Drugs of the Future 2010, 35(5): 373-378
Copyright © 2010 Prous Science, S.A.U. or its licensors. All rights reserved.
CCC: 0377-8282/2010
DOI: 10.1358/dof.2010.35.5.1508523

MONOGRAPH

TANEZUMAB

Rec INN; USAN

Anti-NGF Monoclonal Antibody
Treatment of Pain
Treatment of Osteoarthritis

PF-04383119
RI-624
RN-624

Immunoglobulin G_2, anti (human nerve growth factor) (human mouse monoclonal RN624 heavy chain), disulfide with human mouse monoclonal RN624 light chain, dimer

Immunoglobulin G_2, anti (human nerve growth factor) humanized mouse monoclonal RN624 [Lys^{71},Ser^{330},Ser^{331}] γ2 heavy chain (135-214')-disulfide with κ light chain (223-223'':224-224'':227-227'':230-230'')-tetrakisdisulfide dimer

Humanized monoclonal IgG_{2a} kappa antibody against human nerve growth factor (NGF)

Immunoglobulin G_2, anti-[Homo sapiens nerve growth factor beta (NGFB)], humanized monoclonal antibody, RN624; γ2 heavy chain (1-447) [humanized VH (Homo sapiens FR/Mus musculus CDR-Homo sapiens IGHJ4*01) [8.7.15] (1-121)-Homo sapiens IGHG2*01, CH2 A115>S, P116>S (122-447)], (135-214')-disulfide with κ light chain (1'-214') [humanized V-KAPPA (Homo sapiens FR/Mus musculus CDR-Homo sapiens IGKJ2*01) [6.3.9] (1'-107')-Homo sapiens IGKC*01 (108'-214')]; (223-223'':224-224'':227-227'':230-230'')-tetradisulfide dimer

CAS: 880266-57-9
EN: 372227

SUMMARY

Current therapies for the treatment of pain and inflammation in diseases such as osteoarthritis largely rely upon the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in combination with opiates such as morphine sulfate. These drugs, however, are ineffective in a large percentage of patients or cause complicated side effects such as gastrointestinal ulceration and respiratory depression. The development of safer, more effective treatments is therefore the goal of much pharmaceutical research. Nerve growth factor (NGF) is a key mediator in the genesis of hypersensitivity and allodynia in states of pain and inflammation and the prevention of the NGF/receptor interaction has been shown to improve pain in a number of preclinical animal models. Pfizer has developed a humanized anti-NGF monoclonal antibody, tanezumab, as a therapy for safe and effective pain relief. Tanezumab works by sequestering NGF, thereby preventing NGF from interacting with its receptors on sensory neurons, which acts to alleviate painful symptoms. Tanezumab has successfully entered human clinical trials and a number of phase II/III trials are ongoing to investigate the safety and efficacy of tanezumab in treating pain related to osteoarthritis, chronic lower back pain and other disease-related chronic pain states for which no wholly effective therapy exists.

K. Haddley. University of Liverpool, School of Biomedical Sciences, Crown St., Liverpool, Merseyside L69 3BX, UK. E-mail: khaddley@liv.ac.uk.

BACKGROUND

Nerve growth factor (NGF), a member of the neurotrophin family, is a critical director of neurite outgrowth in the developing peripheral nervous system (PNS) (1). The role of NGF in the adult is well documented as a key mediator in sensitization to noxious stimuli and hyperalgesia, as well as playing a central role in the development of allodynia (pain sensation from a non-noxious stimulus) (2-4). In addition, elevated levels of NGF are present in tissues during inflammation and injury. NGF binds to two distinct but interacting receptors on sensory neurons in the PNS: the $p75^{NTR}$, a low-affinity NGF receptor that also binds other neurotrophins such as brain-derived neurotrophic factor (BDNF), and the high-affinity NGF receptor TrkA, which is found exclusively on dorsal root ganglion (DRG) neurons. In a murine model of pain, $p75^{NTR}$ receptor knockout did not affect the response to acute pain, suggesting that the effects of NGF in painful stimuli were mediated by the TrkA receptor; however, in a second model of pain, blockade of the $p75^{NTR}$ receptor attenuated electrical signaling in sensory neurons, suggesting that the two NGF receptors might mediate different types or degrees of pain, for example acute and chronic pain (reviewed in 5). The DRG sensory neurons are a major component of the nociceptive pathway(s). DRG nociceptors synapse with second-order pain neurons in the spinal cord to relay pain signals from the periphery and somatic tissues to the central nervous system (CNS). Upon binding to the TrkA receptor, NGF initiates a number of intracellular signaling cascades, including the mitogen-activated protein kinase (MAPK), extracellular-signal regulated kinase 1 and 2 (ERK-1/2), and the phosphoinositide 3-kinase (PI3K) pathways, all of which alter the activity of downstream mediators of gene expression, such as cAMP-dependent response

