BRIEFING DOCUMENT

JOINT MEETING OF THE ARTHRITIS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

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ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

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LIST OF ABBREVIATIONS

Terms that are also in the glossary are hyperlinked.

Abbreviation	Term
ACR	American College of Rheumatology
ADA	anti-drug (tanezumab) antibodies
ANCOVA	analysis of covariance model
APTC	Antiplatelet Trialists' Collaboration
BID	bis in diem (twice a day)
BLA	Biologics license application
BMI	body mass index
BOCF	baseline observation carried forward
BWS	best-worst scaling
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CI	confidence interval
CLBP	chronic low back pain
Cmax	maximum observed concentration
CMC	Chemistry Manufacturing and Controls
CR	controlled release
CTx1	collagen type 1 C-telopeptide
CV	Cardiovascular
DAAP	Division of Anesthesiology, Addiction Medicine, and Pain Medicine
DCE	discrete-choice experiment
ECG	Electrocardiogram
eGFR	estimated glomerular filtration rate
ETASU	Elements To Assure Safe Use
FDA	Food and Drug Administration
GI	Gastrointestinal
HCP	Healthcare Provider
IENF	intraepidermal nerve fiber
IgG2	immunoglobulin G Type 2
IMEDS	Innovation in Medical Evidence and Development Surveillance
IND	Investigational New Drug
ITT	intent-to-treat
IV	Intravenous
JSN	joint space narrowing
JSW	joint space width
KL	Kellgren-Lawrence
LOCF	last observation carried forward
LS	least squares
MACE	major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	myocardial infarction

Abbreviation	Term
mL	Milliliter
MRI	magnetic resonance imaging
N	total number, total sample size
NA	Not applicable
ND	not determined
NGF	nerve growth factor
NRS	numerical rating scale
NSAIDs	nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
ON	osteonecrosis
OPG	osteoprotegerin
OMERACT	Outcome Measures in Rheumatology
PCH	partial clinical hold
PD	pharmacodynamics
PGA-OA	Patient Global Assessment of osteoarthritis
PK	pharmacokinetics
PO	oral administration
PT	(MedDRA) Preferred Term
Q12H	every 12 hours
Q8W	every 8 weeks
QTc	corrected QT interval
RANKL	receptor activator of nuclear factor kappa-B ligand
REMS	Risk Evaluation and Mitigation Strategy
RPOA	rapidly progressive osteoarthritis
SC	subcutaneous
SD	standard deviation
SE	standard error
SIF	subchondral insufficiency fracture
TE	Treatment-emergent
TJR	total joint replacement
TKR	total knee replacement
Tmax	time to first occurrence of Cmax
TrkA	tropomyosin-related kinase A
UK	United Kingdom
US	United States
USPI	United States Prescribing Information
Wks	Weeks
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

INTRODUCTION AND REVIEWER GUIDE

This document is organized with a gray, boxed summary of key points for each major section indicated below. Detailed data presentation and discussion is provided in the remainder of each section.

- Executive Summary (Section 1)
- Therapeutic Context and Unmet Medical Need (Section 2.1)
- Clinical Pharmacology Overview (Section 3.1)
- Efficacy Overview (Section 4.1)
- Safety Overview (Section 5.1)
    - Joint Safety Overview (Section 5.3.2.1)
    - Peripheral Neurological Safety Overview (Section 5.3.2.2.1)
    - Sympathetic Neurological Safety Overview (Section 5.3.2.2.2)

Technical terms are defined in the glossary in Section 9 and are linked from the first use in the document.

Note to Reader:

- In this document, the leading designation of "A409" in the tanezumab study protocol numbers has been omitted, for example, Study A4091011 has been referred to simply as Study 1011.
- Studies have been categorized as those conducted prior to 2015 (pre-2015) and studies conducted during or after 2015 (post-2015).

1. EXECUTIVE SUMMARY

This briefing document is provided to the FDA in advance of the Advisory Committee meeting and supports the tanezumab Biologics License Application (BLA) submitted to the FDA on 18 December 2019 for the treatment of moderate to severe osteoarthritis (OA) pain in adult patients for whom use of other analgesics is ineffective or not appropriate. The Sponsor is seeking approval of tanezumab 2.5 mg, administered subcutaneously (SC) at 8-week intervals. The proposed Risk Evaluation and Mitigation Strategy (REMS), labeling, and postmarketing studies are subject to FDA review and discussion with the Sponsor.

1.1. Osteoarthritis Therapeutic Context

OA is a chronic, progressive, disease of the joint that causes disability largely due to unrelenting pain and has a high unmet medical need (ie, a condition whose treatment is not addressed adequately by available therapy). OA is prevalent: approximately 31 million adults in the United States (US) have symptomatic OA, and this number is rising, likely related to the aging population and obesity. Pain from chronic OA presents a substantial burden to the patient and a high socioeconomic burden to society as it can lead to loss of function, disability, increased risk of comorbidities, and reduced quality of life.

Not all patients with OA, especially those with moderate to severe disease, achieve adequate pain relief with currently available treatment options (such as nonsteroidal anti-inflammatory drugs [NSAIDs] or opioids) or are unable or unwilling to take them due to risk factors, such as cardiovascular (CV) or gastrointestinal (GI) pre-conditions, toxicities, or concerns of opioid abuse or addiction (Section 2.1). These risks increase markedly with chronic use and are further amplified in the elderly, the most common population with OA. Pain is one of the key barriers to maintaining physical activity, and can lead to progressive loss of function, and increase in mortality when a person is no longer able to walk or live independently.[1] NSAIDs and opioids carry risks serious enough in proportion to the potential benefit of the drug, that the FDA has required all approved labels for NSAIDs and opioids to carry a Boxed Warning advising prescribers to assess the risks and benefits of using these drugs and recommends using them at the lowest dose for the shortest duration (See Appendix 2). Limited treatment options for treating moderate to severe pain have led to an over reliance on opioids which has contributed to the opioid epidemic. New innovative treatment options are needed to address the “pain epidemic” and the burden of chronic pain on society and its devastating consequences on the individual.[2]

1.2. Tanezumab Clinical Development Program for OA

Tanezumab is a humanized immunoglobulin G Type 2 (IgG2) monoclonal antibody directed against nerve growth factor (NGF) with high binding affinity and specificity. As such, tanezumab is a novel, non-opioid, peripheral NGF inhibitor that decreases pathological pain processing with a mechanism distinct from NSAIDs and opioids, without functional central nervous system activity, and with no known risk of abuse and dependence.

The first partial clinical hold (June/July 2010) was due to adverse events described by investigators as reports of osteonecrosis (ON) which led to total joint replacement (TJR). An FDA Arthritis Advisory Committee meeting was held on 12 March 2012 to discuss safety issues possibly related to anti-NGF drugs. Data including an overall benefit-risk assessment

of tanezumab, risk mitigation measures and future clinical development proposals were presented to the Committee who voted in favor of continuing the clinical development program for tanezumab.

The second partial clinical hold placed on all anti-NGF programs in December 2012 was due to concerns about the potential for adverse effects on the Sympathetic Nervous System of mature animals. This second partial clinical hold was lifted following FDA's review of comprehensive additional analyses of available clinical and non-clinical data, execution of additional non-clinical studies, and implementation of increased surveillance and assessment.

When the Phase 3 clinical development program was reinitiated in 2015, two placebo-controlled studies (1056 and 1057) were conducted to evaluate the efficacy and safety of tanezumab with SC administration administered at 8-week intervals in patients with moderate to severe OA pain of the hip or knee who had failed to respond to other analgesics or who were unable to tolerate or could not take these analgesics due to contraindications, or who were specifically unwilling to take opioid medications. In addition, a long term active-controlled study (1058) was conducted that was designed to evaluate joint safety of SC administration of tanezumab with 56 weeks of treatment compared to NSAIDs but also included efficacy outcomes.

1.3. Key Efficacy Conclusions

Tanezumab 2.5 mg administered SC every 8 weeks resulted in clinically meaningful and sustained reduction in pain and improvement in function compared to placebo:

- In the intended patient population, tanezumab 2.5 mg SC resulted in significant improvement over placebo in all three co-primary efficacy measures (change from baseline in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain, WOMAC Physical Function, and Patient Global Assessment of OA (PGA-OA) in Study 1056, and in two of the three co-primary efficacy measures (change from baseline in WOMAC Pain and WOMAC Physical Function) in Study 1057.

- The improvement in WOMAC Pain with tanezumab 2.5 mg SC in Studies 1056 and 1057 was considered to be a substantial clinically meaningful improvement according to published definitions. This was evidenced by a significantly greater proportion of patients achieving ≥50% reduction in pain (approximately 50% patients) compared with placebo (approximately 36% patients).

- The onset of pain relief in Studies 1056 and 1057 occurred within the first week of the initial dose of tanezumab 2.5 mg SC, with a significantly greater reduction in Daily Average Pain Score compared with placebo. A reduction with tanezumab in WOMAC Pain and improvement in WOMAC Physical Function was sustained throughout the 8-week dosing interval, and persisted over approximately one year of treatment in long-term studies. Tolerance requiring escalating doses was not detected.

- The efficacy of tanezumab 2.5 mg SC was similar regardless of patient gender, age, Body Mass Index (BMI) category ≥25 kg/m^2, index joint (hip or knee), disease duration, disease severity, and geographic region.

- The degree of improvement in the co-primary endpoints with tanezumab 2.5 mg SC was similar to, but not significantly greater than, NSAID treatment in the long-term active-controlled Study 1058. In contrast to Studies 1056 and 1057, patients in this study were receiving a stable dose of an NSAID prior to and during screening, before being randomized at baseline to switch to tanezumab or to continue NSAID treatment. Otherwise, the patient populations were similar.

1.4. Key Safety Conclusions

- Tanezumab 2.5 mg SC was generally well-tolerated. The overall incidence of adverse events with tanezumab during the treatment period was not notably different from placebo treatment. Overall incidences of deaths, serious adverse events and discontinuations due to an adverse event with tanezumab were low and similar to placebo.

- Adverse events considered likely associated with tanezumab 2.5 mg SC treatment were rapidly progressive OA (RPOA), joint swelling, abnormal peripheral sensation (paresthesia, hypoesthesia, and burning sensation), carpal tunnel syndrome, and peripheral edema (edema peripheral and peripheral swelling).

- Joint safety events were the primary safety issues identified for tanezumab. In the post-2015 studies (which included a pre-defined prospective analysis of joint safety, comprehensive risk mitigation measures and surveillance focused on joint safety over the course of study treatment and for approximately 24 weeks after the treatment period in post-treatment follow-up) approximately 3% of the patients treated with tanezumab 2.5 mg, had an adjudicated joint safety endpoint. Tanezumab increased the risk for developing RPOA, observed as accelerated loss of articular and/or meniscal cartilage in a joint (RPOA-1) or abnormal bone loss and/or destruction including limited or total collapse of a subchondral surface (RPOA-2). The incidences of adjudicated events of RPOA-1 and RPOA-2 as well as TJRs, were dose-dependent, being lower with tanezumab 2.5 mg compared to tanezumab 5 mg. The risk differences for tanezumab 2.5 mg for RPOA relative to NSAIDs were generally similar over time.

    - **RPOA-1** was the most common type of adjudicated event included in the primary composite joint safety endpoint. The incidence of RPOA-1 at 2.3% in tanezumab 2.5 mg treated-patients was statistically significantly higher than the incidence of 1.1% in NSAID-treated patients.

    - The incidence of **RPOA- 2** with tanezumab 2.5 mg was low (0.4%) and not statistically significantly different from NSAID-treated patients (0.1%).

    - There were no RPOA-1 or RPOA-2 events in placebo-treated patients.

    - The incidence of **TJR** was 5.5% in tanezumab 2.5 mg treated-patients, 4.5% in placebo-treated patients, and 2.6% in NSAID- treated patients. In the tanezumab 2.5 mg and NSAID treatment groups, the adjudication outcome for most TJRs was normal progression of OA (4.8% and 2.2%, respectively).

- Across treatment groups, the majority (85%; 32 out of 36 joints in the tanezumab 2.5 mg group) of RPOA-1 affected joints did not undergo a TJR within the observation period (treatment period plus approximately 24-weeks safety follow-up) while approximately 50% (3 out of 6 joints in the tanezumab 2.5 mg group) of the RPOA-2 events were associated with a TJR during the observation period. Events occurred most frequently in knee and hip joints that had significant underlying structural OA and rarely occurred in the shoulder joint (no tanezumab 2.5 mg patients) or in joints without pre-existing OA.

- In the pre-2015 studies, more than 90 days of NSAID use in conjunction with tanezumab administration was associated with an increase in the incidence of RPOA. In the post-2015 studies, NSAID use was limited to no more than 10 days per 8-week dosing interval. Co-administration of tanezumab and NSAIDs is not recommended due to the potential for an increased risk of joint safety events and this is reflected in the proposed prescribing information (see Appendix 1).

- There were no serious neurological and no CV, renal, hepatic, or hypersensitivity safety concerns identified with tanezumab 2.5 mg treatment in over 1456 patient-years of exposure (over 5937 patient-years exposure with tanezumab at all doses in OA patients). Adverse event profiles in subgroups evaluated for intrinsic and extrinsic factors were consistent with the profile in the overall population. Tanezumab was not associated with clinically meaningful changes in laboratory values, vital signs, or electrocardiograms (ECGs). In addition, treatment with tanezumab 2.5 mg SC was not associated with potential drug abuse, dependence or withdrawal.

1.5. The Voice of the Patient

Patient-centered care fosters shared decision making between the patient and the healthcare provider (HCP) and places patients' preferences and treatment goals at the forefront when deciding on treatment options, weighing carefully the benefits and associated risks.

Based on the results of the US patient preference study, achieving pain and symptom relief was most important to patients, followed by avoiding physical dependence, avoiding risk of a myocardial infarction (MI), and then avoiding risk of severe joint problems. The key finding from this study was that patients were more willing to accept risk of serious joint problems than risk of physical dependence with opioids, indicating patients prefer the attributes of tanezumab over those of opioids.

1.6. Proposed Postmarketing Risk Management

The proposed comprehensive postmarketing risk management strategy includes the following key components:

- Routine and additional risk mitigation:

    - US Prescribing Information (USPI) and Medication Guide including a boxed warning for RPOA and TJR

  - Restricted distribution program (ie, risk evaluation and mitigation strategy [REMS] program)
  - Healthcare provider RPOA Imaging Guide
- Routine and additional safety surveillance:
  - Adverse event monitoring including enhanced follow-up for all joint safety adverse events
  - Safety surveillance study to assess long-term safety

Notable requirements of the proposed REMS include:

- Certification of prescribers, healthcare settings, and pharmacies to ensure that stakeholders involved in the prescribing, dispensing, and administration of tanezumab are educated about the increased risk of RPOA with tanezumab and the REMS program requirements necessary to ensure safe use.
- Baseline and annual radiographs to ensure that patients with relevant pre-existing or new onset conditions do not initiate or continue tanezumab treatment, respectively.
- Required patient counseling and enrollment in the REMS to ensure patients are educated about the increased risk of RPOA with tanezumab, including the need to avoid the use of NSAIDs.
- Appropriate monitoring of patients during treatment to ensure early identification of RPOA and to ensure that patients are discontinued if they don't receive clinically important improvement after 2 doses.

Additionally, tanezumab will only be administered within a certified healthcare setting after confirmation that both prescriber and patient are enrolled and eligible in the REMS program.

1.7. Benefit-Risk Conclusion

The benefit of tanezumab 2.5 mg is seen in a population of patients for whom current treatments are ineffective or are clinically not appropriate because of contraindications or co-morbidities, lack of tolerability or due to patient choice/unwillingness to take opioids. These difficult-to-treat patients are not served by current therapies and there remains unmet medical need. This is the reality for many Americans suffering from OA, and contributes to diminished physical functioning and reduced quality of life. For tanezumab 2.5 mg, the risk of joint safety is not life-threatening, occurs at a low incidence and is manageable through labeling, REMS with Elements To Assure Safe Use (ETASU), and a postmarketing safety surveillance study to further characterize the risk in the post-approval setting. In totality, with a positive benefit-risk profile, tanezumab will fill this important unmet need for those patients that meet the indication *for the treatment of moderate to severe osteoarthritis (OA) pain in adult patients for whom use of other analgesics is ineffective or not appropriate*. Tanezumab is appropriate for this subset of patients and the decision whether to initiate and

continue tanezumab should be shared by the HCP and patient based upon these benefit-risk considerations.

2. PRODUCT BACKGROUND

2.1. Therapeutic Context and Unmet Medical Need

- Osteoarthritis (OA) is a prevalent, progressive disease associated with significant disability, reduced quality of life, and high socioeconomic burden, especially in those patients with moderate to severe disease.
- Additional options are needed for patients with moderate to severe OA who do not adequately respond to or cannot tolerate currently available treatments as.
    1. Current guideline-recommended pharmacological treatment options include NSAIDs (topical/oral), intra-articular steroids, and tramadol – but not all patients adequately respond to these current treatment options
    2. Tolerability or safety concerns, such as increased risk of adverse cardiovascular (CV) or gastrointestinal (GI) events, preclude or limit use of these treatment options in some patients.
    3. Opioids are not the answer – opioids are not recommended by treatment guidelines because of both toxicity concerns and potential for dependence. Despite the on-going opioid crisis, their use in this patient population nonetheless persists to a high degree. Specifically, an analysis from 2017 showed non-tramadol opioids remain the most frequently prescribed pain medications for OA (52.7%) which reflects a decline from an analysis in 2008 (71.7%)
- Tanezumab 2.5 mg is intended for use in these patients – those who have no other medical treatment options.

OA is a chronic, progressive, disabling disease of the joint. The hallmark signs and symptoms of OA are joint pain, stiffness, and reduced range of motion. Risk factors for OA include increased age, obesity, female gender, trauma, and high impact sports.[3] Recent estimates indicate that approximately 31 million adults in the United States (US) are affected with OA.[4] The prevalence of OA is expected to increase as the population ages and as the rate of obesity rises.[3] Up to 63% of OA patients have moderate to severe OA depending on the population studied and the criteria used to assess severity. [5-9]

Globally, estimates in 2016 suggest OA of the knee and hip is the 12th leading cause of disability, as measured by years of life lost due to disability,[10] and between 1990 and 2010 was the fourth most rapidly rising cause of disability just behind diabetes, Alzheimer's disease, and benign prostatic hyperplasia.[11] Patients with moderate to severe OA are particularly impacted. In the 2009 US National Health and Wellness Survey, as OA severity increased, workers reported more frequent pain, poorer quality of life, greater use of specific healthcare resources (including hospitalizations), and reduced productivity.[7] Likewise, an analysis of the Adelphi Disease Specific program database demonstrated that disease severity had a significant impact on functional outcomes, productivity, employment, and productivity

costs. For example, patients with self-reports of severe OA were nearly twice as likely to be unemployed and for those that were employed, there was a 2.25-fold greater work impairment, in terms of percent time lost, for patients with severe OA than for those with mild OA.[7]

As well as directly affecting physical function, OA disability may also lead to secondary morbidity and mortality. In a population-based study, the severity of OA disability was associated with a significant increase in all-cause mortality and serious CV disease events.[12] Given the high prevalence, and the disability, morbidity, and mortality associated with OA, the Osteoarthritis Research Society International (OARSI) has recommended to the FDA that OA be designated a serious disease.[1]

The recent (2019) OARSI[13] and American College of Rheumatology (ACR; 2019)[14] OA treatment guidelines recommend non-pharmacological methods such as education and self-management, exercise, weight loss (if overweight or obese), and walking aids.

With respect to pharmacological interventions, NSAIDs are recommended by the recent OARSI and ACR treatment guidelines for hip and knee OA, with topical NSAIDs to be considered prior to use of oral NSAIDs, depending upon the affected joint.[13,14] The guidelines recommend use of oral NSAIDs at the lowest effective dose for the shortest possible period of time due to their safety.[13,14] The primary safety concerns are serious upper GI complications, such as ulcers and bleeding, and acute MI and heart failure.[15] This may be of particular concern when treating older patients with OA based on a systematic review that showed that the risks of GI toxicity are elevated in the elderly population.[16] All NSAIDs have the potential to induce acute kidney injury, and patients with OA especially those with a history of co-morbid conditions, including hypertension, heart failure, and diabetes mellitus, and NSAID users are at three-fold higher risk compared with non-NSAID users in the general population.[15] These safety concerns are an important consideration when treating OA patients and as described in product labeling, the use of oral NSAIDs is preferably restricted to the lowest effective dose for the shortest duration possible. Short-term use however, is unlikely to adequately address the needs of patients with a long-term condition.

Intra-articular corticosteroids are conditionally recommended by both guidelines,[13,14] with evidence of short-term efficacy with single injections showing improvement in pain in the injected joint over the first several weeks, but not beyond.[17-20] There is minimal evidence to suggest the efficacy of intra-articular corticosteroids is maintained with repeat injections over the long term.[21,22] Moreover, there is evidence that repeat intra-articular corticosteroid injections may have a deleterious effect on the joint and enhance the progression of OA,[23] but this has not been seen in other studies.[24] Intra-articular hyaluronic acid is conditionally recommended in the OARSI (for knee only) but not ACR guidelines.[13,14]

The OARSI guideline recommends against the use of acetaminophen due to limited efficacy in OA and a signal for possible hepatotoxicity,[13] while the ACR guideline conditionally recommends acetaminophen as it may be appropriate for short term, episodic use in those who cannot take NSAIDs.[14]

The ACR and OARSI guidelines do not recommend the use of opioids due to concerns about a high risk of toxicity and potential for dependence, and limited or no relevant benefits of long-term use of opioids for OA symptoms, although the ACR does recognize that they may be used under certain circumstances, particularly when other options have been exhausted. Tramadol was not specifically discussed in the OARSI guideline but was conditionally recommended in the ACR guideline.[14] A metanalysis identified the most common adverse events associated with opioid treatment in OA patients are nausea, constipation, dizziness, somnolence and vomiting.[25] These adverse events often cause patients to stop taking their opioids, which can further limit the usefulness of opioids in the long term.[25] In a recent metanalysis, patients taking opioids were almost 4-fold more likely to discontinue treatment due to adverse events compared to placebo-treated patients.[26] In addition, there is significant risk for overdose deaths, misuse, abuse, and addiction. In the US, between 1999 and 2010, prescription opioid–related overdose deaths increased substantially in parallel with increased prescribing of opioids,[27] although there is evidence that opioid prescribing in the US has decreased in recent years.[28] In 2016, opioid-involved drug overdoses accounted for 42,249 deaths, over 40% (17,087) involving prescription opioids.[29] In 2018, an estimated 1.7 million individuals in the US had opioid use disorder (addiction) associated with prescription opioids,[30] and in 2013 the Centers for Disease Control and Prevention (CDC) estimated that the total economic burden of prescription opioid misuse in the US was $78.5 billion.[31] In the chronic pain population, a recent systematic review evaluating the effectiveness and risks of long-term opioid therapy for chronic pain identified the prevalence of dependence in the primary care setting ranged from 3-26% and the prevalence of addiction in pain clinics ranged from 2-14%.[32] In a more recent metanalysis it was estimated that 4.7% of pain patients prescribed opioid therapy were associated with a new diagnosis of opioid dependence or abuse.[33]

Looking at clinical practice in the US, NSAIDs and opioids are the most commonly prescribed pain medications for OA. In a large 2008 analysis of a claims database of over 100,000 patients with diagnosed OA in the US, 56.7% of patients received prescriptions for pain medications. Of those receiving a prescription during 2008, non-tramadol opioids were the most frequently prescribed pain medication for OA (71.7%) followed by NSAIDs (65.4%) and tramadol (17.3%).[34] In an analysis of US prescription claims data from August 2016 to July 2017 from 439,416 patients diagnosed with OA, 73.3% received a prescription in the past year. Of those receiving a prescription, non-tramadol opioids were still the most frequently prescribed pain medication for OA (50.8%) followed by NSAIDs (42.1%) and tramadol (20.9%).[35] Finally, a recent study utilized a different methodology to characterize prescribing patterns in 841 patients with mild (n=382), moderate (n=302), or severe (n=157) OA pain seen between February and May 2017 by physicians who participated in the US Adelphi Disease Specific Program.[36] While NSAIDs (including COX-2-specific inhibitors) were the most frequent current treatment across the OA patients (57.6% of patients), 32.5% of patients with severe OA pain were currently taking opioids, compared with 9.7% of patients with mild OA pain.[36] These data show that the use of opioids in OA is still widespread, despite guideline recommendations against opioid use in OA, and the CDC guideline for opioid prescribing for chronic pain that recommend non-opioid, or non-pharmacologic treatment options over opioids.[37]

A 2008 claims-based analysis demonstrated a substantial proportion of patients with OA either switched, augmented, or discontinued their initial therapy: two-thirds within 2 months and >90% within 6 months.[38] The observed high rates of therapy switching and discontinuation, especially within a short time frame after treatment initiation, would be consistent with inadequate pain relief, potentially intolerable adverse effects, or both. Consistent with this, in the EU National Health and Wellness Survey only 30% of OA patients taking pain medications reported being satisfied or very satisfied with it and the level of satisfaction was similar between the different classes of prescription medication.[39] In a second study, 54% of patients with OA of the knee were identified as having inadequate pain relief which was defined as having moderate to severe pain despite being on pain medication.[40] Moreover, 48% of patients with inadequate pain relief reported dissatisfaction with their response to treatment, and 38% reported dissatisfaction with tolerability to the medication.[40]

Joint replacement is an important treatment option for OA in patients with more severely affected functional status. There were nearly 1 million total knee or hip replacements in the US in 2010,[41] a number expected to grow to approximately 1.5 million in 2020.[42] According to the CDC, in 2010 total knee replacement (TKR) was the most frequently performed inpatient procedure on adults aged 45 years or older.[43] A recent study compared TKR with non-surgical treatments (including exercise, education, dietary advice, insoles and pain medication). The TKR group had improved pain and functional outcomes compared to non-surgical treatment, but also had a higher number of serious adverse events than the non-surgical treatment group.[44] While, the majority of patients have positive outcomes after TJR, in a systematic review 7-23% and 10-34% of patients report an unfavorable long-term pain outcome following total hip and knee replacement respectively.[45]

Additional non-opioid options are needed for patients with moderate to severe OA who do not adequately respond or cannot tolerate currently available treatments or who may be at increased risk for safety events associated with these treatments. Not all patients adequately respond to current treatment options, and many with moderate to severe OA become dependent on chronic opioids for pain relief. Moreover, tolerability or safety concerns, such as CV or GI events, or potential for abuse or dependence can limit the use of currently available treatments.

2.2. Mechanism of Action

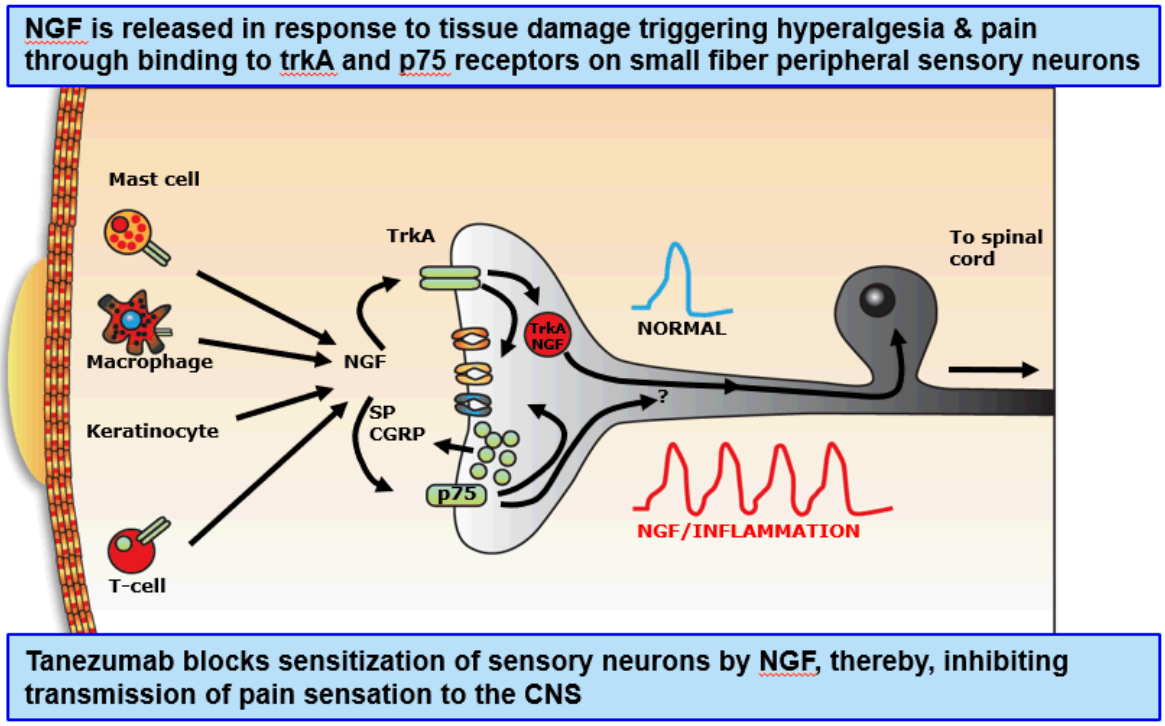
Tanezumab, a humanized IgG2 monoclonal antibody, is an NGF inhibitor that binds with high affinity and specificity to NGF.

NGF is produced and released by peripheral tissues in response to noxious stimuli such as tissue damage, inflammation, and in chronic pain states.[46] NGF stimulates the release and actions of inflammatory mediators that in turn stimulate increased synthesis and/or release of NGF.[47,48] NGF plays an important role in modulation of the pain response by binding to tropomyosin-related kinase A (TrkA; high affinity) or p75 (low affinity) neurotrophin receptors, resulting in modulation of several pain signaling pathways.[48-50]

Monoclonal antibodies (such as tanezumab) directed against NGF (NGF inhibitors) act peripherally by inhibiting the interaction of NGF with TrkA and/or p75 receptors.[48,50] This

mechanism is distinct from that of other currently available analgesics including opioids and NSAIDs.

Figure 1. Tanezumab Mechanism of Action



Adapted from Hefti FF et al. Trends Pharmacol Sci. 2006;27(2):85-91.[51]

2.3. Regulatory History

Apr 2004	**Tanezumab IND Filed**
Jun/Jul 2010 – Aug 2012	**Partial Clinical Hold** FDA's Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) placed tanezumab on partial clinical hold (PCH) and subsequently the entire NGF inhibitor class (December 2010) on PCH due to adverse events initially described by investigators as ON that in some cases resulted in TJR. It was subsequently determined that the investigator-reported events of ON were primarily RPOA. • Jul 2011: NGF inhibitor sponsors submitted responses to PCH • Mar 2012: FDA convened Arthritis Advisory Committee to discuss the benefit-risk profile of the NGF inhibitor class. The Committee voted in favor of continued clinical development of tanezumab. • Jul 2012: Sponsor submitted a Complete Response detailing risk mitigation plans for future studies. • Aug 2012: FDA removed the PCH on tanezumab allowing studies to resume.
Dec 2012 – Mar 2015	**Partial Clinical Hold** FDA's DAAP placed another PCH on all NGF inhibitor development programs due to concerns about adverse changes in the sympathetic nervous system morphology of mature animals. During 2013-2014, the sponsor conducted a comprehensive series of nonclinical studies to investigate the effects of tanezumab on the sympathetic nervous system (see Section 2.5for more details). • Feb 2015: Sponsor submitted a Complete Response addressing sympathetic nervous system concerns. • Mar 2015: FDA removed the PCH on tanezumab allowing studies to resume. • Per agreement with the FDA, subsequent clinical studies of tanezumab included risk mitigation measures for joint safety and additional safety measures to monitor for and manage patients who may develop evidence of clinically important sympathetic nervous system dysfunction.
May 2017	FDA granted the tanezumab development program **Fast Track Designation**, on the basis that tanezumab has the potential to treat a serious condition and fill an unmet medical need.
Aug 2017	FDA and the Center for Drug Evaluation and Research (CDER) Medical Policy Council provided additional comments on the review of a Breakthrough Application (previously denied in May 2017) requesting additional safety data for a minimum of 2 years to assess potential toxicities with chronic use of tanezumab. In subsequent communications, FDA informed the sponsor as an alternative to 2-year safety data as part of the application, the sponsor should propose a plan for collecting additional safety data in the postmarketing setting beyond routine pharmacovigilance.
Jan 2018	FDA confirmed a REMS **with elements to assure safe use (ETASU)** will be necessary to ensure that the benefits of the drug outweigh the risks of RPOA and possible sympathetic autonomic neuropathy.
2018-2019	There were several interactions with FDA over the course of 2018 and 2019 to align on the submission strategy and presentation of data in the BLA.
Dec 2019	The sponsor has followed FDA advice and the **BLA was submitted via Rolling Submission** with the final component dispatched to FDA on 18 December 2019.

2.4. Clinical Development Program and Study Design

Approximately 13,270 patients have been treated with at least one dose of tanezumab in the 39 Phase 1 to 3 clinical studies submitted for the BLA:

- 20 OA studies (including 4 Phase 1/2 studies and 16 Phase 3 studies) to investigate the analgesic efficacy and safety of tanezumab in adult patients with moderate to severe OA of the hip or knee;
- 19 other studies including:
  - 2 Phase 1 healthy volunteer studies;
  - 14 Phase 1/2/3 proof-of-concept, dose ranging or safety and efficacy studies to investigate tanezumab in a variety of pain conditions not being sought as indications at this time (including 5 studies in adult patients with chronic low back pain [CLBP]);
  - 2 observational safety studies monitoring neurological development in infants who were exposed to tanezumab in-utero.
  - 1 observational safety study in patients from tanezumab studies who underwent a TJR.

Of the 20 OA studies, all four Phase 1/2 studies and 13 of the 16 Phase 3 studies were conducted pre-2015 primarily using an intravenous (IV) route of administration for tanezumab. Some of these studies were terminated early due to the partial clinical holds from 2010 to 2015. When the Phase 3 clinical development program was re-initiated in 2015, three OA studies were conducted to evaluate the efficacy and safety of SC administration of tanezumab. The same formulation of tanezumab was used for both IV and SC administration in Phase 3 studies. SC administration was selected for development and is proposed for commercialization for ease of use in a clinical practice setting.

All of the Phase 3 OA studies were randomized, double-blind (or dose-blinded for uncontrolled studies), multicenter, fixed-dose, parallel-group studies. They followed a similar overall design, although they differed in aspects of patient selection (eg, the index joint as knee or hip, and the required inadequacy of prior analgesics), and study treatment (the doses of tanezumab and the duration of treatment). Schematics of individual efficacy studies are provided in Section 4.

The Phase 3 OA studies evaluated tanezumab doses of 2.5 mg, 5 mg, or 10 mg. Tanezumab (or matching placebo where applicable) was administered by study personnel by SC (in the thigh or abdomen) or IV injection once every 8 weeks. Active comparator (or placebo matching the active comparator) was self-administered orally by the patient during the treatment period in active-controlled studies.

2.5. Overview of Key Nonclinical Safety Findings

- A comprehensive evaluation of the potential effects of long term NGF inhibition on bone/joint homeostasis and selected sensory nerve morphometrics in multiple species (mouse, rat, and monkey) showed no adverse effect of tanezumab or its murine precursor, muMab911, on morphology, nerve density, or microvasculature of the knee and hip joints or nerve regeneration following injury at exposures equal to or greatly exceeding (up to approximately 5916 times, based on C_{av}) the human exposure at the dose of 2.5 mg SC every 8 weeks.[52]

- Tanezumab treatment for up to 1 month in rats and 6 months in monkeys was associated with lower sympathetic ganglion volume and lower average size of post-ganglionic sympathetic neurons at exposures approximately ≥28 times the human exposure. All effects were completely reversible following an 8- to 10-month dosing-free recovery period. In a separate cardiovascular function study in monkeys, administration of tanezumab at exposures up to approximately 5227 times the human exposure did not cause any functional changes in the cardiovascular system controlled by the sympathetic nervous system. In the absence of neuronal cell death and adverse functional effects, the effects of tanezumab on the sympathetic nervous system were considered non-adverse.[53]

- In monkey reproduction studies at exposures approximately 37 times the human exposure, administration of tanezumab to pregnant monkeys during organogenesis resulted in increased postnatal mortality, increased incidence of stillbirths, and developmental neurotoxicity in offspring.[54]

The nonclinical toxicology program included single-dose studies in cynomolgus monkeys, and repeat-dose studies of up to 1 month in duration in rats and up to 6 months in monkeys. In addition to the bone/joint evaluations conducted as part of repeat-dose general toxicity studies using normal animals, a series of mechanistic studies were conducted to further investigate bone/joint safety. An extensive evaluation of the peripheral nervous system, including stereology (quantitative) and morphological (qualitative) assessments as well as sympathetic control of cardiovascular function, was conducted in 2 species (rat and monkey). The potential for developmental and reproductive toxicity was assessed in fertility and embryo-fetal development studies in rats, and in two separate modified pre- and postnatal development toxicity studies in cynomolgus monkeys. Tanezumab was also evaluated in vitro for hemocompatibility and tissue cross-reactivity.

Several studies were conducted in animals to investigate the mechanism of RPOA Type 2. In normal healthy animals (mouse, rat, and monkey), multiple dose administration of tanezumab or its murine precursor (muMab911) at exposures equal to or greatly exceeding human therapeutic levels (up to 5916x the exposure in humans at the dose of 2.5 mg SC every 8 weeks, based on C_{av}) had no effect on morphology, nerve density and microvasculature of the knee and hip joints, or nerve regeneration following injury.[52] Studies in models of bone pain revealed no effect of NGF inhibition on bone innervation, bone remodeling, or fracture

healing.[55-59] Treating rats subjected to surgically induced medial meniscal tear with tanezumab did not recapitulate the atrophic bone destruction associated with RPOA in clinical studies;[60] although anti-NGF treatment early in the disease process influenced weight-bearing and drove additional cartilage damage, secondary changes in subchondral bone were instead hypertrophic (subchondral bone thickening, with osteophytes present). No destructive changes were noted in rats with medial meniscal tear treated with anti-NGFs when weight bearing was prevented.

There is no accepted pathophysiology for the tanezumab-related joint destruction. Although there may be speculation related to the effect of NGF inhibition on osteoclasts, it has been reported in the rat monoiodoacetate model that treatment with muMab911 partially inhibits the induced increase in osteoclast number while not affecting cartilage damage. This might have a beneficial effect on subchondral bone in OA.[61] Inhibition of TrkA signaling has also been shown to impair load-induced bone formation in mice.[62] Preliminary data from an ongoing study in the same model has shown lower load-induced bone formation rate in muMab911-treated mice compared with untreated controls, suggesting a potential effect of NGF inhibition on osteoblast function, while having no effect on osteoblast count or biomarkers of osteoclast recruitment and/or function (receptor activator of nuclear factor kappa-B ligand [RANKL], osteoprotegerin [OPG], RANKL/OPG ratio, and collagen type 1 C-telopeptide [CTx1]).[35]

2.6. Overview of Biopharmaceutics

- The tanezumab commercial formulation consists of compendial excipients commonly used in the pharmaceutical industry.
- The 2.5 mg/mL tanezumab drug product is prepared as a sterile liquid. The liquid bulk drug product is formulated at 2.5 mg/mL tanezumab in 10 mM histidine buffer (pH 6.0), 84 mg/mL trehalose dihydrate, 0.05 mg/mL edetate disodium dihydrate, and 0.1 mg/mL polysorbate 20. The product is filled in single-dose, prefilled syringes and is intended for SC administration delivered by a healthcare provider (HCP).
- Only 2 formulations have been utilized with tanezumab throughout development, both of which are liquid formulations and use precedented compendial excipients. Chemistry Manufacturing and Controls (CMC) Analytical Comparability exercises were performed to support process changes, and each comparability exercise demonstrated that the changes made resulted in drug substance with a similar product quality profile. A clinical pharmacokinetics (PK) comparability study comparing the two processes was not considered necessary to confirm analytical comparability. This was supported by comparable noncompartmental PK results across clinical studies that used the two process formulations.

3. CLINICAL PHARMACOLOGY

3.1. Overview

- The characterization of tanezumab pharmacokinetics (PK) following SC administration in the thigh or abdomen is consistent with other IgG2 monoclonal antibodies (Section 3.2):
- Mean effective half-life ~22 days and time to maximum observed concentration (Tmax) 8 to 12 days.
- No dose adjustment is required for site of administration, age, weight, sex, race, renal or hepatic impairment.
- Assessment of tanezumab PK-QTc interval relationship and limited central nervous system penetration indicate these are of no clinical relevance (Section 3.3).
- Tanezumab is minimally immunogenic: no detectable clinical consequences of treatment-emergent (TE) anti-tanezumab antibodies (Section 3.4).

3.2. Pharmacokinetic Characterization

Following single and steady-state dosing of tanezumab 2.5 mg SC, the typical time to reach maximum concentration (T_{max}) values range from 8 to 12 days. The accumulation index at steady-state is approximately 1.2, and the effective half-life is approximately 22 days. There is modest variability in PK and a limited overlap in exposures between tanezumab 2.5 and 5 mg dose.

Absolute bioavailability of tanezumab following SC administration is estimated to be between 62% and 76%. The maximum plasma concentration (C_{max}) following SC tanezumab dose was approximately 3-fold lower compared to the same dose administered via the IV route. The observed single-dose IV and SC data and steady-state simulations from the population PK analyses indicate that despite the lower bioavailability, tanezumab plasma concentrations measured from Week 4 post-dose are similar between the IV and SC routes.

As tanezumab is expected to be metabolized primarily by catabolic degradation following endocytosis by the mononuclear phagocytic system, it is expected that hepatic impairment will not have a clinically relevant effect on the PK of tanezumab. Clinical studies have not been conducted to evaluate the effect of hepatic impairment on the PK of tanezumab.

Renal clearance is not considered important for elimination of monoclonal antibodies due to their large size and inefficient filtration through the glomerulus. Based on population PK analysis that included creatinine clearance as covariate, no dose adjustment is required in patients with mild to moderate renal impairment. Tanezumab PK has not been studied in patients with severe renal impairment.

The population PK analysis also indicated that dose adjustment for age, weight, sex, or race, is not necessary. Furthermore, the site of injection (ie, abdomen or thigh) had no impact on the PK of tanezumab in the patient population.

Additionally, clinically relevant drug-drug interactions are not expected since tanezumab is expected to be cleared by catabolism following endocytosis by the mononuclear phagocytic system and not to affect cytochrome P450 enzymes expression.

3.3. Pharmacodynamic Characterization

Pharmacokinetic-target characterization indicated that following tanezumab treatment, total NGF concentrations in blood increased from baseline in an approximately dose-proportional manner possibly due to the longer half-life of the tanezumab-NGF complex compared to free NGF. Upon termination of tanezumab treatment, the total NGF concentrations begin approaching baseline concentrations with an effective half-life similar to tanezumab.

3.4. Pharmacodynamic (Safety) Characterization

Based on the absorption, distribution, and elimination properties of tanezumab in plasma and in cerebrospinal fluid, tanezumab is not expected to result in pharmacologically active concentrations in the central nervous system. This is supported by non-human primate data indicating that tanezumab concentrations in cerebrospinal fluid were approximately 0.1% of the plasma tanezumab concentrations.[63] Under the assumption that this estimate is similar to that in humans, pharmacokinetic-pharmacodynamic (PK-PD) model-based predictions indicated that there would be less than 1% suppression of NGF in the cerebrospinal fluid, indicating that tanezumab has no relevant functional central nervous system activity. This is consistent with the correspondence received from FDA.[64]

As expected for monoclonal antibodies in general,[65] tanezumab does not result in prolongation of the QTc interval, based on an exposure-response analysis. This analysis assessed the QTc interval over tanezumab concentrations that were up to 100-fold higher than the population PK model- predicted steady-state C_{max} value for 2.5 mg tanezumab administered SC every 8 weeks.

Immunogenicity

Over an 80-week period, the overall incidence of patients producing anti-drug antibody (ADA) to tanezumab when treated with a 2.5 mg SC dose of tanezumab every 8 weeks for 48 weeks was less than 10%. Generally, the samples that were evaluated for neutralizing ADA within the treatment-emergent (TE) ADA positive patient population were determined to be neutralizing ADA positive. Assessment of TE ADA impact on population PK following SC administration in OA patient populations indicated a 7% increase in total clearance in the TE ADA positive population relative to the TE ADA negative population.

To assess ADA impact on WOMAC Pain Subscale response, a clinically meaningful response was defined as a change from Baseline in WOMAC Pain Subscale score reduction of ≥30% at Week 16 and TE ADA+ patients were classified according to whether the first TE ADA+ titer was identified within (ie, ≤16 weeks) or after 16 weeks. Based on limited data obtained in patients producing ADA to tanezumab, there was no evidence of a meaningful

difference in the proportion of responders between patients with or without TE ADA to tanezumab.

Furthermore, no meaningful differences were observed in the overall incidence of TE adverse events, serious adverse events or specifically adverse events categorized as hypersensitivity or injection site reactions, between patients with or without TE ADA to tanezumab.

In the longer duration Study 1058, the incidence of TE ADA+ patients increased gradually with increasing study duration. Of patients who became TE ADA+ by Week 80, 95% (ie, 80 of 84 patients) had developed TE ADA within 8 weeks of the final dose that was administered at Week 48 for tanezumab 2.5 mg treatment group. For TE ADA+ patients in the 2.5 mg treatment group, median ADA titer values appeared to increase from baseline and plateaued by Week 8. Post Week 16 to Week 80, median ADA titer values appeared to fluctuate about the plateau and did not appreciably decline or increase.

The immunogenicity has only been studied for the once every 8-week dosing regimen and thereby precludes any comparison with other more frequent or less frequent dosing regimens. For further information on safety and benefit-risk assessment please see Section 5 and Section 8, respectively.

3.5. Rationale for Phase 3 Dose Selection: Tanezumab 2.5 mg at an 8-Week Dosing Interval

Phase 2 dose-ranging studies and associated PK/PD and dose-response analysis supported 2.5 mg as the lowest dose for inclusion in Phase 3 studies.

Doses lower than 2.5 mg were evaluated in two Phase 1/2 OA studies (Studies 1006, 1008). Both studies administered tanezumab IV and used weight-based dosing (µg/kg). For a 100 kg patient, a 10 µg/kg and 25 µg/kg doses equated to 1 mg and 2.5 mg, respectively.

Results indicated that doses below 2.5 mg had limited magnitude and duration of efficacy which was not sustained over an 8-week interval (Studies 1006, 1008). There was also a noticeable increase in responder rate in comparison to placebo when the tanezumab dose was increased from 10 µg/kg (1 mg) to 25 µg/kg (2.5 mg) in Study 1008.

The end of Phase 2 PK/PD and dose-response analyses supported 1) the choice of tanezumab 2.5 mg as the lowest dose in the subsequent Phase 3 programs, 2) the 8-week dosing interval, and 3) the conclusion that administration of the same IV and SC dose would be therapeutically similar at primary efficacy timepoints. The selection of 2.5 mg every 8 weeks as the lowest dose for Phase 3 was discussed at the end of Phase 2 discussions with the FDA, and was included in Phase 3 protocols.

The results of Phase 3 dose-response and PK/PD analyses were consistent with the end of Phase 2 data, and are discussed in Section 4.4.7.

4. EFFICACY

4.1. Overview

- Tanezumab 2.5 mg administered SC every 8 weeks resulted in a clinically meaningful and sustained reduction in pain and improvement in function compared to placebo in patients with moderate to severe OA pain for whom use of other analgesics was ineffective or not appropriate.
- Patients in Studies 1056 and 1057 had moderate to severe OA at baseline, with mean ± standard deviation [SD]) (Section 4.4.1.2):
    - WOMAC Pain score (11 point Numerical Rating Scale [NRS]) 6.9 ±1.1
    - WOMAC Physical Function score (11 point NRS) 7.0 ±1.0
    - PGA-OA (5-point Likert Scale) 3.5 ± 0.6
- Most patients (77%) had Kellgren-Lawrence (KL) radiographic severities of Grade 3 or 4, and 24% met criteria for a severe cohort (Section 4.4.1.2).
- Tanezumab 2.5 mg SC resulted in significant improvement over placebo in all three co-primary efficacy measures (WOMAC Pain, WOMAC Physical Function and PGA-OA) in Study 1056, and in two of the three co-primary efficacy measures (WOMAC Pain and WOMAC Physical Function) in Study 1057 (Section 4.4.1.3).
- With tanezumab 2.5 mg SC, approximately 50% patients demonstrated a substantial clinically meaningful improvement in pain (≥50% reduction in the WOMAC Pain Subscale) versus approximately 36% with placebo, while approximately 67% achieved a moderately important clinically meaningful improvement (≥30% reduction) versus approximately 56% with placebo (Section 4.4.1.4).
- The onset of pain relief was within one week of initiating therapy (Section 4.4.1.5).
- Reduction in pain and improvement in function was sustained throughout the 8-week SC injection cycle (Section 4.4.1.6).
- Substantial evidence of efficacy and a consistent treatment effect was replicated across the IV and SC clinical programs (Section 4.4.2).
- The efficacy of tanezumab 2.5 mg SC was similar regardless of patient gender, age, BMI category ≥25 kg/m^2, index joint (hip or knee), disease duration, disease severity, and geographic region (Section 4.4.3).
- Tanezumab 2.5 mg SC provided persistent treatment effects over approximately one year of treatment in long-term studies. Tolerance was not observed and dose adjustments are not required (Section 4.4.6).

- Across all studies and assessments, there was no meaningful difference between tanezumab 2.5 mg and 5 mg doses (Section 4.5).
- Dose-Response and pharmacokinetics/pharmacodynamics (PK/PD) analyses support the dose regimen of tanezumab 2.5 mg SC dose every 8 weeks for OA patients and comparability between SC and IV administration (Section 4.4.7).

4.2. Efficacy Database

Efficacy data were derived from seven completed, randomized, controlled, double-blinded Phase 3 OA studies, and one long-term open-label dose-blinded extension study.

Four of these studies were placebo-controlled, included treatment with the tanezumab 2.5 mg dose, and provide the key evidence of efficacy:

- **Placebo-Controlled Studies 1056 and 1057:** These post-2015 studies provide the substantive evidence of efficacy versus placebo for the proposed tanezumab dose (2.5 mg) and route of administration (SC) in the intended patient population with moderate to severe OA pain for whom use of other analgesics (acetaminophen and NSAIDs, and tramadol or non-tramadol opioids) was ineffective or not appropriate.[66-68]
- **Placebo-Controlled Studies 1011 and 1014**: These pre-2015 studies provide additional evidence of efficacy versus placebo for tanezumab 2.5 mg administered IV, in a similar patient population also with limited treatment options.[69,70]

The remaining four studies did not include the tanezumab 2.5 mg dose or were not placebo-controlled, but provide supportive evidence of efficacy:

- **Placebo- and Active-Controlled Studies 1015 and 1018:** These pre-2015 studies compared tanezumab 5 mg and 10 mg IV to placebo and naproxen 500 mg BID,[71] and are included here because they fed into the long-term uncontrolled extension Study 1016.
- **Long-Term Uncontrolled Extension Study 1016:** Patients participating in Studies 1011, 1014, 1015 or 1018 (parent studies) were eligible to continue open-label, dose-blinded tanezumab IV treatment in this extension study over a period of approximately 2 years.
- **Long-Term Active-Controlled Study 1058:** This post-2015 study evaluated the joint safety and efficacy of tanezumab 2.5 mg and 5 mg SC versus NSAIDs over 56 weeks of treatment.

Data for each set of studies are presented in Sections 4.4.1, 4.4.2, 4.4.4, 4.4.5, and 4.4.6 respectively. A pool of Studies 1056, 1057, 1011, and 1014 was used to analyze tanezumab efficacy in pre-defined subgroups and is presented in Section 4.4.3. Dose response and PK/PD data were derived from the Phase 3 placebo-controlled studies and are discussed in Section 4.4.7.

Other Phase 3 OA studies are not presented in this section either because they were terminated early due to the partial clinical hold and provide limited efficacy information or, because they did not include the proposed patient population and/or dosing regimen and did not feed into the extension study or provide long-term data.

4.3. Study Design

4.3.1. Overall Study Design

Overall design features of the efficacy studies are summarized in Table 1. Study schematics are provided at the start of each results section.

