



1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

March 10, 2021

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**Comments for the Food and Drug Administration's Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee Regarding Biologics License Application 761130 for Tanezumab
Docket No. FDA-2021-N-0134**

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, submits these comments to the Food and Drug Administration's (FDA's) Arthritis Advisory Committee (AAC) and the Drug Safety and Risk Management Advisory Committee (DSaRMAC) regarding the biologics license application (BLA) 761130, tanezumab subcutaneous injection, submitted by Pfizer Inc., for the proposed indication of relief of signs and symptoms of moderate-to-severe osteoarthritis (OA) in adult patients for whom use of other analgesics is ineffective or not appropriate. Such comments were solicited by the agency in a notice published in the *Federal Register* on February 16, 2021 (Docket No. FDA-2021-N-0134).¹

Public Citizen strongly opposes approval of tanezumab for the proposed indication because the totality of the evidence from three published pivotal phase 3 randomized clinical trials that tested tanezumab in the intended target patient population demonstrates that the drug fails to provide clinically meaningful benefit but does dramatically increase the rates of rapidly progressive OA (RPOA) and other types of serious joint damage and of total joint replacements in a dose- and duration-dependent manner. As a result, the risks of the drug far outweigh its benefits.

The following are key points regarding the three published pivotal phase 3 randomized clinical trials discussed in our comments:

- (1) With respect to the efficacy data, we note the following:
 - (a) For the two smaller, placebo-controlled trials — one with a 16-week (two-dose) treatment phase and the other with a 24-week (three-dose) treatment phase — for those co-primary efficacy endpoints that did show statistically significant improvements in the tanezumab groups compared with the placebo groups, the point

¹ 65 FR 9512-9513.

estimates for the differences of least squares mean versus placebo for these co-primary efficacy outcomes were small and the lower bounds of the 95% confidence intervals were very small. Such small statistically significant differences indicate that tanezumab at the tested dose on average provided little clinically meaningful benefit.

- (b) For the placebo-controlled trials with a 24-week (three-dose) treatment phase, the trial failed to show statistically significant improvement in the tanezumab 2.5-milligram (mg) group compared with the placebo group on all three prespecified co-primary efficacy endpoints and thus failed to demonstrate that this dose is efficacious compared with placebo according to the prespecified statistical plan.
- (c) For the two smaller, placebo-controlled trials, if the subjects in the placebo group had received a daily regimen of oral non-steroidal anti-inflammatory drugs (NSAIDs — for the vast majority who were not intolerant to and did not have a contraindication to NSAIDs) or even daily acetaminophen, including on the days when the primary efficacy endpoint assessments were made, the differences on these primary efficacy outcome measures between the tanezumab groups and the control group undoubtedly would have been even smaller.
- (d) In the real-world setting, most patients with moderate-to-severe OA who have inadequate relief from currently available oral analgesics, such as those enrolled in the two smaller, placebo-controlled trials, likely would be treated with one or more of the currently available FDA-approved oral analgesics or other standard non-pharmacologic interventions that were not provided to the placebo-group subjects during the treatment phase of this trial. Therefore, any assessment of the overall safety and effectiveness of tanezumab must be based on clinical trials of tanezumab that include an active-comparator group.
- (e) The third large active-comparator controlled trial with a 54-week (seven-dose) treatment phase provided a much more appropriate control group for assessing the efficacy (and safety) of tanezumab for relief of signs and symptoms of moderate-to-severe OA in adult patients for whom use of other analgesics is ineffective or not appropriate. In addition, the longer duration of exposure to the tanezumab and the much greater subject enrollment in this trial relative to the two placebo-controlled trials allowed for a much more robust assessment of the efficacy (and safety) of this drug for the proposed indication.

The efficacy data from the active-comparator trial demonstrated that in comparison with oral NSAIDs, tanezumab at a dosage of 2.5 mg and 5 mg every eight weeks failed to meet the prespecified efficacy outcomes or provide any clinically meaningful benefit for the relief of signs and symptoms of moderate-to-severe OA of the knee or hip in adult patients for whom use of other analgesics is ineffective or not appropriate.

- (2) With respect to the safety data, we note the following:

- (a) Tanezumab caused accelerated joint damage after as little as two 2.5-mg doses.
- (b) The long-term safety and efficacy phase 3, active-comparator trial clearly demonstrated that tanezumab causes a dramatic, statistically significant, and clinically important increase in the rate of serious adverse joint events and total joint replacements in a dose- and duration-dependent manner.

Strikingly, the observation time-adjusted rates of the primary composite joint safety endpoint (adjudicated RPOA type 1 or 2, primary osteonecrosis, subchondral insufficiency fracture, or pathologic fracture) in the tanezumab 2.5-mg group and tanezumab 5-mg group were approximately *2.5 times higher* and *nearly five times higher*, respectively, than the rate in the NSAID group. Likewise, the observation time-adjusted rates of total joint replacement in the tanezumab 2.5-mg group and tanezumab 5-mg group were approximately *two times higher* and *three times higher*, respectively, than the rate in the NSAID group.

- (c) The occurrence of the adverse joint events caused by tanezumab is not rare.
- (d) Despite the robust risk-mitigation strategies that were employed in all three phase 3 clinical trials and intended to minimize the risk of adverse joint events, an unacceptably high number of serious joint adverse events still occurred. In a real-world setting, where there would not be the same rigorous screening and monitoring of patients that occurs for subjects enrolled in a clinical trial and where the drug is likely to be prescribed for uses not approved by the FDA (so-called off-label uses), the incidence of such serious adverse joint events almost certainly would be significantly higher.

We therefore urge the committees to recommend that the FDA not approve the BLA for tanezumab. A drug that accelerates the joint destruction of the underlying OA disease that it is intended to treat but lacks any evidence of clinically meaningful benefit in comparison to use of a placebo or oral NSAIDs obviously should never be approved by the FDA. It is baffling why the FDA felt it needed to bring the BLA for this drug before your committees.

The following is a more detailed discussion of the evidence supporting our opposition to FDA approval of tanezumab.

A. Background

Nerve growth factor (NGF) is a protein that is believed to play a significant role in pain sensation in adults through several mechanisms, including increased sensitization of the nerves that transmit pain signals at the site of tissue injury.² Tanezumab is an anti-NGF monoclonal antibody that prevents NGF from binding to its receptors. It has been studied as a potential

² Barker PA, Mantyh P, Arendt-Nielsen L, et al. Nerve growth factor signaling and its contribution to pain. *J Pain Res.* 2020 May 26;13:1223-1241.

treatment for chronic pain, including pain associated with OA,^{3,4,5,6} low back pain,⁷ and neuropathic pain,⁸ among other conditions.

