Efficacy and Safety of Anti–Nerve Growth Factor Antibody Therapy for Hip and Knee Osteoarthritis

A Meta-analysis

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Background: The efficacy and safety of anti-nerve growth factor (NGF) antibody therapy used for osteoarthritis (OA) pain are controversial.

Purpose: To evaluate the efficacy and safety of anti-NGF antibody therapy via a meta-analysis of randomized controlled trials (RCTs). **Study Design:** Systematic review; Level of evidence, 1.

Methods: PubMed, the Cochrane Central Register of Controlled Trials, Embase, and the Web of Science databases were searched for RCTs assessing anti-NGF antibody treatments for hip and knee OA. A total of 623 records were retrieved from the databases. A random-effects model was used to assess primary and secondary outcomes. Bias was assessed using the Cochrane Collaboration tool, funnel plots, and the Egger test. Subgroup analyses were used to assess the efficacy and safety of the independent variables. Sensitivity analysis was conducted to evaluate the effectiveness of tanezumab and the effectiveness of anti-NGF antibodies compared to active comparator drugs. We present the effects of dose, administration mode, and treatment duration on the efficacy and safety of anti-NGF antibody therapy.

Results: There were 19 RCTs included in our meta-analysis. Anti-NGF antibody treatment showed significant improvements on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for pain, physical function, and stiffness as well as on a patient global assessment (PGA). The overall standardized mean differences were as follows: WOMAC pain (-0.31 [95% CI, -0.36 to -0.26]; Z = 11.75; P < .001; $l^2 = 38\%$), WOMAC physical function (-0.36 [95% CI, -0.41 to -0.30]; Z = 12.67; P < .001; $l^2 = 44\%$), WOMAC stiffness (-3.59 [95% CI, -4.87 to -2.30]; Z = 5.47; P < .001; $l^2 = 98\%$), and PGA (-0.28 [95% CI, -0.34 to -0.22]; Z = 9.39; P < .001; $l^2 = 50\%$). Anti-NGF antibody treatment resulted in a greater incidence of adverse events (risk ratio, 1.09 [95% CI, 1.06 to 1.12]; Z = 5.60; P < .001; $l^2 = 0\%$). The incidence of serious adverse events was similar between the treatment and control groups (risk ratio, 1.15 [95% CI, 0.98 to 1.34]; Z = 1.71; P = .09; $l^2 = 0\%$).

Conclusion: Anti-NGF antibody treatment significantly relieved pain and improved function in patients with hip and knee OA. However, no conclusion could be drawn regarding the optimal treatment plan for anti-NGF antibodies when all 3 variables (dose, administration mode, and treatment duration) were combined in the analyses.

Keywords: anti-NGF antibody; osteoarthritis; RCTs; meta-analysis

Osteoarthritis (OA) affects approximately 250 million people worldwide and is a major cause of pain and disability among older adults.^{20,22} OA is a burden on both individual persons and developed countries, with an effect representing 1.0% to 2.5% of the average gross domestic product.^{15,20,31}

Joint pain and stiffness are the most common symptoms of OA in patients.²⁰ Most guidelines recommend a combination of nonpharmacological and analgesic treatments for OA symptoms.^{15,21,25} Nonsteroidal anti-inflammatory drugs (NSAIDs) are highly recommended.²⁵ Because NSAIDs may cause side effects, safety is important when choosing treatments for OA.²⁰

Nerve growth factor (NGF) is an essential protein for the growth and maintenance of sympathetic and sensory nerves²⁸ and plays a role in the modulation of nociceptive

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sensitization.¹¹ Inflamed tissues resulting from arthritis increase the expression of NGF, thus increasing pain sensation.^{8,23,42,43} Anti-NGF antibodies have reduced pain-related behaviors in arthritis animal models,⁴² providing support for anti-NGF antibody therapy for OA pain in humans.¹⁶ NGF inhibitors in the advanced phases of development for OA include tanezumab, fasinumab, and fulranumab. Tanezumab is a human immunoglobulin G2 monoclonal anti-NGF antibody that blocks the interaction of NGF with its receptors tropomyosin receptor kinase A (TrkA) and p75.¹ Fasinumab is a fully human high-affinity monoclonal anti-NGF antibody ⁴¹; fasinumab has a subpicomolar binding affinity for NGF and does not detectably bind to most other members of the neurotrophin family, including brain-derived neurotrophic factor and neurotrophin-3.41 Fulranumab is a human recombinant immunoglobulin G2 monoclonal anti-NGF antibody that specifically neutralizes the biological actions of NGF.³²

Although meta-analyses of anti-NGF antibody therapy for relieving OA pain have been published,^{9,36,37,44} the appropriate dose, administration mode, and treatment duration have not been assessed. The purpose of this study was to present a meta-analysis assessing dose, administration mode, and treatment duration on the efficacy and safety of anti-NGF antibodies for the treatment of hip and knee OA.

METHODS

Search Strategy

This meta-analysis was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines,³⁰ and the study protocol was registered with PROSPERO (registration identification CRD42021242967). We searched for relevant double-blind randomized controlled trials (RCTs) in PubMed, Embase, the Web of Science, and the Cochrane Central Register of Controlled Trials databases between inception and March 21, 2021, using a detailed search strategy (Appendix 1). There were no language restrictions.

Inclusion Criteria

The inclusion criteria were as follows: (1) full-text RCT articles; (2) patients with OA of the knee or hip according to the American College of Rheumatology criteria, ranked grade \geq 2 according to the Kellgren-Lawrence classification for OA severity; (3) administration of anti-NGF antibodies at any dose versus a placebo or active comparator drug (if both a placebo and active comparator drug were used, only

the placebo results were included in the analysis); (4) outcomes of the standardized mean difference (SMD) or mean difference between baseline and the endpoint in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; pain, physical function, and/or stiffness subscales) and patient global assessment (PGA) scores; and (5) safety data (including the incidence of adverse events [AEs] and serious AEs [SAEs]).

Data Extraction

There were 2 investigators (Y.G. and Z.H.) who independently extracted data from RCTs including the study name, pain condition, sample size, mean age of participants, percentage of included women, content of the experimental and control interventions, and outcomes. When the same research appeared in different articles, only the most complete set of data was selected. Disagreements were arbitrated by a third investigator (Y.H.). The SMDs for outcomes between baseline and the endpoint were pooled. If the mean, standard deviation (SD), or standard error of the mean were not obtainable from the text, values were extracted from diagrams and tables.

Numeric values that were only available from graphs or charts were extracted using GetData Graph Digitizer (Version 2.26; https://apps.automeris.io/wpd/index.zh_CN.html). When only the standard error of the mean was reported, the SD was estimated using the equation $SD = SE \times \sqrt{n}$, where n is the number of patients. SE,standard error.

Quality and Risk-of-Bias Assessments

The quality of the RCTs was independently evaluated by 2 investigators (Y.G. and Z.H.) using the Cochrane Collaboration tool, funnel plots, and the Egger test for assessing the risk of bias.¹³ A judgment of "yes" indicated a low risk of bias, "no" indicated a high risk of bias, and "unclear" indicated an unclear or unknown risk of bias. When the same research appeared in different articles, only the most complete set of data was selected. The remaining duplicate data were eliminated. Any disagreements regarding data extraction and quality assessment between the 2 investigators were resolved via a consensus or, if necessary, by a third investigator (Y.H.).

Data and Statistical Analyses

The meta-analysis was performed using Review Manager (Version 5.4; Cochrane) and Stata (Version 16.0; Stata-Corp). SMD changes from baseline to the endpoint in WOMAC scores (pain, physical function, and stiffness) and

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PGA scores were determined. Secondary outcomes were the incidences of AEs and SAEs. Control groups used either a placebo or active comparator drug. In studies that included results from both placebos and active comparator drugs, only placebo results were extracted.

We conducted subgroup analyses to assess the effects of anti-NGF antibody dose, administration mode, and treatment duration on efficacy and safety. A sensitivity analysis was performed on RCTs that assessed fixed-dose tanezumab. Data from RCTs comparing anti-NGF antibodies and active comparator drugs were extracted separately for the sensitivity analysis.

Continuous outcomes are presented as SMDs with 95% CIs, and dichotomous data are presented as risk ratios (RRs) with 95% CIs. A random-effects model was used to assess variations in the meta-analysis characteristics. Heterogeneity was determined using the I^2 statistic. The significance of pooled effects was evaluated via the Z test. The threshold of significance was set at P < .05.

RESULTS

Study Characteristics

A total of 623 records were retrieved from the databases. Of these, 47 RCTs met initial eligibility criteria. Ultimately, 19 double-blind $\mathrm{RCTs}^{\$}$ were included in this meta-analysis (Figure 1).

The characteristics of the included RCTs are shown in Table 1. The RCTs were double-blind, parallel-group, and placebo or active comparator drug-controlled studies. In the 19 RCTs, 13 used tanezumab^{||}, 4 used fulranumab,^{23,27,32,33} and 2 used fasinumab.^{10,41} In addition, 10 included only intravenous (IV) injections,[¶] 8 included only subcutaneous (SC) injections,^{3,10,18,23,27,32,33,34} and 1 included both modes.⁴ There were 4 studies that included active comparator drug controls,^{14,18,27,40} and 6 studies reported outcomes at 8 weeks.^{2,4,14,29,40,41}

Most of the RCTs used fixed-dose drugs, but 3 studies used weight-adjusted drugs.^{26,29,41} According to the methods of a previous meta-analysis,⁹ the classification of drug metering in the literature, and a comparison of drug doses in different studies, we divided drug doses into 3 levels. The low-dose subgroup included tanezumab (10 μ g/kg, 25 μ g/kg, and 2.5 mg), fulranumab (1 mg every 4 weeks and 3 mg every 8 weeks), and fasinumab (0.03 mg/kg, 1 mg, and 3 mg). The moderate-dose subgroup included tanezumab (50 μ g/kg and 5 mg), fulranumab (3 mg every 4 weeks and 6 mg every 8 weeks), and fasinumab (0.1 mg/kg and 6 mg). The high-dose subgroup included tanezumab (100 μ g/kg, 200 μ g/kg, and 10 mg), fulranumab (10 mg every 8 weeks), and fasinumab (0.3 mg/kg and 9 mg).



Figure 1. Study selection flowchart. RCT, randomized controlled trial.

Risk of Bias

The assessment of the risk of bias in the RCTs is shown in Figure 2. A total of 7 studies had insufficient information about random sequence generation and allocation concealment, 2,4,6,7,14,40,41 4 lacked information regarding blinding of participants, 4,14,18,40 7 lacked information regarding blinding of outcome assessors, 4,14,18,27,32,33,40 and 5 showed a high risk of bias for incomplete outcome data. 2,4,14,23,27 All RCTs showed a low risk of selective reporting bias. Other biases in the RCTs were unclear (all research was sponsored by pharmaceutical companies).[#] Overall, the quality of the reported trials was high.

WOMAC Pain Score

A total of 17 studies^{**} were assessed to determine anti-NGF antibody treatment effects on WOMAC pain scores (Figure 3).

[§]References 2–7, 10, 14, 18, 23, 26, 27, 29, 32–35, 40, 41.

References 2, 3, 4, 5, 6, 7, 14,18, 26, 29, 34, 35, 40.

[¶] References 2, 5, 6, 7, 14, 26, 29, 35, 40, 41.

[#]References 2–7, 10, 14, 18, 23, 26, 27, 29, 32–35, 40, 41.

^{**}References 2–4, 6, 7, 10, 14, 18, 23, 26, 27, 29, 33–35, 40, 41.

| Lead Author (Year) | Type of OA | Sample Size, n | Female Sex, % | ${\rm Patient}~{\rm Age},^b{\rm y}$ | Outcomes |
|--------------------------------|---------------|-------------------|------------------|---|--|
| Lane ²⁶ (2010) | Knee | 444 | 59.0 | $\begin{array}{l} \label{eq:tau} \mbox{Tanezumab IV (10 $\mu g/kg$): 58.3 ± 8.3 \\ \mbox{Tanezumab IV (25 $\mu g/kg$): 59.9 ± 8.1 \\ \mbox{Tanezumab IV (50 $\mu g/kg$): 60.4 ± 7.7 \\ \mbox{Tanezumab IV (100 $\mu g/kg$): 57.1 ± 8.2 \\ \mbox{Tanezumab IV (200 $\mu g/kg$): 58.4 ± 7.6 \\ \end{array}$ | PGA, WOMAC (pain, physical function, stiffness), AEs, SAEs |
| Nagashima ²⁹ (2011) | Knee | 83 | 68.7 | Placebo: 58.1 ± 7.7 Tanezumab IV (10 μg/kg): 59.3 ± 3.6 Tanezumab IV (25 μg/kg): 57.3 ± 4.7 Tanezumab IV (50 μg/kg): 60.7 ± 6.3 Tanezumab IV (100 μg/kg): 58.1 ± 7.0 Tanezumab IV (200 μg/kg): 60.0 ± 4.2 | WOMAC (pain, physical function, stiffness), AEs, SAEs |
| Brown ⁷ (2012) | Knee | 690 | 60.9 | Tatesbo: 53.4 ± 5.6 Tanezumab IV (2.5 mg q8wk): 60.8 Tanezumab IV (5 mg q8wk): 62.1 Tanezumab IV (10 mg q8wk): 61.4 Placebo: 62.2 | PGA, WOMAC (pain, physical function), AEs, SAEs |
| Brown ⁶ (2013) | Hip | 621 | 61.8 | Tanezumab IV (2.5 mg q8wk): 62.4 Tanezumab IV (5 mg q8wk): 61.8 Tanezumab IV (10 mg q8wk): 63.3 Placebo: 61.9 | PGA, WOMAC (pain, physical function), AEs, SAEs |
| Sanga ³² (2013) | Knee or hip | 466 | 57.5 | Fulranumab SC (1 mg q4wk): 61.2 ± 9.23 Fulranumab SC (3 mg q8wk): 60.5 ± 8.86 Fulranumab SC (3 mg q4wk): 60.8 ± 9.42 Fulranumab SC (6 mg q8wk): 60.7 ± 8.96 Fulranumab SC (10 mg q8wk): 61.4 ± 9.50 Placebo: 61.3 ± 8.26 | AEs, SAEs |
| Spierings ⁴⁰ (2013) | Knee or hip | 610 | 62.5 | Tanezumab IV (5 mg q8wk): 57.8 Tanezumab IV (10 mg q8wk): 57.0 Oxycodone CR (10-40 mg q12 h): 57.6 Placebo: 57.2 | PGA, WOMAC (pain, physical function, stiffness), AEs, SAEs |
| Balanescu ² (2014) | Knee or hip | 604 | 77.6 | Tanezumab IV (2.5 mg q8wk) + DSR oral (75 mg BID): 62.1 Tanezumab IV (5 mg q8wk) + DSR oral (75 mg BID): 62.2 Tanezumab IV (10 mg q8wk) + DSR oral (75 mg BID): 63.1 Placebo + DSR: 62 3 | PGA, WOMAC (pain, physical function), AEs, SAEs |
| Brown ⁵ (2014) | Knee or hip | 219 | 59.4 | Tanezumab IV (5 mg q8wk): 57.8 ± 8.3 Tanezumab IV (10 mg q8wk): 58.0 ± 9.0 Placebo: 56.3 ± 10.2 | AEs, SAEs |
| Ekman ¹⁴ (2014) | Knee or hip | 1668 | 61.9 | Study 1015 • Tanezumab IV (5 mg q8wk): 61.1 ± 10.1 • Tanezumab IV (10 mg q8wk): 61.1 ± 10.3 • Naproxen oral (500 mg BID): 61.4 ± 10.0 • Placebo: 60.9 ± 10.1 Study 1018 • Tanezumab IV (5 mg q8wk): 59.8 ± 9.6 • Tanezumab IV (10 mg q8wk): 59.2 ± 10.3 • Naproxen oral (500 mg BID): 60.3 ± 10.5 • Placebo: 60.1 ± 9.4 | PGA, WOMAC (pain, physical function), AEs, SAEs |
| Tiseo ⁴¹ (2014) | Knee | 215 | 68.8 | Fasinumab IV (0.03 mg/kg): 59.0 ± 9.24 Fasinumab IV (0.1 mg/kg): 60.3 ± 7.55 Fasinumab IV (0.3 mg/kg): 58.8 ± 9.23 Placebo: 59 1 ± 8.84 | WOMAC (pain, physical function), AEs |
| Schnitzer ³⁵ (2015) | Knee or hip | 2700 | 70.5 | Tanezumab IV (5 mg q8wk): 61.9 ± 9.7 Tanezumab IV (10 mg q8wk): 62.0 ± 10.0 Tanezumab IV (5 mg q8wk) + NSAID oral (BID): 61.7 ± 10.2 Tanezumab IV (10 mg q8wk) + NSAID oral (BID): 61.3 ± 10.0 Placebo + NSAID: 61.3 ± 9.3 | PGA, WOMAC (pain, physical function), AEs, SAEs |
| Mayorga ²⁷ (2016) | Knee or hip | 196 | 56.1 | Fulranumab SC (3 mg q4wk): 58.8 ± 9 Fulranumab SC (9 mg q4wk): 58.6 ± 10 Oxycodone CR (BID): 60.9 ± 9 Placebo: 59.2 ± 9 | PGA, WOMAC (pain, physical function, stiffness), AEs, SAEs |

| TABLE 1 | | | | | | | | | | | |
|--------------------|------------|---------------|--|--|--|--|--|--|--|--|--|
| Characteristics of | f Included | $Studies^{a}$ | | | | | | | | | |

| Lead Author (Year) | Type of OA | Sample Size, n | Female Sex, % | Patient Age, ^{b} y | Outcomes |
|--------------------------------|---------------|-------------------|------------------|---|--|
| Sanga ³³ (2017) | Knee or hip | 401 | 59.0 | Fulranumab SC (1 mg q4wk): 60.8 ± 9.19 Fulranumab SC (3 mg q8wk): 60.7 ± 8.80 Fulranumab SC (3 mg q4wk): 60.8 ± 9.67 Fulranumab SC (6 mg q8wk): 60.9 ± 9.33 Fulranumab SC (10 mg q8wk): 62.2 ± 9.59 Placeba: 61.0 ± 8.29 | PGA, WOMAC (pain, physical function), AEs, SAEs |
| Birbara ⁴ (2018) | Knee or hip | 1057 | 66.5 | Tanezumab SC (2.5 mg q8wk): 61.0 Tanezumab SC (5 mg q8wk): 60.3 Tanezumab SC (10 mg q8wk): 58.2 Tanezumab IV (10 mg q8wk): 59.6 Placebo: 61.3 | PGA, WOMAC (pain, physical function), AEs, SAEs |
| Dakin ¹⁰ (2019) | Knee or hip | 419 | 64.6 | Fasinumab SC (1 mg q4wk): 60.7 ± 8.9 Fasinumab SC (3 mg q4wk): 60.7 ± 8.9 Fasinumab SC (6 mg q4wk): 60.1 ± 7.9 Fasinumab SC (9 mg q4wk): 61.5 ± 7.8 Placebo: 60.1 ± 7.2 | WOMAC (pain, physical function), AEs |
| Kelly ²³ (2019) | Knee or hip | 245 | 62.0 | Fulranumab SC (1 mg q4wk): 62.0 ± 10.14 Fulranumab SC (3 mg q4wk): 63.0 ± 9.59 Placebo: 64.4 ± 8.63 | WOMAC (pain), AEs, SAEs |
| Schnitzer ³⁴ (2019) | Knee or hip | 696 | 65.1 | Tanezumab SC (2.5 mg): 60.9 Tanezumab SC (2.5 mg/5 mg): 61.2 Placebo: 60.4 | PGA, WOMAC (pain, physical function), AEs, SAEs |
| Berenbaum ³ (2020) | Knee or hip | 849 | 69.1 | Tanezumab SC (2.5 mg q8wk): 65.2 ± 8.4 Tanezumab SC (5 mg q8wk): 65.2 ± 10.2 Placebo: 64.2 ± 9.6 | PGA, WOMAC (pain, physical function), AEs, SAEs |
| Hochberg ¹⁸ (2021) | Knee or hip | 2996 | 65.2 | Tanezumab SC (2.5 mg q8wk): 60.3 ± 9.2 Tanezumab SC (5 mg q8wk): 61.2 ± 9.6 Open-label NSAID oral: 60.3 ± 9.5 | PGA, WOMAC (pain, physical function), AEs, SAEs |

^{*a*}AE, adverse event; BID, twice a day; CR, controlled release; DSR, diclofenac sustained release; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; PGA, patient global assessment; q12h, once every 12 hours; q4wk, once every 4 weeks; q8wk, once every 8 weeks; SAE, serious adverse event; SC, subcutaneous; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

^{*b*}Data are shown as mean or mean \pm SD.

 TABLE 2

 Subgroup Analysis of WOMAC Pain Scores According to Dose, Administration Mode, and Treatment Duration^a

| Dose/Mode/ Duration | SMD (95% CI) | Z Value | P Value | I ² Value |
|------------------------|--------------------------|------------|---------|-------------------------|
| Low/IV/16 wk | -0.39 (-0.62 to -0.17) | 3.42 | .0006 | 45% |
| Low/IV/8 wk | -0.22 (-0.48 to 0.05) | 1.61 | .11 | 0% |
| Low/SC/24 wk | -0.16 (-0.36 to 0.04) | 1.53 | .13 | NA |
| Low/SC/16 wk | -0.08 (-0.17 to 0.01) | 1.74 | .08 | 0% |
| Low/SC/8 wk | -0.45 (-0.97 to 0.07) | 1.71 | .09 | NA |
| Moderate/IV/16 wk | -0.34 (-0.43 to -0.25) | 7.48 | <.00001 | 0% |
| Moderate/IV/8 wk | -0.40 (-0.53 to -0.27) | 6.17 | <.00001 | 0% |
| Moderate/SC/24 wk | -0.21 (-0.41 to -0.01) | 2.02 | .04 | NA |
| Moderate/SC/16 wk | -0.10 (-0.19 to -0.01) | 2.26 | .02 | 0% |
| Moderate/SC/8 wk | -0.41 (-0.94 to 0.12) | 1.51 | .13 | NA |
| High/IV/16 wk | -0.42 (-0.55 to -0.28) | 5.99 | <.00001 | 55% |
| High/IV/8 wk | -0.40 (-0.53 to -0.28) | 6.38 | <.00001 | 0% |
| High/SC/16 wk | -0.23 (-0.58 to 0.12) | 1.30 | .19 | 20% |
| High/SC/8 wk | -0.31 (-0.36 to -0.26) | 1.68 | .09 | NA |
| | | | | |

^aBolded *P* values indicate statistical significance (P < .05). IV, intravenous; NA, not applicable; SC, subcutaneous; SMD, standardized mean difference; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. The results demonstrated a significant decrease in pain (SMD, -0.31 [95% CI, -0.36 to -0.26]; Z = 11.75; P < .00001; $I^2 = 38\%$).

There were 9 studies that reported only intravenous (IV) administration,^{††} 7 that reported only subcutaneous (SC) administration, ^{3,10,18,23,27,33,34} and 1 that reported both administration modes.⁴ The WOMAC pain score was reported at 8 weeks in 6 studies,^{2,4,14,29,40,41} at 16 weeks in 13 studies,^{‡‡} and at 24 weeks in 1 study.³ To directly compare the effects of dose, administration mode and treatment duration combined on the outcome indicators, we divided the RCTs into 14 subgroups. The results are shown in Table 2 and Appendix 2 (Figure A1). The results of the subgroup analysis showed that the IV administration of a high-dose anti-NGF over a period of 16 weeks significantly improved the WOMAC pain score (SMD= -0.42; [95% CI, -0.55 to -0.28]; Z = 5.99; P < .00001; $I^2 = 55\%$).

Table 1 (continued)

^{††}References 2, 6, 7, 14, 26, 29, 35, 40, 41.

^{‡‡}References 2, 6, 7, 10, 14, 18, 23, 26, 27, 33, 34, 35, 41.



Figure 2. Risk of bias of the included studies. + = low risk; - = high risk; ? = unclear risk.

WOMAC Physical Function Score

A total of 16 studies^{§§} were assessed to determine anti-NGF antibody treatment effects based on the WOMAC physical function score (Figure 4). The overall physical function score significantly improved (SMD, -0.36 [95% CI, -0.41 to -0.30]; Z = 12.67; P < .00001; $I^2 = 44\%$) (Figure 4).

There were 9 studies that reported only IV administration^{||||} 6 that reported only SC administration,^{3,10,18,27,33,34} and 1 that reported both modes.⁴ The WOMAC physical function score was reported at 8 weeks in 6 studies,^{2,4,14,29,40,41} at 16 weeks in 12 studies,^{¶¶} and at 24 weeks in 1 study.³ To directly compare the combined effects of dose, administration mode, and treatment duration on the outcome indicators, we divided the RCTs into 14 subgroups. The results are shown in Table 3 and Appendix 2 (Figure A2). The results of the subgroup analysis showed that IV administration of a moderate dose of anti-NGF antibody treatment over a period of 8 weeks significantly improved the WOMAC physical function score (SMD, -0.46 [95% CI, -0.58 to -0.33]; Z = 7.01; P < .00001; $I^2 = 0\%$).

WOMAC Stiffness Score

A total of 4 studies^{26,27,29,40} assessed anti-NGF antibody treatment on WOMAC stiffness scores (Figure 5). The overall stiffness score significantly improved (SMD, -3.59 [95% CI, -4.87 to -2.30]; Z = 5.47; P < .00001; $I^2 = 98\%$) (Figure 5).

PGA Score

A total of 13 studies^{##} were assessed to determine anti-NGF antibody treatment effects on the PGA score. The overall PGA score significantly improved (SMD, -0.28[95% CI, -0.34 to -0.22]; Z = 9.39; P < .00001; $I^2 = 50\%$) (Figure 6).

There were 7 studies that reported only IV administration, 2,6,7,14,26,35,40 5 that reported only SC administration, 3,18,27,33,34 and 1 that reported both modes.⁴ PGA scores were reported at 8 weeks in 4 studies, 2,4,14,40 at 16 weeks in 10 studies, a and at 24 weeks in 1 study.³ To directly compare the combined effects of dose, administration mode, and treatment duration on the outcome indicators, we divided the RCTs into 14 subgroups. The results are shown in Table 4 and Appendix 2 (Figure A3). The results of the subgroup analysis showed that IV administration of a moderate dose of anti-NGF antibody treatment over a period of 8 weeks significantly improved the PGA score (SMD, -0.45 [95% CI, -0.58 to -0.31]; Z = 6.63; P < .00001; $I^2 = 0\%$).

Adverse Events

AEs were reported in all RCTs.^b Nausea, arthralgia, paresthesia, hypoesthesia, and headache were the most frequently reported AEs in the treatment groups. The overall incidence of patients with AEs was higher in the anti-NGF

^{§§}References 2–4, 6, 7, 10, 14, 18, 26, 27, 29, 33–35, 40, 41.

^{III}References 2, 6, 7, 14, 26, 29, 35, 40, 41.

^{¶¶}References 2, 6, 7, 10, 14, 18, 26, 27, 33, 34, 35, 41.

^{##}References 2–4, 6, 7, 14, 18, 26, 27, 33–35, 40.

^aReferences 2, 6, 7, 14, 18, 26, 27, 33, 34, 35, 40.

^bReferences 2–7, 10, 14, 18, 23, 26, 27, 29, 32–35, 40, 41.

| | Exp | eriment | tal | c | ontrol | | : | Std. Mean Difference | | Std. Mean Difference |
|--|----------|-------------|-------|-------|--------|------------|--------|------------------------|------|--|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | Year | IV, Random, 95% Cl |
| Lane 2010 Tanezumab 10 µg/kg IV [26] | -30.1 | 19.79 | 74 | -16.2 | 20.51 | 14 | 0.7% | -0.69 [-1.27, -0.11] 2 | 2010 | |
| Lane 2010 Tanezumab 25 µg/kg IV [26] | -36 | 19.05 | 75 | -16.2 | 20.51 | 15 | 0.7% | -1.02 [-1.59, -0.44] 2 | 2010 | |
| Lane 2010 Tanezumab 200 µg/kg IV [20] | -39.0 | 19.52 | 72 | -16.2 | 20.51 | 14 | 0.6% | -1.27[-1.01, -0.01] 2 | 2010 | |
| Lane 2010 Tanezumab 50 µg/kg IV [26] | -29 | 20.36 | 72 | -16.2 | 20.51 | 15 | 0.7% | -0.62 [-1.19, -0.06] 2 | 2010 | |
| Nagashima 2011 Tanezumab 25 µg/kg IV [29] | -34.6 | 20.41 | 15 | -23.2 | 21.4 | 3 | 0.2% | -0.53 [-1.78, 0.73] 2 | 2011 | |
| Nagashima 2011 Tanezumab 10 µg/kg IV [29] | -20 | 20.95 | 15 | -23.2 | 21.4 | 2 | 0.1% | 0.14 [-1.33, 1.62] 2 | 2011 | |
| Nagashima 2011 Tanezumab 50 µg/kg IV [29] | -24.8 | 20.41 | 15 | -23.2 | 21.4 | 3 | 0.2% | -0.07 [-1.31, 1.17] 2 | 2011 | · · · · · · · · · · · · · · · · · · · |
| Nagashima 2011 Tanezumab 100 µg/kg IV[29] | -32.6 | 20.44 | 16 | -23.2 | 21.4 | 3 | 0.2% | -0.44 [-1.68, 0.81] 2 | 2011 | |
| Nagashima 2011 Tanezumab 200 µg/kg IV [29] | -42 | 20.65 | 154 | -23.2 | 21.4 | 51 | 0.1% | -0.80 [-2.27, 0.67] 2 | 2011 | |
| Brown 2012 Tanezumab10 mg IV [7] | -3.1 | 2.85 | 154 | -2.4 | 2.85 | 51 | 1.7% | -0.23 [-0.35, 0.09] 2 | 2012 | |
| Brown 2012 Tanezumab 5 mg IV [7] | -3.3 | 2.87 | 156 | -2.4 | 2.85 | 52 | 1.7% | -0.31 [-0.63, 0.00] 2 | 2012 | |
| Spierings 2013 Tanezumab 5 mg IV [40] | -3.58 | 2.79 | 161 | -2.62 | 2.85 | 71 | 2.0% | -0.34 [-0.62, -0.06] 2 | 2013 | |
| Brown 2013 Tanezumab 2.5 mg IV [6] | -2.9 | 2.83 | 151 | -1.62 | 2.85 | 51 | 1.7% | -0.45 [-0.77, -0.13] 2 | 2013 | |
| Brown 2013 Tanezumab 10 mg IV [6] | -3.37 | 3 | 150 | -1.62 | 2.85 | 51 | 1.6% | -0.59 [-0.91, -0.27] 2 | 2013 | |
| Spierings 2013 Tanezumab 10 mg IV [40] | -3.58 | 2.82 | 150 | -2.62 | 2.85 | 70 | 1.9% | -0.34 [-0.62, -0.05] 2 | 2013 | |
| Brown 2013 Lanezumab 5 mg IV [6] | -3.31 | 2.82 | 150 | -1.62 | 2.85 | 10 | 1.7% | -0.60 [-0.92, -0.27] 2 | 2013 | |
| Balanescu Tanezumah 2.5 mg IV+DSR week 8 [2] | -2.0 | 2.01 | 157 | -1.9 | 21 | 51 | 1.7% | -0.36 [-0.69, 0.16] 2 | 2014 | |
| Ekman 2014a Tanezumab 5 mg IV week 8 [14] | -3.57 | 2.87 | 206 | -2.36 | 2.88 | 103 | 2.3% | -0.42 [-0.66, -0.18] 2 | 2014 | |
| Ekman 2014b Tanezumab 5 mg IV week 8 [14] | -3.2 | 2.76 | 211 | -1.99 | 2.89 | 105 | 2.4% | -0.43 [-0.67, -0.19] 2 | 2014 | |
| Balanescu 2014 Tanezumab 2.5 mg IV+DSR [2] | -2.09 | 2.26 | 157 | -1.68 | 2.34 | 51 | 1.7% | -0.18 [-0.50, 0.14] 2 | 2014 | |
| Balanescu Tanezumab 5 mg IV+DSR week 8 [2] | -2.23 | 2.08 | 150 | -1.54 | 2.1 | 51 | 1.7% | -0.33 [-0.65, -0.01] 2 | 2014 | |
| Tiseo 2014 Fasinumab 0.1 mg/kg IV week 8 [41] | -3.4 | 2.54 | 53 | -1.9 | 1.74 | 18 | 0.7% | -0.63 [-1.17, -0.08] 2 | 2014 | |
| Tiseo 2014 Fasinumab 0.03 mg/kg IV [41] | -2.7 | 1.89 | 53 | -2.4 | 2.18 | 18 | 0.8% | -0.15 [-0.69, 0.38] 2 | 2014 | |
| Ekman 2014b Tanezumab 10 mg IV [14] | -3.14 | 2.59 | 207 | -2.23 | 2.59 | 103 | 2.3% | -0.35 [-0.59, -0.11] 2 | 2014 | |
| Tiseo 2014 Fasinumab 0.3 mg/kg IV [41] | -3.2 | 2.24 | 54 | -2.4 | 2.18 | 19 | 0.8% | -0.36 [-0.88, 0.17] 2 | 2014 | |
| Balanescu 2014 Tanezumab 10 mg IV+DSR [2] | -2.25 | 2.29 | 145 | -1.68 | 2.34 | 50 | 1.6% | -0.25 [-0.57, 0.08] 2 | 2014 | |
| Ekman 2014a Tanezumab 10 mg IV week 8 [14] | -3.8 | 2.58 | 207 | -2.36 | 2.88 | 104 | 2.3% | -0.54 [-0.77, -0.30] 2 | 2014 | |
| Ekman 2014b Tanezumab 10 mg IV week 8 [14] | -2.79 | 2.88 | 208 | -1.99 | 2.89 | 104 | 2.4% | -0.28 [-0.51, -0.04] 2 | 2014 | |
| Balanescu Tanezumab 10 mg IV+DSR week 8 [2] | -2.29 | 2.05 | 145 | -1.54 | 2.1 | 51 | 1.7% | -0.36 [-0.68, -0.04] 2 | 2014 | |
| Tiseo 2014 Fasinumab 0.3 mg/kg IV week 8 [41] | -3.5 | 2.42 | 54 | -1.9 | 1.74 | 19 | 0.8% | -0.70 [-1.23, -0.16] 2 | 2014 | |
| Ekman 2014a Tanezumab 5 mg IV [14] | -3.44 | 2.58 | 206 | -2.23 | 2.59 | 104 | 2.3% | -0.47 [-0.71, -0.23] 2 | 2014 | |
| Ekman 2014b Tanezumab 5 mg IV [14] | -2.95 | 3.2 | 211 | -1.81 | 3.18 | 105 | 2.4% | -0.36 [-0.59, -0.12] 2 | 2014 | |
| Balanescu 2014 Tanezumab 5 mg IV+DSR [2] | -2.19 | 2.33 | 150 | -1.68 | 2.34 | 51 | 1.7% | -0.22 [-0.54, 0.10] 2 | 2014 | |
| Schnitzer 2015b Tanezumab 10 mg IV+celecoxib[3 | 5]-2.41 | 2.07 | 254 | -1.47 | 2.56 | 64 | 2.0% | -0.43 [-0.71, -0.15] 2 | 2015 | |
| Schnitzer 2015a Tanezumab 10 mg IV [35] | -2.02 | 2.56 | 288 | -1.44 | 2.52 | 70 | 2.1% | -0.23 [-0.49, 0.03] 2 | 2015 | |
| Schnitzer 2015a Tanezumab 10 mg IV+naproxen[3 | 5]-2.36 | 2.56 | 288 | -1.44 | 2.52 | 71 | 2.1% | -0.36 [-0.62, -0.10] 2 | 2015 | |
| Schnitzer 2015b Tanezumab 10 mg IV [35] | -2.05 | 2.55 | 254 | -1.47 | 2.56 | 64 | 2.0% | -0.23 [-0.50, 0.05] 2 | 2015 | |
| Schnitzer 2015a Tanezumab 5 mg IV [35] | -1.88 | 2.19 | 285 | -1.44 | 2.52 | 71 | 2.1% | -0.19[-0.45, 0.07] 2 | 2015 | |
| Schnitzer 2015b Tanezumab 5 mg IV - 1351 | -2.13 | 2.10 | 256 | -1.44 | 2.52 | 64 | 2.1% | -0.21 [-0.49 0.06] 2 | 2015 | |
| Schnitzer 2015b Tanezumab 5 mg IV+celecoxib [35 | -2.22 | 2.56 | 256 | -1.47 | 2.56 | 64 | 2.0% | -0.29 [-0.57, -0.02] 2 | 2015 | |
| Mayorga 2016 Fulranumab 3 mg SC [27] | -2.78 | 2.49 | 48 | -3.01 | 2.63 | 24 | 0.9% | 0.09 [-0.40, 0.58] 2 | 2016 | |
| Mayorga 2016 Fulranumab 9 mg SC [27] | -3.03 | 2.56 | 50 | -3.01 | 2.63 | 24 | 0.9% | -0.01 [-0.49, 0.48] 2 | 2016 | |
| Sanga 2017 Fulranumab 1 mg SC q4wk [33] | -2.3 | 3.18 | 70 | -2.18 | 4.15 | 12 | 0.6% | -0.04 [-0.65, 0.58] 2 | 2017 | |
| Sanga 2017 Fulranumab 3 mg SC q8wk [33] | -1.98 | 3.49 | 69 | -2.18 | 4.15 | 12 | 0.6% | 0.06 [-0.56, 0.67] 2 | 2017 | |
| Sanga 2017 Fulranumab 3 mg SC q4wk [33] | -2.24 | 3.46 | 60 | -2.18 | 4.15 | 12 | 0.6% | -0.02 [-0.63, 0.60] 2 | 2017 | |
| Sanga 2017 Fulranumab 10 mg SC q8wk[33] | -2.58 | 3.45 | 66 | -2.18 | 4.15 | 11 | 0.6% | -0.11 [-0.75, 0.53] 2 | 2017 | |
| Birbara 2018 Tanezumab 10 mg SC [4] | -3.92 | 2.78 | 86 | -2.73 | 2.21 | 18 | 0.8% | -0.44 [-0.95, 0.07] 2 | 2018 | |
| Birbara 2018 Tanezumab 5 mg SC [4] | -3.8 | 2.7 | 63 | -2.73 | 2.21 | 18 | 0.8% | -0.41 [-0.94, 0.12] 2 | 2018 | |
| Birbara 2018 Tanezumab 10 mg IV [4] | -3.6 | 2.47 | 84 | -2.73 | 2.21 | 18 | 0.8% | -0.36 [-0.87, 0.16] 2 | 2018 | |
| Birbara 2018 Tanezumab 2.5 mg SC [4] | -3.88 | 2.58 | 74 | -2.73 | 2.21 | 18 | 0.8% | -0.45 [-0.97, 0.07] 2 | 2018 | |
| Kelly 2019 Fulranumab 1 mg SC [23] | -2.73 | 4.41 | 81 | -3.07 | 4.32 | 40 | 1.3% | 0.08 [-0.30, 0.46] 2 | 2019 | |
| Dakin 2019 Fasinumab 1 mg SC [10] | -3.5 | 2.1 | 75 | -2.4 | 2.4 | 17 | 0.8% | -0.51 [-1.04, 0.03] 2 | 2019 | |
| Schnitzer 2019 Tanezumah 2.5 mg SC [34] | -3.23 | 3 42 | 231 | -2.4 | 3 46 | 116 | 2.5% | -0.47 [-0.39, 0.10] 2 | 2019 | |
| Dakin 2019 Fasinumab 6 mg SC [10] | -3.1 | 2.3 | 77 | -2.4 | 2.4 | 18 | 0.8% | -0.30 [-0.81, 0.22] 2 | 2019 | |
| Kelly 2019 Fulranumab 3 mg SC [23] | -3.89 | 4.65 | 83 | -3.07 | 4.32 | 41 | 1.3% | -0.18 [-0.55, 0.20] 2 | 2019 | |
| Schnitzer 2019 Tanezumab 2.5/5 mg SC [34] | -3.37 | 3.43 | 233 | -2.64 | 3.46 | 116 | 2.5% | -0.21 [-0.44, 0.01] 2 | 2019 | |
| Dakin 2019 Fasinumab 9 mg SC [10] | -3.8 | 2.5 | 79 | -2.4 | 2.4 | 18 | 0.8% | -0.56 [-1.08, -0.04] 2 | 2019 | |
| Berenbaum 2020 Tanezumab 2.5 mg SC [3] | -2.7 | 2.86 | 283 | -2.24 | 3.02 | 141 | 2.7% | -0.16 [-0.36, 0.04] 2 | 2020 | |
| Berendaum 2020 Tanezumab 5 mg SC [3] Hochberg 2021 Tanezumab 2 5 mg SC [19] | -2.85 | 2.86 | 284 | -2.24 | 3.02 | 141 409 | 2.7% | -0.21 [-0.41, -0.01] 2 | 2020 | |
| Hochberg 2021 Tanezumab 5 mg SC [18] | -3.33 | 3.38 | 998 | -3.07 | 3.46 | 498 | 3.9% | -0.04 [-0.15, 0.06] 2 | 2021 | - |
| the second s | 0.00 | 0.00 | 500 | 0.01 | 0.40 | | 0.070 | 0.00[0.10,0.00] 2 | | . |
| Total (95% CI) | | | 10960 | | | 4163 | 100.0% | -0.31 [-0.36, -0.26] | | • |
| Heterogeneity: Tau ² = 0.01; Chi ² = 109.45, df = 68 (| P = 0.00 | 01); l² = : | 38% | | | | | | _ | -2 -1 0 1 2 |
| Test for overall effect: Z = 11.75 (P < 0.00001) | | | | | | | | | | Favours [experimental] Favours [control] |