Table 1. Listing of Tanezumab Osteoarthritis Efficacy Studies

Study Type	Study	N	Index Joint[a]	Study Design	Treatment Duration [Primary Efficacy Analysis] in Weeks (No. Doses)	Tan Route Of Admin	Tan Doses (mg every 8 weeks)			Comparator	
							2.5	5	10	PBO	NSAID
Placebo-Controlled Studies that Included the Tanezumab 2.5 mg Dose											
Placebo Controlled	1056	696	K/H	R, DB	16 [16] (2)	SC	✓	✓[b]	–	✓	–
	1057	849	K/H	R, DB	24 [24] (3)	SC	✓	✓	–	✓	–
	1011	690	K	R, DB	24 [16] (3)	IV	✓	✓	✓	✓	–
	1014	621	H	R, DB	24 [16] (3)	IV	✓	✓	✓	✓	–
Supportive IV Studies											
Placebo and Active Controlled	1015	828	K	R, DB	16 [16] (2)	IV	–	✓	✓	✓	✓[c]
	1018	840	K/H	R, DB	16 [16] (2)	IV	–	✓	✓	✓	✓[c]
Long-Term Studies											
Long-Term Uncontrolled	1016	2142[d]	K/H	R, B, Ex + StOC	104 [24,48] (13)	IV	✓	✓	✓	-	–
Long-Term Active Controlled	1058	2996	K/H	R, DB	56 [16] (7)	SC	✓	✓	–	-	✓[e]

B = Dose blinded; DB = Double-Blinded; Ex = Extension Study; H = Hip; K = Knee; N = Number of patients (ITT population); R = Randomized; StOC = Standard of care.
a. Identified by the Investigator at screening as the most painful protocol specified joint (knee or hip) meeting ACR criteria, with x-ray confirmation, and with a qualifying WOMAC Pain score.
b. These patients received 2.5 mg tanezumab for the first dose, and 5 mg for the second dose.
c. Naproxen 500 mg BID.
d. Of these, 827 patients received tanezumab for the first time in Study 1016, following treatment with PBO or comparator in parent Studies 1011, 1014, 1015 and 1018.
e. Naproxen 500 mg BID, Celecoxib 100 mg BID, or Diclofenac Extended Release 75 mg BID.

4.3.2. Key Inclusion Criteria

Patients enrolled in Studies 1056, 1057, 1011, and 1014 had moderate to severe OA of the hip or knee based on clinical and radiographical findings. Patients were also required to meet eligibility criteria related to pain, physical function, and global well-being (Table 2).

Studies 1056, 1057, 1011, and 1014 all enrolled patients for whom use of other analgesics was ineffective or not appropriate, although the criteria were more stringent in Studies 1056, and 1057 as part of the joint safety risk mitigation strategy for post-2015 studies (Table 2):

Table 2. Summary of Key Inclusion Criteria in Efficacy Studies 1056, 1057, 1011, 1014

Criteria	Post-2015 SC Studies 1056 and 1057	Pre-2015 IV Studies 1011 and 1014
Demographics	Male or female ≥18 years BMI ≤39 kg/m^2	Male or female ≥18 years BMI ≤39 kg/m^2
Meet ACR Classification Criteria	Yes	Yes
Kellgren-Lawrence criteria	≥2	≥2
WOMAC Pain[a] in index joint at Screening	≥5	≥4
WOMAC Pain[a] in index joint at Baseline	≥5	≥5
Increase in WOMAC Pain[a] in index joint at Baseline for patients taking pain medications before Screening	Not applicable	≥1
WOMAC Physical Function[a] in index joint at Baseline	≥5	≥4
Patient Global Assessment[a] at Baseline	Fair, poor or very poor	Fair, poor or very poor
Ineffective or not appropriate other analgesics[b]	APAP ineffective *and* NSAID ineffective/ unable, *and ≥1 of:* Tramadol ineffective/ unable *or* Opioid ineffective/ unable/ unwilling	Non-opioids ineffective / unable / unwilling *or* candidate for invasive intervention

ACR = American College of Rheumatology; APAP = Acetaminophen; BMI = Body Mass Index
a. Descriptions of WOMAC Pain, WOMAC Physical Function and Patient Global Assessment measures can be found in Table 3.
b. 'Ineffective'=Specified medication not providing adequate pain relief; 'Unable'=Patient unable to take specified medication due to contraindications or inability to tolerate; 'Unwilling'=Patient unwilling to take specified medication.

For Studies 1015 and 1018, the baseline demographic and disease criteria were the same as for Studies 1011 and 1014, however there were no criteria with respect to the adequacy of prior analgesics.

For Study 1058, the baseline demographic and disease criteria, and criteria with respect to adequacy of prior acetaminophen, tramadol and non-tramadol opioids were the same as for Studies 1056 and 1057. However, unlike Studies 1056 and 1057, patients in Study 1058

were required to be receiving and tolerating a stable therapeutic dose of NSAID prior to entering the study and through the screening period, before being randomized at baseline to switch to tanezumab or to continue NSAID treatment. Therefore, patients in Study 1058 were presumably receiving some treatment benefit from NSAIDs; however, relief was sub-optimal since patients were still required to meet the baseline disease severity criteria.

In Studies 1056, 1057, and 1058, evidence that medications were ineffective or not appropriate (and that patients in Study 1058 were receiving stable doses of NSAIDs) was sourced by the investigator from medical records and/or patient's recall (if sufficiently detailed). The required level of evidence to establish that subjects met these eligibility criteria was based upon the investigator's judgment. Medication names and classes, route of administration, dates of use, and protocol qualifying reason for prior drug treatments for OA were entered into the appropriate page of the case report form (CRF). If one or more of the medications could not be used due to contraindication, or if the subject refused to take the medication due to fear of known side effects, this was to be clearly documented with supporting details in patient source documents. In Studies 1011 and 1014, investigators recorded whether patients met the eligibility criteria on the CRF, with no further documentation required.

4.3.3. Concomitant OA Treatment and Rescue Therapy

Patients in all controlled Phase 3 OA studies were required to discontinue all non-study pain medications for OA (with a pre-specified washout during the screening period).

Acetaminophen was available in all controlled Phase 3 OA studies as a rescue medication with minor differences in dosing rules between studies (3000 mg or 4000 mg per day for ≤3 or ≤5 days per week during the treatment period, increasing to ≤7 days per week for Weeks 17 to 56 of the treatment period for Study 1058). Patients were to discontinue use of rescue medication within 24 or 48 hours before a study visit.

Occasional use of analgesics (eg, NSAID, acetaminophen) for non-OA pain was permitted in situations such as outpatient diagnostic procedures (eg, colonoscopy, dental procedures) or limited accidental injury (eg, ankle sprains, minor fractures, minor burns/sunburns). Patients were counseled to avoid scheduling prospective procedures requiring pain medications within 48 hours before a study visit. Limits on the use of NSAIDs in these circumstances were applied in Studies 1056, 1057 and 1058:

- Studies 1056 and 1057: Permitted occasional NSAID use not exceeding a cumulative total of 30 days between Day 1 (Baseline) and Week 24 (Study 1056), or 40 days between Day 1 and Week 32 (Study 1057), or an aggregate of 10 days of use during each 8-week dosing interval of either study.

- Study 1058: Prohibited use of NSAIDs and cyclooxygenase-2 inhibitors (COX-2) selective inhibitors (outside of oral investigational product) through the Week 64 visit.

Patients were permitted to take daily low dose aspirin (typically ≤325 mg/day) for non-analgesic or non-arthritic reasons (if at a stable dose for at least 30 days before the Initial

Pain Assessment Period) in Studies 1011, 1014, 1015 and 1018, and for CV prophylaxis without restriction in Studies 1056, 1057, and 1058.

In uncontrolled Study 1016, concomitant analgesics for the pain of OA were considered standard of care and were permitted at the Investigator's discretion.

With respect to lifestyle, patients were instructed to maintain their normal daily routine, including stable doses of permitted medications and exercise program. Patients were also permitted to continue with stable non-pharmacologic activities (eg, massage, physical therapy and psychological therapy) during the study. Patients were cautioned against initiating or altering strenuous exercise regimens during the study as this may influence efficacy, safety and laboratory results.

4.3.4. Primary and Secondary Endpoints

The pre-defined co-primary efficacy endpoints for the controlled Phase 3 efficacy studies were the change from baseline to Week 16 (Studies 1056, 1011, 1014, 1015, 1018, and 1058) or Week 24 (Study 1057) in the following (defined in Table 3):

- WOMAC Pain subscale score (11 point NRS);
- WOMAC Physical Function score (11 point NRS);
- PGA-OA score (5 point scale ranging from 'very good' to 'very poor').

A key secondary efficacy endpoint was defined as the percentage of patients with ≥50% reduction from baseline in WOMAC Pain at Week 16 in Studies 1056 and 1058, and at Week 24 in Study 1057. Additional key secondary endpoints defined in Study 1057 were WOMAC Pain Subscale change from Baseline to Week 2, and Weekly Average Pain Score (based on daily diary) in the index joint change from Baseline to Week 1. The Outcome Measures in Rheumatology (OMERACT)-OARSI Responder Index (defined in Table 3) at Week 16 was defined as a key secondary endpoint in Studies 1011, 1014, 1015 and 1018.

4.3.5. Efficacy Scales and Measures

Table 3. Efficacy Scales and Measures Used in Tanezumab Osteoarthritis Studies

<table>
<tr><th>Endpoint</th><th>Description</th></tr>
<tr><td>WOMAC Pain Subscale[72-74]</td><td>The WOMAC Pain Subscale is comprised of 5 questions regarding the amount of pain experienced due to OA in the index joint (selected study knee or hip) in the past 48 hours. The scores for each question, and the overall WOMAC Pain Subscale score (the mean from the 5 questions), range from 0 to 10 on a NRS, with higher scores indicating higher pain.</td></tr>
<tr><td>WOMAC Physical Function Subscale</td><td>The WOMAC Physical Function Subscale is comprised of 17 questions regarding the degree of difficulty experienced due to OA in the index joint in the past 48 hours. The scores for each question, and the overall WOMAC Physical Function Subscale score (the mean from the 17 questions), range from 0 to 10 on a NRS, with higher scores indicating worse function. This refers to the patient's ability to move around and perform usual activities of daily living.</td></tr>
<tr><td>PGA-OA[75,76]</td><td>For the PGA, depending on the index joint, patients answered the following question: "Considering all the ways your osteoarthritis in your knee/hip affects you, how are you doing today?" Patients rated their condition using the following scale:
<table>
<tr><td>1 – Very Good</td><td>Asymptomatic and no limitation of normal activities</td></tr>
<tr><td>2 – Good</td><td>Mild symptoms and no limitation of normal activities</td></tr>
<tr><td>3 – Fair</td><td>Moderate symptoms and limitation of some normal activities</td></tr>
<tr><td>4 – Poor</td><td>Severe symptoms and inability to carry out most normal activities</td></tr>
<tr><td>5 – Very Poor</td><td>Very severe symptoms which are intolerable and inability to carry out all normal activities</td></tr>
</table></td></tr>
<tr><td>OMERACT-OARSI Responder Index.[77]</td><td>A composite endpoint utilizing the change from Baseline to Week 16 in the three co-primary endpoints of WOMAC Pain Subscale, WOMAC Physical Function Subscale, and the PGA-OA. A patient was classified as a responder if, either:
The change (improvement) from Baseline to Week 16 ≥50% (percentage change) and ≥2 (absolute change) in either the WOMAC Pain or physical function subscales, OR
At least 2 of the following 3 being true:
The change (improvement) from Baseline to Week 16 ≥20% (percentage change) and ≥1 (absolute change) in the WOMAC Pain Subscale.
The change (improvement) from Baseline to Week 16 ≥20% (percentage change) and ≥1 (absolute change) in the WOMAC Physical Function Subscale.
The change (improvement) from Baseline to Week 16 ≥20% (percentage change) and ≥1 (absolute change) in the PGA-OA (note: from the 5 point Likert scale, any change of ≥1 will also be a change of ≥20%).</td></tr>
<tr><td>Patient Daily / Weekly Pain Assessment</td><td>Diary assessments of pain in the index joint were completed by the patients at approximately the same time each day (or each week). Average pain over the preceding 24 hours was assessed using an 11-point NRS ranging from zero (no pain) to 10 (worst pain or worst possible pain) captured through interactive response technology.</td></tr>
<tr><td colspan="2">NRS = Numerical Rating Scale</td></tr>
</table>

4.3.6. Statistical Methods and Definitions

Each study had a pre-specified analysis plan to control type I error at 5% in comparing tanezumab groups to placebo or NSAID groups. This applied to co-primary and key secondary endpoints and used step-down or graphical testing procedures.

Efficacy analyses were carried out on the intent-to-treat (ITT) population defined as all randomized patients who received at least 1 dose of IV or SC study medication (either tanezumab or matching placebo).

An analysis of covariance model (ANCOVA) was used for the co-primary endpoints and other continuous variables (including for subgroup analysis) with a model term for study added for pooled analyses of multiple studies. Missing data were handled by a multiple imputation approach, based on the patient's baseline score (for missing data resulting from discontinuation due to death, adverse events or insufficient clinical response) or last score (for all other reasons). For binary endpoints such as responder rates, a logistic regression model was used with missing data imputed by the mixed baseline observation carried forward/last observation carried forward (BOCF/LOCF) approach.

A modified treatment-policy estimand was applied in the integrated efficacy analysis. All data collected for efficacy assessments were included in the main analysis for the co-primary endpoints, regardless of whether rescue medication was used. Specifically, data collected within 8 weeks (per pre-defined window rules) after treatment discontinuation were included and data collected more than 8 weeks after treatment discontinuation (per a predefined windowing rule) were treated as missing.

To aid in assessing consistency with the overall effect, efficacy in pre-defined standard subgroups was analyzed using pooled data from placebo-controlled Studies 1056, 1057, 1011, and 1014. Pooling compatibility was based on the studies having a similar design, similar intended duration of treatment (16 to 24 weeks) of tanezumab monotherapy, a placebo control, a 16-week or 24-week primary efficacy endpoint, and subjects with similar baseline characteristics. The subgroup analysis was based on the 3 co-primary endpoints and used the same approach as for the overall analyses of the co-primary endpoints.

For subgroup analysis, patients with the most severe symptoms were defined as those with a baseline WOMAC Pain Subscale score ≥7, WOMAC Physical Function Subscale score ≥7 and PGA-OA assessment of "Poor" or "Very Poor.

Note that patients who received tanezumab 2.5 mg/5 mg in Study 1056 were included in the tanezumab 5 mg treatment group for the pooled data presentations.

4.4. Efficacy Results

4.4.1. Placebo-Controlled SC Studies 1056 and 1057

Studies 1056 and 1057 provided the substantive evidence of efficacy and were of similar design except for a longer treatment duration and later efficacy analysis point in Study 1057 (24 weeks versus 16 weeks in accordance with European Medicines Agency guidelines), the tanezumab dose groups (2.5 mg and 5 mg in Study 1057, versus 2.5 mg and 2.5 mg to 5 mg titration in Study 1056), and the region (North America for Study 1056, and Europe and Japan for Study 1057).

4.4.1.1. Study Schematic

Figure 2. Schematic Showing Design of Study 1056

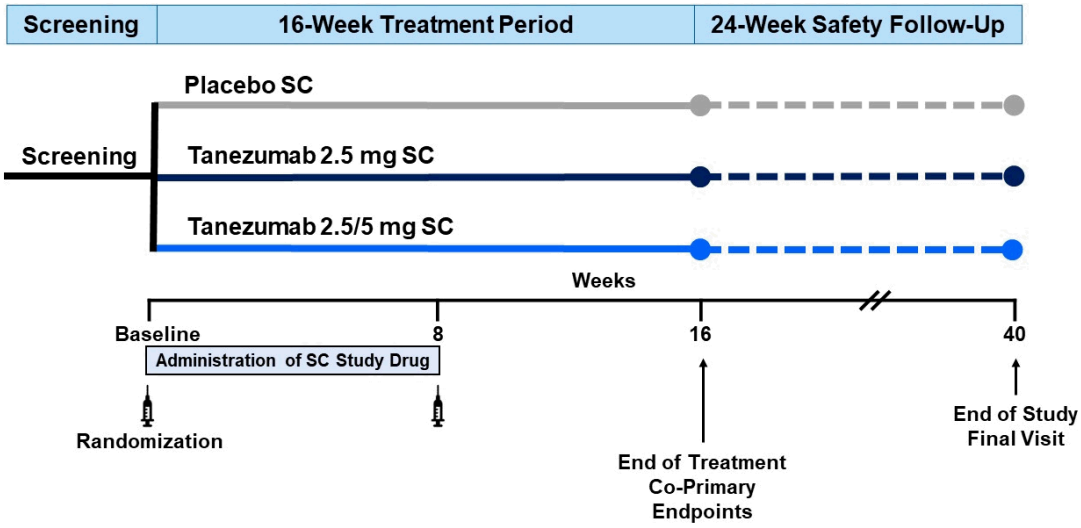
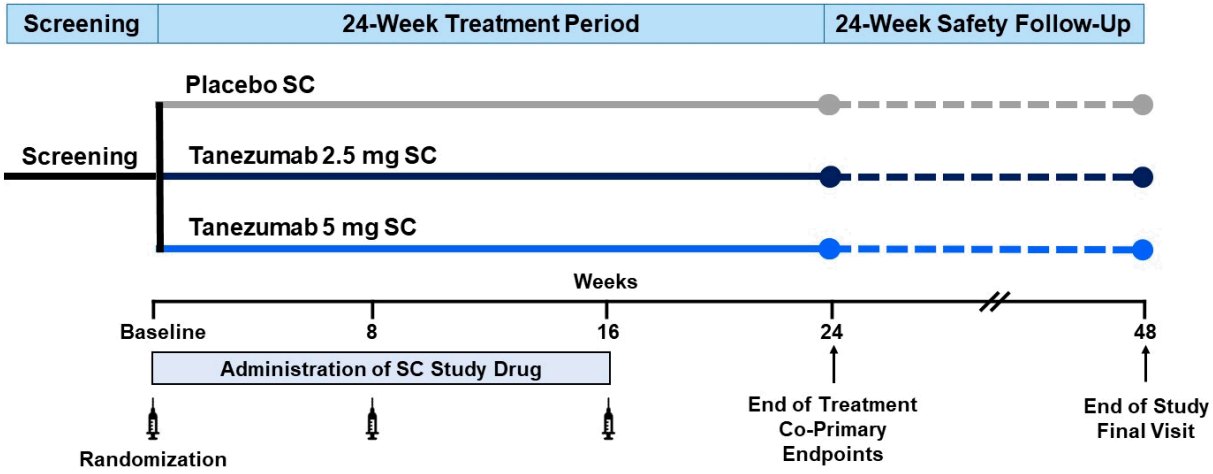


Figure 3. Schematic Showing Design of Study 1057



4.4.1.2. Study Population

4.4.1.2.1. Patients' Prior Experience of Analgesic Medications for OA

Reflecting the intended patient population, patients in Studies 1056 and 1057 had failed to respond to other analgesics, or were unable to tolerate or could not take these analgesics due to contraindications, or were specifically unwilling to take opioid medications.

- Patients in Studies 1056 and 1057 had prior inadequate pain relief with acetaminophen, and most (approximately 90%) had prior inadequate pain relief with NSAIDs (with the remainder either intolerant of, or with a contraindication for NSAIDs) (Table 4).

- The qualifying opioid pain medication in Study 1056 was predominantly a non-tramadol opioid (76% versus 32% tramadol), whereas in Study 1057 the reverse was seen (75% tramadol versus 34% non-tramadol) (Table 4). This likely reflects the different region in which these studies were conducted. The difference in prescribing cultures, regulations, and healthcare systems of those regions[78,79] may favor the prescription of tramadol rather than other opioids in Europe and Japan.[34,39,80-82] Note that patients may have qualified with non-tramadol opioid and/or tramadol so totals do not add up to 100%.

Combinations of reasons for protocol qualifying failed medications in Studies 1056 and 1057 included the following:

- Most commonly, patients indicated inadequate pain relief for all classes of medications: 42% in Study 1056 and 54% in Study 1057.

- Approximately 4-5% of patients had a contraindication to NSAIDs, opioids, and/or tramadol.

- Approximately 20-26% of patients did not have a contraindication to a medication but were unable to tolerate NSAIDs, opioids, and/or tramadol.

- The percentage of patients who were unwilling to take an opioid was 37% in Study 1056 and 16% in Study 1057.

The proportion of patients taking each class of medication and the reason(s) that each of these treatments for OA was unacceptable was balanced between treatment groups in the individual studies (data not shown).

Table 4. Protocol Qualifying Reason for Prior Drug Treatments for OA in Studies 1056 and 1057

	Study 1056 N=696 n (%)	Study 1057 N=849 n (%)
Number (%) of patients with any qualifying pain medication	696 (100)	849 (100)
Acetaminophen	694 (99.7)	849 (100)
Inadequate Pain Relief	693 (99.6)[a]	849 (100)
Intolerability	1 (0.1)	0
NSAID – Oral	695 (99.9)	848 (99.9)
Contraindication	24 (3.4)	34 (4.0)
Inadequate Pain Relief	631 (90.7)	741 (87.3)
Intolerability	61 (8.8)	95 (11.2)
Opioids	531 (76.3)	291 (34.3)
Contraindication	9 (1.3)	2 (0.2)
Inadequate Pain Relief	185 (26.6)	98 (11.5)
Intolerability	94 (13.5)	57 (6.7)
Unwilling to take	257 (36.9)	136 (16.0)
Tramadol	223 (32.0)	633 (74.6)
Contraindication	1 (0.1)	1 (0.1)
Inadequate Pain Relief	180 (25.9)	455 (53.6)
Intolerability	42 (6.0)	172 (20.3)
Unwilling to take	NA	11 (1.3)

ITT population
Totals for the number of Patients at a higher level are not necessarily the sum of those at the lower levels since a patient may report two or more different medications within the higher level category.
a. Three (3) patients were not assessed for adequacy of pain relief to acetaminophen; one of these patients was recorded as unable to tolerate acetaminophen.

In Studies 1056 and 1057, 65 to 70% patients continued taking their prior analgesic medication(s) during the Screening Period, as permitted by the protocols. These medication(s) were to be discontinued beginning at least 48 hours prior to the initial pain assessment period (the seven days prior to Baseline). Of note, the mean WOMAC Pain score either did not change or increased slightly from Screening to Baseline across the subgroups of patients who: a) were using protocol-qualifying medications during the Screening Period or b) were not taking any OA medications due to inadequate pain relief, intolerability, contraindication, or unwillingness to take analgesics. This observation corroborates the reporting by patients that these analgesics were not providing adequate pain relief.

4.4.1.2.2. Demographic Characteristics

The age and gender balance of patients in Studies 1056 and 1057 were broadly similar and reflected OA epidemiology and risk factors; some differences in race, ethnicity and region resulted in a broad range of typical OA patients across the two studies.

- The mean age of patients across Studies 1056 and 1057 was approximately 63 years with a good representation of elderly patients aged ≥65 years and very elderly patients aged ≥75 years (Table 5). The proportion of females (67%) was higher than males in both studies.

- Although the majority of patients across Studies 1056 and 1057 were White and Non-Hispanic, there was representation of Black or African American patients (in Study 1056), Asian patients (predominantly in Study 1057), and Hispanic patients (predominantly in Study 1056).

Demographic characteristics were well balanced across treatment groups in the individual studies (data not shown).

Table 5. Baseline Demographic Characteristics in Studies 1056 and 1057

Demographic Characteristic		Study 1056 (N=696) n(%)	Study 1057 (N=849) n(%)
Age (years)	<18	0	0
	18-44	29 (4.2%)	20 (2.4%)
	45-64	425 (61.1%)	371 (43.7%)
	≥65	242 (34.8%)	458 (53.9%)
	≥75	57 (8.2%)	122 (14.4%)
	Mean (SD)	60.8 (9.6)	64.9 (9.4)
Gender	Male	243 (34.9%)	262 (30.9%)
	Female	453 (65.1%)	587 (69.1%)
Race	White	504 (72.4%)	740 (87.2%)
	Black or African American	153 (22.0%)	0
	Asian	26 (3.7%)	106 (12.5%)
	Other/Unknown	13 (1.9%)	3 (0.4%)
Ethnicity	Hispanic or Latino	119 (17.1%)	48 (5.7%)
	Not Hispanic or Latino	577 (82.9%)	801 (94.3%)
Region	North America	696 (100.0%)	0
	Europe	0	743 (87.5%)
	Japan	0	106 (12.5%)

ITT population

4.4.1.2.3. Baseline Disease Characteristics

As expected per the study eligibility criteria, patients enrolled in Studies 1056 and 1057 had moderate/severe pain and functional impairment before enrollment (Table 6).

- The patients in Study 1057 had a lower WOMAC Pain score at baseline compared with patients in Study 1056. However, there was good representation of patients with the most severe symptoms in both studies, and most patients had a KL Grade of 3 or 4 in the index joint.

- Patients in both studies typically had long-standing disease with a mean duration of approximately 8 years.

- The index joint was most often a knee in Studies 1056 and 1057 (84.1%), and approximately 80% patients had OA in more than one joint (Table 30).

Baseline disease characteristics were similar across treatment groups in the individual studies (data not shown).

Table 6. Baseline Disease Characteristics in Studies 1056 and 1057

Baseline Disease Characteristic		Study 1056 (N=696) n(%)	Study 1057 (N=849) n(%)
Index Joint	Hip	102 (14.7%)	144 (17.0%)
	Knee	594 (85.3%)	705 (83.0%)
KL Grade of Index Joint	0	0	2 (0.2%)
	1	1 (0.1%)	0
	2	184 (26.5%)	166 (19.6%)
	3	304 (43.7%)	375 (44.2%)
	4	206 (29.6%)	306 (36.0%)
Disease Duration (Years)	Mean (SD)	9.3 (8.4)	7.5 (7.0)
WOMAC Pain (0-10 NRS)	Mean (SD)	7.2 (1.2)	6.6 (0.9)
WOMAC Physical Function (0-10 NRS)	Mean (SD)	7.3 (1.1)	6.7 (0.9)
PGA-OA (1 -5 Likert Scale)	Mean (SD)	3.5 (0.6)	3.6 (0.6)
Severe Cohort[a]	Yes	216 (31.0%)	157 (18.5%)

ITT population
a. The severe cohort was defined as patients with a baseline WOMAC Pain score ≥ 7, WOMAC Physical Function score ≥ 7 and PGA-OA = "Poor" (score of 4) or "Very Poor" (score of 5)

4.4.1.2.4. Disposition

A large majority (approximately 90%) of patients in Studies 1056 and 1057 completed their tanezumab treatment (Table 7). The most common reasons for discontinuation were 'insufficient clinical response', 'withdrawal by subject', and 'other'.

The incidence of withdrawal from treatment due to insufficient clinical response through the end of treatment was lower for patients treated with tanezumab compared with placebo for both tanezumab doses in both studies (Table 7); this difference versus placebo was significant for tanezumab 2.5/5 mg in Study 1056 ($p \leq 0.05$) and tanezumab 2.5 mg and 5 mg in Study 1057 ($p \leq 0.01$).

Table 7. Reasons for Treatment Discontinuation in Studies 1056 and 1057

Study 1056	Placebo (N=232) n (%)	Tanezumab 2.5 mg (N=231) n(%)	Tanezumab 2.5/5 mg (N=233) n(%)
All Reasons	**40 (17.2)**	**23 (10.0)**	**24 (10.3)**
Adverse Event	3 (1.3)	1 (0.4)	3 (1.3)
Death	0	0	0
Lost to Follow-Up[a]	3 (1.3)	2 (0.9)	3 (1.3)
Withdrawal By Subject[b]	8 (3.4)	6 (2.6)	3 (1.3)
Insufficient Clinical Response	13 (5.6)	6 (2.6)	4 (1.7)
Protocol Violation	1 (0.4)	2 (0.9)	0
Other[c]	12 (5.2)	6 (2.6)	11 (4.7)
Study 1057	**Placebo (N=282) n(%)**	**Tanezumab 2.5 mg (N=283) n(%)**	**Tanezumab 5 mg (N=284) n(%)**
All Reasons	**44 (15.6)**	**26 (9.2)**	**29 (10.2)**
Adverse Event	9 (3.2)	7 (2.5)	4 (1.4)
Death	0	0	2 (0.7)
Lost to Follow-Up[a]	0	1 (0.4)	0
Withdrawal By Subject [b]	14 (5.0)	13 (4.6)	17 (6.0)
Insufficient Clinical Response	18 (6.4)	2 (0.7)	3 (1.1)
Protocol Violation	3 (1.1)	2 (0.7)	1 (0.4)
Other[c]	0	1 (0.4)	2 (0.7)

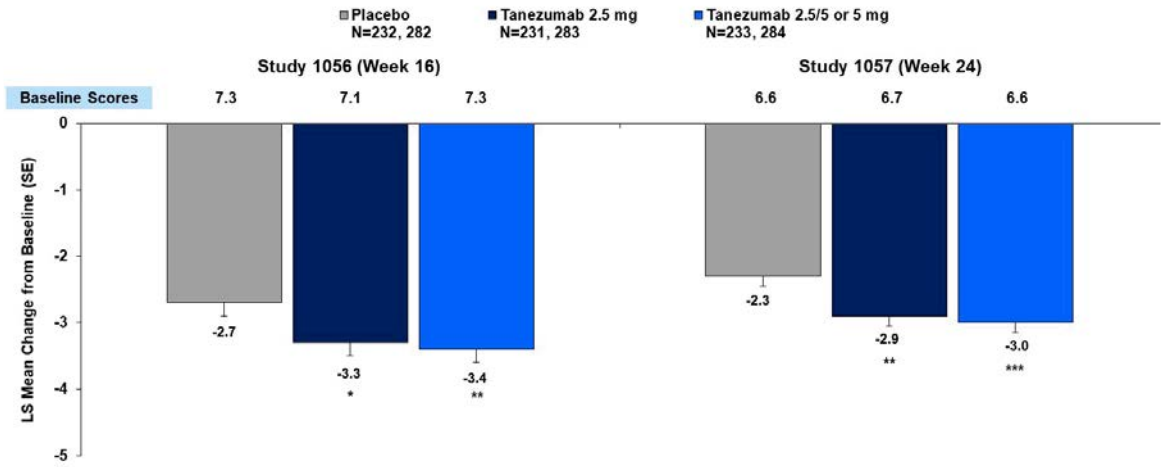
ITT population
The incidences of withdrawal by reason were determined through completion of the 16-week treatment period (Study 1056) or through completion of the 24-week treatment period (Study 1057).
a. Patient failed to return to the study site and repeated attempts to contact them were unsuccessful.
b. Patient no longer interested in participating in the study for personal reasons.
c. Primary reason not one of the other categories (eg, a move, or change in life or work circumstances).

4.4.1.3. Results for Co-Primary Endpoints

Tanezumab 2.5 mg administered SC every 8 weeks provides consistent and clinically important improvement in pain and function.

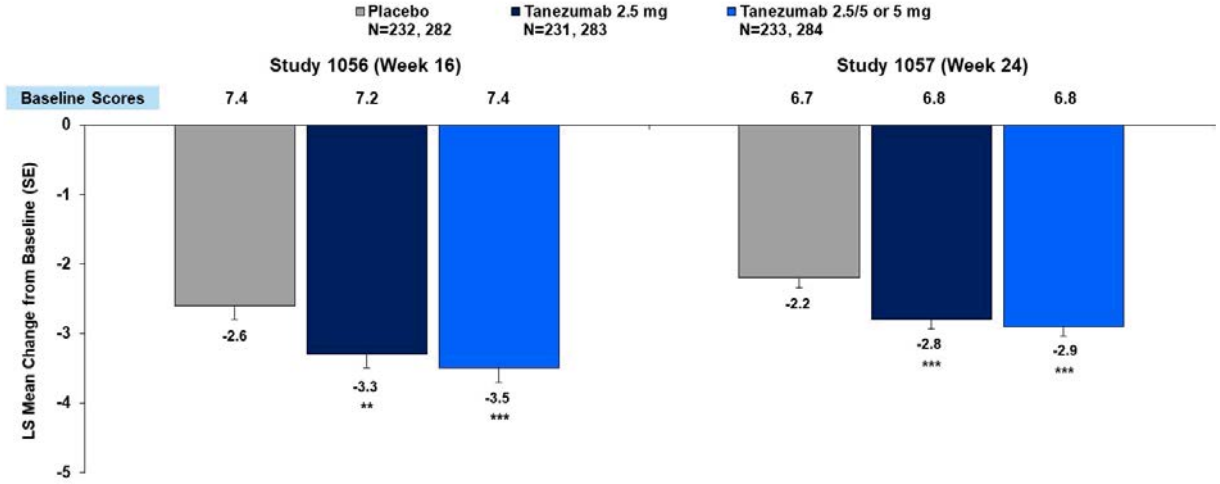
- In Study 1056, tanezumab 2.5 mg and 2.5 mg/5 mg resulted in significant improvement over placebo at Week 16 for all three co-primary endpoints (Figure 4, Figure 5, and Figure 6).
- In Study 1057, tanezumab 2.5 mg resulted in significant improvement over placebo at Week 24 for two of the three co-primary endpoints (WOMAC Pain and WOMAC Physical Function). Tanezumab 5 mg resulted in significant improvement over placebo for all three co-primary endpoints (Figure 4, Figure 5, and Figure 6).
- Both tanezumab doses resulted in significant improvement over placebo for all three co-primary endpoints at Week 16 in Study 1057 ($p<0.05$; data not shown).

Figure 4. Co-Primary Endpoints: WOMAC Pain Subscale - Change From Baseline at Week 16 in Study 1056 and Week 24 in Study 1057



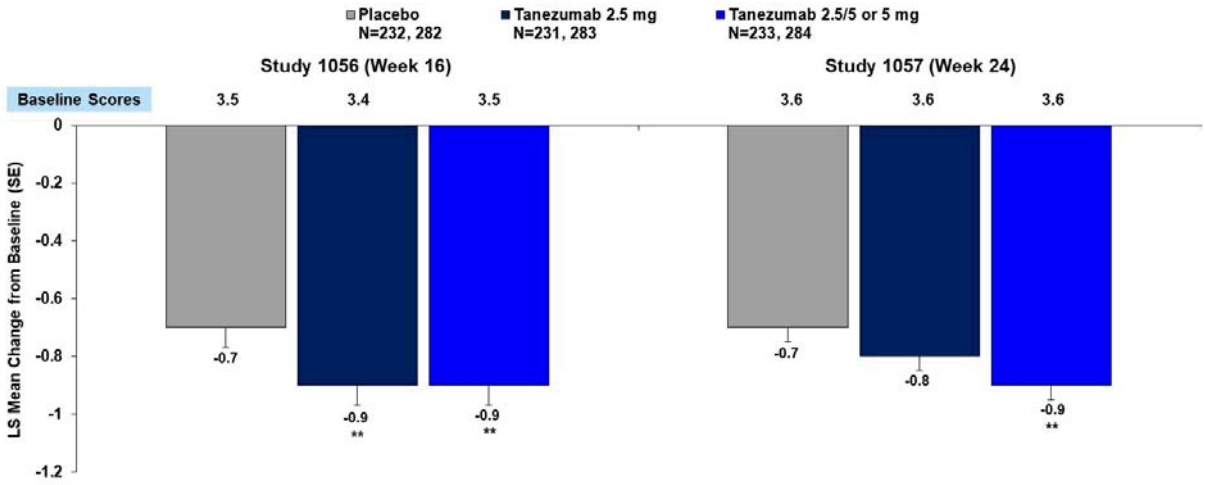
ITT population, Multiple Imputation; *p≤0.05, **p≤0.01, ***p≤0.001 versus placebo

Figure 5. Co-Primary Endpoints: WOMAC Physical Function Subscale - Change From Baseline at Week 16 in Study 1056 and Week 24 in Study 1057



ITT population, Multiple Imputation; *p≤0.05, **p≤0.01, ***p≤0.001 versus placebo

Figure 6. Co-Primary Endpoints: PGA-OA - Change From Baseline at Week 16 in Study 1056 and Week 24 in Study 1057



ITT population, Multiple Imputation; *p≤0.05, **p≤0.01, ***p≤0.001 versus placebo

4.4.1.4. Results for Key Secondary and Additional Endpoints

Approximately half of patients treated with tanezumab 2.5 mg SC demonstrated a 50% or greater reduction in the WOMAC Pain Subscale (a 'substantial improvement'), defined as a key secondary endpoint (Figure 7).

- 55% and 45% patients treated with tanezumab 2.5 mg demonstrated ≥50% improvement in the WOMAC Pain Subscale from baseline to Week 16 in Study 1056 and Week 24 in Study 1057, which was significantly greater than the proportion in the placebo group (approximately 36%; p=0.0011 and p=0.0023 respectively).

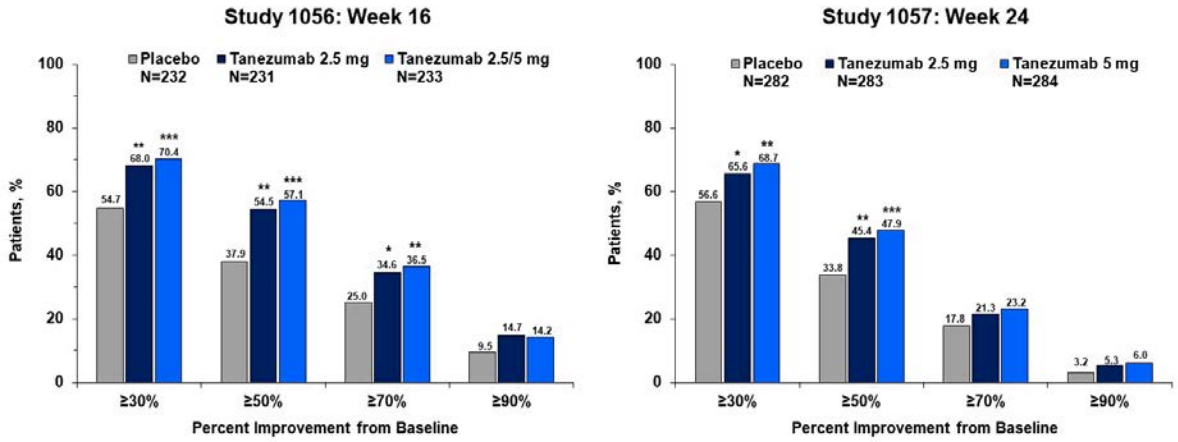
The proportions of patients with ≥30%, ≥70% and ≥90% improvement in the WOMAC Pain Subscale were additional secondary endpoints (Figure 7).

- Approximately 67% patients treated with tanezumab 2.5 mg, demonstrated ≥30% improvement in the WOMAC Pain Subscale from baseline to Week 16 in Study 1056 and Week 24 in Study 1057, which was significantly greater than the proportion in the placebo group (approximately 56%; p=0.0065 and p=0.0201 respectively).

An improvement from baseline in the WOMAC Pain Subscale of ≥30% was considered to be clinically meaningful or 'moderately important improvement', and ≥50% was considered to be a 'substantial improvement' based on published definitions.[83]

Note that key secondary endpoints in Study 1057 could not be formally tested per the pre-specified graphical testing procedure since tanezumab 2.5 mg was not significantly different from placebo at Week 24 for all three co-primary endpoints. Results for these key secondary endpoints are presented based on nominal (unadjusted) p-values, as are results for other secondary endpoints. 'Significant' refers to a nominal p-value ≤0.05.

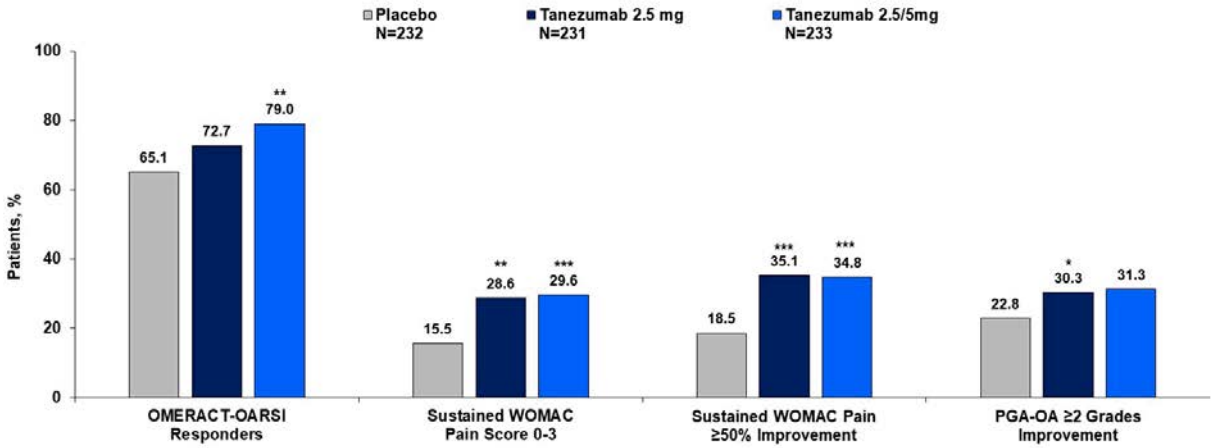
Figure 7. Categorical Change in WOMAC Pain From Baseline at Week 16 in Study 1056 and Week 24 in Study 1057



ITT population, Mixed BOCF/LOCF; *p≤0.05, **p≤0.01, ***p≤0.001 versus placebo

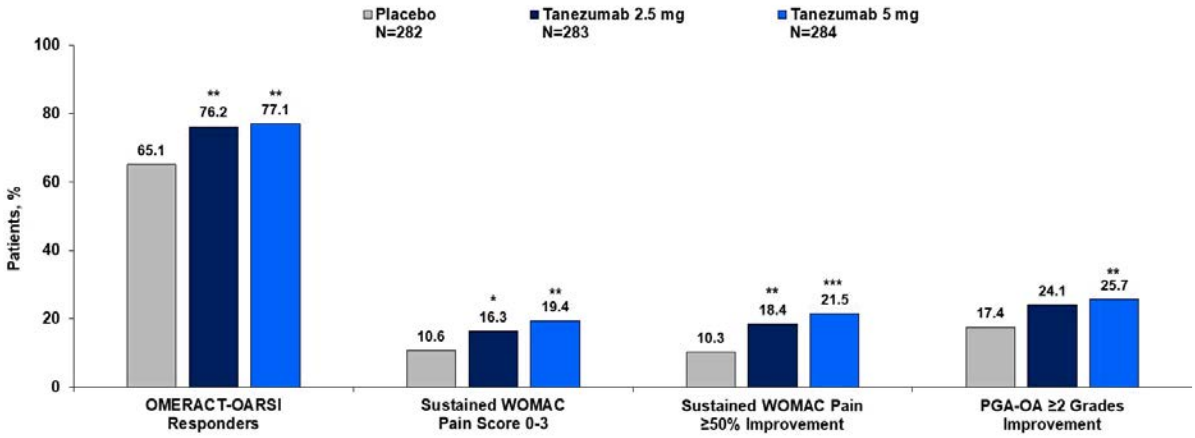
The results for co-primary and key secondary efficacy variables in Studies 1056 and 1057 were supported by results from additional categorical endpoints which also showed significant improvement with tanezumab over placebo Figure 8 and Figure 9 respectively. Sustained improvement in WOMAC pain was defined as a score of 0-3 or ≥50% reduction in score from Week 4 to Week 16 (Study 1056) or Week 24 (Study 1057). OMERACT-OARSI response is a composite endpoint defined in Table 3.

Figure 8. Additional Categorical Endpoints at Week 16 in Study 1056: OMERACT-OARSI, Sustained WOMAC Pain Response, and PGA-OA ≥2 Grades Improvement



ITT population, Mixed BOCF/LOCF; *p≤0.05, **p≤0.01, ***p≤0.001 versus placebo

Figure 9. Additional Categorical Endpoints at Week 24 in Study 1057: OMERACT-OARSI, Sustained WOMAC Pain Response, and PGA-OA ≥2 Grades Improvement



ITT population, Mixed BOCF/LOCF; *p≤0.05, **p≤0.01, ***p≤0.001 versus placebo

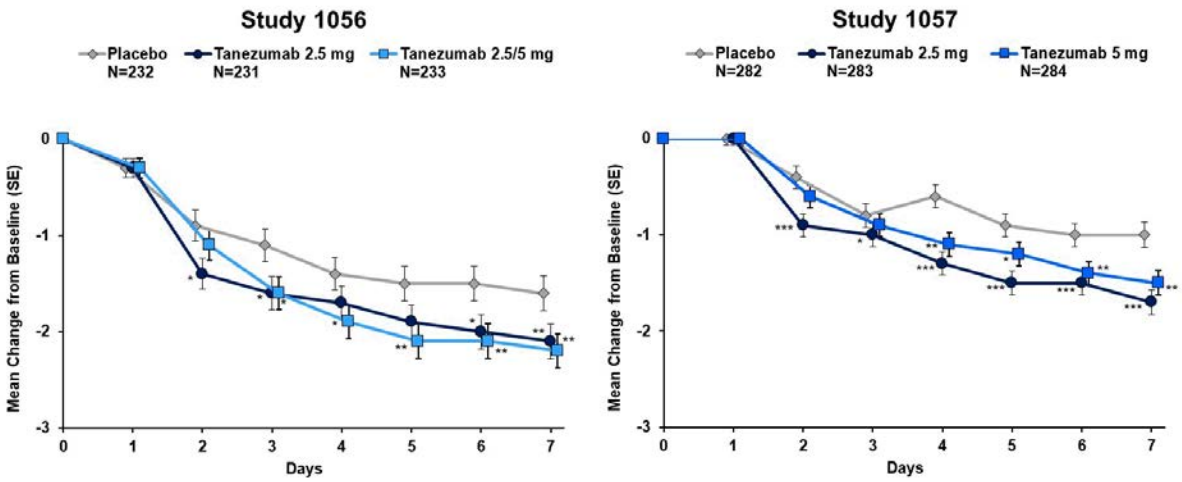
4.4.1.5. Onset of Efficacy Over Days 1 to 7

The onset of pain relief was within the first week after the initial dose of tanezumab 2.5 mg SC.

As WOMAC Pain, WOMAC Physical Function and PGA-OA were first assessed at Week 2, the onset of pain relief was assessed using daily pain diaries for Days 1 through 7 following the initial dose of study medication.

- Daily pain was significantly lower with tanezumab compared to placebo within one week of initiating therapy in Studies 1056 and 1057 (Figure 10) with no indication of a significant difference in the onset of pain relief with different tanezumab doses. Note that in Study 1056, both treatment groups received tanezumab 2.5 mg over this time period.

Figure 10. Onset of Efficacy: Daily Average Pain Diaries – Change From Baseline Over Days 1 to 7 in Studies 1056 and 1057



ITT population, Multiple Imputation; *p≤0.05, **p≤0.01, ***p≤0.001 versus placebo

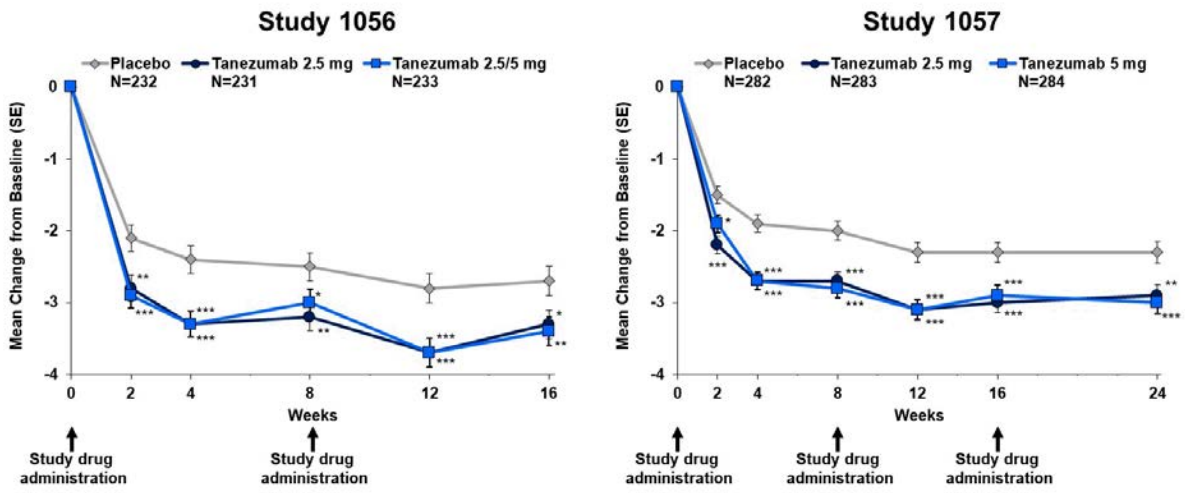
4.4.1.6. Efficacy Across 8-week Dose Intervals

Reduction in pain and improvement in function with tanezumab 2.5 mg SC was sustained throughout the 8-week injection cycle.

- Tanezumab provided significant reduction in WOMAC Pain versus placebo from Week 2 (first post-dose assessment) or Week 4 (second post-dose assessment) following treatment initiation in Studies 1056 and 1057 (Figure 11). Responses typically reached a maximum within 4 weeks of the first dose of tanezumab, were largely maintained up to re-administration at Week 8. There was some small fluctuation in response level that was consistent with the 8-week dose interval and was not considered to be clinically meaningful.

Results for WOMAC Physical Function, PGA-OA, and Weekly Average Pain Score were consistent with these data for WOMAC Pain (data not shown).

Figure 11. Efficacy Time Course: WOMAC Pain Subscale – Change from Baseline Across the 8-Week Dosing Interval in Studies 1056 and 1057



ITT population, Multiple Imputation; *p≤0.05, **p≤0.01, ***p≤0.001 versus placebo

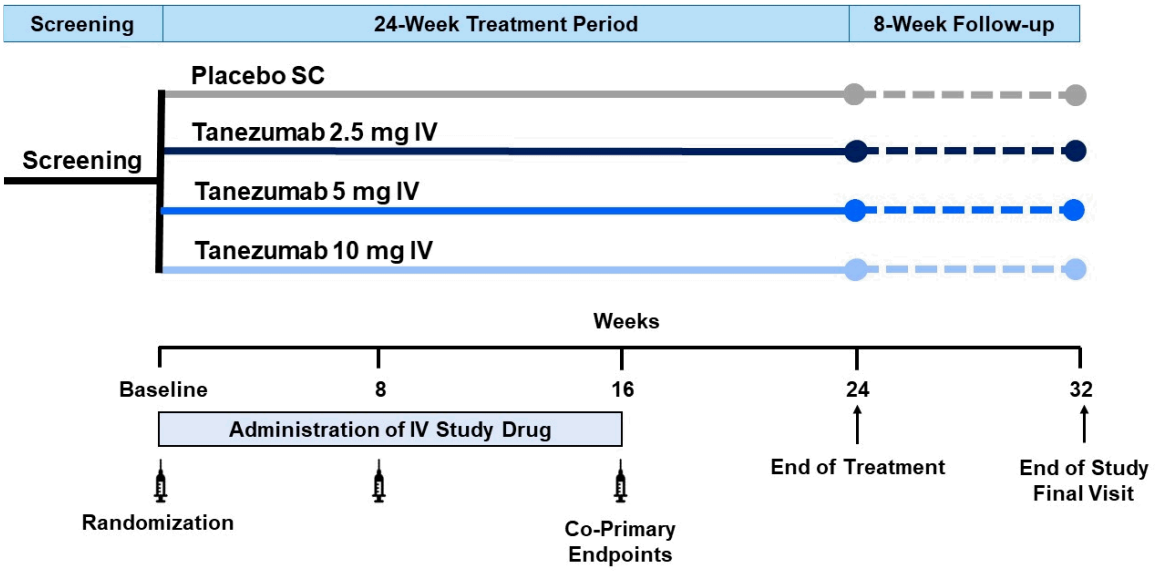
The selection of an 8-week dosing interval was further supported by PK/PD model based predictions (Section 4.4.7). Alternative dose intervals were not tested in the clinical studies.

4.4.2. Placebo-Controlled IV Studies 1011 and 1014

Studies 1011 and 1014 provide additional evidence of efficacy versus placebo for tanezumab 2.5 mg IV. They were 24-week, placebo controlled studies identical to each other apart from the required index joint (knee versus hip). Studies 1011 and 1014 (in addition to Studies 1015 and 1018) were parent studies for the long-term uncontrolled extension Study 1016.

