

# Nerve growth factor antibody for the treatment of osteoarthritis pain and chronic low-back pain: mechanism of action in the context of efficacy and safety

Martin Schmelz<sup>a</sup>, Patrick Mantyh<sup>b</sup>, Anne-Marie Malfait<sup>c</sup>, John Farrar<sup>d</sup>, Tony Yaksh<sup>e</sup>, Leslie Tive<sup>f</sup>, Lars Viktrup<sup>g,\*</sup>

## Abstract

Chronic pain continues to be a significant global burden despite the availability of a variety of nonpharmacologic and pharmacologic treatment options. Thus, there is a need for new analgesics with novel mechanisms of action. In this regard, antibodies directed against nerve growth factor (NGF-Abs) are a new class of agents in development for the treatment of chronic pain conditions such as osteoarthritis and chronic low-back pain. This comprehensive narrative review summarizes evidence supporting pronociceptive functions for NGF that include contributing to peripheral and central sensitization through tropomyosin receptor kinase A activation and stimulation of local neuronal sprouting. The potential role of NGF in osteoarthritis and chronic low-back pain signaling is also examined to provide a mechanistic basis for the observed efficacy of NGF-Abs in clinical trials of these particular pain states. Finally, the safety profile of NGF-Abs in terms of common adverse events, joint safety, and nerve structure/function is discussed.

**Keywords:** Nerve growth factor, Mechanism of action, Chronic pain, Osteoarthritis, Chronic low-back pain

## 1. Introduction

Chronic pain is a significant global burden, affecting approximately 30% of the adult population.<sup>32</sup> Patients exhibit a reduced quality of life due to chronic pain and the negative impact it can have on sleep, physical function, productivity, mental health, and social interaction.<sup>12</sup> As a result, and due to the ineffectiveness of single interventions, a multidisciplinary approach incorporating both nonpharmacologic and pharmacologic interventions is recommended for many chronic pain conditions.<sup>81,110</sup> Despite this recommendation and the availability of a variety of treatment options, chronic pain continues to be undermanaged and represents a significant public health concern.<sup>81</sup> There remains,

therefore, an unmet need for safe and effective treatments for moderate-to-severe chronic pain.

For nearly 20 years, monoclonal antibodies against nerve growth factor (NGF-Abs) have been investigated for the treatment of chronic pain, and 3 NGF-Abs (fasinumab, fulranumab, and tanezumab) have advanced into phase 2 clinical testing (note Johnson and Johnson discontinued the fulranumab development program in 2016 as part of a reprioritization of its drug pipeline). Although NGF-Abs have been studied in both nociceptive and neuropathic conditions including osteoarthritis (OA), chronic low-back pain (CLBP), peripheral neuropathy, urological chronic pelvic pain syndromes, and cancer pain, the most consistent reports of analgesia have occurred in clinical trials of inflammatory nociceptive-type pain associated with OA and CLBP.<sup>6</sup> The purpose of this narrative review, therefore, is to detail the mechanism of action of NGF-Abs in terms of analgesia and safety, particularly in the context of CLBP and OA.

## 2. Methods

Studies cited in this narrative review were obtained through PubMed searches and the authors' familiarity with the published literature in their respective fields. PubMed was searched for both preclinical and clinical articles related to "NGF and pain." Articles published within the past 10 years were prioritized, although older articles of significance were also included.

Clinical trials of NGF-Abs in OA and CLBP (**Table 1**) were identified through a systematic search of the PubMed database on December 21, 2017, for English language publications with the following terms in the title: "tanezumab," "RN624," "fasinumab," "REGN475," "fulranumab," or "JNJ-42160443." Trials were included in the table if they reported on a phase 2 or phase 3 clinical trial in patients with OA or CLBP, contained an anti-NGF-Ab monotherapy treatment arm, and contained an active comparator.

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<sup>a</sup> Department of Experimental Pain Research Mannheim, University of Heidelberg, Heidelberg, Germany, <sup>b</sup> Department of Pharmacology, Cancer Center, University of Arizona, Tucson, AZ, United States, <sup>c</sup> Department of Internal Medicine, Division of Rheumatology, Rush University, Chicago, IL, United States, <sup>d</sup> Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, PA, United States, <sup>e</sup> Department of Anesthesiology and Pharmacology, University of California at San Diego, La Jolla, CA, United States, <sup>f</sup> Medical Affairs, Pfizer, New York, NY, United States, <sup>g</sup> Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, United States

\*Corresponding author. Address: Lilly Research Laboratories, Eli Lilly and Company, DC 1546, 88/4, Lilly Corporate Center, Indianapolis, IN 46285. Tel.: 317-652-4947; fax: 317-433-4901. E-mail address: viktrup\_lars@lilly.com (L. Viktrup).

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**Table 1**  
**Summary of phase 2/3 randomized, placebo-controlled, and active-controlled clinical trials of NGF-Ab monotherapy for the treatment of OA or CLBP.**