Figure 3. Forest plot of changes from baseline to the endpoint for the Western Ontario and McMaster Universities Osteoarthritis Index pain score. DSR, diclofenac sustained release; IV, intravenous; IV, inverse variance; q4wk, once every 4 weeks; q8wk, once every 8 weeks; SC, subcutaneous; Std. Mean Difference, standardized mean difference.

| | Exp | erimen | tal | c | ontrol | | 5 | Std. Mean Difference | | Std. Mean Difference |
|--|-----------|------------|-----------|-------|--------|-------|--------|----------------------|------|--|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% Cl | Year | IV, Random, 95% CI |
| Lane 2010 Tanezumab 50 µg/kg IV [26] | -30.8 | 20.36 | 72 | -15.2 | 19.65 | 15 | 0.8% | -0.76 [-1.33, -0.20] | 2010 | |
| Lane 2010 Tanezumab 10 µg/kg IV [26] | -30.1 | 19.79 | 74 | -15.2 | 19.65 | 14 | 0.7% | -0.75 [-1.33, -0.16] | 2010 | |
| Lane 2010 Tanezumab 25 µg/kg IV [26] | -34.9 | 19.05 | 75 | -15.2 | 19.65 | 15 | 0.8% | -1.02 [-1.60, -0.45] | 2010 | |
| Lane 2010 Tanezumab 200 µg/kg IV [26] | -43.8 | 18.92 | 74 | -15.2 | 19.05 | 14 | 0.7% | -1.32 [-1.92 -0.71] | 2010 | |
| Nagashima 2011 Tanezumab 25 µg/kg IV [29] | -31.4 | 20.95 | 15 | -22.9 | 20.06 | 3 | 0.2% | -0.39 [-1.64, 0.86] | 2010 | · · · · · · · · · · · · · · · · · · · |
| Nagashima 2011 Tanezumab 200 µg/kg IV [29] | -40.3 | 20.87 | 6 | -22.9 | 20.06 | 3 | 0.1% | -0.75 [-2.21, 0.71] | 2011 | · · · · · · · · · · · · · · · · · · · |
| Nagashima 2011 Tanezumab 100 µg/kg IV [29] | -32.1 | 20.56 | 16 | -22.9 | 20.06 | 3 | 0.2% | -0.43 [-1.67, 0.81] | 2011 | · · · · · · · · · · · · · · · · · · · |
| Nagashima 2011 Tanezumab 50 µg/kg IV [29] | -24.3 | 20.95 | 15 | -22.9 | 20.06 | 3 | 0.2% | -0.06 [-1.30, 1.18] | 2011 | |
| Nagashima 2011 Tanezumab 10 µg/kg IV [29] | -18.1 | 21.38 | 15 | -22.9 | 20.06 | 2 | 0.1% | 0.21 [-1.26, 1.69] | 2011 | |
| Brown 2012 Tanezumab 5 mg IV [7] | -3 | 2.75 | 156 | -2 | 2.85 | 52 | 1.8% | -0.36 [-0.67, -0.04] | 2012 | |
| Brown 2012 Tanezumab10 mg IV[7] | -2.8 | 2.85 | 154 | -2 | 2.85 | 51 | 1.8% | -0.28 [-0.60, 0.04] | 2012 | |
| Spierings 2013 Tanezumab 10 mg IV [40] | -3.06 | 2.57 | 150 | -1.91 | 2.00 | 70 | 2.0% | -0.44 [-0.72, -0.15] | 2012 | |
| Brown 2013 Tanezumab 5 mg IV [6] | -2.88 | 2.45 | 150 | -1.39 | 2.36 | 52 | 1.7% | -0.61 [-0.93, -0.29] | 2013 | |
| Spierings 2013 Tanezumab 5 mg IV [40] | -3.05 | 2.54 | 161 | -1.91 | 2.73 | 71 | 2.0% | -0.44 [-0.72, -0.16] | 2013 | |
| Brown 2013 Tanezumab 2.5 mg IV [6] | -2.57 | 2.58 | 151 | -1.39 | 2.36 | 51 | 1.7% | -0.47 [-0.79, -0.14] | 2013 | |
| Brown 2013 Tanezumab 10 mg IV [6] | -3 | 2.62 | 156 | -1.39 | 2.36 | 51 | 1.7% | -0.63 [-0.95, -0.30] | 2013 | |
| Balanescu Tanezumab 2.5 mg IV+DSR week 8 [2] | -1.74 | 2.13 | 157 | -1.46 | 2.1 | 51 | 1.8% | -0.13 [-0.45, 0.18] | 2014 | |
| Tiseo 2014 Fasinumab 0.03 mg/kg IV week 8 [41] | -2.8 | 2.07 | 53 | -1.8 | 1.95 | 18 | 0.8% | -0.48 [-1.03, 0.06] | 2014 | |
| Balanescu Tanezumah 10 mg IV+DSR week 8 [2] | -3.4 | 2.57 | 04 145 | -1.6 | 1.95 | 51 | 1.7% | -0.30 [-0.62 0.02] | 2014 | |
| Ekman 2014a Tanezumab 10 mg IV veek 8 [14] | -3.41 | 2.58 | 206 | -1.94 | 2.58 | 103 | 2.3% | -0.57 [-0.81, -0.33] | 2014 | |
| Ekman 2014b Tanezumab 10 mg IV week 8 [14] | -2.55 | 2.88 | 208 | -1.55 | 2.6 | 104 | 2.4% | -0.36 [-0.59, -0.12] | 2014 | |
| Tiseo 2014 Fasinumab 0.1 mg/kg IV [41] | -3.4 | 2.28 | 53 | -2.3 | 2.3 | 18 | 0.8% | -0.48 [-1.02, 0.06] | 2014 | |
| Ekman 2014b Tanezumab 5 mg IV [14] | -2.68 | 3.05 | 211 | -1.45 | 3.04 | 105 | 2.4% | -0.40 [-0.64, -0.17] | 2014 | _ - _ |
| Balanescu 2014 Tanezumab 5 mg IV+DSR [2] | -2.16 | 2.33 | 150 | -1.53 | 2.34 | 51 | 1.7% | -0.27 [-0.59, 0.05] | 2014 | |
| Ekman 2014a Tanezumab 5 mg IV [14] | -3.09 | 2.73 | 206 | -1.84 | 2.73 | 103 | 2.3% | -0.46 [-0.70, -0.22] | 2014 | |
| Tiseo 2014 Fasinumab 0.1 mg/kg IV week 8 [41] | -3.4 | 2.32 | 53 | -1.8 | 1.95 | 18 | 0.8% | -0.71 [-1.26, -0.16] | 2014 | |
| Ekman 2014a Tanezumab 5 mg IV+DSR week 8 [14] | -2.2 | 2.00 | 206 | -1.40 | 2.1 | 103 | 2.3% | -0.35 [-0.66, -0.03] | 2014 | |
| Ekman 2014b Tanezumab 5 mg IV week 8 [14] | -2.8 | 2.75 | 200 | -1.54 | 2.50 | 105 | 2.3% | -0.49 [-0.73, -0.25] | 2014 | _ |
| Balanescu 2014 Tanezumab 10 mg IV+DSR [2] | -2.23 | 2.29 | 145 | -1.53 | 2.34 | 50 | 1.7% | -0.30 [-0.63, 0.02] | 2014 | |
| Tiseo 2014 Fasinumab 0.3 mg/kg IV [41] | -3.1 | 2.18 | 54 | -2.3 | 2.3 | 19 | 0.9% | -0.36 [-0.88, 0.17] | 2014 | |
| Ekman 2014b Tanezumab 10 mg IV [14] | -2.45 | 3.03 | 208 | -1.45 | 3.04 | 104 | 2.4% | -0.33 [-0.57, -0.09] | 2014 | |
| Tiseo 2014 Fasinumab 0.03 mg/kg IV [41] | -2.9 | 1.78 | 53 | -2.3 | 2.3 | 18 | 0.8% | -0.31 [-0.85, 0.23] | 2014 | |
| Ekman 2014a Tanezumab 10 mg IV [14] | -2.82 | 2.73 | 206 | -1.84 | 2.73 | 103 | 2.4% | -0.36 [-0.60, -0.12] | 2014 | |
| Balanescu 2014 Tanezumab 2.5 mg IV+DSR [2] | -2.05 | 2.26 | 157 | -1.53 | 2.34 | 51 | 1.8% | -0.23 [-0.54, 0.09] | 2014 | |
| Schnitzer 2015a Tanezumab 5 mg IV (135) | -1.86 | 2.53 | 285 | -1.38 | 2.09 | 71 | 2.2% | -0.19[-0.45, 0.07] | 2015 | |
| Schnitzer 2015b Tanezumab 5 mg IV 1351 | -2.05 | 2.4 | 256 | -1.42 | 2.56 | 64 | 2.1% | -0.26 [-0.53, 0.02] | 2015 | |
| Schnitzer 2015b Tanezumab 5 mg IV+celecoxib [35 | -2.22 | 2.56 | 256 | -1.42 | 2.56 | 64 | 2.1% | -0.31 [-0.59, -0.04] | 2015 | |
| Schnitzer 2015a Tanezumab 10 mg IV+naproxen [3 | 5]-2.26 | 2.72 | 288 | -1.38 | 2.69 | 71 | 2.2% | -0.32 [-0.58, -0.06] | 2015 | |
| Schnitzer 2015b Tanezumab 10 mg IV [35] | -2.04 | 2.39 | 254 | -1.42 | 2.56 | 64 | 2.1% | -0.26 [-0.53, 0.02] | 2015 | |
| Schnitzer 2015b Tanezumab 10 mg IV+celecoxib [3 | 5]-2.42 | 2.55 | 254 | -1.42 | 2.56 | 64 | 2.0% | -0.39 [-0.67, -0.12] | 2015 | |
| Schnitzer 2015a Tanezumab 10 mg IV [35] | -1.9 | 2.88 | 288 | -1.38 | 2.69 | 70 | 2.2% | -0.18 [-0.44, 0.08] | 2015 | |
| Mayorga 2016 Fulranumab 9 mg SC [27] | -3.09 | 2.62 | 50 | -2.99 | 2.7 | 24 | 1.0% | -0.04 [-0.52, 0.45] | 2016 | |
| Sanga 2017 Fulranumab 3 mg SC (27) | -2.35 | 3.57 | 69 | -2.99 | 3.15 | 12 | 0.7% | -0.03 [-0.64, 0.58] | 2010 | |
| Sanga 2017 Fulranumab 1 mg SC q4wk [33] | -2.46 | 3.76 | 70 | -2.2 | 3.15 | 12 | 0.7% | -0.07 [-0.68, 0.54] | 2017 | |
| Sanga 2017 Fulranumab 10 mg SC q8wk [33] | -3.43 | 3.49 | 66 | -2.2 | 3.15 | 11 | 0.6% | -0.35 [-0.99, 0.29] | 2017 | |
| Sanga 2017 Fulranumab 3 mg SC q4wk [33] | -2.87 | 3.55 | 68 | -2.2 | 3.15 | 12 | 0.7% | -0.19 [-0.80, 0.42] | 2017 | |
| Sanga 2017 Fulranumab 6 mg SC q8wk [33] | -2.41 | 3.57 | 69 | -2.2 | 3.15 | 12 | 0.7% | -0.06 [-0.67, 0.55] | 2017 | |
| Birbara 2018 Tanezumab 10 mg IV [4] | -3.12 | 2.2 | 84 | -2.24 | 1.95 | 18 | 0.9% | -0.40 [-0.92, 0.11] | 2018 | |
| Birbara 2018 Tanezumab 2.5 mg SC [4] | -3.29 | 2.58 | 74 | -2.24 | 1.95 | 18 | 0.9% | -0.42 [-0.94, 0.10] | 2018 | |
| Birbara 2018 Tanezumab 10 mg SC [4] | -3.51 | 2.7 | 63 | -2.24 | 1.95 | 10 | 0.9% | -0.93 [-1.45, -0.40] | 2018 | |
| Dakin 2019 Fasinumah 3 mg SC [10] | -3.3 | 2.7 | 78 | -2.24 | 2.3 | 17 | 0.9% | -0.52 [-1.05, 0.12] | 2019 | |
| Dakin 2019 Fasinumab 1 mg SC [10] | -3.2 | 2.3 | 75 | -2.1 | 2.3 | 17 | 0.9% | -0.47 [-1.01, 0.06] | 2019 | |
| Schnitzer 2019 Tanezumab 2.5 mg SC [34] | -3.22 | 3.37 | 231 | -2.56 | 3.42 | 116 | 2.5% | -0.19 [-0.42, 0.03] | 2019 | |
| Dakin 2019 Fasinumab 9 mg SC [10] | -3.5 | 2.5 | 80 | -2.1 | 2.3 | 18 | 0.9% | -0.56 [-1.08, -0.05] | 2019 | |
| Schnitzer 2019 Tanezumab 2.5/5 mg SC [34] | -3.45 | 3.31 | 233 | -2.56 | 3.42 | 116 | 2.5% | -0.27 [-0.49, -0.04] | 2019 | |
| Dakin 2019 Fasinumab 6 mg SC [10] | -3 | 2.5 | 76 | -2.1 | 2.3 | 18 | 0.9% | -0.36 [-0.88, 0.15] | 2019 | |
| Berenbaum 2020 Tanezumab 2.5 mg SC [3] | -2.7 | 2.69 | 283 | -2.11 | 2.67 | 141 | 2.7% | -0.22 [-0.42, -0.02] | 2020 | |
| Hochberg 2021 Tapezumab 5 mg SC [3] | -2.02 | 3.03 | 204 | -2.11 | 2.07 | 41 | 2.1% | -0.24 [-0.45, -0.04] | 2020 | - |
| Hochberg 2021 Tanezumab 2.5 mg SC [18] | -3.27 | 3.47 | 1002 | -3.08 | 3.46 | 498 | 3.6% | -0.05 [-0.16, 0.05] | 2021 | -+ |
| | | | | | | | | | | |
| Total (95% CI) | | | 10800 | | | 4078 | 100.0% | -0.36 [-0.41, -0.30] | | |
| Heterogeneity: Tau ² = 0.02; Chi ² = 118.14, df = 66 (| (P < 0.00 | 001); l² = | = 44% | | | | | | | -2 -1 0 1 2 |
| l est for overall effect: Z = 12.67 (P < 0.00001) | | | | | | | | | | Favours [experimental] Favours [control] |

Figure 4. Forest plot of changes from baseline to the endpoint for the Western Ontario and McMaster Universities Osteoarthritis Index physical function score. DSR, diclofenac sustained release; IV, intravenous; IV, inverse variance; q4wk, once every 4 weeks; q8wk, once every 8 weeks; SC, subcutaneous; Std. Mean Difference, standardized mean difference.

 TABLE 3

 Subgroup Analysis of WOMAC Physical Function Scores

 According to Dose, Administration Mode, and Treatment

 Duration^a

| Dose/Mode/ Duration | SMD (95% CI) | Z Value | P Value | I ² Value |
|------------------------|----------------------------------|------------|---------|-------------------------|
| Low/IV/16 wk | -0.37 (-0.60 to -0.14) | 3.12 | .002 | 71% |
| Low/IV/8 wk | -0.22 (-0.48 to 0.05) | 1.61 | .11 | 0% |
| Low/SC/24 wk | -0.22 (-0.42 to -0.02) | 2.12 | .03 | NA |
| Low/SC/16 wk | -0.24 (-0.41 to -0.06) | 2.64 | .008 | 0% |
| Low/SC/8 wk | -0.42 (-0.94 to 0.10) | 1.59 | .11 | NA |
| Moderate/IV/16 wk | -0.36 (-0.45 to -0.27) | 8.01 | <.00001 | 0% |
| Moderate/IV/8 wk | -0.46 (-0.58 to -0.33) | 7.01 | <.00001 | 0% |
| Moderate/SC/24 wk | -0.24 (-0.45 to -0.04) | 2.35 | .02 | NA |
| Moderate/SC/16 wk | -0.13 (-0.22 to -0.03) | 2.70 | .007 | 0% |
| Moderate/SC/8 wk | -0.41 (-0.93 to 0.12) | 1.51 | .13 | NA |
| High/IV/16 wk | -0.44 (-0.59 to -0.30) | 5.95 | <.00001 | 60% |
| High/IV/8 wk | -0.44 (-0.57 to -0.32) | 6.99 | <.00001 | 0% |
| High/SC/16 wk | $-0.30 \; (-0.62 \; to \; 0.02)$ | 1.84 | .07 | 6% |
| High/SC/8 wk | $-0.36\;(-0.41\;to\;-0.30)$ | 3.46 | <.00001 | NA |
| | | | | |

^aBolded *P* values indicate statistical significance (P < .05). IV, intravenous; NA, not applicable; SC, subcutaneous; SMD, standardized mean difference; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

antibody treatment groups than in the control groups. RRs for AEs were significantly increased (RR, 1.09 [95% CI, 1.06-1.12]; Z = 5.60; P < .00001; $I^2 = 0\%$) (Figure 7).

There were 10 studies that reported only IV administration,^c 8 that reported only SC administration,^{3,10,18,23,27,32,33,34} and 1 that reported both modes.⁴ To directly compare the combined effects of dose and administration mode on outcome indicators, we divided the RCTs into 6 subgroups. The results are shown in Table 5 and Appendix 2 (Figure A4). The results of the subgroup analysis showed that IV administration of a low dose of anti-NGF antibodies significantly increased the incidence of AEs (RR, 1.28 [95% CI, 1.05-1.55]; Z = 2.44; P = .01; $I^2 = 0\%$).

Additionally, 17 studies^{*d*} were assessed to determine anti-NGF antibody treatment effects on SAEs. Increased OA, osteonecrosis, and arthralgia were the most commonly reported SAEs in all treatment groups. Compared with the control groups, the incidence of SAEs in the anti-NGF antibody treatment groups did not increase significantly (RR, 1.15 [95% CI, 0.98-1.34]; Z = 1.71; P = .09; $I^2 = 0\%$) (Figure 8).

There were 9 studies that reported only IV administration, 7 that reported only SC administration, and 1 that reported both modes. To directly compare the combined effects of dose and administration mode on the outcome indicators, we divided the RCTs into 6 subgroups. The results are shown in Table 6 and Appendix 2 (Figure A5). The results of the subgroup analysis showed that in all treatment groups, the incidence of SAEs did not significantly increase.

Sensitivity Analysis

A sensitivity analysis was performed on 9 RCTs^{2-7,14,18,35} that assessed fixed-dose tanezumab (Table 7 and Appendix 3). The analysis revealed significant improvements in the overall WOMAC pain score (SMD, -0.27 [95% CI, -0.32 to -0.21]; Z = 9.51; P < .001; $I^2 = 32\%$), WOMAC physical function score (SMD, -0.31 [95% CI, -0.37 to -0.25]; Z = 10.12; P < .001; $I^2 = 42\%$), and PGA score (SMD, -0.24 [95% CI, -0.30 to -0.17]; Z = 7.44; P < .001; $I^2 = 47\%$) (Table 7). The proportion of the fixed-dose tanezumab group that discontinued treatment because of AEs was significantly higher than that of the control group (RR, 1.12 [95% CI, 1.08 to 1.15]; Z = 6.15; P < .001; $I^2 = 0\%$). Compared with the control group, the incidence of SAEs in the fixed-dose tanezumab group did not significantly increase (RR, 1.14 [95% CI, 0.97 to 1.34]; Z = 1.55; P = .12; $I^2 = 0\%$).

A sensitivity analysis of 4 RCTs with active comparator drugs was performed (Appendix 4). There were 2 RCTs^{27,40} that used controlled-release oxycodone and 2 RCTs^{14,18} that used NSAIDs as active comparator drug controls. There were significant improvements in the WOMAC pain score (SMD, -0.21 [95% CI, -0.31 to -0.11]; Z = 3.99; P < .001; $I^2 = 54\%$), WOMAC physical function score (SMD, -0.24) $[95\% \text{ CI}, -0.34 \text{ to } -0.13]; Z = 4.40; P < .001; I^2 = 56\%), \text{ and}$ PGA score (SMD, -0.20 [95% CI, -0.32 to -0.09]; Z = 3.45; $P = .0006; I^2 = 63\%$). The results of the sensitivity analysis showed that there was no significant difference in the rate of treatment discontinuation due to AEs between the Anti-NGF antibody group and the active comparator drugs group (RR, 0.94 [95% CI, 0.85 to 1.04]; Z = 1.14; P = 0.26; $I^2 = 73\%$). Compared to the control group, the incidence of SAEs in the fixed-dose tanezumab group did not significantly increase (RR, 1.20 [95% CI, 0.90 to 1.61]; Z = 1.22; P = .22; $I^2 = 9\%$).

Publication Bias

Asymmetry in the funnel plots indicated a publication bias (Figure 9). The *P* value from the Egger test¹³ was <.001 for the WOMAC pain score, indicating an inflation of SMD values due to publication bias.

DISCUSSION

According to our results, anti-NGF antibody therapy was an effective type of treatment for OA. The pooled results showed a significant reduction in the change in WOMAC pain (SMD, -0.31 [95% CI, -0.36 to -0.26]; Z = 11.75; P < .00001; $I^2 = 38\%$), WOMAC physical function (SMD, -0.36 [95% CI, -0.41 to -0.30]; Z = 12.67; P < .00001; $I^2 = 44\%$), WOMAC stiffness (SMD, -3.59 [95% CI, -4.87 to -2.30]; Z = 5.47; P < .00001; $I^2 = 98\%$), and PGA scores (SMD, -0.28 [95% CI, -0.34 to -0.22]; Z = 9.39; P < .00001; $I^2 = 50\%$). In contrast to good treatment effects, the incidence of AEs also increased (RR, 1.09 [95% CI, 1.06 to 1.12]; Z = 5.60; P < .00001; $I^2 = 0\%$).

There have been reports on the use of the anti-NGF antibodies tanezumab, fulranumab, and fasinumab to treat hip and/or knee OA pain.^{10,18,33} However, there is still

^cReferences 2, 5, 6, 7, 14, 26, 29, 35, 40, 41

^dReferences 2–7, 14, 18, 23, 26, 27, 29, 32–35, 40.

| | Experimental Control | | | | Std. Mean Difference | | Std. Mean Difference | | | |
|---|----------------------|----------|-----------|--------|----------------------|-------|----------------------|-------------------------|------|--|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% C | Year | IV. Random, 95% CI |
| Lane 2010 Tanezumab 25 µg/kg IV [26] | -37.7 | 2 | 75 | -16.3 | 2.4 | 15 | 6.8% | -10.26 [-11.89, -8.63] | 2010 | |
| Lane 2010 Tanezumab 50 µg/kg IV [26] | -34.5 | 2.4 | 72 | -16.3 | 2.4 | 14 | 7.1% | -7.52 [-8.80, -6.23] | 2010 | |
| Lane 2010 Tanezumab 200 µg/kg IV [26] | -47.8 | 2.4 | 72 | -16.3 | 2.4 | 14 | 6.4% | -13.01 [-15.08, -10.94] | 2010 | |
| Lane 2010 Tanezumab 100 µg/kg IV [26] | -42.7 | 2.2 | 74 | -16.3 | 2.4 | 15 | 6.6% | -11.72 [-13.56, -9.87] | 2010 | _ - _ |
| Lane 2010 Tanezumab 10 µg/kg IV [26] | -33.5 | 2.3 | 74 | -16.3 | 2.4 | 15 | 7.2% | -7.36 [-8.60, -6.12] | 2010 | |
| Nagashima 2011 Tanezumab 10 µg/kg IV [29] | -21.59 | 21.42 | 15 | -19.69 | 22.94 | 3 | 7.2% | -0.08 [-1.32, 1.16] | 2011 | + |
| Nagashima 2011 Tanezumab 25 µg/kg IV [29] | -39.81 | 21.73 | 15 | -19.69 | 22.94 | 3 | 7.1% | -0.88 [-2.16, 0.41] | 2011 | |
| Nagashima 2011 Tanezumab 50 µg/kg IV [29] | -22.37 | 21.73 | 15 | -19.69 | 22.94 | 3 | 7.2% | -0.12 [-1.36, 1.12] | 2011 | + |
| Nagashima 2011 Tanezumab 100 µg/kg IV[29] | -30.48 | 21.44 | 16 | -19.69 | 22.94 | 3 | 7.2% | -0.48 [-1.72, 0.77] | 2011 | |
| Nagashima 2011 Tanezumab 200 µg/kg IV[29] | -29.36 | 22.22 | 6 | -19.69 | 22.94 | 2 | 6.8% | -0.38 [-2.00, 1.24] | 2011 | |
| Spierings 2013 Tanezumab 5 mg IV [40] | -3.01 | 2.66 | 161 | -1.85 | 2.73 | 71 | 7.6% | -0.43 [-0.71, -0.15] | 2013 | - |
| Spierings 2013 Tanezumab 10 mg IV [40] | -3.27 | 2.69 | 150 | -1.85 | 2.73 | 70 | 7.6% | -0.52 [-0.81, -0.24] | 2013 | - |
| Mayorga 2016 Fulranumab 3 mg SC [27] | -3.39 | 2.77 | 48 | -3.06 | 2.91 | 24 | 7.6% | -0.12 [-0.61, 0.37] | 2016 | + |
| Mayorga 2016 Fulranumab 9 mg SC [27] | -3.05 | 2.76 | 50 | -3.06 | 2.91 | 24 | 7.6% | 0.00 [-0.48, 0.49] | 2016 | + |
| Total (95% CI) | | | 843 | | | 276 | 100.0% | -3.59 [-4.872.30] | | ◆ |
| Heterogeneity: $Tau^2 = 5.60$: Chi ² = 640.60, df = | = 13 (P | < 0.000 |)1): 2 = | 98% | | | | | | |
| Test for overall effect: $7 = 5.47$ (P < 0.0001) | 10 (1 | - 0.0000 | ,,,, | 0070 | | | | | | -10 -5 0 5 10 |
| 103(10) 010141 01002 2 - 0.47 (F < 0.00001) | | | | | | | | | | Favours [experimental] Favours [control] |

Figure 5. Forest plot of changes from baseline to the endpoint for the Western Ontario and McMaster Universities Osteoarthritis Index–stiffness score.