4.4.2.1. Study Schematic

Figure 12. Schematic Showing Design of Studies 1011 and 1014



4.4.2.2. Study Population

Patients in Studies 1011 and 1014 had moderate to severe OA and limited treatment options, with non-opioid analgesics from one or more classes ineffective or not appropriate (Section 4.3.2).

The baseline demographic characteristics of patients in Studies 1011 and 1014 were similar to each other and to Studies 1056 and 1057, and were well balanced across treatment groups. The mean age of patients in Studies 1011 and 1014 was approximately 62 years old with 40% patients aged ≥65 years and 12% aged ≥75 years; 61% patients were female, 86% were White, 11% were Black or African American, and 91% were non-Hispanic. Both studies were conducted in North America.

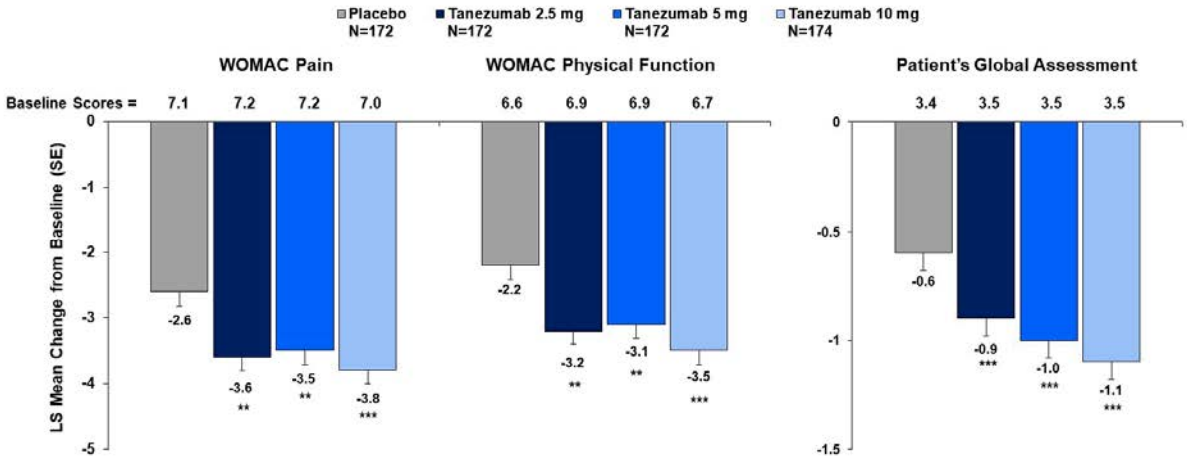
The baseline disease severity characteristics of patients in Studies 1011 and 1014 were also similar to each other and were well balanced across treatment groups. The baseline WOMAC Pain, WOMAC Physical Function, and PGA-OA scores in Studies 1011 and 1014 (approximately 7.2, 6.8, and 3.5 respectively), and the proportion of patients with the most severe OA symptoms (26%) were similar to those in Studies 1056 and 1057. However, a lower proportion of patients in Studies 1011 and 1014 had the most severe radiographic OA in the index joint (KL Grade 4; 16%) compared with patients in Studies 1056 and 1057 (33%). Reflecting inclusion criteria, the index joint was a knee in all patients in Study 1011, and a hip in all patients in Study 1014.

The overall rate of discontinuation from treatment was higher in Studies 1011 and 1014 (28% in tanezumab treatment groups and 51% in the placebo group) compared with Studies 1056 and 1057 (10% in tanezumab treatment groups and 16% in the placebo group). However, like Studies 1056 and 1057, the primary reason for discontinuation in Studies 1011 and 1014 was insufficient clinical response, with a lower incidence in the tanezumab treatment groups (17%) compared to the placebo group (42%); this difference versus placebo was significant for all tanezumab doses in Studies 1011 and 1014 ($p<0.01$).

4.4.2.3. Results for Co-primary Endpoints

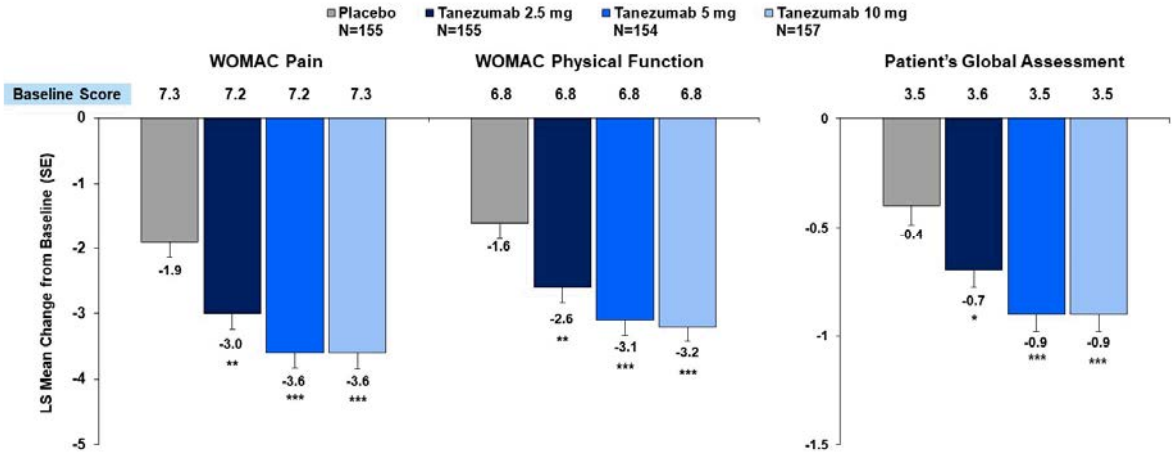
In Studies 1011 and 1014, tanezumab 2.5 mg, 5 mg and 10 mg IV were statistically superior to placebo at Week 16 for all three co-primary endpoints (Figure 13 and Figure 14).

Figure 13. Co-Primary Endpoints: Change From Baseline at Week 16 in Study 1011



ITT population, Multiple Imputation; *p≤0.05, **p≤0.01, ***p≤0.001 versus placebo

Figure 14. Co-Primary Endpoints: Change From Baseline at Week 16 in Study 1014



ITT population, Multiple Imputation; *p≤0.05, **p≤0.01, ***p≤0.001 versus placebo

Although the pre-specified analysis for Studies 1011 and 1014 was Week 16, data are also available for Week 24 in these studies. All three tanezumab doses resulted in significant improvement over placebo in WOMAC Pain and WOMAC Physical Function at Week 24 in both studies. For PGA-OA at Week 24, the treatment difference versus placebo reached significance for tanezumab 5 mg in Study 1014 and for tanezumab 2.5 mg and 10 mg in Study 1011, but not for tanezumab 2.5 mg in Study 1014 (data not shown).

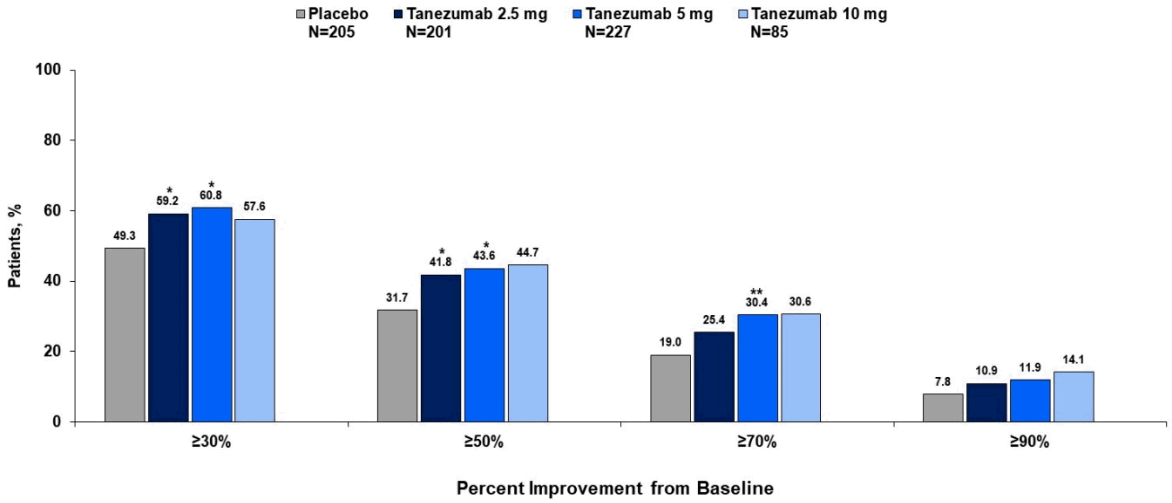
4.4.3. Subgroup Analysis in Placebo-Controlled Studies 1056, 1057, 1011, and 1014

Pooled data from placebo-controlled studies (Studies 1056, 1057, 1011 and 1014) were used for subgroup analyses to maximize the number of patients per subgroup and allow meaningful analysis. The treatment groups for the pooled placebo-controlled studies were

well balanced with respect to baseline demographics and disease characteristics (data not shown).

Tanezumab 2.5 mg provided significant relief compared to placebo for the subgroup of individuals with severe OA (as defined by a baseline WOMAC Pain Subscale score ≥7, WOMAC Physical Function Subscale score ≥7 and PGA-OA assessment of "Poor" or "Very Poor") for all three co-primary endpoints. The reduction in WOMAC pain score was clinically significant as shown by the significantly higher percent of patients with ≥30% and ≥50% improvement with tanezumab versus placebo (Figure 15).

Figure 15. Categorical Change in WOMAC Pain From Baseline at Week 16 in Patients With Severe OA: Studies 1011, 1014, 1056 and 1057 Pooled.



ITT Population; Mixed BOCF/LOCF; *p≤0.05, **p≤0.01, ***p≤0.001 versus placebo

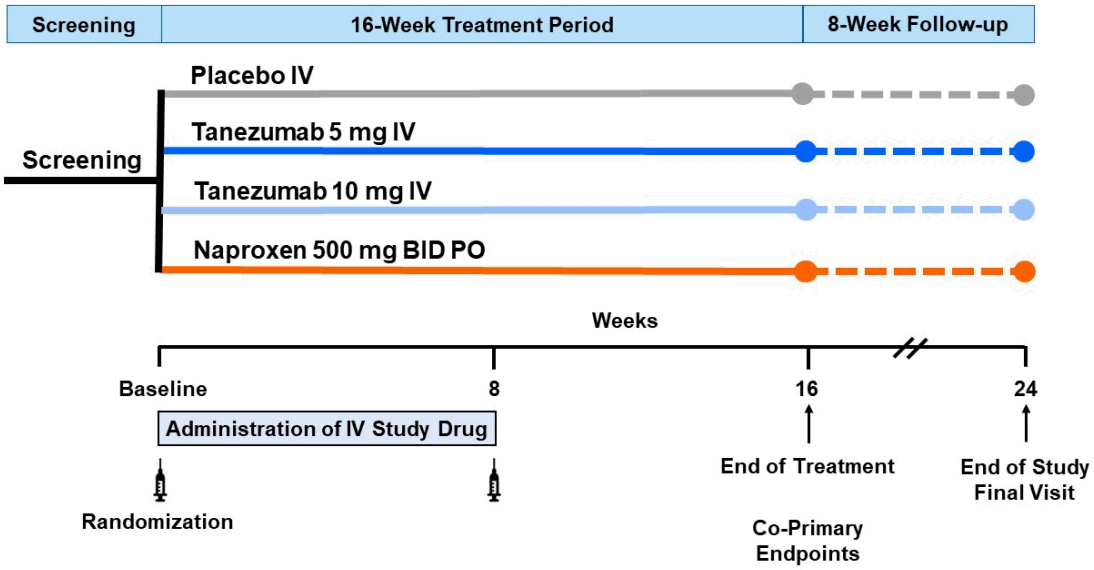
Tanezumab 2.5 mg also provided significant improvement compared to placebo for WOMAC Pain irrespective of gender, age (including the elderly aged ≥65 years), BMI category ≥25 kg/m^2, index joint (hip or knee), disease duration, baseline pain and function, overall disease severity, baseline KL grade, and region (North America, Europe, or Japan). Tanezumab 2.5 mg did not provide significant improvement compared to placebo in other subgroups with smaller sample sizes and/or high placebo responses (eg, male patients aged ≥65 years, BMI <25 kg/m^2, Black race, and Hispanic ethnicity). The results for WOMAC Physical Function were consistent with those for the WOMAC Pain Subscale, and results for PGA-OA were generally consistent but with some minor variations.

4.4.4. Supportive IV Studies 1015 and 1018

Studies 1015 and 1018 provide supportive evidence of tanezumab efficacy for the 5 mg and 10 mg IV doses versus placebo and naproxen, although they did not include the tanezumab 2.5 mg IV dose. They are included here because (in addition to Studies 1011 and 1014) they were parent studies for the long-term uncontrolled extension Study 1016. They were 16-week placebo- and active-controlled studies differing by index joint only (knee versus knee or hip). The primary objective for both studies was for statistical comparison versus placebo, with comparison to naproxen as a secondary objective.

4.4.4.1. Study Schematic

Figure 16. Schematic Showing Design of Studies 1015 and 1018



4.4.4.2. Study Population

Like the other studies, patients in Studies 1015 and 1018 had moderate to severe OA (Section 4.3.2). The baseline demographic and disease severity characteristics, overall rate of discontinuation, and reasons for discontinuation for patients in Studies 1015 and 1018 were similar to each other and to Studies 1011 and 1014.

The mean age of patients in Studies 1015 and 1018 was approximately 60 years, with 34% patients aged ≥65 years and 8% aged ≥75 years; 62% patients were female, 85% were White, 12% were Black or African American, and 81% were non-Hispanic. Both studies were conducted in North America.

The mean baseline WOMAC Pain, WOMAC Physical Function, and PGA-OA scores in Studies 1015 and 1018 were approximately 7.3, 6.9, and 3.4 respectively. These baseline scores, as well as the proportion of patients with the most severe OA symptoms (24%) and the proportion of patients with most severe radiographic OA in the index joint (KL Grade 4; 12%) were similar to those in Studies 1011 and 1014. Reflecting inclusion criteria, the index joint was a knee in all patients in Study 1015. Although patients with either hip or knee OA were permitted in Study 1018, 81% had a knee as an index joint.

The overall rate of discontinuation in Studies 1015 and 1018 (26% in tanezumab treatment groups) was similar to that in Studies 1011 and 1014. Also similarly to Studies 1011 and 1014, the primary reason for discontinuation in Studies 1015 and 1018 was insufficient clinical response, with a lower incidence in the tanezumab treatment groups (12%) compared to the placebo group (25%); this difference versus placebo was significant for both tanezumab doses in Studies 1015 and 1018 ($p<0.01$).

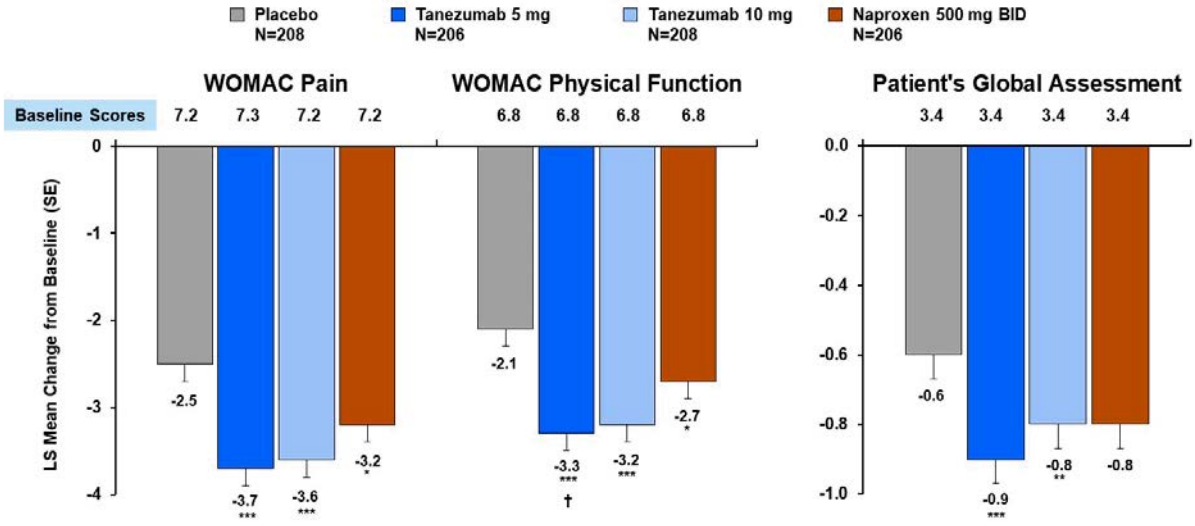
4.4.4.3. Results for Co-primary Endpoints

Tanezumab 5 mg and 10 mg IV were statistically superior to placebo at Week 16 for all three co-primary endpoints in Studies 1015 (Figure 17) and 1018 (Figure 18).

Naproxen 500 mg BID was statistically superior to placebo for WOMAC Pain and WOMAC Physical Function in Study 1015, but for none of the co-primary endpoints in Study 1018.

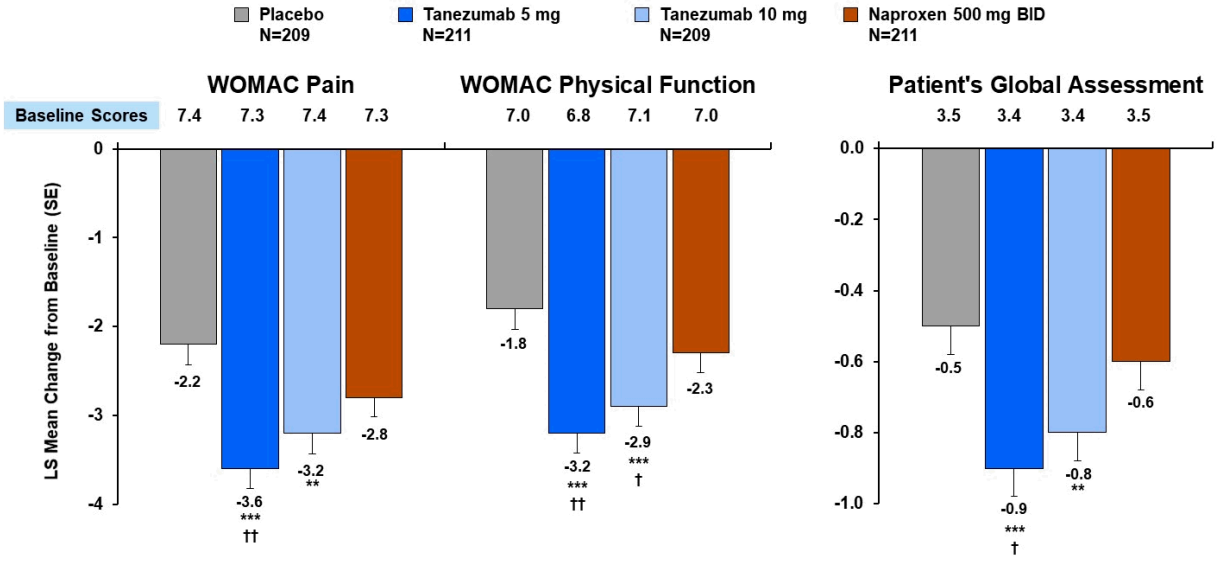
Improvements with tanezumab over naproxen were statistically significant with tanezumab 5 mg for WOMAC Physical Function in Study 1015 and for all 3 co-primary endpoints in Study 1018. However, improvements with tanezumab 10 mg over naproxen were not statistically significant in Study 1015, and were significant only for WOMAC Physical Function in Study 1018. Therefore, superiority could not be declared for tanezumab over naproxen due to the pre-specified step-down testing procedure in each study.

Figure 17. Co-Primary Endpoints: Change From Baseline at Week 16 in Study 1015



ITT population; Multiple Imputation
*p≤0.05; **p≤0.01; ***p≤0.001 versus placebo; †p≤0.05; ††p≤0.01; †††p≤0.001 versus naproxen

Figure 18. Co-Primary Endpoints: Change From Baseline at Week 16 in Study 1018



ITT population; Multiple Imputation
*p≤0.05; **p≤0.01; ***p≤0.001 versus placebo; †p≤0.05; ††p≤0.01; †††p≤0.001 versus naproxen

4.4.5. Long-Term Uncontrolled Extension Study 1016

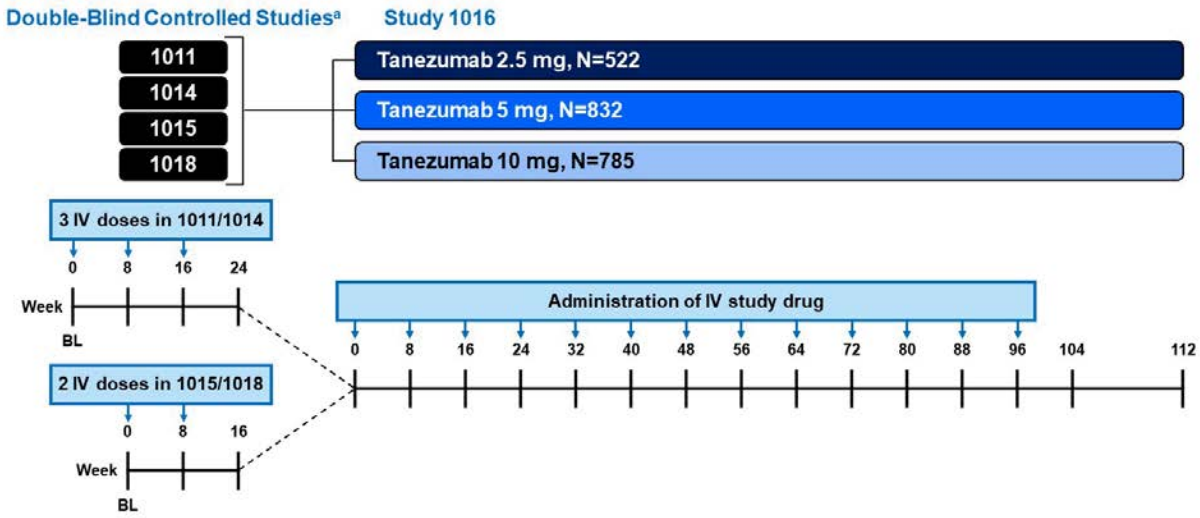
Study 1016 was an uncontrolled dose-blinded safety follow-up study to the Phase 3 OA parent Studies 1011, 1014, 1015, and 1018 and, in combination with the parent studies, provides long-term efficacy data. Patients who entered Study 1016 received 24 weeks of treatment in parent Studies 1011 and 1014, or 16 weeks of treatment in parent Studies 1015 and 1018 (tanezumab 2.5 mg, tanezumab 5 mg, tanezumab 10 mg, placebo or active comparator) followed by up to 104 weeks of tanezumab treatment in Study 1016.

Patients who received tanezumab in the parent study continued with the same dose of tanezumab in Study 1016. Patients who received placebo or comparator in the parent study were randomized to receive tanezumab 2.5 mg, 5 mg, or 10 mg in a 1:1:1 ratio in Study 1016.

Study 1016 was terminated early due to the partial clinical hold. As a result, more than 50% of patients were not treated at Week 40 and did not have WOMAC Pain Subscale data. Therefore, analyses beyond Week 32 were not performed.

4.4.5.1. Study Schematic

Figure 19. Schematic Showing Design of Extension Study 1016



a. Patients randomized to placebo or naproxen treatment in the double-blind parent study were re-randomized in a 1:1:1 ratio to tanezumab 2.5 mg , tanezumab 5 mg or tanezumab 10 mg treatment in the 1016 study. Patients randomized to tanezumab in the double-blind parent study continued tanezumab treatment at the same dose level in the 1016 study

4.4.5.2. Study Population

The population of Study 1016 consisted of patients with moderate to severe OA who were previously enrolled in Studies 1011, 1014, 1015, and 1018. Consequently, the demographic and baseline disease characteristics were consistent with those studies. Overall, a higher proportion of patients in Study 1016 had the knee as the index joint (ranging from 68.0% to 77.9% across the treatment groups) compared to the hip (22.1% to 32.0%).

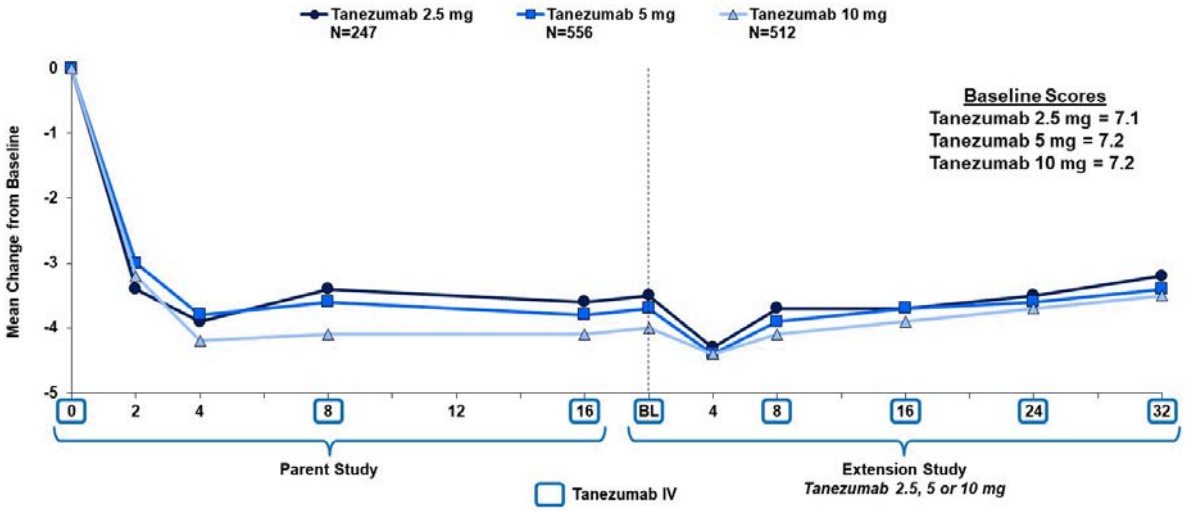
4.4.5.3. Results for Co-Primary Endpoints and WOMAC Pain Responder Analysis

Data from the long-term uncontrolled Study 1016 demonstrated persistent treatment effects through Week 32 for WOMAC Pain, WOMAC Physical Function, PGA-OA, WOMAC Responder Analysis, and additional secondary efficacy measures.

- The maximum change from baseline in WOMAC Pain was achieved by Week 4 in the parent studies. This level of response was maintained throughout the remainder of the parent studies, temporarily increased further on transferring to extension Study 1016, and was then largely maintained through Week 32 (Figure 20).

- The results for the change in the WOMAC Physical Function Subscale and PGA-OA were consistent with those for the WOMAC Pain Subscale (data not shown).

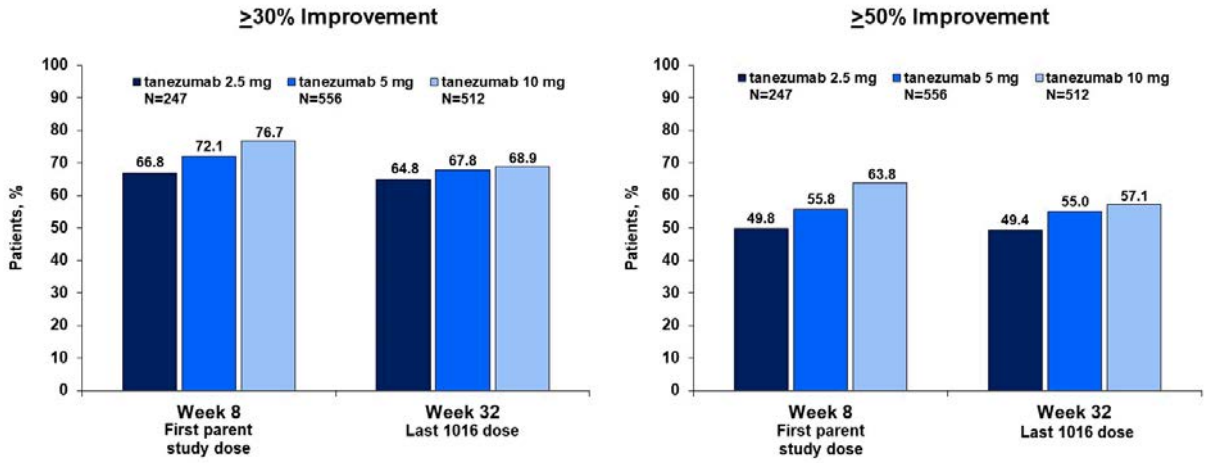
Figure 20. Long-Term Efficacy: Change From Baseline in WOMAC Pain Over Time in Double-Blind Parent Studies 1011, 1014, 1015, and 1018 Through Uncontrolled Extension Study 1016[a]



a. Patients treated with tanezumab in the parent study and continued to receive the same dose in Study 1016. ITT population; Multiple Imputation

Eight weeks after the first dose of tanezumab in the parent studies, a high percentage of patients treated with tanezumab showed ≥30% and ≥50% improvement from baseline in the WOMAC Pain Subscale (approximately 67% and 50% patients respectively for tanezumab 2.5 mg). This level of response was maintained through to Week 32 of the extension study (Figure 21). No clinically important differences among the tanezumab doses were evident over the extended duration of therapy.

Figure 21. Long-Term Efficacy: ≥30% and ≥50% Improvement From Baseline in WOMAC Pain at Week 8 in Double-Blind Parent Studies 1011, 1014, 1015, and 1018 and Week 32 in Uncontrolled Extension Study 1016[a]



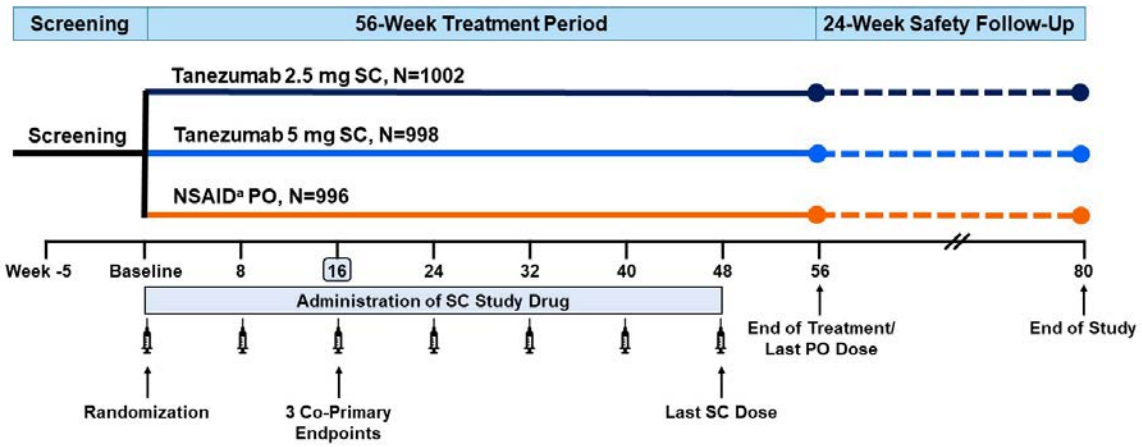
a. Patients treated with tanezumab in the parent study and continued to receive the same dose in Study 1016 ITT population; Mixed BOCF/LOCF

4.4.6. Long-Term Active-Controlled Study 1058

Study 1058 was designed primarily to assess the joint-related safety outcomes of tanezumab 2.5 mg or 5 mg SC versus oral NSAID treatment consisting of naproxen 500 mg BID, celecoxib 100 mg BID or prolonged release diclofenac 75 mg BID over 56 weeks of treatment. An assessment of comparative efficacy at Week 16 was subsequently added as a second primary study objective, even though the study design was suboptimal for efficacy comparisons.

4.4.6.1. Study Schematic

Figure 22. Schematic Showing Design of Study 1058



Telephone contact at Weeks 12, 20, 28, 36, 44, 52, 60, 68, 72 and 76
a. NSAID = celecoxib 100 mg BID, naproxen 500 mg BID or diclofenac extended release 75 mg BID

4.4.6.2. Study Population

4.4.6.2.1. Patient's Prior Experience of Analgesic Medications for OA

Per eligibility criteria (Section 4.3.2), the patient population in Study 1058 was required to be taking and tolerating NSAIDs and receiving at least some efficacy benefit. In addition, patients were required to have had an unsatisfactory experience with acetaminophen, opioids or tramadol, or be unwilling to take the medication in the case of opioids (Table 8).

Table 8. Protocol Qualifying Reason for Prior Drug Treatments for OA in Study 1058

	Study 1058 (N=2996) n (%)
Number (%) of subjects with any qualifying pain medication	2996 (100.0)
Acetaminophen	2995 (100)
NSAID - Oral	NA[a]
Opioids	2079 (69.4)
Contraindication	15 (0.5)
Inadequate Pain Relief	690 (23.0)
Intolerability	412 (13.8)
Unwilling to take	997 (33.3)
Tramadol	1328 (44.3)
Contraindication	9 (0.3)
Inadequate Pain Relief	893 (29.8)
Intolerability	426 (14.2)
Unwilling to take	1 (0.0)

ITT population
Totals for the number of Patients at a higher level are not necessarily the sum of those at the lower levels since subjects may report two or more different medications within the higher level category.
a. patients were required to be receiving and tolerating a stable therapeutic dose of NSAID prior to entering the study and through the screening period.

4.4.6.2.2. Demographic Characteristics

Study 1058 was conducted in 17 countries [most patients were enrolled at sites in the US (78.4%), Japan (6.7%), Ukraine (2.6%), or Brazil (2.2%)]. Overall, the patient demographic characteristics were similar to those in Studies 1056 and 1057, with some variation in racial balance and ethnicity largely reflecting the region in which the study was conducted (Table 9).

The treatment groups in Study 1058 were well balanced with respect to baseline demographic characteristics, disease characteristics, and protocol qualifying prior drug treatments for OA (data not shown).

Table 9. Baseline Demographic Characteristics in Study 1058

Demographic Characteristic		Study 1058 (N=2996) n (%)
Age (years)	<18	0
	18-44	142 (4.7%)
	45-64	1844 (61.5%)
	≥65	1010 (33.7%)
	≥75	204 (6.8%)
	Mean (SD)	60.6 (9.4)
Gender	Male	1043 (34.8%)
	Female	1953 (65.2%)
Race	White	2097 (70.0%)
	Black or African American	514 (17.2%)
	Asian	304 (10.1%)
	Other/Unknown	81 (2.7%)
Ethnicity	Hispanic or Latino	552 (18.4%)
	Not Hispanic or Latino	2444 (81.6%)
Region	North America	2350 (78.4%)
	Europe	32 (1.1%)
	Japan	200 (6.7%)
	Rest of World	414 (13.8%)
ITT Population		

4.4.6.2.3. Baseline Disease Characteristics

Overall, the baseline disease characteristics in Study 1058 were similar to those in Studies 1056 and 1057 (Table 10).

Table 10. Baseline Disease Characteristics in Study 1058

Baseline Disease Characteristic		Study 1058 (N=2996) n (%)
Index Joint	Hip	443 (14.8%)
	Knee	2553 (85.2%)
KL Grade of Index Joint	0	5 (0.2%)
	1	7 (0.2%)
	2	892 (29.8%)
	3	1425 (47.6%)
	4	667 (22.3%)
Disease Duration (Years)	Mean (SD)	8.8 (8.3)
WOMAC Pain (0-10 NRS)	Mean (SD)	7.0 (1.1)
WOMAC Physical Function (0-10 NRS)	Mean (SD)	7.1 (1.1)
PGA-OA (1 -5 Likert Scale)	Mean (SD)	3.5 (0.6)
Severe Cohort[a]	Yes	796 (26.6%)

ITT population
a. The severe cohort was defined as patients with a baseline WOMAC Pain score ≥ 7, WOMAC Physical Function score ≥ 7 and PGA-OA = "Poor" (score of 4) or "Very Poor" (score of 5)

4.4.6.2.4. Disposition

The overall proportion of patients who discontinued tanezumab treatment in Study 1058 was approximately 55% to 58% over the 56-week treatment period in both tanezumab and NSAID treatment groups. Approximately 22% of the patients discontinued treatment after failing to meet the protocol-specified efficacy criteria at Week 16 (Table 11). The incidence of withdrawal from treatment due to insufficient clinical response was significantly lower for patients treated with tanezumab (6.0% for tanezumab 2.5 mg) compared with NSAIDs (9.1%) in Study 1058 ($p<0.01$). Adverse events leading to discontinuation in Study 1058 are discussed in Section 5.3.1.5.

Table 11. Reasons for Treatment Discontinuation in Study 1058

	Tanezumab 2.5 mg (N=1002) n (%)	Tanezumab 5 mg (N=998) n (%)	NSAIDs (N=996) n (%)
All Reasons	555 (55.4%)	579 (58.0%)	550 (55.2%)
Adverse Event	74 (7.4%)	104 (10.4%)	58 (5.8%)
Death	2 (0.2%)	3 (0.3%)	0
Lost to Follow-Up	14 (1.4%)	11 (1.1%)	11 (1.1%)
Withdrawal By Subject	63 (6.3%)	62 (6.2%)	55 (5.5%)
Insufficient Clinical Response	60 (6.0%)	63 (6.3%)	91 (9.1%)
Protocol Violation	18 (1.8%)	31 (3.1%)	27 (2.7%)
Patient Meets Protocol-Specified Criteria for Discontinuation	224 (22.4%)	207 (20.7%)	220 (22.1%)
Other[a]	100 (10.0%)	98 (9.8%)	88 (8.8%)

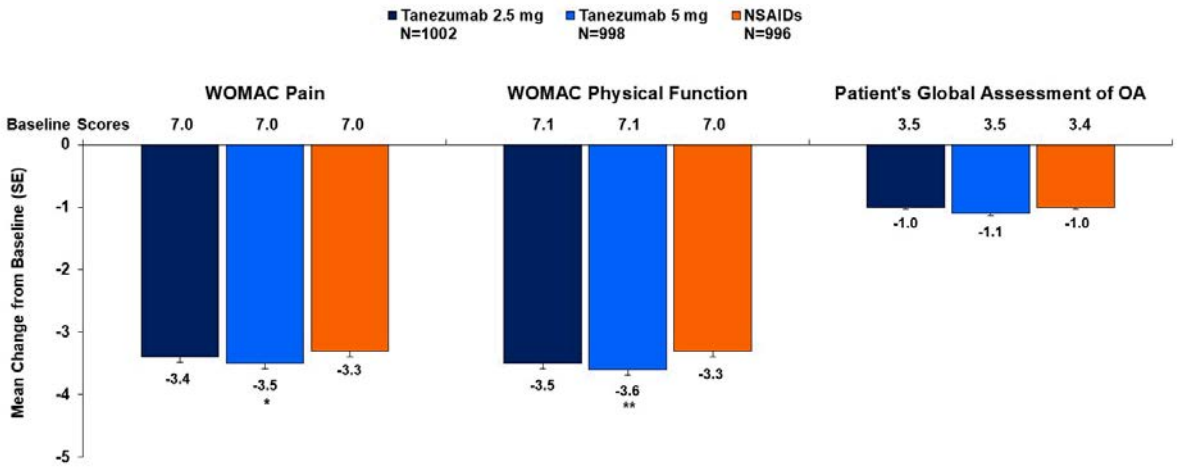
ITT population
a. 'Other' included changes in personal circumstances that prevented the patient from further participation, such as a house move or change in life or work circumstances, also joint replacement surgery and entering safety extension study.

4.4.6.3. Results for Co-primary Endpoints

In Study 1058, the efficacy results with tanezumab 2.5 mg or 5 mg at Week 16 were similar to NSAID treatment but did not demonstrate superiority. No significant differences were detected between tanezumab 2.5 mg and NSAIDs across the 3 co-primary efficacy measures. Improvements with tanezumab 5 mg reached statistical significance versus NSAIDs for WOMAC Pain and WOMAC Physical Function but not for PGA-OA (Figure 23).

All treatment groups responded nearly equally well to double-blind study medication as evidenced by a greater than 3-point mean improvement in WOMAC Pain scores (from a baseline value of approximately 7), in contrast to the patients' protocol qualifying pre-randomization WOMAC Pain score indicating that the same NSAIDs (open-label) provided no apparent efficacy benefit over approximately 30 days of treatment between the screening and baseline pain assessments. The reason for this discrepancy is not clear.

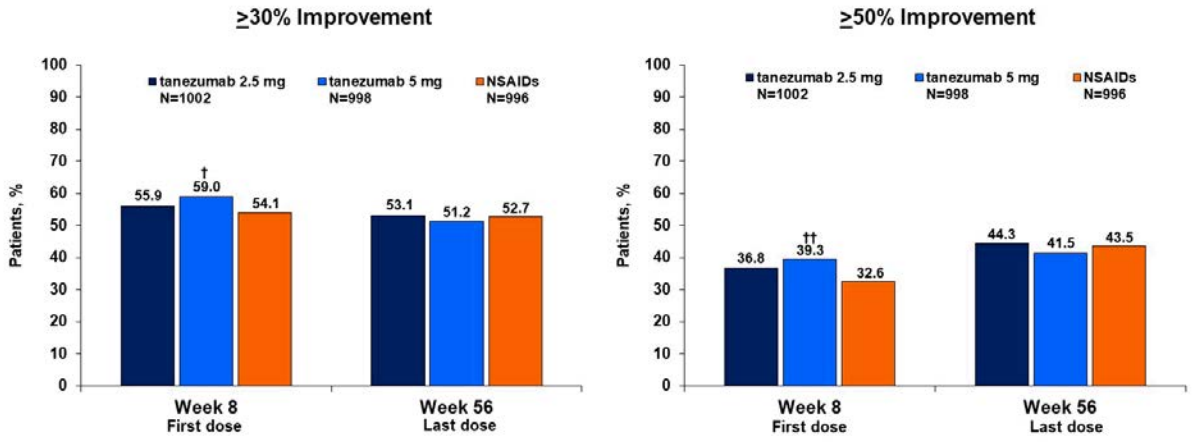
Figure 23. Co-Primary Endpoints: Change From Baseline at Week 16 in Study 1058



ITT population, Multiple Imputation; *p≤0.05, **p≤0.01, ***p≤0.001 versus NSAIDs

The response rates were stable across the 56-week treatment period demonstrating that the effects of tanezumab are persistent over extended treatment periods. The analysis of categorical improvement in WOMAC pain ≥30% and ≥50% following the first dose of SC study medication (Week 8) to the final dose (Week 56) is shown in Figure 24.

Figure 24. Long-Term Efficacy: ≥30% and ≥50% Improvement From Baseline in WOMAC Pain at Week 8 and Week 56 in Study 1058



Week 8 is 8 weeks after the first dose and immediately before the second dose; Week 56 is 8 weeks after the last dose.
ITT population; Mixed BOCF/LOCF; †p≤0.05; ††p≤0.01; †††p≤0.001 versus NSAIDs

4.4.7. Phase 3 Dose-Response and Pharmacokinetic/Pharmacodynamic (PK/PD) Analyses

The Week 16 dose- and exposure-response model-predicted estimates of the treatment differences for tanezumab 2.5 mg versus placebo were:

- Weekly Average Pain Score: -0.75 (95% confidence interval (CI) -0.84, -0.69);
- WOMAC Pain Subscale: -0.85 (95% CI -0.92, -0.79); and
- WOMAC Physical Function Subscale: -0.91 (95% CI -1.00, -0.85).

The analyses show tanezumab 2.5 mg to be a dose providing clinically relevant efficacy for the majority of the population. The average increase in effect for tanezumab 5 mg over 2.5 mg across these endpoints was small (10 to 20%).

From the PK/PD modelling and associated sensitivity analyses, tanezumab doses below 2.5 mg are predicted to be in the linear part of the dose- and exposure-response relationships, such that reducing the dose by half would approximately halve the efficacy. Therefore, any meaningful lowering of dose would provide inadequate efficacy for a majority of the population.

Consistent with the end of Phase 2 model-based predictions (Section 3.5), simulations from the Phase 3 PK/PD model support that an every 8-week SC dose regimen provides a balance between the rate of onset of effect and minimizing fluctuation across the dosing interval.

- Population PK/PD model-based predictions were performed of the placebo-corrected change from baseline in weekly average pain score versus time profile for a typical

patient following tanezumab SC administration of 1.25, 2.5 or 3.75 mg total dose every 4, 8 or 12 weeks, respectively. More frequent dosing (ie, SC administration every 4 weeks) is predicted to have less-fluctuation in the placebo-corrected weekly average pain score across the dosing interval and a slower onset rate of the treatment effect. The opposite is predicted to occur with less frequent administration (ie, SC administration every 12 weeks).

Simulations from a population PK/PD model support the lack of need for dose adjustment for intrinsic factors including those potentially impacting the PD, eg, age, race, KL grade, site of OA or sensitivity to NSAID.

The population PK/PD model-based analyses of the Phase 3 weekly pain score over time identified a small difference (0.1 to 0.14 point decrease on an 11 point scale) in treatment effect due to PK related differences for SC versus IV dosing. However, the dose-response analyses of primary endpoints (WOMAC Pain and Physical Function) and weekly pain score at Week 16 found that, after inclusion of other statistically significant covariates such as the baseline score and age, neither inadequate treatment response to other analgesics in the SC study participants or patients' average drug exposure had any impact on treatment effect compared with placebo.

4.5. Efficacy Discussion

In Studies 1056 and 1057, patients with moderate to severe OA pain for whom the use of other analgesics (ie, acetaminophen, NSAIDs and opioids) was ineffective or not appropriate received the proposed registration dose (tanezumab 2.5 mg every 8 weeks) via the proposed route of administration (SC). These studies therefore provide substantial evidence of efficacy for the proposed indication; important corroborating support is provided by IV Studies 1011 and 1014. The latter two studies investigated the efficacy of tanezumab 2.5 mg IV in patients for whom non-opioid medications (ie, acetaminophen and NSAIDs) were ineffective or not appropriate or who were candidates for an invasive intervention.

Per study eligibility criteria, patients enrolled in the efficacy studies had moderate/severe pain and functional impairment with OA of the knee or hip. There was good representation of patients with the most severe symptoms and radiographic severity.

The age and gender distribution of patients in Studies 1056, 1057, 1011, and 1014 reflected the expected patient population based on the epidemiology of OA.[1,84] Although the majority of patients in the studies were White and Non-Hispanic, there was reasonable representation of Black or African American, Asian, and Hispanic patients, with overall proportions approximating the general US population.[85] The populations across the individual efficacy studies were similar with respect to baseline gender and age; small variations with respect to race and ethnicity between individual studies largely reflected the region in which the study was conducted.

Both tanezumab doses (2.5 mg and 5 mg SC) resulted in significant improvement over placebo at the pre-specified timepoints of Week 16 in Study 1056 and Week 24 in Study 1057 for the three co-primary endpoints except for one comparison (PGA-OA for tanezumab 2.5 mg in Study 1057 at Week 24). In Study 1057, as in the other placebo-controlled studies,

both tanezumab doses 2.5 mg and 5 mg resulted in significant improvement over placebo for all three co-primary endpoints at Week 16.

In Studies 1011 and 1014, all tanezumab doses (2.5 mg, 5 mg, and 10 mg IV) resulted in significant improvement over placebo at Week 16 for all three co-primary endpoints. This provides support for the results of Studies 1056 and 1057 and demonstrates consistency of efficacy across the SC and IV program (Table 12).

Although none of the individual efficacy studies were designed to compare tanezumab doses, there was a trend in the data for the three co-primary endpoints which suggested a modest additional improvement with tanezumab 5 mg over tanezumab 2.5 mg. However, in post-hoc analysis there was no significant difference in treatment effect (versus placebo) between tanezumab doses in individual placebo-controlled studies or pools ($p>0.05$). This was supported by PK/PD dose response analyses which predicted only a small increase in effect for tanezumab 5 mg over 2.5 mg.

Table 12. Summary of Treatment Differences for Tanezumab Versus Placebo for Co-Primary Endpoints at Landmark Analysis Point[a] in Studies 1056, 1057, 1011, and 1014

Route	Study and Tanezumab Dose	WOMAC Pain Subscale	WOMAC Physical Function Subscale	PGA-OA
SC	Study 1056 (Knee & Hip OA)			
	Tanezumab 2.5 mg	✓	✓	✓
	Tanezumab 2.5/5 mg	✓	✓	✓
SC	Study 1057 (Knee & Hip OA)			
	Tanezumab 2.5 mg	✓	✓	×
	Tanezumab 5 mg	✓	✓	✓
IV	Study 1011 (Knee OA)			
	Tanezumab 2.5 mg	✓	✓	✓
	Tanezumab 5 mg	✓	✓	✓
	Tanezumab 10 mg	✓	✓	✓
IV	Study 1014 (Hip OA)			
	Tanezumab 2.5 mg	✓	✓	✓
	Tanezumab 5 mg	✓	✓	✓
	Tanezumab 10 mg	✓	✓	✓

ITT population, Multiple Imputation
✓ indicates $p\leq0.05$ versus placebo; × indicates $p>0.05$ versus placebo ($p=0.0909$)
a. Week 16 for Study 1056, 1011, and 1014; Week 24 for Study 1057

The prespecified analysis for Studies 1011 and 1014 was Week 16, however data are available for Week 24 in these studies to compare to the Week 24 data for Study 1057. At Week 24 in Studies 1011 and 1014, all tanezumab doses resulted in significant improvement over placebo in WOMAC Pain and WOMAC Physical Function but, similarly to Study 1057, results were inconsistent for PGA-OA. This may have been due to greater use of imputed data at Week 24 compared with Week 16, as more patients withdrew from the studies over time.

The efficacy of tanezumab 2.5 mg was clinically meaningful according to published definitions (based on the proportion of patients with ≥30% and ≥50% reduction in WOMAC Pain Subscale score). This, and additional categorical analyses, demonstrated a consistent clinically meaningful response across the placebo-controlled studies, and across multiple assessments of symptomatic OA disease (Table 13 and Table 14).

Table 13. Summary of Analyses for Tanezumab 2.5 mg Versus Placebo for 30/50/70/90% Improvement in WOMAC Pain Subscale in Studies 1056, 1057, 1011, and 1014

Route	Study	% Improvement from Baseline[a]			
		≥30%	≥50%	≥70%	≥90%
SC	Study 1056	✓	✓	✓	×
SC	Study 1057	✓	✓	×	×
IV	Study 1011	✓	✓	✓	✓
IV	Study 1014	✓	✓	✓	✓

ITT population, Mixed BOCF/LOCF

✓ indicates p≤0.05 for Odds Ratio versus placebo; × indicates p>0.05 for Odds Ratio versus placebo

a. Improvement from Baseline to Week 16 (Studies 1056, 1011, and 1014) or Week 24 (Study 1057)

Table 14. Summary of Analyses for Tanezumab 2.5 mg Versus Placebo for Additional Responder Endpoints in Studies 1056, 1057, 1011, and 1014

Route	Study	Sustained WOMAC Pain Scores 0-3[a]	Sustained ≥50% Improvement WOMAC Pain[a]	OMERACT-OARSI Responder Index[b]	≥ 2 Grade Improvement in PGA-OA[b]
SC	Study 1056	✓	✓	×	✓
SC	Study 1057	✓	✓	✓	×
IV	Study 1011	✓	✓	✓	✓
IV	Study 1014	✓	✓	✓	×

ITT population, BOCF/LOCF

✓ indicates p≤0.05 for Odds Ratio versus placebo; × indicates p>0.05 for Odds Ratio versus placebo

a. Sustained over Weeks 4 to 16 (Studies 1056, 1011, and 1014) or Weeks 4 to 24 (Study 1057)

b. Change from Baseline to Week 16 (Studies 1056, 1011, and 1014) or Week 24 (Study 1057)

In subgroup analysis of the pooled placebo-controlled studies (1056, 1057, 1011 and 1014), no demographic or baseline disease characteristics were identified that significantly affected efficacy, and consequently no dose adjustments are required. This is supported by simulations from population PK/PD modelling. Importantly in terms of clinical relevance for the intended patient population, tanezumab 2.5 mg SC was effective in the subgroup of patients with the most severe OA.

The onset of efficacy in Studies 1056 and 1057 was achieved within one week of the initial tanezumab dose based on significant improvement in pain recorded in daily diaries.

Maximum responses were typically evident within 4 weeks of the first dose of tanezumab, were largely maintained up to re-administration at Week 8. These data support the proposed 8-week dose interval. Further support was provided by the PK/PD model for alternative dosing regimens which suggest that an 8-week dosing interval provides the best balance between onset of effect and fluctuation across the dosing interval.

