any rash' in the tanezumab treatment groups was 1.5% compared to 0.6% in the NSAID treatment group.
- The frequency of potential hypersensitivity events with tanezumab was higher in the broader placebo-controlled pool including the SC and IV studies. These data suggest that the IV route of administration is associated with an increased frequency of potential hypersensitivity events.

9.8. Injection Site Reaction

The data described in this section are based on analyses performed by the Applicant.

Background

Because the intended route of administration for tanezumab is SC, the analyses for injection site reaction focus on the OA post-2015 study pools where study drug was administered SC.

Analysis

In the OA post-2015 placebo-controlled pool, there were 11 injection site reactions reported across the treatment groups. The incidence in the tanezumab 2.5 mg, 2.5/5 mg and 5 mg treatment groups was 0.2% (n=1), 0.9% (n=2) and 1.4% (n=4), respectively compared with 0.4% (n=2) in the placebo group. Injection site pain and erythema were the most frequently reported preferred terms. There were no serious or severe injection site reactions reported. One patient in the tanezumab 5 mg treatment group discontinued treatment due to an AE of injection site erythema.

In the active-controlled SC OA Study 1058, the incidence of injection site reaction AEs the same (0.5%) in all treatment groups. The most frequently reported injection site reaction AEs were erythema, hemorrhage, pain, and swelling. There were no serious or severe injection site reactions or discontinuations due to these reactions.

Most of the injection site reactions occurred soon after the first injection of study medication, although in the tanezumab treatment groups, additional events occurred after the second injection of study medication.

The Applicant found that in analyses of pre-2015 clinical trials, where tanezumab was generally administered IV, the incidence of infusion site reactions was also low.

Conclusion

The administration of SC tanezumab was associated with a low incidence of injection site reactions. Reactions were typically mild in severity and generally transient.

9.9. Abnormal Peripheral Sensation

Neurological Consultation

In all tanezumab studies, peripheral neurological safety was monitored and evaluated through assessment of AEs, neurological examinations by investigators at each clinic visit, and by referring patients for neurological consultation if they met pre-specified criteria. In pre-2015 studies, a neurologic consultation was required for any AE suggestive of new or worsening peripheral neuropathy or any AE of abnormal peripheral sensation or for a clinically significant change on a patients' neurologic examination. In post-2015 studies, neurologic consultation was required if the AEs or neurologic examination changes were reported as 1) a SAE or 2) an AE which has resulted in the patient being withdrawn from the study, or 3) an AE ongoing at the end of the patient's participation in the study, or 4) an AE of severe intensity. As a result of the change in requirements for neurologic consultation, neurological consultation was requested for fewer patients in post-2015 studies compared to pre-2015 studies.

Analysis

Data from the analyses conducted by the Applicant are presented in this section of the review. The analyses run by the FDA safety statistician did not reproduce the exact numbers the Applicant presented but are very close and the minor differences would not impact the interpretation of the results and the overall conclusion.

The frequency of APS events was higher with tanezumab compared to both the placebo and the NSAIDs comparators during the treatment period. Dose-effect was observed. There were no notable differences between tanezumab and comparators after the cessation of treatment. The most commonly reported APS were hypoesthesia, paresthesia, and carpal tunnel syndrome (Table 87, Table 88, Table 89, and Table 90).

Table 87. Frequency of TEAE of Abnormal Peripheral Sensation, All Causalities (Placebo-Controlled SC OA Studies 1027, 1056, and 1057)

Up to End of Study					
Subjects evaluable for AEs	**Placebo N=586 n (%)**	**Tan 2.5 mg N=602 n (%)**	**Tan 2.5/5 mg N=219 n (%)**	**Tan 5 mg N=347 n (%)**	**Tan 10 mg N=86 n (%)**
With any APS AE[1]	16 (2.7)	37 (6.1)	9 (4.1)	22 (6.3)	12 (14.0)
Paresthesia	7 (1.2)	15 (2.5)	3 (1.4)	14 (4.0)	6 (7.0)
Hypoesthesia	8 (1.4)	15 (2.5)	5 (2.3)	9 (2.6)	6 (7.0)
CTS	0	4 (0.7)	0	1 (0.3)	0
Burning sensation	1 (0.2)	1 (0.2)	0	2 (0.6)	0
During Treatment Period					
Subjects evaluable for AEs	**Placebo N=586 n (%)**	**Tan 2.5 mg N=602 n (%)**	**Tan 2.5/5 mg N=219 n (%)**	**Tan 5 mg N=347 n (%)**	**Tan 10 mg N=86 n (%)**
With any APS AE[1]	12 (2.0)	29 (4.8)	7 (3.2)	20 (5.8)	11 (12.8)
During Follow-up Period					
Subjects evaluable for AEs	**Placebo N=545 n (%)**	**Tan 2.5 mg N=564 n (%)**	**Tan 2.5/5 mg N=215 n (%)**	**Tan 5 mg N=322 n (%)**	**Tan 10 mg N=80 n (%)**
With any APS AEs[1]	5 (0.9)	9 (1.6)	3 (1.4)	3 (0.9)	1 (1.3)

Source: Prepared by Anjelina Pokrovnichka using data from Applicant's tables 4.1.3.c from BLA amendment submitted on May 12, 2020, page 2545, Table 4.1.1.c, from Appendix Table 2 – Neurological Safety, page 443, and Table 4.1.2.c from BLA amendment submitted on May 12, 2020, page 2544

Abbreviations: APS, abnormal peripheral sensation; CTS, carpal tunnel syndrome; PT, preferred term; TEAE, treatment-emergent adverse event

[1] Excluding sciatica

Table 88. Frequency of TEAE of Abnormal Peripheral Sensation, All Causalities (Placebo-Controlled IV OA Studies 1011, 1014, 1015, 1018, 1026, 1027, and 1030)

Up to End of Study						
Subjects evaluable for AEs	**Placebo N=1029 n (%)**	**Tan 2.5 mg N=327 n (%)**	**Tan 5 mg N=977 n (%)**	**Tan 10 mg N=1056 n (%)**	**Nap N=417 n (%)**	**Oxy N=158 n (%)**
With any APS AE[1]	33 (3.2)	30 (9.2)	85 (8.7)	134 (12.7)	22 (5.3)	4 (2.5)
Paresthesia	17 (1.7)	13 (4.0)	53 (5.4)	64 (6.1)	11 (2.6)	1 (0.6)
Hypoesthesia	9 (0.9)	13 (4.0)	28 (2.9)	28 (2.7)	10 (2.4)	2 (1.3)
CTS	1 (0.1)	6 (1.8)	9 (0.9)	19 (1.8)	1 (0.2)	0
Burning sensation	1 (0.1)	0	6 (0.6)	17 (1.6)	3 (0.7)	0
…	33					95
During Treatment Period						
Subjects evaluable for AEs	**Placebo N=1029 n (%)**	**Tan 2.5 mg N=327 n (%)**	**Tan 5 mg N=977 n (%)**	**Tan 10 mg N=1056 n (%)**	**NAP N=417 n (%)**	**Oxy N=158 n (%)**
With any APS AE[1]	33 (3.2)	30 (9.2)	85 (8.7)	132 (12.5)	22 (5.3)	4 (2.5)
During Follow-up Period						
Subjects evaluable for AEs	**Placebo N=305 n (%)**	**Tan 2.5 mg N=47 n (%)**	**Tan 5 mg N=268 n (%)**	**Tan 10 mg N=352 n (%)**	**NAP N=63 n (%)**	**Oxy N=122 n (%)**
With any APS AE[1]	0	1 (2.1)	0	6 (1.7)	1 (1.6)	0

Source: Prepared by Anjelina Pokrovnichka using data from Applicant's Table 4.1.3.b, Table 4.1.1.b, and Table 4.1.2.b, pages 471, 441, and 465

Abbreviations: AE, adverse event; APS, abnormal peripheral sensation; CTS, carpal tunnel syndrome; IV, intravenous; Nap, naproxen; OA, osteoarthritis; Oxy, oxycodone; PT, preferred term; Tan, tanezumab; TEAE, treatment-emergent adverse event

[1] Excluding sciatica

Table 89. Frequency of TEAE of Abnormal Peripheral Sensation, All Causality (Active-Controlled SC OA Study 1058)

During up to End of Study			
Subjects evaluable for AEs	**NSAIDs N=996 n%**	**Tan 2.5 mg N=1002 n%**	**Tan 5 mg N=998 n%**
With any APS AE[1]	47 (4.7)	61 (6.1)	93 (9.3)
Hypoesthesia	19 (1.9)	30 (3.0)	29 (2.9)
Paresthesia	14 (1.4)	18 (1.8)	32 (3.2)
CTS	7 (0.7)	16 (1.6)	31 (3.1)
During Treatment Period			
Subjects evaluable for AEs	**NSAIDs N=996 n%**	**Tan 2.5 mg N=1002 n%**	**Tan 5 mg N=998 n%**
With any APS AE[1]	42 (4.2)	59 (5.9)	85 (8.5)
During Follow-up Period			
Subjects evaluable for AEs	**NSAIDs N=887 n%**	**Tan 2.5 mg N=880 n%**	**Tan 5 mg N=885 n%**
With any APS AE[1]	8 (0.9)	5 (0.6)	11 (1.2)

Source: Prepared by Anjelina Pokrovnichka using data from Applicant's Table 4.1.3.m, Table 4.1.1.m, and Table 4.1.2.m, pages 477, 453, and 470
Abbreviations: AE, adverse event; APS, abnormal peripheral sensation; CTS, carpal tunnel syndrome; NSAID, nonsteroidal anti-inflammatory drug; PT, preferred term; SC, subcutaneous; Tan, tanezumab; TEAE, treatment-emergent adverse event
[1] Excluding sciatica

Table 90. Frequency of TEAE of Abnormal Peripheral Sensation, All Causalities (Active-Controlled IV OA Studies 1017 and 1025)

Parameter	**NSAID N=691 n (%)**	**Tan 5 mg N=541 n (%)**	**Tan 10 mg N=542 n (%)**	**Tan + NSAID N=1530 n (%)**
With any APS AE[1]	**48 (6.9)**	**77 (14.2)**	**95 (17.5)**	**224 (14.6)**
Paresthesia	16 (2.3)	34 (6.3)	39 (7.2)	114 (7.5)
Hypoesthesia	14 (2.0)	25 (4.6)	29 (5.4)	74 (4.8)
CTS	5 (0.7)	9 (1.7)	22 (4.1)	24 (1.6)

Source: Prepared by Anjelina Pokrovnichka using data from Applicant's Table 4.1.1.l, page 452
Abbreviations: AE, adverse event; APS, abnormal peripheral sensation; CTS, carpal tunnel syndrome; NSAID, nonsteroidal anti-inflammatory drug; PT, preferred term; Tan, tanezumab; TEAE, treatment-emergent adverse event
[1] Excluding sciatica
The table includes events that occurred during the entire study duration. As there were no events that occurred during the follow-up period, the number of events during entire study and during treatment was the same.

The events of abnormal peripheral sensation occurred at a higher frequency and tended to manifest earlier with the IV route than with the SC route of tanezumab administration. The start day was on or before 8 to 16 weeks after the first tanezumab dose. A dose-response relationship (i.e., earlier start day for higher doses) was noted only in the IV placebo-controlled studies. No dose response was observed for the duration of the APS events. For most of the patients, the APS events resolved. For more than half of the patients, the symptoms of APS resolved while the treatment was still ongoing. However, there were patients for which the events have not resolved at the end of their participation in the study (on or off-treatment). More patients in the tanezumab than the placebo and the NSAID treatments in the corresponding study pools did not experience

resolution of symptoms. For the 2.5 mg SC tanezumab dose, unresolved AEs of APS at the end of patient participation in the study were reported by 17% versus 8% in the placebo and 25% versus 14% in the NSAIDs groups in the corresponding study pools.

Table 91. Start Day of APS Events During Treatment Period (Controlled OA Studies)

Placebo-Controlled OA Studies				
Days, median (min, max)	**Placebo**	**Tan 2.5 mg**	**Tan 5 mg**	**Tan 10 mg**
SC Study pool	N=586	N=602	N=347	N=86
	43	**57**	59	62
	(1, 126)	**(2, 151)**	(1, 158)	(14, 92)
IV Study pool	N=1029	N=327	N=977	N=1056
	29	**46**	36	15
	(1, 117)	**(1, 175)**	(2, 169)	(1, 172)
Active-Controlled OA Studies				
Days, median (min, max)	**NSAIDs**	**Tan 2.5 mg**	**Tan 5 mg**	**Tan 10 mg**
SC Study pool	N=996	N=1002	N=998	-
	52	**97**	106	**-**
	(1, 406)	**(2, 359)**	(1, 384)	
IV Study pool	N=691	**-**	N=541	N=542
	50	-	54	50
	(1, 316)		(1, 358)	(1, 337)

Abbreviations: APS, abnormal peripheral sensation; IV, intravenous; max, maximum; min, minimum; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; SC, subcutaneous; Tan, tanezumab
SC placebo-controlled pool includes Studies 1027, 1056, and 1057
IV placebo-controlled pool includes Studies 1011, 1014, 1015, 1018, 1026, 1027, and 1030
SC active-controlled pool includes Study 1058
IV active-controlled pool includes Studies 1017 and 1025
Excludes events of sciatica.
Source: Created by Anjelina Pokrovnichka using data from the following Applicant's analysis tables:
For placebo-controlled SC studies: Applicant's Table 4.1.4.c, Table 4.1.7.c, Table 4.3.1.c, and Table 4.3.7.c from ISS Appendix Tables 2 – Neurological safety, pages 485, 530, 600, and 826
For placebo-controlled IV studies: Applicant's Table 4.1.4.b, Table 4.1.7.b, Table 4.3.1.b, and Table 4.3.7.b from ISS Appendix Tables 2 – Neurological safety, pages 478, 526, 578, and 735
For active-controlled SC study: Applicant's Table 4.1.4.m, Table 4.1.7.m, Table 4.3.1.m, and Table 4.3.7.m from ISS Appendix Tables 2 – Neurological safety, pages 510, 543, 650, and 1134
For active-controlled IV studies: Applicant's Table 4.1.4.l, Table 4.1.7.l, Table 4.3.1.l, and Table 4.3.7.l from ISS Appendix Tables 2 – Neurological safety, pages 498, 537, 632, and 984

Table 92. Duration of APS Events During the Treatment Period (Controlled OA Studies)

Placebo-Controlled OA Studies				
Days, median (min, max)	**Placebo**	**Tan 2.5 mg**	**Tan 5 mg**	**Tan 10 mg**
SC Study pool	N=586	N=602	N=347	N=86
	44	**31**	16	17
	(1, 484)	**(1, 264)**	(1, 358)	(1, 100)
IV Study pool	N=1029	N=327	N=977	N=1056
	29	**54**	33	31
	(1, 401)	**(1, 185)**	(1, 305)	(1, 183)
Active-Controlled OA Studies				
Days, median (min, max)	**NSAIDs**	**Tan 2.5 mg**	**Tan 5 mg**	**Tan 10 mg**
SC Study pool	N=996	N=1002	N=998	**-**
	73	**72**	74	**-**
	(1, 502)	**(1, 474)**	(1, 530)	
IV Study pool	N=691	**-**	N=541	N=542
	54	-	76	57
	(1, 345)		(3, 391)	(1, 379)

Source: Created by Anjelina Pokrovnichka using data from Applicant's analysis tables listed as source documents for Table 91.
Abbreviations: APS, abnormal peripheral sensation; IV, intravenous; max, maximum; min, minimum; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; SC, subcutaneous; Tan, tanezumab
SC placebo-controlled pool includes Studies 1027, 1056, and 1057
IV placebo-controlled pool includes Studies 1011, 1014, 1015, 1018, 1026, 1027, and 1030
SC active-controlled pool includes Study 1058
IV active-controlled pool includes Studies 1017 and 1025
Excludes events of sciatica.

