Development of pain therapies targeting nerve growth factor signal transduction and the strategies used to resolve safety issues

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ABSTRACT — Therapeutic agents commonly used in the management of chronic pain have limited effectiveness and may be associated with issues of dependence and tolerability. Thus, a large unmet medical need exists for the development of safe and effective therapeutics for treatment of chronic pain. A novel approach includes identification of intracellular signals involved in the pain transduction pathway, such as nerve growth factor (NGF). Monoclonal antibodies targeting NGF, such as tanezumab, fulranumab and fasinumab, have been investigated for the treatment of chronic pain conditions. Due to unexpected joint adverse events in clinical studies and concerns about sympathetic nervous system toxicity in animals, these agents were placed on 2 separate partial clinical holds, which were subsequently lifted after rigorous evaluations were conducted to understand how inhibition of NGF impacts safety. To share learnings regarding the rigorous evaluation of clinical and nonclinical safety data which contributed to the removal of these partial clinical holds, this article reviews the rationale for developing agents that target NGF as potential treatments for chronic pain, describes nonclinical and clinical studies of these agents, and describes strategies used to evaluate whether inhibition of NGF has negative effects on joint or sympathetic nervous system safety.

Key words: Nerve growth factor antibody, Tanezumab, Fasinumab, Fulranumab

INTRODUCTION

A large unmet medical need exists for the development of safe and effective therapeutics for treatment of chronic pain (Institute of Medicine, 2011). Therapeutic agents commonly used in the management of chronic pain include nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids (Kissin, 2010). These compounds have limited effectiveness and issues of dependence, tolerability, and overall safety have been associated with standard pain therapies (Bjordal et al., 2004).

One approach to selecting appropriate new targets for the development of potential pain treatments is through the identification of intracellular signals involved in the pain transduction pathway. For example, nerve growth factor (NGF) has been identified as an important key mediator in the pain pathway. The development of NGF monoclonal antibodies (mAbs) binding to NGF represents a novel approach to the treatment of chronic pain using a mechanism-based approach (Hefti et al., 2006; Woolf and Max, 2001). For example, tanezumab (Pfizer Inc.), fulranumab (Janssen Pharmaceuticals LLC), and fasinumab (Regeneron Pharmaceuticals Inc. and Teva Pharmaceuticals Inc.) are mAbs targeted against NGF that have been investigated for treatment of chronic pain conditions, including osteoarthritis (OA), chronic low back pain (CLBP), and cancer pain (Balanescu et al., 2014; Brown et al., 2012, 2013; Ekman et al., 2014; Gimbel et al., 2014; Katz et al., 2011; Kivitz et al., 2013; Lane et al., 2010; Mayorga et al., 2016; Nagashima et al., 2011; Sanga et al., 2013, 2016; Schnitzer et al., 2015, 2011; Sopata et al., 2015; Spierings et al., 2013; Tiseo et al., 2014). In 2010, the US Food and Drug Administration (FDA) placed a partial clinical hold on the clinical development of all NGF...
antibodies due to adverse events initially described as osteonecrosis (Janssen Research and Development LLC, 2012; Pfizer Inc., 2012; Regeneron Pharmaceuticals Inc. and Arthritis Advisory Committee Meeting, 2012). Despite these initial reports, blinded external adjudication analyses determined that tanezumab treatment was not associated with an increase in osteonecrosis but was associated with an increase in rapidly progressive OA (RPOA) (Hochberg et al., 2016; Pfizer Inc., 2012). Based on these findings, and clinical analyses which identified a number of risk mitigation procedures intended to reduce the risk of RPOA with tanezumab (Hochberg et al., 2016; Pfizer Inc., 2012), the FDA lifted the joint safety partial clinical hold on tanezumab in 2012. A second class-wide partial clinical hold was implemented by FDA in December 2012 due to nonclinical data showing morphologic changes in the sympathetic nervous system. In 2015, FDA lifted the partial clinical hold on tanezumab due to a number of new nonclinical studies and clinical data analyses undertaken to understand how inhibition of NGF impacts sympathetic nervous system safety (Pfizer Inc., 2015). Although the clinical development of tanezumab was stopped for over 4 years in total due to the two partial clinical holds, tanezumab clinical trials resumed in July 2015 and include clinical risk mitigation measures related to joint safety and sympathetic nervous system safety that were agreed to with FDA. To share our learnings from the rigorous evaluation of clinical and nonclinical safety, we herein review the rationale for targeting the NGF signal transduction pathway for treatment of chronic pain, nonclinical and clinical studies of NGF mAbs, and strategies used to evaluate safety concerns associated with these agents to remove the partial clinical holds.

