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Efficacy and safety of tanezumab versus naproxen in the treatment of chronic low back pain

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ABSTRACT

Tanezumab is a humanized monoclonal antibody that specifically inhibits nerve growth factor as a treatment for chronic pain. This phase IIB study investigated the efficacy and safety of tanezumab for chronic low back pain vs placebo and naproxen. Patients (N = 1347) received intravenous tanezumab (5, 10, or 20 mg every 8 weeks), naproxen (500 mg twice daily), or placebo. The primary efficacy end point was mean change in daily average low back pain intensity (LBPI) from baseline to week 16. Secondary end points included mean change from baseline to week 16 in the Roland Morris Disability Questionnaire and Patient's Global Assessment (PGA) of low back pain. Tanezumab 10 and 20 mg had similar efficacy profiles and significantly improved LBPI, Roland Morris Disability Questionnaire, and PGA scores vs both placebo and naproxen ($P \leqslant .05$). Tanezumab 5 mg provided improvement of PGA scores vs placebo ($P \leqslant .05$), and naproxen resulted in significant improvement of LBPI vs placebo ($P \leqslant .05$). Adverse event incidence was comparable across tanezumab doses but higher than with placebo or naproxen. Arthralgia, pain in extremity, headache, and paresthesia were the most commonly reported adverse events by tanezumab-treated patients. The most frequently reported adverse events resulting in discontinuation of tanezumab treatment were arthralgia and paresthesia; the highest frequency was observed with tanezumab 20 mg (both 1.4%). Serious adverse event incidence was similar across treatments. In conclusion, tanezumab provided significantly greater improvement in pain, function, and global scores vs placebo and naproxen in patients with chronic low back pain.

1. Introduction

More than two thirds of adults experience an episode of low back pain in their lifetime [3]. According to the 2002 National Center for Health Statistics survey, 26.4% of individuals in the United States reported low back pain within the previous 3 months [13,31]. Prognosis is usually good, and approximately 90% of these individuals recover within a 3-month period, often within a few weeks [3]. However, for some, chronic low back pain (>3 months) may develop, causing significant morbidity, disability, and lost productivity [22,23]. Chronic low back pain has a heterogeneous etiology that may include osteoarthritis (OA) of the spine, disc disease or injury, muscle strain, and radiculopathy [10,13], although the precise pathogenesis is typically unclear, as nearly 90% of low back pain cases are described as nonspecific [32]. Given the lack of a specific diagnosis, therapeutic measures are generally aimed at providing symptomatic relief.

Treatment of chronic low back pain is a difficult clinical problem [8–10]. Generally, treatment of chronic low back pain involves a multimodal approach utilizing both pharmacological (single or multiple agents) and nonpharmacological measures [8,9]. Pharmacological treatment often includes use of opioids and/or nonsteroidal anti-inflammatory drugs (NSAIDs) despite only modest efficacy [2,4,8]. NSAIDs and opioids are often associated with poor tolerability due to central nervous system, cardiovascular, or gastrointestinal adverse events [10,14,27]. In addition, there are insufficient data from clinical trials demonstrating benefit from long-term use [41]. Although evidence indicates that skeletal muscle relaxants and tricyclic muscle relaxants provide some relief of low back pain, effects were modest at best [8]. Because effectiveness for

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most interventions has not been demonstrated conclusively in controlled settings or with chronic treatment, therapeutic management of chronic low back pain varies widely [8]. Thus, there remains a significant need for new agents in the management of chronic low back pain.

The neurotrophin, nerve growth factor (NGF), is essential for neuronal differentiation and survival during prenatal and early postnatal development [33]. In adults, however, NGF is a key mediator of the generation and potentiation of pain signals after tissue injury and inflammation [21]. Elevated NGF levels are associated with increased pain perception in several chronic pain conditions [50]. As such, NGF inhibition is a promising target in the search for novel pain therapeutics [1,24,50].

Tanezumab, a high-affinity humanized monoclonal antibody against NGF, inhibits NGF binding to its receptors, tropomyosin-related kinase A (TrkA) and p75 (low-affinity NGF receptor) [1]. Tanezumab has been previously reported to reduce chronic pain resulting from OA of the knee or hip, chronic low back pain, and interstitial cystitis [7,17,18,27,30]. In patients with chronic low back pain, a single intravenous (IV) infusion of tanezumab provided greater analgesic efficacy than placebo or naproxen [27]. To confirm and extend these findings, the current study investigated the efficacy and safety of IV tanezumab administered every 8 weeks at 3 fixed doses (5, 10, or 20 mg) vs placebo or naproxen 500 mg twice daily.

2. Methods

This was a large, randomized, double-blind, placebo- and active-controlled, multicenter, parallel-group, phase IIB study of patients with chronic low back pain (ClinicalTrials.gov identifier NCT00876187). The study was conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The protocol was reviewed and approved by an institutional review board for all study sites. Written informed consent was obtained from each patient before the initiation of protocol-specified procedures.