Table 93. Unresolved Events of APS During the Treatment Period (Controlled OA Studies)

Placebo-Controlled OA Studies				
Patients with any APS	**Placebo**	**Tan 2.5 mg**	**Tan 5 mg**	**Tan 10 mg**
SC Study pool	**N=12**	**N=29**	**N=20**	**N=11**
n (%) of subjects with unresolved APS events	1 (8%)	**5 (17%)**	2 (10%)	7 (64%)
IV Study pool	N=33	N=30	N=85	N=132
n (%) of subjects with unresolved APS events	7 (21%)	**19 (63%)**	34 (40%)	41 (31%)
Active-Controlled OA Studies				
Patients with any APS	**NSAIDs**	**Tan 2.5 mg**	**Tan 5 mg**	**Tan 10 mg**
SC Study pool	**N=42**	**N=59**	**N=85**	**-**
n (%) of subjects with unresolved APS events	6 (14%)	**15 (25%)**	21 (25%)	**-**
IV Study pool	N=48	**-**	N=77	N=95
n (%) of subjects with unresolved APS events	17 (35%)	-	33 (43%)	40 (42%)

Source: Created by Anjelina Pokrovnichka using data from Applicant's analysis tables listed as source documents for Table 91
Abbreviations: APS, abnormal peripheral sensation; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; SC, subcutaneous; Tan, tanezumab
SC placebo-controlled pool includes Studies 1027, 1056, and 1057
IV placebo-controlled pool includes Studies 1011, 1014, 1015, 1018, 1026, 1027, and 1030
SC active-controlled pool includes Study 1058
IV active-controlled pool includes Studies 1017 and 1025
Excludes events of sciatica.
Patients with any APS were used as the denominator.

Table 94. Patients With APS Events Who Discontinued Treatment/Study Due to APS Events (Controlled OA Studies)

Placebo-Controlled OA Studies				
	Placebo	**Tan 2.5 mg**	**Tan 5 mg**	**Tan 10 mg**
SC Study pool	**N=586**	**N=602**	**N=347**	**N=86**
n (%) of subjects who d/c due to APS events	0	**0**	1 (0.3%)	0
IV Study pool	N=1029	N=327	N=977	N=1056
n (%) of subjects who d/c due to APS events	1 (0.1%)	**2 (0.6%)**	5 (0.5%)	13 (1.2%)
Active-Controlled OA Studies				
	NSAIDs	**Tan 2.5 mg**	**Tan 5 mg**	**Tan 10 mg**
SC Study pool	**N=996**	**N=1002**	**N=998**	**-**
n (%) of subjects who d/c due to APS events	4 (0.4%)	**3 (0.3%)**	15 (1.5%)	**-**
IV Study pool	N=691	**-**	N=541	N=542
n (%) of subjects who d/c due to APS events	4 (0.6%)	-	11 (2%)	19 (3.5%)

Source: Created by Anjelina Pokrovnichka using data from Applicant's Table 4.1.10.b, Table 4.1.10.c, Table 4.1.10.l, Table 4.1.10.m from ISS Appendix Tables 2 – Neurological safety, pages 458, 460, 463, 464
Abbreviations: APS, abnormal peripheral sensation; d/c, discontinued; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; SC, subcutaneous; Tan, tanezumab
SC placebo-controlled pool includes Studies 1027, 1056, and 1057
IV placebo-controlled pool includes Studies 1011, 1014, 1015, 1018, 1026, 1027, and 1030
SC active-controlled pool includes Study 1058
IV active-controlled pool includes Studies 1017 and 1025
Excludes events of sciatica.
Includes up to the end of the study observation period.
The denominator used to calculate percentages is the number of randomized patients for each treatment group in the corresponding study pools.

Objective Measures of Peripheral Nerve Function

The effect of tanezumab administration on peripheral nerve function was prospectively evaluated in three separate studies that included objective tests of sensory nerve function or cutaneous small nerve fiber density. The duration of exposure to tanezumab in these studies was short and ranged from one to three doses and two of the studies were impacted by the clinical hold resulting in a relatively small number of evaluable patients. Nevertheless, the limited data available do not demonstrate notable effect on sensory-motor nerve conduction or cutaneous small fiber nerve density with tanezumab treatment as compared to placebo treatment.

Study 1026 was conducted in patients with OA to evaluate the effect of tanezumab administration on peripheral nerve function and included assessments of nerve conduction velocity and intraepidermal nerve fiber density (IENFD) in skin biopsies from the distal leg. The study was prematurely discontinued due to the clinical hold. Tanezumab doses of 5 mg (N=73) and 10 mg (N=74) administered IV every 8 weeks for up to 24 weeks (three doses) were compared to placebo (N=72) in this study. The administration of either dose of tanezumab did not meaningfully affect sensory-motor nerve conduction or cutaneous small fiber nerve density as compared to placebo treatment. The prespecified clinically important decrease of ≥2 IENF/mm in a tanezumab group relative to placebo-treated patients was not observed. Study 1040 was an extension study for patients who completed Study 1026 but was substantially impacted by the partial clinical hold with total of 21 patients enrolled, 11 received tanezumab and 10 received placebo.

Study 1031 was conducted in patients with painful diabetic peripheral neuropathy and included IENFD assessments from skin biopsy sites in the thigh and distal leg. Two doses of tanezumab 20 mg SC were planned to be administered in this study and compared to placebo treatment at Week 16. This study was terminated early due to the clinical hold, enrolling 46% of the planned sample size, with the majority of patients receiving a single dose of SC study medication. Many patients declined the Week 16 (or Early Termination) biopsy, thus the number of patients with Baseline and Week 16 data were small (between 12 and 16 patients). Both the observed case and the last observation carried forward analyses showed a small decline in IENFD at Week 16 relative to Baseline in the tanezumab treatment group for both locations (thigh and distal leg) while the placebo treatment group had a small increase in IENFD at both locations. The differences between the treatments, were not statistically significant. The decline in the IENF density in the tanezumab treatment group is difficult to interpret due to the small number of patients.

Study 1046 was conducted in healthy volunteers (N=28) and included assessments of IENFD in the thigh and distal leg comparing baseline to Week 16. Single administration of 20 mg SC tanezumab was compared to placebo in this study. No meaningful changes in IENF density were observed between treatment groups.

9.10. Sympathetic Dysfunction

Background

Because neuronal atrophy in the sympathetic ganglia was noted in animal studies, post-2015 clinical studies included the following procedures to evaluate the effects of tanezumab on the sympathetic nervous system:

- Survey of autonomic symptoms to exclude patients who may have had an autonomic neuropathy.
- Assessments of orthostatic hypotension and bradycardia at each clinic visit.
- Periodic ECG assessments and autonomic symptom questionnaires.
- Consultations with cardiologists and neurologist for possible events of sympathetic neuropathy.
- Assessment of AEs considered potentially associated with sympathetic autonomic neuropathy, such as syncope, bradycardia, orthostatic hypotension, anhidrosis or hypohidrosis, was performed at each clinical visit. A pool of these five events was pre-specified as Tier 1 in the analyses.

Of note, the diagnosis of autonomic neuropathy in clinical practice is extremely challenging because the associated clinical presentation includes symptoms and objective findings that are not specific. For example, the survey of autonomic symptoms questions about nausea, diarrhea, constipation, lightheadedness, erectile dysfunction, sweating of hands and feet, dry mouth and eyes. In addition, it is unknown at what level of the sympathetic neuron depletion symptoms will occur. Therefore, the analysis of adverse events from clinical studies that could represent sympathetic dysfunction is suboptimal and does not allow for definitive conclusions on the sympathetic safety in humans.

Analysis

Table 95 presents the observation-adjusted rates for Tier 1 sympathetic AEs in pooled analysis from post-2015 placebo-controlled studies.

Table 95. Observation-Time Adjusted Tier 1 Sympathetic AEs up to End of Study, Post-2015 Placebo-Controlled Study Pool (1056 and 1057)

Number of Subjects /Observation Time (rate per 1000 subject-years) Preferred Term	Placebo (N=514)	Tanezumab 2.5 mg (N=528)	Tanezumab 2.5/5 mg (N=219)	Tanezumab 5 mg (N=284)
With Any Adverse Event	8/393.9 (20.3)	12/412.2 (29.1)	2/161.9 (12.4)	11/238.2 (46.2)
Bradycardia	7/394.4 (17.7)	7/414.7 (16.9)	1/162.4 (6.2)	6/240.4 (25)
Orthostatic hypotension	1/395.6 (2.5)	4/414.6 (9.6)	1/162 (6.2)	4/239.5 (16.7)
Hypohidrosis	0 /396.1 (0)	1/416 (2.4)	0 /162.6 (0)	0 /241.7 (0)
Syncope	0 /396.1 (0)	0 /416.5 (0)	0 /162.6 (0)	1/241.6 (4.1)

Source: Applicant's Table 5.2.7.c1 from ISS Appendix Tables 2, page 2256
Abbreviation: AE, adverse event

The observation-time adjusted rates for up to end of study for any Tier 1 sympathetic AEs was similar between the placebo and tanezumab 2.5 mg but higher for the tanezumab 5 mg treatment group. The imbalance was primarily driven by higher rates of bradycardia and orthostatic hypotension in the tanezumab treatment groups. Dose response was observed for both of these events. Of note, the overall numbers were very small and the tanezumab 2.5/5 mg and tanezumab 5 mg dose groups each were represented in a single study.

The mean start day ranged between 100 and 120 across the treatment groups. No patient discontinued because of these events. Most events resolved, including all orthostatic events in the tanezumab-treated patients.

The number of patients who required sympathetic function consultations was similar across tanezumab and placebo treatment groups. No patient in any treatment group was considered to have a sympathetic neuropathy.

Table 96 presents the observation-adjusted rates for Tier 1 sympathetic AEs in Study 1058.

Table 96. Observation-Time Adjusted Tier 1 Sympathetic AEs up to End of Study, Active-Controlled Post-2015 Study 1058

Number of Subjects /Observation Time (per 1000 Subject-Years) Preferred Term	NSAID (N=996)	Tanezumab 2.5 mg (N=1002)	Tanezumab 5 mg (N=998)
Any adverse event	37/999.2 (37)	26/1013.4 (25.7)	36/996.8 (36.1)
Bradycardia	21/1009.6 (20.8)	12/1024.6 (11.7)	18/1009.5 (17.8)
Orthostatic hypotension	12/1008 (11.9)	10/1019 (9.8)	16/1001.5 (16)
Syncope	4/1013.2 (3.9)	5/1025.8 (4.9)	1/1013 (1)
Hypohidrosis	0 /1015.8 (0)	0 /1028.3 (0)	1/1013 (1)

Source: Applicant's Table 5.2.7.m from ISS Appendix Tables 2, page 2257
Abbreviation: AE, adverse event

The observation time-adjusted rate for any Tier 1 sympathetic AEs were similar across NSAID and tanezumab 5 mg treatment groups and less in tanezumab 2.5 mg treatment group. The decrease rates for the tanezumab 2.5 mg treatment group compared to NSAID was driven by a lower rate of bradycardia. The observation time-adjusted rates for orthostatic hypotension, hypohidrosis, and syncope were similar for tanezumab treatment groups and the NSAID treatment group.

The mean start day was around Day 170 and similar between the treatment groups. Most events resolved. Only one patient from the NSAID group discontinued because of syncope.

The number of patients who required sympathetic function consultations was similar across tanezumab and NSAIDs treatment groups. No patient in any treatment group was considered to have a sympathetic neuropathy.

Conclusion

Tanezumab was not found to be associated with an increased risk of sympathetic disfunction. Adverse events of possible sympathetic dysfunction (syncope, bradycardia, orthostatic hypotension, anhidrosis or hypohidrosis) occurred at low frequency and were balanced across the treatment groups.

