OPEN

Relative Efficacy and Safety of Tanezumab for Osteoarthritis

A Systematic Review and Meta-analysis of Randomized-Controlled Trials

Bocheng Zhang, PhD,*† Xiaoyuan Tian, PhD,*† Zhenan Qu, MD,‡ Jiaming Liu, MD, † and Liang Yang, PhD*

Objectives: The aim of this meta-analysis was to evaluate the efficacy and safety of tanezumab for the treatment of patients with knee or hip osteoarthritis (OA).

Methods: PubMed, Embase, Cochrane Central Register of Controlled Trials, and Web of Science were searched from inception to July 2020. Randomized-controlled trials comparing tanezumab with placebo or nonsteroidal anti-inflammatory drugs in patients with OA. Two investigators identified studies and independently extracted data, and conventional meta-analyses were conducted with Review Manager 5.3. The outcomes were pain relief, functional improvement, and risk of adverse events (AEs).

Results: A total of 8 articles, comprising 9 randomized-controlled trials, were included. Overall, tanezumab was superior to placebo for relieving pain and improving function, as well as in the patient's global assessment. Tanezumab also had significant advantages over nonsteroidal anti-inflammatory drugs for relieving pain and improving function, as well as in the patient's global assessment. Significantly more patients discontinued treatment because of AEs after treatment with tanezumab. However, the differences in serious AEs and total joint replacement were not significant. Moreover, tanezumab-treated patients experienced significantly more rapid progression of osteoarthritis.

Discussion: Tanezumab can alleviate pain and improve function for patients with OA of the hip or knee. Although tanezumab does not

Received for publication March 22, 2021; revised August 21, 2021; accepted September 3, 2021.

From the *Second Affiliated Hospital; †Graduate School, Dalian Medical University; and ‡Affiliated Zhongshan Hospital, Dalian University, Dalian, Liaoning, China. B.Z., X.T., and Z.Q. contributed equally to this study.

- B.Z. and X.T.: carried out the literature search and statistical analysis; collected, analyzed, and interpreted the data; wrote the manuscript. Z.Q.: resolved differences and performed statistical analysis. J.L.: wrote and critically revised the manuscript. L.Y.: led the design and contributed to language correction.

The authors declare no conflict of interest.

- Reprints: Liang Yang, PhD, Second Affiliated Hospital, Dalian Medical University, Dalian, Liaoning 116000, China (e-mail: yangliangyang@ 126.com).
- Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www. clinicalpain.com.
- Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI: 10.1097/AJP.0000000000000986

cause serious AEs, rapid progression of OA occurred in a small number of participants, so more clinical trials are needed to explore its safety.

Key Words: osteoarthritis, tanezumab, meta-analysis, randomizedcontrolled trials

(Clin J Pain 2021;37:914-924)

steoarthritis (OA) is the most common form of arthritis, affecting ~302 million people worldwide, and is a cause of disability in the elderly.¹ OA is characterized by pathology involving the whole joint, including cartilage degradation, bone remodeling, osteophyte formation, and synovial inflammation, leading to pain, stiffness, swelling, and loss of normal joint function.² Pain is the main symptom of OA, which seriously affects the patient's quality of life. Pain accounts for large societal costs and morbidity across all societies and is clearly inadequately controlled with current biomedical and psychosocial strategies. At present, nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line drugs to treat OA. However, these drugs can cause serious adverse events (SAEs), such as gastrointestinal bleeding, peptic ulcers, and cardiovascular effects, and the pain relief effect of NSAIDs is not obvious in the treatment of severe pain.³

In recent years, neurotrophic factors, which are secreted proteins that promote the growth and survival of neurons, have received increasing attention as novel targets for the treatment of chronic pain; examples of neurotrophic factors include nerve growth factor (NGF), brain-derived neurotrophic factor, neurotrophin-3, and neurotrophin-4.4 By far, the most advanced strategy to target neurotrophic factors for OA pain is the approach that uses neutralizing antibodies against NGF. NGF has become an important target for developing analgesics because of the well-documented role of NGF in pain, as it has been found to be highly overexpressed in human pain states, including OA.5 Tanezumab, a humanized monoclonal antibody, specifically targets and inhibits NGF from binding with its receptors, neurotrophic tyrosine kinase receptor type 1 and p57. At present, there are some clinical trials using tanezumab to treat OA, and they have achieved good results in analgesia and functional improvement, but rapidly progressive osteoarthritis (RPOA) occurred in a small number of participants.6

Previously, there have been 3 meta-analyses on the treatment of OA with tanezumab.^{7–9} Their results suggested



FIGURE 1. Preferred reporting items for systematic reviews and meta-analysis flowchart for the searching for and identifying included studies.

that tanezumab had obvious advantages over placebo or NSAIDs in analgesia and functional improvement, but the relationship between tanezumab and RPOA has not been analyzed. Therefore, the goal of our meta-analysis was to combine the results of previous clinical trials to analyze the effectiveness and safety of tanezumab in the treatment of OA and to further analyze the correlation between tanezumab and RPOA events.

METHODS

Protocol and Registration

This systematic review and meta-analysis study was implemented following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,¹⁰ and the protocol was registered with Prospero, an international prospective register of systematic reviews (CRD42020200793).

Search Strategy

We systematically searched the Cochrane Central Register of Controlled Trials, PubMed, Embase and Web of Science (from inception to July 15, 2020) using a combination of relevant terms, including tanezumab, osteoarthrosis, placebo, and randomized-controlled trial (RCT), without restrictions on the language (Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/CJP/A826). Ongoing and unpublished studies were searched in the clinical trial registry (ClinicalTrials.gov). In addition, references of the retrieved papers and reviews were manually reviewed.

Inclusion/Exclusion Criteria

The inclusion criteria were as follows: (1) RCTs with an average of at least 100 participants per arm¹¹; (2) studies on only participants with OA of the hip or knee according to the American College of Rheumatology criteria and grade 2 or higher based on the Kellgren-Lawrence grading system^{12,13}; (3) studies comparing tanezumab at any dose and any route with placebo or NSAIDs; (4) studies reporting pain (Western Ontario and McMaster Universities (WOMAC) pain, function (WOMAC physical functional), patient's global assessment (PGA) or AEs (RPOA events, total joint replacement [TJR]) events, patients who discontinued treatment because of adverse events (AE) and SAE outcomes; and (5) studies published in any language.

The following studies were excluded: (1) secondary analyses, including pooled analyses; (2) studies where the follow-up time was <1 week; (3) studies using tanezumab combined with other drugs; (4) studies for pain in the joints caused by other conditions such as rheumatoid arthritis or other autoimmune disorders and postoperative pain; and (5) abstracts only (insufficient data).

Study Selection and Data Extraction

The selection of literature and decisions about including studies were carried out independently by 2 review

| References | Funding Source | Design | Study Duration (wk) | No. Randomized and Treated (N on Tanezumab) | Joint Affected | Primary Outcome Extracted | NCT Number |
|----------------------------------|-------------------|--------------------------|---------------------------|---|-------------------|--|---------------|
| Berenbaum et al ³³ | Commercial | Multicentre, Parallel | 48 | 849 (567) | Hip or knee | WOMAC pain, WOMAC physical function, PGA | NCT02709486 |
| Brown et al ³⁴ | Commercial | Parallel | 32 | 690 (518) | Knee | WOMAC pain, WOMAC physical function, PGA | NCT00733902 |
| Brown et al ³⁵ | Commercial | Parallel | 32 | 621 (466) | Hip | WOMAC pain, WOMAC physical function, PGA | NCT00744471 |
| Ekman et al ³⁶ | Commercial | Parallel | 24 | 828 (414) | Knee | WOMAC pain, WOMAC physical function, PGA | NCT00830063 |
| Ekman et al ³⁶ | Commercial | Parallel | 24 | 840 (420) | Hip or knee | WOMAC pain, WOMAC physical function, PGA | NCT00863304 |
| Schnitzer et al ³⁸ | Commercial | Multicentre, Parallel | 16 | 2700 (1083) | Hip or knee | WOMAC pain, WOMAC physical function, PGA | NCT00809354 |
| Schnitzer et al ³⁹ | Commercial | Multicentre, Parallel | 16 | 696 (464) | Hip or knee | WOMAC pain, WOMAC physical function, PGA | NCT02697773 |
| Spierings et al ⁴⁰ | Commercial | Multicentre, Parallel | 18 | 610 (311) | Hip or knee | WOMAC pain | NCT00985621 |
| NCT02528188 | Commercial | Multicentre, Parallel | 80 | 2996 (2000) | Hip or knee | WOMAC pain, WOMAC physical function, PGA | NCT02528188 |

NCT indicates national clinical trial; PGA, patient's global assessment; RCT, randomized-controlled trial; WOMAC, The Western Ontario and McMaster Universities

authors (B.Z. and X.T.). We obtained the full text for the studies to determine inclusion in our review. If there were multiple reports that described the same trial, only the most recent or complete study was included.

Relevant data from selected studies were independently extracted according to inclusion criteria by 2 review authors (B.Z. and X.T.). The following data were extracted: author, published year, type of funding support, duration of study, study design, sample size, types of joints affected, and types of measures used for the outcomes. We also extracted data from participants at baseline, including sex, mean age, dose of tanezumab, route of administration, and type of control used. A third review author (Z.Q.) resolved any disagreements about study selection and data extraction.

The primary outcome measures of interest were mean change in the WOMAC pain, the WOMAC physical function, and the PGA at the baseline and endpoint. The secondary outcome measures comprised patients who discontinued treatment because of AEs, number of SAEs, RPOA events, and TJR events. If the mean, SD or standard error of the mean were not attainable in the text of the articles, we extracted values from the diagrams and tables as needed.¹⁴

Quality Assessment

Two review authors (B.Z. and X.T.) independently assessed the risk of bias for each study using the Cochrane risk of the bias assessment tool.¹⁴ The tool includes seven specific domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and "other sources of bias." Each domain was

assigned a score of low risk of bias, high risk of bias or unclear risk of bias. We resolved disagreements by consensus.

Statistical Analysis

A conventional meta-analysis was conducted to compare tanezumab with placebo or NSAIDs using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK). We used risk ratios (RRs) and 95% confidence intervals (CIs) for dichotomous data based on the number of events in the control and intervention groups of each study. For continuous data, we calculated the mean differences (MDs) and 95% CIs between the tanezumab and control groups. WOMAC pain and WOMAC physical function scores were converted to a common scale from 0 (no pain or disability) to 10 (worst possible pain or disability) before meta-analysis. The heterogeneity of the effect size across the studies was tested using the χ^2 test (P < 0.1 was considered heterogeneous) and I^2 statistic ($I^2 > 50\%$ was considered heterogeneous). If there was significant heterogeneity between studies, a random-effects model was used; otherwise, a fixedeffects model was used. Subgroup analysis was based on the dose of tanezumab and the type of control group. The overall effect was tested using a Z score with the significance set at P < 0.05. We used funnel plots to assess publication bias if more than 10 trials were included in any particular pooled analysis.

RESULTS

Study Selection

The PRISMA flowchart of study selection is shown in Figure 1. We identified 227 studies from database searches and 22 additional records from other sources. After

TABLE 2. Baseline Patient Characteristics

| | | | | | | Kellgrer | I-Lawrence G | rade (%) |
|-------------------------------|----------------------------|------|---------|---------------|------------------------------------|------------|--------------|------------|
| References | Intervention | N | Age (v) | Female (%) | Duration Since Diagnosis (v) | 2 | 3 | 4 |
| Paranhaum | Top (2.5 mg SC) | 282 | 65.2 | 108 (70.0) | <u> </u> | 40 (17.3) | 121 (46.2) | 101 (25 7) |
| et al ³³ | 1 all (2.5 llig, 5C) | 283 | 05.2 | 198 (70.0) | 0.0 | 49 (17.3) | 131 (40.3) | 101 (33.7) |
| | Tan (5 mg, SC) | 284 | 65.2 | 193 (68.0) | 6.7 | 58 (20.4) | 121 (42.6) | 105 (37.0) |
| | Placebo | 282 | 64.2 | 196 (69.5) | 7.4 | 59 (20.9) | 123 (43.6) | 100 (35.5) |
| Brown et al ³⁴ | Tan (2.5 mg, IV) | 172 | 60.8 | 94 (54.7) | 7.3 | 64 (37.2) | 74 (43.0) | 31 (18.0) |
| | Tan (5 mg, IV) | 172 | 62.1 | 101 (58.7) | 7.5 | 64 (37.2) | 89 (51.7) | 18 (10.5) |
| | Tan (10 mg, IV) | 174 | 61.4 | 106 (60.9) | 9.5 | 71 (40.8) | 77 (44.3) | 26 (14.9) |
| | Placebo | 172 | 62.2 | 119 (69.2) | 8.2 | 68 (39.5) | 82 (47.7) | 22 (12.8) |
| Brown et al ³⁵ | Tan (2.5 mg, IV) | 155 | 62.4 | 101 (65.2) | 6.0 | 71 (45.8) | 53 (34.2) | 31 (20.0) |
| | Tan (5 mg, IV) | 154 | 61.8 | 92 (59.7) | 6.3 | 72 (46.8) | 54 (35.1) | 27 (17.5) |
| | Tan (10 mg, IV) | 157 | 63.3 | 88 (56.1) | 5.6 | 67 (42.7) | 58 (36.9) | 32 (20.4) |
| | Placebo | 155 | 61.9 | 103 (66.5) | 5.6 | 73 (47.1) | 56 (36.1) | 26 (16.8) |
| Ekman et al ³⁶ | Tan (5 mg, IV) | 206 | 61.1 | 122 (59.2) | 7.9 | 76 (36.9) | 108 (52.4) | 22 (10.7) |
| | Tan (10 mg, IV) | 208 | 61.1 | 128 (61.5) | 8.5 | 98 (47.1) | 90 (43.3) | 20 (9.6) |
| | Naproxen | 206 | 61.4 | 129 (62.6) | 7.2 | 99 (48.1) | 89 (43.2) | 18 (8.7) |
| | Placebo | 208 | 60.9 | 120 (57.7) | 9.0 | 89 (42.8) | 91 (43.8) | 28 (13.5) |
| Ekman B et al ³⁶ | Tan (5 mg, IV) | 211 | 59.8 | 134 (63.5) | 6.4 | 104 (49.3) | 77 (36.5) | 30 (14.2) |
| | Tan (10 mg, IV) | 209 | 59.2 | 128 (61.2) | 6.8 | 101 (48.3) | 72 (34.4) | 36 (17.2) |
| | Naproxen | 211 | 60.3 | 136 (64.5) | 7.7 | 110 (52.1) | 84 (39.8) | 17 (8.1) |
| | Placebo | 209 | 60.1 | 136 (65.1) | 6.3 | 107 (51.2) | 79 (37.8) | 22 (10.5) |
| Schnitzer et al ³⁸ | Tan (5 mg, IV) | 541 | 61.9 | 392 (72.5) | 7.3 | 181 (33.5) | 191 (35.3) | 169 (31.2) |
| | Tan (10 mg, IV) | 542 | 62.0 | 392 (72.3) | 7.1 | 187 (34.5) | 203 (37.5) | 152 (28.0) |
| | Tan+NSAID* | 536 | 61.7 | 363 (67.7) | 7.0 | 183 (34.2) | 212 (39.6) | 139 (26.0) |
| | Tan+NSAID* | 542 | 61.3 | 369 (68.1) | 7.4 | 161 (29.7) | 218 (40.2) | 163 (30.1) |
| | Placebo+NSAID* | 539 | 61.3 | 388 (72.0) | 7.5 | 197 (36.5) | 217 (40.3) | 125 (23.2) |
| Schnitzer et al ³⁹ | Tan (2.5 mg, SC) | 231 | 60.9 | 145 (62.8) | 6.4 | 60 (26.0) | 101 (43.7) | 69 (29.9) |
| | Tan (2.5/5 mg, SC) | 233 | 61.2 | 151 (64.8) | 7.2 | 59 (25.4) | 105 (45.3) | 68 (29.3) |
| | Placebo | 232 | 60.4 | 157 (67.7) | 6.9 | 65 (28.0) | 98 (42.2) | 69 (29.7) |
| Spierings et al ⁴⁰ | Tan (5 mg, IV) | 161 | 57.8 | 96 (59.6) | 7.6 | 78 (48.4) | 60 (37.3) | 23 (14.3) |
| 1 0 | Tan (10 mg, IV) | 150 | 57.0 | 94 (62.7) | 7.5 | 73 (48.7) | 55 (36.7) | 22 (14.7) |
| | Oxycodone | 158 | 57.6 | 99 (62.7) | 6.2 | 80 (50.6) | 55 (34.8) | 23 (14.6) |
| | Placebo | 141 | 57.2 | 92 (65.2) | 7.4 | 67 (47.5) | 56 (39.7) | 18 (12.8) |
| NCT02528188 | Tan | 1002 | 60.3 | 637 (63.6%) | None | None | None | None |
| (unpublished) | (2.5 mg, SC) | | | ` ' | | | | |
| / | Tan (5 mg, SC) | 998 | 61.2 | 654 (65.5) | None | None | None | None |
| | Placebo+NSAID [†] | 996 | 60.3 | 662 (66.5) | None | None | None | None |