In 2010, the FDA placed a clinical hold on the development programs for tanezumab as a treatment for OA and chronic low back pain because randomized clinical trials of the drug found that it was associated with unusual and unexpected joint-related adverse events that had been reported as osteonecrosis and avascular necrosis, all of which led to joint replacement. There were also several cases of pathological (non-trauma-related) bone fracture.⁹ These serious joint and bone adverse events all occurred in tanezumab-group subjects, with none in placebo-group subjects or active-comparator-group subjects. After further analysis and adjudication of the joint-related adverse events, Pfizer characterized many of these events as RPOA.¹⁰

On March 12, 2012, the FDA convened a meeting of the AAC to consider these serious tanezumab-induced adverse events, as well as similar safety concerns about two other anti-NGF monoclonal antibodies that were being developed.¹¹ At that meeting Public Citizen urged the FDA to permanently suspend the clinical development of these anti-NGF agents for the treatment of pain because of the dramatic, serious safety signal seen in clinical trials of these agents demonstrating an unusually high incidence of rapid joint destruction.¹² At that time, the AAC committee members concluded the following:

³ Lane NE, Schnitzer TJ, Birbara CA, et al. Tanezumab for the treatment of pain from osteoarthritis of the knee. *N Engl J Med*. 2010 Oct 14;363(16):1521-31.

⁴ Schnitzer TJ, Easton R, Pang S, et al. Effect of tanezumab on joint pain, physical function, and patient global assessment of osteoarthritis among patients with osteoarthritis of the hip or knee: A randomized clinical trial. *JAMA*. 2019;322(1):37-48.

⁵ Berenbaum F, Blanco FJ, Guermazi A, et al. Subcutaneous tanezumab for osteoarthritis of the hip or knee: efficacy and safety results from a 24-week randomised phase III study with a 24-week follow-up period. *Ann Rheum Dis*. 2020;79(6):800-810.

⁶ Hochberg MC, Carrino JA, Schnitzer TJ, et al. Long-term safety and efficacy of subcutaneous tanezumab versus nonsteroidal antiinflammatory drugs for hip or knee osteoarthritis: A randomized trial. *Arthritis Rheumatol*. 2021 Feb 3. doi: 10.1002/art.41674. Online ahead of print.

⁷ Markman JD, Bolash RB, McAlindon TE, et al. Tanezumab for chronic low back pain: a randomized, double-blind, placebo- and active-controlled, phase 3 study of efficacy and safety. *Pain*. 2020;161(9):2068–2078.

⁸ Bramson C, Herrmann DN, Carey W, et al. Exploring the role of tanezumab as a novel treatment for the relief of neuropathic pain. *Pain Med*. 2015;16(6):1163-76.

⁹ Food and Drug Administration. Background materials; meeting of the Arthritis Advisory Committee. March 12, 2012. <https://wayback.archive-it.org/7993/20170405210029/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM295202.pdf>. Accessed March 7, 2021.

¹⁰ Pfizer. Tanezumab: Arthritis Advisory Committee briefing document. February 8, 2012. Available at <https://wayback.archive-it.org/7993/20170405210034/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM295205.pdf>. Accessed March 7, 2021.

¹¹ Food and Drug Administration. Background materials; meeting of the Arthritis Advisory Committee. March 12, 2012. <https://wayback.archive-it.org/7993/20170405210029/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM295202.pdf>. Accessed March 7, 2021.

¹² Carome MA, Wolfe SM. Testimony to the FDA's Arthritis Advisory Committee on safety issues related to anti-nerve growth factor agents. March 12, 2012. <https://mkus3lurbh3lbztg254fzode-wpengine.netdna-ssl.com/wp-content/uploads/2007.pdf>. Accessed March 7, 2021.

- (1) The adverse events of painful, rapid joint destruction seen in clinical studies of anti-NGF agents that were under development for the treatment of pain due to a variety of disorders occurred with an unusually high incidence in the populations studied and were unusually severe compared with joint-related events that occur in these populations.
- (2) Destructive joint events had been identified as a safety signal in the tanezumab clinical programs and RPOA type 2 was a relatively distinct finding in the tanezumab studies.
- (3) The risk-benefit profile of tanezumab/NSAID combination therapy was unfavorable compared with NSAID treatment alone and with tanezumab monotherapy.
- (4) More studies were required to make a final determination as to whether the risk-benefit profile of tanezumab monotherapy in the treatment of OA is favorable compared to treatment with placebo, NSAIDS, or extended-release oxycodone.
- (5) There was a role for ongoing development of anti-NGF agents for treatment of pain in conditions such as OA.¹³

In August 2012, the FDA lifted the clinical hold on tanezumab, allowing resumption of clinical trials of the drug for OA and all other chronic pain conditions.¹⁴ But in December 2012, the FDA placed another partial clinical hold on clinical trials of tanezumab, except for those in subjects with cancer pain, due to concerns about adverse changes in the sympathetic nervous system of mature animals administered the drug.¹⁵

In March 2015, after reviewing safety data from additional animal studies, the FDA lifted the partial hold on the clinical trials of tanezumab.¹⁶ Notably, subsequent clinical trials implemented detailed strategies that were intended to minimize the risk of adverse joint events, including the following:

Risk minimization: (1) exclusion of chronic concomitant NSAID use; (2) exclusion of tanezumab doses that had been explored and did not demonstrate benefit over lower doses in the condition under study; (3) exclusion of subjects with evidence of RPOA or risk factors for RPOA; and (4) exclusion of subjects who are not suitable candidates for total joint replacement.

¹³ Food and Drug Administration. Summary minutes of the Arthritis Advisory Committee Meeting. March 12, 2012. <https://wayback.archive-it.org/7993/20170404145629/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM307879.pdf>. Accessed March 7, 2021.

¹⁴ Pfizer. Clinical protocol: A phase 3 randomized, double-blind, placebo-controlled, multicenter study of the analgesic efficacy and safety of a dose titration regimen for the subcutaneous administration of tanezumab in subjects with osteoarthritis of the hip or knee. https://clinicaltrials.gov/ProvidedDocs/73/NCT02697773/Prot_000.pdf. Accessed March 8, 2021.

¹⁵ *Ibid.*

¹⁶ Garde D. FDA removes the brakes on Pfizer and Lilly's pain drug. Fierce Biotech. March 23, 2015. <https://www.fiercebiotech.com/regulatory/fda-removes-brakes-on-pfizer-and-lilly-s-pain-drug>. Accessed March 8, 2021.

Risk identification and management: (1) evaluation and follow-up for severe joint pain; (2) extended post-treatment follow-up; (3) a program-level Central Radiograph Reader and subject-level stopping criteria; (4) an Adjudication Committee; and (5) a Data Monitoring Committee (DMC) and protocol-level stopping rules.