| | Exc | periment | al | c | ontrol | | : | Std. Mean Difference | | Std. Mean Difference |
|--|----------|------------------------|----------|-------|--------|-------|--------|----------------------|------|--|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV. Random, 95% Cl | Year | IV. Random, 95% Cl |
| Lane 2010 Tanezumab 50 µg/kg IV[26] | -17.5 | 14.42 | 72 | -9.2 | 15.38 | 15 | 0.9% | -0.56 [-1.13, -0.00] | 2010 | |
| Lane 2010 Tanezumab 100 µg/kg IV [26] | -23.7 | 13.76 | 74 | -9.2 | 15.38 | 14 | 0.8% | -1.03 [-1.62, -0.43] | 2010 | · · · · · · · · · · · · · · · · · · · |
| Lane 2010 Tanezumab 200 µg/kg IV [26] | -21 | 14.42 | 72 | -9.2 | 15.38 | 15 | 0.9% | -0.80 [-1.37, -0.23] | 2010 | |
| Lane 2010 Tanezumab 10 µg/kg IV[26] | -16.3 | 14.62 | 74 | -9.2 | 15.38 | 14 | 0.8% | -0.48 [-1.05, 0.10] | 2010 | |
| Lane 2010 Tanezumab 25 µg/kg IV[26] | -23.6 | 13.86 | 75 | -9.2 | 15.38 | 15 | 0.8% | -1.01 [-1.59, -0.44] | 2010 | |
| Brown 2012 Tanezumab 5 mg IV [7] | -0.9 | 0.87 | 156 | -0.5 | 0.74 | 52 | 1.9% | -0.47 [-0.79, -0.16] | 2012 | |
| Brown 2012 Tanezumab10 mg IV[7] | -1 | 0.74 | 154 | -0.5 | 0.74 | 51 | 1.9% | -0.67 [-1.00, -0.35] | 2012 | |
| Brown 2012 Tanezumab 2.5 mg IV [7] | -0.8 | 0.74 | 154 | -0.5 | 0.74 | 51 | 1.9% | -0.40 [-0.72, -0.08] | 2012 | |
| Brown 2013 Tanezumab 5 mg IV [6] | -0.78 | 0.86 | 150 | -0.34 | 0.74 | 52 | 1.9% | -0.53 [-0.85, -0.21] | 2013 | |
| Spierings 2013 Tanezumab 5 mg IV [40] | -0.9 | 0.89 | 161 | -0.52 | 0.95 | 71 | 2.2% | -0.42 [-0.70, -0.13] | 2013 | |
| Spierings 2013 Tanezumab 10 mg IV[40] | -1 | 0.99 | 150 | -0.52 | 0.95 | 70 | 2.2% | -0.49 [-0.78, -0.20] | 2013 | |
| Brown 2013 Tanezumab 10 mg IV [6] | -0.81 | 0.87 | 156 | -0.34 | 0.74 | 51 | 1.9% | -0.56 [-0.88, -0.24] | 2013 | |
| Brown 2013 Tanezumab 2.5 mg IV [6] | -0.66 | 0.86 | 151 | -0.34 | 0.74 | 51 | 1.9% | -0.38 [-0.70, -0.06] | 2013 | |
| Ekman 2014a Tanezumab 5 mg IV [14] | -0.87 | 1 | 205 | -0.53 | 1 | 103 | 2.6% | -0.34 [-0.58, -0.10] | 2014 | |
| Ekman 2014b Tanezumab 5 mg IV [14] | -0.73 | 1.02 | 211 | -0.39 | 1.01 | 105 | 2.6% | -0.33 [-0.57, -0.10] | 2014 | |
| Balanescu 2014 Tanezumab 5 mg IV+DSR [2] | -0.52 | 0.86 | 150 | -0.34 | 0.86 | 51 | 1.9% | -0.21 [-0.53, 0.11] | 2014 | |
| Balanescu Tanezumab 5 mg IV+DSR week 8[2] | -0.65 | 0.86 | 150 | -0.32 | 0.86 | 51 | 1.9% | -0.38 [-0.70, -0.06] | 2014 | |
| Ekman 2014a Tanezumab 5 mg IV week 8[14] | -0.95 | 0.86 | 205 | -0.52 | 0.86 | 103 | 2.6% | -0.50 [-0.74, -0.26] | 2014 | |
| Ekman 2014b Tanezumab 5 mg IV week 8 [14] | -0.87 | 0.87 | 211 | -0.43 | 1.16 | 105 | 2.6% | -0.45 [-0.69, -0.21] | 2014 | |
| Balanescu 2014 Tanezumab 10 mg IV+DSR[2] | -0.58 | 0.84 | 145 | -0.34 | 0.86 | 50 | 1.9% | -0.28 [-0.61, 0.04] | 2014 | |
| Ekman 2014a Tanezumab 10 mg IV [14] | -0.73 | 1.01 | 207 | -0.53 | 1 | 103 | 2.6% | -0.20 [-0.44, 0.04] | 2014 | |
| Ekman 2014b Tanezumab 10 mg IV [14] | -0.72 | 1.01 | 208 | -0.39 | 1.01 | 104 | 2.6% | -0.33 [-0.56, -0.09] | 2014 | |
| Ekman 2014a Tanezumab 10 mg IV week 8 [14] | -0.96 | 0.86 | 207 | -0.52 | 0.86 | 103 | 2.6% | -0.51 [-0.75, -0.27] | 2014 | |
| Ekman 2014b Tanezumab 10 mg IV week 8 [14] | -0.79 | 0.87 | 208 | -0.43 | 1.16 | 104 | 2.6% | -0.37 [-0.61, -0.13] | 2014 | |
| Balanescu Tanezumab 10 mg IV+DSR week 8 [2] | -0.62 | 0.84 | 145 | -0.32 | 0.86 | 50 | 1.9% | -0.35 [-0.68, -0.03] | 2014 | |
| Balanescu 2014 Tanezumab 2.5 mg IV+DSR [2] | -0.52 | 0.88 | 157 | -0.34 | 0.86 | 51 | 1.9% | -0.20 [-0.52, 0.11] | 2014 | |
| Balanescu Tanezumab 2.5 mg IV+DSR week 8 [2] | -0.48 | 0.88 | 157 | -0.32 | 0.86 | 51 | 1.9% | -0.18 [-0.50, 0.13] | 2014 | |
| Schnitzer 2015a Tanezumab 5 mg IV[35] | -0.54 | 0.84 | 285 | -0.54 | 0.84 | 71 | 2.4% | 0.00 [-0.26, 0.26] | 2015 | |
| Schnitzer 2015a Tanezumab 5 mg IV+naproxen [35 | -0.62 | 0.84 | 280 | -0.54 | 0.84 | 71 | 2.4% | -0.10 [-0.36, 0.17] | 2015 | |
| Schnitzer 2015b Tanezumab 5 mg IV[35] | -0.67 | 0.8 | 256 | -0.54 | 0.8 | 64 | 2.3% | -0.16 [-0.44, 0.11] | 2015 | |
| Schnitzer 2015b Tanezumab 5 mg IV+celecoxib[35 | -0.74 | 0.8 | 256 | -0.54 | 0.8 | 64 | 2.3% | -0.25 [-0.52, 0.03] | 2015 | |
| Schnitzer 2015a Tanezumab 10 mg IV+naproxen[3 | 5] -0.72 | 0.85 | 288 | -0.54 | 0.84 | 71 | 2.4% | -0.21 [-0.47, 0.05] | 2015 | - |
| Schnitzer 2015b Tanezumab 10 mg IV[35] | -0.59 | 0.8 | 254 | -0.54 | 0.8 | 64 | 2.3% | -0.06 [-0.34, 0.21] | 2015 | |
| Schnitzer 2015b Tanezumab 10 mg IV+celecoxib[3: | 5] -0.75 | 0.8 | 254 | -0.54 | 0.8 | 64 | 2.3% | -0.26 [-0.54, 0.01] | 2015 | |
| Schnitzer 2015a Tanezumab 10 mg IV[35] | -0.61 | 0.85 | 288 | -0.54 | 0.84 | 70 | 2.4% | -0.08 [-0.34, 0.18] | 2015 | |
| Mayorga 2016 Fulranumab 3 mg SC [27] | -3.07 | 2.84 | 48 | -2.84 | 2.98 | 24 | 1.1% | -0.08 [-0.57, 0.41] | 2016 | |
| Mayorga 2016 Fulranumab 9 mg SC [27] | -3.16 | 3.11 | 50 | -2.84 | 2.98 | 24 | 1.1% | -0.10 [-0.59, 0.38] | 2016 | |
| Sanga 2017 Fulranumab 1 mg SC q4wk [33] | -2.2 | 3.6 | 70 | -2.12 | 3.84 | 12 | 0.8% | -0.02 [-0.63, 0.59] | 2017 | |
| Sanga 2017 Fulranumab 3 mg SC q8wk [33] | -2.4 | 3.41 | 69 | -2.12 | 3.84 | 12 | 0.8% | -0.08 [-0.69, 0.53] | 2017 | |
| Sanga 2017 Fulranumab 6 mg SC q8wk [33] | -2.4 | 3.41 | 69 | -2.12 | 3.84 | 12 | 0.8% | -0.08 [-0.69, 0.53] | 2017 | |
| Sanga 2017 Fulranumab 3 mg SC q4wk [33] | -2.52 | 3.3 | 68 | -2.12 | 3.84 | 12 | 0.8% | -0.12 [-0.73, 0.50] | 2017 | |
| Sanga 2017 Fulranumab 10 mg SC q8wk[33] | -2.69 | 3.33 | 66 | -2.12 | 3.84 | 11 | 0.7% | -0.17 [-0.80, 0.47] | 2017 | |
| Birbara 2018 Tanezumab 2.5 mg SC[4] | -1.06 | 0.95 | /4 62 | -0.78 | 0.85 | 18 | 1.0% | -0.30 [-0.81, 0.22] | 2018 | |
| Birbara 2018 Tanezumab 5 mg SC [4] | -0.95 | 1.01 | 03 | -0.78 | 0.85 | 18 | 1.0% | -0.19 [-0.72, 0.33] | 2018 | |
| Birbara 2018 Tanezumab 10 mg IV (+) | -0.9 | 1.01 | 84 | -0.78 | 0.85 | 18 | 1.0% | -0.12 [-0.63, 0.39] | 2018 | |
| Sebaitzer 2010 Tanezumab 2 E mg SC[4] | -1.00 | 1.1 | 221 | -0.76 | 0.00 | 116 | 0.70/ | -0.20 [-0.79, 0.23] | 2010 | |
| Schnitzer 2019 Tanezumab 2.5 mg SC[34] | -0.07 | 1.10 | 231 | -0.65 | 1.17 | 116 | 2.7% | -0.19 [-0.41, 0.03] | 2019 | |
| Berenhaum 2020 Tanezumah 5 mg SC [34] | -0.9 | 1.17 | 200 | -0.03 | 1.17 | 141 | 2.1% | -0.21 [-0.44, 0.01] | 2019 | |
| Berenbaum 2020 Tanezumab 2.5 mg SC [3] | -0.9 | 1.01 | 204 | -0.72 | 1.01 | 141 | 2.5% | -0.10[-0.30, 0.02] | 2020 | -+ |
| Hochberg 2021 Tanezumah 5 mg SC [3] | -0.02 | 1.01 | 203 | -0.94 | 1.01 | 498 | 3.0% | -0.02[-0.30, 0.10] | 2020 | + |
| Hochberg 2021 Tanezumab 3 fing 30 [18] | -0.97 | 1.21 | 1002 | -0.94 | 1.21 | 450 | 3.0% | -0.02 [-0.13, 0.06] | 2021 | + |
| Hochoorg 2021 Tanezuniab 2.5 mg 30 [10] | -0.90 | 1.21 | 1002 | 10.54 | 1.21 | 450 | 3.5% | -0.02 [-0.12, 0.09] | 2021 | |
| Total (95% CI) | | | 10104 | | | 3884 | 100.0% | -0.28 [-0.34, -0.22] | | ♦ |
| Heterogeneity: Tau ² = 0.02: Chi ² = 102.42. df = 51 (| P < 0.00 | 001): I ² = | 50% | | | | | | - | |
| Test for overall effect: Z = 9.39 (P < 0.00001) | | | | | | | | | | -1 -0.5 0 0.5 1 |
| , | | | | | | | | | | Favours (experimental) Favours (control) |

Figure 6. Forest plot of changes from baseline to the endpoint for the patient global assessment score. DSR, diclofenac sustained release; IV, intravenous; IV, inverse variance; q4wk, once every 4 weeks; q8wk, once every 8 weeks; SC, subcutaneous; Std. Mean Difference, standardized mean difference.

| Dose/Mode/Duration | SMD | (95% CI) | Z Value | P Value | I^2 Value |
|------------------------|-------|--------------------|---------|---------|-----------------|
| Low-dose/IV/16 wk | -0.42 | (-0.63 to -0.21) | 3.92 | <.0001 | 32% |
| Low-dose/IV/8 wk | -0.18 | (-0.50 to 0.13) | 1.13 | 0.26 | NA |
| Low-dose/SC/24 wk | -0.1 | (-0.30 to 0.10) | 0.96 | 0.34 | NA |
| Low-dose/SC/16 wk | -0.05 | (-0.14 to 0.05) | 1.02 | 0.31 | 0% |
| Low-dose/SC/8 wk | -0.3 | (-0.81 to 0.22) | 1.13 | 0.26 | NA |
| Moderate-dose/IV/16 wk | -0.27 | (-0.37 to -0.16) | 4.9 | <.00001 | $\mathbf{27\%}$ |
| Moderate-dose/IV/8 wk | -0.45 | (-0.58 to -0.31) | 6.63 | <.00001 | 0% |
| Moderate-dose/SC/24 wk | -0.18 | (-0.38 to 0.02) | 1.72 | 0.08 | NA |
| Moderate-dose/SC/16 wk | -0.06 | (-0.16 to 0.03) | 1.32 | 0.19 | 0% |
| Moderate-dose/SC/8 wk | -0.19 | (-0.72 to 0.33) | 0.73 | 0.48 | NA |
| High-dose/IV/16 wk | -0.34 | (-0.48 to -0.20) | 4.73 | <.00001 | 57% |
| High-dose/IV/8 wk | -0.42 | (-0.54 to -0.29) | 6.34 | <.00001 | 0% |
| High-dose/SC/16 wk | -0.13 | (-0.51 to 0.26) | 0.64 | 0.52 | 0% |
| High-dose/SC/8 wk | -0.28 | (-0.79 to 0.23) | 1.08 | 0.28 | NA |
| | | | | | |

 TABLE 4

 Subgroup Analysis of PGA Scores According to Dose, Administration Mode, and Treatment Duration^a

^{*a*}Bolded P values indicate statistical significance (P < .05). IV, intravenous; NA, not applicable; SC, subcutaneous; SMD, standardized mean difference.

controversy over the effectiveness and safety of this treatment. The optimal dose, administration mode, and treatment duration of each drug have not been determined for this therapy in a clinical setting.

The therapeutic effects and safety of anti-NGF antibody treatment from 19 RCTs were assessed for hip and knee OA pain. Pooled results showed significant reductions in WOMAC scores for pain, physical function, and stiffness as well as in PGA scores. These changes show the clinical significance of anti-NGF antibody treatment for hip and/or knee OA. The results are consistent with previous RCTs indicating that anti-NGF antibody drugs have a significant effect on pain relief and functional improvement in patients with hip and/or knee OA pain. 18,35 It may be that NGF plays a key role in the process of pain generation under chronic pain conditions.^{39,42} Anti-NGF antibodies have the potential to normalize noxious hyperactivity and produce pain relief in a clinical environment.⁴² These drugs may reduce the concentration of free NGF, prevent NGF from binding to TrkA, or prevent TrkA from being activated and thus play a role in pain treatment.^{12,24} Our meta-analysis showed that the incidence of AEs in the treatment group was higher than that in the control group, but the incidence of SAEs was similar between the 2 groups.

We believe that the overall research quality was high. Most of the RCTs in this study were low risk in terms of random sequence generation, allocation of hidden information, blinding, and selective reporting. However, there were 5 high-risk studies in terms of the completeness of the results.^{2,4,14,23,27} All the studies were sponsored by pharmaceutical companies, which could have an effect on the findings. Our results indicate that a large number of unpublished studies and studies reporting nonsignificant results have led to publication bias.

High doses of anti-NGF antibodies improve OA pain but increase the incidence of AEs. Our meta-analysis focused on the effect of dose, administration mode, and treatment duration on the treatment of OA pain. Our subgroup analysis of the effects of the 3 combined variables showed that there was no unique treatment that achieved an optimal therapeutic effect. High doses of anti-NGF antibodies via IV administration over a 16-week treatment period significantly improved pain scores. Moderate doses of anti-NGF antibodies via IV administration over an 8-week treatment period significantly improved physical function scores. Low doses of anti-NGF antibodies via IV administration over a 16-week treatment period significantly improved PGA scores. In general, the IV administration of anti-NGF antibodies was a more effective treatment method compared to SC administration. Low doses of anti-NGF antibodies had the highest incidence of AEs using IV administration. Moderate doses of anti-NGF antibodies had the lowest incidence of AEs using SC administration. The incidence of AEs in all treatment groups was higher than that in the control groups. An indirect comparison of the incidence of AEs in subgroup analyses showed that the incidence of AEs with SC administration was lower than that of the corresponding dose with IV administration. In all treatment groups, the incidence of SAEs was similar to that in the control groups. This finding is consistent with the results of the direct comparison between the IV and SC administrations of tanezumab.⁴

RCTs that assessed the SC administration of tanezumab as a new treatment method^{4,18,33} allowed us to conduct a sensitivity analysis on fixed doses of tanezumab. Results of the analysis showed that tanezumab effectively relieved pain, improved physical function and stiffness, and improved PGA scores. Birbara et al⁴ examined the effects of the IV versus SC administration of tanezumab for the treatment of OA pain. Their results showed that there was no significant difference in the effectiveness of the 2 administration modes. Our sensitivity analysis showed that medium- and high-dose tanezumab had the most significant improvement in pain with IV administration. High doses of tanezumab had the most significant improvement in physical function with SC administration, and high doses of tanezumab had the most significant improvement in PGA scores with IV administration. Although our results

| | Experin | nental | Contr | ol | | Risk Ratio | | Risk Ratio |
|--|-----------------|-------------------------|--------|-------|--------|---------------------|------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | Year | M-H, Random, 95% Cl |
| Lane 2010 Tanezumab 100 µg/kg IV [26] | 51 | 74 | 8 | 15 | 0.3% | 1.29 [0.79, 2.13] | 2010 | |
| Lane 2010 Tanezumab 200 µg/kg IV [26] | 58 | 74 | 9 | 15 | 0.5% | 1.31 [0.85, 2.01] | 2010 | |
| Lane 2010 Tanezumab 25 µg/kg IV [26] | 49 | 74 | 8 | 15 | 0.3% | 1.24 [0.75, 2.05] | 2010 | |
| Lane 2010 Tanezumab 50 µg/kg IV [26] | 44 | 74 | 8 | 15 | 0.3% | 1.11 [0.67, 1.86] | 2010 | |
| Lane 2010 Tanezumab 10 µg/kg IV [26] | 51 | /4 | 8 | 14 | 0.4% | 1.21 [0.75, 1.95] | 2010 | |
| Nagashima 2011 Tanezumab 10 µg/kg IV [29] | 9 N 9 | 15 | 3 | 3 | 0.3% | 0.00 [0.39, 1.10] | 2011 | |
| Nagashima 2011 Tanezumah 200 ug/kg W122 | 0 6 | 6 | 2 | 4 | 0.1% | 1 33 [0 72 2 44] | 2011 | |
| Nagashima 2011 Tanezumab 25 ug/kg IV [29] | 4 | 15 | 2 | 3 | 0.1% | 0.40 [0.13, 1.28] | 2011 | · · · · · · · · · · · · · · · · · · · |
| Nagashima 2011 Tanezumab 50 µg/kg IV [29] | 9 | 15 | 3 | 3 | 0.3% | 0.68 [0.39, 1.18] | 2011 | |
| Brown 2012 Tanezumab10 mg IV [7] | 104 | 174 | 28 | 58 | 1.0% | 1.24 [0.92, 1.66] | 2012 | + |
| Brown 2012 Tanezumab 2.5 mg IV [7] | 100 | 172 | 27 | 57 | 0.9% | 1.23 [0.91, 1.66] | 2012 | + |
| Brown 2012 Tanezumab 5 mg IV [7] | 95 | 172 | 28 | 57 | 1.0% | 1.12 [0.84, 1.51] | 2012 | - - |
| Sanga 2013 Fulranumab 10 mg SC q8wk [32] | 42 | 78 | 8 | 16 | 0.3% | 1.08 [0.63, 1.83] | 2013 | |
| Sanga 2013 Fulranumab 1 mg SC q4wk [32] | 36 | 77 | 8 | 16 | 0.3% | 0.94 [0.54, 1.61] | 2013 | |
| Sanga 2013 Fulranumab 3 mg SC q4wk [32] | 50 | 79 | 8 | 16 | 0.3% | 1.27 [0.75, 2.12] | 2013 | |
| Sanga 2013 Fulranumab 3 mg SC q8wk [32] | 47 | 76 | 8 | 15 | 0.3% | 1.16 [0.70, 1.92] | 2013 | |
| Sanga 2013 Fulranumab 6 mg SC q8wk [32] | 45 | 78 | 8 | 15 | 0.3% | 1.08 [0.65, 1.80] | 2013 | |
| Brown 2013 Tanezumab 10 mg IV[6] | 89 | 157 | 22 | 51 | 0.7% | 1.31 [0.93, 1.85] | 2013 | |
| Brown 2013 Tanezumab 2.5 mg IV [6] | 90 | 155 | 23 | 52 | 0.8% | 1.31 [0.94, 1.83] | 2013 | |
| Brown 2013 Tanezumab 5 mg IV [6] | 84 | 154 | 23 | 52 | 0.7% | 1.23 [0.88, 1.73] | 2013 | |
| Spierings 2013 Tanezumab 10 mg IV [40] | 61 | 150 | 25 | 70 | 0.6% | 1.14 [0.79, 1.65] | 2013 | |
| Balanescu 2014 Tanezumab 10 mg IV+DSP | 21 71 | 145 | 20 | 50 | 0.7% | 1.27 [0.69, 1.62] | 2013 | |
| Balanescu 2014 Tanezumab 2.5 mg IV+DSR | 2) 71 [2] 73 | 145 | 18 | 51 | 0.5% | 1.44 [0.95, 2.19] | 2014 | |
| Balanescu 2014 Tanezumab 5 mg IV+DSR[2] | 1 72 | 150 | 18 | 51 | 0.5% | 1.36 [0.91, 2.04] | 2014 | |
| Brown 2014 Tanezumab 10 mg IV 15 | 48 | 74 | 20 | 36 | 0.7% | 1.17 [0.83, 1.64] | 2014 | |
| Brown 2014 Tanezumab 5 mg IV [5] | 41 | 73 | 19 | 36 | 0.6% | 1.06 [0.74, 1.54] | 2014 | |
| Ekman 2014a Tanezumab 10 mg IV [14] | 122 | 208 | 50 | 104 | 1.6% | 1.22 [0.97, 1.54] | 2014 | |
| Ekman 2014a Tanezumab 5 mg IV[14] | 107 | 206 | 49 | 104 | 1.4% | 1.10 [0.87, 1.40] | 2014 | - |
| Ekman 2014b Tanezumab 10 mg IV[14] | 101 | 209 | 42 | 104 | 1.1% | 1.20 [0.91, 1.57] | 2014 | |
| Ekman 2014b Tanezumab 5 mg IV[14] | 101 | 211 | 43 | 105 | 1.2% | 1.17 [0.89, 1.53] | 2014 | + |
| Tiseo 2014 Fasinumab 0.03 mg/kg IV[41] | 37 | 56 | 11 | 18 | 0.5% | 1.08 [0.71, 1.63] | 2014 | |
| Tiseo 2014 Fasinumab 0.1 mg/kg IV [41] | 39 | 52 | 12 | 18 | 0.6% | 1.13 [0.78, 1.62] | 2014 | |
| Tiseo 2014 Fasinumab 0.3 mg/kg IV [41] | 39 | 52 | 12 | 19 | 0.6% | 1.19 [0.81, 1.73] | 2014 | |
| Schnitzer 2015 Tanezumab 10 mg IV[35] | 399 | 542 | 91 | 135 | 5.2% | 1.09 [0.96, 1.24] | 2015 | Ľ |
| Schnitzer 2015 Tanezumab 10 mg IV +NSAIL | 0[35] 400 | 542 | 91 | 135 | 5.2% | 1.09 [0.96, 1.24] | 2015 | |
| Schnitzer 2015 Tanezumab 5 mg IV (33) | 405 | 541 | 91 | 134 | 5.3% | 1.10 [0.97, 1.25] | 2015 | |
| Mayoraa 2016 Eulranumah 2 ma SC [27] | 30 | 330 | 10 | 135 | 0.9% | 0.92 [0.61, 1.15] | 2015 | |
| Mayorga 2016 Fulranumab 9 mg SC [27] | 41 | 40 50 | 10 | 24 | 1.4% | 1 04 [0 81 1 32] | 2016 | |
| Sanga 2017 Fulranumab 10 mg SC g8wk [33] | 68 | 78 | 14 | 16 | 2.0% | 1.00 [0.81, 1.22] | 2017 | <u> </u> |
| Sanga 2017 Fulranumab 1 mg SC g4wk [33] | 66 | 77 | 14 | 15 | 3.2% | 0.92 [0.78, 1.08] | 2017 | |
| Sanga 2017 Fulranumab 3 mg SC q4wk [33] | 74 | 79 | 14 | 16 | 2.2% | 1.07 [0.88, 1.30] | 2017 | - - |
| Sanga 2017 Fulranumab 3 mg SC q8wk [33] | 72 | 76 | 13 | 15 | 2.0% | 1.09 [0.89, 1.34] | 2017 | + |
| Sanga 2017 Fulranumab 6 mg SC q8wk [33] | 72 | 78 | 14 | 16 | 2.2% | 1.05 [0.87, 1.28] | 2017 | |
| Birbara 2018 Tanezumab 10 mg SC ^[4] | 36 | 86 | 10 | 18 | 0.4% | 0.75 [0.47, 1.22] | 2018 | |
| Birbara 2018 Tanezumab 2.5 mg SC ^[4] | 35 | 74 | 9 | 18 | 0.3% | 0.95 [0.56, 1.59] | 2018 | |
| Birbara 2018 Tanezumab 5 mg SC [4] | 31 | 63 | 9 | 18 | 0.3% | 0.98 [0.58, 1.66] | 2018 | |
| Birbara 2018 Tanezumab 10 mg IV[4] | 44 | 84 | 9 | 18 | 0.3% | 1.05 [0.63, 1.74] | 2018 | |
| Dakin 2019 Fasinumab 9 mg SC [10] | 48 | 83 | 11 | 20 | 0.4% | 1.05 [0.68, 1.63] | 2019 | |
| Kelly 2019 Fulranumab 1 mg SC [23] | 62 | 81 | 26 | 41 | 1.2% | 1.21 [0.93, 1.57] | 2019 | |
| Kelly 2019 Fulranumab 3 mg SC [23] | 60 | 83 | 25 | 40 | 1.1% | 1.16 [0.88, 1.52] | 2019 | |
| Schnitzer 2019 Tanezumab 2.5/5 mg SC [34] | 40 | 231 | 10 | 110 | 0.3% | 1.20 [0.74, 2.14] | 2019 | |
| Dakin 2019 Fasinumah 1 mg SC [10] | 54 | 233 | 11 | 21 | 0.3% | 1 21 [0 78 1 88] | 2019 | |
| Dakin 2019 Fasinumab 3 mg SC [10] | 52 | 84 | 11 | 20 | 0.5% | 1.13 [0.73, 1.73] | 2019 | |
| Dakin 2019 Fasinumab 6 mg SC [10] | 55 | 85 | 12 | 21 | 0.5% | 1.13 [0.76, 1.69] | 2019 | |
| Berenbaum 2020 Tanezumab 2.5 mg SC [3] | 184 | 283 | 89 | 141 | 3.6% | 1.03 [0.88, 1.20] | 2020 | + |
| Berenbaum 2020 Tanezumab 5 mg SC [3] | 198 | 284 | 89 | 141 | 3.9% | 1.10 [0.95, 1.28] | 2020 | + |
| Hochberg 2021 Tanezumab 2.5 mg SC [18] | 681 | 1002 | 333 | 498 | 14.9% | 1.02 [0.94, 1.10] | 2021 | + |
| Hochberg 2021 Tanezumab 5 mg SC [18] | 744 | 998 | 333 | 498 | 16.4% | 1.11 [1.04, 1.20] | 2021 | * |
| | | | | | | | | |
| Total (95% CI) | | 10199 | | 3742 | 100.0% | 1.09 [1.06, 1.12] | | ۲ |
| Total events | 6429 | | 2084 | | | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 40.58$, df = | 61 (P = 0.98 | 3); I ² = 0% |) | | | | - | 0.2 0.5 1 2 5 |
| l est for overall effect: $Z = 5.60 (P < 0.00001)$ | | | | | | | | Favours [experimental] Favours [control] |

Figure 7. Forest plot of differences in adverse event rates between the experimental and control groups. DSR, diclofenac sustained release; IV, intravenous; M-H, random Mantel-Haenszel random-effects model; q4wk, once every 4 weeks; q8wk, once every 8 weeks; SC, subcutaneous.

 $\begin{array}{c} {\rm TABLE~5}\\ {\rm Subgroup~Analysis~of~Adverse~Events~According~to~Dose}\\ {\rm and~Administration~Mode}^a \end{array}$

| Dose/Mode | RR (95% CI) | Z Value | P Value | I^2 Value |
|-------------|-------------------|---------|---------|-------------|
| Low/IV | 1.28 (1.05-1.55) | 2.44 | .01 | 0% |
| Low/SC | 1.02 (0.95-1.09) | 0.55 | .58 | 0% |
| Moderate/IV | 1.11 (1.04-1.19) | 2.96 | .003 | 0% |
| Moderate/SC | 1.08 (1.03-1.14) | 3.01 | .003 | 0% |
| High/IV | 1.15(1.07 - 1.23) | 4.04 | <.0001 | 0% |
| High/SC | 1.00 (0.87-1.14) | 0.05 | .96 | 0% |

^aBolded P values indicate statistical significance (P < .05). IV, intravenous; RR, risk ratios; SC, subcutaneous.

are consistent with the observation that a higher dose of tanezumab provides improved efficacy,³⁸ our findings of the effectiveness of IV administration on treatment outcomes differ from the results of Birbara et al.⁴ Considering that only one study used a high dose of tanezumab (10 mg) with SC administration,⁴ we believe that additional studies comparing different administration modes should be performed.

Our sensitivity analysis demonstrated that compared with oxycodone,^{27,40} and NSAIDs,^{14,18} anti-NGF antibodies significantly improved pain scores, physical function scores, and PGA scores. There was no significant difference in the incidence of AEs for anti-NGF antibodies compared to analgesics.^{14,18,27,40}

| | Experim | ental | Contr | rol | | Risk Ratio | Risk Ratio |
|---|------------|------------|--------|-------|--------|-----------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI Y | ear M-H, Random, 95% Cl |
| Lane 2010 Tanezumab 100 µg/kg IV [26] | 0 | 74 | 0 | 15 | | Not estimable 2 | 010 |
| Lane 2010 Tanezumab 200 µg/kg IV [26] | 2 | 74 | 1 | 15 | 0.5% | 0.41 [0.04, 4.19] 2 | 010 |
| Lane 2010 Tanezumab 25 µg/kg IV [26] | 1 | 74 | 0 | 15 | 0.2% | 0.64 [0.03, 15.01] 2 | 010 |
| Lane 2010 Tanezumab 50 µg/kg IV [26] | 0 | 74 | 0 | 15 | | Not estimable 2 | 010 |
| Lane 2010 Tanezumab 10 µg/kg IV [26] | 0 | 74 | 0 | 14 | | Not estimable 2 | 010 |
| Nagashima 2011 Tanezumab 10 µg/kg IV [29] | 1 | 15 | 0 | 3 | 0.3% | 0.75 [0.04, 15.17] 2 | 011 |
| Nagashima 2011 Tanezumab 100 µg/kg IV [29] | 0 | 16 | 0 | 3 | | Not estimable 2 | 011 |
| Nagashima 2011 Tanezumab 200 µg/kg IV [29] | 0 | 6 | 0 | 4 | | Not estimable 2 | D11 |
| Nagashima 2011 Tanezumab 25 µg/kg IV [29] | 1 | 15 | 0 | 3 | 0.3% | 0.75 [0.04, 15.17] 2 | 011 |
| Nagashima 2011 Tanezumab 50 µg/kg IV [29] | 0 | 15 | 0 | 3 | | Not estimable 2 | 011 |
| Brown 2012 Tanezumab10 mg IV [7] | 3 | 174 | 1 | 58 | 0.5% | 1.00 [0.11, 9.43] 2 | 012 |
| Brown 2012 Tanezumab 2.5 mg IV[7] | 3 | 172 | 1 | 57 | 0.5% | 0.99 [0.11, 9.37] 2 | 012 |
| Brown 2012 Tanezumab 5 mg IV [7] | 4 | 172 | 1 | 57 | 0.5% | 1.33 [0.15, 11.62] 2 | 012 |
| Sanga 2013 Fulranumab 10 mg SC q8wk[32] | 1 | 78 | 0 | 16 | 0.2% | 0.65 [0.03, 15.18] 2 | 013 |
| Sanga 2013 Fulranumab 1 mg SC q4wk[32] | 0 | 77 | 0 | 16 | | Not estimable 2 | 013 |
| Sanga 2013 Fulranumab 3 mg SC q4wk[32] | 0 | 79 | 0 | 16 | | Not estimable 2 | 013 |
| Sanga 2013 Fulranumab 3 mg SC q8wk[32] | 0 | 76 | 0 | 15 | | Not estimable 2 | 013 |
| Sanga 2013 Fulranumab 6 mg SC q8wk[32] | 1 | 78 | 1 | 15 | 0.3% | 0.19 [0.01, 2.91] 2 | 013 |
| Brown 2013 Tanezumab 10 mg IV[6] | 6 | 157 | 2 | 51 | 1.0% | 0.97 [0.20, 4.68] 2 | 013 |
| Brown 2013 Tanezumab 2.5 mg IV [6] | 7 | 155 | 2 | 52 | 1.0% | 1.17 [0.25, 5.48] 2 | 013 |
| Brown 2013 Tanezumab 5 mg IV [6] | 5 | 154 | 2 | 52 | 1.0% | 0.84 [0.17, 4.22] 2 | 013 |
| Spierings 2013 Tanezumab 10 mg IV [40] | 4 | 150 | 1 | 70 | 0.5% | 1.87 [0.21, 16.40] 2 | 013 |
| Spierings 2013 Tanezumab 5 mg IV[40] | 2 | 161 | 1 | /1 | 0.4% | 0.88 [0.08, 9.57] 2 | |
| Balanescu 2014 Tanezumab 10 mg IV+DSR[2] | 10 | 145 | 3 | 50 | 1.6% | 1.15 [0.33, 4.01] 2 | |
| Balanescu 2014 Tanezumab 2.5 mg IV+DSR[2] | 12 | 157 | 3 | 51 | 1.6% | 1.30 [0.38, 4.42] 2 | |
| Balanescu 2014 Tanezumab 5 mg IV+DSR [2] | 8 | 150 | 2 | 51 | 1.1% | 1.30 [0.30, 6.20] 2 | |
| Brown 2014 Tanezumab 10 mg IV (5) | 3 | 74 | 0 | 36 | 0.3% | 3.45 [0.18, 65.12] 2 | 014 |
| Brown 2014 Tanezumab 5 mg IV [5] | 0 | 73 | 0 | 30 | 4 60/ | Not estimable 2 | |
| Ekman 2014a Tanezumab Tu mg IV(14) | 0 | 208 | 4 | 104 | 1.0% | 0.75 [0.22, 2.60] 2 | |
| Ekman 2014a Tanezumab 5 mg IV [14] | 1 | 200 | 4 | 104 | 1.7% | 0.00 [0.20, 2.95] 2 | |
| Ekman 2014b Tanezumab To mg IV[14] | 4 | 209 | 2 | 104 | 0.9% | 1.00 [0.19, 5.35] 2 | |
| Sobsitzer 2015 Tanezumab 10 mg IV [35] | 3 | 542 | 11 | 105 | 0.0% | 1.04 [0.55, 4.40] 2 | |
| Schnitzer 2015 Tanezumab 10 mg IV (55) | 40 | 542 | 11 | 135 | 6.6% | 1.04 [0.55, 1.96] 2 | |
| Schnitzer 2015 Tanezumab 5 mg IV [35] | 1 04 | 542 | 10 | 134 | 5.7% | 1.45 [0.79, 2.07] 2 | 15 |
| Schnitzer 2015 Tanezumab 5 mg IV +NSAID [35] | 54 | 536 | 10 | 134 | 6.4% | 1.03 [0.00, 2.11] 2 | 15 |
| Mayorga 2016 Eulranumah 3 mg SC [27] | 0 | 48 | | 24 | 0.470 | Not estimable 2 | 016 |
| Mayorga 2016 Fulranumab 9 mg SC [27] | 1 | 50 | 1 | 24 | 0.3% | 0.48 [0.03, 7, 35] 2 | 016 |
| Sanga 2017 Fulranumah 10 mg SC g8wk[33] | 25 | 78 | 3 | 16 | 2.2% | 1 71 [0 59 4 98] 2 | |
| Sanga 2017 Fulranumab 1 mg SC q4wk[33] | 11 | 77 | 2 | 15 | 1.3% | 1.07 [0.26, 4.35] 2 | 117 |
| Sanga 2017 Fulranumab 3 mg SC q4wk[33] | 26 | 79 | 3 | 16 | 2.2% | 1.76 [0.60, 5.10] 2 | |
| Sanga 2017 Fulranumab 3 mg SC g8wkl33 | 14 | 76 | 2 | 15 | 1.3% | 1.38 [0.35, 5.46] 2 | 017 |
| Sanga 2017 Fulranumab 6 mg SC g8wk[33] | 20 | 78 | 3 | 16 | 2.1% | 1.37 [0.46, 4.06] 2 | 017 |
| Birbara 2018 Tanezumab 10 mg SC [4] | 0 | 86 | 0 | 18 | | Not estimable 2 | 018 |
| Birbara 2018 Tanezumab 2.5 mg SC [4] | 2 | 74 | 1 | 18 | 0.4% | 0.49 [0.05, 5.07] 2 | 018 |
| Birbara 2018 Tanezumab 5 mg SC [4] | 0 | 63 | 0 | 18 | | Not estimable 2 | 018 |
| Birbara 2018 Tanezumab 10 mg IV [4] | 1 | 84 | 1 | 18 | 0.3% | 0.21 [0.01. 3.27] 2 | 018 |
| Kelly 2019 Fulranumab 3 mg SC[23] | 3 | 83 | 2 | 40 | 0.8% | 0.72 [0.13, 4.16] 2 | 019 |
| Schnitzer 2019 Tanezumab 2.5/5 mg SC[34] | 4 | 231 | 2 | 116 | 0.9% | 1.00 [0.19, 5.40] 2 | 019 |
| Schnitzer 2019 Tanezumab 2.5 mg SC [34] | 4 | 233 | 2 | 116 | 0.9% | 1.00 [0.19, 5.36] 2 | 019 |
| Kelly 2019 Fulranumab 1 mg SC[23] | 8 | 81 | 3 | 41 | 1.5% | 1.35 [0.38, 4.82] 2 | 019 |
| Berenbaum 2020 Tanezumab 2.5 mg SC [3] | 11 | 283 | 13 | 141 | 4.1% | 0.42 [0.19, 0.92] 2 | |
| Berenbaum 2020 Tanezumab 5 mg SC [3] | 24 | 284 | 14 | 141 | 6.3% | 0.85 [0.45, 1.59] 2 | |
| Hochberg 2021 Tanezumab 2.5 mg SC [18] | 78 | 1002 | 33 | 498 | 16.0% | 1.17 [0.79, 1.74] 2 | 021 + |
| Hochberg 2021 Tanezumab 5 mg SC [18] | 110 | 998 | 33 | 498 | 17.7% | 1.66 [1.14, 2.42] 2 | 021 |
| Total (95% CI) | | 9702 | | 3605 | 100.0% | 1.15 [0.98, 1.34] | ► |
| Total events | 644 | | 194 | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 20.71, df = 41 | (P = 1.00) |); I² = 0% | | | | | 0.01 0.1 1 10 100 |
| Test for overall effect: Z = 1.71 (P = 0.09) | | | | | | | Favours [experimental] Favours [control] |

Figure 8. Forest plot of differences in serious adverse event rates between the experimental and control groups.

