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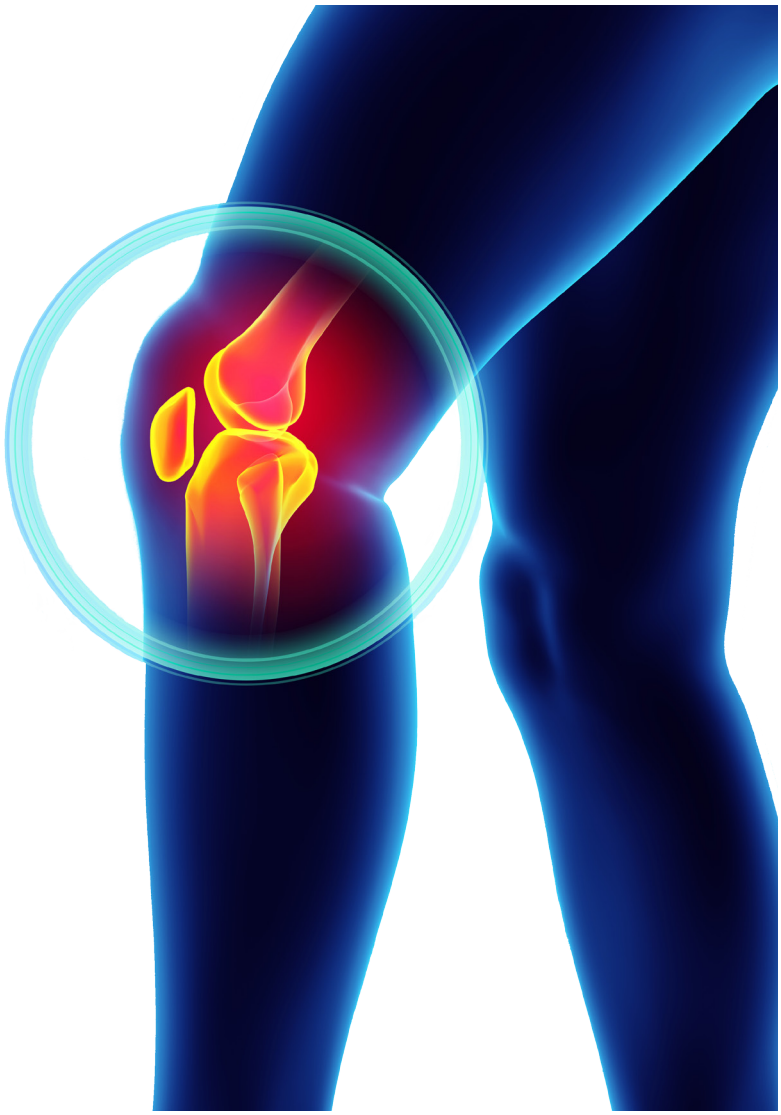
Monoclonal Antibodies for Osteoarthritis of the Hip or Knee



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Methods

These bulletins are not systematic reviews and do not involve critical appraisal or include a detailed summary of study findings. Rather, they present an overview of the technology and its associated available evidence. They are not intended to provide recommendations for or against a particular technology.

Industry is invited to review these bulletins, and a draft of each one is reviewed by at least one clinical expert.

Literature Search Strategy

A limited literature search was conducted using the following bibliographic databases: MEDLINE via OVID, PubMed, Embase via OVID, and the Cochrane Library. Grey literature was identified by searching relevant sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters). No methodological filters were applied. The search was limited to English, French, and Chinese-language documents.

Summary

- Osteoarthritis (OA) is a common and chronic disease of the synovial joints caused by biomechanical factors, inflammation, and joint tissue damage. The current therapeutic options include non-pharmacologic therapy and topical analgesics, followed by oral analgesics and injectable agents, followed by surgery for end-stage disease. OA typically affects the knees, hips, hands, spine, and feet.
- Treatment with anti-nerve growth factors monoclonal antibodies (anti-NGFs) may improve joint pain and physical function, as nerve growth factor is associated with chronic pain conditions, and is elevated in the joints of patients with osteoarthritis. Within the indication of OA, anti-NGFs are currently being studied exclusively for hip or knee OA.
- Initially, three anti-NGFs were in development for use in various chronic pain conditions, including osteoarthritis of the hip or knee. These anti-NGFs were tanezumab, fulranumab, and fasinumab. In 2016, development was discontinued for fulranumab, and future plans for the development of the drug are unknown. There are four ongoing trials on fasinumab for hip or knee OA, most of which are in the recruitment phase. Tanezumab will be reviewed by the US FDA with "fast track" designation for OA and chronic low back pain. For hip and knee OA, tanezumab is being studied for both subcutaneous and intravenous (IV) administrations.
- As tanezumab is the most advanced in clinical development among all three anti-NGFs, this bulletin provides evidence on its efficacy and safety. Additional safety information is provided for the other two drugs.
- IV tanezumab was found to be statistically significantly more effective than the placebo and active comparators (nonsteroidal anti-inflammatory drugs and oxycodone) for three key outcomes — Tanezumab provided a reduction in pain, functional improvement, and improvement in patient's global assessment of OA.
- An increase in the frequency of adverse events (AEs) involving abnormalities of peripheral sensation such as paresthesia, dysesthesia, and others was noted for all three anti-NGFs compared with the placebo. There were no statistically significant differences in serious adverse events for IV tanezumab compared with the placebo and the active comparators (nonsteroidal anti-inflammatory drugs and oxycodone). Withdrawals due to AEs were higher with IV tanezumab and with the anti-NGFs compared with the placebo.
- Lower doses of IV tanezumab provided similar efficacy (with fewer AEs) as higher doses.
- Given that the unit cost of biologics are usually high, tanezumab will likely result in a significant additive cost to health care systems and payers. Furthermore, OA patients are a clinically heterogeneous population; hence, it will be important to identify the appropriate patient population for whom tanezumab will be effective.

