Peripheral Nerve Safety of Nerve Growth Factor Inhibition by Tanezumab: Pooled Analyses of Phase III Clinical Studies in over 5000 Patients with Osteoarthritis

Running heading: Neurological Safety of Nerve Growth Factor Inhibition by Tanezumab in Patients with Osteoarthritis

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Abstract

Background

Tanezumab, a humanized anti-nerve growth factor antibody, was developed for the treatment of pain associated with osteoarthritis. Due to its mechanism of action, peripheral nerve safety was assessed in all clinical studies.

Objectives

To summarize the neurological safety of intravenous (IV) and subcutaneous (SC) tanezumab versus placebo in patients with osteoarthritis.

Methods

Data were pooled from 3,389 patients across seven studies that investigated IV administration, and from 1,840 patients across three studies that investigated SC administration. The treatment period of each study ranged 16–24 weeks, and follow-up periods ranged 8–24 weeks. Neurological safety evaluations focused on adverse events (AEs) of abnormal peripheral sensation (APS), neurologic examinations, and consultations.

Results

Across datasets, the incidence of AEs of APS was higher in tanezumab groups versus placebo. Paresthesia and hypoesthesia were the most frequently reported AEs in tanezumab-treated patients, versus placebo. In both datasets, most AEs were of mild severity, resolved, and rarely resulted in discontinuation. In all treatment groups in both IV and SC studies, over 90% of patients had no new or worsened neurological examination abnormalities at the last study visit. Across datasets, mononeuropathy was diagnosed more frequently in tanezumab groups versus placebo. Polyneuropathy was diagnosed in ≤0.9% of patients in tanezumab and placebo groups.

Conclusions

Tanezumab IV or SC had an increased incidence of AEs of APS, such as paresthesia and hypoesthesia, and diagnoses of mononeuropathy versus placebo. However, tanezumab was not associated with generalized peripheral neuropathy.

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Key Points

- The peripheral nerve safety of tanezumab, a nerve growth factor inhibitor, was compared to placebo in pooled data from 5229 patients with osteoarthritis. Based on the overall neurological safety profile, the data suggest that tanezumab does not have an adverse effect on the underlying peripheral nervous system.
- An increased incidence of adverse events of abnormal peripheral sensation was observed in patients who received tanezumab, compared with placebo.
- Tanezumab was associated with increased diagnoses of mononeuropathy, compared with placebo. The incidence of polyneuropathy diagnoses was similar in tanezumab and placebo groups.

1 Introduction

During embryogenesis, nerve growth factor (NGF) is a survival factor for nociceptive sensory and sympathetic neurons, signaling through tyrosine kinase receptor A (trkA) and the low-affinity receptor $p75^{NTR}$ [1-3]. During maturation and throughout adulthood, trkA and $p75^{NTR}$ continue to be expressed in subpopulations of post-ganglionic sympathetic neurons and peptide-rich nociceptive sensory neurons. During postnatal maturation of sensory neurons, NGF switches its role from a survival factor to that of a pro-nociceptive mediator [2, 4]. Expression of NGF is increased in injured or inflamed tissues in chronic pain conditions such as osteoarthritis (OA) and contributes to the painful manifestations of this disease [2].

Tanezumab is a potent and selective humanized monoclonal antibody against NGF that has been investigated in multiple large, randomized, placebo-controlled clinical trials for the treatment of OA pain in adult patients. During the clinical development program, the route of tanezumab administration transitioned from intravenous (IV) to subcutaneous (SC) injection to provide a more convenient dose administration for the patients and a predicted improvement in the overall benefit/risk profile. Randomized controlled trials of IV or SC tanezumab in patients with OA have demonstrated that tanezumab improves pain, physical function, and the patient's global assessment of OA versus placebo [5-11]. These studies also showed a higher incidence of adverse events (AEs) of abnormal peripheral sensation (APS), compared with placebo [6-12].

Pooled data from nine studies of IV or SC administration of tanezumab in 5229 patients with moderate-to-severe OA were analyzed to investigate the peripheral neurological safety of tanezumab versus placebo. These studies represent all of the phase 3 placebo-controlled studies of tanezumab in patients with OA. We have previously reported the peripheral neurological safety of tanezumab versus nonsteroidal anti-inflammatory drugs in patients with OA[13]. The general and joint safety of tanezumab in this patient population has been reported elsewhere[14-16].

On October 26, 2021, Pfizer Inc. and Eli Lilly and Company announced discontinuation of the tanezumab global clinical development program as a result of the outcomes of regulatory reviews of tanezumab for the treatment of OA pain by the U.S. Food and Drug Administration and European Medicines Agency [17, 18].

2 Methods

2.1 Participants

Nine studies were included in the analysis: six with IV administration, two with SC administration, and one with both IV and SC administration (**Table 1**). Each of the nine phase III placebo-controlled studies enrolled patients with moderate-to-severe OA with an index joint of the hip or knee. Although patients may have had OA in several joints, the index joint was the most painful joint at screening that met study inclusion criteria. Full inclusion and exclusion criteria for each study have been published [6-12] and are briefly summarized in **Supplementary Table 1**.

Data were pooled from six phase III studies of IV tanezumab and one study that investigated both IV and SC administration arms (only IV data were used in this pool) [6-9, 12]. Data were separately pooled from two phase III studies of SC tanezumab and one study that investigated both IV and SC administration (only SC data were used in this pool) [9-11]. In all studies of IV and SC tanezumab, study drug or placebo was administered every 8 weeks.

2.2 Safety Endpoints

Patient-level datasets were prepared separately for the treatment period and for the treatment period and follow-up period combined for the IV and SC pools as described. Datasets were analyzed separately with summary statistics.

2.2.1 Adverse Events

A prespecified group of 27 symptomatic and neuropathy-related AEs was designated as AEs of APS and was assessed in several analyses (**Supplementary Table 2**). Each of these AEs were reported as Medical Dictionary for Regulatory Activities preferred terms, which is the standard practice for AE reporting in regulatory submissions. The incidence, start day, and severity of AEs of APS were analyzed for the treatment period of each study. The maximum severity of AEs of APS were graded by the study investigators as mild (did not interfere with the patient's usual function), moderate (interfered to some extent with patient's usual function) or severe (interfered significantly with patient's usual function). The duration and resolution of AEs of APS reported during the treatment period were analyzed up to the end of the follow-up period of each study. Discontinuations due to AEs of APS were analyzed for AEs reported up to the end of the follow-up period of each study.

2.2.2 Neurological Examinations

Standardized neurologic examinations were performed during the screening period, at baseline, and at each study visit by an investigator who had been trained on the examination. Neurologic examination results were reported using the Neuropathy Impairment Score [19].

2.2.3 Neurological Consultations

Patients were referred for a local neurological consultation if they met prespecified criteria. In the IV studies, a neurologic consultation was required for any AE suggestive of new or worsening peripheral neuropathy, any AE of APS, pain in the extremities suggestive of neuropathic pain, or for a clinically significant change on a patient's neurologic examination. In the SC studies, neurologic consultation was required if the AE of APS or neurologic examination changes were reported as a serious AE, an AE which resulted in the patient being withdrawn from the study, an AE ongoing at the end of the patient's participation in the study, or an AE of severe intensity. Neurological consultations were also performed for patients with a non-neuropathic AE that the investigator considered medically important.

The consulting neurologist was asked to take a thorough neurologic history, to perform a complete neurologic examination, to formulate a diagnostic impression and plan, and to record these in a written consultation report. If there was evidence of new or worsened peripheral neuropathy based on the patient's neurologic history and neurologic examination, the neurologist was encouraged to pursue appropriate laboratory and electrodiagnostic testing to confirm or refute the diagnosis and attempt to establish an etiology for the presumed peripheral neuropathy.

The outcomes of neurological consultations related to APS were assessed separately for pre-2015 IV and post-2015 SC studies. In the post-2015 SC studies, peripheral neurological consultations and associated clinical data were reviewed by a blinded external neurologist with expertise in neuromuscular disorders. The external expert neurologist diagnosed each patient with a primary diagnosis and any additional diagnoses warranted by the reported AEs, neurological consultation, and clinical data. In the pre-2015 IV studies, patients whose neurologic consultations were categorized by the investigator as having signs or diagnostic evidence of peripheral neuropathy were evaluated by an external expert neurologist or a sponsor neurologist and assigned a primary diagnosis.

The protocol for neurological consultations in study A4091027, which included both IV and SC administration and was conducted in 2010, was similar to that used in the IV pooled studies. Consequently, data for the IV treatment groups of this study were included in the IV pooled dataset. Neurological consultation data for the SC groups of study A4091027 were not included in the SC pooled dataset owing to the different consultation assessment procedures in this study, compared with the post-2015 SC studies.