element-binding protein (CREB), c-Fos, c-Jun and nuclear factor NF-κB (reviewed in 6).

Existing therapies for pain and inflammation mostly rely on the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and opiates such as morphine, but these are largely ineffective or cause severe side effects for a broad range of patients when used to target chronic conditions such as osteoarthritis or visceral inflammation. Following the advent of several preclinical studies that demonstrated successful amelioration of hypersensitivity in animal models, therapies that interfere with NGF signaling, including receptor blockade, NGF capture and inhibition of downstream NGF receptor signaling, have become attractive targets for pharmaceutical intervention in the treatment of chronic pain and inflammatory disease (5).

Pfizer has developed a humanized anti-NGF monoclonal antibody, tanezumab, which targets both types of NGF receptor by reducing the availability of free NGF, thereby demonstrating NGF-specific effects. It has already undergone successful phase I clinical trials for safety and efficacy in humans and is currently being studied in phase II and III clinical investigations in the treatment of osteoarthritis of the knee and hip, visceral inflammation, bone cancer-related pain and chronic lower back pain (7).

PRECLINICAL PHARMACOLOGY

Antibody-based anti-NGF therapies have been extensively studied in animal models of pain and inflammation and include the use of antibodies that sequester NGF or block the binding of NGF to its receptors. The majority of nerve fibers innervating bone express the NGF receptors TrkA and $p75^{NTR}$, which could, in part, explain the development of hypersensitivity to cancer-related bone pain. In a murine model of prostate cancer-induced bone pain, canine prostate carcinoma ACE-1 cells were injected into the intramedullary space of the left mouse femur to induce tumor formation and tumor-related pain. Anti-NGF treatment of these animals using an antibody that sequestered NGF to prevent it binding to NGF receptors (mAb911; Rinat Neuroscience Corporation [now owned by Pfizer]) attenuated bone cancer pain more effectively than opiates such as morphine. Pain indices were assessed by guarding and flinching behavior monitored over a fixed time period of 2 min. In treated mice, time spent guarding was significantly reduced (from 7.7 ± 0.8 to 1.2 ± 0.4 s), as was spontaneous flinching behavior (from 11.9 ± 1.2 to 2.1 ± 0.7 s) (8, 9). In a similar model, osteolytic murine sarcoma NCTC 2472 cells were injected into left mouse femur and mice were treated with mAb911 to assess efficacy and monitor markers of peripheral and central sensitization. This study reported that anti-NGF treatment did not alter disease progression or bone modeling, but did reduce levels of elevated biomarkers associated with pain, such as the expression of activating transcription factor 3 (ATF-3; a marker of neuronal injury), dynorphin and the immediate early gene *FOS*. In addition, macrophage infiltration in the periphery (an indication of inflammation) was reduced by treatment (10).

Tanezumab administration reduced pain-associated behaviors in a rodent model of postoperative pain. An i.p. or i.v. injection of tanezumab (0.008-0.6 mg/kg or 0.1-1.0 mg/kg, respectively) was given 12-16 h prior to surgical hind paw incision (1 cm) and weight-bearing activity was analyzed 24 h following surgery to assess postoperative pain. The effect of tanezumab was both dose- (≥ 0.1 mg/kg i.v. and ≥ 0.044 mg/kg i.p.) and time-dependent, showing good efficacy in attenuating pain-related behaviors when applied prior to surgery, but not if applied postsurgically (11).