Risk characterization: (1) comprehensive evaluation of OA medical history prior to study entry; (2) scheduled radiographic assessments during the studies; (3) surgical and post-operative total joint replacement outcomes; and (4) biomarker determinations.¹⁷

B. Review of three published pivotal phase 3 randomized clinical trials of tanezumab in adult patients with moderate to severe OA for whom use of other analgesics was ineffective or not appropriate

1. Efficacy and Safety of a Subcutaneous Tanezumab Titration Dosing Regimen in Subjects With Moderate to Severe Osteoarthritis of the Hip or Knee (study ID# A4091056; ClinicalTrials.gov identifier NCT02697773; Schnitzer et al, *Journal of the American Medical Association (JAMA)*, 2019)^{18,19}

Design overview

The first pivotal phase 3 clinical trial, study A4091056, was a randomized, double-blind, placebo-controlled, multicenter trial that was conducted from January 2016 to May 2018 (last subject visit) in the U.S., Canada, and Puerto Rico. Subjects were aged 18 years and older and diagnosed as having hip or knee OA according to American College of Rheumatology criteria with radiographic confirmation at screening (Kellgren-Lawrence grade ≥ 2). Additional key inclusion criteria included the following:

- An index joint (defined as the most painful hip or knee at screening) Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC) Pain subscale score of 5 or greater (on an 11-point numerical rating scale from 0 = no pain to 10 = extreme pain) at both screening and baseline;
- A baseline WOMAC Physical Function subscale score of 5 or greater (on an 11-point numerical rating scale from 0 = no difficulty to 10 = extreme difficulty);
- A baseline global assessment of osteoarthritis (PGA-OA) rating of fair, poor, or very poor (on a scale from 1 = very good to 5 = very poor); and
- A documented history of (1) insufficient pain relief from acetaminophen; (2) insufficient pain relief from, intolerance to, or contraindication to NSAIDs; and (3) insufficient pain

¹⁷ Pfizer. Clinical protocol: A phase 3 randomized, double-blind, placebo-controlled, multicenter study of the analgesic efficacy and safety of a dose titration regimen for the subcutaneous administration of tanezumab in subjects with osteoarthritis of the hip or knee.

https://clinicaltrials.gov/ProvidedDocs/73/NCT02697773/Prot_000.pdf. Accessed March 8, 2021.

¹⁸ ClinicalTrials.gov. Efficacy and safety of a subcutaneous tanezumab titration dosing regimen in subjects with moderate to severe osteoarthritis of the hip or knee. <https://clinicaltrials.gov/ct2/show/study/NCT02697773>. Accessed March 8, 2021.

¹⁹ Schnitzer TJ, Easton R, Pang S, et al. Effect of tanezumab on joint pain, physical function, and patient global assessment of osteoarthritis among patients with osteoarthritis of the hip or knee: A randomized clinical trial. *JAMA*. 2019;322(1):37-48.

relief from, intolerance to, or contraindication to tramadol or other opioids (or were unwilling to take opioids).

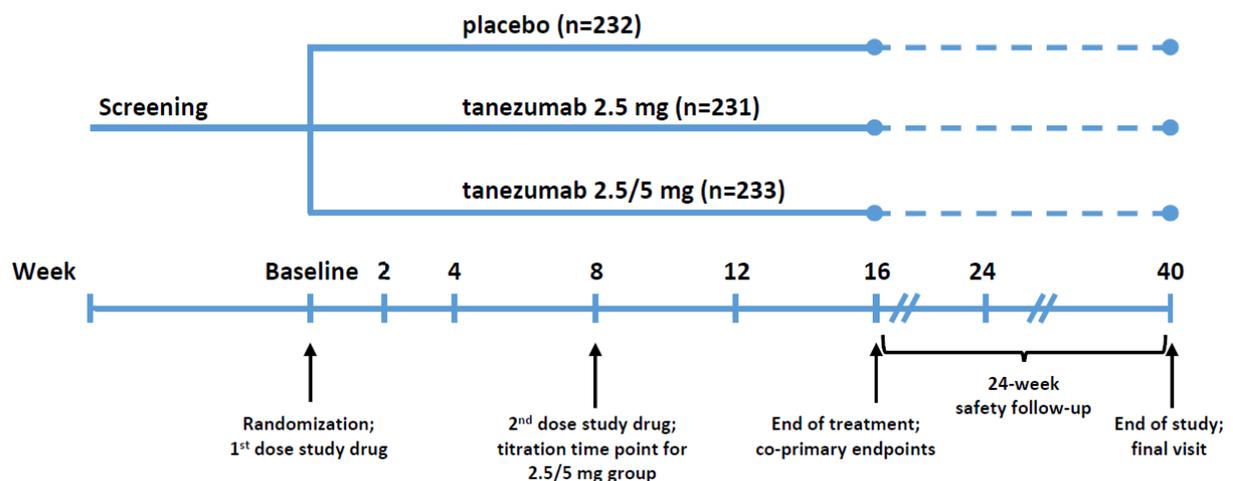
Patients with radiographic evidence of prespecified joint safety concerns (e.g., rapidly progressive OA, subchondral insufficiency fracture, osteonecrosis, pathologic fracture) in any major joint on screening radiographs, as determined by a central reader, were excluded.

Subjects were randomly assigned to receive by subcutaneous administration either tanezumab, 2.5 mg, at baseline (time 0) and week 8 (n = 231); tanezumab, 2.5 mg, at baseline and 5 mg at week eight (n = 233); or placebo at baseline and week eight (n = 232) (two doses total for each group). Analgesics were prohibited except as follows: NSAIDs for non-OA conditions were permitted for up to 10 days per eight-week period between baseline and week 24, but not within 48 hours of a study visit (at which WOMAC Pain and Physical Function subscale scores and PGA-OA scores were assessed for efficacy outcomes). Rescue medication with acetaminophen was allowed up to 3,000 mg/d and for three or fewer days per week during the treatment period, but not within 24 hours of a study visit. Standard-of-care treatment for OA pain was permitted 16 weeks after the last study drug dose.

The three co-primary efficacy endpoints were the changes from baseline to week 16 in WOMAC Pain subscale scores, WOMAC Physical Function subscale scores, and PGA-OA scores. Under the prespecified statistical plan, a tanezumab group was considered superior to the placebo group only if all three co-primary endpoints were statistically significant. A key secondary efficacy endpoint was the WOMAC Pain responder rate of 50% or greater at week 16, defined as the proportion of patients with a 50% or greater reduction from baseline in WOMAC Pain subscale score at week 16.

Following the 16-week treatment phase, subjects were followed for 24 weeks for safety outcomes.

The following figure provides a summary of the study design (excerpted from the supplemental materials for Schnitzer et al, *JAMA*, 2019):



Key efficacy and safety data

Of note, more than 99% of subjects had inadequate pain relief with acetaminophen and 91% had inadequate pain relief with oral NSAIDs prior to enrollment.

Public Citizen's comment

Importantly, inadequate pain relief does not necessarily mean no pain relief with these medications.

As shown in the following table excerpted from Schnitzer et al, *JAMA*, 2019, statistically significant improvements on the three co-primary efficacy endpoints were seen in both tanezumab groups compared with the placebo group.