The safety of anti-NGF antibodies has been a concern in clinical applications.¹⁷ Our meta-analysis showed that the frequency of drug withdrawal because of AEs in the

TABLE 6 Subgroup Analysis of Serious Adverse Events According to Dose and Administration Mode^a

| Dose/Mode | RR (95% CI) | Z Value | P Value | I^2 Value |
|-------------|------------------------------|---------|---------|-------------|
| Low/IV | 1.09 (0.49-2.39) | 0.20 | .84 | 0% |
| Low/SC | 0.97 (0.70-1.36) | 0.16 | .88 | 3% |
| Moderate/IV | 1.10(0.76 - 1.60) | 0.50 | .62 | 0% |
| Moderate/SC | 1.34 (0.99-1.80) | 1.92 | .05 | 2% |
| High/IV | 1.12(0.79 - 1.59) | 0.61 | .54 | 0% |
| High/SC | $1.34\ (0.52 \hbox{-} 3.47)$ | 0.61 | .54 | 0% |

^aIV, intravenous; RR, risk ratios; SC, subcutaneous.

treatment group was higher than that in the control group and that the incidence of SAEs was similar between the 2 groups. In multiple studies, a lower incidence of AEs in the placebo group or placebo combined with NSAID group compared to the anti-NGF antibody group or anti-NGF antibody combined with NSAID group was reported.^{2,35} Several studies reported that the frequency of treatment discontinuation because of AEs with anti-NGF antibodies is similar to or lower than the rates observed with NSAIDs.^{14,27,35,40} Our safety data showed that the incidence of drug withdrawal because of AEs and SAEs meets the prescribed standards.^{14,27,35,40} We found that anti-NGF antibody treatments are well tolerated and safe.

The most common AEs associated with the use of anti-NGF antibodies include peripheral edema, joint and limb pain, and peripheral neuropathy.^{12,33,35,41} Less than 10% of patients have neuropathy.¹² Symptoms of abnormal peripheral sensation are usually mild to moderate,

TABLE 7 Sensitivity Analysis of Fixed-Dose Tanezumab a

| Outcome | SMD or RR (95% CI) | Z Value | P Value | I^2 Value |
|-------------------------|------------------------|---------|---------|-----------------|
| WOMAC pain | | | | |
| Low dose/IV | -0.28 (-0.47 to -0.10) | 3.04 | .002 | 0% |
| Low dose/SC | -0.11 (-0.21 to -0.01) | 2.06 | .04 | 15% |
| Moderate dose/IV | -0.33 (-0.42 to -0.24) | 7.47 | <.00001 | 0% |
| Moderate dose/SC | -0.12 (-0.21 to -0.03) | 2.71 | .007 | 1% |
| High dose/IV | -0.33 (-0.42 to -0.25) | 7.66 | <.00001 | 0% |
| High dose/SC | -0.44 (-0.95 to 0.07) | 1.68 | .09 | NA |
| WOMAC physical function | | | | |
| Low dose/IV | -0.32 (-0.51 to -0.14) | 3.44 | .0006 | 0% |
| Low dose/SC | -0.14 (-0.26 to -0.02) | 2.38 | .02 | 26% |
| Moderate dose/IV | -0.36 (-0.44 to -0.27) | 8.09 | <.00001 | 0% |
| Moderate dose/SC | -0.18 (-0.29 to -0.06) | 3.03 | .002 | $\mathbf{24\%}$ |
| High dose/IV | -0.36 (-0.44 to -0.27) | 8.17 | <.00001 | 0% |
| High dose/SC | -0.93 (-1.45 to -0.40) | 3.46 | .0005 | NA |
| PGA | | | | |
| Low dose/IV | -0.33 (-0.51 to -0.15) | 3.52 | .0004 | 0% |
| Low dose/SC | -0.06 (-0.15 to 0.02) | 1.48 | .14 | 0% |
| Moderate dose/IV | -0.27 (-0.37 to -0.17) | 5.22 | <.00001 | $\mathbf{27\%}$ |
| Moderate dose/SC | -0.10 (-0.20 to 0.00) | 1.90 | .06 | 13% |
| High dose/IV | -0.29 (-0.40 to -0.18) | 5.13 | <.00001 | 39 % |
| High dose/SC | -0.28 (-0.79 to 0.23) | 1.08 | .28 | NA |
| AEs | | | | |
| Low dose/IV | 1.28 (1.05 to 1.55) | 2.44 | .01 | 0% |
| Low dose/SC | 1.02 (0.95 to 1.09) | 0.55 | .58 | 0% |
| Moderate dose/IV | 1.12 (1.04 to 1.20) | 3.07 | .002 | 0% |
| Moderate dose/SC | 1.11 (1.04 to 1.19) | 3.01 | .001 | 0% |
| High dose/IV | 1.14 (1.06 to 1.22) | 3.67 | .0002 | 0% |
| High dose/SC | 0.75 (0.47 to 1.22) | 1.15 | .25 | NA |
| SAEs | | | | |
| Low dose/IV | 1.21 (0.50 to 2.91) | 0.42 | .68 | 0% |
| Low dose/SC | 0.78 (0.40 to 1.51) | 0.75 | .45 | 47% |
| Moderate dose/IV | 1.10 (0.76 to 1.60) | 0.50 | .62 | 0% |
| Moderate dose/SC | 1.25 (0.75 to 2.08) | 0.87 | .38 | 41% |
| High dose/IV | 1.14 (0.80 to 1.63) | 0.74 | .46 | 0% |
| High dose/SC | Not estimable | NA | NA | NA |

^aBolded P values indicate statistical significance (P < .05). AE, adverse event; IV, intravenous; NA, not applicable; PGA, patient global assessment; RR, risk ratios; SAE, serious adverse event; SC, subcutaneous; SMD, standardized mean difference; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.



Figure 9. Funnel plots with pseudo–95% Cls. Funnel plot of changes from baseline to the endpoint for the Western Ontario and McMaster Universities Osteoarthritis Index–pain score. IV, inverse variance.

transient in nature, and without continuous changes on neurological examination, and most AEs disappeared before the end of the study by Dietz et al.¹²

Early clinical trial studies have shown that rapidly progressive OA is a potential SAE.^{3,17,35} The United States Food and Drug Administration concluded that tanezumab was unrelated to an increased risk of osteonecrosis.^{19,36} Schnitzer et al^{34,35} showed that joint safety events were rare and most were considered normal OA progression. No joint safety event was judged to be osteonecrosis, a subchondral insufficiency fracture, or a pathological fracture.³⁵ The incidence of rapidly progressive OA may be related to the dose of tanezumab.³⁴ SAEs in clinical trials of anti-NGF antibodies should be monitored to determine the overall risk-benefit ratio of anti-NGF antibodies in controlling OA pain.

We found that anti-NGF antibodies provided pain relief and improved physical function in patients with OA as well as had acceptable AEs. Compared with classic OA analgesics (oxycodone and NSAIDs), anti-NGF antibodies improved treatment outcomes better. There were significant improvements in the WOMAC pain score (SMD, -0.21 [95% CI, -0.31 to -0.11]; Z = 3.99; P < .001; $I^2 = 54\%$), WOMAC physical function score (SMD, -0.24 [95% CI, -0.34 to -0.13]; Z = 4.40; P < .001; $I^2 = 56\%$), and PGA score (SMD, -0.20 [95% CI, -0.32 to -0.09]; Z = 3.45; P = .0006; $I^2 =$ 63%). Our results may provide an important foundation for investigating anti-NGF antibody treatment policies.

This meta-analysis had several limitations. First, few RCTs examining fulranumab and fasinumab were available, which may have affected outcomes. Second, RCTs did not distinguish between knee and hip outcomes. Third, most of the RCTs that we included only reported the outcome indicators at 16 weeks, and more outcome indicators at different treatment durations are needed to increase the reliability of the results. Fourth, there was only 1 study that directly compared the IV and SC administrations of tanezumab. Fifth, the WOMAC stiffness scores were highly heterogeneous ($I^2 = 98\%$), and few RCTs reported on this outcome indicator. Finally, all RCTs were sponsored by pharmaceutical companies, possibly introducing funding bias.

CONCLUSION

Our meta-analysis showed that anti-NGF antibodies could effectively relieve pain, improve physical function, reduce stiffness, and improve the PGA score in patients with knee and hip OA. We found that the AEs caused by anti-NGF antibody treatment were temporary and mild in nature and were usually well tolerated. SAEs were not considered to be related to the use of anti-NGF antibodies. However, no conclusion can be drawn regarding the optimal treatment plan for anti-NGF antibodies based on an analysis of the combined effect of the study variables on treatment outcomes. Additional RCTs are necessary to provide information on the combined effect of dose, administration mode, and treatment duration on the effectiveness and safety of anti-NGF antibody treatment.

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APPROVAL STATEMENT

All studies included in this meta-analysis had been published and declared ethical approval, and we did not collect or utilize any raw data of these results, therefore no ethical approval was needed for this meta-analysis study. This meta-analysis was conducted on the basis of the Preferred Reporting Items for Systematic Reviews and Meta-analysis.

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APPENDIX 1

| | Search Strategy | Results |
|-----|--|---------|
| Pub | med | |
| #1 | "Osteoarthritis"[Mesh] | 65487 |
| #2 | Osteoarthr* | 101226 |
| #3 | OA[Title/Abstract] | 37442 |
| #4 | "Degenerative Arthriti*" | 1410 |
| #5 | Arthroses [Title/Abstract] | 512 |
| #6 | Arthrosis [Title/Abstract] | 5511 |
| #7 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 ((("Nerve Growth Factor"[Mesh]) OR "fasimimab" | 118192 |
| #8 | [Supplementary Concept]) OR "fulranumab" [Supplementary Concept]) OR "tanezumab" [Supplementary Concept] | 7347 |
| #9 | "nerve growth factor"[Title/Abstract] | 18874 |
| #10 | NGF[Title/Abstract] | 15932 |
| #11 | fasinumab[Title/Abstract] | 19 |
| #12 | REGN475[Title/Abstract] | 3 |
| #13 | fulranumab[Title/Abstract] | 19 |
| #14 | tanezumab [Title/Abstract] | 105 |
| #15 | RN624 MAb[Title/Abstract] | 6 |
| #16 | RN624[Title/Abstract] | 2 |
| #17 | RI 624[Title/Abstract] | 123 |
| #18 | #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 | 23396 |
| #19 | #7 AND #18 | 286 |
| #20 | (randomized controlled trial[pt] | 1254914 |
| | OR controlled clinical trial[pt]OR randomized[tiab] OR placebo[tiab] OR clinical trials as | |
| | topic[mesh:noexp] OR randomly[tiab] OR trial[ti]) NOT | |
| | (animals [mh] NOT (humans [mh] AND animals[mh])) | |
| #21 | #19 AND #20 | 66 |
| The | Cochrane Central Register of Controlled Trials (CENTRAL) | |
| #1 | MeSH descriptor: [Osteoarthritis] explode all trees | 7704 |
| #2 | (osteoarthr*) | 19224 |
| #3 | (OA): ti,ab,kw | 6306 |
| #4 | "Degenerative Arthriti*" | 1 |
| #5 | (Arthrosis): ti,ab,kw | 652 |
| #6 | (Arthroses): ti,ab,kw | 40 |
| #7 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 | 20285 |
| #8 | MeSH descriptor: [Nerve Growth Factor] explode all trees | 87 |
| #9 | (NGF): ti,ab,kw OR ("nerve growth factor"):ti,ab,kw | 512 |
| #10 | (SAR164877):ti,ab,kw | 6 |
| #11 | (REGN475): ti,ab,kw | 19 |
| #12 | (fasinumab): ti,ab,kw | 22 |
| #13 | #10 OR #11 OR #12 | 30 |
| #14 | (fulranumab): ti,ab,kw | 23 |
| #15 | (JNJ 42160443): ti,ab,kw | 16 |
| #16 | #14 OR #15 | 35 |
| #17 | (tanezumab): ti,ab,kw | 117 |
| #18 | (RN624): ti,ab,kw | 15 |
| #19 | (RI 624): ti,ab,kw | 3 |
| #20 | (PF 04383119): ti,ab,kw | 13 |
| #21 | #17 OR #18 OR #19 OR #20 | 126 |
| #22 | #8 OR #9 OR #13 OR #16 OR #21 | 642 |
| #23 | #7 AND #22 | 134 |
| EM | BASE | |
| #1 | osteoarthritis'/exp | 139060 |
| #2 | oa:ab,ti | 58777 |
| #3 | 'degenerative arthriti*' | 1751 |
| #4 | osteoarthr* | 163396 |
| #5 | arthroses:ab,ti | 600 |

(continued)

(continued)

| | Search Strategy | Results |
|-----|---|---------|
| #6 | arthrosis:ab,ti | 7481 |
| #7 | nerve growth factor'/exp | 27373 |
| #8 | nerve growth factor antibody'/exp | 615 |
| #9 | #7 OR #8 | 27611 |
| #10 | 'fasinumab'/exp | 66 |
| #11 | 'fulranumab'/exp | 84 |
| #12 | 'tanezumab'/exp | 409 |
| #13 | ngf:ab,ti | 19411 |
| #14 | 'nerve growth factor':ab,ti | 21860 |
| #15 | fasinumab:ab,ti | 22 |
| #16 | fulranumab:ab,ti | 37 |
| #17 | tanezumab:ab,ti | 202 |
| #18 | regn475: ab,ti | 5 |
| #19 | sar164877: ab,ti | 1 |
| #20 | jnj 42160443': ab,ti | 3 |
| #21 | rn624: ab,ti | 2 |
| #22 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 | 192383 |
| #23 | #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR # 19 OR #20 OR #21 | 35541 |
| #24 | #22 AND #23 | 697 |
| | 'crossover procedure':de OR 'double-blind procedure':de OR | |
| | 'randomized controlled trial':de OR 'single-blind procedure':de | |
| | OR random*:de,ab,ti OR factorial*:de,ab,ti OR | |
| #25 | crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti | 2715860 |
| #26 | #24 AND #25 | 241 |
| Web | o of Science | |
| #1 | TOPIC: (Osteoarthr*) | 82281 |
| #2 | TOPIC: (OA) | 36559 |
| #3 | TOPIC: ("Degenerative Arthriti*") | 726 |
| #4 | TOPIC: (Arthrosis) | 1975 |
| #5 | TOPIC: ("nerve growth factor") | 100295 |
| #6 | TOPIC: ("nerve growth factor") | 16664 |
| #7 | TOPIC: (NGF) | 9626 |
| #8 | TOPIC: (fasinumab) | 19 |
| #9 | TOPIC: (fulranumab) | 29 |
| #10 | TOPIC: (tanezumab) | 222 |
| #11 | TOPIC: (REGN475) | 3 |
| #12 | TOPIC: (RN624) | 2 |
| #13 | TOPIC: (RN 624) | 3 |
| #14 | #12 OR #13 | 5 |
| #15 | TOPIC: (RI 624) | 9 |
| #16 | TOPIC: (PF-04383119) | 1 |
| #17 | #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #14 OR #15 OR | 19129 |
| | #16 | |
| #18 | #5 AND #17 | 419 |
| | TS= clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR | 0000001 |
| #19 | TS=tollow-up stud* OK TS=prospective stud* OK TS=random* OK TS=placebo* OK TS= (single blind*) OR | 3398291 |
| | IIS= (double blind*) | 100 |
| #20 | #18 AND #19 | 182 |

APPENDIX 2

| Study or Subaroup | Exp | eriment SD | al Total | Mean | Control SD | Total | S Weight | td. Mean Difference IV. Random, 95% CI Y | Std. Mean Difference ear IV. Random. 95% Cl |
|--|-------------------------------|-----------------------|--------------|----------------|---------------|------------|---------------|--|--|
| low-dose&IV&week 16 Lane 2010 Tanezumah 10 uniko IV (24) | -30.1 | 19.79 | 74 | -16.2 | 20.51 | 14 | 0.7% | -0.691-1.27 -0.111 2 | 10 |
| Lane 2010 Tanezumab 25 µg/kg IV 124 Brown 2012 Tanezumab 25 µg/kg IV 124 | -36 | 19.05 | 75 | -16.2 | 20.51 | 15 | 0.7% | -1.02 [-1.59, -0.44] 21 | 10 |
| Brown 2013 Tanezumab 2.5 mg IV/H Balanescu 2014 Tanezumab 2.5 mg IV/H | -2.9 | 2.83 | 151 | -1.62 | 2.85 | 51 | 1.7% | -0.45 [-0.77, -0.13] 21 | 113 |
| Tiseo 2014 Fasinumab 0.03 mg/kg IV ^[4] Subtratal (95% CI) | -2.7 | 1.89 | 53 | -2.4 | 2.18 | 18 | 0.8% | -0.15[-0.69, 0.38] 21 | 014 • |
| Heterogeneity: Tau ^a = 0.03; Chi ^a = 9.08, df = 5 (P = Test for overall effect: Z = 3.42 (P = 0.0006) | 0.11); (| = 45% | | | | 200 | 1.2.10 | | |
| Iow-dose&IV&week 8 | 34.6 | 20.41 | 16 | .21.2 | 21.4 | | 0.2% | 0.531478.0791.3 | |
| Nagashima 2011 Tanezumab 10 µg/kg IV I21 Relacency Tanezumab 10 µg/kg IV I21 | -20 | 20.95 | 15 | -23.2 | 21.4 | 2 | 0.1% | 0.14 [-1.33, 1.62] 21 | |
| Tiseo 2014 Fasinumab 0.03 mg/kg IV week 8141 Subtotal (95% CI) | -2.6 | 2.01 | 53 | -1.9 | 1.74 | 18 | 0.8% | -0.36 [-0.89, 0.18] 21 | 014 |
| Heterogeneity: Tau ² = 0.00; Chi ² = 0.83, df = 3 (P = Test for overall effect: Z = 1.61 (P = 0.11) | 0.84) <u>:</u> I ⁴ | * = 0% | 240 | | | 14 | 2.174 | 10.22 [10.46, 0.00] | |
| low-dose&SC&week 24 | | | | | | | | | |
| Berenbaum 2020 Tanezumab 2.5 mg SC PI Subtotal (95% CI) Heterogeneity: Not applicable Text for overall effect: Z = 1.53 (P = 0.13) | -2.7 | 2.86 | 283 283 | -2.24 | 3.02 | 141 141 | 2.7% 2.7% | -0.16 [-0.36, 0.04] 2 -0.16 [-0.36, 0.04] | 120 |
| low-dose&SC&week 16 | | | | | | | | | |
| Sanga 2017 Fulranumab 1 mg SC q4wki34 Sanga 2017 Fulranumab 3 mg SC g8wki34 | -2.3 | 3.18 3.49 | 70 69 | -2.18 | 4.15 | 12 12 | 0.6% | -0.04 [-0.65, 0.58] 21 | 017 017 |
| Kelly 2019 Fulranumab 1 mg SC [2] Dakin, 2019 Easinumab 1 mg SC [3] | -2.73 | 4.41 | 81 | -3.07 | 4.32 | 40 | 1.3% | 0.08 [-0.30, 0.46] 2 | 119 |
| Dakin 2019 Fasinumab 3 mg SC IIII Scholtzer 2019 Tagestumab 2 5 mg SC IIII | -3.4 | 2.4 | 78 | -2.4 | 2.4 | 18 | 0.8% | -0.41 [-0.93, 0.10] 2 | 19 |
| Hochberg 2021 Tanezumab 2.5 mg SCIM Subtotal (955, CI) | -3.22 | 3.39 | 1002 | -3.07 | 3.46 | 498 | 3.9% | -0.04 [-0.15, 0.06] 21 | 121 |
| Heterogeneity: Tau ^a = 0.00; Chi ^a = 6.01, df = 6 (P = Test for overall effect: Z = 1.74 (P = 0.08) | 0.42); 1 | *= 0% | 1000 | | | 113 | 10.379 | -0.00 [-0.17, 0.01] | |
| low-dose&SC&week 8 | | | | | | | | | |
| Birbara 2018 Tanezumab 2.5 mg SC H Subtotal (95% CI) Heterogeneity: Not applicable | -3.88 | 2.58 | 74 | -2.73 | 2.21 | 18 18 | 0.8% | -0.45 [-0.97, 0.07] 20 -0.45 [-0.97, 0.07] | 118 |
| Test for overall effect: Z = 1.71 (P = 0.09) | | | | | | | | | |
| moderate-dose&IV&week 16 Lane 2010 Tanezumab 50 µg/kg IV (24) | -29 | 20.36 | 72 | -16.2 | 20.51 | 15 | 0.7% | -0.62 [-1.19, -0.06] 2 | 010 |
| Brown 2012 Tanezumab 5 mg IV (1) Brown 2013 Tanezumab 5 mg IV (4) | -3.3 -3.31 | 2.87 2.82 | 156 150 | -2.4 | 2.85 2.85 | 52 52 | 1.7% 1.7% | -0.31 [-0.63, 0.00] 21 -0.60 [-0.92, -0.27] 21 | 012 |
| Ekman 2014a Tanezumab 5 mg IV(14) Tiseo 2014 Fasinumab 0.1 mg/kg, IV(14) | -3.44 | 2.58 | 206 53 | -2.23 | 2.59 | 104 18 | 2.3% | -0.47 [-0.71, -0.23] 21 -0.40 [-0.94, 0.14] 21 |)14 |
| Ekman 2014b Tanezumab 5 mg IV (H) Balanescu 2014 Tanezumab 5 mg IV +DSB PI | -2.95 | 3.2 | 211 | -1.81 | 3.18 | 105 | 2.4% | -0.36 [-0.59, -0.12] 20 | 114 |
| Schnitzer 2015b Tanezumab 5 mg IV 198 Schnitzer 2015b Tanezumab 5 mg IV calecovib 115 | -2.02 | 2.56 | 256 | -1.47 | 2.56 | 64 | 2.0% | -0.21 [-0.49, 0.06] 2 | 115 |
| Schnitzer 2015a Tanezumab 5 mg IV (38) | -1.88 | 2.19 | 285 | -1.44 | 2.52 | 71 | 2.1% | -0.19 [-0.45, 0.07] 21 | 115 |
| Subtotal (95% CI) | -2.13 | 2.18 | 2075 | -1.44 | 2.52 | 667 | 19.5% | -0.34 [-0.43, -0.25] | • |
| Heterogeneity: Tau ^a = 0.00; Chi ^a = 7.34, df = 10 (P Test for overall effect: Z = 7.48 (P < 0.00001) | = 0.69); | P = 0% | | | | | | | |
| moderate-dose&IV&week 8 Nagashima 2011 Tanezumab 50 µg/kg IV I™ | -24.8 | 20.41 | 15 | -23.2 | 21.4 | 3 | 0.2% | -0.07 [-1.31, 1.17] 20 | 011 |
| Spierings 2013 Tanezumab 5 mg IV I ⁴⁴ Ekman 2014a Tanezumab 5 mg IV week 8 I ¹⁴ | -3.58 | 2.79 | 161 206 | -2.62 | 2.85 | 71 103 | 2.0% | -0.34 [-0.62, -0.06] 21 | 113 |
| Ekman 2014b Tanezumab 5 mg IV week 8 I ¹⁴¹ Balanescu Tanezumab 5 mg IV+DSR week 8 III | -3.2 | 2.76 | 211 | -1.99 | 2.89 | 105 | 2.4% | -0.43 [-0.67, -0.19] 20 | 114 |
| Tiseo 2014 Fasinumab 0.1 mg/kg IV week 8 [41] Subtrat (95% C1) | -3.4 | 2.54 | 53 | -1.9 | 1.74 | 18 | 0.7% | -0.63 [-1.17, -0.08] 21 | 014 |
| Heterogeneity: Tau ^a = 0.00; Chi ^a = 1.38, df = 5 (P = Test for overall effect: Z = 6.17 (P < 0.00001) | 0.93); (| *= 0% | 100 | | | 551 | | | |
| moderate-dose&SC&week 24 Berenbaum 2020 Tanezumab 5 mg SC I제 | -2.85 | 2.86 | 284 | -2.24 | 3.02 | 141 | 2.7% | -0.21 [-0.41, -0.01] 2 | 120 |
| Subtotal (95% CI) Heterogeneity: Not applicable | | | 284 | | | 141 | 2.7% | -0.21 [-0.41, -0.01] | • |
| Test for overall effect: Z = 2.02 (P = 0.04) | | | | | | | | | |
| Mayorga 2016 Fulranumab 3 mg SC I ²⁷ I | -2.78 | 2.49 | 48 | -3.01 | 2.63 | 24 | 0.9% | 0.09 [-0.40, 0.58] 2 | 116 |
| Sanga 2017 Fufranumab 6 mg SC q8wkji3j Sanga 2017 Fufranumab 3 mg SC q4wkji3j | -2.29 | 3.49 | 69 68 | -2.18 | 4.15 | 12 12 | 0.6% | -0.03 [-0.64, 0.58] 21 -0.02 [-0.63, 0.60] 21 | 117 |
| Dakin 2019 Fasinumab 6 mg SC [14] Kelly 2019 Fulranumab 3 mg SC [14] | -3.1 | 2.3 4.65 | 77 83 | -2.4 | 2.4 | 18 41 | 0.8% | -0.30 [-0.81, 0.22] 21 -0.18 [-0.55, 0.20] 21 | 019 |
| Schnitzer 2019 Tanezumab 2.5/5 mg SC (H) Hochberg 2021 Tanezumab 5 mg SC (H) | -3.37 | 3.43 3.38 | 233 998 | -2.64 | 3.46 | 116 498 | 2.5% | -0.21 [-0.44, 0.01] 21 | 019 |
| Subtotal (95% CI) Heterogeneity: Tau ² = 0.00; Chi ² = 2.59, df = 6 (P = | 0.86); 1 | = 0% | 1576 | | | 721 | 10.7% | -0.10 [-0.19, -0.01] | • |
| Test for overall effect: Z = 2.26 (P = 0.02) | | | | | | | | | |
| Birbara 2018 Tanezumab 5 mg SC14 Schotel (955) CD | -3.8 | 2.7 | 63 | -2.73 | 2.21 | 18 | 0.8% | -0.41 [-0.94, 0.12] 2 | 018 |
| Heterogeneity: Not applicable Test for overall effect: Z = 1.51 (P = 0.13) | | | 65 | | | 10 | 0.075 | -0.41 [-0.34, 0.12] | |
| high-dose&IV&week 16 | | | | | | | | | |
| Lane 2010 Tanezumab 100 µg/kg IV [24] Lane 2010 Tanezumab 200 µg/kg IV [24] | -39.6 | 18.93 19.52 | 74 72 | -16.2 | 20.51 20.51 | 14 15 | 0.6% | -1.21 [-1.81, -0.61] 21 -1.37 [-1.97, -0.78] 21 | 10 |
| Brown 2012 Tanezumab10 mg IV ITI Brown 2013 Tanezumab 10 mg IV IVI | -3.6 | 2.85 | 154 | -2.4 | 2.85 | 51 | 1.7% | -0.42 [-0.74, -0.10] 2 | 112 |
| Ekman 2014b Tanezumab 10 mg IV IHI Tineo 2014 Encloymeth 0.2 molice Multi | -2.62 | 3.17 | 208 | -1.81 | 3.18 | 104 | 2.4% | -0.25 [-0.49, -0.02] 20 | 114 |
| Balanescu 2014 Tanezumab 10 mg IV+DSR I ²¹ | -2.25 | 2.29 | 145 | -1.68 | 2.34 | 50 | 1.6% | -0.25 [-0.57, 0.08] 21 | 114 |
| Schnitzer 2015b Tanezumab 10 mg IV1+1 Schnitzer 2015b Tanezumab 10 mg IV+celecoxib) | -3.14 | 2.59 | 254 | -1.47 | 2.59 | 64 | 2.3% | -0.43 [-0.71, -0.15] 2 | 115 |
| Schnitzer 2015a Tanezumab 10 mg IV (21) Schnitzer 2015a Tanezumab 10 mg IV+naproxen(x) | -2.02 9 -2.36 | 2.56 2.56 | 288 288 | -1.44 | 2.52 | 70 | 2.1% | -0.23 [-0.49, 0.03] 21 -0.36 [-0.62, -0.10] 21 | 115 |
| Schnitzer 2015b Tanezumab 10 mg IV IM Subtotal (95% CI) | -2.05 | 2.55 | 254 2148 | -1.47 | 2.56 | 64 676 | 2.0% 20.0% | -0.23 [-0.50, 0.05] 21 -0.42 [-0.55, -0.28] | • |
| Heterogeneity: Tau ² = 0.03; Chi ² = 24.23, df = 11 (F Test for overall effect: Z = 5.99 (P < 0.00001) | P = 0.01) | ; I ² = 55 | % | | | | | | |
| high-dose&IV&week 8 Nanashima 2011 Tanagumah 100 uniko IV/21 | -32.6 | 20.44 | 16 | -23.2 | 21.4 | 3 | 0.2% | 0.441-188-0.811-2 | |
| Nagashima 2011 Tanezumab 200 µg/kg IV(2*) Solariana 2012 Tanezumab 10 mp IV(2*) | -42 | 20.65 | 6 | -23.2 | 21.4 | 3 | 0.1% | -0.80 [-2.27, 0.67] 2 | |
| Ekman 2014a Tanezumab 10 mg IV week 8 I141 | -3.8 | 2.58 | 207 | -2.36 | 2.88 | 104 | 2.3% | -0.54 [-0.77, -0.30] 21 | 114 |
| Balanescu Tanezumab 10 mg IV+DSR week 8 [14] | -2.29 | 2.88 | 145 | -1.99 | 2.69 | 51 | 1.7% | -0.28 [-0.51, -0.04] 21 | 114 |
| Birbara 2014 Fashumac 0.3 mg/kg TV week 8 (4) Birbara 2018 Tanezumab 10 mg IV (4) Birbara (655) 67 | -3.6 | 2.42 | 54 84 | -1.9 | 2.21 | 19 | 0.8% | -0.70 [-1.23, -0.16] 21 -0.36 [-0.87, 0.16] 21 | 118 |
| Subtotal (95% CI) Heterogeneity: Tau ² = 0.00; Chi ² = 4.01, df = 7 (P = Test for overall effect: Z = 6.38 (P < 0.00001) | 0.78): 1 | = 0% | 870 | | | 372 | 10.1% | -0.40 [-0.53, -0.28] | |
| high-dose&SC&week 16 | | | | | | | | | |
| Mayorga 2016 Fulranumab 9 mg SC I ²¹ Sanga 2017 Fulranumab 10 mg SC q8wkl ³³ | -3.03 -2.58 | 2.56 3.41 | 50 66 | -3.01 -2.18 | 2.63 4.15 | 24 11 | 0.9% 0.6% | -0.01 [-0.49, 0.48] 21 -0.11 [-0.75, 0.53] 21 | 016 |
| Dakin 2019 Fasinumab 9 mg SC(10) Subtotal (95% CI) | -3.8 | 2.5 | 79 195 | -2.4 | 2.4 | 18 53 | 0.8% | -0.56 [-1.08, -0.04] 2 -0.23 [-0.58, 0.12] | 019 |
| Heterogeneity: Tau ^a = 0.02; Chi ^a = 2.48, df = 2 (P = Test for overall effect: Z = 1.30 (P = 0.19) | 0.29); 1 | = 20% | | | | | | | |
| high-dose&SC&week 8 | 1 gen | 294.0 | 10220 | 2020 | 12-12-1 | 1000 | 1912320 | 727702233-55-52-54 | |
| Birbara 2018 Tanezumab 10 mg SC H Subtotal (95% CI) | -3.92 | 2.78 | 86 86 | -2.73 | 2.21 | 18 18 | 0.8% 0.8% | -0.44 [-0.95, 0.07] 21 -0.44 [-0.95, 0.07] | 018 |
| Heterogeneity: Not applicable Test for overall effect: Z = 1.68 (P = 0.09) | | | | | | | | | 5 m 2 |
| Total (95% CI) Heterogeneity: Tau ^a = 0.01; Chi ^a = 109.45, df = 68 (| P = 0.0 | 01); i*=: | 10960 38% | | | 4163 | 100.0% | -0.31 [-0.36, -0.26] | • |
| Test for overall effect: Z = 11.75 (P < 0.00001) Test for suboroup differences: Chi ² = 49.24, df = 13 | (P < 0.0 | 00011.1 | * = 73.6 | 16 | | | | | Favours [experimental] Favours [control] |

Figure A1. Subgroup analysis of WOMAC pain scores according to dose, administration mode, and treatment duration.