*Naproxen or celecoxib. †Naproxen, celecoxib or diclofenac.

IV indicates intravenously; NCT, national clinical trial; NSAID, nonsteroidal anti-inflammatory drug; SC, subcutaneously; Tan, tanezumab.

removing duplicates, we assessed 129 studies and excluded 106 studies based on the titles and abstracts. We assessed the full text of 26 possibly eligible papers, and excluded studies included 12 conference abstracts, ^{15–26} 3 papers with an insufficient sample size, ^{27–29} 1 duplicate study, ³⁰ 1 not relevant study, ³¹ and 1 incomplete study. ³² Finally, we included 8 eligible papers (9 studies) in the quantitative analysis and meta-analysis. ^{33–40}

Study Characteristics

The characteristics of the included studies are shown in Table 1, and the details of the baseline patient characteristics are shown in Table 2. This review includes 8 papers reporting 9 RCTs and has a sample size of 10830 participants. A total of 6243 patients were included in the intervention group. One record reported on the results of 2 separate RCTs.³⁶ One record provided results posted online but not published in a peer-reviewed journal.³⁷ All studies were phase III clinical trials, and patients in the intervention

group received 2.5/5/10 mg tanezumab every 8 weeks, administered intravenously or subcutaneously. The control groups were placebo, NSAIDs (naproxen or celecoxib) and oxycodone, but oxycodone did not meet the inclusion criteria, so we excluded the oxycodone group in this review. The duration of the studies was 16 to 80 weeks. Only knee, hip or both knee and hip OA were evaluated in the included studies. In 2 studies, only the knee joint was evaluated.^{34,36} The hip joint was evaluated in 1 study.³⁶ The remaining studies included both the hip and knee joints simultaneously. All studies reported receiving funding from pharmaceutical companies that produced study drugs. All studies were registered on the ClinicalTrials.gov website.

Risk of Bias Among the Included Studies

The risk of bias assessment for all of the studies is shown in Figure 2. All studies had 2 or more domains that were judged as having an unclear risk of bias. Randomized sequence generation was implemented adequately in 3 studies,^{33,38,39}



FIGURE 2. Risk of bias in the selected studies.

although all of them reported being RCTs. Allocation concealment was implemented adequately in 2 studies.^{38,39} All included studies successfully reported blinding of participants, and personnel were at low risk of performance bias. Four studies reported blinding of outcome assessors at unclear risk of bias of detection bias.^{33–35,40} All studies were funded by companies that produced tanezumab and were at unclear risk of bias for the other sources of domain bias. Visual cues in funnel plots indicated that there was no conclusive evidence of publication bias (Supplementary Fig. 1, Supplemental Digital Content 2, http://links.lww.com/CJP/A827).

Effects on Joint Pain

All included studies evaluating analgesic efficacy utilized WOMAC pain reduction as the primary or secondary outcome. First, we compared the mean change between the tanezumab group and placebo group. Tanezumab was significantly superior to placebo (MD = -0.91, 95% CI = -1.10 to $-0.72, P < 0.00001; I^2 = 0\%$) (Fig. 3). In the subgroup analysis, the effect tended to rise with the increase in the dose of the drug (MDs of -0.66/-0.96/-1.05 at 2.5 mg/5 mg/10 mg, respectively). Similar results were obtained in the tanezumab group and NSAID group (MD = -0.49, 95% CI = -0.66 to $-0.31, P < 0.00001; I^2 = 0\%$) (Supplementary Fig. 2, Supplemental Digital Content 3, http://links.lww.com/CJP/A828). The above results showed that tanezumab had superior analgesic effects compared with placebo and NSAIDs.

Effects on Physical Function

All studies reported comprehensive WOMAC physical function outcome data. The WOMAC physical function

scores were significantly different between the tanezumab group and placebo group (MD = -0.93, 95% CI = -1.10 to -0.75, P < 0.00001; $I^2 = 0\%$) (Fig. 4). In the dose-response subgroup analysis, the 10 mg group had a superior physical function score (MDs of -0.76/-0.94/-1.02 at 2.5 mg/5 mg/ 10 mg, respectively). Compared with NSAIDs, tanezumab also showed good results in functional improvements (MD = -0.53, 95% CI = -0.71 to -0.35, P < 0.00001; $I^2 = 0\%$) (Supplementary Fig. 3, Supplemental Digital Content 4, http://links. lww.com/CJP/A829).

PGA

All studies report data on PGA. PGA of OA was assessed using a 5-point Likert scale (1 = very good and 5 = very poor). The reduction in PGA scores was significantly larger between the tanezumab group and placebo group (MD = -0.31, 95% CI = -0.37 to -0.25, P < 0.00001; $I^2 = 0\%$ (Fig. 5). In the dose-response subgroup analysis, as the dose increased, the improvement effect over placebo was more obvious (MDs of -0.21/-0.31/-0.38 at 2.5 mg/5 mg/ 10 mg, respectively). PGA also showed some improvement in the overall comparison between the tanezumab and NSAID groups (MD = -0.08, 95% CI = -0.14 to -0.02, P = 0.008; $I^2 = 0\%$) (Supplementary Fig. 4, Supplemental Digital Content 5, http://links.lww.com/CJP/A830). However, in the subgroup analysis, the PGA improvement was not statistically significant when comparing the 10 mg tanezumab versus NSAIDs (MD = -0.08, 95% CI = -0.18to -0.01, P = 0.09; $I^2 = 0\%$) (Supplementary Fig. 4, Supplemental Digital Content 5, http://links.lww.com/CJP/A830).

| | tan | ezuma | ab | pl | acebo |) | | Mean Difference | Mean Difference |
|-----------------------------------|----------|--------------------|-----------|------------------------------------|---------|----------------------|--------|--|--|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | IV. Fixed, 95% CI |
| 1.1.1 2.5 mg | | | | | | | | | |
| Berenbaum 2020 | -2.7 | 2.86 | 283 | -2.24 | 2.85 | 141 | 11.1% | -0.46 [-1.04, 0.12] | |
| Brown 2012 | -3.16 | 3.15 | 172 | -2.43 | 3.15 | 57 | 4.2% | -0.73 [-1.67, 0.21] | |
| Brown 2013 | -2.9 | 3.11 | 155 | -1.62 | 3.11 | 52 | 3.9% | -1.28 [-2.26, -0.30] | |
| Schnitzer 2020 | -3.23 | 3.41 | 231 | -2.64 | 3.46 | 116 | 6.3% | -0.59 [-1.36, 0.18] | |
| Subtotal (95% CI) | | | 841 | | | 366 | 25.4% | -0.66 [-1.04, -0.28] | • |
| Heterogeneity: Chi ² = | 2.06, df | = 3 (P | = 0.56 |): ² = 0 ⁰ | % | | | | |
| Test for overall effect: | Z = 3.40 |) (P = 1 | 0.0007 | | | | | | |
| | | 8 | | | | | | | |
| 1.1.2 5 mg | | | | | | | | | |
| Berenbaum 2020 | -2.85 | 2.86 | 284 | -2.24 | 2.85 | 141 | 11.1% | -0.61 [-1.19, -0.03] | |
| Brown 2012 | -3.27 | 3.15 | 172 | -2.43 | 3.15 | 57 | 4.2% | -0.84 [-1.78, 0.10] | |
| Brown 2013 | -3.31 | 3.1 | 154 | -1.62 | 3.11 | 51 | 3.8% | -1.69 [-2.67, -0.71] | |
| Ekman 2014A | -3.44 | 2.87 | 206 | -2.23 | 2.88 | 104 | 8.0% | -1.21 [-1.89, -0.53] | |
| Ekman 2014B | -2.95 | 3.2 | 211 | -1.81 | 3.16 | 105 | 6.7% | -1.14 [-1.88, -0.40] | |
| Schnitzer 2020 | -3.37 | 3.43 | 233 | -2.64 | 3.46 | 116 | 6.3% | -0.73 [-1.50, 0.04] | |
| Spierings 2013 | -3.58 | 2.79 | 161 | -2.62 | 2.85 | 71 | 5.9% | -0.96 [-1.75, -0.17] | |
| Subtotal (95% CI) | | | 1421 | | | 645 | 46.1% | -0.96 [-1.25, -0.68] | ♦ |
| Heterogeneity: Chi ² = | 4.69, df | = 6 (P | = 0.58 |); ² = 0 ⁰ | % | | | i kananan a kanana kanan a | 22.5 |
| Test for overall effect: | Z = 6.66 | 6 (P < 1 | 0.0000 | 1) | | | | | |
| | | | | · | | | | | |
| 1.1.3 10 mg | | | | | | | | | |
| Brown 2012 | -3.62 | 3.17 | 174 | -2.43 | 3.15 | 58 | 4.2% | -1.19 [-2.13, -0.25] | |
| Brown 2013 | -3.37 | 3.13 | 157 | -1.62 | 3.11 | 52 | 3.9% | -1.75 [-2.73, -0.77] | |
| Ekman 2014A | -3.14 | 2.88 | 208 | -2.23 | 2.88 | 104 | 8.1% | -0.91 [-1.59, -0.23] | |
| Ekman 2014B | -2.62 | 3.18 | 209 | -1.81 | 3.16 | 104 | 6.7% | -0.81 [-1.55, -0.07] | |
| Spierings 2013 | -3.58 | 2.82 | 150 | -2.62 | 2.85 | 70 | 5.7% | -0.96 [-1.77, -0.15] | |
| Subtotal (95% CI) | | | 898 | | | 388 | 28.5% | -1.05 [-1.41, -0.69] | • |
| Heterogeneity: Chi2 = | 2.67. df | = 4 (P | = 0.61 | : 1 ² = 0 ⁰ | % | | | | |
| Test for overall effect: | Z = 5.72 | 2 (P <) | 0.0000 | 1) | | | | | |
| | | - - | | | | | | | 85 |
| Total (95% CI) | | | 3160 | | | 1399 | 100.0% | -0.91 [-1.10, -0.72] | • |
| Heterogeneity: Chi2 = | 11.79. d | f = 15 | (P = 0.0) | 59); l ² = | 0% | | | | |
| Test for overall effect: | Z = 9.29 |) (P < 1 | 0.0000 | 1) | 88939 | | | | -4 -2 0 2 4 |
| Test for subaroup diffe | erences | Chi ² = | 2.37.0 | f = 2 (F | P = 0.3 | 1), ² = | 15.7% | | Favours (tanezumab) Favours (placebo) |
| of obout out of this | | | | | 0.0 | | | | i aroaro [tanozaniab] i aroaro [biaoebo] |

FIGURE 3. Forest plots of the mean change in Western Ontario and McMaster Universities Osteoarthritis Index pain after treatment with tanezumab versus placebo (mean ± SD). CI indicates confidence interval.

Safety

The safety of tanezumab was investigated in 4 aspects: the number of patients who discontinued treatment because of AEs, SAEs, and the number of RPOA events and TJR events. All 9 studies reported patients who discontinued treatment because of AEs and SAEs. Five studies^{33,37-40} reported patients who experienced RPOA events, and 8 studies^{33–36,38–40} reported patients who experienced TJR events.