Condition	Treatments	N	Primary endpoint duration	Pain index†	Function index‡	PGA index§
<b>Osteoarthritis</b>						
Mayorga et al., <sup>73</sup> 2016 Fulranumab phase 2	Placebo	48	12 wk	-3.02 (0.37)	-2.92 (0.39)	-3.07 (0.42)
	Fulranumab 3 mg (IV Q4w)	48		-2.92 (0.36)††	-3.05 (0.38)††	-3.63 (0.40)
	Fulranumab 9 mg (IV Q4w)	50		-2.83 (0.36)††	-2.84 (0.37)††	-3.78 (0.42)†
	Oxycodone-CR (20-50 mg BID)	50		-1.37 (0.37)***	-1.38 (0.38)**	-2.58 (0.42)
Ekman et al., <sup>31</sup> 2014¶	Placebo	208	16 wk	-2.23 (0.20)	-1.84 (0.19)	-0.53 (0.07)
	Tanezumab 5 mg (IV Q8w)	206		-3.44 (0.20)***,††	-3.09 (0.19)***,†††	-0.87 (0.07)***,†
	Tanezumab 10 mg (IV Q8w)	208		-3.14 (0.20)***	-2.82 (0.19)***,†	-0.73 (0.07)*
	Naproxen 500 mg (BID)	206		-2.67 (0.20)	-2.30 (0.19)	-0.65 (0.07)
Ekman et al., <sup>31</sup> 2014¶	Placebo	209	16 wk	-1.81 (0.22)	-1.45 (0.21)	-0.39 (0.07)
	Tanezumab 5 mg (IV Q8w)	211		-2.95 (0.22)***,††	-2.68 (0.21)***,††	-0.73 (0.07)***,†
	Tanezumab 10 mg (IV Q8w)	209		-2.62 (0.22)**	-2.45 (0.21)***,†	-0.72 (0.07)***,†
	Naproxen 500 mg (BID)	211		-2.26 (0.22)	-1.91 (0.21)	-0.54 (0.07)
Spierings et al., <sup>109</sup> 2013¶¶	Placebo	141	8 wk	-2.62 (0.24)	-1.91 (0.23)	-0.52 (0.08)
	Tanezumab phase 3					
	Tanezumab 5 mg (IV Q8w)	161		-3.58 (0.22)***	-3.05 (0.20)***	-0.90 (0.07)***
	Tanezumab 10 mg (IV Q8w)	150		-3.58 (0.23)***	-3.06 (0.21)***	-1.00 (0.08)***
Spierings et al., <sup>109</sup> 2013¶¶	Placebo	137	8 wk	-2.28 (0.26)	-1.67 (0.24)	-0.51 (0.08)
	Tanezumab phase 3					
	Tanezumab 5 mg (IV Q8w)	153		-3.14 (0.24)†††	-2.78 (0.22)†††	-0.90 (0.07)†††
	Tanezumab 10 mg (IV Q8w)	149		-2.81 (0.24)†	-2.52 (0.23)††	-0.79 (0.08)†††
Schnitzer et al., <sup>102</sup> 2015#	Placebo	285	16 wk	-1.88†	-1.86††	-0.54
	Tanezumab phase 3					
	Tanezumab 5 mg (IV Q8w)	288		-2.02†††	-1.90††	-0.54
	Tanezumab 10 mg (IV Q8w)	283		-1.44	-1.38	-0.61
Schnitzer et al., <sup>102</sup> 2015#	Placebo	256	16 wk	-2.02††	-2.05††	-0.67
	Tanezumab phase 3					
	Tanezumab 5 mg (IV Q8w)	254		-2.05††	-2.04††	-0.59
	Tanezumab 10 mg (IV Q8w)	256		-1.47	-1.42	-0.54
<b>Chronic low back pain</b>						
Katz et al., <sup>53</sup> 2011 Tanezumab phase 2	Placebo	41	6 wk	-1.96	-3.93	NA
	Tanezumab 200 µg/kg (single IV)	88		-3.37***,††	-7.70***,†††	NA
	Naproxen 500 mg (BID)	88		-2.54	-4.69	NA
Kivitz et al., <sup>57</sup> 2013 Tanezumab phase 2	Placebo	230	16 wk	-1.25 (0.16)	-1.75 (0.29)	-0.40 (0.06)
	Tanezumab phase 2					
	Tanezumab 5 mg (IV Q8w)	232		-1.58 (0.16)	-2.37 (0.29)	-0.58 (0.06)*
	Tanezumab 10 mg (IV Q8w)	295		-2.06 (0.14)***,†	-3.18 (0.26)***,††	-0.65 (0.05)***,†
	Tanezumab 20 mg (IV Q8w)	295		-2.18 (0.14)***,††	-2.80 (0.26)**,†	-0.67 (0.05)***,†
Naproxen 500 mg (BID)	295		-1.66 (0.11)*	-2.07 (0.26)	-0.50 (0.05)	

\* \*\*, and \*\*\* =  $P \leq 0.05$ ,  $P \leq 0.01$ , and  $P \leq 0.001$ , respectively, vs placebo. †, ††, and ††† =  $P \leq 0.05$ ,  $P \leq 0.01$ , and  $P \leq 0.001$ , respectively, vs active comparator. Data shown as mean and standard error (if available in original publication).

† Based on WOMAC Pain subscale for OA trials and Low Back Pain Intensity scale for CLBP trials. Both tools assess pain on an 11-point NRS with higher scores indicating greater pain.

‡ Based on WOMAC Physical Function subscale for OA trials (an 11-point NRS) and the Roland Morris Disability Questionnaire for CLBP trials (a 25-point NRS). For both tools, a higher score indicates worse function.

§ Based on a 5-point scale from 1 = very good to 5 = very poor except for the study reported by Mayorga et al., which used an 11-point NRS from 0 = very good to 10 = very bad.

¶ Two separate trials were reported by Ekman et al. 2014.

¶¶ In the study reported by Spierings et al., comparisons of tanezumab vs placebo were performed in all randomized patients who received  $\geq 1$  dose of study medication. Because of a clinical hold implemented before all patients completed the study, comparisons of tanezumab vs oxycodone-CR and oxycodone-CR vs placebo were performed in patients who received  $\geq 1$  dose of study medication and had a WOMAC Pain score for week 8 that was collected before June 23, 2010.

# In the study reported by Schnitzer et al., comparisons between tanezumab and NSAID were performed separately for naproxen and for celecoxib.

BID, twice daily; CLBP, chronic low-back pain; IV, intravenous; NRS, numeric rating scale; OA, osteoarthritis; PGA, patient global assessment; Q4w, every 4 weeks; Q8w, every 8 weeks; Q12h, every 12 hours; SC, subcutaneous; wk, week; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

### 3. Rationale for nerve growth factor in pain

Nerve growth factor was initially identified as a neuronal survival factor (ie, neurotrophin) during embryogenesis. Other neurotrophins include brain-derived growth factor (BDNF), neurotrophin 3 (NT-3), and neurotrophin 4 (NT-4).<sup>11</sup> During development, neurotrophins are secreted by target tissues and bind with high affinity to a member of the tropomyosin-related kinase (Trk) receptor family and to the low-affinity p75 neurotrophin receptor on the neuronal cell surface, resulting in activation of several signaling pathways (eg, phospholipase C, mitogen-activated protein kinase, and phosphoinositide 3-kinase pathways) that

stimulate neuronal survival, sprouting, and growth.<sup>11,26</sup> Brain-derived growth factor and NT-4 bind to TrkB receptors throughout the CNS that play a role in memory, learning, and synaptic plasticity.<sup>11</sup> NT-3 binds TrkC that is highly expressed in proprioceptive sensory neurons.<sup>58</sup> Nerve growth factor binds TrkA that is expressed in many sensory and sympathetic fibers and regulates survival of these neurons.<sup>16,70</sup> Nociceptors are particularly dependent on NGF signaling since mutations in the genes for NGF or TrkA result in congenital insensitivity to pain.<sup>24,28</sup> In the postnatal period, TrkA expression declines and sensory neurons require substantially less NGF for survival.<sup>70,80</sup> However, a large number of neurons continue to express TrkA in adulthood. In adult rats, for

example, TrkA+ cells make up about 40% of neurons in the dorsal root ganglion (DRG) and include thin myelinated A $\delta$  fibers and peptidergic unmyelinated C fibers (ie, those that express pronociceptive peptides such as substance P and calcitonin gene-related peptide [CGRP]) that innervate skin, viscera, muscle, and bone.<sup>5,70</sup> A similar proportion of TrkA+ neurons are found in human DRG.<sup>96</sup> The concept of NGF as a viable target for pain management did not begin to arise until NGF's continued functions in the mature nervous system were delineated, functions that include roles in nerve sprouting/remodeling and in pain modulation.

