TANEZUMAB

ARTHRITIS ADVISORY COMMITTEE

BRIEFING DOCUMENT

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EXECUTIVE SUMMARY

Tanezumab and other anti-nerve growth factor (NGF) monoclonal antibodies may offer an important breakthrough in the treatment of chronic pain and are under clinical investigation for the treatment of pain associated with osteoarthritis or other chronic pain conditions. In 2010, the Division of Analgesia, Anesthetic, and Addiction Products of the Food and Drug Administration placed a partial clinical hold on tanezumab clinical development and subsequently to all anti-NGF antibodies due to adverse events initially described as osteonecrosis all of which resulted in total joint replacement.

Over the past year, Pfizer gathered and analyzed all relevant data regarding these events from completed clinical studies and from the studies that were discontinued due to the partial clinical hold. The investigation and analyses related to joint-safety were comprehensive and based on tanezumab monotherapy exposure in over 6400 patients and tanezumab with concomitant non-steroidal anti-inflammatory drug (NSAID) therapy in 3400 patients. There were over 5000 patients who received tanezumab treatment alone or in combination with NSAIDs for 6 months or longer. A brief summary of the findings and conclusions follows.

During conduct of Phase 3 clinical studies in patients with osteoarthritis, the signal event that raised concerns about the joint-related safety of tanezumab was investigator-reported adverse events described as osteonecrosis that led to total joint replacement. Initially, all patients with investigator-reported osteonecrosis had been treated with tanezumab monotherapy or tanezumab/NSAID combination therapy. Subsequently, additional adverse events described as osteonecrosis were reported by investigators not only for patients treated with tanezumab monotherapy or tanezumab/ NSAID combination therapy, but also for patients treated with NSAIDs alone. In addition, investigator reports of osteonecrosis were also received for patients treated with tanezumab in a randomized, non-controlled, long-term study of chronic low back pain. In total, investigators reported 87 adverse events initially described as osteonecrosis in the tanezumab clinical development program.

Because osteoarthritis and osteonecrosis have some radiologic similarities and can co-exist at certain stages, an Adjudication Committee of medical experts in these disease areas was initially formed to examine the 87 investigator reports described as osteonecrosis in a treatment-blinded fashion to understand the nature of these adverse events. The scope of the Adjudication Committee was then expanded from an examination of adverse events described as osteonecrosis to include all other patients who underwent total joint replacement in the tanezumab clinical development program. Sufficient information was available for the Adjudication Committee to examine 249 of the 386 patients with all-cause total joint replacements which included all 87 adverse events initially described by investigators as osteonecrosis.

The Adjudication Committee determined that only two of the 87 investigator reports of osteonecrosis in the tanezumab clinical program were correctly diagnosed. Both adjudicated cases of osteonecrosis occurred in patients with osteoarthritis. One of these patients received tanezumab 5 mg and the other tanezumab 10 mg. The remaining investigator-reported osteonecrosis adverse events were adjudicated to be events of rapidly progressive

osteoarthritis (34/87 patients, 39.1%), normal progression of osteoarthritis (14/87 patients, 16.1%), worsening osteoarthritis but insufficient information to distinguish the rate of progression (3/87 patients, 3.4%), other diagnoses such as subchondral insufficiency fracture and end-stage osteoarthritis without progression (21/87 patients, 24.1%), or there was insufficient information available for the Adjudication Committee to make a decision or reach consensus (13/87 patients, 14.9%).

Patients with rapidly progressive osteoarthritis were not only identified by the Adjudication Committee in patients for whom investigators reported an adverse event of osteonecrosis, but were also found in patients who underwent a total joint replacement related to worsening osteoarthritis.

Of the 249 patients adjudicated in total, there were 68 patients identified with rapidly progressive osteoarthritis in the tanezumab clinical program. Of this total, 67 patients were participating in one of the Phase 3 osteoarthritis studies and 1 patient was participating in a Phase 2 chronic low back pain study. A majority of patients identified with rapidly progressive osteoarthritis had advanced osteoarthritis of the affected joint prior to treatment and experienced an increase in pain in the period of time after the Baseline study visit to the onset of the reported event. In 9 of these patients, rapidly progressive osteoarthritis was evident prior to study enrollment and treatment with study medication. The Adjudication Committee determined there were 10 patients with a subchondral insufficiency fracture in the absence of evidence of rapidly progressive osteoarthritis and an additional 13 of the 68 patients (19%) with adjudicated outcome of rapidly progressive osteoarthritis who had suggestive or definitive evidence of a subchrondral insufficiency fracture in association with or preceding the event of rapidly progressive osteoarthritis.

The majority of patients adjudicated with rapidly progressive osteoarthritis received tanezumab/NSAID combination treatment (n=47) or tanezumab monotherapy (n=20). The remaining patient adjudicated with rapidly progressive osteoarthritis was treated with naproxen alone. The patient with chronic low back pain adjudicated with rapidly progressive osteoarthritis of the knee had severe lateral osteoarthritis in this joint prior to study entry and was treated with tanezumab 20 mg monotherapy. There were a total of 13 all-cause total joint replacements reported for patients participating in the Phase 2 chronic low back pain studies.

In patients with osteoarthritis, the rate of rapidly progressive osteoarthritis increased in a dose-related manner from 0 events/1000 patient-years to 11 events/1000 patient-years with tanezumab 2.5 to 10 mg monotherapy. The rate of rapidly progressive osteoarthritis with all tanezumab monotherapy doses combined was elevated above placebo and active comparator treatment. The rate of rapidly progressive osteoarthritis was further increased over tanezumab monotherapy by greater than three-fold in patients treated with tanezumab/ NSAID combination therapy.

The rate of all-cause joint replacements in patients with osteoarthritis was comparable among placebo, active comparator, and tanezumab monotherapy treatment groups ranging from 32 to 44 events/1000 patient-years. The rate of all-cause total joint replacements did not

increase in relation to increasing tanezumab monotherapy doses. The event rate of all-cause total joint replacements with tanezumab/NSAID combination treatment was 2.4- to 3-fold greater than any of the other treatment groups.

The mechanisms responsible for rapidly progressive osteoarthritis associated with tanezumab treatment are uncertain but may result in part from reduced joint pain leading to increased joint loading and over-use and thus accelerate further damage to a susceptible joint. One of the additional factors involved may be the pre-existing condition of subchondral bone. Patients with an atrophic form of osteoarthritis, greater subchondral bone pathology, and/or susceptibility for subchondral insufficiency fractures may be more at risk for rapidly progressive osteoarthritis with mechanical joint-overloading resulting from the pain reduction associated with tanezumab treatment. This effect may be further exacerbated in the presence of NSAIDs due to interference with normal bone repair processes. There were no patients with or without total joint replacement presenting with loss of protective sensitivity following treatment with tanezumab in the clinical development program. No evidence was found for a direct effect of tanezumab on bone, cartilage, joint vasculature, or joint innervation that would lead to accelerated joint damage was found in non-clinical studies.

In addition to the investigation of bone and joint-related safety, the general safety profile and the efficacy results with tanezumab were evaluated to assess the emerging benefit-risk profile of this agent. The results demonstrate tanezumab monotherapy relieves pain and improves function to a clinically meaningful extent over both placebo and NSAID treatment. In a preliminary study, the efficacy of tanezumab was greater than oxycodone controlled-release (CR) in the treatment of osteoarthritis as well. Tanezumab 5 mg and 10 mg in combination with naproxen 500 mg BID, celecoxib 100 mg BID or diclofenac sustained-release (SR) 75 mg BID provided superior efficacy in the treatment of osteoarthritis when compared to any of these NSAIDs administered alone. However, tanezumab/ NSAID combination therapy did not show a meaningful efficacy improvement over tanezumab monotherapy.

Encouraging Phase 2 efficacy results with tanezumab have also been observed in chronic low back pain, neuropathic pain, and visceral pain with preliminary safety results considered acceptable in these populations. The emerging data indicate further clinical investigation is warranted.

To reduce the risk of rapidly progressive osteoarthritis in future studies of patients with osteoarthritis or other chronic pain conditions, measures to optimize further the benefit-risk of tanezumab therapy and strategies for increased patient surveillance have been developed as an outgrowth of the joint-related safety analyses outlined above. The measures outlined below would be applicable to future clinical studies of osteoarthritis patients as well as other chronic pain patients with some modifications as deemed appropriate depending on the patient population selected for study.

1. Exclude chronic concomitant NSAID use with tanezumab

2. Exclude tanezumab 10 mg from further investigation in osteoarthritis and application of a more cautious approach to escalated doses in other non-osteoarthritic chronic pain conditions

3. Exclude patients with pre-existing rapidly progressive osteoarthritis from treatment with tanezumab

4. Discontinue patients who do not respond adequately to initial doses of tanezumab

5. Treat only those patients who have inadequate response or are intolerant to first-line therapy or patients who have contraindications for existing standard of care

Based on the assessments of risk and benefit, we conclude that further clinical investigation of tanezumab in osteoarthritis and other forms of chronic pain is warranted with the protection of additional risk management and surveillance measures.

Chronic pain affects millions of adults in the United States. For many patients, treatment of chronic pain is inadequate in part due to the limitations in the availability of effective treatments and inadequate patient and clinician knowledge about the best ways to manage chronic pain. Our intent is to affirm with the Arthritis Advisory Committee the benefits and risks of proceeding with further clinical studies of tanezumab and determine how best to bring this promising therapy to patients with debilitating chronic pain.

1. GENERAL INTRODUCTION AND REGULATORY HISTORY

This Briefing Document has been prepared by Pfizer Inc. in preparation for the Arthritis Advisory Committee, Meeting to be held in Silver Spring, MD on March 12, 2012. This meeting of the Arthritis Advisory Committee will consider investigational programs in the anti-NGF drug class which are being conducted by multiple sponsors. Pfizer is the drug Sponsor for tanezumab, a recombinant humanized IgG2 monoclonal antibody directed against human NGF.

The objective of this Briefing Document is to provide the available safety data regarding progressive joint diseases and total joint replacements that have been reported and evaluated during the tanezumab clinical trial program to date. For general background and context, brief information is also included on the clinical and pathological descriptions of progressive joint diseases, the pharmacology of the anti-NGF class, the relevant non-clinical bone and joint data and the overall tanezumab efficacy and safety profile observed to date. Finally, an overall benefit-risk assessment of tanezumab, risk management and surveillance measures, and future clinical development plans are provided for the Committee's consideration.

The Biological Investigational New Drug (BB-IND) application for tanezumab was submitted to FDA in April 2004 for indications related to the treatment of moderate to severe, acute and/or chronic pain including musculoskeletal, visceral, and neuropathic pain. Following an End of Phase 2 Meeting in April 2008, Pfizer initiated a Phase 3 clinical development program in moderate-to-severe osteoarthritis with tanezumab by intravenous (IV) administration. Phase 2 studies in other chronic pain conditions were also initiated.

On April 9, 2010, Pfizer notified FDA of actions being taken as a result of investigator reports of adverse events described as osteonecrosis leading to total joint replacement during the conduct of the Phase 3 clinical studies in patients with osteoarthritis, all of whom were treated with tanezumab monotherapy or tanezumab/NSAID combination therapy.

On June 22, 2010, FDA placed the tanezumab osteoarthritis program on clinical hold and to suspend further clinical investigation.

On July 16, 2010 FDA informed Pfizer that studies in chronic low back pain, diabetic peripheral neuropathy and interstitial cystitis were also being placed on clinical hold. At that time, studies in cancer pain and chronic pancreatitis were allowed to continue.

On December 23, 2010, FDA informed Pfizer that all other anti-NGF antibody programs were being placed on partial clinical hold due to an adverse event report of osteonecrosis in a chronic low back pain study from another sponsor's investigational program. Based on reports of osteonecrosis in two separate anti-NGF antibody programs, FDA indicated that studies were now acceptable only in patients with terminal cancer pain.

Pfizer received a Partial Clinical Hold Letter for the anti-NGF class on January 24, 2011. To address the deficiencies contained this letter Pfizer prepared a Clinical Hold Complete Response for tanezumab that was submitted to FDA on July 1, 2011.

2. BACKGROUND INFORMATION ON RELEVANT BONE AND JOINT DISORDERS

The information provided in Section 2 is intended to provide a brief summary as well as compare and differentiate the bone and joint disorders that are subsequently discussed in this Briefing Document specifically with respect to the tanezumab development program.

2.1. Osteonecrosis

Investigator reports of adverse events initially described as osteonecrosis in tanezumab clinical trials of patients with osteoarthritis were received beginning in 2009 and continued through 2010. The number of reported events of osteonecrosis exceeded the expected background incidence rate of osteonecrosis, even in light of the report by Cooper et al. indicating osteoarthritis was a risk factor for osteonecrosis.[1] The initial reports of osteonecrosis were evident only in patients who had been exposed to tanezumab monotherapy alone or tanezumab/NSAID combination therapy. Subsequently, adverse events described as osteonecrosis were also reported in patients who received NSAIDs alone in the clinical program.

Osteonecrosis (or avascular necrosis) is a syndrome caused by a primary event of vascular occlusion resulting in a segment of bone death (infarction). This process usually occurs in an otherwise normal joint most often the femoral head although other joints such as the knee, shoulder, and ankle can be affected as well.[2,3,4,5] The presence of bone infarction gradually leads to secondary osteoarthritis over a period of years. Histological evaluation shows necrotic bone with considerable reparative/reactive changes.

By contrast, osteoarthritis in general but even more so, rapidly progressive osteoarthritis, are initiated by articular cartilage failure and fragmentation of the underlying bone. Bone fragmentation and deprivation of blood supply leads to secondary osteonecrosis. Histological evaluation of these fragments show necrotic bone but there is no evidence of a reactive or reparative change. Focal osteonecrosis is not an uncommon finding in patients with end-stage osteoarthritis.[6,7]

Although the underlying pathophysiology is different, there can be considerable radiologic similarity between late stages of osteonecrosis and end stage osteoarthritis or rapidly progressive osteoarthritis. Because osteoarthritis and osteonecrosis have some radiologic similarities and can co-exist at certain stages, an Adjudication Committee of medical experts in these disease areas was formed to examine the reports received in the tanezumab clinical development program in a treatment-blinded fashion.

The Adjudication Committee determined that only two of the investigator reports of primary osteonecrosis in the tanezumab clinical program were correctly diagnosed. Both adjudicated events of primary osteonecrosis occurred in patients with osteoarthritis. The remainder of the investigator-reported adverse events initially described as osteonecrosis were adjudicated to be events of rapidly progressive osteoarthritis (39.1%), normal progression of osteoarthritis (16.1%), worsening osteoarthritis but insufficient information to distinguish rate of

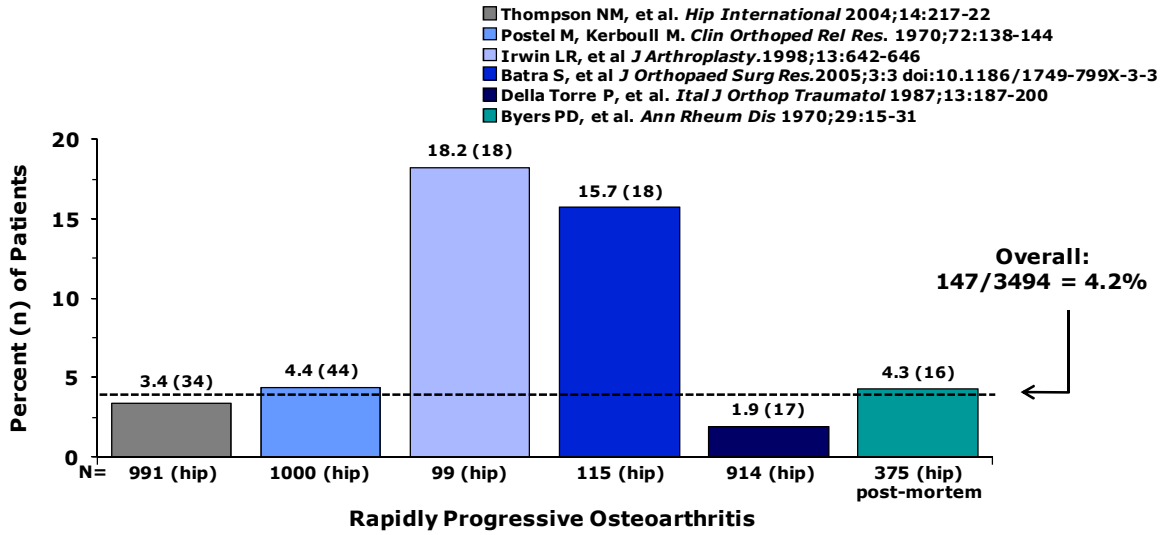
progression (3.4%) other diagnoses such as subchondral insufficiency fracture (24.1%) or there was insufficient information available for the Committee to make a decision or reach consensus (14.9%). Importantly, patients with rapidly progressive osteoarthritis were not only identified by the Adjudication Committee in patients for whom investigators reported an adverse event of osteonecrosis, but were also found in patients who underwent a total joint replacement related to worsening osteoarthritis. Thus, on the basis of event adjudication, investigator-reports of osteonecrosis were not often correct regarding the diagnosis of this condition and were inadequate alone for identifying patients with rapidly progressive osteoarthritis.

2.2. Rapidly Progressive Osteoarthritis

Rapidly progressive osteoarthritis of the hip was first described by Forestier in 1957 and subsequently described in as many as a dozen studies as atrophic osteoarthritis, rapidly destructive osteoarthritis, rapidly destructive arthropathy, rapidly progressive hip disease, or rapidly destructive coxarthrosis.[8,9,10,11,12,13,14,15,16,17,18,19,20] Rapidly progressive hip osteoarthritis is characterized by patients who typically present with hip pain, often severe, with radiographs that show rapid joint space narrowing as a result of chrondrolysis from a prior radiograph and, subsequently, an osteolytic phase with severe progressive atrophic bone destruction involving the femoral head and the acetabulum. There can be marked flattening of the femoral head and loss of subchondral bone in the weight-bearing area and in some cases the femoral head appears sheared off. Osteophytes are typically conspicuously small or absent. Bone sclerosis is often present at sites of impaction of the femoral head and the acetabulum, subchondral detritus is invariably present and bone fragmentation and debris are commonly observed that can lead to synovitis. Lequesne proposed that patients with 2 mm/year or greater of joint space narrowing or loss of more than 50% of the joint space within 1 year should be considered to have rapidly progressive osteoarthritis.[8,10,13,18] Due to a lack of longitudinal studies, it is not clear what proportion of patients with rapid loss of joint space (chondrolysis) will progress to have bone destruction. Rapid progression of osteoarthritis has also been described in the shoulder and the knee.[21,22]

The incidence of rapidly progressive osteoarthritis in the overall osteoarthritis population is not well defined. For rapid progression of hip osteoarthritis, the prevalence ranges from approximately 2% to 18% based on clinical case series analyses (Figure 1).[11,12,14,15,16,23] These published studies were supplemented by two analyses we conducted on rapid progression of knee osteoarthritis from two studies; the Osteoarthritis Initiative Study and a large 2-year Pfizer study recently completed in a development program outside of tanezumab. These analyses are described in more detail in Section 6.5.7. The percentage of patients with rapidly progressive osteoarthritis of the knee was 3.5% (41/1174 patients) in the Osteoarthritis Initiative Study and 1.1% (16/1457 patients) in the Pfizer study.

Figure 1. Percent of Patients with Rapidly Progressive Osteoarthritis of the Hip from Published Clinical Case Series Evaluations



Rapidly progressive osteoarthritis is part of the natural spectrum of osteoarthritis progression as evidenced by multiple studies evaluating radiographic progression of osteoarthritis of the knee or hip over 1 to 2 yrs.[9,24,25,26,27,28]

The pathophysiology of rapidly progressive osteoarthritis is not understood. Various mechanisms have been proposed including; ischemia, venous statis, local nutritional deficiencies, synovitis, mechanical overloading, NSAID use (see discussion on analgesic arthropathy below) or corticosteroid use, intra-articular deposition of hydroxyappatitie or pyrophosphate crystals and subchondral insufficiency fractures.[13,16,20,29,30]

For patients who undergo arthroplasty due to rapidly progressive osteoarthritis, there is a possibility for increased need of transfusion and trend toward longer operating times particularly in patients who have significant bone destruction with acetabular involvement.[13,23,31] The mid- to long-term outcome of total joint replacement in patients with rapidly progressive osteoarthritis has been evaluated in three studies with mean follow-up of 2 to 12 years. The clinical results and the observed longevity of the implants across these studies indicate that total hip arthroplasty performed for rapidly progressive osteoarthritis is not substantially different from those performed for more common end-stage osteoarthritis disease including those cases with more advanced joint destruction (acetabular involvement).[31,32,33]

2.3. Subchondral Insufficiency Fractures

Subchondral insufficiency fractures can affect the hip, knee, or shoulder, result in severe pain, and lead to acute onset of osteoarthritis or rapidly progressive osteoarthritis.[29,30,34,35,36,37,38,39,40,41,42,43]

In patients with osteoarthritis, isolated microfractures are often observed in the superficial eburnated (or sclerotic) lesion (in areas of thin or absent cartilage). These fractures are distinct from subchondral insufficiency fractures based on the lack of a linear fracture line and the presence of typical osteoarthritic changes, including loss of cartilage in the subchondral area, osteophyte formation, bone cysts and sclerosis.

Most of the reported cases of hip subchondral insufficiency fractures are unilateral although a recent study reports a case of bilateral hip subchondral insufficiency fractures.[35] This condition is most often seen in older/elderly women some with osteoporosis or osteopenia and who are overweight but can be seen in normal young adults as well and in some instances associated with increased physical activity.[35,36,37]

Subchondral insufficiency fractures of the femoral head are reported to be a cause of acute onset and rapidly progressive osteoarthritis that had been attributed to either osteonecrosis or osteoarthritis.[29,30,34,38] In a histopathological assessment of over 7718 femoral heads surgically removed (7349 with preoperative diagnosis of osteoarthritis and 369 with preoperative diagnosis of osteonecrosis), subchondral insufficiency fracture was diagnosed in 6.5% of the femoral heads (501/7718) overall with a prevalence of 6.3% (460/7349) for those with preoperative osteoarthritis diagnosis and 11.1% (41/369) for those with preoperative osteonecrosis diagnosis.[38]

In the knee, subchondral insufficiency fractures have been commonly mis-identified as spontaneous osteonecrosis. Spontaneous osteonecrosis of the knee (SPONK) was first described by Ahlback et al. in 1968 and since that original report there have been additional investigations and two reviews written on this condition.[3,44,45] Spontaneous osteonecrosis of the knee is almost always unilateral and is most commonly localized to the medial femoral condyle although the lateral femoral condyle, tibial condyles, and the patella are also susceptible. However, in 2009 Mears et al. published a study demonstrating that spontaneous osteonecrosis of the knee is in fact not an osteonecrotic condition and was misnamed.[40] Rather than caused by bone death, their results led to the conclusion that spontaneous osteonecrosis of the knee is caused by osteoporosis and subchondral insufficiency fractures as suggested by previous evaluations with MRI and by evaluation of histological specimens in which only localized evidence of osteonecrosis as a result of subchondral insufficiency fractures could be found.[41,42, 43]

2.4. Neurogenic Arthropathy (Charcot Joint)

On the basis of joint damage and appearance, rapidly progressive osteoarthritis and neurogenic arthropathy (Charcot joint) bear a strong resemblance. A similar presentation of joint destruction is seen in patients with tabes dorsalis. The key difference is whether there is also evidence of severe neuropathy and loss of protective sensitivity in the weight-bearing joints. Typically, these neurological deficits are readily evident in patients with Charcot joint and allow for the differential diagnosis. For example, individuals with severe diabetic peripheral neuropathy[46,47] or with congenital insensitivity to pain (CIPA) of hereditary sensory and autonomic neuropathy (HSAN) IV due to TrkA mutation or HSAN V due to NGF mutation,[48,49,50,51,52,53,54] have significant propensity for fracture, dislocation of

multiple joints, and infection of joints often occurring in a repetitive manner. These and other forms of chronic joint abuse, contribute to the common presence of neurogenic arthropathy. Work in animal models indicates neurectomy of the primary articular nerves alone does not result in joint damage unless accompanied by anterior cruciate ligament transection and resulting joint instability.[55] Anterior cruciate ligament transection alone is known to produce significant experimental osteoarthritis although at a much reduced rate of progression.

2.5. Analgesia-Induced Arthropathy

The possibility that reduced joint pain (with all other sensation intact) may result in increased joint loading and use and thus accelerate further damage to a susceptible joint was first reported with the introduction of the NSAIDs in the late-1960s. There were case reports or observational studies indicating the use of NSAIDs, particularly indomethacin, was causally associated with a severe, rapidly destructive arthropathy involving both femoral and acetabular components of the hip osteoarthritis.[56,57,58,59,60] These reports described similar radiographic findings of severe bone attrition, paucity of osteophytes, frequent protrusio acetabuli, and disproportionate retention of joint space - so called 'analgesic' or 'indomethacin hip'. Suggested mechanisms for these observations included increased joint loading and overuse of compromised joints rendered less painful by NSAIDs or direct cartilage and bone toxicity. Evidence was never provided from these studies that the patients affected actually had significant pain relief or that pain relief increased their level of activity or function with NSAID use, thus, linking analgesia to increased mechanical insult and in turn mechanical insult to accelerated joint damage.

3. MECHANISM OF ACTION AND PRECLINICAL PHARMACOLOGY

Inhibition of NGF has emerged as a novel molecular target from research on the biology and pathophysiology that underlie the many facets of chronic pain. NGF levels are increased substantially following tissue damage, inflammation, and in chronic pain states.[61,62,63] Administration of exogenous NGF elicits pain and long-lasting hyperalgesia to heat and mechanical stimulation,[64,65] and the physiological relevance of NGF is highlighted by genetic evidence in humans who have embryonic developmental deficiencies due to mutation in NGF or an NGF receptor.[48,49] Finally, inhibition of NGF reduces pain and hyperalgesia across a number of animal models of pain.[62,66,67]

NGF acts through two types of receptors: the TrkA tyrosine kinase receptor and the p75 neurotrophin receptor (p75NTR). Tanezumab inhibits the binding of NGF to both of these receptors. Peripheral nociceptors strongly express TrkA and p75NTR receptors and are developmentally and functionally dependent on NGF. NGF continues to play a major role in pain processing after the primary nociceptors no longer have absolute dependency on NGF in the postnatal period. This latter function is limited to a subpopulation of small unmyelinated peptidic sensory neurons that synthesize substance P and calcitonin gene-related peptide (CGRP), and express the high affinity NGF receptor TrkA.[62,63]

Tanezumab binds to human NGF with both high affinity and specificity. The apparent equilibrium constant (K_D) was tighter than 2 pM at 25°C by surface plasmon resonance (Biacore) and 2 pM at 23°C by the solution-based Kinetic Exclusion Assay (KinExA).[68] The ability to support neuronal survival *in vitro* is historically seen as a highly sensitive assay for NGF. Conversely, inhibition of this effect with tanezumab produces an assay with high sensitivity that has only recently been superseded by ELISA methods. The IC50 of tanezumab determined in this assay was 20 pM, equivalent to the recombinant human NGF (rhNGF) concentration (15 pM). Thus, the affinity of tanezumab for NGF is <20 pM and is comparable to the affinity of the TrkA receptor for NGF. Cross-reactivity of tanezumab was evaluated for other structurally-related members of the neurotrophin gene family, brain-derived neurotrophic factor, neurotrophin-3 or neurotrophin-4/5, the genetically unrelated neurotrophic factor, glial cell-derived nerve growth factor, and vascular endothelial growth factor. In all cases, there was greater than one-thousand fold lower affinities as compared to NGF.

Tanezumab inhibits hyperalgesia in animal models. Tanezumab and/or its murine precursor have been shown to reduce pain–related behaviors in rodent models of pathological pain including arthritis, cancer pain, bone fracture, and post surgical pain. Treatment with tanezumab or its murine precursor, MuMAb911 significantly decreased the nociceptive response as compared with the vehicle group in rats with an aggressive inflammatory arthritis induced by administration of complete Freund's adjuvant.[69]

The efficacy of MuMAb911 was demonstrated in two murine models of bone cancer pain.[70,71] These studies demonstrated that administration of MuMAb911 to mice bearing intrafemoral grafts of either an osteolytic sarcoma cell line or an osteoblastic prostate tumor cell line significantly reduced behaviors associated with both ongoing and movement-evoked

pain. The efficacy of MuMAb911 on all pain-related measures was comparable to or exceeded that seen with administration of morphine. Administration of MuMAb911 did not affect tumor growth, innervation density, or bone remodeling in any case. Similarly, recently published studies have shown administration of MuMAb911 decreases pain behaviors in animal models of bone fracture-induced pain[72,73] and in a model initiated by tibia fracture that seems to replicate many features of Complex Regional Pain Syndrome.[74]

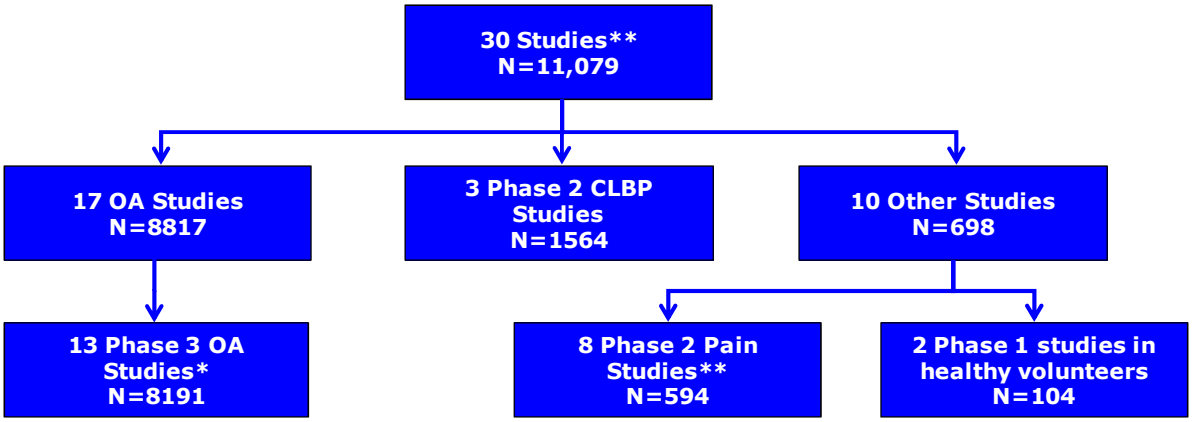
4. CLINICAL DEVELOPMENT PROGRAM

4.1. Overview

Throughout this summary document, clinical studies are identified or referenced by the last four digits of their full study number. The full study numbers can be found in the Table of Clinical Studies located in Appendix 1. For example, Study A4091011 will be referred to as Study 1011.

A total of 30 clinical studies involving over 11,000 subjects have been conducted with tanezumab to date (Figure 2). The greatest proportion of these studies was in patients with osteoarthritis of the knee or hip.

Figure 2. Tanezumab Clinical Development Program



*Includes Studies 1040 and 1032 (total N=22); the Phase 3 osteoarthritis analysis set (N=8169) excludes these 2 studies

**Includes studies of diabetic peripheral neuropathy, post-herpetic neuralgia, interstitial cystitis, prostatitis, endometriosis, chronic pancreatitis, & bunionectomy; excludes 2 ongoing studies in metastatic bone pain

Osteoarthritis (OA); chronic low back pain (CLBP)

A total of 17 clinical studies overall, 4 Phase 2 studies and 13 Phase 3 studies, were initiated to provide evidence of efficacy and safety of tanezumab with IV or SC administration for the relief of the signs and symptoms of osteoarthritis alone or in combination with NSAIDs. These studies are summarized in Table 1 and additional study details can be found in Appendix 1. Both IV and SC routes of administration with tanezumab at fixed dose levels of 2.5 mg, 5 mg, and 10 mg every 8 weeks were evaluated in Phase 3 clinical studies of osteoarthritis patients. The conduct of the Phase 3 studies was affected to varying extents by the clinical hold placed on the tanezumab osteoarthritis program on June 23, 2010.

In addition to the osteoarthritis studies, 11 Phase 2 studies were conducted to examine the efficacy and safety of tanezumab in other musculoskeletal, neuropathic, and visceral chronic pain conditions and 2 Phase 2 studies in metastatic bone pain are ongoing. In these studies, tanezumab was administered by IV or SC administration every 8 weeks at fixed doses ranging 1 mg to 20 mg or equivalent body-weight adjusted doses. These studies are summarized in Table 2 and additional study details can be found in Appendix 1. The

conduct of the Phase 2 studies was impacted to varying extents by the clinical hold implemented on July 16, 2010 on the tanezumab chronic pain program.

Table 1. Summary of Tanezumab Osteoarthritis Studies

Study No. – Population	Duration (Weeks)	No. of Patients	Treatments
Phase 3 Studies with tanezumab IV administration			
1011 – Knee OA	24	690	tanezumab 2.5, 5, or 10 mg or placebo
1014 – Hip OA	24	621	tanezumab 2.5, 5, or 10 mg or placebo
1015 – Knee OA	16	828	tanezumab 5 or 10 mg, naproxen 500 mg BID or placebo matching active oral and IV study drug
1016[1,3] – Knee or hip OA	112	2142	tanezumab 2.5, 5, or 10 mg
1017[1] – Knee or hip OA	24	604	tanezumab 2.5, 5, or 10 mg or placebo add-on therapy with diclofenac SR 75 mg BID
1018 – Knee or hip OA	16	840	tanezumab 5 or 10 mg, naproxen 500 mg BID or placebo matching active oral and IV study drug
1025[1] – Knee or hip OA	56	2700	tanezumab 5 or 10 mg monotherapy, with placebo matching active oral study drug, tanezumab 5 or 10 mg add-on therapy with NSAIDs (naproxen 500 mg BID or celecoxib 100 mg BID) or NSAID monotherapy with placebo matching active IV study drug
1026[2] – Knee or hip OA	24	219	tanezumab 5 or 10 mg or placebo
1030[2] – Knee or hip OA	16	610	tanezumab 5 or 10 mg, oxycodone controlled release 10-40 mg BID or placebo matching active oral and IV study drug
1040[2,4] – Knee or hip OA	56	21	tanezumab 5 or 10 mg plus standard of care or placebo plus standard of care
Phase 2 Studies with tanezumab IV administration			
1006 – Knee OA	8	121	tanezumab 3,10, 30, 100, 300, or 1000 µg/kg or placebo
1008 – Knee OA	16	440	tanezumab 10, 25, 50, 100, or 200 µg/kg or placebo
1009[5] – Knee OA	56	281	tanezumab 50 µg/kg
1022 – Knee OA	8	83	tanezumab 10, 25, 50, 100, or 200 µg/kg or placebo
Phase 3 Studies with tanezumab SC administration			
1027[2] – Knee OA	16	379	tanezumab 2.5, 5, or 10 mg SC, tanezumab 10 mg IV or placebo
1032[2] – Knee OA	56	1	tanezumab 2.5, 5, or 10 mg
1043[1] – Knee or hip OA	56	678	tanezumab 2.5, 5, or 10 mg

[1] Study affected by the FDA clinical hold; fully enrolled, duration of treatment objective was not achieved
[2] Study affected by the FDA clinical hold; enrollment and duration of treatment objectives were not achieved
[3] Randomized, double-blind, long-term extension study for patients who participated in Studies 1011, 1014, 1015 or 1018; patients receiving tanezumab in a controlled study were maintained on same treatment, patients receiving placebo or naproxen were re-randomized in a balanced fashion to one of the 3 tanezumab dose regimens; tanezumab exposure determinations for Study 1016 do not include exposure in Studies 1011, 1014, 1015 or 1018 for patients who received tanezumab continuously throughout both studies
[4] Double-blind, long-term extension study for patients who participated in Study 1026, patients continued to receive same treatment with standard of care as determined by the investigator
[5] Open-label long-term extension study for patients who participated in Study 1008

Table 2. Summary of Tanezumab Chronic Pain Studies

Study No. – Population	Duration (Weeks)	No. of Patients	Treatments
Phase 2 Studies with tanezumab IV or SC Administration			
1003[1] – Metastatic bone pain	8	59	tanezumab IV 10 mg plus standard of care opioids or placebo plus standard of care opioids
1004 – Chronic low back pain	8	217	tanezumab IV 200 µg/kg, naproxen 500 mg BID or placebo matching active oral and IV study drug
1005 – Post-herpetic neuralgia	8	96	tanezumab IV 50 or 200 µg/kg or placebo
1007 – Bunionectomy	8	50	tanezumab IV 10, 30, 100, 300, 1000 µg/kg or placebo
1010 – Interstitial cystitis	8	64	tanezumab IV 200 µg/kg or placebo
1012 – Chronic low back pain	16	1347	tanezumab IV 5, 10, or 20 mg, naproxen 500 mg BID or placebo matching active oral and IV study drug
1019 – Abacterial chronic prostatitis	8	62	tanezumab IV 20 mg or placebo
1023 – Endometriosis	8	47	tanezumab IV 15 mg or placebo
1029[1, 5] – Metastatic bone pain	56	19	tanezumab IV 10 mg plus standard of care opioids
1031[3] – Peripheral diabetic neuropathy	16	73	tanezumab SC 20 mg or placebo
1035[3] – Interstitial cystitis	16	200	tanezumab SC 1, 2.5, 10, or 20 mg plus standard of care or placebo plus standard of care
1039[2,4] – Chronic low back pain	56	848	tanezumab IV 10 or 20 mg for 24 weeks followed by tanezumab SC 10 or 20 mg for 32 weeks
1044[3] – Chronic pancreatitis	8	2	tanezumab SC 20 mg plus standard of care or placebo plus standard of care

[1] Study ongoing and not affected by the FDA clinical hold
[2] Study affected by the FDA clinical hold; fully enrolled, duration of treatment objective was not achieved
[3] Study affected by the FDA clinical hold; enrollment and duration of treatment objectives were not achieved
[4] Randomized, double-blind, long-term extension study for patients who participated in Study 1012; patients receiving tanezumab 10 mg or 20 mg in the controlled study were maintained on same treatment, patients receiving placebo, naproxen or tanezumab 5 mg were re-randomized in a 1:2 ratio to tanezumab 10 mg or 20 mg; tanezumab exposure determinations for Study 1039 do not include exposure in Study 1012 for patients who received tanezumab continuously throughout both studies
[5] Open-label extension study for patients who participated in Study 1003

4.2. Data Presentation, Analysis Plan and Statistical Methods

4.2.1. Data Presentation

The endpoints selected for analysis included both investigator-reported and adjudicated outcomes. Outcomes of interest reported up to February 5, 2011 were included in the analyses described below. Investigator-reported outcomes included serious adverse events, adverse events, and non-drug study procedures of osteonecrosis, osteonecrosis with total

joint replacement, and all other total joint replacements attributed to causes other than osteonecrosis such as osteoarthritis or injury, or unspecified.

All investigator-reports of adverse events described as osteonecrosis were a serious adverse event whether or not a total joint replacement also occurred as a result of the adverse event. Total joint replacements attributed by investigators to other causes were reported as serious adverse events, adverse events, or non-drug study procedures. Total joint replacements from all of these categories were analyzed. Analyses were also conducted on adverse events related to fractures.

4.2.2. Analysis Plan

All investigator reports of osteonecrosis or total joint replacements related to worsening osteoarthritis or other reasons occurred in patients who participated in either the Phase 3 osteoarthritis studies or the Phase 2 chronic low back studies. As a result, the outcomes of interest were analyzed and are summarized only for these two components of the tanezumab development program in subsequent sections. To supplement these primary analyses, the outcomes of interest were also analyzed over the entire development program in which the Phase 3 osteoarthritis studies were combined with the Phase 2 chronic low back pain studies, the Phase 2 osteoarthritis studies, and all other Phase 1/2 studies.

The analysis of the Phase 3 osteoarthritis studies was further subdivided as warranted into two components; (1) the controlled Phase 3 osteoarthritis studies (Studies 1011, 1014, 1015, 1017, 1018, 1025, 1026, 1027 and 1030) and (2) the non-controlled long-term Phase 3 osteoarthritis studies (Studies 1016 and 1043). Finally, all reports of osteonecrosis or all-cause total joint replacements in the Phase 2 chronic low back pain studies occurred in one study – a non-controlled long-term study (Study 1039). As a result, this study is examined alone in selected analyses.

The analysis of the Phase 3 osteoarthritis studies did not include Study 1032 (N=1) or Study 1040 (N=21). The enrollment in studies were substantially impacted by the clinical hold and given their lower priority we were unable to complete study closeout and database unblinding procedures on these 2 studies in time to include them in analyses provided in the Clinical Hold Complete Response submitted to FDA on July 1, 2011.

Patients receiving tanezumab monotherapy were analyzed separately from patients receiving tanezumab in combination with NSAID treatment due to the differential risks observed. This included both patients randomized to tanezumab/NSAID combination treatment in controlled studies and those treated with tanezumab and receiving NSAIDs concomitantly for any period of time at the discretion of the investigator in non-controlled long-term studies.

4.2.3. Statistical Methods

For the events examined, the treatment exposure-adjusted event rates (events per 1000 patient-years [pt-yrs]) are provided. Treatment group comparisons of tanezumab versus placebo or the active comparator were made by determination of the risk difference [i.e., the attributable (or absolute) risk] and the 95% confidence intervals (CI) were determined. The

calculations of the 95% CI for the risk difference of the crude incidence were based upon the exact difference for two binomial samples.[75] The calculation of the 95% CI for the risk difference for the exposure-adjusted event rate was based on the poisson model with identity link, and model terms for exposure and exposure-by-treatment.[76] Confidence intervals and p-values were not produced in the poisson model, where the number of events was zero in either treatment group of a comparison.

Treatment group comparisons of tanezumab versus placebo or the active comparator for time to event endpoints were made using the Wilcoxon test (separate analyses for each two-group comparison). Kaplan-Meier estimates of 1st, 2nd, 5th and 10th percentiles of time to osteonecrosis or total joint replacement were determined for each treatment group.

Dose response relationships were evaluated using logistic regression for the binary data, and poisson model with log link and log exposure as an offset variable for the exposure-adjusted data. Dose response analyses were performed separately for tanezumab monotherapy (using placebo as a 0 mg tanezumab dose) and tanezumab+NSAID (using active comparator as a 0 mg tanezumab dose).

The Number Needed to Harm (NNH) is the number of patients that would need to be treated, such that the number of patients with a risk-factor event in a treatment group would be 1 more than in a reference treatment group. The Number Needed to Treat (NNT) is similarly defined, but for an efficacy response event. The NNH and NNT are defined as the inverse (reciprocal) of the risk difference, for example an event rate of 15% in a treatment group of interest, and 10% in a reference treatment group would give an NNH/NNT of 1/(0.15-0.10) =20.

4.3. Patient Exposure

A total of 11,079 subjects participated in the tanezumab clinical program comprising 30 studies conducted to date. Of this total, 6410 patients were treated with tanezumab monotherapy and 3400 were treated with tanezumab in combination with NSAID treatment.

A total of 8169 patients were treated in the Phase 3 osteoarthritis studies and 1564 were treated in the Phase 2 chronic low back studies. In the Phase 3 osteoarthritis studies, 1029 patients received placebo treatment (exposure up to 6 months; 313 total patient-years of exposure), 4273 patients received tanezumab monotherapy (exposure up to 2 years; 2613 total patient-years of exposure), 3028 patients received tanezumab/NSAID combination therapy which includes patients who were either randomized to combination therapy or received concomitant NSAID therapy in a non-controlled long-term study (exposure up to 2 years; 2082 total patient-years of exposure), and 1266 patients were treated with active comparator (exposure up to 1 year; 661 total patient-years of exposure); 700 patients were treated with naproxen 500 mg BID, 256 were treated with celecoxib 100 mg BID, 152 patients were treated with diclofenac sustained release (SR) 75 mg BID, 158 patients were treated with oxycodone CR.