Patients Who Discontinued Treatment Because of AEs

The tanezumab group had a significantly increased number of patients who discontinued treatment because of AEs compared with those in the placebo and NSAIDs groups (RR = 1.36, 95% CI = 1.09 to 1.70, P = 0.006; $I^2 = 16\%$) (Fig. 6A).

SAEs

SAEs were defined as events resulting in hospitalization (initial or prolonged), disability or permanent damage, congenital abnormality or birth defect of offspring, life-threatening events or death. There were no significant differences in the number of participants reporting SAEs between the tanezumab group and the placebo or NSAIDs group (RR = 1.18, 95% CI = 0.97 to 1.45, P = 0.53; $I^2 = 0\%$) (Fig. 6B).

RPOA Events

There were significantly increased RPOA events in the tanezumab group compared with those in the placebo and NSAIDs groups (RR = 9.2, 95% CI = 2.59 to 32.71, P = 0.0006; $I^2 = 0\%$) (Fig. 6C). In the subgroup analysis, we found that the incidence of RPOA was the highest in the 5 mg tanezumab group (RR = 6.49, P = 0.001; $I^2 = 0\%$) but was not statistically significant in the 2.5 and 10 mg tanezumab groups compared with that in the control group (Supplementary Fig. 5, Supplemental Digital Content 6, http://links.lww.com/CJP/A831).

TJR

There were no significant differences in the TJR events between the tanezumab group and the placebo or NSAIDs group (RR = 1.04, 95% CI = 0.77 to 1.42, P = 0.78; $I^2 = 14\%$) (Fig. 6D).

DISCUSSION

This systematic review and meta-analysis evaluated the safety and effectiveness of tanezumab in the analgesic effect of OA patients, and 9 RCTs with a total of 10,830 participants were included. The 3 different doses of tanezumab, compared with placebo, significantly improved the WOMAC pain, WOMAC physical function, and PGA, and similar results were also obtained for the comparison

Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

| | tan | ezuma | b | pl | acebo | | | Mean Difference | | Me | an Differe | nce | |
|--|-----------|-------------|------------------|-----------------------|-------|-------|--------|----------------------|----|----------------|------------|------|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | | IV. | Fixed. 95 | % CI | |
| 2.1.1 2.5 mg | | | | | | | | | | | | | |
| Berenbaum 2020 | -2.7 | 2.86 | 283 | -2.11 | 2.85 | 141 | 9.2% | -0.59 [-1.17, -0.01] | | | - | | |
| Brown 2012 | -2.81 | 2.89 | 172 | -2.05 | 2.89 | 57 | 4.1% | -0.76 [-1.63, 0.11] | | - | - | | |
| Brown 2013 | -2.57 | 2.49 | 155 | -1.39 | 2.49 | 52 | 5.0% | -1.18 [-1.96, -0.40] | | | - | | |
| Schnitzer 2020 | -3.22 | 3.37 | 231 | -2.56 | 3.42 | 116 | 5.3% | -0.66 [-1.42, 0.10] | | - | - | | |
| Subtotal (95% CI) | | | 841 | | | 366 | 23.6% | -0.76 [-1.12, -0.40] | | | • | | |
| Heterogeneity: Chi ² = | 1.51. df | = 3 (P | = 0.68) | $ ^{2} = 0^{0}$ | 6 | | | | | | | | |
| Test for overall effect: | Z = 4.14 | + (P < (| 0.0001) | | | | | | | | | | |
| | | 1 | | | | | | | | | | | |
| 2.1.2 5 mg | | | | | | | | | | | | | |
| Berenbaum 2020 | -2.82 | 2.86 | 284 | -2.11 | 2.85 | 141 | 9.2% | -0.71 [-1.29, -0.13] | | 8 . | - | | |
| Brown 2012 | -3.01 | 2.89 | 172 | -2.05 | 2.89 | 57 | 4.1% | -0.96 [-1.83, -0.09] | | | | | |
| Brown 2013 | -2.88 | 2.48 | 154 | -1.39 | 2.49 | 51 | 4.9% | -1.49 [-2.28, -0.70] | | | - | | |
| Ekman 2014A | -3.09 | 2.73 | 206 | -1.84 | 2.74 | 104 | 7.3% | -1.25 [-1.90, -0.60] | | _ | - | | |
| Ekman 2014B | -1.95 | 2.47 | 211 | -1.4 | 2.46 | 105 | 9.2% | -0.55 [-1.13, 0.03] | | | - | | |
| Schnitzer 2020 | -3.45 | 3.31 | 233 | -2.56 | 3.42 | 116 | 5.4% | -0.89 [-1.64, -0.14] | | | | | |
| Spierings 2013 | -3.05 | 2.54 | 161 | -1.91 | 2.73 | 71 | 5.5% | -1.14 [-1.89, -0.39] | | _ | _ | | |
| Subtotal (95% CI) | | | 1421 | | | 645 | 45.6% | -0.94 [-1.20, -0.69] | | | • | | |
| Heterogeneity: Chi ² = | 5.42, df | = 6 (P | = 0.49) | ; l ² = 09 | 6 | | | | | | | | |
| Test for overall effect: | Z = 7.15 | 5 (P < (| 0.00001 | 0 | | | | | | | | | |
| | | ÷ | | 1 | | | | | | | | | |
| 2.1.3 10mg | | | | | | | | | | | | | |
| Brown 2012 | -3.29 | 2.9 | 174 | -2.05 | 2.89 | 58 | 4.1% | -1.24 [-2.10, -0.38] | | | - | | |
| Brown 2013 | -3 | 2.51 | 157 | -1.39 | 2.49 | 52 | 5.0% | -1.61 [-2.39, -0.83] | | | | | |
| Ekman 2014A | -2.82 | 2.74 | 208 | -1.84 | 2.74 | 104 | 7.3% | -0.98 [-1.62, -0.34] | | _ | - | | |
| Ekman 2014B | -1.97 | 2.46 | 209 | -1.4 | 2.46 | 104 | 9.1% | -0.57 [-1.15, 0.01] | | | - | | |
| Spierings 2013 | -3.06 | 2.57 | 150 | -1.91 | 2.73 | 70 | 5.3% | -1.15 [-1.91, -0.39] | | _ | - | | |
| Subtotal (95% CI) | | | 898 | | | 388 | 30.9% | -1.02 [-1.34, -0.71] | | | | | |
| Heterogeneity: Chi ² = | 4.89. df | = 4 (P | = 0.30) | ; l ² = 18 | 3% | | | | | | | | |
| Test for overall effect: | Z = 6.38 | B (P <) | 0.00001 | 1) | | | | | | | | | |
| 90000000000000000000000000000000000000 | 1913 1915 | 0.49 - 1933 | 00817353500 0 | (T) | | | | | | | | | |
| Total (95% CI) | | | 3160 | | | 1399 | 100.0% | -0.93 [-1.10, -0.75] | | | • | | |
| Heterogeneity: Chi2 = | 13.03. d | f = 15 | (P = 0.6) | 50); l ² = | 0% | | | - | | | _ | | |
| Test for overall effect: | | | | | | | | | -4 | -2 | 0 | 2 | 4 |
| root for oronall oncot. | Z = 10.3 | 38 (P < | 0.0000 |)1) | | | | | | - | 0 | - | - |

FIGURE 4. Forest plots of mean change in Western Ontario and McMaster Universities Osteoarthritis Index physical function after treatment with tanezumab versus placebo (mean \pm SD). CI indicates confidence interval.

of tanezumab with NSAIDs. In the subgroup analysis, we found that compared with placebo or NSAIDs, tanezumab at 10 mg had the best therapeutic effect, but 10 mg of tanezumab, compared with NSAIDs, did not significantly improve the PGA. In the safety evaluation, we found that the occurrence of patients who discontinued treatment because of AEs and experienced RPOA events was significantly higher in the tanezumab group than in the placebo and NSAID groups, and with the increase in the dose of tanezumab, the occurrence of RPOA events also increased. In SAEs and TJR events, there were no significant differences between the intervention group and the control group.

In 2015, a systematic review evaluating the safety of 3 antibodies, namely, tanezumab, fulranumab, and fasinumab, to NGF in the treatment of OA was published.⁷ The review included published and unpublished studies of 10 placebocontrolled trials, and 7 involved tanezumab. Efficacy outcomes showed that tanezumab, compared with placebo, resulted in statistically significant improvements in all components of the PGA and the WOMAC scale, including pain and physical function subscales. To obtain an overall view of safety, studies with tanezumab reported a higher rate of patients who discontinued treatment because of AEs in the higher dose groups than in the placebo groups, and the lower dose ranges were similar to those reported with placebo. No significant differences were reported for SAEs between the tanezumab and placebo groups.⁷ In 2016 and 2017, 2 meta-analyses obtained similar results on the effectiveness and safety of tanezumab in the treatment of OA.^{8,9} On this basis, their results showed that there was a higher incidence of abnormal peripheral sensations and peripheral neuropathy in the tanezumab group than in the placebo group. Compared with results from previous metaanalyses, our results are similar in effectiveness and safety. At the same time, we analyzed the relationship between the use of tanezumab and the occurrence of joint safety incidents, including RPOA and TJR events.

Tanezumab, also known as RN624, in animal models of pain was highly effective at relatively low doses, and controlled animal tolerability and safety studies did not reveal any AEs. On this basis, 2 clinical trials were quickly carried out to test the efficacy of tanezumab in acute or chronic pain. The results of these phase I clinical trials showed that tanezumab has a good analgesic effect on chronic pain and has good safety and tolerability, but the analgesic effect in acute pain is not obvious.^{29,41} In 2006, RPOA events occurred in a small percentage of patients, particularly in patients who received concomitant treatment with NSAIDs. The Food and Drug Administration (FDA) imposed a partial clinical hold on noncancer pain-related tanezumab studies because of unexpected AEs.⁴² However, there are few studies on the mechanism of RPOA, and there is no effective method to prevent or reduce the occurrence of such AEs. Our analysis results showed that tanezumab has a certain correlation with the occurrence of RPOA in the treatment of OA.

| Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI IV, Fixed, 95% CI 3.1.1 2.5 mg Berenbaum 2020 -0.82 1.01 283 -0.72 1.01 141 9.3% -0.10 [-0.30, 0.10] Brown 2012 -0.82 0.92 172 -0.51 0.92 57 5.1% -0.32 [-0.59, 0.05] Schnitzer 2020 -0.87 1.16 231 -0.65 1.17 116 5.7% -0.22 [-0.48, 0.04] Subtotal (95% CI) 841 366 25.4% -0.21 [-0.34, -0.09] -0.49 -0.72 1.01 141 9.4% -0.22 [-0.48, 0.04] Berenbaum 2020 -0.9 1.01 284 -0.72 1.01 141 9.4% -0.38 [-0.36, -0.07] -0.34 [-0.38, 0.02] -0.34 [-0.38, 0.02] -0.34 [-0.38, 0.10] -0.34 [-0.56, 0.10] -0.34 [-0.56, 0.10] -0.34 [-0.56, 0.10] -0.34 [-0.56, 0.10] -0.34 [-0.56, 0.21] -0.35 [-0.51, 0.01] -0.34 [-0.57, 0.02] -0.35 [-0.51, 0.01] -0.34 [-0.56, 0.22] +0.37 [-0.20] | | tan | ezuma | ab | pl | acebo | | | Mean Difference | Mean Difference |
|--|-----------------------------------|----------|--------------------|----------|-----------------------|----------|----------------------|--------|----------------------|---------------------------------------|
| 3.1.2.5 mg Berenbaum 2020 $-0.82 \ 1.01 \ 283 \ -0.72 \ 1.01 \ 141 \ 9.3\% \ -0.10 \ [-0.30, 0.10] Brown 2013 -0.66 \ 0.87 \ 155 \ -0.34 \ 0.87 \ 52 \ 5.2\% \ -0.32 \ [-0.59, -0.03] Brown 2013 -0.66 \ 0.87 \ 155 \ -0.34 \ 0.87 \ 52 \ 5.2\% \ -0.32 \ [-0.59, -0.09] Heterogeneity: Ch2 = 2.25, df = 3 \ (P = 0.52); P = 0% Test for overall effect: Z = 3.40 (P = 0.0007) 3.1.2 5 mg Berenbaum 2020 -0.9 \ 1.01 \ 284 \ -0.72 \ 1.01 \ 141 \ 9.4\% \ -0.18 \ [-0.38, 0.02] Brown 2012 -0.86 \ 0.92 \ 172 \ -0.51 \ 0.92 \ 57 \ 5.1\% \ -0.34 \ [-0.59, -0.16] Berenbaum 2020 -0.9 \ 1.01 \ 284 \ -0.72 \ 1.01 \ 141 \ 9.4\% \ -0.18 \ [-0.38, 0.02] Brown 2012 -0.86 \ 0.92 \ 172 \ -0.51 \ 0.92 \ 57 \ 5.1\% \ -0.34 \ [-0.58, -0.10] Brown 2013 -0.78 \ 0.87 \ 154 \ -0.39 \ 11 \ 105 \ 7.0\% \ -0.34 \ [-0.58, -0.10] Ekman 2014A -0.73 \ 1.02 \ 211 \ -0.39 \ 11 \ 105 \ 7.0\% \ -0.34 \ [-0.58, -0.10] Spherings 2013 -0.9 \ 1.17 \ 233 \ -0.68 \ 1.17 \ 116 \ 5.7\% \ -0.38 \ [-0.64, -0.12] Brown 2012 -1 \ 0.92 \ 174 \ -0.51 \ 0.92 \ 58 \ 5.2\% \ -0.49 \ [-0.76, -0.22] Brown 2012 -1 \ 0.92 \ 174 \ -0.51 \ 0.92 \ 58 \ 5.2\% \ -0.49 \ [-0.76, -0.22] Brown 2012 -1 \ 0.92 \ 174 \ -0.51 \ 0.92 \ 58 \ 5.2\% \ -0.47 \ [-0.74, -0.20] Brown 2012 -1 \ 0.92 \ 174 \ -0.51 \ 0.92 \ 58 \ 5.2\% \ -0.47 \ [-0.74, -0.20] Brown 2012 -1 \ 0.92 \ 174 \ -0.51 \ 0.92 \ 58 \ 5.2\% \ -0.47 \ [-0.74, -0.20] Brown 2013 \ -0.81 \ 0.88 \ 157 \ -0.39 \ 11 \ 104 \ 6.9\% \ -0.20 \ [-0.44, 0.42] Brown 2013 \ -0.81 \ 0.88 \ 157 \ -0.39 \ 10 \ 104 \ 6.9\% \ -0.20 \ [-0.44, 0.42] Brown 2013 \ -0.81 \ 0.88 \ 157 \ -0.39 \ 10 \ 104 \ 6.9\% \ -0.20 \ [-0.44, 0.42] Brown 2013 \ -0.81 \ 0.88 \ 157 \ -0.39 \ 10 \ 0.\% \ -0.33 \ [-0.57, -0.21] Bubtotal (95\% Cl) \ 898 \ 388 \ 29.5\% \ -0.38 \ [-0.48, -0.26] Heterogeneity: Ch2 = 3.93, df = 4 (P = 0.42); P = 0\%Test for overall effect: Z = 6.67 \ (P = 0.000)1Total (95% Cl) \ 3160 \ 1399 \ 100.0\% \ -0.31 \ [-0.37, -0.25]Heterogeneity: Ch2 = 12.96, df = 15 \ (P = 0.61); P = 0\%Test for overall effect: Z = 5$ | Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI |
| Berenbaum 2020 -0.82 1.01 283 -0.72 1.01 141 9.3% -0.10 [-0.30, 0.10] Brown 2012 -0.82 0.92 172 -0.51 0.92 57 5.1% -0.31 [-0.59, 0.05] Schnitzer 2020 -0.87 1.16 231 -0.65 1.17 116 5.7% -0.22 [-0.48, 0.04] Subtotal (95% CI) 841 366 25.4% -0.21 [-0.34, -0.09] Heterogeneity: Chi ² = 2.25, df = 3 ($P = 0.52$); $P = 0\%$ Test for overall effect: Z = 3.40 ($P = 0.0007$) 3.1.2 5 mg Berenbaum 2020 -0.9 1.01 284 -0.72 1.01 141 9.4% -0.18 [-0.38, 0.02] Brown 2012 -0.86 0.92 172 -0.51 0.92 57 5.1% -0.35 [-0.63, -0.07] Brown 2013 -0.78 0.87 154 -0.34 0.87 51 5.1% -0.44 [-0.72, -0.16] Ekman 2014A -0.87 1 206 -0.53 1.01 104 6.9% -0.34 [-0.58, 0.10] Schnitzer 2020 -0.9 1.17 233 -0.65 1.17 116 5.7% -0.25 [-0.51, 0.01] Schnitzer 2020 -0.9 1.17 233 -0.65 1.17 116 5.7% -0.38 [-0.64, -0.12] Brown 2013 -0.78 0.99 161 -0.52 0.95 71 5.7% -0.38 [-0.64, -0.12] Subtotal (95% CI) 1421 645 45.0% -0.31 [-0.74, -0.20] Heterogeneity: Chi ² = 3.10, df = 6 ($P = 0.80$); $P = 0\%$ Test for overall effect: Z = 6.60 ($P < 0.00001$) 3.1.3 10 mg Brown 2013 -0.81 0.88 157 -0.34 0.87 52 5.2% -0.47 [-0.74, -0.20] Ekman 2014A -0.73 1.01 208 -0.53 1.01 104 6.9% -0.20 [-0.76, -0.22] Heterogeneity: Chi ² = 3.93, df = 4 ($P = 0.42$); $P = 0\%$ Test for overall effect: Z = 6.47 ($P < 0.00001$) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 ($P = 0.61$); $P = 0\%$ Test for overall effect: Z = 6.66 ($P < 0.00001$) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 ($P = 0.61$); $P = 0\%$ Test for overall effect: Z = 6.86 ($P < 0.00001$) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 ($P = 0.61$); $P = 0\%$ Test for overall effect: Z = 5.66 ($P < 0.00001$) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 ($P = 0.61$); $P = 0\%$ Test for overall effect: Z = 5.66 ($P < 0.00001$) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 2.96, | 3.1.1 2.5 mg | | | | | | | | | |
| Brown 2012 -0.82 0.92 172 -0.51 0.92 57 5.1% -0.31 [-0.59, -0.03] Brown 2013 -0.66 0.87 155 -0.34 0.87 52 5.2% -0.32 [-0.59, -0.05] Schnitzer 2020 -0.87 1.16 231 -0.65 1.17 116 5.7% -0.22 [-0.48, 0.04] Subtotal (95% CI) 841 366 25.4% -0.21 [-0.34, -0.09] Heterogeneity: Chi ² = 2.25, df = 3 ($P = 0.52$); $P = 0\%$ Test for overall effect: Z = 3.40 ($P = 0.52$); $P = 0\%$ Test for overall effect: Z = 6.60 ($P < 0.52$); $P = 0\%$ Test for overall effect: Z = 6.60 ($P < 0.52$); $P = 0\%$ Test for overall effect: Z = 6.60 ($P < 0.500$); $P = 0\%$ Test for overall effect: Z = 6.60 ($P < 0.500$); $P = 0\%$ Test for overall effect: Z = 6.60 ($P < 0.0001$) 3.13 10 mg Brown 2012 -1 0.92 174 -0.51 0.92 58 5.2% -0.49 [-0.76, -0.22] Erwan 2014A -0.73 1.01 208 -0.53 1.01 104 6.9% -0.31 [-0.74, -0.20] Erwan 2013 -0.18 0.88 161 -0.52 0.95 71 5.7% -0.38 [-0.64, -0.12] Subtotal (95% CI) 1421 645 45.0% -0.31 [-0.77, -0.26] Erwan 2014B -0.73 1.01 208 -0.53 1.01 104 6.9% -0.20 [-0.44, 0.04] Erwan 2014B -0.73 1.01 208 -0.53 1.01 104 6.9% -0.20 [-0.44, 0.04] Erwan 2014B -0.73 1.01 208 -0.53 1.01 104 6.9% -0.20 [-0.44, 0.04] Erwan 2014B -0.72 1.01 209 -0.39 1 104 7.0% -0.33 [-0.77, -0.20] Erwan 2013 -0.41 0.88 157 -0.34 0.87 52 5.2% -0.47 [-0.74, -0.20] Erwan 2013 -0.41 0.88 150 -0.52 0.95 70 5.3% -0.48 [-0.75, -0.21] Subtotal (95% CI) 898 388 29.5% -0.38 [-0.49, -0.26] Heterogeneity: Chi ² = 3.93, df = 4 ($P = 0.42$); $P = 0\%$ Test for overall effect: Z = 6.47 ($P < 0.0001$) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 ($P = 0.61$); $P = 0\%$ Test for overall effect: Z = 6.47 ($P < 0.0001$) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 ($P = 0.61$); $P = 0\%$ Test for overall effect: Z = 6.80 df = 2 ($P = 0.16$); $P = 0\%$ Test for overall effect: Z = 6.80 df = 2 ($P = 0.16$); $P = 0\%$ Test for overall effect: Z = 6.80 df = 2 ($P = 0.61$); $P = 0\%$ Test for overall effect: Z = 6.80 df = 2 ($P = 0.61$); | Berenbaum 2020 | -0.82 | 1.01 | 283 | -0.72 | 1.01 | 141 | 9.3% | -0.10 [-0.30, 0.10] | |
| Brown 2013 -0.66 0.87 155 -0.34 0.87 52 5.2% -0.32 [-0.59, -0.05] Schnitzer 2020 -0.87 1.16 231 -0.65 1.17 116 5.7% -0.22 [-0.48, 0.04] Subtotal (95% CI) 844 366 25.4% -0.21 [-0.34, -0.09] Heterogeneity: Chi ² = 2.25, df = 3 (P = 0.52); $P = 0\%$ Test for overall effect: Z = 3.40 (P = 0.0007) 3.1.2 5 mg Berenbaum 2020 -0.9 1.01 284 -0.72 1.01 141 9.4% -0.18 [-0.38, 0.02] Brown 2012 -0.86 0.92 172 -0.51 0.92 57 5.1% -0.35 [-0.63, -0.07] Brown 2013 -0.78 0.87 154 -0.34 0.87 51 5.1% -0.44 [-0.72, -0.16] Ekman 2014A -0.87 1 206 -0.53 1.01 104 6.9% -0.34 [-0.58, -0.10] Schnitzer 2020 -0.9 1.17 233 -0.65 1.17 116 5.7% -0.25 [-0.51, 0.01] Schnitzer 2020 -0.9 1.17 233 -0.65 1.17 116 5.7% -0.25 [-0.51, 0.01] Schnitzer 2020 -0.9 1.17 233 -0.65 1.17 116 5.7% -0.25 [-0.51, 0.01] Subtotal (95% CI) 1421 -0.51 0.92 58 5.2% -0.49 [-0.76, -0.22] Brown 2013 -0.81 0.88 157 -0.34 0.87 52 5.2% -0.49 [-0.76, -0.22] Brown 2013 -0.81 0.88 157 -0.34 0.87 52 5.2% -0.49 [-0.76, -0.22] Ekman 2014A -0.73 1.01 208 -0.53 1.01 104 6.9% -0.20 [-0.44, 0.04] Ekman 2014B -0.72 1.01 209 -0.39 1 104 7.0% -0.33 [-0.77, -0.09] Spierings 2013 -1 0.98 150 -0.52 0.95 70 5.3% -0.48 [-0.75, -0.21] Subtotal (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); P = 0% Test for overall effect: Z = 6.47 (P < 0.0001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); P = 0% Test for overall effect: Z = 6.86 df = 2 (P = 0.16); P = 45.7% Test for overall effect: Z = 9.68 (P < 0.00001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); P = 0% Test for overall effect: Z = 9.68 (P < 0.00001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); P = 0% Test for overall effect: Z = 9.68 (P < 0.00001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); P = 0% Test for overall effect: Z | Brown 2012 | -0.82 | 0.92 | 172 | -0.51 | 0.92 | 57 | 5.1% | -0.31 [-0.59, -0.03] | |
| Schnitzer 2020 0.87 1.16 231 -0.65 1.17 116 5.7% -0.22 [-0.48, 0.04] Subtotal (95% CI) 841 366 25.4% -0.21 [-0.34, -0.09] Heterogeneity: Ch ² = 2.25, df = 3 (P = 0.52); P = 0% Test for overall effect: Z = 3.40 (P = 0.0007) 3.1.2 5 mg Berenbaum 2020 -0.9 1.01 284 -0.72 1.01 141 9.4% -0.18 [-0.38, 0.02] Brown 2012 -0.86 0.92 172 -0.51 0.92 57 5.1% -0.35 [-0.63, 0.07] Brown 2013 -0.78 0.87 15 4-0.34 0.87 51 5.1% -0.34 [-0.72, -0.16] Ekman 2014A -0.87 1 206 -0.53 1.01 104 6.9% -0.34 [-0.58, 0.10] Schnitzer 2020 -0.9 1.17 233 -0.65 1.17 116 5.7% -0.25 [-0.51, 0.01] Splerings 2013 -0.9 0.89 161 -0.52 0.95 71 5.7% -0.38 [-0.44, -0.12] Heterogeneity: Ch ² = 3.10, df = 6 (P = 0.80); P = 0% Test for overall effect: Z = 6.60 (P < 0.00001) 3.1.3 10 mg Brown 2012 -1 0.92 174 -0.51 0.92 58 5.2% -0.49 [-0.76, -0.22] Brown 2013 -0.81 0.88 157 -0.34 0.87 52 5.2% -0.47 [-0.74, -0.20] Ekman 2014A -0.73 1.01 208 -0.53 1.01 104 6.9% -0.20 [-0.44, 0.04] Ekman 2014A -0.73 1.01 209 -0.39 1 104 7.0% -0.33 [-0.75, -0.21] Brown 2013 -0.81 0.88 157 -0.34 0.87 52 5.2% -0.47 [-0.74, -0.20] Ekman 2014B -0.72 1.01 209 -0.39 1 104 7.0% -0.33 [-0.75, -0.21] Subtotal (95% CI) 898 388 29.5% -0.38 [-0.48, -0.26] Heterogeneity: Ch ² = 12.96, df = 15 (P = 0.61); P = 0% Test for overall effect: Z = 6.47 (P < 0.00001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Ch ² = 12.96, df = 15 (P = 0.61); P = 0% Test for overall effect: Z = 6.86, df = 2 (P = 0.16), P = 45.7% Test for overall effect: Z = 0.68, df = 2 (P = 0.16), P = 45.7% | Brown 2013 | -0.66 | 0.87 | 155 | -0.34 | 0.87 | 52 | 5.2% | -0.32 [-0.59, -0.05] | |
| Subtotal (95% CI) 841 366 25.4% -0.21 [$\overline{0}$.34, -0.09] Heterogeneity: Ch ² = 2.25, df = 3 (P = 0.52); P = 0% Test for overall effect: Z = 3.40 (P = 0.0007) 3.1.2 5 mg Berenbaum 2020 -0.9 1.01 284 -0.72 1.01 141 9.4% -0.18 [-0.38, 0.02] Brown 2012 -0.86 0.92 172 -0.51 0.92 57 5.1% -0.35 [-0.63, -0.07] Brown 2013 -0.78 0.87 154 -0.34 0.87 51 5.1% -0.44 [-0.72, -0.16] Ekman 2014A -0.87 1 206 -0.53 1.01 104 6.9% -0.34 [-0.58, -0.10] Schnitzer 2020 -0.9 1.17 233 -0.65 1.17 116 5.7% -0.28 [-0.64, -0.12] Subtotal (95% CI) 1421 645 45.0% -0.31 [-0.41, -0.22] Heterogeneity: Ch ² = 3.10, df = 6 (P = 0.80); P = 0% Test for overall effect: Z = 6.60 (P < 0.00001) Signings 2013 -0.81 0.88 157 -0.34 0.87 52 5.2% -0.49 [-0.76, -0.22] Brown 2012 -1 0.92 174 -0.51 0.92 58 5.2% -0.49 [-0.76, -0.22] Brown 2013 -0.81 0.88 157 -0.34 0.87 52 5.2% -0.49 [-0.76, -0.22] Brown 2013 -0.81 0.88 157 -0.34 0.87 52 5.2% -0.49 [-0.76, -0.22] Brown 2013 -0.81 0.88 157 -0.34 0.87 52 5.2% -0.49 [-0.76, -0.22] Brown 2013 -0.81 0.88 157 -0.34 0.87 52 5.2% -0.49 [-0.76, -0.22] Brown 2013 -0.81 0.88 157 -0.34 0.87 52 5.2% -0.49 [-0.76, -0.22] Brown 2014 -0.72 1.01 209 -0.39 1 104 6.9% -0.20 [-0.44, 0.04] Ekman 2014A -0.73 1.01 208 -0.52 0.95 70 5.3% -0.48 [-0.75, -0.21] Subtotal (95% CI) 888 388 29.5% -0.38 [-0.48, -0.26] Heterogeneity: Ch ² = 12.96, df = 15 (P = 0.61); P = 0% Test for overall effect: Z = 6.47 (P < 0.00001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Ch ² = 12.96, df = 15 (P = 0.61); P = 0% Test for overall effect: Z = 6.86, df = 2 (P = 0.16), P = 45.7% Test for overall effect: Z = 9.66 (P < 0.00001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Ch ² = 12.96, df = 15 (P = 0.61); P = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Ch ² = 12.96, df = 15 (P = 0.61); P = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Favours funezumba Favours fuleaceabal | Schnitzer 2020 | -0.87 | 1.16 | 231 | -0.65 | 1.17 | 116 | 5.7% | -0.22 [-0.48, 0.04] | |