Several lines of evidence helped establish a role for NGF in pain signaling, including the observation that NGF levels are increased in animal models of chronic pain.<sup>87,88,107</sup> In addition, administration of exogenous NGF, overexpression of NGF, or inhibition of NGF degradation induces mechanical and thermal hyperalgesia in otherwise normal rodent models.<sup>2,25,65,89,101</sup> Elevated NGF levels are also observed in humans with chronic pain conditions, and intradermal or intramuscular injection of NGF causes allodynia and hyperalgesia in healthy subjects.<sup>27,113</sup> Similarly, inhibition of NGF activity through NGF-Abs has been shown to attenuate hyperalgesia in a variety of animal models, including autoimmune arthritis, bone cancer pain, OA, and bone fracture pain.<sup>46,59,61,79,105,106,120</sup> Likewise, inhibition of other aspects of the NGF pathway, including TrkA and p75<sup>NTR</sup>, provides analgesia in rodent models of inflammatory and OA pain, providing further evidence for a role of NGF signaling in pain.<sup>4,48,84</sup> These findings have spurred additional research into understanding the role of NGF in chronic pain.

#### 4. Pronociceptive actions of nerve growth factor

Nerve growth factor is released by immune cells as part of the inflammatory response after peripheral injury. Nonimmune cells such as endothelial cells, pericytes, chondrocytes, and synoviocytes are possible sources of NGF in some conditions.<sup>17,41,77</sup> Although the role of NGF in chronic pain signaling is not fully understood, it is believed to contribute to chronic pain by promoting neuronal sensitization (ie, increased nervous system excitability) and, possibly, by driving local neuronal sprouting at sites of inflammation and, possibly, within the central nervous system.<sup>16,70</sup>

Sensitization is believed to be a key process in many chronic pain states that are characterized by exaggerated responses to otherwise innocuous or mildly noxious stimuli (ie, allodynia and hyperalgesia).<sup>104</sup> Peripheral sensitization manifests as hyperexcitability of peripheral nociceptors, largely believed to be due to the action of inflammatory mediators that promote depolarization of the nociceptor.<sup>56,83</sup> Central sensitization can result from continuous nociceptive input that manifests as hyperexcitability of wide dynamic range neurons in the dorsal horn.<sup>119</sup> This hyperexcitability is due to prolonged or repeated depolarization of the neurons through a variety of processes including (1) activation or modulation of membrane channels or receptors; (2) release of pronociceptive factors; (3) loss of local inhibitory regulation; and (4) excitatory input into the dorsal horn from bulbospinal projections.<sup>119</sup> Chronic inflammation can lead to persistent peripheral and central sensitization through the processes above and also by inducing changes in the phenotype of primary nociceptive neurons. In animal models of chronic inflammation, for example, primary afferents in the DRG and postganglionic sympathetic fibers can exhibit a neuropathic-like phenotype and enhanced sprouting into affected peripheral sites and the DRG itself.<sup>22,23,36,50</sup>

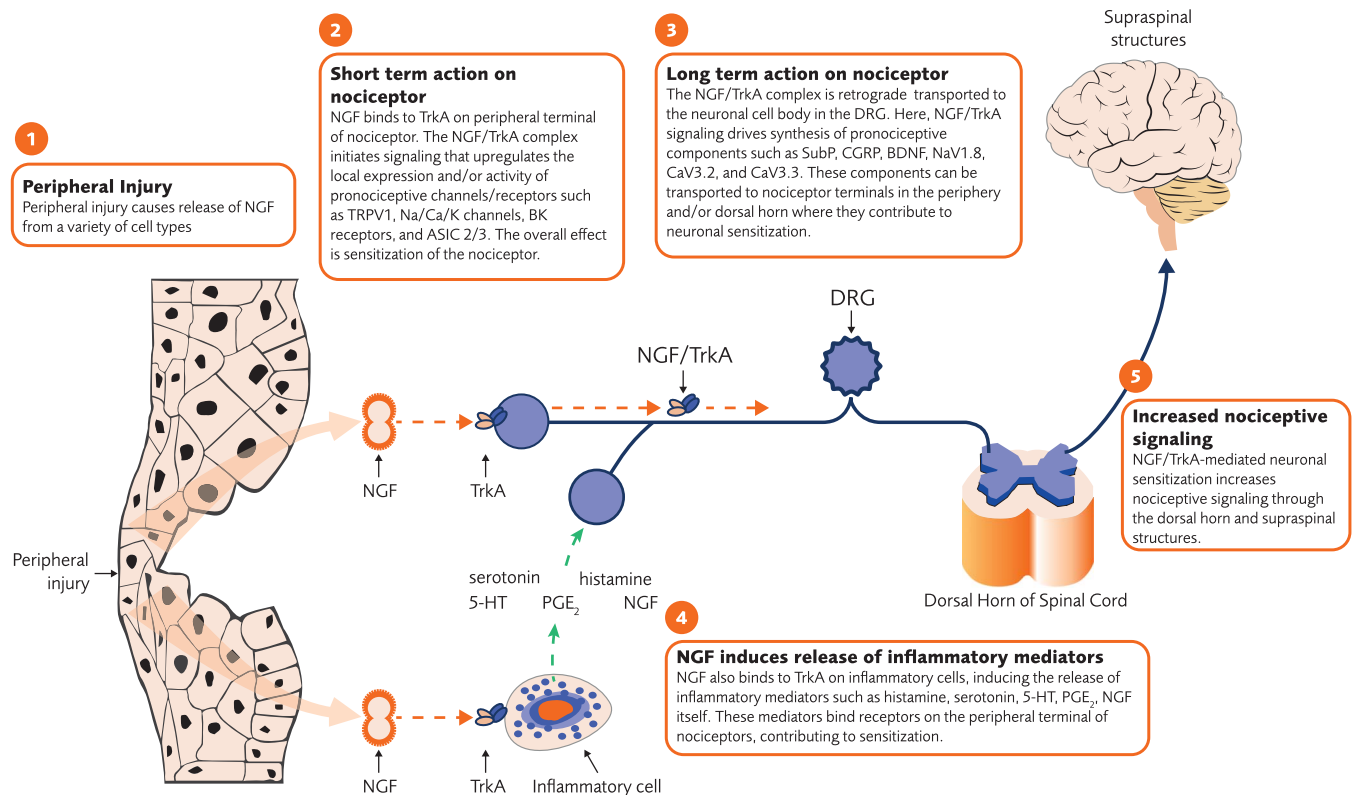
Nerve growth factor-induced sensitization of skin nociceptors has been confirmed in humans. Microneurography reveals that axonal branches within an NGF injection zone exhibit hyperexcitability, including reduced activation thresholds, compared with

branches of the same parent axon outside the injection zone.<sup>85</sup> In addition, intradermal injection of NGF results in local priming within human skin, evidenced by an increase in ultraviolet-B irradiation-induced hyperalgesia and, in many subjects, non-evoked pain.<sup>98</sup> Nerve growth factor is believed to contribute to acute peripheral sensitization directly through its binding to TrkA receptors on the peripheral terminal of nociceptors and on the surface of inflammatory cells, and to central sensitization indirectly through its downstream effects on transcription (**Fig. 1**).