NGF BIOLOGY AND ROLE IN PAIN SIGNALING

NGF was first isolated and described based on observations of increased production of nerve fibers in tumors grafted onto chick embryos (Bueker, 1948). NGF has a key role in the developing nervous system, where it promotes growth and development of specific populations of primary sensory and sympathetic neurons and contacts with their targets (Mantyh et al., 2011). NGF is also critical for survival of these neurons since NGF inhibition during development leads to a marked loss of sensory and sympathetic neurons due to an increase in the magnitude of naturally occurring cell death (Gorin and Johnson, 1979; Levi-Montalcini and Booker, 1960).

In the adult, NGF is no longer required for survival of primary sensory or sympathetic neurons, but it has a role in pain signaling through the binding of NGF to its receptors, tropomyosin-related kinase A (trkA; high affinity) and p75 (low affinity) (Mantyh et al., 2011). These receptors are expressed on the peripheral terminals of A-delta and unmyelinated C-fibers (Bennett et al., 1998; Hefti et al., 2006; Mantyh et al., 2011). When bound, the NGF:trkA complex is internalized into the fibers and transported to cell bodies in dorsal root ganglia where it activates transcription factors that control expression of modulators involved in pain signaling. These include a number of receptors and ion channels at the membrane surface, including transient receptor potential vanilloid 1 (TRPV1), acid-sensing ion channels 2 and 3, endothelin receptors, bradykinin receptors, voltage-gated sodium, and calcium channels, delayed rectifier potassium currents, increased synthesis of peptides (e.g. substance P and calcitonin gene-related peptide [CGRP]) and putative mechano-transducers (Delcroix et al., 2003; Kendall et al., 1995; Mantyh et al., 2011; Miller and Kaplan, 2001; Woolf, 1996).

Tissue NGF levels are increased in pain states, including inflammatory pain (McMahon, 1996; Wu et al., 2007), leading to both peripheral sensitization of nociceptors and central sensitization of dorsal horn neurons responding to noxious stimuli (McMahon, 1996) (see Fig. 1). In studies investigating administration of NGF, injection of NGF caused behavioral hyperalgesia in rats and long-lasting pain sensitivity in humans (Dyck et al., 1997; Lewin et al., 1994; Svensson et al., 2003). Conversely, blocking NGF activity via administration of NGF antibody or Trk A immunoglobulin G (IgG) fusion protein decreased pain-related behavior in animal models (Shelton et al., 2008; Zahn et al., 2004). NGF-antibody treatment significantly reduced bone cancer pain-related behaviors in animal models of early and late stage cancer (Halvorson et al., 2005; Sevcik et al., 2005). Administration of NGF antibody also reversed established hyperalgesia in a rodent model of autoimmune arthritis (Shelton et al., 2005). Thus, blockade of NGF is a promising therapeutic approach for treatment of chronic pain (Mantyh et al., 2011).

Tanezumab is a humanized IgG2Aa mAb targeted against NGF with high selectivity and specificity for NGF that is currently in development for treatment of chronic pain (Abdiche et al., 2008; Mantyh et al., 2011). Tanezumab binds NGF and inhibits NGF interaction with its receptors (Abdiche et al., 2008; Mantyh et al., 2011). Fullranumab and fasinumab are recombinant, fully human, NGF mAbs that bind to NGF and have also been studied in patients with chronic pain (Mayorga et al., 2016; Sanga et al., 2013, 2016; Tiseo et al., 2014). Based on current published data, there do not appear to be substan-
tial differences in the general safety profiles among NGF mAbs.