Background

The 2013 Global Burden of Disease study estimated that, worldwide, 242 million people were living with symptomatic and activity-limiting osteoarthritis (OA) of the hip or knee.[1] In Canada, OA affects more than 10% of the population aged 15 years or older. Of these Canadians, 12% experience pain in their hips, 29% in their knees, and 29% in both.[2] The prevalence of knee and hip OA is higher in women than men.[3] In addition to the hip and knees, OA can also affect hands, spine, and feet.[3]

Osteoarthritis is a painful disease of the synovial joints with symptoms including joint pain, stiffness, and restricted mobility. These symptoms may lead to a diminished quality of life.[1,4] OA is caused by a variety of factors, including biomechanical factors, inflammation, and joint tissue damage.[5]

The symptomatic presentation of OA is diverse and heterogeneous. OA ranges from mild disability (intermittent pain; minimal difficulty performing daily activities) to severe disability (chronic pain; progressive irreversible structural damage and loss of function).OA patients have increased risks of comorbidities like cardiovascular disease.[6] A 2014 Statistics Canada report showed that 48% of people with OA (any joint) experienced symptoms and were diagnosed in the same year, 42% had symptoms at least a year before diagnosis, and for approximately 10%, symptoms emerged after they had been diagnosed, a pattern consistent with hip and knee OA.[7] Among the various symptoms of OA, pain is the key criterion for clinical diagnosis, as well as the key reason people seek treatment for hip or knee OA.[8,9]

Current guidelines recommend a combination of both pharmacological and non-pharmacological treatments for the management of OA.[10-12] Both pharmacological and non-pharmacological treatments are intended to reduce pain, improve functional mobility, and delay or avoid joint replacement surgery.[13] However, current standards of care have not adequately managed chronic pain in a significant proportion of OA patients.[13,14]

Currently, there are various novel products and approaches in development, both pharmacological and non-pharmacological, for the management of OA, such as beta nerve growth factor (NGF) inhibitors[a].[16] Beta NGF is a neurotrophin needed for the normal development of the sympathetic nervous system and the sensory neurons responsible for pain and temperature sensation.[17] Injury, inflammation, and chronic pain conditions are associated with the up regulation of NGF levels.[13] NGF levels are elevated in the joints of OA patients, suggesting that NGF also contributes to osteoarthritic pain.[13] In OA patients, treatment with anti-NGFs may improve joint pain and physical function.[17] Given the prevalence of OA and the unmet medical needs of patients with OA under the current standard of care, anti-NGFs (if proven safe and effective) may be used in a large number of patients with OA who have hip or knee pain.

The Technology

Initially, there were three anti-NGF monoclonal antibodies in development for osteoarthritic pain: tanezumab, fulranumab, and fasinumab.

- **Tanezumab** (RN624), developed by Pfizer and Eli Lilly, is a humanized immunoglobulin G type 2 monoclonal antibody with high specificity for NGF. It inhibits the binding of NGF to its receptors, p75 and tropomyosin receptor kinase A.[18] Tanezumab was initially investigated as an intravenous (IV) infusion and was later investigated as a subcutaneous (SC) injection.[18-26]
- **Fasinumab** (REGN475), developed by Regeneron and Teva, is a fully human monoclonal antibody that has high affinity and selectivity directed against NGF.[27]
- **Fulranumab** (JNJ-42160443), developed by Janssen and Amgen, is a human recombinant immunoglobulin G2 monoclonal antibody that specifically inhibits the biological actions of NGF.[28]

Since the early 2000s, tanezumab, fulranumab, and fasinumab have been studied in patients with chronic hip or knee OA. However, in 2010, the FDA put a clinical hold[b] on all anti-NGFs (for all indications except cancer pain) because of reports of rapidly progressive OA and osteonecrosis with the use of tanezumab, which was causing the need for joint replacements.[30,31] Independent adjudication committees from Pfizer and Janssen reviewed the records of patients with osteoarthritis or chronic low back pain (CLBP) who had developed osteonecrosis. It was determined that the reported cases were instances of either normal or rapid progression of osteoarthritis. The rapid progression of osteoarthritis was deemed a safety signal associated with increasing doses of tanezumab or fulranumab, pre-existing subchondral insufficiency

[a] In February 2018, CADTH published an environmental scan on emerging non-opioid drugs for pain. The scan provides background information on alternative drugs in the pipeline with a potential to reduce or eliminate the use of opioids.[15]

[b] A "clinical hold" is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation.[29]

fractures, and concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs).[31] The hold was lifted subject to conditions, including increased patient surveillance for joint adverse events (AEs) and sympathetic nervous system dysfunction; limits on NSAID use during treatment with anti-NGFs; a restriction to patients who were unresponsive or intolerant to multiple standard-of-care analgesics; dose limitations in patients with OA; and pre-enrolment radiographic imaging to exclude patients with pre-existing shoulder, hip, and knee joint abnormalities.[32,33] A second clinical hold was placed on the entire anti-NGF class in December 2012 after peripheral nervous system effects were reported in animals.[34] The clinical hold was lifted in 2015 after the FDA conducted a review of nonclinical data.[30,35]

In June 2017, the US FDA granted "fast track" designation[c] to tanezumab in order to expedite the review of its clinical efficacy and safety for the management of chronic pain in patients with OA and in patients with CLBP.[37] A total of eight phase III clinical trials on intravenous (IV) tanezumab in patients with hip or knee OA have been completed.[18,20-24,38] There are three ongoing phase III clinical trials on subcutaneous (SC) tanezumab for patients with OA, which are expected to be completed in 2018 or 2019.[39-41]

Janssen announced on March 31, 2016, that it was discontinuing the development program for fulranumab in osteoarthritic pain. As such, it terminated its licensing agreement with Amgen and has returned all rights back to Amgen.[42] It is unclear if Amgen is pursuing the development of fulranumab. As of April 24, 2018, fulranumab is not noted as a drug on Amgen's pipeline.[43]

In October 2016, fasinumab was put on a clinical hold by the FDA due to safety concerns, more specifically because of a case of arthropathy. According to the manufacturer, the incidence of arthropathy was found to be potentially dose-dependent. There are four ongoing phase III clinical trials on fasinumab in patients with hip or knee OA, of which, two are recruiting patients; one is not yet recruiting patients; and one is active, but not recruiting patients. All the trials are estimated to be completed in 2020.[44-47] In May 2018, following the recommendation from an independent data monitoring committee, Regeneron announced that clinical trials on fasinumab for OA will be modified based on the risk benefit assessment. This means that trials with higher dose regimens will be discontinued, and only clinical trials with lower dose regimens will be continued.[48]

Given that tanezumab is the most advanced in clinical development among all three anti-NGFs, this bulletin will only provide evidence on the efficacy of tanezumab in patients with hip or knee OA; however, evidence on the safety of all three anti-NGFs (tanezumab, fulranumab, and fasinumab) will be presented.