Binding of NGF to TrkA on the nociceptor peripheral terminal has both short-term and long-term consequences. In the short-term, the NGF/TrkA complex initiates signaling that increases the expression and/or activity of a variety of ion channels and receptors at the membrane surface including transient receptor potential cation channel subfamily V member 1 (TRPV1), voltage-gated sodium and calcium channels, delayed rectifier potassium channels, bradykinin receptors, and acid-sensing ion channels 2 and 3.<sup>62,63,68,121</sup> These changes result in nociceptor depolarization and immediate local peripheral sensitization. For example, NGF/TrkA signaling has been shown to increase activity of TRPV1 and produce thermal hypersensitivity within minutes of TrkA binding.<sup>49</sup> In the long-term component, the NGF/TrkA complex is internalized and retrogradely transported to the neuronal cell body in the DRG, where it initiates transcriptional signaling that increases the synthesis of peptides involved in nociception such as substance P, CGRP, BDNF, and the nociceptor-specific ion channels Na<sub>v</sub>1.8, Ca<sub>v</sub>3.2, and Ca<sub>v</sub>3.3.<sup>33,64,70,75,90,108</sup> These newly synthesized receptors, channels, and peptides are then transported from the DRG to the nerve terminals in both the periphery and the dorsal horn, where they undergo translational processing and contribute to peripheral and central sensitization that can take hours to days to become evident.<sup>70</sup> One example involves NGF-dependent upregulation of BDNF in the dorsal horn. BDNF binds to TrkB receptors on primary afferent neurons leading to glutamate release, and on second order afferent neurons leading to glutamate receptor phosphorylation and resulting in neuronal depolarization.<sup>15,19</sup> This effectively lowers the threshold potential of second-order afferent neurons, making them more responsive to primary nociceptive input that manifests as persistent thermal and mechanical central hypersensitivity.<sup>55,118</sup>

Nerve growth factor binding to TrkA receptors on inflammatory cells stimulates the release of inflammatory mediators such as histamine, serotonin, 5-hydroxytryptamine, PGE<sub>2</sub>, and NGF itself.<sup>45,70,72</sup> Many of these mediators are known to bind receptors on the peripheral terminal of nociceptors and initiate signaling that causes nociceptor sensitization.<sup>38</sup> Thus, binding to inflammatory cells is another mechanism by which NGF promotes peripheral sensitization.

As mentioned earlier, NGF may also contribute to pain hypersensitivity by increasing sensory nerve terminal density at the site of injury through stimulation of local neuronal sprouting. Administration of NGF stimulates axonal sprouting of the rat sciatic nerve *in vitro* that is accompanied by thermal hyperalgesia *in vivo*.<sup>97</sup> Studies in mouse models of bone cancer pain and joint pain have also shown increased sprouting of TrkA+ sensory neurons and the formation of painful neuroma-like structures, which can be inhibited by NGF-Ab administration.<sup>36,50,51,71</sup> Nerve growth factor-induced neuronal sprouting within the DRG and dorsal horn may also play a role in pain hypersensitivity. In a rodent model of chronic mirror pain, peripheral nerve injury has been shown to cause release of NGF from satellite glia in the affected DRG, which may even spread to the contralateral DRG to induce synapse-like structures within CGRP+ fibers.<sup>21</sup> Overexpression, through injection of NGF-expressing adenovirus, of NGF in the dorsal horn of adult rats causes peptidergic axonal



**Figure 1.** Pronociceptive actions of NGF. 5-HT, 5-hydroxytryptamine; ASIC, acid-sensing ion channels; BDNF, brain-derived neurotrophic factor; BK, bradykinin; Ca, calcium; CGRP, calcitonin gene-related peptide; DRG, dorsal root ganglion; K, potassium; Na, sodium; NGF, nerve growth factor; PGE<sub>2</sub>, prostaglandin E<sub>2</sub>; SubP, substance P; TrkA, tropomyosin receptor kinase A; TRPV1, transient receptor potential cation channel subfamily V member 1.

sprouting throughout the dorsal horn and into the ventral horn and lateral funiculus that is accompanied by thermal and mechanical hyperalgesia.<sup>66,95</sup> Nerve growth factor also induces sprouting/remodeling of TrkA+ sympathetic nerves, and because increased sympathetic tone is associated with certain chronic pain conditions and is believed to contribute to long-term pain hypersensitivity, this may represent another pronociceptive action of NGF.<sup>18,37,51,71</sup>

Overall, the evidence reviewed supports pronociceptive functions for NGF that include contributing to sensitization of peripheral and central sensory neurons and, potentially, driving local neuronal sprouting at the site of injury, within the DRG, and possibly within the dorsal horn. These functions of NGF boost the ability of nociceptive pathways to overcome adaptive processes, which typically limit the nociceptor to transient responses, and discharge (both evoked and spontaneously) under inflammatory conditions. Because of the key actions of NGF in the periphery and DRG, blockage of NGF action through NGF-Abs could have both peripheral and central effects on neuronal sensitization and pain despite not appreciably crossing the blood-brain barrier and without having any overt anti-inflammatory activity.

**5. Role of nerve growth factor in osteoarthritis pain**

Osteoarthritis is a musculoskeletal condition with progressive loss of articular cartilage as a prominent feature, although contemporary models recognize that important structural and pathological changes occur in the entire joint organ including subchondral bone, menisci, synovium, joint capsule, and periarticular ligaments and muscles.<sup>67</sup> Pain is often a symptom of OA, although

the degree of joint damage is uncoupled from the production of pain.<sup>8,82</sup> Pain may originate from nearly any tissue within the joint because most, with the exception of articular cartilage, are densely innervated by nociceptive A and C fibers.<sup>74</sup> A population of sensory C fibers that do not respond to mechanical stimuli within the normal joint are also present (ie, silent nociceptors).<sup>74</sup>

Quantitative sensory testing reveals that patients with OA have lower pressure pain thresholds at the affected joint compared with healthy controls.<sup>112</sup> This suggests peripheral sensitization plays a role in OA pain. This sensitization is believed to be due to hyperexcitability of nociceptors that typically respond to mechanical stress within the joint and silent nociceptors, which become mechanosensitive in the OA joint.<sup>74</sup> Quantitative sensory testing also shows that OA patients have lower pressure pain thresholds than healthy controls at unaffected sites, suggesting a role for central sensitization in OA pain.<sup>112</sup> As discussed earlier, central sensitization can result from persistent nociceptive input (ie, sensitized nociceptors). However, central sensitization can also result from neuropathic damage to the nerves themselves, possibly due to material from the degenerating/remodeling joint.<sup>47</sup> Indeed, although OA pain is believed to be predominantly nociceptive in origin, a population of OA patients (estimates vary greatly between 5% and 65%) can show aspects of neuropathic pain (eg, burning, numbness, and tingling), and the OA population is likely a heterogeneous mix of pain states.<sup>10,86</sup>