Table 2. Change From Baseline to Week 16 in WOMAC Pain Subscale, WOMAC Physical Function Subscale, and Patient Global Assessment of Osteoarthritis (Co-primary End Points)^a

Scale	Tanezumab		Placebo (n = 232)
	2.5 mg (n = 231)	2.5/5 mg (n = 233)	
WOMAC Pain^b			
Baseline Pain score, mean (range)	7.1 (4.8 to 10.0)	7.3 (5.0 to 10.0)	7.3 (4.2 to 10.0)
Least squares change from baseline, mean (95% CI)	-3.23 (-3.67 to -2.79)	-3.37 (-3.81 to -2.93)	-2.64 (-3.08 to -2.19)
Difference of least squares vs placebo, mean (95% CI)	-0.60 (-1.07 to -0.13)	-0.73 (-1.20 to -0.26)	
P value	.01	.002	
WOMAC Physical Function^c			
Baseline Physical Function score, mean (range)	7.2 (5.1 to 9.9)	7.4 (3.2 to 9.9)	7.4 (4.4 to 10.0)
Least squares change from baseline, mean (95% CI)	-3.22 (-3.66 to -2.79)	-3.45 (-3.88 to -3.03)	-2.56 (-3.00 to -2.12)
Difference of least squares vs placebo, mean (95% CI)	-0.66 (-1.14 to -0.19)	-0.89 (-1.37 to -0.42)	
P value	.007	<.001	
Patient Global Assessment of Osteoarthritis^d			
Baseline score, mean (range)	3.4 (2 to 5)	3.5 (3 to 5)	3.5 (3 to 5)
Least squares change from baseline, mean (95% CI)	-0.87 (-1.02 to -0.72)	-0.90 (-1.05 to -0.75)	-0.65 (-0.80 to -0.50)
Difference of least squares vs placebo, mean (95% CI)	-0.22 (-0.39 to -0.05)	-0.25 (-0.41 to -0.08)	
P value	.01	.004	

In addition, the proportion of subjects with a 50% or greater reduction from baseline in WOMAC Pain subscale scores at week 16 was 54.5% and 57.1% in the tanezumab 2.5-mg and tanezumab 2.5/5-mg groups, respectively, compared with 37.9% in the control group subjects, differences that were statistically significant ($P = .001$ for both comparisons).

Public Citizen's comments

Regarding the efficacy data for this trial, we would like to highlight the following points:

- (1) The point estimates for the differences of least squares mean versus placebo for the three co-primary efficacy outcomes were small: only -0.60 and -0.73 on the 0-to-10 scale for the WOMAC Pain subscale scores, -0.66 and -0.89 on the 0-to-10 scale for Physical Function subscale scores, and -0.22 and -0.25 on the 1-to-5 scale for the PGA-OA scores for the tanezumab 2.5-mg and tanezumab 2.5/5-mg groups, respectively.***

Also, the lower bounds for the 95% confidence intervals for these differences generally were very small: only -0.13 and -0.26 on the 0-to-10 scale for the WOMAC Pain subscale scores, -0.19 and -0.42 on the 0-to-10 scale for Physical Function subscale scores, and -0.05 and -0.08 on the 1-to-5 scale for the PGA-OA scores for the tanezumab 2.5-mg and tanezumab 2.5/5-mg groups, respectively).

Such small statistically significant differences indicate that tanezumab at the tested doses on average provided little clinically meaningful benefit.

- (2) If the subjects in the placebo group had received a daily regimen of oral NSAIDs (for the vast majority who were not intolerant to and did not have a contraindication to NSAIDs) or even daily acetaminophen, including on the days when the primary efficacy endpoint assessments were made, the differences on these primary efficacy outcome measures between the tanezumab groups and the control group undoubtedly would have been even smaller.***
- (3) In the real-world setting, most patients with moderate-to-severe OA who have inadequate relief from currently available oral analgesics, like those enrolled in this trial, likely would be treated with one or more of the currently available FDA-approved oral analgesics or other standard non-pharmacologic interventions that were not provided to the placebo-group subjects during the treatment phase of this trial. Therefore, any assessment of the overall safety and effectiveness of tanezumab must be based on clinical trials of tanezumab that include an active comparator.***

The following table excerpted from Schnitzer et al, *JAMA*, 2019 shows that adverse joint events, including RPOA and the need for total joint replacement, occurred with higher frequency in the tanezumab groups in a generally dose-dependent manner:

Table 4. Summary of Overall Adverse Events, Neurological Adverse Events (AEs), and Joint Safety Outcomes

	Treatment Period (0-16 wk), No. (%)			Up to End of Study (0-40 wk), No. (%)		
	Tanezumab		Placebo (n = 232)	Tanezumab		Placebo (n = 232)
	2.5 mg (n = 231)	2.5/5 mg (n = 233)		2.5 mg (n = 231)	2.5/5 mg (n = 233)	
Joint Safety Outcomes						
Patients with adjudicated joint safety events						
Normal osteoarthritis progression				8 (3.5)	17 (7.3)	5 (2.2)
Rapidly progressive OA type 1 ^d				3 (1.3)	1 (0.4)	0
Rapidly progressive OA type 2 ^e				2 (0.9)	0	0
Other (eg, preexisting subchondral insufficiency fracture) ^f				1 (0.4)	0	0
Patients with ≥1 total joint replacement				8 (3.5)	16 (6.9) ^g	4 (1.7)
Joints replaced						
Knee				3	10	4
Hip				5	7	0

^d Rapidly progressive osteoarthritis (OA) type 1 is defined as a significant loss of joint space width ≥ 2 mm (predicated on optimal joint positioning) within approximately 1 year, without gross structural failure. One patient with rapidly progressive OA type 1 in the tanezumab, 2.5/5mg, treatment group had a total joint replacement.

^e Rapidly progressive OA type 2 is defined as abnormal bone loss or destruction, including limited or total collapse of at least 1 subchondral surface, that is not normally present in conventional end-stage osteoarthritis. One patient with rapidly progressive OA type 2 in the tanezumab, 2.5mg, treatment group had a total joint replacement.

^f A condition was adjudicated as “preexisting” if it was not identified by the central reader at screening but the adjudication committee determined it to be preexisting after reviewing all available postbaseline clinical and imaging information for the joint safety event in question.

^g One patient had 2 joint replacements.

Notably, RPOA occurred only in tanezumab-group subjects (2.5 mg: n = 5, 2.2%; 2.5/5mg: n = 1, 0.4%), and the incidence of total joint replacements was four (1.7%), eight (3.5%), and 16 (6.9%) in the placebo group, tanezumab 2.5-mg group, and tanezumab 2.5/5-mg group, respectively.

Public Citizen's comments

Regarding the joint safety data for this trial, we would like to highlight the following points:

- (1) Tanezumab caused accelerated joint damage after as little as two 2.5-mg doses.***
- (2) Given that moderate-to-severe OA is a chronic condition for which tanezumab would be used for much longer durations, the cumulative incidence of such serious adverse joint events in the real-world setting would clearly be far greater than that seen during this trial.***
- (3) Despite the robust risk-mitigation strategies that were employed in this trial and intended to minimize the risk of adverse joint events, a significant number of serious joint adverse events still occurred. In a real-world setting, where there would not be the same rigorous screening and monitoring of patients that occurs for subjects enrolled in a clinical trial and where the drug is likely to be prescribed for uses not approved by the FDA (so-called off-label uses), the incidence of such serious adverse joint events almost certainly would be significantly higher.***

2. Study of the Analgesic Efficacy and Safety of Subcutaneous Tanezumab in Subjects With Osteoarthritis of the Hip or Knee (study ID# A4091057; ClinicalTrials.gov identifier NCT02709486; Berenbaum et al, *Ann Rheum Dis*, 2020)^{20,21}

Design overview

The second pivotal phase 3 clinical trial, study A4091057, was a randomized, double-blind, placebo-controlled, multicenter trial conducted from March 2016 to November 2018 in Europe and Japan. The key inclusion criteria were identical to study A4091056, and patients with radiographic evidence of prespecified joint safety concerns (e.g., RPOA, atrophic or hypotrophic OA, subchondral insufficiency fracture, spontaneous osteonecrosis of the knee, osteonecrosis or pathological fracture) on screening radiographs, as determined by centralized readers, were excluded.