DEVELOPMENT OF TANEZUMAB

Administration of NGF inhibitors, including muM-ab911, the murine precursor to tanezumab, reduced pain-related behaviors in several animal models of pain, including reduced withdrawal latency to radiant heat in a plantar incision model (Zahn et al., 2004), pain associated with auto-immune arthritis (Ghilardi et al., 2012; Shelton et al., 2005), bone fracture pain (Jimenez-Andrade et al., 2011, 2007; Koewler et al., 2007; Sabsovich et al., 2008), and significant reduction in bone cancer pain-related behaviors (Halvorson et al., 2005; Sevcik et al., 2005). No changes in bone innervation, bone remodeling, or fracture healing were detected during these studies (Ghilardi et al., 2012; Halvorson et al., 2005; Jimenez-Andrade et al., 2011, 2007; Koewler et al., 2007; Sabsovich et al., 2008; Sevcik et al., 2005).

The fact that NGF inhibition reduced pain-related behavior without causing detrimental effects on bone or joint parameters in nonclinical studies led to the development of a humanized form of the antibody for evaluation in clinical trials. A Biological Investigational New Drug application was submitted to the FDA in 2004 for investigation of tanezumab in indications related to the treatment of moderate to severe, acute, and/or chronic pain (Pfizer Inc., 2012). Tanezumab was subsequently evaluated in several clinical trials of chronic pain conditions. For example, in patients with moderate to severe OA of the knee or hip, tanezumab significantly reduced pain and improved physical function and Patient’s Global Assessment (PGA) (Balanescu et al., 2014; Brown et al., 2014, 2012, 2013; Ekman et al., 2014; Gimbel et al., 2014; Katz et al., 2011; Kivitz et al., 2013; Lane et al., 2010; Nagashima et al., 2011; Schnitzer et al., 2015, 2011; Spierings et al., 2013). Specifically, across 3 co-primary measures of efficacy (Western Ontario and McMaster Universities Osteoarthritis Pain and Physical Function subscales and PGA of OA), tanezumab provided significant improvement over place-
bo (Balanescu et al., 2014; Brown et al., 2012, 2013; Ekman et al., 2014; Lane et al., 2010; Nagashima et al., 2011; Schnitzer et al., 2015; Spierings et al., 2013). Similarly, in studies comparing efficacy of tanezumab to an NSAID active comparator, treatment with naproxen 500 mg twice daily (b.i.d.) or celecoxib 100 mg b.i.d., tanezumab provided significantly greater improvement (Ekman et al., 2014; Schnitzer et al., 2015). Compared with oxycodone controlled-release (CR) formulation, tanezumab resulted in significant clinical improvement vs both placebo and oxycodone CR in pain, physical function, and PGA in patients with OA whereas oxycodone CR failed to provide significant improvement vs placebo in any of the efficacy measures (Spierings et al., 2013). In studies conducted to evaluate efficacy and safety of tanezumab added to an oral NSAID regimen in patients with moderate to severe OA of the knee and/or hip, the addition of tanezumab to NSAID therapy resulted in significant improvements in pain, function, and global assessments in these patients (Balanescu et al., 2014; Schnitzer et al., 2015) but the addition of tanezumab 5 mg or 10 mg to NSAID treatment did not provide substantial benefit over tanezumab 5 mg or 10 mg monotherapy, respectively (Pfizer Inc., 2012). In addition, the frequency of RPOA was more common in patients receiving tanezumab plus NSAID than in those receiving tanezumab monotherapy or NSAIDs alone (Hochberg et al., 2016; Pfizer Inc., 2012).

Tanezumab has also been evaluated in other types of chronic pain. For example, tanezumab demonstrated clinically and statistically superior efficacy relative to placebo and naproxen in patients with CLBP (Katz et al., 2011; Kivitz et al., 2013). In addition, tanezumab provided significant pain reduction in patients with diabetic peripheral neuropathy (Bramson et al., 2015).