In a rodent model of arthritic pain, where arthritis was induced by intradermal injection of complete Freund's adjuvant (CFA) at the base of the tail, rats received mAb911 (10 mg/kg i.v.) or the humanized and affinity-matured version (tanezumab; 1.8 mg/kg i.v.) on days 14 and 19 following injection of CFA. When assessed on day 18 and compared to saline-treated controls, animals treated with mAb911 had a decrease of 74% in vocalization in response to paw manipulation (a measure of pain response), while animals treated with tanezumab had a decrease of 79%. In parallel and used as an analgesic comparator, treatment with the NSAID indomethacin (3 mg/kg/day) reduced vocalization by 68% when compared to saline-treated controls. In the same experiment, by day 24, animals treated with mAb911 showed a 91% reduction in vocalizations, those treated with indomethacin did not show further improvement, and strikingly, those treated with tanezumab no longer vocalized in response to mechanical stimulation. This study also reported that the onset of the effect of anti-NGF treatment (tanezumab) was dose-dependent, with higher doses (10 mg/kg) reversing arthritic hyperalgesia within 24 h (12).

Anti-NGF therapy was also examined in a rat tibia fracture model in which allodynia is a major phenotype and which is used to mimic complex regional pain syndrome (CRPS) type I in humans. Rats received anti-NGF (mAb911; 10 mg/kg i.p.) or vehicle on days 17 and 24 post-fracture. Anti-NGF treatment reduced neuropeptide (substance P [SP] and calcitonin gene-related peptide [CGRP]) levels in sciatic nerve and reduced nociceptive sensitization, but did not decrease hind paw edema, warmth or cytokine production. The authors concluded that anti-NGF therapy may be useful for treating some but not all of the symptoms associated with CRPS type I (13). Similar experiments in a murine closed femur fracture model assessed spontaneous and palpation-evoked guarding and flinching behavior over a 2-min period at 1, 2, 4, 8, 12 and 18 days post-fracture. Treatment with anti-NGF antibody (mAb911; 10 mg/kg i.p. on days 1 and 6 post-fracture) significantly reduced time spent guarding (> 50% decrease) and flinching (> 40% decrease) in measurements of both spontaneous and mechanical evoked pain, as measured on days 2, 8 and 12, and showed greater analgesic potential than s.c. administration of 10 mg/kg morphine sulfate. In addition, palpation in fracture mice on day 2 following fracture (maximal pain) induced significant levels of c-Fos and dynorphin expression in the spinal cord (7.4 ± 1.3 $c\text{-}Fos^+$ neurons laminae I-II, 17.8 ± 2.7 $c\text{-}Fos^+$ neurons laminae III-VI and 7.5 ± 0.4 DYN^+ laminae III-VI) compared to nonfracture mice (1.5 ± 0.8 $c\text{-}Fos^+$ neurons laminae I-II, 1.5 ± 0.6 $c\text{-}Fos^+$ neurons laminae III-VI and 1.4 ± 0.3 DYN^+ laminae III-VI), which was significantly attenuated in fracture mice treated with anti-NGF therapy (3.0 ± 0.6 $c\text{-}Fos^+$ neurons laminae I-II, 6.2 ± 1 $c\text{-}Fos^+$ neurons laminae III-VI and 5.4 ± 0.6 DYN^+ laminae III-VI) (14).

PHARMACOKINETICS AND METABOLISM

In animal models, tanezumab had a plasma half-life ($t_{1/2}$) of several days, low clearance (Cl) and a volume of distribution (V_d) only slightly higher than the blood volume (5, 7). In 2008, Abdiche et al. used four unique biosensors to determine the in vitro binding profile of

tanezumab. Tanezumab formed a highly stable interaction with NGF, with a slow dissociation rate constant (K_d; 2 x 10^{-6}/s), an affinity (K_D) in the single-digit picomolar range and an association rate constant (K_a) of 2 x 10^5-2 x 10^6/M/s (15).

SAFETY

All preclinical studies performed in rodent models reported no adverse events (AEs) for anti-NGF treatment (8-14). Two preclinical assessments of safety and efficacy were also conducted in cynomolgus monkeys. In one, tanezumab (1, 10, 20 or 30 mg/kg i.v.) was given as a single dose (n = 6). In the second, tanezumab (1, 10, 20 or 30 mg/kg i.v.) was given once a week for 26 weeks (n = 4-6). In the first study, all animals survived for the period of study (2 weeks) and showed no signs of toxicity compared to vehicle-treated controls. In the second study, antibodies against tanezumab could be detected in the plasma of 6 of 28 monkeys (mostly at the highest dose) and 1 animal died due to a pronounced monkey anti-human antibody response. Treatment with tanezumab at 30 mg/kg for 23 weeks or 1 or 10 mg/kg for 26 weeks had no AEs on the evaluated parameters, which included body weight, blood pressure, respiratory rate, body temperature, ophthalmology, electrocardiograms, clinical pathology, gross pathology, organ weights and ratios, standard histopathology and specialized neurohistopathology (16).