Regulatory Status

In June 2017, the US FDA granted tanezumab "fast track" designation to expedite the review of its clinical efficacy and safety for the management of chronic pain in patients with hip or knee OA and in patients with CLBP.[37]

Cost and Administration

The cost for tanezumab is unavailable as this product is not marketed in any country.

Tanezumab was initially investigated as an intravenous infusion; a subcutaneous injection was subsequently developed.[18-26] The doses used in the completed phase III clinical trials for IV tanezumab were 2.5 mg, 5 mg, or 10 mg administered every eight weeks.[13] The doses used in the ongoing phase III clinical trials for SC tanezumab are 2.5 mg and 5 mg, administered every eight weeks.[39-41]

Target Population

For OA, tanezumab has been studied in adults with hip or knee OA who do not respond to or who are intolerant to currently available pain medications.[13,49]

Current Practice

Multimodal interventions (i.e., a combination of pharmacological and non-pharmacological treatments) are generally recommended for the treatment of pain in OA.[10-12,50] The goal of the treatment is to achieve pain control with minimum AEs, while maintaining or improving joint mobility and function, and affording an improved health-related quality of life.[51]

Most clinical practice guidelines recommend non-pharmacological therapies in addition to pharmacological treatments.[10-12,50] In general, recommended non-pharmacological options include exercise, joint protection, use of assistive devices,

[c] "Fast track" is a process designed by the FDA to facilitate the development, and expedite the review of, drugs to treat serious conditions that fill an unmet medical need. The purpose is to get important new drugs to the patient earlier. [36]

thermal therapy, physical therapy, neuromuscular training, or education and self-management such as psychosocial interventions (e.g., cognitive behavioural therapy). Recommended pharmacological treatment options include topical NSAIDs; oral NSAIDs; and analgesics like acetaminophen, corticosteroids, or tramadol.[12] Other pharmacological options are available but are either not recommended or the evidence on these pharmacological options is inconclusive. These include non-tramadol opioids, capsaicin, glucosamine, intra-articular hyaluronate, platelet rich plasma, and stem cell therapy.[10,12] Pharmacological treatment options are often associated with AEs, especially their long-term use. NSAIDs are associated with risks of gastrointestinal, cardiovascular, and renal complications, while opioids are associated with the risks of falls, confusion, respiratory depression, diversion, overdose, misuse, or opioid use disorder.[13,52,53]

Summary of the Evidence

Evidence on the efficacy of one anti-NGF, tanezumab, is included in this report. Evidence on the safety of all three anti-NGFs (tanezumab, fulranumab, and fasinumab) is presented separately.

Study Characteristics

EFFICACY

Systematic Review and Meta-Analysis on Intravenous Tanezumab

Evidence of the safety and efficacy of intravenous tanezumab used in knee or hip OA is based on a meta-analysis by Chen et al.[13] The meta-analysis by Chen et al. included nine reports for a total of 10 randomized controlled trials (RCT) on tanezumab (one report contained two RCTs). All 10 RCTs were parallel-design double-blind, placebo or active-controlled trials. The 10 RCTs enrolled a total of 7,665 patients.[13] The meta-analysis included eight phase III studies, one phase II study, and one phase I/II study. Tanezumab was administered intravenously in all the included studies, and was studied in patients with hip or knee OA.[13,18,20-25,54,55] The dose of tanezumab in all eight phase III trials was 5 mg or 10 mg every 8 weeks; three phase III trials also studied 2.5 mg of tanezumab every 8 weeks. In the other two trials (phase II and phase I/IIa), the dose of tanezumab was 10 mcg/kg to 200 mcg/kg. One RCT added tanezumab to oral diclofenac sustained release; two RCTs compared tanezumab with a placebo and naproxen; one RCT compared tanezumab with a placebo and oxycodone; and one RCT compared tanezumab monotherapy with tanezumab combined with an NSAID. The primary end points in the RCTs were mean change from baseline to end point in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain, WOMAC physical function, patient's global assessment (PGA), withdrawals due to adverse events (WDAEs), and SAEs.[13] Only published trials, and those written in English, were included in the meta-analysis.[13] Although the systematic review retrieved five active-controlled RCTs, Chen et al. did not analyze these studies in detail; only the comparisons with a placebo were meta-analyzed.[18,20-22] Table 1 presents the inclusion and exclusion criteria for the meta-analysis by Chen et al. Table 2 presents the study characteristics of the 10 RCTs included in Chen et al.

Information on the analysis of tanezumab versus active comparators is based on a systematic review and meta-analysis (SR/MA) of RCTs on all three anti-NGFs, which was conducted by Schnitzer and Marks.[14] The inclusion criteria for the SR/MA by Schnitzer and Marks were patients 40 years old to 80 years old with a Kellgren-Lawrence grade of ≥ 2 and stable NSAID or opioid use, with a diagnosis of OA of the knee in one trial and a diagnosis with knee or hip OA in the other trial.[14] As such, the SR/MA by Schnitzer and Marks included an analysis of the five RCTs that compared tanezumab with active comparators (naproxen, celecoxib, and oxycodone).[18,20-22] (See Table 2 for the study characteristics of the five studies with active comparators that were described by Chen et al.)

SAFETY

Extension Studies on Intravenous Tanezumab

In addition to the RCTs included in the meta-analysis by Chen et al., there are two extension studies (one phase III and one phase II) on IV tanezumab, for which the phase III was terminated prematurely as a result of the US FDA's clinical hold.[26,38,56] The study characteristics are presented in Table 3.