Adverse events related to abnormalities in peripheral sensation have been reported by patients in tanezumab clinical studies (Balanescu et al., 2014; Brown et al., 2014, 2012, 2013; Ekman et al., 2014; Gimbel et al., 2014; Katz et al., 2011; Kivitz et al., 2013; Lane et al., 2010; Nagashima et al., 2011; Schnitzer et al., 2015, 2011; Spierings et al., 2013). Paresthesia (pins and needles sensation) was most frequently reported followed by hypoesthesia (numbness) and burning sensation (Balanescu et al., 2014; Brown et al., 2014, 2012, 2013; Ekman et al., 2014; Gimbel et al., 2014; Katz et al., 2011; Kivitz et al., 2013; Lane et al., 2010; Nagashima et al., 2011; Pfizer Inc., 2012; Schnitzer et al., 2015, 2011; Spierings et al., 2013). These adverse events were more frequently reported by patients receiving tanezumab alone or in combination with NSAID treatment than in patients receiving either placebo or active comparator. In general, the incidence of adverse events related to abnormal peripheral sensation was greatest in patients who received treatment with tanezumab in combination with an NSAID (Balanescu et al., 2014; Brown et al., 2014, 2012, 2013; Ekman et al., 2014; Gimbel et al., 2014; Katz et al., 2011; Kivitz et al., 2013; Lane et al., 2010; Nagashima et al., 2011; Schnitzer et al., 2015, 2011; Spierings et al., 2013). The adverse events were generally mild to moderate in severity and resolved before last patient contact.

In addition to evaluating pain-related behaviors, nonclinical studies have been conducted to determine the dependence of adult sympathetic neurons on NGF. These studies indicated an apparent loss of neurons with NGF blockade, although no studies ever revealed images of dead or dying neurons (Bjerre et al., 1975; Goedert et al., 1978; Gorin and Johnson, 1980; Johnson et al., 1982; Ruberti et al., 2000; Ruit et al., 1990). More recently, in-depth studies examining the effects of tanezumab on the sympathetic nervous system in cynomolgus monkeys demonstrated that tanezumab was associated with smaller ganglion volume, smaller average neuron size/area, and lower estimated total neuron counts (Belanger et al., 2017; Butt et al., 2014). These changes did not progress over time or persist with continued exposure to tanezumab and were completely reversible (Belanger et al., 2017; Butt et al., 2014). Specifically, treatment with tanezumab followed by an untreated recovery phase indicated that the apparent loss of neurons associated with tanezumab treatment was temporary and not due to an actual loss of neurons since neuron counts or size/area after recovery were similar for vehicle-treated animals and those treated with tanezumab (Belanger et al., 2017; Butt et al., 2014) (see Table 1). Despite intensive evaluation, there was no evidence of neuronal apoptosis or necrosis in these studies. Similarly, assessment of the effects of tanezumab on the function of the sympathetic nervous system indicated no changes in the sympathetic control of cardiovascular function occurred in response to tanezumab (Belanger et al., 2017).

**KEY REGULATORY EVENTS IN THE DEVELOPMENT OF TANEZUMAB**

Nonclinical data from studies conducted prior to the entry of tanezumab into clinical trials did not show any adverse effects on bone or joint. Nonclinical studies evaluating pain-related behavior did not result in any changes in bone innervation, bone remodeling, or fracture healing (Halvorson et al., 2005; Jimenez-Andrade et al., 2007;
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<th>Table 1. Stereologic assessments of the superior cervical ganglion from cynomolgus monkeys administered vehicle (controls) or tanezumab at 1.2 mg/kg/8 weeks for 1, 3, and 6 months and 6 months followed by an 8 to 10 month non-dosing recovery period.</th>
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NE, not evaluated; S.D., standard deviation
*p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001, tanezumab treated vs control
Koewler et al., 2007; Sabsovich et al., 2008; Sevcik et al., 2005). Similarly, inhibition of NGF during fracture healing did not inhibit callus formation, bridging, or mechanical strength (Jimenez-Andrade et al., 2007; Koewler et al., 2007). In a model of complex regional pain syndrome caused by a tibial fracture, which is associated with pronounced bone loss, treatment with NGF antibody attenuated the bone loss (Sasovich et al., 2008). Likewise, the inhibition of NGF with muMab911 in animal models of osteolytic or osteoblastic tumor-induced bone remodeling had no effect on bone remodeling while decreasing pain behaviors (Halvorson et al., 2005; Sevcik et al., 2005). Thus, the occurrence of adverse events initially described as osteonecrosis reported during conduct of clinical studies of tanezumab was unexpected (Hochberg, 2015).