9.11. Composite Joint Safety Endpoint

Adjudication

Outcome for Patients Evaluated by the Adjudication Committee

Table 97. Adjudication Outcome for Patients Evaluated by the Adjudication Committee—Subject Level (Osteoarthritis Post-2015 Studies 1056, 1057, and 1058)

Parameter	Patients With Joint Event(s) Evaluated by Adjudication Committee N=451
Adjudication outcome	
Primary osteonecrosis	3
Worsening osteoarthritis	385
Rapidly progressive osteoarthritis	124
Rapidly progressive osteoarthritis type 1	100
Rapidly progressive osteoarthritis type 2	24
Normal progression	259
Not enough information to distinguish rapid and normal	2
Subchondral insufficiency fracture	18
Pathologic fracture	0
Other	45
Not enough information for diagnosis	0

Source: prepared by clinical reviewer Anjelina Pokrovnichka using data from Applicant's analyses
Includes patients with events up to end of the follow-up period or 26 weeks after the end of the treatment period, whichever is later.
Three additional RPOA1 events, not displayed in this table, occurred after the 26-weeks end of treatment follow-up period in patients who received tanezumab 5 mg.

Descriptive

Analyses of CJSE by Number of Doses

Because the number of doses received is a post-baseline variable that may be affected by treatment, the descriptive analyses included in this section are exploratory and should be interpreted with caution.

Descriptive summaries of the number of observed CJSE by the total number of doses received in Studies 1056 and 1057 are shown in Table 98 and Table 99.

Table 98. CJSE Summary by Dose Received (Study 1056)

Parameter	Placebo	Tan 2.5	Tan 2.5/5
N	233	232	233
Total number of subjects with CJSE	0	5	1
Total number of doses received (number of CJSE subjects)			
0	1 (0)	1 (0)	0 (0)
1	26 (0)	10 (0)	14 (0)
2	206 (0)	221 (5)	219 (1)

Source: DB7 reviewer using adadj.xpt from ISS-joint-safety-analysis pool and adsl.xpt from the ISS-all-study pool.
Abbreviations: CJSE, composite joint safety endpoint; Tan, tanezumab
This summary was tabulated by randomization arm. Fourteen subjects who were randomized to the Tan 2.5/5 arm received only the first dose of Tan 2.5 and were categorized as Tan 2.5 in the primary CJSE analysis.

Table 99. CJSE Summary by Dose Received (Study 1057)

Parameter	Placebo	Tan 2.5	Tan 5
N	282	283	284
Total number of subjects with CJSE	0	5	11
Total number of doses received (number of CJSE subjects)			
1	17 (0)	8 (0)	9 (0)
2	23 (0)	11 (0)	11 (1)
3	242 (0)	264 (5)	264 (10)

Source: DB7 reviewer using adadj.xpt from ISS-joint-safety-analysis pool and adsl.xpt from the ISS-all-study pool.
Abbreviations: CJSE, composite joint safety endpoint; Tan, tanezumab
Note: All randomized subjects received study treatment as randomized in Trial 1057.

In Study 1056, 92.6% of the randomized subjects received two doses of randomized treatment, and in Study 1057, 90.6% of the randomized subjects received three doses of randomized treatment. These subjects account for 21 out of 22 CJSE events in these two studies. Because the subjects who received the maximum number of doses may be different from the subjects who received fewer doses, and because over 90% of the subjects received the maximum number of pre-specified doses, any analysis of CJSE by number of doses in studies 1056 and 1057 would be difficult to interpret. Because no clinical data were available beyond the study duration of Trial 1056/1057 (16/24-week treatment plus 24-week follow up), the risk of CJSE associated with tanezumab compared to placebo beyond this period is unknown.

Descriptive summaries of the number of observed CJSE by the total number of doses received in Study 1058 are shown in Table 100.

Table 100. CJSE Summary by Dose Received (Study 1058)

Parameter	NSAID	Tan 2.5	Tan 5
N	1008	1008	1005
Total number of subjects with CJSE	15	39*	72*
Total number of doses received (number of CJSE subjects)			
0*	12 (0)	6 (0)	7 (0)
1	81 (0)	73 (1)	79 (1)
2†	334 (1)	319 (6)	303 (8)
3	50 (3)	61 (10)	73 (12)
4	27 (2)	33 (2)	34 (0)
5	23 (0)	28 (1)	35 (0)
6	34 (0)	24 (0)	38 (6)
7	447 (9)	464 (19)	436 (45)

Source: DB7 reviewer using adadj.xpt from ISS-joint-safety-analysis pool and adsl.xpt from the ISS-all-study pool.
Abbreviations: CJSE, composite joint safety endpoint; Tan, tanezumab
* Twelve, six, and seven subjects in the NSAID, Tan 2.5, and Tan 5 arms, respectively, were randomized but did not receive study treatment.
† Subjects who did not respond in the WOMAC Pain subscale at the 30% level or greater at Week 16 and at the 15% level or greater at either Week 2, 4, or 8 were discontinued from treatment. Week 16 approximately corresponds to the end of the second dose.

The number of received doses of randomized treatment in Study 1058 followed a bi-modal distribution with peaks at 2 doses (31.6% of randomized subjects) and 7 doses (44.6%). This bi-modal distribution was caused by the fact that subjects who did not meet the responder criteria (decrease in the WOMAC Pain subscale score by 30% level or greater at Week 16 and by 15% or greater at either Week 2, 4, or 8) were discontinued from treatment at that time. Therefore, subjects who received three or more doses (responders) may be different in measured and unmeasured characteristics than subjects who received fewer than three doses (non-responders + subjects who discontinued treatment early for other reasons). Because the number of doses received by any subject is a post-randomization characteristic that was affected by study design (pre-specified discontinuation due to lack of efficacy) and possibly by other post-randomization characteristics, it is not possible to conduct an adequate analysis to explore the association between the risk of CJSE and the number of doses received by a patient. CJSE events were recorded after as few as one dose of randomized treatment; however, it is unclear whether this risk increases with additional doses. Furthermore, because no clinical data are available beyond the study duration of Trial 1058 (56-week treatment plus 24-week follow up), the risk of CJSE associated with tanezumab compared to NSAID beyond this period is unknown.

CJSE in Index Versus Non-index Joints (Table 104)

A non-index joint was affected in more patients treated with tanezumab than those treated with NSAID. The primary CJSE occurred in non-index joints in approximately 40% of the patients in the tanezumab 2.5 mg and NSAID treatment groups compared to 70% of the patients in the tanezumab 5 mg treatment group. Events of RPOA1, RPOA2, and ON occurred in non-index joint in 60% of the patients treated with tanezumab (71/118) and 27% in patients treated with NSAIDs (3/11). Events of SIF in non-index joint occurred more frequently in the NSAIDs treatment group, 57% in patients treated with tanezumab (8/14) and 75% in patients treated with NSAIDs (3/4).

Clinical Signs and Symptoms Prior to a CJSE (Table 104)

Among patients randomized to tanezumab, arthralgia and joint swelling superficially appeared to correlate with CJSE. A total of 42 out of 620 (6.8%) subjects who experienced arthralgia or joint swelling and also experienced CJSE; 36 out of these 42 subjects experienced arthralgia and joint swelling prior to CJSE. However, as described in CJSE clinical presentation below, only 1% of cases that went for adjudication were triggered by the clinical investigator because of clinical presentation. Among patients who did not experience arthralgia or joint swelling, a smaller proportion 88 out of 2411 (3.6%), experienced CJSE. This pattern was not observed among patients randomized to NSAIDs: 1 out of 161 (0.6%) subjects who experienced arthralgia or joint swelling also experienced CJSE, and 14 out of 834 (1.7%) who did not experience arthralgia or joint swelling experienced CJSE. Note that even if arthralgia and joint swelling are associated with CJSE among patients taking tanezumab, no data are available to show whether discontinuing treatment after an AE of arthralgia or joint swelling influences the risk of CJSE.

Type of Joint Affected (Table 104)

For most patients with a primary CJSE, with no difference between the treatment groups, the knee was the affected joint (107/145, or 74%), followed by the hip (35/145, or 24%), and the shoulder (3/145, or 2%). Of note, about 85% of the patients across the treatment groups enrolled in study with knee as their index joint.

CJSE Resulting in TJR (Table 104)

Across the treatment groups with primary CJSE, only 23% had a TJR surgery. Joint replacement surgery was more frequently seen as an outcome in patients with substantial loss/destruction of bone, such as RPOA2 and ON. Approximately 15% of the patients with RPOA 1 and 20% of the patients with SIF versus 60% of the patients with RPOA 2 underwent TJR. Two of the three patients with adjudicated ON underwent TJR.

Evolution of the Destructive Process in RPOA1 Cases After Study Drug Discontinuation

To assess whether the risk mitigation scheme is likely to be effective, it is important to characterize the trajectory of joint adverse events in patients who developed RPOA1 and stopped drug. Thus, the Applicant was asked to submit an analysis that captured the outcome of RPOA1 cases on imaging studies performed after the event was identified.

If the patient was still in the treatment period when RPOA1 was detected, treatment was discontinued, and follow-up images collected during the early termination follow-up period. If the RPOA1 event was first detected after the patient has completed the Treatment period, follow-up images were collected at the protocol-specified imaging time points during the 24-week safety follow-up period.

In their response dated March 13, 2020, the Applicant clarified that the Adjudication Committee alone made the determination of whether an event of RPOA1 had progressed to a more severe category. Pfizer explained that the Committee's assessment was made upon imaging and other available documentation. The Applicant reports that cases sent for adjudication were reviewed by the Adjudication Committee after all images collected for each case were available, thus, the

final adjudication classification reflects the most severe outcome observed among all images. The Applicant reports that 99 out of 101 cases with RPOA1 adjudication outcome were assessed upon review of all collected images and ended up as RPOA1. Therefore, the Applicant concludes that there is little evidence of event progression after treatment discontinuation.

Superficially, the assertion that the RPOA1 adjudicated cases did not progress supports a conclusion that RPOA does not progress after treatment discontinuation. However, we note that adequate follow-up imaging, after the date when RPOA1 was identified, are available in a fairly small number of patients who developed RPOA1. Across all three post-2015 OA studies, there were 101 patients with an adjudicated endpoint of RPOA1 of which the majority (89 patients) were enrolled in Study 1058. Follow-up images were available for 67 out of the 101 RPOA1 events (66%). For 58 out of the 67 patients with available follow-up images, the RPOA1 diagnosis was made on imaging obtained at end-of-treatment or early-termination visit. For 48 out of 101 patients with RPOA1 event, the follow-up image was performed ≥4 months after the RPOA1 event was first identified (Table 101). For most of the events with no available follow-up images, the RPOA1 event was detected at the final study visit or the last visit of the early termination period.

Table 101. Follow-up Imaging for RPOA Type 1 Events (Studies 1056, 1057, and 1058)

RPOA 1 Events in Studies 1056, 1057, and 1058 (N=101)	
RPOA 1 events with available follow-up images	Duration between RPOA 1 first identified and follow-up imaging
67 (66%)	Any time point after RPOA 1
48 (47%)	≥4 months after RPOA 1
13 (13%)	≥6 months after RPOA 1

Source: Medical reviewer Anjelina Pokrovnichka
Abbreviation: RPOA, rapidly progressive osteoarthritis

Given the latency to many of the joint events, we conclude that the available data do not adequately inform the fate of patients who develop RPOA1.

CJSE Clinical Presentation

The CJSE were largely clinically silent. A total of 451 patients had a joint safety event evaluated by the adjudication committee. The imaging studies of all 451 patients were evaluated by the Central Reader. Approximately 56% (254/451) of the cases qualified for adjudication because of an event identified by the Central Reader on imaging, 43% (191/451) because of a TJR with no qualifying findings based on imaging, and 1% because of event identified by an investigator (6/451). Most of the qualifying cases identified by the Central Reader were detected on images required as part of the protocol-specified safety follow-up (241/254, or 95%) and only a small number (13/254, or 5%) on images requested "for cause" (Table 102). These findings suggest that for most of the possible/probable joint events, the radiographic changes were not associated with clinical signs or symptoms. As 70% of the cases with an adjudicated joint event (100 out of 145) were RPOA1, a diagnostic entity describing decrease in joint space width without bone destruction, the lack or correlation between the radiographic and the clinical presentation is not unexpected. RPOA1 is considered the early stage of the rapidly progressing OA. Because the surgical management becomes more complex and challenging if the process advances to bone loss and severe joint destruction, detecting the RPOA at an early stage is important. However,

due to its 'salient' presentation, early detection of RPOA1 requires frequent, high quality imaging surveillance.

Table 102. Joint Safety Events Evaluated by the Adjudication Committee

Joint Safety Events—Reason for Evaluation by the Adjudication Committee	Number of Patients (451)
Events identified by the CR (all possible/probable primary ON, RPOA, SIF [including stress/recent fractures], and pathologic fracture)	254
Events identified by the CR on images required as part of the safety follow-up	241
Events identified by the CR on images obtained 'for cause' by the investigator: • To evaluate increased severe and persistent joint pain[1] • To evaluate concerning findings on examination and/or patient complaints[1]	13
Events identified by the investigator or Applicant as medically important that were not evaluated by the CR	0
Events of TJR (no CR findings of a possible/probable joint safety event)	191
Evaluated by the CR	191
Not evaluated by the CR	0
Other (specify) events identified by the investigator for adjudication that were evaluated by the CR[1]	6

Source: Applicant's Table 1 from the response to the information request submitted April 20, 2020
Abbreviations: AC, adjudication committee; CR, central reader; ON, osteonecrosis; RPOA, rapidly progressive osteoarthritis; SIF, subchondral insufficiency fracture; TJR, total joint replacement
[1] Unable to summarize reason for 'for cause' MRI, investigators were not required to indicate the specific reason for requesting "for cause" imaging.

Imaging Modality of Choice for Detection of RPOA: X-Ray Versus MRI

The Applicant proposes to use annual knee and hip radiographs for the joint event surveillance that would be part of the REMS program. Data from post-2015 OA studies were examined to determine if the RPOA diagnosis was established on X-ray or MRI imaging.