The efficacy of tanezumab was persistent in long-term active-controlled Study 1058 and long-term uncontrolled Study 1016, with little difference observed between tanezumab doses. The magnitude of pain relief provided by tanezumab treatment was associated with a substantial reduction in OA-related physical disability, improving both function associated with daily living and overall well-being. Since efficacy was maintained, there was no evidence of tolerance, and consequently no dose adjustments are required.

Neither dose of tanezumab was superior to NSAID treatment at the Week 16 landmark analysis in long-term Study 1058, although WOMAC Pain and WOMAC Physical Function scores were significantly improved with tanezumab 5 mg relative to NSAIDs. The magnitude of pain relief across all treatment groups observed after the first dose of study medication was maintained to the final dose (56 weeks of treatment). The unexpected improvement seen during the study for those patients continuing NSAID treatment may reflect an anticipation of benefit from blinded SC study medication. This study did not include a placebo group as that was considered impractical due to the long-term treatment duration of the study.

Supportive Studies 1015 and 1018 included placebo and naproxen 500 mg BID control arms and tested tanezumab 5 mg and 10 mg doses. Significantly improved treatment effects versus placebo were demonstrated for all three co-primary endpoints in both studies for both tanezumab doses (ie, 6 out of 6 contrasts for each dose), but not for naproxen (2/6 contrasts). In a direct comparison, statistical significance was not reached for tanezumab 10 mg versus naproxen across all three co-primary endpoints in either study, and predefined statistical testing procedures were not met. Therefore, superiority of tanezumab 5 mg over naproxen could not be concluded despite significantly greater treatment effects for tanezumab 5 mg in all three co-primary endpoints in Study 1018.

4.6. Efficacy Conclusions

Tanezumab 2.5 mg administered by SC injection every 8 weeks provided clinically meaningful and sustained reduction in pain and improvement in function compared to placebo in the intended patient population with moderate to severe OA pain for whom use of other analgesics was ineffective or not appropriate. Onset of pain relief occurred within the first week of treatment. Efficacy was sustained throughout the 8-week dose interval and persisted over approximately one year of treatment in long-term studies. Tolerance requiring escalating doses was not detected. Tanezumab 2.5 mg was effective in patients with the most severe OA and other subgroups. There was no meaningful difference between tanezumab 2.5 mg and tanezumab 5 mg. The degree of improvement in the co-primary endpoints with tanezumab 2.5 mg SC was similar to, but not significantly greater than, that with NSAID measured in patients who were on a stable dose of NSAID before being randomized at baseline to switch to tanezumab or to continue NSAID treatment.

5. SAFETY

5.1. Overview

- The safety profile of tanezumab was determined by evaluating the safety data from 17,779 patients across 39 clinical studies, focusing on the 16 Phase 3 studies in OA which included 9732 OA patients who received at least one dose of tanezumab.
- Tanezumab 2.5 mg SC was generally well-tolerated. The overall incidence of adverse events during the treatment period was not notably different than placebo. Incidences of deaths, serious adverse events, and discontinuations due to an adverse event were low and similar to placebo (Section 5.3.1 and Section 5.3.1.3).
- Adverse events considered likely associated with tanezumab 2.5 mg SC treatment were abnormal peripheral sensation (4.2%; includes paresthesia, hypoesthesia, and burning sensation), rapidly progressive OA (2.7%; includes RPOA-1 and RPOA-2), joint swelling (2.5%), peripheral edema (1.7%; includes edema peripheral and peripheral swelling), and carpal tunnel syndrome (0.5%) (Section 5.3.1.6).
- Joint safety events including adjudicated RPOA-1, RPOA-2, and total joint replacements (TJRs) were the primary safety issues identified for tanezumab. Incidences were dose-dependent and further increased with concomitant chronic NSAID use. The incidences of RPOA-1 and TJR were higher with tanezumab 2.5 mg SC (2.3% and 5.5%, respectively) than placebo (0% and 4.5%, respectively) and NSAIDs (1.1% and 2.6%, respectively). The incidence of RPOA-2 with tanezumab 2.5 mg was low (0.4%) and not statistically significantly different from NSAIDs (0.1%). The risk differences for tanezumab 2.5 mg for RPOA relative to NSAIDs were generally similar over time. Joint safety events occurred most frequently in knee and hip joints that had significant underlying structural OA (Section 5.3.2.1).
- No serious neurological safety concerns were identified with tanezumab treatment. Adverse events of abnormal peripheral sensation (eg, paresthesia) were associated with tanezumab 2.5 mg treatment. The majority of these adverse events were mild or moderate in severity and resolved by end of study. There was no evidence for an increased risk of peripheral polyneuropathy, or sympathetic autonomic neuropathy compared to placebo (Section 5.3.2.2).
- No cardiovascular (CV) safety concerns were identified with tanezumab treatment (Section 5.3.1.4).
- Tanezumab treatment did not lead to an increased risk for adverse events in other organ systems including renal or hepatic and was not associated with clinically meaningful changes in laboratory values, vital signs, or ECGs (Section 5.3.4).
- Tanezumab 2.5 mg SC was not associated with an increased risk of hypersensitivity events (Section 5.3.2.3). Tanezumab treatment was not associated with an increased incidence of adverse events indicative of potential drug abuse, dependence, or withdrawal (Section 5.3.4).
- Adverse event profiles in subgroups evaluated for intrinsic and extrinsic factors were consistent with the profile in the overall population (Section 5.3.3.1).
- Based on the totality of the safety data, tanezumab 2.5 mg SC (administered every 8 weeks) has an acceptable safety profile when appropriate risk mitigation strategies are followed (discussed in Section 7.4) for those patients with moderate to severe OA pain for whom use of other analgesics is ineffective or not appropriate.

5.2. Evaluation of Safety

5.2.1. Safety Database

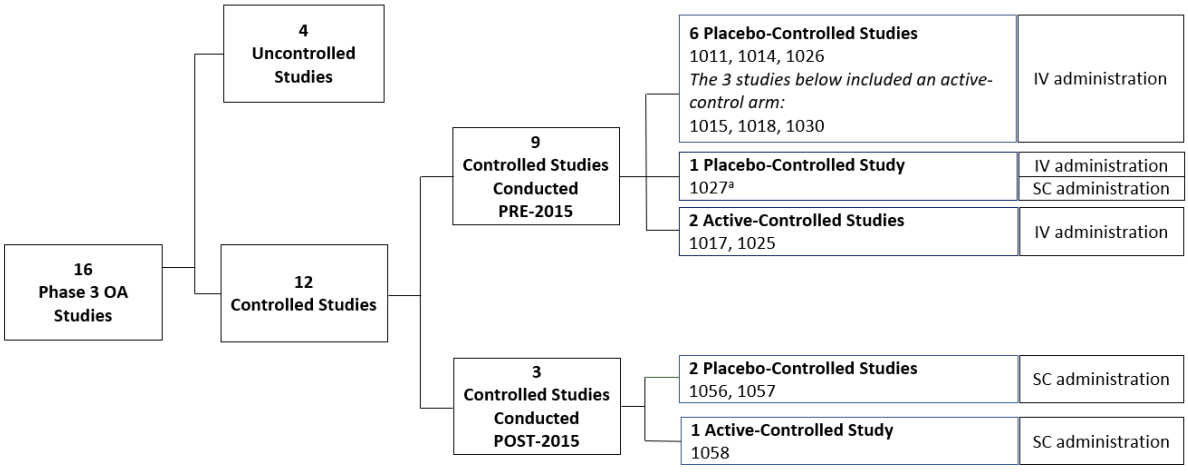
This section focuses on the pooled datasets of the 16 Phase 3 OA studies (including both IV and SC studies). In the Phase 3 OA studies, 9732 OA patients received at least one dose of tanezumab (5937 patient-years of exposure). A total of 1604 patients (across the Phase 3 controlled clinical studies) received the proposed dose of tanezumab 2.5 mg administered SC every eight weeks. Of these, 804 patients were exposed to tanezumab for at least 24 weeks, and 374 patients were exposed for at least 56 weeks.

The overall safety database, comprising safety data from 17,779 patients, also included four Phase 1/2 studies in OA and 19 other studies (see Section 2.4).

5.2.2. Pooling of Studies

Figure 25 provides an overview of the 16 Phase 3 OA studies included in the pooled datasets used to evaluate safety. Due to differences in study design (eg, placebo-controlled versus active-controlled versus uncontrolled; studies using SC versus IV administration; study duration; assessment of joint and neurological safety in pre- versus post-2015 studies) different pools of studies were used to evaluate different safety topics. Details and rationale of the pools used to evaluate general safety and special safety topics are provided below.

Figure 25. Overview of Phase 3 OA Studies For Safety Evaluations



a. Study 1027 included placebo, 3 tanezumab SC dose groups and 1 tanezumab IV dose group.

General Safety

While data from all patients receiving tanezumab in the overall safety database were reviewed to determine the overall safety profile, the two main safety populations discussed in Section 5.3.1 on general safety focus on the Phase 3 OA placebo-controlled studies (treatment duration up to 24 weeks) and include:

1. All patients (N = 3614) receiving tanezumab either by IV or SC administration in the nine Phase 3 placebo-controlled OA studies (OA placebo-controlled [SC + IV] pool) and;

2. A sub-set of patients (N = 1254) receiving tanezumab by SC administration only, in three Phase 3 placebo-controlled OA studies; Studies 1027, 1056, and 1057 (OA placebo-controlled SC pool).

An overview of adverse events (Section 5.3.1), serious adverse events (Section 5.3.1.2) and adverse events leading to discontinuation (Section 5.3.1.5) are provided for both the OA placebo-controlled (SC + IV) pool and the OA placebo-controlled SC pool. However, most discussions in the general safety section are focused on the OA placebo-controlled SC pool, as it provides the most relevant safety information for prescribers regarding the intended patient population and the indicated route of SC administration. An overview of adverse events, serious adverse events, and adverse events leading to discontinuation are also provided for the OA active-controlled SC Study (Study 1058; treatment duration 56 weeks).

To provide a more comprehensive understanding of infrequent events, such as deaths and major adverse cardiovascular events (MACE), data from the larger pool of all 12 Phase 3 placebo- and active-controlled OA studies (OA controlled pool) are provided in these sections.

An overview of datasets/pools used for the evaluation of general safety is provided in Table 15.

Special Safety Topics

For special safety topics, additional pools of OA studies (other than those used for general safety evaluations) were evaluated due to the nature of the data being summarized. The rationale and details of the safety pools used for these special topics are summarized below and in Table 15.

- Joint Safety

For the pre-2015 studies, a retrospective, blinded assessment of joint safety was conducted after Investigator-reported adverse events of ON became the signal event raising concern of a potential joint safety issue with tanezumab treatment. Based on the findings in the pre-2015 studies, post-2015 studies included a pre-defined prospective analysis of joint safety. In addition, post-2015 studies included comprehensive risk mitigation measures (characterization, identification/management, and minimization) and surveillance focused on joint safety. Therefore, conclusions regarding the joint safety profile of tanezumab are primarily based on post-2015 data (Studies 1056, 1057, and 1058). The pooling strategy designed to assess joint safety consists of combined groups of studies from post-2015 Phase 3 OA studies. Key data on joint safety from the pre-2015 OA studies are presented in Section 5.3.2.1.1.2. Further details on joint safety assessments in the post-2015 studies are provided in Section 5.3.2.1.1.3.

- Peripheral Neurological Safety

While data from a number of pools were reviewed to evaluate adverse events of abnormal peripheral sensation, data from the OA placebo-controlled post-2015 pool (Studies 1056 and

1057) and the OA active-controlled SC study (Study 1058) are discussed in the Peripheral Neurological Safety section (Section 5.3.2.2.1). Neurological consultations related to abnormal peripheral sensation from the OA placebo-controlled post-2015 pool are discussed in Section 5.3.2.2.1.4.

- Sympathetic Neurological Safety

While data from a number of pools were reviewed to evaluate possible sympathetic neurological findings, the post-2015 studies were the primary focus since these studies included assessments of sympathetic neurologic safety that were not included in the pre-2015 studies (further details are provided in Section 5.3.2.2.2). In the post-2015 studies, consultations were required for pre-specified sympathetic nervous system adverse events (bradycardia, orthostatic hypotension, syncope, anhidrosis, and hypohidrosis). Consultations from the OA placebo-controlled post-2015 pool are discussed in Section 5.3.2.2.2.3.

Table 15. Details of Datasets/Pools Discussed in This Document for Each Safety Topic

Pool/Study Name	Description	General Safety	Special Safety
All Phase 3 OA Studies N=13,537	This dataset includes 16 OA controlled and uncontrolled studies (includes IV and SC studies).	• Exposure	
OA Controlled Pool N=12,032	This is the largest controlled OA dataset and includes the 12 controlled OA studies (includes IV and SC studies).	• Deaths • MACE	
OA Placebo-controlled (SC + IV) Pool N=5732	This placebo-controlled dataset includes all 9 placebo-controlled studies that used either SC or IV route of administration. Three of these studies included an active-control arm. This pool was evaluated to support general safety conclusions from the individual SC and IV pools (Data from the IV pool are not provided in this document).	• Overview of adverse events • Serious adverse events • Adverse events leading to discontinuation	
OA Placebo-controlled SC Pool N=1840	This placebo-controlled dataset includes only the 3 placebo-controlled studies that used SC route of administration. This dataset was the primary pool used for the interpretation of the general safety of tanezumab including determination of adverse events considered likely associated with tanezumab treatment (ADRs).	• Overview of adverse events • Serious adverse events • Adverse events leading to discontinuation • Common adverse events • Determination of adverse events likely associated with tanezumab treatment	
OA Active-controlled SC Study N=2996	This is the only active-controlled study that used SC route of administration.	• Overview of adverse events • Serious adverse events • Adverse events leading to discontinuation	• Peripheral Neurological Safety • Joint Safety
OA Placebo-controlled Post-2015 (SC) Pool N=1545	This placebo-controlled dataset includes the 2 placebo-controlled studies that were conducted post-2015 and used SC route of administration.		• Peripheral Neurological Safety • Joint Safety • Sympathetic Neurological Safety • Potential Hypersensitivity • Injection Site Reactions
OA Controlled Post-2015 (SC) Pool N=4541	This controlled dataset includes the 3 placebo- and active-controlled OA studies conducted post-2015.		• Joint Safety

All Phase 3 OA Studies: 1011, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030, 1032, 1040, 1043, 1056, 1057, 1058
OA Controlled Studies: 1011, 1014, 1015, 1017, 1018, 1025, 1026, 1027, 1030, 1056, 1057, 1058
OA Placebo-controlled (SC + IV) Studies: 1011, 1014, 1015, 1018, 1026, 1027, 1030, 1056, 1057
OA Placebo-controlled SC Studies: 1027, 1056, 1057
OA Active-controlled SC Study 1058
OA Placebo-controlled Post-2015 (SC) Studies: 1056, 1057
OA Controlled Post-2015 (SC) Studies: 1056, 1057, 1058

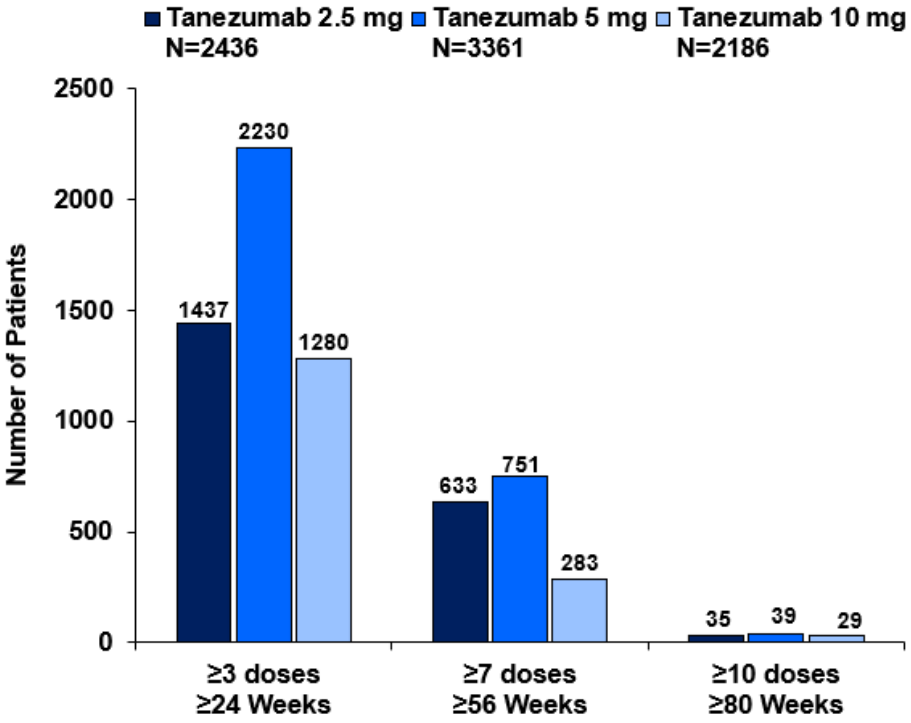
5.2.3. Tanezumab Exposure Across All Phase 3 OA Studies

Across all Phase 3 OA studies (see Table 15), 8202 patients received from one to 11 doses of monotherapy tanezumab (2.5 mg, 2.5/5 mg, 5 mg or 10 mg; either SC or IV); 3255 patients received one or two doses, 4947 patients received three or more doses, and 1667 patients received seven or more doses.

The total number of patients who received from three to 11 doses of tanezumab 2.5 mg (IV or SC) was 1437, and the total number of patients who received seven or more doses of tanezumab 2.5 mg was 633 (Figure 26).

The total number of patients (across the Phase 3 controlled clinical studies) who received the proposed dose of tanezumab 2.5 mg administered SC every eight weeks was 1604. Of these, 804 patients were exposed to tanezumab for at least 24 weeks (three doses), and 374 patients were exposed for at least 56 weeks (seven doses).

Figure 26. Treatment Exposure Duration With Tanezumab 2.5 mg, 5 mg and 10 mg Dosing Across All Phase 3 OA Studies



OA Studies: 1011, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030, 1032, 1040, 1043, 1056, 1057, 1058.
Tanezumab 2.5/5 mg treatment group (N=219) received 2 doses and is not shown.

5.2.4. Patient Demographics and Disease Characteristics

Baseline patient demographics and disease characteristics were generally balanced across treatment groups with no clinically relevant differences noted in each of the major safety pools. Ranges of mean baseline patient demographics and disease characteristics among the placebo, tanezumab 2.5 mg, and tanezumab 5 mg treatment groups in the placebo-controlled

pools, and the tanezumab 2.5 mg, tanezumab 5 mg and NSAID groups in the active-controlled study, are provided in Table 16.

Table 16. Baseline Patient Demographics and Disease Characteristics for General Safety Pools/Datasets

Range Across Treatment Groups[a]	OA Placebo-Controlled (SC + IV) Pool N=5732	OA Placebo-Controlled SC Pool N=1840	OA Active-Controlled SC Study N=2996
Age			
Mean age (years)	61.0 – 62.4	62.3 – 64.3	60.3 – 61.2
≥65 years (%)	37.1 – 40.9	42.0 – 55.6	32.1 – 36.2
≥75 years (%)	8.6 – 9.9	10.6 – 15.0	5.5 – 8.0
Gender			
Female (%)	61.8 – 65.4	66.0 – 68.3	63.6 – 66.5
Race			
White (%)	82.6 – 86.0	79.0 – 86.2	68.3 – 71.3
Black or African American (%)	9.8 – 12.1	2.3 – 11.9	16.2 – 18.7
Asian (%)	3.1 – 3.8	7.8 – 10.4	9.5 – 11.0
Mean Disease Duration			
OA (years)	7.3 – 7.8	8.0 – 8.9	8.5 – 9.1
Baseline Disease Severity (Kellgren-Lawrence Grade of the Index Joint)			
KL Grade 3 (%)	40.9 – 42.7	42.2 – 44.9	47.4 – 47.8
KL Grade 4 (%)	18.4 – 26.6	30.7 – 32.3	21.5 – 22.7

OA Placebo-controlled Studies (SC + IV) 1011, 1014, 1015, 1018, 1026, 1027, 1030, 1056, 1057.
OA Placebo-controlled SC Studies 1027, 1056, 1057.
OA Active-controlled SC Study 1058.
a. Range of means or rates across the following treatment groups for the OA placebo-controlled (SC + IV) pool and the OA placebo-controlled SC pool: placebo, tanezumab 2.5 mg and tanezumab 5 mg. Range of means or rates across the following treatment groups for the OA active-controlled SC study: tanezumab 2.5 mg, tanezumab 5 mg and NSAID.

5.2.5. Patient Evaluation and Disposition

The rates of both completion of treatment and completion of the study as well as rates of discontinuation were reflective of when the studies were conducted (post-2015 or pre-2015). As a result of the partial clinical hold, many pre-2015 studies were terminated by the Sponsor prior to their completion and account for the majority of patient discontinuations from treatment and/or study. The range of rates across treatment groups of patients discontinuing study, in addition to the discontinuation rates in the placebo (or active comparator) and tanezumab 2.5 mg groups, for each major pool are shown in Table 17, along with the reasons for discontinuation.

Table 17. Patient Evaluation and Disposition for General Safety Pools/Datasets

	OA Placebo-Controlled (SC + IV) Pool			OA Placebo-Controlled SC Pool			OA Active-Controlled SC Study		
	Range[a] N=5732	Placebo N=1543	Tanezumab 2.5 mg N=929	Range[a] N=1840	Placebo N=586	Tanezumab 2.5 mg N=602	Range[a] N=2996	Tanezumab 2.5 mg N=1002	NSAID N=996
Discontinued Study (%)[b]	14.2 – 91.8	**65.8**	**48.5**	14.2 – 90.7	**25.1**	**24.4**	24.0 – 27.0	**26.0**	**24.0**
Adverse Event	0 – 10.1	2.1	2.2	0 – 1.5	0.9	1.5	0.8 – 2.3	2.3	0.8
Death	0 – 0.9	0.1	0	0 – 0.9	0	0	0 – 0.4	0.4	0
Lost to Follow-up	0.9 – 2.5	0.9	1.2	0.6 – 3.5	1.7	1.8	2.1 – 3.1	2.5	3.1
Study Terminated by Sponsor	0 – 58.2	11.5	6.0	0 – 79.1	8.7	9.3	0	0	0
Withdrawal by Subject	5.0 – 7.7	7.4	6.0	5.0 – 10.4	8.0	7.0	9.7 – 10.4	9.7	10.0
Insufficient Clinical Response	1.8 – 17.9	17.9	7.8	1.2 – 2.6	2.6	2.3	1.9 – 2.2	1.9	2.2
Protocol Violation	0 – 1.2	0.8	1.2	0 – 1.2	0.2	0.2	0.4 – 0.6	0.4	0.4
Other[c]	4.1 – 60.9	25.2	24.2	0.9 – 4.1	3.1	2.3	7.4 – 9.1	8.9	7.4

OA Placebo-controlled (SC + IV) Studies 1011, 1014, 1015, 1018, 1026, 1027, 1030, 1056, 1057.
OA Placebo-controlled SC Studies 1027, 1056, 1057.
OA Active-controlled SC Study 1058.
a. Range of rates across treatment groups for each pool. OA Placebo-controlled (SC + IV) pool: Placebo, Tanezumab 2.5, 2.5/5, 5 and 10 mg, Naproxen 500 mg BID and Oxycodone CR 10-40 mg Q12H; OA Placebo-controlled SC pool: Placebo, Tanezumab 2.5, 2.5/5, 5 and 10 mg; OA Active-controlled SC study: Tanezumab 2.5, 5 mg and NSAID.
b. Includes patients who rolled over into an extension study, discontinued due to the clinical hold, or discontinued due to other reasons.
c. Includes patient-specific reasons such as a change in work schedule, relocation or family obligation that does not allow the patient to continue.

5.2.6. General Adverse Event Data Interpretation

The primary comparisons to placebo were conducted using the tanezumab 2.5 and 5 mg dose levels since these treatments included the largest number of patients. Tanezumab 2.5 mg is the proposed indicated dose.

For the OA placebo-controlled SC pool, data for tanezumab 2.5/5 mg (one dose of 2.5 mg followed by the second dose of 5 mg) and 10 mg dose levels came from single studies and, therefore, due to the limited number of patients the results for these doses should be interpreted with caution. In some of the analyses in this pool of placebo-controlled SC studies, the adverse event incidence rate with tanezumab 10 mg was substantially lower as compared to the tanezumab 2.5 mg and 5 mg dose levels, likely due to the shorter duration of the study that included this dose (following the partial clinical hold in 2010 most patients received only 1 dose of study medication); lower incidence rates with tanezumab 10 mg are not discussed in the sections with these analyses. The data for tanezumab 2.5/5 mg, are provided as an independent dose group.

The primary assessment of adverse events was based on those that occurred during the treatment period. Data in the follow-up and up to end of study periods were evaluated as well to determine if imbalances in events occurred after the conclusion of treatment. Table 18 provides definitions of these study periods.

Table 18. Definition of Study Periods

	Pre-2015 Studies	Post-2015 Studies
Treatment Period	Time from 1st dose of SC/IV study drug to the last treatment period visit or to the time of transfer to an extension study[a]	Time from 1st dose of study drug to the last treatment period visit (if the patient completed the treatment period) or to the date of withdrawal from treatment (if the patient did not complete the treatment period)
Follow-up Period	Time from the day after the treatment period ends to the date of study completion or discontinuation (if such a period exists for a given patient). During this period, patients were followed for safety outcomes but no study treatment was administered.	
Up to End of Study[b]	Treatment period + Follow up Period	
Up to End of Study and Post-Study	Treatment period + Follow up Period + Any Time After Study Completion	

a. The following are long-term extension studies that received patients from other studies: 1016 (received patients from 1011, 1014, 1015, and 1018); 1032 (received patients from 1027), and 1040 (received patients from 1026). Patients continued to be treated in these studies. There were no post-2015 extension studies where patients continued to be treated.
b. For post-2015 joint safety event summaries and analyses, the Up to End of Study period (primary study period) went to the end of the follow-up period or 26 weeks after the end of the treatment period, whichever was later, with the intent of capturing relevant events. Sensitivity analyses were performed using all events reported, including those after the primary study period.

5.2.7. Statistical Methods

The majority of safety analyses were descriptive in nature (eg, incidence of adverse events) unless there were pre-specified hypotheses associated with the parameters. A pool of five adverse events (bradycardia, syncope, orthostatic hypotension, anhidrosis, or hypohidrosis), potentially associated with sympathetic autonomic neuropathy, were pre-specified as "Tier 1

adverse events" and were subjected to inferential testing for statistical significance with p-values and 95% CIs provided for between-group comparisons. Adverse events with an incidence of ≥2% in any treatment groups were considered "Tier 2 adverse events" and risk differences between groups were assessed via point estimates and 95% CIs.

For the post-2015 studies, statistical analyses were conducted for adjudicated joint safety endpoints, TJRs, and joint space width (JSW). The Up to End of Study period (primary study period) went to the end of the follow-up period or 26 weeks after the end of the treatment period, whichever was later, with the intent of capturing relevant events. Event rates were calculated by treatment group and difference/ratio of treatment groups were subjected to inferential testing with p-values and 95% CIs provided for between-group comparisons. Kaplan-Meier analysis was performed for time to events.

Two retrospective MACE analyses were conducted and the risk difference for the primary composite endpoint and individual MACE components was calculated with 95% CIs provided for between-group comparisons.

5.3. Safety Results

5.3.1. Overview of Adverse Events

The overall incidence of adverse events in the OA placebo-controlled (SC + IV) pool (N = 5732) during the treatment period was similar among tanezumab and the active-controlled treatments; however, these treatments had a higher incidence of adverse events than was observed with placebo (Table 19). The incidence of serious adverse events and discontinuations due to adverse events was similar among placebo and tanezumab 2.5 mg and 5 mg treatments.

In the OA placebo-controlled SC pool (N = 1840), the overall incidence of patients with one or more adverse events and serious adverse events during the treatment period was not notably different across the treatments, although the incidence of severe adverse events was generally higher with tanezumab than with placebo treatment. Discontinuations from treatment and/or study due to an adverse event were low and similar across the treatments (Table 20).

In the OA active-controlled SC Study 1058 (N = 2996), the overall incidence of patients with one or more adverse events, serious adverse events, and severe adverse events during the treatment period was not notably different between tanezumab 2.5 mg and NSAIDs, but all were higher with tanezumab 5 mg. The incidence of discontinuations from treatment and/or from the study due to an adverse event was higher with both tanezumab doses compared to NSAIDs (Table 20).

Table 19. Overview of Adverse Events (All Causalities) During the Treatment Period in the OA Placebo-Controlled (SC + IV) Pool

	Placebo	Tanezumab				Naproxen	Oxycodone CR
	N=1543	2.5 mg N=929	2.5/5 mg N=219	5 mg N=1324	10 mg N=1142	500 mg BID N=417	10-40 mg Q12H N=158
Number (%) of Patients	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Patients with adverse events	717 (46.5)	505 (54.4)	103 (47.0)	678 (51.2)	591 (51.8)	213 (51.1)	95 (60.1)
Patients with serious adverse events	29 (1.9)	21 (2.3)	3 (1.4)	29 (2.2)	23 (2.0)	12 (2.9)	3 (1.9)
Patients with severe adverse events	39 (2.5)	36 (3.9)	6 (2.7)	42 (3.2)	46 (4.0)	19 (4.6)	4 (2.5)
Patients discontinued from treatment due to adverse events[a]	39 (2.5)	19 (2.0)	1 (0.5)	31 (2.3)	52 (4.6)	27 (6.5)	16 (10.1)
Patients discontinued from treatment and/or study due to adverse events[b]	41 (2.7)	22 (2.4)	1 (0.5)	35 (2.6)	56 (4.9)	28 (6.7)	16 (10.1)

OA Placebo-controlled Studies (SC + IV) 1011, 1014, 1015, 1018, 1026, 1027, 1030, 1056, 1057. Studies 1015, 1018, 1030 included patients receiving active control.
a. Patients who have an adverse event record that indicates that the adverse event caused the patient to be discontinued from the treatment.
b. Patients who have an adverse event record that indicates that the adverse event caused the patient to be discontinued from the treatment and/or study.
Adverse events defined as Treatment-Emergent.

Table 20. Overview of Adverse Events (All Causalities) During the Treatment Period in the OA Placebo-Controlled SC Pool and the OA Active-Controlled SC Study

	OA Placebo-Controlled SC Pool (Duration up to 24 weeks)					OA Active-Controlled SC Study (Duration 56 weeks)		
	Placebo	Tanezumab				Tanezumab		NSAID
	N=586	2.5 mg N=602	2.5/5 mg N=219	5 mg N=347	10 mg N=86	2.5 mg N=1002	5 mg N=998	N=996
Number (%) of Patients	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Patients with adverse events	303 (51.7)	315 (52.3)	103 (47.0)	190 (54.8)	34 (39.5)	629 (62.8)	670 (67.1)	601 (60.3)
Patients with serious adverse events	9 (1.5)	13 (2.2)	3 (1.4)	9 (2.6)	0	51 (5.1)	80 (8.0)	46 (4.6)
Patients with severe adverse events	10 (1.7)	13 (2.2)	6 (2.7)	13 (3.7)	0	45 (4.5)	68 (6.8)	45 (4.5)
Patients discontinued from treatment due to adverse events[a]	12 (2.0)	8 (1.3)	1 (0.5)	4 (1.2)	0	74 (7.4)	103 (10.3)	58 (5.8)
Patients discontinued from treatment and/or study due to adverse events[b]	13 (2.2)	11 (1.8)	1 (0.5)	5 (1.4)	0	75 (7.5)	105 (10.5)	59 (5.9)

OA Placebo-controlled SC Studies 1027, 1056, 1057; OA Active-controlled SC Study 1058.
a. Patients who have an adverse event record that indicates that the adverse event caused the patient to be discontinued from the treatment.
b. Patients who have an adverse event record that indicates that the adverse event caused the patient to be discontinued from the treatment and/or study.
Adverse events defined as Treatment-Emergent.

5.3.1.1. Common Adverse Events

The adverse event profile of tanezumab across all pools generally demonstrated a consistent pattern with a dose-related increase in the incidence of several specific types of adverse events when compared to placebo or NSAID treatments. Safety findings in the IV studies were generally consistent with those in the SC studies, but discussion of common adverse events and adverse events likely related to tanezumab use (adverse drug reactions) are focused on the OA placebo-controlled SC pool, as it provides the most relevant adverse event data for prescribers regarding the intended patient population.

During the treatment period in the OA placebo-controlled SC pool, among the adverse events that occurred in ≥2% of patients in any treatment group (Table 21), the only events that occurred at a higher incidence (ie, 95% CI excluded 0) in the 2.5 mg or 5 mg tanezumab groups relative to placebo were peripheral edema, joint stiffness, hypoesthesia and paresthesia. The incidence of peripheral edema, hypoesthesia and paresthesia demonstrated a dose relationship, and these events are considered likely associated with tanezumab use (discussed further in Section 5.3.1.6).

Review of the adverse events of peripheral edema and peripheral swelling concluded that the terms represent the same medical concept, and, therefore, an additional analysis was conducted to determine the incidence of these two events combined (see Section 5.3.1.6). Clinical review of adverse events of lower frequency did not reveal additional safety issues with the exception of burning sensation and carpal tunnel syndrome which, based on the totality of the data, were also considered events likely associated with tanezumab use.

Overall, the majority of adverse events occurring during the treatment period were mild or moderate in severity with similar proportions reported across treatment groups. Severe events were infrequently reported with a similar proportion in the placebo (1.7%) and tanezumab 2.5 mg (2.2%) treatment groups and a higher proportion in the other tanezumab groups (2.7 to 3.7%). The only severe event that was reported by more than 1 patient in a treatment group was arthralgia; placebo (0.5%), tanezumab 2.5 mg (0.2%) and tanezumab 5 mg (2.0%).

Table 21. Incidence of Adverse Events (≥2%) During the Treatment Period (All Causalities) in the OA Placebo-Controlled SC Pool

	Placebo	Tanezumab			
Number of patients evaluable for adverse events	**N=586**	**2.5 mg N=602**	**2.5/5 mg N=219**	**5 mg N=347**	**10 mg N=86**
Number (%) of patients: by Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
With any adverse event	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)
Nasopharyngitis	33 (5.6)	44 (7.3)	11 (5.0)	23 (6.6)	0
Back pain	22 (3.8)	28 (4.7)	6 (2.7)	18 (5.2)	0
Fall	14 (2.4)	26 (4.3)	4 (1.8)	8 (2.3)	0
Headache	27 (4.6)	26 (4.3)	7 (3.2)	14 (4.0)	5 (5.8)
Joint swelling	10 (1.7)	15 (2.5)	4 (1.8)	10 (2.9)	2 (2.3)
Musculoskeletal pain	15 (2.6)	14 (2.3)	2 (0.9)	8 (2.3)	1 (1.2)
Pain in extremity	10 (1.7)	14 (2.3)	7 (3.2)	7 (2.0)	3 (3.5)
Paraesthesia	6 (1.0)	14 (2.3)	3 (1.4)	14 (4.0)	6 (7.0)

Table 21. Incidence of Adverse Events (≥2%) During the Treatment Period (All Causalities) in the OA Placebo-Controlled SC Pool

	Placebo	Tanezumab			
Number of patients evaluable for adverse events	**N=586**	**2.5 mg N=602**	**2.5/5 mg N=219**	**5 mg N=347**	**10 mg N=86**
Upper respiratory tract infection	9 (1.5)	14 (2.3)	3 (1.4)	7 (2.0)	0
Osteoarthritis[a]	10 (1.7)	13 (2.2)	1 (0.5)	13 (3.7)	0
Hypoaesthesia	5 (0.9)	11 (1.8)	3 (1.4)	8 (2.3)	5 (5.8)
Urinary tract infection	4 (0.7)	10 (1.7)	3 (1.4)	2 (0.6)	2 (2.3)
Diarrhoea	7 (1.2)	9 (1.5)	5 (2.3)	4 (1.2)	0
Bronchitis	8 (1.4)	7 (1.2)	0	3 (0.9)	2 (2.3)
Influenza	7 (1.2)	7 (1.2)	0	9 (2.6)	1 (1.2)
Oedema peripheral	1 (0.2)	6 (1.0)	6 (2.7)	6 (1.7)	0
Joint stiffness	1 (0.2)	4 (0.7)	5 (2.3)	2 (0.6)	0
Peripheral swelling	5 (0.9)	4 (0.7)	2 (0.9)	5 (1.4)	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)

OA Placebo-controlled SC Studies 1027, 1056, 1057.
Adverse events are shown by descending frequency by the tanezumab 2.5 mg treatment group.
Adverse events defined as Treatment-Emergent.
a. Investigator reported event not based on adjudicated outcome.
MedDRA v21.1 coding dictionary applied.

During the follow-up period, the overall incidence of adverse events was higher in the tanezumab 2.5 mg and 5 mg treatment groups (37.2% and 36.3%, respectively) than in the placebo group (32.3%), primarily due to a higher incidence of musculoskeletal adverse events. The most frequently reported events included arthralgia (placebo: 7.2%, tanezumab 2.5 mg: 8.5%, tanezumab 5 mg: 9.0%), back pain (placebo: 2.2%, tanezumab 2.5 mg: 2.7%, tanezumab 5 mg: 3.1%), osteoarthritis (placebo: 1.7%, tanezumab 2.5 mg: 2.0%, tanezumab 5 mg: 2.8%) and RPOA (placebo: 0%, tanezumab 2.5 mg: 1.1%, tanezumab 5 mg: 2.2%). During the follow-up period, the incidence of nervous system adverse events such as paresthesia and hypoesthesia was low (<1%) and generally similar between the placebo, tanezumab 2.5 mg and tanezumab 5 mg groups.

5.3.1.2. Serious Adverse Events

In the OA placebo-controlled SC pool during the treatment period, the overall incidence of serious adverse events was ≤2.6% and not notably different with tanezumab relative to placebo treatment. There was no obvious pattern in the types of serious adverse events that occurred. The only serious adverse events that occurred in ≥2 patients across the tanezumab 2.5 and 5 mg treatment groups combined were osteoarthritis and arthralgia (Table 22). None of the serious adverse events were considered treatment-related by the Investigator.

Table 22. Incidence of Serious Adverse Events (≥2 Patients in Any Treatment Group) During the Treatment Period (All Causalities) in the OA Placebo-Controlled SC Pool

	Placebo	Tanezumab			
Number of patients evaluable for adverse events	**N=586**	**2.5 mg N=602**	**2.5/5 mg N=219**	**5 mg N=347**	**10 mg N=86**
Number (%) of patients: by Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
With any adverse event	9 (1.5)	13 (2.2)	3 (1.4)	9 (2.6)	0
Osteoarthritis[a]	2 (0.3)	2 (0.3)	0	2 (0.6)	0
Arthralgia	0	0	1 (0.5)	1 (0.3)	0

OA Placebo-controlled SC Studies 1027, 1056, 1057.
Adverse events are shown by descending frequency by the tanezumab 2.5 mg treatment group.
Adverse events defined as Treatment-Emergent.
a. Investigator reported event not based on adjudicated outcome.
MedDRA v21.1 coding dictionary applied.

Because serious adverse events are less common, data from the OA placebo-controlled (SC + IV) pool are presented so that the evaluation includes a larger patient population. The overall incidence of serious adverse events in the OA placebo-controlled (SC + IV) pool during the treatment period was low (≤2.3%) and similar across the tanezumab and placebo treatment groups (Table 23).

Table 23. Incidence of Serious Adverse Events (≥2 Patients in Any Treatment Group) During the Treatment Period (All Causalities) in the OA Placebo-Controlled (SC + IV) Pool

	Placebo	Tanezumab				Naproxen	Oxycodone CR
Number of patients evaluable for adverse events	**N=1543**	**2.5 mg N=929**	**2.5/5 mg N=219**	**5 mg N=1324**	**10 mg N=1142**	**500 mg BID N=417**	**10-40 mg Q12H N=158**
Number (%) of patients: by Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
With any serious adverse event	29 (1.9)	21 (2.3)	3 (1.4)	29 (2.2)	23 (2.0)	12 (2.9)	3 (1.9)
Osteoarthritis[a]	4 (0.3)	3 (0.3)	0	3 (0.2)	0	0	0
Pneumonia	1 (0.1)	1 (0.1)	0	2 (0.2)	1 (0.1)	0	0
Angina pectoris	2 (0.1)	0	0	0	0	0	0
Arthralgia	0	0	1 (0.5)	2 (0.2)	1 (0.1)	0	0
Asthma	2 (0.1)	0	0	0	0	0	0
Cellulitis	0	0	0	0	2 (0.2)	0	0
Osteonecrosis[a]	0	0	0	0	2 (0.2)	0	0

OA Placebo-controlled Studies (SC + IV) 1011, 1014, 1015, 1018, 1026, 1027, 1030, 1056, 1057.
Studies 1015, 1018, 1030 included patients receiving active control.
Adverse events are shown by descending frequency by the tanezumab 2.5 mg treatment group.
Adverse events defined as Treatment-Emergent.
a. Investigator reported event not based on adjudicated outcome.
MedDRA v21.1 coding dictionary applied.

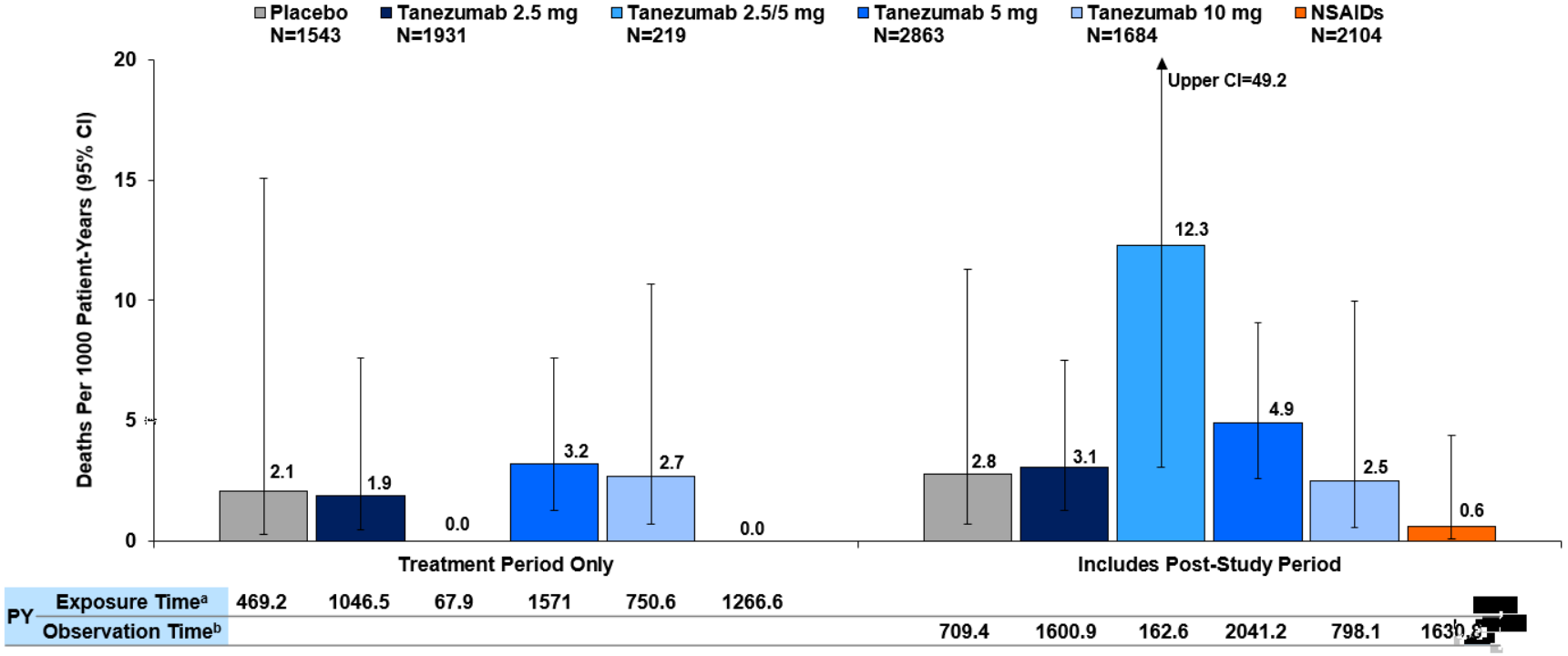
In the OA active-controlled SC Study (Study 1058), the overall incidence of serious adverse events was not notably different between the tanezumab 2.5 mg treatment group (5.1%) and NSAID group (4.6%) but was higher in the tanezumab 5 mg group (8.0%). With the exception of a higher incidence of serious adverse events related to the musculoskeletal system (arthralgia, osteoarthritis, and RPOA), there was no obvious pattern in the types of serious adverse events that occurred with tanezumab treatment compared with NSAIDs.

5.3.1.3. Deaths

The OA controlled pool (SC + IV) provides the largest dataset in patients with OA to evaluate the risk of death with tanezumab in the intended patient population. In this pool, the incidence rate of death up to the end of study and post-study was similar with tanezumab 2.5 mg (3.1/1000 patient-years) and placebo (2.8/1000 patient-years). The incidence rate of death was not notably different across all tanezumab dose levels (range 2.5 to 4.9/1000 patient-years) and placebo. The death rate in the NSAID group was unexpectedly low (0.6/1000 patient-years) compared with placebo (Figure 27).

During the treatment period only, in the OA controlled pool (SC + IV), the exposure-adjusted incidence rate of death was low and not notably different across the placebo (2.1/1000 patient-years) and tanezumab treatments (range 1.9 to 3.2/1000 patient-years). No deaths were reported with NSAID treatment (Figure 27).

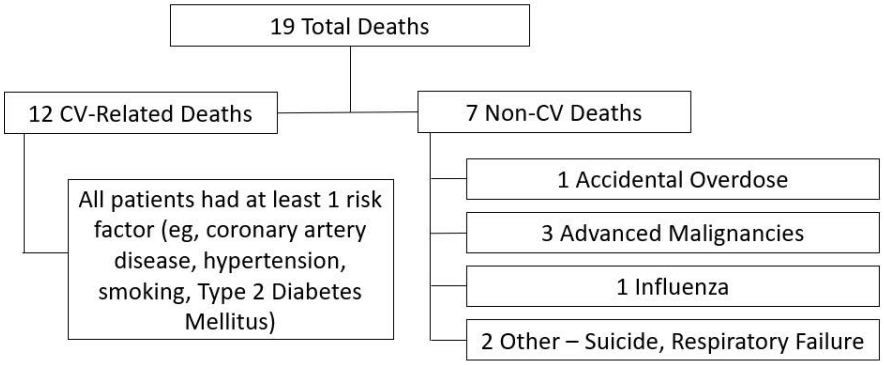
Figure 27. Overview of Deaths up to End of Study and Post-Study in the OA Controlled Pool



OA Controlled Studies 1011, 1014, 1015, 1017, 1018, 1025, 1026, 1027, 1030, 1056, 1057, 1058.
PY = patient-years
a. Exposure-adjusted rate/1000 patient-years. Exposure defined as a) if the patient experienced the event: time from first IV/SC dose to the date of death. b) if the patient did not experience the event: Time from first IV/SC dose to the end of treatment visit date for patients who completed the treatment period or up to the withdrawal from treatment date for patients who withdrew from the treatment period.
b. Observation time-adjusted rate/1000 patient-years. Observation time defined as: a) if the patient experienced the event: time from first IV/SC dose to the date of death. b) if the patient did not experience the event: Time from first IV/SC dose to the end of study.
Data from the following treatment groups are not shown: tanezumab (2.5 mg/5 mg/10 mg)+NSAID groups and oxycodone group

Up to the end of study and post-study, the most commonly reported fatal events with tanezumab monotherapy, were possibly related to CV disease. All of these patients had at least one risk factor for CV death (eg, coronary artery disease, hypertension, smoking, or type 2 diabetes mellitus). Since the most frequently reported fatal events were related to CV disease, retrospective MACE analyses were conducted and are discussed in Section 5.3.1.4. Non-CV deaths with tanezumab monotherapy, occurred due to a variety of causes with no discernible pattern (Figure 28).

Figure 28. Causes of Death With Tanezumab Monotherapy up to the End of Study and Post-Study in the OA Controlled Pool



OA Controlled Studies: 1011, 1014, 1015, 1017, 1018, 1025, 1026, 1027, 1030, 1056, 1057, 1058.

5.3.1.4. Major Adverse Cardiovascular Events (MACE) Analyses

The most frequently reported fatal events were possibly related to CV disease. Therefore, two retrospective MACE analyses were conducted based on the Antiplatelet Trialists' Collaboration (APTC)[86] published definition and include incidence rates of the primary CV events of CV death, non-fatal stroke, and non-fatal myocardial infarction (MI). Analyses included a composite incidence rate for all three terms and individual incidence rates for each of the components.

The two analyses differed in the method of identification of MACE events as the tanezumab clinical study program did not have pre-specified analyses or blinded prospective external adjudication and case assignment of events. In the first analysis (denoted as Analysis #1), non-fatal MI and non-fatal stroke events were assigned based on selection of Investigator-reported PTs for serious adverse events that were consistent with the definitions published by the Standardized Data Collection for Cardiovascular Trials Initiative (SCTI) and US FDA.[87] CV death was defined as any death resulting from an acute MI, sudden cardiac death, death due to heart failure, death due to stroke, death due to CV procedure, death due to CV hemorrhage, and death due to other CV causes (eg, pulmonary embolism). Death cases were assigned as meeting the definition of CV death based on the Sponsor's review of all available data for each case to determine the primary cause of death.

For the second analysis (denoted as Analysis #2), case assignment of MACE was determined retrospectively by a blinded external adjudication committee at C5Research at Cleveland Clinic. The Adjudication Committee at C5Research used the same published definitions of

CV death, non-fatal stroke, and non-fatal MI that were developed by SCTI and the US FDA and reviewed cases blinded to study treatment received.

Overall, the data from both MACE analyses provide similar conclusions and do not demonstrate a CV signal with tanezumab. While the incidence rates for some endpoints varied between the two analyses, the number of events was low, and the incidence rates for all endpoints were similar across treatment groups. There was no dose response noted across tanezumab treatment groups, which would have been anticipated if there was a true treatment effect based on the dose-responsive pattern noted with adverse events considered related to tanezumab use (Adverse Drug Reactions; see Section 5.3.1.6).

In the OA controlled pool, the observation time-adjusted incidence rates up to the end of the study and including the post-study period for any composite MACE was variable across treatment groups, with no treatment group having more than 11 total events in Analysis #1 and 9 total events in Analysis #2. The incidence rates of any composite MACE event, CV death, non-fatal MI, and non-fatal stroke across the treatment groups for Analysis #1 and Analysis #2 are shown in Table 24.