Serious joint safety adverse events led the FDA to place all NGF inhibitors on partial clinical hold in 2010 for all studies except those evaluating cancer pain (Center for Drug Evaluation and Research, 2012a, 2012b; Pfizer Inc., 2012). As a result of the unexpected joint-related adverse events, an adjudication committee of medical experts, including a bone pathologist, orthopedic surgeons, and rheumatologists, was formed to review these events (Hochberg, 2015). The committee, blinded to treatment, examined the investigator reports described as osteonecrosis and cases of total joint replacement for which radiology images within approximately 9 months of the surgery date were available to understand the nature of these events (Hochberg, 2015). A total of 249 cases (87 cases reported as osteonecrosis and 162 cases of total joint replacement) were adjudicated by the committee. Based on the adjudication and classification of these events, only 2 (0.8%) of 249 cases were adjudicated as primary osteonecrosis. Worsening OA was adjudicated in 200 (80.3%) of 249 cases altogether, and was considered to be RPOA in 68 (27.3%) of the cases (Hochberg, 2015).

Following this analysis of joint-related adverse events, Pfizer outlined measures to reduce risk of RPOA in future clinical studies of tanezumab (Pfizer Inc., 2012). These measures were to be used in clinical studies of patients with OA as well as other chronic pain conditions, although some modifications would be necessary depending on the study design and patient population involved in the study (Pfizer Inc., 2012). These measures include the exclusion of chronic concomitant NSAID use with tanezumab; the exclusion of tanezumab 10 mg from further investigation in OA; a cautious approach to tanezumab doses ≥ 10 mg in non-OA chronic pain conditions; discontinuation of patients who do not respond adequately to initial doses of tanezumab; exclusion of patients with pre-existing RPOA or risk factors associated with RPOA identified on x-ray from treatment with tanezumab; and treatment of patients who have inadequate response or are intolerant to multiple classes of analgesics or patients who have contraindications for existing standard of care (Pfizer Inc., 2012). On August 28, 2012, the FDA lifted the partial clinical hold on tanezumab related to joint safety issues (Schnitzer et al., 2015).

In December 2012, the FDA placed a second partial clinical hold on the NGF mAbs, tanezumab, fulranumab and fasminumab due to nonclinical data showing anatomical changes suggestive of neuronal cell death in the sympathetic nervous system of mature animals (Pfizer Inc., 2015). These effects consisted of decreased ganglion volume, decreased neuron size/area, and decreased neuron count in rats and monkeys. As described earlier, in-depth studies were conducted in cynomolgus monkeys to evaluate whether tanezumab had an adverse effect on the sympathetic nervous system (Belanger et al., 2017). Tanezumab was associated with non-progressive, reversible changes in ganglion volume, average neuron size/area, and lower estimated total neuron counts, but no significant changes in sympathetic control of cardiovascular function (Belanger et al., 2017). These changes were temporary and not associated with any evidence of neuronal apoptosis or necrosis (Belanger et al., 2017; Bjerre et al., 1975). Evidence of clinically important effects on the sympathetic nervous system have not been identified in previously completed tanezumab clinical studies (Pfizer Inc., 2015).

In March 2015, FDA lifted the partial clinical hold on tanezumab related to nonclinical data on the sympathetic nervous system (Pfizer Inc., 2015). Clinical trials of tanezumab have resumed and there are currently 6 active studies of tanezumab in patients with OA, CLBP, or bone metastasis cancer pain as of this writing.