According to the Adjudication Committee Charter, the definition for primary ON included both radiographic and MRI characteristics. The definitions for RPOA1 and RPOA2 were based on radiographic (x-ray) criteria. The Adjudication Committee had both radiographs and MRIs as well as the Central Reader's assessments of the radiographs and MRIs available for their deliberations. Based on the adjudication process, the Applicant stated that it is difficult to assess whether the Adjudication Committee considered the radiographic and/or the MRI findings during the adjudication process.

In Studies 1056 and 1057 (N=1545), MRIs were not included as part of the scheduled, protocol-specified imaging but they could be requested for cases with discordant pain or ambiguous/equivocal X-ray findings. For only a small proportion of the patients enrolled in studies 1056 and 1057 (35/1545 or 2.3%), the Central Reader requested an MRI to complete the safety assessment. In these studies, there was a total of 116 patients who had a possible/probable joint safety event or total joint replacement evaluated by the Adjudication Committee (116/1545 or 7.5%).

In Study 1058, the protocol required MRIs at screening for knee and hip joints and at follow-up visits for any patient who had a knee or hip with a baseline KL Grade of 3 or 4. These MRIs were not routinely read for surveillance during the course of the study. The Applicant states that

"MRIs were performed in Study 1058 so they would be available for reading if equivocal radiographic findings were identified." Follow-up MRIs were read only under the following circumstances:

- To confirm a diagnosis of RPOA1 that was established on X-ray (to determine if the apparent loss of joint space width observed on radiograph could be explained by cartilage damage and/or meniscal extrusion as opposed to positional changes).
- To complete the radiographic assessment for cases with discordant pain to X-ray findings and for cases in which the MRI was requested "for cause.'
- To prepare qualifying events for adjudication, available radiographs and MRIs for all joints for the given patient were read by the Central Reader.

In a response to Information Request submitted March 24, 2020, the Applicant reported that 335 of 2996 (11%) patients had a possible/probable joint safety event or total joint replacement evaluated by the Adjudication Committee.

Of those patients, the Central Reader read both follow-up X-rays and MRIs to complete the safety assessment for only 188 patients (188/2996 or 6.3%) according to the response provided to Question 2f. This represents slightly more than half of the cases adjudicated. The breakdown of the radiographic and the MRI findings follow:

- Nine patients, or 4.8% (9/188), had no X-ray findings but did have MRI findings of joint safety event (RPOA, SIF, or ON)
- One hundred seventy-nine patients, or 95% (179/188) had equivocal X-ray findings but a joint safety event was identified on their MRI. For majority of these patients (107/179, or 60%), the Central Reader identified RPOA1 on the MRI imaging

In Study 1058 (N=2996), the Central Reader identified 386/2996 radiographs with possible/probable RPOA1. For 132/386 (34%) of these radiographs, the RPOA1 diagnosis was not confirmed by the MRI findings (Information provided by Applicant in their response to information request submitted on March 24, 2020, Question 2c). Of note, MRIs were required to confirm any diagnosis of RPOA1 made on X-ray imaging in Study 1058, which means that both X-ray and MRIs were read in at least 386 out of the 2996 patients enrolled in Study 1058, contradicting the response provided to Question 2f (188/2996 having both X-ray and MRIs read).

The fact that a small number of patients required an MRI to complete the safety assessment is reassuring. Nevertheless, because the pathophysiologic process by which tanezumab causes joint destruction is unknown, the correlating findings on imaging studies are uncharted. Therefore, it is unknown whether findings that are detectable on MRI but not on X-ray, for example atypical bone marrow edema, could be an early sign indicating that the destructive process has been triggered. Review of the narratives for several cases revealed that retrospectively read MRIs, while preparing a case for adjudication, identified joint safety events that were not seen on series of X-ray images until later into the destruction process.

For example, review of the narrative for Subject (b) (6) 67-year-old female adjudicated with RPOA2 in the index left knee, revealed that atypical large area of bone marrow edema was the first finding identifiable on MRI but not on X-ray imaging. The MRIs for this patient were read after the diagnosis of RPOA2 was established on X-ray in preparation of the case for the Adjudication Committee.

- Patient entered study with left knee (baseline KLG3) as the index joint and received 6 out of the 7 blinded study drug doses (treatment administered was tanezumab 5 mg).
- Screening X-ray was determined to be qualifying for enrollment. MRI was obtained at screening but not read until RPOA2 of the left knee was detected on X-ray at the end of the treatment period visit; the retrospectively read baseline MRI indicated bone marrow edema/lesion left knee; no other comments were provided in the narrative.
- Protocol required Week 24 X-ray indicated no possible or probable joint safety findings. The MRI obtained on this visit was subsequently read as no possible or probable joint safety findings, but large area of bone marrow edema medial left femur and tibia not typical for OA and bone marrow edema/lesion of right knee.
- Protocol required Week 56 X-ray indicated RPOA2 in the left knee. The MRI obtained on that visit was subsequently read and confirmed the diagnosis of RPOA2 in the left knee.

Subject (b) (6) from Study 1058, who received seven doses of tanezumab 5 mg, developed a joint safety event in her right shoulder classified as RPOA2 requiring TJR. The event was identified on MRI obtained on Day 345 but was not detectable on X-rays on Day 147, Day 352, and Day 373.

Subject (b) (6) from Study 1058 treated with tanezumab 5 mg had a primary ON of left and right knee, and right hip, described on the screening MRI that was retrospectively read by the Central Reader. Series of X-rays in this patient were reported as "'no possible or probable joint safety event present." This patient underwent bilateral knee replacement surgeries. The adjudication outcome was "normal OA progression."

One other piece of evidence supports that plain radiographs may lack the sensitivity to detect significant joint disease. Our review of several narratives identified cases in which one or more exclusionary conditions were identified on retrospectively read MRIs obtained at baseline, such as pre-existing ON and/or SIF (from Study 1058, Subject (b) (6) Subject (b) (6) and Subject (b) (6)). These conditions were not detected on serial X-rays, including baseline and per-protocol scheduled follow-up X-rays until the subject met the criteria for evaluation by the Adjudication Committee. These cases were detected when, in preparing the case for adjudication, the Central Reader retrospectively read all available images, including the MRI images that were obtained but not read.

In conclusion, the imaging surveillance in post-2015 OA studies was primarily based on radiographic assessments and MRIs were obtained and/or read in rare instances. As a result, the number of patients with MRI readings was substantially smaller than the number of patients with X-ray readings. Due to this imbalance, the data from the tanezumab studies, do not allow to make any definitive conclusions about superior specificity and/or sensitivity of one imaging modality over the other for the detection of the joint destruction signal. The development program was not structured to answer this question. Nevertheless, recent literature (Fleming 2017 and Price 2019) suggests that MRI may be a superior technique to detect RPOA at an earlier stage. This conception is supported by joint safety findings identified on retrospectively read MRIs in tanezumab studies that were not appreciable on series of X-ray images.

Joint Case Ascertainment—Discrepancies Between Adjudication Committee and Central Reader

The Central Reader reported 241 patients with a joint event meeting the criteria for a primary CJSE event. However, the Adjudication Committee reported 145 patients as having met the criteria for a primary CJSE (Table 103). The Central Readers were highly trained board-certified musculoskeletal radiologists guided by an imaging atlas. The Central Reader's assessment was primarily based on imaging supplemented with pain diary scores. In contrast, the Adjudication Committee was provided with a dossier that included clinical summaries, imaging reports, operative reports (if applicable), and pathology results (when available). As the Applicant explained, the Adjudication Committee's remit was to assess the totality of the available clinical and imaging information, including the possible contribution of pre-existing conditions, traumatic events, and/or concomitant procedures, when assigning a final adjudication outcome to be used for analyses. Nevertheless, the discrepancy between the Central Reader and the Adjudication Committee categorization of the joint safety events illustrates the complexity and the uncertainty of the classification process, alluding to the challenges that would be faced in clinical practice. We further note that most CJSEs were defined solely on the basis of imaging findings.

Because the joint safety analyses were based on the final adjudication categorization of the events, sensitivity analyses were performed to examine if the outcomes would differ if a different trigger, Central Reader versus Adjudicators, was used for event detection.

Table 103 provides a summary by treatment group of the primary joint safety outcome based on joint safety events identified by the Central Reader versus joint safety event identified by the Adjudication Committee.

Table 103. Joint Safety Outcomes Central Reader Versus Adjudication Committee Classification (Post-2015 OA Studies)

	Placebo N=514	Tan 2.5 mg N=1530	Tan 2.5/5 mg N=219	Tan 5 mg N=1282	NSAID N=996
Parameter			n (%)		
Primary CJSE by CR, N=241	3 (0.6)	81 (5.3)	3 (1.4)	129 (10.1)	25 (2.5)
RPOA1 by CR	2 (0.4%)	43 (2.8)	2 (0.9)	71 (5.5)	13 (1.3)
RPOA2 By CR	0	7 (0.5)	0	21 (1.6)	0
SIF by CR	0	25 (1.6)	0	30 (2.3)	8 (0.8)
ON by CR	1 (0.2%)	6 (0.4)	1 (0.5)	7 (0.5)	4 (0.4)
Pathologic fracture by CR	0	0	0	0	0
Primary CJSE by AC, N=145	0	49 (3.2)	1 (0.5)	80 (6.2)	15 (1.5)
RPOA1 by AC	0	35 (2.3)	1 (0.5)	54 (4.2)	10 (1.0)
RPOA2 by AC	0	6 (0.4)	0	17 (1.3)	1 (0.1)
SIF by AC	0	7 (0.5)	0	7 (0.5)	4 (0.4)
ON by AC	0	1 (0.1)	0	2 (0.2)	0
Pathologic fracture by AC	0	0	0	0	0

Source: Applicant's Table 2 and Table 3 provided in response to information request dated April 20, 2020
Abbreviations: AC, adjudication committee; CR, central reader; NSAID, nonsteroidal anti-inflammatory drug; ON, osteonecrosis; RPOA, rapidly progressive osteoarthritis; RPOA 1, rapidly progressive osteoarthritis type 1; RPOA 2, rapidly progressive osteoarthritis type 2; SIF, subchondral insufficiency fracture; TJR, total joint replacement

Across the treatment groups, a larger number of primary CJSE were identified based on the Central Reader's assessment relative to the Adjudication Committee's assessment. However, the pattern for the composite and the individual components across the treatment groups remains the same, except for the SIF outcome. Therefore, the conclusion about the joint safety risk associated with tanezumab treatment relative to placebo and NSAIDs treatments does not change.

Tables With Descriptive Statistics for CJSE

Table 104. Details of Adjudicated Primary CJSE, Subject Level (Post-2015 OA Studies 1056, 1057, and 1058)

Parameter	Tan 2.5 mg (N=1530)	Tan 5 mg (N=1282)	NSAID (N=996)	All Treatment Groups[1] (N=4541)
Primary joint composite endpoint (n)	49	80	15	145[1]
Associated with TJR (n%)				
Yes	7 (14.3)	22 (27.5)	4 (26.7)	34 (23.4)[1]
No	42 (85.7)	58 (72.5)	11 (73.3)	111 (76.6)
Joint(s) affected (n%)				
Knee	37 (75.5)	58 (72.5)	12 (80.0)	107 (73.8)
Hip	12 (24.5)	20 (25.0)	2 (13.3)	35 (24.1)[1]
Shoulder	0	2 (2.5)	1 (6.7)	3 (2.1)
Index	28 (57.1)	25 (31.3)	9 (60.0)	63 (43.4)[1]
Non-index	21 (42.9)	55 (68.8)	6 (40.0)	82 (56.6)
KLG of affected joint at baseline (n%)				
Not available	0	2 (2.5)	1 (6.7)	3 (2.1)
0	3 (6.1)	6 (7.5)	1 (6.7)	10 (7.1)
1	6 (12.2)	14 (17.5)	1 (6.7)	21 (14.5)
2	16 (32.7)	30 (37.5)	5 (33.3)	51 (35.2)
3	19 (38.8)	24 (30.0)	6 (40.0)	50 (34.5)[1]
4	5 (10.2)	4 (5.0)	1 (6.7)	10 (6.9)
WOMAC pain at baseline (n%)				
<7	18 (36.7)	35 (43.8)	6 (40.0)	60 (41.4)[1]
≥7	31 (63.3)	45 (56.3)	9 (60.0)	85 (58.6)
Study period event detected (n%)				
During treatment	19 (38.8)	46 (57.4)	8 (53.3)	73 (50.3)
During follow-up	29 (59.2)	29 (36.3)	5 (33.4)	64 (44.2)
During safety follow-up	21 (42.9)	17 (21.3)	5 (33.4)	44 (30.4)[1]
During early term follow-up	8 (16.3)	12 (15.0)	0	20 (13.8)
After follow-up[2]	1 (2.0)	5 (6.3)	2 (13.3)	8 (5.5)[1]
AEs of arthralgia/joint swelling prior to event (n%)				
Yes	13 (26.5)	23 (28.8)	1 (6.7)	37 (25.5)
No	36 (73.5)	57 (71.3)	14 (93.3)	108 (74.5)[1]

Source: Table created by the medical reviewer Anjelina Pokrovnichka using data submitted by the Applicant on March 30, 2020.
Abbreviations: AE, adverse event; CJSE, composite joint safety endpoint; KLG, Kellgren-Lawrence grade; OA, osteoarthritis; NSAID, nonsteroidal anti-inflammatory drug; Tan, tanezumab; TJR, total joint replacement; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index
Includes events up to the end of the follow-up period or 26 weeks after the end of the treatment period, whichever is later. The denominator is the number of that outcome.
The single subject from the tanezumab 2.5/5 mg treatment group had an adjudicated event of RPOA 1 in the index hip joint with a baseline KLG of 4, which was detected during the follow-up period; the event resulted in TJR.
[1] Placebo, N=514 with zero events and tanezumab 2.5/5 mg, N=219 with one event are not presented as separate columns but are included in the All Treatment Groups column
[2] Includes events that occurred within 2 weeks after patients (1) completed follow-up (safety or early termination), or (2) discontinued from follow-up (safety or early termination).