Table 24. Observation Time-Adjusted MACE Events up to End of Study and Post-Study (All Causalities) in the OA Controlled Pool

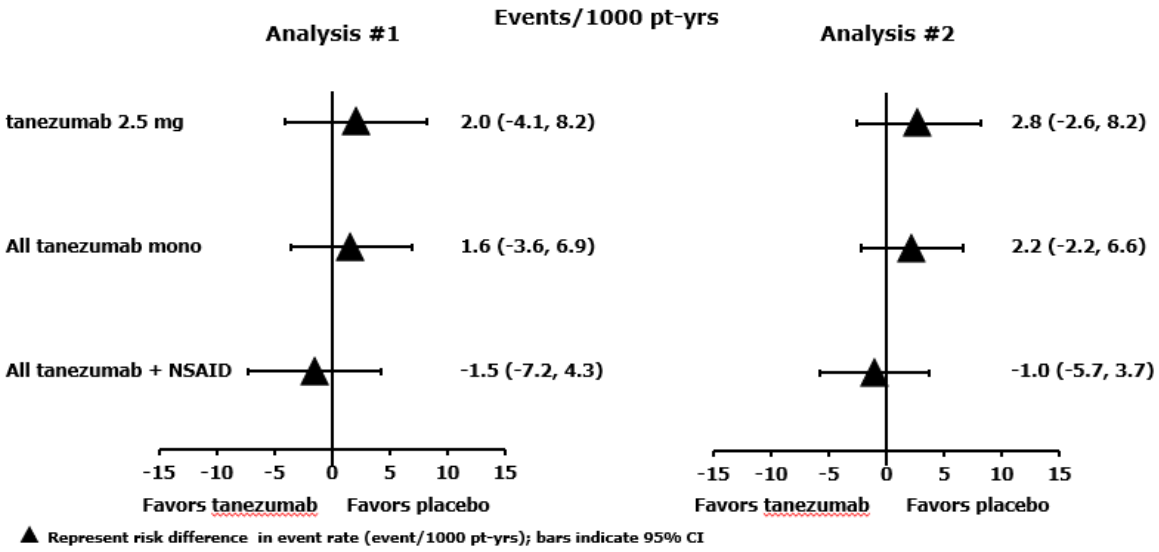
Number of Patients/Observation Time (rate per 1000 patient-years)	Placebo	Tanezumab						NSAID
		2.5 mg	2.5/5 mg	5 mg	10 mg	All Tanezumab Monotherapy	All Tanezumab + NSAID	
	N=1543	N=1931	N=219	N=2863	N=1684	N=6697	N=1530	N=2104
Events Based on Investigator-reported PTs – Analysis #1								
With any Composite MACE Event	3/708.1 (4.2)	10/1598.9 (6.3)	0/162.6 (0)	11/2039.7 (5.4)	6/797.2 (7.5)	27/4598.3 (5.9)	3/1082.2 (2.8)	9/1627.7 (5.5)
CV death	1/709.3 (1.4)	3/1600.9 (1.9)	0/162.6 (0)	7/2040.7 (3.4)	2/798.1 (2.5)	12/4602.3 (2.6)	1/1082.4 (0.9)	1/1630.8 (0.6)
Non-Fatal MI	1/708.5 (1.4)	5/1599.6 (3.1)	0/162.6 (0)	1/2040.2 (0.5)	0/798.1 (0)	6/4600.5 (1.3)	0/1082.3 (0)	7/1627.6 (4.3)
Non-Fatal Stroke	1/708.8 (1.4)	2/1600.2 (1.2)	0/162.6 (0)	3/2039.4 (1.5)	4/797.2 (5)	9/4599.3 (2)	2/1082.1 (1.8)	1/1630.3 (0.6)
Events Based on External Adjudication at C5Research – Analysis #2								
With any Composite MACE Event	2/708.1 (2.8)	9/1598.8 (5.6)	0/162.6 (0)	8/2039.3 (3.9)	6/797.6 (7.5)	23/4598.2 (5)	2/1082.1 (1.8)	7/1628.4 (4.3)
CV death	0/709.3 (0)	2/1600.9 (1.2)	0/162.6 (0)	2/2040.5 (1)	2/798.1 (2.5)	6/4602 (1.3)	0/1082.3 (0)	1/1630.8 (0.6)
Non-Fatal MI	1/708.5 (1.4)	4/1599.8 (2.5)	0/162.6 (0)	3/2040 (1.5)	0/798.1 (0)	7/4600.5 (1.5)	0/1082.3 (0)	5/1628.3 (3.1)
Non-Fatal Stroke	1/708.8 (1.4)	3/1599.9 (1.9)	0/162.6 (0)	3/2039.4 (1.5)	4/797.6 (5)	10/4599.5 (2.2)	2/1082.1 (1.8)	1/1630.3 (0.6)

OA Controlled Studies: 1011, 1014, 1015, 1017, 1018, 1025, 1026, 1027, 1030, 1056, 1057, 1058.
Observation time defined as: a) If patient experienced the event: Time from first IV/SC dose to the date of first occurrence of the event. b) If the patient did not experience the event: Time from first IV/SC dose to the end of Study.
All Tanezumab Monotherapy is combined group of tanezumab 2.5, 2.5/5, 5 and 10 mg.
Tanezumab 2.5 mg + NSAID, tanezumab 5 mg + NSAID, tanezumab 10 mg + NSAID and oxycodone treatment groups are not shown.

In Analysis #1, the composite MACE incidence rate was similar in the placebo, all tanezumab monotherapy, and NSAID groups. In Analysis #2, the composite MACE incidence rate was similar in the all tanezumab monotherapy and NSAID groups; the event rate in the placebo group was numerically lower but the 95% CIs for the risk differences between the placebo group and the tanezumab treatment groups included zero. In both analyses, the composite MACE rate was lowest in the all tanezumab + NSAID group, and there was no dose response noted across the tanezumab monotherapy treatment groups or the tanezumab + NSAID treatment groups.

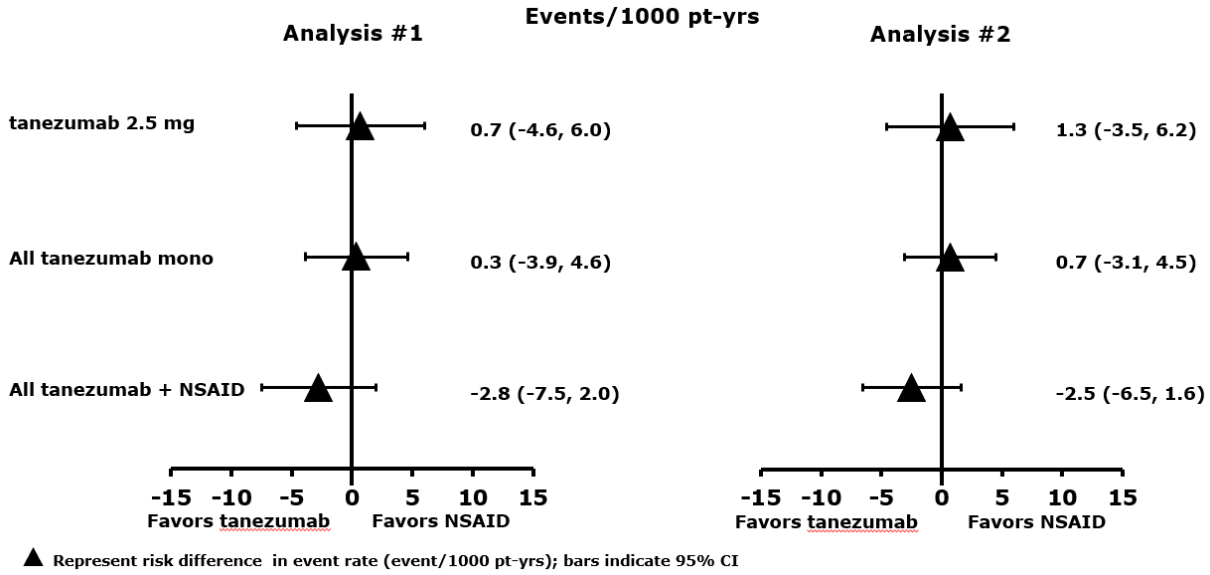
Forest plots of the risk difference with 95% CIs for any composite MACE are shown in Figure 29 for tanezumab versus placebo and in Figure 30 for tanezumab versus NSAID, with data shown for both Analysis #1 and Analysis #2.

Figure 29. Risk Differences for Any Composite MACE up to End of Study and Post-Study Between Tanezumab and Placebo in the OA Controlled Studies



OA Controlled Studies: 1011, 1014, 1015, 1017, 1018, 1025, 1026, 1027, 1030, 1056, 1057, 1058.
pt-yrs = patient-years

Figure 30. Risk Differences for Any Composite MACE up to End of Study and Post-Study Between Tanezumab and NSAID in the OA Controlled Studies



OA Controlled Studies: 1011, 1014, 1015, 1017, 1018, 1025, 1026, 1027, 1030, 1056, 1057, 1058.
pt-yrs = patient-years
'All tanezumab + NSAID' data comes from Studies 1017 and 1025 where tanezumab was evaluated in combination with oral NSAID.

CV Events with NSAIDs from Similar OA Clinical Studies

A primary finding in the tanezumab OA program was the uncharacteristically low incidence of CV death in patients receiving NSAIDs compared to those receiving placebo or tanezumab. The MACE analyses also demonstrate a lower than anticipated incidence rate for composite MACE in the NSAID group. This is at variance from numerous previous studies where concerns have been raised regarding the adverse CV effects of NSAIDs[88,89] as well as FDA-mandated NSAID class labeling which includes a Boxed warning for elevated CV risk. However, it is noteworthy that the majority of patients receiving NSAIDs (in Studies 1025 and 1058) were already on a stable dose prior to initiating the study, and this may have played a role in these findings. Collectively, there were 5,696 patients treated in these two studies, and they included the majority of NSAID monotherapy patients in the tanezumab program (78.6%). The risk for NSAID-associated CV events in these patients may have been lower in the tanezumab studies than anticipated, as a recent meta-analysis of real world use of NSAIDs in 446,763 individuals, including 61,460 with acute MI, found that the risk for acute MI was greatest during the first month of NSAID use.[90]

5.3.1.5. Adverse Events Leading to Discontinuation

The majority of adverse events leading to discontinuation that occurred in more than two patients across the tanezumab 2.5 mg, 5 mg, and placebo treatment groups were related to either the musculoskeletal system or the nervous system.

Discontinuations in the OA placebo-controlled (SC + IV) pool are summarized in Table 25. Adverse events that led to discontinuation of treatment and/or study in more than two patients across the placebo, tanezumab 2.5 mg and tanezumab 5 mg treatment groups included, arthralgia (0.5% in the placebo group and 0.4% in each of the tanezumab groups), osteoarthritis (0.3% in the placebo and tanezumab 2.5 mg treatment groups), and hypoesthesia (0.3% in the tanezumab 5 mg group).

Discontinuations in the OA placebo-controlled SC pool are summarized in Table 26. The incidence of adverse events leading to discontinuation of treatment and/or study was low and not notably different in the tanezumab treatment groups compared to the placebo group. The only adverse events that led to discontinuation of treatment and/or study in more than two patients in a treatment group were arthralgia and osteoarthritis, although the highest incidence of discontinuation due to arthralgia was in the placebo group (1.2%). Three patients (0.5%) in the tanezumab 2.5 mg dose group discontinued due to osteoarthritis.

Discontinuations in the OA active-controlled SC study are summarized in Table 26. Tanezumab treatment led to a higher rate of discontinuation of treatment and/or study than NSAID treatment. The imbalance was primarily due to an increase in musculoskeletal events such as arthralgia (0.6%, 1.1% and 0.5% in the tanezumab 2.5 mg, tanezumab 5 mg and NSAID groups, respectively), osteoarthritis (1.2%, 1.9% and 0.3% in the tanezumab 2.5 mg, tanezumab 5 mg, and NSAID groups, respectively), and RPOA (1.2%, 1.7% and 0.3% in the tanezumab 2.5 mg, tanezumab 5 mg, and NSAID groups, respectively).

Table 25. Overview of Adverse Events Leading to Discontinuation (All Causalities) in the OA Placebo-Controlled (SC + IV) Pool

	Placebo	Tanezumab				Naproxen	Oxycodone CR
	N=1543	2.5 mg N=929	2.5/5 mg N=219	5 mg N=1324	10 mg N=1142	500 mg BID N=417	10-40 mg Q12H N=158
Number (%) of Patients							
Patients discontinued from treatment due to adverse events[a]	39 (2.5)	19 (2.0)	1 (0.5)	31 (2.3)	52 (4.6)	27 (6.5)	16 (10.1)
Patients discontinued from treatment and/or study due to adverse events[b]	41 (2.7)	22 (2.4)	1 (0.5)	35 (2.6)	56 (4.9)	28 (6.7)	16 (10.1)

OA Placebo-controlled Studies: 1011, 1014, 1015, 1018, 1026, 1027, 1030, 1056, 1057.
Studies 1015, 1018, 1030 included patients receiving active control.
a. Patients who have an adverse event record that indicates that the adverse event caused the patient to be discontinued from the treatment.
b. Patients who have an adverse event record that indicates that the adverse event caused the patient to be discontinued from the treatment and/or study.
Adverse events defined as Treatment-Emergent.

Table 26. Overview of Adverse Events Leading to Discontinuation (All Causalities) in the OA Placebo-Controlled SC Pool and the OA Active-Controlled SC Study

	OA Placebo-Controlled SC Pool (Treatment Duration up to 24 weeks)[a]					OA Active-Controlled SC Study (Treatment Duration 56 weeks)[a]		
	Placebo	Tanezumab				Tanezumab		NSAID
	N=586	2.5 mg N=602	2.5/5 mg N=219	5 mg N=347	10 mg N=86	2.5 mg N=1002	5 mg N=998	N=996
Number (%) of Patients								
Patients discontinued from treatment due to adverse events[b]	12 (2.0)	8 (1.3)	1 (0.5)	4 (1.2)	0	74 (7.4)	103 (10.3)	58 (5.8)
Patients discontinued from treatment and/or study due to adverse events[c]	13 (2.2)	11 (1.8)	1 (0.5)	5 (1.4)	0	75 (7.5)	105 (10.5)	59 (5.9)

OA Placebo-controlled SC Studies: 1027, 1056, 1057; OA Active-controlled SC Study 1058.
a. Post-treatment follow-up duration: up to 24 weeks.
b. Patients who have an adverse event record that indicates that the adverse event caused the patient to be discontinued from the treatment.
b. Patients who have an adverse event record that indicates that the adverse event caused the patient to be discontinued from the treatment and/or study.
c. Adverse events defined as Treatment-Emergent.

5.3.1.6. Adverse Events Considered Likely Associated With Tanezumab Use

Based on the totality of tanezumab safety data, all adverse events underwent internal clinical and safety review to apply medical judgment in determining adverse events likely associated with tanezumab use (adverse drug reactions). In addition, adjudicated joint safety event data were evaluated to determine joint specific adverse events likely associated with tanezumab use, as these events were not always reported as adverse events with accurate diagnoses.

For adverse events likely associated with tanezumab use, event terms representing the same medical concept or condition were grouped together and an overall pooled incidence was reported. The adverse events of paresthesia, hypoesthesia, and burning sensation were grouped together under the term "abnormal peripheral sensation". Adverse events of edema peripheral and peripheral swelling were grouped together under the term "peripheral edema". Adjudicated joint safety events of RPOA-1 and RPOA-2 were grouped together under the term "RPOA". Based on this analysis, the adverse events shown in Table 27 are considered likely associated with tanezumab use.

The majority of the safety data (excluding RPOA) presented in Table 27 is based on 602 patients with OA who received tanezumab 2.5 mg for up to 24 weeks and 586 patients who received placebo for up to 24 weeks in the placebo-controlled SC studies (Studies 1027, 1056, 1057). For adjudicated RPOA, the incidence is based on 514 OA patients who received placebo (for up to 24 weeks) and 1530 OA patients who received tanezumab 2.5 mg (for up to 56 weeks) in the placebo- and active-controlled SC studies with adjudicated joint safety outcomes (Studies 1056, 1057, 1058).

Table 27. Adverse Events Likely Associated With Tanezumab Use (Adverse Drug Reactions) in Patients Receiving Tanezumab 2.5 mg SC

System Organ Class	Terms Used for Groups of Adverse Events Considered Likely Associated with Tanezumab Use (ADR Term)	Frequency n/N (%)	
		Placebo	Tanezumab 2.5 mg SC
Nervous system disorders	Abnormal peripheral sensation[1]	10/586 (1.7)	25/602 (4.2)
	Carpal tunnel syndrome	0/586 (0)	3/602 (0.5)
Musculoskeletal and connective tissue disorders	Rapidly progressive osteoarthritis[2]	0/514 (0)	41/1530 (2.7)
	Joint swelling	10/586 (1.7)	15/602 (2.5)
General disorders and administration site conditions	Peripheral edema[3]	6/586 (1.0)	10/602 (1.7)

Event terms that represent the same medical concept or condition were grouped together and reported as a single adverse reaction in the table above.
[1]Includes: paraesthesia, hypoaesthesia, and burning sensation.
[2]Includes: adjudicated rapidly progressive osteoarthritis type 1 and type 2.
[3]Includes: oedema peripheral and peripheral swelling.

5.3.2. Safety Topics of Special Interest

Adverse events of special interest for the tanezumab program included joint safety and neurological safety (peripheral and sympathetic). Since potential hypersensitivity and injection site reactions represent specific potential concerns with administration of injectable therapeutic proteins, these topics were also evaluated as safety topics of special interest.

5.3.2.1. Joint Safety

- Osteoarthritis (OA) is a heterogeneous disease in its genesis, rate of progression, severity of symptoms, and the degree of structural joint damage at the time of total joint replacement (TJR). A minority of patients with various etiologies for their OA will experience more rapid and destructive forms of joint disease necessitating arthroplasty.
- Joint safety events including rapidly progressive osteoarthritis (RPOA) were the primary safety findings identified for tanezumab during both the treatment and follow-up periods. Analyses of these events were primarily conducted using adjudicated joint safety events from the post-2015 OA studies (Studies 1056, 1057 and 1058).
- RPOA-1 was the most common type of adjudicated event included in the primary composite endpoint. There was a dose-dependent increase in RPOA-1 in the tanezumab groups compared to the NSAID group (tanezumab 2.5 mg: 2.3%; NSAID: 1.1%, and placebo: 0%). RPOA-1 most frequently occurred in knee (83%) joints that had Kellgren-Lawrence (KL) Grade 2 or 3 OA at baseline (77%). There were 19 RPOA-1 events (18%) that occurred in joints with KL Grade 1 OA at baseline. In the tanezumab 2.5 mg treatment group, 32 of the 36 affected joints did not undergo TJR during the treatment or post-treatment, safety follow-up period of ~24 weeks. The characteristics of joints and patients with RPOA-1 and Normal Progression of OA were generally similar. No patients with follow-up imaging had an adjudicated RPOA-1 event progress to an adjudicated RPOA-2 event.
- The incidence of adjudicated RPOA-2 in the tanezumab 2.5 mg group was low (0.4%) and not statistically significantly different from NSAIDs (0.1%). There were no RPOA-2 events in placebo-treated patients. Most (~80%) RPOA-2 events occurred in joints that had KL Grade 3 or 4 OA at baseline. Events rarely occurred in joints without pre-existing OA.
- The risk differences for tanezumab 2.5 mg for RPOA relative to NSAIDs were generally similar over time based on analyses of Study 1058.
- Subgroup analyses indicated that patients with more severe structural OA at baseline tended to have a higher incidence of joint safety endpoints.
- More patients in the tanezumab groups underwent TJRs than patients in the placebo group, although the treatment differences between the tanezumab and placebo groups were not statistically significant. There was a dose-dependent increase in TJRs in the tanezumab groups relative to the NSAID group with the highest rate of TJR occurring in the tanezumab 5 mg group. Most TJRs were in joints with KL Grade 3 or 4 at baseline and were associated with events adjudicated as Normal Progression of OA.
- Retrospective joint safety analyses of the pre-2015 studies found that more than 90 days of continuous NSAID use in conjunction with tanezumab administration was associated with an increase in the incidence of RPOA and TJR events. Limited NSAID use of no more than 10 days per 8-week dosing interval (in post-2015 studies) was not associated with an increased risk of such events.

5.3.2.1.1. Background Information

5.3.2.1.1.1. Rapidly Progressive Osteoarthritis – Key Risk for Tanezumab

Osteoarthritis is a heterogeneous disease in its genesis, rate of progression, severity of symptoms, and the degree of structural joint damage at the time of TJR. A widely used method of assessing structural progression of OA in the knee or hip is the measurement of radiographic joint space width (JSW).[91,92] Measurement of joint space narrowing (JSN) over time has been shown to be sensitive for monitoring structural changes in the joint due to OA, but requires proper joint positioning and radiographic techniques that are reproducibly followed.[93-97] The rate of JSN in a typical joint with OA is on the order of 0.15 mm/year.[91] However, JSN occurs at varying rates among individual patients or joint(s) within a given patient with OA. Atypical courses of JSN including "slow" and "rapid" progressors have been described in patients with knee or hip OA.[93] For example, in a study of over 600 patients with knee OA, 2% were found with JSN of 2.1 mm over 2 years.[93] A minority of patients with OA will experience a rapid and more destructive form of joint disease necessitating arthroplasty with etiologies attributable to one of the following: (1) trauma, (2) septic arthritis, (3) neurogenic arthropathy (Charcot joint), (4) ON, (5) idiopathic RPOA, (6) crystal-induced arthropathy, or (7) concurrent rheumatoid or psoriatic arthritis.[98]

Idiopathic RPOA of the hip was first described in the European literature in 1957 and characterized further with differing nomenclatures in many subsequent studies. [95-97,99-107] Rapidly progressive hip OA was characterized in patients who typically presented with hip pain, often severe, with sequential radiographs showing rapid loss of JSW and, subsequently, an osteolytic phase with severe progressive atrophic bone destruction involving the femoral head and the acetabulum. Marked flattening of the femoral head and loss of subchondral bone in the weight-bearing area was often noted and, in some cases, the femoral head appeared to be sheared off. The prevalence of RPOA in the OA patient population is not well understood. The Sponsor previously reported the background incidence of RPOA in the knee over a 2-4 year period was in the range of 1-3% based on the analysis of two large OA studies.[108] Furthermore, due to the lack of large scale longitudinal studies, it is not clear what proportion of patients with rapid JSN will progress to bone destruction, or even if these are a continuum of a single disease process or represent two different disease processes. Indeed, in the current program, as described below, the occurrence of rapid JSW did not predict the progression to bone destruction nor the subsequent need for TJR.

RPOA has also been associated with analgesic drug treatment. Following the introduction of NSAIDs in the late-1960s, case reports and retrospective observational studies began to emerge suggesting that NSAIDs, particularly indomethacin, were associated with a severe, rapidly destructive arthropathy involving both femoral and acetabular components of the hip, so-called 'analgesic hip' or 'indomethacin hip'.[109 110 111 112 113 114] As described in Section 5.3.2.1.3, in the current program there were cases of RPOA associated with NSAID treatment. In addition, retrospective observational studies have also suggested that intra-articular steroids may also lead to rapid progression of OA in some patients. For instance, Simeone et al describe more rapid progression of OA and collapse of the joint associated with steroid/anesthetic injections in the hip.[115] Kompel and colleagues report similar findings in an uncontrolled retrospective observational study, with evidence of RPOA and other joint safety events following with intra-articular steroid injections in the hip and knee.[23] On the

other-hand, a long-term prospective trial with intra-articular injections of corticosteroids in the knee every three months over two years with magnetic resonance imaging (MRI) surveillance, revealed a small but significant decrease in cartilage thickness, that was less than the cross-sectional difference between one KL Grade that had been measured in a prior natural history study; there was no evidence of RPOA-like changes.[21,24] Additional work is necessary to determine the exact causality of the joint safety findings that have been seen with intra-articular steroid injection.[116]

Finally, RPOA has been seen in clinical trials with anti-NGF antibodies, including tanezumab.[117] In the pre-2015 tanezumab clinical program, initial cases of joint damage reported by clinical Investigators as adverse events of ON were subsequently determined to be RPOA, normal progression of OA, or another joint condition by an external Adjudication Committee (see Section 5.3.2.1.1.2).[108] As discussed above, published investigations on idiopathic RPOA, based largely on case series analyses, describe patients who exhibited rapid JSN followed by bone loss. However, as it is not clear what proportion of patients with rapid JSN will progress to have bone destruction, the tanezumab Adjudication Committee took a conservative approach in their assessment of joint safety events in the tanezumab program and subdivided RPOA into type 1 (RPOA-1), or rapid JSN using the definition proposed by Lequesne who proposed that patients with 2 mm/year or greater of JSN within 1 year should be considered to have RPOA, and RPOA type 2 (RPOA-2) defined as abnormal bone loss or destruction, including limited or total collapse of at least one subchondral surface, which is not normally present in conventional end-stage OA.[118] As RPOA-1 requires measurement of JSN, the diagnosis of RPOA-1 can only be established when prior images are available to allow longitudinal assessment.[119] On the other hand, RPOA-2 can be identified on the basis of destruction of bone not normally present in end stage OA.[120]

In summary, progression of OA is variable from patient to patient, with a small proportion progressing at a much faster rate, as measured by JSN. More rapid and destructive forms of OA have been identified, including idiopathic RPOA, in which there is rapid JSN and subsequent destruction of the subchondral bone. While the prevalence of RPOA is not well understood, retrospective studies suggested it may occur in 1-3% of OA patients. RPOA has been as associated with analgesic drug treatment, including NSAIDs, intra-articular steroids, and also anti-NGF antibodies, including tanezumab.

5.3.2.1.1.2. Key Joint Safety Results from Pre-2015 Studies

Analyses of joint safety events were primarily conducted using adjudicated joint safety events from the post-2015 OA studies (Section 5.3.2.1.1.3). Below, is a summary of the key joint safety results from the pre-2015 studies (data previously shared at the meeting of the Arthritis Advisory Committee in March 2012[108])

- Investigator-reported adverse events of ON became the signal event that raised concern of a potential joint safety issue with tanezumab treatment in pre-2015 Phase 3 clinical studies. A retrospective, blinded assessment of joint safety events in pre-2015 studies was subsequently conducted by an external Adjudication Committee of medical experts in

ON and OA. Since prospective imaging was not included in pre-2015 study protocols, available images and clinical information were collected post-hoc for adjudication.

- In a treatment-blinded fashion, the Adjudication Committee examined all 87 patients who had an adverse event report of ON. In addition to these reports of ON, there were an additional 299 patients with TJRs related to OA (N=292) or to joint injury or infection (N=7) that were reported by the Investigator. Of these additional patients, 162 (54.2%) had sufficient information to be reviewed by the Adjudication Committee, bringing the total number of patients reviewed by the Adjudication Committee in pre-2015 studies to 249 out of 386 patients (64.5%) with a joint safety event.

- The blinded Adjudication Committee determined that only 2 of the 87 Investigator reports of ON in the pre-2015 tanezumab clinical program were correctly diagnosed. The majority (98%) of the remaining Investigator-reported ON adverse events were adjudicated to be events of RPOA, normal progression of OA or other diagnoses such as subchondral insufficiency fracture (SIF) or end-stage OA without progression.

- Of the 249 patients adjudicated in total, there were 68 patients identified with RPOA in the pre-2015 tanezumab clinical program. Table 28 summarizes the incidence of RPOA and All-Cause TJRs (includes patients with TJR, regardless of causality, and patients with reported ON without TJR) in the pre-2015 Phase 3 OA studies. In the pre-2015 studies:

    - The rate of RPOA increased in a dose-related manner.

    - The rate of RPOA with all tanezumab monotherapy doses combined was elevated above placebo and active comparator treatment.

    - The rate for RPOA was not significantly greater for tanezumab 2.5 mg or 5 mg monotherapy compared with the rate for active comparator. The rate of RPOA was significantly greater for tanezumab 10 mg monotherapy compared with the rate for active comparator. Because of this, the 10 mg dose strength was not included in the post-2015 studies.

    - The rate of RPOA was further increased over tanezumab monotherapy by greater than three-fold in patients treated with tanezumab/chronic NSAID combination therapy.

    - The rate of All-Cause TJRs in patients with OA was comparable among placebo, active comparator, and tanezumab monotherapy treatment groups ranging from 32 to 47 events/1000 patient-years. The rate of All-Cause TJRs did not increase in relation to increasing tanezumab monotherapy dose strengths. The event rate of All-Cause TJRs with tanezumab/NSAID combination treatment was 2.42- to 2.7-fold greater than any of the other treatment groups.

Table 28. RPOA and All-Cause Total Joint Replacements in the Pre-2015 Phase 3 OA Studies

	Placebo	Tanezumab			Tanezumab + NSAID[a]			Active Comparator[b]
	N=1029	2.5 mg N=604	5 mg N=1771	10 mg N=1898	2.5 mg N=587	5 mg N=1249	10 mg N=1192	N=1266
Total exposure (patient-years)	**313**	**373**	**1116**	**1125**	**381**	**877**	**823**	**661**
Incidence of RPOA n(%)[c]	0 (0.0)	0 (0.0)	7 (0.4)	12 (0.6)	6 (1.0)	16 (1.3)*†	25 (2.1)*†	1 (0.1)
RPOA Event rates (events/1000 patient-years)[d]	0	0	6	11†	16†	18†	30†	2
Incidence of All-Cause TJR n(%)[e]	10 (1.0)	15 (2.5)	52 (2.9)*	49 (2.6)*	34 (5.8)*†	88 (7.1)*†	96 (8.1)*†	28 (2.2)
All-Cause TJR Event rates (events/1000 patient-years)[f]	32	40	47	44	89*†	100*†	117*†	42

Studies 1011, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030, and 1043

a. NSAID = naproxen 500 mg BID, celecoxib 100 mg BID or diclofenac SR 75 mg BID in controlled studies and patients receiving any concomitant NSAID with tanezumab in on-controlled long-term studies

b. Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID

c. Dose-response for crude incidence; p=0.005 tanezumab monotherapy, p<0.001 combination therapy

d. Dose-response for event rate; p=0.012 dose-response tanezumab monotherapy, p<0.001 tanezumab/NSAID combination therapy

e. Dose-response for crude incidence: p=0.032 tanezumab monotherapy, p<0.001 tanezumab/NSAID combination therapy

f. Dose-response for event rate; p=0.553 dose-response tanezumab monotherapy, p<0.001 combination therapy

Risk difference: *p≤0.05 versus placebo, †p≤0.05 versus active comparator

5.3.2.1.1.3. Joint Safety Assessments in Post-2015 Studies

The conclusions regarding the joint safety profile of tanezumab are primarily based on the post-2015 data due to the prospective assessment of joint safety and increased level of surveillance included in the post-2015 studies.

Based on the findings in the pre-2015 studies, post-2015 studies included a pre-defined prospective analysis of joint safety, comprehensive risk characterization, mitigation measures, and surveillance focused on joint safety – protocol-specified screening and post-baseline imaging.

- All post-2015 studies included prospectively scheduled radiographic assessments with standardized positioning to facilitate reproducibility and accuracy of JSW measurements, important for characterization of RPOA-1.

- Program-level central, musculoskeletal radiologists (Central Readers) read all imaging in a standardized manner according to an imaging atlas and Charter. Central Readers reviewed radiology images at screening, for assessment of eligibility (including determination of KL Grade), and identification of exclusionary joint conditions, and after randomization for diagnosis of joint conditions that would warrant further evaluation by the Adjudication Committee. In addition, Central Readers read all imaging collected for cause during the studies (including MRIs) and to prepare cases for adjudication.

- Details of radiographic and MRI assessments for post-2015 studies were as follows:

    - Radiographs of both knees, hips, and shoulders were performed at screening and approximately every 24 weeks depending on the individual protocol.

    - Across Studies 1056, 1057 and 1058, a total of 13,797 patients were radiographically screened. The 3 most commonly defined radiographic exclusionary findings on knee radiographs were severe knee malalignment (2.8%), SIF (2.2%) and atrophic OA (1.8%). The 3 most commonly defined radiographic exclusionary findings on hip radiographs were ON (1.2%), atrophic OA (0.4%) and RPOA-2 (0.4%).

    - For Studies 1056 and 1057, MRIs were performed for cause, but were not routinely performed.

    - For Study 1058, MRIs of hips and knees were performed at screening for all patients. Those patients who had a hip and/or knee with a KL Grade 3 or 4 at screening had post-baseline MRIs of their hips and knees collected at Weeks 24, 56, and 80.

    - MRIs were not used to determine eligibility of patients at screening.

- An external, blinded Adjudication Committee reviewed all possible or probable joint-related safety events (see Section 5.3.2.1.1.4 for further details on the review of joint safety events by the Adjudication Committee).

In addition, for post-2015 studies:

- Study inclusion criteria were designed to enroll patients with more severe OA who were unresponsive to or intolerant of multiple standard of care analgesics including acetaminophen, NSAIDs, tramadol, and opioids.
- Patients with evidence of risk factors for RPOA, such as atrophic OA and SIF, were excluded from studies.
- Only tanezumab 2.5 mg and 5 mg doses were evaluated as higher doses showed no additional benefit in pre-2015 studies.
- Patients who did not achieve adequate pain relief (≥30% decrease from baseline in WOMAC Pain subscale at Week 16 plus 1 additional visit prior to Week 16 with a decrease ≥15%) were discontinued from treatment with study medication in longer-term studies.
- Retrospective joint safety analyses for the pre-2015 studies found that more than 90 days of NSAID use in conjunction with tanezumab administration was associated with an increase in the incidence of RPOA and TJR events. Therefore, chronic concomitant NSAID use was excluded in post-2015 studies.
- Studies included a 24-week post-treatment follow-up period, as well as evaluation and follow-up for patients who reported severe persistent pain.
- Patients who received SC investigational product in Studies 1056, 1057, or 1058 and had an actual or planned TJR during the study, were eligible to enroll in the TJR Safety Follow-up Study 1064. The objective of this study was to provide data regarding the outcome of the patients' TJR surgeries.

5.3.2.1.1.4. Review of Joint Safety Events and Total Joint Replacements in Post-2015 OA Studies

A blinded external Adjudication Committee reviewed joint safety events; it consisted of experts in orthopedic surgery, rheumatology, orthopedic pathology, or musculoskeletal radiology with expertise in patients with end stage OA and ON.

The Adjudication Committee reviewed all possible or probable joint-related safety events which included the following:

- Those identified by the central readers for imaging (Central Reader).
- TJRs - regardless of whether or not there was an associated adverse event or potential joint safety event identified with imaging.
- Investigator-reported adverse events (potential events, based on clinical findings or imaging results) of ON, RPOA, SIF, or pathologic fracture (the 4 components of the

primary composite joint safety endpoint utilized in the post-2015 studies and discussed in the next section).

Prior to the Adjudication Committee's review of a given event, the Committee was provided with a blinded narrative summary which was produced from available source documentation including, as applicable for the event, progress reports from the Investigator, orthopedic consult reports, operative reports, radiology reports, and pathology reports. The Adjudication Committee was provided with available radiographs and MRI images for review as well as the Central Reader's reports for the available images. When available, results from the central pathologist's assessment of specimens collected from consenting patients who had a TJR were provided to the Adjudication Committee for their consideration during their adjudication review.

Each potential event was reviewed independently by the Adjudication Committee members. If there was agreement by four of the four Adjudication Committee members (or four out of five Adjudication Committee members prior to November 2018) on the categorization of the potential events, the event was considered closed. If fewer than four of the Adjudication Committee members agreed on the categorization of the potential event, the case was re-reviewed by the Adjudication Committee at a subsequent meeting and consensus agreement was sought. At that meeting, at least four of the four members needed to be present to review the case and at least three of whom needed to agree on the categorization of the event for the case to be considered closed. The rationale for the categorization was captured. There were no events that did not have at least three committee members agree on the adjudication categorization for the event.

5.3.2.1.1.5. Joint Safety Endpoints in Post-2015 Studies

Assessment of joint safety included analyses of adjudicated joint safety endpoints, TJRs, and JSW.

In total, there were six pre-specified joint safety adjudication categories (Table 29).

Table 29. Joint Safety Adjudication Categories

1.		Primary ON
2.		Worsening OA
	2a.	RPOA (RPOA-1 or RPOA-2)
	2b.	Normal Progression of OA
	2c.	Not enough information to distinguish between RPOA and normal progression of OA
3.		SIF
4.		Pathological Fracture
5.		Other (diagnosis specified)
6.		Not enough information to specify a diagnosis

Highlighted in blue are adjudication outcomes included in the primary composite joint safety endpoint.

For events assessed as 'Worsening OA' the Adjudication Committee further classified these cases as RPOA, 'Normal Progression of OA' or 'Not enough information to distinguish between RPOA and normal progression of OA'. For events assessed as RPOA, the Adjudication Committee further classified these cases as RPOA-1 or RPOA-2 as follows:

- **RPOA-1**: These were events that the Adjudication Committee considered to have significant loss of JSW (≥2 mm) within approximately 1 year without gross structural failure. The threshold of 2 mm was an absolute value, not a projected value based on loss of JSW in intervals less than 12 months. In addition, this measurement was predicated on optimal positioning and other technical issues associated with the radiological assessment.

- **RPOA-2**: These were events that were considered to have abnormal loss or destruction of bone including limited or total collapse of at least 1 subchondral surface (eg, medial femoral condyle) that is not normally present in conventional end-stage OA. Type 2 events could have been identified based on a single radiograph demonstrating abnormal destruction or collapse of bone. In order to establish a joint as being affected with RPOA-2, there should not have been preceding or concurrent radiographic evidence of ON.

Normal progression of OA was assigned to possible/probable joint safety events that the Adjudication Committee deemed followed a normal course for OA progression and did not meet the criteria for any of the joint safety outcomes or have another diagnosis.

The primary joint safety endpoint was the incidence of patients with any of the adjudication outcomes of RPOA-1 or RPOA-2, SIF, primary ON, or pathological fracture (primary composite endpoint) (shown highlighted in blue in Table 29).

Secondary joint safety endpoints included: incidence of individual adjudication outcomes of RPOA-1, RPOA-2, SIF, primary ON, pathologic fracture, and incidence of TJR.

Two additional adjudication outcomes were available: 'Other' which included a diagnosis and allowed the Adjudication Committee to specify a different outcome for events that did not meet the endpoint definitions and 'Not enough information to specify a diagnosis', but there were no events assigned to this category (Table 29).

If a patient had multiple adjudicated outcomes, the primary outcome for a patient was identified with the following hierarchy: primary ON, RPOA-2, SIF, pathological fracture, RPOA-1, not enough information to determine RPOA versus normal progression of OA, other, normal progression of OA. If a patient had multiple of the same outcomes, any associated with a TJR were chosen as the primary. In case of multiple such events existing, the one with the earliest date was selected, and if multiple events still existed, the event in the joint with the lowest KL grade was selected. For the 'All Outcomes, Patient-level' analyses, all unique event types were included for a given patient with the exception of outcomes of normal progression of OA and Other. These outcomes were only included if the patient did not have one of the outcomes included in the primary joint safety endpoint. Patients with more than one event with the same adjudication outcome were only included once per adjudication outcome.

5.3.2.1.2. Baseline Disease Status

Across the OA controlled post-2015 studies (Studies 1056, 1057 and 1058), the majority of patients had multiple joints with OA; approximately 78% of patients had ≥1 joint of KL

Grade 3 or 4, and 2 or more joints with KL Grade ≥2, indicating moderate to severe OA at baseline (Table 30).

Table 30. Baseline Disease Status in the OA Controlled Post-2015 Studies

	Placebo	Tanezumab			NSAID
n (%)	N=514	2.5 mg N=1530	2.5/5 mg N=219	5 mg N=1282	N=996
Index Joint					
Knee	434 (84.4)	1291 (84.4)	189 (86.3)	2566 (84.7)	852 (85.5)
Hip	80 (15.6)	239 (15.6)	30 (13.7)	465 (15.3)	144 (14.5)
KL Grade of the Index Joint					
0	0	2 (0.1)	0	4 (0.3)	1 (0.1)
1	0	3 (0.2)	0	2 (0.2)	3 (0.3)
2	124 (24.1)	410 (26.8)	56 (25.6)	361 (28.2)	291 (29.2)
3	221 (43.0)	714 (46.7)	98 (44.7)	595 (46.4)	476 (47.8)
4	169 (32.9)	401 (26.2)	64 (29.2)	320 (25.0)	225 (22.6)
Maximum KL Grade of Any Joint					
0	0	0	0	0	0
1	0	1 (0.1)	0	0	0
2	86 (16.7)	329 (21.5)	48 (21.9)	280 (21.8)	239 (24.0)
3	242 (47.1)	752 (49.2)	99 (45.2)	645 (50.3)	503 (50.5)
4	186 (36.2)	448 (29.3)	72 (32.9)	357 (27.8)	254 (25.5)
Shoulder OA at Baseline[a]					
Yes	20 (3.9)	107 (7.0)	15 (6.8)	82 (6.4)	55 (5.5)
Number of Joints with KL Grade ≥2					
0	0	1 (0.1)	0	0	0
1	101 (19.6)	358 (23.4)	45 (20.5)	262 (20.4)	219 (22.0)
2	278 (54.1)	824 (53.9)	116 (53.0)	722 (56.3)	560 (56.2)
3	87 (16.9)	202 (13.2)	34 (15.5)	186 (14.5)	124 (12.4)
4	48 (9.3)	145 (9.5)	24 (11.0)	112 (8.7)	93 (9.3)

OA Controlled Post-2015 Studies 1056, 1057, 1058
a. Shoulder OA at Baseline is based on the Investigator's assessment of musculoskeletal history

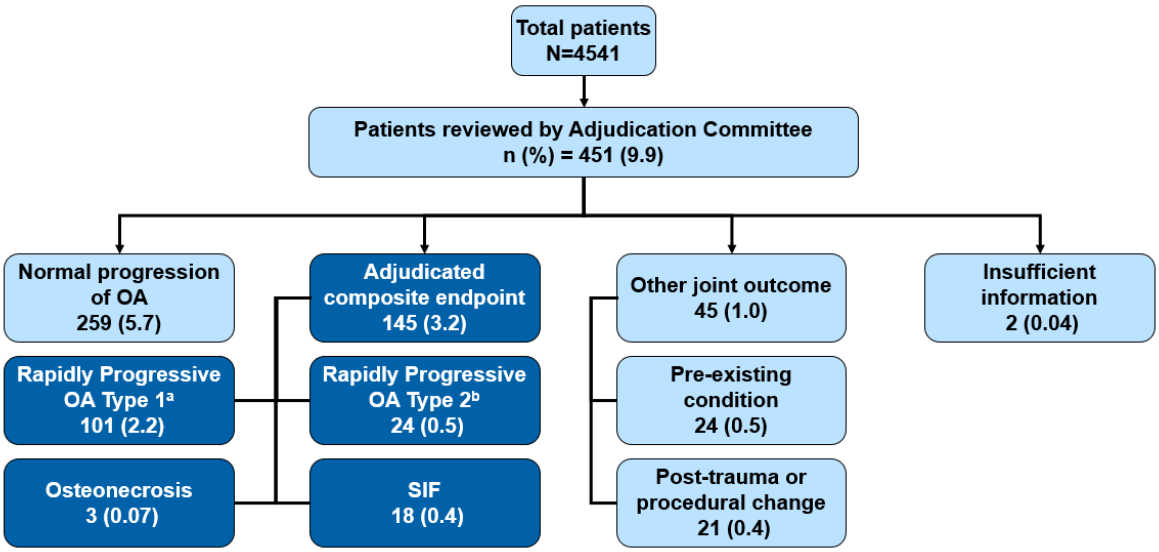
5.3.2.1.3. Adjudicated Joint Safety Events

As shown in Figure 31, across Studies 1056, 1057 and 1058 which included a total of 4541 patients (across all treatment groups: tanezumab 2.5 mg, tanezumab 5 mg, tanezumab 2.5/5 mg and NSAID), 451 patients (9.9%) had joint safety events that were reviewed by the Adjudication Committee and 145 (3.2%) had an adjudicated joint safety outcome included in the primary composite joint safety endpoint (an event of ON, RPOA-1, RPOA-2, SIF, or pathological fracture; patient-level by primary outcome). Of the 145 patients with an adjudicated outcome included in the primary composite endpoint (primary outcome), the majority (100 patients with primary outcome of RPOA-1, 69%; 101 patients with any RPOA-1 event) had events that were classified as RPOA-1; 24 patients (17%) had events classified as RPOA-2; 18 patients (12%) had events classified as SIF; and three patients (2%) had events classified as ON. The most commonly reported adjudication outcome of the 451 patients reviewed was 'normal progression of OA' (259 patients, 57%). A total of 45 patients (10%) had an adjudication outcome of 'Other' and within this group the two main diagnoses (0.004%) were 'pre-existing condition' or 'post-trauma or procedural change'. There were

two patients for whom there was insufficient information to determine rapid versus normal progression of OA. No patient had an adjudication outcome of pathological fracture.

Of the 145 total patients with adjudicated outcomes in the primary composite endpoint, 9 patients (6%) had more than 1 affected joint (1 patient in the tanezumab 2.5 mg group, 7 patients in the tanezumab 5 mg group and 1 patient in the NSAID group) and in 3 patients (2%) the affected joint was the shoulder (2 patients in the tanezumab 5 mg group and 1 patient in the NSAID group).

Figure 31. Identification of and Adjudication of Joint Safety Events in OA Controlled Post-2015 Studies



OA Controlled Post-2015 Studies 1056, 1057, 1058 (Composite Endpoint – Primary Outcome; Individual Components – All Outcomes)
a. Defined as a significant loss of JSW ≥2 mm (predicted on optimal joint positioning) within approximately 1 year, without gross structural failure.
b. Defined as abnormal bone loss or destruction, including limited or total collapse of at least 1 subchondral surface, which is not normally present in conventional end-stage OA.

- Summary of Adjudication Endpoints

A summary of the adjudicated composite endpoint as well as the individual components of the composite endpoint, broken down by treatment group, is shown in Figure 32. Statistical analyses of the adjudication endpoints are provided in the next section.

Primary Composite Endpoint

Across Studies 1056, 1057 and 1058, there were no adjudicated joint safety endpoints included in the primary composite endpoint identified in placebo-treated patients compared to events in 49 patients (3.2%) and 80 patients (6.2%) in the tanezumab 2.5 mg and 5 mg treatment groups, respectively, and 15 patients (1.5%) in the NSAID-treatment group. The

treatment differences relative to NSAIDs for both the tanezumab 2.5 mg and 5 mg treatment groups were statistically significant.

- RPOA-1

There was a dose-dependent increase in adjudicated events of RPOA-1 in the tanezumab treatment groups compared to the NSAID treatment group. The treatment differences relative to NSAIDs for both the tanezumab 2.5 mg and 5 mg treatment groups were statistically significant. The majority of adjudicated events included in the primary composite endpoint were RPOA-1 events.

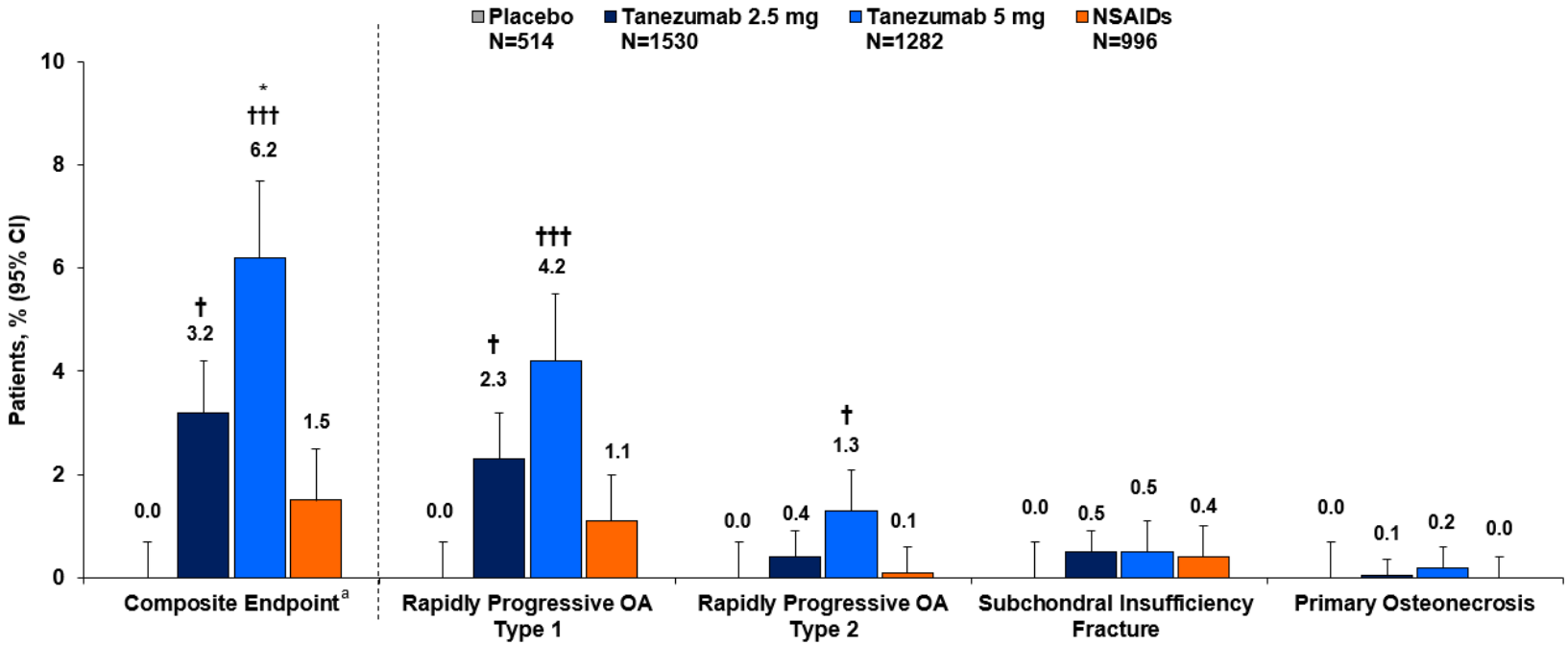
- RPOA-2

The incidence of adjudicated events of RPOA-2 with tanezumab 2.5 mg was low (0.4%) and not statistically significantly different from NSAIDs (0.1%). Adjudicated events of RPOA-2 were significantly increased in patients treated with tanezumab 5 mg (1.3%) relative to patients treated with NSAIDs (0.1%).

- SIF and ON

For SIF and ON, the event rates were similar across treatment groups.

Figure 32. Summary of Adjudication Outcomes for the OA Controlled Post-2015 Studies



OA Controlled Post-2015 Studies 1056, 1057 and 1058 (Composite Endpoint-Primary Outcome; Individual Components-All outcomes)
Data not shown for Study 1056 2.5/5 mg treatment group: Composite endpoint, 0.5%; RPOA-1, 0.5%; RPOA-2, 0%; SIF, 0%; ON, 0%.
*p≤0.05, **p≤0.001, ***p≤0.001 versus placebo (based on comparisons of data from Studies 1056/1057).
†p≤0.05, ††p≤0.01; †††p≤0.001 versus NSAIDs (based on comparisons of data from Study 1058).
a. No patients adjudicated with pathological fracture.

- Statistical Analyses of Adjudicated Joint Safety Endpoints for the Post-2015 Placebo-Controlled OA Pool and the OA Active-Controlled Study

Overall summaries of adjudicated joint safety endpoints for Studies 1056, 1057, and 1058, were performed at the patient-level using incidence and observation-time adjusted rates. Because of the differences in study duration and comparators between the placebo-controlled studies and active-controlled study, statistical analyses of adjudicated joint safety endpoints were not conducted for the entire pool of post-2015 studies. Statistical analyses were conducted separately for the OA post-2015 placebo-controlled studies (Studies 1056 and 1057) and OA active-controlled Study 1058. For most summaries and analyses, joint safety events occurring within 26 weeks after the end of the treatment period were included (Table 31). In analyses of observation-time adjusted rates the observed treatment group differences were similar to analyses based on the incidence of joint safety events.

In the OA placebo-controlled post-2015 studies, there were no adjudicated joint safety endpoints included in the primary composite endpoint identified in the placebo-treated patients compared to events in 10 patients (1.9%) and 9 patients (3.2%) in the tanezumab 2.5 and 5 mg treatment groups, respectively. The incidence and risk difference for the primary composite endpoint were highest with tanezumab 5 mg treatment. The risk difference (3.17%) for the incidence was statistically significantly higher in patients treated with tanezumab 5 mg compared to placebo-treated patients (p=0.0367). The risk difference (1.89%) for the primary composite endpoint with tanezumab 2.5 mg trended higher (p=0.0841) relative to placebo treatment.

In the OA active-controlled Study 1058, the incidence and risk difference for the primary composite endpoint, were highest in the tanezumab 5 mg treatment group and increased relative to the NSAID treatment group in both the tanezumab 5 and 2.5 mg treatment groups.