The Phase 3 osteoarthritis studies summarized above included 9 controlled studies and 2 non-controlled long-term studies. The summary of treatment exposure in the 9 controlled Phase 3 osteoarthritis studies is provided in Table 3. The mean duration of exposure was lowest in the placebo treatment group and highest in patients receiving tanezumab/NSAID combination therapy. Of the 7491 patients who were randomized and treated in these studies, 79.4% of the patients had 4 months or longer of treatment exposure, 50.6% had 6 months or longer of treatment exposure and 8.3% had 1 year or more of treatment exposure.

Table 3. Duration of Exposure and Total Patient-Years of Exposure in the Controlled Phase 3 Osteoarthritis Studies

	Number (%) of Patients by Treatment Group			
	placebo (N=1029)	tanezumab monotherapy[1] (N=3666)	tanezumab[1] + NSAID[2] (N=1530)	active comparator[3] (N=1266)
Duration of Exposure – N (%)				
≥ 4 weeks	932 (90.6)	3509 (95.7)	1494 (97.6)	1201 (94.9)
≥ 8 weeks	866 (84.2)	3349 (91.4)	1444 (94.4)	1148 (90.7)
≥ 16 weeks	656 (63.8)	2950 (80.5)	1344 (87.8)	997 (78.8)
≥ 24 weeks	233 (22.6)	1707 (46.6)	1261 (82.4)	586 (46.3)
≥ 32 weeks	32 (3.1)	869 (23.7)	1059 (69.2)	466 (36.8)
≥ 40 weeks	3 (0.3)	717 (19.6)	712 (46.5)	363 (28.7)
≥ 48 weeks	0 (0.0)	529 (14.4)	517 (33.8)	266 (21.0)
≥ 56 weeks	0 (0.0)	255 (7.0)	238 (15.6)	126 (10.0)
Maximum Patient Exposure (Days)	333	470	479	515
Mean Patient Exposure (Days)	111	173	258	190
Median Patient Exposure (Days)	113	155	251	137
Total Patient-Years of Exposure	313	1740	1083	661

[1] All tanezumab doses combined: 2.5, 5, 10 mg, Studies 1011, 1014, 1015, 1017, 1018, 1025, 1026, 1027 & 1030
[2] NSAID = naproxen 500 mg BID, celecoxib 100 mg BID or diclofenac SR 75 mg BID
[3] Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID

A total of 2820 patients participated in the non-controlled long-term Phase 3 osteoarthritis studies (Table 4). Neither study included placebo or active comparator. There were 1872 total patient-years of exposure to tanezumab treatment in these studies combined with maximum exposure reaching nearly 20 months (589 days). The mean duration of exposure was 242 days and the median duration of exposure was 225 days. A total of 79.9% of the patients had at least 6 months of tanezumab treatment exposure and 22.5% had at least 1 year of exposure to tanezumab. Tanezumab exposure determinations for Study 1016 do not include exposure in Studies 1011, 1014, 1015 or 1018 for patients who received tanezumab continuously throughout both studies.

Table 4. Duration of Exposure and Total Patient-Years of Exposure in the Non-Controlled Long-Term Phase 3 Osteoarthritis Studies

	Number (%) of Patients by Treatment Group			
	tanezumab 2.5 mg (N=752)	tanezumab 5 mg (N=1054)	tanezumab[1] 10 mg (N=1014)	tanezumab all doses (N=2820)
Duration of Exposure – N (%)				
≥ 4 weeks	745 (99.1)	1046 (99.2)	1003 (98.9)	2794 (99.1)
≥ 8 weeks	733 (97.5)	1022 (97.0)	984 (97.0)	2739 (97.1)
≥ 16 weeks	699 (93.0)	974 (92.4)	932 (91.9)	2605 (92.4)
≥ 24 weeks	601 (79.9)	848 (80.5)	804 (79.3)	2253 (79.9)
≥ 32 weeks	483 (58.2)	609 (57.8)	559 (55.1)	1606 (57.0)
≥ 40 weeks	287 (38.2)	394 (37.4)	354 (34.9)	1035 (36.7)
≥ 48 weeks	196 (26.1)	237 (22.5)	201 (19.8)	634 (22.5)
≥ 56 weeks	119 (15.8)	133 (12.6)	95 (9.4)	347 (12.3)
≥ 64 weeks	52 (6.9)	59 (5.6)	44 (4.3)	155 (5.5)
Maximum Patient Exposure (Days)	576	589	574	589
Mean Patient Exposure (Days)	249	244	236	242
Median Patient Exposure (Days)	226	225	225	225
Total Patient-Years of Exposure	512	704	655	1872

An additional 38 patients had 72 weeks or more of treatment exposure
Tanezumab exposure determinations for Study 1016 do not include exposure in Studies 1011, 1014, 1015 or 1018 for patients who received tanezumab continuously throughout both studies
Studies 1016 and 1043

A total of 1564 patients participated in the Phase 2 chronic low back pain studies with a total exposure of 887 patient-years (Studies 1004, 1012 and 1039 – see Table 2). All of the long-term exposure of chronic low back pain patients to tanezumab occurred in the non-controlled long-term Phase 2 chronic low back pain study (Study 1039). There were 848 patients enrolled in this study; 599 (70.6%) of whom were exposed to tanezumab 10-20 mg treatment for 6 months. There were 463 total patient-years of exposure in the study. The mean and median duration of exposure was 199 and 201 days, respectively. The longest treatment duration in the study was 406 days. Tanezumab exposure determinations for Study 1039 do not include exposure in Studies 1012 for patients who received tanezumab continuously throughout both studies.

4.4. Baseline Patient Demographics and Disease Characteristics

Table 5 summarizes the pooled demographic characteristics for the patients who participated in the 9 controlled Phase 3 osteoarthritis studies. In these studies, age, race, and gender were similar across treatment groups. The demographic characteristics for each individual study were also consistent with the pooled summaries with no differences across treatment groups. The patients were predominately female with a mean age over 60 years. About one-third of the patients were 65 years or older. The demographic characteristics of patients enrolled in the non-controlled long-term Phase 3 osteoarthritis studies were similar.

Table 5. Baseline Demographic Characteristics in the Controlled Phase 3 Osteoarthritis Studies

Baseline Characteristic	placebo (N=1029)	tanezumab monotherapy[1] (N=3666)	tanezumab[1] + NSAID[2] (N=1530)	active comparator[3] (N=1266)
Age – years				
Mean (SD)	60.3 (10.4)	60.8 (10.2)	61.8 (9.9)	60.8 (9.7)
Range	25-88	20-93	28-93	28-92
≥65 years - N (%)	353 (34.3)	1293 (35.3)	613 (40.1)	436 (34.4)
≥75 years - N (%)	75 (7.3)	322 (8.8)	149 (9.7)	100 (7.9)
Race/Ethnic Origin				
White - N (%)	872 (84.7)	2920 (79.7)	1176 (76.9)	1006 (79.5)
Black - N (%)	127 (12.3)	446 (12.2)	124 (8.1)	146 (11.5)
Asian - N (%)	11 (1.1)	157 (4.3)	138 (9.0)	64 (5.1)
Other - N (%)	19 (1.8)	143 (3.9)	92 (6.0)	50 (3.9)
Gender				
Female - N (%)	656 (63.8)	2345 (64.0)	1083 (70.8)	870 (68.7)
Body Mass Index - kg/m^2				
Mean (SD)	30.4 (4.8)	30.4 (4.9)	30.3 (4.7)	30.7 (4.7)
Range	16.7 – 39.8	16.2 – 63.2	16.5 – 42.3	16.3 – 39.5

[1] All tanezumab doses combined: 2.5, 5, 10 mg; Studies 1011, 1014, 1015, 1017, 1018, 1025, 1026, 1027 & 1030
[2] NSAID = naproxen 500 mg BID, celecoxib 100 mg BID or diclofenac SR 75 mg BID
[3] Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID

Table 6 summarizes the osteoarthritis disease characteristics for patients who were treated in the controlled Phase 3 osteoarthritis studies. The patient population was characterized by significant radiological and symptomatic osteoarthritis at study entry. Over 15% of the patients were identified with Kellgren-Lawrence Grade 4 osteoarthritis. Approximately 3% of patients in each treatment group had undergone one or more total joint replacements prior to study participation. The pain scores were close to the severe category on average. The percentage of patients who rated their global assessment of osteoarthritis as poor or very poor approached 40%. The Baseline disease characteristics of patients enrolled in the non-controlled long-term Phase 3 osteoarthritis studies were similar.

Table 6. Baseline Disease Status in the Controlled Phase 3 Osteoarthritis Studies

Baseline Characteristic	placebo (N=1029)	tanezumab monotherapy[1] (N=3666)	tanezumab[1] + NSAID[2] (N=1530)	active comparator[3] (N=1266)
Disease Duration – years				
Mean (SD)	7.5 (8.3)	7.4 (8.0)	7.0 (7.2)	7.2 (7.8)
Median	5.0	4.8	4.8	4.7
Range	0.0 - 51.3	0.0 - 59.6	0.0 - 46.8	0.0 - 49.8
Index Joint – N (%)				
Knee	800 (77.7)	2828 (77.1)	1251 (81.8)	1070 (84.5)
Hip	229 (22.3)	838 (22.9)	279 (18.2)	196 (15.5)
Kellgren Lawrence Grade – N (%)				
Grade 2	468 (45.5)	1495 (40.8)	558 (36.5)	554 (43.8)
Grade 3	410 (39.8)	1433 (39.1)	631 (41.2)	513 (40.5)
Grade 4	137 (13.3)	698 (19.0)	339 (22.2)	199 (15.7)
Joints with Osteoarthritis – N (%)				
Unilateral knee or hip	664 (64.5)	2308 (63.0)	888 (58.1)	781 (61.7)
Knee or hip and ≥ 1 additional joint	365 (35.5)	1358 (37.0)	642 (42.0)	485 (38.3)
WOMAC Pain (scale: 0-10)				
Mean (SD)	7.3 (1.4)	7.0 (1.5)	6.2 (1.6)	6.8 (1.6)
WOMAC Physical Function (scale: 0-10)				
Mean (SD)	6.9 (1.6)	6.8 (1.6)	6.3 (1.6)	6.6 (1.6)
Patient's Global Assessment – N (%)				
Fair	614 (59.7)	2200 (60.0)	951 (62.2)	759 (60.0)
Poor	343 (33.3)	1225 (33.4)	466 (30.5)	421 (33.3)
Very Poor	66 (6.4)	208 (5.7)	80 (5.2)	68 (5.4)
Medical History – N (%)				
Total joint replacement	23 (2.2)	120 (3.3)	42 (2.7)	43 (3.4)

[1] All tanezumab doses combined: 2.5, 5, 10 mg; Studies 1011, 1014, 1015, 1017, 1018, 1025, 1026, 1027 & 1030
[2] NSAID = naproxen 500 mg BID, celecoxib 100 mg BID or diclofenac SR 75 mg BID
[3] Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID

In the Phase 2 chronic low back pain studies, women out-numbered men only slightly and the mean age of the population was 53 years, about a decade younger than patients participating in the osteoarthritis studies. Approximately, 25% of the patients had a medical history of osteoarthritis and 3.7% had undergone one or more total joint replacements prior to study entry.

4.5. Patient Disposition

Table 7 provides a summary of all patients who completed treatment and the reasons for early study termination in the 9 controlled Phase 3 osteoarthritis studies. Study termination by the Sponsor (due to the clinical hold) and treatment failure (i.e. lack of efficacy) were the most common reasons for study termination in the placebo, tanezumab monotherapy, and active comparator treatments groups. Study termination by the Sponsor (due to the clinical hold) and withdrawals due to adverse events were the most common reasons for study termination in the tanezumab/NSAID combination treatment group. Withdrawals due to adverse events generally increased as a function of the tanezumab dose administered (2.5, 5, or 10 mg) and at any given dose of tanezumab, the addition of an NSAID further increased the incidence of discontinuation due to adverse events. Withdrawals due to treatment failure were lowest in patients treated with tanezumab monotherapy or tanezumab/NSAID combination therapy.

Table 7. Patient Disposition in the Controlled Phase 3 Osteoarthritis Studies

	Number (%) of Patients by Treatment Group			
	placebo (N=1029)	tanezumab monotherapy[1] (N=3666)	tanezumab[1] + NSAID[2] (N=1530)	active comparator[3] (N=1266)
Total Completed	471	2037	168	402
Deaths	1 (0.1)	2 (0.1)	2 (0.1)	0 (0.0)
Total Withdrawn	556 (54.0)	2096 (57.2)	1358 (88.8)	864 (68.2)
Treatment Failure	259 (25.2)	374 (10.2)	82 (5.4)	158 (12.5)
Adverse Event	27 (2.6)	247 (6.7)	204 (13.3)	101 (8.0)
Withdrawn Consent	63 (6.1)	256 (7.0)	135 (8.8)	103 (8.1)
Protocol Violation	10 (1.0)	65 (1.8)	43 (2.8)	21 (1.7)
Lost to Follow-up	6 (0.6)	52 (1.4)	32 (2.1)	11 (0.9)
Other	14 (1.4)	39 (1.1)	25 (1.6)	12 (0.9)
Study terminated by Sponsor	177 (17.2)	1062 (29.0)	837 (54.7)	458 (36.2)

[1] All tanezumab doses combined: 2.5, 5, 10 mg; Studies 1011, 1014, 1015, 1017, 1018, 1025, 1026, 1027 & 1030
[2] NSAID = naproxen 500 mg BID, celecoxib 100 mg BID or diclofenac SR 75 mg BID
[3] Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID

The incidence of withdrawal due to treatment failure or an adverse event was just under 6% and 7%, respectively, with all doses of tanezumab combined (2.5-10 mg) in the non-controlled long-term Phase 3 osteoarthritis studies. A total of 2138 patients (75.8%) were withdrawn due to study termination resulting from the clinical hold.

In the two Phase 2 controlled chronic low back pain studies, the overall incidence of withdrawal was 43.5%, 35.6%, and 35.0% with placebo (N=271), tanezumab monotherapy (N=910), and naproxen 500 mg BID treatment (N=383), respectively. The incidence of withdrawal due to adverse events was 5.9%, 7.0%, and 3.4% with placebo, tanezumab monotherapy, and naproxen 500 mg BID treatment, respectively. The incidence of withdrawal due to treatment failure was 24.7%, 13.2%, and 19.1% with placebo, tanezumab monotherapy, and naproxen 500 mg BID treatment, respectively. Both studies were completed prior to the clinical hold. A total of 848 patients were entered into the non-controlled, long-term Phase 2 chronic low back pain study. The incidence of withdrawal due to treatment failure or an adverse event was just under 3% and 7%, respectively. None of the patients actively participating in the study was afforded the opportunity to complete one year of treatment due to the clinical hold leading to study termination by the sponsor.

5. INVESTIGATOR-REPORTED OSTEONECROSIS AND ALL-CAUSE TOTAL JOINT REPLACEMENTS

During conduct of Phase 3 clinical studies in patients with osteoarthritis, the signal event that raised concerns about the joint-related safety of tanezumab was investigator reported adverse events described as osteonecrosis. Initially, all patients with investigator reported osteonecrosis had been treated with tanezumab monotherapy or tanezumab/NSAID combination therapy. Subsequently, additional events of osteonecrosis were reported not only for patients treated with tanezumab monotherapy or tanezumab/NSAID combination therapy, but also for patients treated with NSAIDs alone. In addition, investigator reports of osteonecrosis were also received for patients treated with tanezumab in a non-controlled, long-term Phase 2 study of chronic low back pain. In total, investigators reported 87 adverse events described as osteonecrosis in the tanezumab clinical development program.

A total of 50 patients (57.5%) with an investigator-reported adverse event of osteonecrosis had undergone a total joint replacement. Total joint replacement was planned, pending, or no decision had been taken in the remainder of the patients at the time this summary was completed. To provide the most conservative assessment, all 87 patients with reported osteonecrosis, irrespective of total joint replacement status were included in analyses described in Section 5.1, further, these patients were included in the analysis of all-cause total joint replacements summarized in Section 5.2. As noted previously, all investigator reports of osteonecrosis were adjudicated and are described in Section 6.

In addition to these reports of osteonecrosis, there were an additional 299 patients with total joint replacements related to osteoarthritis (N=292) or to joint injury or infection (N=7) that were reported by investigators in the tanezumab clinical development program. These 386 patients form the basis of the discussion of investigator-reported events and adjudication outcomes in subsequent sections of this document.

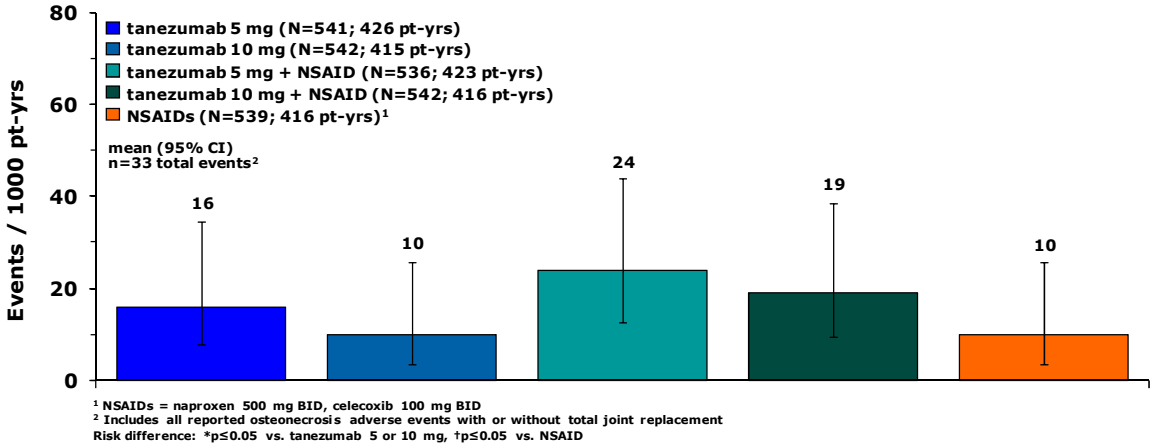
The statistical analyses provided are based on 385 patients with a total joint replacement evident in the clinical studies analyzed. The analysis of the Phase 3 osteoarthritis studies did not include Study 1032 (N=1) or Study 1040 (N=21). The enrollment in these studies were substantially impacted by the clinical hold and given their lower priority we were unable to complete study closeout and database unblinding procedures on these two studies in time to include them in analyses provided in the Clinical Hold Complete Response submitted to FDA on July 1, 2011. Subsequent to the finalization of this analysis plan, one patient with a total joint replacement related to osteoarthritis was reported in Study 1040 (bringing the total number of patients with an all-cause joint replacement to 386). However, this event is included in the descriptive statistics of adjudication outcomes and all-cause total joint replacements.

The results of Study 1025 provided the first indication of the relationship between randomized treatment (tanezumab monotherapy, tanezumab/NSAID combination therapy, or NSAID treatment alone) and adverse events described as osteonecrosis or a total joint replacement for any cause. A total of 33 investigator-reported osteonecrosis adverse events

and 150 all-cause total joint replacements occurred in Study 1025; approximately 40% of the total number of events over the entire tanezumab program.

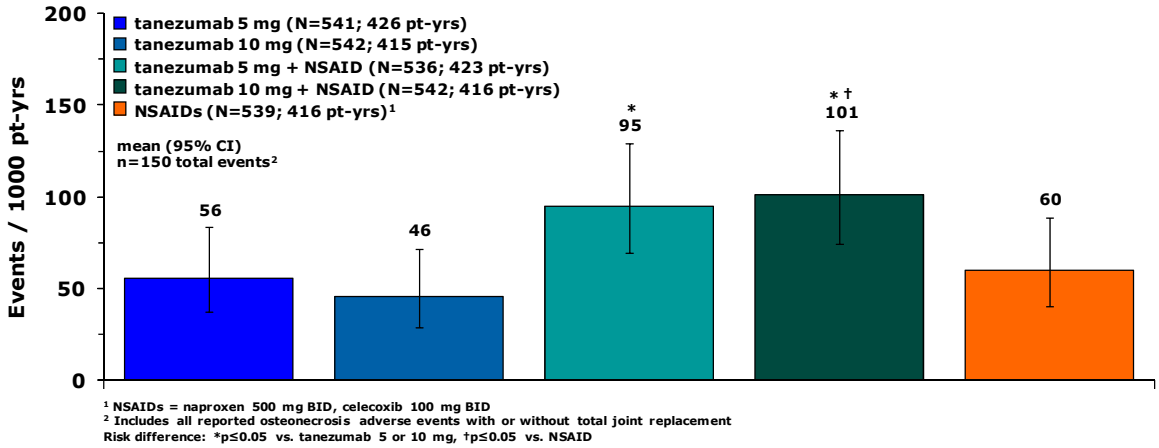
Study 1025 was a large (N=2700) randomized active-controlled Phase 3 study in patients with osteoarthritis of the knee or hip. Patients were required to be receiving naproxen 500-1000 mg daily or celecoxib 200 mg daily, receiving some benefit, and tolerating treatment prior to study entry in order to be eligible to participate in the study. Patients were randomized to one of five treatment groups (1) tanezumab 5 mg monotherapy, (2) tanezumab 10 mg monotherapy, (3) tanezumab 5 mg plus NSAID treatment, (4) tanezumab 10 plus NSAID treatment, or (5) NSAID treatment alone. The NSAIDs used in the study were naproxen 500 mg BID or celecoxib 100 mg BID. The distribution of investigator-reported adverse events of osteonecrosis across the treatment groups are shown in Figure 3. The results suggested that investigator-reported osteonecrosis was more common in patients receiving tanezumab/NSAID combination treatment than those receiving tanezumab or NSAID monotherapy.

Figure 3. Rates of Investigator-Reported Osteonecrosis in Study 1025



These treatment differences became more evident when patients with a total joint replacement for any cause were assessed (Figure 4). The rate of all-cause total joint replacements in Study 1025 was up to two-fold greater with tanezumab/NSAID combination therapy compared to patients receiving treatment with tanezumab or NSAID monotherapy. The event rates of all-cause total joint replacements were similar between tanezumab monotherapy and NSAID treatment.

Figure 4. Rates of All-Cause Total Joint Replacements in Study 1025



Given the results in Study 1025, patients receiving tanezumab/NSAID combination therapy were analyzed separately from patients treated with tanezumab monotherapy in all subsequent analyses of investigator-reported osteonecrosis adverse events, all-cause total joint replacements, or adjudicated outcomes. This included both patients randomized to tanezumab/NSAID combination treatment in controlled studies and those treated with tanezumab and receiving NSAIDs concomitantly at the discretion of the investigator in non-controlled long-term studies.

5.1. Investigator-Reported Osteonecrosis

Investigators reported the occurrence of osteonecrosis adverse events in 87 patients. Eighty-one (81) of these patients were participating in the Phase 3 osteoarthritis program and the remaining 6 patients were participating in the Phase 2 chronic low back pain program.

There were 80 patients with a reported adverse event of osteonecrosis affecting one joint and 7 patients with more than one joint affected. Six of the 7 patients with multiple reports of osteonecrosis were enrolled in an osteoarthritis clinical study.

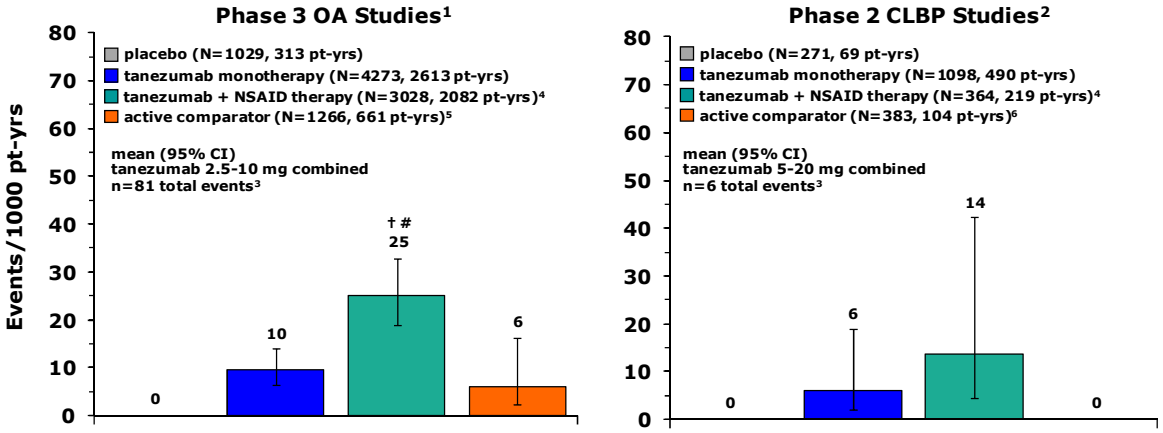
Of the 80 patients with a reported adverse event of osteonecrosis affecting one joint, the hip was most commonly affected (n=42) followed by the knee (n=29), shoulder (n=7), ankle (n=1), and foot (1). In the 7 remaining patients with more than 1 affected joint, 10 were reported in the hip and 5 in the shoulder.

A total of 50 patients (57.5%) with an investigator-reported adverse event of osteonecrosis had undergone a total joint replacement at last contact. Total joint replacement was planned, pending, or no decision had been taken in the remainder of the patients at the time this summary was completed. The event of reported osteonecrosis of the foot (second and third metarsal joints) was adjudicated as a Freiberg infraction and the patient underwent corrective surgery without total joint replacement. The event of reported osteonecrosis of the ankle was

adjudicated as post-traumatic osteoarthritis. No corrective surgery had been performed on the joint.

All of the 87 patients with reported osteonecrosis participated in either the Phase 3 osteoarthritis program or the Phase 2 chronic low back pain program. There were no events in other Phase 2 chronic pain studies or in the Phase 2 osteoarthritis studies. The rate of investigator-reported osteonecrosis adverse events in the Phase 3 osteoarthritis studies and the Phase 2 chronic low back pain studies are shown in Figure 5. The results are normalized for exposure to account for studies of differing duration and hazard rates. The doses of tanezumab were combined for this display.

Figure 5. Rates of Investigator-Reported Osteonecrosis in the Phase 3 Osteoarthritis Studies and Phase 2 Chronic Low Back Pain Studies



[1] Phase 3 osteoarthritis (OA) studies (analysis set): 1011, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030, & 1043
[2] Phase 2 chronic low back pain (CLBP) studies: 1004, 1012, & 1039
[3] Includes all reported osteonecrosis adverse events with or without total joint replacement
[4] Patients receiving concomitant NSAID treatment with tanezumab in long-term studies are included in the tanezumab + NSAID treatment groups
[5] Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID
[6] Active comparator = naproxen 500 mg BID
Risk Difference: †p ≤ 0.05 vs. active comparator, #p ≤ 0.05 vs. tanezumab monotherapy, comparisons to placebo (zero events) could not be made

The rate of investigator-reported osteonecrosis adverse events across the treatment groups in the Phase 3 osteoarthritis studies or the Phase 2 chronic low back pain studies were similar to that first observed in Study 1025 alone (see Figure 3). The rate of reported osteonecrosis with tanezumab/NSAID combination treatment was over two-fold greater compared to patients receiving treatment with either tanezumab monotherapy or active comparator alone in osteoarthritis patients. The event rates of investigator-reported osteonecrosis were greater with tanezumab monotherapy when compared to active comparator treatment alone and both treatments were associated with a higher event rate compared to placebo treatment. No investigator-reported adverse events of osteonecrosis were reported in osteoarthritis patients receiving placebo treatment.

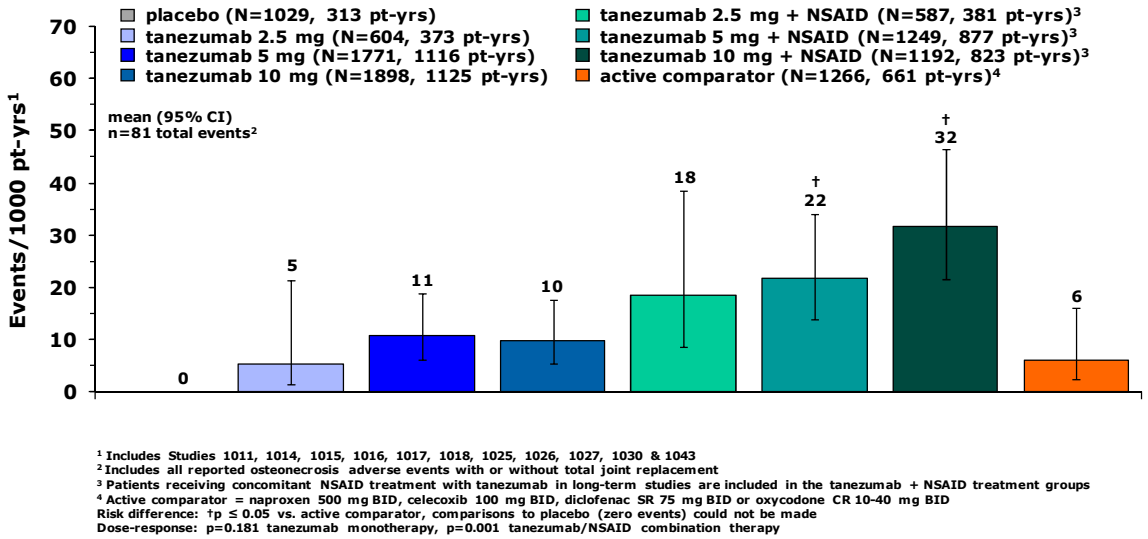
Tanezumab/NSAID combination treatment was also associated with the highest rate of investigator-reported osteonecrosis in the Phase 2 chronic low back pain studies. The rate of investigator-reported osteonecrosis with tanezumab monotherapy was greater than with placebo or active comparator treatment in these studies. However, there were no investigator-reported osteonecrosis adverse events with any of the treatments in the two

short-term Phase 2 chronic low back pain studies where placebo, tanezumab, and active comparator treatment were all included as treatment arms. All six investigator-reported osteonecrosis adverse events occurred in the non-controlled long-term Phase 2 chronic low back pain study. Tanezumab was the only treatment evaluated in this study. The event rates with tanezumab monotherapy or tanezumab/NSAID combination therapy when estimated with exposure in this study alone were 12 events/1000 pt-yrs and 14 events/1000 pt-yrs, respectively.

Investigator-reported osteonecrosis accounted for less than one-quarter (22.5%) of all-cause total joint replacements. The pattern of investigator-reported osteonecrosis and all-cause total joint replacements was similar across the treatment groups suggesting a commonality of investigator reports of osteonecrosis and total joint replacements related to worsening osteoarthritis (Figure 5 and Figure 7).

The rate and incidence of investigator-reported osteonecrosis by tanezumab dose in the Phase 3 osteoarthritis studies is summarized in Figure 6 and Table 8.

Figure 6. Rates of Investigator-Reported Osteonecrosis by Dose of Tanezumab in the Phase 3 Osteoarthritis Studies



[1] Includes Studies 1011, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030 & 1043
[2] Includes all reported osteonecrosis adverse events with or without total joint replacement
[3] Patients receiving concomitant NSAID treatment with tanezumab in long-term studies are included in the tanezumab + NSAID treatment groups
[4] Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID
Risk difference: †p ≤ 0.05 vs. active comparator, comparisons to placebo (zero events) could not be made
Dose-response: p=0.181 tanezumab monotherapy, p=0.001 tanezumab/NSAID combination therapy

The rate of investigator-reported osteonecrosis was not significantly related to the dose of tanezumab when administered as monotherapy. The event rates with tanezumab 5 and 10 mg monotherapy doses were greater than active comparator treatment and the rates in all active treatments were greater than placebo treatment. When administered in combination with NSAID treatment, increasing doses of tanezumab were associated with an increasing incidence of investigator-reported osteonecrosis. Also, the incidence rates with all tanezumab doses when combined with NSAID administration were elevated compared to placebo, all tanezumab monotherapy, and active comparator treatments.

Table 8. Investigator-Reported Osteonecrosis Adverse Events in the Phase 3 Osteoarthritis Studies

	placebo	tanezumab monotherapy			tanezumab + NSAID[1]			Active Comparator[2]
		2.5 mg	5 mg	10 mg	2.5 mg	5 mg	10 mg	
N	**1029**	**604**	**1771**	**1898**	**587**	**1249**	**1192**	**1266**
Total exposure (pt-yrs)	**313**	**373**	**1116**	**1125**	**381**	**877**	**823**	**661**
n (%)								
	0 (0.0)	2 (0.3)	12 (0.7)	11 (0.6)	7 (1.2)	19 (1.5)* #	26 (2.2)* #	4 (0.3)
Event rates (events/1000 pt-yrs)								
	0	5	11	10	18	22#	32#	6

Studies 1011, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030, & 1043
[1] 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 non-controlled long-term studies
[2] Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID
Risk difference: * $p \leq 0.05$ vs. placebo, # $p \leq 0.05$ vs. active comparator; event rate comparisons to placebo (zero events) could not be made
Dose-response for crude incidence: p=0.056 tanezumab monotherapy, p<0.001 tanezumab/NSAID combination therapy
Dose-response for event rate: p=0.181 dose-response tanezumab monotherapy, p=0.001 combination therapy

In the non-controlled long-term Phase 2 chronic low back pain study, the incidence of investigator-reported osteonecrosis with tanezumab 10 mg monotherapy, tanezumab 20 mg monotherapy, tanezumab 10 mg/NSAID combination therapy, tanezumab 20 mg/NSAID combination treatment were 0.5% (1 event/194 patients), 0.7% (2 events/290 patients), 0.8% (1 event/127 patients) and 0.8% (2 events/237 patients), respectively. The corresponding event rates were 10, 14, 14, and 14 events/1000 pt-yrs, respectively.

5.2. All-Cause Total Joint Replacements

Investigators reported 386 patients in the tanezumab clinical development program who underwent a total joint replacement. This total includes all 87 patients with reported osteonecrosis discussed in Section 5.1 although only 50 of these patients (57.5%) had undergone a total joint replacement.

Table 9 summarizes the treatment distribution of all-cause total joint replacements by affected joint in the Phase 3 osteoarthritis studies and the Phase 2 chronic low back pain studies. Total knee replacements were more common than total hip replacements but as a proportion of the overall patients enrolled with knee osteoarthritis versus hip osteoarthritis, there was a greater incidence of total hip replacements. Total shoulder replacements were reported only in patients treated with tanezumab monotherapy or tanezumab/ NSAID combination therapy. In the Phase 3 osteoarthritis studies, approximately 3% of patients had a history of unilateral or bilateral shoulder osteoarthritis.

Table 9. All-Cause Total Joint Replacements in the Phase 3 Osteoarthritis Studies and the Phase 2 Chronic Low Back Pain Studies; Affected Joints

joints affected; n (%)	placebo (N=1300)	tanezumab monotherapy[1] (N=5183)	tanezumab[1] + NSAID[2] (N=3400)	active comparator[3] (N=1653)
All-cause total joint replacements	11	143	259	32
Knee	6 (54.5)	68 (47.6)	164 (63.3)	22 (68.8)
Hip	5 (45.5)	69 (48.3)	79 (30.5)	10 (31.2)
Shoulder[4]	0 (0.0)	6 (4.2)	13 (5.0)	0 (0.0)
Other (foot, ankle, wrist)[5]	0 (0.0)	0 (0.0)	3 (1.2)	0 (0.0)

Studies 1004, 1011, 1012, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030, 1039, 1040, & 1043
[1] All tanezumab doses combined: 2.5, 5, 10, and 20 mg
[2] NSAID = naproxen 500 mg BID, celecoxib 100 mg BID or diclofenac SR 75 mg BID
[3] Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID
[4] In the controlled Phase 3 OA studies 216/7491 (2.9%) patients had unilateral or bilateral shoulder OA at study entry
[5] 1 foot affected; reported osteonecrosis, no associated total joint replacement, adjudicated as Freiberg infraction
1 ankle affected; reported osteonecrosis, no associated total joint replacement, adjudicated as post-traumatic OA
1 wrist affected; reported as total joint replacement, distal radial-ulnar joint prosthesis, not adjudicated

Of the 386 patients with an all-cause total joint replacement, the affected joint was the same as the index joint (the joint under study) in 216 patients and a different joint in 170 patients. In these 170 patients, there was definitive or suggestive evidence of osteoarthritis in the affected joint of 127 patients (74.7%), insufficient information to make a determination in 34 patients (20.0%), another joint abnormality in 6 patients (3.5%), and evidence of a normal joint or minimal osteoarthritis in 3 patients (1.8%).

In the 13 patients with a total joint replacement who participated in the Phase 2 chronic low back pain studies, 11 (84.6%) had definitive or suggestive evidence of osteoarthritis in the affected joint; there was insufficient information to make a determination in the remaining 2 patients.

Of the 386 patients with total joint replacement attributed to any cause in the tanezumab program, 329 (85.2%) patients had a single joint affected. The remaining 57 (14.8%) patients had more than one all-cause total joint replacement.

Table 10 summarizes the treatment distribution for patients with multiple all-cause total joint replacements. The highest incidence of patients with multiple total joint replacements was evident in the patients treated with tanezumab/NSAID combination therapy. There was little difference in incidence among the placebo, tanezumab monotherapy and active comparator treatments. All but one patient with multiple total joint replacements was participating in a Phase 3 osteoarthritis study. One patient who underwent bilateral hip replacement was enrolled in a chronic low back pain study.

Table 10. All-Cause Total Joint Replacements in the Phase 3 Osteoarthritis Studies and the Phase 2 Chronic Low Back Pain Studies; Patients with Multiple Total Joint Replacements

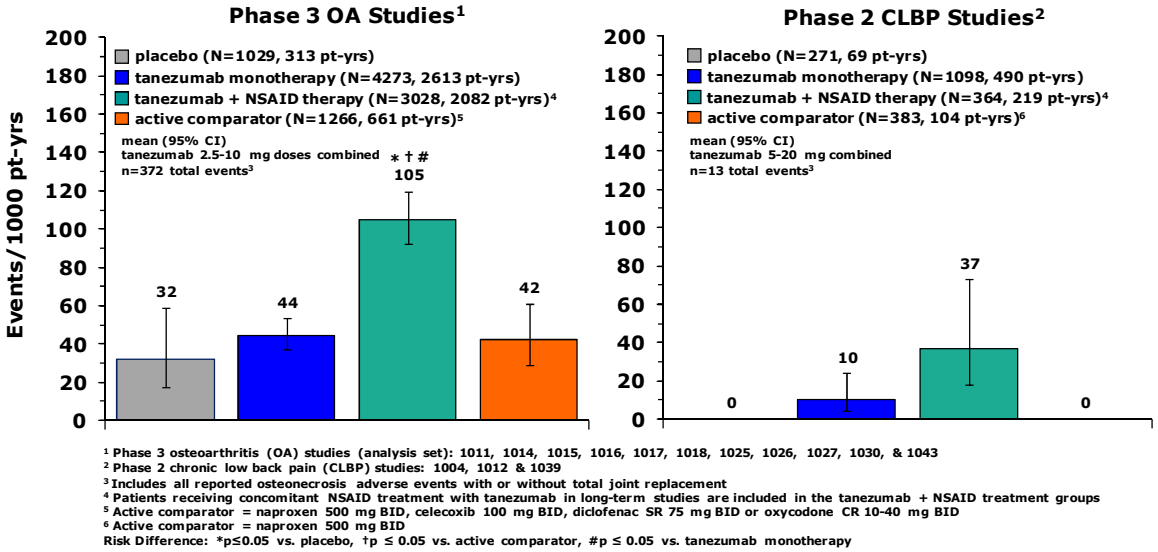
n (%)	placebo (N=1300)	tanezumab monotherapy[1] (N=5183)	tanezumab[1] + NSAID[2] (N=3400)	active comparator[3] (N=1653)
No total joint replacement	1290 (99.2)	5061 (97.7)	3174 (93.4)	1625 (98.3)
1 total joint replacement	9 (0.7)	102 (2.0)	194 (5.7)	24 (1.5)
2 or more total joint replacements	1 (0.1)	20 (0.4)	33 (1.0)	4 (0.2)

Studies 1004, 1011, 1012, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030, 1039, 1040, & 1043
[1] All tanezumab doses combined: 2.5, 5, 10, & 20 mg.
[2] 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 non-controlled long-term studies
[3] Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID.

5.2.1. Analysis of Treatment Effects

All of the 386 patients who underwent a total joint replacement participated in either the Phase 3 osteoarthritis studies or the Phase 2 chronic low back pain studies. There were no total joint replacements in other Phase 2 chronic pain studies or in the Phase 2 osteoarthritis studies. The rate of all-cause total joint replacements in the Phase 3 osteoarthritis studies and the Phase 2 chronic low back pain studies are shown in Figure 7. The results are normalized for exposure to account for studies of differing duration and hazard rates. The doses of tanezumab were combined for this display.

Figure 7. Rates of All-Cause Total Joint Replacements in the Phase 3 Osteoarthritis Studies and Phase 2 Chronic Low Back Pain Studies



[1] Phase 3 osteoarthritis (OA) studies (analysis set): 1011, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030, & 1043
[2] Phase 2 chronic low back pain (CLBP) studies: 1004, 1012 & 1039
[3] Includes all reported osteonecrosis adverse events with or without total joint replacement
[4] Patients receiving concomitant NSAID treatment with tanezumab in long-term studies are included in the tanezumab + NSAID treatment groups
[5] Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID
[6] Active comparator = naproxen 500 mg BID
Risk Difference: *p≤0.05 vs. placebo, †p ≤ 0.05 vs. active comparator, #p ≤ 0.05 vs. tanezumab monotherapy

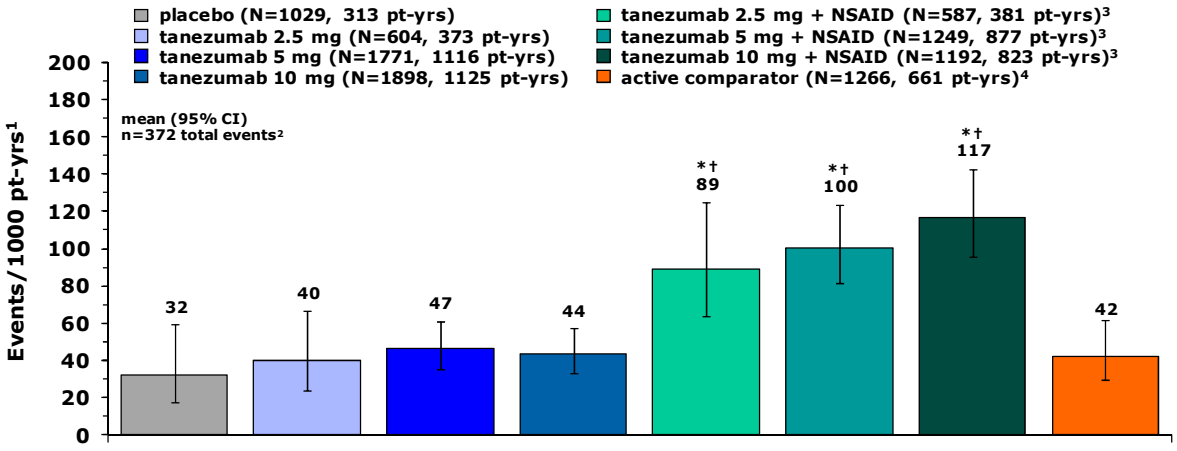
The distribution of all-cause total joint replacements across the randomized treatment groups in the Phase 3 osteoarthritis studies or the Phase 2 chronic low back pain studies were similar to that first observed in Study 1025 alone (see Figure 4). In the Phase 3 osteoarthritis studies,

the rate of all-cause total joint replacements in patients treated with placebo, tanezumab monotherapy, or active comparator were comparable. The rate of all-cause total joint replacements with tanezumab/ NSAID combination therapy was over two-fold greater than with the monotherapy treatment regimens.