Subjects were randomly assigned to receive by subcutaneous administration either tanezumab at a dose of 2.5 mg (n = 283), tanezumab at a dose of 5 mg (n = 284), or placebo (n = 282) at baseline, eight weeks and 16 weeks (three doses total for each group). Analgesics were prohibited except as follows: NSAIDs for self-limited non-OA conditions were permitted for up to 10 days per eight-week period between baseline and week 32, but not within 48 hours or five half-lives (whichever was greater) of a study visit for efficacy assessments. Rescue medication

²⁰ ClinicalTrials.gov. Study of the analgesic efficacy and safety of subcutaneous tanezumab in subjects with osteoarthritis of the hip or knee. <https://clinicaltrials.gov/ct2/show/NCT02709486>. Accessed March 8, 2021.

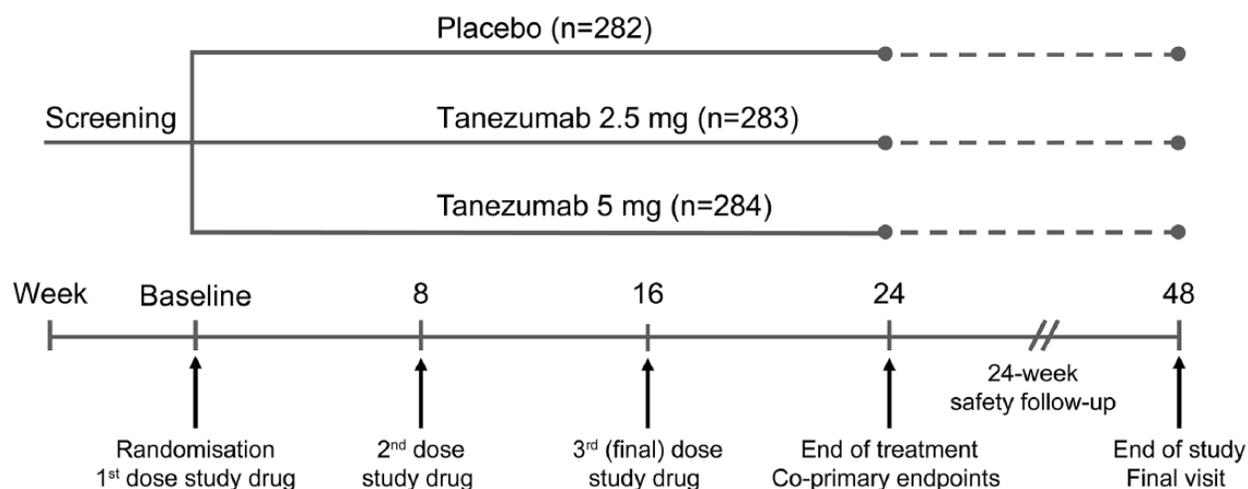
²¹ Berenbaum F, Blanco FJ, Guermazi A, et al. Subcutaneous tanezumab for osteoarthritis of the hip or knee: efficacy and safety results from a 24-week randomised phase III study with a 24-week follow-up period. *Ann Rheum Dis*. 2020;79(6):800-810.

with acetaminophen was allowed up to 4,000 mg/d (or as permitted by local or national labelling) for five or fewer days per week up to week 24, and then as needed until week 32, but not within 24 hours of a study visit for efficacy assessments. Standard of care treatment for OA pain was permitted after week 32.

The three co-primary efficacy endpoints were the changes from baseline to week 24 in WOMAC Pain subscale scores, WOMAC Physical Function subscale scores, and PGA-OA scores. Under the prespecified statistical plan, a tanezumab group was considered superior to the placebo group only if all three co-primary endpoints were statistically significant. A key secondary efficacy endpoint was the WOMAC Pain responder rate of 50% or greater at week 24.

Following the 24-week treatment phase, subjects were followed for 24 additional weeks for safety outcomes.

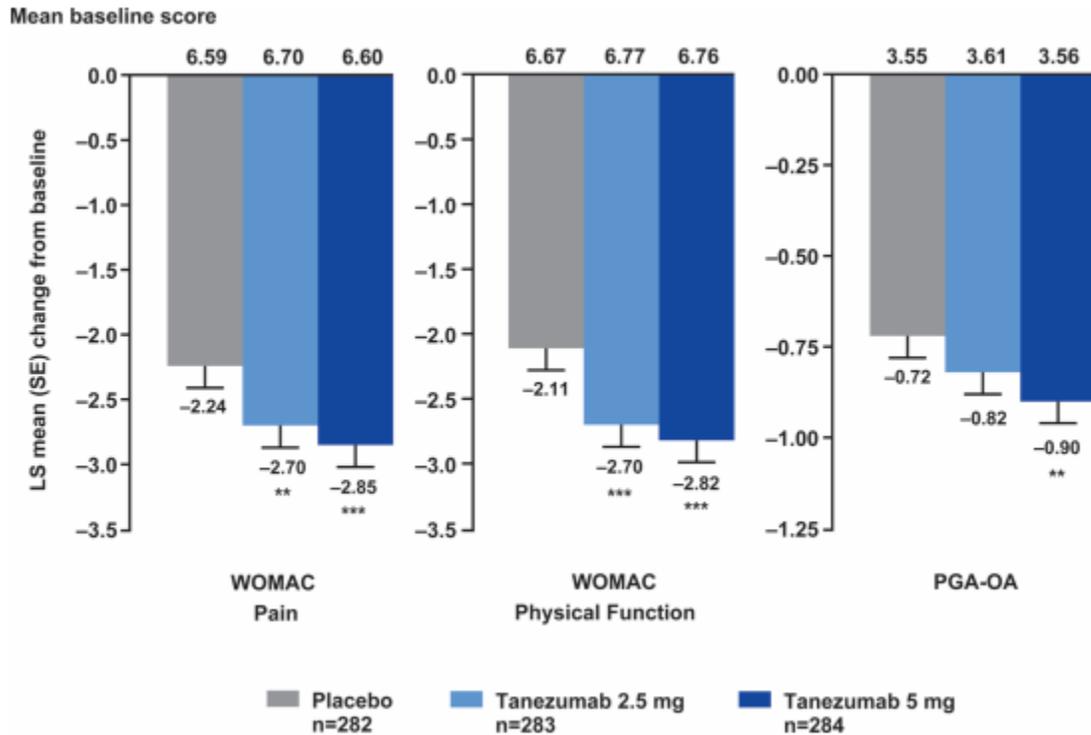
The following figure provides a summary of the study design (excerpted from Berenbaum et al, *Ann Rheum Dis*, 2020):



Key efficacy and safety data

Mean baseline WOMAC Pain subscale scores were 6.6, 6.7, and 6.6 for the placebo, tanezumab 2.5-mg, and tanezumab 5-mg groups, respectively. Mean baseline WOMAC Physical Function subscale scores were 6.7, 6.8, and 6.8 for the placebo, tanezumab-2.5 mg, and tanezumab 5-mg groups, respectively.