| Heterogeneity: Ch ² = 2.25, df = 3 (P = 0.52); P = 0% Test for overall effect: Z = 3.40 (P = 0.0007) 3.1.2 5 mg Berenbaum 2020 - 0.9 1.01 284 -0.72 1.01 141 9.4% -0.18 [-0.38, 0.02] Brown 2012 - 0.86 0.92 172 - 0.51 0.92 57 5.1% -0.35 [-0.63, -0.07] Brown 2013 - 0.78 0.87 154 -0.34 0.87 51 5.1% -0.44 [-0.72, -0.16] Ekman 2014A - 0.87 1 206 -0.53 1.01 104 6.9% -0.34 [-0.58, -0.10] Ekman 2014B -0.73 1.02 211 -0.39 1 105 7.0% -0.34 [-0.58, -0.10] Schnitzer 2020 -0.9 1.17 233 -0.65 1.17 116 5.7% -0.25 [-0.51, 0.01] Spierings 2013 -0.9 0.89 161 -0.52 0.95 71 5.7% -0.38 [-0.64, -0.12] Subtotal (95% CI) 1421 645 45.0% -0.31 [-0.41, -0.22] Heterogeneity: Chi ² = 3.10, df = 6 (P = 0.80); P = 0% Test for overall effect: Z = 6.60 (P < 0.00001) 3.1.3 10 mg Brown 2012 -1 0.92 174 -0.51 0.92 58 5.2% -0.49 [-0.76, -0.22] Brown 2013 -0.81 0.88 157 -0.34 0.87 52 5.2% -0.47 [-0.74, -0.20] Ekman 2014A -0.73 1.01 208 -0.53 1.01 104 6.9% -0.33 [-0.57, -0.09] Spierings 2013 -1 0.98 150 -0.52 0.95 70 5.3% -0.48 [-0.75, -0.21] Subtotal (95% CI) 898 388 29.5% -0.38 [-0.49, -0.26] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); P = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); P = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Total (95% CI) 3160 129 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); P = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Total (95% CI) 3160 1299 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); P = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Favours [Ianezumable Favours [Ianezbol] | Subtotal (95% CI) | | | 841 | | | 366 | 25.4% | -0.21 [-0.34, -0.09] | • |
| Test for overall effect: $Z = 3.40$ (P = 0.0007) 3.1.2 5 mg Berenbaum 2020 -0.9 1.01 284 -0.72 1.01 141 9.4% -0.18 [-0.38, 0.02] Brown 2012 -0.86 0.92 172 -0.51 0.92 57 5.1% -0.35 [-0.63, -0.07] Brown 2013 -0.78 0.87 154 -0.34 0.87 51 5.1% -0.44 [-0.72, -0.16] Ekman 2014A -0.87 1 206 -0.53 1.01 104 6.9% -0.34 [-0.58, -0.10] Schnitzer 2020 -0.9 1.17 233 -0.65 1.17 116 5.7% -0.25 [-0.51, 0.01] Spierings 2013 -0.9 0.89 161 -0.52 0.95 71 5.7% -0.38 [-0.44, -0.12] Subtotal (95% CI) 1421 645 45.0% -0.31 [-0.41, -0.22] Heterogeneity: Chi ² = 3.10, df = 6 (P = 0.80); l ² = 0% Test for overall effect: Z = 6.60 (P < 0.00001) 3.13 10 mg Brown 2012 -1 0.92 174 -0.51 0.92 58 5.2% -0.49 [-0.76, -0.22] Brown 2013 -0.81 0.88 157 -0.34 0.87 52 5.2% -0.47 [-0.74, -0.20] Ekman 2014A -0.73 1.01 208 -0.53 1.01 104 6.9% -0.20 [-0.44, 0.04] Ekman 2014B -0.72 1.01 209 -0.39 1 104 7.0% -0.33 [-0.57, -0.09] Spierings 2013 -1 0.98 150 -0.52 0.95 70 5.3% -0.48 [-0.75, -0.21] Subtotal (6% CI) 898 388 29.5% -0.38 [-0.49, -0.26] Heterogeneity: Chi ² = 3.93, df = 4 (P = 0.42); l ² = 0% Test for overall effect: Z = 6.47 (P < 0.00001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.26] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 0.66 (P < 0.00001) Total (95% CI) 3160 1299 100.0% -0.31 [-0.37, -0.26] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 0.68 (P < 0.00001) Total (95% CI) 3160 1299 100.0% -0.31 [-0.37, -0.26] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 0.68 (P < 0.00001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.26] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 0.68 (P < 0.00001) Total (95% CI) 3160 Table 10.50 0 0.5 1 Favours [Jacebol] | Heterogeneity: Chi ² = | 2.25, df | = 3 (P | = 0.52 | ; l ² = 09 | % | | | | 1.0.00 |
| 3.1.2 5 mg Berenbaum 2020 $-0.9 \ 1.01 \ 284 \ -0.72 \ 1.01 \ 141 \ 9.4\% \ -0.18 [-0.38, 0.02]$ Brown 2012 $-0.86 \ 0.92 \ 172 \ -0.51 \ 0.92 \ 57 \ 5.1\% \ -0.35 [-0.63, -0.07]$ Brown 2013 $-0.78 \ 0.87 \ 154 \ -0.34 \ 0.87 \ 51 \ 5.1\% \ -0.44 \ [-0.72, -0.16]$ Ekman 2014A $-0.87 \ 1 \ 206 \ -0.53 \ 1.01 \ 104 \ 6.9\% \ -0.34 \ [-0.58, -0.10]$ Schnitzer 2020 $-0.9 \ 1.17 \ 233 \ -0.65 \ 1.17 \ 116 \ 5.7\% \ -0.25 \ [-0.51, 0.01]$ Subtotal (95% CI) $1421 \ 645 \ 45.0\% \ -0.31 \ [-0.41, -0.22]$ Heterogeneity: Chi ² = 3.10, df = 6 (P = 0.80); P = 0% Test for overall effect: Z = 6.60 (P < 0.00001) 3.1.3 10 mg Brown 2012 $-1 \ 0.92 \ 174 \ -0.51 \ 0.92 \ 58 \ 5.2\% \ -0.49 \ [-0.76, -0.22]$ Brown 2013 $-0.81 \ 0.88 \ 157 \ -0.38 \ 1.01 \ 104 \ 6.9\% \ -0.20 \ [-0.44, -0.20]$ Ekman 2014B $-0.72 \ 1.01 \ 209 \ -0.39 \ 1 \ 104 \ 7.0\% \ -0.33 \ [-0.76, -0.22]$ Brown 2013 $-0.81 \ 0.88 \ 157 \ -0.39 \ 1 \ 104 \ 6.9\% \ -0.26 \ [-0.44], -0.20]$ Ekman 2014B $-0.72 \ 1.01 \ 209 \ -0.39 \ 1 \ 104 \ 7.0\% \ -0.33 \ [-0.75, -0.21]$ Subtotal (95% CI) $898 \ 388 \ 29.5\% \ -0.48 \ [-0.75, -0.21]$ Heterogeneity: Chi ² = 3.93, df = 4 (P = 0.42); P = 0\% Test for overall effect: Z = 6.47 (P < 0.00001) Total (95% CI) $3160 \ 1399 \ 100.0\% \ -0.31 \ [-0.37, -0.25]$ Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); P = 0\% Test for overall effect: Z = 9.66 (P < 0.00001) Total (95% CI) $3160 \ 1399 \ 100.0\% \ -0.31 \ [-0.37, -0.25]$ Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); P = 0\% Test for overall effect: Z = 9.66 (P < 0.00001) Total (95% CI) $3160 \ 1399 \ 100.0\% \ -0.31 \ [-0.37, -0.25]$ Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); P = 0\% Test for overall effect: Z = 9.66 (P < 0.00001) Total (95\% CI) $3160 \ 1399 \ 100.0\% \ -0.31 \ [-0.37, -0.25]$ Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); P = 0\% Test for overall effect: Z = 9.66 (P < 0.00001) Total (95\% CI) $3160 \ 1399 \ 100.0\% \ -0.31 \ [-0.37, -0.25]$ Heterogeneity: Chi ² = 1.66, df = 2 (P = 0.16); P = 0\% | Test for overall effect: | Z = 3.40 |) (P = 1 | 0.0007) | | | | | | |
| 3.1.2 5 mg Berenbaum 2020 -0.9 1.01 284 -0.72 1.01 141 9.4% -0.18 [-0.38, 0.02] Brown 2012 -0.86 0.92 172 -0.51 0.92 57 5.1% -0.35 [-0.63, 0.07] Brown 2013 -0.78 0.87 154 -0.34 0.87 51 5.1% -0.44 [-0.72, -0.16] Ekman 2014A -0.87 1 206 -0.53 1.01 104 6.9% -0.34 [-0.58, -0.10] Schnitzer 2020 -0.9 1.17 233 -0.65 1.17 116 5.7% -0.25 [-0.51, 0.01] Spierings 2013 -0.9 0.89 161 -0.52 0.95 71 5.7% -0.38 [-0.64, 0.12] Subtotal (95% CI) 1421 645 45.0% -0.31 [-0.41, -0.22] Heterogeneity: Chi ² = 3.10, df = 6 (P = 0.80); $l^2 = 0\%$ Test for overall effect: Z = 6.60 (P < 0.00001) 3.1.3 10 mg Brown 2012 -1 0.92 174 -0.51 0.92 58 5.2% -0.49 [-0.76, -0.22] Ekman 2014A -0.73 1.01 208 -0.53 1.01 104 6.9% -0.20 [-0.44, 0.04] Ekman 2014A -0.73 1.01 208 -0.53 1.01 104 6.9% -0.20 [-0.44, 0.04] Ekman 2014A -0.73 1.01 208 -0.53 1.01 104 6.9% -0.20 [-0.44, 0.04] Ekman 2014A -0.73 1.01 208 -0.53 1.01 104 6.9% -0.20 [-0.44, 0.04] Ekman 2014B -0.72 1.01 209 -0.39 1 104 7.0% -0.33 [-0.57, -0.98] Subtotal (95% CI) 898 388 29.5% -0.38 [-0.49, -0.26] Heterogeneity: Chi ² = 3.93, df = 4 (P = 0.42); $l^2 = 0\%$ Test for overall effect: Z = 6.67 (P < 0.00001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); $l^2 = 0\%$ Test for overall effect: Z = 9.66 (P < 0.00001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); $l^2 = 0\%$ Test for overall effect: Z = 9.66 (P < 0.00001) Exators uboroup differences: Chi ² = 3.68, df = 2 (P = 0.16), $l^2 = 45.7\%$ | | | 8 | 2.5 | | | | | | |
| Berenbaum 2020 -0.9 1.01 284 -0.72 1.01 141 9.4% -0.18 [-0.38, 0.02] Brown 2012 -0.86 0.92 172 -0.51 0.92 57 5.1% -0.35 [-0.63, -0.07] Brown 2013 -0.78 0.87 154 -0.34 0.87 51 5.1% -0.44 [-0.72, -0.16] Ekman 2014A -0.87 1 206 -0.53 1.01 104 6.9% -0.34 [-0.58, -0.10] Schnitzer 2020 -0.9 1.17 233 -0.65 1.17 116 5.7% -0.25 [-0.51, 0.01] Subtotal (95% CI) 1421 645 45.0% -0.31 [-0.41, -0.22] Heterogeneity: Chi ² = 3.10, df = 6 (P = 0.80); $ ^2 = 0\%$ Test for overall effect: Z = 6.60 (P < 0.00001) 3.1.3 10 mg Brown 2012 -1 0.92 174 -0.51 0.92 58 5.2% -0.49 [-0.76, -0.22] Brown 2013 -0.81 0.88 157 -0.34 0.87 52 5.2% -0.47 [-0.74, -0.20] Ekman 2014A -0.73 1.01 208 -0.53 1.01 104 6.9% -0.23 [-0.44, 0.04] Ekman 2014B -0.72 1.01 209 -0.39 1 104 7.0% -0.33 [-0.57, -0.29] Subtotal (95% CI) 898 388 29.5% -0.38 [-0.49, -0.26] Heterogeneity: Chi ² = 3.93, df = 4 (P = 0.42); $ ^2 = 0\%$ Test for overall effect: Z = 6.67 (P < 0.00001) Total (95% CI) 3160 139 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); $ ^2 = 0\%$ Test for overall effect: Z = 9.66 (P < 0.00001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 3.93, df = 4 (P = 0.42); $ ^2 = 0\%$ Test for overall effect: Z = 9.66 (P < 0.00001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); $ ^2 = 0\%$ Test for overall effect: Z = 9.66 (P < 0.00001) Fast for suboroup differences: Chi ² = 3.68, df = 2 (P = 0.16), $ ^2 = 45.7\%$ | 3.1.2 5 mg | | | | | | | | | |
| Brown 2012 -0.86 0.92 172 -0.51 0.92 57 5.1% -0.35 [-0.63, -0.07] Brown 2013 -0.78 0.87 154 -0.34 0.87 51 5.1% -0.34 [-0.72, -0.16] Ekman 2014A -0.87 1 206 -0.53 1.01 104 6.9% -0.34 [-0.58, -0.10] Ekman 2014B -0.73 1.02 211 -0.99 1 105 7.0% -0.34 [-0.58, -0.10] Schnitzer 2020 -0.9 1.17 233 -0.65 1.17 116 5.7% -0.25 [-0.51, 0.01] Spierings 2013 -0.9 0.89 161 -0.52 0.95 71 5.7% -0.38 [-0.64, -0.12] Subtotal (95% Cl) 1421 645 45.0% -0.31 [-0.41, -0.22] Heterogeneity: Ch ² = 3.10, df = 6 (P = 0.80); l ² = 0% Test for overall effect: Z = 6.60 (P < 0.00001) Situatal (95% Cl) 898 157 -0.34 0.87 52 5.2% -0.49 [-0.76, -0.22] Brown 2013 -0.81 0.88 157 -0.34 0.87 52 5.2% -0.47 [-0.74, -0.20] Ekman 2014A -0.73 1.01 208 -0.53 1.01 104 6.9% -0.20 [-0.44, 0.04] Ekman 2014B -0.72 1.01 209 -0.39 1 104 7.0% -0.33 [-0.57, -0.09] Spierings 2013 -1 0.98 150 -0.52 0.95 70 5.3% -0.48 [-0.49, -0.26] Heterogeneity: Ch ² = 3.93, df = 4 (P = 0.42); l ² = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Total (95% Cl) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Ch ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Total (95% Cl) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Ch ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Total (95% Cl) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Ch ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Total (95% Cl) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Ch ² = 3.68 df = 2 (P = 0.16), l ² = 45.7% | Berenbaum 2020 | -0.9 | 1.01 | 284 | -0.72 | 1.01 | 141 | 9.4% | -0.18 [-0.38, 0.02] | |
| Brown 2013 -0.78 0.87 154 -0.34 0.87 51 5.1% -0.44 [-0.72, -0.16] Ekman 2014A -0.87 1 206 -0.53 1.01 104 6.9% -0.34 [-0.58, -0.10] Schnitzer 2020 -0.9 1.17 233 -0.65 1.17 116 5.7% -0.25 [-0.51, 0.01] Spierings 2013 -0.9 0.89 161 -0.52 0.95 71 5.7% -0.38 [-0.64, -0.12] Subtotal (95% CI) 1421 645 45.0% -0.31 [-0.41, -0.22] Heterogeneity: Chi ² = 3.10, df = 6 (P = 0.80); l ² = 0% Test for overall effect: Z = 6.60 (P < 0.00001) 3.1.3 10 mg Brown 2012 -1 0.92 174 -0.51 0.92 58 5.2% -0.49 [-0.76, -0.22] Brown 2013 -0.81 0.88 157 -0.34 0.87 52 5.2% -0.47 [-0.74, -0.20] Ekman 2014A -0.73 1.01 208 -0.53 1.01 104 6.9% -0.20 [-0.44, 0.04] Ekman 2014A -0.73 1.01 208 -0.53 1.01 104 6.9% -0.20 [-0.44, 0.04] Ekman 2014B -0.72 1.01 209 -0.39 1 104 7.0% -0.38 [-0.49, -0.26] Heterogeneity: Chi ² = 3.93, df = 4 (P = 0.42); l ² = 0% Test for overall effect: Z = 9.66 (f = 0.0001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 9.66 (f = 2.00001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 9.66 (f = 2.00001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 9.66 (f = 2.00001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 9.66 (f = 2.00001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 9.66 (f = 2.00001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 9.66 (f = 2.00001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 9.66 (f = 2.00001) | Brown 2012 | -0.86 | 0.92 | 172 | -0.51 | 0.92 | 57 | 5.1% | -0.35 [-0.63, -0.07] | |