3 Results

3.1 Adverse Events of Abnormal Peripheral Sensation

In both the SC and IV datasets, AEs of APS were reported more frequently in the tanezumab groups compared with placebo (**Table 2**). In both datasets, paresthesia and hypoesthesia were the most frequently reported individual AE of APS in tanezumab-treated patients, compared with placebo. In the SC dataset paresthesia was reported for 1.0%, 2.3%, 1.4%, 4.0%, and 7.0% of patients, and hypoesthesia for 0.9%, 1.8%, 1.4%, 2.3% and 5.8% of patients in the placebo, tanezumab 2.5, 2.5/5 (2.5 mg at baseline and 5 mg at Week 8), 5, and 10 mg groups, respectively. In the IV dataset paresthesia was reported for 1.7%, 4.0%, 5.4%, and 6.0% of patients, and hypoesthesia for 0.9%, 4.0%, 2.9%, and 2.5% of patients in the placebo, tanezumab 2.5, 5, and 10 mg groups, respectively. Frequencies for all other AEs of APS were typically less than 1% across the treatment groups in both datasets, except for carpal tunnel syndrome in the tanezumab groups of the IV pooled data (0.9–1.7%), and decreased vibratory sense, neuropathy peripheral and sensory disturbance (all 1.2%) in the tanezumab 10 mg group of the SC pooled data.

3.2 Severity of AEs of APS

In the SC dataset, the majority of AEs of APS were mild in severity across the treatment groups, and no severe events, defined as those that interfered significantly with a patient's usual function, were reported (**Figure 1A**). In the IV dataset, severe AEs of APS were reported in the placebo and tanezumab 2.5, 5, and 10 mg groups with frequencies of 0%, 0.6%, 0.1%, and 0.4% of patients, respectively (**Figure 1B**). The remaining AEs of APS were of mild or moderate severity, with the majority classified as mild (**Figure 1B**).

3.3 Start Day and Duration of AEs of APS

In the SC dataset, the mean start day for AEs of APS (i.e., the time when the AE was first reported, expressed as the number of days since the baseline study medication administration) showed no clear pattern

(**Table 3**). With the exception of the 2.5/5 mg group), the median duration of any AE of APS for the tanezumab groups was similar to or shorter than that for the placebo group (**Table 4**).

In the IV-dataset, start days for any AE of APS and some individual AEs such as carpal tunnel syndrome, paresthesia, and hypoesthesia were generally earlier for higher doses of tanezumab compared with lower doses (**Table 3**). In general, the median duration of any AE of APS in the tanezumab treatment groups was similar to or longer than the duration in the placebo treatment group (**Table 4**).

3.4 Resolution of AEs of APS

In the SC dataset, the majority of patients had AE resolution in the placebo, tanezumab 2.5, 2.5/5, and 5 mg treatment groups but not in the tanezumab 10 mg treatment group (**Figure 2A**). Patients in the tanezumab 10 mg group reporting hypoesthesia or paresthesia had less frequent resolution compared with the other treatment groups (resolution rates for hypoesthesia 100%, 90.9%, 66.7%, 87.5%, and 40.0% and paresthesia 100%, 85.7%, 100%, 92.9%, and 33.3% in the placebo, tanezumab 2.5, 2.5/5, 5, and 10 mg groups, respectively). In the IV dataset, the majority of patients had resolution of AEs of APS in the placebo, tanezumab 5, and 10 mg groups but not in the tanezumab 2.5 mg group (**Figure 2B**). In the tanezumab 2.5 mg group, patients with AEs of hypoesthesia or paresthesia had less frequent resolution compared with the other treatment groups (resolution rates for hypoesthesia 77.8%, 38.5%, 53.6%, and 53.8% and paresthesia 76.5%, 53.8%, 71.7%, and 69.8% in the placebo, tanezumab 2.5, 5, and 10 mg groups, respectively).

In the SC dataset, 46.2%, 53.8%, 28.6% and 64.7% of patients in the placebo, tanezumab 2.5, 2.5/5, and 5 mg treatment groups had AE resolution during the treatment period (**Supplementary Figure 1**). After completion of treatment, 30.8%, 30.8%, 57.1% and 23.5% of patients in the placebo, tanezumab 2.5, 2.5/5, and 5 mg treatment groups had AE resolution. In the IV dataset, 68.6%, 28.1%, 52.3% and 56.7% of patients in the placebo, tanezumab 2.5, 5 and 10 mg treatment groups had AE resolution during the treatment period. After completion of treatment, 5.7%, 9.4%, 2.3% and 6.0% of patients in the placebo, tanezumab 2.5, 5 and 10 mg treatment groups had AE resolution.

3.5 Discontinuations Due to AEs of APS

In the pooled SC studies, only one patient, in the tanezumab 5 mg group, discontinued due to an AE of APS (hypoesthesia, **Table 5**). In the pooled IV studies, the incidence of any AE of APS that led to discontinuation for placebo-treated patients was 0.2%, and that for patients treated with tanezumab 2.5, 5, and 10 mg was 0.6%,

0.5%, and 1.3%, respectively (**Table 5**). Hypoesthesia and paresthesia were the most frequently reported AEs leading to discontinuation.

3.6 Neurological Examinations

For all treatment groups in the pooled SC dataset, at the last assessment in the study, a large majority (≥92%) of patients had no new or worsened neurological examination abnormalities (**Table 6**). Few (<1.0%) patients had new or worsened neurological examination abnormalities that were considered clinically significant. Overall, the neurological examination findings were similar in the tanezumab treatment groups and placebo treatment group. At the last assessment, higher tanezumab doses were not associated with higher frequencies of new or worsened neurological abnormalities that were considered clinically significant, compared with lower doses.

In the IV pooled studies, a large majority (≥90%) of patients had no new or worsened neurological examination abnormalities for all treatment groups at the last assessment in the study (**Table 6**). Few (<1.0%) patients had new or worsened neurological examination abnormalities that were considered clinically significant. Overall, the neurological examination findings were similar in the tanezumab treatment groups and placebo treatment group.

3.7 Neurological Consultations

In the post-2015 SC pooled data, patients in the tanezumab 2.5 (3.2%) and 5 mg (2.1%) groups required neurologic consultations more frequently compared with patients in the placebo group (1.4%) (**Table 7**). However, the frequency of any neurologic diagnosis was <1.5% in any group. The blinded expert neurologist's diagnoses from most frequent to least frequent were radiculopathy, mononeuropathy, polyneuropathy, neurologic symptoms but no clinically significant signs, no neuropathic signs or symptoms, and plexopathy. Radiculopathy and mononeuropathy were diagnosed more frequently in the tanezumab 2.5 and 5 mg groups (1.1–1.3% and 1.1–1.3%, respectively) compared with the placebo group (0.4% and 0.2%, respectively). Polyneuropathy was diagnosed with similar frequency in the tanezumab 2.5 and 5 mg groups (0.2 and 0%, respectively) and placebo group (0.2%). For the diagnoses of radiculopathy, mononeuropathy, and polyneuropathy, a higher frequency of a diagnosis was not associated with a higher tanezumab dose.

In the IV pooled data, the incidence of patients categorized as having a new/worsened peripheral neuropathy (based on clinically significant examination findings or diagnostic test abnormalities) and assigned a

primary neurologic diagnosis was 0.9%, 4.0%, 2.1%, and 3.2% for the placebo, tanezumab 2.5, 5, and 10 mg groups, respectively (**Table 7**). Mononeuropathy was the most common diagnosis, observed in 0.6%, 2.4%, 1.4%, and 1.7% of patients across the placebo, tanezumab 2.5, 5, and 10 mg groups, respectively. The majority of mononeuropathies were diagnosed as carpal tunnel syndrome. Polyneuropathy or radiculopathy were each diagnosed in <1% of patients in any group. Plexopathy was not diagnosed in any patient. The incidence of these diagnoses was greater in tanezumab groups than in the placebo group.

4 Discussion

These data summarizing the neurological safety of tanezumab, an anti-NGF therapy, in over 5000 patients with OA across the nine phase 3 randomized placebo-controlled clinical trials provides important information for this drug class in patients with chronic pain conditions. The large number of patients who received placebo in these studies also provides an unprecedented dataset detailing the natural history of nerve function in patients with OA. Although NGF is not required for neuronal survival beyond the early post-natal period [4], treatment with an anti-NGF antibody could theoretically have posed a risk to the peripheral nervous system, so all of these studies utilized robust assessments of neurological safety.

In both the IV and SC pooled data, during the treatment period, the overall incidence of AEs of APS was ≤12.8%. The incidence of these AEs was higher in the tanezumab groups compared to the placebo groups, though the fact that between 2-3% of placebo-treated patients reported these AEs deserves mention since most studies of OA patients do not report detailed neurologic findings. Most AEs were mild, and fewer were moderate, with very few patients reporting severe events during the treatment period in tanezumab groups. Most of the events reported were resolved in both sets of pooled data during treatment or upon completion of treatment.

The incidence of AEs of APS was lower after tanezumab SC administration than after IV administration. Unlike the SC pooled dataset, in the IV pooled dataset the start dates of any AEs of APS were earlier for higher doses of tanezumab compared to lower doses, and for some individual AEs such as carpal tunnel syndrome, paresthesia, and hypoesthesia. The duration of any AEs of APS for the tanezumab treatment groups was generally similar to or shorter than that for the placebo treatment group in the SC pool. In the IV pool, the duration of AEs of APS in the tanezumab treatment groups was generally similar to or longer than the duration in the placebo treatment group. For comparable treatment groups (e.g., tanezumab 2.5 mg for each route of administration) the duration of any AE of APS was generally shorter for the SC treatment group than for the IV treatment group.