Studies on Anti-NGFs (Including Fulranumab and Fasinumab)

The SR/MA by Schnitzer and Marks, and one phase II/III RCT on fasinumab, were used to provide evidence on the safety of the anti-NGFs.[14,57]

The SR/MA by Schnitzer and Marks included two phase II RCTs on fulranumab.[14] One RCT with a sample size of 196 patients compared fulranumab 3 mg every four weeks or fulranumab 9 mg every four weeks, with a placebo or oxycodone 10 mg to 50 mg twice daily. The other RCT (which had a sample size of 466 patients) compared fulranumab 1 mg every four weeks, fulranumab 3 mg every four weeks, fulranumab 3 mg every eight weeks, fulranumab 6 mg every eight weeks, and fulranumab 10 mg every eight weeks, with a placebo.[14]

The SR/MA by Schnitzer and Marks also included one phase II RCT on fasinumab.[14] This RCT had a sample size of 217 patients and compared fasinumab 0.03 mg/kg every eight weeks, fasinumab 0.1 mg/kg every eight weeks, and fasinumab 0.3 mg/kg every eight weeks with a placebo.[14]

A placebo-controlled phase II/III RCT on fasinumab conducted by Maloney et al. was published in 2016 (after the SR/MA by Schnitzer and Marks). A total of 419 patients were randomized to 1 mg fasinumab SC every four weeks, 3 mg fasinumab SC every four weeks, 6 mg fasinumab SC every four weeks, 9 mg fasinumab SC every four weeks, or to the placebo. The numbers of patients in each group were not reported.[57]

Table 1: Inclusion and Exclusion Criteria for the Systematic Review and Meta-Analysis by Chen Et Al.[13]

Inclusion Criteria	Exclusion Criteria

Study design:
• RCT
Study population:
• ≥ 18 years
• BMI of ≤ 39 kg/m^2
• Knee or hip OA
• Kellgren-Lawrence grade of ≥ 2 (on a 0 to 4 scale)[a]
• Candidacy for invasive interventions[b]
• WOMAC pain subscale score in the index knee of ≥ 4 (on a 0 to10 scale) at screening, and ≥ 5 at baseline, an increase of ≥ 1 after washout of prior analgesic treatment
Intervention and comparator:
• Tanezumab versus placebo
• Tanezumab versus active comparator
Outcomes:
• Mean change from baseline to end point in
  ◦ WOMAC[c] pain
  ◦ WOMAC physical functional
  ◦ PGA
• WDAEs
• SAEs
	• Pregnant or intended to get pregnant during the study
	• Any condition that could confound OA pain assessment
	• Rheumatoid arthritis, fibromyalgia, or other autoimmune disorders
	• Significant cardiac, neurologic, or psychiatric conditions

BMI = body mass index; OA = osteoarthritis; PGA = patient's global assessment; RCT = randomized controlled trial; SAEs = serious adverse events; WDAEs = withdrawals due to adverse events; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

[a] A Kellgren-Lawrence grade is a method of classifying the radiographic severity of knee OA using five grades: a score of 2 (signs of OA) indicates definite osteophytes without reduction of the joint space; a score of 3 (moderate signs of OA) indicates diminished joint space; and a score of 4 (severe signs of OA) indicates greatly reduced joint space.[25]

[b] For example, intra-articular injections or total knee arthroplasty.

[c] WOMAC is an instrument widely used to measure symptoms and physical disability of OA of the hip or knee.[58] WOMAC evaluates pain, stiffness, and physical function with five, two, and 17 questions, respectively.[58] The WOMAC pain subscale is rated on a numerical rating scale of zero to 10, with lower scores indicating lower levels of symptoms or physical disability.[58]

Table 2: Study Characteristics of the Ten Randomized Controlled Trials Included in Chen Et Al.[13]

Author, Year	Study Phase, Study Duration, Sample Size	Population	Intervention and Comparators	Outcomes
Balanescu et al., 2014[18]	Phase III 24 weeks N = 604	Moderate-to-severe knee or hip OA ≥ 18 years BMI of ≤ 39 kg/m^2 Kellgren-Lawrence grade ≥ 2[a] WOMAC pain ≥ 4 Tolerating stable DSR 150 mg/day[b]	TNZ IV 2.5 mg + DSR 75 mg[b] (n = 157) TNZ IV 5 mg + DSR 75 mg[b] (n = 150) TNZ IV 10 mg + DSR 75 mg[b] (n = 145) Placebo + DSR 75 mg[b] (n = 152)	WOMAC pain WOMAC physical Function PGA
Brown et al., 2012[24]	Phase III 32 weeks N = 697	Knee OA Kellgren-Lawrence grade ≥ 2[a] WOMAC pain ≥ 5 WOMAC physical function ≥ 4 PGA ≥ 3 Inadequate relief from non-opiate medications or candidacy for invasive interventions	TNZ IV 2.5 mg (n = 172) TNZ IV 5 mg (n = 172) TNZ IV 10 mg (n = 174) Placebo (n = 172)	WOMAC pain WOMAC physical Function PGA
Brown et al., 2013[23]	Phase III 32 weeks N = 627	Hip OA WOMAC pain ≥ 4 WOMAC physical function ≥ 4 PGA "fair," "poor," or "very poor" Inadequate relief from non-opiate medications or candidacy for invasive interventions	TNZ IV 2.5 mg (n = 155) TNZ IV 5 mg (n = 154) TNZ IV 10 mg (n = 157) Placebo (n = 155)	WOMAC pain WOMAC physical Function PGA
Brown et al., 2014[c54]	Phase III 32 weeks N = 219	Knee or hip OA ≥ 18 years WOMAC pain ≥ 4 PGA "fair," "poor," or "very poor"	TNZ IV 5 mg (n = 73) TNZ IV 10 mg (n = 74) Placebo (n = 72)	Nerve conduction attributes Heat rate variability with deep breathing
Ekman et al., 2014A[21]	Phase III 24 weeks N = 828	Knee OA ≥ 18 years BMI ≤ 39 kg/m^2 Kellgren-Lawrence grade ≥ 2[a] WOMAC pain ≥ 4 WOMAC physical function ≥ 4 PGA "fair," "poor," or "very poor"	TNZ IV 5 mg (n = 206) TNZ IV 10 mg (n = 208) Naproxen 500 mg (n = 206) Placebo (n = 208)	WOMAC pain WOMAC physical Function PGA
Ekman et al., 2014B[21]	Phase III 24 weeks N = 840	Knee or hip OA ≥ 18 years BMI ≤ 39 kg/m^2 Kellgren-Lawrence grade ≥ 2[a] WOMAC pain ≥ 4 WOMAC physical function ≥ 4 PGA "fair," "poor," or "very poor"	TNZ IV 5 mg (n = 211) TNZ IV 10 mg (n = 209) Naproxen 500 mg (n = 211) Placebo (n = 209)	WOMAC pain WOMAC physical Function PGA