Table 105. Details of Adjudicated RPOA1, Subject-Level (Post -2015 OA Studies 1056, 1057, and 1058)

Parameter	Tan 2.5 mg (N=1530)	Tan 5 mg (N=1282)	NSAID (N=996)	All Treatment Groups[1] (N=4541)
Primary joint composite endpoint (n)	35	54	10	100[1]
Associated with TJR (n%)				
Yes	4 (11.4)	8 (14.8)	2 (20.0)	15 (15.0)[1]
No	31 (88.6)	46 (85.2)	8 (80.0)	85 (85.0)
Joint(s) affected (n%)				
Knee	29 (82.9)	46 (85.2)	8 (80.0)	83 (83.0)
Hip	6 (17.1)	7 (13.0)	2 (20.0)	16 (16.0)[1]
Shoulder	0	1 (1.9)	0	1 (1.0)
Index	19 (54.3)	17 (31.5)	8 (80.0)	45 (45.0)[1]
Non-index	16 (45.7)	37 (68.5)	2 (20.0)	55 (55.0)
KLG of affected joint at baseline				
Not available	0	1 (1.9)	0	1 (1.0)
0	2 (5.7)	2 (3.7)	0	4 (4.0)
1	6 (17.1)	11 (20.4)	1 (10.0)	18 (18.0)
2	13 (37.1)	25 (46.3)	4 (40.0)	42 (42.0)
3	14 (40.0)	15 (27.8)	5 (50.0)	35 (35.0)[1]
4	0	0	0	0
WOMAC pain at baseline				
<7	13 (37.1)	22 (40.7)	2 (20.0)	38 (38.0)[1]
≥7	22 (62.9)	32 (59.3)	8 (80.0)	62 (62.0)
Study period event detected				
During treatment	13 (37.1)	30 (55.6)	5 (50.0)	48 (48.0)
During follow-up	21 (60.0)	23 (42.6)	4 (40.0)	49 (49.0)[1]
During safety follow-up	14 (40.0)	12 (22.2)	4 (40.0)	31 (31.0)[1]
During early term follow-up	7 (20.0)	11 (20.4)	0	18 (18.0)
After follow-up[2]	1 (2.9)	1 (1.9)	1 (10.0)	3 (3.0)
AEs of arthralgia/joint swelling prior to event				
Yes	11 (31.4)	16 (29.6)	1 (10.0)	28 (28.0)
No	24 (68.6)	38 (70.4)	9 (90.0)	72 (72.0)[1]

Source: Table created by the medical reviewer Anjelina Pokrovnichka using data submitted by the Applicant on March 30, 2020.
Abbreviations: AE, adverse event; CJSE, composite joint safety endpoint; KLG, Kellgren-Lawrence grade; OA, osteoarthritis; NSAID, nonsteroidal anti-inflammatory drug; Tan, tanezumab; TJR, total joint replacement; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

[1] Placebo, N=514 with zero RPOA1 events and tanezumab 2.5/5 mg, N=219 with one RPOA1 event are not presented as separate columns but are included in the 'All Treatment Groups' column.

[2] Includes events that occurred within 2 weeks after patients (1) completed follow-up (safety or early termination), or (2) discontinued from follow-up (safety or early termination).

Table 106. Details of Adjudicated RPOA Type 2, Subject Level (Post -2015 OA Studies 1056, 1057, and 1058)

Parameter	Tan 2.5 mg (N=1530)	Tan 5 mg (N=1282)	NSAID (N=996)	All Treatment Groups[1] (N=4541)
Primary joint composite endpoint (n)	6	17	1	24
Associated with TJR (n%)				
Yes	3 (50.0)	10 (58.8)	1 (100.0)	14 (58.3)
No	3 (50.0)	7 (41.2)	0	10 (41.7)
Joint(s) affected (n%)				
Knee	3 (50.0)	6 (35.3)	0	9 (37.5)
Hip	3 (50.0)	10 (58.8)	0	13 (54.2)
Shoulder	0	1 (5.9)	1 (100.0)	2 (8.3)
Index	5 (83.3)	6 (35.3)	0	11 (45.8)
Non-index	1 (16.7)	11 (64.7)	1 (100.0)	13 (54.2)
KLG of affected joint at baseline				
Not available	0	1 (5.9)	1 (100.0)	2 (8.3)
0	0	2 (11.8)	0	2 (8.3)
1	0	1 (5.9)	0	1 (4.2)
2	0	1 (5.9)	0	1 (4.2)
3	1 (16.7)	8 (47.1)	0	9 (37.5)
4	5 (83.3)	4 (23.5)	0	9 (37.5)
WOMAC pain at baseline				
<7	2 (33.3)	6 (35.3)	1 (100.0)	9 (37.5)
≥7	4 (66.7)	11 (64.7)	0	15 (62.5)
Study period event detected (n%)				
During treatment	2 (33.3)	11 (64.8)	0	13 (54.2)
During follow-up	4 (66.7)	3 (17.6)	0	7 (29.2)
During safety follow-up	4 (66.7)	2 (11.8)	0	6 (25.0)
During early term follow-up	0	1 (5.9)	0	1 (4.2)
After follow-up[2]	0	3 (17.6)	1 (100.0)	4 (16.6)
AEs of arthralgia/joint swelling prior to event				
Yes	2 (33.3)	4 (23.5)	0	6 (25.0)
No	4 (66.7)	13 (76.5)	1 (100.0)	18 (75.0)

Source: Table created by the medical reviewer Anjelina Pokrovnichka using data submitted by the Applicant on March 30, 2020.
Abbreviations: AE, adverse event; CJSE, composite joint safety endpoint; KLG, Kellgren-Lawrence grade; OA, osteoarthritis; NSAID, nonsteroidal anti-inflammatory drug; Tan, tanezumab; TJR, total joint replacement; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

[1] Placebo, N=514 and tanezumab 2.5/5 mg, N=219 are not presented as separate columns but are included in the 'All Treatment Groups' column. There were no RPOA2 events in those two groups.

[2] Includes events that occurred within 2 weeks after patients (1) completed follow-up (safety or early termination), or (2) discontinued from follow-up (safety or early termination).

Table 107. Details of Adjudicated Subchondral Insufficiency Fracture, Subject Level (Post -2015 OA Studies 1056, 1057, and 1058)

Parameter	Tan 2.5 mg (N=1530)	Tan 5 mg (N=1282)	NSAID (N=996)	All Treatment Groups[1] (N=4541)
Primary joint composite endpoint (n)	7	7	4	18
Associated with TJR (n%)				
Yes	0	3 (42.9)	1 (25.0)	4 (22.2)
No	7 (100.0)	4 (57.1)	3 (75.0)	14 (77.8)
Joint(s) affected (n%)				
Knee	5 (71.4)	6 (85.7)	4 (100.0)	15 (83.3)
Hip	2 (28.6)	1 (14.3)	0	3 (16.7)
Shoulder	0	0	0	0
Index	4 (57.1)	2 (28.6)	1 (25.0)	7 (38.9)
Non-index	3 (42.9)	5 (71.4)	3 (75.0)	11 (61.1)
KLG of affected joint at baseline				
Not available	0	0	0	0
0	0	1 (14.3)	1 (25.0)	2 (11.1)
1	0	1 (14.3)	0	1 (5.6)
2	3 (42.9)	4 (57.1)	1 (25.0)	8 (44.4)
3	4 (57.1)	1 (14.3)	1 (25.0)	6 (33.3)
4	0	0	1 (25.0)	1 (5.6)
WOMAC pain at baseline				
<7	2 (28.6)	5 (71.4)	3 (75.0)	10 (55.6)
≥7	5 (71.4)	2 (28.6)	1 (25.0)	8 (44.4)
Study period event detected (n%)				
During treatment	4 (57.1)	3 (42.9)	3 (75.0)	10 (55.6)
During follow-up	3 (42.9)	3 (42.9)	1 (25.0)	7 (38.8)
During safety follow-up	2 (28.6)	3 (42.9)	1 (25.0)	6 (33.3)
During early term follow-up	1 (14.3)	0	0	1 (5.6)
After follow-up[2]	0	1 (14.29)	0	1 (5.6)
AEs of arthralgia/joint swelling prior to event				
Yes	0	3 (42.9)	0	3 (16.7)
No	7 (100.0)	4 (57.1)	4 (100.0)	15 (83.3)

Source: Table created by the medical reviewer Anjelina Pokrovnichka using data submitted by the Applicant on March 30, 2020.
Abbreviations: AE, adverse event; CJSE, composite joint safety endpoint; KLG, Kellgren-Lawrence grade; OA, osteoarthritis; NSAID, nonsteroidal anti-inflammatory drug; Tan, tanezumab; TJR, total joint replacement; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index
*Placebo, N=514 and tanezumab 2.5/5 mg, N=219 are not presented as separate columns but are included in the 'All Treatment Groups' column. There were no events of RPOA2 in those two groups.
[2] Includes events that occurred within 2 weeks after patients (1) completed follow-up (safety or early termination), or (2) discontinued from follow-up (safety or early termination).

Adjudicated Joint Safety Outcomes—Joint Level

Table 108. Adjudicated Joint Safety Outcomes—Joint-Level (Safety: OA Controlled Post-2015 Studies 1056, 1057, and 1058)

	Placebo (N=514)	Tanezumab 2.5 mg (N=1530)	Tanezumab 2.5/5 mg (N=219)	Tanezumab 5 mg (N=1282)	Tanezumab 2.5 and 5 mg Combined (N=3031)	NSAID (N=996)
Potential events analyzed by the Adjudication Committee [n]	28	173	19	246	438	57
Joint safety events						
Rapidly Progressive OA [n (%)]	0	42 (24.3)	1 (5.3)	77 (31.3)	120 (27.4)	12 (21.1)
Rapidly Progressive OA type 1 [n (%)]	0	36 (20.8)	1 (5.3)	58 (23.6)	95 (21.7)	11 (19.3)
Rapidly Progressive OA type 2 [n (%)]	0	6 (3.5)	0	19 (7.7)	25 (5.7)	1 (1.8)
Primary Osteonecrosis [n (%)]	0	1 (0.6)	0	3 (1.2)	4 (0.9)	0
Pathological Fracture [n (%)]	0	0	0	0	0	0
Subchondral Insufficiency Fracture [n (%)]	0	7 (4.0)	0	7 (2.8)	14 (3.2)	4 (7.0)
Not Enough Information to Determine Rapid vs. Normal Progression of OA [n (%)]	0	2 (1.2)	0	0	2 (0.5)	0
Normal Progression of OA [n (%)]	24 (85.7)	108 (62.4)	18 (94.7)	128 (52.0)	254 (58.0)	31 (54.4)
Other Joint Outcome [n (%)]	4 (14.3)	13 (7.5)	0	31 (12.6)	44 (10.0)	10 (17.5)

The denominator is number of potential events.
Includes TJR or adjudicated event up to the end of the follow-up period or 26 weeks after the end of the treatment period, whichever is later.

Source: Applicant's Table 49 from ISS, page 200
Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis

Analysis of Changes in Joint Space Width

In Study 1058, the Applicant performed prespecified statistical analyses of the radiographic change from Baseline to Weeks 56 and 80 in the Joint Space Width (JSW) for patients with KL grades of 2 or 3 in the index joint, regardless of whether the patient experienced an adjudicated joint safety event. Measurements in the knee and hip were analyzed separately. For patients with an index joint of a knee, where both medial and lateral measurements were collected, if the Baseline medial JSW was less than or equal to the Baseline lateral JSW, the medial view was followed through the study for these analyses. If the Baseline lateral JSW was less than the Baseline medial JSW, the lateral view was followed through the study for these analyses. The Applicant selected the medial knee compartment for this analysis as, typically, this compartment is the most sensitive to changes in JSW.

In summary, at Week 56, the tanezumab 5 mg dose was associated with greater decreases in JSW in the medial compartment of the index knee compared with NSAID treatment. At Week 80, both tanezumab 2.5 mg and 5 mg doses were associated with greater decreases in JSW in the medial compartment of the index knee compared with NSAID treatment. Statistical significance was observed for the difference with the 5 mg dose. Statistically significant differences were not observed for the index hip or the lateral compartment of index knee.

A decrease in the least squares (LS) mean minimum JSW in the medial compartment of the index knee was observed across treatment groups at Week 56 (-0.26 mm, -0.43 mm, and -0.25 mm for the tanezumab 2.5 mg, tanezumab 5 mg, and NSAID treatment groups, respectively) and Week 80 (-0.36 mm, -0.44 mm, and -0.26 mm for the tanezumab 2.5 mg, tanezumab 5 mg, and NSAID treatment groups, respectively). There was a significantly greater LS mean decrease in the tanezumab 5 mg treatment group compared with the NSAID treatment group at Weeks 56 (p=0.0014) and 80 (p=0.0068). In patients with Baseline KL grade 2 or 3, no significant differences were observed in decrease from Baseline in LS mean JSW of the lateral compartment

of the index knee. Similar results were observed when the analysis was conducted for patients with Baseline KL grade 3 only.

At Week 56, the LS mean minimum JSW of the index hip decreased for all treatment groups, with the greatest LS mean decrease in the tanezumab 5 mg treatment group (-0.34 mm, -0.52 mm, and -0.32 mm for the tanezumab 2.5 mg, tanezumab 5 mg, and NSAID treatment groups, respectively). JSW was further decreased at Week 80, with the greatest LS mean decrease in the tanezumab 2.5 mg treatment group (-0.56 mm, -0.43 mm, and -0.37 mm for the tanezumab 2.5 mg, tanezumab 5 mg, and NSAID treatment groups, respectively). There were no significant differences in the decrease in JSW of the index hip for either tanezumab treatment group compared with NSAID at Week 56 or Week 80. However, the sample size evaluated was relatively small (approximately 5% of the total population).

To account for measurement error, significant progression of OA was defined using the Bland-Altman method, as proposed by OARSI-OMERACT. Progression was defined as 1.96 times the within-patient standard deviation (SD) of the change in JSW. The incidence of patients with JSW narrowing greater than or equal to these values was shown (with KL grades of 2 or 3 in the index joint and separately with KL grade of 3 in the index knee) and analyzed using logistic regression for binary data, when considering Baseline JSW as a covariate.