| Study or Subgroup | Exp | eriment SD | tai Totai | Mean | Control SD | Total | 5 Weight | td. Mean Difference IV. Random. 95% CI | Year | Std. Mean Difference IV. Random, 95% CI |
|---|-------------------|---------------------------|--------------|-------|---------------|------------------|------------------------|--|-----------|--|
| low-dose&IV&week 16 Lane 2010 Tanezumab 10 uo/ko IVI2N | -30.1 | 19.79 | 74 | -15.2 | 19.65 | 14 | 0.7% | -0.75 [-1.330.16] | 2010 | |
| Lane 2010 Tanezumab 25 µg/kg (VI24 | -34.9 | 19.05 | 75 | -15.2 | 19.65 | 15 | 0.8% | -1.02 [-1.60, -0.45] | 2010 | |
| Brown 2012 Tanezumab 2.5 mg IVI/I Brown 2013 Tanezumab 2.5 mg IVI/I | -2.8 | 2.85 | 154 | -2 | 2.85 | 51 51 | 1.8% | -0.28 [-0.60, 0.04] -0.47 [-0.79, -0.14] | 2012 2013 | |
| Tiseo 2014 Fasinumab 0.03 mg/kg 1VHI | -2.9 | 1.78 | 53 | -2.3 | 2.3 | 18 | 0.8% | -0.31 [-0.85, 0.23] | 2014 | |
| Balanescu 2014 Tanezumab 2.5 mg IV+DSRIPI 4ochberg 2021 Tanezumab 2.5 mg SCIPI | -2.05 | 2.26 | 157 | -1.53 | 2.34 | 51 498 | 1.8% | -0.23 [-0.54, 0.09] | 2014 | -1 |
| Subtotal (95% CI) | | | 1666 | | | 698 | 11.2% | -0.37 [-0.60, -0.14] | | • |
| Heterogeneity: Tau ^a = 0.06; Chi ^a = 20.67, df = 6 (P : Test for overall effect: Z = 3.12 (P = 0.002) | = 0.002 | t; I² = 71 | % | | | | | | | |
| ow-dose&IV&week 8 | | | | | | | | | | |
| Nagashima 2011 Tanezumab 10 µg/kg IVI24 Nagashima 2011 Tanezumab 25 µg/kg IVI24 | -18.1 | 21.38 20.95 | 15 15 | -22.9 | 20.06 | 23 | 0.1% | 0.21 [-1.26, 1.69] -0.39 [-1.64, 0.86] | 2011 2011 | |
| Balanescu Tanezumab 2.5 mg IV+DSR week 8121 | -1.74 | 2.13 | 157 | -1.46 | 2.1 | 51 | 1.8% | -0.13 [-0.45, 0.18] | 2014 | |
| Tiseo 2014 Fasinumab 0.03 mg/kg TV week 8141 Subtotal (95% CI) | -2.8 | 2.07 | 53 240 | -1.8 | 1.95 | 18 | 0.8% | -0.48 [-1.03, 0.06] -0.22 [-0.48, 0.05] | 2014 | • |
| leterogeneity: Tau ² = 0.00; Chi ² = 1.62, df = 3 (P = | 0.65); (| * = 0% | | | | | | | | |
| en dess 82C8 met 24 | | | | | | | | | | |
| Berenbaum 2020 Tanezumab 2.5 mg SCI ³ | -2.7 | 2.69 | 283 | -2.11 | 2.67 | 141 | 2.7% | -0.22 [-0.42, -0.02] | 2020 | - |
| Jubtotal (95% CI) | | | 283 | | | 141 | 2.7% | -0.22 [-0.42, -0.02] | | |
| Fest for overall effect: Z = 2.12 (P = 0.03) | | | | | | | | | | |
| ow-dose&SC&week 16 | | | | | | | | | | |
| Sanga 2017 Fulranumab 3 mg SC q8wki34 Sanga 2017 Fulranumab 1 mg SC q8wki33 | -2.31 | 3.57 | 69 70 | -2.2 | 3.15 | 12 | 0.7% | -0.03 [-0.64, 0.58] | 2017 | |
| Dakin 2019 Fasinumab 3 mg SCIIII | -3.3 | 2.3 | 78 | -2.1 | 2.3 | 17 | 0.9% | -0.52 [-1.05, 0.01] | 2019 | |
| Dakin 2019 Fasinumab 1 mg SC(III) | -3.2 | 2.3 | 231 | -2.1 | 2.3 | 17 | 0.9% | -0.47 [-1.01, 0.06] | 2019 | |
| Subtotal (95% CI) | | 0.01 | 523 | 2.00 | 0.76 | 174 | 5.6% | -0.24 [-0.41, -0.06] | 2010 | • |
| teterogeneity: Tau ² = 0.00; Chi ² = 2.70, df = 4 (P = fest for overall effect: Z = 2.64 (P = 0.008) | 0.61); 1 | * = 0% | | | | | | | | |
| ow-dose&/V&week 8 | | | | | | | | | | |
| 3irbara 2018 Tanezumab 2.5 mg SC III Subtotal (95% CD | -3.29 | 2.58 | 74 | -2.24 | 1.95 | 18 | 0.9% | -0.42 [-0.94, 0.10] | 2018 | - |
| Heterogeneity: Not applicable | | | 14 | | | 18 | 0.9% | -u.az (-0.94, 0.10) | | |
| est for overall effect: Z = 1.59 (P = 0.11) | | | | | | | | | | |
| noderate-dose&IV&week 16 ane 2010 Tanezumah 60 uniter 5/104 | -30.6 | 20.24 | 72 | .15 0 | 19.65 | 15 | 0.8% | -0.761.1 32 -0.24 | 2010 | |
| srown 2012 Tanezumab 5 mg IV m | -3 | 2.75 | 156 | -2 | 2.85 | 52 | 1.8% | -0.36 [-0.67, -0.04] | 2012 | |
| Brown 2013 Tanezumab 5 mg IV HI | -2.88 | 2.45 | 150 | -1.39 | 2.36 | 52 | 1.7% | -0.61 [-0.93, -0.29] | 2013 | |
| Ekman 2014b Tanezumab 5 mg IV (H) | -2.68 | 3.05 | 211 | -1.45 | 3.04 | 105 | 2.4% | -0.40 [-0.64, -0.17] | 2014 | |
| Balanescu 2014 Tanezumab 5 mg IV+DSR(2) | -2.16 | 2.33 | 150 | -1.53 | 2.34 | 51 | 1.7% | -0.27 [-0.59, 0.05] | 2014 | |
| Schnitzer 2015a Tanezumab 5 mg IVI+naproxenus | -2.16 | 2.51 | 280 | -1.38 | 2.69 | 71 | 2.2% | -0.31 [-0.57, -0.04] | 2014 | |
| Schnitzer 2015a Tanezumab 5 mg Mir4 | -1.86 | 2.53 | 285 | -1.38 | 2.69 | 71 | 2.2% | -0.19 [-0.45, 0.07] | 2015 | |
| Schnitzer 2015b Tanezumab 5 mg IV+celecoxib(24) | -2.22 | 2.56 | 256 | -1.42 | 2.56 | 64 | 2.1% | -0.31 [-0.59, -0.04] | 2015 | - |
| Subtotal (95% CI) determents: Taud = 0.00; Chil = 8.05; df = 10 (P) | = 0.621 | 17 = 026 | 2075 | | | 666 | 20.0% | -0.36 [-0.45, -0.27] | | • |
| est for overall effect: Z = 8.01 (P < 0.00001) | - 0.02), | 1-016 | | | | | | | | |
| noderate-dose&IV&week 8 | | | | | | | | | | |
| Nagashima 2011 Tanezumab 50 µg/kg IV I ²⁹ Selerings, 2013 Tanezumab 5 mg IVI#I | -24.3 | 20.95 | 15 | -22.9 | 20.06 | 3 | 0.2% | -0.06 [-1.30, 1.18] | 2011 | |
| liseo 2014 Fasinumab 0.1 mg/kg IV week 8[4] | -3.4 | 2.32 | 53 | -1.8 | 1.95 | 18 | 0.8% | -0.71 [-1.26, -0.16] | 2014 | |
| Balanescu Tanezumab 5 mg IV+DSR week 814 | -2.2 | 2.08 | 150 | -1.46 | 2.1 | 50 | 1.7% | -0.35 [-0.68, -0.03] | 2014 | |
| Ekman 2014b Tanezumab 5 mg IV week 814 | -2.8 | 2.5 | 211 | -1.55 | 2.6 | 105 | 2.4% | -0.49 [-0.73, -0.25] | 2014 | - |
| Subtotal (95% CI) seterogeneity: Tau ² = 0.00: Chi ² = 1.69. df = 5 (P = | 0.891:1 | ² = 0% | 796 | | | 350 | 9.4% | -0.46 [-0.58, -0.33] | | • |
| Test for overall effect: Z = 7.01 (P < 0.00001) | | | | | | | | | | |
| noderate-dose&SC&week 24 | | | | | | | | | | |
| Subtotal (95% CI) | -2.82 | 3.03 | 284 | -2.11 | 2.67 | 141 | 2.7% | -0.24 [-0.45, -0.04] | 2020 | • |
| feterogeneity: Not applicable [est for overall effect: Z = 2.35 (P = 0.02) | | | | | | | | | | 2.4 |
| noderste dosa8508week 16 | | | | | | | | | | |
| Mayorga 2016 Fulranumab 3 mg SCIII1 | -2.99 | 2.56 | 48 | -2.99 | 2.7 | 24 | 1.0% | 0.00 [-0.49, 0.49] | 2016 | |
| Sanga 2017 Fulranumab 6 mg SC q8wkisii | -2.41 | 3.57 | 69 | -2.2 | 3.15 | 12 | 0.7% | -0.06 [-0.67, 0.55] | 2017 | |
| Schnitzer 2019 Tanezumab 2.5/5 mg SC(34) | -3.45 | 3.31 | 233 | -2.56 | 3.42 | 116 | 2.5% | -0.27 [-0.49, -0.04] | 2019 | |
| Dakin 2019 Fasinumab 6 mg SCIM forthern 2021 Tanezumab 5 mg SCIM | -3 | 2.5 | 76 | -2.1 | 2.3 | 18 | 0.9% | -0.36 [-0.88, 0.15] | 2019 | |
| Subtotal (95% CI) | -3.39 | 3,47 | 1492 | -3.00 | 3,40 | 680 | 9.3% | -0.13 [-0.22, -0.03] | 2021 | • |
| <pre>leterogeneity: Tau² = 0.00; Chi² = 3.08, df = 5 (P = 'est for overall effect: Z = 2.70 (P = 0.007)</pre> | 0.69); 1 | * = 0% | | | | | | | | |
| moderate-dose&SC&week 8 | | | | | | | | | | |
| lirbara 2018 Tanezumab 5 mg SC ¹⁴ Subtotal (95% CI) | -3.29 | 2.7 | 63 63 | -2.24 | 1.95 | 18 18 | 0.9% | -0.41 [-0.93, 0.12] | 2018 | - |
| leterogeneity: Not applicable | | | | | | | | | | |
| est for overall effect: $Z = 1.51$ ($P = 0.13$) | | | | | | | | | | |
| agh-dose&IV&week 16 ane 2010 Tanezumab 200 µo/kg IV⊯i | -43.8 | 19.52 | 72 | -15.2 | 19.65 | 15 | 0.7% | -1.45 [-2.05, -0.85] | 2010 | · |
| ane 2010 Tanezumab 100 µg/kg IV I24 | -40.5 | 18.93 | 74 | -15.2 | 19.65 | 14 | 0.7% | -1.32 [-1.92, -0.71] | 2010 | |
| Rown 2012 Tanezumab10 mg IVm Brown 2013 Tanezumab 10 mg IVm | -3.3 | 2.61 | 154 | -2 | 2.85 | 51 51 | 1.7% | -0.48 [-0.81, -0.16] -0.63 [-0.95, -0.30] | 2012 2013 | |
| alanescu 2014 Tanezumab 10 mg IV+DSRI2I | -2.23 | 2.29 | 145 | -1.53 | 2.34 | 50 | 1.7% | -0.30 [-0.63, 0.02] | 2014 | |
| Iseo 2014 Fasinumab 0.3 mg/kg IVI41 Ikman 2014b Tanezumab 10 mg IVI41 | -3.1 | 2.18 | 54 208 | -2.3 | 2.3 | 19 | 0.9% | -0.36 [-0.88, 0.17] -0.33 [-0.67, -0.09] | 2014 2014 | |
| Ekman 2014a Tanezumab 10 mg IVI14 | -2.82 | 2.73 | 206 | -1.84 | 2.73 | 103 | 2.4% | -0.36 [-0.60, -0.12] | 2014 | |
| Schnitzer 2015a Tanezumab 10 mg IV+naproxen M Schnitzer 2015b Tanezumab 10 mg IV/31 | -2.26 | 2.72 | 288 | -1.38 | 2.69 | 71 64 | 2.2% | -0.32 [-0.58, -0.06] | 2015 | |
| Schnitzer 2015b Tanezumab 10 mg IV+celecoxibI31 | 1 -2.42 | 2.55 | 254 | -1.42 | 2.56 | 64 | 2.0% | -0.39 [-0.67, -0.12] | 2015 | |
| Schnitzer 2015a Tanezumab 10 mg IV (49) Subtotal (95% Cl) | -1.9 | 2.88 | 288 2153 | -1.38 | 2.69 | 70 676 | 2.2% | -0.18 [-0.44, 0.08] -0.44 [-0.59, -0.30] | 2015 | • |
| teterogeneity: Tau ² = 0.04; Chi ² = 27.72, df = 11 (P fest for overall effect: Z = 5.95 (P < 0.00001) | = 0.00 | 4); l ^a = 6 | 0% | | | | | | | 2.5 |
| high-dose&IV&week 8 | | | | | | | | | | |
| lagashima 2011 Tanezumab 200 µg/kg IV I21 | -40.3 | 20.87 | 6 | -22.9 | 20.06 | 3 | 0.1% | -0.75 [-2.21, 0.71] | 2011 | |
| agashima 2011 Tanezumab 100 µg/kg IV i24 spierings 2013 Tanezumab 10 mg IV iati | -32.1 | 20.58 | 16 | -22.9 | 20.06 | 3 | 0.2% | -0.43 [-1.67, 0.81] -0.44 [-0.72 -0.15] | 2011 2013 | |
| Ekman 2014a Tanezumab 10 mg IV week 81141 | -3.41 | 2.58 | 206 | -1.94 | 2.58 | 103 | 2.3% | -0.57 [-0.81, -0.33] | 2014 | |
| xman 2014b Tanezumab 10 mg IV week 8141 iseo 2014 Fasinumab 0.3 mo/kg IV week 8141 | -2.55 | 2.88 | 208 54 | -1.55 | 2.6 | 104 | 2.4% | -0.36 [-0.59, -0.12] -0.65 [-1.19, -0.12] | 2014 2014 | |
| alanescu Tanezumab 10 mg IV+DSR week 8(2) | -2.08 | 2.05 | 145 | -1.46 | 2.1 | 51 | 1.7% | -0.30 [-0.62, 0.02] | 2014 | |
| Brbara 2018 Tanezumab 10 mg IVPI Subtotal (95% CI) | -3.12 | 2.2 | 84 869 | -2.24 | 1.95 | 18 371 | 0.9% | -0.40 [-0.92, 0.11] -0.44 [-0.57, -0.32] | 2018 | • |
| teterogeneity: Tau ² = 0.00; Chi ² = 3.09, df = 7 (P = fast for overall effect: 7 = 6.00 (P = 0.00001) | 0.88); 1 | * = 0% | | | | 1000 | | | | 08 |
| les: na Uveras enec: 2 = 0.99 (P < 0.00001) | | | | | | | | | | |
| nign-dose&SC&week 16 | -3.09 | 2.62 | 50 | -2.99 | 27 | 24 | 1.0% | -0.04 [-0.52, 0.45] | 2016 | |
| Mayorga 2016 Fulranumab 9 mg SCI21 | -3.43 | 3.49 | 66 | -2.2 | 3.15 | 11 | 0.6% | -0.35 [-0.99, 0.29] | 2017 | |
| Mayorga 2016 Fulranumab 9 mg SCI21 Sanga 2017 Fulranumab 10 mg SC q8wk I24 | -35 | 2.5 | 80 196 | -2.1 | 2.3 | 18 53 | 0.9% | -0.56 [-1.08, -0.05] -0.30 [-0.62, 0.021 | 2019 | • |
| Mayorga 2016 Fulranumab 9 mg SC대기 Sanga 2017 Fulranumab 10 mg SC q8wk I며 Dakin 2019 Fasinumab 9 mg SC대의 Subtotal (95% CI) | | | 100 | | | ~ | | and a south a start | | |
| Mayorga 2016 Fulranumab 9 mg SC (2017 Sanga 2017 Fulranumab 10 mg SC (2004 (2017 Jakin 2019 Fashiumab 9 mg SC (2019 Subtotal (95% CI) fetorogeneity: Tau ² = 0.01; Chi ² = 2.14, df = 2 (P = | 0.34); 1 | * = 6% | | | | | | | | |
| Mayonga 2016 Fulkanumab 9 mg SCP1 Sanga 2017 Purtanumab 10 mg SC q9xk Pil Dakin 2019 Fasinumab 9 mg SCPM Subtati (195% CI) 4eterogeneity: Tau ^p = 0.01; Chi ^p = 2.14, df = 2 (P = feat for overall effect 2 = 1.84 (P = 0.07) | 0.34); 1 | ² = 6% | | | | | | | | |
| Mayonga 2016 Fulranumab 9 mg SCIP1 Sanga 2017 Fulranumab 10 mg SC glek (J4) Jakin 2019 Fasimumab 9 mg SCIM Subtotal (95% C0) 4eterogeneity: Tau ⁴ = 0.01; Chi ² = 2.14, df = 2 (P = fext for overall effect: $Z = 1.84$ (P = 0.07) tigh-doce&SC&week 8 Kibera 2018 Tanezumab 10 mg SCIM | 0.34); 1 | 1.21 | 86 | -2.24 | 1.95 | 18 | 0.9% | -0.93 [-1.450.40] | 2018 | |
| Algorga 2016 Fulranumado 9 mg SCP1 Saga 2017 Fulranumado 9 mg SCP1 Salahi 2019 Fairsinumado 9 mg SCP1 Salahi 2019 Fairsinumado 9 mg SCP1 Salahi 2019 Fairsinumado 9 mg SCP1 Salahi 2010 Salahi 2010 SCP1 Salahi 2010 ScP1 | 0.34); I -3.51 | * = 6% 1.21 | 86 86 | -2.24 | 1.95 | 18 18 | 0.9% 0.9% | -0.93 [-1.45, -0.40] -0.93 [-1.45, -0.40] | 2018 | - |
| Algorga 2016 Fulranumab 9 mg SCP1 balan 2016 Fulranumab 9 mg SCP1 balan 2019 Faissunab 9 mg SCP1 balan 2019 Faissunab 9 mg SCP1 balan 2019 Faissunab 9 mg 2014 2, 14, df = 2 (P = test for overall effect 2 = 1.84 (P = 0.07) tigh-dose&SC&week 8 linebara 2018 Toinezamab 10 mg SC14 balanda (295-07) teatorogeneity. Not applicable ends for overall effect 2 = 3.46 (P = 0.0005) | 0.34); I -3.51 | ² = 6% 1.21 | 86 86 | -2.24 | 1.95 | 18 18 | 0.9% 0.9% | -0.93 [-1.45, -0.40] -0.93 [-1.45, -0.40] | 2018 | - |
| Mayonga 2017 Furturnuma 9 mg SCP1 Mayonga 2017 Furturnuma 9 mg SCP1 Santosal (1954). Critical (1955). Cri | 0.34); I -3.51 | * = 6% 1.21 | 86 86 | -2.24 | 1.95 | 18 18 4078 | 0.9% 0.9% 100.0% | -0.93 [-1.45, -0.40] -0.93 [-1.45, -0.40] -0.36 [-0.41, -0.30] | 2018 | = |

Figure A2. Subgroup analysis of WOMAC physical function scores according to dose, administration mode, and treatment duration.

| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV. Random, 95% C | IV. Random. 95% Cl |
|---|-----------|-----------------------|-------------|-------|-------|------------|-----------|--|--------------------|
| Balanescu 2014 Tanezumab 2.5 mg IV+DSR [2] | -0.52 | 0.88 | 157 | -0.34 | 0.86 | 51 | 1.9% | -0.20 [-0.52, 0.11] | |
| Brown 2012 Tanezumab 2.5 mg IV [7] Brown 2013 Tanezumab 2.5 mg IV [6] | -0.8 | 0.74 | 154 | -0.5 | 0.74 | 51 | 1.9% | -0.40 [-0.72, -0.08] | |
| Lane 2010 Tanezumab 10 µg/kg IV [26] | -16.3 | 14.62 | 74 | -9.2 | 15.38 | 14 | 0.8% | -0.48 [-1.05, 0.10] | |
| Lane 2010 Tanezumab 25 µg/kg IV [26] Subtotal (95% CI) | -23.6 | 13.86 | 75 | -9.2 | 15.38 | 15 182 | 0.8% | -1.01 [-1.59, -0.44] -0.42 [-0.63, -0.21] | • |
| Heterogeneity: Tau ^a = 0.02; Chi ^a = 5.89, df = 4 (P = Test for overall effect: Z = 3.92 (P < 0.0001) | 0.21); P | = 32% | | | | | | | |
| low-dose&IV&week 8 | | | | | | | | | |
| Balanescu Tanezumab 2.5 mg IV+DSR week 8 [2] Subtotal (95% CI) | -0.48 | 0.88 | 157 | -0.32 | 0.86 | 51 | 1.9% | -0.18 [-0.50, 0.13] -0.18 [-0.50, 0.13] | - |
| Heterogeneity: Not applicable | | | | | | | | | |
| low-dose&\$C&week 24 | | | | | | | | | |
| Berenbaum 2020 Tanezumab 2.5 mg SC [3] | -0.82 | 1.01 | 283 | -0.72 | 1.01 | 141 | 2.9% | -0.10 [-0.30, 0.10] | - |
| Subtotal (95% CI) | | | 283 | | | 141 | 2.9% | -0.10 [-0.30, 0.10] | - |
| Test for overall effect: Z = 0.96 (P = 0.34) | | | | | | | | | |
| low-dose&SC&week 16 | | | | | | | | | |
| Hochberg 2021 Tanezumab 2.5 mg SC [18] Sanga 2017 Fulranumab 1 mg SC g4wk [33] | -0.96 | 1.21 3.6 | 1002 | -0.94 | 1.21 | 498 | 3.9% | -0.02 [-0.12, 0.09] -0.02 [-0.63, 0.59] | |
| Sanga 2017 Fulranumab 3 mg SC q8wk[33] | -2.4 | 3.41 | 69 | -2.12 | 3.84 | 12 | 0.8% | -0.08 [-0.69, 0.53] | |
| Schnitzer 2019 Tanezumab 2.5 mg SC [34] Subtotal (95% CI) | -0.87 | 1.16 | 231 1372 | -0.65 | 1.17 | 116 638 | 2.7% 8.2% | -0.19 [-0.41, 0.03] -0.05 [-0.14, 0.05] | • |
| Heterogeneity: Tau ² = 0.00; Chi ² = 1.87, df = 3 (P = Test for overall effect: Z = 1.02 (P = 0.31) | 0.60); P | * = 0% | | | | | | | |
| low-dose&SC&week 8 | | | | | | | | | |
| Birbara 2018 Tanezumab 2.5 mg SC[4] Subtotal (95% CI) | -1.06 | 0.95 | 74 | -0.78 | 0.85 | 18 | 1.0% | -0.30 [-0.81, 0.22] | |
| Heterogeneity: Not applicable Test for overall effect: 7 = 1 13 (P = 0.26) | | | | | | 10 | 1.076 | -0.00 [*0.01; 0.22] | |
| moderate-dose&IV&week 16 | | | | | | | | | |
| Balanescu 2014 Tanezumab 5 mg IV+DSR [2] | -0.52 | 0.86 | 150 | -0.34 | 0.86 | 51 | 1.9% | -0.21 [-0.53, 0.11] | |
| Brown 2012 Tanezumab 5 mg IV [7] Brown 2013 Tanezumab 5 mg IV [6] | -0.9 | 0.87 | 156 | -0.5 | 0.74 | 52 52 | 1.9% | -0.47 [-0.79, -0.16] -0.53 [-0.85, -0.21] | |
| Ekman 2014a Tanezumab 5 mg IV [14] | -0.87 | 1 | 205 | -0.53 | 1 | 103 | 2.6% | -0.34 [-0.58, -0.10] | |
| Ekman 2014b Tanezumab 5 mg IV [14] Lane 2010 Tanezumab 50 ug/kg IV [26] | -0.73 | 1.02 | 211 | -0.39 | 1.01 | 105 | 2.6% | -0.33 [-0.57, -0.10] -0.56 [-1.13, -0.00] | |
| Schnitzer 2015a Tanezumab 5 mg IV [35] | -0.54 | 0.84 | 285 | -0.54 | 0.84 | 71 | 2.4% | 0.00 [-0.26, 0.26] | |
| Schnitzer 2015a Tanezumab 5 mg IV+naproxen [35 Schnitzer 2015b Tanezumab 5 mg IV[35] | -0.62 | 0.84 | 280 | -0.54 | 0.84 | 71 | 2.4% | -0.10 [-0.36, 0.17] | |
| Schnitzer 2015b Tanezumab 5 mg IV+celecoxib [35 | -0.74 | 0.8 | 256 | -0.54 | 0.8 | 64 | 2.3% | -0.25 [-0.52, 0.03] | |
| Subtotal (95% CI) Heterogeneity: Tau ² = 0.01; Chi ² = 12.35, df = 9 (P Test for overall effect: Z = 4.90 (P < 0.00001) | = 0.19); | ² = 27% | 2021 | | | 648 | 21.2% | -0.27 [-0.37, -0.16] | • |
| moderate-dose&IV&week 8 | | | | | | | | | |
| Balanescu Tanezumab 5 mg IV+DSR week 8 [2] | -0.65 | 0.86 | 150 | -0.32 | 0.86 | 51 | 1.9% | -0.38 [-0.70, -0.06] | |
| Ekman 2014a Tanezumab 5 mg IV week 8 [14] Ekman 2014b Tanezumab 5 mg IV week 8 [14] | -0.95 | 0.86 | 205 | -0.52 | 0.86 | 103 | 2.6% | -0.50 [-0.74, -0.26] -0.45 [-0.69, -0.21] | |
| Spierings 2013 Tanezumab 5 mg IV [40] | -0.9 | 0.89 | 161 | -0.52 | 0.95 | 71 | 2.2% | -0.42 [-0.70, -0.13] | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 0.38, df = 3 (P = | 0.94); P | * = 0% | 121 | | | 330 | 9.3% | -0.45 [-0.58, -0.31] | • |
| Test for overall effect: Z = 6.63 (P < 0.00001) | | | | | | | | | |
| moderate-dose&SC&week 24 Berenbaum 2020 Tanezumab 5 mg SC [3] | -0.9 | 1.01 | 284 | -0.72 | 1.01 | 141 | 2.9% | -0.18 [-0.38, 0.02] | - |
| Subtotal (95% CI) | | | 284 | | | 141 | 2.9% | -0.18 [-0.38, 0.02] | - |
| Heterogeneity: Not applicable Test for overall effect: Z = 1.72 (P = 0.08) | | | | | | | | | |
| moderate-dose&SC&week 16 | | | | | | | | | |
| Hochberg 2021 Tanezumab 5 mg SC [18] Mayorga 2016 Fulranumab 3 mg SC [27] | -0.97 | 1.21 | 998 48 | -0.94 | 1.21 | 498 | 3.9% | -0.02 [-0.13, 0.08] -0.08 [-0.57, 0.41] | |
| Sanga 2017 Fulranumab 3 mg SC q4wk [33] | -2.52 | 3.3 | 68 | -2.12 | 3.84 | 12 | 0.8% | -0.12 [-0.73, 0.50] | |
| Sanga 2017 Fulranumab 6 mg SC q8wk [33] Schnitzer 2019 Tanezumab 2 5/5 mg SC [34] | -2.4 | 3.41 | 233 | -2.12 | 3.84 | 12 | 0.8% | -0.08 [-0.69, 0.53] -0.21 [-0.44, 0.01] | |
| Subtotal (95% CI) | | | 1416 | | 1212 | 662 | 9.2% | -0.06 [-0.16, 0.03] | • |
| Heterogeneity: Tau ^a = 0.00; Chi ^a = 2.26, df = 4 (P = Test for overall effect: Z = 1.32 (P = 0.19) | 0.69); P | * = 0% | | | | | | | |
| moderate-dose&SC&week 8 Bidbara 2018 Tananumah 5 ma SC (4) | -0.05 | 0.97 | 63 | 0.78 | 0.85 | 10 | 1.0% | 0 10 10 72 0 331 | |
| Subtotal (95% CI) | -0.00 | 0.07 | 63 | -9-10 | 0.00 | 18 | 1.0% | -0.19 [-0.72, 0.33] | - |
| Heterogeneity: Not applicable Test for overall effect: Z = 0.73 (P = 0.47) | | | | | | | | | |
| high-dose&IV&week 16 | | | | | | | | | |
| Balanescu 2014 Tanezumab 10 mg IV+DSR [2] Brown 2012 Tanezumab 10 mg IV 71 | -0.58 | 0.84 | 145 | -0.34 | 0.86 | 50 | 1.9% | -0.28 [-0.61, 0.04] | |
| Brown 2013 Tanezumab 10 mg IV[6] | -0.81 | 0.87 | 156 | -0.34 | 0.74 | 51 | 1.9% | -0.56 [-0.88, -0.24] | |
| Ekman 2014a Tanezumab 10 mg IV[14] | -0.73 | 1.01 | 207 | -0.53 | 1 | 103 | 2.6% | -0.20 [-0.44, 0.04] | |
| Lane 2010 Tanezumab 100 µg/kg IV [14] | -23.7 | 13.76 | 74 | -9.2 | 15.38 | 14 | 0.8% | -1.03 [+1.62, -0.43] | |
| Lane 2010 Tanezumab 200 µg/kg IV [26] | -21 | 14.42 | 72 | -9.2 | 15.38 | 15 | 0.9% | -0.80 [-1.37, -0.23] | |
| Schnitzer 2015a Tanezumab 10 mg IV[35] Schnitzer 2015a Tanezumab 10 mg IV+naprovent3 | -0.61 | 0.85 | 288 | -0.54 | 0.84 | 70 | 2.4% | -0.08 [-0.34, 0.18] -0.21 [-0.47, 0.05] | |
| Schnitzer 2015b Tanezumab 10 mg IV [35] | -0.59 | 0.8 | 254 | -0.54 | 0.8 | 64 | 2.3% | -0.06 [-0.34, 0.21] | |
| Schnitzer 2015b Tanezumab 10 mg IV+celecoxib[3 Subtotal (95% CI) | 6] -0.75 | 0.8 | 254 2100 | -0.54 | 0.8 | 64 657 | 2.3% | -0.26 [-0.54, 0.01] -0.34 [-0.48, -0.20] | • |
| Heterogeneity: Tau ^a = 0.03; Chi ^a = 23.18, df = 10 (F Test for overall effect: Z = 4.73 (P < 0.00001) | P = 0.01) | ; l ^a = 57 | % | | | | | · · · · · · · · · · · · · · · · · · · | |
| high-dose&IV&week 8 | | | | | | | | | |
| Balanescu Tanezumab 10 mg IV+DSR week 8 [2] Birbara 2018 Tanezumab 10 mg IV/M | -0.62 | 0.84 | 145 | -0.32 | 0.86 | 50 18 | 1.9% | -0.35 [-0.68, -0.03] | |
| Ekman 2014a Tanezumab 10 mg IV week 8 [14] | -0.96 | 0.86 | 207 | -0.52 | 0.85 | 103 | 2.6% | -0.51 [-0.75, -0.27] | |
| Ekman 2014b Tanezumab 10 mg IV week 8 [14] Splatings 2013 Tanezumab 10 mg IV (40) | -0.79 | 0.87 | 208 | -0.43 | 1.16 | 104 | 2.6% | -0.37 [-0.61, -0.13] | |
| Subtotal (95% CI) | -1 | 0.99 | 794 | -0.52 | 0.95 | 345 | 10.2% | -0.42 [-0.54, -0.29] | • |
| Heterogeneity: Tau ² = 0.00; Chi ² = 2.43, df = 4 (P = Test for overall effect: Z = 6.34 (P < 0.00001) | 0.66); P | *= 0% | | | | | | | |
| high-dose&SC&week 16 | | | | | | | | | |
| Mayorga 2016 Fulranumab 9 mg SC [27] | -3.16 | 3.11 | 50 | -2.84 | 2.98 | 24 | 1.1% | -0.10 [-0.59, 0.38] | |
| Sanga 2017 Fulranumab 10 mg SC q8wk[33] Subtotal (95% CI) | -2.69 | 3.33 | 66 116 | -2.12 | 3.84 | 11 35 | 0.7% | -0.17 [-0.80, 0.47] -0.13 [-0.51, 0.26] | - |
| Heterogeneity: Tau ² = 0.00; Chi ² = 0.02, df = 1 (P = Test for overall effect: Z = 0.64 (P = 0.52) | 0.88); P | * = 0% | | | | | - 14 14 | | |
| high-dose&SC&week 8 | | | | | | | | | |
| ingit doucadouncer o | | 11 | 86 | -0.78 | 0.85 | 18 | 1.0% | -0.28 [-0.79, 0.23] | |
| Birbara 2018 Tanezumab 10 mg SC [4] | -1.08 | | - | | | | | 10 M 10 M 10 M 10 M 10 | |
| Birbara 2018 Tanezumab 10 mg SC [4] Subtotal (95% Cl) Heterogeneity: Not applicable | -1.08 | | 86 | | | 18 | 1.0% | -0.28 [-0.79, 0.23] | |
| Birbara 2018 Tanezumab 10 mg SC [4] Subtotal (95% Cl) Heterogeneity: Not applicable Test for overall effect: Z = 1.08 (P = 0.28) | -1.08 | | 86 | | | 18 | 1.0% | -0.28 [-0.79, 0.23] | |
| By the constant of the second | -1.08 | 0012 12 - | 86 10104 | | | 3884 | 1.0% | -0.28 [-0.79, 0.23] | • |

Figure A3. Subgroup analysis of PGA scores according to dose, administration mode, and treatment duration.