Table 31. Summary of the Adjudicated Primary Composite Endpoint, RPOA-1, RPOA-2, Primary ON and SIF for the OA Placebo-Controlled Post-2015 Pool and the OA Active-Controlled SC Study

	Placebo-Controlled Post-2015 Pool				Active Controlled SC Study		
	Placebo	Tanezumab			Tanezumab		NSAID
	N=514	2.5 mg N = 528	2.5/5 mg N = 219	5 mg N = 284	2.5 mg N=1002	5 mg N=998	N = 996
Observation time: Primary Composite Endpoint (patient-years)	396.1	414.8	162.4	239.9	1017.1	992.9	1011.1
Length of Study/Observation Period[a]	40-48 weeks				80 weeks		
Planned number of injections of SC study medication	Study 1056: 2 doses Study 1057: 3 doses				7 doses		
	n (%) [95% CI] Risk difference versus placebo (%[95% CI]) p-value versus placebo for risk difference				n (%) [95% CI] Risk difference versus NSAID (%[95% CI]) p-value versus NSAID for risk difference		
Primary Composite Joint Safety Endpoint[b]	0 (0.0) [0.0, 0.7]	10 (1.9) [0.9, 3.5] 1.89 [-0.05, 4.71] 0.0841	1 (0.5) [0.0, 2.5] 0.46 [-1.63, 4.47] 0.6962	9 (3.2) [1.5, 5.9] 3.17 [0.56, 7.18] 0.0367	39 (3.9) [2.8, 5.3] 2.39 [0.58, 4.68] 0.0123	71 (7.1) [5.6, 8.9] 5.61 [3.55, 8.14] <0.0001	15 (1.5) [0.8, 2.5]
RPOA-1	0 (0.0) [0.0, 0.7]	6 (1.1) [0.4, 2.5] 1.14 [-0.68, 3.85] 0.2381	1 (0.5) [0.0, 2.5] 0.46 [-1.63, 4.47] 0.6962	5 (1.8) [0.6, 4.1] 1.76 [-0.54, 5.51] 0.1834	29 (2.9) [1.9, 4.1] 1.79 [0.16, 3.92] 0.0366	49 (4.9) [3.7, 6.4] 3.81 [1.99, 6.12] 0.0001	11 (1.1) [0.6, 2.0]
RPOA-2	0 (0.0) [0.0, 0.7]	3 (0.6) [0.1, 1.7] 0.57 [-1.15, 3.20] 0.4863	0 (0.0) [0.0, 1.7] 0.00 [-1.94, 3.89] 1.000	3 (1.1) [0.2, 3.1 1.06 [-1.08, 4.67] 0.3774]	3 (0.3) [0.1, 0.9] 0.20 [-0.76, 1.71] 0.6168	14 (1.4) [0.8, 2.3] 1.30 [0.17, 2.97] 0.0388	1 (0.1) [0.0, 0.6]
Primary ON	0 (0.0) [0.0, 0.7]	0 (0.0) [0.0, 0.7] 0.00 [-1.61, 2.55] 1.0000	0 (0.0) [0.0, 1.7] 0.00 [-1.94, 3.89] 1.0000	1 (0.4) [0.0, 1.9] 0.35 [-1.59, 3.82] 0.7330	1 (0.1) [0.0, 0.6] 0.10 [-0.74, 1.51] 0.7245	1 (0.1) [0.0, 0.6] 0.10 [-0.74, 1.52] 0.7182	0 (0.0) [0.0, 0.4]
SIF	0 (0.0) [0.0, 0.7]	1 (0.2) [0.0, 1.1] 0.19 [-1.45, 2.77] 0.7560	0 (0.0) [0.0, 1.7] 0.00 [-1.94, 3.89] 1.0000	0 (0.0) [0.0, 1.3] 0.00 [-1.84, 3.39] 1.0000	6 (0.6) [0.2, 1.3] 0.20 [-0.96, 1.90] 0.6824	7 (0.7) [0.3, 1.4] 0.30 [-0.86, 2.03] 0.5632	4 (0.4) [0.1, 1.0]

OA Placebo-controlled Post-2015 Studies: 1056, 1057; OA Active-controlled SC Study: 1058 (Composite Endpoint – Primary Outcome; Individual Components – All Outcomes)
[a]Observation period was the period from Baseline up to the end of the safety follow-up period or 26 weeks after the end of the treatment period, whichever is later.
[b]RPOA, primary ON, SIF, pathologic fracture
No patients had an adjudicated outcome of pathologic fracture.

5.3.2.1.3.1. RPOA-1

5.3.2.1.3.1.1. Characterization of RPOA-1 Events

Across the OA controlled post-2015 studies, there were a total of 106 adjudicated RPOA-1 events in 101 total patients with an RPOA-1 event. RPOA-1 most frequently occurred in the knee (83%) and the majority (85%) of affected joints did not undergo TJR within the treatment period or 24-week follow-up period. In the tanezumab 2.5 mg treatment group, 4 of the 36 joints (11%) with RPOA-1 (all of which were KL Grade 2 or 3 at baseline) had a TJR. Most (82/106) RPOA-1 events occurred in joints that had radiographic evidence of OA with KL Grade 2 or 3 OA at baseline, although there were four events in joints that were KL Grade 0 at baseline (two each in the tanezumab 2.5 mg and 5 mg treatment groups). No events of RPOA-1 occurred in joints that were KL Grade 4 at baseline (Table 32). One explanation for this is joints with KL Grade 4 at baseline likely do not have at least 2 mm of joint space available so the criteria for RPOA-1 could not be met.

Table 32. Characteristics of Adjudicated RPOA-1 Events in the OA Controlled Post-2015 Studies (Joint-Level)

	Placebo N=514	Tanezumab 2.5 mg N=1530	Tanezumab 2.5/5 mg N=219	Tanezumab 5 mg N=1282	NSAID N=996
n (%)					
Any RPOA-1 Event	0	36 (2.4)	1 (0.5)	58 (4.5)	11 (1.1)
TJR (yes)	0	4 (0.3)	1 (0.5)	9 (0.7)	2 (0.2)
Affected Joint					
Knee	0	30 (2.0)	0	49 (3.8)	9 (0.9)
Hip	0	6 (0.4)	1 (0.5)	8 (0.6)	2 (0.2)
Shoulder	0	0	0	1 (0.1)	0
Index Joint	0	19 (1.2)	1 (0.5)	21 (1.6)	9 (0.9)
Baseline KL Grade of Affected Joint					
Not Available	0	0	0	1 (0.1)	0
0	0	2 (0.1)	0	2 (0.2)	0
1	0	7 (0.5)	0	11 (0.9)	1 (0.1)
2	0	13 (0.8)	0	27 (2.1)	5 (0.5)
3	0	14 (0.9)	1 (0.5)	17 (1.3)	5 (0.5)
4	0	0	0	0	0

OA Controlled Post-2015 Studies 1056, 1057, 1058.
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.

To provide some clinical context for the RPOA-1 events, characteristics of the joints and patients who had RPOA-1 were compared to those with Normal Progression of OA for the tanezumab 2.5 mg and NSAID groups (Table 33). In general, the profiles of patients and joints with RPOA-1 or Normal Progression of OA were similar across treatment groups. A few minor differences were observed between the two event types. First, across treatment groups a higher percentage of RPOA-1 events occurred in knee joints than for Normal Progression of OA events. In addition, the percentage of RPOA-1 events occurring in the

index joint was lower for the tanezumab 2.5 mg treatment group relative to NSAIDs, although most RPOA-1 events in both treatment groups occurred in joints that were KL Grade 2 or 3 at baseline.

Differences were noted in the post-baseline musculoskeletal exam data. At Screening, across treatment group and outcomes, ~80% of the affected joints had an abnormality identified with the most common findings being pain on motion, crepitus, tenderness, and decreased range of motion. Across both treatment groups, a change in the post-baseline musculoskeletal exam occurred more frequently in joints with RPOA-1 than for those with Normal Progression of OA.

Table 33. Comparison of Adjudicated RPOA-1 and Normal Progression of OA Events in the OA Controlled Post-2015 Studies

Joint-Level Summary	Tanezumab 2.5 mg and NSAID N=172	
	RPOA-1 N=46 Patients n=47 Affected Joints	Normal Progression of OA N=126 Patients n=139 Affected Joints
Affected Joint: Knee	83%	66%
Index Joint:	Tanezumab 2.5 mg: 53% NSAID: 82%	Tanezumab 2.5 mg: 74% NSAID: 81%
KL Grade	79% KL Grade 2 or 3	86% KL Grade 3 or 4
Abnormal MSK Exam at Screening[a]	**81%**	**87%**
Pain on motion	53%	66%
Crepitus	47%	42%
Tenderness	32%	38%
Decreased range of motion	30%	45%
Change in MSK Exam Post-Baseline[a,b]	**36%**	**20%**
Clinically significant	15%	13%

OA Controlled Post-2015 Studies 1056, 1057, and 1058.
MSK = musculoskeletal
Includes adjudicated events up to the end of the follow-up period or 26 weeks after the end of the treatment period, whichever is later.
a. Knee and hip joints only.
b.Includes musculoskeletal examination results up to and including the date of the adjudicated outcome.

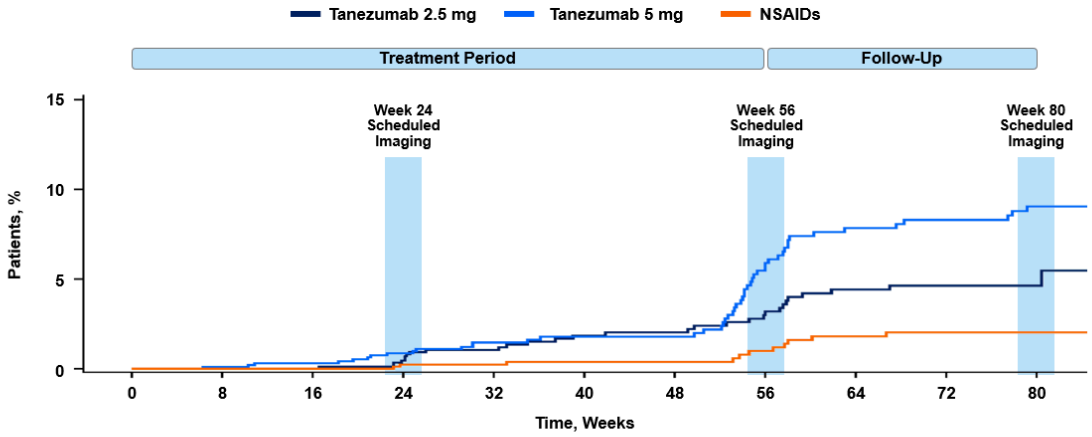
5.3.2.1.3.1.2. Timing of Adjudicated RPOA-1 Events

Across the post-2015 OA studies, 89 of 101 total patients with RPOA-1 events (88%) had the RPOA-1 event in Study 1058. Study 1058 had a 56-week treatment period and included seven administrations of SC study medication and a 24-week follow-up period.

The analysis of time to RPOA-1 events and plot of time to RPOA-1 events in Study 1058 (Figure 33) indicated statistically significant differences between both the tanezumab 2.5 mg and 5 mg treatment groups versus the NSAID treatment group. The increases in events observed around Week 24 and Week 56 generally correspond to the timing of Study 1058 protocol-specified imaging visits (Figure 33). After Week 24, the shape of the curves for the tanezumab 2.5 mg and NSAID groups were generally similar. This contrasts with the tanezumab 5 mg group which had a larger increase in events at Week 56. For patients who had a possible joint safety event identified during the treatment period, treatment was

stopped, and these patients were monitored for an additional 24 weeks. For the patients with follow-up imaging, there were no patients who had an adjudicated RPOA-1 event that progressed to an adjudicated RPOA-2 event.

Figure 33. Plot of Time to Adjudicated RPOA-1 Events in the OA Active-Controlled SC Study 1058

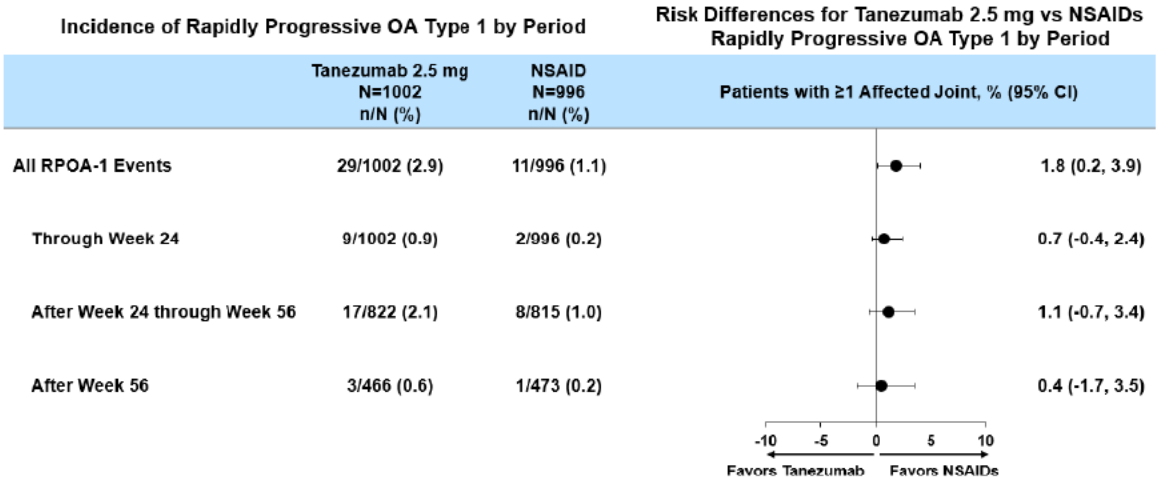


Week		0	24	56	80
Patients	2.5 mg	1002	855	489	259
	5 mg	998	873	450	238
	NSAIDs	996	866	489	254

Tanezumab 2.5 mg versus NSAID p = 0.0043
Tanezumab 5 mg versus NSAID p<0.0001

To further evaluate the timing of RPOA-1 events in Study 1058, the incidence of RPOA-1 events and risk differences for tanezumab 2.5 mg versus NSAIDs was summarized by the interval during the 80-week observation period the RPOA-1 event was identified (Figure 34). The intervals consisted of: 1) period from baseline through the Week 24 imaging visit; 2) the period after the Week 24 imaging visit through the Week 56 imaging visit; and 3) the period after the Week 56 imaging visit. Most RPOA-1 events in both treatment groups occurred after the Week 24 imaging visit through the Week 56 imaging visit. When comparing the values across treatment groups for the first two periods on the forest plot, the risk differences were similar, whereas, the risk difference was decreased to 0.4% for the period after the Week 56 imaging visit. This finding suggests the risk difference for RPOA-1 relative to NSAIDs did not increase throughout the 80-week observation period.

Figure 34. Risk Differences for RPOA-1 by Study Period in the OA Active-Controlled SC Study 1058 (Patient-Level)



Week 24 and Week 56 imaging visits defined as Study Days 169 and 393, respectively, +/- 4 weeks.

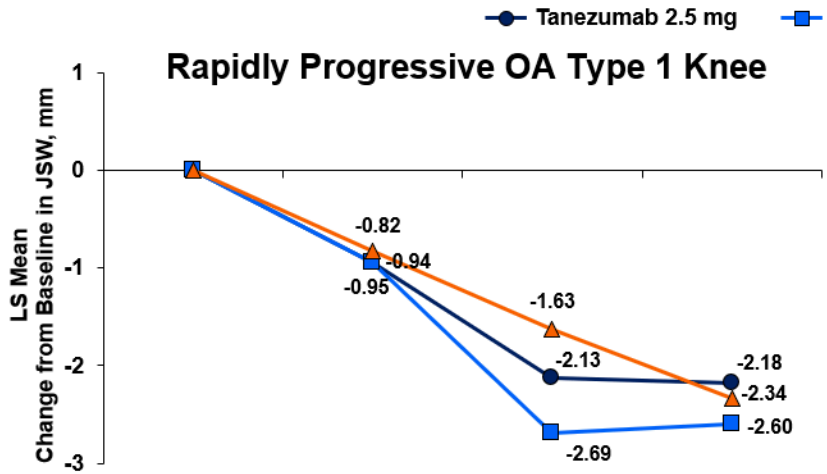
5.3.2.1.3.1.3. Joint Space Width

- Joint Space Width Changes in Affected and Unaffected Knees of Patients with RPOA-1

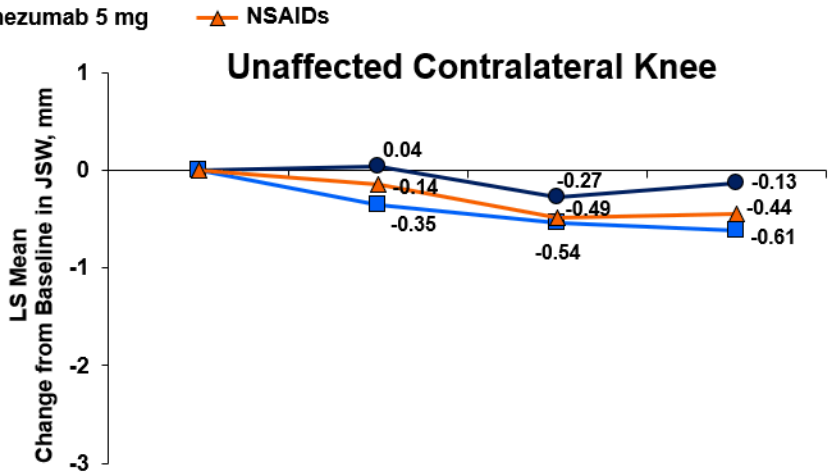
To supplement the assessment of RPOA-1 which is based on radiographic assessment of JSW and assess whether patients with RPOA-1 in one knee also had changes in their unaffected knee, the change from Baseline in JSW in the knee with RPOA-1 and the contralateral knee for patients in Study 1058 was analyzed. Figure 35 shows the absolute magnitude of the changes from Baseline in medial JSW for joints with adjudicated RPOA-1 compared to the contralateral joints without RPOA-1. The tables at the bottom of the figure provide the number of joints that were analyzed at each time point (Figure 35).

The magnitude of the LS mean changes from Baseline in medial JSW were larger for the joints with adjudicated RPOA-1 than for the joints without adjudicated RPOA-1. There were no statistically significant treatment differences between the tanezumab-treated patients and the NSAID-treated patients for the analyses of change from baseline in medial JSW for the affected knees or the unaffected contralateral knees, although numbers are small.

Figure 35. Change From Baseline in Medial Joint Space Width for Knee Joints With Adjudicated RPOA-1 Versus Contralateral Knee Without RPOA-1 in OA Active-Controlled SC Study 1058



	Baseline (Medial JSW Median)	Number of Knees		
		Week 24	Week 56	Week 80
2.5 mg	24 (3.9 mm)	22	13	9
5 mg	38 (3.5 mm)	36	28	16
NSAIDs	8 (3.9 mm)	7	5	2



	Baseline (Medial JSW Median)	Number of Knees		
		Week 24	Week 56	Week 80
2.5 mg	22 (4.0 mm)	21	12	8
5 mg	33 (2.3 mm)	32	26	14
NSAIDs	7 (2.1 mm)	6	4	2

Includes all baseline KL Grades except for KL Grade 4

5.3.2.1.3.1.4. RPOA-1 Subgroup Analyses and Risk Factor Identification

Subgroup analyses for demographic factors, baseline disease severity, selected adverse events, efficacy response at Week 16, sensory examinations in lower extremities, and other factors such as concomitant medications (eg, concomitant CV prophylactic aspirin use (≤325 mg), intra-articular corticosteroid use, bisphosphonate use, and concomitant acetaminophen use) and selected medical history related to bone health (eg, history of osteopenia or osteoporosis, baseline dual energy x-ray absorptiometry assessments), indicated that there were few factors that seemed to occur in a pattern that was different between patients with or without RPOA-1. No characteristic other than structural severity of the affected joint at baseline was associated with the occurrence of RPOA-1. Analyses showed that across the treatment groups patients with more severe OA at baseline (maximum KL Grade in any joint = 3) tended to have a higher incidence of adjudicated RPOA-1 events. In approximately one-third of patients who had an RPOA-1 event, adverse events of arthralgia or joint swelling were associated with the event compared to approximately 20% of patients with no RPOA-1 event who had one of these adverse events.

As discussed in Section 5.3.2.1.1.2, in the pre-2015 studies, more than 90 days of NSAID use in conjunction with tanezumab administration was associated with an increase in the incidence of RPOA and All-Cause TJR events. In the post-2015 studies, limited NSAID use of no more than 10 days per 8-week dosing interval was not associated with an increased risk of RPOA or TJR. However, given the data from the pre-2015 studies, co-administration of tanezumab and NSAIDs is not recommended due to the potential for an increased risk of joint safety events and this is reflected in the proposed prescribing information.

5.3.2.1.3.1.5. RPOA-1 Risk Differences

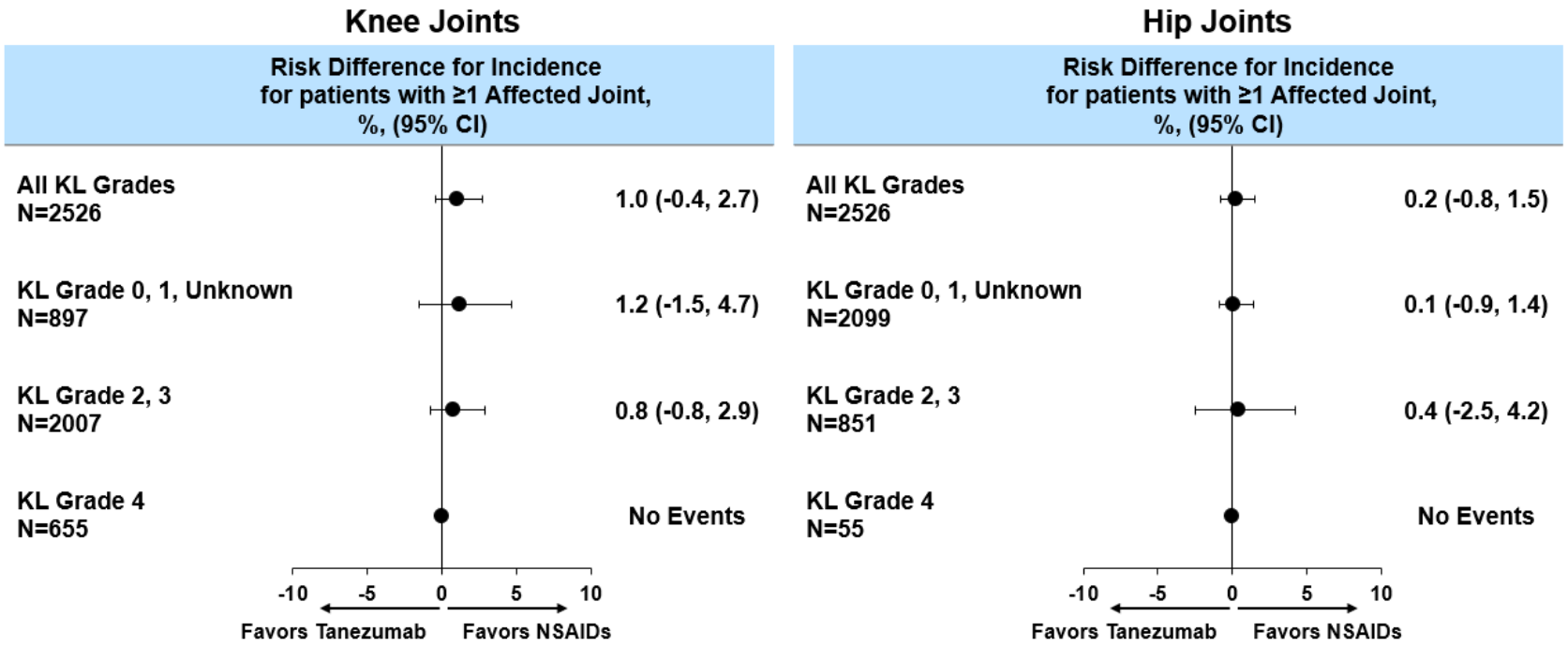
To further characterize the association of patients who have more severe structural OA at baseline tending to have a higher incidence of RPOA-1, analyses of the risk differences for developing RPOA-1 in the knee or hip, in patients treated with tanezumab 2.5 mg relative to both placebo and NSAIDs were evaluated by baseline KL Grade of the affected joint. Table 34 provides the incidence for RPOA-1 by the affected joint type (knee or hip) and baseline KL grade of the affected joint. Across the treatment groups, the highest incidences of RPOA-1 were observed in patients with a KL Grade 2 or 3 knee or hip at baseline. No events occurred in joints that were KL Grade 4 at baseline. The risk differences relative to NSAIDs were similar for patients with KL grades ≤3 for both joints (Figure 36).

Table 34. Risk Differences for Adjudicated RPOA-1 for Knees and Hips by Baseline KL Grade of Affected Joint in the OA Controlled Post-2015 Studies (Patient-Level)

	Number (Incidence) of RPOA-1 Endpoint[a]		
	Placebo N=514	Tanezumab 2.5 mg N=1530	NSAID N=996
Any Baseline KL grade			
Knee	0 (0.0)	29 (1.9)	9 (0.9)
Hip	0 (0.0)	6 (0.4)	2 (0.2)
Baseline KL grade 0, 1 or unknown [patients with KL Grade 0, 1, or unknown at baseline]			
Knee	0 (0.0) [n=174]	8 (1.4) [n=553]	1 (0.3) [n=334]
Hip	0 (0.0) [n=419]	1 (0.1) [n=1274]	0 (0.0) [n=825]
Baseline KL grade 2 or 3 [patients with KL grade 2 or 3 joint at baseline]			
Knee	0 (0.0) [n=395]	22 (1.8) [n=1198]	8 (1.0) [n=809]
Hip	0 (0.0) [n=190]	5 (1.0) [n=519]	2 (0.6) [n=332]
Baseline KL grade 4 [patients with KL grade 4 joint at baseline]			
Knee	0 (0.0) [n=171]	0 (0.0) [n=415]	0 (0.0) [n=240]
Hip	0 (0.0) [n=17]	0 (0.0) [n=40]	0 (0.0) [n=15]

OA Controlled Post-2015 Studies: 1056, 1057, and 1058
a. Patients with at least one affected joint

Figure 36. Risk Differences for Adjudicated RPOA-1 by Baseline KL Grade of Affected Joint: Tanezumab 2.5 mg Versus NSAIDs in the OA Controlled Post-2015 Studies (Patient-Level)



OA Controlled Post-2015 Studies: 1056, 1057 and 1058
Patients can be represented on more than one KL subcategory

5.3.2.1.3.2. RPOA-2

5.3.2.1.3.2.1. Characterization of RPOA-2 Events

Across the OA controlled post-2015 studies, there were a total of 26 adjudicated RPOA-2 events in 24 patients. Across the treatment groups in the OA controlled post-2015 studies, the affected joint was approximately evenly split between the hip and knee with only two patients having the shoulder as the affected joint (one each in the tanezumab 5 mg and NSAID treatment groups). Approximately half (14/26) of the RPOA-2 events occurred in joints that eventually had a TJR at some point during the treatment period or 24-week safety follow-up period. Most (20/26) RPOA-2 events occurred in joints that had radiographic evidence of KL Grade 3 or 4 OA at baseline. There were two events in joints that were KL Grade 0 at baseline (both in the tanezumab 5 mg treatment group; Table 35).

Table 35. Characteristics of Adjudicated RPOA-2 Events in the OA Controlled Post-2015 Studies (Joint-Level)

	Placebo N=514	Tanezumab 2.5 mg N=1530	Tanezumab 5 mg N=1282	NSAID N=996
n (%)				
Any RPOA-2 Event	0	6 (0.4)	19 (1.5)	1 (0.1)
TJR (yes)	0	3 (0.2)	10 (0.8)	1 (0.1)
Affected Joint				
Knee	0	3 (0.2)	8 (0.6)	0
Hip	0	3 (0.2)	10 (0.8)	0
Shoulder	0	0	1 (0.1)	1 (0.1)
Index Joint	0	5 (0.3)	8 (0.6)	0
Baseline KL Grade of Affected Joint				
Not Available	0	0	1 (0.1)	1 (0.1)
0	0	0	2 (0.2)	0
1	0	0	1 (0.1)	0
2	0	0	1 (0.1)	0
3	0	1 (0.1)	8 (0.6)	0
4	0	5 (0.3)	6 (0.5)	0

OA Controlled Post-2015 Studies 1056, 1057, 1058.
Data not shown for Study 1056 2.5/5 mg treatment group – there were no RPOA-2 events in this group.
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.

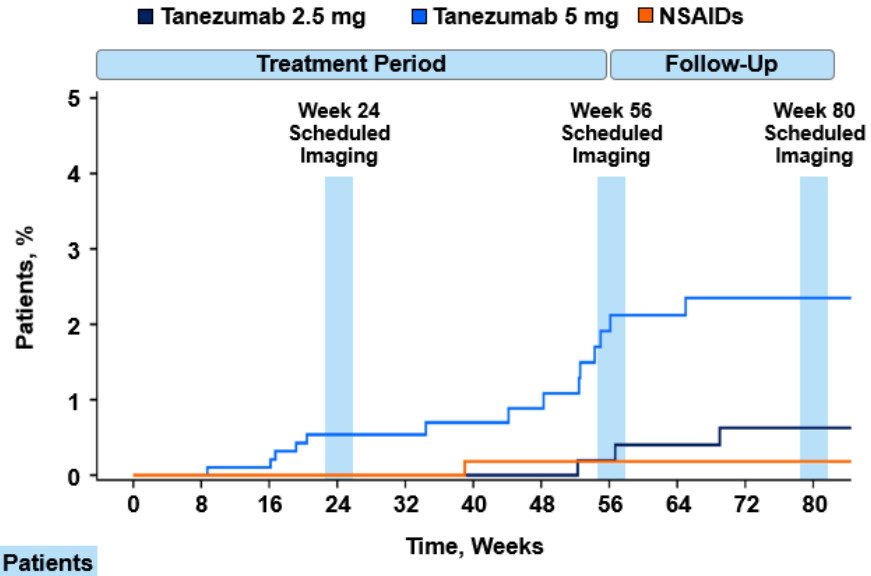
5.3.2.1.3.2.2. Timing of Adjudicated RPOA-2 Events

The time to adjudicated RPOA-2 events from Study 1058 was analyzed and Kaplan-Meier estimates of the time to event were produced. Study 1058 had a 56-week treatment period and included 7 administrations of SC study medication and a 24-week follow-up period.

The general profile of the Kaplan-Meier curve indicates the tanezumab 5 mg treatment group had an earlier increase in RPOA-2 events than the other treatment groups in Study 1058

(Figure 37). For comparisons between treatment with tanezumab 5 mg and NSAIDs, a statistically significant difference (p=0.0007) was observed. The analysis of time to RPOA-2 and plot of time to RPOA-2 showed a trend for a treatment difference between tanezumab 2.5 mg and NSAID but the difference was not statistically significant (p=0.3246). The RPOA-2 events in both the tanezumab 2.5 mg and NSAID treatment groups occurred after the Week 24 visit and closer to the end of the study.

Figure 37. Plot of Time to Adjudicated RPOA-2 Events in the OA Active-Controlled SC Study 1058

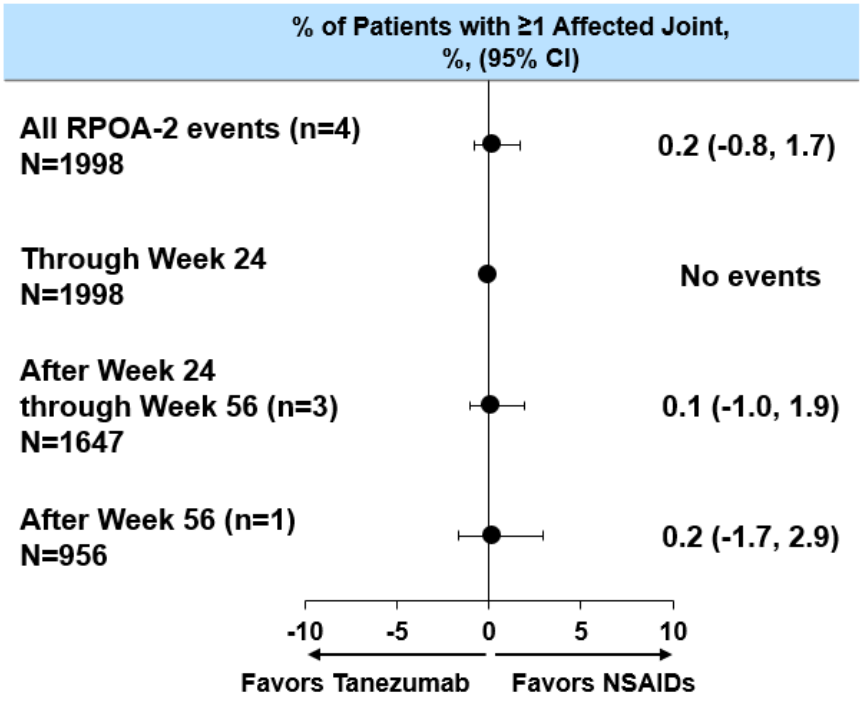


Patients				
2.5 mg	1002	859	494	264
5 mg	998	877	465	249
NSAIDs	996	868	492	259

Tanezumab 2.5 mg versus NSAID p = 0.3246
Tanezumab 5 mg versus NSAID p = 0.0007

Similar to the analyses conducted for RPOA-1 events by study period, the risk differences for developing RPOA-2 for tanezumab 2.5 mg versus NSAID by study period are shown in Figure 38. As shown in the Kaplan Meier analyses for RPOA-2, the events all occurred after the Week 24 imaging visit. The risk differences relative to NSAIDs was 0.2% or less in all study periods indicating the risk differences were similar throughout the 80-week observation period.

Figure 38. Risk Differences for RPOA-2 by Study Period in the OA Active-Controlled SC Study 1058 (Patient-Level)



Forest Plot: Week 24 and Week 56 imaging visits defined as Study Days 169 and 393, respectively, +/- 4 weeks.

5.3.2.1.3.2.3. RPOA-2 Subgroup Analyses and Risk Factor Identification

Subgroup analyses for demographic factors, baseline disease severity, selected adverse events, efficacy response at Week 16, sensory examinations in lower extremities, and other factors such as concomitant medications and selected medical history related to bone health, indicated no characteristic other than structural severity of the affected joint at baseline was associated with the occurrence of RPOA-2.

In approximately one-third of patients who had an RPOA-2 event, adverse events of arthralgia or joint swelling were associated with the event compared to approximately 20% of patients with no RPOA-2 event who had one of these adverse events.

5.3.2.1.3.2.4. RPOA-2 Risk Differences

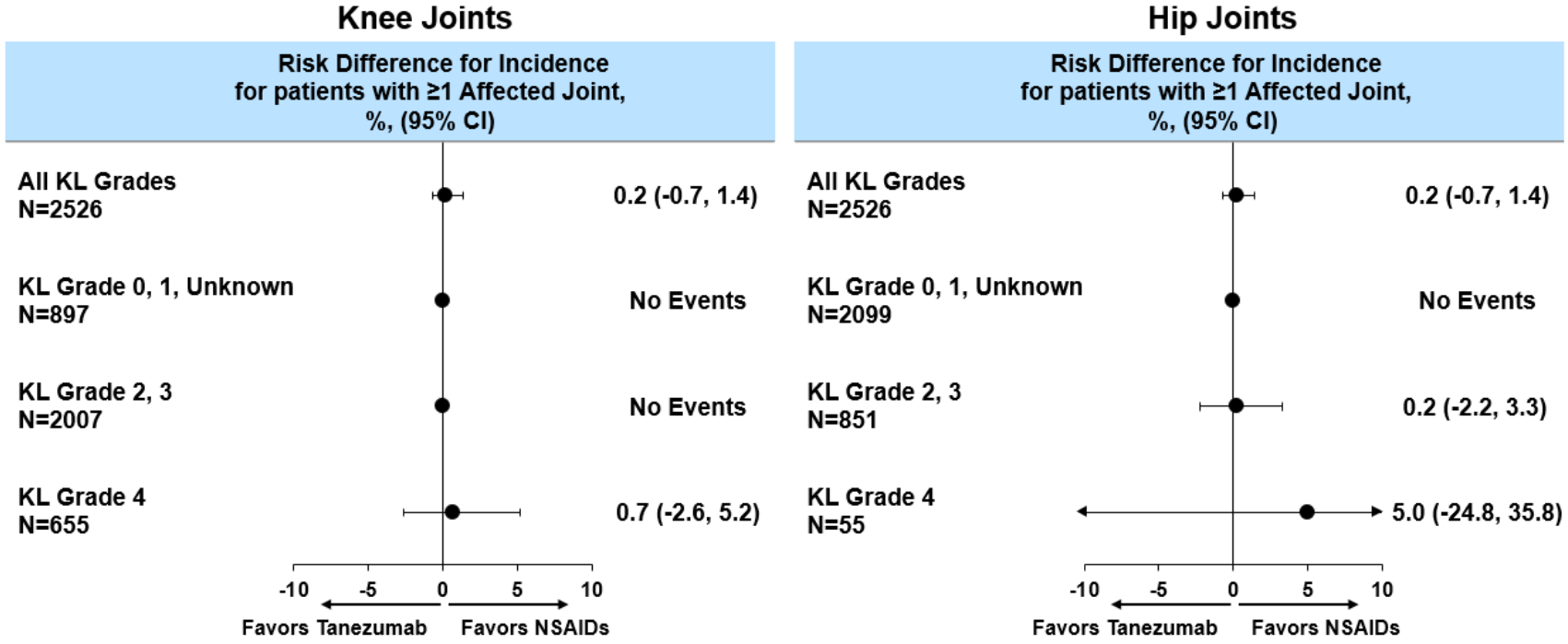
The evaluation of incidence of adjudicated RPOA-2 and risk differences for tanezumab 2.5 mg versus NSAIDs for developing RPOA-2 in the knee or hip by KL Grade in the affected joint is shown in Table 36 and Figure 39. The overall number of RPOA-2 events in the tanezumab 2.5 mg treatment group was low with 6 total events; 3 occurring in the knee and 3 occurring in the hip. The forest plot for the hips shows the risk difference of 5% for patients with KL Grade 4 hips is the least favorable. The risk differences for patients with the other KL grades in the knee and hip joints which had RPOA-2 events were less than 1%.

Table 36. Risk Difference for Adjudicated RPOA-2 for Knees and Hips by Baseline KL Grade of Affected Joint in the OA Controlled Post-2015 Studies (Patient-Level)

	Number (Incidence) of RPOA-2 Endpoint[a]		
	Placebo N=514	Tanezumab 2.5 mg N=1530	NSAID N=996
Any Baseline KL grade			
Knee	0 (0.0)	3 (0.2)	0 (0.0)
Hip	0 (0.0)	3 (0.2)	0 (0.0)
Baseline KL grade 0, 1 or unknown [patients with KL Grade 0, 1, or unknown at baseline]			
Knee	0 (0.0) [n=174]	0 (0.0) [n=553]	0 (0.0) [n=334]
Hip	0 (0.0) [n=419]	0 (0.0) [n=1274]	0 (0.0) [n=825]
Baseline KL grade 2 or 3 [patients with KL grade 2 or 3 joint at baseline]			
Knee	0 (0.0) [n=395]	0 (0.0) [n=1198]	0 (0.0) [n=809]
Hip	0 (0.0) [n=190]	1 (0.2) [n=519]	0 (0.0) [n=332]
Baseline KL grade 4 [patients with KL grade 4 joint at baseline]			
Knee	0 (0.0) [n=171]	3 (0.7) [n=415]	0 (0.0) [n=240]
Hip	0 (0.0) [n=17]	2 (5.0) [n=40]	0 (0.0) [n=15]

OA Controlled Post-2015 Studies 1056, 1057, and 1058
a. Patients with at least one affected joint

Figure 39. Risk Differences for Adjudicated RPOA-2 by Baseline KL Grade of Affected Joint: Tanezumab 2.5 mg Versus NSAIDs in the OA Controlled Post-2015 Studies (Patient-Level)



OA Controlled Post-2015 Studies: 1056, 1057, and 1058

5.3.2.1.4. Total Joint Replacements

In total, across the treatment groups for all three post-2015 studies, 248 patients had at least one TJR. As shown in Figure 40 (left side of figure), more patients in the tanezumab treatment groups underwent TJRs than patients in the placebo treatment group, although the treatment differences between the tanezumab and placebo treatment groups were not statistically significant. There was a dose-dependent increase in TJRs in the tanezumab treatment groups relative to the NSAID treatment group.

- As discussed in Section 5.3.2.1.1.4, the Adjudication Committee reviewed TJRs to determine if the replaced joint may have also had a joint safety endpoint present. Across all treatment groups, the adjudication outcome for most TJRs was normal progression of OA (~82%). As shown in Figure 40 (right side of figure) the incidence of patients who had joints replaced and normal progression of OA was similar in the placebo- and tanezumab 2.5 mg-treated patients with the incidence in both of these treatment groups being higher than the NSAID treatment group. The incidences of patients who had joints replaced and an adjudicated event of RPOA-1 or RPOA-2, were similar between the tanezumab 2.5 mg and NSAID treatment groups.

- As noted above in Section 5.3.2.1.2, the majority of patients had multiple joints with OA. Of the 248 patients who had a TJR, 26 patients had two or more TJRs. The proportion of patients who had their index joint replaced was generally similar in the placebo- (~87%), tanezumab 2.5 mg- (~88%), and NSAID-treated patients (~85%). In the tanezumab 5 mg treatment group, the proportion of patients with a TJR in their index joint was ~77%. Non-index joints that were replaced also often had evidence of OA at baseline.

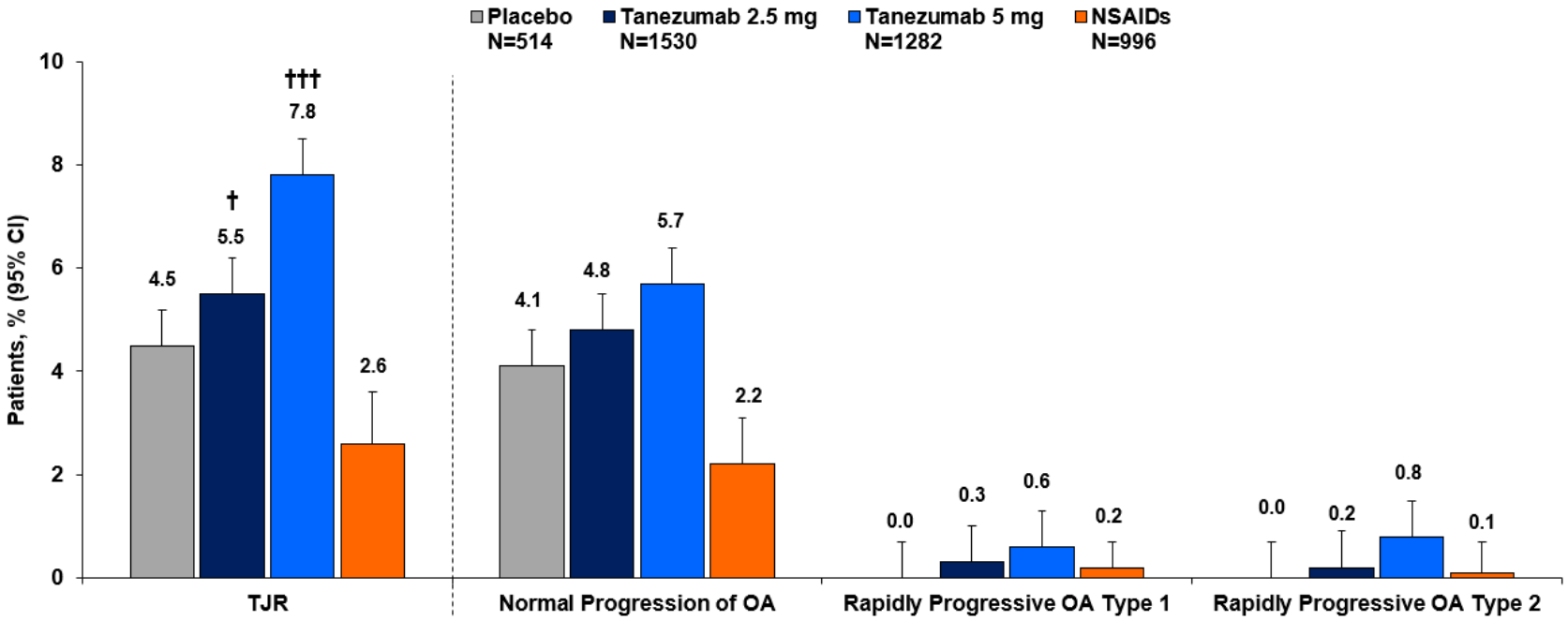
- Across the OA controlled post-2015 studies, over 85% of the TJRs occurred in joints that were KL Grade 3 or 4 at study baseline. No patients treated with tanezumab 2.5 mg had a TJR of a joint with KL Grade 0 at study baseline. There were two TJRs (1.8%), both in patients treated with tanezumab 5 mg, that occurred in joints that were KL Grade 0 at baseline. One patient had a TJR of his right hip. The patient's right knee was KL Grade 2 and right hip was KL Grade 0 at study baseline. The adjudication outcome for the TJR event was Other-post-traumatic subchondral fracture due to the patient accidently falling from the bed of a truck and causing a subchondral fracture that progressed to the patient needing a TJR. The second patient had a TJR in her right hip. The patient's right knee was KL Grade 4 and right hip was KL Grade 0 at study baseline but developed pain during the course of the study. The adjudication outcome for this event was RPOA-2.

- No associations between factors included in subgroup analyses, other than structural severity, and the incidence of TJR were observed.

- There were no differences in the outcome of TJR surgeries across treatment groups in patients who participated in the TJR Safety Follow-up study (data not shown).

- Based on the adjudication outcomes associated with TJRs and the outcome of TJR surgeries in the tanezumab 2.5 mg and NSAID treatment groups, there does not appear to be any qualitative differences in the TJRs in these treatment groups.

Figure 40. Total Joint Replacements in the OA Controlled Post-2015 Studies



OA Controlled Post-2015 Studies 1056, 1057, 1058.
Data not shown for Study 1056 2.5/5 mg treatment group: 15 TJRs/219 patients (6.8%).
Rate difference: *p ≤0.05, ** p ≤0.01, *** p ≤0.001 versus placebo (based on comparison of data from Studies 1056 and 1057).
Rate difference: † p ≤0.05, †† p ≤0.01, ††† p ≤0.001 versus NSAID (based on comparisons of data from Study 1058).

5.3.2.1.4.1. Total Joint Replacement Risk Differences

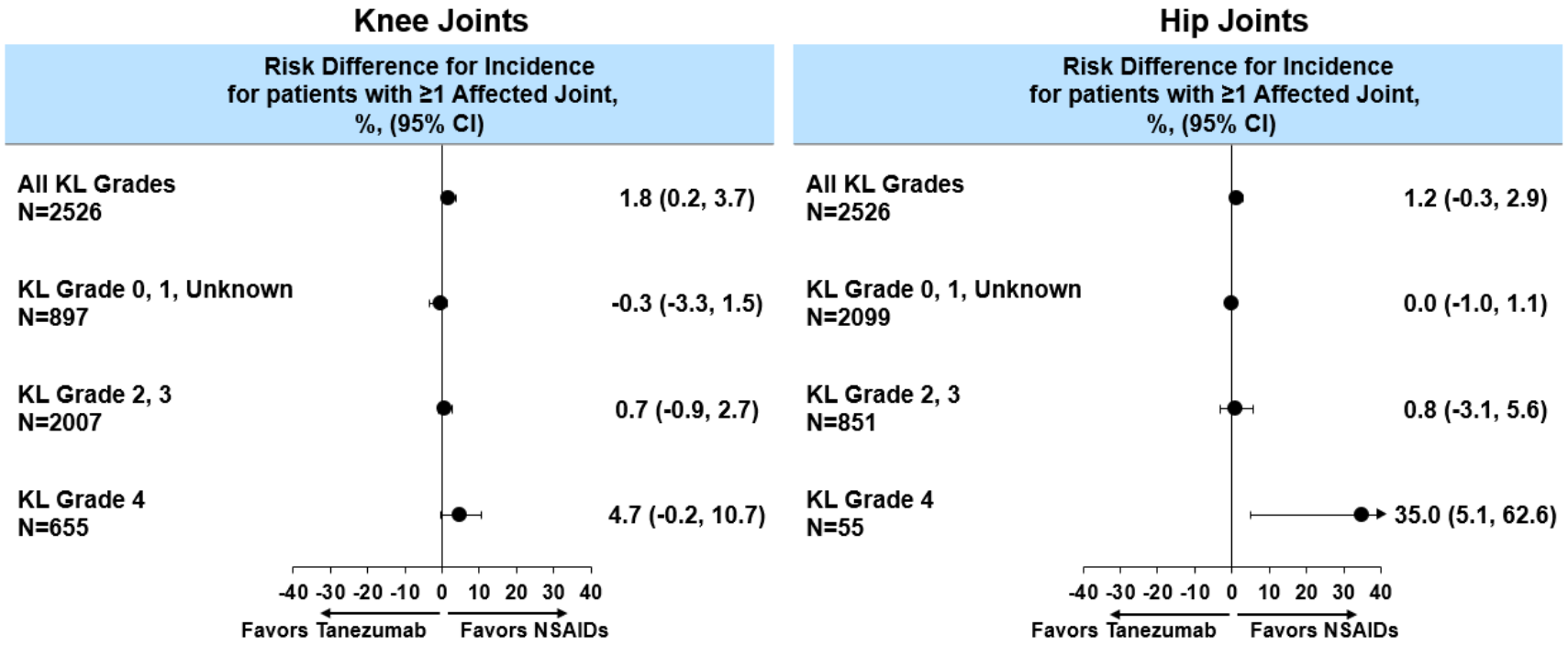
The evaluation of incidence of TJR and risk differences for tanezumab 2.5 mg versus NSAIDs for TJR in the knee or hip by KL Grade in the affected joint is shown in Table 37 and Figure 41. The forest plot for the hips shows the risk difference of 35% for patients with KL Grade 4 hips is the least favorable.

Table 37. Risk Differences for Total Joint Replacement for Knees and Hips by Baseline KL Grade of Affected Joint in the OA Controlled Post-2015 Studies (Patient-Level)

	Number (Incidence) of TJR[a]		
	Placebo N=514	Tanezumab 2.5 mg N=1530	NSAID N=996
Any Baseline KL grade			
Knee	11 (2.1)	50 (3.3)	15 (1.5)
Hip	12 (2.3)	33 (2.2)	10 (1)
Baseline KL grade 0, 1 or unknown [patients with KL Grade 0, 1, or unknown at baseline]			
Knee	1 (0.6) [n=174]	0 (0.0) [n=553]	1 (0.3) [n=334]
Hip	0 (0.0) [n=419]	0 (0.0) [n=1274]	0 (0.0) [n=825]
Baseline KL grade 2 or 3 [patients with KL grade 2 or 3 joint at baseline]			
Knee	5 (1.3) [n=395]	20 (1.7) [n=1198]	8 (1.0) [n=809]
Hip	11 (5.8) [n=190]	20 (3.9) [n=519]	10 (3) [n=332]
Baseline KL grade 4 [patients with KL grade 4 joint at baseline]			
Knee	6 (3.5) [n=171]	30 (7.2) [n=415]	6 (2.5) [n=240]
Hip	2 (11.8) [n=17]	14 (35) [n=40]	0 (0.0) [n=15]

OA Controlled Post-2015 Studies: 1056, 1057, and 1058
a. Patients with at least one affected joint

Figure 41. Risk Differences for Total Joint Replacement by Baseline KL Grade of Affected Joint: Tanezumab 2.5 mg Versus NSAIDs in the OA Controlled Post-2015 Studies (Patient-Level)



OA Controlled Post-2015 Studies: 1056, 1057, and 1058
Patients can be represented in more than one KL subcategory

5.3.2.2. Neurological Safety

5.3.2.2.1. Peripheral Neurological Safety

- There was a dose-responsive increase in the incidence of adverse events of abnormal peripheral sensation such as burning sensation, carpal tunnel syndrome, hypoesthesia, and paresthesia in tanezumab-treated patients. The increased incidence of adverse events of abnormal peripheral sensation in the tanezumab treatment groups was mainly due to an increased incidence of the reported symptoms of hypoesthesia and paresthesia. The majority of the adverse events of abnormal peripheral sensation were mild or moderate in severity and resolved by end of study. Adverse events of abnormal peripheral sensation infrequently led to discontinuation.

- Although adverse events of abnormal peripheral sensation were more frequent in the tanezumab 2.5 mg group compared with placebo and NSAID groups, additional evaluations including neurologic examinations and neurologic consultations for patients meeting specific neurologic monitoring criteria provided no evidence for an increased risk of peripheral polyneuropathy in tanezumab-treated patients.

- In addition, results from three studies did not demonstrate an adverse effect of tanezumab (up to 20 mg) compared to placebo, on distal, small sensory nerve fibers (using intraepidermal nerve fiber [IENF] density assessments) - robust quantitative evidence for absence of a neuropathic safety signal.