Using the Bland-Altman method, the proportion of patients with progression of OA in the index knee (medial compartment OA, Baseline KL grade 2 or 3) at Week 56 was highest in the tanezumab 5 mg treatment group (11.5%), followed by the tanezumab 2.5 mg treatment group (5.2%) and the NSAID treatment group (3.9%). Statistical significance was reached for the tanezumab 5 mg treatment group compared with the NSAID treatment group (p=0.0035). At Week 80, the proportion of progressors was highest in the tanezumab 5 mg treatment group (12.7%), followed by the tanezumab 2.5 mg treatment group (6.9%) and the NSAID treatment group (3.4%); the difference was significant when comparing the tanezumab 5 mg treatment group to the NSAID treatment group (p=0.0008). Of note, the proportion of progressors at Week 80 compared to Week 56 remained stable for the NSAIDs (3.9% at Week 56 vs. 3.4% at Week 80) compared to some increase in the tanezumab 2.5 mg (5.2% at Week 56 vs. 6.9% at Week 80) and tanezumab 5 mg (11.5% at Week 56 vs. 12.7% at Week 80) treatment groups. When comparing patients treated with tanezumab to those treated with NSAID, no significant differences were observed in the proportion of patients with progression of OA in the lateral compartment of the index knee (Baseline KL grade 2 or 3, or Baseline KL grade 3 only) at Week 56 or 80.

9.12. Total Joint Replacement

OA Studies

Details Not Included in Section III.4.7

The number of patients with TJR in post-2015 OA studies occurring within 26 weeks after the end of the treatment period was 248. An additional 10 patients had TJRs that occurred after the 26 weeks after the end-of-treatment period, bringing the total number to 258 patients.

Patients with TJR were evaluated by the Adjudication Committee to identify joint safety endpoints. Only a small proportion of patients with TJR were adjudicated to have a joint safety endpoint (34/248). Most of the joint endpoints associated with TJR were RPOA1 and RPOA2 (29/34) with similar distribution between the two categories. Most of the patient who had TJR associated with joint safety endpoint were treated with tanezumab (30/34).

Unusual joint replacement surgeries, such TJR of the shoulder, and TJR in joints that were documented to be healthy at baseline (KL Grade of 0 or 1) were observed in more patients who received tanezumab treatment. There were six TJR of a shoulder joint, one in patient treated with tanezumab 2.5 mg, four in patients treated with tanezumab 5 mg, and one in patient treated with NSAID. Six patients underwent TJR in a joint with documented KL Grade of 0 or 1 at baseline. Five of the six patients received tanezumab 5 mg treatment and one received placebo treatment.

Comparing TJR in Pre- and Post-2015 OA Studies

Reporting of TJR surgeries followed the same rules in the pre- and post-2015 studies. There was no appreciable difference in the rate of TJR between tanezumab and comparators in pre-2015 OA studies according to the analysis performed by the Applicant (Table 116). However, in the post-2015 OA studies (1056 and 1058), the rate of TJR was 2- to 3-fold higher with tanezumab than with placebo or NSAID treatment. It is not clear why a TJR signal was not detected in pre-2015 studies.

The Kaplan-Meier plots for post-2015 OA studies show that the separation of the TJR curves between tanezumab and comparators begins to be appreciable after the end of treatment and picks at the end of the 24-week follow up period (Figure 4 and Figure 6). To investigate if the longer duration of the follow up period in post-2015 studies (24 versus 8 weeks) was the reason for TJR signal to emerge in the post-2015 studies, TJR analysis with truncated observation period (treatment + 8 weeks of follow up instead of treatment + 24 weeks of follow up) were carried on (Table 109, Table 110, and Table 111). However, the TJR signal in these modified analyses was not lost; the 8-week results were very similar to the full study results.

Table 109. All-Cause TJRs in Study 1056—Observation Period Truncated to Include 8 Weeks of Safety Follow-up

Parameter	Placebo	Tan 2.5	Tan 2.5/5
N	232	245	219
Number of subjects with TJR (IR*÷100 PY)	4 (2.48)	9 (5.27)	15 (9.29)
Number of subjects with **TJR within 8 weeks after end treatment period**	1	4	5

Source: DB7
Abbreviations: IR, incidence rate; PY, person-years; Tan, tanezumab; TJR, total joint replacement
Observation period included a cutoff of 8 weeks after the end of the treatment period (defined as 8 weeks after the last dose).

Table 110. All-Cause TJRs in Study 1057—Observation Period Truncated to Include 8 Weeks of Safety Follow-up

Parameter	Placebo	Tan 2.5	Tan 5
N	282	283	284
Number of subjects with TJR (IR*÷100 PY)	21 (9.00)	25 (10.22)	20 (8.33)
Number of subjects with **TJR within 8 weeks after the end of treatment period**	6	5	5

Source: DB7
Abbreviations: IR, incidence rate; PY, person-years; Tan, tanezumab; TJR, total joint replacement
Observation period included a cutoff of 8-week after the end of treatment period (end of treatment period is defined as 8 weeks after the last dose is administered).

Table 111. All-Cause TJRs in Study 1058—Observation Period Truncated to Include 8 Weeks of Safety Follow-up

Parameter	NSAID	Tan 2.5	Tan 5
N	996	1002	998
Number of subjects with TJR (IR*÷100 PY)	26 (2.57)	56 (5.47)	82 (8.17)
Number of subjects with **TJR within 8 weeks after end treatment period**	18	30	42

Source: DB7
Abbreviations: PY, person-years; Tan tanezumab; TJR, total joint replacement
Observation period included a cutoff of 8 weeks after the end of the treatment period (defined as 8 weeks after last dose administered).

TJR Outcome Study (Study 1064)

The literature suggests that operative outcomes for total joint replacements performed in the setting of RPOA2 may be worse than in ordinary end-stage OA, presumably due to more bone loss. The Applicant conducted an observational study (Study 1064) to describe the post-operative outcome of patients who underwent a total knee, hip, or shoulder replacement while participating in tanezumab Studies A4091056, A4091057, and A4091058.

This 24-week observational study evaluated the post-operative outcome of 150 out of the 258 patients (58%) who underwent a TJR surgery in the parent studies. A small proportion of the 150 patients enrolled in Study 1064 had a TJR associated with a joint safety event (12/150 or 8%). Thus, there was a small number of patients to inform whether surgical outcomes were worse in the setting of RPOA. The study consisted of a smaller number of patients treated during the parent study with placebo (N=20), NSAIDs (N=17), or tanezumab 2.5 mg/5 mg (N=8) compared to patients treated with tanezumab 2.5 mg (N=52) or tanezumab 5 mg (N=53). The duration of treatment in parent studies varied. There were 14 patients who had at least one additional TJR after enrolling in this study. Evaluations included surgeon's assessment of procedural difficulty during surgery, complications after surgery, and any post-surgical additional or corrective procedures that were performed. This study also evaluated patient-reported questionnaires rating their satisfaction with various aspects of the surgery at Week 24 and questionnaires rating levels of pain, physical function, and stiffness in the joint at Week 24.

Although there were few incidences overall, procedural difficulty/complication during surgery, post-surgical complications, and additional or corrective procedures occurred mostly in patients who received tanezumab in the parent study. The number of patients with TJR due to a joint safety event of advanced destruction (RPOA2/ON) was too small (9/150) to allow any

meaningful assessment of the impact of bone stock loss on the outcome of TJR surgery in this patient population. Also, as this was not a randomized study, and the management of patients post-surgery was not standardized, any safety comparisons between treatment groups based on treatment assignment in parent study are at best exploratory.

Histopathology

The number of patients with TJR surgery was 258. The Applicant reported that histopathology was available for 97 out of the 258 patients (38%) who underwent TJR (71/207 or 34% for tanezumab-treated patients, 11/26 NSAID-treated patients, and 15/25 or 60% for the placebo-treated patients).

Summary of Key Outcomes

- Surgical procedural difficulties were reported only in subjects who received tanezumab in parent studies.
  - Surgeon description/rating of the procedure was available for 122 out of 150 TJR surgeries. Surgical procedural difficulties (minor complications) were reported for 6/122 TJR. All six subjects received tanezumab in parent study. Two of the six subjects had TJR associated with adjudicated RPOA2.
- Post-surgical complications were reported only in subjects who received tanezumab in parent studies.
  - Post-surgical complications reported as an AE occurred in six out of the 150 TJR. All six subjects received tanezumab in parent study and had a TJR that was not associated with adjudicated joint safety event.
- Corrective post-surgical procedures were reported for nine patients who received tanezumab and one patient who received NSAID in parent studies.
- Patients' self-reported outcomes regarding their satisfaction with various aspects of the surgery and their levels of pain, physical function, and stiffness in the joint at Week 24 were generally similar across the treatment groups within each assessment.
- Incidence of adverse events, SAEs, and severe adverse events were similar for patients treated with tanezumab or NSAIDs in the parent studies but were higher compared to patients treated with placebo.

CLBP Studies

Total joint replacements (TJR) in adjudicated joint safety database for post-2015 CLBP studies are summarized in Table 112.

- All eight TJR cases were reported in the 10 mg dose group.
- Of those eight cases, six (75%) were adjudicated as CJSE, including two cases of RPOA1, three cases of RPOA2, and one case of SIF, and two were in the other category indicated as meniscal tear and trauma.
- Joints replaced were knee (four cases), hip (two cases), and shoulder (two cases) joints. The baseline KLG was 0 in one case, 1 in three cases, 2 in two cases, and unknown KLG in two cases. TJR joints with a baseline KLG of 0 or 1 accounted for 4 of all 8 joints involved and 4 of 6 joints with known baseline KLG.

- TJR occurred during treatment (four cases) and after treatment (two cases during scheduled safety follow-up after dropout from treatment and two cases after dropout from scheduled safety follow-up period).

The cases of TJR in the back pain population accentuate the safety concerns with rapidly progressive joint destruction leading to total joint replacement involving relatively healthy joints and dose-related increase in risk to joint toxicity at higher dose of tanezumab.

Table 112. Summary of TJRs

Study	1059	1063	Pooled
Tanezumab dose		Tan 10 mg	
Number of patients treated	N=502	N=93	N=595
TJRs	**7** (1.4%)	1 (1.1%)	8 (1.3%)
TJR Joint(s) affected			
Knee	4		4
Hip	1	1	2
Shoulder	2		2
Baseline KL grade			
Not available	2		2
0	1		1
1	2	1	3
2	2		2
Study period for TJR occurrence			
Treatment period	3	1	4
After dropout from safety follow-up	2		2
Follow-up after dropout from treatment	2		2

Data sources: Table 14.5.1.1.3 on pages 3694 to 3695 in the report for Study 059 and Table 14.5.1.1.3 on page 811-812 in the report for Study 063.
Source: Created by the clinical reviewer, Christina Fang
Abbreviations: KL, Kellgren-Lawrence; Tan, tanezumab; TJR, total joint replacement

9.13. Joint Safety in Chronic Low Back Pain Studies

Pre-2015 Study

Only one pre-2015 study (039) had 10 cases (12 joints) adjudicated by the Adjudication Committee based on events of total joint replacement (TJR) and osteonecrosis (ON) reported by the Investigator.

- The adjudicated outcomes included four events of worsening OA-normal progression, two events of worsening OA-insufficient information on progression, two events of pathological findings due to trauma, one event of worsening OA-rapidly progressive OA type 2 (RPOA2), one event of subchondral insufficiency fracture (C). None of the seven reported ON events were adjudicated as primary ON due to lack of evidence or insufficient information.
- The adjudicated outcomes for cases of SIF and RPOA2 were based on comparison of two MRIs conducted five months apart after the end of treatment (four 20 mg doses) for the patient with SIF, and one MRI during treatment and one MRI after the end of treatment

(four 5 mg doses) for the RPOA2 patient, who had history of OA. Neither patients had baseline imaging available for comparison.

Post-2015 Study

Adjudicated joint safety data for post-2015 studies are summarized in two separate tables, one for patients with adjudicated joint safety outcomes and one for joints with Composite joint safety endpoint (CJSE) outcomes.

- CJSE cases included no cases in the placebo group (2 doses given in 16 weeks) and the celecoxib group, one case (0.2%) in the tramadol group, six cases (1.0%) in the tanezumab 5 mg (Tan 5) group, and 15 cases (2.5%) in the tanezumab 10 mg (Tan 10) group. Of the 22 CJSE cases 21 were reported in patients treated with tanezumab.
- Specific CJSE cases included RPOA1 reported in six cases (1.0%) at 5 mg dose and seven cases (1.2%) at 10 mg dose of tanezumab, RPOA2 in three cases (0.5%) at 10 mg dose, and SIF in five cases (0.8%) at 10 mg dose.
- A total of 25 joints had CJSE outcomes involving knee joints (20 of 25, or 80%), and hip and shoulder joints.
- The baseline Kellgren-Lawrence Grade (KLG) was KLG=0 for six joints (24%), KLG=1 for eight joints (32%), KLG=2 for nine joints (36%), and KLG unknown for two joints. Joints identified by CJSE with a baseline KLG of 0 or 1 counted for 14 (56%) of all 25 CJSE joints or 14 (61%) of 23 joints with known baseline KLG.

Joint safety data obtained from the CLBP population confirmed the findings from OA studies, suggested close association between tanezumab treatment and evidence of rapidly progressive joint destruction leading to total joint replacement involving relatively healthy joints, and suggested dose-related increase in risk to joint toxicity at higher dose of tanezumab.