As shown in the following figure excerpted from Berenbaum et al, *Ann Rheum Dis*, 2020, compared with the placebo group, statistically significant improvements on all three co-primary efficacy endpoints were seen in the tanezumab 5-mg group. However, the tanezumab 2.5-mg group subjects did not do statistically significantly better than placebo subjects for all three co-primary efficacy endpoints. Specifically, there was not a statistically significant improvement for the PGA-OA endpoint.



p≤0.01; *p≤0.001 vs placebo

Therefore, from the predefined gatekeeping strategy, because the PGA-OA endpoint was not met for the tanezumab 2.5-mg group, further hypothesis testing of the key secondary endpoints for both tanezumab treatment groups could not be performed.

Without adjustment for multiple comparisons, the proportion of subjects with a 50% or greater reduction from baseline in WOMAC Pain subscale scores at week 24 was 45.4% and 47.9% in the tanezumab 2.5-mg and tanezumab 5-mg groups, respectively, compared with 33.8% in the control group, differences that were nominally statistically significant (nominal p≤0.01 for the tanezumab 2.5-mg group and nominal p≤0.001 for the tanezumab 5-mg group versus placebo).

Public Citizen's comments

Regarding the efficacy data for this trial, we would like to highlight the following points:

- (1) For the tanezumab 2.5-mg group, the trial failed to show statistically significant improvement compared with the placebo group on all three prespecified co-primary efficacy endpoints and thus failed to demonstrate that this dose is efficacious compared with placebo according to the prespecified statistical plan.***
- (2) For the tanezumab 5-mg group, as with first trial, the point estimates for the differences of least squares mean versus placebo for the three co-primary efficacy outcomes were small: only -62 on the 0-to-10 scale for the WOMAC Pain subscale score, -0.71 on the 0-to-10 scale for Physical Function subscale score, and -0.19 on the 1-to-5 scale for the PGA-OA score.***

Such differences indicate that tanezumab at the 5-mg dose provided little clinically meaningful benefit compared with placebo.

- (3) Once again, if the subjects in the placebo group had received a daily regimen of oral NSAIDs (for the vast majority who were not intolerant to and did not have a contraindication to NSAIDs) or even daily acetaminophen, including on the days when the primary efficacy endpoint assessments were made, the differences on these primary efficacy outcome measures between the tanezumab 5-mg group and the control group undoubtedly would have been even smaller.***
- (4) In the real-world setting, most patients with moderate-to-severe OA who have inadequate relief from currently available oral analgesics, like those enrolled in this trial, likely would be treated with one or more of the currently available FDA-approved oral analgesics or other standard non-pharmacologic interventions that were not provided to the placebo-group subjects during the treatment phase of this trial. Therefore, any assessment of the overall safety and effectiveness of tanezumab must be based on clinical trials of tanezumab that include an active-comparator group.***

By the end of the safety follow-up period, RPOA was observed in 1.4% (4/283) and 2.8% (8/284) of subjects in the tanezumab 2.5-mg and tanezumab 5-mg groups, respectively, and none in the placebo group. Total joint replacements were similarly distributed across all three groups (6.7% to 7.8%).

Public Citizen's comments

Regarding the joint safety data for this trial, we would like to highlight the following points:

- (1) Given that moderate-to-severe OA is a chronic condition for which tanezumab would be used for much longer durations, the cumulative incidence of such serious adverse joint events in the real-world setting would clearly be far greater than that seen during this trial.***
- (2) Again, despite the robust risk-mitigation strategies that were employed in this trial and intended to minimize the risk of adverse joint events, a significant number of serious joint adverse events still occurred. In a real-world setting, where there would not be the same rigorous screening and monitoring of patients that occurs for subjects enrolled in a clinical trial and where the drug is likely to be prescribed for off-label uses, the incidence of such serious adverse joint events almost certainly would be significantly higher.***

3. Long Term Safety and Efficacy Study of Tanezumab in Subjects With Osteoarthritis of the Hip or Knee (study ID# A4091058; ClinicalTrials.gov identifier NCT02528188; Hochberg, et al, *Arthritis Rheumatol*, 2021)^{22,23}

Design overview

The third pivotal phase 3 clinical trial, study A4091058, was a randomized, double-blind, double-dummy, active-controlled, multicenter trial conducted from July 2015 to February 2019 in the U.S., Europe, Latin America, and Asia-Pacific region. The subject population for this trial was very similar to those enrolled in studies A4091056 and A4091057. Subjects were aged 18 years and older and diagnosed as having hip or knee OA according to American College of Rheumatology criteria with radiographic confirmation at screening (Kellgren-Lawrence grade ≥ 2). Additional key inclusion criteria included the following:

- Received a stable dose of an oral NSAID for 30 or more days before screening with a documented history of (1) inadequate pain relief with acetaminophen and (2) inadequate pain relief with, contraindication to, or intolerance of opioid analgesics or tramadol (or unwillingness to take opioid analgesics);
- An index joint WOMAC Pain subscale score of 5 or greater at baseline while receiving stable doses of oral NSAIDs for two or more weeks prior to randomization;
- A baseline WOMAC Physical Function subscale score of 5 or greater; and
- A baseline PGA-OA rating of fair, poor, or very poor.

²² ClinicalTrials.gov. Long term safety and efficacy study of tanezumab in subjects with osteoarthritis of the hip or knee. <https://clinicaltrials.gov/ct2/show/NCT02528188>. Accessed March 8, 2021.

²³ Hochberg MC, Carrino JA, Schnitzer TJ, et al. Long-term safety and efficacy of subcutaneous tanezumab versus nonsteroidal antiinflammatory drugs for hip or knee osteoarthritis: A randomized trial. *Arthritis Rheumatol*. 2021 Feb 3. doi: 10.1002/art.41674. Online ahead of print.

Patients with radiographic evidence of prespecified joint safety concerns (i.e., destructive arthropathy characteristic of RPOA, atrophic OA, subchondral insufficiency fracture, primary osteonecrosis, or pathologic fracture) in any in any hip, knee, or shoulder joint were excluded.

After receiving stable open-label oral NSAIDs (naproxen, 500 mg twice daily; celecoxib 100 mg twice daily; or diclofenac extended release, 75 mg twice daily) for at least the last two weeks of the screening period, subjects were randomly assigned to receive one of the following interventions:

- Tanezumab 2.5 mg subcutaneously administered at baseline and every eight weeks through week 48 (seven doses total) (n = 1,002);
- Tanezumab 5 mg subcutaneously administered at baseline and every eight weeks through week 48 (seven doses total) (n = 998); or
- Oral NSAID twice daily (one of aforementioned three regimens) for 56 weeks (n = 996);

Subjects in the tanezumab groups also received oral placebo matching NSAID tablets twice daily, and subjects in the NSAID control group also received subcutaneous placebo injections matching tanezumab at baseline and every eight weeks through week 48.