Author, Year	Study Phase, Study Duration, Sample Size	Population	Intervention and Comparators	Outcomes
Lane et al., 2010[25]	Phase II 26 weeks N = 450	Knee OA 40 to 75 years Kellgren-Lawrence grade ≥ 2[a] Walking-pain measure of the WOMAC 50 to90[d] Inadequate relief from non-opiate medications or candidacy for invasive interventions	TNZ IV 10 mcg/kg (n = 74) TNZ IV 25 mcg/kg (n = 74) TNZ IV 50 mcg/kg (n = 74) TNZ IV 100 mcg/kg (n = 74) TNZ IV 200 mcg/kg (n = 74) Placebo (n = 74)	Knee pain while walking PGA of response to therapy
Nagashimaet al., 2011[55]	Phase I/IIa 13 to17 weeks N = 83	Knee OA 35 to 75 years (Japanese) Kellgren-Lawrence grade ≥ 2[a] Walking-pain (index knee pain) measure of the WOMAC 50 to 90[d] Inadequate relief from non-opiate medications or candidacy for invasive interventions	TNZ IV 10 mcg/kg (n = 15) TNZ IV 25 mcg/kg (n = 15) TNZ IV 50 mcg/kg (n = 15) TNZ IV 100 mcg/kg (n = 16) TNZ IV 200 mcg/kg (n = 6) Placebo (n = 16)	Index knee pain intensity WOMAC subscales
Schnitzeret al., 2015[20]	Phase III 16 weeks N = 2,700	Knee or hip OA ≥ 18 years BMI ≤ 39 kg/m^2 Kellgren-Lawrence grade ≥ 2[a] WOMAC pain ≥ 4 WOMAC physical function ≥ 4 PGA "fair," "poor," or "very poor" Stable NSAID use with some benefit	TNZ IV 5 mg (n = 541) TNZ IV 10 mg (n = 542) TNZ IV 5 mg + NSAID (n = 536) TNZ IV 10 mg + NSAID (n = 542) Placebo + NSAID (n = 539)	WOMAC pain WOMAC physical Function PGA
Spierings et al., 2013[22]	Phase III 16 weeks N = 614	Knee or hip OA Kellgren-Lawrence grade ≥ 2[a] WOMAC Pain score ≥ 4 PGA "fair," "poor," or "very poor" Regular use of analgesics (opioid or non-opioid, other than acetaminophen) Inadequate relief from non-opiate medications or candidacy for invasive interventions	TNZ IV 5 mg (n = 161) TNZ IV 10 mg (n = 150) Oxycodone 10 mg to 40 mg (n = 158) Placebo (n = 141)	WOMAC pain

BMI = body mass index; DSR = diclofenac sustained release; IV = intravenous; NSAID = non-steroid anti-inflammatory drugs; OA = osteoarthritis; PGA = patient's global assessment; TNZ = tanezumab; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

[a] A Kellgren-Lawrence grade of ≥ 2 on a 0 to 4 scale. The Kellgren-Lawrence grade is a method of classifying the radiographic severity of knee OA using five grades: a score of 2 (signs of OA) indicates definite osteophytes without reduction of the joint space; a score of 3 (moderate signs of OA) indicates diminished joint space; and a score of 4 (severe signs of OA) indicates greatly reduced joint space.[25]

[b] Taken orally (75 mg twice daily).

[c] The study was stopped prematurely due to the US FDA's clinical hold.

[d] Pain while walking on a flat surface (the walking-pain measure of the WOMAC rated between 50 and 90 on a visual analogue scale that ranged from 0 to 100, with 100 indicating maximal pain).

Table 3: Study Characteristics of Two Extension Studies[26,38]

Author, Year	Study Design, Study Phase, Study (Treatment) Duration, Sample Size	Population	Intervention and Comparators	Outcomes
Bello et al., 2012[38a] (Abstract)	Non-controlled, randomized, dose-blinded extension study Phase III 80 weeks N = 2,142	Patients enrolled in placebo-controlled and active comparator, multiple-dose phase III parent studies of tanezumab for the treatment of hip or knee OA. Eligible patients were enrolled up to 12 weeks after their last dose of study medication in the parent study.	TNZ IV 2.5 mg (n = 522) TNZ IV 5 mg (n = 832) TNZ IV 10 mg (n = 788)	WOMAC pain WOMAC physical function PGA AEs Physical and neurological examinations Laboratory tests
Schnitzer et. al., 2011[26]	Open-label, multiple-dose extension study Phase II 56 weeks N = 281	Patients who previously participated in studies of tanezumab for the treatment of knee OA (i.e., the phase II study by Lane et al.).[25b] Patients who had received at least two doses of tanezumab in the parent study by Lane et al., and were followed for at least eight weeks.	TNZ IV 50 mcg/kg (n = 281) on days 1 and 56, with subsequent dose administered at eight-week intervals, for up to a total of eight infusions	All observed or volunteered AEs SAEs Laboratory test, vital signs, physical and neurological examinations Efficacy outcomes: • overall knee pain • WOMAC index subscales • SGA of response to therapy

AE = adverse events; IV = intravenous; OA = osteoarthritis; PGA = patient's global assessment; TNZ = tanezumab; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; SAE = serious adverse events.

[a] The study was terminated prematurely due to the US FDA's clinical hold.

[b] Lane et.al was included in the systematic review and meta-analysis by Chen et. al. (see Table 2).

Results

EFFICACY

Intravenous Tanezumab Versus Placebo: Results from the Systematic Review and Meta-Analysis by Chen Et Al.[13]

Pain: Pain, measured by WOMAC, was the primary or secondary outcome of all the included studies.[13] All of the eight phase III RCTs used a numerical rating scale of zero to 10 (where a decreasing score represented a reduction in pain),[13,18,20-24,54] while the phase II and phase I/IIa studies used a zero mm to 100 mm visual analogue scale (VAS). The VAS results were converted to the numerical rating scale for analysis by Chen et al.[13,25,55] Tanezumab statistically significantly reduced pain compared with the placebo by approximately a one point difference (5,879 patients; mean difference [MD] = −0.98; 95% confidence interval [CI], −1.18 to −0.79; P < 0.00001).[13]

Physical Function: All of the 10 included RCTs measured changes in WOMAC physical function using the numerical rating scale of zero to 10 (where a lower score represented less limitation of physical function). A statistically significant difference was observed between tanezumab and the placebo (6,078 patients; MD = −1.10; 95% CI, −1.28 to −0.92; P < 0.00001), favouring tanezumab over the placebo for functional improvement by approximately one point.[13]