The results of clinical trials in humans suggest that tanezumab is generally well tolerated, with minor, transient AEs, including headache, diarrhea, muscle cramps and abdominal pain. AEs of abnormal peripheral sensation, such as hyperesthesia, hypoesthesia, dysesthesia or paresthesia, were reported by 13.5% of treated patients in an osteoarthritis study, 12.5% of patients in a chronic lower back pain study and 29.4% of patients in the interstitial cystitis study (17-22).

CLINICAL STUDIES

Tanezumab has successfully entered phase I, II and III trials for use in the treatment of neuropathic and chronic pain and inflammation associated with a number of clinical disorders. All completed, ongoing and currently proposed trials are or have been sponsored by Pfizer (U.S. and Japan). An interventional, nonrandomized, open-label phase I bioavailability study was carried out in healthy volunteers to determine whether s.c. administration of tanezumab resulted in lower drug exposure compared to i.v. administration. Healthy volunteers aged 18-55 years (N = 76) were enrolled and received 1 of 4 treatments: 10 mg i.v., 5 mg s.c., 10 mg s.c. and 19 mg s.c. Primary outcome measures included bioavailability, AEs and immunogenic response. Assessment of NGF levels was performed as a secondary outcome measure. This study was completed in June 2009, although currently there are no data available (23).

A second randomized, double-blind, placebo-controlled phase I study to examine the density of intraepidermal nerve fibers following s.c. administration of tanezumab in healthy volunteers is ongoing. The study began in January 2010 and primary outcome data to assess nerve fiber density and safety, tolerability and immunogenicity were collected in April 2010. Secondary outcome measures will assess the pharmacokinetic profile. Healthy volunteers aged 18-55 years (N = 28) were enrolled and received tanezumab (20 mg s.c.) or a drug-free formulation (placebo) (24).

The safety and efficacy of tanezumab as a therapy for treating pain associated with osteoarthritis of the knee was also investigated in a randomized, double-blind, placebo-controlled, dose-escalation phase I study. The study enrolled 34 adults, 10 of whom received placebo and the remainder received a single dose of tanezumab (0.03-0.3 mg i.v.). Pain was subjectively assessed daily using the visual analog scale (VAS) and joint function was assessed on the Western Ontario and McMaster Universities arthritis index (WOMAC) at weeks 1, 2 and 4 postinjection. All patients receiving tanezumab reported decreased levels of pain, but the treatment was most effective in those receiving doses of 0.1 mg/kg and above ($P < 0.05$), with more than half of those patients showing a 50% improvement in summed pain intensity differences (SPID) within 2 weeks. In 7 of 12 patients, improvements in SPID scores were stable for up to 90 days. WOMAC scores determined that in the placebo group 20% of patients responded while over 83% of patients receiving tanezumab responded. WOMAC function scores decreased by 7 ± 6 points in the placebo group, 33 ± 7 points in the 0.1 mg/kg group and 23 ± 7 points in the 0.3 mg/kg group ($P < 0.05$). Single doses of up to 0.3 mg/kg were well tolerated, with minor AEs such as headache, diarrhea, muscle cramps and abdominal pain (17). This study was further extended to include a greater number of patients (27 on 0.1 mg/kg i.v., 26 on 0.3 mg/kg i.v. and 26 on placebo). In this extension, patients receiving 0.1 mg/kg tanezumab did not show a significant improvement in pain scores on the VAS scale up to 2 weeks following injection compared to the placebo group; however, by days 21-56, significant improvement in walking pain was noted for both dose groups, and between days 28 and 56 the patients on the lower dose displayed significant improvements on the WOMAC scale. In this extension, although AEs in the treatment groups were greater than those receiving placebo, no serious AEs were reported (25).