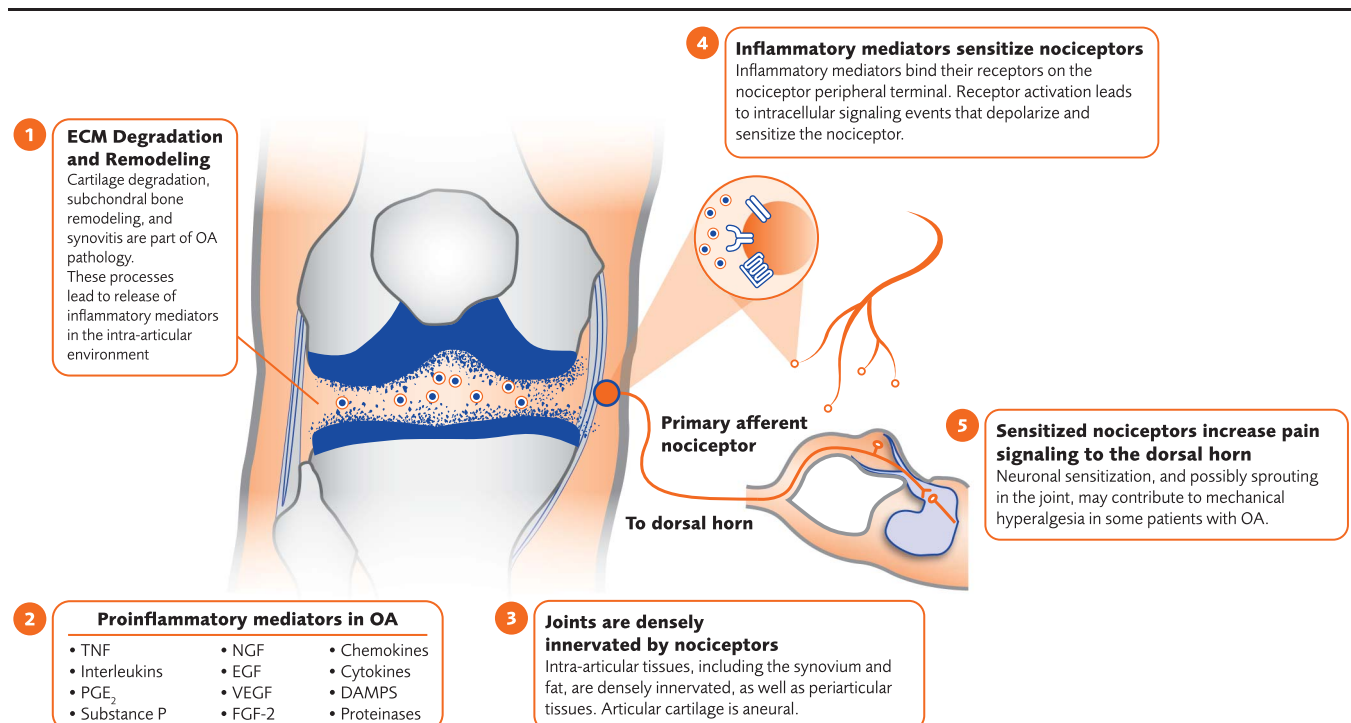
A potential role for NGF in the pathogenesis of OA pain is based on its ability to facilitate peripheral and central sensitization. The release of several nociceptor-sensitizing inflammatory mediators, including NGF, during cartilage degradation, bone remodeling, and the synovial inflammation process likely plays an important role in mechanical hyperalgesia in some patients with OA pain



(Fig. 2).<sup>78</sup> Nerve growth factor levels are increased in synovial specimens from patients with advanced OA compared with specimens from non-OA controls, and in specimens from patients exhibiting symptomatic chondropathy compared with specimens from patients exhibiting asymptomatic chondropathy.<sup>111</sup> These observations suggest a correlation between levels of NGF and the presence of pain in OA. Notably, mechanical stress has been shown to increase expression and release of NGF from murine cartilage explants *in vitro*.<sup>91</sup> Fibroblasts and chondrocytes are among the potential sources of NGF within the joint.<sup>91,111</sup>

In addition to neuronal sensitization, NGF-dependent neuronal sprouting may potentially contribute to the pathogenesis of OA pain. In a murine model of arthritic inflammation, for example, sensory and sympathetic nerve fibers of geriatric mice undergo significant ectopic nerve sprouting and remodeling, resulting in the formation of nonmalignant neuroma-like formations that have been shown to cause chronic and severe pain in neuronal injury models.<sup>36,51</sup> Administration of NGF-Ab attenuates sprouting in the joint and pain-related behavior in these animals.<sup>36</sup> Patients with symptomatic knee OA also exhibit increased nerve-fiber density, NGF levels, and TrkA levels in the synovium compared with age-matched asymptomatic controls.<sup>54</sup> However, the extent to which NGF drives sprouting in the human OA joint, and the role of sprouting in human OA pain,<sup>29,69,116,117</sup> has not been clearly established. Moreover, sprouting is not required to induce hyperalgesia in humans by NGF,<sup>42</sup> and it is only one facet of the complex interplay between chronic inflammation and nociceptive sensitization as indicated by increased OA pain and IL-6 signaling in patients with diabetes.<sup>30</sup> It is clear, however, that NGF plays a role in OA pain pathogenesis, as evidenced by the demonstrated ability of NGF-Abs to attenuate pain (or pain-related behavior) in animal models of OA, pilot veterinary (cat and dog) trials of degenerative joint disease, and in clinical trials of OA.<sup>77,103</sup>

Tanezumab, fulranumab, and fasinumab have each demonstrated efficacy in randomized, placebo-controlled, phase 2 or 3 clinical trials in patients with moderate-to-severe pain due to OA of the knee or hip. Systematic reviews detailing the efficacy of NGF-Abs in OA clinical trials have been published elsewhere.<sup>20,52,103</sup> Here, we summarize the efficacy of NGF-Abs in phase 2 or 3 randomized controlled clinical trials that used an active comparator arm in addition to placebo (**Table 1**). A single phase 2 study demonstrated statistically significant improvement in WOMAC Pain and Physical Function scores with IV fulranumab (3 or 9 mg administered at baseline, week 4, and week 8) at week 12 compared with oral oxycodone-controlled release (20–50 mg twice daily).<sup>73</sup> Surprisingly, there was no difference between placebo and either fulranumab regimen in this study, complicating interpretation of the oxycodone vs fulranumab comparison. The study was also limited by low sample size due to early termination. A single phase 3 study also demonstrated statistically significant improvement in WOMAC Pain, WOMAC Physical Function, and patients' global disease assessment with IV tanezumab (5 or 10 mg at baseline and week 8) at week 8 compared with placebo and with oral oxycodone-controlled release (10–40 mg twice daily).<sup>109</sup> Three phase 3 studies have compared IV tanezumab (5 or 10 mg administered at baseline and week 8) to placebo and either oral naproxen (500 mg twice daily) or oral celecoxib (100 mg twice daily) after 16 weeks of treatment.<sup>31,102</sup> The 5-mg regimen consistently provided significant improvement over NSAID for WOMAC Pain and Physical Function. By contrast, the 10-mg regimen consistently improved function compared with NSAID, but improvements over naproxen with respect to pain failed to reach the level of statistical significance in 2 of the studies.<sup>31</sup> Overall, standard effects sizes on the WOMAC Pain subscale for the tanezumab 5- and 10-mg regimens have been estimated at 0.24 (0.15, 0.32;  $P < 0.001$ ) and 0.22 (0.13, 0.30;  $P < 0.001$ ), respectively, vs all comparators



