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Nerve safety of tanezumab, a nerve growth factor inhibitor for pain treatment

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ABSTRACT

Objective: To evaluate peripheral nerve safety and clinical efficacy of tanezumab in patients with painful osteoarthritis.
Methods: Patients received intravenous tanezumab 5 mg, tanezumab 10 mg, or placebo every 8 weeks for 24 weeks. Neurological safety was evaluated via a composite score (nerve conduction attributes and heart rate variability with deep breathing; $\Sigma 5NC + HR_{db}$), intraepidermal nerve fiber (IENF) density, and clinical assessments. Efficacy and general safety were also evaluated.
Results: The study was stopped prematurely by an FDA partial clinical hold (joint safety issues in other studies). Differences in change from baseline to Week 24 in $\Sigma 5NC + HR_{db}$ were not significant. Tanezumab 5 mg vs placebo exceeded the prespecified clinically important difference using last observation carried forward imputation, but not with observed data or when patients with evidence of neuropathy at baseline were excluded. No significant differences were found in individual nerve conduction measures. No treatment exceeded the prespecified clinically important decrease in IENF. Tanezumab resulted in significant improvement in pain, physical function, and Patient's Global Assessment. Safety was similar to previous tanezumab clinical trials.
Conclusions: Tanezumab has a modulating effect on pain, does not appear to increase neurological safety signals, and offers a potentially promising, novel approach in treatment of pain.

1. Introduction

Nerve growth factor (NGF) has been of great interest, initially from a fundamental biological standpoint [1] and more recently for its potential role in human therapeutics. In the prenatal and early post-natal periods, NGF is required for survival of certain peripheral sympathetic and nociceptive neuronal populations [2]. In adult mammals, NGF is not required for survival of these neuronal populations and the role of NGF shifts to modulation of nociceptive neuronal activity [3]. From a therapeutic standpoint, NGF was evaluated as a treatment for diabetic sensorimotor polyneuropathy but failed to demonstrate efficacy [4]. Instead, NGF administration resulted in long-lasting mechanical and thermal hyperalgesia, allodynia, hypersensitivity, and generalized muscle pain [4–6].

NGF is released by inflammatory and mast cells following injury, binds tropomyosin-related kinase A (trkA; high affinity) and p75 (low affinity) receptors, and facilitates pain signaling (Fig. 1) [3]. Elevated NGF levels are found in serum of patients with chronic pain and within injured or inflamed tissue [4,6–17].

Recently, pain therapy development has focused on selective NGF inhibition. Tanezumab, a humanized immunoglobulin G type 2

Abbreviations: 5 HT, serotonin; 5NC, 5 individual NC tests; ASIC3, acid-sensing ion channel 3; BDNF, brain-derived neurotrophic factor; BR2, bradykinin receptor; CB1, cannabinoid receptor 1; CGRP, calcitonin gene-related peptide; CI, confidence interval; CMAP, compound muscle action potential; DRG, dorsal root ganglia; H+, proton; HRdb, heart rate deep breathing; IENF, intraepidermal nerve fiber; IPAP, Initial Pain Assessment Period; ITT, intent-to-treat; IV, intravenous; LLF, lower limb function; LOCF, last observation carried forward; LSM, least squares mean; MNCV, motor nerve conduction velocity; MNDL, motor nerve distal latency; NaV 1.8, voltage-gated sodium channel 1.8; NC, nerve conduction; nd, normal deviate; NGF, nerve growth factor; NIS, neuropathy impairment score; NIS-R, NIS muscle stretch reflexes; NIS-S, NIS sensation; NIS-W, NIS weakness; NRS, numeric rating scale; NSC, neuropathy symptoms and change; NV, neurology visit; OA, osteoarthritis; P2X3, purinergic 2X receptor 3; p75, low-affinity p75 neurotrophin receptor; PGA, Patient's Global Assessment; PPAS, per-protocol analysis set; RV, recruitment site visit; SD, standard deviation; SE, standard error; SNAP, sensory nerve action potential; SP, substance P; trkA, tropomyosin-related kinase A; TrpA1, transient receptor potential ankyrin subtype 1; TrpV1, transient receptor potential vanilloid 1; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

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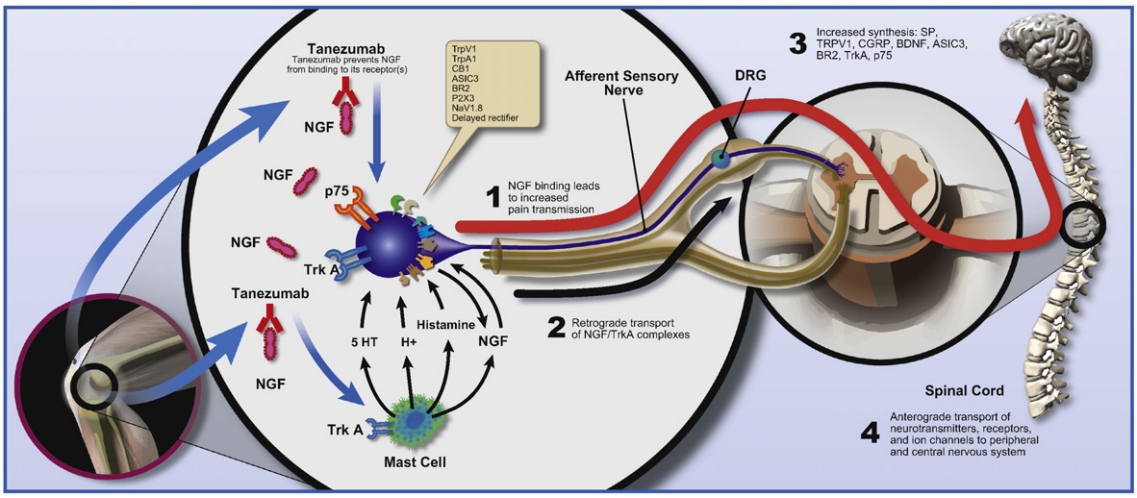