| Ekman 2014A -0.87 1 206 -0.53 1.01 104 6.9% -0.34 $[-0.58, -0.10]$ Ekman 2014B -0.73 1.02 211 -0.39 1 105 7.0% -0.34 $[-0.58, -0.10]$ Schnitzer 2020 -0.9 1.17 233 -0.65 1.17 116 5.7% -0.25 $[-0.51, 0.01]$ Spierings 2013 -0.9 0.89 161 -0.52 0.95 71 5.7% -0.38 $[-0.64, -0.12]$ Heterogeneity: Chi ² = 3.10, df = 6 (P = 0.80); l ² = 0% Test for overall effect: Z = 6.60 (P < 0.00001) 3.1.3 10 mg Brown 2012 -1 0.92 174 -0.51 0.92 58 5.2% -0.49 $[-0.76, -0.22]$ Brown 2013 -0.81 0.88 157 -0.34 0.87 52 5.2% -0.47 $[-0.74, -0.20]$ Ekman 2014A -0.73 1.01 208 -0.53 1.01 104 6.9% -0.20 $[-0.44, 0.04]$ Ekman 2014A -0.73 1.01 208 -0.53 1.01 104 6.9% -0.20 $[-0.44, 0.04]$ Ekman 2014A -0.73 1.01 208 -0.52 0.95 70 5.3% -0.48 $[-0.75, -0.21]$ Subtotal (95% CI) 898 388 29.5% -0.38 $[-0.49, -0.26]$ Heterogeneity: Chi ² = 3.93, df = 4 (P = 0.42); l ² = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Total (95% CI) 3160 1399 100.0\% -0.31 $[-0.37, -0.25]$ Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Total (95% CI) 3160 1399 100.0\% -0.31 $[-0.37, -0.25]$ Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Total (95% CI) 3160 1399 100.0\% -0.31 $[-0.37, -0.25]$ Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Favours (banezumab) Favours [blaeebol] | Brown 2013 | -0.78 | 0.87 | 154 | -0.34 | 0.87 | 51 | 5.1% | -0.44 [-0.72, -0.16] | |
| Ekman 2014B -0.73 1.02 211 -0.39 1 105 7.0% -0.34 [-0.58, -0.10] Schnitzer 2020 -0.9 1.17 233 -0.65 1.17 116 5.7% -0.25 [-0.51, 0.01] Spierings 2013 -0.9 0.89 161 -0.52 0.95 71 5.7% -0.38 [-0.64, -0.12] Subtotal (95% CI) 1421 645 45.0% -0.31 [-0.41, -0.22] Heterogeneity: Chi ² = 3.10, df = 6 (P = 0.80); l ² = 0% Test for overall effect: Z = 6.60 (P < 0.00001) 3.1.3 10 mg Brown 2012 -1 0.92 174 -0.51 0.92 58 5.2% -0.49 [-0.76, -0.22] Brown 2013 -0.81 0.88 157 -0.34 0.87 52 5.2% -0.47 [-0.74, -0.20] Ekman 2014A -0.73 1.01 208 -0.53 1.01 104 6.9% -0.20 [-0.44, 0.04] Ekman 2014B -0.72 1.01 209 -0.39 1 104 7.0% -0.33 [-0.57, -0.09] Spierings 2013 -1 0.98 150 -0.52 0.95 70 5.3% -0.48 [-0.75, -0.21] Subtotal (95% CI) 898 388 29.5% -0.38 [-0.49, -0.26] Heterogeneity: Chi ² = 3.93, df = 4 (P = 0.42); l ² = 0% Test for overall effect: Z = 6.47 (P < 0.00001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Fotal (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Favours [Idaezbol] | Ekman 2014A | -0.87 | 1 | 206 | -0.53 | 1.01 | 104 | 6.9% | -0.34 [-0.58, -0.10] | |
| Schnitzer 2020 -0.9 1.17 233 -0.65 1.17 116 5.7% -0.25 [-0.51, 0.01] Spierings 2013 -0.9 0.89 161 -0.52 0.95 71 5.7% -0.38 [-0.64, -0.12] Subtotal (95% CI) 1421 645 45.0% -0.31 [-0.41, -0.22] Heterogeneity: Chi ² = 3.10, df = 6 (P = 0.80); l ² = 0% Test for overall effect: $Z = 6.60 (P < 0.00001)$ 3.1.3 10 mg Brown 2012 -1 0.92 174 -0.51 0.92 58 5.2% -0.49 [-0.76, -0.22] Brown 2013 -0.81 0.88 157 -0.34 0.87 52 5.2% -0.47 [-0.74, -0.20] Ekman 2014A -0.73 1.01 208 -0.53 1.01 104 6.9% -0.20 [-0.44, 0.04] Ekman 2014B -0.72 1.01 209 -0.39 1 104 7.0% -0.33 [-0.57, -0.99] Spierings 2013 -1 0.98 150 -0.52 0.95 70 5.3% -0.48 [-0.75, -0.21] Subtotal (95% CI) 898 388 29.5% -0.38 [-0.49, -0.26] Heterogeneity: Chi ² = 3.93, df = 4 (P = 0.42); l ² = 0% Test for overall effect: $Z = 6.47 (P < 0.00001)$ Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: $Z = 9.66 (P < 0.00001)$ Total (95% CI) 3160 539 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: $Z = 9.66 (P < 0.00001)$ Total (95% CI) 500 0.5 1 Favours [tanezumab] Favours [blacebo] | Ekman 2014B | -0.73 | 1.02 | 211 | -0.39 | 1 | 105 | 7.0% | -0.34 [-0.58, -0.10] | |
| Spierings 2013 -0.9 0.89 161 -0.52 0.95 71 5.7% -0.38 [-0.64, -0.12] Subtotal (95% CI) 1421 645 45.0% -0.31 [-0.41, -0.22] Heterogeneity: Chi ² = 3.10, df = 6 (P = 0.80); l ² = 0% Test for overall effect: Z = 6.60 (P < 0.00001) 3.1.3 10 mg Brown 2012 -1 0.92 174 -0.51 0.92 58 5.2% -0.49 [-0.76, -0.22] Brown 2013 -0.81 0.88 157 -0.34 0.87 52 5.2% -0.47 [-0.74, -0.20] Ekman 2014A -0.73 1.01 208 -0.53 1.01 104 6.9% -0.20 [-0.44, 0.04] Ekman 2014B -0.72 1.01 209 -0.39 1 104 7.0% -0.33 [-0.57, -0.99] Spierings 2013 -1 0.98 150 -0.52 0.95 70 5.3% -0.48 [-0.75, -0.21] Subtotal (95% CI) 898 388 29.5% -0.38 [-0.49, -0.26] Heterogeneity: Chi ² = 3.93, df = 4 (P = 0.42); l ² = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Test for subnorup differences: Chi ² = 3.68, df = 2 (P = 0.16), l ² = 45.7% Fayours [tanezumab] Fayours [blacebo] | Schnitzer 2020 | -0.9 | 1.17 | 233 | -0.65 | 1.17 | 116 | 5.7% | -0.25 [-0.51, 0.01] | |
| Subtotal (95% CI) 1421 645 45.0% -0.31 [-0.41 , -0.22] Heterogeneity: Chi ² = 3.10, df = 6 (P = 0.80); l ² = 0% Test for overall effect: Z = 6.60 (P < 0.00001) | Spierings 2013 | -0.9 | 0.89 | 161 | -0.52 | 0.95 | 71 | 5.7% | -0.38 [-0.64, -0.12] | |
| Heterogeneity: $Ch^{12} = 3.10$, $df = 6$ (P = 0.80); $l^{2} = 0\%$ Test for overall effect: Z = 6.60 (P < 0.00001) 3.1.3 10 mg Brown 2012 -1 0.92 174 -0.51 0.92 58 5.2% -0.49 [-0.76, -0.22] Brown 2013 -0.81 0.88 157 -0.34 0.87 52 5.2% -0.47 [-0.74, -0.20] Ekman 2014A -0.73 1.01 208 -0.53 1.01 104 6.9% -0.20 [-0.44, 0.04] Ekman 2014B -0.72 1.01 209 -0.39 1 104 7.0% -0.33 [-0.57, -0.09] Spierings 2013 -1 0.98 150 -0.52 0.95 70 5.3% -0.48 [-0.75, -0.21] Subtotal (95% CI) 898 388 29.5% -0.38 [-0.49, -0.26] Heterogeneity: Chi ² = 3.93, df = 4 (P = 0.42); l ² = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Test for subgroup differences: Chi ² = 3.68, df = 2 (P = 0.16), l ² = 45.7% Favours [tanezumab] Favours [tanezumab | Subtotal (95% CI) | | | 1421 | | | 645 | 45.0% | -0.31 [-0.41, -0.22] | ◆ |
| Test for overall effect: $Z = 6.60 (P < 0.00001)$ 3.1.3 10 mg Brown 2012 -1 0.92 174 -0.51 0.92 58 5.2% -0.49 [-0.76, -0.22] Brown 2013 -0.81 0.88 157 -0.34 0.87 52 5.2% -0.47 [-0.74, -0.20] Ekman 2014A -0.73 1.01 208 -0.53 1.01 104 6.9% -0.20 [-0.44, 0.04] Ekman 2014B -0.72 1.01 209 -0.39 1 104 7.0% -0.33 [-0.57, -0.09] Spierings 2013 -1 0.98 150 -0.52 0.95 70 5.3% -0.48 [-0.75, -0.21] Subtotal (95% Cl) 898 388 29.5% -0.38 [-0.49, -0.26] Heterogeneity: Chi ² = 3.93, df = 4 (P = 0.42); l ² = 0% Test for overall effect: $Z = 6.47 (P < 0.00001)$ Total (95% Cl) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: $Z = 9.66 (P < 0.00001)$ Test for subgroup differences: Chi ² = 3.68, df = 2 (P = 0.16), l ² = 45.7% Favours [tanezumab] Favours [tanezu | Heterogeneity: Chi ² = | 3.10, df | = 6 (P | = 0.80 | ; l ² = 09 | % | | | | |
| 3.1.3 10 mg Brown 2012 -1 0.92 174 -0.51 0.92 58 5.2% -0.49 [-0.76, -0.22] Brown 2013 -0.81 0.88 157 -0.34 0.87 52 5.2% -0.47 [-0.74, -0.20] Ekman 2014A -0.73 1.01 208 -0.53 1.01 104 6.9% -0.20 [-0.44, 0.04] Ekman 2014B -0.72 1.01 209 -0.39 1 104 7.0% -0.33 [-0.57, -0.09] Spierings 2013 -1 0.98 150 -0.52 0.95 70 5.3% -0.48 [-0.75, -0.21] Subtotal (95% Cl) 898 388 29.5% -0.38 [-0.49, -0.26] Heterogeneity: Chi ² = 3.93, df = 4 (P = 0.42); l ² = 0% Test for overall effect: Z = 6.47 (P < 0.00001) Total (95% Cl) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Test for subgroup differences: Chi ² = 3.68, df = 2 (P = 0.16), l ² = 45.7% Favours [tanezumab] Favours [t | Test for overall effect: | Z = 6.60 |) (P < 1 | 0.0000 | 1) | | | | | |
| 3.1.3 10 mg Brown 2012 -1 0.92 174 -0.51 0.92 58 5.2% -0.49 [-0.76, -0.22] Brown 2013 -0.81 0.88 157 -0.34 0.87 52 5.2% -0.47 [-0.74, -0.20] Ekman 2014A -0.73 1.01 208 -0.53 1.01 104 6.9% -0.20 [-0.44, 0.04] Ekman 2014B -0.72 1.01 209 -0.39 1 104 7.0% -0.33 [-0.57, -0.09] Spierings 2013 -1 0.98 150 -0.52 0.95 70 5.3% -0.48 [-0.75, -0.21] Subtotal (95% Cl) 898 388 29.5% -0.38 [-0.49, -0.26] Heterogeneity: Chi ² = 3.93, df = 4 (P = 0.42); l ² = 0% Test for overall effect: Z = 6.47 (P < 0.00001) Total (95% Cl) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Test for subgroup differences: Chi ² = 3.68, df = 2 (P = 0.16), l ² = 45.7% Favours [tanezumab] Favours [tan | | | • | | | | | | | |
| Brown 2012 -1 0.92 174 -0.51 0.92 58 5.2% -0.49 [-0.76, -0.22] Brown 2013 -0.81 0.88 157 -0.34 0.87 52 5.2% -0.47 [-0.74, -0.20] Ekman 2014A -0.73 1.01 208 -0.53 1.01 104 6.9% -0.20 [-0.44, 0.04] Ekman 2014B -0.72 1.01 209 -0.39 1 104 7.0% -0.33 [-0.57, -0.09] Spierings 2013 -1 0.98 150 -0.52 0.95 70 5.3% -0.48 [-0.75, -0.21] Subtotal (95% CI) 898 388 29.5% -0.38 [-0.49, -0.26] Image: Chi² = 3.93, df = 4 (P = 0.42); l² = 0% Test for overall effect: Z = 6.47 (P < 0.00001) | 3.1.3 10 mg | | | | | | | | | |
| Brown 2013 -0.81 0.88 157 -0.34 0.87 52 5.2% -0.47 [-0.74, -0.20] Ekman 2014A -0.73 1.01 208 -0.53 1.01 104 6.9% -0.20 [-0.44, 0.04] Ekman 2014B -0.72 1.01 209 -0.39 1 104 7.0% -0.33 [-0.57, -0.09] Spierings 2013 -1 0.98 150 -0.52 0.95 70 5.3% -0.48 [-0.75, -0.21] Subtotal (95% CI) 898 388 29.5% -0.38 [-0.49, -0.26] Heterogeneity: Chi ² = 3.93, df = 4 (P = 0.42); l ² = 0% Test for overall effect: Z = 6.47 (P < 0.00001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Test for subaroup differences: Chi ² = 3.68, df = 2 (P = 0.16), l ² = 45.7% Favours [tanezumab] Favours [| Brown 2012 | -1 | 0.92 | 174 | -0.51 | 0.92 | 58 | 5.2% | -0.49 [-0.76, -0.22] | |
| Ekman 2014A -0.73 1.01 208 -0.53 1.01 104 6.9% -0.20 [-0.44, 0.04] Ekman 2014B -0.72 1.01 209 -0.39 1 104 7.0% -0.33 [-0.57, -0.09] Spierings 2013 -1 0.98 150 -0.52 0.95 70 5.3% -0.48 [-0.75, -0.21] Subtotal (95% CI) 898 388 29.5% -0.38 [-0.49, -0.26] Heterogeneity: Chi ² = 3.93, df = 4 (P = 0.42); l ² = 0% Test for overall effect: Z = 6.47 (P < 0.00001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Test for subaroup differences: Chi ² = 3.68, df = 2 (P = 0.16), l ² = 45.7% Favours [tanezumab] Favours [tanezum | Brown 2013 | -0.81 | 0.88 | 157 | -0.34 | 0.87 | 52 | 5.2% | -0.47 [-0.74, -0.20] | |
| Ekman 2014B -0.72 1.01 209 -0.39 1 104 7.0% -0.33 [-0.57, -0.09] Spierings 2013 -1 0.98 150 -0.52 0.95 70 5.3% -0.48 [-0.75, -0.21] Subtotal (95% CI) 898 388 29.5% -0.38 [-0.49, -0.26] Heterogeneity: Chi ² = 3.93, df = 4 (P = 0.42); l ² = 0% Test for overall effect: Z = 6.47 (P < 0.00001) Total (95% CI) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Test for subgroup differences: Chi ² = 3.68, df = 2 (P = 0.16), l ² = 45.7% Favours [tanezumab] Favours [tanezumab] Fa | Ekman 2014A | -0.73 | 1.01 | 208 | -0.53 | 1.01 | 104 | 6.9% | -0.20 [-0.44, 0.04] | |
| Spierings 2013 -1 0.98 150 -0.52 0.95 70 5.3% -0.48 [-0.75, -0.21] Subtotal (95% Cl) 898 388 29.5% -0.38 [-0.49, -0.26] Heterogeneity: Chi ² = 3.93, df = 4 (P = 0.42); l ² = 0% Test for overall effect: Z = 6.47 (P < 0.00001) Total (95% Cl) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Test for subgroup differences: Chi ² = 3.68, df = 2 (P = 0.16), l ² = 45.7% Favours [tanezumab] Favours [t | Ekman 2014B | -0.72 | 1.01 | 209 | -0.39 | 1 | 104 | 7.0% | -0.33 [-0.57, -0.09] | |
| Subtotal (95% Cl) 898 388 29.5% -0.38 [-0.49, -0.26] Heterogeneity: Chi ² = 3.93, df = 4 (P = 0.42); l ² = 0% Test for overall effect: Z = 6.47 (P < 0.00001) | Spierings 2013 | -1 | 0.98 | 150 | -0.52 | 0.95 | 70 | 5.3% | -0.48 [-0.75, -0.21] | |
| Heterogeneity: Chi ² = 3.93, df = 4 (P = 0.42); l ² = 0% Test for overall effect: Z = 6.47 (P < 0.00001) Total (95% Cl) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 9.66 (P < 0.00001) Test for subgroup differences: Chi ² = 3.68, df = 2 (P = 0.16), l ² = 45.7% Favours [tanezumab] Favours [tan | Subtotal (95% CI) | | | 898 | | | 388 | 29.5% | -0.38 [-0.49, -0.26] | ◆ |
| Test for overall effect: Z = 6.47 (P < 0.00001) | Heterogeneity: Chi ² = | 3.93, df | = 4 (P | = 0.42 | ; 1 ² = 09 | % | | | | |
| Total (95% Cl) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% -1 -0.5 0 0.5 1 Test for subgroup differences: Chi ² = 3.68, df = 2 (P = 0.16), l ² = 45.7% Favours [tanezumab] Favours [tanezumab] Favours [tanezumab] | Test for overall effect: | Z = 6.47 | (P <) | 0.0000 | 1) | | | | | |
| Total (95% Cl) 3160 1399 100.0% -0.31 [-0.37, -0.25] Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% -1 -0.5 0 0.5 1 Test for overall effect: Z = 9.66 (P < 0.00001) | | | | | | | | | | 1021 |
| Heterogeneity: Chi ² = 12.96, df = 15 (P = 0.61); l ² = 0% Test for overall effect: Z = 9.66 (P < 0.00001) | Total (95% CI) | | | 3160 | | | 1399 | 100.0% | -0.31 [-0.37, -0.25] | ◆ |
| Test for overall effect: $Z = 9.66 (P < 0.00001)$ -1 -0.5 0 0.5 1 Test for subgroup differences: Chi ² = 3.68. df = 2 (P = 0.16), l ² = 45.7% Favours [tanezumab] Favours [tanezumab] | Heterogeneity: Chi ² = | 12.96. d | f = 15 | (P = 0.0 | 61); l ² = | 0% | | | | |
| Test for subgroup differences: Chi ² = 3.68, df = 2 (P = 0.16), l ² = 45.7% Favours [tanezumab] Favours [clacebo] | Test for overall effect: | Z = 9.66 | 6 (P < 1 | 0.0000 | 1) | 1211/201 | | | | -1 -0.5 0 0.5 1 |
| | Test for subaroup diffe | erences: | Chi ² = | 3.68. 0 | f = 2 (F | P = 0.1 | 6), l ² = | 45.7% | | Favours [tanezumab] Favours [placebo] |