A randomized, placebo-controlled, parallel-arm, double-blind, multiple-dose phase II investigation on the safety and efficacy of tanezumab as a therapy for osteoarthritis of the knee was completed in October 2009 (26). Patients (age range: 40-78 years) with moderate to severe osteoarthritis-related pain who did not respond to treatment with NSAIDs or who were candidates for joint replacement were included in the study (N = 450). There were 5 treatment cohorts, each receiving tanezumab 10, 25, 50, 100 or 200 µg/kg i.v. on day 1 and day 56 and a placebo group. Primary outcome measures, taken between weeks 2 and 16, assessed walking knee pain, and secondary outcome measures included overall knee pain, occurrence of AEs and WOMAC scoring. All treatment groups showed significant improvement in walking-related pain compared to placebo-treated controls. Baseline measurement in all groups ranged from 68.1 to 72.4 points, and significant improvement was observed in all treatment groups (–17.0 ± 3 to –28.0 ± 3.3 points compared to placebo; $P < 0.001$), with the greatest effect seen in those treated with higher doses. Improvements in WOMAC subscale scores were also noted across all groups compared to placebo ($P < 0.001$). Overall physical function, pain and stiffness were significantly and dose-dependently improved by week 12 in all treatment groups compared to controls (> 50% improvement compared to placebo; $P < 0.001$), and beneficial gains were maintained at week 16. Treatment of approximately 6% of patients was discontinued due to AEs;

however, no serious AEs were recorded and the most common AEs in the treatment groups were headache (8.9%), upper respiratory tract infection (7.3%) and paresthesia (6.8%). The results of this trial suggested that administration of tanezumab once every 8 weeks resulted in a significant benefit for patients with painful osteoarthritis of the knee, as assessed by responder index measures and WOMAC scores (18, 19, 27).

A randomized, placebo-controlled, double-blind, dose-escalation phase I/II study of the safety, tolerability, efficacy and pharmacokinetics of a single dose of tanezumab in osteoarthritis-related knee pain in Japanese patients was completed in December 2009 (28). Primary outcome measures assessed safety, WOMAC and VAS scores for walking and overall knee pain. Secondary outcome measures of pharmacokinetics included peak plasma concentrations, volume of distribution, half-life and renal clearance. The results of this trial have not yet been published. In addition, a randomized, double-blind, placebo-controlled, multicenter phase III study examining the safety and efficacy of tanezumab in patients with osteoarthritis of the knee was carried out by Pfizer and was completed in 2009 (29). Primary outcome measures included WOMAC scores at 16 weeks and overall global assessment of pain. Secondary outcome measures included safety and self-assessment of pain. Patients (N = 697) were separated into 4 cohorts receiving tanezumab at 2.5, 5 or 10 mg i.v. every 8 weeks and a placebo control group. The results of this trial have not yet been published.

Other numerous phase III studies investigating the use of tanezumab in treating osteoarthritis of the knee or hip are ongoing or in the recruitment phase and include: efficacy and safety of s.c. administration (an s.c./i.v. bridging study) (30), an extension study in osteoarthritis (31), a long-term safety study in arthritis patients (32), the effect of treatment on nerve function in arthritis (33) and a number of studies to compare tanezumab efficacy alone or compared to that of naproxen or oxycodone in osteoarthritis of the hip and knee (34-37). Phase II and III extension studies are also recruiting or planned to assess the safety of s.c. administration in patients with osteoarthritis (38, 39).

In addition to a role in osteoarthritis-related pain and inflammation, tanezumab is also being investigated for prospective use in treating other types of pain, such as chronic lower back pain and interstitial cystitis. A randomized, double-blind, multiple-dose, active- and placebo-controlled phase II study of the analgesic potential of tanezumab in chronic lower back pain is currently recruiting (40). Efficacy will be assessed over 16 weeks and primary outcome measures are low back pain intensity (LBPI), as measured by an 11-point numeric rating scale (NRS), compared to placebo and active (naproxen)-treated groups. Secondary outcome measures include: further assessment of pain, Roland-Morris Disability Questionnaire Scores (RMDQS), safety and pharmacokinetic analysis. Initial data have been recorded from 217 patients (age range: 50-52 years; n = 88 tanezumab [5-20 mg twice at 8-week intervals with oral placebo for naproxen twice daily]; n = 88 naproxen [500 mg twice daily with 2 i.v. injections of placebo for tanezumab at 8-week intervals]; n = 41 placebo [both i.v. placebo injections and oral placebo daily]). The mean baseline LBPI was the same across all groups (6.5-6.7). When measured at 6 weeks the mean decrease in baseline was significantly greater for tanezumab (–3.37) compared to naproxen (–2.54) or nonactive placebo (–1.96) controls. Response to treatment was also significantly greater in patients treated with tanezumab (57%) compared to naproxen (34%) or nonactive placebo (4.9%) controls. Tanezumab also fared significantly better in improved RMDQS (–7.70) compared to either naproxen (–4.69) or nonactive placebo (–3.93) controls. Further improvement and enhanced favorability for the action of tanezumab were also noted at week 12. AEs including dysesthesia, hyperesthesia and paresthesia were reported in 11.4%, 3.4% and 2.4% of patients, respectively, on tanezumab, naproxen and placebo (20, 21). An additional phase II/III study assessing long-term treatment with tanezumab in chronic lower back pain is currently recruiting from the above study (41).