Patient's Global Assessment: Data on PGA were reported in nine of the 10 trials, and PGA was assessed using a five-point Likert scale (with 1 meaning very good and 5 meaning very poor). A statistically significantly greater reduction in PGA score was observed with tanezumab versus the placebo (5,366 patients; MD = −0.27; 95% CI, −0.34 to −0.20; P < 0.00001).[13]

Tables 4a, 4b, and 4c provide mean baseline to end-point changes of WOMAC pain, WOMAC physical function, and PGA after the tanezumab treatment versus the placebo. It should be noted that patients in the phase III RCTs received fixed doses of tanezumab (2.5 mg, 5 mg, or 10 mg of IV tanezumab), and patients in the phase II RCTs received doses based on weight (10 mcg/kg, 25 mcg/kg, 50 mcg/kg, 100 mcg/kg or 200 mcg/kg of IV tanezumab). The phase II and phase III data were pooled by Chen et al., the results combined according to sub-groups for low dose (10 mcg/kg and 25 mcg/kg in phase II trials, and 2.5 mg in phase III trials), moderate dose (50 mcg/kg in phase II trials, and 5 mg in phase III trials), and high dose (100 mcg/kg and 200 mcg/kg in phase II trials, and 10 mg in phase III trials).

Table 4a: Mean Baseline to End-Point Changes in Western Ontario and McMaster Universities Osteoarthritis Index Pain after Tanezumab Treatment Versus Placebo[13]

Dose Subgroup	Low Dose[a]	Moderate Dose[b]	High Dose[c]	All Doses Combined
Sample size	Tanezumab (n = 641) Placebo (n = 84)	Tanezumab (n = 1,722) Placebo (n =760)	Tanezumab (n = 1,804) Placebo (n = 768)	Tanezumab (n = 4,167) Placebo (n = 1,712)
Study weight (%)	14.8	41.8	43.4	100
Mean difference[d] (95% CI) tanezumab IV vs. placebo	−0.97 (−1.47 to −0.46)	−0.94 (−1.25 to −0.64)	−1.03 (−1.32 to −0.73)	−0.98 (−1.18 to −0.79)
Heterogeneity	I^2 = 25%	I^2 = 0%	I^2 = 43%	I^2 = 5%

CI = confidence interval; IV = intravenous; vs = versus.

[a] Studies include Balanescu et al. 2014, Brown et al. 2012, Brown et al. 2013, Lane et al. 2010, and Nagashima et al. 2011[18,23-25,55] (see Table 2 for study characteristics).

[b] Studies include Balanescu et al. 2014, Brown et al. 2012, Brown et al. 2013, Brown et al. 2014, Ekman et al. 2014 A and B, Lane et al. 2010, Nagashima et al. 2011, Schnitzeret al. 2015, and Spierings et al. 2013[18,20-25,54,55] (see Table 2 for study characteristics).

[c] Studies include Balanescu et al. 2014, Brown et al. 2012, Brown et al. 2013, Brown et al. 2014, Ekman et al. 2014 A and B, Lane et al. 2010, Nagashima et al. 2011, Schnitzeret al. 2015, and Spierings et al. 2013[18,20-25,54,55] (see Table 2 for study characteristics).

[d] Using a fixed effect model.

Table 4b: Mean Baseline to End-Point changes in Western Ontario and McMaster Universities Osteoarthritis Index Physical Function after Tanezumab Treatment Versus Placebo[13]

Dose Subgroup	Low Dose[a]	Moderate Dose[b]	High Dose[c]	All Doses Combined
Sample size	Tanezumab (n = 641) Placebo (n =185)	Tanezumab (n = 1,722) Placebo (n = 860)	Tanezumab (n = 1,804) Placebo (n = 866)	Tanezumab (n = 4,167) Placebo (n =1,911)
Study weight (%)	13.4	43	43.6	100
Mean difference[d] (95% CI) tanezumab IV vs. placebo	−1.11 (−1.60 to −0.62)	−1.06 (−1.33 to −0.78)	−1.14 (−1.32 to −0.87)	−1.10 (−1.28 to −0.92)
Heterogeneity	I^2 = 42%	I^2 = 0%	I^2 = 47%	I^2 = 15%

CI = confidence interval; IV = intravenous; vs = versus.

[a] Studies include Balanescu et al. 2014, Brown et al. 2012, Brown et al. 2013, Lane et al. 2010, and Nagashima et al. 201118,23-25,55 (see Table 2 for study characteristics).

[b] Studies include Balanescu et al. 2014, Brown et al. 2012, Brown et al. 2013, Brown et al. 2014, Ekman et al. 2014 A and B, Lane et al. 2010, Nagashima et al. 2011, Schnitzeret al. 2015, and Spierings et al. 201318,20-25,54,55 (see Table 2 for study characteristics).

[c] Studies include Balanescu et al. 2014, Brown et al. 2012, Brown et al. 2013, Brown et al. 2014, Ekman et al. 2014 A and B, Lane et al. 2010, Nagashima et al. 2011, Schnitzeret al. 2015, and Spierings et al. 201318,20-25,54,55 (see Table 2 for study characteristics).

[d] Using a fixed effect model.

Table 4c: Mean Baseline to End-point Changes in Patient's Global Assessment after Tanezumab Treatment Versus Placebo[13]

Dose Subgroup	Low Dose[a]	Moderate Dose[b]	High Dose[c]	All Doses Combined
Sample size	Tanezumab (n = 462) Placebo (n = 153)	Tanezumab (n = 1,643) Placebo (n = 737)	Tanezumab (n = 1,636) Placebo (n = 735)	Tanezumab (n = 3,741) Placebo (n = 1, 625)
Study weight (%)	10.4	45.2	44.4	100
Mean difference[d] (95% CI) tanezumab IV vs. placebo	−0.23 (−0.45 to −0.01)	−0.29 (−0.39 to −0.18)	−0.27 (−0.37 to −0.16)	−0.27 (−0.34 to −0.20)
Heterogeneity	I^2 = 0%	I^2 = 0%	I^2 = 0%	I^2 = 0%

CI = confidence interval; IV = intravenous; vs = versus.

[a] Studies include Balanescu et al. 2014, Brown et al. 2012, and Brown et al. 2013[18,23,24] (see Table 2 for study characteristics).