For tanezumab 2.5, 2.5/5, and 5 mg treatment groups, the AE resolution rates were higher in the SC dataset than in the IV dataset. It should be noted that the tanezumab 10 mg group of the SC pool was derived entirely from study A4091027, which was terminated early due to a clinical hold, with <10% of patients completing treatment and a small number of patients (n=86), compared to the other treatment groups. This may explain the larger percentage of unresolved AEs in the tanezumab 10 mg SC group compared to the tanezumab

10 mg IV group, which included many more patients. The IV studies also had shorter follow-up periods than the SC studies, which may have been a factor in the comparatively lower resolution rates in the IV dataset. Discontinuations were infrequent and lower in the OA placebo-controlled SC pool compared to the IV pool. The SC route of administration was also associated with fewer neurologic examination changes than the IV route of administration.

Across both pooled datasets and for all treatment groups, a large majority (≥90%) of patients had no new or worsened neurological examination abnormalities at the last study visit, and few (≤0.8%) had new or worsened neurological examination abnormalities that were considered clinically significant. Across study pools, mononeuropathy was diagnosed more frequently in the tanezumab groups compared with the placebo groups. Polyneuropathy was diagnosed in less than 1% of patients.

The mechanism by which tanezumab causes abnormal sensation events is unknown. It may be that tanezumab unmasks previously existing compressive neuropathies, such as carpal tunnel syndrome and radiculopathies, by only having an effect on partly injured nerves such as those at compression sites. It could also be that, at focal compression sites, the blood–nerve barrier becomes more permeable and, therefore, access to antibodies may be increased. Changes in sensory perception may be related to the way normal sensory nerves alter their signaling in response to decreased NGF stimulation. For example, there could be changes in the balance of sensory neuron activation between those neurons with trkA (NGF responsive; in the skin only 30% of neurons are trkA positive) and those without trkA (NGF unresponsive). In addition, downstream systems, such as sodium, calcium, or acid sensing channels, could respond to decreased NGF signaling and, in turn, alter sensory perception.

Although patients reported abnormal peripheral sensation events more frequently in tanezumab treatment groups than in placebo treatment groups, based on the overall neurological safety profile, the data do not suggest that tanezumab has an adverse effect on the underlying peripheral nervous system. As noted above, changes in sensory perception might occur by altered signaling by normal nerves in the presence of decreased NGF and the adverse events were typically transient and resolved during ongoing treatment. In addition, there was minimal impact on the clinical neurological examinations over the course of the studies and compared to placebo, and there was no increase in the diagnosis of polyneuropathy in patients undergoing neurologic consultation. The peripheral neurologic safety of tanezumab studied with quantitative assessments such as nerve conduction study parameters, intra-epidermal nerve fiber (IENF) density and quantitative sensory testing support a lack of adverse effects of tanezumab on the underlying peripheral nervous system. One of the OA IV

studies (Study A4091026) utilized prospective nerve conduction parameters and IENF density assessments and did not demonstrate a detrimental effect of tanezumab 5 mg or 10 mg on the underlying peripheral nervous system [5]. Similarly, in a tanezumab study of patients with painful diabetic neuropathy, quantitative sensory testing and IENF density assessments did not demonstrate an adverse effect of tanezumab 20 mg vs placebo despite the presence of underlying diabetic peripheral neuropathy [20].

The studies in this pooled analysis illustrate the importance of thoroughly assessing peripheral nerve safety when there may be a potential issue. Our studies show that there was a lack of a tanezumab-associated peripheral nerve safety signal in the large number of patients studied. Our data are supported by published studies of the other anti-NGF drugs, albeit in smaller populations and in less detail. Previous studies of fasinumab and fulranumab, two anti-NGF antibodies, also showed increased incidences of paresthesia and hypoesthesia versus placebo [21-23]. These findings are particularly important for the field of chronic pain research even though development of the initial anti-NGF monoclonal antibodies (e.g. tanezumab, fulranumab and fasinumab) has been discontinued, since chronic pain treatment based on the NGF system (e.g. MEDI7352) continues to be studied [24-26].

5 Conclusions

These data indicate that IV or SC tanezumab was associated with an increased incidence of AEs of APS, compared with placebo. These events were mild or moderate in severity and rarely led to discontinuation. Mononeuropathy was diagnosed with an increased frequency in tanezumab groups compared with placebo, but tanezumab was not associated with an increased incidence of polyneuropathy. The data support the predicted improvement in the overall neurological safety profile that was a factor in the transition from IV to SC administration during the tanezumab development program. These data also suggest that tanezumab, as given in these studies, does not have an adverse effect on the underlying peripheral nervous system.

Statements and Declarations

(i) Role of the Funder/Sponsor

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

(ii) Competing Interests

DRC has served as a consultant for AlgoTX, Amgen Inc., Annexon Biosciences, Boehringer Ingelheim, Cigna Health Management, Inc., CSL Behring, Grifols S.A., Johnson & Johnson, Nervosave, Nurobio, Octapharma AG, Passage Bio, Pfizer Inc., Pharnext SAS, Roche, Seattle Genetics Inc., ValenzaBio. He sits on the Data Safety Monitoring Board for Anavex Life Sciences Corp, Passage Bio, PledPharma AB, Hansa Medical AB, Mitsubishi Tanabe Pharma Corporation. Through Johns Hopkins University, receives royalties for technology licensing from AstraZeneca Pharmaceuticals, LP, Genentech Inc., Levicept Inc., Seattle Genetics, Inc., Merrimack Pharmaceuticals. He sits on the Scientific Advisory Board for AlgoTx and Sinomab. MK is director of Neurophysiology Consulting Ltd and QTMS Science Ltd. During the past 5 years he has been an adhoc consultant and the speaker bureau for Eli Lilly, GSK, Levicept, Marks & Clerk Law, Merck, Neursentis, Pfizer, Richmond Pharmaceuticals Ltd and Roche. KG has served as a consultant for Argenx, Annexon, Janssen, Pfizer and UCB Pharma. MTB, AH, GCP, PG and CRW own stock in and are full-time employees of Pfizer. L.V. owns stocks in and is a full-time employee of Eli Lilly and Company.

(iii) Data Sharing

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

(iv) Ethics Approval

The protocol for each clinical trial was approved by an institutional review board or independent ethics committee at each participating investigational center. The studies were conducted in compliance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice Guidelines.

(v) Consent

All patients provided written informed consent before entering the studies. Consent for publication was not applicable.

(vi) Author's Contributions

Mark Brown: Conceptualization, Data curation, Investigation, Methodology, Supervision, Visualization, Writing – review & editing

David Cornblath: Investigation, Supervision, Writing – review & editing

Martin Koltzenburg; Investigation, Supervision, Writing – review & editing

Kenneth Gorson; Investigation, Supervision, Writing – review & editing

Anne Hickman: Conceptualization, Data curation, Investigation, Methodology, Supervision, Visualization, Writing – review & editing

Glenn C. Pixton: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Visualization, Writing – review & editing

Puneet Gaitonde: Data curation, Investigation, Methodology, Supervision, Visualization, Writing – review & editing

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Christine West: Conceptualization, Data curation, Investigation, Methodology, Supervision, Visualization, Writing – review & editing

(vii) Code Availability

Not applicable

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Tables and Figures

Table 1 Studies included in the analyses

Study ID	Index joint	Treatment period (weeks)	Follow-up period (weeks)	Treatments
A4091011	Knee	24	8	Tanezumab 2.5 mg IV Tanezumab 5 mg IV Tanezumab 10 mg IV Placebo IV
A4091014	Hip	24	8	Tanezumab 2.5 mg IV Tanezumab 5 mg IV Tanezumab 10 mg IV Placebo IV
A4091015	Knee	16	8	Tanezumab 5 mg IV Tanezumab 10 mg IV Naproxen 500 mg BID PO Placebo matching PO and IV
A4091018	Hip or knee	16	8	Tanezumab 5 mg IV Tanezumab 10 mg IV Naproxen 500 mg BID PO Placebo matching PO and IV
A4091026	Hip or knee	24	8	Tanezumab 5 mg IV Tanezumab 10 mg IV Placebo IV
A4091027[a]	Knee	16	8	Tanezumab 2.5 mg SC Tanezumab 5 mg SC Tanezumab 10 mg SC Tanezumab 10 mg IV Placebo IV and SC
A4091030	Hip or knee	16	8	Tanezumab 5 mg IV Tanezumab 10 mg IV Oxycodone CR 10–40 mg PO BID Placebo matching PO and IV
A4091056	Hip or knee	16	24	Tanezumab 2.5 mg SC Tanezumab 2.5/5 mg SC[b] Placebo SC