2.1. Study population

Key inclusion criteria were: duration of chronic low back pain of $\geqslant$3 months requiring regular use of analgesic medication (>4 days per week for the past month), including immediate-release opioids (in which the average daily opioid dose [for a 7-day period] did not exceed a morphine equivalent dose of 30 mg/d) but excluding acetaminophen, gabapentin, or pregabalin as the sole analgesics used for chronic low back pain; primary location of low back pain between the 12th thoracic vertebra and the lower gluteal folds, with or without radiation into the posterior thigh (Quebec Task Force on Spinal Disorders category 1 or 2 [39]); average low back pain intensity (LBPI) score of $\geqslant$4 (on an 11-point numerical rating scale) while receiving current treatment; and Patient's Global Assessment (PGA) of low back pain of fair, poor, or very poor.

Key exclusion criteria were: history of lumbosacral radiculopathy within the past 2 years, vertebral fracture, major trauma, or back surgery in the past 6 months; significant cardiac, neurological, or other pain, or psychological conditions; known history of rheumatoid arthritis, seronegative spondyloarthropathy, Paget's disease of the spine, pelvis, or femur, fibromyalgia, tumors or infections of the spinal cord; and any condition that might preclude NSAID use. Patients also were excluded if extended-release (ER) opioids or long-acting opioids such as oxycodone controlled release, oxymorphone ER, hydromorphone, transdermal fentanyl, or methadone had been used within 3 months of screening.

2.2. Study design

The study consisted of a screening period of up to 30 days (for discontinuation and washout of all prohibited pain medications), 16 weeks of treatment, and 8 weeks of additional follow-up. Study visits were conducted at screening, baseline (randomization; day 0), and weeks 2, 4, 8, 12, 16, and 24. A safety extension study (NCT00924664) was available to those patients who desired and were eligible for additional treatment after completion of 16 weeks of treatment and 2 dose administrations of the assigned treatment in the current study or who had exited the study due to lack of efficacy.

Patients received a stipend to compensate them for time and travel. Eligible patients underwent a minimum 2-day washout period for all analgesic medications except rescue medication (500 mg acetaminophen, as needed, up to a maximum of 3000 mg/d and discontinued 24 hours before the baseline visit) before the initial pain assessment period. During the initial pain assessment period (the 5 days before randomization/baseline assessment), patients recorded daily LBPI scores on an 11-point numerical rating scale ranging from 0 (no pain) to 10 (worst possible pain) using an interactive voice response system (IVRS; PharmaNet Development Group, Princeton, NJ). The patients were to describe their pain during the past 24 hours and to conduct the self-assessment in the evening before midnight.

Patients with a mean daily average LBPI score $\geqslant$4 were randomized in a 2:2:3:3:3 ratio to one of the following treatments: placebo, tanezumab 5 mg, tanezumab 10 mg, tanezumab 20 mg, or naproxen in a double-blind and double-dummy fashion. Tanezumab or matching placebo were administered by IV infusion over 5 minutes (slow IV push) at baseline and again at week 8. All patients received oral study medication (naproxen or matching placebo) on a daily basis throughout the study.

2.3. Efficacy

Efficacy was assessed as the mean change in the daily average LBPI score from baseline to week 16 and was recorded daily using the IVRS. Secondary end points were the mean change from baseline (days −4 to 0) to week 16 (days 107 to 113) in the Roland-Morris Disability Questionaire (RMDQ) score (range, 0 to 24 with a lower score indicating better function) [42]; the mean change from baseline to week 16 in PGA (5-point scale, 1 = very good, 5 = very poor); the percentage of patients with a $\geqslant$30%, $\geqslant$50%, $\geqslant$70%, or $\geqslant$90% improvement in LBPI from baseline at week 16; and the chronic low back pain responder index at week 16. PGA of low back pain was assessed using a scale that was adapted from scales developed by Pharmacia (Pfizer Inc, New York, NY) and used previously in a variety of clinical trials in the assessment of osteoarthritis, rheumatoid arthritis, and chronic low back pain [27,48]. The chronic low back pain responder index is a composite score calculated from the LBPI, RMDQ, and PGA of low back pain efficacy measures, with response defined as a reduction of $\geqslant$30% in mean daily average LBPI score from baseline, a decrease of $\geqslant$30% in PGA of low back pain from baseline, and no worsening (increase) in RMDQ score from baseline [5,47]. All concomitant treatments for chronic low back pain (including NSAIDs, selective cyclooxygenase-2 [COX-2] inhibitors, antidepressants, anticonvulsants, corticosteroids, and muscle relaxants) were prohibited throughout the duration of the study. In the event of inadequate pain relief for chronic low back pain during the double-blind treatment period, patients were allowed to take rescue medication (acetaminophen; up to 3000 mg/d, up to 3 days/week) beginning at the randomization visit. Patients recorded rescue medication usage daily using the IVRS. Patients were required to discontinue rescue medication at least 24 hours before any scheduled study visit.