Tanezumab/NSAID combination treatment was also associated with the highest rate of all-cause total joint replacements in the Phase 2 chronic low back pain studies. The rate of all-cause total joint replacements with tanezumab monotherapy was greater than with placebo or active comparator treatment in these studies. However, there were no total joint replacements with any of the treatments in the two short-term Phase 2 chronic low back pain studies in which placebo, tanezumab, and active comparator treatment were all included as treatment arms. All 13 total joint replacements occurred in the non-controlled long-term Phase 2 chronic low back pain study. Tanezumab was the only treatment evaluated in this study. The event rates with tanezumab monotherapy or tanezumab/NSAID combination therapy when estimated with the exposure in this study alone were 21 events/1000 pt-yrs and 37 events/1000 pt-yrs, respectively.

The rate and incidence of all-cause total joint replacements by tanezumab dose in the Phase 3 osteoarthritis studies are summarized in Figure 8 and Table 11.

Figure 8. Rates of All-Cause Total Joint Replacements by Dose of Tanezumab in the Phase 3 Osteoarthritis Studies



There was no observed relationship of all-cause total joint replacements to the dose of tanezumab when administered as monotherapy. All tanezumab monotherapy doses were comparable to active comparator treatment and the rate of all-cause total joint replacements with all doses of tanezumab monotherapy and active comparator treatment were generally similar to placebo treatment. When administered in combination with NSAID treatment, increasing doses of tanezumab were associated with an increasing rate of all-cause total joint replacement and the rate with all tanezumab doses when combined with NSAID administration were elevated two- to three-fold compared to placebo, all tanezumab monotherapy, and active comparator treatments.

Table 11. All-Cause Total Joint Replacements in the Phase 3 Osteoarthritis Studies

	placebo	tanezumab monotherapy			tanezumab + NSAID[1]			Active Comparator[2]
		2.5 mg	5 mg	10 mg	2.5 mg	5 mg	10 mg	
N	**1029**	**604**	**1771**	**1898**	**587**	**1249**	**1192**	**1266**
Total exposure (pt-yrs)	**313**	**373**	**1116**	**1125**	**381**	**877**	**823**	**661**
n (%)								
	10 (1.0)	15 (2.5)	52 (2.9)*	49 (2.6)*	34 (5.8)* #	88 (7.1)* #	96 (8.1)* #	28 (2.2)
Event rates (events/1000 pt-yrs)								
	32	40	47	44	89* #	100* #	117* #	42

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

[1] 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 non-controlled long-term studies

[2] Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID

Risk difference: * $p \leq 0.05$ vs. placebo, # $p \leq 0.05$ vs. active comparator

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

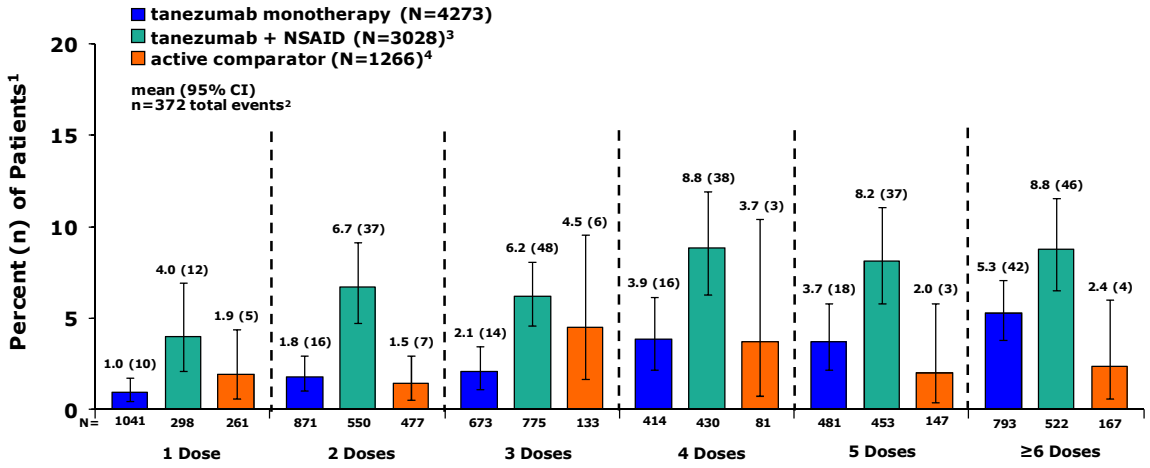
Dose –response for event rate; p=0.553 dose-response tanezumab monotherapy, p<0.001 combination therapy

In the non-controlled long-term Phase 2 chronic low back pain study, the incidence of all cause total joint replacements with tanezumab 10 mg monotherapy, tanezumab 20 mg monotherapy, tanezumab 10 mg/NSAID combination therapy, tanezumab 20 mg/NSAID combination treatment were 1.6% (3 events/194 patients), 0.7% (2 events/290 patients), 3.9% (5 events/127 patients) and 1.3% (3 events/237 patients), respectively. The corresponding event rates were 31, 14, 67 and 21 events/1000 pt-yrs, respectively.

5.2.2. Incidence of All-Cause Total Joint Replacements as Function of the Number of Tanezumab Doses Administered

The relationship of all-cause total joint replacements to the number of tanezumab doses administered (or matched placebo with oral active comparator treatment) is shown Figure 9. The results show modest increases in the incidence of all-cause total joint replacements over the range of 1 to > 6 doses of tanezumab administered (8 to $\geq$48 weeks of treatment) as monotherapy or when given in combination with NSAIDs. A similar pattern is observed with active comparator treatment. These data suggest the risk of all-cause total joint replacement is increasing over time in the study population as would be anticipated for patients with osteoarthritis and is minimally affected by the duration of tanezumab therapy.

Figure 9. Incidence of All-Cause Total Joint Replacements by the Number of Tanezumab Doses Administered in the Phase 3 Osteoarthritis Studies



1 Studies 1011, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030 & 1043. The placebo treatment group is not shown.
2 Includes all reported osteonecrosis adverse events with or without total joint replacement
3 tanezumab + NSAID group includes patients from 1016 and 1043 with ≥1 day of concomitant NSAID use
4 Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID

5.2.3. All-Cause Total Joint Replacements in Clinical Trials and Observational Studies

A number of clinical trials and observational studies were examined to provide context for the rate of total joint replacements observed in the tanezumab clinical program. These analyses as summarized in Table 12 indicate that among individuals with osteoarthritis, the estimated event rate of total joint replacement is on the order of 23 to 74 events/1000 person-yrs compared to 0.4 to 2.2 events/1000 person-yrs in the general population, and 5.8 events/1000 person-yrs in individuals with a diagnosis of chronic low back pain.

While direct comparisons are not possible, there is reasonably good agreement with regard to the total joint replacement event rates in patients with osteoarthritis across these various sources of information despite varying methodologies. The event rates of all-cause total joint replacements observed with placebo, tanezumab monotherapy, or active comparator treatment in the tanezumab program do not differ substantially from those observed elsewhere. The all-cause total joint replacement event rates with tanezumab/NSAID combination therapy exceed the event rates found in all of the sources evaluated.

Table 12. Summary of Total Joint Replacement Event Rates Among Patients from Other Clinical Trials or Observational Studies

Population	Number of Subjects	Mean Follow-up time (yrs)	Total Joint Replacements (n)	Rate of Total Joint Replacement (Events per 1000 person-yrs)
Clinical Studies – OA Patients				
Dougados et al.[77]	507	2.296	87	58
CLASS	5,785	0.577	108	32
Celecoxib Long-Term Safety Study*	2,920	1.200	119	34
Osteoarthritis Initiative – progression cohort**	1,170	3.000	106	30
Hawker et al.[78]	2,128	5.200	254	23
Retrospective Analyses of Claims Databases – OA cohorts				
LifeLink Health Plan Claims Database	7,931	5.000	2,948	74
United HealthCare Claims Database				
Entire OA cohort	1,413,816	1.864	101,506	39
Moderate to severe OA cohort	781,424	1.812	65,728	46
THIN				
Entire OA cohort	55,638	2.58	7,873	55
Moderate to severe OA cohort	33,407	2.76	6,030	65
Retrospective Analyses of Claims Databases – General (non-OA) cohorts				
LifeLink Health Plan Claims Database	562,447	5.000	6,055	2.2
United HealthCare Claims Database	1,185,602	2.119	1,024	0.4
Retrospective Analyses of Claims Databases – Chronic Low Back Pain cohort				
LifeLink Health Plan Claims Database	53,729	5.000	1,571	5.8

* person-time was unavailable, but imputed based on subject counts lost in each given 3 month interval and assuming that a subject, on average, was lost 1.5 months into the three month window

** based on one-, two-, and three-year visit data

A number of clinical trials and observational studies were examined to provide context for the incidence of multiple total joint replacements observed in the tanezumab clinical program. These analyses as summarized in Table 13 and Table 14 indicate that among individuals with osteoarthritis, a small proportion of patients undergo multiple total joint replacements similar to the observations made in the tanezumab clinical development program.

Table 13. Incidence of Total Joint Replacements Reported as Serious Adverse Events in Celecoxib Long-Term Studies: Osteoarthritis Patients

n (%)	No total joint replacement N (%)	1 total joint replacement N (%)	2 or more total joint replacements N (%)
Celecoxib Long-Term Arthritis Safety Study (CLASS)* (N=5785 OA patients)	5,638 (98.1)	98 (1.7)	10 (0.2)
Celecoxib Long-Term Open-Label Safety Study (N=2920 OA patients)**	2,801 (95.9)	111 (3.8)	8 (0.4)

* Of the 108 total joint replacements, 60 (55.6%) were unilateral total knee replacements, 36 (33.3%) were unilateral total hip replacements, 2 (1.9%) were unilateral shoulder replacements, 8 (7.4%) were bilateral knee replacements and 2 (1.9%) were bilateral hip replacements. Mean patient exposure was approximately 7 months.

** Of the 119 patients with total joint replacements, 49 (41.2%) were unilateral total knee replacements, 57 (47.9%) were unilateral total hip replacements, and 5 (4.2%) were unilateral shoulder replacements. The remaining 8 patients (6.7%) underwent bilateral total hip replacement (n=2), bilateral knee total replacement (n=5), or contralateral knee and hip replacement (n=1). This was a 2-year open-label study. Mean or median exposure was not reported; 50.2% of patients completed the study

Table 14. Incidence of Total Joint Replacements in Patients with Osteoarthritis of the Knee or Hip: Analysis of Healthcare Claims Database

Location of Total Joint Replacements in Patients with a Diagnosis of Knee or Hip OA and Continuously Enrolled in the Same Healthcare Plan				
Results over 1 Year (2009)				
n (%)	**Unilateral Total Knee Replacement**	**Bilateral Total Knee Replacement**	**Unilateral Total Hip Replacement**	**Bilateral Total Hip Replacement**
Hip OA (N=3420)	47 (1.4)	3 (0.1)	1235 (36.4)	70 (2.1)
Knee OA (N=15762)	2150 (13.6)	172 (1.1)	152 (1.0)	8 (0.1)
Results over 5 Years (2005-2009)				
Hip OA (N=1321)	67 (5.1)	8 (0.6)	639 (48.4)	161 (12.2)
Knee OA (N=6384)	1581 (24.8)	375 (5.9)	168 (2.6)	31 (0.5)

6. ADJUDICATION OUTCOMES

6.1. Adjudication Process and Event Classification

An Adjudication Committee consisting of external orthopedic surgeons, rheumatologists, and an orthopedic pathologist with expertise in patients with end stage osteoarthritis and osteonecrosis was assembled to review adverse events described as osteonecrosis and total joint replacements related to osteoarthritis or joint injury from the tanezumab clinical program. The Adjudication Committee met 7 times from September 2010 through April 2011 to review the blinded joint safety information. The Adjudication Committee was comprised of 6 members: Dr. David Hungerford[a] (chairman), Dr. Steven Abramson[b], Dr. Marc Hochberg[c], Dr. Edward McCarthy[d], Dr. Bernard Stulberg[e], and Dr. Eric Vignon[f]. Dr. Stulberg had limited availability to work with the committee and only participated in the first meeting in September 2010.

The Adjudication Committee was asked to review all events of reported osteonecrosis and all cases of total joint replacements for which radiology images within 9 months of the surgery date were able to be obtained.

The adjudication categories for the events were the following:

1. Primary osteonecrosis
2. Worsening osteoarthritis
   For events of worsening osteoarthritis, the event was further categorized:
   a. Rapid progression of osteoarthritis (type 1 [2a-1] or type 2 [2a-2])
   b. Normal progression of osteoarthritis
   c. Not enough information to distinguish between rapidly progressive osteoarthritis and normal progression of osteoarthritis
3. Other (with diagnosis specified)
4. Not enough information to distinguish between primary osteonecrosis and worsening osteoarthritis or specify another diagnosis

The Adjudication Committee considered the following radiologic characteristics to be suggestive of primary osteonecrosis: 1) lucency with an abnormally large amount of sclerosis and flattening of the bone; 2) crescent sign referring to a thin, curvilinear lucent line

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[a] Former Chief of the Division of Arthritis Surgery at Johns Hopkins and Chief of Orthopaedics at The Good Samaritan Hospital, Baltimore, MD; Professor of Orthopaedic Surgery, The Johns Hopkins University School of Medicine.

[b] Senior Vice President and Vice Dean for Education, Faculty and Academic Affairs, Professor of Medicine and Pathology and Director of the Division of Rheumatology, New York University Medical Center

[c] Professor of Medicine, Head, Division of Rheumatology & Clinical Immunology, University of Maryland School of Medicine, Baltimore, MD

[d] Professor of Pathology, Professor of Orthopaedic Surgery, Department of Pathology, The Johns Hopkins University School of Medicine

[e] Professor of Surgery, Department of Orthopaedic Surgery, Cleveland Clinic

[f] Professor of Rheumatology, Department Head of Rheumatology, Université Claude Bernard, Lyon, France

parallel and inverted to the critical margin of a bone representing a fracture in the margin of a disk of articular cartilage and underlying subchondral bone; and 3) a lack of joint space narrowing.

For events assessed as worsening osteoarthritis-rapid progression (rapidly progressive osteoarthritis), the Adjudication Committee further classified these events as type 1 or type 2. Type 1 events were those that the adjudication committee considered to have significant loss of joint space width (≥1 mm) in less than approximately 1 year. Type 2 events were those which were considered to have abnormal loss/destruction of bone that is not normally present in end-stage osteoarthritis which in the most severe form was catastrophic bone failure and joint destruction. Some cases adjudicated to rapidly progressive type 2 were based on a single x-ray demonstrating abnormal destruction of bone for which technically the rapidity of the destruction could not be determined. These cases were included with the other type 2 cases where serial radiographs were present since both groups were considered to have abnormal loss/destruction of bone that is not normally present in end-stage osteoarthritis.

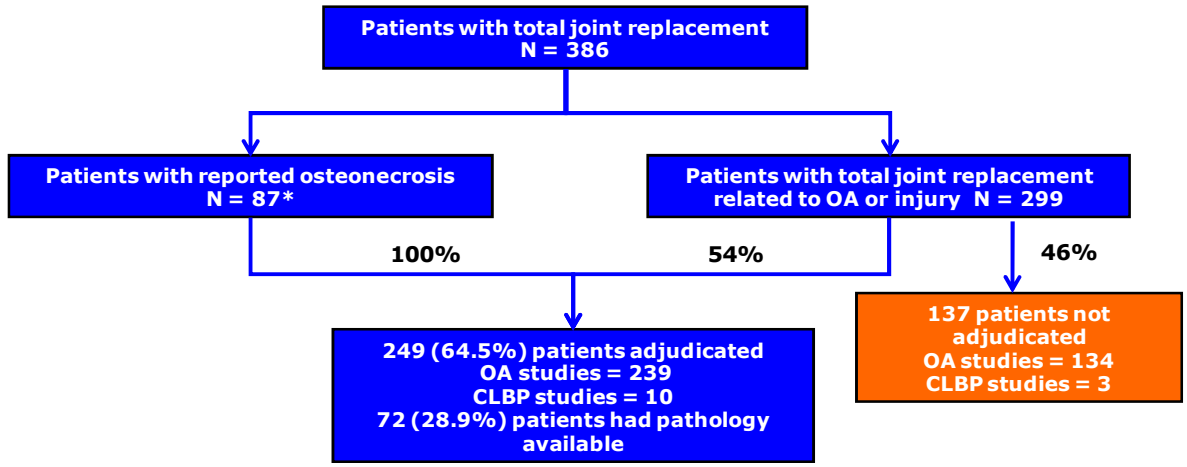
Four Adjudication Committee members were required to provide a final assessment for an event in order to have a final committee assessment assigned. It was required that 3 committee members agree on the final assessment of the event for a given category to be designated as the collective Adjudication Committee's final assessment.

The analyses of adjudicated outcomes are provided at the patient level. That is, for patients who had more than one adjudicated event, one assessment for that patient was included in the analyses. For patients who had a reported adverse event of osteonecrosis plus a total joint replacement in another joint, the Adjudication Committee assessment for the event of reported osteonecrosis was included. For patients who had multiple reports of osteonecrosis or total joint replacements adjudicated, the worst adjudication assessment was utilized if the final assessments for each of the individual joint events were different. The following order was used to determine the worst assessment: Primary osteonecrosis (Category 1), Worsening osteoarthritis (rapidly progressive, type 2 [Category 2a-2]), Worsening osteoarthritis (rapidly progressive, type 1 [Category 2a-1]), Worsening osteoarthritis (insufficient information to distinguish between rapid and normal progression, Category 2c), Other (diagnosis of a condition that was not pre-existing, Category 3), Worsening osteoarthritis (normal progression, Category 2b).

6.2. Characteristics of the Events Adjudicated

Of the 386 patients who had a reported adverse event of osteonecrosis and/or underwent a total joint replacement, the Adjudication Committee reviewed events from a total of 249 (64.5%) patients (Figure 10).

Figure 10. Flow Diagram of Adjudicated Events



*50 patients (57.5%) underwent total joint replacement

All 87 patients who had a reported event(s) of osteonecrosis were adjudicated and they made up 34.9% (87/249) of the total number of adjudicated events. The Adjudication Committee also reviewed events from 54.2% (162/299) of the patients who underwent a total joint replacement(s) not associated with osteonecrosis (159 total joint replacements due to osteoarthritis and 3 total joint replacements due to joint injury or infection). Total joint replacements related to osteoarthritis or joint injury/infection accounted for 65.1% (162/249) of the adjudicated events. Pathology specimens were available for 23/87 (26.4%) patients with reported osteonecrosis and 49/162 (30.2%) patients with a total joint replacement related to osteoarthritis or joint injury/infection.

Despite much effort to obtain relevant information including radiographic scans for all patients with reported total joint replacement, information sufficient to allow adjudication could not be obtained for 137 patients. The reasons for this included refusal by the clinical site to obtain the information, inability of the clinical site to make contact with the patient, inability of clinical site to obtain the information from the source, or refusal by the patient to allow release of the information among others.

To determine whether the 249 patients who were adjudicated were representative of all patients who underwent total joint replacement, demography, disease severity, study treatment and duration and characteristics of the event for this patient cohort were compared to the 137 non-adjudicated patients. The groups were comparable in all respects.

The majority of adjudicated patients (239/249 patients; 96.0%) were enrolled in the Phase 3 osteoarthritis clinical studies; the remaining 10 patients were enrolled in the non-controlled long-term Phase 2 chronic low back pain study.

6.3. Summary of Adjudication Outcomes by Original Investigator Report

In 188 of the 249 patients adjudicated, the categorization by the Adjudication Committee was unanimous (75.5%). In addition, there was agreement on the categorization by a majority of the Adjudication Committee members for an additional 54 patients (21.7%). The Adjudication Committee failed to reach consensus on the categorization of 7 patients (2.8%).

The distribution of patients with adjudication outcomes based on the original report from the investigator is summarized below in Table 15.

Of the 87 patients with reported osteonecrosis adverse events, 2 (2.3%) were adjudicated to have primary osteonecrosis (Category 1). One event occurred in the right shoulder and the second in the right hip. Both events were reported by investigators based on radiologic findings from routinely scheduled end-of-study x-rays.

Of the pathology specimens available for examination by an Adjudication Committee member (E. McCarthy), none were consistent with diagnosis of primary osteonecrosis.

Table 15. Incidence of Adjudication Outcomes Categorized by the Investigator Report

n (%)	Reported osteonecrosis N = 87	Total joint replacement related to osteoarthritis or joint injury/ infection N = 162	Total N = 249
Primary osteonecrosis (1)	2 (2.3)	0 (0.0)	2 (0.8)
Worsening osteoarthritis (2)	51 (58.6)	149 (92.0)	200 (80.3)
Other (3)	21 (24.1)	8 (4.9)	29 (11.7)
Not enough information to distinguish osteonecrosis from worsening osteoarthritis (4)	8 (9.2)	3 (1.9)	11 (4.4)
Lack of consensus*	5 (5.8)	2 (1.2)	7 (2.8)

* Fewer than 3 Adjudication Committee members agreed on the final assessment

Worsening osteoarthritis (Category 2) was the most frequent general adjudication outcome for both investigator-reported osteonecrosis adverse events (51/87; 58.6%) and total joint replacements related to osteoarthritis or joint injury/infection (149/162; 92.0%).

Table 16 provides the further categorization of adjudicated events assessed as worsening osteoarthritis. Approximately one-half (119/200; 47.8%) of the patients with worsening osteoarthritis were adjudicated to have normal progression of osteoarthritis (Category 2b). The incidence of an adjudication outcome of worsening osteoarthritis-normal progression was 64.8% (105/162 patients) in those patients for whom the investigator reported a total joint replacement related to osteoarthritis or joint injury/infection and 16.1% (14/87 patients) for those patients with investigator-reported osteonecrosis.

Table 16. Incidence of Adjudication Outcomes Summarized by Investigator Report

	Reported osteonecrosis N = 87	Total joint replacement related to osteoarthritis or joint injury/ infection N = 162	Total N = 249
Worsening osteoarthritis (2)	51 (58.6)	149 (92.0)	200 (80.3)
Rapid progression (2a-1)*	3 (3.5)	8 (4.9)	11 (4.4)
Rapid progression (2a-2)†	31 (35.6)	26 (16.0)	57 (22.9)
Normal progression (2b)‡	14 (16.1)	105 (64.8)	119 (47.8)
Insufficient information to distinguish between rapid and normal progression (2c)§	3 (3.5)	10 (6.2)	13 (5.2)

∗ Category 2a-1 = worsening osteoarthritis, rapidly progressive, type 1
† Category 2a-2 = worsening osteoarthritis, rapidly progressive, type 2
‡ Category 2b = worsening osteoarthritis, normal progression
§ Category 2c = worsening osteoarthritis, insufficient information to distinguish between rapid and normal progression

Similarly, adjudicated outcomes of rapidly progressive osteoarthritis were identified irrespective of whether the investigator reported the event as osteonecrosis or a total joint replacement related to osteoarthritis or joint injury/infection. The incidence of an adjudicated outcome of rapid progressively osteoarthritis (type 1 and type 2) was 21.0% (34/162 patients) in those patients for whom the investigator reported a total joint replacement related to osteoarthritis or joint injury/infection and 39.1% (34/87 patients) in those patients with investigator-reported osteonecrosis.

Given the lack of specificity of investigator reports to an adjudication outcome, the adjudication results provided in subsequent sections by treatment group are summarized without regard to the original investigator report.

There were a total of 29 (11.6%) patients with events adjudicated to the Other category (3). The diagnoses provided by the Adjudication Committee for the cases in the Other category were as follows:

1. Subchondral insufficiency fracture (10/29; 34.5%)
2. End-stage osteoarthritis (6/29; 20.7%)
3. Shoulder conditions (4/29; 13.8% [chronic rotator cuff arthropathy, tendon rupture, chondrolysis, and recurrent trauma to shoulder])
4. Pre-existing osteonecrosis (3/29; 10.3%; all occurred in the hip joint)
5. Normal osteoarthritis (2/29; 6.9%)
6. Subchondral fracture secondary to a fall (1/29; 3.4%)
7. Pre-existing femoral neck fracture (1/29; 3.4%)
8. Freiburg infraction (1/29; 3.4%)
9. Post-traumatic ankle osteoarthritis (1/29; 3.4%)

All 10 events adjudicated as subchondral insufficiency fracture occurred in the knee. Nine of the patients were enrolled in an osteoarthritis clinical study and the subchondral insufficiency fracture occurred in the index joint in 4 of these patients. In the other 5 patients, the

subchondral insufficiency fracture occurred in the contralateral knee to the patient's index knee. The tenth patient who was diagnosed with a subchondral insufficiency fracture was enrolled in a chronic low back pain study. There were 13 additional patients adjudicated with rapidly progressive osteoarthritis of the knee or hip in association with an evident subchondral insufficiency fracture.

There were 11 (4.4%) events which the Adjudication Committee indicated there was not enough information to definitively assess the event (Category 4). For a majority of these events, there were either no radiology images available for review or the images were of poor quality. There were 7 (2.8%) events which the committee did not reach a consensus on the final assessment. For the events where a consensus was not achieved, none of the Adjudication Committee members assessed them as primary osteonecrosis.

In the non-controlled long-term Phase 2 chronic low back pain study (N=848), the Adjudication Committee reviewed events from 10 of the 13 patients with an all-cause total joint replacement. None of the events were adjudicated as primary osteonecrosis. Five patients (0.6%) were adjudicated with worsening osteoarthritis. Three patients (0.4%) were diagnosed with a condition in the Other category. These diagnoses included: post-traumatic subchondral fracture secondary to trauma, subchondral fracture, and post-traumatic osteoarthritis of the ankle. One patient (0.1%) was adjudicated to the category of insufficient information to distinguish osteonecrosis from worsening osteoarthritis and the Adjudication Committee did not reach consensus on the event for one other patient.

6.4. Adjudication Outcomes – Primary Osteonecrosis

There were two events in the Phase 3 osteoarthritis studies adjudicated as primary osteonecrosis. The right shoulder in a 66 year-old female who received tanezumab 10 mg monotherapy was adjudicated with primary osteonecrosis. The patient was asymptomatic and the event was reported by the investigator from a scheduled end of study x-ray. The second adjudicated event of primary osteonecrosis occurred in the right hip of a 58 year-old male who received tanezumab 5 mg monotherapy. This patient was also asymptomatic and the event was reported by the investigator from a scheduled end of study x-ray.

There were a total of 10 patients most of whom received tanezumab/NSAID combination treatment in the Phase 3 osteoarthritis studies who were adjudicated to the category of not enough information to distinguish between primary osteonecrosis and worsening osteoarthritis by the Adjudication Committee. Inclusion of these events with the 2 adjudicated events of osteonecrosis in a sensitivity analysis did not materially impact the results with tanezumab monotherapy but did result in unfavorable comparisons of tanezumab/NSAID combination therapy to the other treatment groups.

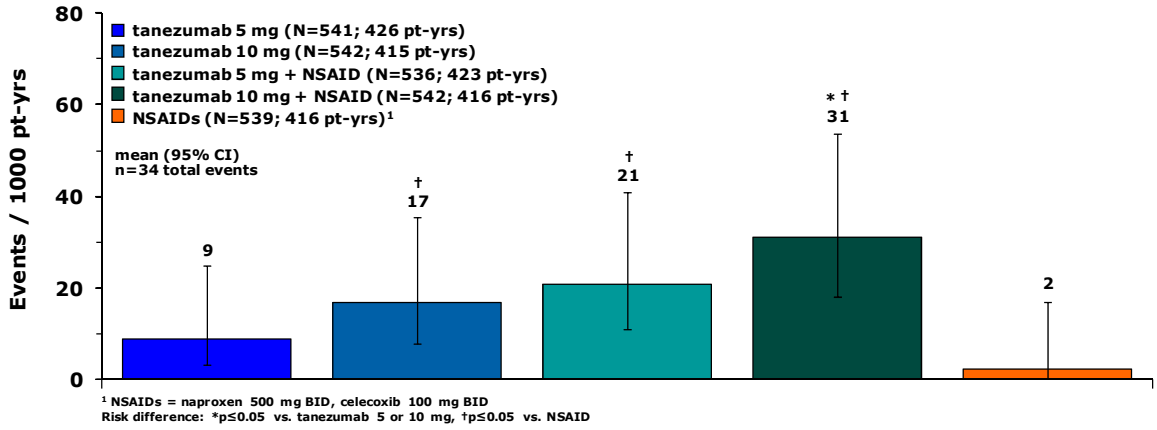
6.5. Adjudication Outcomes – Rapidly Progressive Osteoarthritis

6.5.1. Analysis of Treatment Effects

There were 68 patients with an adjudication outcome of rapidly progressive osteoarthritis. Of these 68 patients, 67 participated in a Phase 3 osteoarthritis study and 1 patient was enrolled in a Phase 2 chronic low back pain study.

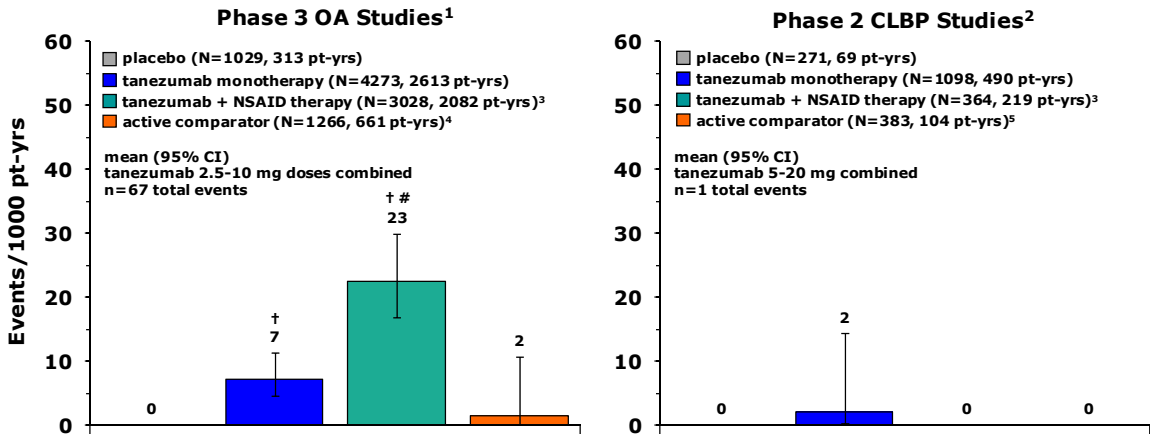
Of the 68 patients with rapidly progressive osteoarthritis, 34 (50%) were participating in Study 1025. In this study, the rate of rapidly progressive osteoarthritis was elevated in all tanezumab treatment groups relative to patients receiving treatment with an NSAID alone (Figure 11). The event rate increased as function of the dose of tanezumab administered and the administration of tanezumab in combination with NSAIDs further increased the rate of rapidly progressive osteoarthritis by two-fold over tanezumab monotherapy for the combined results of 5 mg and 10 mg.

Figure 11. Rates of Rapidly Progressive Osteoarthritis in Study 1025



The rate of rapidly progressive osteoarthritis in the Phase 3 osteoarthritis studies and the Phase 2 chronic low back pain studies are shown in Figure 12. In osteoarthritis patients, the rate of rapidly progressive osteoarthritis with tanezumab monotherapy was elevated above active comparator treatment. The rate of rapidly progressive osteoarthritis in patients receiving tanezumab in combination with NSAIDs was further increased above tanezumab alone and greatly exceeded placebo and active comparator treatment. The one patient adjudicated with rapidly progressive osteoarthritis in the Phase 2 chronic low back pain studies received tanezumab 20 mg monotherapy. This patient experienced rapidly progressive osteoarthritis in the left knee. There was severe lateral osteoarthritis in this knee prior to study entry.

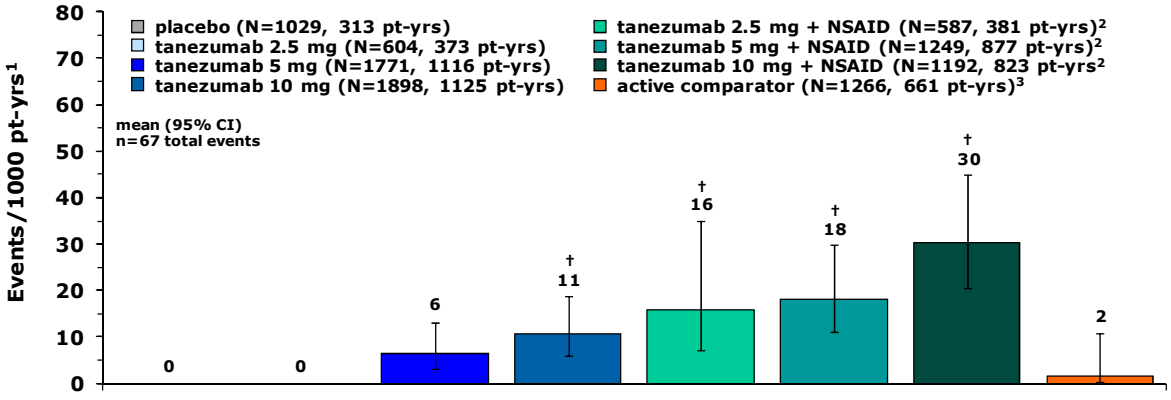
Figure 12. Rates of Rapidly Progressive Osteoarthritis in the Phase 3 Osteoarthritis Studies and Phase 2 Chronic Low Back Pain Studies



[1] Phase 3 osteoarthritis (OA) studies (analysis set): 1011, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030, & 1043
[2] Phase 2 chronic low back pain (CLBP) studies: 1004, 1012 & 1039
[3] Patients receiving concomitant NSAID treatment with tanezumab in long-term studies are included in the tanezumab + NSAID treatment groups
[4] Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID
[5] Active comparator = naproxen 500 mg BID
Risk Difference: †p ≤ 0.05 vs. active comparator, #p ≤ 0.05 vs. tanezumab monotherapy, comparisons to placebo (zero events) could not be made

The rate and incidence of rapidly progressive osteoarthritis by tanezumab dose in the Phase 3 osteoarthritis studies are summarized in Figure 13 and Table 17.

Figure 13. Rates of Rapidly Progressive Osteoarthritis by Dose of Tanezumab in the Phase 3 Osteoarthritis Studies



[1] Includes Studies 1011, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030 & 1043
[2] Patients receiving concomitant NSAID treatment with tanezumab in long-term studies are included in the tanezumab + NSAID treatment groups
[3] Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID
Risk difference: †p ≤ 0.05 vs. active comparator, analyses vs. placebo (zero events) could not be made
Dose response: p=0.012 tanezumab monotherapy, p<0.001 tanezumab/NSAID combination therapy

There was an observed relationship of rapidly progressive osteoarthritis to the dose of tanezumab when administered as monotherapy ranging from 0 events/1000 pt-yrs with tanezumab 2.5 mg to 11 events/1000 pt-yrs with tanezumab 10 mg. The rate of rapidly progressive osteoarthritis with tanezumab 2.5 mg was similar to active comparator treatment. On the basis of crude incidence or event rates normalized to treatment exposure, the risk of rapidly progressive osteoarthritis was greater with tanezumab 5 mg or 10 mg monotherapy in

comparison to placebo or active comparator treatment. The difference between the event rate with tanezumab 10 mg and active comparator treatment was statistically significant.

When administered in combination with NSAID treatment, there was an increased incidence of rapidly progressive osteoarthritis with the dose of tanezumab and all combination treatments were elevated compared to placebo, all tanezumab monotherapy, and active comparator treatments. Tanezumab 10 mg/NSAID combination treatment was associated with the highest rate of rapidly progressive osteoarthritis.

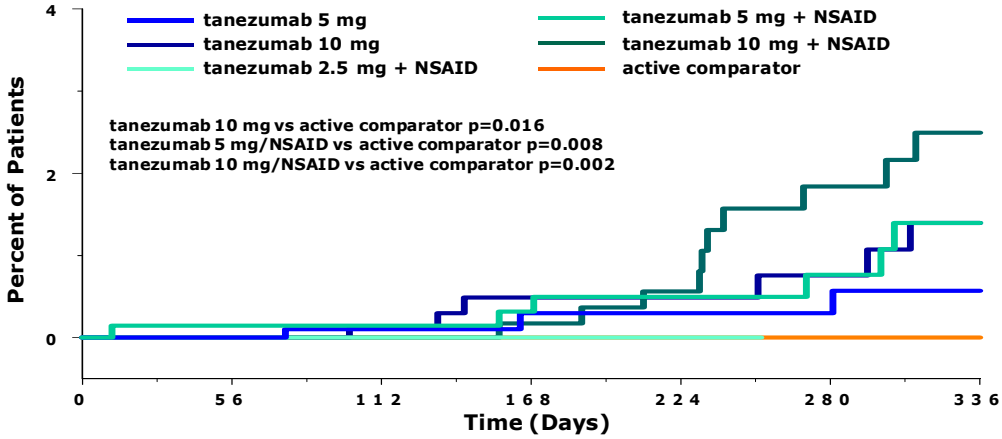
Table 17. Rapidly Progressive Osteoarthritis in the Phase 3 Osteoarthritis Studies

	placebo	tanezumab			tanezumab + NSAID[1]			Active Comparator[2]
		2.5 mg	5 mg	10 mg	2.5 mg	5 mg	10 mg	
N	**1029**	**604**	**1771**	**1898**	**587**	**1249**	**1192**	**1266**
Total exposure (pt-yrs)	**313**	**373**	**1116**	**1125**	**381**	**877**	**823**	**661**
n (%)								
	0 (0.0)	0 (0.0)	7 (0.4)	12 (0.6)	6 (1.0)	16 (1.3)* #	25 (2.1)* #	1 (0.1)
Event rates (events/1000 pt-yrs)								
	0	0	6	11#	16#	18#	30#	2

Studies 1011, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030, & 1043
[1] 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 non-controlled long-term studies
[2] Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID
Risk difference: * $p \leq 0.05$ vs. placebo, # $p \leq 0.05$ vs. active comparator, event rate comparisons to placebo (zero events) could not be made
Dose-response for crude incidence; p=0.005 tanezumab monotherapy, p<0.001 combination therapy
Dose-response for event rate; p=0.012 dose-response tanezumab monotherapy, p<0.001 tanezumab/NSAID combination therapy

The time to event analysis of total joint replacement due to rapidly progressive osteoarthritis comparing tanezumab monotherapy or tanezumab/NSAID combination therapy to active comparator treatment is shown in Figure 14. In this analysis, all studies that included tanezumab monotherapy or combination therapy with NSAIDs and active comparator treatment groups were pooled for analysis. The time to event curves with tanezumab 10 mg monotherapy and for tanezumab 5 mg or 10 mg in combination with NSAIDs were significantly elevated when compared to active comparator treatment by log-rank test.

Figure 14. Time to Event Analysis of Rapidly Progressive Osteoarthritis Versus Active Comparator Treatment in the Controlled Phase 3 Osteoarthritis Studies



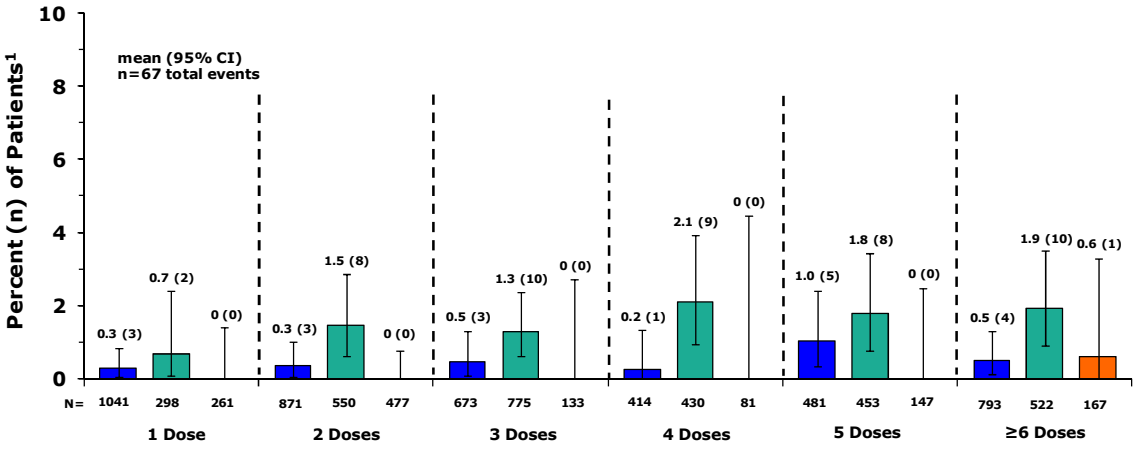
At Risk							
tanezumab 5 mg	1119	1044	919	493	404	369	270
tanezumab 10 mg	1109	1001	880	478	396	348	259
active comparator	1266	1148	997	586	466	363	266
tanezumab 2.5 mg + NSAID	157	154	143	135	88	0	0
tanezumab 5 mg + NSAID	686	648	602	567	492	360	264
tanezumab 10 mg + NSAID	687	642	599	559	479	352	253

6.5.2. Incidence of Rapidly Progressive Osteoarthritis as Function of the Number of Tanezumab Doses Administered

The relationship of rapidly progressive osteoarthritis to the number of tanezumab doses administered is shown in Figure 15. The results show modest increases in the incidence of rapidly progressive osteoarthritis over the range of 1 to > 6 doses of tanezumab administered (8 to ≥48 weeks of treatment) as monotherapy or when given in combination with NSAIDs. The results largely mirror those for all-cause total joint replacements as shown in Figure 9.

These data indicate the incidence of rapidly progressive osteoarthritis is not increasing by duration of therapy to the degree suggested by the time to event (event = total joint replacement) analysis would suggest (Figure 14). The time of total joint replacement occurred more often toward the later portion of the studies because patients with planned surgeries were excluded from enrolling in the tanezumab osteoarthritis studies, there was likely a need for some level of exposure to treatment before the effect/symptoms on the joint would present which then would be followed by an assessment by, or referral to an orthopedic surgeon, scheduling of the surgical procedure, and finally the total joint replacement.

Figure 15. Incidence of Rapidly Progressive Osteoarthritis by the Number of Tanezumab Doses Administered in the Phase 3 Osteoarthritis Studies



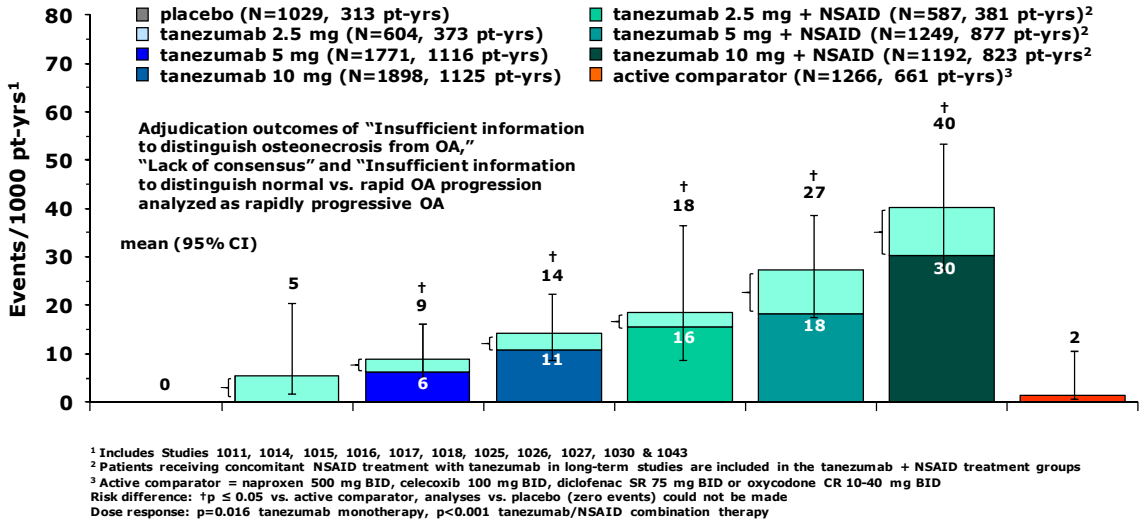
[1] Studies 1011, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030 & 1043. The placebo treatment group is not shown.
[2] tanezumab + NSAID group includes patients from 1016 and 1043 with ≥1 day of concomitant NSAID use
[3] Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID

6.5.3. Sensitivity Analysis

A sensitivity analysis was carried out on the endpoint of rapidly progressive osteoarthritis. In this analysis all patients categorized as (1) insufficient information to distinguish osteonecrosis from osteoarthritis (2) lack of consensus by the Adjudication Committee and (3) insufficient information to distinguish rapid progression of osteoarthritis from normal progression were added to adjudicated events of rapidly progressive osteoarthritis. The results of the sensitivity analysis are shown in Figure 16.

