

Randomized, Double-Blind, Placebo-Controlled Trial of Intraarticular Trans-Capsaicin for Pain Associated With Osteoarthritis of the Knee

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Objective. To assess the efficacy and safety of high-purity synthetic trans-capsaicin (CNTX-4975) in patients with chronic moderate-to-severe osteoarthritis (OA)–associated knee pain.

Methods. In this phase II multicenter double-blind study, patients ages 45–80 years who had stable knee OA were randomized in a 2:1:2 ratio to receive a single intraarticular injection of placebo, CNTX-4975 0.5 mg, or CNTX-4975 1.0 mg. The primary efficacy end point was area under the curve (AUC) for change from baseline in daily Western Ontario and McMaster Universities Osteoarthritis Index pain with walking score (range 0–10, 0 = none and 10 = extreme) through week 12. Secondary efficacy end points included a similar AUC analysis of outcomes in patients treated with CNTX-4975 0.5 mg, and evaluations extending to 24 weeks.

Results. Efficacy was evaluated in 172 patients (placebo group, n = 69; CNTX-4975 0.5 mg group, n = 33; CNTX-4975 1.0 mg group, n = 70). At week 12, greater decreases in the AUC for the pain score were observed with CNTX-4975 in the 0.5 mg and 1.0 mg groups versus placebo (0.5 mg group least squares mean difference [LSMD] –0.79, $P = 0.0740$; 1.0 mg group LSMD –1.6, $P < 0.0001$). Significant improvements were maintained at week 24 in the 1.0 mg group (LSMD –1.4, $P = 0.0002$). Treatment-emergent adverse events were similar in the placebo and CNTX-4975 1.0 mg groups.

Conclusion. In this study, CNTX-4975 provided dose-dependent improvement in knee OA–associated pain. CNTX-4975 1.0 mg produced a significant decrease in OA knee pain through 24 weeks; CNTX-4975 0.5 mg significantly improved pain at 12 weeks, but the effect was not evident at 24 weeks.

INTRODUCTION

Knee osteoarthritis (OA) affects >10% of individuals ages 60 years and older, and current treatment options for pain control are considered inadequate (1,2). Management includes nonpharmacologic and pharmacologic options, many of which have at least short-term benefits (3,4). Intraarticular therapies, including injections of viscosupplements and glucocorticoids, may have limited efficacy (3–6). In a randomized clinical trial, intraarticular injection of glucocorticoids every 12 weeks for 2 years was associated with significantly greater loss of cartilage volume compared to placebo, with no significant difference in knee pain (6). Whether the loss of cartilage volume has clinical significance is unknown.

Pharmacologic treatments have been recommended for properly selected patients, but they carry risks of adverse effects involving the gastrointestinal, cardiovascular, renal, and central nervous systems (3). The presence of comorbidities may make individuals with knee OA more susceptible to these adverse effects, thus limiting treatment options (3,7). A total knee joint replacement often provides longer-term benefits. However, this surgery entails serious risks, and many patients continue to have pain and disability following surgery (7,8). In addition, many patients are not candidates for major surgery (8). Therefore, there is an unmet need for effective therapies to mitigate risks and provide effective pain management.

Capsaicin, the pungent ingredient in chili peppers, is a potent agonist for the transient receptor potential cation channel

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subfamily V member 1 (TRPV1) (9). TRPV1 is a nonspecific cation channel that opens with exposure to heat, acid, and certain fatty acids (10). Within the peripheral nervous system, this channel is selectively expressed on the terminals of nociceptors (pain sensory fibers). After a brief period of activation, capsaicin induces a long-term desensitization of nociceptors related to calcium influx into the nociceptive nerve terminals (A δ and C fibers). This desensitization is likely due to a reversible retraction of innervation (9,11). Based on studies of the skin, it is known that the nociceptors grow back during a period of weeks to months (12,13). In the meantime, there is a profound attenuation of pain sensibility but not of other sensory functions (11). A topical formulation of capsaicin has been approved by the US Food and Drug Administration for the treatment of postherpetic neuralgia (14,15).

In this study, the strategy was to take advantage of the selective long-term analgesic effects of capsaicin to address the moderate-to-severe pain associated with OA of the knee. An injectable form of highly purified trans-capsaicin, CNTX-4975, was developed using proprietary technology. A single intraarticular injection of CNTX-4975 was expected to provide rapid-onset long-term analgesia, with a duration of effect commensurate with the time required for the nociceptors to regenerate. Because trans-capsaicin at a concentration needed to affect the nociceptors is confined to the joint, the effects were expected to be restricted to within the joint. The elimination half-life of CNTX-4975 is <4 hours (data on file; Centrexion Therapeutics Corp.), which establishes a favorable ratio of pharmacokinetic and pharmacodynamic properties, namely, a brief systemic exposure with the prospect of long-term clinical benefit.

We report findings from the TRIUMPH study, a phase IIb randomized, double-blind, placebo-controlled, dose-ranging trial (ClinicalTrials.gov identifier: NCT02558439) designed to evaluate the efficacy and safety of a single intraarticular injection of CNTX-4975 for up to 24 weeks in patients with chronic, stable, moderate-to-severe OA knee pain in whom previous treatment was not successful.