A randomized, double-blind, placebo-controlled, dose-ranging phase II study to determine the safety and efficacy of tanezumab in the treatment of pain associated with interstitial cystitis/painful bladder syndrome is in the recruitment stage and will be completed by April 2011 (42). The primary outcome measure is the change in mean daily pain assessed over a 7-day period (at week 16), as measured by an 11-point NRS. Secondary endpoints include change in micturition variables from baseline and assessment of any AEs. Patients (age range: 21-85 years) receive a single dose of tanezumab (200 µg/kg i.v.; n = 34) or placebo (n = 30). At week 6, tanezumab significantly reduced mean daily pain score and frequency of urgency to urinate compared to placebo. Transient, mild and reversible AEs included headache (20.6%), paresthesia (17.6%) and abnormal peripheral sensation (29.4%) (22).

Further ongoing clinical studies investigating the use of tanezumab in treating disease-related pain are recruiting and include: pain relief in adults with diabetic peripheral neuropathy (43) and an open-label extension in breast cancer-related pain (44). Finally, a randomized, double-blind, placebo-controlled, parallel-group, proof-of-concept phase II study investigating the efficacy and safety of a 20-mg dose of tanezumab in the treatment of pain associated with chronic bacterial prostatitis enrolled 62 male patients and was completed in January 2010, but the results have not yet been reported (45).

Two phase III clinical trials in the recruitment stage are assessing the efficacy of tanezumab when used in conjunction with other analgesics to treat pain arising from osteoarthritis of the knee and hip, including combination with ciclofenac (46) or NSAIDs (47). A phase II investigation on the potential use of tanezumab as add-on therapy to opiates in treating bone cancer-related pain is also currently recruiting (48).

SOURCE

Pfizer, Inc. (US).

DISCLOSURES

The author states no conflicts of interest.

REFERENCES

1. Thoenen, H., Barde, Y.A., Davies, A.M., Johnson, J.E. *Neurotrophic factors and neuronal death.* Ciba Found Symp 1987, 126: 82-95.