5.3.2.2.1.1. Assessments

Throughout the tanezumab clinical program, peripheral neurological safety was evaluated based on (1) a group of adverse events designated as adverse events of abnormal peripheral sensation (which contains both symptomatic and neuropathy-related adverse event terms), standardized structured neurologic examinations by Investigators and (2) consultations by a local neurologist if the patient met protocol-specified criteria for consultation. In the pre-2015 and post-2015 OA studies, patients with peripheral neuropathy were excluded from study participation and in the post-2015 studies, patients with autonomic neuropathy were also excluded. Study 1058 provided the longest controlled neurologic safety data, consisting of 56 weeks of double-blind treatment with tanezumab or an NSAID and 24 weeks of safety follow-up. In the post-2015 studies, a blinded external expert neurologist reviewed clinical and consultation data for patients undergoing consultation and assigned pre-specified diagnoses based on the totality of the patient's clinical data. Adverse event terms mostly reflecting patient symptoms are less rigorous data than diagnoses made following expert review of all of the patient's relevant clinical data. Changes in sensation following tanezumab treatment may result from expected decreases in NGF binding to its receptors on sensory nerves and do not necessarily imply that there has been a detrimental effect on the underlying peripheral nervous system. Finally, as described below, a number of pre-2015 studies assessed objective measures of peripheral nerve safety such as IENF density assessments.

In all tanezumab studies, peripheral neurological safety was monitored and evaluated through the following:

1. Assessment of adverse events of abnormal peripheral sensation. For a full list of adverse events of abnormal peripheral sensation please refer to Appendix 3.

2. Neurological Examinations by Investigators – Standardized Assessments

    - Neurological exams were performed at each clinic visit and were reported using the Neuropathy Impairment Score (NIS), a validated instrument used in clinical studies to assess the strength of groups of muscles of the head and neck, upper limbs, and lower limbs, deep tendon reflexes and sensation (touch pressure, vibration, joint position sense and pin prick) of both index fingers and both great toes.

3. Neurological Consultations

    - In pre-2015 studies, a neurologic consultation was required for any adverse event suggestive of new or worsening peripheral neuropathy or any adverse event 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 adverse events or neurologic examination changes noted above were reported as 1) a serious adverse event or 2) an adverse event which resulted in the patient being withdrawn from the study or 3) an adverse event ongoing at the end of the patient's participation in the study or 4) an adverse event of severe intensity. In these studies, peripheral neurological consultations and associated clinical data were reviewed by a blinded external neurologist with expertise in peripheral neuromuscular neurology. This neurologist diagnosed each patient with a primary diagnosis as warranted by the reported adverse events, neurological consultation and clinical data.

4. Studies with Quantitative Nerve Safety Assessments

    - Three of the pre-2015 studies examined objective measures of peripheral nerve safety including assessments of small unmyelinated nerve fibers with IENF density in healthy volunteers (Study 1046), patients with diabetic peripheral neuropathy (Study 1031), or OA patients (Study 1026) with tanezumab treatment relative to placebo. Study 1026 assessed OA patients objectively using nerve conduction study parameters.

5.3.2.2.1.2. Adverse Events of Abnormal Peripheral Sensation

- OA Placebo-controlled Post-2015 Pool (Studies 1056 and 1057)

During the treatment period, adverse events of abnormal peripheral sensation were more frequently reported in the tanezumab treatment groups compared to the placebo treatment

group. The incidence of patients reporting any adverse events of abnormal peripheral sensation increased with increasing tanezumab dose. Symptoms of paresthesia and hypoesthesia were the most frequently reported events with tanezumab compared to placebo (Table 38). The exposure-adjusted rates (rate per 1000 patient-years) for adverse events of abnormal peripheral sensation, showed a pattern similar to the unadjusted incidence rates. The majority of these events were mild across the treatment groups (92%, 74% and 76% in the placebo, tanezumab 2.5 mg and tanezumab 5 mg treatment groups, respectively), and no severe events were reported. The median duration of any adverse event of abnormal peripheral sensation during the treatment period in the tanezumab 2.5 mg group (31 days) was similar to that in the placebo group (29 days).

The majority of the patients with adverse events of abnormal peripheral sensation whose resolution status was known (ie, all patients except one in the tanezumab 2.5 mg group whose resolution was unknown) had event resolution by the end of study: 92%, 85% and 88% in the placebo, tanezumab 2.5 mg and tanezumab 5 mg treatment groups, respectively. A minority of patients reported to have an adverse event of abnormal peripheral sensation had at least one event which did not resolve by the end of study: 8%, 15% and 12% in the placebo, tanezumab 2.5 mg, and tanezumab 5 mg treatment groups, respectively. Altogether there were 7 patients in the post-2015 placebo-controlled studies reported to have abnormal peripheral sensation adverse events that were ongoing at the end of study. Six of these patients had adverse events related to abnormal sensation in the hands (3 with hand paresthesia and 3 with carpal tunnel syndrome). In 4 of the 7 patients, the blinded expert neurologist considered the diagnosis associated with the adverse event was preexisting before the start of the study which might partially explain the lack of adverse event resolution during the study. Details regarding when adverse events of abnormal peripheral sensation resolved during the study are as follows: All events resolved during treatment in 46%, 54% and 65% in the placebo, tanezumab 2.5 mg, and tanezumab 5 mg treatment groups, respectively. At least 1 event resolved after treatment but without treatment discontinuation in 31%, 31% and 24% in the placebo, tanezumab 2.5 mg and tanezumab 5 mg treatment groups, respectively. At least 1 event resolved after treatment when treatment was discontinued in 15%, 0% and 0% in the placebo, tanezumab 2.5 mg and tanezumab 5 mg treatment groups, respectively.

No patient in the tanezumab 2.5 mg treatment group discontinued due to adverse events of abnormal peripheral sensation. No patient in any treatment group reported a serious adverse event of abnormal peripheral sensation.

- OA Active-controlled SC Study (Study 1058)

During the treatment period, a higher proportion of patients receiving tanezumab reported adverse events of abnormal peripheral sensation compared to patients treated with an NSAID. The incidence of adverse events increased with increasing tanezumab dose. Symptoms of hypoesthesia, paresthesia, and carpal tunnel syndrome were the most frequently reported individual events in the tanezumab treatment groups compared to the NSAID treatment group. For the other individual adverse events of abnormal peripheral sensation, frequencies were typically less than 1% across the treatments but were more

frequently reported with tanezumab compared to NSAID treatment (Table 38). The exposure-adjusted adverse event incidence rates (rate per 1000 patient-years) showed a similar pattern to the unadjusted incidence rates.

The majority of patients reporting adverse events of abnormal peripheral sensation had events that were mild in severity (76%, 74% and 73% in the NSAID, tanezumab 2.5 mg and tanezumab 5 mg treatment groups, respectively). Severe adverse events of abnormal peripheral sensation were reported in the NSAID treatment group (2%), in the tanezumab 2.5 mg (2%), and in the tanezumab 5 mg treatment groups (3%). The remaining patients reported adverse events of abnormal peripheral sensation that were of moderate severity.

The majority of the patients with adverse events of abnormal peripheral sensation whose resolution status was known (ie, all patients except one in the tanezumab 2.5 mg group whose resolution was unknown) had event resolution by the end of study: 87% in the NSAID treatment group, 74% in tanezumab 2.5 mg treatment group, and 77% in the tanezumab 5 mg treatment group. A minority of patients reported to have an adverse event of abnormal peripheral sensation had at least one event which did not resolve by the end of study: 13%, 26% and 23% in the NSAID, tanezumab 2.5 mg, and tanezumab 5 mg treatment groups, respectively. The majority of patients with unresolved adverse events were reported to have carpal tunnel syndrome (23/43 patients; 53%) and the unresolved carpal tunnel syndrome incidence was similar across the tanezumab and NSAID treatment groups. Details regarding when adverse events of abnormal peripheral sensation resolved during the study are as follows: All events resolved during treatment in 61%, 38% and 42% in the NSAID, tanezumab 2.5 mg, and tanezumab 5 mg treatment groups, respectively. At least 1 event resolved after treatment but without treatment discontinuation in 7%, 15% and 13% in the NSAID, tanezumab 2.5 mg, and tanezumab 5 mg treatment groups, respectively. At least 1 event resolved after treatment when treatment was discontinued in 20%, 21% and 21% in the NSAID, tanezumab 2.5 mg, and tanezumab 5 mg treatment groups, respectively.

Altogether, 4 patients (0.4%) in each of the tanezumab 2.5 mg and NSAID treatment groups and 15 patients (1.5%) in the tanezumab 5 mg treatment group discontinued due to adverse events of abnormal peripheral sensation. For the tanezumab 2.5 mg group, 2 patients discontinued due to bilateral carpal tunnel syndrome, 1 patient discontinued due to hypoesthesia and 1 patient discontinued due to sciatica. In Study 1058 one patient (0.1%) in the tanezumab 2.5 mg treatment was reported to have carpal tunnel syndrome as a serious adverse event; no patients in the tanezumab 5 mg or NSAID groups were reported to have serious adverse events of abnormal peripheral sensation.

Table 38. Incidence of Adverse Events of Abnormal Peripheral Sensation During the Treatment Period (All Causalities) in the OA Placebo-Controlled Post-2015 Pool and the OA Active-Controlled SC Study

	Placebo-Controlled Post-2015 Pool (Studies 1056, 1057)				Active-Controlled SC Study (Study 1058)		
	Placebo	Tanezumab			Tanezumab		NSAID
Number (%) of Subjects by Preferred Term	N=514	2.5 mg N=528	2.5/5 mg N=219	5 mg N=284	2.5 mg N=1002	5 mg N=998	N=996
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	13 (2.5)	27 (5.1)	7 (3.2)	17 (6.0)	62 (6.2)	90 (9.0)	46 (4.6)
Paraesthesia	6 (1.2)	13 (2.5)	3 (1.4)	12 (4.2)	18 (1.8)	30 (3.0)	13 (1.3)
Hypoaesthesia	5 (1.0)	9 (1.7)	3 (1.4)	6 (2.1)	27 (2.7)	28 (2.8)	18 (1.8)
Carpal tunnel syndrome	0	3 (0.6)	0	1 (0.4)	16 (1.6)	27 (2.7)	6 (0.6)
Sciatica	1 (0.2)	3 (0.6)	0	1 (0.4)	3 (0.3)	8 (0.8)	4 (0.4)
Decreased vibratory sense	3 (0.6)	1 (0.2)	1 (0.5)	1 (0.4)	8 (0.8)	5 (0.5)	7 (0.7)
Neuralgia	0	1 (0.2)	0	1 (0.4)	0	0	1 (0.1)
Neuropathy peripheral	0	0	0	1 (0.4)	2 (0.2)	3 (0.3)	0
Burning sensation	1 (0.2)	0	0	0	1 (0.1)	3 (0.3)	3 (0.3)
Hypoaesthesia oral	1 (0.2)	0	0	0	0	1 (0.1)	0
Allodynia	0	0	0	0	0	1 (0.1)	0
Dysaesthesia	0	0	0	0	0	3 (0.3)	1 (0.1)
Hyperaesthesia	0	0	0	0	0	0	1 (0.1)
Peripheral sensory neuropathy	0	0	0	0	1 (0.1)	0	0
Sensory disturbance	0	0	0	0	0	0	1 (0.1)
Sensory loss	0	0	0	0	0	1 (0.1)	1 (0.1)

Adverse events defined as Treatment-Emergent.
Abnormal Peripheral Sensation includes Allodynia, Axonal neuropathy, Burning sensation, Carpal tunnel syndrome, Decreased vibratory sense, Demyelinating polyneuropathy, Dysaesthesia, Formication, Hyperaesthesia, Hyperpathia, Hypoaesthesia, Hypoaesthesia oral, Intercostal neuralgia, Neuralgia, Neuritis, Neuropathy peripheral, Paraesthesia, Paraesthesia oral, Peripheral sensorimotor neuropathy, Peripheral sensory neuropathy, Polyneuropathy, Polyneuropathy chronic, Sciatica, Sensory disturbance, Sensory loss, Tarsal tunnel syndrome, Thermohypoaesthesia.
MedDRA v21.1 coding dictionary applied.

5.3.2.2.1.3. Neurological Examinations by Investigators at Last Assessment

For the OA placebo-controlled post-2015 pool and the OA active-controlled SC study, a large majority of patients across the treatment groups had no new or worsened neurological examination abnormalities at the last assessment (≥92% and ≥94%, respectively). In these studies, other patients had new or worsened neurological examination abnormalities at the last assessment that the Investigator considered not to be clinically significant (≤7% and ≤6%, respectively and reported with similar frequencies across the treatment groups). In these studies, few patients in any treatment group (<1.0 % in the OA placebo-controlled post-2015 pool and in the OA active-controlled SC study) had neurological deficits in the neurologic examination at the last assessment considered clinically significant by the Investigator.

5.3.2.2.1.4. Neurologic Consultations

As shown in Table 39, in the OA placebo-controlled post-2015 pool (Studies 1056 and 1057), patients in the tanezumab 2.5 mg and 5 mg treatment groups required neurologic consultations more frequently than patients in the placebo treatment group. Neurologic consultations were performed in the majority of these patients across the treatment groups. In this study pool, the frequency of any individual diagnosis was low (<1.5% for any diagnosis in any treatment group). A blinded expert neurologist's diagnoses from most frequent to least frequent were: radiculopathy, mononeuropathy, polyneuropathy, neurologic symptoms but no clinically significant signs, no neuropathic signs or symptoms, and plexopathy. Radiculopathy and mononeuropathy were diagnosed more frequently in the tanezumab treatment groups than in the placebo treatment group. Polyneuropathy was diagnosed with similar frequency in the tanezumab treatment groups and placebo treatment group. For the diagnoses of radiculopathy, mononeuropathy, and polyneuropathy, a tanezumab dose-response was not observed.

The clinical presentation of radiculopathy (2/2 in placebo and 11/11 across the tanezumab treatment groups) and mononeuropathy (1/1 in placebo and 8/10 across the tanezumab treatment groups) was sensory in the majority of patients. Radiculopathy (1/2 in placebo and 8/11 across the tanezumab treatment groups) and mononeuropathy (0/1 in placebo and 7/10 across the tanezumab treatment groups) was considered new in most patients.

The clinical presentation of polyneuropathy was sensory in all the patients (1/1 in placebo and 2/2 across the tanezumab treatment groups). Polyneuropathy was considered pre-existing in all patients (1/1 in placebo and 2/2 across the tanezumab treatment groups).

Table 39. Neurologic Consultations in the OA Placebo-Controlled Post-2015 Studies

	Placebo N=514	Tanezumab 2.5 mg N=528	Tanezumab 2.5/5 mg N=219	Tanezumab 5 mg N=284
	n (%)	n (%)	n (%)	n (%)
Patients requiring neurologic consultations	7 (1.4)	17 (3.2)	4 (1.84)	6 (2.1)
Neurologic consult performed for this patient?				
Yes	6 (1.2)	10 (1.9)	4 (1.8)	4 (1.4)
Expert Primary Diagnosis[a]	7 (1.4)	17 (3.2)	3 (1.4)	6 (2.1)
Mononeuropathy	1 (0.2)	7 (1.3)	0	3 (1.1)
Carpal Tunnel Syndrome	1 (0.2)	5 (0.9)	0	2 (0.7)
Other	0	2 (0.4)	0	1 (0.4)
Plexopathy	1 (0.2)	0	0	0
Polyneuropathy	1 (0.2)	1 (0.2)	1 (0.5)	0
Radiculopathy	2 (0.4)	7 (1.3)	1 (0.5)	3 (1.1)
No neuropathic symptoms or signs	1 (0.2)	0	1 (0.5)	0
Neuropathic symptoms but no clinically significant signs	1 (0.2)	2 (0.4)	0	0
Diagnosis Missing	0	0	1 (0.5)	0

OA Placebo-Controlled Post-2015 Studies 1056 and 1057

a. Diagnosis based on blinded review by external neurology expert for patients with at least 1 adverse event requiring neurologist consult regardless of whether or not a neurologic consultation was performed.

5.3.2.2.1.5. Nerve Safety Studies

Assessment of small unmyelinated nerve fibers with IENF density in three studies provided no evidence for a reduction in cutaneous small fiber density in healthy volunteers, patients with diabetic peripheral neuropathy, or OA patients with tanezumab treatment relative to placebo. One of these studies (Study 1026) also assessed OA patients using nerve conduction studies and found no meaningful effects with tanezumab relative to placebo (Table 40).

Table 40. Summary of Results From Nerve Safety Studies

Patient Population	Study Description	Summary of Study Results
OA [Study 1026]	Phase 3, randomized, double-blind, placebo-controlled study designed to evaluate the effect of tanezumab (5 mg or 10 mg) administration on peripheral nerve function in patients with OA.	IENF density in the distal leg and replicate nerve conduction studies assessing motor and sensory nerve parameters and heart rate deep breathing were performed at Baseline and Week 24/Early Termination. This study was terminated early due to the 2010 clinical hold, enrolling 59% of the planned sample size. Administration of tanezumab 5 mg or 10 mg IV at 8-weekly intervals for up to 24 weeks did not meaningfully affect sensory or motor nerve conduction parameters, autonomic nerve function (heart rate deep breathing), or cutaneous small fiber (IENF density) as compared to placebo treatment.
Healthy Volunteers [Study 1046]	Phase 1, randomized, double-blind (Sponsor-Open), placebo-controlled study to examine the density of IENF after a single SC administration of tanezumab (20 mg) in healthy volunteers.	IENF density assessments were made at Baseline, Week 2, and Week 16 or Early Termination in skin biopsies from the thigh and distal leg. The data indicated that IENF density was stable and reproducible over 16 weeks in healthy volunteers and that SC administration of tanezumab does not appear to cause a reduction in IENF density in the area of the injection site or cause a systemic reduction in IENF density in healthy volunteers.
Painful Diabetic Neuropathy [Study 1031]	Phase 2 randomized, double-blind, placebo-controlled, multicenter, parallel group, proof of concept study of the analgesic effects of tanezumab (20 mg) in adult patients with diabetic peripheral neuropathy.	IENF density was assessed from skin biopsies in the distal thigh and distal leg at Baseline and Week 16/Early Termination. This study was terminated early due to the 2010 clinical hold, enrolling 46% of the planned sample size and with the majority (92%) of patients receiving a single dose of SC study medication. There was no evidence suggesting that tanezumab 20 mg treatment resulted in worsening of diabetic peripheral neuropathy. No significant changes were observed in the IENF density with tanezumab treatment.

The results of these nerve safety studies are important because neurotoxic agents and diseases which injure peripheral nerves (eg, diabetes mellitus) typically demonstrate symmetric polyneuropathic changes which begin in the distal extremities and progress proximally as nerve injury continues. Evaluation of distal, small sensory nerve fibers by IENF density assessments is a sensitive method to detect small fiber loss, which are the nerve fibers presumed most at risk with tanezumab. This technique was assessed in three tanezumab studies including healthy volunteers, neurologically normal OA patients, and patients with painful diabetic neuropathy (a patient population with small sensory fiber peripheral neuropathy at baseline) with tanezumab doses up to 20 mg. None of these studies demonstrated an adverse effect of tanezumab compared to placebo on IENF density, which is quantitative evidence for absence of a neuropathic safety signal. The nerve conduction study data in patients with OA treated with placebo, tanezumab 5 mg, or tanezumab 10 mg for up to 24 weeks likewise demonstrated the lack of an adverse effect based on objective nerve conduction test parameters, a quantitative, well-validated method to assess peripheral nerve safety of large fiber populations. In summary, these tests were sensitive objective assessments of peripheral nerve safety designed to detect a neuropathic safety signal following tanezumab treatment, but no such signal was observed.

5.3.2.2.2. Sympathetic Neurological Safety

- Adverse events of possible decreased sympathetic function occurred at low incidence with similar incidences across the tanezumab and placebo treatment groups.
- The incidence of adverse events of possible decreased sympathetic function which required consultation was also similar across tanezumab and placebo treatment groups.
- No patients were considered by the Investigator to have a sympathetic neuropathy following consultation.
- There was no data to suggest that tanezumab was associated with an increased risk for sympathetic autonomic neuropathy.

5.3.2.2.2.1. Assessments

Multiple procedures and analyses across the entire clinical program were used to evaluate the effects of tanezumab on the sympathetic nervous system. In both pre-2015 and post-2015 studies, adverse events of possible decreased sympathetic function (such as syncope, bradycardia, orthostatic hypotension, anhidrosis and hypohidrosis) were evaluated. In post-2015 studies, the Survey of Autonomic Symptoms questionnaire was used during the Screening period to exclude patients who may have had an autonomic neuropathy. Additionally, in post-2015 studies, program-wide assessments of orthostatic hypotension and bradycardia were implemented and protocol-specified consultations with cardiologists and neurologists were conducted to evaluate patients for possible sympathetic neuropathy.

Sympathetic nervous system safety was monitored and evaluated through assessment of adverse events such as syncope, bradycardia, orthostatic hypotension, anhidrosis or hypohidrosis at each clinical visit, orthostatic blood pressure assessment at each clinic visit, periodic protocol-specified ECG assessments (to quantitatively assess bradycardia during screening and on-study based on pre-specified criteria), autonomic symptom questionnaires and referral of patients for neurological or cardiologic consultation to evaluate for sympathetic neuropathy if they met pre-specified criteria as described in the individual post-2015 study protocols. For a complete list of adverse events of decreased sympathetic function and those which required consultation, please refer to Appendix 3.

If a local consultation indicated presence of a sympathetic neuropathy, an external neurologist at Mayo Clinic with expertise in sympathetic neuropathy assessment would have performed an additional evaluation of the patient. No patients required this additional evaluation at the Mayo Clinic.

The post-2015 studies were the primary focus for the assessment of sympathetic nervous system safety.

5.3.2.2.2.2. Adverse Events of Possible Decreased Sympathetic Function

During the treatment period, in the OA placebo-controlled post-2015 pool, the overall frequency of adverse events of possible decreased sympathetic function reported was similar across tanezumab 2.5 mg and 5 mg treatment groups (5.1% to 5.3%) and placebo (4.5%) treatment group. Diarrhea, bradycardia, nausea, and orthostatic hypotension were the most commonly reported events, but each was reported in ≤1.4% in any of these treatment groups. The remaining possible decreased sympathetic function adverse events were reported in ≤1.0% in the tanezumab 2.5 mg, and 5 mg treatment groups (Table 41). The exposure-adjusted rates for any adverse event of possible decreased sympathetic function showed a similar pattern to the unadjusted rates.

Table 41. Incidence of Adverse Events of Possible Sympathetic Nervous System During the Treatment Period (All Causalities) in the OA Placebo-Controlled Post-2015 Pool

Number (%) of Subjects: by Preferred Term	Placebo N=514	Tanezumab 2.5 mg N=528	Tanezumab 2.5/5 mg N=219	Tanezumab 5 mg N=284
	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	23 (4.5)	27 (5.1)	11 (5.0)	15 (5.3)
Diarrhoea	7 (1.4)	6 (1.1)	5 (2.3)	4 (1.4)
Nausea	5 (1.0)	6 (1.1)	1 (0.5)	0
Bradycardia	3 (0.6)	4 (0.8)	0	4 (1.4)
Orthostatic hypotension	1 (0.2)	3 (0.6)	1 (0.5)	3 (1.1)
Sinus bradycardia	3 (0.6)	3 (0.6)	3 (1.4)	0
Urinary incontinence	4 (0.8)	2 (0.4)	1 (0.5)	2 (0.7)
Vomiting	1 (0.2)	2 (0.4)	2 (0.9)	1 (0.4)
Abdominal discomfort	0	1 (0.2)	0	0
Hypohidrosis	0	1 (0.2)	0	0
Pollakiuria	0	1 (0.2)	0	1 (0.4)
Presyncope	0	1 (0.2)	0	0
Syncope	0	0	0	1 (0.4)

OA Placebo-controlled Post-2015 Studies 1056, 1057.
Adverse events defined as Treatment-Emergent.
Adverse Events of Sympathetic Nervous System: Abdominal discomfort, Anal Incontinence, Anhidrosis, Blood pressure orthostatic decreased, Bradycardia, Diarrhoea, Dizziness postural, Early satiety, Ejaculation delayed, Ejaculation disorder, Ejaculation failure, Heart rate decreased, Hypertonic bladder, Hypohidrosis, Micturition urgency, Nausea, Nocturia, Orthostatic hypotension, Pollakiuria, Presyncope, Respiratory distress, Respiratory failure, Sinus bradycardia, Syncope, Urinary hesitation, Urinary incontinence, Vomiting.
MedDRA v21.1 coding dictionary applied.

5.3.2.2.2.3. Sympathetic Function Consultations

Across the treatment groups up to the end of study for the OA placebo-controlled post-2015 pool, the number of patients who required sympathetic function consultations either for at least one orthostatic hypotension episode requiring consultation or for another pre-specified sympathetic adverse event (bradycardia, syncope, anhidrosis or hypohidrosis) was similar across tanezumab and placebo treatment groups. The total unique number of patients (n/%) requiring consultation in the placebo, tanezumab 2.5 mg, tanezumab 2.5/5 mg, and

tanezumab 5 mg treatment groups were 13/514 (2.5%), 10/528 (1.9%), 5/219 (2.3%), and 8/284 (2.8%), respectively (Table 42).

Across these treatment groups, bradycardia was the most common adverse event requiring consultation, followed by single patients with orthostatic hypotension, syncope, and hypohidrosis. Consultations were performed in the majority of patients requiring them in the placebo (11/13; 85%), tanezumab 2.5 mg (7/10; 70%), tanezumab 2.5/5 mg (5/5; 100%), and tanezumab 5 mg (5/8; 63%) treatment groups. The reason a consult was not performed was typically that the patient refused consultation.

No patient in any treatment group was considered to have a sympathetic neuropathy based on the principal Investigator's assessment of the patient's clinical and consultation data.

Table 42. Sympathetic Function Consultations in the OA Placebo-Controlled Post-2015 Pool

	Placebo N=514	Tanezumab 2.5 mg N=528	Tanezumab 2.5/5 mg N=219	Tanezumab 5 mg N=284
	n (%)	n (%)	n (%)	n (%)
Number of patients requiring consult	13 (2.5)	10 (1.9)	5 (2.3)	8 (2.8)
Orthostatic hypotension	0	0	1 (0.5)	0
Bradycardia	13 (2.5)	9 (1.7)	4 (1.8)	7 (2.5)
Syncope	0	0	0	1 (0.4)
Hypohidrosis	0	1 (0.2)	0	0
Consult Completed	11 (2.1)	7 (1.3)	5 (2.3)	5 (1.8)
Sympathetic neuropathy present per Investigator				
Yes	0	0	0	0
No	11	8	5	5
Missing (ie, no consult)	2	2	0	3

OA Placebo-controlled Post-2015 Studies 1056, 1057.
No patients were reported to have anhidrosis.

5.3.2.3. Potential Hypersensitivity and Injection Site Reactions

Evaluations of potential hypersensitivity events and injection site reactions were primarily determined in the OA placebo-controlled post-2015 pool (Studies 1056 and 1057) and the OA active-controlled SC study (Study 1058), to evaluate these events with SC administration and to align with the immunogenicity assessments conducted in the post-2015 studies.

Tanezumab is not associated with an increased risk for clinically concerning potential hypersensitivity events. No anaphylaxis or other serious hypersensitivity events were observed with tanezumab.

The overall incidence of tanezumab injection site reaction adverse events in OA clinical studies was low (≤0.5%) and was not different from placebo at the intended dose and

regimen of 2.5 mg SC given every 8 weeks. There were no serious or severe events, and no events leading to discontinuation with tanezumab 2.5 mg during the treatment period.

5.3.3. Safety in Special Groups and Situations

5.3.3.1. Intrinsic/Extrinsic Factors

Tanezumab safety data in discrete patient populations based on age (≥65 and ≥75 years old), gender, race, ethnicity, body mass index, baseline estimated glomerular filtration rate (eGFR) category and geographic region were evaluated. The adverse event profile for these subgroups was consistent with the profile in the overall population. No special precautions regarding the safe use of tanezumab in any of the above patient subpopulations are needed.

5.3.4. Summaries of Other Safety Data for Tanezumab

This section summarizes the safety of tanezumab in other organ systems or special patient populations, in addition to those described previously and findings from the analyses of clinical laboratory values, vital signs and ECG data.

Renal	Tanezumab had no clinically relevant adverse effects on renal function, based on evaluation of renal adverse events and changes in eGFR.
Hepatic	Tanezumab treatment did not lead to an increased risk for drug induced liver injury. No cases meeting the biochemical criteria of Hy's law were observed.
Clinical Laboratory Abnormalities, Vitals, and ECG	Tanezumab treatment was not associated with clinically meaningful changes in laboratory values, vital signs, or ECG (including QTc). There was a small, dose dependent increase in the median change from baseline for alkaline phosphatase in the tanezumab treatment groups compared to the placebo and NSAIDs groups; the clinical relevance of this finding is unknown.
Potential Drug Abuse, Dependence or Withdrawal	Tanezumab treatment was not associated with an increased incidence of adverse events indicative of potential drug abuse, dependence or withdrawal.
Pregnancy	Based on findings from animal studies, tanezumab may cause fetal harm when administered to a pregnant woman and therefore tanezumab use is contraindicated during pregnancy. Seven infants, born to female patients who received tanezumab and were followed for neurological abnormalities up to 60 weeks of age, had no clinically significant abnormalities, including neurological development abnormalities, identified. The proposed label provides contraindication for pregnancy.

5.4. Safety Conclusions

Tanezumab 2.5 mg administered SC was generally well-tolerated. The overall incidence of adverse events during the treatment period was not notably different than placebo. Incidences of deaths, serious adverse events and discontinuations due to an adverse event were low and similar to placebo.

Adverse events considered likely associated with tanezumab 2.5 mg treatment are RPOA (RPOA-1 and RPOA-2), joint swelling, abnormal peripheral sensation (including paresthesia,

hypoesthesia, and burning sensation), carpal tunnel syndrome, peripheral edema (including edema peripheral and peripheral swelling).

Joint safety events including adjudicated RPOA-1, RPOA-2, and TJRs were the primary safety issues identified for tanezumab; incidences were dose-dependent. The incidences of RPOA-1 and TJR were higher with tanezumab 2.5 mg than placebo and NSAIDs. The incidence of RPOA-2 with tanezumab 2.5 mg was low and not statistically significantly different from NSAIDs. Most RPOA-1 and RPOA-2 events occurred in joints with radiographic evidence of OA at baseline. The risk of RPOA was increased 3-fold when tanezumab was administered concomitantly with chronic use of NSAIDs.

There were no serious neurological and no CV safety concerns identified with tanezumab 2.5 mg treatment. Furthermore, renal and hepatic function were not altered by tanezumab nor were there imbalances in adverse events in the renal and hepatic systems. Adverse event profiles in subgroups evaluated for intrinsic and extrinsic factors were consistent with the profile in the overall population. Treatment with tanezumab was not associated with an increased risk for hypersensitivity events or injection site reactions and was not associated with potential drug abuse, dependence or withdrawal. Tanezumab was not associated with clinically meaningful changes in laboratory values, vital signs, or ECGs.

Based on the totality of the safety data, tanezumab 2.5 mg SC (administered every 8 weeks) has an acceptable safety profile when appropriate risk mitigation strategies are followed (discussed in Section 7.4) for those patients with moderate to severe OA pain for whom use of other analgesics is ineffective or not appropriate.

6. PATIENT PREFERENCE STUDY

A patient preference study was conducted to quantify preferences for attributes of potential analgesic treatments for moderate to severe OA, and to evaluate OA patients' willingness to accept safety risks in exchange for treatment benefit.[121] This large prospective study used discrete-choice experiment (DCE) and best-worst scaling (BWS) methods to elicit patients' preferences and was conducted in partnership with Research Triangle Institute (RTI) Health Solutions, a leader in this field. The study was conducted separately in both the US and UK and included patients diagnosed with moderate to severe OA and/or chronic low back pain (CLBP). However, the Sponsor agrees with FDA that the US data on patients with OA is most relevant for the current BLA. Therefore, data from the UK and from patients without OA are not being presented. The study design followed current best practices and FDA guidance.[122,123] Additionally, the study protocol was peer-reviewed by IMI-PREFER, an international public-private collaboration under the Innovative Medicines Initiative (IMI) designed to establish recommendations on the use of patient preference studies for benefit-risk decisions.[124] A number of studies have been conducted with OA patients to understand their relative preferences for different efficacy and safety characteristics associated with drug treatment – often focusing on risk attributes of NSAIDs.[125-129] In general, these studies have shown that in addition to efficacy, risks associated with NSAIDs including CV risks are key drivers of patient preference.[126,128,129]

The study was designed to elicit tradeoffs that patients with moderate to severe OA in the US were willing to make among attributes of three current or proposed treatment options – NGF inhibitors, NSAIDs, and opioids– that were identified as being important to patients. The choice of treatment attributes in the quantitative preference study was informed by qualitative research conducted by the same investigators. Four patient focus groups were conducted in the US, with a total of 30 patients, to identify treatment features that were important to them. This qualitative work identified what treatment attributes of opioid and nonopioid pain treatments for OA were most important to patients and influenced their treatment choices.

Primary data collection using the self-administered online survey instrument was conducted using a nationwide patient panel from 04 February 2019 to 20 March 2019.

6.1. Selection Criteria

Enrolled patients were not from the tanezumab clinical studies. The US study sample (n=400) was drawn from a sample of patients from an online panel using a detailed screening survey to identify patients with a medical history consistent with moderate to severe OA with inadequate treatment response —or intolerance—to prior treatment with three classes of pain treatment. Inclusion/exclusion criteria were as follows:

- Inclusion
    - Aged 18 years or older.
    - US resident.

- Had a self-reported physician diagnosis of hip or knee OA only, or concurrent OA and CLBP, received at least 3 months ago.
- Had self-reported moderate to severe pain in the hip, or knee, defined as a self-assessed rating of 5 or greater on average in the past week on an 11-point numeric pain scale ranging from 0 (no pain) to 10 (worst possible pain).
- Had taken or tried 3 or more classes of pain treatment in the past 2 years, OR have taken or tried 2 prior classes of pain treatment and for whom NSAIDs are contraindicated or were unwilling to take opioids.

- Exclusion
  - Had a self-reported physician 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.
  - Had pain as a result of having had surgery in the past 3 months.

6.2. Discrete Choice Experiment Attributes

Treatment attributes for the DCE were chosen based on the patient focus groups and on characteristics that differentiate NGF inhibitors from NSAIDs and opioids. One key safety risk from each of the three classes of pain treatment were selected. Final OA treatment attributes for the DCE were:

- Pain and symptom control (Patient Global Assessment; Poor, Fair, Good, Very Good)
- Risk of physical dependence (annual risk; 0%, 5%, 25%)
- Risk of heart attack (annual risk; 0%, 0.2%, 0.5%)
- Risk of severe rapidly progressive joint problems requiring TJR (annual risk; 0%, 0.5%, 4%).
- Mode and frequency of administration (oral pills 2 or more times a day, oral pills once a day, injection every 4 weeks, injections every 8 weeks).

6.3. Best-Worst Scaling Attributes

Only one key safety risk for each class of treatment was included in the DCE because there is a limit to the number of attributes that can be included in such an experiment. However, drugs in each of the three treatment classes are likely associated with risks beyond those included in the DCE. Therefore, an object-case BWS exercise was incorporated in the survey instrument to elicit patients' assessments of the relative importance of additional potential treatment-related risks that may be associated with the drugs in the three treatment classes. The three risk attributes from the DCE (risk of having a heart attack, risk of physical

dependence, and risk of joint problems) were also included in the BWS to create a link between the two preference-elicitation methods.

The items included in the BWS exercise were as follows:

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

6.4. Patient Comprehension

The Sponsor undertook a number of steps to ensure that patients understood the risks/attributes being tested prior to completing the DCE exercise. Patients were provided with a description of each of the three key risks, including the risk of severe joint problems (RPOA), in lay language so that they understood the event and could make informed decisions when selecting a response. In addition, patient comprehension of the attributes in both the DCE and BWS was assessed through qualitative pretest interviews. Comprehension of the DCE attributes was also assessed using comprehension questions in the survey. The comprehension assessments showed that patients understood attributes. Attribute comprehension in this survey was comparable to that observed in similar preference studies.

6.5. Discrete Choice Experiment and Best-Worse Scaling Methods

The conditional relative importance of each attribute was calculated as the difference between the preference weight for the highest and lowest level of each attribute. For example, the conditional relative importance of the risk of physical dependence was 2.68 and was calculated as the difference between the preference weight on the most preferred level (0%, preference weight = 1.185) and the preference weight on the least preferred level (25%, preference weight = -1.498). Likewise, the conditional relative importance for symptom control was 4.01 and was calculated as the difference between the preference weight for "Very good" (preference weight = 1.557) and the preference weight for "Poor" (preference weight = -2.453).

Conditional relative importance estimates were then rescaled to express the relative importance of each attribute relative to a fixed round number. The attribute with the largest conditional relative importance (symptom control in this case) was set to 10, and the conditional importance of each of the other attributes are rescaled relative to that attribute. For example, the conditional relative importance for physical dependence was rescaled to equal 6.69 (10 x the conditional relative importance of risk of physical dependence [2.68] divided by the conditional relative importance of symptom control [4.01]). Standard errors and 95% confidence intervals for these differences were calculated using the delta method.

6.6. Results

6.6.1. Baseline Characteristics

There were 400 OA patients in the US sample, with 201 having OA only, and 199 with comorbid OA and CLBP.

A comparison of baseline characteristics between the US study sample and the study populations of studies 1056 and 1057 is contained in Table 43. The mean age in study 1056 and the proportion of females in both clinical studies was similar to those of the US OA patients included in the preference study. In terms of OA characteristics, pain rating and time since OA diagnosis in study 1057, but not study 1056, was similar to the preference sample. Patients in the preference study had a higher proportion of responses of "Very Poor" for the PGA-OA at Baseline compared with the study populations. However, it should be noted that that survey participants were responding to the question "What would you expect your level of OA symptom control to be if you did not take any medicines?"

Overall, Table 43 shows that the preference study criteria were effective in recruiting respondents who were similar to the tanezumab study populations, and representative of the target population for tanezumab.

Table 43. Baseline Characteristics for OA Patients in the US Patient Preference Study and Participants From Tanezumab Studies 1056 and 1057

Characteristic	US OA Patients	Tanezumab Study Participants	
		Study 1056 n (%)	Study 1057 n (%)
N	400	696	849
Age (years)			
Mean (years)	65.5	60.8	64.9
Sex			
Male	34.0%	34.9%	30.9%
Female	66.0%	65.1%	69.1%
Ethnic Group			
African American	3.8%	22.0%	0.0%
Asian American	1.0%	3.7%	12.5%
Caucasian / White	94.5%	72.4%	87.2%
Hispanic	2.0%	---	---
Native American or American Indian	2.0%	---	---
Other	0.5%	1.9%	0.4%
Prefer not to answer	0%	---	---

Table 43. Baseline Characteristics for OA Patients in the US Patient Preference Study and Participants From Tanezumab Studies 1056 and 1057

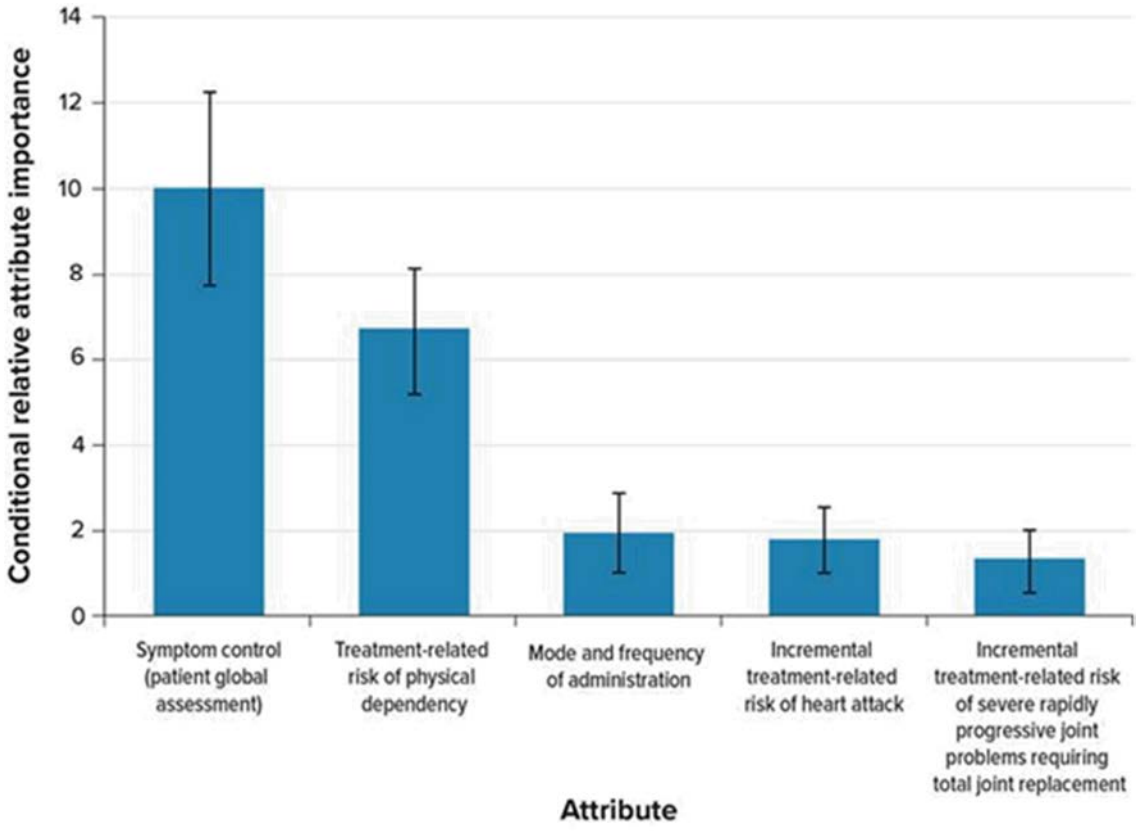
Characteristic	US OA Patients	Tanezumab Study Participants	
		Study 1056 n (%)	Study 1057 n (%)
OA Pain Rating			
WOMAC Pain subscale score at baseline (mean)	6.4	7.2	6.62
Time since OA diagnosis			
Mean range across study arms (years)	---	9.1 to 9.5	6.7 to 8.2
Five or more years ago	50.0%	---	---
PGA-OA at Baseline			
VERY GOOD	1 (0.3%)	0 (0)	1 (0.1)2
GOOD	17 (4.7%)	1 (0.1)	1 (0.1)
FAIR	101 (28.0%)	403 (57.9)	413 (48.8)
POOR	150 (41.6%)	255 (36.6)	375 (44.3)
VERY POOR	92 (25.5%)	37 (5.3)	57 (6.7)

6.6.1.1. Discrete Choice Experiment Results

Estimates of the conditional relative importance of the attributes in the DCE are presented in Table 44 and Figure 42.

In Figure 42, treatment attributes are presented according to the relative importance patients placed on them in making a treatment decision. Achieving pain and symptom relief was most important to patients, followed by avoiding physical dependence, mode and frequency of administration, avoiding risk of an MI, and then avoiding risk of severe joint problems.

Figure 42. Discrete-Choice Experiment Scaled Conditional Attribute Relative Importance in the United States; Respondents With Moderate-to Severe OA (N = 400)



Note: The vertical bars surrounding each mean preference weight represent the 95% confidence intervals around the point estimate.

Comparisons between two specific attributes can be summarized by dividing the point estimates of relative importance. For example, symptom control was approximately 1.5 (ie, 10/6.69=1.5) times as important as the risk of physical dependence. Similarly, symptom control was 6 (10/1.76) times more important than the risk of heart attack, and 9 (10/1.29) times more important than the risk of severe joint problems. Examination of the confidence intervals shows symptom control and risk of physical dependence were both statistically significantly more important than mode and frequency of administration, risk of heart attack, and risk of severe rapidly progressive joint problems requiring TJR.

Table 44. Discrete-Choice Experiment Scaled Conditional Attribute Relative Importance in the United States; Respondents With Moderate-to-Severe OA (N = 400)

Attribute	Worst level/least preferred	Best level/most preferred	Order of importance	Mean	95% CI	
Symptom control (patient global assessment)	Poor	Very good	1	10.00	7.75	12.25
Treatment-related risk of physical dependence	250 people out of 1,000 (25%)	No risk (0%)	2	6.69	5.22	8.16
Mode and frequency of administration	Injection every 8 weeks	Oral pills once a day	3	1.95	1.02	2.88
Incremental treatment-related risk of heart attack	5 people out of 1,000 (0.5%)	No additional risk (0%)	4	1.76	1.00	2.53
Incremental treatment-related risk of severe rapidly progressive joint problems requiring TJR	40 people out of 1,000 (4%)	No additional risk (0%)	5	1.29	0.54	2.05

Note: The conditional relative importance estimate for each attribute is scaled such that the attribute with the highest conditional relative importance—symptom control—is set to 10. The conditional importance of each of the other attributes is scaled relative to the conditional importance of the attribute with the highest conditional relative importance. The standard errors and the 95% CI for these differences were calculated using the delta method.

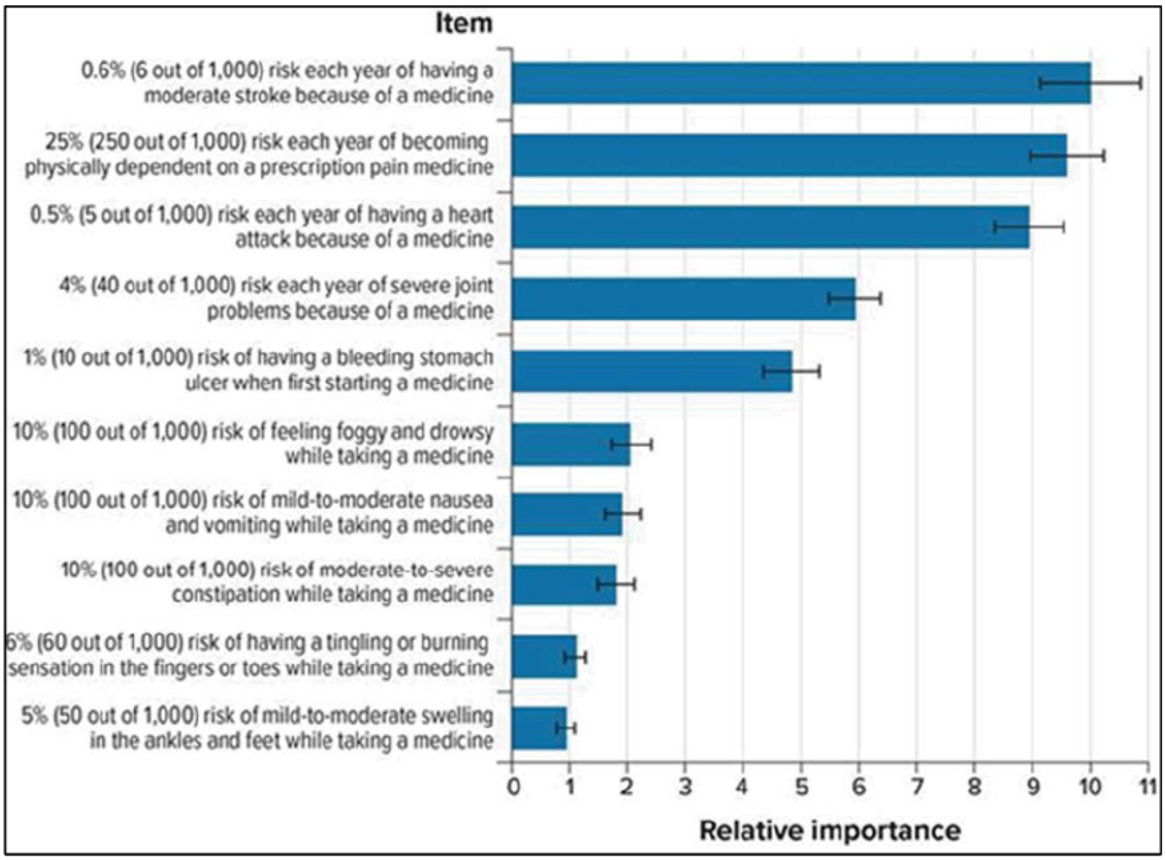
The estimates of the conditional relative importance presented in Table 44 indicate that avoiding a 4% annual risk of severe joint problems or avoiding a 0.5% annual risk of heart attack has much less impact on patient choice than improving symptom control from poor to very good, implying that patients would be willing to accept much more than a 4% increase in the annual risk of severe joint problems or more than a 0.5% increase in the risk of heart attack to achieve very good symptom control. In addition, these results indicate that patients would be willing to accept more than a 4% risk of severe joint problems or more than a 0.5% annual risk of heart attack to avoid the risk of physical dependence.

6.6.2. Best-Worst Scaling Results

Figure 43 presents findings from the BWS exercise. For patients, a 0.6% increased annual risk of having a moderate stroke because of a medicine was the most important risk to avoid relative to all other risks included in the BWS exercise. This was followed by the three risks included in both the DCE and the BWS (risk of physical dependence, risk of heart attack, and risk of severe joint problems requiring TJR). The ranking of these three risks was consistent across the DCE and BWS; that is avoiding a 25% annual risk of physical dependence was more important than avoiding a 0.5% risk of having a heart attack which, in turn, was more important than avoiding a 4% annual risk of severe joint problems. The least important risks

to avoid were a 6% risk of having a tingling or burning sensation in the fingers or toes while taking a medicine and a 5% risk of mild-to-moderate swelling in the ankles and feet while taking a medicine.

Figure 43. Best-Worst Scaling Relative Importance in the United States (N = 400)



Note: The horizontal bars surrounding each relative importance weight estimate denote the 95% CI (computed by the delta method).

6.6.2.1. Conclusion

The key finding of the patient preference study was that US OA patients placed much more importance on avoiding the risk of physical dependence compared to avoiding the risk of severe joint problems. This was seen in both the DCE and BWS scaling exercises. Patients were willing to accept some level of each type of risk to improve pain symptom control; however, patients are more willing to accept the risk of joint problems likely to be associated with NGF-inhibitor products than they are willing to accept the risk of dependency associated with opioids when the level of symptom control is the same for both treatment types. In addition, patients are no less willing to accept the risk of severe joint problems likely to be associated with NGF-inhibitor products than they are willing to accept CV risks likely associated with NSAIDs. These results suggest that patients, on average, prefer alternative pharmacological treatments for pain to treatments with characteristics reported for opioids and that they view NGF-inhibitor products as acceptable alternatives to both NSAIDs and opioids, despite the risks associated with NGF-inhibitor medications.

FDA has issued guidance that patients can and should bring their own experiences to bear in helping the Agency evaluate the benefit-risk profile of medicines.[123] Quantitative preference data conveys the voice of the patient population as scientific data that can be used for regulatory decision-making. The preferences within a patient population may be very diverse, and a population-based, quantitative patient preference study may capture that range of perspectives much better than single-patient testimony. This has led to quantitative patient preference studies being recognized as a significant step in the direction of incorporating patients' benefit preferences and risk tolerance into the existing evidence-based regulatory process.[130]

7. PROPOSED POSTMARKETING RISK MANAGEMENT

The proposed comprehensive postmarketing risk management strategy is detailed in this section and includes the following key components:

- Routine and additional risk mitigation:
  - USPI and Medication Guide including a boxed warning for the increased risk of RPOA and potential need for a TJR
  - Restricted distribution program (ie, REMS program)
  - Healthcare provider RPOA Imaging Guide
- Routine and additional safety surveillance:
  - Adverse event monitoring including enhanced follow-up for all joint safety adverse events
  - Safety surveillance study to assess long-term safety

7.1. Strategy for Proposed Prescribing Information

The proposed labelling for tanezumab, including the USPI and associated Medication Guide for patients, will communicate all safety risks for tanezumab and will provide guidance on the appropriate use of tanezumab in the postmarketing setting, including the proposed risk minimization measures for RPOA (See Appendix 1 for relevant excerpts). These measures were primarily informed by the procedures and processes used to monitor and mitigate joint damage in patients with OA in the post-2015 clinical studies and are intended to ensure the benefit-risk profile of tanezumab is maintained in the postmarketing setting. Key risk minimization measures are as follows:

- Use of tanezumab at 2.5 mg as this is an efficacious dose with the most favorable benefit-risk profile.
- Patients with pre-existing RPOA, SIF, ON, or atrophic OA should not use tanezumab because it may increase the risk of developing new or worsening RPOA. Bilateral radiographs of knees and hips are required prior to treatment initiation to assess for these risk factors.
- Patients should be monitored at each visit for signs and symptoms of RPOA and repeat radiographs should be obtained if clinically warranted.
- Administration of tanezumab with NSAIDs and for 16 weeks after the last dose is not recommended, given the 3-fold-increase in risk of RPOA with long-term concomitant use. While safety data demonstrate that short-term concomitant use of NSAIDs (up to 10 days in an 8-week period) does not lead to an increased risk for RPOA, in an abundance of caution, any NSAID use is not recommended. A contraindication to

NSAID use with tanezumab has not been suggested due to the recognition that some patients will benefit from acute use of NSAIDs for acute illness or injury. Safety data from clinical studies related to short-term use will be provided in the USPI and REMS educational materials, so that HCPs can make appropriate decisions on short-term NSAID use if the benefit-risk is deemed favorable in individual situations.