Public Citizen's comments

Regarding the design of this trial, we would like to highlight the following points:

- (1) The inclusion of the active-comparator NSAID control group in this trial provided a much more appropriate control group for assessing the safety and efficacy of tanezumab for relief of signs and symptoms of moderate-to-severe OA in adult patients for whom use of other analgesics is ineffective or not appropriate.***
- (2) The longer duration of exposure to the tanezumab and the much greater subject enrollment in this trial relative to the two placebo-controlled trials allowed for a much more robust assessment of the safety and efficacy of this drug.***

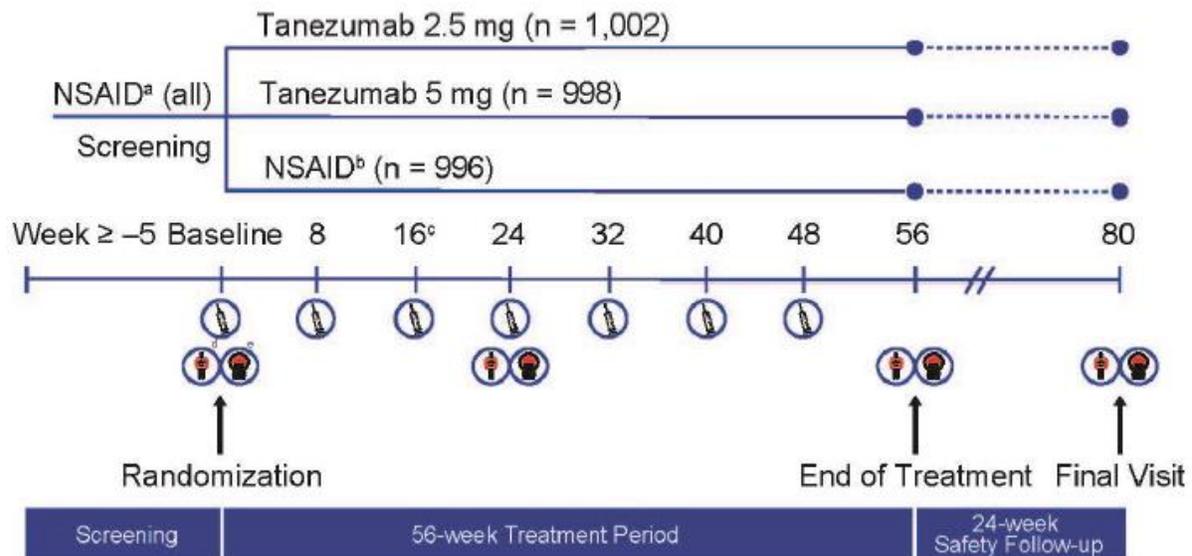
Rescue therapy with acetaminophen was allowed in subjects with inadequate pain relief up to 3,000 mg/d up to week 16 and as needed thereafter to week 64, but not within 24 hours of a study visit for efficacy assessments. Use of non-assigned NSAIDs was prohibited through week 64, but analgesics were permitted occasionally for self-limiting conditions unrelated to OA, but not within 48 hours or five half-lives (whichever was greater) of study visits for efficacy assessments.

Radiographs of bilateral hips, knees, and shoulders were obtained during the screening period and at weeks 24, 56, and 80 to monitor occurrence of joint safety events and were evaluated by trained central readers. Magnetic resonance imaging (MRI) of each hip and knee was performed at screening in all patients; follow-up MRIs of each hip and knee were obtained at weeks 24, 56,

and 80 in patients with Kellgren-Lawrence grade ≥ 3 in any hip/knee and at the discretion of the investigators or central readers throughout the study.

The primary composite joint safety endpoint over the 80-week trial period (56-week treatment period plus 24-week follow-up period) comprised adjudicated RPOA type 1 or 2, primary osteonecrosis, subchondral insufficiency fracture, or pathologic fracture. The three co-primary efficacy endpoints were change from baseline to week 16 in WOMAC Pain subscale scores, WOMAC Physical Function subscale scores, and PGA-OA scores. Under the prespecified statistical plan, between-group differences for all three co-primary efficacy endpoints had to be significant for the co-primary endpoint to be significant. A key secondary efficacy endpoint was the WOMAC Pain responder rate of 50% or greater at week 16.

The following figure provides a summary of the study design (excerpted from Hochberg, et al, *Arthritis Rheumatol*, 2021):



 SC study drug

 X-ray  MRI

Key efficacy and safety data

The mean (standard deviation) baseline WOMAC Pain subscale scores were 7.0 (1.1) for all three trial groups. Mean baseline WOMAC Physical Function subscale scores were 7.1 (1.1) for both tanezumab groups and 7.0 (1.1) for the NSAID group.

Public Citizen's comment

Importantly, given these baseline WOMAC Pain subscale and WOMAC Physical Function subscale scores on oral NSAID treatment, most of the subjects in this trial reasonably could be characterized as having had inadequate pain relief with NSAIDs at the time of randomization.

The excerpted data from Table 4 of Hochberg, et al, *Arthritis Rheumatol*, 2021, below shows results for the three co-primary efficacy endpoints. The tanezumab 5-mg group did not do statistically significantly better than the NSAID group for all three co-primary efficacy endpoints. Specifically, there was not a statistically significant improvement from baseline for the PGA-OA endpoint. For the tanezumab 5-mg group, there were statistically significantly greater improvements from baseline (least squares mean difference [95% CI]) in WOMAC Pain subscale score (−0.26 [−0.46, −0.05]; $P = 0.015$) and WOMAC Physical Function score (−0.31 [−0.52, −0.11]; $P = 0.003$) compared with the NSAID group. For the tanezumab 2.5-mg group, there were no statistically significant improvements from baseline for any of the three co-primary efficacy endpoints compared with the NSAID group.

Table 4. Change from baseline to week 16 in WOMAC Pain subscale, WOMAC Physical Function subscale, and patient's global assessment of osteoarthritis (co-primary efficacy endpoints)

Efficacy endpoint	Tanezumab 2.5 mg (n = 1,002)	Tanezumab 5 mg (n = 998)	NSAID (n = 996)
WOMAC Pain^a			
Mean (range) baseline score	7.01 (3.6–10.0)	7.02 (1.6–10.0)	6.96 (2.6–10.0)
Least squares mean (95% CI) change from baseline	−3.22 (−3.43, −3.01)	−3.33 (−3.54, −3.12)	−3.07 (−3.29, −2.86)
Difference of least squares means (95% CI) vs. NSAID	−0.15 (−0.36, 0.06)	−0.26 (−0.46, −0.05)	–
<i>P</i> value	NS	0.015	–
WOMAC Physical Function^b			
Mean (range) baseline score	7.09 (1.5–10.0)	7.08 (1.1–10.0)	6.99 (2.4–10.0)
Least squares mean (95% CI) change from baseline	−3.27 (−3.48, −3.05)	−3.39 (−3.60, −3.17)	−3.08 (−3.29, −2.86)
Difference of least squares means (95% CI) vs. NSAID	−0.19 (−0.40, 0.02)	−0.31 (−0.52, −0.11)	–
<i>P</i> value	NS	0.003	–
Patient's global assessment of OA^c			
Mean (range) baseline score	3.49 (1–5)	3.46 (2–5)	3.44 (1–5)
Least squares mean (95% CI) change from baseline	−0.96 (−1.03, −0.88)	−0.97 (−1.05, −0.90)	−0.94 (−1.01, −0.86)
Difference of least squares means (95% CI) vs. NSAID	−0.02 (−0.09, 0.06)	−0.04 (−0.11, 0.04)	–
<i>P</i> value	NS	NS	–

In addition, the proportions of patients who achieved $\geq 50\%$ reduction from baseline in the WOMAC Pain subscale score at week 16 were 54.9%, 56.5%, and 51.5% in the tanezumab 2.5-mg, tanezumab 5-mg, and NSAID groups, respectively. After 56 weeks, corresponding WOMAC Pain 50% response rates were 44.3%, 41.5%, and 43.5%.