PATIENTS AND METHODS

Patient characteristics. Patients were enrolled between August 2015 and April 2016 at 22 sites in the US. Eligible patients were adults ages 45–80 years who had a body mass index (BMI) of ≤ 45 kg/m², radiographic evidence of chronic OA (Kellgren/Lawrence [K/L] grade 2–4) (16) in the index knee, moderate-to-severe pain in the index knee that was stable for ≥ 2 months prior to screening, and a mean pain score of 5–9 (range 0–10, 0 = none and 10 = extreme) at screening and baseline (day 1) according to the question in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (17) that addresses pain with walking. The mean pain score in the contralateral knee had to be ≤ 3 .

Additionally, patients must have had an inadequate response, an adverse event resulting in discontinuation of prior treatment, or

an absolute or relative contraindication (based on product labeling) to what would otherwise be standard-of-care treatment(s). Prior standard-of-care may have included ≥ 1 of the following: systemic nonsteroidal antiinflammatory drugs (NSAIDs) (oral, rectal, or injection), opioid analgesics (oral or transdermal), intraarticular glucocorticoid, or intraarticular hyaluronic acid.

Exclusion criteria included pain in the index knee from a joint disease other than OA; pain in the nonindex knee rated at >3 according to the WOMAC pain with walking score; topical capsaicin, glucocorticoid injection, or intraarticular viscosupplementation in the index knee within 90 days of screening; joint replacement surgery at any time or open surgery on the index knee during the preceding 12 months; arthroscopic surgery on the index knee within 3 months of screening; non-OA chronic pain that required use of analgesic medications (e.g., pregabalin, duloxetine); current use of opioids for any condition other than OA of the index knee (maximum dose of 15 mg/day of hydrocodone [or equivalent]); secondary OA of the knee due to traumatic injury; significant current or past instability (e.g., cruciate ligament tear or rupture or previous repair) or malalignment (>10 degrees varus or valgus) of the index knee; documented history of neuropathic arthropathy or finding of bony fragmentation in the index knee with imaging; regular use of anticoagulant blood thinners (except low-dose aspirin or clopidogrel); or ulcer or open wound anywhere on the index knee.

Study design. Patients were randomly assigned in a 2:1:2 ratio to 1 of 3 treatment groups (placebo, CNTX-4975 0.5 mg, or CNTX-4975 1.0 mg) and stratified for balance across treatment groups by K/L grade (2–3 and 4 [$\leq 10\%$ had grade 4]) and BMI (<30 kg/m² and ≥ 30 kg/m²). Randomization schedules were computer-generated using a permuted block algorithm that randomly allocated study drug to the randomization numbers. The numbers generated were assigned sequentially using a central interactive response system as patients entered the study. No one involved in study conduct had access to the randomization schedule before official unblinding of assignments. A central reader assessed all radiographs at baseline to determine the K/L grade. All patients, investigators, and study personnel involved in the conduct of the study (including data management personnel and the sponsor) were blinded with regard to treatment assignment, except for a randomization statistician and programmer from the contract research organization who had access to randomization code, a pharmacist who prepared study drug and provided a labeled syringe of masked study drug product for administration, and a pharmacy clinical research associate.

This study consisted of a screening period, a single treatment day (day 1), and a 24-week follow-up period. At the investigators' discretion, patients could be premedicated using an opioid, NSAID, or local anesthetic (e.g., ethyl chloride, topical or subcutaneous lidocaine), with a maximum of 2 premedications. After 15 minutes of joint cooling with a wrap placed around the knee,

patients received 15 ml of intraarticular 2% lidocaine, without epinephrine, for the purpose of (in order of importance): 1) achieving the targeted concentration of capsaicin, 2) improving distribution of capsaicin within the joint, and 3) decreasing the initial pain associated with injection. Cooling was reapplied for 30 minutes and then the study drug was provided in a vehicle consisting of polyethylene glycol 300, which was diluted to 30% (volume/volume) at the point of care with sterile water for injection. A single intraarticular injection (4 ml) of placebo (vehicle control), CNTX-4975 0.5 mg, or CNTX-4975 1.0 mg was administered. The CNTX-4975 and placebo injections were identical in appearance and viscosity. Injection into the joint was confirmed by ultrasound and/or joint fluid aspiration. Cooling was removed for injection and then reapplied immediately for 30 minutes–1 hour. Patients were advised not to take a hot bath or shower or to expose the injected knee to external heat within 24 hours after the injection.

Throughout the study, patients were permitted to take oral rescue medications (see Supplementary Table 1, on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40894/abstract>) for OA pain in the index knee. Rescue medication was not permitted within 12 hours preceding any planned posttreatment study visit. Use of topical medication for OA knee pain during the trial was not permitted. Physical therapy was not permitted within 30 days prior to screening and throughout the study.

Patients used an interactive web-based response system to record index knee pain felt with walking during the previous 24 hours. Patients rated their pain daily from baseline to week 12 and weekly from week 12 to 24. In-clinic assessments were conducted at weeks 4, 8, 12, 16, and 24, and telephone assessments were conducted on day 3 and at weeks 14, 18, and 22.

This study was conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation Guidelines for Good Clinical Practice, and applicable regulations of the country in which the study was conducted. The protocol was approved by the institutional review board (IRB) at each academic center, or a central IRB (Sterling IRB, Atlanta, GA) at nonacademic sites that were able to have a central review, prior to study initiation. Written informed consent was provided at the screening visit, before study-related procedures were initiated.