The results of the sensitivity analysis differ from assessment of adjudicated outcomes of rapidly progressive osteoarthritis alone (Figure 13) in that the event rate with tanezumab 2.5 mg monotherapy exceeds active comparator treatment and a significant difference is evident between tanezumab 5 mg monotherapy and active comparator treatment. However, the sensitivity analysis does not alter the conclusions that are reached regarding the effects of tanezumab treatment.

Figure 16. Sensitivity Analysis of Rapidly Progressive Osteoarthritis in the Phase 3 Osteoarthritis Studies



¹ Includes Studies 1011, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030 & 1043
² Patients receiving concomitant NSAID treatment with tanezumab in long-term studies are included in the tanezumab + NSAID treatment groups
³ Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID
Risk difference: †p ≤ 0.05 vs. active comparator, analyses vs. placebo (zero events) could not be made
Dose response: p=0.016 tanezumab monotherapy, p<0.001 tanezumab/NSAID combination therapy

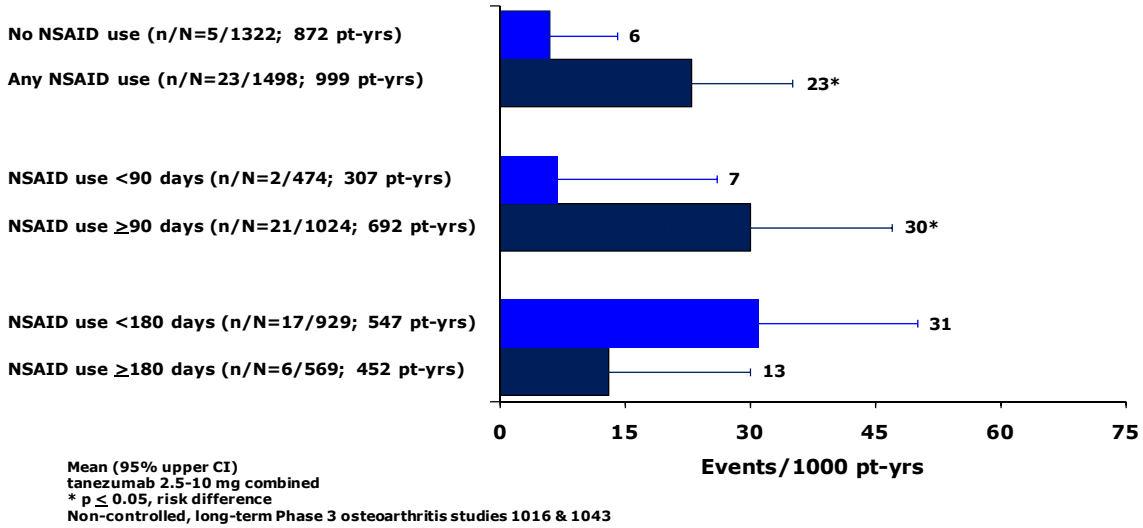
6.5.4. Effect of Duration of NSAID Treatment

Patients participating in the controlled Phase 3 osteoarthritis studies were randomized to treatment with tanezumab/NSAID combination therapy and, therefore, their use of NSAIDs was not confounded by the progression of joint disease and requirement for additional analgesia. Per-protocol in the non-controlled long-term Phase 3 osteoarthritis studies and the non-controlled long-term Phase 2 chronic low back pain study, patients were permitted to receive NSAID treatment if warranted based on the clinical judgment of the investigator.

A total of 827 patients (55.2%) began receiving NSAIDs within one week of the start of participation in one of the non-controlled long-term Phase 3 osteoarthritis studies and 963 patients (64.3%) within one month of study initiation. The remaining patients began NSAID therapy after one month of study initiation. Based on the time that NSAID treatment was initiated as function of study entry it seems unlikely that NSAID use was confounded by progression of osteoarthritis and the need for additional pain relief as a result in most patients (i.e., NSAID use was not being used as a result of rapidly progressive osteoarthritis).

In the non-controlled long-term Phase 3 osteoarthritis studies, 1498 patients used NSAIDs concomitantly with tanezumab and 1322 patients did not use NSAIDs. The rate of rapidly progressive osteoarthritis was significantly greater in concomitant NSAID users as compared to non-users (Figure 17). These data are consistent with the observations regarding tanezumab/NSAID combination therapy in the controlled Phase 3 osteoarthritis studies.

Figure 17. Effect of NSAID use with Tanezumab on the Rate of Rapidly Progressive Osteoarthritis in the Non-Controlled Long-Term Phase 3 Osteoarthritis Studies

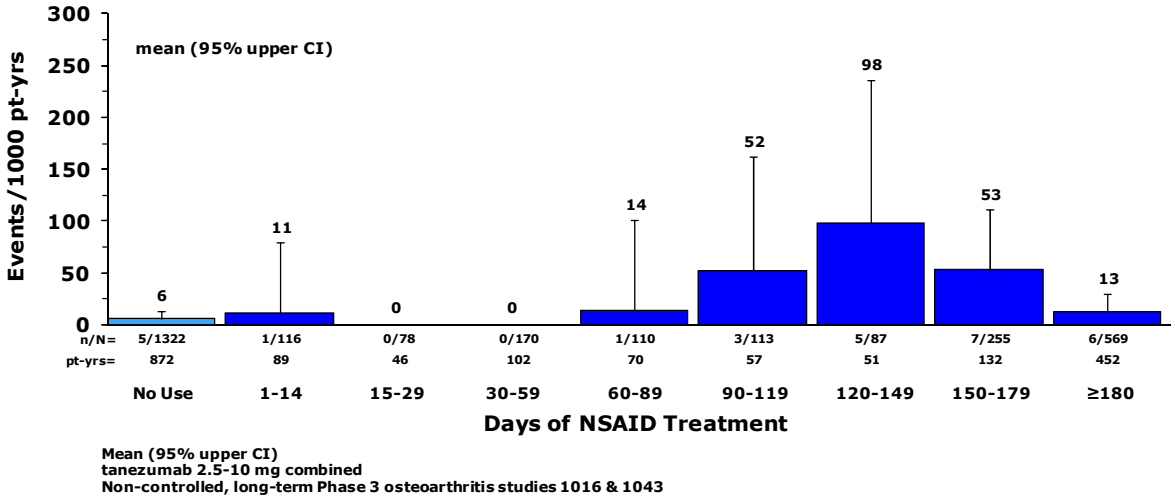


In those patients receiving tanezumab and concomitantly using NSAIDs, the risk of rapidly progressive osteoarthritis was related to duration of NSAID therapy. The rate of rapidly progressive osteoarthritis in patients who used NSAIDs for less than 90 days was comparable to NSAID non-users and significantly lower than patients who used NSAIDs for a period of 90 days or more. In contrast, no differences were evident in the rate of rapidly progressive osteoarthritis when duration of NSAID use of less than 180 days was compared to 180 days or more.

The effect of duration of concomitant NSAID administration with tanezumab was further evaluated by examining NSAID use in 15-30 day intervals as shown in Figure 18. This more detailed analysis confirms the pattern of increased risk of rapidly progressive osteoarthritis when NSAIDs are used concomitantly with tanezumab for periods of greater than 90 days.

The rate of rapidly progressive osteoarthritis type 2 by NSAID use in the non-controlled long-term Phase 3 osteoarthritis studies was 19 events/1000 pt-yrs (n/N = 19/1498; 999 pt-yrs) in NSAID users and 6 events (n/N = 5/1322; 872 pt-yrs) in non-NSAID users. The rate of rapidly progressive osteoarthritis type 1 in these respective cohorts was 4 and 0 events/ 1000 pt-yrs.

Figure 18. Duration of Concomitant NSAID use with Tanezumab: Effect on the Incidence of Rapidly Progressive Osteoarthritis in the Non-Controlled Long-Term Phase 3 Osteoarthritis Studies



6.5.5. Characterization of Adjudicated Events of Rapidly Progressive Osteoarthritis

There were a total of 68 patients identified by adjudication with rapidly progressive osteoarthritis. Of this total, 67 patients were participating in one of the Phase 3 osteoarthritis studies and 1 patient was participating in a chronic low back pain study. Over 90% of these patients experienced an increase in pain in the period of time after the Baseline study visit to the onset of the reported event.

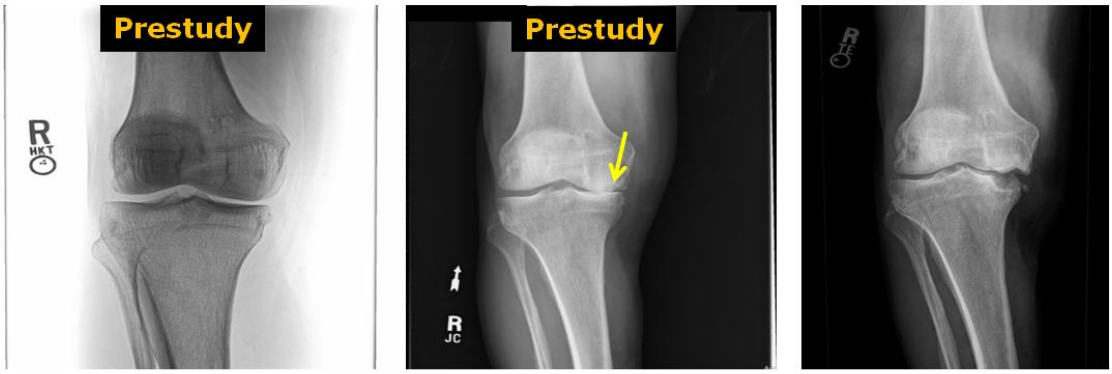
The Adjudication Committee concluded that 9 adjudicated events of rapidly progressive osteoarthritis occurred prior to the patient entering a Phase 3 osteoarthritis study and receiving study medication. These patients are listed in Table 18. The events were equally split between type 1 (4 events) and type 2 (5 events) rapidly progressive osteoarthritis. Five of the patients were randomized to tanezumab/NSAID combination treatment or receiving NSAIDs concomitantly. An example of a patient adjudicated with pre-existing rapidly progressive osteoarthritis is shown in Figure 19.

Table 18. Patients Adjudicated with Pre-Existing Rapidly Progressive Osteoarthritis

Study	Patient	Treatment
1014	**10951003**	tanezumab 10 mg
1025	**10621007**	tanezumab 10 mg
1025	**11571002**	tanezumab 10 mg + NSAID
1025	**13171020**	tanezumab 5 mg
1025	**13261002**	tanezumab 5 mg + NSAID
1016	**10391013**	tanezumab 5 mg*
1016	**10351004**	tanezumab 10 mg
1043	**10531004**	tanezumab 2.5 mg*
1043	**10331016**	tanezumab 5 mg*

*Patient used NSAIDs concomitantly with study medication

Figure 19. Serial Radiographs of the Right Knee in a Patient Adjudicated with Pre-Existing Rapidly Progressive Osteoarthritis



A 63-year-old man received 2 doses of tanezumab 5 mg IV every 8 weeks (14-Apr-10, 10-Jun-10).
Considering the 9-Dec-09 and 01-Apr-10 knee x-rays, rapidly progressive OA was present prior to study entry and dosing.

The Adjudication Committee determined there were 10 patients with a subchondral insufficiency fracture in the absence of evidence of rapidly progressive osteoarthritis (Section 6.6). In addition, the Adjudication Committee identified 19% of the patients (13/68 patients) with an adjudicated outcome of rapidly progressive osteoarthritis who had suggestive or definitive evidence of a subchrondral insufficiency fracture in association with or preceding the event of rapidly progressive osteoarthritis. Of these 13 patients, the knee was the affected joint in 11 patients and there was definitive evidence of a subchondral insufficiency fracture of the medial (n=10) or lateral (n=1) femoral condyle coincident with the determination of rapidly progressive osteoarthritis or was pre-existing prior to study entry (n=2). Rapidly progressive osteoarthritis was adjudicated as type 2 (osteolysis) in 8 of these patients and type 1 in 3 patients. The remaining 2 patients were identified with rapidly progressive osteoarthritis type 2 and possible subchondral insufficiency fracture of the hip.

Table 19 provides a summary of patient characteristics for those patients with adjudicated outcome of rapidly progressive osteoarthritis. Eighty-four percent (57/68) of the patients with rapidly progressive osteoarthritis were women, whereas the overall study population in the tanezumab clinical program was approximately 65% women. The distribution of patients less than 65 years of age (54.4%) and those 65 years of age or older (45.6%) was similar to the overall study population. Of the 38 patients with rapidly progressive osteoarthritis of the hip in the tanezumab clinical program, 32 (84%) were women and the average age was 64 years (range 50-80 yrs) and, thus, had strong resemblance to patients at risk naturally for rapidly progressing osteoarthritis.

Table 19. Characteristics of Patients with Rapidly Progressive Osteoarthritis

n (%)		N = 68
Gender		
	Female	57 (83.8)
	Male	11 (12.6)
Age		
	<65 years	37 (54.4)
	≥65 years	31 (45.6)
Affected Joint		
	Hip	38 (55.9)
	Knee	27 (39.7)
	Shoulder	3 (4.4)
Kellgren-Lawrence Grade of Affected Joint		
	Grade 2	6 (8.8)
	Grade 3	29 (42.6)
	Grade 4	20 (29.4)
	Unknown	13 (19.1)

The index joint was the affected joint in 44 patients (64.7%). Evidence to establish that osteoarthritis was present in the affected joint prior to treatment was available for 58 patients and suggestive evidence in 3 additional patients (89.7% of the patients overall). There was no available information to make a determination in 6 patients. The final patient in this cohort had minimal to no osteoarthritis in the affected joint. However, the patient experienced a subchondral insufficiency fracture that was evident prior to the determination of rapidly progressive osteoarthritis. One patient participating in the non-controlled long-term Phase 2 chronic low back pain study was adjudicated with rapidly progressive osteoarthritis in the left knee. The patient was a 76-year-old woman with a history of chronic low back pain and osteoarthritis in unspecified multiple joints since 2003. Magnetic resonance imaging (MRI) scan before the surgery showed a complex tear of the medial and lateral meniscus, superimposed on moderate medial and advanced (bone on bone) lateral compartment degenerative arthritis. The patient had been treated with tanezumab 20 mg and prior to that, tanezumab 5 mg in the controlled chronic low back pain parent study.

Of the 68 patients adjudicated with rapidly progressive osteoarthritis, the Kellgren-Lawrence score of the affected joint prior to study entry was available or determined by the Adjudication Committee for 55 patients (80.8%). In 89.1% of these 55 patients, the Kellgren-Lawrence Grade of the affected joint was Grade 3 or 4 (Table 19). In the Phase 3 osteoarthritis population, 58.2% of patients had Kellgren-Lawrence Grade 3 or 4 of the index

joint. A total of 20 patients (36.4%) had Kellgren-Lawrence Grade 4 osteoarthritis in the affected joint and 29 patients (52.7%) had Kellgren-Lawrence Grade 3 osteoarthritis in the affected joint. The remaining 6 patients had Kellgren-Lawrence Grade 2 osteoarthritis. Thus, the majority of patients with adjudicated rapidly progressive of osteoarthritis had significant disease severity prior to study entry compared to the study population overall.

The hip was the affected joint in 38 patients (55.9%), the knee in 27 patients (39.7%) and the shoulder in 3 patients (4.4%). In the Phase 3 osteoarthritis population, the knee was the index joint (most symptomatic or bothersome) at Baseline in 79% of the patients and the hip in 21% of patients. In the 38 patients (40 hips) with rapidly progressive osteoarthritis of the hip, 30 hips were determined to be concentric joint space narrowing, 5 had mild dyplasia, 1 had moderate dysplasia and could not be determined in 4 hips due to the degree of joint destruction. None of the hip images were clearly hypertrophic and the large majority were atrophic osteoarthritis.

There were 11 events of type 1 rapidly progressive osteoarthritis ($\geq$1 mm joint space narrowing over the course of 1 year) and 57 events of type 2 rapidly progressive osteoarthritis (abnormal loss/destruction of bone). The one patient identified with rapidly progressive osteoarthritis while on active comparator (naproxen 500 mg BID) treatment was a bilateral knee type 2 event. Of these 68 events, serial x-rays or MRI images were available for 50 patients to determine the approximate time-course of the event. The mean interval was 9.7 months (range 1-24 months). The interval between the initial and final radiographic image was 7.4 (range 3-18) months for the 11 type 1 rapidly progressive osteoarthritis events and 10.2 (range 1-24) months for 39 of 57 type 2 rapidly progressive osteoarthritis events where antecedent x-rays were available.

6.5.6. Subgroup Analyses

The subgroup or discriminant analyses listed in Table 20 were conducted to identify patients who were at greater risk for rapidly progressive osteoarthritis. The same subgroup or dicriminant analyses were conducted with the outcome of all-cause total joint replacement or the adjudication outcome of worsening osteoarthritis-normal progression. The results with latter outcomes were used to judge whether the subgroup or discriminant analyses were specific for rapidly progressive osteoarthritis and would differentiate patients with elevated risk for this condition or generally mirror patients at risk for proceeding to total joint replacement for any reason.

Some subgroups with an elevated incidence of rapidly progressive were identified but not uniquely so. In most of the same subgroups the risk of total joint replacement for any reason or due to normal progression of osteoarthritis were elevated as well. There was an increased incidence of rapidly progressive osteoarthritis, total joint replacements related to normal progression, or all-cause total joint replacements associated with increasing age, index joint of the hip, Kellgren-Lawrence Grade 3 or 4 of the index joint, multiple joint osteoarthritis, an adverse event of arthralgia, joint swelling, abnormal peripheral sensation, or pain in extremity, analgesics or anti-inflammatory drug use prior to the study or use of opioid analgesics or corticosteroids during the study.

Table 20. Subgroup or Discriminant Analyses Conducted to Assess the Risk of Rapidly Progressive Osteoarthritis

Demographic Characteristics 1. age 2. gender 3. BMI Concomitant medications 1. low dose aspirin 2. acetaminophen 3. opioid analgesics 4. proton pump inhibitors 5. bisphosphonates 6. corticosteroids Prior Medication Use 1. Analgesics 2. NSAIDs	Disease Characteristics 1. index joint (knee vs. hip) 2. history of multiple joint OA 3. history of total joint replacement 3. Kellgren-Lawrence Grade at Baseline 4. history of osteopenia/osteoporosis 5. baseline WOMAC Pain severity (moderate vs. severe) 6. baseline WOMAC Physical Function severity (moderate vs. severe) 7. baseline Patient's Global Assessment (fair vs. poor/very poor) Efficacy response 1. maximum improvement in WOMAC Pain (<50% vs. ≥50%) 2. maximum improvement in WOMAC Physical Function (<50% vs. ≥50%) Adverse Events 1. arthralgia 2. joint swelling 3. abnormal peripheral sensations 4. pain in extremity 5. fractures 6. back pain

Baseline symptomatic disease severity, magnitude of efficacy response, an adverse event of back pain or osteoporosis/osteopenia, concomitant use of acetaminophen, proton pump inhibitors, bisphosphonates, or body mass index were not observed to elevate the risk of any joint-related outcome.

There was an increased incidence of all-cause total joint replacements alone in patients with history of total joint replacement, patients taking low-dose aspirin or an adverse event of fracture.

There was an increased incidence of rapidly progressive osteoarthritis alone in women and trends for an increased incidence in patients with a history of osteoporosis/osteopenia; however, there were very few patients in this subgroup.

6.5.7. Application of the Adjudication Classification used for the Tanezumab Program to Other Osteoarthritis Studies

The incidence of rapidly progressive osteoarthritis in the overall osteoarthritis population is not well defined. We evaluated the incidence of rapidly progressive knee osteoarthritis in patients participating in the Osteoarthritis Initiative (OAI) Study.

The OAI Study is a nationwide multicenter four-year observational study of men and women with knee osteoarthritis or at risk for developing knee osteoarthritis. The OAI Study has recruited two primary cohorts, one with symptomatic knee osteoarthritis at baseline followed for worsening of the disease (progression cohort) and another without symptomatic knee osteoarthritis, but selected on the basis of having specific characteristics which give them an increased risk of developing incident symptomatic knee osteoarthritis during the study (incidence cohort).

Bilateral knee radiographs of the progression cohort from the OAI Study were obtained and reviewed by a member of the tanezumab Adjudication Committee (E. Vignon) to classify the events with the adjudication categories utilized by the Adjudication Committee. A program which allows for visualization of the radiology images from a given patient in the same screen for comparison and an accurate measurement of the minimum joint space width to determine the one year joint space narrowing was used. The focus of this evaluation was to determine if rapidly progressive osteoarthritis was present in this cohort of patients.

A total of 1391 patients were evaluated. After removing patients who had only a baseline radiograph and those patients who had a knee replacement prior to the baseline of study, there were 1174 patients (2348 paired radiographs) classified with the tanezumab adjudication categories. Rapidly progressive osteoarthritis (Category 2a) was identified in 41 patients (3.5%). Thirty-nine of the patients (3.3%) had type 1 rapidly progressive osteoarthritis and 2 patients (0.2%) had type 2 rapidly progressive osteoarthritis.

A similar analysis was carried out in 1457 patients with knee osteoarthritis who participated in a 2-year Pfizer study of radiographic progression. Patients with Kellgren-Lawrence Grade 2 (641 patients, 44%) and Grade 3 (816 patients, 56%) at baseline were enrolled into the study and underwent x-ray evaluation on an annual basis. There were 16 patients categorized with rapidly progressive osteoarthritis or 1.1% (16/1457 patients); 14 with type 1 rapidly progressive osteoarthritis (joint space narrowing $\geq$ 1 mm per year) and 2 with type 2 rapidly progressive osteoarthritis. There were 3 patients with a subchondral insufficiency fracture.

In both studies described above a small percentage of patients were identified with rapidly progressive osteoarthritis, predominately type 1. The Adjudication Committee identified 4 (3.1%) patients with type 1 rapidly progressive osteoarthritis in the 127 patients with knee osteoarthritis they examined from the tanezumab program although not all of these patients had a baseline x-ray to make a determination of joint space narrowing. In the same group of patients, however, there were 23 patients (16.1%) adjudicated with type 2 rapidly progressive osteoarthritis. These comparisons indicate that rapidly progressive osteoarthritis type 2 is a relatively distinct finding in the tanezumab studies.

6.6. Adjudication Outcomes – Other Diagnoses

Patients adjudicated to Other Diagnosis with subchondral insufficiency fracture are listed in Table 21. Seven patients with a subchondral insufficiency fracture were treated with tanezumab in combination with NSAIDs, two received tanezumab monotherapy and one patient was treated with an NSAID alone. Thus, similar to other observations, tanezumab/ NSAID combination treatment was associated with an excess number of patients with a subchondral insufficiency fracture.

Table 21. Patients with Subchondral Insufficiency Fractures

Study	Patient	Treatment	Joint
1025	**13031032**	NSAID	Right knee (index joint)
1025	**13001016**	tanezumab 10 mg	Left knee (index joint)
1025	**12201001**	tanezumab 10 mg + NSAID	Left knee (index joint was right knee)
1025	**13031003**	tanezumab 10 mg + NSAID	Right knee (index joint)
1017	**10521001**	tanezumab 2.5 mg + NSAID	Left knee (index joint was right knee)
1016	**10351021**	tanezumab 5 mg*	Left knee (index joint was right knee)
1016	**10941005**	tanezumab 5 mg*	Left knee (index joint was right knee)
1016	**12081002**	tanezumab 5 mg*	Left knee (index joint was right knee)
1016	**10601028**	tanezumab 10 mg	Left knee (index joint)
1039 (CLBP)	**10981004**	tanezumab 20 mg*	Right knee

* Patient used NSAIDs concomitantly with study medication

7. MECHANISM OF RAPIDLY PROGRESSIVE OSTEOARTHRITIS

As outlined in Section 2 the mechanisms involved in rapidly progressive osteoarthritis are poorly understood. Following the introduction of NSAIDs in the late 1960s for the treatment osteoarthritis, reports began to appear associating NSAID treatment, most prominently indomethacin, with rapidly progressive osteoarthritis. The proposed mechanism(s) underlying these observations included increased joint loading and overuse of compromised joints rendered less painful and/or a direct detrimental effect of these agents on cartilage and/or bone.[56,57,58,59,60] Neither of these effects were shown conclusively to result in rapidly progressive osteoarthritis and a cause and effect relationship of NSAIDs with rapidly progressive osteoarthritis was never established. However, there has been clear demonstration in several studies that reductions in pain with NSAID administration alone are sufficient to increase the load on degenerative portion of osteoarthritic joints.[79,80,81] Tanezumab has been extensively investigated pre-clinically to determine whether NGF inhibition results in any direct effects on bone, cartilage, joint vasculature or joint innervation that would lead to accelerated joint damage.

The clinical peripheral neurological safety profile of tanezumab was also evaluated to determine whether there was any apparent relationship to adverse joint-related outcomes. On the basis of joint damage and appearance, rapidly progressive osteoarthritis and neurogenic arthropathy (Charcot joint) bear a strong resemblance. The key difference is whether there is also evidence of severe neuropathy and loss of protective sensitivity in the weight-bearing joints. Typically, these neurological deficits are readily evident in patients with Charcot joint and allow for the differential diagnosis.

Finally, given the greater magnitude of pain relief in tanezumab-treated patients compared to those receiving NSAIDs, we examined whether reduced pain and improvements in function predisposes patients to a total joint replacement for any cause or specifically to rapidly progressive osteoarthritis in patients when treated with tanezumab alone or tanezumab/ NSAID combination therapy.

7.1. Non-Clinical Assessments of Tanezumab on Bone and Joints

Tanezumab or a murine precursor antibody (MuMAb911) was administered to three species (primate, rat, and mouse) for varying durations up to six months at large multiples of the clinical exposure. Hip and stifle joints were assessed using standard histological methods including: hematoxylin and eosin (H&E), toluidine blue, and modified Goldner's trichrome stains, on both decalcified and undecalcified sections; in-life magnetic resonance imaging (MRI); post-life specialized imaging (quantitative micro-computed tomography (CT)); and serum bone biomarkers (osteocalcin, procollagen type 1 aminoterminal propeptide [P1NP] and carboxyterminal cross-linking telopeptide of bone collagen [CTX-1]). No adverse changes to bone or joint were detected following exposure to tanezumab or MuMAb911, and no evidence was found to indicate NGF inhibition alone has a direct effect on bone, cartilage, joint vascularization, or joint innervation that would lead to joint destruction.

Articular cartilage was assessed on H&E and toluidine blue stained sections. There were no effects of tanezumab or MuMAb911 treatment on any component of articular cartilage including chondrocytes and matrix in all three species.

One of the key non-clinical evaluations was the assessment of subchondral bone in sexually mature primates dosed weekly with tanezumab intravenously at supratherapeutic exposures for 6 months. Decalcified bone histomorphology using H&E and toluidine blue stains, and undecalcified bone using modified Goldner's trichrome were evaluated by a board certified pathologist using light and polarized light microscopy. The primary assessment of the decalcified bone by the pathologist suggested thicker subchondral bone in one of two high dose male groups compared to concurrent control animals. No changes were evident in the female dose groups compared to concurrent controls. To assure a comprehensive evaluation, additional micro-CT image analysis was conducted using specific regions of interest in the lateral and medial tibial plateaus. In this quantitative analysis, subchondral bone thickness in one high-dose male group was statistically significant, confirming the initial histo-morphologic assessment. Since thicker subchondral bone might indicate an early change in the development of arthritis, we closely evaluated the morphology of the subchondral bone in which no evidence for an active process was found; subchondral bone in all animals examined using light and polarized light microscopy consisted of normal lamellar bone laid down over many remodeling cycles coupled with quiescent bone surfaces. These findings confirm that subchondral bone was thickened prior to dosing and thus not considered to be treatment related.

To assess the potential impact of anti-NGF exposure on bone vasculature, Factor VIII immunohistochemistry (IHC) was incorporated with close histomorphologic examination of open physes in rapidly growing rodents. This anatomic location is an active site for angiogenesis and is a known target of anti-vascular endothelial growth factor (VEGF) agents resulting in physeal dysplasia. Treatment with tanezumab or MuMAb911 did not demonstrate any evidence of physeal dysplasia in the rodent growth plate. The basis for this conclusion comes from a lack of morphological changes in long bone physes and metaphyses from both rats (after 4 weeks exposure) and mice (after 12 weeks exposure) with proper organization of cells (chondrocytes) in the physes, and no impact on longitudinal bone growth based on quantitation of bone length using x-rays. Most of the growth plates from the nonhuman primate study were closed due to their sexual maturity, and therefore, could not be assessed for physeal dysplasia; however, no changes were noted in Factor VIII staining in bone. These data are strongly suggestive that anti-NGF administration does not behave like anti-VEGF agents with respect to anti-angiogenic properties in bone.

To assess the potential impact of anti-NGF exposure on peripheral nerve fibers in bone, decalcified sections of bone were evaluated by PGP 9.5 IHC. Histomorphologic assessments were completed in all three species. No changes were seen in any bone or joint tissue in response to anti-NGF treatment.

In addition to the studies outlined above, the effects of anti-NGF therapy have been examined in several nonclinical models of bone pain that involve significant bone remodeling. Anti-NGF treatment produced pain relief with no change in bone innervation,

bone remodeling or fracture healing[70,71,72,73,74]. Two of these studies examined inhibition of NGF during fracture healing and found no inhibition of callus formation, bridging or mechanical strength.[72,73] In a model of complex regional pain syndrome caused by a tibial fracture, where there is a pronounced loss of bone, inhibition of NGF results in a modest sparing of that bone loss, leading to more preserved bone.[74] There are several papers reporting on tumor-induced bone remodeling, either osteolytic or osteoblastic, that found no effect on this bone remodeling following inhibition of NGF.[70,71] In each of the above studies, there are measurable pain behaviors, and treatment with anti-NGF gives a significant decrease in those behaviors indicating that NGF was, indeed, inhibited sufficiently to give an antihyperalgesic effect.

In a recent study examining the dynamic changes that accompany aggressive inflammatory arthritis induced by complete Freund's adjuvant in the rodent, large increases in macrophages, aberrant vasculature, and sensory and sympathetic fibers at the synovial-meniscal junction were described accompanying an increase in pain-related behaviors.[82] Treatment with MuMAb911 prevented the increase in ectopic sprouting of nerve fibers as well as the pain behaviors while having no effect on the vasculature or macrophage number. Correspondingly, use and weight-bearing in the arthritic joint improved by up to 50% and 75%, respectively compared to vehicle-treated animals. There was also no effect on innervation, vasculature, or macrophages in the contralateral, uninflamed joint. The results of this study indicate ectopic sprouting of sensory and sympathetic nerve fibers occurs in the painful arthritic joint and may be involved in the generation and maintenance of arthritic pain and lend further support to the conclusion that NGF inhibitors are anti-hyperalgesic rather than analgesic.

The studies summarized above are likely to be directly relevant to tanezumab as in each of these studies the antibody used to inhibit NGF was the murine precursor to tanezumab.

7.2. Neurogenic Arthropathy (Charcot Joint)

There were no patients with or without total joint replacement presenting with loss of protective sensitivity following treatment with tanezumab in the clinical development program. Given this observation, it seems unlikely that rapidly progressive osteoarthritis with tanezumab administration is the result of neurogenic arthropathy to the degree seen in patients with diabetic neuropathy or other neurological conditions leading to loss of protective sensitivity and joint destruction.

As summarized in Section 3, NGF is critical to peripheral nociceptor development and differentiation during the fetal and early post-natal growth periods, but thereafter these neurons lose their absolute dependence on NGF. NGF continues to play a major role in pain processing in adults although this function is limited to a subpopulation of small unmyelinated peptidic sensory neurons. Non-clinical studies with tanezumab or the murine precursor have shown no detrimental effect of NGF inhibition on normal innervation but do show reduction in aberrant bone and joint innervation in experimental models of bone cancer pain[83] and arthritis.[82] Intraepidermal nerve fiber density measurements in normal human volunteers, patients with peripheral diabetic neuropathy, or osteoarthritis patients treated with

1 to 3 doses of tanezumab confirm that NGF blockade in adults has no significant effect on the viability of small fiber sensory neurons.

Some patients receiving tanezumab report abnormal peripheral sensations (tingling, numbness, or a burning sensation) that typically occur after the first administration of the drug and then resolve in most patients with continued administration of tanezumab (Section 10.5). Unlike known neurotoxic agents, these symptoms do not characteristically worsen with repeated administration of tanezumab and few patients discontinue treatment due to the severity of the symptoms. Non-clinical findings and intraepidermal nerve fiber density measurements in human subjects are also not suggestive of a neurotoxic effect resulting from NGF blockade.

Although the mechanism(s) responsible for abnormalities in peripheral sensation with tanezumab are unclear, a higher incidence of total joint replacement or rapidly progressive osteoarthritis is found in patients reporting abnormal peripheral sensations. However, there were also patients who experienced abnormal peripheral sensations and did not undergo total joint replacement and conversely, patients who underwent total joint replacement and did not report any abnormal peripheral sensations. As a result, it has not been possible to establish whether these neurological and joint-related findings are linked in any way by a common pharmacologic mechanism or represent unrelated pharmacologic effects.

Finally, altered joint proprioception and more recently worsening vibratory perception in the plantar region of the feet mediated by large myelinated sensory neurons have been implicated in the progression of osteoarthritis.[84,85]

Extensive neurological examination of tanezumab-treated patients has shown small and transient worsening of proprioception or vibratory sensation in the great toe of a low percentage of patients. Patients with either abnormality were not predisposed to a greater risk of total joint replacement than those with consistently normal neurological exam findings while receiving tanezumab treatment. Nonetheless, subclinical or minor clinical somatosensory effects of tanezumab or perhaps deficits localized to a specific joint that may be sufficient to result in joint destruction cannot be ruled out with the existing data.

7.3. Relationship of Pain Reduction and All-Cause Total Joint Replacements or Rapidly Progressive Osteoarthritis (Analgesic Arthropathy)

An association of pain relief and all-cause total joint replacements or rapidly progressive osteoarthritis alone was analyzed by several approaches. One such analysis is discussed below. The results are emblematic of all other analyses conducted. Table 22 summarizes those patients undergoing a total joint replacement who reported a pain score of two or less on a 0-10 numerical rating scale (corresponding to no pain or very mild) in the same joint at consecutive clinic visits during treatment but prior to the event. The pain score for the patients enrolling in the Phase 3 osteoarthritis studies was 6-7 on average prior to receiving study medication (0-10 numerical rating scale). In contrast to those patients treated with placebo or an active comparator, approximately 20-40% of patients treated with tanezumab alone or in combination with an NSAID reported minimal to no pain in their index knee or

hip joint over 2 consecutive clinic visits (i.e., a 4 month interval) only to subsequently undergo total joint replacement in the same joint.

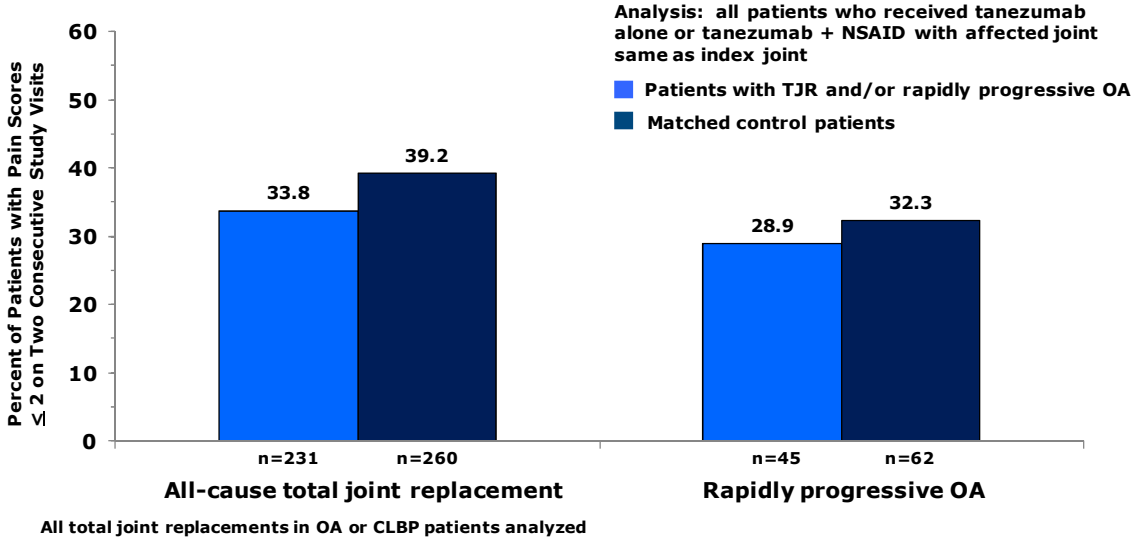
Table 22. Incidence of Minimal to No Pain in Patients Undergoing All-Cause Total Joint Replacement

Index joint was affected joint				
% (n/N)	**placebo**	**tanezumab monotherapy**	**tanezumab + NSAID**	**active comparator**
Patients with total joint replacement and pain score ≤ 2 at consecutive visits preceding the event	0.0% (0/10)	39.1% (66/169)	19.4% (12/62)	0.0% (0/22)

A similar analysis was carried out on patients who received tanezumab monotherapy or tanezumab treatment in combination with NSAIDs to determine the proportion of patients reporting the same level of pain reduction in their index joint but did not undergo either total joint replacement or were not affected by rapidly progressive osteoarthritis. These reference-matched control groups consisted of patients from the same study matched to each patient with a total joint replacement or to each patient with rapidly progressive osteoarthritis. The patients were identified using propensity scores estimated from a logistic regression model which included the following covariates: age, gender, body mass index, Kellgren-Lawrence Grade of the index joint, osteoarthritis disease severity, and number of IV/SC doses of study medication the patient received.

As shown in Figure 20, the proportion of patients reporting minimal to no pain in their index joint in the matched control cohorts was similar to patients affected by a total joint replacement related to any cause or patients with an adjudicated event of rapidly progressive osteoarthritis. These results were corroborated and extended using the same approach for the evaluation of the WOMAC Pain subscale item "pain when walking on a flat surface," "pain when going up or down stairs" and the WOMAC Physical Function subscale.

Figure 20. Incidence of Minimal to No Index Joint Pain Following Tanezumab Administration in Patients with an All-Cause Total Joint Replacement or Rapidly Progressive Osteoarthritis: Comparison to Matched Control



These results, substantiated by other analyses including the observation that some patients found with rapidly progressive osteoarthritis reported only a modest level of pain relief (<30% reduction – see Section 12) when treated with tanezumab, indicate that pain relief and mechanical overloading of a joint may play a role in the deleterious effects of tanezumab. However, this mechanism alone does not appear to explain all of the clinical observations and other contributing factors must be important as well. Of particular note is the large excess of total joint replacements or adjudicated events of rapidly progressive osteoarthritis observed in patients treated with tanezumab in combination with NSAIDs versus tanezumab monotherapy with little apparent differences in the magnitude of pain relief between these two treatment groups.

One of the additional factors involved may be the pre-existing integrity of subchondral bone. Patients with an atrophic form of osteoarthritis, greater subchondral bone pathology and/or susceptibility for subchondral insufficiency fractures may be more at risk for rapidly progressive osteoarthritis with mechanical joint-overloading resulting from the pain reduction associated with tanezumab treatment. This effect may be further exacerbated in the presence of NSAIDs due to interference with normal bone repair processes.[86,87] A similar interaction may explain the large increase in the number of patients treated with tanezumab/ NSAID combination therapy who underwent total joint replacement for reasons other than rapidly progressive osteoarthritis. Worsening microfractures in sclerotic or eburnated bone in the more typical hypertrophic form of osteoarthritis may lead to severe pain and result in a patient's decision to pursue a total joint replacement although the radiologic appearance of the joint would be more typical of end-stage osteoarthritis.[88,89] Evidence to support this mechanical/bone susceptibility hypothesis can be gleaned from published studies evaluating the effect of NSAIDs as a potential cause of analgesic arthropathy or rapidly progressive osteoarthritis, published studies examining the effect of NSAIDs on fracture healing, the

prevalence of subchondral bone defects and subchondral insufficiency fractures in osteoarthritis, the association of tanezumab/NSAID treatment with subchondral insufficiency fractures (Section 6.6) and the effect of tanezumab/ NSAID combination treatment on the incidence of fractures (Section 10.4).

Further, the identification of 9/68 events of pre-existing rapidly progressive osteoarthritis together with the demography and disease characteristics of those patients receiving treatment with tanezumab and adjudicated with rapidly progressive osteoarthritis indicate that an interaction of tanezumab with existing rapidly progressive osteoarthritis or pre-disposing factors may be critically important in initiating or accelerating the process. A large proportion of tanezumab-treated patients with rapidly progressive osteoarthritis were women with an atrophic or hypotrophic form of osteoarthritis of the hip. This predominant phenotype is analogous to that described for patients with rapidly progressive osteoarthritis in all of the published studies on this condition.

8. EFFICACY OF TANEZUMAB IN THE TREATMENT OF OSTEOARTHRITIS

Ten Phase 3 studies were conducted in patients with osteoarthritis of the knee or hip to provide evidence for the efficacy and safety of tanezumab by IV administration in the treatment of the signs and symptoms of osteoarthritis (Table 1). The data provided in this summary are from the Phase 3 osteoarthritis Studies 1011, 1014, 1015, 1018, 1025 and 1030 which were all double-blind, placebo- and/or active-controlled trials of 16 weeks or greater in duration, and intended to enroll 150 or more patients per treatment group. Studies 1011, 1014, 1015 and 1018 were completed as planned and not impacted by the clinical hold. Study 1025 was fully enrolled but the intended 1-year duration of treatment objective was impacted by the clinical hold. Both enrollment and duration of treatment objectives for Study 1030 were impacted by the clinical hold.

The studies included in this analysis of efficacy were randomized, double-blind, double-dummy, placebo- and/or active-controlled studies. Studies 1011, 1014, 1015, 1018 and 1030 were designed to evaluate tanezumab monotherapy, Study 1025 examined tanezumab monotherapy and tanezumab therapy in combination with naproxen 500 mg BID or celecoxib 100 mg BID. In all studies, all pain medications which would confound the assessment of efficacy were prohibited. Only acetaminophen at doses of 4 gm per day for no more than 3 days per week was allowed as rescue medication.