Fig. 1. Schematic showing the pathways and neurotransmitters modulated by NGF in pain perception. 5 HT, serotonin; ASIC3, acid-sensing ion channel 3; BDNF, brain-derived neurotrophic factor; BR2, bradykinin receptor; CB1, cannabinoid receptor 1; CGRP, calcitonin gene-related peptide; DRG, dorsal root ganglia; H^+, proton; NaV 1.8, voltage-gated sodium channel 1.8; NGF, nerve growth factor; P2X3, purinergic 2X receptor 3; p75, low-affinity p75 neurotrophin receptor; SP, substance P; TrkA, tropomyosin-related kinase A receptor; TrpA1, transient receptor potential ankyrin subtype 1; TrpV1, transient receptor potential vanilloid 1.

monoclonal antibody, has high selectivity and specificity for NGF [18]. By tightly binding NGF, tanezumab prevents interaction between NGF and its receptors, thereby disrupting ongoing pain signaling [3,10,18].

The potential clinical utility of tanezumab is supported by studies in patients with osteoarthritis (OA), chronic low back pain, interstitial cystitis, and diabetic peripheral neuropathy [19–29]. Tanezumab provided significant improvements in pain, physical function, and global assessment, although some patients reported transient abnormalities in cutaneous sensation (commonly, paresthesia or hypoesthesia or, in some instances, burning pain or allodynia). An important question has been whether NGF inhibition is safe for the adult human peripheral nervous system.

This study was conducted to evaluate neurological safety and clinical efficacy of tanezumab in a human pain state (painful OA). Neurological safety assessments included evaluation of nerve conduction (NC), autonomic nerve, and cutaneous innervation parameters via well-accepted approaches used extensively to evaluate neuropathy and neuropathic disease progression [30,31].

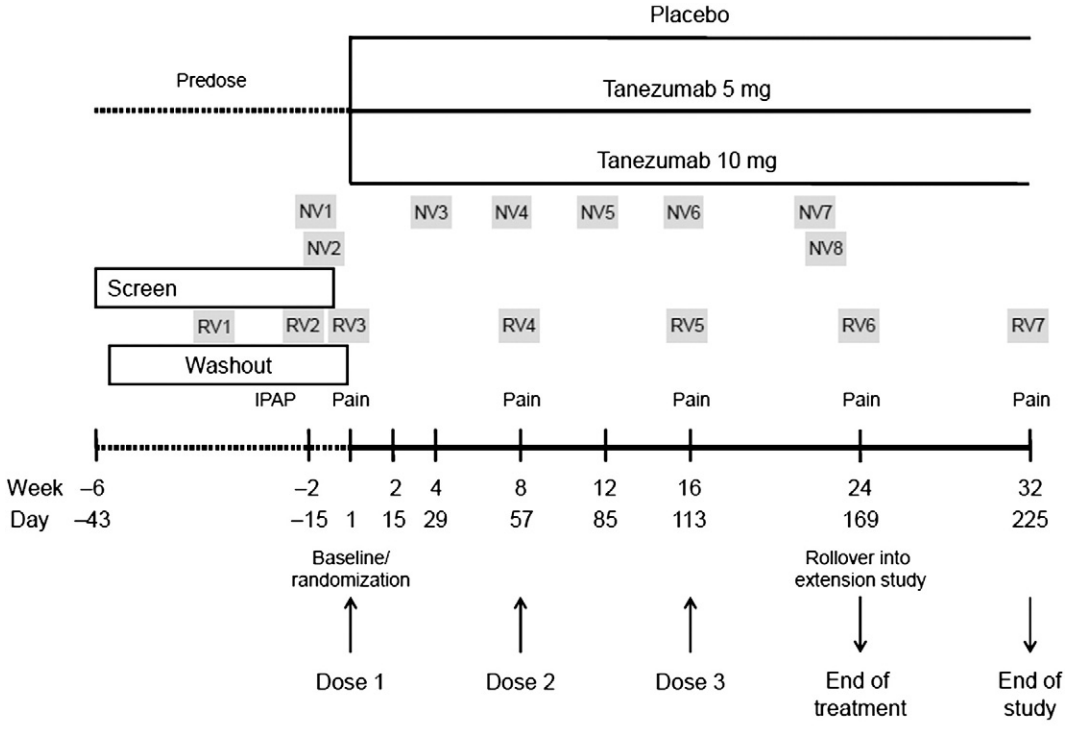

Fig. 2. Study design.