Efficacy and safety evaluations. The primary efficacy end point was area under the curve (AUC) for the change from baseline through week 12 in daily WOMAC pain with walking scores in patients treated with CNTX-4975 1.0 mg versus placebo. Secondary efficacy end points included a similar AUC analysis of scores in patients treated with CNTX-4975 0.5 mg and an evaluation of 24-week outcomes. Time points for the primary and secondary efficacy variables were changed from week 4 to week 12 in a protocol amendment to better address the study objectives using data collected for a longer period of time. Week 12 was selected because it is considered to be a criterion for considering

whether a therapy addresses “chronic” pain (18). This amendment was made prior to database lock and unmasking of the data.

Prespecified exploratory efficacy analyses of both doses of CNTX-4975 versus placebo were performed to ascertain the mean changes from baseline in WOMAC scores addressing pain with walking (range 0–10), knee stiffness (range 0–20), and physical function (range 0–170) at each visit through week 24, and to assess the frequency of use of rescue medication for the index knee pain throughout the study period. Additional analyses included the Patient Global Impression of Change (PGIC) (7-point scale ranging from very much improved to very much worse) (19) at each postinjection visit, and an adapted Patient-Specific Functional Scale (PSFS) to assess functional activity of the index knee (range 0–10, 0 = able to perform activity and 10 = unable to perform the activity at the same level as before injury or problem) (20).

Safety assessments included monitoring for treatment-emergent adverse events (TEAEs), serious adverse events, and laboratory abnormalities. Procedural pain ratings (range 0–4, 0 = none and 4 = severe) were obtained at different intervals up to 2 hours postinjection of study drug. The number needed to treat (NNT), defined as the average number of patients treated to prevent 1 unfavorable outcome, and the number needed to harm (NNH), defined as the number of patients treated before 1 patient has an adverse event beyond what would occur with placebo, were assessed at 12 and 24 weeks.

Statistical analysis. For an effect size of 0.45, a sample size of 157 evaluable patients (63 each in the placebo and CNTX-4975 1.0 mg groups and 31 in the CNTX-4975 0.5 mg group) was needed to achieve 80% statistical power for a significant dose–placebo comparison using a 2-sided test at the 10% significance level (prespecified alpha level, $P \leq 0.10$). Assuming a 10% dropout rate, the initial planned enrollment was 173 patients, with 69 each in the placebo and CNTX-4975 1.0 mg groups and 35 in the CNTX-4975 0.5 mg group. For consistency with the method of sample size estimation and the study’s power to detect a statistical difference in the primary end point, all analyses were performed using a prespecified alpha level of 0.10, with corresponding 90% confidence intervals (90% CIs).

Demographics, baseline characteristics, and safety end points were analyzed in the safety population, which included all patients who received any study medication. All efficacy end points were analyzed in the modified intent-to-treat population, which included all randomized patients who had ≥ 1 postbaseline efficacy assessment.

Primary and secondary efficacy end points were analyzed by analysis of covariance, with treatment as the main effect and with sex, pooled site, baseline K/L grade, baseline BMI, and baseline WOMAC knee pain with walking score as covariates. AUCs for pain rating values were converted to the 0–10 pain rating scale. The AUC was calculated using a time-weighted average standardized by length of time in the study for each patient through

week 12 or 24, depending on the end point. Standardization was performed by dividing a patient's total AUC by their time in the study, which allowed comparison of average daily pain for both completers and noncompleters to avoid attributing a low AUC value to patients who discontinued the study early. This method was also used to calculate a rescue-adjusted AUC for daily WOMAC pain with walking scores, removing scores from days when rescue medication was used. In the event of missing pain scores, the difference in time was considered in the calculation. If there were days missing in a study week, the calculated average for that study week included only nonmissing values; if no values were recorded for the study week, the average weekly WOMAC score for that study week was recorded as missing.

Exploratory efficacy end points of mean changes from baseline in WOMAC scores (for pain with walking, knee stiffness, and physical function) and PSFS scores were analyzed using a mixed model for repeated measures (MMRM). The MMRM included the same covariates as the primary analysis model. Study week and treatment by study week interaction were included as categorical variables. An unstructured within-patient covariance matrix was used. Least squares mean difference (LSMD) and 90% CIs were

provided for each study week by treatment group. This analysis included all available data on patients who completed the study and those who discontinued early. In this analysis population, loss to follow-up was minimal, as few patients in each treatment group discontinued the study early and none discontinued because of an adverse event.

A responder analysis was performed for the PGIC, in which patients with significant clinical improvement (very much improved or much improved) in the index knee were compared to patients in all other categories. Proportions were compared between each CNTX-4975 treatment group and the placebo group using Pearson's chi-square test or Fisher's exact test. All analyses were performed using SAS version 9.3 or later. For safety assessments, no formal inferential statistical analyses were performed.