Tanezumab was administered by IV injection at the Baseline clinic visits and at 8 week intervals thereafter. In all studies, patients completed efficacy assessments at Screening, Baseline and Week 2, 4, 8, 12, 16 clinic visits and 8-week intervals thereafter for studies where tanezumab was administered in more than two clinic visits. In all studies except Study 1025, patients completed an average daily pain assessment in the evening via an interactive voice response system. In all studies with exception of Study 1025, patients recorded their daily use of acetaminophen rescue medication in the same manner.

All patients were required to have a diagnosis of knee or hip osteoarthritis by ACR criteria and meet protocol-specified levels of symptomatic disease severity in order to participate in a Phase 3 study of tanezumab. Additional study specific entry criteria included the patient's experience with and response to medications used to treat the signs of symptoms of osteoarthritis. Some studies required patients to be intolerant or insufficiently responsive to NSAIDs and/or to be candidates for invasive procedures such as intra-articular injections or joint replacement while others required that patients were receiving NSAID treatment and receiving at least some benefit prior to study entry.

8.1. Assessment of Efficacy

The analysis of efficacy with tanezumab in the treatment of the signs and symptoms of osteoarthritis incorporated data from a large number of primary and secondary endpoints.

The 3 co-primary efficacy endpoints were change from Baseline to Week 16 with the following:

- WOMAC Pain subscale

- WOMAC Physical Function subscale
- Patient's Global Assessment of Osteoarthritis

The secondary efficacy endpoints included the following:

- WOMAC Pain subscale (Week 2, 4, 8, & 12 analyses)
- WOMAC Physical Function subscale (Week 2, 4, 8, & 12 analyses)
- Patient's Global Assessment of Osteoarthritis (Week 2, 4, 8, & 12 analyses)
- Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) responder index (Week 2, 4, 8, 12, & 16 analyses)
- Treatment response defined as a reduction from Baseline in the WOMAC Pain subscale of ≥30%, ≥50%, ≥70% and ≥90% (Week 2, 4, 8, 12, & 16 analyses)
- Treatment response defined as an improvement from Baseline of ≥2 points in the Patient's Global Assessment of Osteoarthritis (Week 2, 4, 8, 12, & 16 analyses)
- WOMAC Stiffness subscale (Week 2, 4, 8, 12, & 16 analyses)
- Incidence and time to discontinuation due to Lack of Efficacy

In Studies 1011, 1014, and 1025, efficacy results were also collected at 8 week intervals beyond Week 16 consistent with longer treatment intervals in these studies.

The Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index is a tri-dimensional, self-administered questionnaire. The patient responds to 24 component items: five regarding pain, two regarding stiffness, and 17 regarding physical function. Patients were to complete the WOMAC subscale questionnaires at Screening (Pain subscale only) and Baseline (Day 1), as well as, at Weeks 2, 4, 8, 12, 16, and 24 (or Early Termination) and prior to study drug administration at all clinic visits.

The Patient's Global Assessments of Osteoarthritis was a self-administered questionnaire. Patients answered the following question: "Considering all the ways the osteoarthritis in your index knee (or hip) affects you, how are you doing today?" Patients rated their condition using a 5-point Likert scale. Patients were to complete the Patient's Global Assessment of Osteoarthritis questionnaire at Baseline and Weeks 2, 4, 8, 12, 16, and 24 (or Early Termination) and prior to study drug administration.

8.2. Statistical Analysis

Unless otherwise denoted, all efficacy analyses were based on the Intent-to-Treat (ITT) Cohort, which was defined as all randomized patients who took at least one dose of IV study medication (either tanezumab or placebo IV). In those studies where a modified ITT (mITT) cohort was defined, ITT analyses were also conducted and there were no material differences in the results between the two cohorts.

The primary analysis was analysis of covariance (ANCOVA), with the model including Baseline score and treatment group as fixed effects, and study site as a random effect. The baseline observation carried forward (BOCF) method was used for imputing missing values. The treatment contrasts (each tanezumab dose versus placebo) were tested in a step down

manner from highest to lowest dose of tanezumab administered. The test for a lower dose group depended on statistical significance being achieved for the previous comparison. The step-down testing strategy was employed within each of the 3 co-primary efficacy endpoints; then an assessment was made over all 3 co-primary endpoints to establish overall significance for each contrast.

For those studies in which tanezumab dose groups were compared to both placebo and active comparator, the treatment contrasts (each tanezumab dose versus placebo, and each tanezumab dose versus active comparator) were tested in a step down manner in order to maintain the overall type I error for multiple comparisons. The order of treatment comparisons was first to test tanezumab 10 mg versus placebo, and if significant at the 5% level then to test both tanezumab 5 mg versus placebo, and tanezumab 10 mg versus the active comparator, and then finally if both of these tests were significant to test tanezumab 5 mg versus the active comparator. To maintain the type I error, the Hochberg procedure was used for the two comparisons of tanezumab 5 mg versus placebo, and tanezumab 10 mg versus the active comparator, whereby if the largest p-value from these two tests was greater than 0.05, then the significance level used for the remaining test would be the 2.5% two-sided level. In the case that none or only one of these two comparisons was significant (at the 2.5% level) then the final comparison (tanezumab 5 mg versus active comparator) would not be tested. The treatment comparison of active comparator versus placebo was also made, but this is not part of the testing strategy described above.

All statistical comparisons were two-sided, and were made at the 5% level of significance (except under the Hochberg adjustment described above). The step-down assessment strategy maintained Type I error at ≤5% within each of the co primary efficacy endpoints and to <5% for all 3 co-primary efficacy endpoints.

Similarly, to control the Type I error at a level of 5% in Study 1025, statistical significance was established using a combination of fixed sequence testing procedure and Hochberg procedure. The testing strategy within each primary endpoint was to first test contrast (1) tanezumab 10 mg plus NSAID versus NSAID. If this was significant at the two-sided 5% level (where tanezumab 10 mg plus NSAID was superior to NSAID), then both contrasts (2) tanezumab 5 mg plus NSAID versus NSAID, and (3) tanezumab 10 mg versus NSAID were tested simultaneously using the Hochberg procedure (with both contrasts being initially made at the two-sided 5% significance level). If both of these contrasts were significant then the final treatment contrast (4) tanezumab 5 mg versus NSAID was made, also at the two-sided 5% significance level. For a contrast to be declared statistically superior to NSAID it needed to be significant for each of the 3 co-primary endpoints. Regardless of the outcome of the primary analyses, the secondary endpoints were tested.

Additional treatment comparisons for tanezumab 5 mg plus NSAID versus tanezumab 5 mg, and tanezumab 10 mg plus NSAID versus tanezumab 10 mg were performed. As these are secondary treatment comparisons, no adjustment for multiple testing was made. Other treatment comparisons are not shown in this report.

In all studies, the analysis of responder endpoints was the logistic regression for binary data, using the covariates of Baseline score and index joint.

8.3. Comparison of Tanezumab Monotherapy to Placebo Treatment: Primary Efficacy Endpoints

Across the 3 co-primary measures of efficacy in the four completed Phase 3 studies, tanezumab doses of 2.5 mg, 5 mg, and 10 mg provided significant improvement over placebo treatment as shown in Table 23 and Table 24. All of the tanezumab doses tested were consistently efficacious. In Studies 1011 and 1014, the degree of mean improvement across the three efficacy domains was similar and generally dose ordered with tanezumab 10 mg providing the greatest mean response in each of the 6 comparisons to placebo treatment although only small differences in the magnitude of response were evident among the three doses of tanezumab. In Studies 1015 and 1018, tanezumab 5 mg provided modestly greater mean improvement over tanezumab 10 mg across most of the co-primary endpoints.

In each of these four studies, the mean Baseline WOMAC Pain subscale scores exceeded 7 on a scale of 0 to 10 indicating a patient population with severe pain on average prior to study entry. The mean reduction in pain with tanezumab treatment was typically 3 points or greater yielding an improvement in pain on average from severe to nearly mild in severity. This reduction in pain was associated with equally impressive improvements in function and global well being.

Naproxen 500 mg BID, the highest approved dose for the management of osteoarthritis signs and symptoms, was included as an active control in Studies 1015 and 1018. In contrast to tanezumab, naproxen treatment did not result in consistent improvement with evidence of efficacy isolated to a significant reduction in pain and function in a single study.

Table 23. Co-Primary Endpoints in Studies 1011 and 1014

	Study 1011			Study 1014		
Treatment Group	**N**	**Baseline**	**Change at Week 16**	**N**	**Baseline**	**Change at Week 16**
WOMAC OA Index: Pain Subscale (LS Mean Score)						
Placebo	154	7.1	-2.4	154	7.3	-1.6
tanezumab 2.5 mg	154	7.2	-3.2*	151	7.2	-2.9***
tanezumab 5 mg	156	7.2	-3.3**	150	7.2	-3.3***
tanezumab 10 mg	154	7.0	-3.6***	156	7.3	-3.4***
WOMAC OA Index: Physical Function Subscale (LS Mean Score)						
placebo	154	6.6	-2.0	154	6.8	-1.4
tanezumab 2.5 mg	154	6.9	-2.8**	151	6.8	-2.6***
tanezumab 5 mg	156	6.9	-3.0***	150	6.8	-2.9***
tanezumab 10 mg	154	6.7	-3.3***	156	6.8	-3.0***
Patient's Global Assessment of Osteoarthritis (LS Mean Score)						
placebo	154	3.4	-0.5	154	3.5	-0.3
tanezumab 2.5 mg	154	3.5	-0.8***	151	3.6	-0.7***
tanezumab 5 mg	156	3.5	-0.9***	150	3.5	-0.8***
tanezumab 10 mg	154	3.5	-1.0***	156	3.5	-0.8***

mITT cohort; BOCF
* $p \leq 0.05$; ** $p \leq 0.01$; ***$p \leq 0.001$ versus placebo treatment

Table 24. Co-Primary Endpoints in Studies 1015 and 1018

	Study 1015			Study 1018		
Treatment Group	**N**	**Baseline**	**Change at Week 16**	**N**	**Baseline**	**Change at Week 16**
WOMAC OA Index: Pain Subscale (LS Mean Score)						
Placebo	200	7.2	-2.2	209	7.4	-1.8
tanezumab 5 mg	202	7.3	-3.5*** $^{++}$	211	7.3	-3.0*** $^{++}$
tanezumab 10 mg	203	7.3	-3.2***	209	7.4	-2.6**
naproxen 500 mg BID	200	7.2	-2.7*	211	7.3	-2.3
WOMAC OA Index: Physical Function Subscale (LS Mean Score)						
Placebo	200	6.9	-1.9	209	7.0	-1.5
tanezumab 5 mg	202	6.9	-3.1*** $^{++}$	211	6.8	-2.7*** $^{++}$
tanezumab 10 mg	203	6.9	-2.9*** $^{+}$	209	7.1	-2.5*** $^{+}$
naproxen 500 mg bid	200	6.9	-2.4*	211	7.0	-1.9
Patient's Global Assessment of Osteoarthritis (LS Mean Score)						
Placebo	200	3.4	-0.5	209	3.5	-0.4
tanezumab 5 mg	202	3.4	-0.9*** $^{+}$	211	3.4	-0.7*** $^{+}$
tanezumab 10 mg	203	3.4	-0.8*	209	3.4	-0.7*** $^{+}$
naproxen 500 mg bid	200	3.4	-0.7	211	3.5	-0.5

mITT cohort (Study 1015 and ITT cohort (Study 1018); BOCF
*p≤0.05; **p≤0.01; ***p≤0.001 versus placebo treatment
$^{+}$p≤0.05; $^{++}$p≤0.01; $^{+++}$p≤0.001 versus naproxen treatment

The efficacy results of Study 1030 are provided in Table 25. This Phase 3 study evaluated the safety and efficacy of tanezumab in patients with osteoarthritis of the hip or knee. The primary objective of the study was to demonstrate superior efficacy of tanezumab 5 mg and 10 mg by IV administration versus placebo treatment and oxycodone controlled release (CR) treatment at Week 16 with WOMAC Pain as the primary efficacy endpoint.

The study was discontinued due to the clinical hold of 23 June 2010. When the study was terminated, 614 (77%) of the originally planned 800 patients were randomized. Approximately 62% (499 patients) of the originally planned 800 patients completed Week 8 of the study and 109 patients completed the full duration of the study. As a result, the landmark analysis of the primary endpoint was amended from Week 16 to Week 8 in the protocol and the statistical analysis plan while the study was blinded. The primary method of imputation was also amended at the same time from BOCF to LOCF. The patient cohort was maintained as ITT which was defined as all randomized patients who received IV study medication (either tanezumab or IV placebo).

Tanezumab 5 mg and 10 mg administration produced significantly greater improvement compared to placebo treatment in the WOMAC Pain subscale as well as the WOMAC Physical Function subscale and the Patient's Global Assessment of Osteoarthritis (Table 25). A similar degree of improvement was observed with both doses.

Oxycodone CR 10 mg to 40 mg BID (20 to 80 daily) was included as an active control in Study 1030. Dose adjustments of oxycodone CR were allowed to be carried out every 1 to 2 days and the dose could be adjusted by up to 50% of the current dose at each increase. The doses were permitted to be increased or decreased throughout the course of the study

according to tolerability and pain relief. In contrast to tanezumab, oxycodone CR treatment failed to provide improvement in any of the efficacy measures summarized in Table 25.

Table 25. Efficacy Results Observed in Study 1030

Study 1030			
Treatment Group	**N**	**Baseline**	**Change at Week 8**
WOMAC OA Index: Pain Subscale (LS Mean Score)			
placebo	141	7.8	-2.6
tanezumab 5 mg	161	7.9	-3.6*** $^{+++}$
tanezumab 10 mg	150	7.6	-3.6*** $^{+++}$
oxycodone CR 10-40 mg BID	158	7.9	-2.6
WOMAC OA Index: Physical Function Subscale (LS Mean Score)			
placebo	141	7.2	-1.9
tanezumab 5 mg	161	7.3	-3.1*** $^{+++}$
tanezumab 10 mg	150	7.0	-3.1*** $^{+++}$
oxycodone CR 10-40 mg BID	158	7.3	-2.1
Patient's Global Assessment of Osteoarthritis (LS Mean Score)			
placebo	141	3.6	-0.5
tanezumab 5 mg	161	3.6	-0.9*** $^{+++}$
tanezumab 10 mg	150	3.6	-1.0*** $^{+++}$
oxycodone CR 10-40 mg BID	158	3.6	-0.6

ITT cohort; LOCF
* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$ versus placebo treatment
$^{+}$ $p \leq 0.05$; $^{++}$ $p \leq 0.01$; $^{+++}$ $p \leq 0.001$ versus oxycodone CR treatment

8.4. Comparison of Tanezumab Monotherapy or Combination Therapy to Active Treatment: Primary Efficacy Endpoints

The efficacy responses with tanezumab monotherapy were compared with treatment with naproxen 500 mg BID in Studies 1015 and 1018 and to oxycodone CR 10-40 mg BID in Study 1030. In each case, these comparisons were pre-specified in the protocol and statistical analysis plans. In addition to these 3 studies, pre-specified comparisons of tanezumab monotherapy to either naproxen 500 mg BID or celecoxib 100 mg BID were made in Study 1025.

Pre-specified comparisons of tanezumab as combination (or adjunctive) therapy with NSAIDs versus NSAID treatment alone were performed in Study 1025. Two different NSAIDs were evaluated in this regard; naproxen 500 mg BID and celecoxib 100 mg BID.

In Study 1025 patients treated with either naproxen 500 mg BID or celecoxib 200 mg/day (100 mg BID or 200 mg QD) and receiving only partial benefit but otherwise tolerating the medications well were randomized in a double-blind, double-dummy fashion to one of five treatment groups; (1) tanezumab 5 mg IV, (2) tanezumab 10 mg IV, (3) tanezumab 5 mg IV plus NSAID, (4) tanezumab 10 mg IV plus NSAID, or (5) NSAID alone (placebo IV). Those patients receiving naproxen prior to study entry (the naproxen cohort) received naproxen 500 mg BID if randomized to treatment groups (3), (4) or (5) or matching placebo treatment if randomized to treatment groups (1) or (2). Similarly, patients receiving celecoxib prior to study entry (the celecoxib cohort) received celecoxib 100 mg BID if randomized to treatment groups (3), (4) or (5) or matching placebo treatment if randomized to treatment groups (1) or (2). For those patients randomized to treatment groups (1) or (2),

their NSAID treatment was tapered off in a double-blind fashion during the course of the first 2 weeks following randomization.

As shown in Table 24 above, in Studies 1015 and 1018 tanezumab 5 mg and 10 mg provided greater improvement over treatment with naproxen 500 mg BID as evidenced by nine of twelve statistically significant contrasts of the co-primary endpoints between tanezumab and naproxen including all 6 contrasts between tanezumab 5 mg and naproxen. Tanezumab 10 mg provided significant improvement over naproxen in the WOMAC Physical Function efficacy measure in both studies and in the Patient's Global Assessment of Osteoarthritis efficacy measure in one study (Study 1018).

Unexpectedly, tanezumab 5 mg was generally associated marginally greater improvement across the efficacy domains when compared to tanezumab 10 mg at the Week 16 landmark analysis in both studies. However, as evidenced by the WOMAC pain subscale results over Weeks 2-16, the efficacy results for the two doses were not the same across the two studies. In Study 1015, tanezumab 10 mg provided greater efficacy than tanezumab 5 mg through the first 8 weeks and then was surpassed by tanezumab 5 mg whereas tanezumab 5 mg marginally but consistently outperformed tanezumab 10 mg throughout in Study 1018.

A key objective of Study 1015 and 1018 was to compare the efficacy of tanezumab 5 mg and 10 mg versus naproxen 500 mg bid for the symptomatic treatment of osteoarthritis. To control the type 2 error rate for multiple comparisons, fixed sequence (step down) testing and the Hochberg procedure were predefined to begin with the highest dose (tanezumab 10 mg) followed by tanezumab 5 mg. As a result, despite replicate statistically significant differences with tanezumab 5 mg versus naproxen across 3 co-primary endpoints, a total of 6 comparisons, it is only possible to conclude statistically that tanezumab was superior to naproxen with respect to physical function in both studies and the patient global assessment in one study.

The co-primary efficacy endpoints in Study 1025 were the WOMAC Pain, WOMAC Physical Function and Patient's Global Assessment of Osteoarthritis at the Week 16 landmark analysis. The efficacy objectives of the study were not impacted by the clinical hold as all but 5 patients had the opportunity to complete 16 weeks (4 months) of treatment. The results of the primary efficacy endpoints are provided in Table 26, Figure 21, and Figure 22. Tanezumab 5 mg and 10 mg produced superior improvement in pain and physical function over both naproxen 500 mg BID and celecoxib 100 mg BID; treatment differences in the Patient's Global Assessment of Osteoarthritis did not reach statistical significance. The observed magnitude of improvement was similar with both doses.

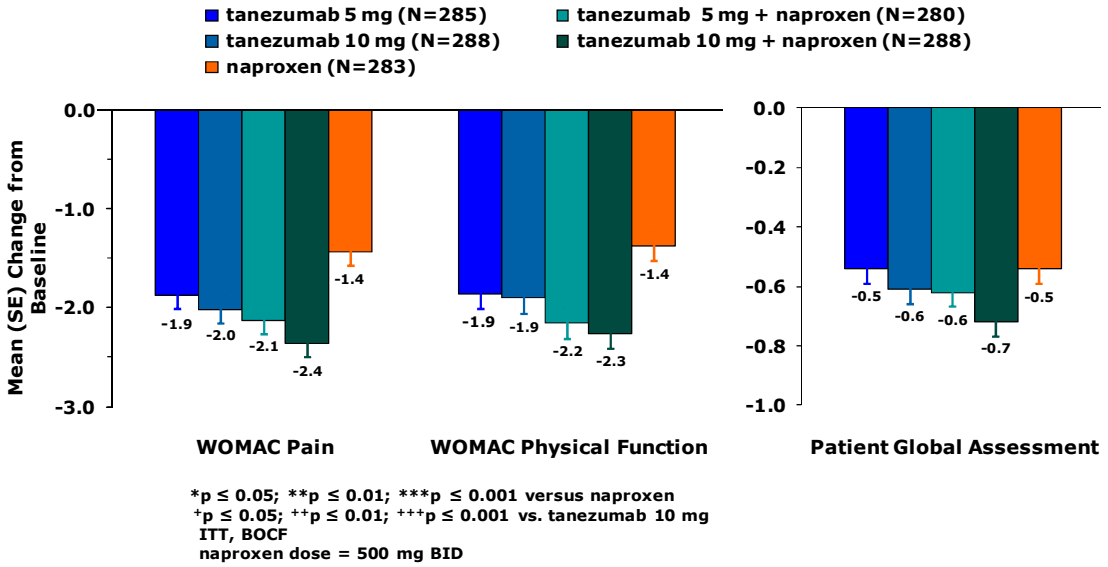
There were two isolated statistically significant differences between tanezumab/NSAID combination therapy and tanezumab monotherapy. Tanezumab 10 mg/NSAID combination therapy was superior to tanezumab 10 mg monotherapy with the WOMAC Physical Function subscale in the naproxen cohort and the Patient's Global Assessment of Osteoarthritis in the celecoxib cohort.

Table 26. Co-Primary Efficacy Endpoints in Study 1025

	Study 1025 Naproxen 500 mg BID Cohort			Study 1025 Celecoxib 100 mg BID Cohort		
Treatment Group	**N**	**Baseline**	**Change at Week 16**	**N**	**Baseline**	**Change at Week 16**
WOMAC OA Index: Pain Subscale (LS Mean Score)						
tanezumab 5 mg	285	6.4	-1.9*	256	6.5	-2.0**
tanezumab 10 mg	288	6.5	-2.0***	254	6.4	-2.1**
tanezumab 5 mg + NSAID	280	6.5	-2.1***	256	6.4	-2.2***
tanezumab 10 mg + NSAID	288	6.3	-2.4***	254	6.3	-2.4***
NSAID	283	6.3	-1.4	256	6.3	-1.5
WOMAC OA Index: Physical Function Subscale (LS Mean Score)						
tanezumab 5 mg	285	6.5	-1.9**	256	6.7	-2.1**
tanezumab 10 mg	288	6.5	-1.9**	254	6.6	-2.0**
tanezumab 5 mg + NSAID	280	6.6	-2.2***	256	6.6	-2.2***
tanezumab 10 mg + NSAID	288	6.4	-2.3*** +	254	6.4	-2.4***
NSAID	283	6.3	-1.4	256	6.5	-1.4
Patient's Global Assessment of Osteoarthritis (LS Mean Score)						
tanezumab 5 mg	285	3.4	-0.5	256	3.4	-0.7
tanezumab 10 mg	288	3.4	-0.6	254	3.5	-0.6
tanezumab 5 mg + NSAID	280	3.4	-0.6	256	3.5	-0.7**
tanezumab 10 mg + NSAID	288	3.4	-0.7**	254	3.4	-0.8** +
NSAID	283	3.4	-0.5	256	3.4	-0.5

ITT cohort, BOCF
* p≤ 0.05; ** p≤ 0.01; *** p≤ 0.001 versus naproxen or celecoxib treatment
+ p≤ 0.05; ++ p≤ 0.01; +++ p≤ 0.001 versus tanezumab treatment

Figure 21. WOMAC Pain and Physical Function Subscales and Patient's Global Assessment of Osteoarthritis: Change from Baseline to Week 16 in Study 1025 – Naproxen Cohort

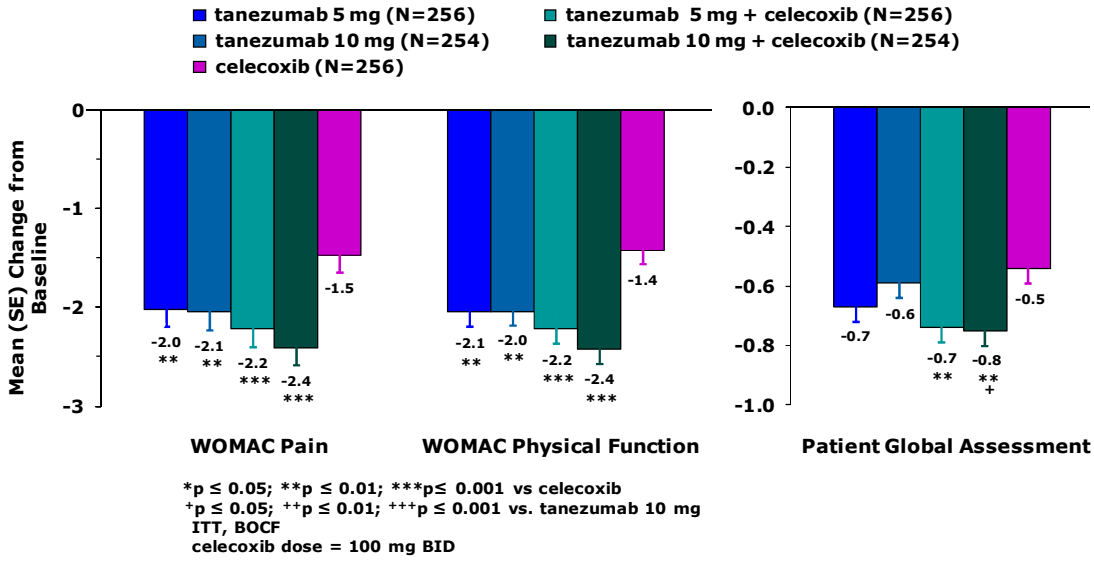


Tanezumab 5 mg or 10 mg in combination with naproxen or celecoxib provided a significant efficacy benefit over treatment with either NSAID alone. A superior reduction in pain and improvement in physical function and global well-being were observed with tanezumab

10 mg when added to either naproxen or celecoxib compared to either drug alone. A similar response was observed with tanezumab 5 mg adjunctive therapy. All treatment comparisons to NSAID treatment alone were statistically superior with exception of the Patient's Global Assessment of Osteoarthritis in the naproxen cohort. The observed magnitude of effect was marginally, but consistently, greater with tanezumab 10 mg/NSAID combination treatment than with tanezumab 5 mg/NSAID combination treatment.

The addition of tanezumab 5 mg or 10 mg to NSAID treatment did not provide substantial benefit over tanezumab 5 mg or 10 mg monotherapy, respectively. Only one statistically significant treatment difference was observed.

Figure 22. WOMAC Pain and Physical Function Subscales and Patient's Global Assessment of Osteoarthritis: Change from Baseline to Week 16 in Study 1025 - Celecoxib Cohort



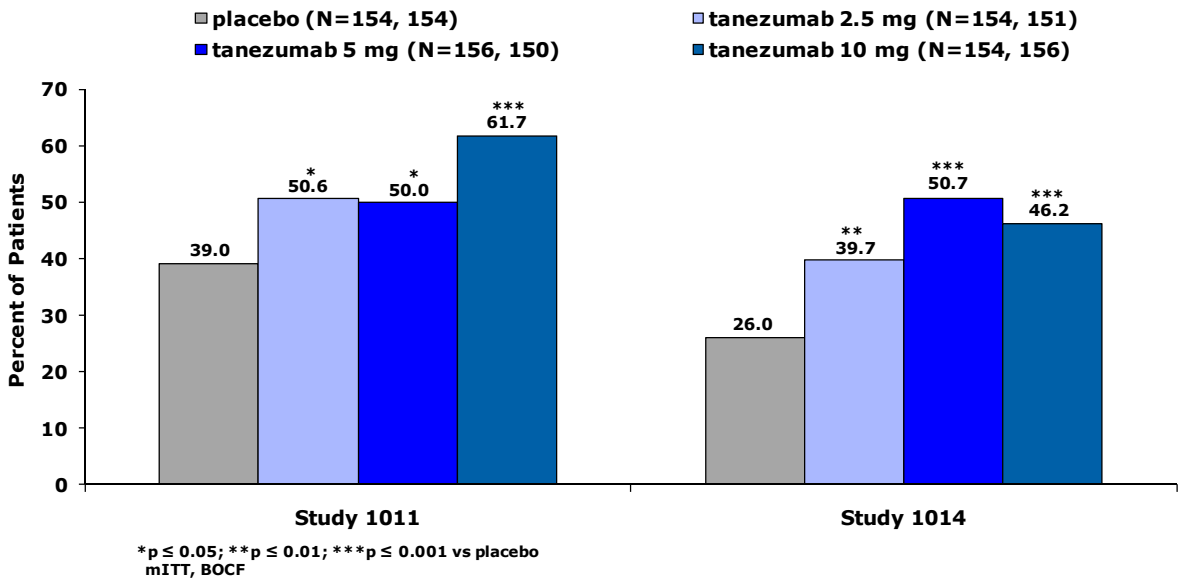
In all of the studies reviewed in this section thus far, tanezumab was compared to NSAID administration. As described above, oxycodone CR was included as the active control in Study 1030. The efficacy results of Study 1030 are provided above in Table 25. A key objective of this study was to demonstrate that tanezumab 5 mg and tanezumab 10 mg were superior, or at a minimum non-inferior, to oxycodone CR in the treatment of osteoarthritis. This objective was achieved. All four comparisons were statistically significant at Week 8; noninferiority of tanezumab 10 mg versus oxycodone CR, superiority of tanezumab 10 mg versus oxycodone CR (p=0.018), non-inferiority of tanezumab 5 mg versus oxycodone CR, and superiority of tanezumab 5 mg versus oxycodone CR (p<0.001). Treatment with tanezumab 10 mg did not provide additional efficacy benefit above that observed with tanezumab 5 mg treatment.

8.5. Responder Analyses

The clinical significance of the reduction in pain with tanezumab treatment was assessed by the evaluation of patient responder rates using a categorical assessment of the WOMAC Pain subscale results, the OMERACT-OARSI Responder Index and a 2-grade or larger categorical improvement in the Patient's Global Assessment of Osteoarthritis. All responder analyses were determined with BOCF imputation unless otherwise noted.

These responder analyses for Studies 1011 and 1014 are summarized in Figure 23 and Table 27. Statistically significant response rates compared to placebo treatment were demonstrated at Week 16 with all tanezumab doses for the percentage of patients with reductions in pain ≥30%, ≥50%, ≥70%, and ≥90% on the WOMAC Pain subscale in both studies with one exception. The odds ratio in favor of tanezumab 10 mg was ≥2 at all response levels. Over 20% of the patients in each study reported a ≥90% reduction in pain at Week 16 with tanezumab 10 mg.

Figure 23. WOMAC Pain Subscale: Patients with a ≥ 50% Reduction in Pain at Week 16 in Studies 1011 and 1014



The proportion of responders based upon the OMERACT-OARSI criteria was also significantly greater with tanezumab compared to placebo treatment. The Week 16 odds ratio in favor of tanezumab treatment ranged from 1.85 with tanezumab 2.5 mg to 3.60 with tanezumab 10 mg. Finally, there was a statistically significant greater proportion of patients with a 2-grade or larger categorical improvement in the Patient's Global Assessment of Osteoarthritis with tanezumab 5 mg and 10 mg compared to placebo treatment at Week 16 in both studies. The improved response with tanezumab 2.5 mg over placebo treatment met statistical significance in Study 1011 only. The odds ratio in favor of tanezumab ranged from 1.96 with tanezumab 5 mg to 5.51 with tanezumab 10 mg. Over 20% of patients treated with either tanezumab 5 mg or 10 mg improved by 2 or more categorical units at Week 16 in both

studies. In summary, there was consistent demonstration of the clinical significance of the analgesic efficacy for all doses of tanezumab across these various response measures. The best results were observed with tanezumab 10 mg.

Table 27. Responder Analyses for Studies 1011 and 1014

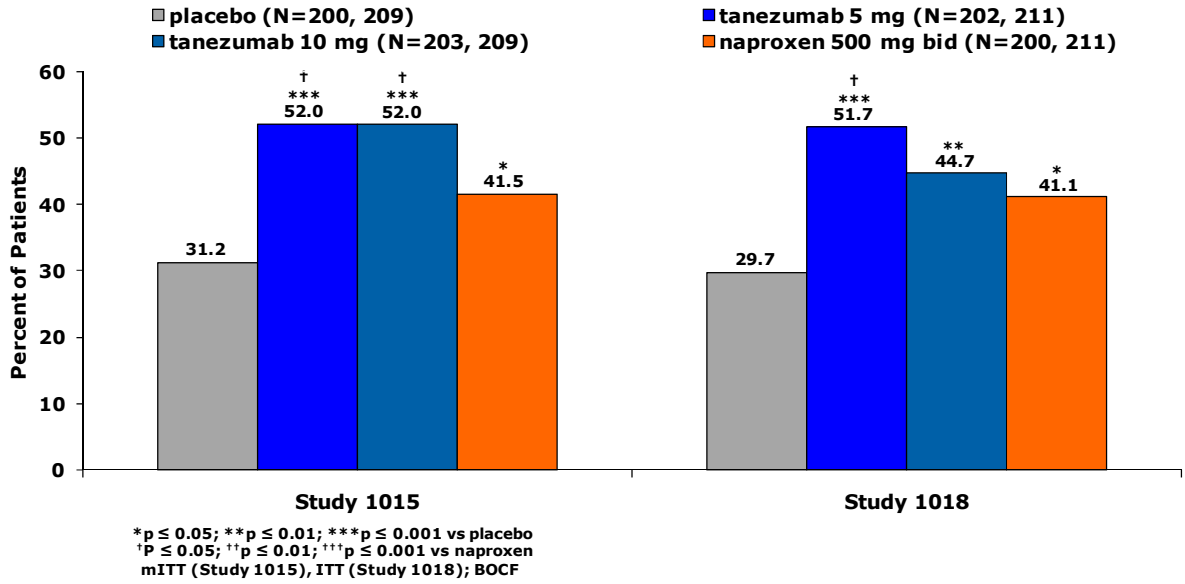
Treatment Group	Study 1011			Study 1014		
	N	Week 16 % of patients	Odds ratio [95% CI] vs placebo	N	Week 16 % of patients	Odds ratio [95% CI] vs placebo
WOMAC OA Index: Pain Subscale (30% response rate)						
placebo	154	51.3		154	32.5	
tanezumab 2.5 mg	154	64.3*	1.72 [1.09, 2.72]	151	56.3***	2.71 [1.70, 4.33]
tanezumab 5 mg	156	65.4*	1.81 [1.15, 2.86]	150	63.3***	3.60 [2.24, 5.78]
tanezumab 10 mg	154	68.2**	2.03 [1.28, 3.23]	156	61.5***	3.41 [2.13, 5.45]
WOMAC OA Index: Pain Subscale (50% response rate)						
placebo	154	39.0		154	26.0	
tanezumab 2.5 mg	154	50.6*	1.62 [1.03, 2.54]	151	39.7**	1.89 [1.16, 3.08]
tanezumab 5 mg	156	50.0*	1.58 [1.00, 2.48]	150	50.7***	2.93 [1.81, 4.75]
tanezumab 10 mg	154	61.7***	2.52 [1.59, 3.98]	156	46.2***	2.49 [1.54, 4.02]
WOMAC OA Index: Pain Subscale (70% response rate)						
placebo	154	23.4		154	13.6	
tanezumab 2.5 mg	154	33.1	1.64 [0.99, 2.72]	151	28.5**	2.54 [1.42, 4.54]
tanezumab 5 mg	156	39.1**	2.14 [1.31, 3.51]	150	36.7***	3.68 [2.09, 6.51]
tanezumab 10 mg	154	44.2***	2.59 [1.58, 4.23]	156	35.3***	3.53 [2.00, 6.24]
WOMAC OA Index: Pain Subscale (90% response rate)						
placebo	154	5.2		154	4.5	
tanezumab 2.5 mg	154	14.9**	3.21 [1.39, 7.44]	151	13.2*	3.20 [1.31, 7.84]
tanezumab 5 mg	156	12.8*	2.69 [1.15, 6.32]	150	18.0***	4.63 [1.95, 11.0]
tanezumab 10 mg	154	24.0***	5.76 [2.58, 12.9]	156	20.5***	5.56 [2.37, 13.1]
OMERACT-OARSI Response Rate						
placebo	154	53.9		154	35.1	
tanezumab 2.5 mg	154	68.2**	1.85 [1.16, 2.94]	151	57.3***	2.48 [1.56, 3.95]
tanezumab 5 mg	156	69.9**	2.00 [1.26, 3.19]	150	65.3***	3.50 [2.18, 5.61]
tanezumab 10 mg	154	70.8**	2.07 [1.29, 3.31]	156	65.8***	3.60 [2.25, 5.76]
Patient's Global Assessment (Patients with ≥ 2 Grade Improvement)						
placebo	154	13.6		154	7.1	
tanezumab 2.5 mg	154	24.7*	2.02 [1.09, 3.74]	151	14.7	2.10 [0.96, 4.58]
tanezumab 5 mg	156	23.7*	1.96 [1.05, 3.65]	150	20.0**	3.27 [1.54, 6.94]
tanezumab 10 mg	154	30.5***	2.93 [1.60, 5.37]	156	27.7***	5.51 [2.66, 11.4]

mITT cohort; BOCF
* p≤ 0.05; ** p≤ 0.01; *** p≤ 0.001 versus placebo treatment

The responder analyses for Studies 1015 and 1018 are summarized in Figure 24 and Table 28. Across all responder indices in Studies 1015 and 1018, tanezumab 5 mg was generally associated with a modest but consistently greater level of improvement over tanezumab 10 mg.

In both studies, statistically significant response rates compared with placebo treatment were demonstrated at Week 16 with both tanezumab doses for the percentage of patients with reductions in pain ≥30%, ≥50%, and ≥70% in the WOMAC Pain subscale. The proportion of patients reporting ≥90% reduction in pain with tanezumab 5 mg or 10 mg was also greater than patients receiving placebo treatment and in Study 1015 the treatment differences met statistical significance. Taken together, over 30% of the patients receiving tanezumab in these two studies reported ≥70% reduction in pain and 13 to 19% had ≥90% response.

Figure 24. WOMAC Pain Subscale: Patients with a ≥ 50% Reduction in Pain at Week 16 in Studies 1015 and 1018



Treatment with naproxen 500 mg BID was associated with improved response rates versus placebo treatment for ≥30% and ≥50% only.

The proportion of responders based upon the OMERACT-OARSI criteria was significantly greater with tanezumab compared to placebo treatment with odds ratio favoring tanezumab treatment ranging from 1.70 to 2.51. There was also a statistically significant greater proportion of patients with a 2-grade or larger categorical improvement in the Patient's Global Assessment of Osteoarthritis with tanezumab 5 mg compared to placebo treatment at Week 16 in both studies and with tanezumab 10 mg in Study 1018.

Across all responder indices, tanezumab 5 mg and 10 mg resulted in consistently greater proportion of responding patients as compared to treatment with naproxen 500 mg BID with many comparisons meeting statistical significance. Tanezumab 5 mg was statistically superior to naproxen treatment in both studies for reductions in pain ≥30%, ≥50%, and ≥70% in the WOMAC Pain subscale, ≥90% in Study 1015, and the OMERACT-OARSI Responder Index in Study 1018. Tanezumab 10 mg was statistically superior to naproxen treatment in Study 1015 for reductions in pain ≥50%, ≥70% and ≥90% in the WOMAC Pain subscale.