A4091057	Hip or knee	24	24	Tanezumab 2.5 mg SC Tanezumab 5 mg SC Placebo SC

CR controlled release, *IV* intravenous, *SC* subcutaneous

[a]Study A4091027 investigated both IV and SC administration. Data from the treatment groups of this study were added to the appropriate IV or SC pooled datasets

[b]Tanezumab 2.5 mg at baseline and 5 mg at Week 8

Table 2 Incidence of adverse events of abnormal peripheral sensation during the treatment period

	Pooled SC studies (*n* = 1840)					Pooled IV studies (*n* = 3389)			
		Tanezumab					Tanezumab		
Patients, *n* (%)	Placebo (*n* = 586)	2.5 mg (*n* = 602)	2.5/5 mg (*n* = 219)	5 mg (*n* = 347)	10 mg (*n* = 86)	Placebo (*n* = 1029)	2.5 mg (*n* = 327)	5 mg (*n* = 977)	10 mg (*n* = 1056)
Any AE of APS	13 (2.2)	31 (5.1)	7 (3.2)	21 (6.1)	11 (12.8)	35 (3.4)	32 (9.8)	86 (8.8)	135 (12.8)
Paresthesia	6 (1.0)	14 (2.3)	3 (1.4)	14 (4.0)	6 (7.0)	17 (1.7)	13 (4.0)	53 (5.4)	63 (6.0)
Hypoesthesia	5 (0.9)	11 (1.8)	3 (1.4)	8 (2.3)	5 (5.8)	9 (0.9)	13 (4.0)	28 (2.9)	26 (2.5)
Carpal tunnel syndrome	0	3 (0.5)	0	1 (0.3)	0	1 (0.1)	5 (1.5)	9 (0.9)	18 (1.7)
Burning Sensation	1 (0.2)	1 (0.2)	0	2 (0.6)	0	1 (0.1)	0	6 (0.6)	17 (1.6)
Decreased vibratory sense	3 (0.5)	1 (0.2)	1 (0.5)	1 (0.3)	1 (1.2)	4 (0.4)	0	2 (0.2)	6 (0.6)
Neuropathy peripheral	0	0	0	1 (0.3)	1 (1.2)	0	2 (0.6)	3 (0.3)	3 (0.3)
Sensory disturbance	0	0	0	0	1 (1.2)	0	0	3 (0.3)	3 (0.3)
Hyperesthesia	0	0	0	0	0	1 (0.1)	1 (0.3)	5 (0.5)	13 (1.2)

AE adverse event, *APS* abnormal peripheral sensation, *IV* intravenous, *SC* subcutaneous
Adverse events reported for ≥1% of patients in any treatment group are shown. The treatment periods ranged 16–24 weeks for studies in both the SC and IV datasets. Each adverse event of abnormal peripheral sensation reported for individual patients is shown. An individual patient may have reported more than one adverse event.

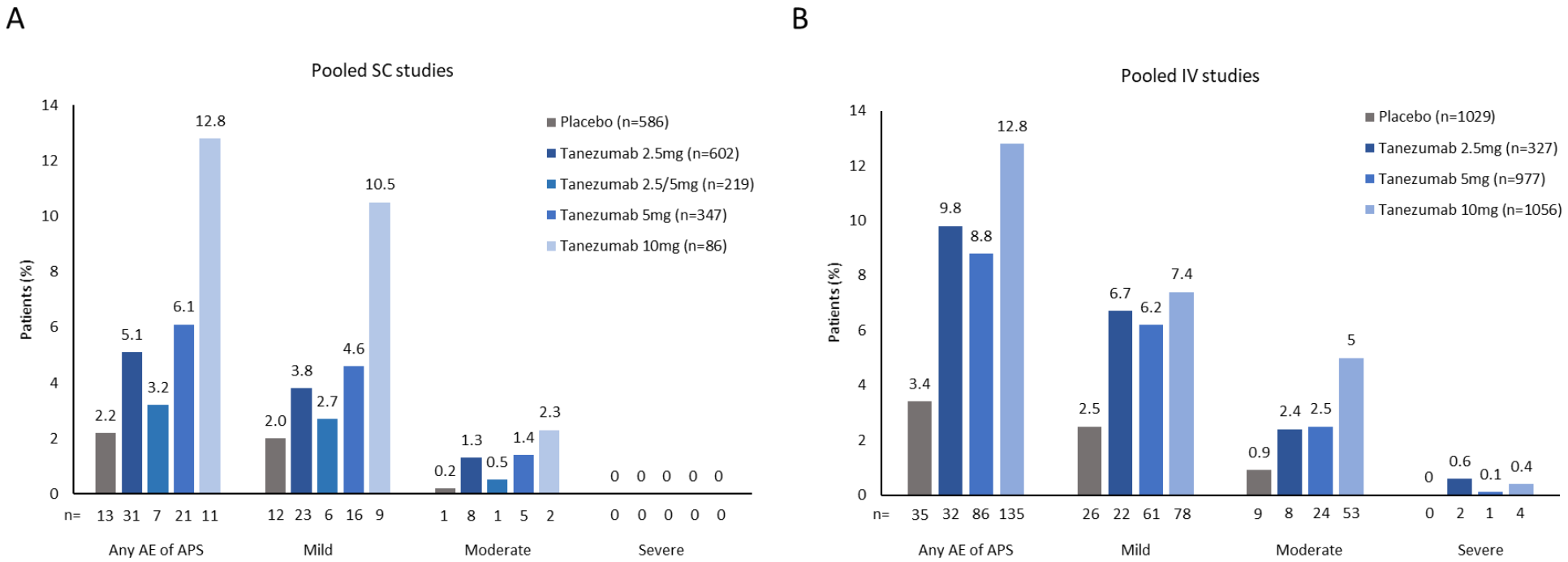

Fig. 1 Severity of adverse events of abnormal peripheral sensation during the treatment period. If the same patient in a given treatment had more than one occurrence in the same preferred term event category, only the most severe occurrence was counted. Any missing severities were imputed as severe unless the patient experienced another occurrence of the same event in a given treatment for which severity was recorded. In this case, the reported severity was summarized. The n for each treatment group reports the total number of patients. The *n* listed below the x-axis reports the number of patients in each category. The treatment periods ranged 16–24 weeks for studies in both the SC and IV datasets. *AE* adverse event, *APS* abnormal peripheral sensation, *IV* intravenous, *SC* subcutaneous

Table 3 Start day of adverse events of abnormal peripheral sensation during the treatment period

	Pooled SC studies (*n* = 1840)					Pooled IV studies (*n* = 3389)			
		Tanezumab					Tanezumab		
Start date, mean (SD), days	Placebo (*n* = 586)	2.5 mg (*n* = 602)	2.5/5 mg (*n* = 219)	5 mg (*n* = 347)	10 mg (*n* = 86)	Placebo (*n* = 1029)	2.5 mg (*n* = 327)	5 mg (*n* = 977)	10 mg (*n* = 1056)
Any AE of APS	45.2 (37.4)	57.3 (46.9)	44.1 (36.6)	71.3 (55.3)	53.0 (28.5)	38.6 (32.5)	56.6 (50.3)	49.5 (43.1)	37.3 (42.0)
Paresthesia	54.2 (43.0)	54.0 (51.1)	29.0 (18.2)	65.5 (58.0)	46.0 (34.5)	33.5 (32.5)	46.3 (46.9)	45.0 (39.5)	33.0 (38.4)
Hypoesthesia	63.2 (69.0)	65.7 (36.1)	34.0 (17.3)	82.1 (65.8)	57.0 (22.7)	54.8 (44.9)	67.7 (44.3)	45.9 (38.7)	51.1 (36.3)
Carpal tunnel syndrome	- (-)	68.3 (63.5)	- (-)	149.0 (-)	- (-)	58.0 (-)	86.8 (65.7)	97.2 (42.7)	52.7 (35.5)
Burning sensation	65.0 (-)	2.0 (-)	- (-)	29.5 (17.7)	- (-)	25.0 (-)	- (-)	34.8 (28.7)	22.1 (25.3)
Decreased vibratory sense	34.0 (21.0)	57.0 (-)	120.0 (-)	120.0 (-)	64.0 (-)	49.3 (27.4)	- (-)	48.5 (47.4)	85.7 (74.2)
Neuropathy peripheral	- (-)	- (-)	- (-)	149.0 (-)	23.0 (-)	- (-)	95.5 (112.4)	85.0 (35.0)	30.7 (14.6)
Sensory disturbance	- (-)	- (-)	- (-)	- (-)	29.0 (-)	- (-)	- (-)	19.3 (16.0)	59.7 (97.3)
Hyperesthesia	- (-)	- (-)	- (-)	- (-)	- (-)	9.0 (-)	2.0 (-)	10.6 (5.4)	12.8 (11.8)

AE adverse event; *APS* abnormal peripheral sensation; *IV* intravenous; *SC* subcutaneous
Start of adverse event is summarized in relation to the beginning of the treatment period. The treatment periods ranged 16–24 weeks for studies in both the SC and IV datasets

Table 4 Duration of adverse events of abnormal peripheral sensation reported during the treatment period

