# Tanezumab Reduces Pain in Women with Interstitial Cystitis/Bladder Pain Syndrome and Patients with Nonurological Associated Somatic Syndromes

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**Abbreviations and Acronyms**

BPS = bladder pain syndrome
CP = chronic prostatitis
CPPS = chronic pelvic pain syndrome
CPSI = Chronic Prostatitis Symptom Index
HADS-A = Hospital Anxiety and Depression Scale-Anxiety
HADS-D = Hospital Anxiety and Depression Scale-Depression
IC = interstitial cystitis
ICSI = Interstitial Cystitis Symptom Index
IV = intravenous
LS = least squares
NGF = nerve growth factor
NRS = numeric rating scale
SC = subcutaneous
UCPPS = urological chronic pelvic pain syndromes

**Purpose:** We performed pooled analyses from 3 small, clinical trials of tanezumab in patients with urological chronic pelvic pain, including chronic prostatitis/chronic pelvic pain syndrome and interstitial cystitis/bladder pain syndrome, to identify patient subpopulations more likely to benefit from tanezumab treatment.

**Materials and Methods:** Pooled analyses included data from 208 patients with interstitial cystitis/bladder pain syndrome or chronic prostatitis/chronic pelvic pain syndrome randomized to placebo (104, 65 [62.5%] female) or tanezumab (104, 63 [60.6%] female) who received 1 dose or more of study medication. Data on tanezumab were from study A4091010 (interstitial cystitis/bladder pain syndrome) on 200 μg/kg intravenous, study A4091019 (chronic prostatitis/chronic pelvic pain syndrome) on 20 mg intravenous and study A4091035 (interstitial cystitis/bladder pain syndrome) on 20 mg subcutaneous. Primary study end points were evaluated using analysis of covariance with gender, study and baseline pain as covariates.

**Results:** For pooled analyses least squares mean (SE) change from baseline in 24-hour pain intensity vs placebo was −0.60 (0.24, 90% CI −0.99, −0.20) overall and −0.99 (0.32, p=0.002) and −0.17 (0.36, p=0.650) for females and males, respectively. The improvement in pain intensity was significant (p=0.011) for patients with symptoms suggesting the concomitant presence of nonurological associated somatic syndromes but not for those with pelvic pain symptoms only (p=0.507).

**Conclusions:** Women with interstitial cystitis/bladder pain syndrome and patients with symptoms suggesting the concomitant presence of nonurological associated somatic syndromes were more likely to experience significant pain reduction with tanezumab than with placebo therapy. In contrast, no difference was reported in response between tanezumab and placebo therapy for men with chronic prostatitis/chronic pelvic pain syndrome symptoms only.

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UROLOGICAL chronic pelvic pain syndromes, including chronic prostatitis/chronic pelvic pain syndrome and interstitial cystitis/bladder pain syndrome, are debilitating and difficult to treat.[1] While current therapies may prove effective in individual patients, many treatments lack evidence from randomized clinical trials demonstrating efficacy in patients with UCPPS.[2–5] Tolerability, safety and dependence concerns also exist for a number of therapies.[6,7] In addition, although some evidence indicates clinical and pathogenic similarities between male IC/BPS and CP/CPPS, clinical trial outcomes vary.[8] Patients with UCPPS express multiple clinical phenotypes, some of which do not respond to a particular therapeutic approach.[9] Thus, better therapies are urgently needed for patients with UCPPS.

Because chronic pelvic pain is a defining characteristic of IC/BPS and CP/CPPS, an approach that targets key modulators of pain signaling may provide better pain relief with a different or improved safety profile. Nerve growth factor is a key modulator of pain perception.[10] NGF inhibition results in reduced pain behaviors in animal models of chronic pelvic pain.[11–13] Elevated NGF levels have been reported in association with UCPPS, including IC/BPS and CP/CPPS.[10,14,15]

Tanezumab is a humanized monoclonal antibody against NGF with high selectivity and specificity.[10,16] Tanezumab prevents NGF from interacting with its receptors, tropomyosin related kinase A (high affinity receptor) and p75 (low affinity receptor).[16] In clinical trials tanezumab reduced pain, and improved function and patient global assessments in chronic pain conditions.[17–20]

Tanezumab was evaluated for the treatment of UCPPS in 3 small clinical trials, including 2 published studies[18,21] and 1 previously unpublished study. Study A4091010 (ClinicalTrials.gov identifier: NCT00601484) evaluated the efficacy and safety of a single dose of tanezumab vs placebo in patients with IC/BPS (clinical diagnosis plus total pelvic pain and urgency/frequency total score of 13 or greater and an ICSI total score of 7 or greater in 62 patients, 89.2% female). Tanezumab showed preliminary efficacy in the treatment of pain associated with IC/BPS.[18] In study A4091019 (ClinicalTrials.gov identifier: NCT00826514) tanezumab marginally improved average daily pain and urinary urgency episode frequency compared with placebo in 62 male patients with CP/CPPS.[21] Study A4091035 (ClinicalTrials.gov identifier: NCT00999518) was a phase IIb study of tanezumab in 200 patients with IC/BPS (85% female).

These studies were small and suggested potential efficacy. Since the studies were similarly designed and used the same primary end point (change from baseline in 24-hour pain intensity), we could combine data using a meta-analytical approach and perform subgroup analyses on pooled data to identify patient populations more likely to benefit from tanezumab.

## MATERIALS AND METHODS

### Study A4091035

Study A4091035 was a randomized, double-blind, placebo controlled, parallel group, dose range finding study (supplementary Appendix 1.1 and supplementary figure 1, http://jurology.com/). Study A4091035 was similar to study A4091010, except some patients received 2 doses of study medication (supplementary Appendix 1.2, http://jurology.com/), the primary end point collection time differed (week 8 in study A4091035 vs week 6), and study A4091035 used subcutaneous dosing, whereas study A4091010 used IV dosing.

Patients were randomized if at visit 2 (randomization) they met the continuation criteria of completed 4 or more average bladder pain scores within any of the 7 days before randomization with a mean average bladder pain intensity score of 4 or greater (on an 11-point NRS), and a mean micturition frequency of 8 or greater per 24 hours during any 3 consecutive days in the previous 7 days. Participants were randomized equally to placebo, 1 mg tanezumab, 2.5 mg tanezumab, 10 mg tanezumab or 20 mg tanezumab SC.

The primary end point was change from baseline to week 8 in average daily pain, measured by an 11-point NRS ranging from 0—no pain to 10—pain as bad as you can imagine, derived from the patient electronic diary (e-diary) (supplementary Appendix 1.3, http://jurology.com/). A key secondary end point was ICSI score. Safety assessments included adverse event monitoring (from time of screening through last clinic visit), vital signs, weight, electrocardiogram and physical examination. If a neurologic adverse event was reported or a clinically significant change noted on examination, the patient was referred to a neurologist for further evaluation.

A preplanned interim analysis was conducted to identify ineffective doses or stop the study for futility based on predefined criteria. This interim analysis was based on change from baseline in mean average daily bladder pain score from baseline to week 8 and performed after 50% of planned patients completed study week 8.

### Pooled Analyses

Overall this analysis included 208 patients randomized to placebo (104) or tanezumab (104; study A4091010—200 μg/kg IV, study A4091019—20 mg IV, study A4091035—20 mg SC groups). The placebo groups were pooled into a single placebo arm and the tanezumab