RESULTS

Patients. A total of 175 eligible patients were enrolled and included in the safety population (placebo, $n = 70$; CNTX-4975 0.5 mg, $n = 34$; CNTX-4975 1.0 mg, $n = 71$) (Figure 1). All patients had radiographic evidence of knee OA (K/L grade 2–4,

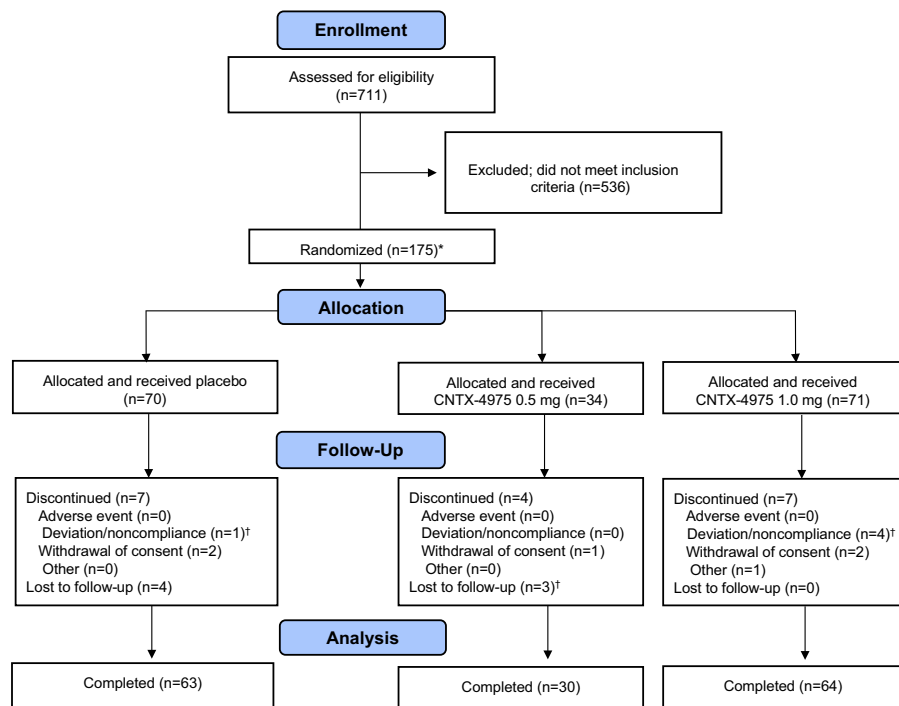


Figure 1. Disposition of the study patients. Reasons for exclusion at screening included Kellgren/Lawrence grade outside of range 2–4 (320 patients [60%]); inability to understand and follow study requirements, including diary entry via computer (64 [12%]); failure to meet the requirement for moderate-to-severe pain (29 [5%]); history of allergic reaction to the planned local anesthesia regimens, polyethylene glycol, or capsaicin (19 [3%]); baseline and screening scores outside of a 5–9 range on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain with walking assessment (12 [2%]); >2-point difference in WOMAC pain with walking score between screening and baseline (11 [2%]); prior participation in an ALGRX4975 or CNTX-4975 study (10 [2%]); and positive urine drug screen or active/past substance use disorder within prior year (10 [2%]). Other inclusion/exclusion criteria each contributed $\leq 1\%$ to exclusions at screening. * = Number of patients in the safety analysis. † Three patients were excluded from the efficacy analysis (modified intent-to-treat population, $n = 172$). One patient was excluded (prior to unblinding) due to deviation/noncompliance, as this patient was injected at 2 different study sites (CNTX-4975 1.0 mg, $n = 1$; placebo, $n = 1$). A third patient was lost to follow-up in the CNTX-4975 0.5 mg group.

as determined by a central reader [radiologist]). Three patients were excluded from the efficacy analysis prior to unblinding: 1 patient entered the study at 2 centers, received 2 injections, and was initially counted as 2 separate patients, and 1 patient received study medication but left the study site and could not be contacted. Thus, 172 patients were included in the modified intent-to-treat population (placebo, $n = 69$; CNTX-4975 0.5 mg, $n = 33$; CNTX-4975 1.0 mg, $n = 70$). A total of 157 patients (90%) completed the study (Figure 1). Demographics and baseline disease characteristics are summarized in Table 1.

Efficacy. In the placebo group, the CNTX-4975 0.5 mg group, and the CNTX-4975 1.0 mg group, the mean baseline scores for pain with walking were 7.4, 7.2, and 7.2, respectively. In the primary AUC efficacy analysis, the reduction in pain scores from baseline through week 12 was significantly greater in the CNTX-4975 1.0 mg group compared to placebo (LSMD -1.6 [90% CI $-2.2, -1.0$], $P < 0.0001$; mean \pm SD change -4.1 ± 2.1 versus -2.6 ± 2.2) (Figure 2). Based on the primary end point and the pooled SD, the Cohen's d standardized effect was calculated as 0.68. A smaller but significant improvement versus placebo was observed with the 0.5 mg dose (LSMD -0.8 [90% CI $-1.5, -0.06$], $P = 0.07$; mean \pm SD change -3.3 ± 2.1). The AUC for change from baseline through week 24 (same efficacy measure as

week 12) showed significant improvements with the CNTX-4975 1.0 mg dose versus placebo (LSMD -1.4 [90% CI $-1.9, -0.77$], $P < 0.001$; mean \pm SD change -3.9 ± 2.2 versus -2.7 ± 2.2), but not with the CNTX-4975 0.5 mg dose (LSMD -0.6 [90% CI $-1.3, 0.15$], $P = 0.19$; mean \pm SD change -3.2 ± 1.9) (Figure 2).