	Pooled SC studies (*n* = 1840)					Pooled IV studies (*n* = 3389)			
		Tanezumab					Tanezumab		
Median duration (min, max), days	Placebo (*n* = 586)	2.5 mg (*n* = 602)	2.5/5 mg (*n* = 219)	5 mg (*n* = 347)	10 mg (*n* = 86)	Placebo (*n* = 1029)	2.5 mg (*n* = 327)	5 mg (*n* = 977)	10 mg (*n* = 1056)
Any AE of APS	29.0 (1, 484)	31.0 (1, 264)	54.0 (24, 143)	16.0 (1, 358)	17.0 (1, 100)	29.0 (1, 401)	53.5 (1, 185)	32.5 (1, 305)	31.0 (1, 183)
Paresthesia	7.0 (1, 211)	28.5 (1, 264)	92.0 (24, 143)	17.5 (2, 87)	17.0 (3, 100)	15.0 (1, 392)	56.0 (3, 185)	27.0 (1, 206)	22.0 (1, 183)
Hypoesthesia	169.0 (29, 280)	29.0 (1, 243)	54.0 (47, 125)	19.0 (1, 157)	4.0 (1, 43)	31.0 (1, 126)	37.0 (2, 113)	49.0 (1, 131)	47.5 (4, 148)
Carpal tunnel syndrome	- (-, -)	31.0 (1, 68)	- (-, -)	1.0 (1, 1)	- (-, -)	401.0 (401, 401)	103.0 (1, 174)	43.0 (1, 305)	50.0 (1, 165)
Burning sensation	14.0 (14, 14)	111.0 (111, 111)	- (-, -)	14.0 (8, 20)	- (-, -)	76.0 (76, 76)	- (-, -)	52.5 (3, 106)	27.0 (8, 143)
Decreased vibratory sense	28.0 (14, 484)	29.0 (29, 29)	53.0 (53, 53)	358.0 (358, 358)	17.0 (17, 17)	46.5 (29, 107)	- (-, -)	50.0 (16, 84)	15.0 (2, 47)
Neuropathy peripheral	- (-, -)	- (-, -)	- (-, -)	1.0 (1, 1)	4.0 (4, 4)	- (-, -)	21.5 (1, 42)	41.0 (1, 112)	44.0 (18, 172)
Sensory disturbance	- (-, -)	- (-, -)	- (-, -)	- (-, -)	86.0 (86, 86)	- (-, -)	- (-, -)	10.0 (8, 46)	26.0 (1, 145)
Hyperesthesia	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)	25.0 (25, 25)	60.0 (60, 60)	9.0 (3, 40)	31.0 (9, 172)

AE adverse event, *APS* abnormal peripheral sensation, *IV* intravenous, *SC* subcutaneous

Patients may have more than one adverse event in each category. The event with maximum duration in each category was summarized. If the event was ongoing at end of study, duration was calculated up to end of study. The treatment periods ranged 16–24 weeks for studies in both the SC and IV datasets

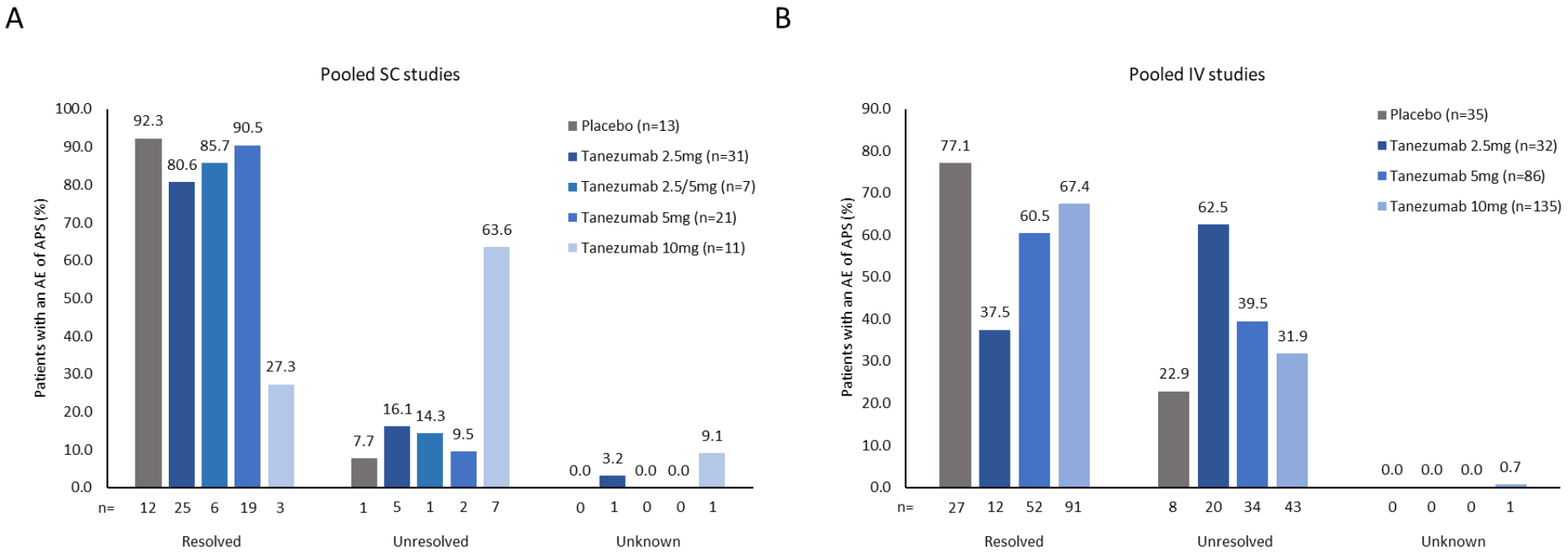

Fig. 2 Resolution of adverse events of abnormal peripheral sensation reported during the treatment period. If the same patient in a given treatment had more than one occurrence in the same preferred term event category, only the most severe occurrence was counted, ranked in order of unresolved, resolved, unknown. Resolution determined by the end of study. The *n* for each treatment group reports the total number of patients with an AE of APS. The *n* listed below the x-axis reports the number of patients in each category. The treatment periods ranged 16–24 weeks for studies in both the SC and IV datasets. *AE* adverse event, *APS* abnormal peripheral sensation, *IV* intravenous, *SC* subcutaneous

Table 5 Discontinuations due to adverse events of abnormal peripheral sensation reported up to end of study

	Pooled SC studies (*n* = 1840)					Pooled IV studies (*n* = 3389)			
		Tanezumab					Tanezumab		
Patients, *n* (%)	Placebo (*n* = 586)	2.5 mg (*n* = 602)	2.5/5 mg (*n* = 219)	5 mg (*n* = 347)	10 mg (*n* = 86)	Placebo (*n* = 1029)	2.5 mg (*n* = 327)	5 mg (*n* = 977)	10 mg (*n* = 1056)
Any AE of APS	0	0	0	1 (0.3)	0	2 (0.2)	2 (0.6)	5 (0.5)	14 (1.3)
Hypoesthesia	0	0	0	1 (0.3)	0	1 (0.1)	1 (0.3)	3 (0.3)	1 (0.1)
Decreased vibratory sense	0	0	0	0	0	0	0	1 (0.1)	0
Neuropathy peripheral	0	0	0	0	0	0	1 (0.3)	0	2 (0.2)
Paresthesia	0	0	0	0	0	0	0	1 (0.1)	3 (0.3)
Burning sensation	0	0	0	0	0	0	0	0	2 (0.2)
Carpal tunnel syndrome	0	0	0	0	0	0	0	0	2 (0.2)
Hyperesthesia	0	0	0	0	0	0	0	0	3 (0.3)
Sciatica	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)

AE adverse event, *APS* abnormal peripheral sensation, *IV* intravenous, *SC* subcutaneous

Table 6 Conclusion from neurological examinations at last study visit

	Pooled SC studies (*n* = 1840)					Pooled IV studies (*n* = 3389)			
		Tanezumab					Tanezumab		
Patients, *n* (%)	Placebo (*n* = 586)	2.5 mg (*n* = 602)	2.5/5 mg (*n* = 219)	5 mg (*n* = 347)	10 mg (*n* = 86)	Placebo (*n* = 1029)	2.5 mg (*n* = 327)	5 mg (*n* = 977)	10 mg (*n* = 1056)
Total	580 (100)	595 (100)	219 (100)	343 (100)	83 (100)	1010 (100)	324 (100)	950 (100)	1032 (100)
No new or worsened abnormality	554 (95.5)	548 (92.1)	206 (94.1)	326 (95.0)	79 (95.2)	921 (91.2)	293 (90.4)	856 (90.1)	929 (90.0)
New/worsened abnormality that was not clinically significant	23 (4.0)	42 (7.1)	13 (5.9)	17 (5.0)	4 (4.8)	88 (8.7)	30 (9.3)	87 (9.2)	95 (9.2)
New/worsened abnormality that was clinically significant	3 (0.5)	5 (0.8)	0	0	0	1 (0.1)	1 (0.3)	7 (0.7)	8 (0.8)

IV intravenous, *SC* subcutaneous
Conclusions from the neurological examination are based on the investigator's assessment. The number of patients shown in the total row includes patients with a neurological examination at last study visit and was used as the denominator for calculation of percentages

Table 7 Results of neurologic consultations and primary diagnoses.