Public Citizen's comments

Regarding the efficacy data for this trial, we would like to highlight the following points:

These efficacy data demonstrate that in comparison to oral NSAIDs, tanezumab at a dosage of 2.5 and 5 mg every eight weeks failed to meet the prespecified efficacy outcomes or provide any clinically meaningful benefit for the relief of signs and symptoms of moderate-to-severe OA of the knee or hip in adult patients for whom use of other analgesics is ineffective or not appropriate. The data on the proportions of patients who achieved $\geq 50\%$ reduction from baseline in the WOMAC Pain subscale score at week 16 and at week 56 are particularly telling.

The excerpted data from Table 3 of Hochberg, et al, *Arthritis Rheumatol*, 2021, below shows that the rates of occurrence of the primary composite joint safety endpoint, RPOA, and the need for total joint replacement were statistically significantly higher in the tanezumab 2.5-mg and tanezumab 5-mg groups than in the NSAID groups. Strikingly, the observation time-adjusted rates of the primary composite joint safety endpoint in the tanezumab 2.5-mg group (38 per 1,000 patient-years) and tanezumab 5-mg group (72 events per 1,000 patient-years) were approximately *2.5 times higher* and *nearly five times higher*, respectively, than the rate in the NSAID group (15 events per 1,000 patient-years) ($P = 0.001$, tanezumab 2.5-mg group versus NSAID group; $P < 0.001$, tanezumab 5-mg group versus NSAID group).

Likewise, the observation time-adjusted rates of total joint replacement in the tanezumab 2.5-mg group (52 per 1,000 patient-years) and tanezumab 5-mg group (80 events per 1,000 patient-years) were approximately *two times higher* and *three times higher*, respectively, than the rate in the NSAID group (26 events per 1,000 patient-years) ($P = 0.003$, tanezumab 2.5-mg group versus NSAID group; $P < 0.001$, tanezumab 5-mg group versus NSAID group).

Table 3. Summary of adjudicated joint safety events and total joint replacements over 80 weeks of observation

Joint safety outcome	Tanezumab 2.5 mg (n = 1,002)	Tanezumab 5 mg (n = 998)	NSAID (n = 996)
Adjudicated for joint safety ^a , No. (%)	116 (11.6)	171 (17.1)	49 (4.9)
Adjudicated as normal progression of OA, No. (%)	66 (6.6)	79 (7.9)	27 (2.7)
Primary composite joint safety endpoint, No. (%) [95% CI]	39 (3.9) [2.8, 5.3]	71 (7.1) [5.6, 8.9]	15 (1.5) [0.8, 2.5]
Observation time, pt-y	1,017	993	1,011
Observation time-adjusted rate/1000 pt-y [95% CI]	38.3 [28.0, 52.5]	71.5 [56.7, 90.2]	14.8 [8.9, 24.6]
Rate difference vs. NSAID [95% CI]	23.5 [9.3, 37.7]	56.7 [38.4, 74.9]	–
<i>P</i> value	0.001	<0.001	–
RPOA1 and RPOA2 combined, No. (%) [95% CI]	32 (3.2) [2.2, 4.5]	63 (6.3) [4.9, 8.0]	12 (1.2) [0.6, 2.1]
Observation time, pt-y	1,018	995	1,012
Observation time-adjusted rate/1,000 pt-y [95% CI]	31.4 [22.2, 44.4]	63.3 [49.5, 81.1]	11.9 [6.7, 20.9]
Rate difference vs. NSAID [95% CI]	19.6 [6.8, 32.4]	51.5 [34.5, 68.5]	–
<i>P</i> value	0.003	<0.001	–
RPOA1 ^b , No. (%) [95% CI]	29 (2.9) [1.9, 4.1]	49 (4.9) [3.7, 6.4]	11 (1.1) [0.6, 2.0]
Observation time, pt-y	1,020	998	1,012
Observation time-adjusted rate/1,000 pt-y [95% CI]	28.4 [19.8, 40.9]	49.1 [37.1, 65.0]	10.9 [6.0, 19.6]
Rate difference vs. NSAID [95% CI]	17.6 [5.4, 29.8]	38.2 [23.1, 53.4]	–
<i>P</i> value	0.005	<0.001	–
RPOA2 ^c , No. (%) [95% CI]	3 (0.3) [0.1, 0.9]	14 (1.4) [0.8, 2.3]	1 (0.1) [0, 0.6]
Observation time, pt-y	1,027	1,010	1,016
Observation time-adjusted rate/1,000 pt-y [95% CI]	2.9 [0.9, 9.1]	13.9 [8.2, 23.4]	1.0 [0.1, 7.0]
Rate difference vs. NSAID [95% CI]	1.9 [–1.9, 5.8]	12.9 [5.4, 20.4]	–
<i>P</i> value	0.32	<0.001	–
Total joint replacement, No. (%) [95% CI]	53 (5.3) [4.0, 6.9]	80 (8.0) [6.4, 9.9]	26 (2.6) [1.7, 3.8]
Observation time, pt-y	1,022	1,004	1,013
Observation time-adjusted rate/1,000 pt-y [95% CI]	51.8 [39.6, 67.9]	79.7 [64.0, 99.2]	25.7 [17.5, 37.7]
Rate difference vs. NSAID [95% CI]	26.2 [9.1, 43.3]	54.0 [33.9, 74.0]	–
<i>P</i> value	0.003	<0.001	–

Public Citizen's comments***Regarding the safety data for this trial, we would like to highlight the following points:***

- (1) This long-term safety and efficacy phase 3 trial clearly demonstrated that tanezumab causes a dramatic, statistically significant, and clinically important increase in the rate of serious adverse joint events in a dose- and duration-dependent manner.***
- (2) The occurrence of these adverse events caused by tanezumab is not rare.***
- (3) Once again, for a third time, despite the robust risk-mitigation strategies that were employed in this trial, a significant number of serious joint adverse events still occurred. In a real-world setting, where there would not be the same rigorous screening and monitoring of patients that occurs for subjects enrolled in a clinical trial and where the drug is likely to be prescribed for off-label uses, the incidence of such serious adverse joint events almost certainly would be significantly higher.***

C. Conclusions

In closing, Public Citizen urges the AAC and DSaRMAC to recommend that the FDA not approve the BLA for tanezumab because the totality of the evidence from the three published pivotal phase 3 randomized clinical trials described above demonstrates that the drug fails to provide clinically meaningful benefit but does dramatically increase the rates of RPOA and other types of serious joint damage and of total joint replacements in a dose- and duration-dependent manner. As a result, the serious risks of the drug far outweigh its benefits.

Put more bluntly, a drug that accelerates the joint destruction of the underlying OA disease that it is intended to treat but lacks any evidence of clinically meaningful benefit in comparison to use of a placebo or oral NSAIDs obviously should never be approved by the FDA. It is baffling why the FDA felt it needed to bring the BLA for this drug before your committees.

Thank you for the opportunity to comment on this important public health issue.



Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group