2. Lewin, G.R., Rueff, A., Mendell, L.M. et al. *Peripheral and central mechanisms of NGF induced hyperalgesia.* Eur J Neurosci 1994, 6: 1903-12.
3. Woolf, C.J., Safieh-Garabedian, B., Ma, Q.P., Crilly, P., Winter, J. *Nerve growth factor contributes to the generation of inflammatory sensory hypersensitivity*. Neuroscience 1994, 62: 327-31.
4. Ma, Q.P., Woolf, C.J. *The progressive tactile hyperalgesia induced by peripheral inflammation is nerve growth factor dependent*. Neuroreport 1997, 8: 807-10.
5. Hefti, F.F., Rosenthal, A., Walicke, P.A. et al. *Novel class of pain drugs based on antagonism of NGF.* Trends Pharmacol Sci 2006, 27(2): 85-91.
6. Pezet, S., McMahon, S.B. *Neurotrophins: Mediators and modulators of pain.* Annu Rev Neurosci 2006, 29: 507-38.
7. Mantyh, P., Tive, L., Shelton, D. *Tanezumab, a humanized anti-nerve growth factor antibody for the treatment of pain.* 28th Annu Sci Meet Am Pain Soc (May 7-9, San Diego) 2009, Abst 275.
8. Halvorson, K.G. et al. *Therapies which attenuate mixed metastatic bone cancer pain*. 11th World Congr Pain (Aug 21-26, Sydney) 2005, Abst 1076-P318.
9. Halvorson, K.G., Kubota, K., Sevcik, M.A. et al. *A blocking antibody to nerve growth factor attenuates skeletal pain induced by prostate tumor cells growing in bone*. Cancer Res 2005, 65(20): 9426-35.
10. Sevcik, M.A., Ghilardi, J.R., Peters, C.M. et al. *Anti-NGF therapy profoundly reduces bone cancer pain and the accompanying increase in markers of peripheral and central sensitization.* Pain 2005, 115(1-2): 128-41.
11. Shelton, D.L., Vergara, G., Pons, J., Ho, W.H., Stratton, J. *Effect of PF04383119 on post-incisional pain following IV or IP administration.* Annu Meet Am Soc Anesthesiol (ASA) (Oct 18-22, Orlando) 2008, Abst A1539.
12. Shelton, D.L., Zeller, J., Ho, W.H., Pons, J., Rosenthal, A. *Nerve growth factor mediates hyperalgesia and cachexia in auto-immune arthritis*. Pain 2005, 116(1-2): 8-16.
13. Sabsovich, I., Wei, T., Guo, T.Z. et al. *Effect of anti-NGF antibodies in a rat tibia fracture model of complex regional pain syndrome type I*. Pain 2008, 138(1): 47-60.
14. Jimenez-Andrade, J.M., Martin, C.D., Koewler, N.J. et al. *Nerve growth factor sequestering therapy attenuates non-malignant skeletal pain following fracture*. Pain 2007, 133(1-3): 183-96.
15. Abdiche, Y.N., Malashock, D.S., Pons, J. *Probing the binding mechanism and affinity of tanezumab, a recombinant humanized anti-NGF monoclonal antibody, using a repertoire of biosensors.* Protein Sci. 2008, 17(8): 1326-35.
16. Shelton, D.L., Zorbas, M., Bales, R., Rogers, B., Pons, J. *Preclinical safety evaluation of PF04383119 after single and multiple-dose administration in monkeys*. Annu Meet Am Soc Anesthesiol (ASA) (Oct 18-22, Orlando) 2008, Abst A597.
17. Lane N. et al. *RN624 (anti-NGF) improves pain and function in subjects with moderate knee osteoarthritis: A phase I study.* 69th Annu Sci Meet Am Coll Rheumatol (Nov 12-17, San Diego) 2005, Abst 1205.
18. Lane, N.E., Schnitzer, T.J., Smith, M.D., Brown, M.T. *Tanezumab relieves moderate to severe pain due to osteoarthritis (OA) of the knee: A phase 2 trial.* 72nd Annu Sci Meet Am Coll Rheumatol (Oct 24-29, San Francisco) 2008, Abst 1989.
19. Lane, N.E., Schnitzer, M.D., Brown, M.T. *Efficacy and safety of PF04383119 in treating moderate to severe pain due to osteoarthritis (OA).* Annu Eur Congr Rheumatol (EULAR) (June 11-14, Paris) 2008, Abst THU0318.
20. Tive, L., Schnitzer, T.J., Katz, N. et al. *Tanezumab, a humanized anti-nerve Growth factor antibody in the treatment of three chronic pain types*. Pain Med (Malden) 2010, 11(2): Abst 151.
21. Katz, N., Borenstein, D., Birbara, C. et al. *Tanezumab, an anti-nerve growth factor (NGF) antibody, for the treatment of chronic low back pain (CLBP) - A randomized, controlled, double-blind, phase 2 trial*. 28th Annu Sci Meet Am Pain Soc (May 7-9, San Diego) 2009, Abst 268.
22. Modwin, R.M., Evans, R.J., Cossons, N. et al. *Efficacy and safety of tanezumab for the treatment of interstitial cystitis.* Eur Urol Suppl 2010, 9(2): Abst 639.