**Figure 2.** Nociceptive components of osteoarthritic knee pain. DAMPS, damage-associated molecular patterns; ECM, extracellular matrix; EGF, epidermal growth factor; FGF-2, fibroblast growth factor-2; NGF, nerve growth factor; OA, osteoarthritis; PGE<sub>2</sub>, prostaglandin E<sub>2</sub>; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

combined (NSAID and oxycodone).<sup>103</sup> There are currently 3 interventional, placebo-controlled clinical trials planned, ongoing, or recently completed on clinicaltrials.gov that examine the efficacy or safety of tanezumab in patients with OA of the knee or hip, and 5 trials of fasinumab (2 of which include active comparators such as naproxen, celecoxib, and diclofenac).

### 6. Potential role of nerve growth factor in chronic low-back pain

The lower back (L1-L5) is a complex structure comprising vertebrae, intervertebral discs that cushion and support vertebrae, facet joints lined with cartilage and lubricated with synovial fluid that connect vertebrae and allow for movement, large muscles that support the spine and power movement, and ligaments and cartilage which provide structural support.<sup>1</sup> Spinal nerve roots exit the spine through the intervertebral foramen, whereas bone, muscle, and facet joints are innervated with nociceptors that respond to injury, inflammation, or mechanical stress.<sup>1</sup> This complexity makes it difficult to identify the specific underlying cause(s) of CLBP in an individual patient, particularly since patients often phenotypically show aspects of both neuropathic and nociceptive pain states (Fig. 3).<sup>7</sup>

A neuropathic component of CLBP can result from mechanical compression of the nerve root by bulging or herniated disc, ligament, or bone spur; irritation of the nerve root by nearby inflammation or degenerative material from a nearby disc or joint; and, potentially, lesions on invasive nociceptive sprouts within a degenerated joint or disc.<sup>7</sup> A nociceptive component can arise

from persistent nociceptor activation and/or sensitization in response to inflammatory processes in a variety of structures including intervertebral discs, facet joints, bones, ligaments, muscles, and organs within the abdominal cavity.<sup>1</sup> Such persistent nociceptive signaling, as discussed earlier, can lead to central sensitization in the dorsal horn. Sensitization is believed to play a role in some forms of CLBP, although the precise contribution of sensitization (and NGF) to the overall pain state is not clearly delineated.<sup>100</sup>

There is, however, a pathophysiological-based rationale for a role of NGF in CLBP in some patients. In contrast to healthy intervertebral discs, for example, media obtained from cultured painful degenerating discs contain increased amounts of proinflammatory nociceptive mediators (including NGF) and can induce neurite growth in CGRP+ neurons in vitro that is blocked by NGF-Abs.<sup>60</sup> In addition, specimens of painful degenerating discs exhibit growth of NGF-expressing blood vessels into the normally avascular disc that is accompanied by growth of adjacent nerves expressing TrkA; effects which are not evident in specimens of degenerating discs from individuals who did not report pain.<sup>34</sup> This demonstrates that NGF can induce neuronal growth into the intervertebral disc, which is typically poorly innervated, but can become densely innervated on degeneration.<sup>35</sup> This suggests that NGF may play a role in painful degenerating discs, although the exact contribution of NGF in CLBP of this, and other, etiologies is not completely understood. It is possible that inflammation and NGF action may affect one or more of several neural components that are in close proximity to the spine including primary afferent fibers to the DRG, neurons