Table 113. Summary of Patients With Adjudicated Joint Safety Outcomes in Post-2015 Studies

Study	059			063			Pooled	
Treatment	Tan 5	Tan 10	Tramadol	Tan 5	Tan 10	Celecoxib	Tan 5	Tan 10
Number of patients treated	N=506	N=502	N=602	N=92	N=93	N=92	N=598	N=595
Number of cases (%)								
Cases analyzed by AC	9 (1.8%)	17 (3.4%)	4 (0.7 %)	2 (2.2%)	2 (2.2%)	1 (1.1%)		
CJSE	5 (1.0%)	13 (2.6%)	1 (0.2%)	1 (1.1%)	2 (2.2%)	0	6 (1.0%)	15 (2.5%)
RPOA	5 (1.0%)	9 (1.8%)	1 (0.2%)	1 (1.1%)	1 (1.1%)	0	6 (1.0%)	10 (1.7%)
RPOA1	5 (1.0%)	7 (1.4%) (2 TJR)	1 (0.2%)	1 (1.1%)	0	0	6 (1.0%)	7 (1.2%) (2 TJR)
RPOA2	0	2 (0.4%) (2 TJR)	0	0	1 (1.1%) (TJR, ON)	0	0	3 (0.5%) (3 TJR)

Study	059			063			Pooled	
SIF	0	4 (0.8%) (1 TJR)	0	0	1 (1.1%)	0	0	5 (0.8%) (1 TJR)
Normal progression of OA	1 (0.2%)	1 (0.2%)	0	0	0	0	1 (0.2%)	1 (0.2%)
Other joint outcomes	3 (0.6%)	3 (0.6%) (2 TJR)	3 (0.5%)	1	0	1	4 (0.7 %)	3 (0.5%) (2 TJR)

Source: Table 79 on pages 265 to 266 in the report for Study 059; Table 45 on page 157 in the report for Study 063.
Abbreviations: AC, adjudication committee; CJSE, composite joint safety endpoint; OA, osteoarthritis; ON, osteonecrosis; RPOA, rapidly progressive osteoarthritis; SIF, subchondral insufficiency fracture; Tan, tanezumab

Table 114. Summary of Joints With CJSE Outcomes in Post-2015 Studies

Study	059					063				Total	
Treatment	Tan 5			Tan 10	Tramadol	Tan 5		Tan 10		Tan 5 or 10g	
No. of patients treated	N=506			N=502	N=602	N=92		N=93			
CJSE outcome	RPOA1	RPOA1	RPOA2	SIF	RPOA1	RPOA1	RPOA2	SIF			
	Joint(s) affected									25 joints	%
Knee	4	9	4	1	2	1				20	80%
Hip	1		1				1			3	12%
Shoulder			2							2	8%
	Baseline KL grade										
Not available			2							2	8%
0	1	2	1	2	1					6	24%
1	1	3		2	0	1	1			8	32%
2	3	4			0	1		1		9	36%

Source: Tables 80-83 on pages 268-271 in the report for Study 059; Sections 12.3.1.3.3.2.1.- 12.3.1.3.3.2.13 on page 158 in the report for Study 063.
Abbreviations: AC, adjudication committee; CJSE, composite joint safety endpoint; KL, Kellgren-Lawrence; RPOA, rapidly progressive osteoarthritis; SIF, subchondral insufficiency fracture; Tan, tanezumab

9.14. Joint Safety in Pre-2015 Studies

The joint destruction signal was identified in pre-2015 studies. However, the proscribed joint safety surveillance in post-2015 studies allowed for a more comprehensive characterization of the signal.

A summary of the key joint safety findings from pre-2015 studies is provided in a bulleted format below:

- A Blinded Adjudication Committee retrospectively reviewed total of 249 cases, including all events of the investigator's reported osteonecrosis (87 events) and 54% of the TJR events (162/299). It was unfortunate that for the remaining 137/299 TJR events, sufficient information to allow adjudication could not be obtained.
- Most of the adjudicated cases (217/249) were from patients enrolled in long-term (1- to 2-years of tanezumab administration) OA studies.
- In contrast to the post-2015 studies, RPOA2 and not RPOA1 was the most prevalent adjudication outcome for joints with rapidly progressing OA (Table 115). The most frequently adjudicated outcome was worsening OA-normal progression (119/249, or 48%), followed by RPOA2 (57/249, or 23%), other (29/249, or 12%), RPOA1 (11/249, or 4%), and ON (2/249, or 0.8%). Subchondral insufficiency fracture (SIF) was included in the 'other' adjudication category. There were 10 events adjudicated as SIF.

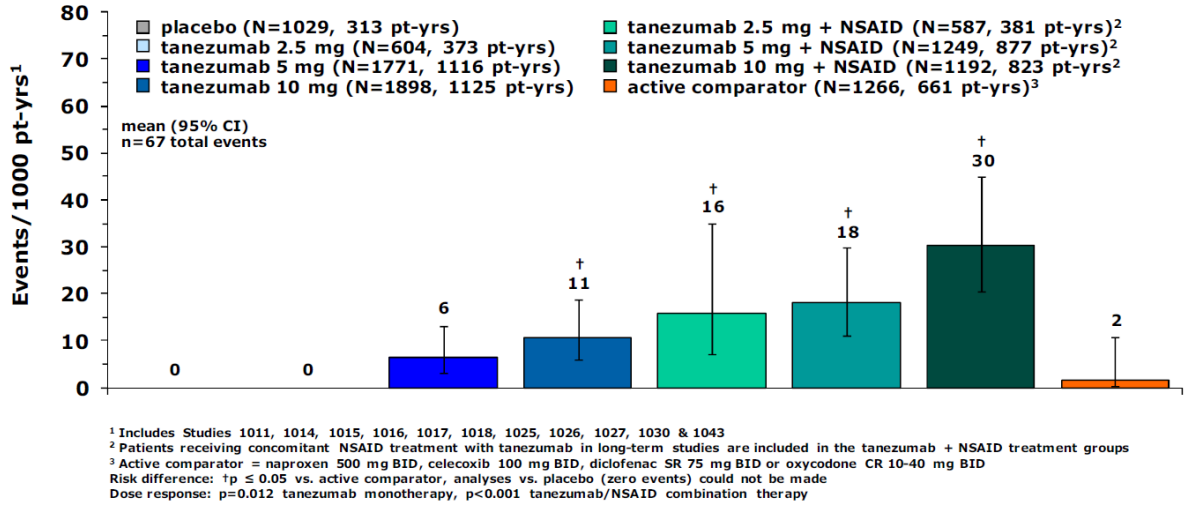
Table 115. Adjudication Outcomes From Pre-2015 Studies

n (%)	Reported ON N=87	TJR N=162	Total N=249
Primary ON	2 (2.3)	0 (0.0)	2 (0.8)
Worsening OA	51 (58.6)	149 (92.0)	200 (80.3)
RPOA Type 1	3 (3.5)	8 (4.9)	11 (4.4)
RPOA Type 2	31 (35.6)	26 (16.0)	57 (22.9)
Normal progression	14 (16.1)	105 (64.8)	119 (47.8)
Insufficient information to distinguish RPOA and normal	3 (3.5)	10 (6.2)	13 (5.2)
Other	21 (24.1)	8 (4.9)	29 (11.7)
Not enough information to distinguish ON from worsening OA	8 (9.2)	3 (1.9)	11 (4.4)
Lack of consensus[1]	5 (5.8)	2 (1.2)	7 (2.8)

Note: Baseline imaging was available for review for 80% of the adjudicated RPOA events.
[1] Fewer than three Adjudication Committee members agreed on the final assessment
Source: Prepared by Anjelina Pokrovnichka using information presented in Table 15 and Table 16 in the 2012 Arthritis Advisory Committee Briefing Document
Abbreviations: OA, osteoarthritis; ON, osteonecrosis; RPOA, rapidly progressive osteoarthritis

The incidence of RPOA increased as a function of the tanezumab dose administered (Figure 23).

Figure 23. Rate of RPOA by Treatment Group in Pre-2015 Phase 3 OA Studies



¹ Includes Studies 1011, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030 & 1043
² Patients receiving concomitant NSAID treatment with tanezumab in long-term studies are included in the tanezumab + NSAID treatment groups
³ Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID
Risk difference: †p ≤ 0.05 vs. active comparator, analyses vs. placebo (zero events) could not be made
Dose response: p=0.012 tanezumab monotherapy, p<0.001 tanezumab/NSAID combination therapy

Source: Applicant's Figure 13 from the 2012 AC briefing document, page 51

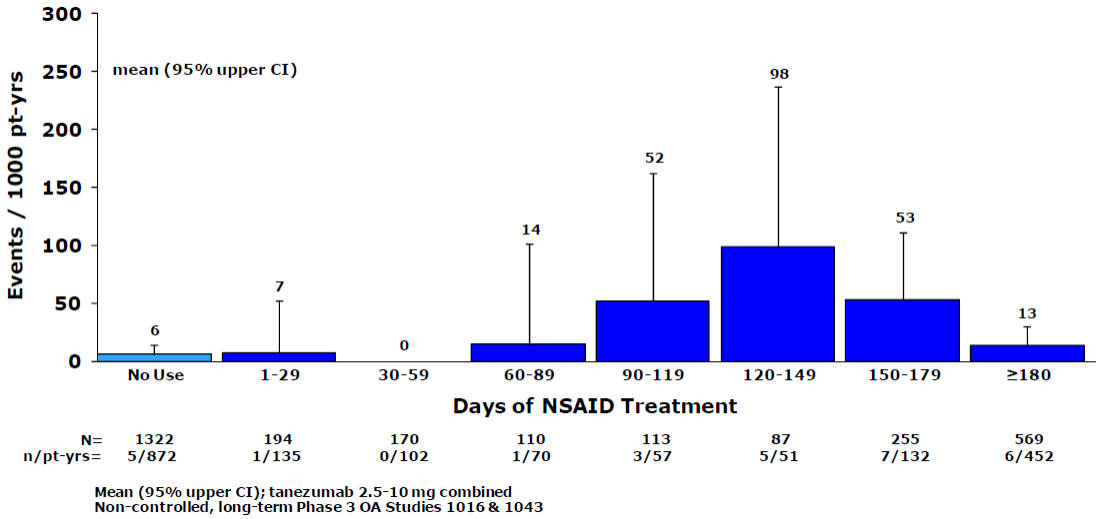
The administration of tanezumab in combination with NSAIDs further increased the incidence rate of RPOA by approximately 3-fold over tanezumab monotherapy (Table 29 and Figure 23). Because of this finding, chronic concomitant use of NSAIDs was prohibited in post-2015 studies.

The incidence of RPOA was significantly higher in subjects randomized to the tanezumab + NSAID combination than in subjects randomized to tanezumab monotherapy treatment groups in pre-2015 studies 1017 and 1025. Thus, the Applicant conducted exploratory analyses to examine if there was an association between the risk of joint adverse events and the duration of concomitant NSAID use. These analyses were conducted to determine if in future tanezumab studies, it would be safe to allow use of NSAIDs on intermittent basis for conditions unrelated to OA.

Per-protocol in the non-controlled, pre-2015 long-term Phase 3 OA studies (1016 and 1043), patients were permitted to receive NSAID treatment if warranted based on the clinical judgment of the investigator. In these studies, 1498 patients used NSAIDs concomitantly with tanezumab and 1322 patients did not use NSAIDs.

The effect of the duration of concomitant NSAID with tanezumab was evaluated by examining NSAID use in 30-day intervals (Figure 24). The Applicant concluded that in patients receiving tanezumab and concomitantly using NSAIDs, the risk of RPOA was related to duration of NSAID therapy. The rate of RPOA in patients who used NSAIDs for less than 90 days was comparable to NSAID non-users and significantly lower than patients who used NSAIDs for a period of 90 days or more. No differences were evident in the rate of RPOA when duration of NSAID use of less than 180 days was compared to use of 180 days or more. Based on these data, occasional use of NSAIDs in future tanezumab studies for up to 60 days over the period of one year was found to be acceptable.

Figure 24. Duration of Concomitant NSAID Use With Tanezumab: Effect on the RPOA in Non-Controlled Phase 3 Pre-2015 OA Studies (1016 and 1043)



Source: Applicant's Figure 3 from complete response to clinical hold July 31, 2012, page 21

- No cases of joint destruction occurred in patients receiving placebo.
- The adjudicated joint events were detected late in treatment: median of 286 days after the first dose and 83 days after the last dose of study medication.
- For RPOA events, the index joint was the affected joint in 65% of the patients.
- For RPOA events, the hip was the affected joint in 38 patients (56%), the knee in 27 patients (40%) and the shoulder in 3 patients (4%). There were several cases with adjudicated outcome in more than one joint.
- RPOA was not restricted only to patients with advanced OA (KLG 3 or 4) but also occurred in KLG 2 joints.
- The rate of all-cause TJRs in patients with OA was comparable among placebo, active comparator, and tanezumab monotherapy treatments with no apparent dose response. The rate of all-cause TJRs in the tanezumab/NSAID combination treatment groups was 2.5-fold greater than any of the other treatment groups (Table 116).

Table 116. Comparative Summary of All-Cause TJRs in Pre- and Post-2015 OA Studies

	Incidence Observation-Time Adjusted Rates N (%) Events/1000 patient-years (pt-years) [95% Confidence Intervals]							
	Pre-2015 Phase 3 OA Studies[a]				Post-2015 Phase 3 OA Studies[b]			
	Placebo N=1029 313 pt-years	Tan 2.5 mg N=604 373 pt-years	Tan 5 mg N=1771 1116 pt-years	Active Comparator[c] N=1266 661 pt-years	Placebo N=514 395 pt-years	Tan 2.5 mg N=1530 1438 pt-years	Tan 5 mg N=1282 1245 pt-years	NSAID N=996 1013 pt-years
All-Cause TJR[d]	10 (1.0) 31.9 [17.2, 59.3]	15 (2.5) 40.2 [24.2, 66.7]	52 (2.9) 46.6 [35.5, 61.2]	28 (2.2) 42.4 [29.3, 61.4]				
TJR[e]					23 (4.5) 58.2 [38.7, 87.5]	84 (5.5) 58.4 [47.2, 72.3]	100 (7.8) 80.3 [66.0, 97.7]	26 (2.6) 25.7 [17.5, 37.7]

[a]Includes Studies 1011, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030, 1043; did not include prospectively scheduled radiographic assessments
[b]Includes Studies 1056, 1057, 1058; included prospectively scheduled radiographic assessments
[c]Includes naproxen, celecoxib, diclofenac SR or oxycodone CR
[d]Total joint replacement (all cause) includes patients with TJR (regardless of causality) or patients with reported ON without TJR
[e]TJR includes patients with TJR (regardless of adjudication outcome)

Source: Applicant's Table 66 from ISS, page 289
Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; Tan, tanezumab; TJR, total joint replacement

9.15. Vital Signs and ECG

Tanezumab treatment (SC and IV) led to a dose-dependent mean decrease from baseline in systolic and diastolic blood pressure that was greater than the decreases seen with placebo or NSAID treatment (Table 117 and Table 118). Changes from baseline in mean heart rate were similar across treatment groups. Table 117 and Table 118 are derived from tables in the Integrated Summary of Safety. The post-baseline rows identified as "mean" appear to be mean change from baseline, not the mean blood pressure at that timepoint.