[b] Studies include Balanescu et al. 2014, Brown et al. 2012, Brown et al. 2013, Brown et al. 2014, Ekman et al. 2014 A and B, Schnitzeret al. 2015, and Spierings et al. 2013[18,20-24,54] (see Table 2 for study characteristics).

[c] Studies include Balanescu et al. 2014, Brown et al. 2012, Brown et al. 2013, Brown et al. 2014, Ekman et al. 2014 A and B, Schnitzeret al. 2015, and Spierings et al. 2013[18,20-24,54] (see Table 2 for study characteristics).

[d] Using a fixed effect model.

Intravenous Tanezumab Versus Active Comparators: Results from the Systematic Review and Meta-Analysis by Schnitzer Et Al.

The meta-analysis by Schnitzer and Marks[14] demonstrated a statistically significantly greater reduction in pain for tanezumab monotherapy compared with the active comparators. This included both tanezumab 5 mg (standardized effect size 0.24; 95% CI, 0.15 to 0.32; P < 0.001) and tanezumab 10 mg (standardized effect size 0.22; 95% CI, 0.13 to 0.30; P < 0.001).[14]

The analysis also demonstrated a statistically significantly greater reduction in pain for tanezumab combined with NSAID compared with NSAID alone. This included both tanezumab 5 mg (standardized effect size 0.28; 95% CI, 0.17 to 0.39; P < 0.001) and tanezumab 10 mg (standardized effect size 0.35; 95% CI, 0.25 to 0.46; P < 0.001).[14]

Low doses (5 mg) of tanezumab and high doses (10 mg) of tanezumab provided similar, and statistically significantly greater, improvement in physical function, as well as a greater reduction in PGA score compared with the active comparators.[14]

SAFETY

Intravenous Tanezumab Versus Placebo: Results from the Systematic Review and Meta-Analysis by Chen Et Al.[13]

Data on WDAEs and SAEs were provided in all 10 RCTs and meta-analyzed by Chen et al. The number of WDAEs was significantly greater after IV tanezumab treatment versus the placebo (6,537 patients; relative risk [RR] = 1.62; 95% CI, 1.29 to 2.03; P < 0.0001). The number of SAEs was not significantly different between tanezumab-treated and placebo-treated patients (7,481 patients; RR = 1.19; 95% CI, 0.94 to1.52; P = 0.15).

The meta-analysis showed that tanezumab-treated patients reported statistically significantly more paresthesia (7,639 patients; RR = 2.55; 95% CI, 1.85 to 3.51; P ≤ 0.00001), arthralgia (7,556 patients; RR = 1.59; 95% CI, 1.28 to 1.98; P ≤ 0.0001), hypoesthesia (7,556 patients; RR = 2.55; 95% CI, 1.70 to 3.83; P ≤ 0.00001), and peripheral edema (6,727 patients; RR = 3.65; 95% CI, 2.35 to 5.68; P ≤ 0.00001). A total of 10 deaths were reported in five RCTs, none of which the investigators considered to be related to the medication.[13]

Intravenous Tanezumab Versus Active Comparators: Results from the Systematic Review and Meta-Analysis by Schnitzer and Marks[14]

No statistically significant difference in the frequency of WDAEs was reported for IV tanezumab compared with NSAIDs (naproxen and celecoxib) (odds ratio [OR] = 1.09; 95% CI, 0.71 to 1.68).[14] There was no statistically significant difference in the incidence of SAEs between IV tanezumab and the active comparators (NSAIDs and oxycodone) (OR = 1.03; 95% CI, not reported).[14]

Of note, the RCT by Spierings et al., in which oxycodone was the active comparator, showed high heterogeneity and was excluded from the meta-analysis of data on WDAEs. It is reported that the withdrawals due to AEs in the oxycodone group were four to eight times higher than with tanezumab.[14]

There were statistically significantly more SAEs and more WDAEs with tanezumab combined with an NSAID compared with NSAID monotherapy (OR = 1.91; 95% CI, 1.39 to 2.61; and OR = 1.39; 95% CI, 1.00 to 1.94; respectively).[14]

Results from the Extension Studies on Intravenous Tanezumab

The study by Bello et al. was stopped prematurely due to the FDA's clinical hold, and limited data are available through an abstract. Mean treatment duration of combined parent and extension studies for tanezumab 2.5 mg, 5 mg, and 10 mg was 353 days, 345 days, and 335 days, respectively. Paresthesia, arthralgia, and hypoesthesia were the most frequently reported treatment-related AEs. Osteonecrosis was reported in 28 of the 2,142 (1.3%) patients, however only one event was adjudicated as osteonecrosis. Concomitant NSAID use was associated with an increased incidence of rapidly progressive osteoarthritis (though data were not available in the abstract). A total of 8.7% (187 of 2,142 patients) underwent total joint replacements; and all-cause total joint replacements frequency was higher in the concomitant NSAID cohort (13.0%, 126 of 969 patients) versus those not taking NSAIDs (5.2%, 61 of 1,173 patients) (statistical significance was not provided in the abstract). [38]

In Schnitzer et al.,[25,26] the incidence of treatment-related AEs was 7.5% (21 of 281 patients). A total of 1.4% (4 of 281 patients) discontinued tanezumab infusions due to treatment-related AEs. The incidence of SAEs was 2.8% (8 of 281 patients) with tanezumab.[26] Paresthesia and hypoesthesia were reported by seven (2.5%) and nine (3.2%) of the 281 patients, respectively.