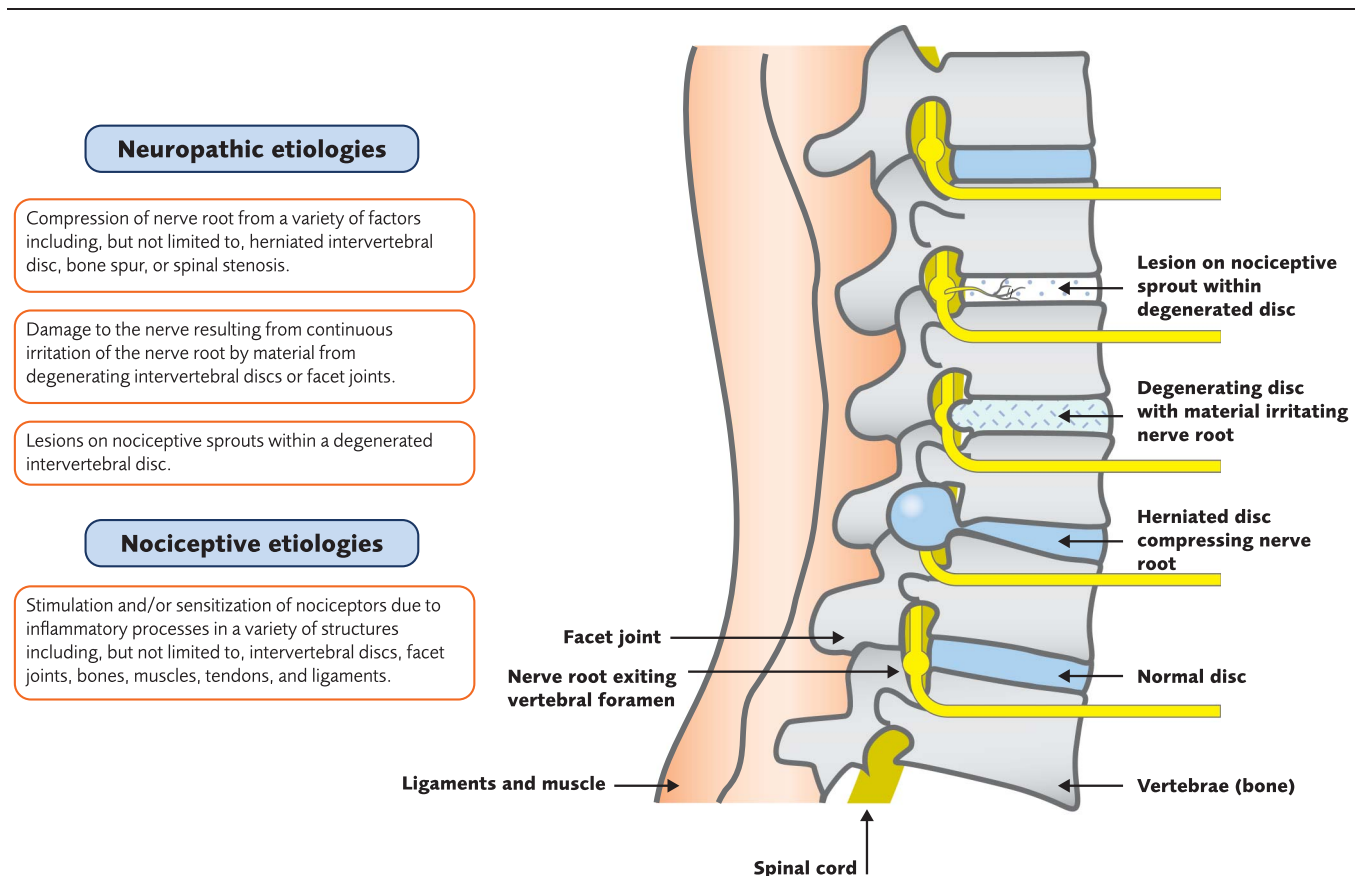


Figure 3. Potential neuropathic and nociceptive components of chronic low-back pain.

within the DRG, efferent nerve roots from the DRG to the spinal cord, or neurons in the spinal cord itself. However, compared with the fairly straight forward rationale for NGF-Abs treatment in OA, there is currently no consensus on a mechanism-oriented therapeutic approach in CLBP. Moreover, therapeutic success also does not necessarily prove involvement in the pathomechanism as clearly exemplified by the reduction of central pain by a peripheral nerve block.<sup>40</sup>

The efficacy observed in some clinical trials of NGF-Abs suggests that NGF plays a role in certain types of CLBP. Tanezumab has demonstrated efficacy in both phase 2 placebo-controlled clinical trials of patients with predominantly nociceptive CLBP conducted to date, which also included oral naproxen (500 mg twice daily) as an active comparator (**Table 1**).<sup>53,57</sup> In an initial proof of concept study, a single IV dose of 200- $\mu$ g/kg tanezumab significantly improved pain (Lower Back Pain Intensity scale) and function (Roland Morris Disability Questionnaire) scores at week 6 compared with placebo and with naproxen.<sup>53</sup> Likewise, in a subsequent study, multiple IV doses of tanezumab (10 or 20 mg administered at baseline and week 8) significantly improved pain, function, and patient global disease assessment at week 16 compared with placebo and with naproxen; no statistically significant differences between naproxen and 5-mg tanezumab were observed.<sup>57</sup> Overall, these results demonstrate the analgesic potential of IV tanezumab in patients with CLBP. Two additional trials are currently underway to assess SC administration of tanezumab (5 or 10 mg) in patients with CLBP compared with placebo and with either oral celecoxib or oral tramadol prolonged release. In contrast to tanezumab, SC fulranumab (1, 3, or 10 mg every 4 weeks, or a 6-mg loading dose followed by 3 mg every 4 weeks) offered no significant efficacy over placebo in terms of pain severity or function (Oswestry Disability Index) after 12 weeks of treatment in a single small phase 2 trial of patients with CLBP. However, it should be noted that there was a strong placebo effect observed in this trial, possibly because patients were permitted to continue adjunctive therapy such as NSAIDs and/or opioids in all study treatment groups.<sup>99</sup> There are currently 2 clinical trials of SC fasinumab vs placebo ongoing or recently completed in patients with CLBP on [clinicaltrials.gov](http://clinicaltrials.gov).

## 7. NGF-Abs safety profile

Although all patients had OA at baseline in clinical trials of OA, unexpected findings in joint morphology that were initially described by study investigators as osteonecrosis led the FDA to place all NGF-Ab programs on partial clinical hold from 2010 to 2012.<sup>43</sup> To better understand the level of risk posed by NGF-Abs, a blinded adjudication process was conducted whereby independent committees of medical experts examined adverse events (AEs) and the pathology of total joint replacements related to OA or joint injury in clinical trials of NGF-Abs.<sup>43,44</sup> In the tanezumab program, 119 of 249 events (47.8%) were conclusively adjudicated as normal OA progression, 68 (27.3%) as rapidly progressive OA (RPOA), and only 2 (0.8%) as primary osteonecrosis.<sup>44</sup> The risk of RPOA increased with increasing dose of tanezumab, use of tanezumab in combination with NSAIDs, and with the presence of pre-existing subchondral insufficiency fractures.<sup>44</sup> Adjudication of joint safety events in other NGF-Ab programs yielded similar findings.<sup>43</sup>

Rapidly progressive OA is an accelerated type of OA that may be characterized by pain, rapid joint space narrowing, and severe progressive atrophic bone changes that typically results in joint replacement.<sup>44</sup> Rapidly progressive OA type 1 is defined as a significant loss of joint space width  $\geq 2$  mm (predicated on

optimal joint positioning) within approximately 1 year, without gross structural failure.<sup>76</sup> Rapidly progressive OA type 2 is defined as abnormal bone loss or destruction, including limited or total collapse of at least one subchondral surface, that is not normally present in conventional end-stage OA.<sup>76</sup> The pathophysiology of RPOA in the context of NGF-Abs is poorly understood, but proposed mechanisms include neuropathic arthropathy, analgesic arthropathy, and pre-existing low bone integrity.<sup>44</sup> Neuropathic arthropathy is caused by joint damage in the nerve that leads to loss of pain sensation and joint instability.<sup>44,114</sup> Patients receiving tanezumab, however, do not exhibit loss of protective pain sensitivity in the joint, making neuropathic arthropathy an unlikely cause of RPOA in this context.<sup>44</sup> Analgesic arthropathy is caused by overuse/mechanical overloading of the joint due to effective analgesia.<sup>44,114</sup> Self-reported pain levels in the index joint, however, did not differ between subjects developing RPOA and those who did not develop RPOA in the tanezumab program, also making analgesic arthropathy unlikely cause.<sup>44</sup> Pre-existing issues with bone integrity, including subchondral insufficiency fractures and atrophic forms of OA, may also contribute to RPOA in the context of NGF-Abs.<sup>44,114</sup> Mechanical overloading due to effective analgesia may exacerbate these pre-existing issues and could explain why the risk of RPOA is increased by the concomitant use of NSAIDs (which may inhibit bone repair) with NGF-Abs.<sup>44,92</sup> It is also possible that NGF may play a role in cartilage repair and load-induced bone formation.<sup>114,115</sup> Inhibition of NGF activity through NGF-Abs would be believed to, potentially, inhibit these processes and contribute to RPOA. These theories, however, are purely speculative at this time, and it is possible that multiple mechanisms play a role in the development of RPOA in the context of NGF-Ab treatment.