FIGURE 5. Forest plots of the mean change in the patient's global assessment after treatment with tanezumab versus placebo (mean \pm SD). CI indicates confidence interval.

RPOA is characterized by pain, with radiographs showing rapid joint space narrowing as a result of chondrolysis and, subsequently, an osteolytic phase with severe progressive atrophic bone that patients with joint space narrowing of $\geq 2 \text{ mm}$ per year or loss of > 50% of the joint space within 1 year. RPOA is common in the hip and shoulder joints, and the pathogenesis of RPOA is still unclear. In the included studies, RPOA mainly occurred in weight bearing joints, mainly in the hip and knee. It was previously believed that subchondral fractures and crystalinduced arthritis could lead to the occurrence of RPOA, but these associations have not been experimentally confirmed. In a rat medial meniscal tear model, application of tanezumab could significantly improve the gait but could cause damage to the articular cartilage. In subsequent studies, tibial amputation could significantly improve the cartilage destruction caused by tanezumab. These data suggest that the application of tanezumab for analgesia and a secondary increase in weight bearing cause damage to the articular cartilage.⁴³ In addition to tanezumab, another anti-NGF called fulranumab also causes RPOA in patients with OA.44

In general, tanezumab, compared with placebo or NSAIDs, has obvious advantages in the analgesia and functional improvement of OA. Our analysis also shows that 10 mg of tanezumab has a better therapeutic effect than 5 or 2.5 mg. The risk of RPOA events is the highest in the 5 mg group. A small number of patients on 2.5 mg experienced

RPOA events, but this result was not statistically significant compared with placebo. Although the incidence of RPOA in the 10 mg group was not statistically significant compared with that in the control group, this may have been because of the small sample size. In the 10 mg group, there are fewer data on RPOA, and more clinical studies are needed to further verify the experimental results. Therefore, low-dose tanezumab, such as 2.5 mg instead of 5 or 10 mg, should be prioritized in subsequent clinical trials. However, to better use tanezumab to treat OA pain, some experiments are needed to study the mechanism of RPOA. However, this meta-analysis has several limitations. First, most of the follow-up periods of the included studies were relatively short, which created some difficulties in assessing the long-term safety of tanezumab. Second, all included studies received funding from the drug manufacturer, which may have had a certain impact on the results.

CONCLUSIONS

This systematic review identified 8 articles to compare 9 RCTs (10830 patients with OA at the hip or knee joint). Tanezumab reduced pain and improved function in patients with OA. Although tanezumab does not cause SAEs, RPOA occurred in a small number of participants, so more clinical trials are needed to explore its safety. Perhaps in the near future, tanezumab can replace NSAIDs as a new generation of painkillers for the treatment of OA.

| Α | tanezumab | | placebo/M | SAID | | Risk Ratio | Risk | Ratio | | |
|-----------------------------------|--------------|----------|---------------|-------|--------|--------------------|---------------------|--------------|-------------|-----|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% Cl | M-H. Fix | ed. 95% Cl | | |
| Berenbaum 2020 | 10 | 567 | 2 | 282 | 2.0% | 2.49 [0.55, 11.27] | | | | |
| Brown 2012 | 23 | 518 | 3 | 172 | 3.4% | 2.55 [0.77, 8.37] | - | | - | |
| Brown 2013 | 18 | 466 | 5 | 155 | 5.6% | 1.20 [0.45, 3.17] | | | | |
| Ekman 2014A | 29 | 414 | 20 | 414 | 15.1% | 1.45 [0.83, 2.52] | | - | | |
| Ekman 2014B | 18 | 420 | 26 | 420 | 19.6% | 0.69 [0.39, 1.24] | | <u>+</u> | | |
| Schnitzer 2014 | 151 | 1083 | 49 | 539 | 49.2% | 1.53 [1.13, 2.08] | | - | | |
| Schnitzer 2020 | 4 | 464 | 3 | 232 | 3.0% | 0.67 [0.15, 2.95] | | | | |
| Spierings 2013 | 6 | 311 | 2 | 141 | 2.1% | 1.36 [0.28, 6.66] | - | | | |
| Total (95% CI) | | 4243 | | 2355 | 100.0% | 1.36 [1.09, 1.70] | | • | | |
| Total events | 259 | | 110 | | | | | | | |
| Heterogeneity: Chi ² = | 8.38, df = 1 | 7 (P = 0 | .30); 12 = 16 | % | | | | | + | - |
| Test for overall effect: | Z = 2.73 (I | P = 0.00 |)6) | | | 0.01 | 0.1 | 1 | 10 | 100 |
| | | | | | | | Favours [tanezumab] | Favours [pla | cebo/NSAID] | |

| В | tanezur | nab | placebo/N | SAID | | Risk Ratio | | | Risk Ratio | | |
|-----------------------------------|--------------|----------|---------------|-------|--------|--------------------|----------|-----|-----------------|----|-----|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | | M | I-H. Fixed. 95% | CI | |
| Berenbaum 2020 | 17 | 567 | 3 | 282 | 2.4% | 2.82 [0.83, 9.54] | | | + | | |
| Brown 2012 | 10 | 518 | 3 | 172 | 2.6% | 1.11 [0.31, 3.98] | | | | _ | |
| Brown 2013 | 18 | 466 | 6 | 155 | 5.3% | 1.00 [0.40, 2.47] | | | | | |
| Ekman 2014A | 13 | 414 | 13 | 414 | 7.6% | 1.00 [0.47, 2.13] | | | - | | |
| Ekman 2014B | 7 | 420 | 13 | 420 | 7.6% | 0.54 [0.22, 1.34] | | 2.2 | | | |
| NCT02528188 | 131 | 2000 | 46 | 996 | 36.0% | 1.42 [1.02, 1.97] | | | | | |
| Schnitzer 2014 | 90 | 1083 | 43 | 539 | 33.7% | 1.04 [0.74, 1.48] | | | - | | |
| Schnitzer 2020 | 8 | 464 | 4 | 232 | 3.1% | 1.00 [0.30, 3.29] | | | | - | |
| Spierings 2013 | 7 | 311 | 2 | 141 | 1.6% | 1.59 [0.33, 7.54] | | | | | |
| Total (95% CI) | | 6243 | | 3351 | 100.0% | 1.18 [0.97, 1.45] | | | • | | |
| Total events | 301 | | 133 | | | | | | | | |
| Heterogeneity: Chi ² = | 7.07, df = 8 | 8 (P = 0 | .53); 12 = 09 | 6 | | | <u> </u> | | | + | |
| Test for overall effect: | Z = 1.64 (I | P = 0.10 |)) | | | 0. | .01 | 0.1 | 1 | 10 | 100 |