- Patients who do not have a satisfactory clinical response after receiving 2 doses should stop treatment with tanezumab, as efficacy data demonstrate no additional benefit is anticipated with further administration.

- Annual re-assessment of benefit-risk, if treatment with tanezumab is continued, including required bilateral radiographs of knees and hips to assess for RPOA or risk factors for RPOA, as not all patients with these events display clinical signs or symptoms. Radiographs will not be required 6 months after treatment initiation, as the Phase 3 clinical trial data did not demonstrate that imaging at this time point would add significantly to the safe use of tanezumab.

- Patients who develop RPOA should be discontinued from tanezumab treatment.

7.1.1. Boxed Warning in Proposed Prescribing Information

The proposed USPI will prominently and clearly describe the increased risk for RPOA and TJR in a boxed warning, including the increased risk associated with concomitant NSAID use.

7.2. Proposed REMS With ETASU

To further mitigate the risk of RPOA, a risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) is proposed to ensure adherence to the labeling requirements and to ensure that prescribers, healthcare settings, pharmacies, and patients understand the risk of RPOA and how to implement the key risk minimization measures prior to treatment initiation and while receiving tanezumab.

Objectives of the REMS include:

- Ensuring HCPs are educated about the increased risk of RPOA associated with the use of tanezumab.

- Ensuring that HCPs are educated on and adhere to the following:

    - Document that baseline and annual radiographs are completed to identify RPOA and risk factors for RPOA by submitting the Patient Enrollment Form and Patient Continuation Form, respectively.

    - Counsel patients on the increased risk of RPOA and the importance of avoiding NSAIDs while being treated with tanezumab and for 16 weeks after the last dose of tanezumab.

- Ensuring safe use of tanezumab by:
    - Ensuring that tanezumab is only administered to enrolled patients in certified healthcare settings after verification of baseline and annual radiographs (after 1 year of treatment), and counseling patients on the importance of avoiding NSAIDs.
- Ensuring patients are informed about:
    - The increased risk of RPOA associated with the use of tanezumab.
    - The requirement for radiographs at baseline and annually thereafter.
    - The importance of avoiding NSAIDs while being treated with tanezumab and for 16 weeks after the last dose of tanezumab.

The key requirements of the REMS program and intended risk mitigation results are summarized in Table 45.

Table 45. Key Requirements of the REMS Program and Intended Risk Mitigation Results

REMS Requirement	Intended Risk Mitigation Result
Prior to Treatment Initiation	
Certification of prescribers, healthcare settings and pharmacies • REMS coordinating center manages and tracks certifications	• Ensure all REMS stakeholders are educated about the risk of RPOA • Ensure all REMS stakeholders understand their associated REMS requirements
Enrollment of patients in the REMS program • Patients and prescribers both sign Patient Enrollment Form and attest that requirements are understood and have been completed	• Ensure patients have been counseled and educated about the risk of RPOA, and understand the actions they need to take to decrease the risk
Baseline radiographs of knees and hips • Attestation of Completion on Patient Enrollment Form	• Ensure patients with pre-existing bone integrity issues do not initiate tanezumab treatment

During Treatment	
Monitor patients for signs and symptoms of RPOA and obtain repeat radiographs if indicated	• Ensure early identification and appropriate management of symptomatic RPOA
Remind patients about RPOA and the need to avoid NSAIDs at each dose • Patients receive new Patient Wallet Card	• Ensure patients remember the risk of RPOA and their actions to take to decrease the risk
Assess patients for clinically important improvement after 2 doses	• Ensure only patients with positive benefit-risk continue to receive tanezumab
Confirm that patients remain authorized to continue therapy prior to each dose • REMS coordinating center must be contacted by certified Healthcare Setting to authorize administration of tanezumab	• Ensure that only eligible patients receive tanezumab
Annual radiographs of knees and hips • Documented on Patient Continuation Form	• Ensure early identification and management of asymptomatic RPOA • Establish new radiographic baseline for future assessments
At All Times	
Report joint safety adverse events to the REMS coordinating center and unenroll the patient	• Ensure RPOA events are reported and key information collected

Additionally, tanezumab will only be administered within a certified healthcare setting after confirmation that both prescriber and patient are enrolled and eligible in the REMS program. Tanezumab will not be dispensed directly to patients as retail pharmacies are not part of the distribution pathway. Tanezumab will be available through a restricted distribution system that will only use two distribution pathways:

1. Wholesaler(s)/distributor(s) distribute tanezumab to a certified healthcare setting to support buy and bill or medical billing models (ie, doctor's office), or

2. Wholesaler(s)/distributors distribute tanezumab to a certified specialty pharmacy to support prescription billing models. The specialty pharmacy dispenses tanezumab

pursuant to a prescription for an individual patient from a prescriber in a certified healthcare setting and sends tanezumab to the healthcare setting.

7.2.1. REMS Requirements for Prescribers

Prescribers must be certified to prescribe tanezumab (further details on the REMS prescriber certification process and REMS training for prescribers, including key risk messages from the REMS educational materials, can be found in Appendix 4). The key risk minimization measures for prescribers include:

- Ensure each patient has received counseling on the risk of RPOA and the REMS requirements prior to treatment initiation by using the Patient Guide and Patient Wallet Card.
- Perform baseline radiographs of the knees and hips to assess for risk factors of RPOA prior to treatment initiation.
- Enroll each patient in the REMS by submitting the Patient Enrollment Form that documents that patient counseling and baseline radiographs have taken place.
- Assess the patient prior to continuing treatment beyond one year by performing annual radiographs of the knees and hips and submitting a Patient Continuation Form.
- Report all joint safety adverse events to the REMS program and unenroll the patient.

7.2.2. REMS Requirements for Healthcare Settings

Healthcare settings must be certified to dispense and administer tanezumab (further details on the REMS healthcare setting certification process and REMS training for healthcare settings can be found in Appendix 4). The key risk mitigation measures for healthcare settings include:

- Ensure that the patient is currently enrolled and authorized to continue therapy by contacting the REMS program to obtain authorization to dispense each dose.
- Ensure that the patient is remined about the risk for RPOA and the need to avoid NSAIDs by providing a new Patient Wallet Card at each tanezumab administration.

7.2.3. REMS Requirements for Pharmacies

Pharmacies must complete the certification process to be able to dispense tanezumab to the certified healthcare setting. The pharmacy must ensure that the prescriber and healthcare setting are certified and the patient is enrolled in the REMS prior to dispensing tanezumab directly to the healthcare setting.

7.2.4. REMS Requirements for Patients

Patients must be enrolled in the REMS prior to being treated with tanezumab. The key requirements for patients include:

- Receive Patient Guide and counseling from a HCP to ensure the patient understands risk of RPOA and REMS requirements for safe use, including avoidance of NSAIDs, prior to treatment initiation.

- Receive Patient Wallet Card at each treatment to serve as a reminder to avoid use of chronic NSAIDs.

- Be assessed for RPOA and risk factors of RPOA by having baseline and annual radiographs of the knees and hips.

- Adhere to the safe use conditions, including avoiding NSAIDs while being treated with tanezumab and for 16 weeks after the last dose.

Further details on patient counseling including key risk messages from the REMS educational materials can be found in Appendix 4.

7.2.5. Assessment of REMS Effectiveness

The Sponsor will conduct assessments to evaluate the effectiveness of the REMS program. The REMS assessment report will be submitted at 6-months, 12-months, and annually thereafter from the date of initial approval of the REMS. The proposed REMS Assessment Plan outlines how the Sponsor will assess the performance of the REMS in meeting its risk mitigation goals and objectives. The proposed plan utilizes both process and outcome indicators to assess program performance. The proposed assessment plan also considers metrics to evaluate aspects related to burden and access challenges due to the program requirements. Appendix 5 describes each goal and objective of the proposed REMS program and its corresponding assessment plan.

The Sponsor will establish a plan for addressing noncompliance with REMS program requirements. Healthcare settings, pharmacies, and wholesaler-distributors will be monitored on an ongoing basis to ensure the requirements of the REMS are being met and corrective actions are being taken if noncompliance is identified by the Sponsor. The Sponsor may receive information via the REMS Administrator, REMS Call Center, REMS Stakeholder Auditor, or other means indicating that a stakeholder is suspected of noncompliance in the tanezumab REMS. Noncompliance investigations will be conducted by the Sponsor and the REMS assessment reports will include a summary and analysis of program compliance.

The Sponsor is also responsible for conducting annual audits. The Sponsor proposes to audit healthcare settings, pharmacies and data from wholesaler-distributors that have distributed tanezumab at 12-months from the date of first commercial distribution and annually thereafter to ensure that all REMS processes and procedures are in place, functioning and support the REMS requirements. To be audited, the healthcare setting or pharmacy must have received at least one shipment of tanezumab in the past 12 months and not have been previously audited in the past three years. The REMS assessment reports will include a summary and analysis of program audit findings.

7.3. Healthcare Provider RPOA Imaging Guide

As another component of risk minimization, the Sponsor will make available a detailed imaging guide for radiologists and other HCPs, as the radiographic features of RPOA and risk factors for RPOA such as SIF, ON and atrophic OA may not be well recognized by all HCPs.

The objective of the imaging guide is to:

- Provide HCPs with detailed imaging information that will be important during attainment and assessment of the required baseline and annual radiographs.
- Provide HCPs with definitions and radiographic examples of RPOA-1, RPOA-2 and risk factors for RPOA that need to be assessed in baseline and annual radiographs.

The Healthcare Professional RPOA Imaging Guide will be made available to radiologists and HCPs through proactive communication and outreach programs.

7.3.1. Rationale for Proposed Postmarketing Radiographic Surveillance

Annual radiographs of knees and hips will be required if patients continue tanezumab treatment for more than one year. Annual radiologic surveillance in the post-2015 studies was effective in early detection of RPOA-2 and minimization of the degree of bone damage as compared to the cases of RPOA-2 in the pre-2015 studies, which did not include systematic radiologic surveillance. Annual radiographic surveillance also allowed for early detection and management of RPOA-1. While some cases of RPOA-2 and RPOA-1 were identified using "for cause" radiographs, routine periodic radiographs were valuable, because not all patients with RPOA-2 or RPOA-1 had clinically meaningful signs or symptoms that signaled the need for a radiograph. Annual radiographs will also provide a new "baseline" for future radiographic assessments. As in the clinical studies, HCPs will be instructed to obtain repeat radiographs of joints that develop new onset persistent pain and/or swelling at any time, as these symptoms could indicate the emergence of RPOA.

It is acknowledged that the proposed radiographic surveillance will likely have higher false positive and false negative error rates in the identification of RPOA-1, in comparison to RPOA-2, in part due to the technical challenges of standardizing joint position of sequential radiographs. While measuring JSW is not customary in clinical practice, JSW can be visually assessed. The imaging guide will provide suggestions for optimal positioning and interpretation of sequential films and it is anticipated that the proposed radiographic surveillance, either annually or for cause, will allow for identification of joints with reductions in JSW consistent with RPOA-1. It is likely that confirmatory radiographs may be needed in some cases to confirm that the narrowing of JSW was not the result of improper joint positioning.

7.4. Proposed Postmarketing Pharmacovigilance

7.4.1. Enhanced Routine Pharmacovigilance

The Sponsor will monitor the real-world safety of tanezumab following its authorization in the US through routine pharmacovigilance that will include continuous intake, review and

summarization of available safety data from the REMS program, clinical studies, spontaneous adverse event reports and published scientific literature. In addition, for all joint safety adverse events, the Sponsor will collect additional follow-up information using a targeted data collection form that will be sent to HCP reporters initially and at one year following the initial report. Safety information, including findings from proposed REMS assessments and audits, will be reviewed for emerging safety signals or for unanticipated findings that suggest that changes to labelling or the REMS program are needed.

7.4.2. Proposed Postmarketing Safety Surveillance Study (Subject to FDA Review and Discussion With the Sponsor)

The Sponsor is committed to obtaining additional safety data after approval, including an assessment of long-term joint safety (ie, use more than 2 years). The Sponsor is consulting with the FDA to align on the optimal study design and has proposed as one of the options, a safety surveillance study using real world electronic healthcare data.

Safety surveillance studies using electronic healthcare databases have been used to successfully monitor the real-world safety of newly approved products across a wide spectrum of therapeutic areas and safety endpoints.[131,132] They are a more rigorous approach to monitoring drug safety than postmarketing spontaneous reports which have limited value for measuring event incidence.[131] In addition, large healthcare databases have been used extensively to study the OA population.[34,133,134]

The proposed safety surveillance study using electronic healthcare data offers several advantages over other study designs:

- Provides clinical, pharmacy and laboratory data from a large number of geographically diverse OA patients using tanezumab and other OA therapies in a real-world setting;
- Allows for data collection from a comparator cohort with similar baseline demographic and disease characteristics to a cohort of patients receiving tanezumab;
- Provides de-identified data on individual patients in a timely manner without the need to obtain informed consent or request data from prescribers and patients.

The proposed study would be conducted using the Innovation in Medical Evidence and Development Surveillance (IMEDS) data network which includes a subset of FDA Sentinel partners and leverages the same healthcare data and analytic tools initially developed by the FDA Sentinel Initiative. The IMEDS is a large data network and is representative of the commercially-insured population in the US. During the time period from 1 January 2014 to 31 December 2018, the IMEDS data network contained approximately 6.9 million OA patients.

The primary research objectives of the proposed study would be to estimate the incidence rate of RPOA-2 and subsequent occurrence of TJR in patients receiving tanezumab and in an appropriate comparison group. RPOA-2 is expected to be identified through ICD-10 codes in the IMEDS data network. Currently, there are no diagnostic codes for RPOA, but the

Sponsor applied to the CDC for new diagnostic codes (ICD-10) for rapidly destructive OA (ie, RPOA-2) in September 2020. It is anticipated that these codes could be available in 2021.

The Sponsor will continue to work with the FDA to design and develop a robust post-approval safety study to assess the long-term safety of tanezumab in a timely manner.

8. BENEFIT RISK ASSESSMENT

8.1. Benefits Profile of Tanezumab

8.2. Assessment of Comparative Benefit-Risk

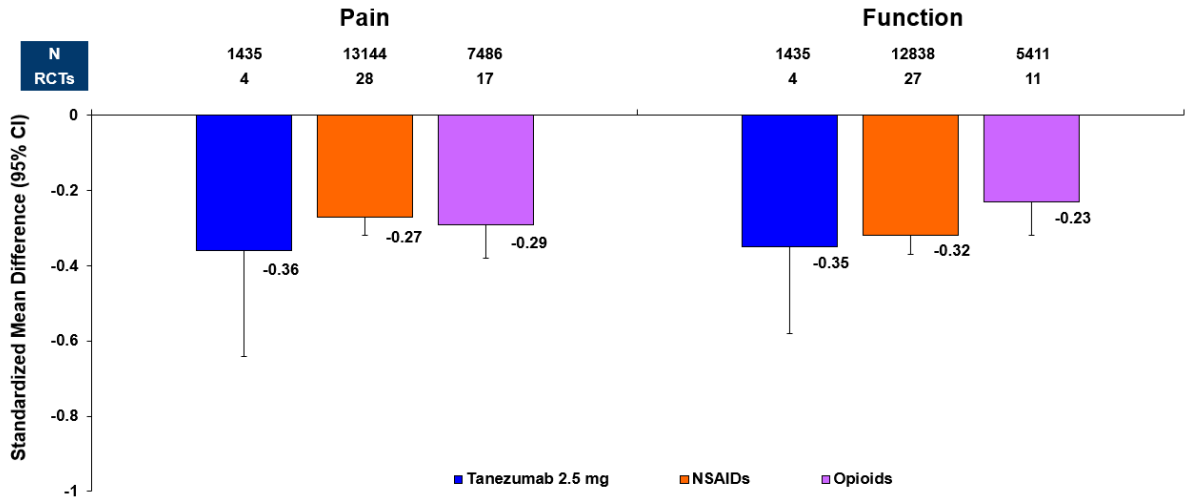
Tufts Medical Center produced a comprehensive, in depth comparative benefit-risk analysis using validated methodology. Below is a summary of the analysis and key findings.

The review included safety and efficacy comparisons of risk differences and standardized mean differences for tanezumab 2.5 mg, NSAIDs, and opioids, in order to provide robust evidence and context of associated risks and treatment benefits compared to NSAIDs and opioids commonly used for the treatment of moderate to severe OA.

The review included randomized controlled studies and categorized findings according to the duration of the study, robustness of the findings, and the strength of the evidence for each finding.

In patients with moderate to severe OA, in the short-term, tanezumab 2.5 mg provided pain relief and functional improvement compared to placebo. These effects were similar to the short-term effects observed in the placebo-controlled studies of NSAIDs and opioids (Figure 44). However, it is noteworthy that the tanezumab patient population had more advanced disease and was more treatment resistant compared to the patient population studied in prior studies with NSAIDs and opioids, and were required to have a history of inadequate pain relief, intolerability, or contraindication with commonly used standard-of-care analgesics including acetaminophen (inadequate pain relief was the only protocol qualifying criteria for acetaminophen), NSAIDs, and either tramadol or opioids (or were unwilling to use opioids).

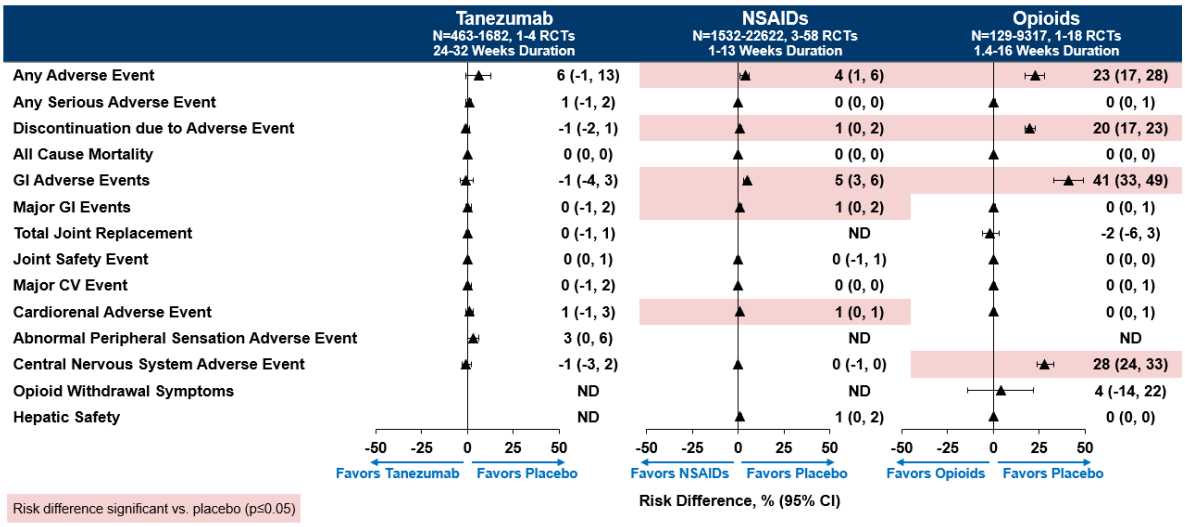
Figure 44. Short-Term Efficacy Across Drug Classes in Placebo- Controlled Studies



The analyses of key safety measures across the classes of medications in shorter-term studies did not identify any unexpected safety concerns for NSAIDs, opioids, or tanezumab (Figure 45). However, the analyses did provide a quantitative (risk difference) comparison of the

safety profiles across the classes of medication. Opioids had the least desirable general safety/tolerability profile as reflected by the risk differences for total adverse events and discontinuations due to adverse events relative to placebo being statistically significantly different from placebo and larger than the risk differences for the NSAID or tanezumab comparisons versus placebo.

Figure 45. Short-Term Safety Across Drug Classes in Placebo-Controlled Studies

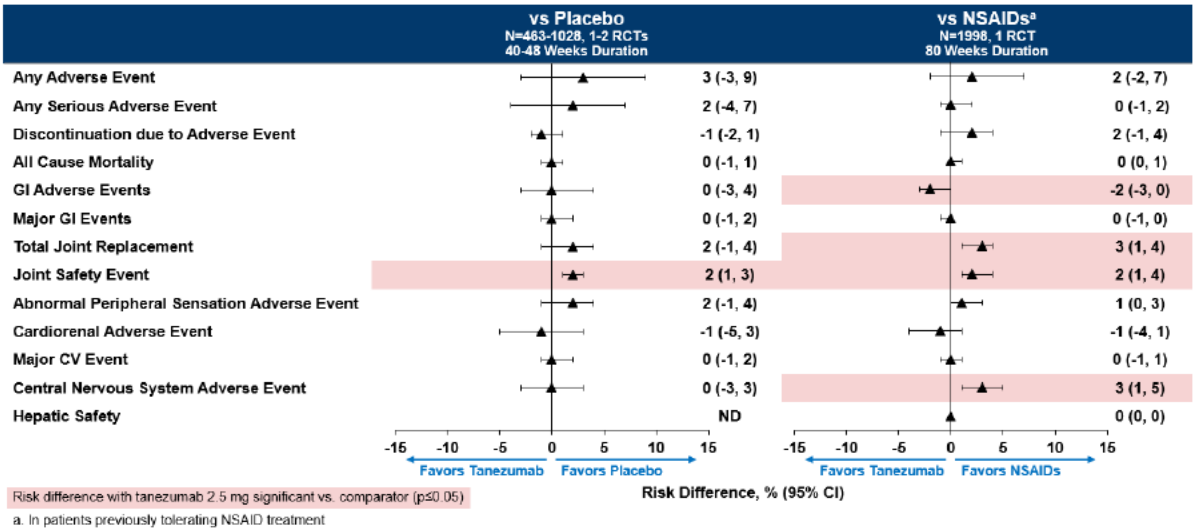


The risk difference for GI-related adverse events favored placebo treatment relative to NSAID treatment. The risk difference for adverse events of abnormal peripheral sensation, paresthesia, and joint safety events favored placebo treatment relative to tanezumab treatment although none of these comparisons reached statistical significance in this analysis of a limited number of studies. The magnitude of the risk differences for these respective different types of adverse events were generally similar suggesting a similar degree of risk for these types of adverse events within each class of medication (tanezumab and NSAIDs).

The risk differences for GI-related and central nervous system-related adverse events with opioids were statistically significantly different relative to placebo treatment with the magnitude of the risk differences being larger than the risk differences for key adverse events associated with NSAIDs or tanezumab suggesting a higher degree of risk for the opioid-associated adverse events.

Based on the post-2015 tanezumab clinical study data, long-term assessments of tanezumab versus placebo (40 to 48 weeks) or NSAIDs (up to 80 weeks) indicated patients receiving tanezumab 2.5 mg were 2% more likely to experience a composite joint safety event. In addition, patients treated with tanezumab 2.5 mg were 3% more likely to undergo TJR than patients treated with NSAIDs (Figure 46). For long-term assessments, no placebo-controlled studies for NSAIDs or opioids met the inclusion criteria of the meta-analysis.

Figure 46. Long-Term Safety of Tanezumab 2.5 mg



Note: Patients treated with NSAID were 3% less likely to have a central nervous system adverse event due to a lower incidence of headache in NSAID treated patients.

To provide an assessment of the long-term risks associated with NSAIDs or opioids, data from a previously published meta-analysis of NSAIDs,[135] a long-term NSAID safety study,[136,137] and a systematic review of observational studies with opioids[32] were evaluated.

There was an increased risk in major vascular events (incidence rate of 5%), major upper GI events (incidence rate of 1.5%), and all-cause mortality (incidence rate of 1.7%) with NSAIDs. Higher doses of NSAIDs were associated with greater risk. [135]

Opioids had the least desirable general safety/tolerability profile as reflected by their association with increased risk for overdose, opioid abuse, fractures, MI, and markers of sexual dysfunction.

Systematic reviews associated with recently published clinical practice guidelines for OA by the ACR[14] and OASRSI[13] had results consistent with the findings of the Tufts Medical Center analysis for NSAIDs and opioids.

The conclusion of Center for Treatment Comparison and Integrative Analysis at Tufts Medical Center analysis of efficacy and safety data for tanezumab, NSAIDs, and opioids indicated that tanezumab has a benefit-risk profile that is acceptable for patients with advanced OA for whom other analgesics are ineffective or not appropriate.

8.3. Overall Conclusion on Benefit to Risk Balance

Key points to consider on the benefit-risk balance for tanezumab that will assist the FDA in applying reasonable scientific and regulatory judgement on the tanezumab application include:

- The efficacy of tanezumab has been established for the treatment of moderate to severe OA pain in adults for whom the use of other analgesics (ie, acetaminophen, NSAIDs and opioids) was ineffective or not appropriate. In placebo-controlled studies with this patient population, approximately 50% of patients had a substantial clinically meaningful improvement in pain while being spared the risks and complications associated with daily NSAID or opioid use.

- Tanezumab is generally well tolerated. The key safety findings were joint safety events including adjudicated RPOA-1, RPOA-2 and TJRs.

- Based on data from the patient preference study, patients were more willing to accept risk of serious joint problems than risk of physical dependence with opioids indicating that patients prefer the attributes of tanezumab over those of opioids.

- The Center for Treatment Comparison and Integrative Analysis at Tufts Medical Center benefit-risk assessment of the safety and efficacy of tanezumab compared to NSAIDs and opioids indicated that tanezumab has a positive benefit-risk profile in the intended patient population.

- The proposed comprehensive postmarketing risk management strategy leverages routine risk management and includes enhancements to the routine pharmacovigilance activities, a proposed REMS, and proposed safety surveillance study to assess long-term safety. The proposed approach was primarily informed by the procedures and processes used to monitor and mitigate joint damage in patients with OA in the post-2015 studies and are intended to ensure the benefit-risk profile is maintained in the postmarketing setting.

- In conclusion, the benefit of tanezumab 2.5 mg is seen in a population of patients for whom current treatments are ineffective or are clinically not appropriate because of contraindications or co-morbidities, lack of tolerability or due to patient choice/unwillingness to take opioids. These difficult-to-treat patients are not served by current therapies and there remains unmet medical need. This is the reality for many Americans suffering from OA, and contributes to diminished physical functioning and reduced quality of life. For tanezumab 2.5 mg, the risk of joint safety is not life-threatening, occurs at a low incidence and is manageable through labelling, REMS with ETASU, and a postmarketing safety surveillance study to further characterize the risk in the post-approval setting. In totality, with a positive benefit-risk profile, tanezumab will fill the important unmet need for those patients that meet the indication for *the treatment of moderate to severe osteoarthritis (OA) pain in adult patients for whom use of other analgesics is ineffective or not appropriate*. Tanezumab is appropriate for this subset of patients and the decision whether to initiate and continue tanezumab should be shared by the HCP and patient based upon these benefit-risk considerations.

9. GLOSSARY

American College of Rheumatology (ACR) Classification Criteria for Osteoarthritis

1986 Osteoarthritis Knee Criteria

Clinical and radiographic criteria for classification of idiopathic osteoarthritis of the knee.

Meets criteria 1, 2 and 3:

1. Knee pain.
2. Presence of at least 1 of the following 3:
    - Age greater than 50 years.
    - Morning stiffness less than 30 minutes in duration.
    - Crepitus.
3. Presence of osteophytes on X-ray.

Osteoarthritis Hip Criteria

Combined clinical and radiographic criteria for osteoarthritis of the hip.

1. Hip pain.
2. AND at least 2 of the 3 following features:
    - Erythrocyte sedimentation rate less than 20 mm/hour.
    - Radiographic femoral or acetabular osteophytes.
    - Radiographic joint space narrowing (superior, axial, and/or medial).

Antidrug Antibodies (ADAs)

- Anti-drug antibodies (ADAs) are made as part of the immune response to a therapeutic antibody.
- ADAs can be described as “neutralizing” and “non-neutralizing”
    - Neutralizing ADAs – ADAs that bind to the area of the variable region that confers antigen specificity or in some way interferes with binding of the therapeutic antibody to its target.
    - Non-neutralizing ADAs – ADAs directed against the non-antigen binding region and do not interfere with the binding of the therapeutic antibody to its target.

Adjudication Committee

- A blinded external committee consisting of 4-5 experts in orthopedic surgery, rheumatology, orthopedic pathology, or radiology with expertise in patients with end-stage OA and ON that reviewed joint safety events.

- The Adjudication Committee reviewed all possible or probable joint related safety events identified by the Central Reader, TJRs, as well as investigator-reported adverse events of ON, RPOA, SIF, or pathologic fracture (potential events).

Atrophic Osteoarthritis

- An OA phenotype characterized by marked loss of joint space without associated osteophyte formation and absence of erosions or other radiographic signs of inflammatory arthritis.

Chronic Pain

- Lasting >3 months.[138]

Composite Joint Safety Endpoint

- Includes any subject with an adjudicated outcome of primary osteonecrosis, RPOA type 1 or type 2, subchondral insufficiency fracture (SIF), or pathological fracture.

Dysesthesia/Dysaesthesia

- Unpleasant spontaneous or evoked sensory phenomena such as burning.

Humanized Antibody

- Humanized antibodies are derived mostly from a human DNA sequence. Only the variable or complementarity determining regions (CDRs) are based on a DNA sequence that originated from a non-human species.[139]

- Humanized antibodies have a lower risk of inducing immune responses in humans, compared with non-human antibodies.[139]

Hyperesthesia/Hyperaesthesia

- Hyperesthesia describes an increased sense of touch or numbness.

Hypoesthesia/Hypoaesthesia

- Hypoesthesia describes a decreased sense of touch or numbness.

Index Joint

- The index joint was identified by the Investigator at screening as the most painful protocol specified joint (knee or hip) meeting American College of Rheumatology (ACR)

criteria, with x-ray confirmation (a Kellgren-Lawrence (KL) x-ray grade of ≥2), and with a qualifying WOMAC Pain score. The KL grade was diagnosed by a Central Reader in post-2015 Studies 1056, 1057, and 1058. In Studies 1011 and 1014 x-rays taken within the last 12 months could be used.

Intent-to-Treat (ITT)

- Clinical study population defined as all randomized patients who received at least one dose of study medication.

Kellgren and Lawrence (KL) Grading System

- A common method of classifying the severity of knee osteoarthritis (OA) using five grades:[140]
  - Grade 0: no radiographic features of OA are present
  - Grade 1: doubtful joint space narrowing (JSN) and possible osteophytic lipping
  - Grade 2: definite osteophytes and possible JSN on anteroposterior weight bearing radiograph
  - Grade 3: multiple osteophytes, definite JSN, sclerosis. Possibly bony deformity
  - Grade 4: large osteophytes, marked JSN, severe sclerosis and definite bony deformity

Major Adverse Cardiovascular Events (MACE)

- A composite endpoint to capture major cardiovascular events.

Monoclonal Antibodies

- A monoclonal antibody (mAb) is an immunoglobulin cloned from a single parent cell.

Nerve Growth Factor (NGF)

- A neurotrophin with a primary role during early (eg, embryonic, postnatal) development and childhood via promotion of neuronal differentiation, maturation, and survival. After childhood, the primary role of NGF switches from neuronal survival to nociception.[50,51]

Nerve Growth Factor (NGF) Receptors

- Tropomyosin-receptor kinase A (TrkA) and p75 are membrane-bound protein receptors with high and low affinity, respectively, for nerve growth factor (NGF).[50]

Numerical Rating Scale (NRS)

- NRS for pain are used to measure pain intensity and commonly used as measures of efficacy in studies of pain treatments including tanezumab studies.

Osteonecrosis (ON)

- ON; or avascular necrosis is caused by a loss of blood supply to a segment of bone, which results in bone death.

Paresthesia/Paraesthesia

- Nonpainful, spontaneous sensory phenomena such as “pins-and-needles” sensation or tingling.

Risk Evaluation and Mitigation Strategies (REMS)

- A drug safety program that the US Food and Drug Administration (FDA) requires for certain medications with serious safety concerns to ensure the benefits of the medication outweigh its risk when labeling alone is not adequate.

Rapidly Progressive Osteoarthritis (RPOA; as defined in tanezumab clinical studies)

- Rapidly progressive osteoarthritis (RPOA) type 1 is defined as a significant loss of JSW ≥2 mm within approximately 1 year, without gross structural failure.[141]

- RPOA type 2 is defined as abnormal bone loss or destruction, including limited or total collapse of at least one subchondral surface, that is not normally present in conventional end-stage OA.[141]

10. APPENDICES

Appendix 1. Excerpts From the Proposed Tanezumab USPI (Draft Subject to FDA Review)

Indication

Treatment of moderate to severe osteoarthritis (OA) pain in adult patients for whom use of other analgesics is ineffective or not appropriate. [proposed indication modified based on discussion with FDA June 2020 at mid cycle meeting].

Box Warning

> Tanezumab increases the risk for developing rapidly progressive osteoarthritis (OA) evidenced by accelerated loss of articular and/or meniscal cartilage (rapidly progressive OA Type 1), or abnormal bone loss and/or destruction, including limited or total collapse of a subchondral surface (rapidly progressive OA Type 2), which leads to an increased risk for total joint replacement. Monitor patients closely for the development of signs and symptoms of rapidly progressive OA during treatment with tanezumab. Discontinue tanezumab if a patient develops rapidly progressive OA.
>
> Tanezumab is not recommended in patients with pre-existing rapidly progressive OA, subchondral insufficiency fracture, osteonecrosis, or atrophic OA because it may increase the risk of developing new or worsening rapidly progressive OA.
>
> Administration of tanezumab with non-steroidal anti-inflammatory drugs (NSAIDs) and for 16 weeks after the last dose of tanezumab is not recommended as chronic use of NSAIDs increases the risk of rapidly progressive OA. Counsel patients who are prescribed tanezumab about the importance of avoiding concomitant NSAID use.
>
> Because of the risk of rapidly progressive OA, tanezumab is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the tanezumab REMS Program.

Warnings and Precautions

Rapidly Progressive Osteoarthritis (OA):

Tanezumab increases the risk for developing rapidly progressive OA evidenced by accelerated loss of articular and/or meniscal cartilage in a joint (rapidly progressive OA Type 1), or abnormal bone loss and/or destruction, including limited or total collapse of a subchondral surface (rapidly progressive OA Type 2), which leads to an increased risk for total joint replacement. Events occurred most frequently in knee and hip joints that had significant underlying OA, and rarely occurred in the shoulder joint or in joints without pre-existing OA.

Tanezumab is not recommended in patients with pre-existing rapidly progressive OA, subchondral insufficiency fracture, osteonecrosis, or atrophic OA because it may increase the risk of developing new or worsening rapidly progressive OA. Bilateral X rays of the knees and hips are required prior to initiation of tanezumab (within 2 months) to exclude the presence of these conditions.

Use of NSAIDs during treatment with tanezumab and for 16 weeks after the last dose of tanezumab is not recommended. The incidence of rapidly progressive OA increases with concomitant chronic use of NSAIDs. Counsel patients who are prescribed tanezumab about the importance of avoiding concomitant NSAID use.

Daily low dose aspirin (≤325 mg) therapy for cardiovascular event prophylaxis did not increase the risk of rapidly progressive OA.

Monitor patients closely for the development of signs and symptoms of rapidly progressive OA during treatment with tanezumab. Symptoms may include new onset, persistent pain or swelling in a joint; however, not all patients will experience these symptoms. It is recommended that an X ray of the affected joint be performed if these symptoms occur. Bilateral X rays of the knees and hips are required annually to exclude the emergence of rapidly progressive OA, subchondral insufficiency fracture and osteonecrosis. Discontinue tanezumab if a patient develops rapidly progressive OA.

Patients who do not have a satisfactory clinical response after receiving 2 doses of tanezumab should stop treatment, as no additional benefit is anticipated with further administration.

Tanezumab Risk Evaluation and Mitigation Strategy (REMS) Program

Tanezumab is available only through a restricted program under a REMS called the Tanezumab REMS Program because of the risk of rapidly progressive OA.

Further information is available at Tanezumab rems.com or by calling 1 844 729 7367 (1 844 TanREMS).

Appendix 2. Excerpts From the Celebrex, Naproxen, Diclofenac, Oxycodone Hydrochloride, and Ultram USPIs

EXCERPTS FROM THE CELEBREX (CELECOXIB CAPSULES) USPI

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8d52185d-421f-4e34-8db7-f7676db2a226

Indication

CELEBREX is a nonsteroidal anti-inflammatory drug indicated for:

- Osteoarthritis (OA)
- Rheumatoid Arthritis (RA)
- Juvenile Rheumatoid Arthritis (JRA) in patients 2 years and older
- Ankylosing Spondylitis (AS)
- Acute Pain (AP)
- Primary Dysmenorrhea (PD)

Box Warning

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events

- Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction, and stroke, which can be fatal. This risk may occur early in the treatment and may increase with duration of use.
- CELEBREX is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.

Gastrointestinal Bleeding, Ulceration, and Perforation

- NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.

EXCERPTS FROM THE NAPROXEN TABLETS USPI

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9225acaa-209f-958b-2c51-9a46995dec33

Indication

Naproxen Sodium is indicated for the treatment of:

- Rheumatoid Arthritis (RA)
- Osteoarthritis (OA)
- Ankylosing Spondylitis (AS)
- Tendonitis, Bursitis
- Acute gout
- Primary dysmenorrhea (PD)
- The Relief of mild to moderate pain

Box Warning

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events:

- Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use.
- Naproxen Sodium is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.

Gastrointestinal Bleeding, Ulceration, and Perforation

- NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.

EXCERPTS FROM THE DICLOFENAC CAPSULES USPI

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=82427c70-58a3-4b8e-a0d5-128c9c1569f8

Indication

Diclofenac Capsules is a nonsteroidal anti-inflammatory drug indicated for:

- management of mild to moderate acute pain (1)
- management of osteoarthritis pain (1)

Box Warning

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events:

- Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use.
- Diclofenac Capsules is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.

Gastrointestinal Bleeding, Ulceration, and Perforation

- NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.

EXCERPTS FROM THE OXYCODONE HYDROCHLORIDE CAPSULES USPI

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=cff0c64a-63f5-4b3c-909a-cdecf6755cbe

Indication

Oxycodone Hydrochloride Capsule are an opioid agonist indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve OXYCODONE HYDROCHLORIDE CAPSULES for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

Box Warning

WARNING: ADDICTION, ABUSE, AND MISUSE: RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

Oxycodone Hydrochloride Capsules expose patients and other users to risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk prior to prescribing Oxycodone Hydrochloride Capsules and monitor all patients regularly for the development of these behaviors and conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- complete a REMS-compliant education program,

- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

Life-threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of Oxycodone Hydrochloride Capsules. Monitor for respiratory depression, especially during initiation of Oxycodone Hydrochloride Capsules or following a dose increase.

Accidental Ingestion

Accidental ingestion of even one dose of Oxycodone Hydrochloride Capsules, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of Oxycodone Hydrochloride Capsules during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction

The concomitant use of Oxycodone Hydrochloride Capsules with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Oxycodone Hydrochloride Capsules and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of Oxycodone Hydrochloride Capsules and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

EXCERPTS FROM THE ULTRAM (TRAMADOL HYDROCHLORIDE TABLET) USPI

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=45f59e6f-1794-40a4-8f8b-3a9415924468

Indication

Ultram is an opioid agonist indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. (1)

Limitations of Use (1)

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve Ultram for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

Box Warning

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; ULTRA-RAPID METABOLISM OF TRAMADOL AND OTHER RISK FACTORS FOR LIFE-THREATENING RESPIRATORY DEPRESSION IN CHILDREN; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

ULTRAM expos es patients and other users to the risks of opioid addiction, abuse and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing ULTRAM, and monitor all patients regularly for the development of these behaviors and conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- complete a REMS-compliant education program, counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

Life-threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of ULTRAM. Monitor for respiratory depression, especially during initiation of ULTRAM or following a dose increase.

Accidental Ingestion

Accidental ingestion of ULTRAM, especially by children, can be fatal.

Ultra-rapid metabolism of Tramadol and other risk factors for life-threatening respiratory depression in children

Life-threatening respiratory depression and death have occurred in children who received tramadol. Some of the reported cases followed tonsillectomy and/or adenoidectomy; in at least one case, the child had evidence of being an ultra-rapid metabolizer of tramadol due to a CYP2D6 polymorphism. ULTRAM is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy. Avoid the us e of ULTRAM in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol.

Neonatal Opioid Withdrawal Syndrome

Prolonged us e of ULTRAM during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid us e is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Interactions with drugs affecting Cytochrome P450 isoenzymes

The effects of concomitant us e or dis continuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol are complex. Us e of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with ULTRAM requires careful consideration of the effects on the parent drug, tramadol, and the active metabolite, M1.

Risks from concomitant use with Benzodiazepines or other CNS depressants

Concomitant us e of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of ULTRAM and benzodiazepines or other CNS depressants for us e in patients for whom alternative treatment options are inadequate. Limit treatment to the minimum effective dosages and durations. Follow patients for signs and symptoms of respiratory depression and sedation.

Appendix 3. Search Criteria Used to Identify Preferred Terms for Special Safety Topics

Table 46. Search Criteria Used to Identify Preferred Terms for Special Safety Topics

Safety Topic	Search Criteria
Peripheral Neurological Safety [Section 5.3.2.2.1]	Adverse events of Abnormal Peripheral Sensation are defined as: Allodynia, Axonal neuropathy, Burning sensation, Carpal tunnel syndrome, Decreased vibratory sense, Demyelinating polyneuropathy, Dysaesthesia, Formication, Hyperaesthesia, Hyperpathia, Hypoaesthesia, Hypoaesthesia oral, Intercostal neuralgia, Neuralgia, Neuritis, Neuropathy peripheral, Paraesthesia, Paraesthesia oral, Peripheral sensorimotor neuropathy, Peripheral sensory neuropathy, Polyneuropathy, Polyneuropathy chronic, Sciatica, Sensory disturbance, Sensory loss, Tarsal tunnel syndrome, Thermohypoaesthesia.
Sympathetic Neurological Safety [Section 5.3.2.2.2]	1. Adverse events of Decreased Sympathetic Function are defined as: Abdominal discomfort, Anal Incontinence, Anhidrosis, Blood pressure orthostatic decreased, Bradycardia, Diarrhoea, Dizziness postural, Early satiety, Ejaculation delayed, Ejaculation disorder, Ejaculation failure, Heart rate decreased, Hypertonic bladder, Hypohidrosis, Micturition urgency, Nausea, Nocturia, Orthostatic hypotension, Pollakiuria, Presyncope, Respiratory distress, Respiratory failure, Sinus bradycardia, Syncope, Urinary hesitation, Urinary incontinence, Vomiting. 2. Adverse events of Decreased Sympathetic Function which required consultation are defined as: Anhidrosis, Bradycardia, Hypohidrosis, Orthostatic hypotension, Syncope.

The most recent version of MedDRA (version 21.1) available at the time of production of the integrated datasets was used for analyses presented in this document.

Appendix 4. Details on the REMS Process and REMS Key Messages

REMS Prescriber Certification Process

Prescribers must be certified to prescribe tanezumab. The prescriber completes the certification process by reviewing the Prescriber Guide, successfully completing the Prescriber Knowledge Assessment, and submitting the Prescriber Enrollment Form to the REMS.

REMS Healthcare Setting Certification Process

Healthcare settings must be certified to dispense and administer tanezumab. The healthcare setting must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS program on behalf of the healthcare setting. The authorized representative completes the healthcare setting certification process by reviewing the REMS Healthcare Setting Guide and submitting the Healthcare Setting Enrollment Form to the REMS. The authorized representative establishes processes and procedures to ensure relevant staff are trained on the REMS requirements (eg, maintaining records documenting staff's completion of training, maintaining records that all REMS processes and procedures are in place and being followed).

REMS Key Messages

Table 47 lists the key messages and supporting messages intended for HCPs and patients, the timing for delivery of each message, and the mode of delivery.

Table 47. REMS Key Messages

Key Messages and Supporting Messages	Message Recipient		Timing of Message				Mode of Delivery
	HCP	Patient	Before first dose	At Each dose	Last dose	Every 12 months if continuing treatment	
Key Message 1 - Rapidly progressive OA is a risk associated with tanezumab.	X	X	X	X*	X*		Prescriber Guide Healthcare Setting Guide Patient Enrollment Form Patient Guide Patient Wallet Card*
Inform of the difference between rapidly progressive OA type 1 and rapidly progressive OA type 2, the signs/symptoms of RPOA, and how to minimize the risk of rapidly progressive OA.	X	X	X	X*	X*		Prescriber Guide Healthcare Setting Guide Patient Guide Patient Enrollment Form Patient Wallet Card*
Tanezumab is not recommended for patients with pre-existing rapidly progressive OA, subchondral insufficiency fracture, osteonecrosis, or atrophic OA because of the increased risk of developing new or worsening rapidly progressive OA.	X		X				Prescriber Guide Healthcare Setting Guide
Patients should tell their HCP if there is a new increase in pain and/or swelling in a joint.	X	X	X	X*	X*		Prescriber Guide Healthcare Setting Guide Patient Guide Patient Enrollment Form Patient Wallet Card*
Key Message 2 -Patients need to avoid NSAIDs while being treated with tanezumab and for 16 weeks after the last dose.	X	X	X	X*	X*		Prescriber Guide Healthcare setting Guide Patient Guide Patient Enrollment Form Patient Wallet Card*
NSAIDs should not be taken while being treated with tanezumab.	X	X	X	X*			Prescriber Guide Healthcare Setting Guide Patient Guide Patient Enrollment Form Patient Wallet Card*

Table 47. REMS Key Messages

Key Messages and Supporting Messages	Message Recipient		Timing of Message				Mode of Delivery
	HCP	Patient	Before first dose	At Each dose	Last dose	Every 12 months if continuing treatment	
NSAIDs should not be taken for 16 weeks after the last dose of tanezumab.	X	X	X	X*	X*		Patient Enrollment Form Patient Guide Patient Wallet Card*
How to identify over-the counter NSAIDs and medicines that contain NSAIDs.		X	X	X*	X*		Patient Guide Patient Wallet Card*
Patients should discuss how to manage breakthrough pain with their physician and patients should tell their HCP if they feel the need to take an NSAID.	X	X	X				Prescriber Guide Healthcare Setting Guide Patient Guide Patient Enrollment Form
Key Message 3 -HCPs need to counsel patients who are prescribed tanezumab using the Patient Guide, Patient Enrollment Form, Patient Wallet Card (regarding Key Messages 1 and 2).	X		X	X*	X*		Prescriber Guide Healthcare Setting Guide Patient Guide Patient Enrollment Form Patient Wallet Card*
Key Message 4 -Understand the baseline and annual X-ray requirements for rapidly progressive OA.	X	X	X				Prescriber Guide Healthcare Setting Guide Patient Guide Patient Enrollment Form
Understand the requirement for baseline bilateral X-rays of the knees and hips.	X	X	X				Prescriber Guide Healthcare Setting Guide Patient Guide Patient Enrollment Form
Understand the requirement for annual X-rays and that a Patient Continuation Form needs to be completed and submitted to the REMS if a patient continues to be treated with tanezumab for longer than a year.	X	X	X			X	Prescriber Guide Healthcare Setting Guide Patient Guide Patient Enrollment Form Patient Continuation Form
*The Patient Wallet Card is packaged within the product carton and given to the patient at each dose.							

Appendix 5. Tanezumab REMS Assessment Plan

Table 48. Tanezumab REMS Assessment Plan

Objective	Requirement	REMS Materials	Assessment Plan Category/domain	Metrics	Data Sources/ Analytical Tools	REMS Assessment Report: Frequency of metric reporting
1. Ensuring healthcare providers are educated about the increased risk of rapidly progressive OA associated with the use of tanezumab.	1) Prescriber certification	1) Prescriber Guide 2) Prescriber Enrollment Form 3) Prescriber Knowledge Assessment	1) Implementation and operations 2) Knowledge of prescribers	1) Number and specialty of certified prescribers 2) Number of prescription orders written by noncertified prescribers and disposition 3) Results of surveys of prescribers regarding their knowledge of the need for baseline and annual X-rays and counseling patients as well as self-reported adherence to these measures.	1) Sponsor REMS database 2) Successful completion of post-training prescriber Knowledge Assessment 3) Evaluation of prescriber surveys	6-month, 12-month, and annual assessment reports
2. Ensuring that healthcare providers are educated on and adhere to the following: a) Document that baseline and annual X-rays are completed to identify rapidly progressive OA and risk factors for rapidly progressive OA by submitting the Patient Enrollment Form and Patient Continuation Form b) Counsel patients on the increased risk of rapidly progressive OA, the importance of avoiding NSAIDS while being treated with tanezumab and for 16 weeks after the last dose of tanezumab.	Safe use conditions	1) Prescriber Guide 2) Patient Enrollment Form 2) Patient Continuation Form	1) Evaluation of safe use conditions 2) Knowledge of prescribers and self-reported adherence to self-use conditions 3) Knowledge of patients and self-reported participation in counseling	1) Number of patients who received tanezumab treatment beyond one year 2) Number of completed Patient Continuation Forms documenting annual X-rays were completed. 3) Results of surveys of prescribers regarding their knowledge of the need for baseline and annual X-rays and counseling patients as well as self-reported adherence to these measures 4) Results of surveys of patients regarding their knowledge of the need for baseline and annual X-rays and self-reported participation in counseling. 5) Results of audits of healthcare settings including summary of findings and any corrective actions taken. 6) Results from electronic healthcare data regarding the proportion of X-rays performed and prescription NSAIDs among tanezumab -treated patients.	1) Sponsor REMS database 2) Surveys of prescribers and patients 3) electronic healthcare data	6-month, 12-month, and annual assessment reports

Table 48. Tanezumab REMS Assessment Plan

Objective	Requirement	REMS Materials	Assessment Plan Category/domain	Metrics	Data Sources/ Analytical Tools	REMS Assessment Report: Frequency of metric reporting
3. Ensuring safe use of tanezumab by: Ensuring that tanezumab is only administered to enrolled patients in certified healthcare settings after verification of baseline and annual X-rays, and counseling patients on the importance of avoiding NSAIDS.	Safe use conditions	1) Patient Enrollment Form 2) Patient Guide 3) Patient Wallet Card	1) Evaluation of safe use conditions 2) Knowledge of prescribers and self-reported adherence to self-use conditions 3) Knowledge of patients and self-reported participation in counseling 4) Knowledge of healthcare settings and self-reported adherence to self-use conditions	1) Number of patients who received tanezumab 2) Number of patients enrolled in the REMS 3) Results of healthcare setting surveys regarding their knowledge of needing to verify the prescriber is certified, healthcare setting is certified, and patient is enrolled. 4) Results of prescriber surveys regarding awareness and utilization of the materials, knowledge of the key risk messages and self-reported adherence to the safe use practices. 5) Results of surveys of patients regarding receipt of counselling and REMS educational materials. 6) Results from electronic healthcare data assessing the proportion of X-rays performed and prescription NSAIDs among tanezumab -treated patients.	1) Sponsor REMS database 2) Survey of healthcare settings 3) Surveys of prescribers 4) Surveys of patients 5) electronic healthcare data	6-month, 12-month, and annual assessment reports
4. Ensuring that patients are informed about: a) the increased risk of rapidly progressive OA associated with the use of tanezumab b) the requirement for X-rays at baseline and annually thereafter c) the importance of NSAIDS while being treated with tanezumab and for 16 weeks after the last dose of tanezumab.	Safe use conditions	1) Patient Enrollment Form 2) Patient Guide 3) Patient Wallet Card	1) Evaluation of safe use conditions 2) Knowledge of patients and self-reported receipt of counseling	1) Number of patients enrolled in the REMS 2) Results of surveys of patients regarding knowledge of increased risk of RPOA with tanezumab, signs and symptoms of RPOA, and the need to avoid NSAIDs during treatment and for 16 weeks after the last dose as well as their self-report regarding receiving counseling from their healthcare provider.	1) Sponsor REMS database 2) Patient surveys	12-month, and annual assessment reports

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