Repeated administration of high-dose NGF-Ab does not have adverse effects on healthy bone and joint tissue from rats, mice, or monkeys<sup>39</sup> and preclinical studies have not identified a risk of accelerated OA with NGF-Ab treatment,<sup>61,120</sup> although RPOA is considered a rare event and no single animal model of OA can fully replicate the progression and consequences of OA in humans. Ongoing NGF-Ab clinical trials have been designed to reduce the risk of RPOA and possibly identify potential mechanisms of RPOA. Tanezumab clinical trials subsequent to the clinical hold, for example, have implemented a risk minimization plan excluding (1) chronic concomitant NSAID use, (2) higher exploratory tanezumab doses that have not demonstrated benefit over lower doses in the condition under study, and (3) subjects with evidence of, or risk factors for, RPOA.<sup>44,94</sup>

A separate FDA partial clinical hold was placed on all NGF-Ab programs from 2012 to 2015 due to anatomical changes seen in the sympathetic nervous system of mature animals (reductions in size and neuronal count). Subsequent enhanced toxicology studies in monkeys did not demonstrate any reduction in neuronal count or sympathetic function, and more detailed analysis of AEs from clinical studies found no evidence of sympathetic function disorder with tanezumab.<sup>9,13</sup> However, a risk minimization plan was implemented in subsequent tanezumab clinical studies excluding patients with suspicion of sympathetic function disorder.

There is some evidence suggesting a role for NGF in bone formation, and thus, there is concern that NGF-Ab therapy might adversely affect bone healing. It is hypothesized that communication between osteoblasts and sensory nerves through NGF/TrkA signaling is essential for load-induced bone formation in mice.<sup>115</sup> In addition, NGF and TrkA are expressed in chondrocytes and osteoblasts near sites of ossification in an animal model of rib fracture, and topical application of NGF enhances fracture

healing in this model.<sup>92</sup> However, blockage of NGF/TrkA signaling using NGF-Abs has not been shown to negatively affect bone healing in mouse models of femur fracture.<sup>59,92</sup>

Although NGF-Abs do not cross the blood–brain barrier under normal conditions, certain situations could arise in the cerebral or spinal cord areas that could potentially increase the cerebrospinal concentration of NGF-Ab. These include disorders such as multiple sclerosis and stroke, and inflammatory conditions such as meningitis and encephalitis. The risk of NGF-Ab use, particularly long-term use, is unknown in these situations.

Overall, NGF-Ab therapy is generally well tolerated for most patients, based on low discontinuation rates due to AEs in clinical trials.<sup>103</sup> The odds ratio for discontinuation due to AEs in clinical trials of OA has been estimated to be 1.50 for NGF-Ab monotherapy (range = 0%–9.2%) compared with placebo (range = 0%–4.2%).<sup>103</sup> This estimate, however, included higher NGF-Ab doses that are no longer being evaluated in phase 3 trials, and rates of withdrawal with lower doses of NGF-Ab were not significantly different from placebo.<sup>103</sup> For all doses, there was no difference in the frequency of serious AEs between NGF-Ab therapy and placebo.<sup>103</sup> The most common AEs in clinical trials of NGF-Abs are peripheral edema, arthralgia, extremity pain, and abnormal peripheral sensations (most often paresthesia or hypoesthesia).<sup>6</sup>

Abnormal peripheral sensations occurred in approximately 5% to 10% of patients but were mostly transient, mild to moderate in severity, and rarely led to study withdrawal.<sup>6</sup> In addition, a high dose of IV tanezumab (10 mg every 8 weeks for 24 weeks) that is no longer being evaluated in clinical studies was not associated with meaningful changes in peripheral nerve conduction velocity or intraepidermal nerve-fiber density at week 24, compared with placebo, in a study of 219 patients with OA, although small differences in nerve safety could not be ruled out due to low patient number.<sup>14</sup> However, successes with recombinant human NGF therapy for the treatment of diabetic neuropathy should give rise to some caution regarding the use of NGF-Abs.<sup>3</sup>

## 8. Discussion

Overall, several lines of evidence demonstrate that NGF has pronociceptive functions that include promotion of neuronal sensitization (both peripheral and central) and stimulation of local neuronal sprouting at sites of inflammation and, possibly, within the CNS. Clinical trials demonstrate that NGF-Abs can provide efficacy in patients with OA pain or CLBP, highlighting the role of NGF-dependent neuronal sensitization and, possibly, sprouting in pain generation and/or maintenance in these conditions. It should be noted that the rationale for NGF, and efficacy of NGF-Abs, is more established in OA than CLBP (for an overview of the efficacy and safety of NGF-Abs in conditions other than OA and CLBP, we refer the reader to recent articles by Chang et al.<sup>16</sup> or Bannwarth and Kostine<sup>6</sup>). However, initial studies with tanezumab in CLBP are promising, although ongoing studies will more clearly define the extent of NGF-Ab efficacy in this condition.

Notably, NGF-Abs have often, but not at all doses examined, demonstrated statistically greater pain relief than both NSAIDs and opioids in head-to-head clinical trials of OA and CLBP. Additional head-to-head studies ongoing or planned will help establish the relative efficacy and safety of NGF-Abs compared with NSAIDs and opioids, which are currently among the most commonly prescribed pharmacologic treatments for chronic pain.<sup>12,93</sup>

NGF-Abs have demonstrated acceptable tolerability in most subjects, as evidenced by low rates of discontinuation in clinical

trials to date.<sup>103</sup> The most common adverse events in clinical trials have been peripheral edema, arthralgia, extremity pain, and abnormal peripheral sensations. Events of abnormal sensation occurred in less than 10% of patients, were mostly mild to moderate in severity, and rarely led to study discontinuation.<sup>6</sup> As discussed previously, however, early clinical trials with NGF-Abs identified a potential risk for RPOA in some patients.<sup>43,44</sup> This spurred changes in NGF-Ab trial design intended to reduce the risk of RPOA and thoroughly assess any impact of NGF-Abs on joint safety. Despite these risk mitigation strategies, careful monitoring of adverse events in ongoing and future NGF-Ab clinical trials is needed to clarify the overall risk-to-benefit ratio, particularly with long-term use, of this emerging class of analgesics.

## Conflict of interest statement

M. Schmelz declares personal fees from Pfizer as consultant in an NGF advisory board. P. Mantyh reports grants from National Institute of Health during the conduct of the study; personal fees and other from Pfizer outside the submitted work; and a patent anti-NGF for the relief of bone cancer pain issued. J. Farrar reports personal fees from Pfizer, Daichi Sankyo, Cara Therapeutics, Biogen, Aptynx, Campbell Alliance, NIH-NIAMS, Analgesic Solutions, Novartis, Aptynx, DepoMed, Jansen, Evadara, and from Wolters Kluwer Health, outside the submitted work. L. Tive is a full-time employee of, and owns stock/option in, Pfizer Inc. L. Viktrup is a full-time employee of Eli Lilly & Co. The remaining authors have no conflicts of interest to declare.

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