23. *Measure exposure of tanezumab in healthy volunteers when administering the drug subcutaneously (NCT00788294).* ClinicalTrials.gov Web site, April 15, 2010.
24. *Study to assess changes in the number of nerves in the skin at the site where tanezumab is injected (NCT01030640).* ClinicalTrials.gov Web site, April 15, 2010.
25. Hefti, F., Mokhtarani, M., Gray, M., Zhao, C., Chan, C. *RN624 (anti.NGF) reduces pain and improves function in subjects with moderate to severe pain from osteoarthritis of the knee*. 25th Annu Sci Meet Am Pain Soc (May 3-6, San Antonio) 2006, Abst 778.
26. *A phase II study looking at moderate to severe osteoarthritis knee pain (NCT00394563).* ClinicalTrials.gov Web site, April 15, 2010.
27. Schnitzer, T.J., Lane, N.E., Smith, M.D., Brown, M.T. *Efficacy and safety of PF04383119 for moderate to severe pain due to osteoarthritis (OA) of the knee: A randomized trial*. 12th World Congr Pain (Aug 17-22, Glasgow) 2008, Abst PT 214.
28. *A phase 1/2A, single dose study of PF-04383119 in Japanese patients with moderate to severe pain from osteoarthritis of the knee (NCT00669409).* ClinicalTrials.gov Web site, April 15, 2010.
29. *Tanezumab in osteoarthritis of the knee (NCT00733902).* ClinicalTrials.gov Web site, April 15, 2010.
30. *Efficacy and safety study of tanezumab subcutaneous administration in osteoarthritis. A subcutaneous/intravenous bridging study (NCT01089725).* ClinicalTrials.gov Web site, April 15, 2010.
31. *Extension study of tanezumab in osteoarthritis (NCT00809783).* ClinicalTrials.gov Web site, April 15, 2010.
32. *Long-term study of the safety of tanezumab in arthritis patients (NCT00960804).* ClinicalTrials.gov Web site, April 15, 2010.
33. *Tanezumab and nerve function in arthritis patients (NCT00863772).* ClinicalTrials.gov Web site, April 15, 2010.
34. *Tanezumab in osteoarthritis of the hip or knee (2) (NCT00853304).* ClinicalTrials.gov Web site, April 15, 2010.
35. *Tanezumab in osteoarthritis of the hip or knee (NCT00985621).* ClinicalTrials.gov Web site, April 15, 2010.
36. *Tanezumab in osteoarthritis of the hip (NCT00744471).* ClinicalTrials.gov Web site, April 15, 2010.
37. *Tanezumab in osteoarthritis of the knee (2) (NCT00830063).* ClinicalTrials.gov Web site, April 15, 2010.
38. *A long term study of the safety of tanezumab when administered by subcutaneous injections (NCT00994890).* ClinicalTrials.gov Web site, April 15, 2010.
39. *Safety extension study of tanezumab when administered by subcutaneous injection to patients with osteoarthritis (NCT01127893).* ClinicalTrials.gov Web site, April 15, 2010.
40. *A study of tanezumab in adults with chronic low back pain (NCT00876187).* ClinicalTrials.gov Web site, April 15, 2010.
41. *Long term safety study of tanezumab in chronic low back pain (NCT00924664).* ClinicalTrials.gov Web site, April 15, 2010.
42. *A study to investigate tanezumab in patients with interstitial cystitis/painful bladder syndrome (NCT00999518).* ClinicalTrials.gov Web site, April 15, 2010.

43. *A study of the analgesic (pain-relief) effects of tanezumab in adult patients with diabetic peripheral neuropathy (NCT01087203).* ClinicalTrials.gov Web site, April 15, 2010.
44. *Open label extension in cancer patients (NCT00830180).* ClinicalTrials.gov Web site, April 15, 2010.
45. *An efficacy and safety study of tanezumab for the treatment of pain associated with chronic bacterial prostatitis (NCT00926514).* ClinicalTrials.gov Web site, April 15, 2010.
46. *Analgesic efficacy and safety of tanezumab added on to diclofenac SR in patients with osteoarthritis of the knee or hip (NCT00864097).* ClinicalTrials.gov Web site, April 15, 2010.
47. *Long-term analgesic efficacy and safety of tanezumab alone or in combination with non-steroidal anti-inflammatory drugs (NSAIDs) versus NSAIDs alone in patients with osteoarthritis of the knee or hip (NCT00809354).* ClinicalTrials.gov Web site, April 15, 2010.
48. *A study of tanezumab as add-on therapy to opioid medication in patients with pain due to cancer that has spread to bone (NCT00545129).* ClinicalTrials.gov Web site, April 15, 2010.