Overview of Results on Anti-NGFs (Including Fulranumab and Fasinumab)

Systematic Review and Meta-Analysis by Schnitzer and Marks[14]

The SR/MA by Schnitzer and Marks showed that the withdrawal odds ratio due to AEs for all groups of patients receiving anti-NGFs (tanezumab, fasinumab, and fulranumab) compared with the placebo was 1.50 (95% CI, 1.01 to 2.23; P = 0.04).[14] No statistically significant differences were reported for SAEs between anti-NGFs and the placebo. Although not quantitatively evaluated, for all three anti-NGF treatments a higher number of abnormal peripheral sensation (paresthesia, dysesthesia, and

others) was reported compared with the placebo. There were no marked imbalances in the incidence of abnormalities associated with the autonomic nervous system reported for any of the three anti-NGFs.[14]

The small sample size and low numbers of AEs and SAEs limited the quantitative analysis of both fulranumab and fasinumab.[14] No statistically significant difference between the placebo and treatment arms was observed for WDAEs in the fulranumab trials (OR = 1.77; 95% CI, 0.74 to 4.22).[14] The odds ratio for WDAEs in the fasinumab groups compared with placebo was 1.53 (95% CI, 0.50 to 4.73), with the highest dose (fasinumab 0.3 mg/kg) showing the greatest number of events.[14]

Randomized Controlled Trial on Fasinumab

In the RCT by Maloney et al., limited safety information was available in the abstract. In fasinumab-treated patients, neuromuscular events (including arthralgia, paresthesia, hypoesthesia, and peripheral edema) occurred more frequently than with the placebo.[57] The numbers of patients with subchondral insufficiency fracture were one, zero, two, zero, and four in the placebo, 1 mg, 3 mg, 6 mg, and 9 mg groups, respectively.[57] One case of rapidly progressive osteoarthritis was reported in each of the 3 mg, 6 mg, and 9 mg fasinumab groups.[57]

STUDY LIMITATIONS

The search strategy for the SR/MA conducted by Chen et al. excluded unpublished trials, which may have resulted in selection bias as trials with positive results are more likely to be published. In addition, the language for the search was restricted to English; hence, trials published in other languages might have been missed. All the included trials were sponsored by pharmaceutical companies.[13] The study population in the SR/MA by Chen et al. included a high proportion of women compared with men, which is expected considering that osteoarthritis affects more women than men.[3,13] Eight of the 10 trials were conducted in the US, and the three studies that reported the ethnicity of the study population reported it to be predominantly as white.[13,20,25,54] These raise questions about the generalizability of the results to the male population and patients of other ethnic origins given that medication efficacy and safety can vary with gender and ethnicity.[59] Furthermore, the patient population included in the individual studies that included patients with both hip and knee OA had predominantly included patients with knee OA, raising further concern about the generalizability of the efficacy results to patients with hip OA.[18,20-22] Patients with cardiac, neurologic, or psychiatric conditions were excluded from the trials.[13] Depending on the interpretation of these definitions, these trials would have likely excluded a large proportion of OA patients who tend to have a high burden of comorbid diseases, especially older patients with OA; again, this would limit the generalizability of the results.[6]

Similar limitations were observed for the SR/MA by Schnitzer and Marks.[14] Additionally, the SR/MA by Schnitzer and Marks had limited data on the safety of fulranumab and fasinumab, with only two studies for fulranumab and one study for fasinumab.[14]

Additionally, the duration of the studies included in the SR/MA by Chen et al. ranged from 16 weeks to 32 weeks, which may not be long enough to assess the long-term changes in the efficacy or safety end points.[13]

Concurrent Developments

Subcutaneous Tanezumab

Three randomized parallel-design, double-blind, phase III clinical trials on SC tanezumab for hip or knee OA are currently ongoing. All of these have completed recruitment and are expected to be completed in 2018 or 2019. Two of these RCTs are placebo controlled, and one is an active-controlled (oral NSAID: naproxen 500 mg, celecoxib 100 mg, or diclofenac 75 mg) trial. A total of 4,570 participants (3,022, 698, and 850 patients) have been recruited for these three trials. The doses of SC tanezumab in all three trials are 2.5 mg and 5 mg. Primary outcomes of all three trials include changes from baseline in WOMAC pain and physical function subscales, and PGA of OA.[39-41]

Other Drugs for Osteoarthritis

MIV-711, an orally administered small molecule targeted to inhibit cathepsin K, is being investigated in phase II trials for OA of the knee.[60]

CNTX-4975, a trans-capsaicin intra-articular injection, acts as an antagonist to TRPV1 receptors and is being investigated in phase II trials for moderate-to-severe OA knee pain.[61]

Ampion, also known as AP-003-C, is an intra-articular injection of low molecular weight fraction of human serum albumin being investigated in phase III trials for pain due to severe OA of the knee.[62]

AXS-02 is an orally administered zoledronic acid that inhibits the activities of osteoclasts. It is being investigated in a phase III trial for knee OA associated with bone marrow lesions.[63]

The cell-mediated gene therapy, Invossa, is an intra-articular injection that is currently being investigated in phase III trials for OA of the knee.[64]

SM04690, an intra-articular injection that inhibits the Wnt pathway, is being investigated in phase II trials for moderately to severely symptomatic OA of the knee.[65]

Sprifermin (AS902330), a recombinant human fibroblast growth factor 18, is being investigated in phase II trials for OA of the knee.[66,67]

Other Indications for the Anti-Nerve Growth Factors

The anti-NGFs discussed in this bulletin are also being investigated for other indications such as chronic lower back pain, radiculopathy, peripheral neuropathic pain, cancer pain, and urological chronic pelvic pain syndromes.[68]

Implementation Issues

Current access to anti-NGFs for osteoarthritis is limited, as patients in Canada are restricted to participation in clinical trials.

OA patients are a clinically heterogeneous population, and the manifestation of symptoms of OA is diverse. Some patients are more affected by joint pain; others complain of stiffness, decreased function, or other symptoms related to, or independent, of pain; and some patients are asymptomatic. Pain is a key reason for seeking treatment of hip or knee OA. Some patients do not respond to, or are intolerant to, currently available pain medications. Hence, it would be important to identify the subset of patients for whom tanezumab will be effective given their unmet needs in terms of hip or knee joint pain control, despite having tried currently available evidence-based treatment for hip or knee OA pain. It is important to establish criteria to determine which patient groups are more likely to benefit from this novel therapy and to guide cessation of therapy.

Another expected major barrier to the uptake of novel monoclonal antibodies therapies for osteoarthritis may be cost. Once tanezumab receives regulatory approval, it will likely result in a significant additive cost to the health care system and payers given that the unit cost of biologics is usually high and that tanezumab may displace drugs that are relatively inexpensive and excluded as benefits on public drug plans (for example, over-the-counter drugs such as acetaminophen and NSAIDs).

Tanezumab is studied for both subcutaneous and intravenous administrations. It is not clear which dosage form is being considered for regulatory approval. Subcutaneous injections may require patient training, patient dexterity, or access to health care professionals for administration. Intravenous administration could become a barrier depending on the availability and accessibility of treatment centres.

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