| low-dose&IV | Events | Total | Events | Total | Weight | Risk Ratio M-H, Random, 95% Cl Year | Risk Ratio M-H, Random, 95% Cl |
|--|---|---|--|--|--|--|-----------------------------------|
| 2010 Terreret 10 8- 8/126 | | | | | 0.49/ | 1 01 10 75 1 051 0010 | |
| Lane 2010 Tanezumab 25 uo/kg IV 126 | 49 | 74 | 8 | 14 | 0.4% | 1.24 [0.75, 1.95] 2010 | |
| Nagashima 2011 Tanezumab 10 µg/kg IV ^[29] | 9 | 15 | 3 | 3 | 0.3% | 0.68 [0.39, 1.18] 2011 | |
| Nagashima 2011 Tanezumab 25 µg/kg IV ^[29] | 4 | 15 | 2 | 3 | 0.1% | 0.40 [0.13, 1.28] 2011 | |
| Brown 2012 Tanezumab 2.5 mg IV 17 | 100 | 172 | 27 | 57 | 0.9% | 1.23 [0.91, 1.66] 2012 | |
| Brown 2013 Tanezumab 2.5 mg IV [6] | 90 | 155 | 23 | 52 | 0.8% | 1.31 [0.94, 1.83] 2013 | |
| Balanescu 2014 Tanezumab 2.5 mg IV+DSR [2] | 73 | 157 | 18 | 51 | 0.5% | 1.32 [0.88, 1.98] 2014 | |
| Fiseo 2014 Fasinumab 0.03 mg/kg TVHI Subtotal (95% CI) | 37 | 718 | 11 | 213 | 0.5% | 1.08 [0.71, 1.63] 2014 | • |
| Total events | 413 | /10 | 100 | 213 | 3.7 70 | 1.15 [0.57, 1.56] | |
| Heterogeneity: Tau ² = 0.01: Chi ² = 8.44, df = 7 (P | = 0.30); P | 2 = 17% | 100 | | | | |
| Fest for overall effect: Z = 1.58 (P = 0.11) | elect, | | | | | | |
| low-dose&SC | | | | | | | |
| Sanga 2013 Fulranumab 3 mg SC q8wk (32) | 47 | 76 | 8 | 15 | 0.3% | 1.16 [0.70, 1.92] 2013 | |
| Sanga 2013 Fulranumab 1 mg SC q4wk [32] | 36 | 77 | 8 | 16 | 0.3% | 0.94 [0.54, 1.61] 2013 | - |
| Sanga 2017 Fulranumab 1 mg SC q4wk [3] | 66 | 77 | 14 | 15 | 3.2% | 0.92 [0.78, 1.08] 2017 | |
| Sanga 2017 Fuiranumab 3 mg SC qdwk (3) Birbara 2018 Tapezumab 2.5 mg SC (d) | 35 | 76 | 13 | 15 | 2.0% | 1.09 [0.89, 1.34] 2017 | |
| Schnitzer 2019 Tanezumab 2.5 mg SC [34] | 33 | 233 | 15 | 116 | 0.3% | 1.10 [0.62, 1.93] 2019 | |
| Dakin 2019 Fasinumab 1 mg SC (10) | 54 | 85 | 11 | 21 | 0.4% | 1.21 [0.78, 1.88] 2019 | |
| Dakin 2019 Fasinumab 3 mg SC [10] | 52 | 84 | 11 | 20 | 0.5% | 1.13 [0.73, 1.73] 2019 | |
| Kelly 2019 Fulranumab 1 mg SC [23] | 62 | 81 | 26 | 41 | 1.2% | 1.21 [0.93, 1.57] 2019 | |
| Berenbaum 2020 Tanezumab 2.5 mg SC [3] | 184 | 283 | 89 | 141 | 3.6% | 1.03 [0.88, 1.20] 2020 | T |
| Hochberg 2021 Tanezumab 2.5 mg SC ^[16] | 681 | 1002 | 333 | 498 | 14.9% | 1.02 [0.94, 1.10] 2021 | 1 |
| Subtotal (95% CI) | 1222 | 2140 | 637 | 910 | 27.0% | 1.02 [0.97, 1.08] | T T |
| Heterogeneity: Tau ² = 0.00: Chi ² = 5.04, df = 10 (| P = 0.89): | $l^2 = 0\%$ | 557 | | | | |
| Test for overall effect: Z = 0.86 (P = 0.39) | | | | | | | |
| noderate-dose&IV | | | | | | | |
| ane 2010 Tanezumab 50 µg/kg IV [24] | 44 | 74 | 8 | 15 | 0.3% | 1.11 [0.67, 1.86] 2010 | |
| Nagashima 2011 Tanezumab 50 µg/kg IV 1291 | 9 | 15 | 3 | 3 | 0.3% | 0.68 [0.39, 1.18] 2011 | |
| Brown 2012 Tanezumab 5 mg IV 171 | 95 | 172 | 28 | 57 | 1.0% | 1.12 [0.84, 1.51] 2012 | |
| Brown 2013 Tanezumab 5 mg IV 161 | 84 | 154 | 23 | 52 | 0.7% | 1.23 [0.88, 1.73] 2013 | |
| Spierings 2013 Tanezumab 5 mg IV (40) | 72 | 161 | 25 | 71 | 0.7% | 1.27 [0.89, 1.82] 2013 | |
| Ekman 2014a Tanezumab 5 mg IV III | 107 | 206 | 49 | 104 | 1.4% | 1.10 [0.87, 1.40] 2014 | |
| Srown 2014 Tanezumab 5 mg IV 14 | 41 | 211 | 19 | 105 | 1.2% | 1.06 [0.74, 1.54] 2014 | |
| Balanescu 2014 Tanezumah 5 mg IV+DSR IZ | 72 | 150 | 18 | 51 | 0.5% | 1.36 [0.91 2.04] 2014 | <u> </u> |
| Tiseo 2014 Fasinumab 0.1 mg/kg. IVI4II | 39 | 52 | 12 | 18 | 0.6% | 1.13 [0.78, 1.62] 2014 | |
| Schnitzer 2015 Tanezumab 5 mg IV [35] | 405 | 541 | 91 | 134 | 5.3% | 1.10 [0.97, 1.25] 2015 | - |
| Schnitzer 2015 Tanezumab 5 mg IV +NSAID [35] | 390 | 536 | 91 | 135 | 5.1% | 1.08 [0.95, 1.23] 2015 | 1 |
| Subtotal (95% CI) | | 2345 | | 781 | 17.7% | 1.11 [1.04, 1.19] | • |
| fotal events | 1459 | 12 - 00/ | 410 | | | | |
| Test for overall effect: Z = 2.96 (P = 0.003) | P = 0.90); | 1. = 0.% | | | | | |
| | | | | | | | |
| noderate-dose&SC | 45 | 78 | 8 | 15 | 0.3% | 1 08 10 65 1 801 2013 | |
| Sanga 2013 Fulranumab 3 mg SC gowk (st) | 40 | 70 | 8 | 16 | 0.3% | 1 27 10 75 2 121 2013 | |
| Javorna 2016 Fulranumab 3 mg SC (27) | 30 | 48 | 18 | 24 | 0.8% | 0.83 [0.61, 1.15] 2016 | |
| Sanga 2017 Fulranumab 3 mg SC q4wkl33 | 74 | 79 | 14 | 16 | 2.2% | 1.07 [0.88, 1.30] 2017 | + |
| Sanga 2017 Fulranumab 6 mg SC q8wk [33] | 72 | 78 | 14 | 16 | 2.2% | 1.05 [0.87, 1.28] 2017 | |
| Birbara 2018 Tanezumab 5 mg SC [4] | 31 | 63 | 9 | 18 | 0.3% | 0.98 [0.58, 1.66] 2018 | |
| Dakin 2019 Fasinumab 6 mg SC IIII | 55 | 85 | 12 | 21 | 0.5% | 1.13 [0.76, 1.69] 2019 | |
| Schnitzer 2019 Tanezumab 2.5/5 mg SCI34 | 40 | 231 | 16 | 116 | 0.3% | 1.26 [0.74, 2.14] 2019 | |
| Reanhaum 2020 Tanazumah 5 mg SCI3 | 108 | 284 | 20 | 141 | 3.9% | 1.10 [0.86, 1.52] 2019 | - |
| Hochberg 2021 Tanezumab 5 mg SCIIN | 744 | 998 | 333 | 498 | 16.4% | 1.11 [1.04, 1.20] 2021 | - |
| | | 2106 | | 921 | 00 40/ | the first that and | |
| Subtotal (95% CI) | | | | | 28.4% | 1.10 [1.04, 1.16] | • |
| fotal events | 1399 | | 546 | | 28.4% | 1.10 [1.04, 1.16] | • |
| subtotal (95% Cl) Fotal events Heterogeneity: Tau ² = 0.00; Chi ² = 4.22, df = 10 (fest for overall effect: Z = 3.38 (P = 0.0007) | 1399 P = 0.94); | ls = 0% | 546 | | 28.4% | 1.10 [1.04, 1.16] | • |
| subtotal (95% CI) Total events teterogeneity: Tau ^a = 0.00; Chi ^a = 4.22, df = 10 (fest for overall effect: Z = 3.39 (P = 0.0007) | 1399 P = 0.94); | Is = 0% | 546 | | 28.4% | 1.10 [1.04, 1.16] | • |
| subtotal (95% Cf) fotal events feterogeneity: Tau ² = 0.00; Chi ² = 4.22, df = 10 (rest for overall effect: Z = 3.39 (P = 0.0007) ligh-dose&IV ane 2010 Tanezumab 100 un/kg IV [24] | 1399 P = 0.94); 51 | I ² = 0% | 546 8 | 15 | 0.3% | 1.10 [1.04, 1.16] | • |
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| substat (95% CI) folal events feterogeneity: Tau ² = 0.00; Chi ² = 4.22, df = 10 (fest for overall effect: Z = 3.30 (P = 0.0007) high-dose&IV ane 2010 Tanezumab 200 µg/kg (V 24 dagashima 2011 Tanezumab 200 µg/kg (V /24 dagashima 2011 Tanezumab 100 µg/kg (V /24 Sizem 20145 Tanezumab 100 µg (V /44 Sizema 20146 Tanezumab 100 µg (V /44 Sizehotal (95% CI) folal events dest for overall effect: Z = 4.04 (P < 0.0001) high-dose&SC anaga 2013 Fulranumab 10 mg SC q@wkiµz] dayorga 2016 Fulranumab 10 mg SC q@wkiµz] dayorga 2017 Fulranumab 10 mg SC q@wkiµz] dayorga 2016 Fulran | 1399 (P = 0.94); 51 58 8 6 104 89 61 48 122 101 39 71 1 400 399 44 1601 (P = 0.98); P = 0.98); 42 41 68 8 36 | 74 74 74 16 6 174 150 74 208 208 208 208 208 208 209 52 145 542 84 2507 1 ² = 0% | 88 99 23 328 225 200 500 500 422 17 17 91 99 429 88 19 91 4 10 | 15 15 3 4 58 51 70 36 104 19 50 36 104 19 50 38 104 19 50 38 817 16 24 4 6 24 4 6 18 817 | 0.3% 0.5% 0.2% 1.0% 0.7% 0.7% 0.7% 0.7% 1.1% 0.6% 0.7% 0.3% 1.4% 2.0% | 1.10 [1.04, 1.16] 1.29 [0.79, 2.13] 2010 1.31 [0.85, 2.01] 2010 0.75 [0.29, 1.92] 2011 1.33 [0.22, 2.44] 2011 1.24 [0.92, 1.66] 2012 1.31 [0.33, 1.65] 2013 1.17 [0.33, 1.64] 2014 1.20 [0.97, 1.54] 2014 1.20 [0.97, 1.54] 2014 1.40 [0.96, 1.24] 2015 1.06 [0.63, 1.83] 2013 1.66 [0.63, 1.83] 2013 1.66 [0.63, 1.83] 2013 1.66 [0.63, 1.83] 2016 1.06 [0.63, 1.82] 2017 1.06 [0.63, 1.22] 2017 1.07 [0.47, 1.22] 2017 | |
| substatu (95% CI) folal events feterogeneity: Tau" = 0.00; Chi ^a = 4.22, df = 10 (feterogeneity: Tau" = 0.00; Chi ^a = 4.22, df = 10 (inter to roverall effect: Z = 3.39 (P = 0.0007) high-dose&IV ane 2010 Tanezumab 200 µg/kg (V IAI lagasthima 2011 Tanezumab 100 µg/kg (V IAI lagasthima 2013 Tanezumab 10 mg IV/IHI Strown 2013 Tanezumab 10 mg IV/IHI Strown 2014 Tanezumab 10 mg IV/IHI Strom 2014 Tanezumab 10 mg IV/IHI Stranz 2014 Tanezumab 10 mg IV/IHI Stranz 2014 Tanezumab 10 mg IV/IHI Stranz 2014 Tanezumab 10 mg IV/IHI Schnitzer 2015 Tanezumab 10 mg IV/IHI Schnitzer 2015 Tanezumab 10 mg IV/IHI Stortal events feterogeneity: Tau" = 0.00; Chi ^a = 5.37, df = 14 (fest for overall effect: Z = 4.04 (P < 0.0001) IngIn-dose&SC Sanga 2017 Fulranumab 10 mg SC µHK Stortar 2015 Fainanumab 10 mg SC IHI Sangu 2017 Fulranumab 10 mg SC IHI Sangu 2015 Fulranumab 10 mg SC IHI Sangu 2017 Fulranumab 10 mg SC IHI S | $\begin{array}{c} 1399\\ 1599\\ 511\\ 58\\ 8\\ 6\\ 6\\ 104\\ 89\\ 61\\ 142\\ 101\\ 399\\ 71\\ 1\\ 1601\\ 399\\ 44\\ 1601\\ 399\\ 44\\ 1601\\ 1098\\ 1098\\ 10\\ 1098\\ 1098\\ 1008\\ 10$ | 74 74 76 6 77 150 74 150 74 150 74 150 74 208 209 52 2542 542 2507 78 84 78 850 78 866 83 375 | 88 99 22 33 282 255 200 422 17 91 91 91 91 91 91 91 91 91 91 | 15 15 3 4 58 51 70 6 104 104 104 105 135 135 135 8 17 16 24 16 24 | 0.3% 0.5% 0.5% 0.7% 1.0% 0.6% 0.7% 1.1% 0.6% 0.6% 0.3% 1.8.6% | 1.10 [1.04, 1.16] 1.29 [0.79, 2.13] 2010 1.31 [0.85, 2.01] 2010 0.75 [0.29, 1.92] 2011 1.33 [0.72, 2.44] 2011 1.34 [0.22, 1.66] 2012 1.31 [0.33, 1.85] 2013 1.14 [0.79, 1.65] 2013 1.17 [0.83, 1.65] 2013 1.17 [0.83, 1.65] 2013 1.17 [0.81, 1.65] 2013 1.19 [0.61, 1.73] 2014 1.20 [0.91, 1.57] 2014 1.40 [0.96, 1.24] 2015 1.05 [0.66, 1.24] 2015 1.05 [0.66, 1.24] 2015 1.05 [0.66, 1.24] 2015 1.05 [0.63, 1.74] 2018 1.15 [1.07, 1.23] 1.06 [0.63, 1.83] 2013 1.04 [0.61, 1.32] 2016 1.05 [0.64, 1.42] 2017 0.75 [0.47, 1.22] 2017 0.75 [0.47, 1.25] 2017 0.75 [0.47, 1.45 | |
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| substatu (95% CI) folal events feterogeneity: Tau ² = 0.00; Ch ² = 4.22, df = 10 (feterogeneity: Tau ² = 0.000; Ch ² = 0.0007) high-dose&IV ane 2010 Tanezumab 100 µg/kg IV (24) lagastima 2011 Tanezumab 200 µg/kg IV (24) lagastima 2011 Tanezumab 100 µg/kg IV (24) lagastima 2011 Tanezumab 100 µg/kg IV (24) lagastima 2013 Tanezumab 100 µg IV (14) listown 2014 Tanezumab 100 µg IV (14) listown 2014 Tanezumab 100 µg IV (14) listown 2014 Tanezumab 100 µg IV (14) lalanescu 2014 Tanezumab 10 µg IV (14) listown 2015 Tanezumab 10 µg IV (14) listown 2016 Tanezumab 10 µg SC (14) listown 2016 Tanezu | $\begin{array}{c} 1399\\ 9(P=0.94);\\ 51\\ 51\\ 58\\ 8\\ 8\\ 8\\ 6\\ 104\\ 89\\ 61\\ 104\\ 122\\ 101\\ 399\\ 71\\ 1\\ 1\\ 122\\ 101\\ 399\\ 71\\ 1\\ 1\\ 9\\ 2\\ 102\\ 1\\ 122\\ 102\\ 1\\ 122\\ 102\\ 1\\ 122\\ 122\\$ | P ² = 0% 74 74 16 6 174 157 145 542 84 2507 78 84 2507 78 83 375 2 = 0% 10199 | 8 8 9 2 2 2 2 2 2 2 2 2 2 2 2 2 | 15 15 3 4 58 51 70 36 104 19 50 36 104 19 50 36 104 19 50 36 104 19 50 51 51 51 51 51 51 51 51 51 51 51 51 51 | 0.3% 0.5% 0.5% 0.1% 0.7% 0.7% 0.7% 0.7% 0.7% 0.6% 0.3% 1.6% 0.3% 18.6% | 1.10 [1.04, 1.16] 1.29 [0.79, 2.13] 2010 1.31 [0.85, 2.01] 2010 0.75 [0.29, 192] 2011 1.33 [0.72, 2.44] 2011 1.24 [0.92, 1.66] 2012 1.37 [0.93, 1.65] 2013 1.17 [0.83, 1.64] 2014 1.22 [0.97, 1.64] 2014 1.22 [0.97, 1.64] 2014 1.29 [0.7, 1.64] 2014 1.29 [0.7, 1.64] 2014 1.90 [0.66, 1.24] 2015 1.06 [0.63, 1.73] 2014 1.15 [1.07, 1.23] 1.08 [0.63, 1.83] 2013 1.04 [0.81, 1.32] 2016 1.05 [0.68, 1.63] 2013 1.06 [0.63, 1.83] 2013 1.06 [0.63, 1.83] 2013 1.06 [0.63, 1.83] 2013 1.06 [0.63, 1.83] 2013 1.06 [0.68, 1.63] 2019 1.06 [0.68, 1.63] 2019 1.06 [0.68, 1.63] 2019 1.06 [0.67, 1.14] | |
| subtotal (95% CI) folal events feterogeneity: Tau ² = 0.00; Chi ² = 4.22, df = 10 (fest for overall effect: Z = 3.80 (P = 0.0007) iigh-dose&IV ane 2010 Tanezumab 200 µgkg (V 24 lagashima 2011 Tanezumab 200 µgkg (V 24 lagashima 2011 Tanezumab 100 µgkg (V 24 lagashima 2014 Tanezumab 100 µg (V 44 kiman 2014b Tanezumab 100 µg (V 44 kiman 2014b Tanezumab 100 µg (V 44 kiman 2014b Tanezumab 100 µg (V 44 litenase 2014 Fanezumab 100 µg (V 44 litenase 2014 Fanezumab 100 µg (V 44 litenase 2016 Tanezumab 100 µg (V 44 litenase 2016 Tanezumab 100 µg (V 44 litenase 2016 Funezumab 100 µg (S (B) kintzer 2015 Fun | 1399 (P = 0.94); 511 58 8 8 6 104 48 8 6 104 146 146 146 146 147 19 7 11 1 10 1 399 44 4 1601 19 235 2 42 245 262); 11 9 20 8 20 8 20 9 20 9 20 9 20 9 20 9 20 | P² = 0% 74 16 6 174 150 744 209 52 201 145 542 84 2507 P² = 0% 83 375 2* = 0% 10199 | 546 8 9 9 2 3 3 28 2 2 5 20 0 0 42 12 17 91 9 14 29 429 8 19 14 429 2 25 20 0 0 11 11 9 1 2 2 2 5 20 0 0 2 2 2 5 20 2 2 5 20 2 2 2 5 20 2 2 2 5 20 5 2 2 2 5 2 2 5 2 5 | 15 15 3 4 58 51 70 36 104 104 104 104 135 51 35 135 135 135 135 135 135 135 1 | 0.3% 0.5% 0.5% 0.7% 0.7% 0.6% 0.7% 0.7% 0.3% 1.6% 0.3% 1.8% 0.3% 4.6% | 1.10 [1.04, 1.16] 1.29 [0.79, 2.13] 2010 1.31 [0.85, 2.01] 2010 0.75 [0.29, 1.92] 2011 1.33 [0.22, 2.44] 2011 1.24 [0.92, 1.66] 2012 1.31 [0.33, 1.65] 2013 1.17 [0.33, 1.64] 2014 1.20 [0.97, 1.54] 2014 1.20 [0.97, 1.54] 2014 1.40 [0.96, 1.57] 2014 1.40 [0.96, 1.57] 2014 1.40 [0.96, 1.24] 2015 1.06 [0.63, 1.83] 2013 1.04 [0.81, 1.32] 2016 1.05 [0.63, 1.83] 2013 1.06 [0.63, 1.83] 2013 1.06 [0.63, 1.83] 2013 1.06 [0.63, 1.12] | |
| subtat (95% CI) folal events feterogeneity: Tau" = 0.00; Chi ^a = 4.22, df = 10 (feterogeneity: Tau" = 0.00; Chi ^a = 0.0007) high-dose&IV ane 2010 Tanezumab 100 µg/kg [V [34] ane 2010 Tanezumab 200 µg/kg [V [34] ane 2010 Tanezumab 100 µg/kg [V [34] Agashima 2011 Tanezumab 100 µg/kg [V [34] Agashima 2011 Tanezumab 100 µg/kg [V [34] Agashima 2011 Tanezumab 100 µg/kg [V [34] Strown 2013 Tanezumab 100 µg/kg [V [34] Strown 2013 Tanezumab 100 µg/kg [V [34] Strown 2014 Tanezumab 100 µg/kg [V [34] Strom 2014 Tanezumab 100 µg [V [44] Strana 2014b Tanezumab 100 µg [V [44] Strana 2014b Tanezumab 100 µg [V [44] Strana 2015 Tanezumab 10 mg [V [44] Strana 2015 Tanezumab 10 mg [V [44] Strana 2015 Tanezumab 10 mg [V [44] Stontizer 2015 Tanezumab 10 mg [V [44] Stontizer 2015 Tanezumab 10 mg [V [44] Stontizer 2015 Tanezumab 10 mg [V [44] Stotal events feterogeneity: Tau" = 0.00; Chi ^a = 5.37, df = 14 (Feterogeneity; Tau" = 0.00; Chi ^a = 1.55, df = 4 (P stotsortal (95% CI) folal events storevental effect: Z = 0.05 (P = 0.96) folal (95% CI) folal events storevental effect: Tau = 4.058, df = 61 | 1399 (P = 0.94); 51 58 8 8 6 104 89 8 61 104 101 101 101 399 49 4 400 89 99 49 400 99 99 49 400 109 99 49 40 40 235 5 205 21 5 6 6 6 6 6 6 6 6 6 6 7 7 8 9 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 | P² = 0% 74 76 74 76 6 174 150 74 157 74 157 74 157 74 157 74 157 74 150 52 542 542 542 542 542 542 542 542 542 542 542 542 560 78 86 375 7= 0% 10199 1; P = 0% | 88992332552004222552004222177911999422988889114101116222084 | 15 15 3 4 58 51 70 36 104 104 104 104 105 135 135 135 18 817 16 24 16 820 94 | 0.3% 0.5% 0.1% 0.2% 0.7% 0.7% 0.7% 0.7% 0.5% 0.3% 1.1% 0.5% 0.3% 1.8.6% | 1.10 [1.04, 1.16] 1.29 [0.79, 2.13] 2010 1.31 [0.85, 2.01] 2010 0.75 [0.29, 1.92] 2011 1.33 [0.22, 2.44] 2011 1.33 [0.22, 2.44] 2011 1.40 [0.21, 2.68] 2013 1.17 [0.33, 1.64] 2014 1.22 [0.97, 1.64] 2014 1.20 [0.61, 1.73] 2014 1.40 [0.61, 1.73] 2014 1.40 [0.61, 1.73] 2014 1.40 [0.61, 1.73] 2014 1.45 [0.63, 1.63] 2013 1.06 [0.63, 1.63] 2013 1.04 [0.61, 1.22] 2016 1.05 [0.68, 1.63] 2019 1.06 [0.68, 1.63] 2019 1.06 [0.68, 1.63] 2019 1.00 [0.87, 1.14] | |

Figure A4. Subgroup analysis of adverse events according to dose and administration mode.

| Study or Subaroup | Events | Total | Events | Total | Weight | M-H. Random. 95% C | M-H, Random, 95% CI |
|--|--|---|---|---|---|---|---|
| ow-dose&IV | | | | | | | |
| alanescu 2014 Tanezumab 2.5 mg IV+DSR I2I | 12 | 157 | 3 | 51 | 1.6% | 1.30 [0.38, 4.42] | ` _ |
| rown 2012 Tanezumab 2.5 mg IV[7] | 3 | 172 | 1 | 57 | 0.5% | 0.99 [0.11, 9.37] | |
| rown 2013 Tanezumab 2.5 mg IV[6] | 7 | 155 | 2 | 52 | 1.0% | 1.17 [0.25, 5.48] | |
| ane 2010 Tanezumab 10 µg/kg IV[26] | 0 | 74 | 0 | 14 | | Not estimable | 12 II |
| ane 2010 Tanezumab 25 µg/kg IVI26] | 1 | 74 | 0 | 15 | 0.2% | 0.64 [0.03, 15.01] | |
| lagashima 2011 Tanezumab 10 µg/kg IV [29] | 1 | 15 | 0 | 3 | 0.3% | 0.75 [0.04, 15.17] | |
| Nagashima 2011 Tanezumab 25 µg/kg IV 129 | 1 | 15 | 0 | 3 | 0.3% | 0.75 [0.04, 15.17] | |
| Subtotal (95% CI) | | 662 | | 195 | 4.0% | 1.09 [0.49, 2.39] | - |
| Total events | 25 | | 6 | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 0.32, df = 5 (F | = 1.00); I | ² = 0% | | | | | |
| Test for overall effect: Z = 0.20 (P = 0.84) | | | | | | | |
| ow-dose&SC | | | | | | | |
| Berenbaum 2020 Tanezumab 2.5 mg SC [3] | 11 | 283 | 13 | 141 | 4.1% | 0.42 [0.19, 0.92] | |
| Birbara 2018 Tanezumab 2.5 mg SC [4] | 2 | 74 | 1 | 18 | 0.4% | 0.49 [0.05, 5.07] | |
| lochberg 2021 Tanezumab 2.5 mg SC[18] | 78 | 1002 | 33 | 498 | 16.0% | 1.17 [0.79, 1.74] | |
| Kelly 2019 Fulranumab 1 mg SC [27] | 8 | 81 | 3 | 41 | 1.5% | 1.35 [0.38, 4.82] | |
| Sanga 2013 Fulranumab 1 mg SC q4wk[32] | 0 | 77 | 0 | 16 | | Not estimable | |
| Sanga 2013 Fulranumab 3 mg SC g8wk[32] | 0 | 76 | 0 | 15 | | Not estimable | |
| Sanga 2017 Fulranumab 1 mg SC q4wk [33] | 11 | 77 | 2 | 15 | 1.3% | 1.07 [0.26, 4.35] | |
| Sanga 2017 Fulranumab 3 mg SC g8wk[33] | 14 | 76 | 2 | 15 | 1.3% | 1.38 [0.35, 5.46] | |
| Schnitzer 2019 Tanezumab 2.5 mg SC [34] | 4 | 233 | 2 | 116 | 0.9% | 1.00 [0.19, 5.36] | |
| Subtotal (95% CI) | | 1979 | | 875 | 25.5% | 0.97 [0.70, 1.36] | • |
| Total events | 128 | | 56 | | | | |
| Heterogeneity: Tau ² = 0.01; Chi ² = 6.19, df = 6 (P | = 0.40); 1 | 2 = 3% | 0.01 | | | | |
| Test for overall effect: Z = 0.16 (P = 0.88) | | | | | | | |
| moderate does PD/ | | | | | | | |
| Relanescu 2014 Tanezumah 5 mg IV+DSP III | 8 | 150 | 2 | 51 | 1 1% | 136/030 6 201 | |
| Rown 2012 Tanezumah 5 mg IV/7 | 4 | 172 | 4 | 57 | 0.5% | 1 33 [0 45 44 63] | |
| Rown 2013 Tanezumah 5 mg M/4 | 4 | 154 | 2 | 52 | 1.0% | 0.84 (0.17, 4.00) | |
| Sown 2013 Tanezumab 5 mg IV (6) | D | 104 | 2 | 52 | 1.0% | 0.64 [0.17, 4.22] | |
| Stown 2014 Tanezumab 5 mg IV IP | 0 | 200 | 0 | 30 | 4 70/ | Not estimable | |
| Ekman 2014b Tanazumah 5 mg IV(14) | 2 | 200 | 4 | 104 | 1.7% | 0.00 [0.20, 2.95] | |
| Exman 2014b Tanezumab 5 mg IV[14] | 3 | 211 | 2 | 105 | 0.8% | 0.75 [0.13, 4.40] | 5 C C C C C C C C C C C C C C C C C C C |
| Lane 2010 Tanezumab 50 µg/kg IV 1291 | 0 | 14 | 0 | 15 | | Not estimable | |
| vagasnima 2011 Tanezumab 50 µg/kg IV 1+71 | 0 | 15 | 0 | 3 | F 70/ | Not estimable | |
| Schnitzer 2015 Tanezumab 5 mg IV[35] | 44 | 541 | 10 | 134 | 5.7% | 1.09 [0.56, 2.11] | |
| Schnitzer 2015 Tanezumab 5 mg IV +NSAID [35] | 54 | 536 | 11 | 135 | 6.4% | 1.24 [0.66, 2.30] | |
| Spierings 2013 Tanezumab 5 mg IVI40 | 2 | 161 | 1 | 71 | 0.4% | 0.88 [0.08, 9.57] | |
| subtotal (95% CI) | | 2293 | | 763 | 17.6% | 1.10 [0.76, 1.60] | T |
| fotal events | 127 | | 33 | | | | |
| Heterogeneity: Tau ^e = 0.00; Chi ^e = 0.69, dt = 7 (P Cost for superall effect: $Z = 0.50$ (P = 0.62) | = 1.00); 1 | * = 0% | | | | | |
| est for overall effect. 2 = 0.50 (F = 0.62) | | | | | | | |
| moderate-dose&SC | | | | | | | |
| Berenbaum 2020 Tanezumab 5 mg SC[3] | 24 | 284 | 14 | 141 | 6.3% | 0.85 [0.45, 1.59] | |
| Birbara 2018 Tanezumab 5 mg SCI4I | 0 | 63 | 0 | 18 | | Not estimable | |
| lochberg 2021 Tanezumab 5 mg SC[18] | 110 | 998 | 33 | 498 | 17.7% | 1.66 [1.14, 2.42] | |
| Kelly 2019 Fulranumab 3 mg SC [23] | 3 | 83 | 2 | 40 | 0.8% | 0.72 [0.13, 4.16] | |
| Mayorga 2016 Fulranumab 3 mg SC[27] | 0 | 48 | 0 | 24 | | Not estimable | |
| Sanga 2013 Fulranumab 3 mg SC q4wk[32] | 0 | 79 | 0 | 16 | | Not estimable | |
| Sanga 2013 Fulranumab 6 mg SC g8wk[32] | 1 | 78 | 1 | 15 | 0.3% | 0.19 [0.01, 2.91] | |
| Sanga 2017 Fulranumab 3 mg SC g4wk[33] | 26 | 79 | 3 | 16 | 2.2% | 1.76 [0.60, 5.10] | |
| Sanga 2017 Fulranumab 6 mg SC g8wk[33] | 20 | 78 | 3 | 16 | 2.1% | 1.37 [0.46, 4.06] | |
| Schnitzer 2019 Tanezumab 2.5/5 mg SC [34] | 4 | 231 | 2 | 116 | 0.9% | 1.00 [0.19, 5.40] | |
| Subtotal (95% CI) | | 2021 | | 900 | 30.2% | 1.34 [0.99, 1.80] | ◆ |
| Total events | 188 | | 58 | | | | |
| Heterogeneity: Tau2 = 0.00; Chi2 = 6.11, df = 6 (F | = 0.41); 1 | ² = 2% | | | | | |
| Test for overall effect: Z = 1.92 (P = 0.05) | | | | | | | |
| high-dose&IV | | | | | | | |
| Salanescu 2014 Tanezumab 10 mg IV+DSRI2 | 10 | 145 | 3 | 50 | 1.6% | 1,15 (0.33, 4 01) | |
| Birbara 2018 Tanezumab 10 mg IV/4 | 1 | 84 | 3 | 18 | 0.3% | 0.21 (0.01 3.27) | |
| Concerned to renormality in ing in init | 3 | 174 | | 59 | 0.5% | 1 00 00 11 0 421 | |
| srown zu iz Tanezuman in ma ioi/i | | | | 51 | 1.0% | 0.97 (0.20 4 69) | |
| Brown 2012 Tanezumab 10 mg IVI/1 | 6 | 157 | | | A 10 100 | | |
| Brown 2012 Tanezumab 10 mg IV14 Brown 2013 Tanezumab 10 mg IV16 Brown 2014 Tanezumab 10 mg IV15 | 6 | 15/ | 2 | 36 | 0.3% | 3 45 10 10 65 101 | |
| Srown 2012 Tanezumab 10 mg IVI1 Srown 2013 Tanezumab 10 mg IVI5 Srown 2014 Tanezumab 10 mg IVI5 Srown 2014 Tanezumab 10 mg IVI5 | 6 | 15/ | 0 | 36 | 0.3% | 3.45 [0.18, 65.12] | ·· |
| Srown 2012 Tanezumab 10 mg IVI1 Srown 2013 Tanezumab 10 mg IVI6 Srown 2014 Tanezumab 10 mg IVI5 Ekman 2014a Tanezumab 10 mg IVI14 Ekman 2014b Tanezumab 10 mg IVI14 | 6 3 6 | 157 74 208 | 2 0 4 | 36 104 | 0.3% | 3.45 [0.18, 65.12] 0.75 [0.22, 2.60] | |
| srown 2012 fanezumab 10 mg IV16 srown 2013 Tanezumab 10 mg IV16 Srown 2014 Tanezumab 10 mg IV15 Ekman 2014b Tanezumab 10 mg IV114 Ekman 2014b Tanezumab 10 mg IV114 Ekman 2014b Tanezumab 10 mg IV114 | 6 3 6 4 | 157 74 208 209 | 2 0 4 2 | 36 104 104 | 0.3% 1.6% 0.9% | 3.45 [0.18, 65.12] 0.75 [0.22, 2.60] 1.00 [0.19, 5.35] | |
| srown 2013 ranezumab 10 mg IVI-1 srown 2013 ranezumab 10 mg IVI61 Srown 2014 Tanezumab 10 mg IVI51 Ekman 2014a Tanezumab 10 mg IVI141 kman 2014b Tanezumab 100 µg/kg IVI261 ane 2010 Tanezumab 100 µg/kg IVI261 | 6 3 6 4 0 | 157 74 208 209 74 | 2 0 4 2 0 | 36 104 104 15 | 0.3% | 3.45 [0.18, 65.12] 0.75 [0.22, 2.60] 1.00 [0.19, 5.35] Not estimable | |
| srown 2013 Tanezumab 10 mg IVI/1 Srown 2013 Tanezumab 10 mg IVI61 Srown 2014 Tanezumab 10 mg IVI61 Skman 2014a Tanezumab 10 mg IVI141 Skman 2014b Tanezumab 10 mg IVI141 Skman 2014b Tanezumab 10 mg IVI141 ane 2010 Tanezumab 200 µg/kg IVI261 Ane 2010 Tanezumab 200 | 6 3 6 4 0 2 | 157 74 208 209 74 74 | 2 0 4 2 0 1 | 36 104 104 15 15 | 0.3% 1.6% 0.9% | 3.45 [0.18, 65.12] 0.75 [0.22, 2.60] 1.00 [0.19, 5.35] Not estimable 0.41 [0.04, 4.19] | |
| stown 2012 I anazumab 10 mg (VI ¹) Stown 2013 Tanazumab 10 mg (VI ⁶) Stown 2014 Tanazumab 10 mg (VI ⁶) Kiman 2014a Tanazumab 10 mg (VI ₁₄) Eknan 2014a Tanazumab 100 µg/kg (VI ²⁶) Jane 2010 Tanazumab 200 µg/kg (VI ²⁶) Jagashima 2011 Tanazumab 100 µg/kg (VI ²⁶) Jagashima 2011 Tanazumab 100 µg/kg (VI ²⁶) | 6 3 6 4 0 2 0 | 157 74 208 209 74 74 16 | 2 0 4 2 0 1 0 | 36 104 104 15 15 3 | 0.3% 1.6% 0.9% | 3.45 [0.18, 65.12] 0.75 [0.22, 2.60] 1.00 [0.19, 5.35] Not estimable 0.41 [0.04, 4.19] Not estimable | |
| stown 2012 ranzezumab 10 mg (VII) Stown 2013 Tanzezumab 10 mg (VII) Stown 2014 Tanzezumab 10 mg (VII) Steman 2014 Tanzezumab 10 mg (VII) Steman 2014 Tanzezumab 10 mg (VII) anze 2010 Tanzezumab 10 mg (VII) Jagashima 2011 Tanzezumab 200 µg/kg (VII) Jagashima 2011 Tanzezumab 200 µg/kg (VII) Jagashima 2011 Tanzezumab 200 µg/kg (VII) | 6 3 6 4 0 2 0 0 | 157 74 208 209 74 74 16 6 | 2 0 4 2 0 1 0 0 | 36 104 104 15 15 3 4 | 0.3% 1.6% 0.9% 0.5% | 3.45 [0.18, 65.12] 0.75 [0.22, 2.60] 1.00 [0.19, 5.35] Not estimable 0.41 [0.04, 4.19] Not estimable | |
| stown 2012 Inanezumab 10 mg (VI ^{II}) stown 2013 Tanezumab 10 mg (VI ^{II}) stown 2014 Tanezumab 10 mg (VI ^{II}) Ekman 2014 Tanezumab 10 mg (VI _I II) Ekman 2014b Tanezumab 10 mg (VI _I II) ane 2010 Tanezumab 200 µg/kg (VI ^{2II}) Jagashima 2011 Tanezumab 200 µg/kg (VI ^{2II}) Jagashima 2011 Tanezumab 200 µg/kg (VI ^{2II}) Schnitzer 2015 Tanezumab 10 mg (VI ^{2II}) | 6 3 6 4 0 2 0 0 46 | 157 74 208 209 74 74 16 6 542 | 2 0 4 2 0 1 0 11 | 36 104 104 15 15 3 4 135 | 0.3% 1.6% 0.9% 0.5% | 3.45 [0.18, 65, 12] 0.75 [0.22, 2.60] 1.00 [0.19, 5.35] Not estimable 0.41 [0.04, 4.19] Not estimable Not estimable | |
| stown 2012 Inanezumab 10 mg (VI ⁴) štown 2013 Tanezumab 10 mg (VI ⁶) štown 2014 Tanezumab 10 mg (VI ⁶) šteman 2014 Tanezumab 10 mg (VI ₁₄) kman 2014b Tanezumab 100 µg/kg (VI26) ane 2010 Tanezumab 200 µg/kg (VI26) kagashima 2011 Tanezumab 200 µg/kg (VI29) kagashima 2011 Tanezumab 200 µg/kg (VI29) Schnitzer 2015 Tanezumab 10 mg (VI39) Schnitzer 2015 Tanezumab 10 mg (VI39) | 6 3 6 4 0 2 0 0 46 1 64 | 157 74 208 209 74 74 16 6 542 542 | 2 0 4 2 0 1 0 11 11 | 36 104 104 15 15 3 4 135 135 | 0.3% 1.6% 0.9% 0.5% 6.2% 6.6% | 3.45 [0.18, 65.12] 0.75 [0.22, 2.60] 1.00 [0.19, 5.35] Not estimable 0.41 [0.04, 4.19] Not estimable 1.04 [0.55, 1.96] 1.45 [0.79, 2.67] | |
| stown 2012 I anezumab 10 mg (VI ^{II}) stown 2013 Tanezumab 10 mg (VI ^{II}) stown 2014 Tanezumab 10 mg (VI ^{II}) kman 2014b Tanezumab 10 mg (VI _I II) kman 2014b Tanezumab 10 mg (VI _I II) kmae 2010 Tanezumab 10 mg (VI _I II) kapashima 2011 Tanezumab 200 µg/kg (VI ^{III}) kapashima 2011 Tanezumab 100 µg/kg (VI ^{III}) schnitzer 2015 Tanezumab 10 mg (VI _I II) schnitzer 2015 Tanezumab 10 mg (VI _I II) spitering 2013 Tanezumab 10 mg (VI _I II) spitering 2013 Tanezumab 10 mg (VI _I II) | 6 3 6 4 0 2 0 0 46 46 4 4 | 157 74 208 209 74 74 16 6 542 542 542 150 | 2 0 4 2 0 1 0 11 11 1 | 36 104 104 15 15 3 4 135 135 70 | 0.3% 1.6% 0.9% 0.5% 6.2% 6.6% 0.5% | 3.45 [0.18, 65.12] 0.75 [0.22, 2.60] 1.00 [0.19, 5.35] Not estimable 0.41 [0.04, 4.19] Not estimable 1.04 [0.55, 1.96] 1.45 [0.79, 2.67] 1.45 [0.79, 2.67] | |
| stown 2012 I anezumab 10 mg (VI ¹) 3rown 2013 Tanezumab 10 mg (VI ¹) 3rown 2014 Tanezumab 10 mg (VI ¹) Ekman 2014 Tanezumab 10 mg (VI ₁) Ekman 2014 Tanezumab 10 mg (VI ₁) ane 2010 Tanezumab 200 µg/kg (VI ²) ane 2010 Tanezumab 200 µg/kg (VI ²) lagashima 2011 Tanezumab 10 mg (V I ³) kagashima 2011 Tanezumab 10 mg (V I ³) Schnitzer 2015 Tanezumab 10 mg (V I ³) Schnitzer 2015 Tanezumab 10 mg (V I ³) Subtotal (95% CI) Cala aunde | 6 3 6 4 0 2 0 0 46 1 64 4 | 157 74 208 209 74 74 16 6 542 542 150 2455 | 2 0 4 2 0 1 0 0 11 11 11 | 36 104 104 15 15 3 4 135 135 70 798 | 0.3% 1.6% 0.9% 0.5% 6.2% 6.6% 0.5% 20.0% | 3.45 [0.18, 65.12] 0.75 [0.22, 2.60] 1.00 [0.19, 5.35] Not estimable 0.41 [0.04, 4.19] Not estimable 1.04 [0.55, 1.96] 1.45 [0.79, 2.67] 1.87 [0.21, 16.40] 1.12 [0.79, 1.59] | |
| stown 2012 I anaczumab 10 mg (VI ^{II}) stown 2013 Tanaczumab 10 mg (VI ^{II}) stown 2014 Tanaczumab 10 mg (VI ^{II}) Exman 2014 Tanaczumab 10 mg (VI _I II) Exman 2014 Tanaczumab 10 mg (VI _I II) anac 2010 Tanaczumab 100 mg (VI _I II) anac 2010 Tanaczumab 200 µg/kg (VI ^{2II}) lagashima 2011 Tanaczumab 200 µg/kg (VI ^{2II}) Schnitzer 2015 Tanaczumab 10 mg (VI _I II) Schnitzer 2015 Tanaczumab 10 mg (VI _I II) Spierings 2013 Tanaczumab 10 mg (VI _I II) Spier | 6 3 6 4 0 2 0 0 46 1 64 4 149 P = 0.941 | 157 74 208 209 74 74 16 6 542 542 542 150 2455 | 2 0 4 2 0 1 1 0 11 11 11 37 | 36 104 104 15 15 3 4 135 135 70 798 | 0.3% 1.6% 0.9% 0.5% 6.2% 6.6% 0.5% 20.0% | 3.45 [0.18, 65.12] 0.75 [0.22, 2.60] 1.00 [0.19, 5.35] Not estimable 0.41 [0.04, 4.19] Not estimable 1.04 [0.55, 1.96] 1.45 [0.79, 2.67] 1.87 [0.21, 16.40] 1.12 [0.79, 1.59] | |
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Figure A5. Subgroup analysis of serious adverse events according to dose and administration mode.