In the analysis of the primary end point adjusted for use of rescue medications, the reduction in rescue-adjusted WOMAC pain with walking scores from baseline through week 12 was significantly greater with CNTX-4975 1.0 mg versus placebo (LSMD -0.9 [90% CI $-1.5, -0.3$], $P = 0.01$; mean \pm SD change -2.75 ± 2.61 versus -1.95 ± 2.16), consistent with results for the primary end point. More rescue medication was taken in the placebo group and the CNTX-4975 0.5 mg group than in the CNTX-4975 1.0 mg group. For patients who took acetaminophen, the mean per patient total dose during the 12 weeks was 21,006 mg in the placebo group ($n = 50$) compared to 13,392 mg in the CNTX-4975 1.0 mg group ($n = 47$). The most commonly taken NSAID was ibuprofen. The mean per patient total ibuprofen dose was greater in the placebo group (9,403 mg; $n = 18$) than in the CNTX-4975 1.0 mg group (7,446 mg; $n = 13$).

In the MMRM analysis, significant improvements in the WOMAC pain with walking score with CNTX-4975 0.5 mg were demonstrated, compared to placebo, at week 12 (LSMD -0.9 [90% CI $-1.7, -0.03$], $P = 0.09$; mean \pm SD change -3.8

Table 1. Demographics and baseline disease characteristics*

	Placebo ($n = 70$)	CNTX-4975 0.5 mg ($n = 34$)	CNTX-4975 1.0 mg ($n = 71$)	Total ($n = 175$)
Age, mean \pm SD years	61 \pm 9	60 \pm 6	59 \pm 8	60 \pm 8
Female	64	59	63	63
BMI				
<30 kg/m ²	33	38	30	33
\geq 30 kg/m ²	67	62	70	67
Index knee				
Right	46	38	51	46
Left	54	62	49	54
K/L grade (index knee)†‡				
2	36	27	45	38
3	53	65	47	53
4	11	9	9	10
WOMAC pain with walking scores§				
Moderate (>4–7)	34	38	47	40
Severe (>7–10)	63	59	54	58
Missing¶	3	3	0	2

* Except where indicated otherwise, values are the percent of patients. BMI = body mass index; K/L = Kellgren/Lawrence; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

† Range 0 (no radiographic features of osteoarthritis are present) to 4 (large osteophytes, marked joint space narrowing, severe sclerosis, and definite bony deformity).

‡ Chi-square test indicated no association ($P = 0.4007$) between treatment and baseline severity.

§ Range 0 (none) to 10 (extreme).

¶ Patients did not have 7 days of response data from baseline to randomization. Calculated baseline value required 7 of 14 days of diary data to calculate baseline pain with walking on a flat surface but did not require a diary entry at baseline.

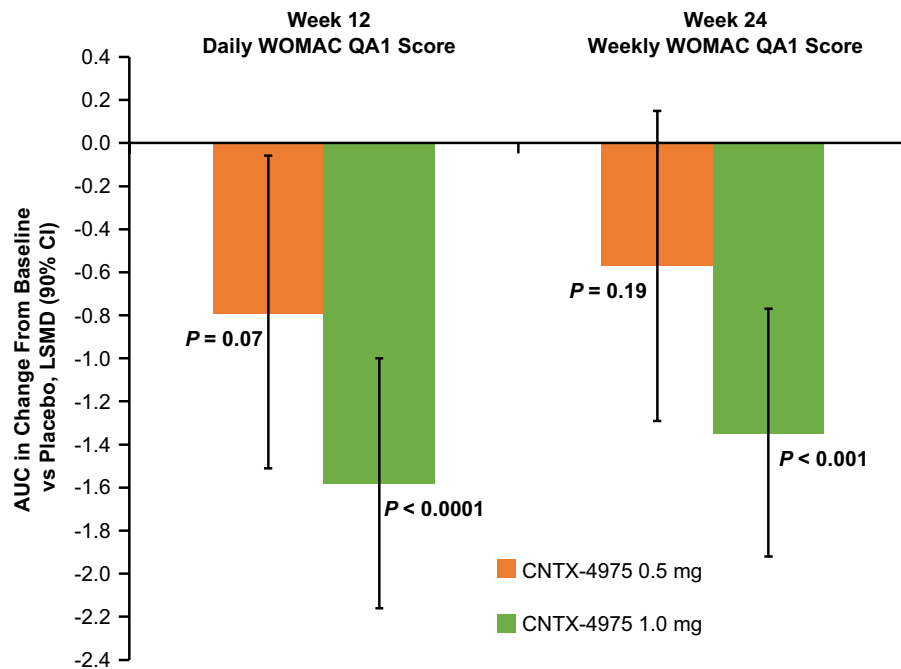


Figure 2. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain with walking on a flat surface (QA1) scores. Standardized area under the curve (AUC), normalized to the 0–10 rating scale, for change from baseline with CNTX-4975 versus placebo in daily pain with walking scores through week 12 and in average weekly pain with walking scores through week 24 were evaluated. Analysis of covariance was performed in the modified intent-to-treat population. LSMD = least squares mean difference; 90% CI = 90% confidence interval.

± 2.5 versus -3.0 ± 2.5), but not at week 24 (LSMD -0.5 [90% CI $-1.5, 0.5$], $P = 0.41$; mean \pm SD change -3.6 ± 2.0 versus -3.0 ± 2.8). At the CNTX-4975 1.0 mg dose, significant divergence from placebo was evident at week 12 (LSMD -1.5 [90% CI $-2.2, -0.8$], $P < 0.001$; mean \pm SD change -4.4 ± 2.6 versus -3.0 ± 2.5) and at week 24 (LSMD -0.9 [90% CI $-1.6, -0.1$], $P = 0.07$; mean \pm SD change -3.3 ± 2.6 versus -3.0 ± 2.8) (Table 2). A significant improvement was evident with the 1.0 mg dose as early as 1 week after treatment (Figure 3). The 1.0 mg dose was associated with significantly improved WOMAC knee stiffness scores (LSMD -2.5 [90% CI $-3.8, -1.2$], $P = 0.001$; mean \pm SD change -6.7 ± 5.2 versus -4.8 ± 6.6) and knee function scores (LSMD -18.3 [90% CI $-28.6, -7.9$], $P = 0.004$; mean \pm SD change -59.3 ± 39.8 versus -46.2 ± 46.0) versus placebo at week 12 (MMRM) (Table 2 and Supplementary Figures 1 and 2, <http://onlinelibrary.wiley.com/doi/10.1002/art.40894/abstract>). Numerical improvements in the CNTX-4975 1.0 mg group versus placebo were observed at week 24 for knee stiffness (LSMD -1.2 [90% CI $-2.5, 0.1$], $P = 0.14$; mean \pm SD change -5.7 ± 5.5 versus -5.1 ± 6.2) and for knee function (LSMD -7.2 [90% CI $-18.3, 3.8$], $P = 0.28$; mean \pm SD change -51.6 ± 44.8 versus -49.4 ± 49.2). The improvements in scores for these WOMAC questions at week 12 with CNTX-4975 0.5 mg versus placebo were not significant.

Based on the PGIC responder analysis, >50% of patients treated with either dose of CNTX-4975 reported significant

improvement (much improved or very much improved) in the index knee at each follow-up visit. At no point did >50% of patients treated with placebo report comparable improvement. Improvements at weeks 4, 8, 12, and 16 in patients receiving the 1.0 mg dose were statistically significant at the prespecified alpha level of ≤ 0.1 versus placebo; improvements at 24 weeks did not reach statistical significance (Supplementary Table 2, <http://onlinelibrary.wiley.com/doi/10.1002/art.40894/abstract>). At weeks 12 and 16, patients achieved significant improvement with CNTX-4975 0.5 mg versus placebo ($P < 0.10$).

On the PSFS, functional activity of the index knee was significantly improved with CNTX-4975 1.0 mg versus placebo at each follow-up visit from week 4 through week 16 ($P < 0.10$ at each time point) (Supplementary Table 3, <http://onlinelibrary.wiley.com/doi/10.1002/art.40894/abstract>). Changes in PSFS score were not significantly different between CNTX-4975 0.5 mg and placebo treatment at any time point.

The NNT to determine $\geq 50\%$ pain improvement was calculated using data from the CNTX-4975 1.0 mg and placebo groups in the modified intent-to-treat population. The NNT at weeks 12 and 24 was 3.6 and 10.3 patients, respectively.

Safety. Ten patients (all at 1 site) were premedicated with ibuprofen prior to injection of the study drug. No other premedications were used. TEAEs were reported by 30%, 47%, and 30% of patients in the placebo, CNTX-4975 0.5 mg, and CNTX-4975 1.0 mg groups, respectively, and were generally

Table 2. Mean change from baseline in weekly average WOMAC scores at weeks 12 and 24*

End point†	Placebo (n = 69)		CNTX-4975 0.5 mg (n = 33)		CNTX-4975 1.0 mg (n = 70)	
	Week 12	Week 24	Week 12	Week 24	Week 12	Week 24
WOMAC pain with walking on a flat surface score‡						
Baseline score, mean ± SD	7.4 ± 0.9		7.2 ± 1.1		7.2 ± 1.2	
Change from baseline, mean ± SD	-3.0 ± 2.5	-3.0 ± 2.8	-3.8 ± 2.5	-3.6 ± 2.0	-4.4 ± 2.6	-3.3 ± 2.6
LSM ± SE	-2.9 ± 0.4	-2.9 ± 0.4	-3.8 ± 0.5	-3.4 ± 0.5	-4.4 ± 0.4	-3.8 ± 0.4
LSMD vs. placebo (90% CI)			-0.9 (-1.7, -0.0)§	-0.5 (-1.5, 0.5)	-1.5 (-2.2, -0.8)¶	-0.9 (-1.6, -0.1)§
WOMAC knee stiffness score#						
Baseline score, mean ± SD	13.1 ± 3.8		12.9 ± 3.3		12.3 ± 3.8	
Change from baseline, mean ± SD	-4.8 ± 6.6	-5.1 ± 6.2	-5.7 ± 5.0	-5.3 ± 4.5	-6.7 ± 5.2	-5.7 ± 5.5
LSM ± SE	-4.4 ± 0.7	-4.8 ± 0.7	-5.2 ± 0.9	-4.6 ± 0.9	-6.9 ± 0.7	-6.0 ± 0.7
LSMD vs. placebo (90% CI)			-0.8 (-2.4, 0.8)	0.3 (-1.4, 1.9)	-2.5 (-3.8, -1.2)¶	-1.2 (-2.5, 0.1)
WOMAC physical function score**						
Baseline score, mean ± SD	114.1 ± 24.7		108.4 ± 24.2		106.9 ± 27.9	
Change from baseline, mean ± SD	-46.2 ± 46.0	-49.4 ± 49.2	-49.3 ± 34.6	-45.7 ± 35.5	-59.3 ± 39.8	-51.6 ± 44.8
LSM ± SE	-46.3 ± 6.0	-50.4 ± 6.2	-51.3 ± 7.4	-46.3 ± 7.8	-64.5 ± 6.0	-57.6 ± 6.2
LSMD vs. placebo (90% CI)			-5.0 (-17.9, 7.9)	4.1 (-9.7, 17.9)	-18.3 (-28.6, -7.9)††	-7.2 (-18.3, 3.8)

* WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; LSMD = least squares mean difference; 90% CI = 90% confidence interval.

† Mixed model for repeated measures in modified intent-to-treat population. Negative numbers reflect a reduction in pain and stiffness and an improvement in function.

‡ Range 0 (none) to 10 (extreme).

§ $P < 0.10$ versus placebo.

¶ $P \leq 0.001$ versus placebo.

Sum of the 2 stiffness responses (range 0–20).

** Sum of the 17 function responses (range 0–170).

†† $P \leq 0.01$ versus placebo.

mild (19%, 29%, and 20%) or moderate (11%, 18%, and 10%) in severity (Table 3). On day 1, TEAEs were reported by 2 patients (3%), 1 patient (3%), and 3 patients (4%), respectively. Only 1 patient in the CNTX-4975 0.5 mg group reported a serious TEAE (intractable shoulder pain from previous OA), which was not considered treatment-related. No deaths were reported.

The most frequent TEAEs, reported by $\geq 5\%$ of patients in any treatment group, are summarized in Table 3. Most TEAEs were considered unrelated to study treatment. Four patients reported 7 TEAEs that were considered possibly or probably related to study medication; there was 1 report each of erythema, peripheral edema, and nausea (on treatment day 1) in the CNTX-4975 0.5 mg group, and dizziness, oral hypoesthesia, malaise, and hypotension (all on treatment day 1) in the CNTX-4975 1.0 mg group. One patient in the CNTX-4975 0.5 mg group developed an effusion that was tapped at 8 and 21 weeks into the study. The investigator did not believe this

was study drug-related, and the patient had no other safety issues. Few laboratory abnormalities were observed, with similar profiles between placebo and CNTX-4975.

Pain was assessed at specific times both immediately before and after injection of intraarticular 2% lidocaine (without epinephrine), and study drug, using a 0–4 categorical scale (0 = no pain and 4 = severe pain). The average pain score before the intraarticular lidocaine injection, while patients were in a resting position, ranged from 1.6 to 1.7 for each of the 3 groups. Ten minutes after lidocaine injection, most patients (70%, 71%, and 66% in the placebo, CNTX-4975 0.5 mg, and CNTX-4975 1.0 mg groups, respectively) reported no procedural pain. The maximal recorded pain score typically occurred 30 minutes after injection of study drug. No-to-moderate pain was recorded in 93%, 85%, and 80% and moderately severe-to-severe pain in 7%, 15%, and 20%, respectively. The maximum average pain scores at rest (range 0–4) before injection were 1.6, 1.7, and 1.7, respectively, and at 30 minutes after injection of study treatment

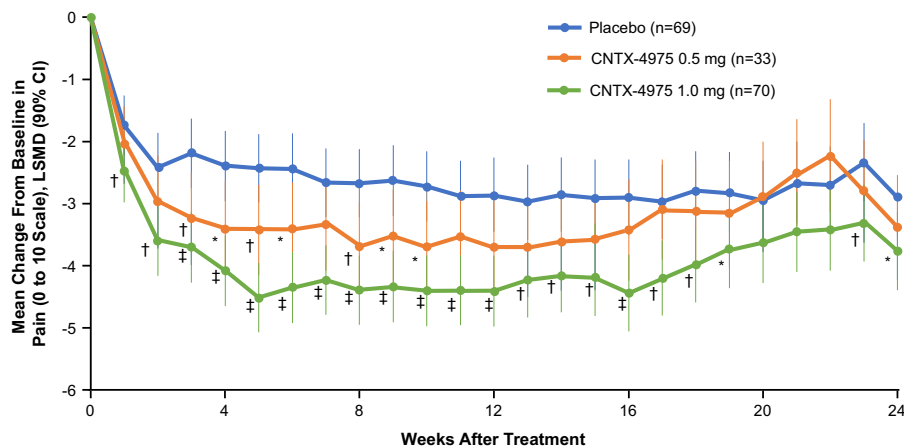


Figure 3. Change in average weekly WOMAC pain with walking scores. Change from baseline in average weekly scores through week 24 in patients treated with CNTX-4975 versus placebo is shown. A mixed model for repeated measures was used in the modified intent-to-treat population. Week 12 was the prespecified landmark end point; other *P* values were considered nominal and are presented for summary purposes only. Baseline scores (range 0–10): placebo 7.4, CNTX-4975 0.5 mg 7.2, CNTX-4975 1.0 mg 7.2. * = *P* < 0.1; † = *P* < 0.05; ‡ = *P* < 0.001, versus placebo. See Figure 2 for definitions.

they were 0.7, 1.2, and 1.6. Pain scores in each group declined to minimal levels in the subsequent 1.5 hours. Supplementary Figure 3 (<http://onlinelibrary.wiley.com/doi/10.1002/art.40894/>) includes a summary of procedural pain. An additional post hoc analysis indicated that procedural pain was not a significant covariate with regard to efficacy.

The NNH was evaluated in the CNTX-4975 1.0 mg and placebo groups. There were a total of 42 TEAEs, with 21 events occurring in each of these groups (Table 3). Based on these events, the NNH at 12 and 24 weeks was 58 and 237 patients, respectively.

DISCUSSION

The findings of this study demonstrated that a single intra-articular injection of CNTX-4975 1.0 mg was effective in providing

significant and clinically meaningful reduction ($\geq 50\%$) in pain that occurs while walking on a flat surface in patients with chronic moderate-to-severe OA knee pain (21,22), with the effect persisting for up to 24 weeks. Onset of improvement was rapid, with significant reduction in pain with walking, compared to placebo, as early as 1 week after treatment. The improvement in pain was associated with a reduction in knee stiffness and an improvement in function, as well as a positive PGIC score, through week 12, compared to placebo. The standardized effect size at 12 weeks for the CNTX-4975 1.0 mg dose using the primary end point was 0.68, which compares favorably to other approved therapies for OA-related knee pain (3). The CNTX-4975 0.5 mg dose was associated with a decrease in pain that was intermediate between that observed with placebo and with the CNTX-4975 1.0 mg dose.

CNTX-4975 1.0 mg was well tolerated, with a safety profile comparable to that of the placebo throughout the study.

Table 3. TEAEs through week 24*

Parameter/TEAE	Placebo (n = 70)	CNTX-4975 0.5 mg (n = 34)	CNTX-4975 1.0 mg (n = 71)
≥ 1 TEAE	21 (30)	16 (47)	21 (30)
≥ 1 serious TEAE	0	1 (3)†	0
Arthralgia	4 (6)	3 (9)	5 (7)
Upper respiratory tract infection	3 (4)	2 (6)	3 (4)
Increased hepatic enzyme	0	2 (6)	1 (1)
Joint effusion	0	3 (9)	0
Osteoarthritis	1 (1)	2 (6)	0

* Values are the number (%) of patients. Treatment-emergent adverse events (TEAEs) reported by $\geq 5\%$ of patients in any treatment group within the safety population are shown. Procedural pain was not counted as a TEAE and therefore is not included.

† Patient reported intractable shoulder pain from previous osteoarthritis, which was not considered treatment-related.

Procedural pain was higher with CNTX-4975 and tapered to minimal levels by 2 hours after injection (Supplementary Figure 3, <http://onlinelibrary.wiley.com/doi/10.1002/art.40894>). There was substantial overlap in postinjection pain with study drug in all 3 arms of the study. No patient withdrew due to an adverse event. Within each group, there was no relationship between procedural pain and outcome.

The AUC method was chosen for evaluation of the primary end point in this study. This method, while generally used in acute pain studies, also applies to chronic pain studies (23). The AUC analysis seemed most appropriate for the following reasons: 1) the profile of CNTX-4975 in previous studies included early onset of action with sustained pain relief through week 24; 2) the AUC method shows the entirety of benefit over time; and 3) the AUC method has potentially greater assay sensitivity because it more accurately shows the effects during the entirety of the study instead of at a single time point. The week-to-week mean numerical pain rating scale scores (Figure 3) were evaluated as a secondary end point using MMRM analysis. At week 12, the time of the designated primary end point, divergence from placebo was highly significant ($P < 0.001$) with the 1 mg dose. By week 18, the treatment effects of CNTX-4975 compared to placebo began to taper, although evidence showed divergence even at week 24 ($P = 0.067$).

The effects of trans-capsaicin are not dependent on ongoing exposure to the drug; the elimination half-life is <4 hours (24), whereas efficacy extends for months following a single injection. This reduces the safety risk of continued drug exposure effects in the long term. Due to the short exposure time and low systemic drug concentrations observed in clinical studies of injectable capsaicin (data on file; Centrexion Therapeutics Corp.), as well as the lipophilic nature of the drug (24), no effect outside of the knee joint is expected. The reduction in pain with the 1.0 mg dose was evident at 24 weeks, although there was a suggestion of diminution of effect after 16 weeks. Onset, maximum effect, and duration of action demonstrated dose dependency. Pain and loss of function are arguably the most important clinical features of OA (2), and an intervention that meaningfully improves pain and function is worth pursuing, given the limited choices currently available to patients.

This study has several limitations. Because it was a small randomized study in a specific population of patients with moderate-to-severe OA knee pain, the findings cannot be generalized to the knee OA population at large. In addition, as a small study, data regarding the safety profile are limited, although the findings are consistent with the safety profile of other capsaicin products.

In conclusion, the present results support the efficacy and safety of the intraarticular injection of trans-capsaicin to manage moderate-to-severe pain associated with knee OA. The findings indicate that further clinical development is warranted.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Stevens had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data. Stevens, Ervin, Nezzar, Nieves, Guedes, Burges, Hanson, Campbell.

ROLE OF THE STUDY SPONSOR

Centrexion Therapeutics Corp facilitated the study design and reviewed and approved the manuscript prior to submission. The authors independently collected the data, interpreted the results, and had the final decision to submit the manuscript for publication. Medical writing assistance was provided by Lauren Gallagher, PhD, and Illyce Nunez, PhD, of Peloton Advantage, LLC, an OPEN Health company, and supported by Centrexion Therapeutics Corp. Publication of this article was not contingent upon approval by Centrexion Therapeutics Corp.

ADDITIONAL DISCLOSURES

Author Ervin is an employee of the Center for Pharmaceutical Research. Authors Nezzar and Nieves were employees of Premier Research during the time the study was conducted.

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