**OTHER NGF ANTIBODIES**

Other NGF antibody therapies have also been investigated for the treatment of chronic pain. Fulranumab (JNJ-42160443) is reported to be a fully human, recombinant, mAb (IgG2) against NGF (Janssen Research and Development LLC, 2012). Fulranumab has been investigated in subjects with moderate to severe chronic pain. As of 2012, 9 clinical studies of fulranumab had been conducted, including 2 phase I/ib studies and 7 phase II studies. The 2 phase I/ib studies include a single-dose, dose escalation study in healthy subjects and a multiple-dose, dose-escalation study in patients with OA knee pain. The 7 phase II studies enrolled patients with
various pain conditions, including cancer-related pain (PAI-2001), OA pain (PAI-2004 Add-on; PAI-2006 Monotherapy), lower back pain (PAI-2003), post-traumatic/neuropathic pain (NPP-2001), diabetic neuropathy (NPP-2002), and interstitial cystitis (PAI-2005) (Janssen Research and Development LLC, 2012). Although all the phase II studies (with the exception of PAI2001) were terminated due to the safety clinical hold in 2010, Janssen reported that fulranumab provided clinically meaningful improvement in pain and a reduction in functional impairment in patients with moderate to severe pain due to OA (Janssen Research and Development LLC, 2012). In 2016, Janssen Pharmaceuticals announced the discontinuation of the development program for fulranumab. This decision was based on strategic portfolio prioritization and was not based on any emerging safety concerns from the phase III clinical studies with fulranumab (Janssen Research and Development LLC, 2016).

Fasinumab (REGN475) is reported to be a fully human IgG4 mAb that specifically binds mature and pro-NGF with cross-reactivity to all mammalian NGFs tested (human, monkey, mouse, and rat NGF) (Regeneron Pharmaceuticals Inc. and Arthritis Advisory Committee Meeting, 2012). In a 24-week, double-blind, placebo-controlled, parallel-group, repeat-dose study in OA patients with walking pain, fasinumab treatment was well tolerated and resulted in statistically significant efficacy in pain measures and physical function versus placebo (Tiseo et al., 2014). In 2016, Regeneron also reported positive results at 16 weeks from a placebo-controlled study evaluating fasinumab in patients with moderate to severe OA pain in the hip or knee (Regeneron Inc., 2016b). An extensive follow-up analysis for joint safety occurred at 36 weeks. At the 36-week analysis, the incidence of adjudicated arthropathies was found to be potentially dose-dependent, with a higher rate of patients experiencing arthropathy in the higher-dose groups (12% [9 mg], 7% [6 mg], 5% [3 mg], 2% [1 mg], and 1% [placebo]). Based on these data, Regeneron and Teva companies are planning to advance only lower doses in the ongoing fasinumab OA pivotal phase III program, subject to discussion with the FDA and other health authorities (Regeneron Inc., 2016a). Also, in a recent study in patients with CLBP, an adverse event of adjudicated arthropathy was reported, prompting the FDA to place fasinumab on clinical hold (Regeneron Inc., 2016a). Based on these results, Regeneron and Teva plan to design a pivotal phase III study in CLBP that excludes patients with advanced OA. The companies plan to submit a program plan for review with the FDA and other health authorities (Regeneron Inc., 2016a).

CONCLUSION

Based on extensive research on the biology and pathophysiology that underlies the many facets of chronic pain, inhibition of NGF has emerged as a novel molecular target. Tanezumab has shown significant efficacy for pain relief in animals and humans in several chronic pain states. The efficacy profile of tanezumab has been well characterized in several chronic pain conditions, indicating tanezumab provides clinically meaningful relief of pain and improvement in function compared with placebo, NSAIDs, and opioids. Issues associated with safety were detected during clinical studies (joint safety) and nonclinical studies (sympathetic nervous system safety). The joint safety issues noted in the initial studies with tanezumab have not been as apparent in studies of fulranumab and fasinumab, most likely due to the much smaller number of patients studied in the fulranumab and fasinumab programs.

Detailed analyses of the effects of NGF inhibition on joints and the sympathetic nervous system were conducted. Through the development of benefit-risk optimization measures and strategies for increased patient surveillance to reduce the risk of joint-related adverse events in future studies of patients with OA or other chronic pain conditions, 2 partial clinical holds were overcome and clinical development of tanezumab and fasinumab has resumed. Further study into the efficacy and safety of NGF antibody therapies may result in pain therapies that target specific and key modulators of pain, thereby providing a much-needed alternative approach to the treatment of chronic pain.

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