Favours [tanezumab] Favours [placebo/NSAID]

| C | C tanezumab pl | | | | | Risk Ratio | | Risk | Ratio | | |
|-----------------------------------|----------------|----------|---------------------------|-------|--------|----------------------|-------|---------------------|--------------------|-------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% C | | M-H, Fix | ed. 95% Cl | | |
| Berenbaum 2020 | 12 | 567 | 0 | 282 | 19.9% | 12.46 [0.74, 209.62] | | - | • | | |
| NCT02528188 | 14 | 2000 | 0 | 996 | 19.9% | 14.45 [0.86, 241.97] | | | • | | |
| Schnitzer 2014 | 11 | 1083 | 0 | 539 | 19.9% | 11.46 [0.68, 194.06] | | <u> </u> | • | | |
| Schnitzer 2020 | 6 | 464 | 0 | 232 | 19.9% | 6.51 [0.37, 115.13] | | | | _ | |
| Spierings 2013 | 1 | 311 | 0 | 141 | 20.5% | 1.37 [0.06, 33.31] | | | | | |
| Total (95% CI) | | 4425 | | 2190 | 100.0% | 9.20 [2.59, 32.71] | | | | | |
| Total events | 44 | | 0 | | | | | | | | |
| Heterogeneity: Chi ² = | 1.59, df = | 4(P = 0) | .81); l ² = 0% | | | | + | | + + + + | | |
| Test for overall effect: | Z = 3.43 (I | P = 0.00 | 006) | | | | 0.005 | 0.1 | 1 10 | 200 | |
| | | | | | | | | Favours [tanezumab] | Favours [placebo/N | SAID] | |

| D | D tanezumab | | placebo/N | SAID | | Risk Ratio | Risk | Ratio | |
|-----------------------------------|--------------|----------|---------------|-------|--------|--------------------|---------------------|-----------------------|-----|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H. Fixed, 95% Cl | M-H. Fix | ed. 95% Cl | |
| Berenbaum 2020 | 42 | 567 | 19 | 282 | 33.3% | 1.10 [0.65, 1.85] | 1 | - | |
| Brown 2012 | 2 | 518 | 1 | 172 | 2.0% | 0.66 [0.06, 7.28] | | | |
| Brown 2013 | 5 | 466 | 3 | 155 | 5.9% | 0.55 [0.13, 2.29] | | <u> </u> | |
| Ekman 2014A | 1 | 414 | 2 | 414 | 2.6% | 0.50 [0.05, 5.49] | | <u> </u> | |
| Ekman 2014B | 0 | 420 | 3 | 420 | 4.6% | 0.14 [0.01, 2.76] | | | |
| Schnitzer 2014 | 43 | 1083 | 25 | 539 | 43.8% | 0.86 [0.53, 1.39] | - | ⊢ | |
| Schnitzer 2020 | 25 | 464 | 4 | 232 | 7.0% | 3.13 [1.10, 8.87] | | | |
| Spierings 2013 | 2 | 311 | 0 | 141 | 0.9% | 2.28 [0.11, 47.09] | | | - |
| Total (95% CI) | | 4243 | | 2355 | 100.0% | 1.04 [0.77, 1.42] | 14 | • | |
| Total events | 120 | | 57 | | | 101 0 0 | | 1.000 | |
| Heterogeneity: Chi ² = | 8.18, df = 1 | 7 (P = 0 | .32); 2 = 14 | % | | | + | + | |
| Test for overall effect: | Z = 0.28 (I | P = 0.78 | 3) | | | 0.01 | 0.1 | 1 10 | 100 |
| | | | | | | | Favours [tanezumab] | Favours [placebo/NSAI | D] |

FIGURE 6. Forest plots of the included studies comparing patients who discontinued treatment because of adverse events (A), serious adverse events (B), rapid progression of osteoarthritis (C), and total joint replacement (D) in patients who received tanezumab versus placebo/nonsteroidal anti-inflammatory drugs. Cl indicates confidence interval.

REFERENCES

1. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Rheumatol.* 2020;72:220–233.

2. Bowden JL, Hunter DJ, Deveza LA, et al. Core and adjunctive interventions for osteoarthritis: efficacy and

models for implementation. Nat Rev Rheumatol. 2020;16: 434-447.

- Conaghan PG, Cook AD, Hamilton JA, et al. Therapeutic options for targeting inflammatory osteoarthritis pain. *Nat Rev Rheumatol.* 2019;15:355–363.
- Malfait AM, Miller RE, Block JA. Targeting neurotrophic factors: novel approaches to musculoskeletal pain. *Pharmacol Ther.* 2020;211:107553.
- Denk F, Bennett DL, McMahon SB. Nerve growth factor and pain mechanisms. *Annu Rev Neurosci.* 2017;40:307–325.
- Hochberg MC. Serious joint-related adverse events in randomized controlled trials of anti-nerve growth factor monoclonal antibodies. *Osteoarthritis Cartilage*. 2015;23:S18–S21.
- Schnitzer TJ, Marks JA. A systematic review of the efficacy and general safety of antibodies to NGF in the treatment of OA of the hip or knee. *Osteoarthritis Cartilage*. 2015;23(suppl 1): S8–S17.
- Kan SL, Li Y, Ning GZ, et al. Tanezumab for patients with osteoarthritis of the knee: a meta-analysis. *PLoS One*. 2016;11: e0157105.
- Chen J, Li J, Li R, et al. Efficacy and safety of tanezumab on osteoarthritis knee and hip pains: a meta-analysis of randomized controlled trials. *Pain Med.* 2017;18:374–385.
- Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6:e1000097.
- Nuesch E, Trelle S, Reichenbach S, et al. Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study. *BMJ*. 2010;341:c3515.
- 12. Altman RD, Hochberg MC, Moskowitz RW, et al, eds. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. *Arthritis Rheum*. 2000;43:1905–1915.
- Kellgren JH, Lawrence JS. Radiological assessment of osteoarthrosis. Ann Rheum Dis. 1957;16:494–502.
- Higgins JPTTJ, Chandler J, Cumpston M, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available at: http://www. training.cochrane.org/handbook. Accessed July 3, 2020.
- 15. Berenbaum F, Blanco FJ, Guermazi A, et al. Subcutaneous tanezumab for osteoarthritis pain: a 24-week phase 3 study with a 24-week follow up. *Ann Rheum Dis.* 2019;78:262–263.
- Berenbaum F, Langford R, Perrot S, et al. Subcutaneous tanezumab 2.5 MG or 5 MG for patients with osteoarthritis of the knee or hip: onset and maintenance of efficacy over 24 weeks. Osteoarthritis Cartilage. 2020;28:S144–S145.
- Bessette L, Schnitzer T, Khan A, et al. Onset and maintenance of efficacy of subcutaneous tanezumab in patients with moderate to severe osteoarthritis of the knee or hip. *Osteoarthritis Cartilage*. 2019;27:S85–S86.
- Birbara CA, Dabezies EJ, Burr AM, et al. Efficacy and safety of subcutaneous tanezumab in patients with knee or hip osteoarthritis (NCT01089725). *Arthritis Rheum.* 2017:69.
- Ekman E, Gimbel J, Bello A, et al. Efficacy and safety of intravenous tanezumab in osteoarthritis hip and knee pain: comparison to placebo and naproxen in two phase III studies (NCT00830063 & NCT00863304). J Pain. 2011;12:P55.
- Fidelholtz J, Tark M, Spierings E, et al. A phase 3 placebo- and oxycodone-controlled study of tanezumab in adults with osteoarthritis. *Arthritis Rheum*. 2011:63.
- Hochberg MC, Carrino J, Schnitzer T, et al. Subcutaneous tanezumab vs NSAID for the treatment of osteoarthritis: efficacy and general safety results from a randomized, doubleblind, active-controlled, 80-week, phase-3 study. *Arthritis Rheumatol.* 2019:71.
- Hochberg MC, Carrino J, Schnitzer T, et al. Subcutaneous tanezumab versus NSAID for the treatment of osteoarthritis: joint safety events in a randomized, double-blind, activecontrolled, 80-week, phase-3 study. *Arthritis Rheumatol.* 2019:71.
- Nagashima H, Suzuki M, Araki S, et al. Preliminary assessment of the safety and efficacy of tanezumab (PF-04383119) in

Japanese patients with moderate to severe osteoarthritis of the knee. Int J Rheum Dis. 2010;13:161.

- 24. Schnitzer TJ, Easton R, Pang S, et al. Efficacy and safety of subcutaneous tanezumab for the treatment of osteoarthritis of the hip or knee. *Br J Pain*. 2019;13:7.
- 25. Spierings ELH, Fidelholtz J, Wolfram G, et al. Efficacy and safety of tanezumab versus placebo and oxycodone in adults with hip or knee osteoarthritis pain (NCT00985621). *Reg Anesth Pain Med.* 2013:38.
- Tive L, Dabezies EJ, Fountaine RJ, et al. Long-term safety and efficacy of subcutaneous tanezumab in patients with knee or hip osteoarthritis (NCT00994890). *Arthritis Rheum.* 2013;65: S911–S912.
- Lane NE, Schnitzer TJ, Birbara CA, et al. Tanezumab for the treatment of pain from osteoarthritis of the knee. N Engl J Med. 2010;363:1521–1531.
- Nagashima H, Suzuki M, Araki S, et al. Preliminary assessment of the safety and efficacy of tanezumab in Japanese patients with moderate to severe osteoarthritis of the knee: a randomized, double-blind, dose-escalation, placebo-controlled study. *Osteoarthritis Cartilage*. 2011;19:1405–1412.
- 29. Walicke PA, Hefti F, Bales R, et al. First-in-human randomized clinical trials of the safety and efficacy of tanezumab for treatment of chronic knee osteoarthritis pain or acute bunionectomy pain. *Pain Rep.* 2018;3:e653.
- 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: 37–48.
- Brown MT, Herrmann DN, Goldstein M, et al. Nerve safety of tanezumab, a nerve growth factor inhibitor for pain treatment. *J Neurol Sci.* 2014;345:139–147.
- Birbara C, Dabezies EJ, Burr AM, et al. Safety and efficacy of subcutaneous tanezumab in patients with knee or hip osteoarthritis. J Pain Res. 2018;11:151–164.
- 33. 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: 800–810.
- Brown MT, Murphy FT, Radin DM, et al. Tanezumab reduces osteoarthritic knee pain: results of a randomized, double-blind, placebo-controlled phase III trial. J Pain. 2012;13: 790–798.
- Brown MT, Murphy FT, Radin DM, et al. Tanezumab reduces osteoarthritic hip pain: results of a randomized, double-blind, placebo-controlled phase III trial. *Arthritis Rheum*. 2013;65: 1795–1803.
- Ekman EF, Gimbel JS, Bello AE, et al. Efficacy and safety of intravenous tanezumab for the symptomatic treatment of osteoarthritis: 2 randomized controlled trials versus naproxen. *J Rheumatol.* 2014;41:2249–2259.
- NCT. Long term safety and efficacy study of tanezumab in subjects with osteoarthritis of the hip or knee. 2015. Available at: https://clinicaltrialsgov/show/NCT02528188. Accessed July 15, 2020.
- Schnitzer TJ, Ekman EF, Spierings EL, et al. Efficacy and safety of tanezumab monotherapy or combined with non-steroidal antiinflammatory drugs in the treatment of knee or hip osteoarthritis pain. *Ann Rheum Dis.* 2015;74:1202–1211.
- 39. Schnitzer TJ, Khan A, Bessette L, et al. Onset and maintenance of efficacy of subcutaneous tanezumab in patients with moderate to severe osteoarthritis of the knee or hip: a 16-week dose-titration study. *Semin Arthritis Rheum.* 2020;50: 387–393.
- Spierings EL, Fidelholtz J, Wolfram G, et al. A phase III placeboand oxycodone-controlled study of tanezumab in adults with osteoarthritis pain of the hip or knee. *Pain*. 2013;154:1603–1612.
- Lane NE, Webster L, Shiao-Ping L. RN624 (anti-NGF) improves pain and function in subjects with moderate knee osteoarthritis: a phase I study. *Arthritis Rheum*. 2005;52:S461.

- 42. Hochberg MC, Tive LA, Abramson SB, et al. When is osteonecrosis not osteonecrosis? Adjudication of reported serious adverse joint events in the tanezumab clinical development program. *Arthritis Rheumatol.* 2016;68:382–391.
- 43. LaBranche TP, Bendele AM, Omura BC, et al. Nerve growth factor inhibition with tanezumab influences weight-bearing and

subsequent cartilage damage in the rat medial meniscal tear model. Ann Rheum Dis. 2017;76:295-302.

44. Sanga P, Katz N, Polverejan E, et al. Long-term safety and efficacy of fulranumab in patients with moderate-to-severe osteoarthritis pain: a phase II randomized, double-blind, placebo-controlled extension study. *Arthritis Rheumatol.* 2017;69:763–773.