	Pooled SC studies* (*n* = 1545)				Pooled IV studies (*n* = 3389)			
		Tanezumab				Tanezumab		
Patients, *n* (%)	Placebo (*n* = 514)	2.5 mg (*n* = 528)	2.5/5 mg (*n* = 219)	5 mg (*n* = 284)	Placebo (*n* = 1029)	2.5 mg (*n* = 327)	5 mg (*n* = 977)	10 mg (*n* = 1056)
Patients requiring consultations	7 (1.4)	17 (3.2)	4 (1.8)	6 (2.1)	9 (0.9)	14 (4.3)	21 (2.1)	36 (3.4)
Total primary diagnoses	7 (1.4)	17 (3.2)	3 (1.4)	6 (2.1)	9 (0.9)	13 (4.0)	21 (2.1)	34 (3.2)
Mononeuropathy	1 (0.2)	7 (1.3)	0	3 (1.1)	6 (0.6)	8 (2.4)	14 (1.4)	18 (1.7)
Carpal tunnel syndrome	1 (0.2)	5 (0.9)	0	2 (0.7)	4 (0.4)	7 (2.1)	12 (1.2)	16 (1.5)
Other mononeuropathy	0	2 (0.4)	0	1 (0.4)	2 (0.2)	1 (0.3)	2 (0.2)	2 (0.2)
Plexopathy	1 (0.2)	0	0	0	0	0	0	0
Polyneuropathy	1 (0.2)	1 (0.2)	1 (0.5)	0	2 (0.2)	3 (0.9)	3 (0.3)	8 (0.8)
Radiculopathy	2 (0.4)	7 (1.3)	1 (0.5)	3 (1.1)	1 (0.1)	2 (0.6)	4 (0.4)	8 (0.8)
No neuropathic symptoms or signs	1 (0.2)	0	1 (0.5)	0	N/A	N/A	N/A	N/A
Neuropathic symptoms but no clinically significant signs	1 (0.2)	2 (0.4)	0	0	N/A	N/A	N/A	N/A
Other	N/A	N/A	N/A	N/A	0	1 (0.3)	0	2 (0.2)
Missing	0	0	1 (0.5)	0	N/A	N/A	N/A	N/A

*Data from the SC groups of study A4091027 were not included as different procedures precluded pooling with the other SC data

Figure 1

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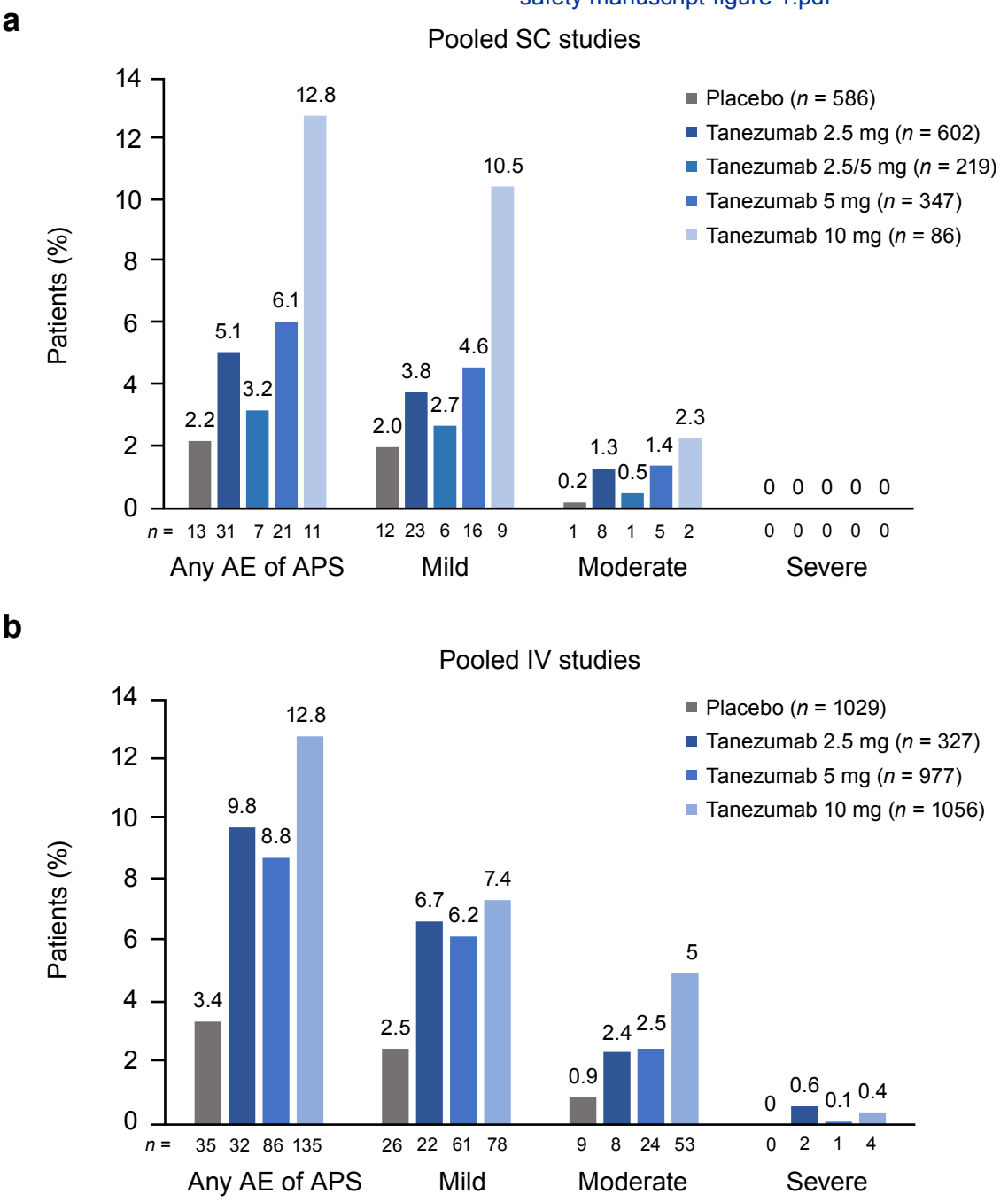

Figure 2

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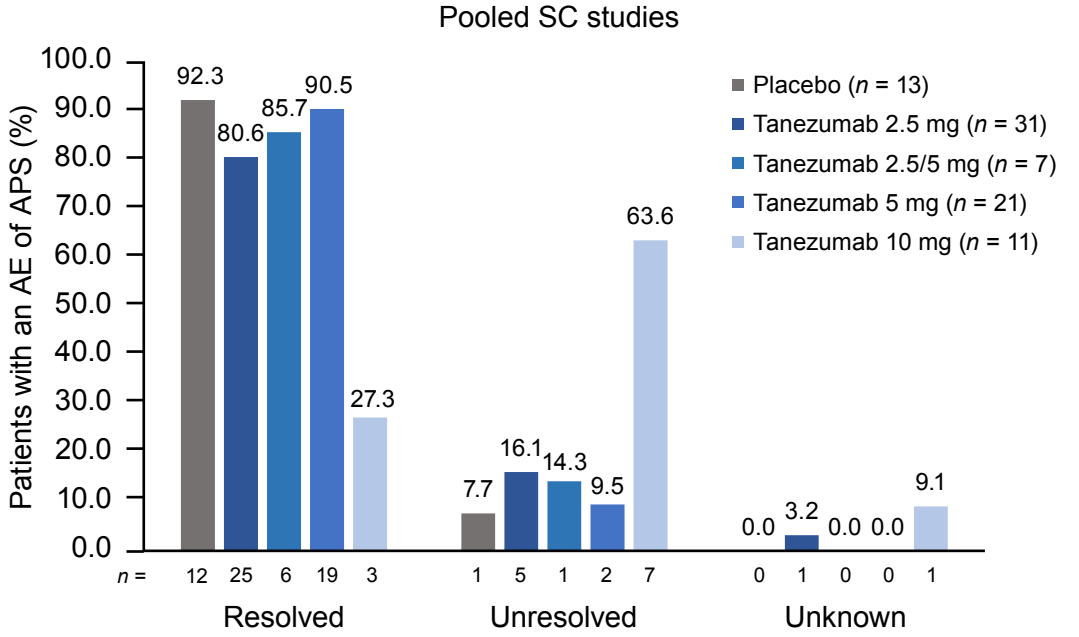
a