Table 28. Responder Analyses for Studies 1015 and 1018

Treatment Group	Study 1015			Study 1018		
	N	Week 16 % of patients	Odds ratio [95% CI] vs placebo	N	Week 16 % of patients	Odds ratio [95% CI] vs placebo
WOMAC OA Index: Pain Subscale (30% response rate)						
placebo	200	42.7		209	39.2	
tanezumab 5 mg	202	65.8*** +	2.63 [1.75, 3.95]	211	62.1*** +	2.56 [1.72, 3.79]
tanezumab 10 mg	203	59.4***	1.98 [1.33, 2.95]	209	52.9**	1.74 [1.18, 2.57]
naproxen 500 mg BID	200	55.5*	1.67 [1.12, 2.49]	211	51.7*	1.66 [1.12, 2.45]
WOMAC OA Index: Pain Subscale (50% response rate)						
placebo	200	31.2		209	29.7	
tanezumab 5 mg	202	52.0*** +	2.45 [1.63, 3.70]	211	51.7*** +	2.57 [1.72, 3.85]
tanezumab 10 mg	203	52.0*** +	2.43 [1.61, 3.67]	209	44.7**	1.93 [1.28, 2.89]
naproxen 500 mg BID	200	41.5*	1.57 [1.04, 2.37]	211	41.1*	1.66 [1.10, 2.49]
WOMAC OA Index: Pain Subscale (70% response rate)						
Placebo	200	22.1		209	19.6	
tanezumab 5 mg	202	39.1*** ++	2.31 [1.49, 3.59]	211	38.9*** +++	2.63 [1.69, 4.09]
tanezumab 10 mg	203	37.6*** +	2.15 [1.39, 3.35]	209	29.3*	1.70 [1.08, 2.68]
naproxen 500 mg BID	200	26.0	1.24 [0.78, 1.96]	211	23.7	1.27 [0.80, 2.03]
WOMAC OA Index: Pain Subscale (90% response rate)						
Placebo	200	8.0		209	8.6	
tanezumab 5 mg	202	18.8** +	2.69 [1.44, 5.00]	211	13.3	1.63 [0.87, 3.06]
tanezumab 10 mg	203	17.8** +	2.50 [1.34, 4.68]	209	13.9	1.72 [0.92, 3.21]
naproxen 500 mg BID	200	11.0	1.41 [0.72, 2.78]	211	9.2	1.07 [0.55, 2.11]
OMERACT-OARSI Response Rate						
placebo	200	50.3		209	42.6	
tanezumab 5 mg	202	66.3***	1.97 [1.32, 2.96]	211	64.9*** +	2.51 [1.69, 3.72]
tanezumab 10 mg	203	63.9**	1.76 [1.18, 2.63]	209	55.8**	1.70 [1.15, 2.51]
naproxen 500 mg BID	200	61.0*	1.55 [1.04, 2.30]	211	53.1*	1.52 [1.03, 2.25]
Patient's Global Assessment (Patients with ≥ 2 Grade Improvement)						
placebo	200	13.5		209	12.4	
tanezumab 5 mg	202	25.2**	2.38 [1.38, 4.11]	211	21.8***	2.74 [1.54, 4.87]
tanezumab 10 mg	203	19.8	1.74 [0.99, 3.04]	209	22.6***	2.68 [1.52, 4.75]
naproxen 500 mg BID	200	19.5	1.56 [0.89, 2.73]	211	19.3*	1.80 [1.01, 3.22]

mITT cohort (Study 1015) and ITT cohort (Study 1018); BOCF
* p≤ 0.05; ** p≤ 0.01; *** p≤ 0.001 versus placebo treatment
+ p≤ 0.05; ++ p≤ 0.01; +++ p≤ 0.001 versus naproxen treatment

In Study 1025, tanezumab 5 mg and 10 mg also resulted in a greater proportion of responding patients compared to naproxen 500 mg BID or celecoxib 100 mg BID (Table 29, Figure 25 and Figure 26). Statistically significant response rates compared to either naproxen or celecoxib treatment were demonstrated at Week 16 with both tanezumab doses for the percentage of patients with reductions in pain ≥30%, ≥50%, and ≥70% with WOMAC Pain subscale. Tanezumab 5 mg also resulted in a higher percentage of patients achieving a ≥90% reduction in pain versus both naproxen and celecoxib while with tanezumab 10 mg the improvement was significant versus naproxen only. The proportion of patients achieving an OMERACT-OARSI response rate with tanezumab 10 mg was significantly greater than celecoxib. There was also a statistically significant greater proportion of patients with a 2-. grade or larger categorical improvement in the Patient's Global Assessment of Osteoarthritis with tanezumab 10 mg compared to naproxen treatment

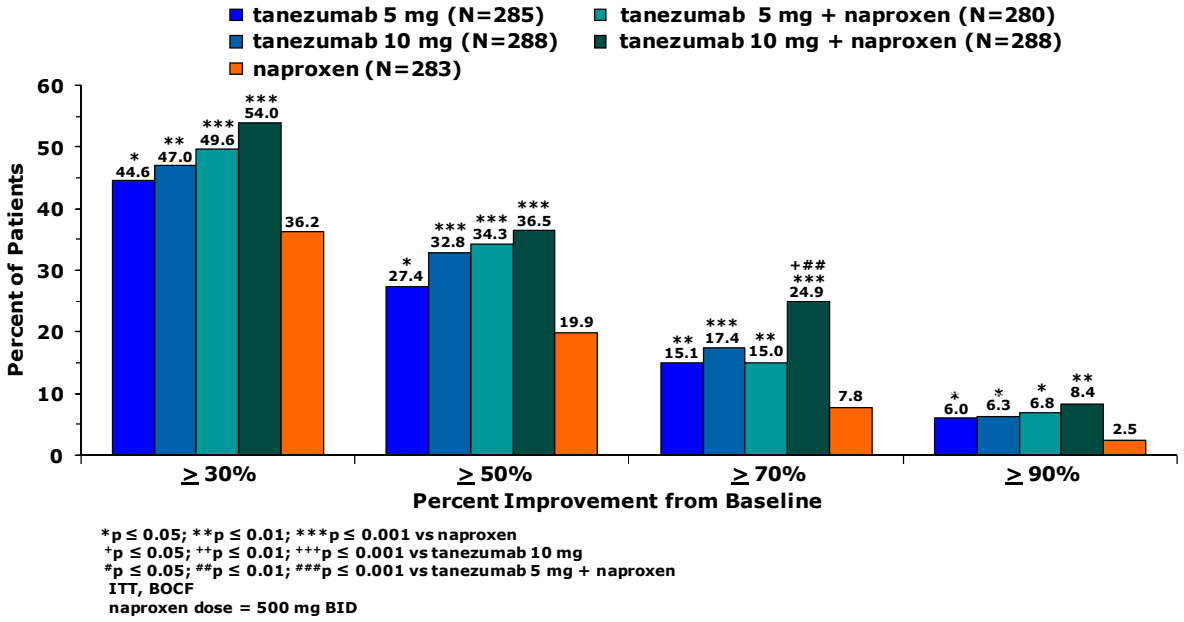
Table 29. Responder Analyses for Study 1025

Treatment Group	Study 1025 Naproxen 500 mg BID Cohort			Study 1025 Celecoxib 100 mg BID Cohort		
	N	Week 16 % of patients	Odds ratio [95% CI] vs naproxen	N	Week 16 % of patients	Odds ratio [95% CI] vs celecoxib
WOMAC OA Index: Pain Subscale (30% response rate)						
tanezumab 5 mg	285	44.6*	1.43 [1.02, 2.00]	256	48.0*	1.44 [1.01, 2.04]
tanezumab 10 mg	288	47.0**	1.58 [1.13, 2.22]	254	48.8*	1.48 [1.04, 2.11]
tanezumab 5 mg + NSAID	280	49.6***	1.76 [1.25, 2.47]	256	52.9**	1.75 [1.23, 2.48]
tanezumab 10 mg + NSAID	288	54.0***	2.08 [1.49, 2.92]	254	54.3***	1.84 [1.29, 2.62]
NSAID	283	36.2		256	39.2	
WOMAC OA Index: Pain Subscale (50% response rate)						
tanezumab 5 mg	285	27.4*	1.53 [1.03, 2.26]	256	35.0**	1.68 [1.14, 2.47]
tanezumab 10 mg	288	32.8***	1.99 [1.35, 2.91]	254	35.0**	1.68 [1.14, 2.47]
tanezumab 5 mg + NSAID	280	34.3***	2.13 [1.45, 3.13]	256	37.6***	1.88 [1.28, 2.76]
naproxen 10 mg + NSAID	288	36.5***	2.33 [1.59, 3.40]	254	42.5***	2.30 [1.57, 3.36]
NSAID	283	19.9		256	24.3	
WOMAC OA Index: Pain Subscale (70% response rate)						
tanezumab 5 mg	285	15.1**	2.15 [1.24, 3.70]	256	20.1***	2.32 [1.39, 3.88]
tanezumab 10 mg	288	17.4***	2.61 [1.53, 4.45]	254	18.1**	2.04 [1.21, 3.44]
tanezumab 5 mg + NSAID	280	15.0**	2.18 [1.26, 3.77]	256	22.0***	2.60 [1.56, 4.32]
tanezumab 10 mg + NSAID	288	24.9***+##	4.03 [2.41, 6.73]	254	24.8***	3.04 [1.84, 5.02]
NSAID	283	7.8		256	9.8	
WOMAC OA Index: Pain Subscale (90% response rate)						
tanezumab 5 mg	285	6.0*	2.55 [1.04, 6.26]	256	7.5*	2.87 [1.18, 6.96]
tanezumab 10 mg	288	6.3*	2.76 [1.13, 6.73]	254	5.9	2.23 [0.89, 5.56]
tanezumab 5 mg + NSAID	280	6.8*	3.01 [1.24, 7.30]	256	7.8*	3.02 [1.25, 7.27]
tanezumab 10 mg + NSAID	288	8.4**	3.70 [1.56, 8.75]	254	12.6*** +	5.10 [2.21, 11.8]
NSAID	283	2.5		256	2.7	
OMERACT-OARSI Response Rate						
tanezumab 5 mg	285	52.3	1.34 [0.96, 1.86]	256	55.1	1.35 [0.95, 1.91]
tanezumab 10 mg	288	53.0	1.38 [0.99, 1.92]	254	55.9*	1.42 [1.00, 2.01]
tanezumab 5 mg + NSAID	280	56.8**	1.61 [1.15, 2.24]	256	59.8**	1.66 [1.17, 2.36]
tanezumab 10 mg + NSAID	288	60.1***	1.82 [1.30, 2.53]	254	63.4***	1.95 [1.37, 2.78]
NSAID	283	45.2		256	47.3	
Patient's Global Assessment (Patients with ≥ 2 Grade Improvement)						
tanezumab 5 mg	285	14.8	1.50 [0.89, 2.55]	256	18.4	1.35 [0.81, 2.26]
tanezumab 10 mg	288	19.1**	2.08 [1.25, 3.46]	254	15.4	0.99 [0.58, 1.69]
tanezumab 5 mg + NSAID	280	16.4*	1.74 [1.03, 2.94]	256	20.0	1.47 [0.88, 2.45]
tanezumab 10 mg + NSAID	288	22.5***	2.67 [1.62, 4.41]	254	18.2	1.40 [0.84, 2.35]
NSAID	283	10.6		256	13.4	

ITT cohort, BOCF
* p≤ 0.05; ** p≤ 0.01; *** p≤ 0.001 versus naproxen or celecoxib treatment
+ p≤ 0.05; ++ p≤ 0.01; +++ p≤ 0.001 versus tanezumab 10 mg treatment
# p≤ 0.05; ## p≤ 0.01; ### p≤ 0.001 versus tanezumab 5 mg + NSAID treatment
OMERACT-OARSI Response: ≥50% and ≥2 points in either the WOMAC Pain or Physical Function subscales, or at least 2 of the following: (1) ≥20% and ≥1 point in the WOMAC Pain subscale; (2) ≥20% and ≥1 point in the WOMAC Physical Function subscale; (3) ≥20% and ≥1 point in the Patient's Global Assessment

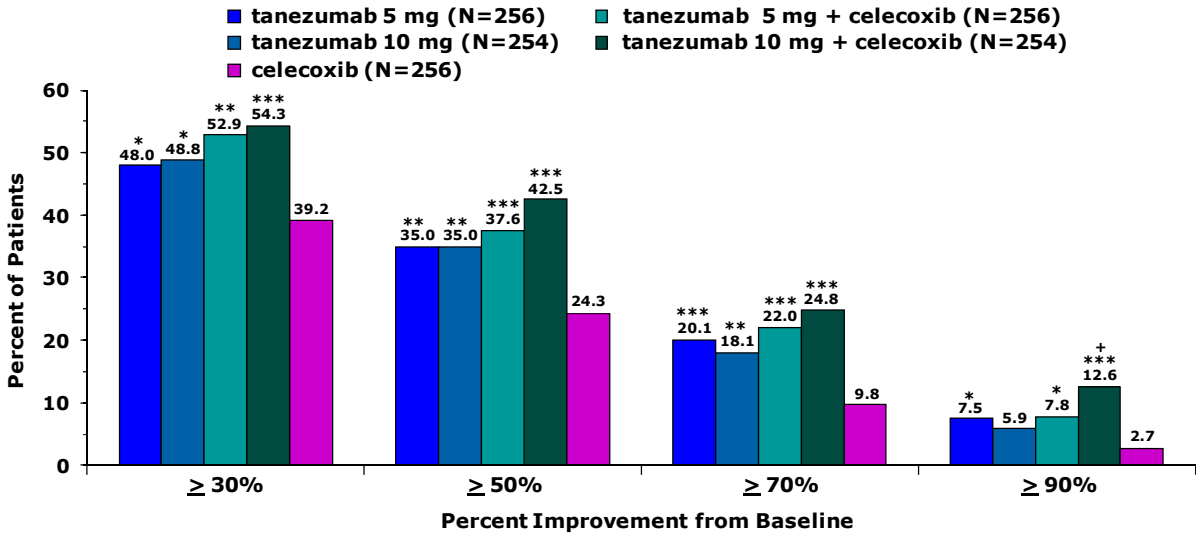
Both tanezumab 5 mg and 10 mg in combination with either naproxen or celecoxib were shown to significantly increase the response rate for ≥30%, ≥50%, ≥70% and ≥90% reductions in pain with WOMAC Pain subscale and with OMERACT-OARSI Responder Index. The response rate based upon a 2-grade or larger categorical improvement in the Patient's Global Assessment of Osteoarthritis was significant for both doses of tanezumab versus naproxen treatment.

Figure 25. WOMAC Pain Subscale: Patients with a ≥ 30%, ≥ 50%, ≥ 70%, or ≥ 90% Reduction in Pain at Week 16 in Study 1025 – Naproxen Cohort



*p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001 vs naproxen
+p ≤ 0.05; ++p ≤ 0.01; +++p ≤ 0.001 vs tanezumab 10 mg
#p ≤ 0.05; ##p ≤ 0.01; ###p ≤ 0.001 vs tanezumab 5 mg + naproxen
ITT, BOCF
naproxen dose = 500 mg BID

Figure 26. WOMAC Pain Subscale: Patients with a ≥ 30%, ≥ 50%, ≥ 70%, or ≥ 90% Reduction in Pain at Week 16 in Study 1025 – Celecoxib Cohort



*p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001 vs celecoxib
+p ≤ 0.05; ++p ≤ 0.01; +++p ≤ 0.001 vs tanezumab 10 mg
ITT, BOCF
celecoxib dose = 100 mg BID

In Study 1030, tanezumab 5 mg and 10 mg resulted in a greater proportion of responding patients compared to both placebo and oxycodone CR treatment at the landmark analysis of Week 8 and with LOCF imputation (Table 30).

Table 30. Responder Analyses for Study 1030

Study 1030			
Treatment Group	**N**	**Week 8 % of patients**	**Odds ratio [95% CI] vs placebo**
WOMAC OA Index: Pain Subscale (30% response rate)			
placebo	141	55.3	
tanezumab 5 mg	161	67.7^{*+++}	1.69 [1.05, 2.70]
tanezumab 10 mg	150	66.0^{+++}	1.58 [0.98, 2.55]
oxycodone CR 10-40 mg BID	158	47.5	0.74 [0.47, 1.17]
WOMAC OA Index: Pain Subscale (50% response rate)			
placebo	141	33.3	
tanezumab 5 mg	161	44.1^{++}	1.59 [0.99, 2.55]
tanezumab 10 mg	150	48.7^{**+++}	1.93 [1.20, 3.11]
oxycodone CR 10-40 mg BID	158	29.7	0.87 [0.53, 1.42]
WOMAC OA Index: Pain Subscale (70% response rate)			
placebo	141	14.9	
tanezumab 5 mg	161	27.3^{**+}	2.25 [1.25, 4.03]
tanezumab 10 mg	150	31.3^{***++}	2.68 [1.50, 4.79]
oxycodone CR 10-40 mg BID	158	17.1	1.24 [0.66, 2.31]
WOMAC OA Index: Pain Subscale (90% response rate)			
placebo	141	3.5	
tanezumab 5 mg	161	12.4^{**++}	4.29 [1.55, 11.87]
tanezumab 10 mg	150	10.7^{*+}	3.26 [1.15, 9.21]
oxycodone CR 10-40 mg BID	158	2.5	0.75 [0.20, 2.88]
OMERACT-OARSI Response Rate			
placebo	141	57.4	
tanezumab 5 mg	161	74.5^{**++}	2.13 [1.30, 3.48]
tanezumab 10 mg	150	70.0^{*+}	1.73 [1.06, 2.80]
oxycodone CR 10-40 mg BID	158	58.9	1.06 [0.66, 1.68]
Patient's Global Assessment (Patients with ≥ 2 Grade Improvement)			
placebo	141	9.2	
tanezumab 5 mg	161	22.4^{***++}	3.43 [1.65, 7.12]
tanezumab 10 mg	150	28.0^{***+++}	4.91 [2.37,10.18]
oxycodone CR 10-40 mg BID	158	10.8	1.30 [0.58, 2.90]

ITT cohort, LOCF
* p≤ 0.05; ** p≤ 0.01; *** p≤ 0.001 versus placebo treatment
$^{+}$ p≤ 0.05; $^{++}$ p≤ 0.01; $^{+++}$ p≤ 0.001 versus oxycodone CR treatment
OMERACT-OARSI Response: ≥50% and ≥2 points in either the WOMAC Pain or Physical Function subscales, or at least 2 of the following: (1) ≥20% and ≥1 point in the WOMAC Pain subscale; (2) ≥20% and ≥1 point in the WOMAC Physical Function subscale; (3) ≥20% and ≥1 point in the Patient's Global Assessment

Tanezumab 5 mg resulted in a significantly greater incidence of responders versus placebo treatment for all response indices with exception of a ≥50% reduction in pain with the WOMAC pain subscale (p=0.053). Similar results were observed with tanezumab 10 mg; the only comparison that failed to meet statistical significance was the ≥30% reduction in pain with the WOMAC pain subscale (p=0.058). Both tanezumab doses were statistically superior to oxycodone CR across all responder indices. Oxycodone CR 10-40 mg BID failed to separate from placebo treatment across all response measures in this study.

8.6. SF-36 Health Survey

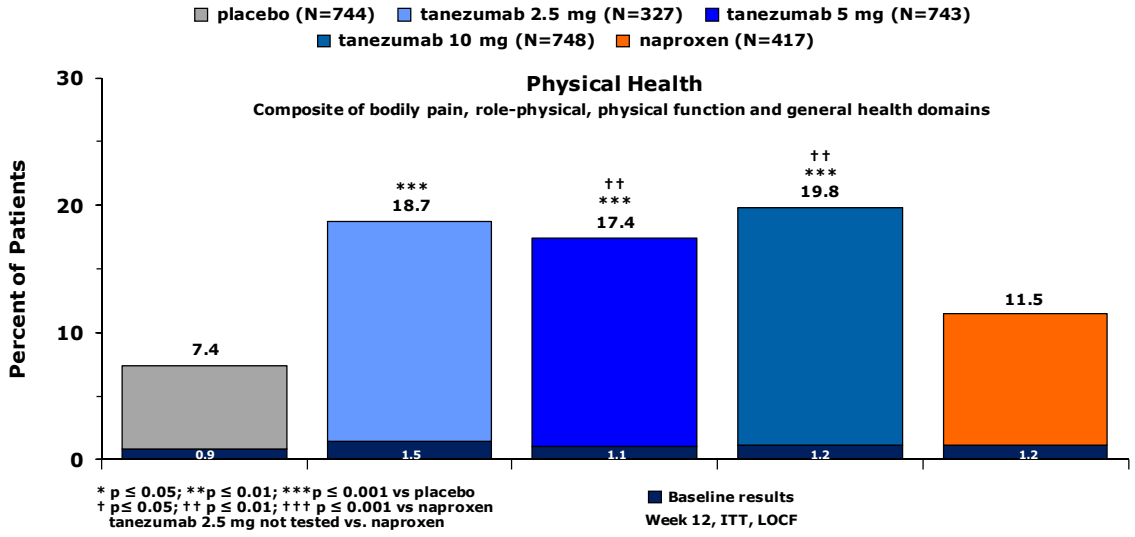
The SF-36 Health Survey was administered to patients in the Phase 3 osteoarthritis studies at Baseline and again after 12 weeks of treatment. The results were used to evaluate the effect of tanezumab treatment on the relative burden of osteoarthritis as compared to the US population normative values. Due to the nature of this disease, particular focus was placed on 4 domains, bodily pain, role-physical, physical function and general health that comprise the Physical Health summary measure. The results for Studies 1011, 1014, 1015, and 1018 combined are summarized in Table 31. The results for the Physical Health Summary measure are shown in Figure 27. A significantly greater proportion of patients reported scores in the bodily pain, role-physical, and physical function domains that met or exceeded the normative scores for the US population with tanezumab 2.5-10 mg treatment. Based on these changes, a significantly greater percentage of tanezumab-treated patients also achieved or exceeded the Physical Health composite normative score for the US population.

Table 31. SF-36 Physical Domains: Percent of Patients with Norm-Based Score ≥ 50 of the US Population at Baseline and after 12 Weeks of Treatment

Percent of Patients with a Norm-Based Score ≥ 50 for the US Population	Bodily Pain Baseline/Wk12	Role-Physical Baseline/Wk12	Physical Function Baseline/Wk12	General Health Baseline/Wk12
placebo (N=744)	1.3 / 15.2	8.6 / 18.4	1.6 / 5.4	48.4 / 53.5
tanezumab 2.5 mg (N=327)	1.5 / 27.2***	4.9 / 24.5**	2.4 / 13.8***	42.8 / 55.4
tanezumab 5 mg (N=743)	1.6 / 31.5*** +++	6.9 / 30.0*** +++	1.3 / 13.3*** ++	47.4 / 60.0**
tanezumab 10 mg (N=748)	1.1 / 31.7*** +++	7.8 / 27.1***++	2.0 / 15.0*** ++	48.1 / 57.2
naproxen 500 mg BID (N=417)	2.2 / 19.9	7.9 / 20.9	1.4 / 7.4	46.8 / 53.5

ITT cohort, LOCF, Studies 1011, 1014, 1015 & 1018
* p≤ 0.05; ** p≤ 0.01; *** p≤ 0.001 versus placebo treatment
+ p≤ 0.05; ++ p≤ 0.01; +++ p≤ 0.001 versus naproxen treatment
tanezumab 2.5 mg not tested vs. naproxen

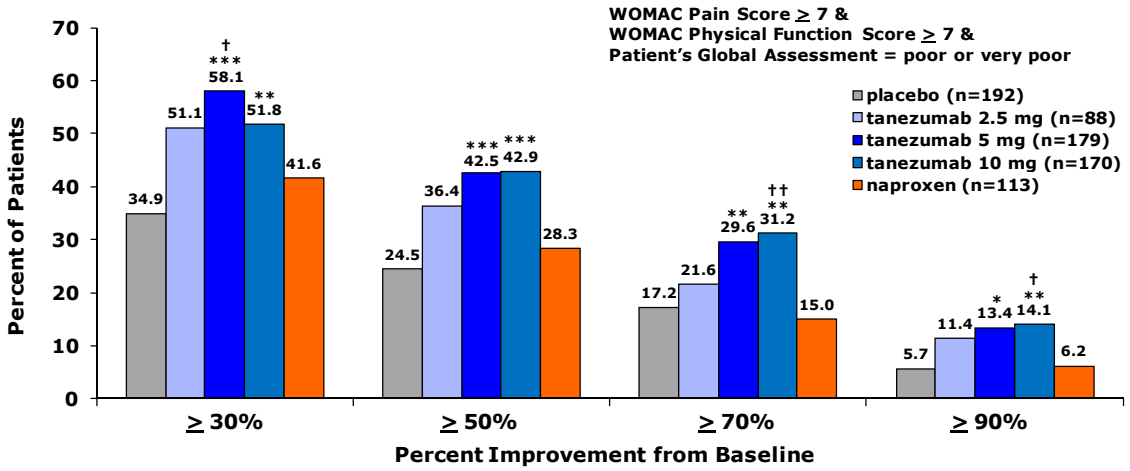
Figure 27. SF-36 Physical Health Composite Measure: Percent of Patients with a Norm-Based Score ≥ 50 of the US Population at Baseline and after 12 Weeks of Treatment



8.7. Efficacy of Tanezumab in Patients with Severe Pain

A prospectively defined analysis of patients participating in Study1011, 1014, 1015, or 1018 was carried out to evaluate the efficacy of tanezumab with severe symptomatic osteoarthritis. Patients defined with severe pain were those with a Baseline WOMAC Pain score ≥ 7 and a WOMAC Physical Function score of ≥ 7 and a score of "poor" or "very poor" in the Patient's Global Assessment of Osteoarthritis. Of the 2979 patient enrolled across the 4 studies, 742 (25.1%) met these criteria for severe disease. Tanezumab 5 mg and 10 mg provided significant and clinically meaningful benefit in this severe patient cohort when compared to placebo treatment. In contrast, there was no evidence that naproxen 500 mg BID was of any benefit to these patients (Figure 28).

Figure 28. WOMAC Pain Subscale: Patients with a ≥ 30%, ≥ 50%, ≥ 70%, or ≥ 90% Reduction in Pain at Week 16: Severe Patients



*p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001 vs. placebo
†p ≤ 0.05; ††p ≤ 0.01; †††p ≤ 0.001 vs. naproxen
[1]Response Rates at Week 16; Studies 1011, 1014, 1015 & 1018; ITT, BOCF; naproxen dose = 500 mg BID

9. EFFICACY OF TANEZUMAB IN THE TREATMENT OF CHRONIC LOW BACK PAIN AND OTHER CHRONIC PAIN CONDITIONS

9.1. Chronic Low Back Pain

The efficacy of tanezumab in chronic low back pain has been evaluated in two Phase 2 studies. The results of one of these studies (Study 1012) are summarized below. This study evaluated the efficacy and safety of multiple doses of tanezumab 5 mg, 10 mg, or 20 mg administered IV every 8 weeks compared to placebo or naproxen 500 mg BID in treating patients with chronic low back pain. The primary endpoint of the study was the mean change in the daily average Low Back Pain Intensity score from Baseline to Week 16 with BOCF imputation. Key secondary efficacy endpoints were the Roland Morris Disability Questionnaire (a measure of function used for low back pain) and Patient Global Assessment of Low Back Pain. As described for the osteoarthritis studies, statistical testing of tanezumab versus treatment with either placebo or naproxen 500 mg BID at the 5% level across these three efficacy endpoints proceeded in a fixed sequence by decreasing tanezumab dose to control the Type 1 error rate.

A total of 1347 patients were randomized and treated and by definition comprised the ITT cohort in the study. The mean age of the study population was approximately 52 years (range 18-89 years). There was a small majority of women (53%) who participated and the average duration of chronic low back pain was approximately 11 years.

Tanezumab 10 mg and 20 mg provided significant improvement across the pain, function, and global efficacy domains at Week 16 compared to both placebo and naproxen treatment (Figure 29). The magnitude of efficacy was similar between these tanezumab doses. The observed treatment differences between tanezumab 5 mg and placebo treatment reached statistical significance for only one of three primary measures of efficacy. Naproxen treatment was associated with a significant reduction in pain versus placebo treatment.

Statistically significant response rates compared to placebo treatment were demonstrated at Week 16 with tanezumab 10 mg and 20 mg for the percentage of patients with reductions in pain ≥30%, ≥50%, ≥70%, and ≥90% in the Low Back Pain Intensity efficacy measure (Figure 30). Tanezumab 20 mg was also statistically superior to naproxen treatment at all response levels and tanezumab 10 mg was superior to naproxen treatment at the ≥70% and ≥90% response levels. The percent of patients with ≥30% and ≥50% reductions in pain were significantly greater with tanezumab 5 mg and naproxen treatment as compared to placebo-treated patients.

Figure 29. Low Back Pain Intensity, Roland-Morris Disability Questionnaire, and Patient's Global Assessment of Low Back Pain: Change from Baseline to Week 16

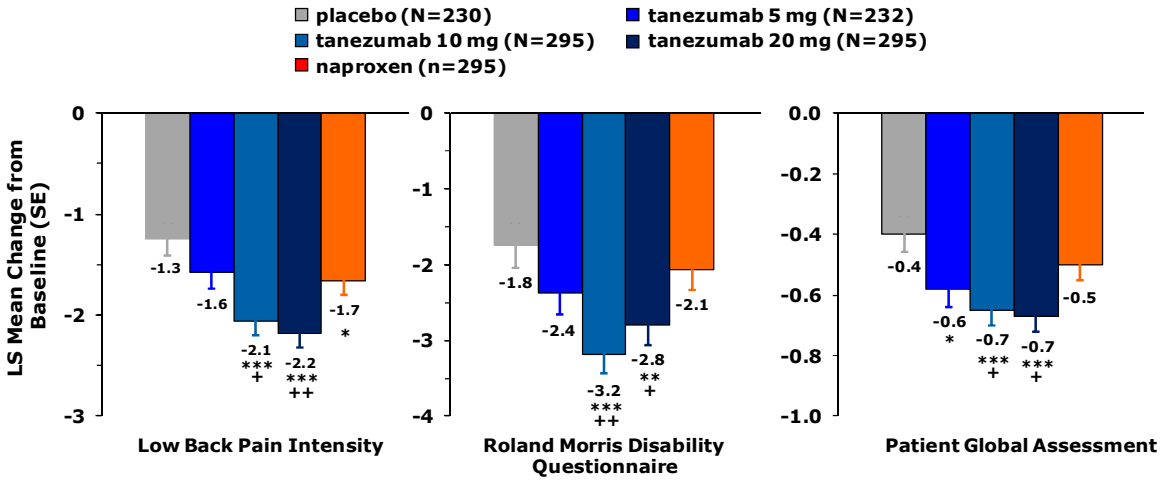
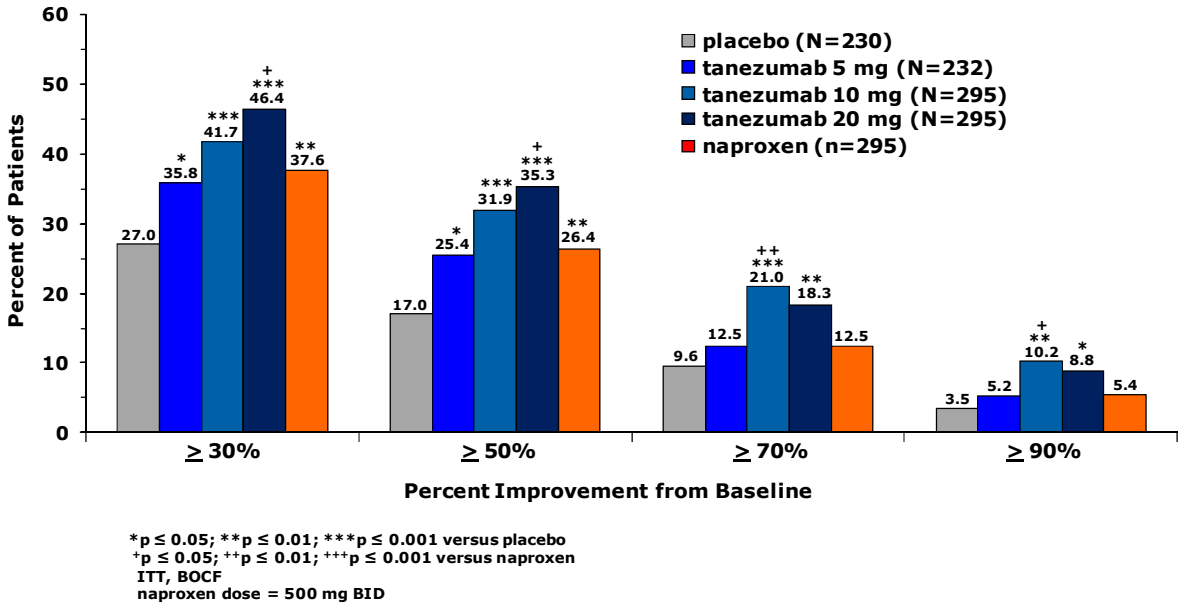


Figure 30. Low Back Pain Intensity: Patients with a ≥ 30%, ≥ 50%, ≥ 70%, or ≥ 90% Reduction in Pain at Week 16



*p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001 versus placebo
+p ≤ 0.05; ++p ≤ 0.01; +++p ≤ 0.001 versus naproxen
ITT, BOCF
naproxen dose = 500 mg BID

The clinical significance of the reduction in pain with tanezumab treatment was assessed by the evaluation of patient responder rates using a categorical assessment of the Low Back Pain Intensity results and the Low Back Pain Responder Index which is a composite endpoint consisting of patients with a ≥30% reduction in Low Back Pain Intensity and in the Patient's

Global Assessment of Low Back Pain and no worsening in the Roland-Morris Disability Questionnaire. These responder analyses were determined with BOCF imputation.

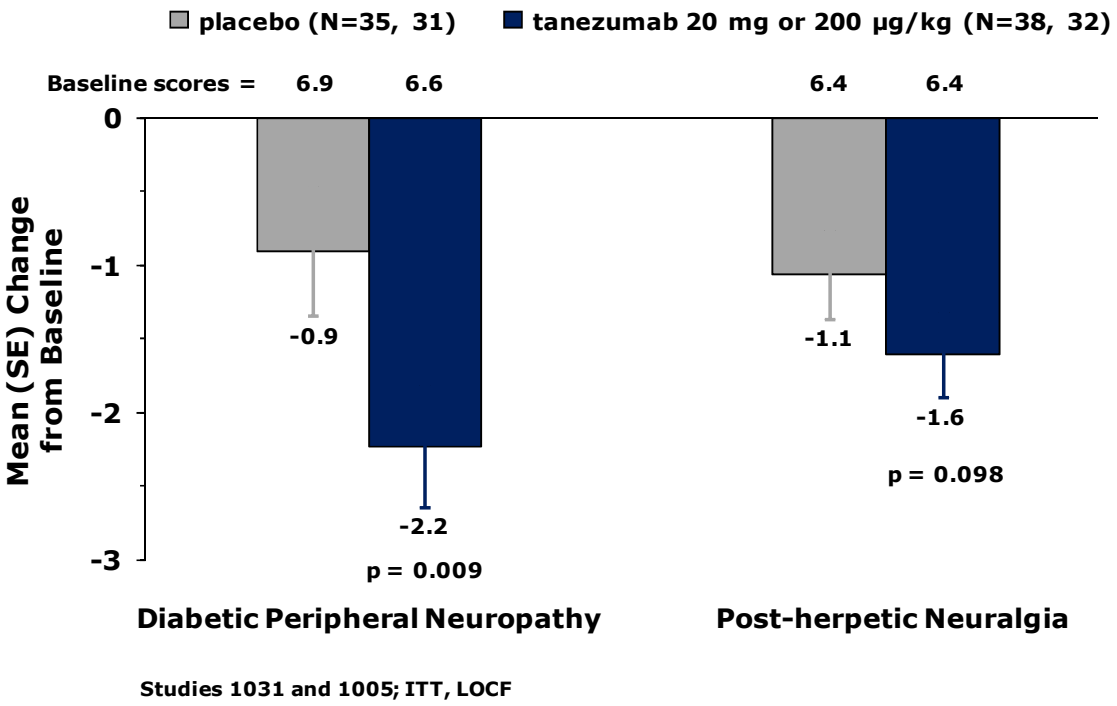
The percentage of patients reaching the Low Back Pain Responder Index criteria at Week 16 with tanezumab 10 mg (30.5%) and 20 mg (30.2%) was significantly greater than with either placebo (19.1%) or naproxen (21.4%). Tanezumab 5 mg and naproxen did not provide meaning improvement in this assessment of efficacy.

9.2. Neuropathic and Visceral Chronic Pain Conditions

Small randomized double-blind controlled Phase 2 studies with tanezumab have been completed in patients with neuropathic pain (post-herpetic neuralgia and diabetic peripheral neuropathy) and visceral pain (interstitial cystititis, prostatitis, and endometriosis) and a study is ongoing metastatic bone pain.

The results of studies conducted in patients with neuropathic pain are shown in Figure 31. A single tanezumab 20 mg fixed dose (used in Study 1031, diabetic peripheral neuropathy) or essentially an equivalent body-weight adjusted dose (200 µg/kg, Study 1005, post-herpetic neuralgia) provided greater pain relief compared to placebo treatment at Week 8 following drug administration.

Figure 31. Efficacy of Tanezumab in Phase 2 Neuropathic Pain Studies

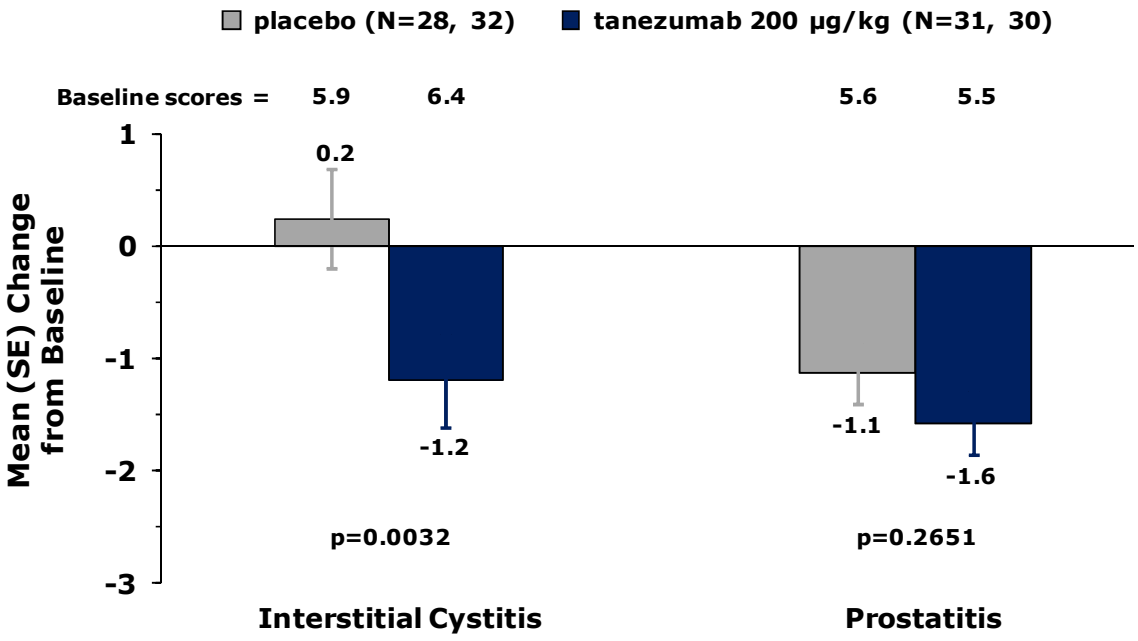


The treatment differences reached statistical significance in patients with diabetic peripheral neuropathy and approached significance in patients with post-herpetic neuralgia. Study 1005 was completed prior to the clinical hold and was intended as a single administration study.

The study also evaluated a tanezumab 50 μg/kg dose; this dose was not efficacious in the study. Study 1031 was intended to evaluate 2 administrations of study medication over a 16 week study interval. Enrollment was interrupted by the clinical hold and few patients had the opportunity to receive the second administration of study medication.

The results of 2 of the 4 studies conducted in patients with visceral pain are shown in Figure 32. A single tanezumab 200 μg/kg dose provided greater pain relief compared to placebo treatment at Week 6 (the predefined primary landmark analysis in these studies) following drug administration. The treatment differences reached statistical significance in patients with interstitial cystitis and approached significance in patients with prostatitis.

Figure 32. Efficacy of Tanezumab in Phase 2 Visceral Pain Studies



Studies 1010 and 1019; ITT, LOCF

Two additional Phase 2 chronic visceral pain studies were conducted. A second study in patients with interstitial cystitis was impacted by the clinical hold and terminated for futility. A study in endometriosis was also terminated for futility following an interim analysis of efficacy.

10. SAFETY OF TANEZUMAB

Based on data from all patient populations who have received tanezumab in clinical studies to date, the adverse drug reactions listed in Table 32 are considered to be expected in patients who are treated with tanezumab.

Table 32. Adverse Drug Reactions in Patients Receiving Tanezumab

System Organ Class	Adverse Drug Reaction	Frequency
General disorders and administration site conditions	Peripheral edema	Common (≥1%, <10%)
Musculoskeletal and connective tissue disorders	Arthralgia Joint swelling Myalgia Pain in extremity	Common (≥1%, <10%)
Nervous system disorders	Burning sensation Carpal tunnel syndrome Hyperesthesia Hypoesthesia Paresthesia	Common (≥1%, <10%)
	Allodynia Peripheral neuropathy	Uncommon (≥0.1%, <1%)

Based on data from the Phase 3 osteoarthritis studies and results of an independent adjudication of investigator-reported adverse events of osteonecrosis and total joint replacements, the risk of rapidly progressive osteoarthritis with tanezumab treatment is greater than with placebo or active comparator treatment. Therefore, in osteoarthritis patients adverse drug reactions expected with tanezumab treatment includes aggravated osteoarthritis and rapidly progressive osteoarthritis in addition to those events listed in Table 32.

The discussion below is focused to the safety profile of tanezumab in patients with osteoarthritis. The safety profile observed in tanezumab to date in other chronic pain patient populations does not differ markedly from the results described below.

Table 33 provides a high level summary of the adverse events in the 9 controlled Phase 3 osteoarthritis studies in which a total of 7491 patients were treated. The incidence of adverse events, withdrawals due to adverse events, and serious adverse events in patients treated with tanezumab monotherapy (2.5-10 mg) was similar to patients receiving active comparator treatment and increased over placebo-treated patients. Across the tanezumab monotherapy doses, the rates of adverse events, withdrawals due to adverse events, and serious adverse events, were similar with tanezumab 5 mg and 10 mg.and elevated in comparison to tanezumab 2.5 mg. Tanezumab/NSAID combination therapy was associated with highest overall incidence rates. The relationship of incidence to the dose of tanezumab administered was similar to that seen with tanezumab monotherapy.

Table 33. Incidence of Adverse Events in the Controlled Phase 3 Osteoarthritis Studies

	Number (%) of Patients			
	placebo N=1029	tanezumab[1] n=3666	tanezumab[1] + NSAID[2] N=1530	active comparator[3] N=1266
Adverse events	461 (44.8)	2165 (59.1)	1006 (65.8)	731 (57.7)
Withdrawals due to adverse events	29 (2.8)	255 (7.0)	204 (13.3)	100 (7.9)
Serious adverse events	25 (2.4)	151 (4.1)	149 (9.7)	69 (5.5)

[1] All tanezumab doses combined: 2.5, 5, 10 mg.
[2] NSAID = naproxen 500 mg BID, celecoxib 100 mg BID or diclofenac SR 75 mg BID.
[3] Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID.
Studies 1011, 1014, 1015, 1017, 1018, 1025, 1026, 1027, and 1030

10.1. Adverse Events

The most common adverse events reported in the controlled Phase 3 osteoarthritis studies are provided in Table 34. The incidence of peripheral edema, upper respiratory tract infection, fall, arthralgia, back pain, pain in extremity, hypoesthesia, and paresthesia were higher in patients receiving tanezumab monotherapy than patients receiving either placebo or active comparator treatment. The incidence of peripheral edema, arthralgia, pain in extremity, and paresthesia increased with increasing doses of tanezumab monotherapy.

The adverse events with increased incidence observed with tanezumab/NSAID combination therapy over either tanezumab monotherapy or active comparator treated included the following: peripheral edema, nasopharynigitis, fall, arthralgia, back pain, osteoarthritis, hypoesthesia, and paresthesia. Of these adverse events, the incidence of peripheral edema, fall, back pain, pain in extremity, and paresthesia increased with increasing doses of tanezumab administered in combination with NSAID treatment.

The adverse events with increased incidence observed with active comparator over tanezumab monotherapy included the following: constipation, nausea, urinary tract infection, nasopharyngitis, osteoarthritis, headache, and hypertension.

Table 34. Incidence of Adverse Events ≥ 3% in the Controlled Phase 3 Osteoarthritis Studies

n (%)	placebo N=1029	tanezumab[1] N=3666	tanezumab[1] + NSAID[2] N=1530	active control[3] N=1266
Any adverse event	461 (44.8)	2165 (59.1)	1006 (65.8)	731 (57.7)
Gastrointestinal Disorders				
Constipation	6 (0.6)	22 (0.6)	8 (0.5)	43 (3.4)
Nausea	20 (1.9)	59 (1.6)	21 (1.4)	46 (3.6)
General Disorders and Administrative Site Conditions				
Peripheral edema	8 (0.8)	171 (4.7)	101 (6.6)	25 (2.0)
Infections and Infestations				
Nasopharyngitis	15 (1.5)	90 (2.5)	83 (5.4)	46 (3.6)
Upper respiratory tract infection	23 (2.2)	140 (3.8)	49 (3.2)	41 (3.2)
Urinary tract infection	20 (1.9)	126 (3.4)	53 (3.5)	49 (3.9)
Injury, Poisoning and Procedural Complications				
Fall	23 (2.2)	98 (2.7)	52 (3.4)	24 (1.9)
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	36 (3.5)	319 (8.7)	160 (10.5)	73 (5.8)
Back pain	17 (1.7)	107 (2.9)	55 (3.6)	33 (2.6)
Osteoarthritis	18 (1.7)	101 (2.8)	93 (6.1)	39 (3.1)
Pain in extremity	25 (2.4)	159 (4.3)	57 (3.7)	27 (2.1)
Nervous System Disorders				
Headache	48 (4.7)	154 (4.2)	60 (3.9)	55 (4.3)
Hypoesthesia	9 (0.9)	136 (3.7)	73 (4.8)	27 (2.1)
Paresthesia	17 (1.7)	212 (5.8)	114 (7.5)	29 (2.3)
Vascular Disorders				
Hypertension	16 (1.6)	58 (1.6)	42 (2.7)	42 (3.3)

[1] Tanezumab doses combined (2.5, 5 and 10 mg); Studies 1011, 1014, 1015, 1017, 1018, 1025, 1026, 1027, & 1030
[2] NSAID = naproxen 500 mg BID, celecoxib 100 mg BID or diclofenac SR 75 mg BID
[3] Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID.

The most common adverse events reported in the non-controlled, long-term Phase 3 osteoarthritis studies events were identical to those seen in the controlled Phase 3 osteoarthritis studies with the exception of the inclusion of joint swelling and musculoskeletal pain and exclusion of headache, hypertension and nasopharyngititis and all gastrointestinal-related adverse events. Dose-related increases in the incidence of peripheral edema, joint swelling, osteoarthritis and paresthesia were observed.

10.2. Adverse Events Causing Withdrawal

The incidence of adverse events most commonly causing withdrawal in the 9 controlled Phase 3 osteoarthritis studies are summarized in Table 35. The incidence of adverse events most commonly causing withdrawal was generally similar between tanezumab monotherapy and active comparator treatment and elevated versus placebo treatment. The highest incidence of adverse events causing withdrawal was observed with tanezumab/NSAID combination therapy.

The most frequent adverse events causing withdrawal in the non-controlled long-term Phase 3 osteoarthritis studies were similar to those seen in the controlled Phase 3 osteoarthritis studies with the exception of the inclusion of carpal tunnel syndrome and the exclusion of hypoesthesia, paresthesia, and reported osteonecrosis.