APPENDIX 3

| | Exp | erimen | ntal | C | ontro | 1 | | Std. Mean Difference | | Std. Mean Difference |
|--|----------|--------------------|--------|-------|-------|-------|--------|----------------------|------|--|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV. Random, 95% CI | Year | IV, Random, 95% Cl |
| low-dose&IV | | | | | | | | | | |
| Brown 2012 Tanezumab 2.5 mg IV [7] | -3.1 | 3.1 | 154 | -2.4 | 2.85 | 51 | 2.3% | -0.23 [-0.55, 0.09] | 2012 | |
| Brown 2013 Tanezumab 2.5 mg IV [6] | -2.9 | 2.83 | 151 | -1.62 | 2.85 | 51 | 2.3% | -0.45 [-0.77, -0.13] | 2013 | |
| Balanescu 2014 Tanezumab 2.5 mg IV+DSR [2] | -2.09 | 2.26 | 157 | -1.68 | 2.34 | 51 | 2.4% | -0.18 [-0.50, 0.14] | 2014 | |
| Subtotal (95% CI) | | | 462 | | | 153 | 7.0% | -0.28 [-0.47, -0.10] | | • |
| Heterogeneity: Tau ² = 0.00; Chi ² = 1.56, df = 2 (P = | 0.46); 1 | $^{2} = 0\%$ | | | | | | | | |
| Test for overall effect: Z = 3.04 (P = 0.002) | | | | | | | | | | |
| | | | | | | | | | | |
| low-dose&SC | | | | | | | | | | |
| Birbara 2018 Tanezumab 2.5 mg SC [4] | -3.88 | 2.58 | 74 | -2.73 | 2.21 | 18 | 1.0% | -0.45 [-0.97, 0.07] | 2018 | |
| Schnitzer 2019 Tanezumab 2.5 mg SC [34] | -3.23 | 3.42 | 231 | -2.64 | 3.46 | 116 | 3.9% | -0.17 [-0.39, 0.05] | 2019 | |
| Berenbaum 2020 Tanezumab 2.5 mg SC[3] | -2.7 | 2.86 | 283 | -2.24 | 3.02 | 141 | 4.4% | -0.16 [-0.36, 0.04] | 2020 | |
| Hochberg 2021 Tanezumab 2.5 mg SC[18] | -3.22 | 3.39 | 1002 | -3.07 | 3.46 | 498 | 7.7% | -0.04 [-0.15, 0.06] | 2021 | |
| Subtotal (95% CI) | | | 1590 | | | 773 | 17.0% | -0.11 [-0.21, -0.01] | | • |
| Heterogeneity: Tau ² = 0.00; Chi ² = 3.52, df = 3 (P = | 0.32); 1 | ² = 159 | 6 | | | | | | | |
| Test for overall effect: Z = 2.06 (P = 0.04) | | | | | | | | | | |
| | | | | | | | | | | |
| moderate-dose&IV | | | | | | | | | | |
| Brown 2012 Tanezumab 5 mg IV [7] | -3.3 | 2.87 | 156 | -2.4 | 2.85 | 52 | 2.4% | -0.31 [-0.63, 0.00] | 2012 | |
| Spierings 2013 Tanezumab 5 mg IV [40] | -3.58 | 2.79 | 161 | -2.62 | 2.85 | 71 | 2.8% | -0.34 [-0.62, -0.06] | 2013 | |
| Brown 2013 Tanezumab 5 mg IV [6] | -3.31 | 2.82 | 150 | -1.62 | 2.85 | 52 | 2.3% | -0.60 [-0.92, -0.27] | 2013 | |
| Ekman 2014b Tanezumab 5 mg IV[14] | -2.95 | 3.2 | 211 | -1.81 | 3.18 | 105 | 3.6% | -0.36 [-0.59, -0.12] | 2014 | |
| Balanescu 2014 Tanezumab 5 mg IV+DSR[2] | -2.19 | 2.33 | 150 | -1.68 | 2.34 | 51 | 2.3% | -0.22 [-0.54, 0.10] | 2014 | |
| Ekman 2014a Tanezumab 5 mg IV[14] | -3.44 | 2.58 | 206 | -2.23 | 2.59 | 104 | 3.6% | -0.47 [-0.71, -0.23] | 2014 | |
| Schnitzer 2015a Tanezumab 5 mg IV [35] | -1.88 | 2.19 | 285 | -1.44 | 2.52 | 71 | 3.2% | -0.19 [-0.45, 0.07] | 2015 | |
| Schnitzer 2015a Tanezumab 5 mg IV+naproxen [35 | -2.13 | 2.18 | 280 | -1.44 | 2.52 | 71 | 3.1% | -0.31 [-0.57, -0.04] | 2015 | |
| Schnitzer 2015b Tanezumab 5 mg IV [35] | -2.02 | 2.56 | 256 | -1.47 | 2.56 | 64 | 2.9% | -0.21 [-0.49, 0.06] | 2015 | |
| Schnitzer 2015b Tanezumab 5 mg IV+celecoxib [35 | -2.22 | 2.56 | 256 | -1.47 | 2.56 | 64 | 2.9% | -0.29 [-0.57, -0.02] | 2015 | |
| Subtotal (95% CI) | | | 2111 | | | 705 | 29.1% | -0.33 [-0.42, -0.24] | | ◆ |
| Heterogeneity: Tau ² = 0.00; Chi ² = 6.27, df = 9 (P = | 0.71); 1 | 2 = 0% | | | | | | | | |
| Test for overall effect: $Z = 7.47$ (P < 0.00001) | | | | | | | | | | |
| , , , , , | | | | | | | | | | |
| moderate-dose&SC | | | | | | | | | | |
| Schnitzer 2019 Tanezumab 2.5/5 mg SC [34] | -3.37 | 3.43 | 233 | -2.64 | 3.46 | 116 | 3.9% | -0.21 [-0.44, 0.01] | 2019 | |
| Berenbaum 2020 Tanezumab 5 mg SC[3] | -2.85 | 2.86 | 284 | -2.24 | 3.02 | 141 | 4.4% | -0.21 [-0.41, -0.01] | 2020 | |
| Hochberg 2021 Tanezumab 5 mg SC[18] | -3.33 | 3.38 | 998 | -3.07 | 3.46 | 498 | 7.7% | -0.08 [-0.18, 0.03] | 2021 | |
| Subtotal (95% CI) | | | 1515 | | | 755 | 16.0% | -0.12 [-0.21, -0.03] | | ◆ |
| Heterogeneity: Tau ² = 0.00; Chi ² = 2.02, df = 2 (P = | 0.36); 1 | 2 = 1% | | | | | | | | |
| Test for overall effect: Z = 2.71 (P = 0.007) | 2.53 | | | | | | | | | |
| | | | | | | | | | | |
| high-dose&IV | | | | | | | | | | |
| Brown 2012 Tanezumab10 mg IV I7I | -3.6 | 2.85 | 154 | -2.4 | 2.85 | 51 | 2.3% | -0.42 [-0.74, -0.10] | 2012 | |
| Brown 2013 Tanezumab 10 mg IV [6] | -3.37 | 3 | 150 | -1.62 | 2.85 | 51 | 2.3% | -0.59 [-0.91, -0.27] | 2013 | |
| Spierings 2013 Tanezumab 10 mg IV [40] | -3.58 | 2.82 | 150 | -2.62 | 2.85 | 70 | 2.8% | -0.34 [-0.62, -0.05] | 2013 | |
| Ekman 2014a Tanezumab 10 mg IV [14] | -3.14 | 2.59 | 207 | -2.23 | 2.59 | 103 | 3.6% | -0.35 [-0.59, -0.11] | 2014 | |
| Ekman 2014b Tanezumab 10 mg IV[14] | -2.62 | 3.17 | 208 | -1.81 | 3.18 | 104 | 3.6% | -0.25 [-0.49, -0.02] | 2014 | |
| Balanescu 2014 Tanezumab 10 mg IV+DSRI2I | -2.25 | 2.29 | 145 | -1.68 | 2.34 | 50 | 2.3% | -0.25 [-0.57, 0.08] | 2014 | |
| Schnitzer 2015b Tanezumab 10 mg IV+celecoxib13 | 51-2.41 | 2.07 | 254 | -1.47 | 2.56 | 64 | 2.9% | -0.43 [-0.71, -0.15] | 2015 | |
| Schnitzer 2015a Tanezumab 10 mg IV [35] | -2.02 | 2.56 | 288 | -1.44 | 2.52 | 70 | 3.1% | -0.23 [-0.49, 0.03] | 2015 | |
| Schnitzer 2015b Tanezumab 10 mg IV (35) | -2.05 | 2.55 | 254 | -1.47 | 2.56 | 64 | 2.9% | -0.23 [-0.50, 0.05] | 2015 | |
| Schnitzer 2015a Tanezumab 10 mg IV+naproxen I3 | 51-2 36 | 2.56 | 288 | -1.44 | 2.52 | 71 | 3.1% | -0.36 [-0.62, -0.10] | 2015 | |
| Birbara 2018 Tanezumah 10 mg IV 14 | -3.6 | 2.47 | 84 | -2 73 | 2.21 | 18 | 1.0% | -0.36 [-0.87 0.16] | 2018 | |
| Subtotal (95% CI) | -0.0 | 2.47 | 2182 | -2.13 | 6.61 | 716 | 29.9% | -0.33 [-0.42, -0.25] | 2010 | ◆ |
| Heterogeneity: $Tau^2 = 0.00$: Chi ² = 5.14. df = 10 (P | = 0.88) | $ ^2 = 0.9$ | 6 | | | | | | | |
| Test for overall effect: $Z = 7.66$ (P < 0.00001) | 0.00), | | - | | | | | | | |
| | | | | | | | | | | |
| high-dose&SC | | | | | | | | | | |
| Birbara 2018 Tanezumab 10 mg SCI4 | -3.92 | 2.78 | 86 | -2.73 | 2.21 | 18 | 1.0% | -0.44 [-0.95, 0.07] | 2018 | |
| Subtotal (95% CI) | 0.02 | 2.10 | 86 | 2.10 | 2.21 | 18 | 1.0% | -0.44 [-0.95, 0.07] | 2010 | |
| Heterogeneity: Not applicable | | | | | | | | | | |
| Test for overall effect: $Z = 1.68 (P = 0.09)$ | | | | | | | | | | |
| ······································ | | | | | | | | | | ~ |
| Total (95% CI) | | | 7946 | | | 3120 | 100.0% | -0.27 [-0.32, -0.21] | | • |
| Heterogeneity: Tau ² = 0.01: Chi ² = 45.64 df = 31 (P | P = 0.04 |): $ ^2 = 3$ | 2% | | | | | in the second | - | |
| Test for overall effect: $Z = 9.51$ (P < 0.00001) | 0.04 | , | - /0 | | | | | | | -1 -0.5 0 0.5 1 |
| Test for subgroup differences: $Chi^2 = 22.80$, df = 5 (| P = 0.0 | 004), 12 | = 78.1 | % | | | | | | Favours [experimental] Favours [control] |

Figure A6. Sensitivity analysis for WOMAC Pain according dose and administration mode in fixed-dose tanezumab trials.

| | Exp | erimen | ital | С | ontrol | | | Std. Mean Difference | | Std. Mean Difference |
|---|-----------|---------------------|--------|-------|--------|-----------|--------|----------------------|------|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV. Random, 95% CI | Year | IV. Random, 95% Cl |
| low-dose&IV | | | | | | | | | | |
| Brown 2012 Tanezumab 2.5 mg IV [7] | -2.8 | 2.85 | 154 | -2 | 2.85 | 51 | 2.5% | -0.28 [-0.60, 0.04] | 2012 | |
| Brown 2013 Tanezumab 2.5 mg IV [6] | -2.57 | 2.58 | 151 | -1.39 | 2.36 | 51 | 2.4% | -0.47 [-0.79, -0.14] | 2013 | |
| Balanescu 2014 Tanezumab 2.5 mg IV+DSR [2] Subtotal (95% CI) | -2.05 | 2.26 | 157 | -1.53 | 2.34 | 51 153 | 2.5% | -0.23 [-0.54, 0.09] | 2014 | • |
| Hotorogonoity: Tau ² = 0.00: Chi ² = 1.19. df = 2./P = | 0.55)-1 | 2 - 0% | 402 | | | 155 | 1.5% | -0.32 [-0.51, -0.14] | | • |
| Test for overall effect: $7 = 3.44$ (P = 0.006) | 0.55), 1 | - 0 % | | | | | | | | |
| | | | | | | | | | | |
| low-dose&SC | | | | | | | | | | |
| Birbara 2018 Tanezumab 2.5 mg SC [4] | -3.29 | 2.58 | 74 | -2.24 | 1.95 | 18 | 1.1% | -0.42 [-0.94, 0.10] | 2018 | |
| Schnitzer 2019 Tanezumab 2.5 mg SC [34] | -3.22 | 3.37 | 231 | -2.56 | 3.42 | 116 | 3.8% | -0.19 [-0.42, 0.03] | 2019 | |
| Berenbaum 2020 Tanezumab 2.5 mg SC[3] | -2.7 | 2.69 | 283 | -2.11 | 2.67 | 141 | 4.2% | -0.22 [-0.42, -0.02] | 2020 | |
| Hochberg 2021 Tanezumab 2.5 mg SC[18] | -3.27 | 3.47 | 1002 | -3.08 | 3.46 | 498 | 6.5% | -0.05 [-0.16, 0.05] | 2021 | |
| Subtotal (95% CI) | 0.001 | 2 | 1590 | | | 113 | 15.7% | -0.14 [-0.26, -0.02] | | • |
| Heterogeneity: $ au^2 = 0.00$; $Chi^2 = 4.05$, $di = 3$ (P = | 0.26); 1 | - = 269 | o | | | | | | | |
| Test for overall effect: $Z = 2.38$ (P = 0.02) | | | | | | | | | | |
| moderate-dose&IV | | | | | | | | | | |
| Brown 2012 Tanezumab 5 mg IV [7] | -3 | 2.75 | 156 | -2 | 2.85 | 52 | 2.5% | -0.36 [-0.67, -0.04] | 2012 | |
| Brown 2013 Tanezumab 5 mg IV [6] | -2.88 | 2.45 | 150 | -1.39 | 2.36 | 52 | 2.4% | -0.61 [-0.93, -0.29] | 2013 | · · · · · · · · · · · · · · · · · · · |
| Spierings 2013 Tanezumab 5 mg IV[40] | -3.05 | 2.54 | 161 | -1.91 | 2.73 | 71 | 2.9% | -0.44 [-0.72, -0.16] | 2013 | |
| Ekman 2014a Tanezumab 5 mg IV[14] | -3.09 | 2.73 | 206 | -1.84 | 2.73 | 103 | 3.5% | -0.46 [-0.70, -0.22] | 2014 | |
| Ekman 2014b Tanezumab 5 mg IV [14] | -2.68 | 3.05 | 211 | -1.45 | 3.04 | 105 | 3.6% | -0.40 [-0.64, -0.17] | 2014 | |
| Balanescu 2014 Tanezumab 5 mg IV+DSR [2] | -2.16 | 2.33 | 150 | -1.53 | 2.34 | 51 | 2.4% | -0.27 [-0.59, 0.05] | 2014 | |
| Schnitzer 2015b Tanezumab 5 mg IV+celecoxib[35 | -2.22 | 2.56 | 256 | -1.42 | 2.56 | 64 | 3.0% | -0.31 [-0.59, -0.04] | 2015 | |
| Schnitzer 2015a Tanezumab 5 mg IV+naproxen[35 | -2.16 | 2.51 | 280 | -1.38 | 2.69 | 71 | 3.2% | -0.31 [-0.57, -0.04] | 2015 | |
| Schnitzer 2015a Tanezumab 5 mg IV [35] | -1.86 | 2.53 | 285 | -1.38 | 2.69 | /1 | 3.2% | -0.19 [-0.45, 0.07] | 2015 | |
| Subtotal (95% CI) | -2.05 | 2.4 | 200 | -1.42 | 2.30 | 704 | 29.7% | -0.26 [-0.55, 0.02] | 2015 | • |
| Heterogeneity: $Tau^2 = 0.00$: $Chi^2 = 6.22$, $df = 9$ (P = | 0.72): 1 | $^{2} = 0\%$ | | | | | 20.170 | 0.00[0.11, 0.21] | | |
| Test for overall effect: $Z = 8.09 (P < 0.00001)$ | 0.12/1 | 070 | | | | | | | | |
| | | | | | | | | | | |
| moderate-dose&SC | | | | | | | | | | |
| Birbara 2018 Tanezumab 5 mg SC [4] | -3.29 | 2.7 | 63 | -2.24 | 1.95 | 18 | 1.1% | -0.41 [-0.93, 0.12] | 2018 | |
| Schnitzer 2019 Tanezumab 2.5/5 mg SC [34] | -3.45 | 3.31 | 233 | -2.56 | 3.42 | 116 | 3.8% | -0.27 [-0.49, -0.04] | 2019 | |
| Berenbaum 2020 Tanezumab 5 mg SC[3] | -2.82 | 3.03 | 284 | -2.11 | 2.67 | 141 | 4.2% | -0.24 [-0.45, -0.04] | 2020 | |
| Hochberg 2021 Tanezumab 5 mg SC[18] | -3.39 | 3.47 | 998 | -3.08 | 3.46 | 498 | 6.5% | -0.09 [-0.20, 0.02] | 2021 | ▲ |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.96$, $df = 3./P$ = | 0 27)-1 | 2 - 240 | 15/6 | | | 113 | 15.0% | -0.10 [-0.29, -0.00] | | • |
| Test for overall effect: $7 = 3.03$ (P = 0.002) | 0.27), 1 | 247 | 0 | | | | | | | |
| 1631 101 0461 all 611601. 2 = 0.00 (F = 0.002) | | | | | | | | | | |
| high-dose&IV | | | | | | | | | | |
| Brown 2012 Tanezumab10 mg IV [7] | -3.3 | 2.61 | 154 | -2 | 2.85 | 51 | 2.4% | -0.48 [-0.81, -0.16] | 2012 | |
| Spierings 2013 Tanezumab 10 mg IV[40] | -3.06 | 2.57 | 150 | -1.91 | 2.73 | 70 | 2.8% | -0.44 [-0.72, -0.15] | 2013 | |
| Brown 2013 Tanezumab 10 mg IV[6] | -3 | 2.62 | 156 | -1.39 | 2.36 | 51 | 2.4% | -0.63 [-0.95, -0.30] | 2013 | |
| Ekman 2014a Tanezumab 10 mg IV [14] | -2.82 | 2.73 | 206 | -1.84 | 2.73 | 103 | 3.5% | -0.36 [-0.60, -0.12] | 2014 | |
| Balanescu 2014 Tanezumab 10 mg IV+DSR[2] | -2.23 | 2.29 | 145 | -1.53 | 2.34 | 50 | 2.4% | -0.30 [-0.63, 0.02] | 2014 | |
| Ekman 2014b Tanezumab 10 mg IV[14] | -2.45 | 3.03 | 208 | -1.45 | 3.04 | 104 | 3.6% | -0.33 [-0.57, -0.09] | 2014 | |
| Schnitzer 2015b Tanezumab 10 mg IV+celecoxib[3 Schnitzer 2015b Tanezumab 10 mg IV/135] | -2.42 | 2.55 | 254 | -1.42 | 2.56 | 54 | 3.0% | -0.39 [-0.67, -0.12] | 2015 | |
| Schnitzer 2015a Tanezumab 10 mg IV (55) Schnitzer 2015a Tanezumab 10 mg IV tagaravania | -1.9 | 2.00 | 288 | -1.38 | 2.09 | 70 | 3.2% | -0.18 [-0.44, 0.08] | 2015 | |
| Schnitzer 2015b Tanezumab 10 mg IV/135 | -2.04 | 2.39 | 254 | -1.42 | 2.56 | 64 | 3.0% | -0.26 [-0.53, 0.02] | 2015 | |
| Birbara 2018 Tanezumab 10 mg IV[4] | -3.12 | 2.2 | 84 | -2.24 | 1.95 | 18 | 1.2% | -0.40 [-0.92, 0.11] | 2018 | |
| Subtotal (95% CI) | | | 2187 | | | 716 | 30.6% | -0.36 [-0.44, -0.27] | | ◆ |
| Heterogeneity: Tau ² = 0.00; Chi ² = 6.17, df = 10 (P | = 0.80); | l ² = 09 | 6 | | | | | | | |
| Test for overall effect: Z = 8.17 (P < 0.00001) | | | | | | | | | | |
| histo desset CO | | | | | | | | | | |
| nign-dose&SC | | 4.04 | | | 4.05 | | 4 400 | 0.001.4.45 0.155 | 00/0 | |
| Birbara 2018 Tanezumab 10 mg SCI4I Subtotal (95% CI) | -3.51 | 1.21 | 86 | -2.24 | 1.95 | 18 | 1.1% | -0.93 [-1.45, -0.40] | 2018 | |
| Heterogeneity: Net applicable | | | 00 | | | 10 | 1.1% | -0.93 [-1.45, -0.40] | | |
| Test for overall effect: $Z = 3.46$ (P = 0.0005) | | | | | | | | | | |
| 1001 01 0401all 61601. 2 = 3.40 (F = 0.0003) | | | | | | | | | | |
| Total (95% CI) | | | 8014 | | | 3137 | 100.0% | -0.31 [-0.37, -0.25] | | |
| Heterogeneity: Tau ² = 0.01; Chi ² = 54.79, df = 32 (f | o = 0.00 | 7); 2 = | 42% | | | | | | | |
| Test for overall effect: Z = 10.12 (P < 0.00001) | | 2 | | | | | | | | -1 -0.5 0 0.5 1 Favours [experimental] Favours [control] |
| Test for subaroup differences: Chi ² = 20.83. df = 5 | (P = 0.0) | 009), I² | = 76.0 | % | | | | | | r avous [experimental] r avours [control] |

Figure A7. Sensitivity analysis for WOMAC Physical Function according dose and administration mode in fixed-dose tanezumab trials.

| | Exp | erimen | tal | С | ontrol | | | Std. Mean Difference | Std. Mean Difference |
|--|------------|-----------------------|-------|-------|--------|-------|--------|---------------------------|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV. Random, 95% CI Year | IV. Random, 95% Cl |
| low-dose&IV | | | | | | | | | |
| Brown 2012 Tanezumab 2.5 mg IV [7] | -0.8 | 0.74 | 154 | -0.5 | 0.74 | 51 | 2.5% | -0.40 [-0.72, -0.08] 2012 | |
| Brown 2013 Tanezumab 2.5 mg IV IM | -0.66 | 0.86 | 151 | -0.34 | 0.74 | 51 | 2.5% | -0.38 [-0.70, -0.06] 2013 | |
| Balanescu 2014 Tanezumab 2.5 mg IV+DSR I/I Subtotal (95% CI) | -0.52 | 0.88 | 15/ | -0.34 | 0.86 | 153 | 2.5% | -0.20 [-0.52, 0.11] 2014 | • |
| Hotorogonoity: Tous = 0.00: Chi2 = 0.01. $df = 2.(P)$ | - 0 62)- 1 | 2 - 0% | 402 | | | 155 | 1.5% | -0.35 [-0.51, -0.15] | • |
| Test for overall effect: $7 = 3.52$ (P = 0.004) | - 0.03), 1 | - 0 % | | | | | | | |
| rest for overall effect. 2 = 5.52 (r = 0.0004) | | | | | | | | | |
| low-dose&SC | | | | | | | | | |
| Birbara 2018 Tanezumab 2.5 mg SC ^[4] | -1.06 | 0.95 | 74 | -0.78 | 0.85 | 18 | 1.2% | -0.30 [-0.81, 0.22] 2018 | |
| Schnitzer 2019 Tanezumab 2.5 mg SCI34I | -0.87 | 1.16 | 231 | -0.65 | 1.17 | 116 | 3.8% | -0.19 [-0.41, 0.03] 2019 | |
| Berenbaum 2020 Tanezumab 2.5 mg SC ^[3] | -0.82 | 1.01 | 283 | -0.72 | 1.01 | 141 | 4.1% | -0.10 [-0.30, 0.10] 2020 | |
| Hochberg 2021 Tanezumab 2.5 mg SC[18] | -0.96 | 1.21 | 1002 | -0.94 | 1.21 | 498 | 6.0% | -0.02 [-0.12, 0.09] 2021 | _ |
| Subtotal (95% CI) | | | 1590 | | | 773 | 15.1% | -0.06 [-0.15, 0.02] | • |
| Heterogeneity: Tau ² = 0.00; Chi ² = 2.85, df = 3 (P = | = 0.42); I | $^{2} = 0\%$ | | | | | | | |
| Test for overall effect: Z = 1.48 (P = 0.14) | | | | | | | | | |
| moderate-doseRIV | | | | | | | | | |
| Brown 2012 Tanazumah E ma IV/171 | 0.0 | 0.97 | 166 | 0.5 | 0.74 | 52 | 2 59/ | 0 47 1 0 70 0 161 2012 | |
| Spierings 2013 Tapezumab 5 mg IV/40 | -0.9 | 0.07 | 161 | -0.5 | 0.74 | 71 | 2.5% | -0.47 [-0.79, -0.10] 2012 | |
| Brown 2013 Tanazumah 5 mg IV/6 | -0.78 | 0.05 | 150 | -0.34 | 0.33 | 52 | 2.5% | -0.53 [-0.85 -0.21] 2013 | |
| Ekman 2014a Tanezumab 5 mg IVIJ | -0.87 | 0.00 | 205 | -0.53 | 1 | 103 | 3.5% | -0.34 [-0.58 -0.10] 2014 | |
| Balanescu 2014 Tanezumab 5 mg IV+DSR I2I | -0.52 | 0.86 | 150 | -0.34 | 0.86 | 51 | 2.5% | -0.21 [-0.53 0.11] 2014 | |
| Ekman 2014b Tanezumab 5 mg IVI14 | -0.73 | 1.02 | 211 | -0.39 | 1.01 | 105 | 3.6% | -0.33 [-0.57, -0.10] 2014 | |
| Schnitzer 2015b Tanezumab 5 mg IV[35] | -0.67 | 0.8 | 256 | -0.54 | 0.8 | 64 | 3.0% | -0.16 [-0.44, 0.11] 2015 | |
| Schnitzer 2015a Tanezumab 5 mg IV(35) | -0.54 | 0.84 | 285 | -0.54 | 0.84 | 71 | 3.2% | 0.00 [-0.26, 0.26] 2015 | |
| Schnitzer 2015a Tanezumab 5 mg IV+naproxen I35 | -0.62 | 0.84 | 280 | -0.54 | 0.84 | 71 | 3.2% | -0.10 [-0.36, 0.17] 2015 | |
| Schnitzer 2015b Tanezumab 5 mg IV+celecoxib 135 | -0.74 | 0.8 | 256 | -0.54 | 0.8 | 64 | 3.0% | -0.25 [-0.52, 0.03] 2015 | |
| Subtotal (95% CI) | | | 2110 | | | 704 | 30.0% | -0.27 [-0.37, -0.17] | • |
| Heterogeneity: Tau ² = 0.01; Chi ² = 12.37, df = 9 (P | = 0.19); | l ² = 27 | % | | | | | | |
| Test for overall effect: Z = 5.22 (P < 0.00001) | | | | | | | | | |
| moderate decol SC | | | | | | | | | |
| Birbara 2018 Tapartumah E ma SC III | 0.05 | 0.07 | 62 | 0.79 | 0.05 | 10 | 1 20/ | 0 10 1 0 72 0 221 2018 | |
| Schnitzer 2019 Tanezumab 2 5/5 mg SCI34 | -0.95 | 1 17 | 233 | -0.76 | 1 17 | 116 | 3.8% | -0.21 [-0.44 0.01] 2019 | |
| Berenhaum 2020 Tanezumah 5 mg SCI3I | -0.9 | 1.01 | 284 | -0.72 | 1.01 | 141 | 4 1% | -0.18 [-0.38 0.02] 2020 | |
| Hochberg 2021 Tanezumab 5 mg SCI18 | -0.97 | 1.21 | 998 | -0.94 | 1.21 | 498 | 6.0% | -0.02 [-0.13, 0.08] 2021 | + |
| Subtotal (95% CI) | | | 1578 | | | 773 | 15.1% | -0.10 [-0.20, 0.00] | • |
| Heterogeneity: Tau ² = 0.00; Chi ² = 3.45, df = 3 (P = | = 0.33); I | ² = 139 | 6 | | | | | | |
| Test for overall effect: Z = 1.90 (P = 0.06) | | | | | | | | | |
| | | | | | | | | | |
| high-dose&IV | | | | | | | | | |
| Brown 2012 Tanezumab10 mg IV ¹⁷ | -1 | 0.74 | 154 | -0.5 | 0.74 | 51 | 2.5% | -0.67 [-1.00, -0.35] 2012 | |
| Brown 2013 Tanezumab 10 mg IVI6 | -0.81 | 0.87 | 156 | -0.34 | 0.74 | 51 | 2.5% | -0.56 [-0.88, -0.24] 2013 | |
| Spierings 2013 Tanezumab 10 mg IV [40] | -1 | 0.99 | 150 | -0.52 | 0.95 | 70 | 2.9% | -0.49 [-0.78, -0.20] 2013 | |
| Ekmon 2014a Tanezumab 10 mg IV+DSR [2] | -0.56 | 1.01 | 145 | -0.34 | 0.00 | 102 | 2.5% | -0.28 [-0.61, 0.04] 2014 | |
| Ekman 2014b Tanezumab 10 mg IVI14 | -0.73 | 1.01 | 207 | -0.33 | 1.01 | 103 | 3.6% | -0.20 [-0.44, 0.04] 2014 | |
| Schnitzer 2015b Tanezumab 10 mg IV 135 | -0.72 | 0.8 | 254 | -0.53 | 0.8 | 64 | 3.0% | -0.06 [-0.34 0.21] 2014 | |
| Schnitzer 2015b Tanezumab 10 mg IV+celecovibl | -0.75 | 0.8 | 254 | -0.54 | 0.8 | 64 | 3.0% | -0.26 [-0.54, 0.01] 2015 | |
| Schnitzer 2015a Tanezumab 10 mg IV location | -0.61 | 0.85 | 288 | -0.54 | 0.84 | 70 | 3.2% | -0.08 [-0.34, 0.18] 2015 | |
| Schnitzer 2015a Tanezumab 10 mg IV+naproxen | 351 -0.72 | 0.85 | 288 | -0.54 | 0.84 | 71 | 3.2% | -0.21 [-0.47, 0.05] 2015 | |
| Birbara 2018 Tanezumab 10 mg IV141 | -0.9 | 1.01 | 84 | -0.78 | 0.85 | 18 | 1.2% | -0.12 [-0.63, 0.39] 2018 | |
| Subtotal (95% CI) | | | 2188 | | | 716 | 31.0% | -0.29 [-0.40, -0.18] | • |
| Heterogeneity: Tau ² = 0.01; Chi ² = 16.45, df = 10 (| P = 0.09 |); l ² = 3 | 9% | | | | | | |
| Test for overall effect: Z = 5.13 (P < 0.00001) | | | | | | | | | |
| high deep 800 | | | | | | | | | |
| high-dose&SC | 4.00 | | | | | 10 | 4 004 | | |
| Birbara 2018 Tanezumab 10 mg SCI4 | -1.08 | 1.1 | 86 | -0.78 | 0.85 | 18 | 1.2% | -0.28 [-0.79, 0.23] 2018 | |
| Haterogeneity: Not applicable | | | 00 | | | 10 | 1.270 | -0.20 [-0.79, 0.23] | |
| Test for overall effect: $7 = 1.08$ (P = 0.28) | | | | | | | | | |
| 100 (F = 0.20) | | | | | | | | | |
| Total (95% CI) | | | 8014 | | | 3137 | 100.0% | -0.24 [-0.30, -0.17] | • |
| Heterogeneity: Tau ² = 0.01; Chi ² = 60.09, df = 32 (| P = 0.00 | 2); ² = | 47% | | | | | | |
| Test for overall effect: Z = 7.44 (P < 0.00001) | | | | | | | | | -1 -U.5 U U.5 1 Eavours (experimental) Eavours (control) |
| Test for subgroup differences: Chi ² = 19.10, df = 5 | (P = 0.0) | 02), I ^z = | 73.8% | | | | | | ravous lexhermental - Lavous [connol] |

Figure A8. Sensitivity analysis for PGA according dose and administration mode in fixed-dose tanezumab trials.