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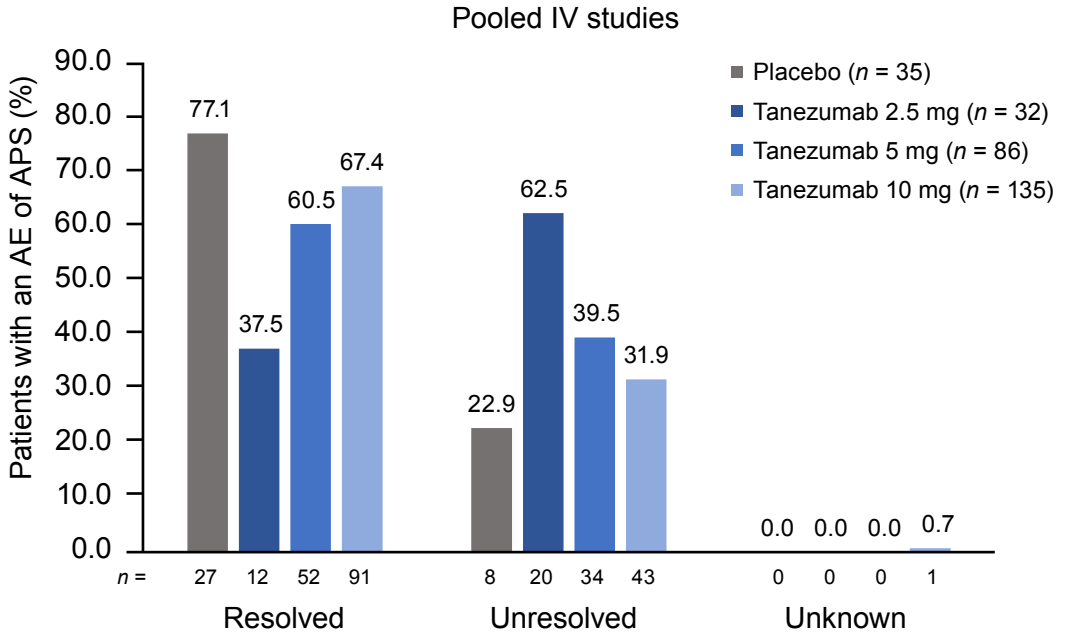

Peripheral Nerve Safety of Nerve Growth Factor Inhibition by Tanezumab: Pooled Analyses of Phase III Clinical Studies in over 5000 Patients with Osteoarthritis

Running heading: Neurological Safety of Nerve Growth Factor Inhibition by Tanezumab in Patients with Osteoarthritis

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Supplementary Table 1 Summary of studies analyzed

Study number (Clinical trial registration; date of registration)	Treatment duration	Treatments	Inclusion criteria	Exclusion criteria
A4091011 (NCT00733902; August 11, 2008)	24 weeks	Tanezumab 2.5 mg IV Tanezumab 5 mg IV Tanezumab 10 mg IV Placebo IV	Diagnosis of OA of the knee according to ACR criteria and X-ray confirmation taken within the previous 12 months with KL X-ray grade >2, and ≥1 of the following: unwillingness or inability to take non-opiate pain medications, inadequate pain relief from non-opiate pain medications, or candidacy for invasive interventions such as intra-articular injections, knee arthroplasty, or knee replacement surgery; WOMAC[a,b] Pain subscale score in the index knee ≥4 at screening and ≥5 at baseline and, in pts who washed out of regularly taken pain medications after screening, an increase ≥1 from screening to baseline; WOMAC Physical Function subscale score ≥4 at baseline; PGA of OA[c] of ‘‘fair,’’ ‘‘poor,’’ or ‘‘very poor,’’ at baseline	Pregnant or intended to become pregnant during the study; had BMI >39 kg/m2; pain syndromes that could confound assessment of pain from OA (e.g., fibromyalgia, systemic lupus erythematosus, or others); or significant cardiac, neurologic, or psychological conditions.
A4091014 (NCT00744471; August 29, 2008)	24 weeks	Tanezumab 2.5 mg IV Tanezumab 5 mg IV Tanezumab 10 mg IV Placebo IV	OA of the hip; ≥1 of the following: unwillingness or inability to take non-opiate pain medications, inadequate pain relief from non-opiate pain medications, or candidacy for invasive interventions such as intra-articular injections or hip surgery such as total joint replacement; WOMAC Pain subscale score of 4 at screening and 5 at baseline, and an increase of 1 from screening to baseline if they had been regularly taking pain medications prior to screening and were required to wash out prior to baseline; WOMAC Physical Function subscale score of 4 at baseline was required for the hip being studied (i.e., the index hip); PGA of OA	Pregnant or intended to become pregnant during the study; had BMI >39 kg/m2; moderate-to-severe pain other than that related to OA; any condition that could confound OA pain assessment; or significant cardiac, neurologic, or psychiatric conditions.

			disease activity as “fair,” “poor,” or “very poor” at baseline was also required	
A4091015 (NCT00830063; January 23, 2009)	16 weeks	Tanezumab 5 mg IV Tanezumab 10 mg IV Naproxen 500 mg BID PO Placebo matching active PO and IV	Aged ≥18 years, BMI ≤39 kg/m2 and diagnosis of knee OA based on the ACR criteria and radiographic confirmation (KL grade ≥2). At screening, eligible pts reported WOMAC Pain score ≥4 in the index joint, with or without analgesic medication. At baseline, pts had to report WOMAC Pain score ≥5 with an increase ≥1 point from screening if they had regularly taken medications (≥4 days.wk) during the month prior to screening; WOMAC Physical Function score ≥4; and a response of fair, poor, or very poor on PGA of OA to be randomized	Key exclusion criteria were similar to studies A4091011 and A4091014, but also included a history of naproxen intolerance, or existence of a medical condition or the use of concomitant medication for which naproxen is contraindicated.
A4091018 (NCT00863304; March 13, 2009)	16 weeks	Tanezumab 5 mg IV Tanezumab 10 mg IV Naproxen 500 mg BID PO Placebo matching active PO and IV	Aged ≥18 years, BMI ≤39 kg/m2 and diagnosis of hip or knee OA based on the ACR criteria and radiographic confirmation (KL grade ≥2). At screening, eligible pts reported WOMAC Pain score ≥4 in the index joint, with or without analgesic medication. At baseline, had to report WOMAC Pain score ≥5 with an increase ≥1 point from screening if they had regularly taken medications (≥4 days/wk) during the month prior to screening; WOMAC Physical Function score ≥4; and a response of fair, poor, or very poor on PGA of OA	Key exclusion criteria were similar to studies A4091011 and A4091014, but also included a history of naproxen intolerance, or existence of a medical condition or the use of concomitant medication for which naproxen is contraindicated.
A4091026 (NCT00863772; March 17, 2009)	24 weeks	Tanezumab 5 mg IV Tanezumab 10 mg IV Placebo IV	≥18 years with diagnosis of knee or hip OA based on ACR criteria; WOMAC Pain subscale score ≥4 for the index joint at screening and baseline; and PGA of OA of fair, poor, or very poor at baseline	Signs of baseline peripheral neuropathy based on prespecified NC and heart rate deep breathing parameters; abnormal baseline neurologic examination; pregnancy; BMI >39 kg/m2; other moderate-to-severe pain that could confound assessments of OA pain; significant heart disease, cancer, neurologic or psychiatric disease; or clinically significant systemic disease that could confound interpretation of NC tests, autonomic testing, or skin biopsy assessments.
A4091027 (NCT01089725; March 11, 2010)	16 weeks	Tanezumab 2.5 mg SC Tanezumab 5 mg SC Tanezumab 10 mg SC	≥18 years old with diagnosis of OA of the knee based on ACR criteria and radiographic confirmation (KL X-ray grade ≥2); and	Pregnancy, nursing, or intent to become pregnant during the study; BMI >39 kg/m2; history of joint disease or recent trauma to the index knee; significant incapacitation,

		Tanezumab 10 mg IV Placebo IV and SC	WOMAC Pain score in the index knee at screening ≥4 and ≥5 at baseline. Pts regularly taking pain medications (≥4 days/wk) during the month prior to screening had to have an increase ≥1 point in WOMAC Pain score between screening and baseline. Pts had WOMAC Physical Function score ≥4 in index knee; PGA of OA of "fair," "poor," or "very poor" at baseline; and ≥1 of the following: unwilling or unable to take non-opiate pain medications (e.g., NSAIDs); inadequate pain relief with non-opiate pain medications; or candidates for or seeking invasive interventions (intra-articular injections, knee arthroplasty, or knee replacement surgery)	fibromyalgia, or regional pain caused by lumbosacral radiculopathy; significant cardiac, neurologic, or psychiatric conditions; planned surgery during the study; or previous exposure to exogenous NGF or NGF antibody.
A4091030 (NCT00985621; September 25, 2009)	16 weeks	Tanezumab 5 mg IV Tanezumab 10 mg IV Oxycodone CR 10–40 mg PO BID Placebo matching active PO and IV	OA of the hip or knee with KL grade ≥2; WOMAC Pain score ≥4 at screening; WOMAC Pain score ≥5 at baseline and an increase of ≥1 following washout of prior analgesic treatment; WOMAC Physical Function score ≥4; PGA of OA of fair, poor, or very poor at baseline; and regular use of analgesics other than acetaminophen for OA pain. In addition, eligible patients had to use non-opioids or opioids up to 90 mg/day in morphine equivalents, but this therapy had not provided adequate pain relief, had not been tolerated, or patient was a candidate for invasive intervention such as total hip or knee replacement.	Pregnancy, nursing, or intent to become pregnant during the study; BMI >39 kg/m2; history of joint disease or recent trauma to the index joint; significant incapacitation, fibromyalgia or regional pain caused by lumbosacral radiculopathy; significant cardiac, neurologic, or psychiatric conditions; planned surgery during the study; opioid abuse or illicit drug use; previous exposure to exogenous NGF or NGF antibody; exposure to opioids in doses exceeding 90 mg/day in morphine equivalents (i.e., oxycodone >60 mg/day) within 30 days prior to screening; history of allergic or anaphylactic reaction to a monoclonal antibody or IgG type-fusion protein; history of intolerance or hypersensitivity to acetaminophen or oxycodone; an existing medical condition for which the use of oxycodone was contraindicated; corticosteroids or intra-articular hyaluronic acid injection to the index hip or index knee within 30 days prior to the initial pain assessment period (the 5 days before randomization); and any other condition, which, in the opinion of the investigator, would put the patient at increased safety risk or would otherwise make the patient unsuitable for the study.
A4091056	16 weeks	Tanezumab 2.5 mg SC Tanezumab 2.5/5 mg SC[d]	≥18 years with a diagnosis of OA with a KL grade ≥2 in the index hip or knee with	Pregnancy, nursing, or intent to become pregnant during the study; BMI >39 kg/m2. A history of non-OA joint