Table 35. Incidence of Adverse Events Causing Withdrawal ≥ 0.5% in the Controlled Phase 3 Osteoarthritis Studies

n (%)	placebo N=1029	tanezumab[1] N=3666	tanezumab[1] + NSAID[2] N=1530	active control[3] N=1266
Any adverse event causing withdrawal	29 (2.8)	255 (7.0)	204 (13.3)	100 (7.9)
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	1 (0.7)	27 (0.7)	26 (1.7)	8 (0.6)
Osteoarthritis	5 (0.5)	23 (0.6)	28 (1.8)	10 (0.8)
Osteonecrosis	0 (0.0)	8 (0.2)	8 (0.5)	2 (0.2)
Nervous System Disorders				
Hypoesthesia	1 (0.1)	9 (0.2)	7 (0.5)	0 (0.0)
Paresthesia	0 (0.0)	14 (0.4)	13 (0.8)	3 (0.2)

[1] Tanezumab doses combined (2.5, 5 and 10 mg); Studies 1011, 1014, 1015, 1017, 1018, 1025, 1026, 1027, & 1030
[2] NSAID = naproxen 500 mg BID, celecoxib 100 mg BID or diclofenac SR 75 mg BID
[3] Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID.

10.3. Serious Adverse Events

A summary of serious adverse events in Sponsor's safety database and occurring in ≥3 patients in any treatment group in the controlled and non-controlled Phase 3 osteoarthritis studies is provided in Table 36. The overall event rate of serious adverse events was highest in patients randomized to tanezumab/NSAID combination therapy (140 events/1000 pt-yrs) compared with the tanezumab monotherapy (110 events/1000 pt-yrs), active comparator (107 events/1000 pt-yrs) and placebo (80 events/1000 pt-yrs). These treatment differences were largely the result of differences in the incidence of the following individual serious adverse events: osteoarthritis, osteonecrosis, arthritis, and arthralgia. Osteoarthritis was the most commonly reported serious adverse event in each treatment group with the highest incidence in patients treated with tanezumab/NSAID combination therapy (37.9 events/1000 pt-yrs), followed by tanezumab monotherapy (21.0 events/1000 pt-yrs), active comparator (16.6 events/1000 pt-yrs) and placebo treatment (9.6 events/1000 pt-yrs).

Serious adverse events of coronary artery disease, small intestinal obstruction, cellulitis, osteomyelitis, foot fracture, pelvic fracture, spinal fracture, tibia fracture, arthritis, back pain, lumbar spinal stenosis, rotator cuff syndrome, synovial cyst, colon cancer, headache, pulmonary embolism and deep vein thrombosis were reported only by patients receiving tanezumab or tanezumab/NSAID combination treatment.

Nine patients experienced pulmonary embolism as a serious adverse event: 7 patients were receiving tanezumab monotherapy and 2 patients were receiving tanezumab/NSAID combination therapy. Five of the patients (4 treated with tanezumab monotherapy and 1 treated with tanezumab/NSAID combination therapy) also had deep vein thrombosis. All nine events were attributed by the investigator to other causes, including extended periods of immobility, post-operative complications, or prior medical history.

Table 36. Rates of Most Frequent Treatment-Emergent Serious Adverse Events (n ≥ 3 in any treatment group) – All Phase 3 Osteoarthritis Studies

Serious Adverse Event by System Organ Class and Preferred Term; n (events/1000 pt-yrs)	placebo N = 1029	tanezumab N =5171	tanezumab + NSAID[1] N = 1530	active comparator[2] N = 1266
Total exposure (pt-yrs)	**313**	**3612**	**1083**	**661**
Blood and Lymphatic System Disorder				
Anemia	0 (0.0)	4 (1.1)	1 (0.9)	1 (1.5)
Cardiac Disorders				
Atrial fibrillation	0 (0.0)	8 (2.2)	4 (3.7)	1 (1.5)
Cardiac arrest	1 (3.2)	3 (0.8)	0 (0.0)	0 (0.0)
Coronary artery disease	0 (0.0)	8 (2.2)	2 (1.8)	0 (0.0)
Gastrointestinal Disorders				
Gastrointestinal hemorrhage	0 (0.0)	3 (0.8)	1 (0.9)	1 (1.5)
Small intestinal obstruction	0 (0.0)	4 (1.1)	0 (0.0)	0 (0.0)
General Disorders				
Chest pain	1 (3.2)	9 (2.5)	3 (2.8)	4 (6.1)
Hepatobiliary Disorders				
Cholelithiasis	0 (0.0)	3 (0.8)	1 (0.9)	3 (4.5)
Infections and Infestations				
Cellulitis	0 (0.0)	9 (2.5)	2 (1.8)	0 (0.0)
Osteomyelitis	0 (0.0)	3 (0.8)	1 (0.9)	0 (0.0)
Pneumonia	1 (3.2)	10 (2.8)	1 (0.9)	1 (1.5)
Sepsis	1 (3.2)	3 (0.8)	0 (0.0)	1 (1.5)
Urinary Tract Infection	0 (0.0)	3 (0.8)	0 (0.0)	1 (1.5)
Injury, Poisoning and Procedural Complication				
Ankle fracture	1 (3.2)	2 (0.6)	3 (2.8)	0 (0.0)
Fall	0 (0.0)	6 (1.7)	2 (1.8)	1 (1.5)
Foot fracture	0 (0.0)	2 (0.6)	3 (2.8)	0 (0.0)
Hip fracture	1 (3.2)	4 (1.1)	0 (0.0)	2 (3.0)
Pelvic fracture	0 (0.0)	3 (0.8)	0 (0.0)	0 (0.0)
Spinal fracture	0 (0.0)	3 (0.8)	1 (0.9)	0 (0.0)
Tendon rupture	0 (0.0)	4 (1.1)	1 (0.9)	1 (1.5)
Tibia fracture	0 (0.0)	5 (1.4)	3 (2.8)	0 (0.0)
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	0 (0.0)	20 (5.5)	7 (6.5)	6 (9.1)
Arthritis	0 (0.0)	5 (1.4)	3 (2.8)	0 (0.0)
Back pain	0 (0.0)	5 (1.4)	1 (0.9)	0 (0.0)
Intervertebral disc protrusion	1 (3.2)	4 (1.1)	2 (1.8)	2 (3.0)
Lumbar spinal stenosis	0 (0.0)	5 (1.4)	1 (0.9)	0 (0.0)
Osteoarthritis	3 (9.6)	76 (21.0)	41 (37.9)	11 (16.6)
Osteonecrosis	0 (0.0)	52[3] (14.4)	24 (22.2)	4 (6.1)
Rotator cuff syndrome	0 (0.0)	3 (0.8)	3 (2.8)	0 (0.0)
Synovial cyst	0 (0.0)	3 (0.8)	1 (0.9)	0 (0.0)
Neoplasms benign, malignant and unspecified				
Breast cancer	0 (0.0)	9 (2.5)	0 (0.0)	1 (1.5)
Colon Cancer	0 (0.0)	3 (0.8)	0 (0.0)	0 (0.0)
Prostrate cancer	0 (0.0)	3 (0.8)	0 (0.0)	1 (1.5)
Nervous System Disorders				
Cerebrovascular accident	0 (0.0)	6 (1.7)	1 (0.9)	1 (1.5)
Headache	0 (0.0)	3 (0.8)	0 (0.0)	0 (0.0)
Respiratory, Thoracic and Mediastinal Disorders				
Chronic obstructive pulmonary disease	0 (0.0)	4 (1.1)	0 (0.0)	1 (1.5)
Pulmonary embolism	0 (0.0)	7 (1.9)	2 (1.8)	0 (0.0)
Vascular disorders				
Deep vein thrombosis	0 (0.0)	5 (1.4)	1 (0.9)	0 (0.0)
Hypertension	0 (0.0)	3 (0.8)	1 (0.9)	0 (0.0)
N (total event rate/1000 pt-yrs)	**25 (80)**	**397(110)**	**152 (140)**	**71 (107)**

[1] Includes only patients randomized to tanezumab/NSAID combination therapy; patients receiving NSAIDs concomitantly in long-term studies are included in the tanezumab monotherapy treatment group; [2] Active comparators = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID; [3] One adverse event of 'osteonecrosis' was changed to 'osteoarthritis' by the investigator following receipt of pathology results and is not included.

Six patients had a serious adverse event of deep vein thrombosis: 5 patients were receiving tanezumab monotherapy and 1 patient was receiving tanezumab/NSAID combination therapy. As noted above, 5 patients also concurrently experienced pulmonary embolism. One event in a patient receiving tanezumab monotherapy occurred approximately 3 months after the patient fell and injured her leg. The remaining events were attributed by the investigator to immobility, compression of vein associated with Baker's cyst, injury or fall, and post-operative complications.

Eleven patients had a serious adverse event of cellulitis: 9 patients were treated with tanezumab monotherapy and 2 with tanezumab/NSAID combination therapy. No events were considered related to study treatment; the majority of the events (9) were to other causes such as injury, insect bites, wounds, or intercurrent illness.

There were 6 patients with a serious adverse event of ankle fracture: 1 treated with placebo, 2 with tanezumab monotherapy or active comparator and 3 with tanezumab/NSAID combination therapy. Causality was attributed to other circumstances, such as fall or injury, in 4 patients; in the remaining 2 patients (both received tanezumab/NSAID combination treatment) causality was unknown. Five patients experienced a serious adverse event of foot fracture: 2 received tanezumab monotherapy and 3 tanezumab/NSAID combination therapy. Three of these events were associated with injuries or pre-existing foot deformities. The remaining 2 events were described as; (1) a fractured third metatarsal on the left foot with no pain leading to excess use but no significant trauma (2) bilateral ankle edema, difficulty with weight-bearing and right second metatarsal and left tibia/fibula fractures.

Eight patients experienced a serious adverse event of tibial fracture: 5 patients were treated with tanezumab monotherapy and 3 with tanezumab/NSAID combination therapy. The location of the fracture was the tibial plateau (4 events), tibial shaft (2 events) or unspecified (2 events). Three events (1 tibial plateau, 1 tibial shaft, 1 unspecified location) were associated with a fall or trip and 1 event (tibial plateau) was diagnosed at the time of total knee replacement for end-stage osteoarthritis. The remaining 4 events (3 in the tanezumab monotherapy treatment group [2 tibial plateau and 1 anterior shaft] and 1 in the tanezumab/NSAID treatment group [distal shaft]) were reported as (1) worsening left knee pain with fracture of the anterior tibial shaft; (2) a tibial plateau stress fracture and osteonecrosis of the right knee, this event was adjudicated as normal progression of osteoarthritis; (3) subchondral insufficiency fracture of the medial tibial plateau and meniscal tear, and (4) bilateral ankle edema, difficulty with weight-bearing and right second metatarsal and left tibia/fibula fractures.

Seven patients had a serious adverse event of hip fracture: 1 patient was treated with placebo, 4 with tanezumab monotherapy, and 2 with active comparator. Six of the events were associated with a fall. The remaining event was described as increased hip pain with movement and fractured hip. Four patients experienced a serious adverse event of spinal fracture; 3 patients had been treated with tanezumab monotherapy and 1 with tanezumab/ NSAID combination therapy. These events were related to a fall (3 events) or motor vehicle accident (1 event). Three patients experienced a serious adverse event of pelvic fracture; all

had been treated with tanezumab monotherapy. These events were related to a fall (2 events) or accident (1 event).

A serious adverse event of tendon rupture occurred in 6 patients; 4 had been treated with tanezumab monotherapy, 1 with tanezumab/NSAID combination therapy and 1 with active comparator. Location of tendon rupture included quadriceps tendon (3 events, all associated with a fall), Achilles tendon (2 events), and tibial-anterior tendon (1 event). The events were related to fall (3 events) or were unspecified (3 events).

Nine patients experienced a fall as a serious adverse event; 6 were treated with tanezumab monotherapy, 2 with tanezumab/NSAID combination therapy and 1 with active comparator. In the tanezumab monotherapy treatment group, 4 of the patients fell on ice, from a ladder, or from tripping over an object. The fifth patient reported a fall after her right knee 'gave out' and was unspecified in the remaining patient. In the tanezumab/NSAID treatment group, one patient fell from a ladder and the cause of the fall in other patient was not reported. One event occurred following total knee replacement (adjudicated as 'not enough information to distinguish between primary osteonecrosis and worsening osteoarthritis) and the other event led to an injured lower back and decompressive lumbar laminectomy. The patient treated with active comparator slipped, injuring the right knee and underwent total knee replacement (this event was not adjudicated).

Sixteen deaths were reported in the Phase 3 osteoarthritis studies. Thirteen of the deaths occurred in patients receiving tanezumab monotherapy or adjunctive therapy with NSAIDs and two deaths occurred in placebo-treated patients. One patient died prior to initiation of study treatment (sudden death). The most frequently reported serious adverse event with a fatal outcome was cardiac arrest (3 tanezumab patients and 1 placebo patient), which were all considered unrelated to treatment. In the tanezumab treatment group, fatal serious adverse events of coronary artery arteriosclerosis, coronary artery disease, cardiopulmonary failure, myocardial ischemia, and pulmonary embolism (1 event each) were reported. Cardio-respiratory arrest, central nervous system lymphoma, demyelinating polyneuropathy, fall, spinal column injury, metastatic pancreatic cancer, pulmonary embolism, gastric cancer and lung carcinoma (1 event each) were reported in the tanezumab/NSAID combination treatment group. In the placebo treatment group, additional fatal serious adverse events of mesothelioma and plural effusion were reported in one patient.

Two patients who experienced deep vein thrombosis and/or pulmonary embolism had a fatal outcome. One patient treated with tanezumab monotherapy experienced deep vein thrombosis and pulmonary embolism one month following bilateral knee replacement. The second patient treated with tanezumab/NSAID combination therapy had a relevant medical history of myocardial ischemia, myocardial fibrosis, chronic pancreatitis and varicose veins and experienced pulmonary embolism approximately 2 months after last dose of study treatment.

10.4. Fractures

10.4.1. Categorization of Fractures

Adverse events and serious adverse events of bone fracture were analyzed in the same manner as investigator reports of osteonecrosis or total joint replacements. All reported adverse events of bone fracture were categorized as follows: (1) traumatic (2) pathological (nontraumatic), (3) osteoporotic, (4) unspecified, and (5) all-cause. There were a sufficient number of fractures categorized as traumatic and all-cause fractures to allow for analyses. There were few pathological and osteoporotic fractures and these are described in a qualitative manner. All categories of fracture were analyzed for the leg and non-leg bones separately to allow comparison with the reporting of fractures in the Osteoarthritis Initiative (OAI) Study. Leg fractures included any bone fracture of the lower extremity, hip joint (including acetabulum) foot and toes. Non-leg fractures included hand, lower arm/wrist, shoulder/ clavicle/scapula, or spine. Patients may have experienced fractures in both non-leg and leg categories. Serious adverse events of fracture are summarized in Section 10.3.

10.4.2. Analysis of Investigator-Reported Fractures

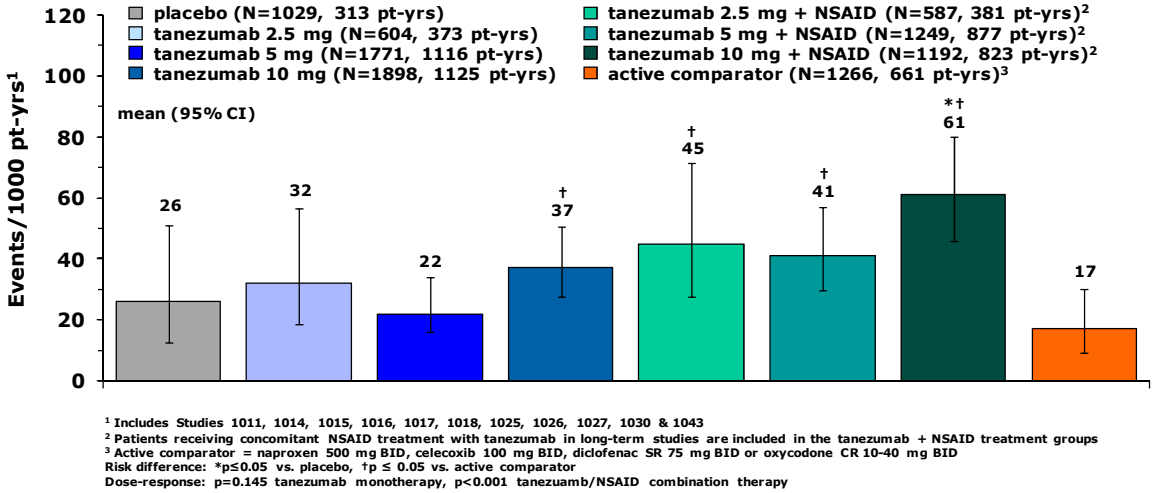
The incidence and rate of fractures in the Phase 3 osteoarthritis studies are summarized in Table 37 and Figure 33. Event rates of fracture were highest in patients receiving any dose of tanezumab in combination with NSAID treatment and those receiving tanezumab 10 mg monotherapy.

Table 37. Summary of Fractures in the Phase 3 Osteoarthritis Studies

	placebo	tanezumab			tanezumab + NSAID[1]			Active Comparator[2]
		2.5 mg	5 mg	10 mg	2.5 mg	5 mg	10 mg	
N	**1029**	**604**	**1771**	**1898**	**587**	**1249**	**1192**	**1266**
Total Exposure (pt-yrs)	**313**	**373**	**1116**	**1125**	**381**	**877**	**823**	**661**
Traumatic								
n (%)	7 (0.7)	9 (1.5)	20 (1.1)	27 (1.4)	12 (2.0)	25 (2.0)#	23 (1.9)#	8 (0.6)
Pathologic								
n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Osteoporotic								
n (%)	0 (0.0)	0 (0.0)	1 (0.1)	3 (0.2)	1 (0.2)	0 (0.0)	3 (0.3)	0 (0.0)
Unspecified/other								
n (%)	1 (0.1)	3 (0.5)	5 (0.3)	12 (0.6)	4 (0.7)	13 (1.0)	25 (2.1)* #	3 (0.2)
All-Cause								
n (%)	8 (0.8)	12 (2.0)	26 (1.5)	42 (2.2)* #	17 (2.9)* #	36 (2.9)* #	50 (4.2)* #	11 (0.9)
events/ 1000 pt-yrs	26	32	23	37#	45 #	41 #	61* #	17

Studies 1011, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030, & 1043
[1] NSAID = naproxen 500 mg BID, celecoxib 100 mg BID or diclofenac SR 75 mg BID.
[2] Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID
risk differences, * $p \leq 0.05$ vs. placebo, # $p \leq 0.05$ vs. active comparator

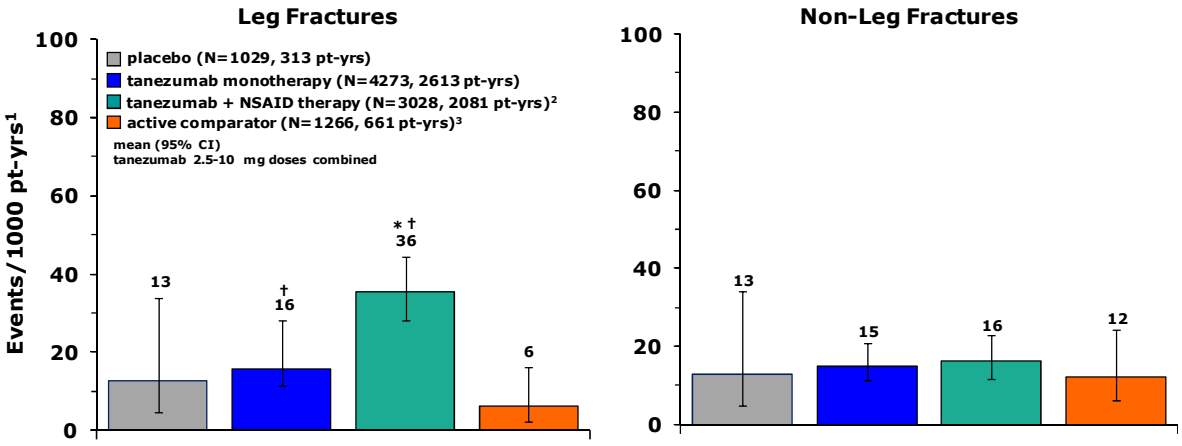
Figure 33. Rates of All-Cause Fractures by Dose in the Phase 3 Osteoarthritis Studies



¹ Includes Studies 1011, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030 & 1043
² Patients receiving concomitant NSAID treatment with tanezumab in long-term studies are included in the tanezumab + NSAID treatment groups
³ Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID
Risk difference: *p≤0.05 vs. placebo, †p ≤ 0.05 vs. active comparator
Dose-response: p=0.145 tanezumab monotherapy, p<0.001 tanezuamb/NSAID combination therapy

The highest rate of fractures was observed in the category of leg fractures in patients treated with tanezumab/NSAID combination therapy. The incidence of all-cause leg and non-leg fractures combined by the dose of tanezumab administered in these studies is shown in Figure 34.

Figure 34. Rates of All-Cause Leg and Non-Leg Fractures in the Phase 3 Osteoarthritis Studies



¹ Includes OA Studies 1011, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030 & 1043
² Patients receiving concomitant NSAID treatment with tanezumab in long-term studies are included in the tanezumab + NSAID treatment group
³ Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID
Risk Difference: *p≤0.05 vs. placebo, †p ≤ 0.05 vs. active comparator

10.4.3. Comparison of Rates of Fracture in the Tanezumab Phase 3 Osteoarthritis Studies to Other Studies

To further investigate the clinical significance of the incidence rates of fracture in the tanezumab program, we analyzed the frequency of fractures in studies of osteoarthritis

patients outside of the tanezumab development program beginning with the NIH-sponsored Osteoarthritis Initiative (OAI) Study. The OAI Study is a nationwide multicenter four-year observational study of men and women with knee osteoarthritis or at risk for developing knee osteoarthritis. The OAI Study has recruited two primary cohorts, one with symptomatic knee osteoarthritis at baseline followed for worsening of the disease (progression cohort) and another without symptomatic knee osteoarthritis, but selected on the basis of having specific characteristics which give them an increased risk of developing incident symptomatic knee osteoarthritis during the study (incidence cohort).

The incidence of fractures recorded in the OAI Study is provided in the Table 38. The incidence of leg fractures ranged from 1.2 to 2.0% per year (or 9 to 20 events/1000 pt-yrs of observation) across the two cohorts. The incidence rates of all-cause leg fractures in the Phase 3 osteoarthritis studies with tanezumab monotherapy are consistent with the values from the OAI Study. The incidence of non-leg fractures in the OAI Study ranged from 2.6% to 4.2% on a yearly basis (or 26 to 42 events/1000 pt-yrs of observation) across both cohorts. The incidence of all-cause non-leg fractures in the tanezumab studies were generally lower even in the studies of longest duration than seen in the OAI Study.

Table 38. Incidence of Fractures in the Osteoarthritis Initiative Study

Time Interval	**Cohort**	**Leg Fracture** n (%)	**Non-leg Fracture** n (%)	**Any Fracture** n (%)
Year 1	Progression (n=1222)	15 (1.2%)	32 (2.6%)	47 (3.8%)
	Incidence (n=3029)	37 (1.2%)	85 (2.8%)	118 (3.9%)
Year 2	Progression (n=1166)	17 (1.5%)	40 (3.4%)	51 (4.4%)
	Incidence (n=2925)	36 (1.2%)	84 (2.9%)	120 (4.1%)
Year 3	Progression (n=1148)	23 (2.0%)	48 (4.2%)	62 (5.4%)
	Incidence (n=2920)	39 (1.3%)	90 (3.1%)	122 (4.2%)

These data were collected at baseline, 12 months, 24 months and 36 months
Cohort 1: Progression = individuals with osteoarthritis of knee at baseline
Cohort 2: Incidence = individuals at risk for development of OA of knee
For Year 1, Year 2 and Year 3, fractures are reported as during the last 12 months.
Patients may have experienced fractures in both non-leg and leg categories.
Non-leg fractures include hand, lower arm/wrist, shoulder/ clavicle/scapula, spine or back
Leg fractures include hip, knee (patella), lower leg/ankle, and foot bones

The rate of fractures in the Celecoxib Long-term Arthritis Safety Study (CLASS) was also reviewed. The incidence of all-cause leg and non-leg fractures combined in patients receiving active comparator (predominately NSAIDs) treatment in the tanezumab Phase 3 osteoarthritis studies was 0.9% (or 17 events/1000 pt-yrs). By comparison, the overall incidence of fractures in a total of 7968 patients (5746 [72%] with a diagnosis of hip or knee osteoarthritis and 2222 [28%] with a diagnosis of rheumatoid arthritis) who received daily NSAID medication in the form of celecoxib 400 mg BID, ibuprofen 800 mg TID, or diclofenac 75 mg BID for a mean follow-up period of approximately 7 months was 1.4% or 25 events/1000 pt-yrs. (4523 total pt-yrs of exposure). Thus, the event rate of fractures with active comparator treatment in the tanezumab osteoarthritis program was reasonably similar to that observed elsewhere with much larger NSAID exposure.

10.5. Peripheral Nerve Safety

Table 39 summarizes the incidence of the most common adverse events of abnormal peripheral sensation in the controlled Phase 3 osteoarthritis studies. Paresthesia (pins and needles sensation) was most frequently reported followed by hypoesthesia (numbness) and burning sensation. These adverse events were frequently reported by patients receiving tanezumab alone or in combination with NSAID treatment when compared to patients receiving either placebo or active comparator treatment. In general, the incidence of adverse events related to abnormal peripheral sensation was greatest in patients who received treatment with tanezumab in combination with an NSAID. The incidence of dysesthesia and decreased vibratory sensation did not exceed 2% in any treatment group; the incidence of dysesthesia was generally similar among treatment groups. Only paresthesia and hypoesthesia were reported in ≥2% of patients in the active comparator treatment group; no adverse event reports exceeded 2% in the placebo treatment group.

Table 39. Abnormal Peripheral Sensations: Incidence of Most Common Adverse Events (≥ 0.5%), Any Adverse Event, Adverse Events Causing Withdrawal, and Serious Adverse Events in the Controlled Phase 3 Osteoarthritis Studies

	placebo	tanezumab			tanezumab + NSAID			Active Comparator
		2.5 mg	5 mg	10 mg	2.5 mg	5 mg	10 mg	
	(N=1029)	(N=401)	(N=1581)	(N=1684)	(N=157)	(N=686)	(N=687)	(N=1266)
Most Common Adverse Events								
Allodynia	0 (0.0)	0 (0.0)	1 (0.1)	13 (0.8)	1 (0.6)	1 (0.1)	2 (0.3)	1 (0.1)
Burning sensation	1 (0.1)	2 (0.5)	15 (0.9)	24 (1.4)	0 (0.0)	8 (1.2)	12 (1.7)	7 (0.6)
Decreased vibratory sensation	4 (0.4)	0 (0.0)	13 (0.8)	9 (0.5)	0 (0.0)	6 (0.9)	7 (1.0)	2 (0.2)
Dysesthesia	4 (0.4)	1 (0.2)	4 (0.3)	14 (0.8)	0 (0.0)	3 (0.4)	5 (0.7)	4 (0.3)
Hyperesthesia	1 (0.1)	1 (0.2)	8 (0.5)	19 (1.1)	0 (0.0)	4 (0.6)	7 (1.0)	0 (0.0)
Hypoesthesia	9 (0.9)	15 (3.7)	54 (3.4)	67 (4.0)	2 (1.3)	36 (5.2)	35 (5.1)	27 (2.1)
Paresthesia	17 (1.7)	14 (3.5)	88 (5.6)	110 (6.5)	4 (2.5)	48 (7.0)	62 (9.0)	29 (2.3)
Adverse Events Causing Withdrawal*								
	1 (0.1)	1 (0.2)	13 (0.8)	21 (1.2)	1 (0.6)	10 (1.5)	11 (1.6)	3 (0.2)
Serious Adverse Events*								
	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.6)	0 (0.0)	1 (0.1)	1 (0.1)

Pooled analysis of controlled Phase 3 osteoarthritis studies 1011,1014,1015,1017, 1018,1025,1026,1027, & 1030
* Includes adverse events of: allodynia, burning sensation, decreased vibratory sense, dysesthesia, formication, hyperesthesia, hyperpathia, hypoesthesia, hypoesthesia facial, hypoesthesia oral, intercostal neuralgia , neuralgia, neuritis, paresthesia, paresthesia oral, sensory disturbance, sensory loss, thermohypoesthesia

Sixty-one (61) patients discontinued study participation due to adverse events of abnormal peripheral sensation. The highest incidence occurred in patients treated with either tanezumab 5 mg or 10 mg in combination with NSAIDs. In the tanezumab 5 mg and 10 mg monotherapy treatment groups, 13 (0.8%) and 21 (1.2%) patients, respectively, discontinued study participation due to an adverse event related to abnormal peripheral sensation. One (0.1%) placebo-treated patient and 3 (0.2%) NSAID-treated patients also withdrew from study participation due to an adverse event of abnormal peripheral sensation. Adverse events of abnormal peripheral sensation were reported as serious in 4 patients (one patient each receiving tanezumab 10 mg monotherapy, tanezumab 2.5 mg or 10 mg in combination with an NSAID, or active comparator).

A summary of peripheral polyneuropathies reported as adverse events in the controlled Phase 3 osteoarthritis studies is provided in Table 40. In general, the incidence of adverse events was low with no individual or total reports exceeding 2.5% in any treatment group.

Table 40. Peripheral Polyneuropathies Reported as Adverse Events, Adverse Events Causing Withdrawal, and Serious Adverse Events in the Controlled Phase 3 Osteoarthritis Studies

n (%)	placebo	tanezumab			tanezumab + NSAID			Active Comparator
		2.5 mg	5 mg	10 mg	2.5 mg	5 mg	10 mg	
	(N=1029)	(N=401)	(N=1581)	(N=1684)	(N=157)	(N=686)	(N=687)	(N=1266)
Adverse Events								
Axonal Neuropathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Demyelinating Polyneuropathy	0 (0.0)	0 (0.0)	2 (0.1)	1 (0.1)	1 (0.6)	0 (0.0)	2 (0.3)	0 (0.0)
Diabetic Neuropathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)
Guillain-Barre Syndrome	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral Neuropathy	0 (0.0)	2 (0.5)	12 (0.8)	14 (0.8)	0 (0.0)	6 (0.9)	10 (1.5)	4 (0.3)
Peripheral Sensory Neuropathy	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral Sensorimotor Neuropathy	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Polyneuropathy	1 (0.1)	0 (0.0)	2 (0.1)	1 (0.1)	1 (0.6)	4 (0.6)	3 (0.4)	2 (0.2)
Toxic Neuropathy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any Adverse Event								
	1 (0.1)	3 (0.7)	19 (1.2)	18 (1.1)	2 (1.3)	10 (1.5)	17 (2.5)	7 (0.6)
Adverse Events Causing Withdrawal								
	0 (0.0)	1 (0.2)	4 (0.3)	4 (0.2)	1 (0.6)	2 (0.3)	4 (0.6)	2 (0.2)
Serious Adverse Events								
	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)

Pooled analysis of controlled Phase 3 osteoarthritis studies 1011, 1014,1015,1017,1018,1025,1026,1027 &1030
As Guillain Barre Syndrome is a demyelinating polyneuropathy, this adverse event term has also been included in this table.

The most frequently reported adverse events across all treatments were peripheral neuropathy and polyneuropathy and the incidence of both were greater in patients receiving tanezumab as compared to treatment with an active comparator or placebo. Few patients withdrew from study participation due adverse events associated with peripheral polyneuropathies but were more common in patients receiving tanezumab treatment. Peripheral polyneuropathy was reported as serious adverse event in 2 patients (one each in the tanezumab 5 mg treatment group and tanezumab 2.5 mg/NSAID combination treatment group).

In all tanezumab studies, patients who report abnormal peripheral sensations and/or have clinically significant neurological exam findings undergo a neurological consultation. In the controlled Phase 3 osteoarthritis studies, a majority of patients in the tanezumab treatment groups whose final neurological consultations were categorized as having a new or worsening peripheral neuropathy based on clinically significant signs or diagnostic tests were diagnosed with some form of mononeuropathy, predominantly carpal tunnel syndrome (a common mononeuropathy of the median nerve) or radiculopathy. A smaller proportion of

patients in the tanezumab treatment groups categorized as having a new or worsening peripheral neuropathy were diagnosed with a polyneuropathy. These results would not be the expected pattern for a neurotoxic compound, which typically would cause a length-dependent polyneuropathy in the majority of affected patients.

11. ASSESSMENT OF EMERGING BENEFIT-RISK OF TANEZUMAB

A comparison between NNT and NNH can be used as a very basic comparison of benefit versus risk for a population of patients who may benefit from a treatment. When the NNH/NNT > 1 or NNT < NNH, then fewer patients need to be treated to achieve benefit than will be treated to have one additional occurrence of an adverse event. However, NNT and NNH by themselves do not account for the patients' value of the benefit or the value of the harm, respectively.

An assessment of the number needed to harm (NNH) with tanezumab in comparison to active comparator for the symptomatic treatment of osteoarthritis is provided in Table 41.

Table 41. NNH with Tanezumab versus Active Comparator in the Treatment of Osteoarthritis

Number of patients treated with tanezumab instead of active comparator[1] to observe 1 additional event	tanezumab monotherapy			tanezumab + NSAID[2]		
	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
Rapidly progressive osteoarthritis	--	316	181	106	83	50
Rapidly progressive osteoarthritis - Sensitivity analysis[3]	397	206	131	90	54	37
All-cause total joint replacements	368	138	270	28	21	17

[1] Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID; Studies 1011, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030, & 1043
[2] 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 non-controlled long-term studies
[3] Events with adjudication outcomes of "Insufficient information to distinguish osteonecrosis from OA," "Lack of consensus" and "Insufficient information to distinguish normal vs. rapid OA progression analyzed as rapidly progressive OA

The NNH were determined for rapidly progressive osteoarthritis from all Phase 3 osteoarthritis studies. NNH determinations for rapidly progressive osteoarthritis were also made based on the results of a sensitivity analysis of all Phase 3 osteoarthritis described in Section 6.5.3. Finally, NNH determinations were made for all-cause total joint replacements.

The NNH for rapidly progressive osteoarthritis favors tanezumab monotherapy over tanezumab/NSAID combination therapy by a wide margin. The NNH for rapidly progressive osteoarthritis with tanezumab 5 mg monotherapy was 1.7-fold greater than that of tanezumab 10 mg monotherapy. There were no adjudicated events of rapidly progressive osteoarthritis with tanezumab monotherapy 2.5 mg. The NNH for rapidly progressive osteoarthritis on the basis of the sensitivity analysis showed a benefit of tanezumab 2.5 mg monotherapy over higher doses of tanezumab monotherapy in osteoarthritis patients. The NNH with tanezumab 5 mg was still favorable when compared to tanezumab 10 mg monotherapy. The NNH for all-cause total joint replacements also favored tanezumab monotherapy over tanezumab/ NSAID combination therapy by over 10-fold. Tanezumab 5 mg monotherapy was associated with the least favorable NNH for all-cause total joint replacements as compared to tanezumab 2.5 mg or 10 mg monotherapy.

In the analysis of NNT, all controlled Phase 3 osteoarthritis studies which included a Week 16 BOCF landmark analysis of tanezumab monotherapy or tanezumab/NSAID combination therapy versus active comparator were examined. The NNT were determined on the basis of observed differences in the WOMAC Pain responder rates of ≥50%, ≥70%, and ≥90% with tanezumab versus active comparator treatment. Studies 1015, 1018 and 1025 were pooled to make the determinations of NNT for tanezumab 5 mg and 10 mg monotherapy versus active comparator. There were no Phase 3 osteoarthritis studies in which both tanezumab 2.5 mg and active comparator were included in the same study to permit a determination of NNT of tanezumab 2.5 mg versus active comparator. Study 1017 was used to make the NNT determination of tanezumab 2.5 mg/NSAID combination therapy versus NSAID treatment alone and Studies 1017 and 1025 were pooled to make the NNT determination of tanezumab 5 mg/NSAID combination therapy or tanezumab 10 mg/NSAID combination therapy versus NSAID treatment alone. The NNT values are provided in Table 42.

Table 42. NNT with Tanezumab versus NSAIDs in the Treatment of Osteoarthritis

Number of patients treated with tanezumab instead of active comparator[1] to observe 1 additional responder	tanezumab monotherapy[2]			tanezumab + NSAID[3]		
	2.5 mg --	5 mg N=852	10 mg N=858	2.5 mg N=157	5 mg N=686	10 mg N=687
WOMAC Pain ≥50% Response	--	10	10	27	8	6
WOMAC Pain ≥70% Response	--	9	11	29	11	7
WOMAC Pain ≥90% Response	--	20	22	26	21	14

[1] Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID
[2] Efficacy determined by BOCF imputation at Week 16 landmark analysis for Studies 1015, 1018, & 1025 combined
[3] Efficacy determined by BOCF imputation at Week 16 landmark analysis for Study 1017 alone (2.5 mg),or Studies 1017, & 1025 combined (5 mg and 10 mg)

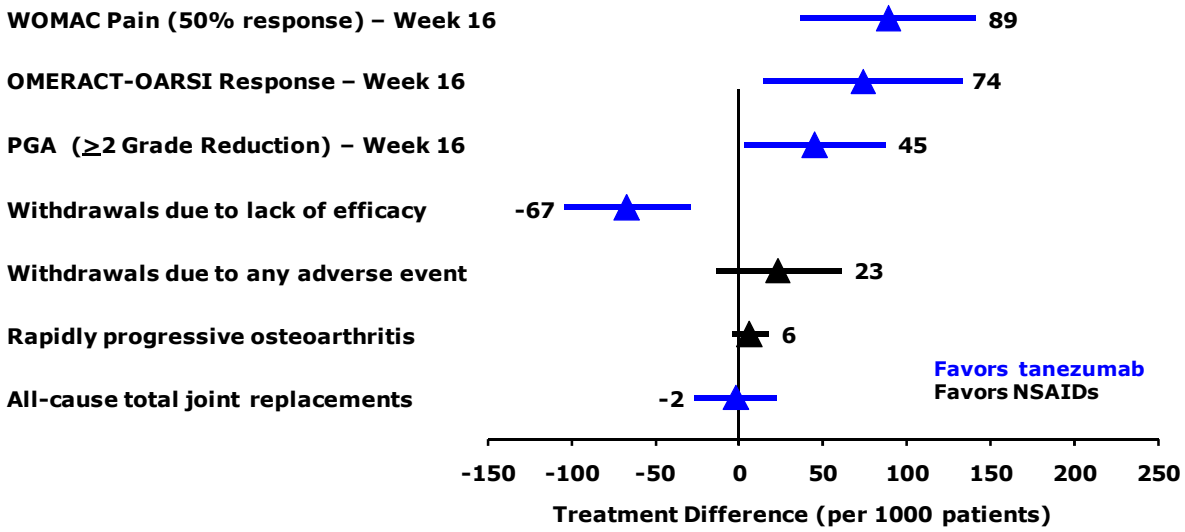
The NNT to observe one additional patient with a WOMAC Pain response rate of 50-90% when treated with tanezumab 5 mg or 10 mg monotherapy instead of an active comparator was on the order 9 to 22 patients and similar across the doses. The NNTs with tanezumab 5 mg or 10 mg monotherapy were marginally higher than with these same doses combined with NSAID treatment.

In summary, the NNT/NNH analyses are most favorable for the continued development of tanezumab 2.5 mg and tanezumab 5 mg monotherapy in the treatment of osteoarthritis.

To corroborate the NNT/NNH analyses above, the benefit and risk outcomes in Study 1025 were evaluated by a different methodology. Study 1025 was a large (N=2700) randomized double-blind NSAID-controlled study which allows for a direct comparison of tanezumab 5 mg and tanezumab 10 mg monotherapy versus NSAID treatment alone as well as a direct comparison of tanezumab/NSAID combination therapy versus NSAID treatment alone without the confounding effects related to pooling of studies.

The treatment differences are provided as graphic displays of the risk difference per 1000 patients treated for each defined comparison. A comparison of benefits and risks of tanezumab 5 mg or 10 mg monotherapy versus NSAID treatment in Study 1025 are provided in Figure 35 and Figure 36, respectively. When benchmarked against NSAID treatment,

Figure 35. Benefit-Risk Differences per 1000 Patients Treated: Tanezumab 5 mg Monotherapy vs. NSAID Treatment in Study 1025

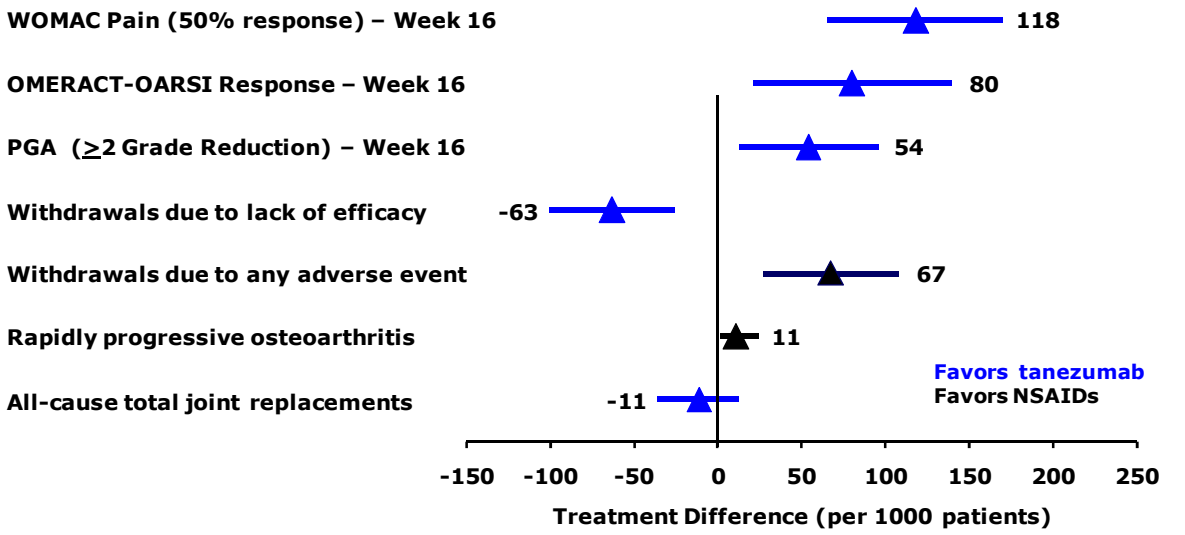


▲ Represent mean treatment difference per 1000 patients; bars indicate 95% CI

PGA = Patient's Global Assessment of Osteoarthritis

OMERACT-OARSI Response: ≥50% and ≥2 points in either the WOMAC Pain or Physical Function subscales, or at least 2 of the following: (1) ≥20% and ≥1 point in the WOMAC Pain subscale; (2) ≥20% and ≥1 point in the WOMAC Physical Function subscale; (3) ≥20% and ≥1 point in the PGA

Figure 36. Benefit-Risk Differences per 1000 Patients Treated: Tanezumab 10 mg Monotherapy vs. NSAID Treatment in Study 1025



▲ Represent mean treatment difference per 1000 patients; bars indicate 95% CI

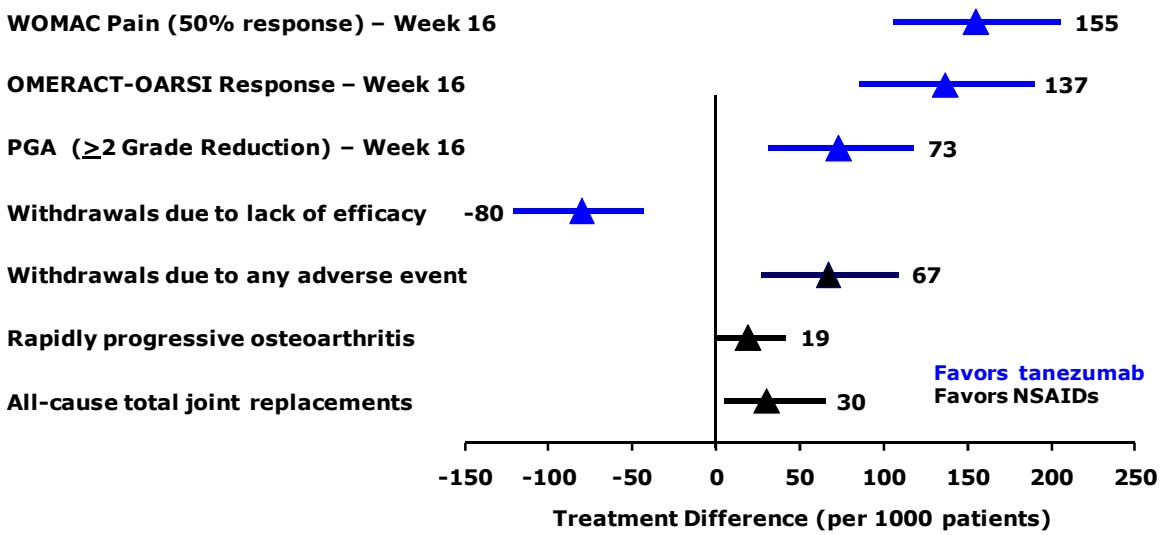
PGA = Patient's Global Assessment of Osteoarthritis

OMERACT-OARSI Response: ≥50% and ≥2 points in either the WOMAC Pain or Physical Function subscales, or at least 2 of the following: (1) ≥20% and ≥1 point in the WOMAC Pain subscale; (2) ≥20% and ≥1 point in the WOMAC Physical Function subscale; (3) ≥20% and ≥1 point in the PGA

tanezumab 5 mg monotherapy is associated with a modest reduction in the number of patients with a clinically meaningful efficacy response in exchange for a reduction in the number of patients with an adverse event causing withdrawal from treatment, rapidly progressive osteoarthritis or all-cause total joint replacement compared to tanezumab 10 mg monotherapy.