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| | Experim | ental | Contr | ol | | Risk Ratio | Risk Ratio |
|--|---|------------------------|--------|-------|--------|--------------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H. Random, 95% CI Year | M-H, Random, 95% Cl |
| low-dose&IV | | | | | | | |
| Brown 2012 Tanezumab 2.5 mg IV [7] | 100 | 172 | 27 | 57 | 1.2% | 1.23 [0.91, 1.66] 2012 | |
| Brown 2013 Tanezumab 2.5 mg IV IPI | 90 | 155 | 23 | 52 | 1.0% | 1.31 [0.94, 1.83] 2013 | |
| Subtotal (95% CI) | 1 73 | 484 | 18 | 160 | 2.9% | 1.32 [0.88, 1.98] 2014 | |
| Total events | 263 | 404 | 68 | 100 | 2.070 | 1.20 [1.00, 1.00] | |
| Heterogeneity: $Tau^2 = 0.00$: $Chi^2 = 0.12$. df = 2 | (P = 0.94); | $^{2} = 0\%$ | 00 | | | | |
| Test for overall effect: Z = 2.44 (P = 0.01) | | | | | | | |
| | | | | | | | |
| low-dose&SC | | | | | | | |
| Birbara 2018 Tanezumab 2.5 mg SC [4] | 35 | 74 | 9 | 18 | 0.4% | 0.95 [0.56, 1.59] 2018 | |
| Schnitzer 2019 Tanezumab 2.5 mg SC [34] | 33 | 233 | 15 | 116 | 0.3% | 1.10 [0.62, 1.93] 2019 | |
| Berenbaum 2020 Tanezumab 2.5 mg SC [3] | 184 | 283 | 89 | 141 | 4.8% | 1.03 [0.88, 1.20] 2020 | |
| Subtotal (95% CI) | 681 | 1592 | 333 | 498 | 19.7% | 1.02 [0.94, 1.10] 2021 | • |
| Total events | 033 | 1332 | 446 | 115 | 20.270 | 1.02 [0.00, 1.00] | |
| Heterogeneity: $Tau^2 = 0.00$: $Chi^2 = 0.17$, df = 3 | (P = 0.98): | $^{2} = 0\%$ | 440 | | | | |
| Test for overall effect: $Z = 0.55$ (P = 0.58) | (, ,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,, | | | | | | |
| | | | | | | | |
| moderate-dose&IV | | | | | | | |
| Brown 2012 Tanezumab 5 mg IVI7I | 95 | 172 | 28 | 57 | 1.3% | 1.12 [0.84, 1.51] 2012 | |
| Spierings 2013 Tanezumab 5 mg IV [40] | 72 | 161 | 25 | 71 | 0.9% | 1.27 [0.89, 1.82] 2013 | |
| Brown 2013 Tanezumab 5 mg IV I6I | 84 | 154 | 23 | 52 | 1.0% | 1.23 [0.88, 1.73] 2013 | |
| Balanescu 2014 Tanezumab 5 mg IV+DSR I ² I | 72 | 150 | 18 | 51 | 0.7% | 1.36 [0.91, 2.04] 2014 | |
| Ekman 2014a Tanezumab 5 mg IV [14] | 107 | 206 | 49 | 104 | 1.9% | 1.10 [0.87, 1.40] 2014 | |
| Brown 2014 Tanezumab 5 mg IV 151 | 41 | 73 | 19 | 36 | 0.8% | 1.06 [0.74, 1.54] 2014 | |
| Ekman 2014b Tanezumab 5 mg IV [14] | 101 | 211 | 43 | 105 | 1.5% | 1.17 [0.89, 1.53] 2014 | |
| Schnitzer 2015 Tanezumab 5 mg IV (35) | 405 | 541 | 91 | 134 | 7.0% | 1.10 [0.97, 1.25] 2015 | |
| Subtotal (95% CI) | 51 390 | 2204 | 91 | 745 | 0.7% | 1.08 [0.95, 1.23] 2015 | • |
| Total events | 1367 | 2204 | 387 | 145 | 21.770 | 1.12 [1.04, 1.20] | - |
| Heterogeneity: $Tau^2 = 0.00$: $Chi^2 = 2.35$, df = 8 | (P = 0.97) | $^{2} = 0\%$ | 001 | | | | |
| Test for overall effect: $Z = 3.07$ (P = 0.002) | (, 0.07), | 070 | | | | | |
| · · · · · · · · · · · · · · · · · · · | | | | | | | |
| moderate-dose&SC | | | | | | | |
| Birbara 2018 Tanezumab 5 mg SC [4] | 31 | 63 | 9 | 18 | 0.4% | 0.98 [0.58, 1.66] 2018 | |
| Schnitzer 2019 Tanezumab 2.5/5 mg SC [34] | 40 | 231 | 16 | 116 | 0.4% | 1.26 [0.74, 2.14] 2019 | |
| Berenbaum 2020 Tanezumab 5 mg SCI3 | 198 | 284 | 89 | 141 | 5.1% | 1.10 [0.95, 1.28] 2020 | |
| Hochberg 2021 Tanezumab 5 mg SC[18] | 744 | 998 | 333 | 498 | 21.6% | 1.11 [1.04, 1.20] 2021 | L |
| Subtotal (95% CI) | 1012 | 15/0 | 447 | 113 | 27.5% | 1.11 [1.04, 1.19] | • |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.42$, $df = 3$ | $(P = 0.94) \cdot 1$ | $ ^2 = 0.0\%$ | 447 | | | | |
| Test for overall effect: $Z = 3.30$ (P = 0.0010) | (1 - 0.34), 1 | - 076 | | | | | |
| | | | | | | | |
| high-dose&IV | | | | | | | |
| Brown 2012 Tanezumab10 mg IV I7I | 104 | 174 | 28 | 58 | 1.3% | 1.24 [0.92, 1.66] 2012 | |
| Brown 2013 Tanezumab 10 mg IV [6] | 89 | 157 | 22 | 51 | 0.9% | 1.31 [0.93, 1.85] 2013 | |
| Spierings 2013 Tanezumab 10 mg IV [40] | 61 | 150 | 25 | 70 | 0.8% | 1.14 [0.79, 1.65] 2013 | |
| Ekman 2014b Tanezumab 10 mg IV [14] | 101 | 209 | 42 | 104 | 1.5% | 1.20 [0.91, 1.57] 2014 | |
| Balanescu 2014 Tanezumab 10 mg IV+DSR I2 | 71 | 145 | 17 | 50 | 0.6% | 1.44 [0.95, 2.19] 2014 | |
| Brown 2014 Tanezumab 10 mg IV [5] | 48 | 74 | 20 | 36 | 1.0% | 1.17 [0.83, 1.64] 2014 | |
| Ekman 2014a Tanezumab 10 mg IV 1141 | 122 | 208 | 50 | 104 | 2.1% | 1.22 [0.97, 1.54] 2014 | |
| Schnitzer 2015 Tanezumab 10 mg IV +NSAIDI | 301 400 | 542 | 91 | 135 | 0.8% | 1.09 [0.96, 1.24] 2015 | |
| Birbara 2018 Tanezumab 10 mg IV [4] | 399 | 942 | 91 | 135 | 0.0% | 1.05 [0.63, 1.24] 2015 | |
| Subtotal (95% CI) | 44 | 2285 | 5 | 761 | 22.3% | 1.14 [1.06, 1.22] | • |
| Total events | 1439 | | 395 | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 3.76, df = 9 | (P = 0.93); | 2 = 0% | | | | | |
| Test for overall effect: Z = 3.67 (P = 0.0002) | | | | | | | |
| | | | | | | | |
| high-dose&SC | | | | | | | |
| Birbara 2018 Tanezumab 10 mg SCI4I | 36 | 86 | 10 | 18 | 0.5% | 0.75 [0.47, 1.22] 2018 | |
| Subiotal (95% CI) | 20 | 86 | 40 | 18 | 0.5% | 0.75 [0.47, 1.22] | |
| I Otal events | 36 | | 10 | | | | |
| Test for overall effect: $7 = 1.15$ (P = 0.25) | | | | | | | |
| | | | | | | | |
| Total (95% CI) | | 8227 | | 3230 | 100.0% | 1.10 [1.06, 1.14] | • |
| Total events | 5051 | | 1753 | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 18.06, df = 3 | 80 (P = 0.96 |); l² = 0% | 6 | | | | 05 07 1 15 0 |
| Test for overall effect: Z = 5.50 (P < 0.00001) | | | | | | | Favours [experimental] Favours [control] |
| Test for subaroup differences: Chi ² = 11.08. df | = 5 (P = 0.0 | 5). l ² = 5 | 4.9% | | | | · · · · · · · · · · · · · · · · · · · |

Figure A9. Sensitivity analysis for AEs according dose and administration mode in fixed-dose tanezumab trials.

| | Experim | ental | Contr | ol | | Risk Ratio | | Risk Ratio |
|---|-------------|------------------------|--------|-------|---------|--------------------|------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H. Random, 95% C | Year | M-H, Random, 95% Cl |
| low-dose&IV | | | | | | | | |
| Brown 2012 Tanezumab 2.5 mg IV [7] | 3 | 172 | 1 | 57 | 0.6% | 0.99 [0.11, 9.37] | 2012 | |
| Brown 2013 Tanezumab 2.5 mg IV [6] | 7 | 155 | 2 | 52 | 1.2% | 1.17 [0.25, 5.48] | 2013 | |
| Balanescu 2014 Tanezumab 2.5 mg IV+DSR[2 | 12 | 157 | 3 | 51 | 1.9% | 1.30 [0.38, 4.42] | 2014 | |
| Subtotal (95% CI) | | 484 | 0 | 160 | 3.1% | 1.21 [0.50, 2.91] | | |
| I otal events | 22 | 2 - 09/ | 6 | | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 0.04, di = 2 Test for everall effect: $\mathbf{Z} = 0.42$ ($\mathbf{P} = 0.69$) | (P = 0.96); | - = 0% | | | | | | |
| Test for overall effect. 2 = 0.42 (F = 0.00) | | | | | | | | |
| low-dose&SC | | | | | | | | |
| Birbara 2018 Tanezumab 2.5 mg SC [4] | 2 | 74 | 1 | 18 | 0.5% | 0.49 [0.05, 5.07] | 2018 | |
| Schnitzer 2019 Tanezumab 2.5 mg SC[34] | 4 | 233 | 2 | 116 | 1.0% | 1.00 [0.19, 5.36] | 2019 | |
| Berenbaum 2020 Tanezumab 2.5 mg SC [3] | 11 | 283 | 13 | 141 | 4.7% | 0.42 [0.19, 0.92] | 2020 | |
| Hochberg 2021 Tanezumab 2.5 mg SC[18] | 78 | 1002 | 33 | 498 | 18.5% | 1.17 [0.79, 1.74] | 2021 | |
| Subtotal (95% CI) | | 1592 | | 773 | 24.8% | 0.78 [0.40, 1.51] | | - |
| Total events | 95 | | 49 | | | | | |
| Heterogeneity: $Tau^2 = 0.20$; $Chi^2 = 5.64$, $df = 3$ | (P = 0.13); | $^{2} = 47\%$ | | | | | | |
| Test for overall effect: Z = 0.75 (P = 0.45) | | | | | | | | |
| medanata daga 8.11/ | | | | | | | | |
| Prove 2012 Topozumat 5 and 1//2 | | 470 | | 57 | 0.00 | 1 22 10 45 14 001 | 2040 | |
| Brown 2012 Tanezumab 5 mg IV[7] | 4 | 1/2 | 1 | 5/ | 0.6% | 1.33 [0.15, 11.62] | 2012 | |
| Brown 2012 Tanazumah 5 mg 1/16 | 2 5 | 154 | 2 | 52 | 1 1 9/ | 0.00 [0.00, 9.57] | 2013 | |
| Ekman 2014a Tanezumah, 5 mg W/14 | 5 | 206 | 2 | 104 | 2 0% | 0.88 [0.26, 2.05] | 2013 | |
| Brown 2014 Tanezumah 5 mg IV15 | 0 | 73 | 4 | 36 | 2.0% | Not estimable | 2014 | |
| Balanescu 2014 Tanezumah 5 mg IV+DSR [2] | 8 | 150 | 2 | 51 | 1 2% | 1 36 [0 30 6 20] | 2014 | |
| Ekman 2014b Tanezumab 5 mg IV(14) | 3 | 211 | 2 | 105 | 0.9% | 0 75 [0 13 4 40] | 2014 | · · · · · · · · · · · · · · · · · · · |
| Schnitzer 2015 Tanezumab 5 mg IV +NSAID I3 | 51 54 | 536 | 11 | 135 | 7.4% | 1.24 [0.66, 2.30] | 2015 | |
| Schnitzer 2015 Tanezumab 5 mg IV [35] | 44 | 541 | 10 | 134 | 6.6% | 1.09 [0.56, 2.11] | 2015 | |
| Subtotal (95% CI) | | 2204 | | 745 | 20.3% | 1.10 [0.76, 1.60] | | ◆ |
| Total events | 127 | | 33 | | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 0.69, df = 7 | (P = 1.00); | ² = 0% | | | | | | |
| Test for overall effect: Z = 0.50 (P = 0.62) | | | | | | | | |
| | | | | | | | | |
| moderate-dose&SC | | | | | | | | |
| Birbara 2018 Tanezumab 5 mg SC[4] | 0 | 63 | 0 | 18 | 4 00/ | Not estimable | 2018 | |
| Schnitzer 2019 Tanezumab 2.5/5 mg SC [34] | 4 | 231 | 2 | 116 | 1.0% | 1.00 [0.19, 5.40] | 2019 | |
| Berenbaum 2020 Tanezumab 5 mg SC[3] | 24 | 284 | 14 | 141 | 7.3% | 0.85 [0.45, 1.59] | 2020 | |
| Subtotal (95% CI) | 110 | 1576 | 33 | 490 | 20.4% | 1.00 [1.14, 2.42] | 2021 | • |
| Total events | 138 | 15/0 | 49 | 115 | 20.7 /0 | 1.20 [0.75, 2.00] | | - |
| Heterogeneity: $Tau^2 = 0.08$: $Chi^2 = 3.39$, $df = 2$ | P = 0.18 | $^{2} = 41\%$ | 45 | | | | | |
| Test for overall effect: $Z = 0.87$ (P = 0.38) | | | | | | | | |
| | | | | | | | | |
| high-dose&IV | | | | | | | | |
| Brown 2012 Tanezumab10 mg IV [7] | 3 | 174 | 1 | 58 | 0.6% | 1.00 [0.11, 9.43] | 2012 | |
| Spierings 2013 Tanezumab 10 mg IV[40] | 4 | 150 | 1 | 70 | 0.6% | 1.87 [0.21, 16.40] | 2013 | |
| Brown 2013 Tanezumab 10 mg IV [6] | 6 | 157 | 2 | 51 | 1.2% | 0.97 [0.20, 4.68] | 2013 | |
| Balanescu 2014 Tanezumab 10 mg IV+DSR [2] | 10 | 145 | 3 | 50 | 1.8% | 1.15 [0.33, 4.01] | 2014 | |
| Ekman 2014a Tanezumab 10 mg IV[14] | 6 | 208 | 4 | 104 | 1.8% | 0.75 [0.22, 2.60] | 2014 | |
| Ekman 2014b Tanezumab 10 mg IV [14] | 4 | 209 | 2 | 104 | 1.0% | 1.00 [0.19, 5.35] | 2014 | |
| Brown 2014 Tanezumab 10 mg IV ISI | 351 04 | <i>[4]</i> | 0 | 36 | 0.3% | 3.45 [0.18, 65.12] | 2014 | |
| Schnitzer 2015 Tanezumab 10 mg IV +NSAID I | 55] 64 | 542 | 11 | 135 | 7.6% | 1.45 [0.79, 2.67] | 2015 | |
| Bithere 2019 Tenerumab 10 mg IV/4 | 40 | 042 | | 135 | 0.4% | 1.04 [0.55, 1.96] | 2015 | |
| Subtotal (95% CI) | | 2285 | | 761 | 22.6% | 1 14 [0 80 1 63] | 2010 | • |
| Total events | 147 | 2200 | 36 | | 22.070 | 1.14 [0.00, 1.00] | | |
| Heterogeneity: $Tau^2 = 0.00$: $Chi^2 = 3.39$, $df = 9$ | P = 0.95): | $^{2} = 0\%$ | 00 | | | | | |
| Test for overall effect: $Z = 0.74$ (P = 0.46) | 0.00/1 | - 14 | | | | | | |
| | | | | | | | | |
| high-dose&SC | | | | | | | | |
| Birbara 2018 Tanezumab 10 mg SC [4] | 0 | 86 | 0 | 18 | | Not estimable | 2018 | |
| Subtotal (95% CI) | | 86 | | 18 | | Not estimable | | |
| Total events | 0 | | 0 | | | | | |
| Heterogeneity: Not applicable | | | | | | | | |
| rest for overall effect: Not applicable | | | | | | | | |
| Total (95% CI) | | 8227 | | 3230 | 100.0% | 1.14 [0.97, 1.35] | | • |
| Total events | 529 | | 173 | | | [| | - |
| Heterogeneity: Tau ² = 0.00; Chi ² = 15.82, df = 2 | 7 (P = 0.96 |); I ² = 0% | 6 | | | | | |
| Test for overall effect: Z = 1.55 (P = 0.12) | | | | | | | | U.U1 U.1 1 10 100 |
| Test for subaroup differences: Chi ² = 1.40. df = | 4 (P = 0.84 |). I ² = 0% | 'n | | | | | ravous [experimental] Favous [control] |

Figure A10. Sensitivity analysis for SAEs according dose and administration mode in fixed-dose tanezumab trials.

APPENDIX 4

| | Experimental | | | Control | | | | Std. Mean Difference | Std. Mean Difference |
|---|--------------|----------------|----------------------|---------|------|-------|--------|---------------------------|--|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV. Random, 95% CI Year | IV. Random, 95% CI |
| Spierings 2013 Tanezumab 10 mg IV[40] | -3.58 | 2.82 | 150 | -2.59 | 2.77 | 79 | 8.5% | -0.35 [-0.63, -0.08] 2013 | |
| Spierings 2013 Tanezumab 5 mg IV [40] | -3.58 | 2.79 | 161 | -2.59 | 2.77 | 79 | 8.6% | -0.35 [-0.63, -0.08] 2013 | |
| Ekman 2014a Tanezumab 10 mg IV[14] | -3.14 | 2.59 | 207 | -2.67 | 2.87 | 103 | 10.1% | -0.17 [-0.41, 0.06] 2014 | |
| Ekman 2014a Tanezumab 5 mg IV [14] | -3.44 | 2.58 | 206 | -2.67 | 2.87 | 103 | 10.0% | -0.29 [-0.52, -0.05] 2014 | |
| Ekman 2014b Tanezumab 10 mg IV[14] | -2.62 | 3.17 | 208 | -2.26 | 3.17 | 103 | 10.1% | -0.11 [-0.35, 0.12] 2014 | |
| Ekman 2014b Tanezumab 5 mg IV [14] | -2.95 | 3.2 | 211 | -2.26 | 3.17 | 104 | 10.1% | -0.22 [-0.45, 0.02] 2014 | |
| Mayorga 2016 Fulranumab 3 mg SC [27] | -2.78 | 2.49 | 48 | -1.21 | 2.62 | 25 | 3.6% | -0.61 [-1.11, -0.12] 2016 | |
| Mayorga 2016 Fulranumab 9 mg SC[27] | -3.03 | 2.56 | 50 | -1.21 | 2.62 | 25 | 3.6% | -0.70 [-1.19, -0.20] 2016 | |
| Hochberg 2021 Tanezumab 2.5 mg SC [18 | 3 -3.22 | 3.39 | 1002 | -3.07 | 3.46 | 498 | 17.6% | -0.04 [-0.15, 0.06] 2021 | |
| Hochberg 2021 Tanezumab 5 mg SC[18] | -3.33 | 3.38 | 998 | -3.07 | 3.46 | 498 | 17.6% | -0.08 [-0.18, 0.03] 2021 | |
| Total (95% CI) | | | 3241 | | | 1617 | 100.0% | -0.21 [-0.31, -0.11] | • • |
| Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 19.54$, | df = 9 (F | P = 0.0 | 2); l ² = | 54% | | | | | -1 -0.5 0 0.5 1 |
| Test for overall effect: Z = 3.99 (P < 0.000 | 1) | | | | | | | | Favours [experimental] Favours [control] |





Figure A12. WOMAC Physical Function score of anti-NGF vs active comparator drugs.

| Exper | iment | al | C | ontrol | | 1 | Std. Mean Difference | Std. Mean Difference |
|--------|--|--|---|---|---|--|---|--|
| ean | SD | Total | Mean | SD | Total | Weight | IV. Random, 95% CI Year | IV. Random, 95% CI |
| -0.9 | 0.89 | 161 | -0.55 | 0.88 | 79 | 9.1% | -0.39 [-0.67, -0.12] 2013 | |
| -1 | 0.99 | 150 | -0.55 | 0.88 | 79 | 8.9% | -0.47 [-0.75, -0.19] 2013 | |
| 0.73 | 1.01 | 207 | -0.65 | 1 | 103 | 10.4% | -0.08 [-0.32, 0.16] 2014 | |
| 0.87 | 1 | 205 | -0.65 | 1 | 103 | 10.3% | -0.22 [-0.46, 0.02] 2014 | |
| 0.72 | 1.01 | 208 | -0.54 | 1.01 | 103 | 10.4% | -0.18 [-0.41, 0.06] 2014 | |
| 0.73 | 1.02 | 211 | -0.54 | 1.01 | 104 | 10.4% | -0.19 [-0.42, 0.05] 2014 | |
| 3.07 | 2.84 | 48 | -1.38 | 3.04 | 25 | 4.2% | -0.57 [-1.07, -0.08] 2016 | |
| 3.16 | 3.11 | 50 | -1.38 | 3.04 | 25 | 4.2% | -0.57 [-1.06, -0.08] 2016 | |
| 0.96 | 1.21 | 1002 | -0.94 | 1.21 | 498 | 16.0% | -0.02 [-0.12, 0.09] 2021 | - |
| 0.97 | 1.21 | 998 | -0.94 | 1.21 | 498 | 16.0% | -0.02 [-0.13, 0.08] 2021 | + |
| | | | | | | | | |
| | | 3240 | | | 1617 | 100.0% | -0.20 [-0.32, -0.09] | \bullet |
| = 9 (P | = 0.00 |)4); l ² = | = 63% | | | | | |
| | | | | | | | | Favours [experimental] Eavours [control] |
| | Exper ean -0.9 -1 0.73 0.87 0.72 0.73 8.07 8.16 0.96 0.97 = 9 (P | Experiment ean SD -0.9 0.89 -1 0.99 0.73 1.01 0.87 1 0.73 1.02 0.73 1.02 0.74 1.21 0.96 1.21 0.97 1. | Experimental ean SD Total 0-9 0.89 161 -1 0.99 150 0.73 1.01 207 0.87 1 205 0.72 1.01 208 0.73 1.02 211 0.07 2.84 48 0.16 3.11 50 0.96 1.21 1002 0.97 1.21 998 3240 = 9 (P = 0.004); I ² = | Experimental Common SD Total Mean ean SD Total Mean -0.55 -0.9 0.89 161 -0.55 .73 1.01 207 -0.65 0.87 1 205 -0.65 0.73 1.01 208 -0.54 0.73 1.02 211 -0.54 0.73 0.07 2.84 48 -1.38 0.16 3.11 50 -1.38 0.96 1.21 1002 -0.94 9.97 1.21 998 -0.94 | Experimental Control ean SD Total Mean SD -0.9 0.89 161 -0.55 0.88 -1 0.99 150 -0.55 0.88 0.73 1.01 207 -0.65 1 0.87 1 205 -0.65 1 0.73 1.01 207 -0.65 1 0.73 1.02 211 -0.54 1.01 0.73 1.02 211 -0.54 1.01 0.74 4.8 -1.38 3.04 0.96 1.21 1002 -0.94 1.21 9.96 1.21 1002 -0.94 1.21 3240 | Experimental Control ean SD Total Mean SD Total 0.9 0.89 161 -0.55 0.88 79 -1 0.99 150 -0.55 1 103 0.73 1.01 207 -0.65 1 103 0.73 1.01 208 -0.54 1.01 103 0.73 1.02 211 -0.54 1.01 103 0.73 1.02 211 -0.54 1.01 104 0.07 2.84 48 -1.38 3.04 25 0.66 1.21 1002 -0.94 1.21 498 0.97 1.21 998 -0.94 1.21 498 0.97 1.21 998 -0.94 1.21 498 0.97 9 0.94 1.21 498 1617 | Experimental Control Stress Total Mean SD Total Meight ean SD Total Mean SD Total Meight e.0.9 SD 161 -0.55 0.88 79 8.9% -1 0.99 150 -0.55 0.88 79 8.9% 0.73 1.01 207 -0.65 1 103 10.4% 0.87 1 205 -0.65 1 103 10.4% 0.73 1.02 211 -0.54 1.01 103 10.4% 0.73 1.02 211 -0.54 1.01 103 10.4% 0.73 1.02 211 -0.54 1.01 104 10.4% 0.73 1.02 211 -1.38 3.04 25 4.2% 0.96 1.21 1002 -0.94 1.21 498 16.0% 9.97 1.21 998 -0.94 1.21 | Experimental Control Std. Mean Difference ean SD Total Weight IV. Random, 95% CI Year 0.9 0.89 161 -0.55 0.88 79 9.1% -0.39 [-0.67, -0.12] 2013 -1 0.99 150 -0.65 0.88 79 8.9% -0.47 [-0.75, -0.12] 2013 0.73 1.01 207 -0.65 1 103 10.4% -0.08 [-0.32, 0.16] 2014 0.87 1 205 -0.65 1 103 10.4% -0.08 [-0.41, 0.06] 2014 0.73 1.02 211 -0.54 1.01 103 10.4% -0.18 [-0.41, 0.06] 2014 0.73 1.02 211 -0.54 1.01 104 10.4% -0.18 [-0.42, 0.05] 2014 0.73 1.02 211 -0.54 1.01 104 10.4% -0.19 [-0.42, 0.06] 2016 0.74 L44 48 1.38 3.04 25 4.2% </td |



| | Experim | ental Control | | Control | | Risk Ratio | Risk Ratio |
|---|------------|---------------|-------------------------|---------|--------|---------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% Cl |
| Ekman 2014a Tanezumab 10 mg IV[14] | 122 | 208 | 52 | 103 | 9.4% | 1.16 [0.93, 1.45] | |
| Ekman 2014a Tanezumab 5 mg IV [14] | 107 | 206 | 52 | 103 | 9.0% | 1.03 [0.82, 1.30] | |
| Ekman 2014b Tanezumab 10 mg IV [14] | 101 | 209 | 55 | 106 | 9.1% | 0.93 [0.74, 1.17] | |
| Ekman 2014b Tanezumab 5 mg IV [14] | 101 | 211 | 55 | 106 | 9.1% | 0.92 [0.73, 1.16] | |
| Hochberg 2021 Tanezumab 2.5 mg SC [18 | 681 | 1002 | 333 | 498 | 15.1% | 1.02 [0.94, 1.10] | + |
| Hochberg 2021 Tanezumab 5 mg SC[18] | 744 | 998 | 333 | 498 | 15.2% | 1.11 [1.04, 1.20] | - |
| Mayorga 2016 Fulranumab 3 mg SC [27] | 30 | 48 | 20 | 25 | 7.1% | 0.78 [0.58, 1.05] | |
| Mayorga 2016 Fulranumab 9 mg SC [27] | 41 | 50 | 20 | 25 | 8.9% | 1.02 [0.81, 1.30] | |
| Spierings 2013 Tanezumab 10 mg IV [40] | 61 | 150 | 50 | 79 | 8.2% | 0.64 [0.50, 0.83] | |
| Spierings 2013 Tanezumab 5 mg IV [40] | 72 | 161 | 50 | 79 | 8.8% | 0.71 [0.56, 0.90] | |
| Total (95% CI) | | 3243 | | 1622 | 100.0% | 0.94 [0.85, 1.04] | • |
| Total events | 2060 | | 1020 | | | | |
| Heterogeneity: Tau ² = 0.02; Chi ² = 33.39, o | f = 9 (P = | 0.0001 |); ² = 739 | 6 | | - | |
| Test for overall effect: $Z = 1.14$ (P = 0.26) | | | | | | | 0.5 0.7 1 1.5 2 |
| | | | | | | | Favours [experimental] Favours [control] |

Figure A14. AEs of anti-NGF vs active comparator drugs.

| | Experimental | | Contr | ol | | Risk Ratio | Risk Ratio |
|--|--------------|-----------------------|--------|-------|--------|--------------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI Year | M-H. Random, 95% CI |
| Spierings 2013 Tanezumab 10 mg IV [40] | 3 | 150 | 2 | 79 | 2.7% | 0.79 [0.13, 4.63] 2013 | · · · · · · · · · · · · · · · · · · · |
| Spierings 2013 Tanezumab 5 mg IV[40] | 4 | 161 | 2 | 79 | 3.0% | 0.98 [0.18, 5.24] 2013 | |
| Ekman 2014a Tanezumab 10 mg IV[14] | 6 | 208 | 3 | 103 | 4.4% | 0.99 [0.25, 3.88] 2014 | |
| Ekman 2014a Tanezumab 5 mg IV[14] | 7 | 206 | 2 | 103 | 3.5% | 1.75 [0.37, 8.27] 2014 | |
| Ekman 2014b Tanezumab 10 mg IV[14] | 4 | 209 | 5 | 106 | 4.9% | 0.41 [0.11, 1.48] 2014 | |
| Ekman 2014b Tanezumab 5 mg IV[14] | 3 | 211 | 4 | 106 | 3.8% | 0.38 [0.09, 1.65] 2014 | |
| Mayorga 2016 Fulranumab 3 mg SC[27] | 0 | 48 | 0 | 25 | | Not estimable 2016 | |
| Mayorga 2016 Fulranumab 9 mg SC ^[27] | 1 | 50 | 1 | 25 | 1.1% | 0.50 [0.03, 7.67] 2016 | |
| Hochberg 2021 Tanezumab 5 mg SC[18] | 110 | 998 | 33 | 498 | 39.5% | 1.66 [1.14, 2.42] 2021 | |
| Hochberg 2021 Tanezumab 2.5 mg SC[18 | ij 78 | 1002 | 33 | 498 | 37.1% | 1.17 [0.79, 1.74] 2021 | |
| Total (95% CI) | | 3243 | | 1622 | 100.0% | 1.20 [0.90, 1.61] | ◆ |
| Total events | 216 | | 85 | | | | 10 35.7 M M |
| Heterogeneity: Tau ² = 0.02; Chi ² = 8.84, d | f = 8 (P = 0 | 0.36); l ² | = 9% | | | | |
| Test for overall effect: Z = 1.22 (P = 0.22) | | | | | | | Favours [experimental] Favours [control] |

Figure A15. SAEs of anti-NGF vs active comparator drugs.

Spierings 2013: oxycodone; Mayorga 2016: oxycodone; Hochberg 2021: open-label oral NSAID (naproxen 500mg twice-daily BID, celecoxib 100mg BID, or diclofenac extended release 75mg BID); Ekman 2014: naproxen