(NCT02697773; March 3, 2016)		Placebo SC	radiographic confirmation by a Central Reader at screening. WOMAC Pain subscale score of ≥5 in the index joint at screening and baseline, WOMAC Physical Function subscale score of ≥5 at baseline, and PGA-OA of "fair," "poor," or "very poor" at baseline. A documented history of insufficient pain relief from acetaminophen; and insufficient pain relief or inability to tolerate or contraindication to nonsteroidal anti-inflammatory drugs (NSAIDs); and insufficient relief from, inability to tolerate or contraindication to either tramadol or other opioids, or unwillingness to take opioids	disease in the index joint, radiographic evidence of rapidly progressive OA, atrophic OA, subchondral insufficiency fractures, osteonecrosis or pathological fracture at screening, or a history of significant trauma or surgery to a knee, hip or shoulder in the year before screening. Fibromyalgia or other moderate-to-severe pain that may confound assessments of OA pain; a history, diagnosis, or signs and symptoms of clinically significant neurological disease or psychiatric disorder, or a known history of alcohol, analgesic, or drug abuse within 2 years of screening.
A4091057 (NCT02709486; March 16, 2016)	24 weeks	Tanezumab 2.5 mg SC Tanezumab 5 mg SC Placebo SC	≥18 years with a diagnosis of OA with a KL grade ≥2 in the index hip or knee with radiographic confirmation by a Central Reader at screening. WOMAC Pain subscale score of ≥5 in the index joint at screening and baseline, WOMAC Physical Function subscale score of ≥5 at baseline, and PGA-OA of "fair," "poor," or "very poor" at baseline. A documented history of insufficient pain relief from acetaminophen; and insufficient pain relief or inability to tolerate or contraindication to nonsteroidal anti-inflammatory drugs (NSAIDs); and insufficient relief from, inability to tolerate or contraindication to either tramadol or other opioids, or unwillingness to take opioids	Pregnancy, nursing, or intent to become pregnant during the study; BMI >39 kg/m2. A history of non-OA joint disease in the index joint, radiographic evidence of rapidly progressive OA, atrophic OA, subchondral insufficiency fractures, osteonecrosis or pathological fracture at screening, or a history of significant trauma or surgery to a knee, hip or shoulder in the year before screening. Fibromyalgia or other moderate-to-severe pain that may confound assessments of OA pain; a history, diagnosis, or signs and symptoms of clinically significant neurological disease or psychiatric disorder, or a known history of alcohol, analgesic, or drug abuse within 2 years of screening.

ACR American College of Rheumatology, *BID* twice a day, *BMI* body mass index, *CR* controlled release, *Ig* immunoglobulin, *IV* intravenous, *KL* Kellgren-Lawrence, *NC* nerve conduction, *NGF* nerve growth factor, *NSAIDs* nonsteroidal anti-inflammatory drugs, *OA* osteoarthritis, *PGA* Patient's Global Assessment, *PO* oral, *pt* patient, *SC* subcutaneous, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

Tanezumab or placebo was administered via IV or SC injection every 8 weeks in all studies

[a]WOMAC was assessed on an 11-point numeric rating scale (greater scores represent greater pain intensity/worsening physical function)

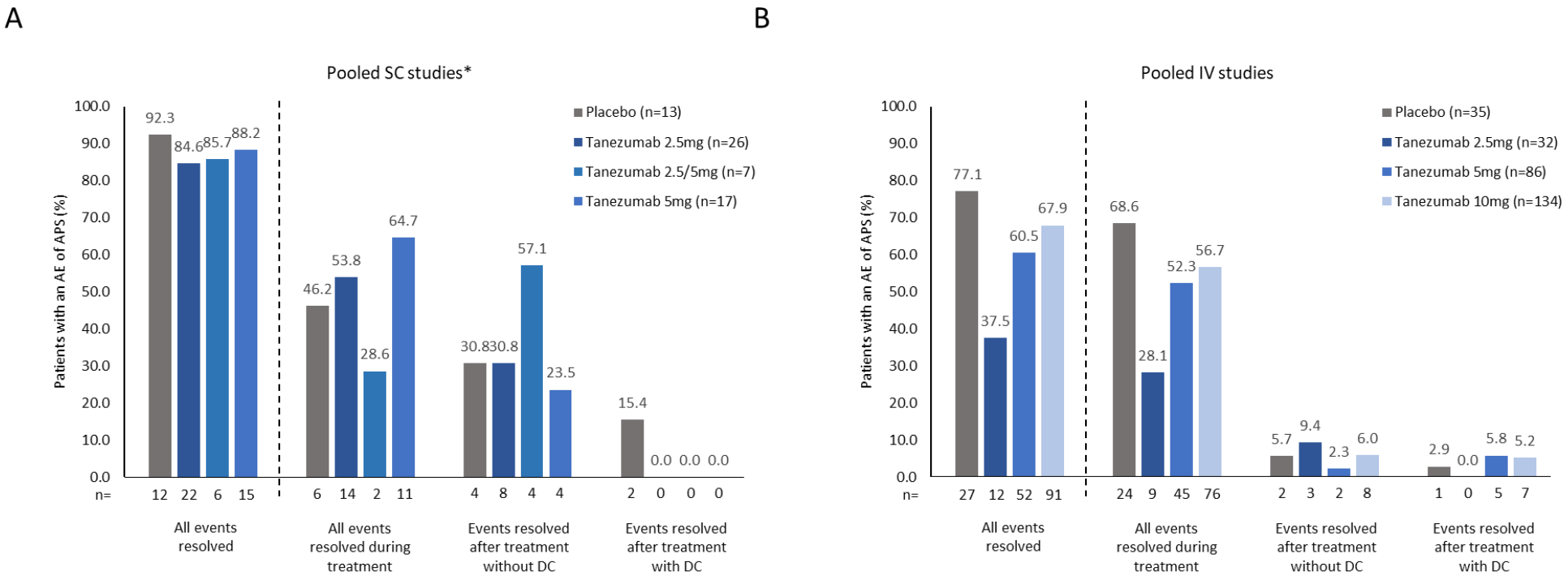
[b]

[c]PGA of OA was assessed on a 5-point scale (1 = very good, 5 = very poor)

[d]Tanezumab 2.5 mg at baseline and 5 mg at week 8

Supplementary Table 2 Adverse events of abnormal peripheral sensation evaluated in each study
Symptomatic adverse events of abnormal peripheral sensation Allodynia, burning sensation, decreased vibratory sense, dysesthesia, formication, hyperaesthesia, hyperpathia, hypoesthesia, hypoesthesia oral, intercostal neuralgia, neuralgia, neuritis, paresthesia, paresthesia oral, sensory disturbance, sensory loss, and thermohypoesthesia
Neuropathy-related adverse events of abnormal peripheral sensation Axonal neuropathy, carpal tunnel syndrome, demyelinating polyneuropathy, neuropathy peripheral, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy, polyneuropathy chronic, sciatica and tarsal tunnel syndrome

Supplementary Figure 1 Resolution timing of adverse events of abnormal peripheral sensation reported during the treatment period



*Data from the SC groups of study A4091027 were not included as different procedures precluded pooling with the other SC data

Includes treatment-emergent events that began during the treatment period. Events with unknown resolution are not shown. The n for each treatment group reports the total number of patients with an AE of APS. The n listed below the x-axis reports the number of patients in each category. The treatment periods ranged 16–24 weeks for studies in both the SC and IV datasets. *AE* adverse event, *APS* abnormal peripheral sensation, *DC* discontinuation of treatment, *IV* intravenous, *SC* subcutaneous