A comparison of benefits and risks of tanezumab (5-10 mg) in combination with NSAIDs versus NSAID treatment alone in Study 1025 is shown in Figure 37. While tanezumab/ NSAID combination therapy results in a large number of patients achieving a clinically meaningful response over NSAID treatment alone, the increased response rate is negated by a greater number of patients experiencing a treatment limiting or irreversible safety outcome. Importantly, tanezumab/NSAID combination treatment does not appear to confer any advantages over tanezumab monotherapy.

Figure 37. Benefit-Risk Differences per 1000 Patients Treated: Tanezumab 5-10 mg /NSAID Combination Therapy vs. NSAID Alone Treatment in Study 1025



▲ Represent mean treatment difference per 1000 patients; bars indicate 95% CI
PGA = Patient's Global Assessment of Osteoarthritis
OMERACT-OARSI Response: ≥50% and ≥2 points in either the WOMAC Pain or Physical Function subscales, or at least 2 of the following: (1) ≥20% and ≥1 point in the WOMAC Pain subscale; (2) ≥20% and ≥1 point in the WOMAC Physical Function subscale; (3) ≥20% and ≥1 point in the PGA

12. BENEFIT-RISK OPTIMIZATION

Based on the thorough assessment of the joint-safety related outcomes, the following measures have been identified to optimize further the benefit-risk profile of tanezumab for continued clinical development of this therapy. The measures outlined below would be applicable to future clinical studies of osteoarthritis patients as well as other chronic pain patients with some modifications as deemed appropriate depending on the patient population selected for study.

1. Exclude chronic concomitant NSAID use with tanezumab

Of the 67 tanezumab-treated patients with an adjudicated event of rapidly progressive osteoarthritis, 47 or approximately 70% were identified in patients who were randomized to tanezumab/NSAID combination treatment or received NSAIDs concomitantly with tanezumab treatment. Given the lack of information regarding the mechanism(s) responsible for the interaction of tanezumab with NSAIDs and the lack of compelling benefit of the tanezumab/NSAID combination therapy over tanezumab monotherapy, there is no reason to continue the development of tanezumab as adjunctive therapy to NSAIDs in the treatment of osteoarthritis or any other chronic pain condition.

The data suggest that short-term treatment with NSAIDs in patients receiving tanezumab is not associated with elevated risk of rapidly progressive osteoarthritis. Therefore, occasional use of NSAIDs to relieve pain appears to be acceptable in situations such as outpatient diagnostic procedures (e.g., dental procedures) or limited accidental injury (e.g., ankle sprains, minor fractures, minor burns/sunburns). Based on the available clinical trial data, NSAIDs can be used concomitantly with tanezumab for a period of up to 90 days over the period of approximately one year without increasing the risk of rapidly progressive osteoarthritis.

2. Exclude tanezumab 10 mg from further investigation in osteoarthritis and application of a more cautious approach to escalated doses in other non-osteoarthritic chronic pain conditions

There were 12 events of rapidly progressive osteoarthritis in patients treated with tanezumab 10 mg monotherapy in the Phase 3 osteoarthritis studies and one event of rapidly progressive osteoarthritis in a chronic low back pain patient treated with tanezumab 20 mg. Taken together, 13 of the 67 (19%) tanezumab-treated patients with rapidly progressive osteoarthritis received tanezumab 10-20 mg monotherapy.

Compared to lower monotherapy doses of 2.5 mg or 5 mg, tanezumab 10 mg was not associated with additional clinical benefit in the treatment of osteoarthritis and the overall safety profile was inferior to lower doses. In addition, the rate of rapidly progressive osteoarthritis was nearly two-fold higher in osteoarthritis patients treated with tanezumab 10 mg versus tanezumab 5 mg. These comparisons support discontinuation of tanezumab 10 mg monotherapy from further clinical development for the treatment of osteoarthritis. The elimination of tanezumab 10 mg in the treatment of osteoarthritis would be an effective

additional step in reducing the risk of rapidly progressive osteoarthritis in this patient population.

In other chronic pain populations the benefit-risk of tanezumab 10 mg monotherapy versus lower doses has not been as definitively characterized and further evaluation of tanezumab 10 mg in chronic pain populations of lower risk for rapidly progressive osteoarthritis would be warranted. For example, in a large chronic low back pain study tanezumab 10 mg was much more efficacious than tanezumab 5 mg while no events of rapidly progressive osteoarthritis were observed in patients treated with either dose. With the exception of chronic low back pain where tanezumab 20 mg was clearly demonstrated to be no more efficacious than tanezumab 10 mg, the same considerations as outlined above for tanezumab 10 mg would be given to the study of tanezumab 20 mg in cancer pain or neuropathic pain.

There were no events of rapidly progressive osteoarthritis in patients treated with tanezumab 2.5 mg monotherapy in the Phase 3 osteoarthritis studies. This dose appears to have a favorable efficacy profile as well when compared to tanezumab 5 mg and may be the optimal initial dose for patients with osteoarthritis thereby reserving tanezumab 5 mg for those who do not respond adequately to tanezumab 2.5 mg or initially present with severe pain.

The steps outlined above account for 60 of the 67 events of rapidly progressive osteoarthritis evident in tanezumab-treated patients. The remaining 7 events of rapidly progressive osteoarthritis associated with tanezumab treatment occurred in osteoarthritis patients treated with tanezumab 5 mg monotherapy. The incidence of rapidly progressive osteoarthritis with tanezumab 5 mg monotherapy was in excess of that observed with active comparator treatment. An additional measure to optimize the benefit-risk profile of tanezumab 2.5 and 5 mg monotherapy for the treatment of osteoarthritis is based on the following considerations.

3. Discontinue patients who do not respond adequately to initial doses of tanezumab

Patients who do not respond to initial doses of tanezumab appear unlikely to respond to subsequent doses and some of these non-responding patients were identified with rapidly progressive osteoarthritis. While not a risk management measure per se, discontinuation of non-responding patients does ensure that the optimal benefit-risk ratio is attained given that patients who do not respond with adequate pain relief after an initial course of tanezumab therapy are being needlessly exposed to risk in the face of no benefit.

Overall, 37.3% (25/67) of tanezumab-treated patients with rapidly progressive osteoarthritis did not respond with a $\geq$30% reduction in pain after 8 or 16 weeks of treatment (1-2 doses of study medication) and yet most went on to receive further treatment. Excluding those events that would be eliminated by virtue of the risk management steps outlined in (1) and (2) above, 3 of the 7 events of rapidly progressive osteoarthritis with tanezumab 5 mg monotherapy occurred in patients who did not report $\geq$30% reduction in pain following their first or second administration of tanezumab. Of these 3 patients, 2 received more than 2 doses of tanezumab. Thus, with early discontinuation of tanezumab treatment, over one-quarter of the events observed with tanezumab 5 mg monotherapy may have been averted.

4. Exclude patients with pre-existing rapidly progressive osteoarthritis from treatment with tanezumab

The evidence accumulated in the analyses of the tanezumab clinical program indicates a proportion of the patients enrolled in the osteoarthritis clinical trials had pre-existing rapidly progressive osteoarthritis prior to study entry and receiving study medication. Tanezumab administration may have further accelerated the disease process. Future clinical studies will be designed to evaluate patients for evidence of rapidly progressive osteoarthritis and exclude patients with rapidly progressive osteoarthritis from treatment with tanezumab. This would include all patients presenting with an unusual amount of bone loss on a single x-ray or rapid loss of cartilage when prior x-rays are available to determine the rate of joint space narrowing. There was one patient treated tanezumab 5 mg monotherapy with pre-existing rapidly progressive osteoarthritis.

In the process of screening patients for rapidly progressive osteoarthritis, it may also be possible to identify patients with joint space narrowing of the hip in the absence of osteophytes (atrophic osteoarthritis) or with pre-existing subchondral insufficiency fractures, and exclude those patients as well on the basis that they are at higher risk for rapidly progressive osteoarthritis.

5. Treat only those patients who have inadequate response or are intolerant to first-line therapy or patients who have contraindications for existing standard of care

In general, previously conducted studies with tanezumab have enrolled patients who meet these criteria. With regard to osteoarthritis patients enrolled in the tanezumab studies, the symptomatic and extent of structural disease appears to be more severe than patients enrolled in previous studies conducted with other agents such as NSAIDs or opioids. However, additional measures to further optimize future osteoarthritis study populations may be appropriate and beneficial, for example, limiting treatment to only patients with severe pain.

The overall effect of the benefit-risk optimization plan outlined above on the incidence of rapidly progressive osteoarthritis in patients with osteoarthritis is shown in Figure 38. The observed incidence of rapidly progressive osteoarthritis is shown for tanezumab-treated patients overall, patients who received tanezumab monotherapy 2.5-10 mg, patients treated with tanezumab 2.5-10 mg/NSAID combination therapy and patients who received an active comparator in the Phase 3 osteoarthritis studies. On the right, are the empirical incidence rates of rapidly progressive osteoarthritis if the risk management plans outlined above had been in place prior to the start of these same studies. The incidence of rapidly progressive osteoarthritis with tanezumab 2.5 mg, tanezumab 5 mg, or both monotherapy doses combined in patients without pre-existing rapidly progressive osteoarthritis and who responded to treatment with a $\geq$30% reduction in WOMAC Pain is comparable to the patients receiving active comparator treatment. The same analyses based on the results the sensitivity analysis for rapidly progressive osteoarthritis (Figure 39) corroborate the results observed with events of adjudicated rapidly progressive osteoarthritis alone.

Figure 38. Rapidly Progressive Osteoarthritis: Observed Results and Effect of the Benefit-Risk Optimization Plan

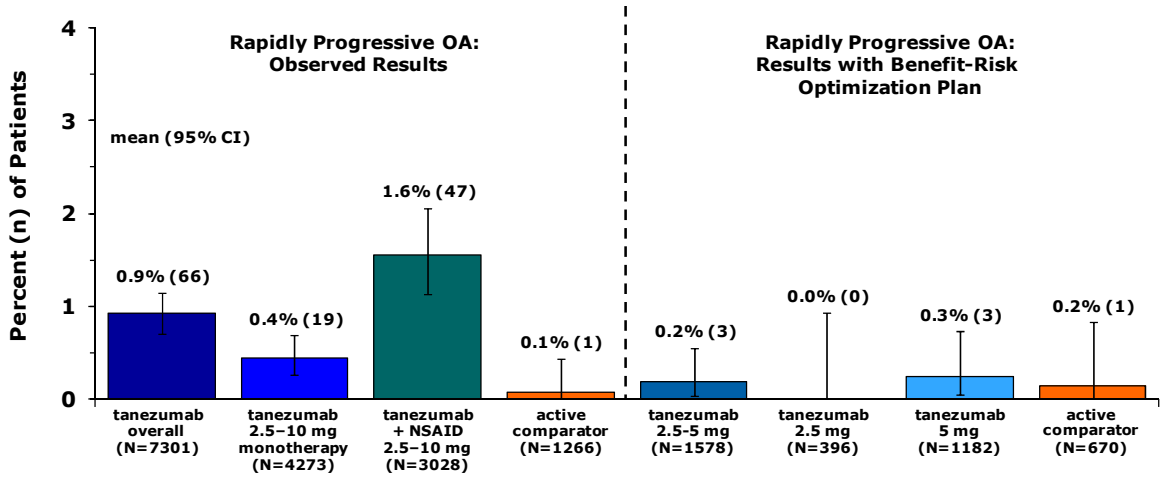
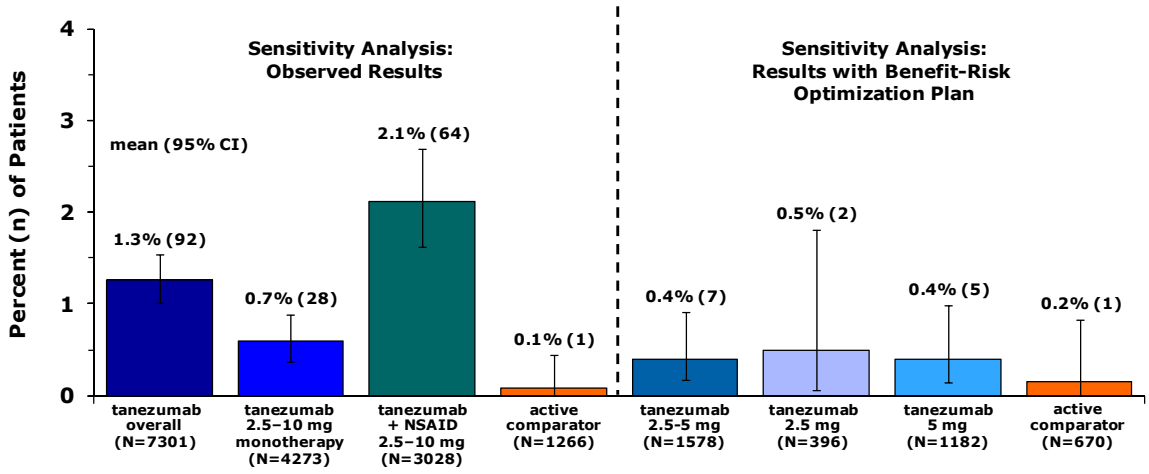


Figure 39. Sensitivity Analysis of Rapidly Progressive Osteoarthritis: Observed Results and the Effect of the Benefit-Risk Optimization Plan



[1] Adjudication outcomes of "Insufficient information to distinguish osteonecrosis from OA," "Lack of consensus" and "Insufficient information to distinguish normal vs. rapid OA progression analyzed as rapidly progressive OA

The components of the benefit-risk optimization plan were also examined using time to event (survival) analysis with the Cox Proportional Hazard Model. The studies evaluated were the same as those used to derive the empirical estimates shown in Figure 38. The Cox Proportional Hazard Model was formulated using additive terms for tanezumab dose (centered at 5 mg) [linear predictor], concomitant NSAID use [categorical covariate/factor], and active comparator treatment [categorical covariate/factor] on log hazard. Based on the model assumptions of covariate independence, the hazard ratios were estimated as 1.96 [1.29-2.96] ($p<0.01$), 3.16 [1.84-5.44] ($p<0.001$) and 0.81 [0.1-6.72], for dose, concomitant NSAID use and active comparator terms, respectively. A reduction in the tanezumab dose from 10 mg to 5 mg while avoiding concomitant NSAID use indicates a 6.2-fold (1.96∗3.16)

decrease in relative hazard for rapidly progressive osteoarthritis.

With implementation of the risk management measures described above, the estimated incidence (95% CI) of rapidly progressive osteoarthritis determined in this analysis weighted over the distribution of exposure times were as follows: 0.16% (0.10%, 0.24%) with tanezumab 2.5 mg alone, 0.22% (0.14%, 0.31%) with tanezumab 5 mg alone, and 0.05% (0.00%, 0.08%) with active comparator. No differences were evident between tanezumab 2.5 mg and tanezumab 5 mg doses given the underlying precision of these estimates and the results lend further support to indicate the effectiveness of the benefit-risk optimization plan as these estimates are substantially lower than the observed rates of rapidly progressive osteoarthritis.

Increased surveillance measures would also be incorporated into all future studies of tanezumab. The measures outlined below would be applicable to future clinical studies of osteoarthritis patients as well as other chronic pain patients with some modifications as deemed appropriate depending on the patient population selected for study.

1. Comprehensive evaluation of osteoarthritis medical history prior to study entry
   - Prestudy assessment of joints with osteoarthritis (range of motion, pain in joints) to establish a baseline status
2. Radiologic assessment of bilateral knee and hip for osteoarthritis structural disease
   - All patients will undergo pre-study bilateral knee and hip x-rays
   - All x-rays assessed by an expert Central Reader to determine patient eligibility for study participation
   - Other joints may be included in pre-study assessments if signs or symptoms indicate presence of osteoarthritis
3. Increased patient monitoring for severe persistent joint pain
   - An interactive voice response system will be utilized to collect information from patients of severe persistent pain in non-index joints on a daily basis
   - Patients with increased, severe, persistent joint pain during the study will undergo additional evaluation
4. Pre-specified adjudication and protocol stopping rules for rapidly progressive osteoarthritis
   - Events identified by Central Reader submitted for Adjudication Committee review
   - A data safety monitoring board will conduct unblinded interim analyses according to pre-specified stopping rules

13. CONCLUSIONS

The investigation and analyses related to joint-safety were comprehensive and based on tanezumab monotherapy exposure in over 6400 patients and tanezumab/NSAID combination therapy in 3400 patients. There were over 5000 patients who received tanezumab treatment alone or in combination with NSAIDs for 6 months or longer. The program was sufficient to define and characterize the adverse event of concern – rapidly progressive osteoarthritis – and evaluate the risk of rapidly progressive osteoarthritis in the context of the overall benefit-risk profile of tanezumab compared to standard of care. The efficacy responses to tanezumab are robust and durable. The longer-term effects of treatment (>1 year) are less certain.

After careful investigation we did not find evidence to indicate tanezumab is associated with an increased risk of osteonecrosis, a disease process quite distinct from osteoarthritis. Of the joint safety events that occurred and were adjudicated in the tanezumab program, all but two were related to osteoarthritis progression, joint injury, or diagnoses other than primary osteonecrosis. Osteonecrosis is a condition that is thought to be primarily caused by vascular insufficiency. There are several papers in the literature that report vascular effects of NGF, but the vast majority of these only indirectly test the potential role of endogenous NGF. The non-clinical investigations we have conducted found no evidence of an effect on the vasculature, bone, or joint in animals treated with large multiples of the clinical dose of tanezumab. Furthermore, there are no described vascular effects in animals that are null for either NGF or TrkA receptor.

The risk of rapidly progressive osteoarthritis with tanezumab monotherapy was well below that observed with tanezumab/NSAID combination therapy but greater than with placebo or active comparator treatment. A majority of patients identified with rapidly progressive osteoarthritis had advanced osteoarthritis of the affected joint prior to treatment. The event rate of all-cause joint replacements was comparable among placebo, active comparator, and tanezumab monotherapy treatment groups. Thus, the overall burden of total joint replacement was not increased in patients receiving tanezumab monotherapy even though a larger proportion of the total joint replacements were associated with greater radiological severity when compared to patients receiving placebo or an active comparator. Despite the possible procedural difficulty, the long-term outcomes of a total joint replacement in a patient with rapidly progressive osteoarthritis have not been shown to be largely different than for typical end-stage disease. Thus, in the situation where an excess frequency of total joint replacements above the background rate has not been observed, the case could be made that an increase in rapidly progressive osteoarthritis with tanezumab treatment represents an important radiological distinction but does not impact the ultimate clinical outcome.

The mechanisms responsible for rapidly progressive osteoarthritis associated with tanezumab treatment are uncertain but may result from interaction of pain relief leading to joint overloading in patients with pre-existing rapidly progressive osteoarthritis or susceptibility to such; the problem can be magnified or accelerated in presence of chronic NSAID administration.

The incidence of patients with rapidly progressive osteoarthritis or with possible risk factors for rapidly progressive osteoarthritis in the overall osteoarthritis population is not well defined. The evidence accumulated in the analyses of the tanezumab clinical program indicates a proportion of the patients enrolled in the clinical trials had pre-existing rapidly progressive osteoarthritis while others were identified with subchondral insufficiency fractures or atrophic osteoarthritis which are reported to be associated with an elevated risk of rapidly progressive osteoarthritis.

The efficacy profile of tanezumab has been well characterized in osteoarthritis and to a lesser extent in other chronic pain conditions. The results indicate tanezumab relieves pain and improves function to a clinically meaningful extent compared to placebo, NSAIDs, and opioids.

Benefit-risk optimization measures and strategies for increased patient surveillance have been developed as an outgrowth of the joint-related safety analyses to reduce the risk of rapidly progressive osteoarthritis in future studies of patients with osteoarthritis or other chronic pain conditions.

Based on the assessments of risk and benefit, we conclude that further clinical investigation of tanezumab is warranted with the additional benefit-risk optimization and surveillance measures employed as outlined in Section 12. Specifically, continued clinical development of tanezumab would include; (1) a limited osteoarthritis indication based upon submission of studies already completed or combined with any additional studies that are considered to be necessary following discussion with FDA, (2) Phase 3 clinical studies in patients with chronic low back pain, and (3) further exploratory development in other chronic pain conditions such as cancer pain, peripheral diabetic neuropathy, interstitial cystitis or chronic pancreatitis.

In osteoarthritis, we would intend to conduct studies to characterize the efficacy and safety of tanezumab 2.5 mg and tanezumab 5 mg monotherapy in patients with significant symptomatic disease inadequately controlled by NSAIDs and/or other forms of standard of care. We would also conduct gait analysis of joint loading or other studies examining the effects of tanezumab on osteoarthritic joints in order to elucidate the mechanism(s) underlying rapidly progressive osteoarthritis. In chronic low back pain patients, the Phase 3 studies would be designed to establish the appropriate therapeutic dose as well as the long-term efficacy and safety of tanezumab monotherapy at doses up to 10 mg in patients with significant symptomatic disease inadequately controlled by NSAIDs and/or other forms of standard of care. In other selected chronic pain conditions, additional short-term (16-week) dose-ranging studies of tanezumab monotherapy or with non-NSAID standard of care up to 20 mg with long-term extension studies for safety are necessary to determine whether full development in these conditions would be warranted.

14. LIST OF APPENDICES

14.1. Appendix 1

Listing of Clinical Studies

Table of Osteoarthritis Studies

Study Number/Title	Treatment (N)	Study Design	Duration of Treatment	Diagnosis and Criteria for Inclusion	Total Patients Randomized and Treated Study Status
Phase 1 and Phase 2 Osteoarthritis Studies					
A4091006 (RN624-CL001) A Phase 1/Phase 2, Randomized, Placebo-Controlled Double-Blind, Dose-Escalation Study of Safety, Pharmaco-kinetics and Efficacy of Single Intravenous Doses of RN624 (tanezumab) in Adults With Moderate-to-Severe Pain From Osteoarthritis of the Knee	Part 1: single-dose escalation tanezumab 3 μg/kg to 1000 μg/kg IV (30) placebo IV (12) Part 2: single-dose parallel group tanezumab 100 μg/kg IV (27) tanezumab 300 μg/kg IV (26) placebo IV (26)	R, PC, DB	8 weeks	Adult Male or Female with Moderate-to-Severe Pain from Osteoarthritis of the Knee	121 Fully Complete
A4091022 A Phase 1/2a, Randomized, Placebo-Controlled, Double Blind Dose-Escalation, Multicenter Study of the Safety, Tolerability, Efficacy and Pharmaco-kinetics, of a Single Intravenous Dose of PF-04383119 (tanezumab) in Japanese Patients with Moderate to Severe Pain from Osteoarthritis of the Knee	Part 1: single-dose escalation tanezumab 10 μg/kg to 200 μg/kg IV (67) placebo IV (16) Part 2: single-dose parallel group tanezumab 10 μg/kg 100 μg/kg IV (61 subset of part 1) placebo IV (16 subset of part 1)	R, PC, DB	8 weeks	Adult Japanese Male or Female with Moderate-to-Severe Pain from Osteoarthritis of the Knee	83 Fully Complete
A4091008 (RN624-CL006) A Randomized, Parallel Arm, Placebo-Controlled, Double-Blind, Multiple-Dose Study of the Safety and Efficacy of RN624 (tanezumab) in Adults with Moderate-to-Severe Pain due to Osteoarthritis of the Knee	tanezumab 10 μg/kg IV q8wks (74) tanezumab 25 μg/kg IV q8wks (75) tanezumab 50 μg/kg IV q8wks (72) tanezumab 100 μg/kg IV q8wks (74) tanezumab 200 μg/kg IV q8wks (72) placebo IV q8wks (73)	R, PC, DB, PG	16 weeks	Adult Male or Female with Moderate-to-Severe Pain from Osteoarthritis of the Knee	440 Fully Complete

Study Number/Title	Treatment (N)	Study Design	Duration of Treatment	Diagnosis and Criteria for Inclusion	Total Patients Randomized and Treated Study Status
A4091009 (RN624-CL007) Open-Label, Multiple-Dose Study of the Safety and Efficacy of RN624 (tanezumab) in Adults with Pain due to Osteoarthritis of the Knee (parent study: A4091008)	tanezumab 50 μg/kg IV q8wks (281)	OL	Up to 1 year	Adult Male or Female with Moderate-to-Severe Pain from Osteoarthritis of the Knee	281 Fully Complete
Phase 3 Controlled Osteoarthritis Studies					
A4091011 A Phase 3 Randomized, Double-Blind, Placebo-Controlled Multicenter Study of the Analgesic Efficacy and Safety of Tanezumab in Patients with Osteoarthritis of the Knee	tanezumab 2.5 mg IV q8wks (172) tanezumab 5 mg IV q8wks (172) tanezumab 10 mg IV q8wks (174) placebo IV q8wks (172)	R, DB, PC, PG	24 weeks	Adult Male or Female with Moderate-to-Severe Pain from Osteoarthritis of the Knee	690 Fully Complete
A4091014 A Phase 3 Randomized, Double-Blind, Placebo-Controlled Multicenter Study of the Analgesic Efficacy and Safety of Tanezumab in Patients with Osteoarthritis of the Hip	tanezumab 2.5 mg IV q8wks (155) tanezumab 5 mg IV q8wks (154) tanezumab 10 mg IV q8wks (157) placebo IV q8wks (155)	R, DB, PC, PG	24 weeks	Adult Male or Female with Moderate-to-Severe Pain from Osteoarthritis of the Hip	621 Fully Complete
A4091015 A Phase 3 Randomized, Double-Blind Placebo and Naproxen Controlled Multicenter Study of the Analgesic Efficacy and Safety of Tanezumab in Patients with Osteoarthritis of the Knee	tanezumab 5 mg IV q8wks (206) tanezumab 10 mg IV q8wks (208) naproxen 500 mg BID PO (206) placebo matching active PO and IV (208)	R, DB, PC, AC, PG	16 weeks	Adult Male or Female with Moderate-to-Severe Pain from Osteoarthritis of the Knee	828 Fully Complete

Study Number/Title	Treatment (N)	Study Design	Duration of Treatment	Diagnosis and Criteria for Inclusion	Total Patients Randomized and Treated Study Status
A4091018 A Phase 3 Randomized, Double-Blind Placebo and Naproxen Controlled Multicenter Study of the Analgesic Efficacy and Safety of Tanezumab in Patients with Osteoarthritis of the Hip or Knee	tanezumab 5 mg IV q8wks (211) tanezumab 10 mg IV q8wks (209) naproxen 500 mg BID PO (211) placebo matching active PO and IV (209)	R, DB, PC, AC, PG	16 weeks	Adult Male or Female with Moderate-to-Severe Pain from Osteoarthritis of the Hip or Knee	840 Fully Complete
A4091017 A Phase 3, Randomized, Double-Blind, Controlled, Multi-Center Study of the Analgesic Efficacy and Safety of Tanezumab Added On to Diclofenac SR in Patients with Osteoarthritis of the Knee or Hip	tanezumab 2.5 mg IV q8wks + diclofenac SR 75 mg BID PO (157) tanezumab 5 mg IV q8wks + diclofenac SR 75 mg BID PO (150) tanezumab 10 mg IV q8wks + diclofenac SR 75 mg BID PO (145) diclofenac SR 75 mg BID PO + placebo IV (152)	R, DB, PC, PG	24 weeks	Adult Male or Female with Moderate-to-Severe Pain from Osteoarthritis of the Hip or Knee	604 Terminated: Complete Enrollment, Incomplete Duration[d]
A4091025 A Phase 3, Multi-Center, Randomized, Double-Blind, Controlled Study of the Long-Term Analgesic Efficacy and Safety of Tanezumab Alone or in Combination with Non-Steroidal Anti-Inflammatory Drugs (NSAIDS[a]) Versus NSAIDS Alone in Patients with Osteoarthritis of the Knee or Hip	NSAID[a] + placebo IV (539) tanezumab 5 mg IV q8wks + placebo PO (541) tanezumab 5 mg IV q8wks+NSAID[a] (536) tanezumab 10 mg IV q8wks+placebo PO (542) tanezumab 10 mg IV q8wks+NSAID[a] (542)	R, DB, AC, PG	56 weeks	Adult Male or Female with Moderate-to-Severe Pain from Osteoarthritis of the Hip or Knee	2700 Terminated: Complete Enrollment, Incomplete Duration[d]
A4091026 A Phase 3 Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Tanezumab on Peripheral Nerve Function in Patients with Osteoarthritis	tanezumab 5 mg IV q8wks (73) tanezumab 10 mg IV q8wks (74) placebo IV q8wks (72)	R, DB, PC, PG	24 weeks	Adult Male or Female with Moderate-to-Severe Pain from Osteoarthritis of the Hip or Knee	219 (369 planned) Terminated: Incomplete Enrollment, Incomplete Duration[d]

Study Number/Title	Treatment (N)	Study Design	Duration of Treatment	Diagnosis and Criteria for Inclusion	Total Patients Randomized and Treated Study Status
A4091027 A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of the Analgesic Efficacy and Safety of Subcutaneous Administration of Tanezumab in Patients with Osteoarthritis of the Knee	tanezumab 2.5 mg SC q8wks (74) tanezumab 5 mg SC q8wks (63) tanezumab 10 mg SC q8wks (86) tanezumab 10 mg IV q8wks (84) placebo IV and SC q8wks (72)	R, DB, PC, PG	16 weeks	Adult Male or Female with Moderate-to-Severe Pain from Osteoarthritis of the Knee	379 (750 planned) Terminated: Incomplete Enrollment, Incomplete Duration[d]
A4091030 A Phase 3 Randomized, Double-Blind, Placebo- and Oxycodone-Controlled, Multicenter Study of the Efficacy and Safety of Tanezumab in Patients with Osteoarthritis of the Knee or Hip	tanezumab 5 mg IV q8wks (161) tanezumab 10 mg IV q8wks (150) oxycodone CR 10 - 40 mg PO q12h (158) placebo matching active PO and IV (141)	R, DB, AC, PG	16 weeks	Adult Male or Female with Moderate-to-Severe Pain from Osteoarthritis of the Hip or Knee	610 (800 planned) Terminated: Incomplete Enrollment, Incomplete Duration[d]
A4091040 A Phase 3, Double-Blind, Placebo-Controlled, Multicenter, Long-Term Safety Study of Tanezumab in Patients with Osteoarthritis of the Knee or Hip (parent study: A4091026)	tanezumab 5 mg IV q8wks + Standard of care (SOC) (7) tanezumab 10 mg IV q8wks + Standard of care (SOC) (4) Standard of care (SOC)[c] + placebo IV (10)	DB, PC, PG	80 weeks	Adult Male or Female with Moderate-to-Severe Pain from Osteoarthritis of the Hip or Knee	21 Terminated: Incomplete Enrollment, Incomplete Duration[d]
Phase 3 Non-Controlled Osteoarthritis Studies					
A4091016 A Phase 3, Multicenter, Randomized, Long-Term Study of the Safety of Tanezumab in Patients with Osteoarthritis of the Knee or Hip (parent studies: A4091011, A4091014, A4091015, A4091018)	tanezumab 2.5 mg IV q8wks (522) tanezumab 5 mg IV q8wks (832) tanezumab 10 mg IV q8wks (788)	R, PG	up to 2 years	Adult Male or Female with Moderate-to-Severe Pain from Osteoarthritis of the Hip or Knee	2142[b] Terminated: Complete Enrollment, Incomplete Duration[d]

Study Number/Title	Treatment (N)	Study Design	Duration of Treatment	Diagnosis and Criteria for Inclusion	Total Patients Randomized and Treated Study Status
A4091032 A Phase 3, Multicenter, Randomized, Long Term Study of the Safety of the Subcutaneous Administration of Tanezumab in Patients with Osteoarthritis of the Knee (parent study : A4091027)	tanezumab 2.5 mg SC q8wks (1) tanezumab 5 mg SC q8wks (0) tanezumab 10 mg SC q8wks (0)	R, PG	56 weeks	Adult Male or Female with Moderate-to-Severe Pain from Osteoarthritis of the Knee	1 Terminated: Incomplete Enrollment, Incomplete Duration[d]
A4091043 A Multicenter, Randomized, Double-Blind, Long Term Study of the Safety of Subcutaneous Administration of Tanezumab in Patients with Osteoarthritis of the Knee or Hip	tanezumab 2.5 mg SC q8wks (230) tanezumab 5 mg SC q8wks (222) tanezumab 10 mg SC q8wks (226)	R, DB, PG	56 weeks	Adult Male or Female with Moderate-to-Severe Pain from Osteoarthritis of the Hip or Knee	678 Terminated: Complete Enrollment, Incomplete Duration[d]

R = randomized; DB = double-blind; PC = placebo-controlled; AC = active-controlled; PG = parallel group; IV = intravenous; SC = subcutaneous; q8wks = every 8 weeks; OL= Open Label; q12 hrs = every 12 hours; PO = oral; CR = controlled release; SOC = standard of care; NA = not applicable

[a] NSAIDs = celecoxib 100 mg PO BID or naproxen 500 mg PO BID

[b] A total of 827 patients (38.6%) received tanezumab for the first time in study A4091016, following treatment with placebo (A4091011, A4091014, A4091015, A4091018) or naproxen (A4091015, A4091018)

[c] Patients randomized to placebo in Study A4091026 received 'Standard of Care' in Study A4091040

[d] Due to Clinical Hold

Table of Chronic Pain Studies

Study Number/Title	Treatment (N)	Study Design	Duration of Treatment	Diagnosis and Criteria for Inclusion	Total Patients Randomized and Treated Study Status
Phase 2 Ongoing Cancer Pain Studies					
A4091003 Phase 2 Randomized, Double-Blind, Placebo-Controlled Multicenter Efficacy and Safety Study of Tanezumab as Add-On Therapy to Opioid Medication In Patients with Pain Due to Bone Metastases	tanezumab 10 mg IV q8wk placebo IV q8wk treatment assignments are blinded	R, DB, PG, AC	8 weeks	Adult Male or Female with Pain Due to Bone Metastases	59 Ongoing
A4091029 A Phase 2, Open-Label Safety Extension Study of Tanezumab in Cancer Patients with Pain Due to Bone Metastases (parent study: A4091003)	tanezumab 10 mg IV q8wk	OL	32 weeks	Adult Male or Female with Pain Due to Bone Metastases	19[a] Ongoing
Phase 2 Controlled Chronic Pain Studies					
A4091004 Phase 2 Randomized, Double-Blind, Placebo and Active Controlled, Multicenter, Parallel Group Proof of Concept Study of the Analgesic Effects of Tanezumab (PF-04383119, formerly RN624) in Adult Patients with Chronic Low Back Pain	tanezumab 200 μg/kg IV (88) naproxen 500 mg BID PO (88) placebo matching active PO and IV (41)	R, DB, PC, AC, PG	8 weeks	Adult Male or Female with Chronic Low Back Pain	217 Fully Complete
A4091005 Phase 2 Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel Group, Proof of Concept Study of the Analgesic Effects of Tanezumab (PF-04383119) in Adult Patients with Post-Herpetic Neuralgia	tanezumab 50 μg/kg IV (33) tanezumab 200 μg/kg IV (32) placebo IV (31)	R, DB, PC, PG	8 weeks	Adult Male or Female with Post-Herpetic Neuralgia	96 Fully Complete

Study Number/Title	Treatment (N)	Study Design	Duration of Treatment	Diagnosis and Criteria for Inclusion	Total Patients Randomized and Treated Study Status
A4091007 (RN624-CL002) A Randomized, Placebo-Controlled, Dose Escalation Study of Safety, Pharmaco-kinetics and Analgesic Efficacy of Intravenous RN624 in Subjects Undergoing First Metatarsal Bunionectomy	tanezumab 10, 30, 100, 300, 1000 µg/kg IV (40) placebo IV (10)	R, DB, PC	8 weeks	Adult Male or Female Undergoing First Metatarsal Bunionectomy	50 Fully Complete
A4091010 A Phase 2, Multicenter, Randomized, Double Blind Placebo Controlled, Parallel Group Proof Of Concept Study Evaluating The Efficacy And Safety Of Tanezumab (PF-04383119) For The Treatment Of Pain Associated With Interstitial Cystitis	tanezumab 200 µg/kg IV (34) placebo IV (30)	R, DB, PC, PG	8 weeks	Adult Male or Female with Pain Associated with Interstitial Cystitis	64 Fully Complete
A4091012 A Randomized, Double-Blind, Multi-Dose, Active- And Placebo-Controlled, Multi-Center, Parallel Group Study of The Analgesic Effects Of Tanezumab In Adult Patients With Chronic Low Back Pain	tanezumab 5 mg IV q8wks (232) tanezumab 10 mg IV q8wks (295) tanezumab 20 mg IV q8wks (295) naproxen 500 mg BID PO (295) placebo matching active PO and IV (230)	R, DB, PC, AC, PG	16 weeks	Adult Male or Female with Chronic Low Back Pain	1347 Fully Complete
A4091019 A Phase 2, Multicenter, Randomized, Double-Blind Placebo-Controlled, Parallel Group Proof-Of-Concept Study Evaluating the Efficacy and Safety of Tanezumab for the Treatment of Pain Associated with Chronic Abacterial Prostatitis	tanezumab 20 mg IV (30) placebo IV (32)	R, DB, PC, PG	8 weeks	Adult Male with Pain Associated with Chronic Abacterial Prostatitis	62 Fully Complete

Study Number/Title	Treatment (N)	Study Design	Duration of Treatment	Diagnosis and Criteria for Inclusion	Total Patients Randomized and Treated Study Status
A4091023 A Phase 2, 16 Week, Multicenter, Randomized, Double Blind Placebo Controlled, Parallel Group Proof of Concept Study Evaluating the Efficacy and Safety of Tanezumab for the Treatment Of Pain Associated with Endometriosis	tanezumab 15 mg IV (22) placebo IV (25)	R, DB, PC, PG	8 weeks	Adult Females with Pain Associated with Endometriosis	47 Fully Complete
A4091031 A Phase 2 Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel Group, Proof of Concept Study of the Analgesic Effects of Tanezumab in Adult Patients with Diabetic Peripheral Neuropathy	tanezumab 20 mg SC q8wks (38) placebo SC q8wks (35)	R, DB, PC, PG	16 weeks	Adult Male or Female with Diabetic Peripheral Neuropathy	73 (160 planned) Terminated: Incomplete Enrollment, Incomplete Duration[b]
A4091035 A Phase 2b, Randomized, Double-Blind, Placebo-Controlled, Dose Ranging Study Evaluating the Efficacy and Safety of Tanezumab for the Treatment of Moderate to Severe Pain Associated with Interstitial Cystitis/ Painful Bladder Syndrome (IC/PBS)	tanezumab 1 mg SC q8wks (41) tanezumab 2.5 mg SC q8wks (37) tanezumab 10 mg SC q8wks (39) tanezumab 20 mg SC q8wks (40) placebo SC q8wks (42)	R, DB, PC, PG	16 weeks	Adult Male or Female with Pain Associated with Interstitial Cystitis	200 (300 planned) Terminated: Incomplete Enrollment, Incomplete Duration[b]
A4091044 A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of the Analgesic Efficacy and Safety of Tanezumab in Patients with Chronic Pancreatitis	tanezumab 20 mg SC (0) placebo SC (2)	R, DB, PC, PG	8 weeks	Adult Male or Female with Chronic Pancreatitis	2 (88 planned) Terminated: Incomplete Enrollment, Incomplete Duration[b]

Study Number/Title	Treatment (N)	Study Design	Duration of Treatment	Diagnosis and Criteria for Inclusion	Total Patients Randomized and Treated Study Status
Phase 2 Non-Controlled Chronic Pain Studies					
A4091039 A Randomized, Multicenter, Long Term Study of the Safety of Tanezumab in Patients with Chronic Low Back Pain (parent study: A4091012)	tanezumab 10 mg IV/SC q8wks (321) tanezumab 20 mg IV/SC q8wks (527)	R, DB	56 weeks	Adult Male or Female with Chronic Low Back Pain	848 Terminated: Complete Enrollment, Incomplete Duration[b]
R = randomized; DB = double-blind; PC = placebo-controlled; AC = active-controlled; PG = parallel group; IV = intravenous; SC = subcutaneous; q8wks = every 8 weeks; OL= Open Label; q12 hrs = every 12 hours; PO = oral; NA = not applicable [a] Recruitment as of 05 Feb 2012 [b] Due to Clinical Hold					

Table of Healthy Volunteer Studies

Study Number/Title	Treatment (N)	Study Design	Duration of Treatment	Diagnosis and Criteria for Inclusion	Total Subjects Randomized and Treated Study Status
A4091013 Pharmacokinetics and Safety of A Single Dose Subcutaneous or Intravenous Administration of Tanezumab in Healthy Volunteers: An Open-Label, Non-Randomized Phase 1 Study	tanezumab 10 mg IV (19) tanezumab 5 mg SC (20) tanezumab 10 mg SC (19) tanezumab 19 mg SC (18)	OL	8 weeks	Healthy Adult Male or Female	76 Fully Complete
A4091046 A Phase 1, Randomized, Double-Blind (Sponsor-Open), Placebo-Controlled Study To Examine The Density Of Intraepidermal Nerve Fibers After A Single Subcutaneous Administration Of Tanezumab In Healthy Volunteers	tanezumab 20 mg SC (14) placebo SC (14)	R, DB, PC, PG	8 weeks	Healthy Adult Male or Female	28 Fully Complete
R = randomized; DB = double-blind; PC = placebo-controlled; PG = parallel group; IV = intravenous; SC = subcutaneous; q8wks = every 8 weeks; OL= Open Label					

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