Table 117. Blood Pressure Change From Baseline During the Treatment Period (OA Placebo-Controlled Studies 1011, 1014, 1015, 1018, 1026, 1027, 1030, 1056, and 1057)

		Placebo (N=1543)	Tan 2.5 mg (N=929)	Tan 5 mg (N=1324)	Tan 10 mg (N=1142)
		Sitting Systolic Blood Pressure (mm Hg)			
Visit	Summary statistics				
Baseline	n	1543	929	1324	1142
	Mean (SD)	128.1 (13.77)	128.8 (13.25)	129.3 (13.74)	127.5 (13.91)
	Median	128.0	130.0	130.0	128.0
	Min, max	(80.0, 182.0)	(89.0, 172.0)	(89.0, 198.0)	(89.0, 175.0)
Week 12	n	1064	810	1051	820
	Mean (SD)	-0.3 (13.18)	-2.4 (12.84)	-2.9 (12.91)	-3.7 (13.46)
	Median	0.0	-2.0	-2.0	-4.0
	Min, max	(-50.0, 70.0)	(-47.0, 51.0)	(-50.0, 58.0)	(-55.0, 41.0)
Week 24	n	578	486	611	369
	Mean (SD)	-1.4 (12.36)	-1.7 (12.92)	-2.1 (12.96)	-3.1 (14.46)
	Median	-1.0	0.0	-2.0	-4.0
	Min, max	(-58.0, 40.0)	(-70.0, 30.0)	(-51.0, 52.0)	(-56.0, 62.0)

		Placebo (N=1543)	Tan 2.5 mg (N=929)	Tan 5 mg (N=1324)	Tan 10 mg (N=1142)
Sitting Diastolic Blood Pressure (mm Hg)					
Baseline	n	1543	929	1324	1142
	Mean (SD)	78.2 (8.75)	78.2 (8.56)	78.1 (9.00)	77.8 (9.13)
	Median	79.0	80.0	80.0	78.0
	Min, max	(44.0, 114.0)	(51.0, 104.0)	(46.0, 113.0)	(49.0, 112.0)
Week 12	n	1064	810	1051	820
	Mean (SD)	-0.3 (8.50)	-1.7 (8.27)	-2.0 (8.78)	-2.4 (8.93)
	Median	0.0	-1.0	-2.0	-2.0
	Min, max	(-35.0, 42.0)	(-32.0, 29.0)	(-34.0, 36.0)	(-37.0, 24.0)
Week 24	n	578	486	611	369
	Mean (SD)	-0.6 (8.42)	-1.0 (8.94)	-1.7 (8.86)	-2.4 (9.34)
	Median	0.0	0.0	-2.0	-2.0
	Min, max	(-25.0, 30.0)	(-39.0, 37.0)	(-30.0, 28.0)	(-30.0, 26.0)

Source: Created by Anjelina Pokrovnichka using data from Applicant's Table 1.10.1 a from ISS Appendix Tables 1, page 13719
Abbreviations: Max, maximum; min, minimum; SD, standard deviation; Tan, tanezumab

Table 118. Blood Pressure Change From Baseline During the Treatment Period (Safety: OA Active-Controlled Studies 1017, 1025, and 1058)

		NSAID (N=1687)	TAN 2.5 mg (N=1002)	TAN 5 mg (N=1539)	TAN 10 mg (N=542)
Sitting Systolic Blood Pressure (mm Hg)					
Visit	Summary statistics				
Baseline	n	1687	1002	1539	542
	Mean (SD)	129.8 (13.72)	128.9 (12.91)	130.1 (13.77)	131.6 (13.99)
	Median	130.0	128.0	130.0	130.0
	Min, max	(80.0, 183.0)	(88.0, 169.0)	(89.0, 182.0)	(87.0, 180.0)
Week 16	n	1156	633	1087	440
	Mean (SD)	-1.2 (13.59)	-3.0 (11.65)	-3.7 (13.46)	-4.9 (13.16)
	Median	0.0	-2.0	-2.0	-5.0
	Min, max	(-64.0, 52.0)	(-50.0, 44.0)	(-53.0, 47.0)	(-54.0, 35.0)
Week 56	n	894	419	868	472
	Mean (SD)	-1.9 (14.56)	-3.3 (11.54)	-2.8 (14.27)	-3.3 (14.61)
	Median	-2.0	-2.0	-2.0	-2.5
	Min, max	(-56.0, 54.0)	(-46.0, 28.0)	(-67.0, 48.0)	(-48.0, 34.0)
Sitting Diastolic Blood Pressure (mm Hg)					
Baseline	n	1687	1002	1539	542
	Mean (SD)	79.1 (8.63)	79.3 (8.56)	79.2 (8.75)	78.9 (8.95)
	Median	80.0	80.0	80.0	80.0
	Min, max	(45.0, 108.0)	(42.0, 112.0)	(50.0, 110.0)	(45.0, 111.0)
Week 16	n	1156	633	1087	440
	Mean (SD)	-0.7 (8.75)	-1.3 (8.15)	-2.2 (8.79)	-3.4 (9.18)
	Median	0.0	-1.0	-2.0	-3.0
	Min, max	(-33.0, 43.0)	(-30.0, 29.0)	(-34.0, 32.0)	(-32.0, 35.0)
Week 56	n	894	419	868	472
	Mean (SD)	-0.8 (9.04)	-2.0 (8.53)	-1.8 (9.20)	-2.0 (9.08)
	Median	0.0	-1.0	-1.0	-1.0
	Min, max	(-30.0, 24.0)	(-28.0, 22.0)	(-35.0, 31.0)	(-39.0, 31.0)

Source: Created by Anjelina Pokrovnichka using data from Applicant's Table 1.10.1 k from ISS Appendix Tables 1, page 13767
Abbreviations: Max, maximum; min, minimum; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; Tan, tanezumab

Tanezumab IV treatment also led to a dose-dependent mean decrease from baseline in systolic and diastolic blood pressure that was greater than the decreases seen with placebo (~1 to 3 mm Hg greater for both systolic and diastolic) or NSAID treatment (~3 to 4 mm Hg greater for systolic and ~1 to 2.5 mm Hg greater for diastolic). Changes from baseline in mean heart rate were similar across treatment groups. Given the potential effects on the sympathetic nervous system identified in animal studies, it is possible that this difference is real. However, the analyses of orthostatic hypotension did not show any significant effect. Since no significant AEs related to hypotension were reported, the effects on blood pressure are not likely to be clinically significant.

In the OA placebo-controlled pool, tanezumab had no effect on the proportion of patients who met the pre-specified ECG threshold categories for elevations or maximal increases from baseline in QTcB or QTcF intervals compared to placebo. In the OA active-controlled studies, the proportion of patients who met the threshold categories for elevations or maximal increases from baseline in QTcB interval or QTcF interval was similar between the tanezumab 2.5 and 5 mg treatment groups and the NSAID treatment group, and higher in the tanezumab 10 mg treatment group. The incidence of patients with a QTcB interval or QTcF interval ≥500 msec or a maximal change from baseline ≥60 msec was low and not notably different across treatment groups in both the placebo- and active-controlled studies.

9.16. Safety in Healthy Volunteers and Other Pain Conditions

The safety of tanezumab in healthy volunteers (studies 1013 and1046) and patients with pain conditions other than OA or CLBP (studies 1003, 1005, 1007, 1010, 1019, 1023, 1029, 1031 and 1035) was consistent with the safety in OA patients. Analogous to the OA studies, tanezumab was associated with a higher frequency of neurosensory events and events of arthralgia.

In general, higher fixed doses of tanezumab, up to 20 mg, were administered in these studies and in some (studies 1005, 1007, 1010), tanezumab was dosed as µg/kg. Some studies used the IV route of administration and others, the SC route. Most were single-dose studies with eight weeks of post-dose safety follow-up. Two doses of tanezumab were administered in studies 1031 and 1035 and four doses in Study 1029. Studies 1013, 1031, and 1046 had a 16-week follow-up period.

Summary of Safety Findings in Healthy Volunteer Studies

In the two healthy volunteer studies (Study 1013 and Study 1046), single 10 mg IV infusion over 1 minute or SC injection (5, 10, 19 or 20 mg) of tanezumab were administered. Most of the reported AEs were events of abnormal peripheral sensation reported at a higher frequency in tanezumab-treated patients.

Joint-related symptoms were reported by three patients from the high tanezumab dose groups in Study 1031.

Subject (b) (6): This 35-year-old male received single dose of tanezumab 19 mg SC. The subject reported mild AEs of pain in extremity (bilateral lower extremities pain) and musculoskeletal discomfort (general joint discomfort) on Study Day 18. The event of pain in

extremity resolved on Study Day 20 and the event of musculoskeletal discomfort resolved on Study Day 26.

Subject (b) (6): This 32-year-old male received tanezumab 19 mg SC. The subject reported severe AE of arthralgia on Study Day 16. The event resolved on Study Day 35.

Subject (b) (6): This 36-year-old male received tanezumab 10 mg IV. The subject reported mild AEs of musculoskeletal pain (bilateral shoulder pain) and arthralgia (bilateral knee pain) on Study Day 11. The event of musculoskeletal pain resolved on Study Day 16 and the event of arthralgia resolved on Study Day 18.

Summary of Safety Findings in Other Pain-Condition Studies

The safety profile of tanezumab was consistent across studies in neuropathic pain (Studies 1005 and 1031), visceral pain (Studies 1010, 1019, 1023 and 1035), and bunionectomy (Study 1007).

The most common AEs in these studies were events of abnormal peripheral sensation which were reported at a higher frequency in tanezumab-treated patients. Two patients from the 20 mg tanezumab dose group in Study 1031 (diabetic peripheral neuropathy population) were diagnosed with new or worsened peripheral neuropathy. Also, in Study 1031, arthralgia, myalgia, and pain in extremity were reported more frequently in tanezumab than in placebo-treated patients. In Study 1019 (chronic pain of nonbacterial prostatitis), arthralgia was reported in seven patients after one dose of 20 mg IV tanezumab versus no patients in the placebo group.

9.17. 120-Day Safety Update

The 120-day safety update was submitted on April 10, 2020. The Applicant reported that a search was conducted of the Global Safety Database for the initial and follow-up reports received from the date of database lock of each post-2015 clinical study (A4091056, A4091057, A4091058, A4091059, A4091063, A4091064) through February 12, 2020. No new important safety information has been identified including no additional adverse events reported or significant updates for prior cases following database lock.

The 120-day safety update also included a follow-up information for a patient from the ongoing observational Study A4091065. Subject ((b) (6), whose mother had tanezumab exposure in the first trimester of pregnancy, was noted to have developmental delay at visits 463 days old and 683 days old. This subject completed an additional follow-up visit when he was 810 days old. The investigator reports speech and language developmental delay with causality attributable to a family history of developmental disorders.

10. REMS Background

Section 505-1 of the Food, Drug, and Cosmetic Act (FDCA), added to the law by the Food Drug Administration Amendments Act of 2007, authorizes the FDA to require applicants or application holders to develop and comply with a risk evaluation and mitigation strategies (REMS) for a drug if the Agency determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. A REMS is a required risk management plan that uses risk

minimization strategies beyond the professional labeling. The elements of a REMS can include: Medication Guide or patient package insert, a communication plan for healthcare providers, certain packaging and safe disposal technologies for drugs that pose a serious risk of abuse or overdose, elements to assure safe use (ETASU), and implementation system. All REMS approved for drugs or biologics under New Drug Applications and Biologics License Applications (BLA) must have a timetable for submission of assessments of the REMS. These assessments are prepared and submitted by the application holder and reviewed by FDA.

A Medication Guide provides FDA approved patient-focused labeling and can be required as part of the approved labeling if FDA determines one or more of the following apply:

- Patient labeling could help prevent serious adverse events.
- The product has serious risks that could affect a patient's decision to use or continue to use the drug.
- Patient adherence to directions is crucial to product effectiveness.

A communication plan consists of FDA-approved materials used to aid a sponsor's implementation of the REMS and/or inform healthcare providers about the serious risk of a drug. This can include, for example, "Dear Healthcare Professional" letters, collaboration with professional societies, and education pieces (such as letters, drug fact sheets) to inform prescribers of the risks and the safe use practices for the drug.

ETASU can include one or more of the following requirements:

- Healthcare providers who prescribe the drug have particular training, experience or special certifications
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- The drug may be dispensed only in certain healthcare settings
- The drug may be dispensed to patients with evidence of safe-use conditions
- Each patient must be subject to monitoring
- Patients must be enrolled in a registry

Because ETASU can impose significant burdens on the healthcare system and potentially impact patient access to treatment, ETASU are required only if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to mitigate a specific serious risk listed in the labeling. Accordingly, the statute [FDCA 505-1(f)(2)] specifies that ETASU:

- Must be commensurate with specific serious risk(s) listed in the labeling.
- Cannot be unduly burdensome on patient access to the drug.
- To minimize the burden on the healthcare delivery system, must, to the extent practicable, conform with REMS elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs.