CNTX-4975 Administration in Subjects With Knee Pain Associated With Osteoarthritis: Results of the Randomized, Double-Blind, Placebo-Controlled, Phase 2b TRIUMPH Study

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INTRODUCTION

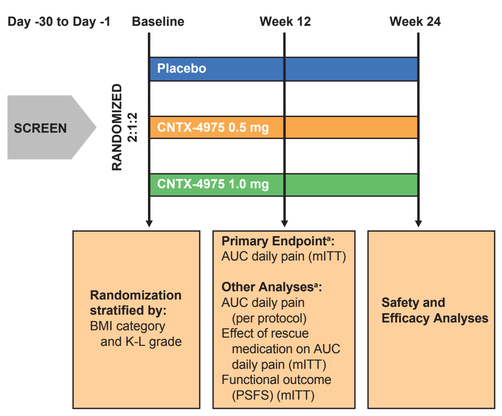
- Osteoarthritis (OA), the most common form of arthritis in the United States, results in significant disability, increased cardiovascular risk, and impaired quality of life[1-3]
- Classic symptoms of OA include chronic joint pain and stiffness, difficulty walking, and reduced physical function[1,2,4]
- The few available treatments for chronic OA pain are associated with adverse events (AEs), and subjects may require long-term treatment with higher doses[1,5,6]
  - Increased cardiovascular risk, renal impairment, hypertension, and gastrointestinal toxicity can occur with common OA therapies[1,5,7]
  - Increased risk of serious AEs and addiction can occur with opioid analgesics[8]
- CNTX-4975 is a highly purified, synthetic *trans*-capsaicin and long-acting, non-opioid analgesic in clinical development for the treatment of knee pain associated with OA
  - CNTX-4975 was developed using proprietary STRATI™ technology (Synthetic TRans cApsaicin ulTra-pure Injection)
- A single intra-articular injection of CNTX-4975 produces analgesia by targeting the transient receptor potential vanilloid 1 (TRPV1) channel to reversibly deactivate the end terminals of primary afferent pain fibers within the joint and capsule
- This presentation describes the efficacy of two dose levels of CNTX-4975 for improving pain with walking and functional outcomes at 12 weeks, and safety results through 24 weeks, for treatment of moderate to severe knee pain associated with OA

METHODS

Study Design

- The TRIUMPH study was a 24-week, randomized, double-blind, placebo-controlled, dose-ranging, multicenter phase 2b clinical trial (NCT02558439) designed to evaluate the efficacy, safety, and tolerability of CNTX-4975 versus placebo in subjects with chronic, moderate to severe knee pain associated with OA (**Figure 1**)
- Subjects who met eligibility criteria were randomized (2:1:2) to receive placebo, CNTX-4975 0.5 mg, or CNTX-4975 1.0 mg as a single intra-articular injection in the index knee
  - Subject randomization was stratified according to Kellgren-Lawrence (K-L) grade (2–3 or 4 [up to 10% of randomized subjects]) and body mass index (BMI; <30 kg/m^2 or ≥30 kg/m^2)

Figure 1. TRIUMPH Study Design



AUC, area under the curve; BMI, body mass index; K-L, Kellgren-Lawrence; mITT, modified intent to treat; PSFS, Patient Specific Function Scale.
[a]All tests of statistical significance were 2 sided (prespecified alpha *P*=0.1).

Key Inclusion Criteria

- Adults 45–80 years of age with chronic, stable, moderate to severe knee pain due to OA
  - Chronic OA of the index knee confirmed by radiographic evidence, with a K-L grade of 2–4
  - Moderate to severe, stable pain associated with OA in the index knee for ≥2 months before screening
- Mean Western Ontario and McMaster Universities Osteoarthritis Index Question A1 (WOMAC A1) pain score between 5 and 9 (inclusive) in the index knee during the week prior to dosing, at screening, and at baseline
- BMI ≤45 kg/m^2
- Prior therapeutic failure and/or intolerability to one or more oral or intra-articular analgesic therapies for OA, defined as follows:
  - No relief or inadequate relief
  - Treatment discontinuations due to AEs
  - Contraindication to medication

Key Exclusion Criteria

- Previous index knee replacement surgery, open surgery of the index knee within 12 months, or arthroscopic surgery of the index knee within 3 months
- Any pain in the index knee due to joint disease other than OA
- Mild pain in the non-index knee while walking
- Any other chronic pain that requires use of analgesic medications
- Secondary OA resulting from acute traumatic injury to the index knee
- Significant current or past instability or misalignment in the index knee
  - Instability (eg, cruciate ligament tear or rupture or previous repair)
  - Misalignment (>10 degrees varus or valgus)
- Use of topical capsaicin, corticosteroid injection, or intra-articular viscosupplementation in the index knee within 90 days
- Current use of opioids for any condition other than OA in the index knee
- Current or prior substance abuse within 1 year or urine drug screen positive for substance abuse
- Moderate to severe depression or anxiety

Efficacy Assessments

- The primary efficacy endpoint of TRIUMPH was the area under the curve (AUC) in change from baseline in daily WOMAC A1 pain scores for placebo versus CNTX-4975 1.0 mg at week 12 in the modified intent-to-treat (mITT) population (reported separately)
  - Subjects rated "pain when walking on a flat surface during the last 24 hours" from 0 (pain absent) to 10 (severe pain) in a daily eDiary
- The following efficacy assessments are included in this presentation:
  - AUC in change from baseline in daily WOMAC A1 pain scores at week 12 for placebo versus CNTX-4975 0.5 mg and CNTX-4975 1.0 mg in the per-protocol population
  - Change from baseline in weekly WOMAC A1 pain scores through week 12 for placebo versus CNTX-4975 0.5 mg and CNTX-4975 1.0 mg in the per-protocol population
    - Weekly average pain scores were calculated from daily WOMAC A1 ratings
  - AUC in change from baseline in daily WOMAC A1 pain scores at week 12 adjusted for use of rescue medications in the mITT population
  - Mean change from baseline in functional outcomes assessed using an adapted Patient Specific Function Scale (PSFS) in the mITT population
    - Subjects rated their level of function on ≤3 activities from 0 (able to perform activity at the same level as before injury or problem) to 10 (unable to perform)

Safety Assessments

- Treatment-emergent AEs (TEAEs), serious AEs, treatment-related AEs, AE severity, and discontinuations due to AEs were assessed from baseline through week 24
- Clinical laboratory parameters were evaluated at screening, baseline, week 12, and week 24

Concomitant Medications

- The study allowed the following concomitant medications for rescue pain relief using the recommended daily doses: acetaminophen, ibuprofen, naproxen, celecoxib, meloxicam, or tramadol

Statistical Analysis

- Efficacy and safety analyses were performed in the following study populations:
  - mITT: randomized subjects who had at least 1 post-baseline efficacy assessment
  - Per-protocol: all subjects in the mITT population who received CNTX-4975 and had no critical deviations from the study protocol
  - Safety: all subjects who received any amount of CNTX-4975 or placebo
- Two sensitivity analyses of the primary efficacy endpoint were conducted in the per-protocol population:
  - Analysis of covariance (ANCOVA) of the standardized AUC of daily WOMAC A1 pain scores at week 12
  - Mixed model for repeated measures (MMRM) analysis of the weekly WOMAC A1 pain scores at week 12 (changed from week 4 to week 12 in a protocol amendment)
- Standardized AUC of daily WOMAC A1 pain scores was adjusted for use of rescue medications using ANCOVA analysis in the mITT population
- Functional outcomes were assessed using the PSFS with MMRM analysis
- Change from baseline in least squares (LS) means, LS differences between treatment and placebo, 90% confidence intervals, and *P* values were obtained from the ANCOVA and MMRM models
- The ANCOVA and MMRM models included treatment as the main effect, and sex, pooled site group 1 (sites grouped smallest to largest sequentially until each pooled site had ≥40 subjects), baseline K-L grade category of the index knee, baseline BMI category, and baseline WOMAC A1 score as covariates
- MMRM models used an unstructured within-subject covariance matrix, with visit and treatment by visit as categorical variables
- All tests of statistical significance were 2 sided (prespecified alpha *P*=0.1)

RESULTS

Subjects

- A total of 175 subjects were randomized to receive a single intra-articular injection of placebo (n=70), CNTX-4975 0.5 mg (n=34), or CNTX-4975 1.0 mg (n=71) in the index knee (**Table 1**)
  - Overall, 89.7% of subjects (n=157) in the safety population completed the 24-week study

Table 1. Subject Disposition at 24 Weeks, n (%)

Placebo (n=70)		CNTX-4975 0.5 mg (n=34)		CNTX-4975 1.0 mg (n=71)	
Completed study	**63 (90.0)**	**Completed study**	**30 (88.2)**	**Completed study**	**64 (90.1)**
Discontinued	**7 (10.0)**	**Discontinued**	**4 (11.8)**	**Discontinued**	**7 (9.9)**
• Lost to follow-up	4 (5.7)	• Lost to follow-up	3 (8.8)	• Protocol deviation	4 (5.6)
• Protocol deviation	1 (1.4)	• Withdrew consent	1 (2.9)	• Withdrew consent	2 (2.8)
• Withdrew consent	2 (2.9)			• Other	1 (1.4)

- Demographics and baseline BMI category, K-L grade severity, and WOMAC A1 pain scores were comparable across treatment groups (**Table 2**)

Table 2. Demographics and Baseline Disease Characteristics of Study Subjects, Safety Population

	Placebo (n=70)	CNTX-4975 0.5 mg (n=34)	CNTX-4975 1.0 mg (n=71)
Age, mean (SD), years	60.6 (8.9)	59.6 (6.4)	59.1 (7.7)
Sex, n (%)			
Male	25 (35.7)	14 (41.2)	26 (36.6)
Female	45 (64.3)	20 (58.8)	45 (63.4)
Race, n (%)			
White	51 (72.9)	24 (70.6)	52 (73.2)
Black or African American	19 (27.1)	10 (29.4)	18 (25.4)
Multiple	0	0	1 (1.4)
Ethnicity, n (%)			
Hispanic/Latino	26 (37.1)	12 (35.3)	25 (35.2)
Not Hispanic/Latino	44 (62.9)	22 (64.7)	46 (64.8)
BMI category, n (%)			
<30 kg/m^2	23 (32.9)	13 (38.2)	21 (29.6)
≥30 kg/m^2	47 (67.1)	21 (61.8)	50 (70.4)
K-L grade (index knee), n (%)			
0	0	0	0
1	0	0	0
2	25 (35.7)	9 (26.5)	32 (45.1)
3	37 (52.9)	22 (64.7)	33 (46.5)
4	8 (11.4)	3 (8.8)	6 (8.5)
Baseline WOMAC A1 severity, n (%)			
Moderate	24 (34.3)	13 (38.2)	33 (46.5)
Severe	44 (62.9)	20 (58.8)	38 (53.5)
Missing	2 (2.9)	1 (2.9)	0

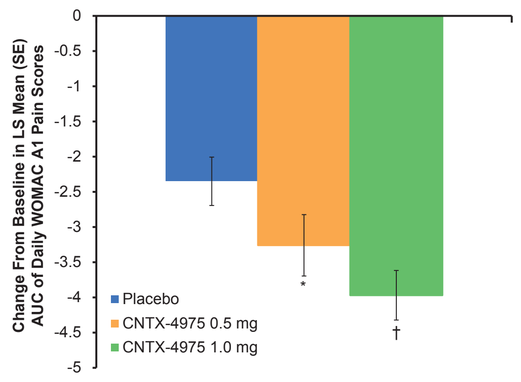
BMI, body mass index; K-L, Kellgren-Lawrence; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

Efficacy

Sensitivity Analysis: Average Daily Pain With Walking (WOMAC A1), Per-Protocol Population

- The per-protocol population included 163 subjects (placebo, n=65; CNTX-4975 0.5 mg, n=30; CNTX-4975 1.0 mg, n=68)
- Mean baseline weekly WOMAC A1 pain scores, which can range from 0 to 10, were 7.44 for placebo, 7.22 for CNTX-4975 0.5 mg, and 7.22 for CNTX-4975 1.0 mg
- At week 12, a statistically significant reduction in standardized AUC based on daily WOMAC A1 pain scores was observed for CNTX-4975 1.0 mg versus placebo (**Figure 2**)
  - The LS mean difference (LSMD) (SE) at week 12 versus placebo was −0.91 (0.45; *P*=0.0455) for CNTX-4975 0.5 mg and −1.61 (0.36; *P*<0.0001) for CNTX-4975 1.0 mg

Figure 2. Change From Baseline in LS Mean (SE) Standardized AUC of Daily WOMAC A1 Pain Scores at Week 12, ANCOVA Analysis, Per-Protocol Population

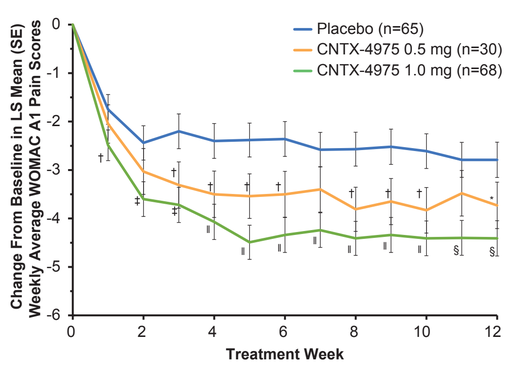


*P<0.05, †P<0.0001, CNTX-4975 versus placebo.
ANCOVA, analysis of covariance; AUC, area under the curve; LS, least squares; SE, standard error; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Sensitivity Analysis: Average Weekly Pain With Walking (WOMAC A1), Per-Protocol Population

- At week 12, the LSMD (SE) in weekly average WOMAC A1 pain scores versus placebo was −0.94 (0.53, *P*=0.08) for CNTX-4975 0.5 mg and −1.62 (0.42, *P*=0.0002) for CNTX-4975 1.0 mg
- Statistically significant reductions in weekly average WOMAC A1 pain score versus placebo were observed as early as week 3 with CNTX-4975 0.5 mg (LSMD: −1.1; *P*=0.04), and this change remained significant during weeks 3–6 (*P*<0.04), weeks 8–10 (*P*<0.04), and week 12 (*P*=0.08) (**Figure 3**)
- Treatment with CNTX-4975 1.0 mg resulted in statistically significant reductions in weekly average WOMAC A1 pain score versus placebo as early as week 1 (LSMD: −0.73; *P*=0.03) and the reductions remained significant at all time points through week 12 (*P*≤0.005) (**Figure 3**)
- The greatest reduction in weekly average WOMAC A1 pain scores with CNTX-4975 1.0 mg versus placebo was observed at week 5 (LSMD: −2.11; *P*<0.0001)

Figure 3. Change From Baseline in LS Mean (SE) Weekly Average WOMAC A1 Scores (Pain With Walking), MMRM Analysis, Per-Protocol Population

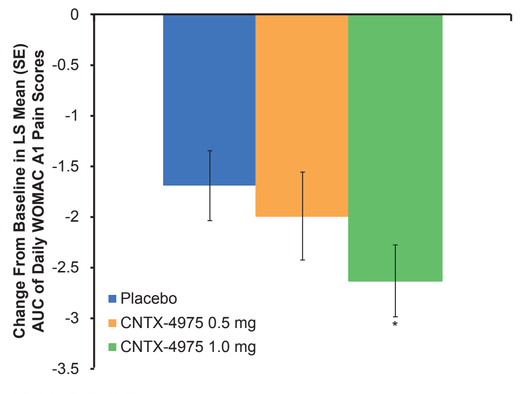


*P<0.10, †P≤0.05, ‡P<0.01, §P<0.001, ǁP<0.0001, CNTX-4975 versus placebo.
LS, least squares; MMRM, mixed model for repeated measures; SE, standard error; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Average Daily Pain With Walking (WOMAC A1) Adjusted for Use of Rescue Medications, mITT Population

- The mITT population included 172 subjects (placebo, n=69; CNTX-4975 0.5 mg, n=33; CNTX-4975 1.0 mg, n=70)
- Mean baseline weekly WOMAC A1 pain scores, which can range from 0 to 10, were 7.42 for placebo, 7.24 for CNTX-4975 0.5 mg, and 7.20 for CNTX-4975 1.0 mg
- When adjusting for use of rescue medications, a statistically significant reduction in week 12 standardized AUC based on daily WOMAC A1 pain scores was observed for CNTX-4975 1.0 mg versus placebo (**Figure 4**)
  - At week 12, LSMD (SE) versus placebo was −0.29 (0.45; *P*=0.51) for CNTX-4975 0.5 mg and −0.93 (0.36; *P*=0.0098) for CNTX-4975 1.0 mg

Figure 4. Change From Baseline in LS Mean (SE) Standardized AUC of Daily WOMAC A1 Pain Scores at Week 12, Adjusted for Use of Rescue Medications, ANCOVA Analysis, mITT Population

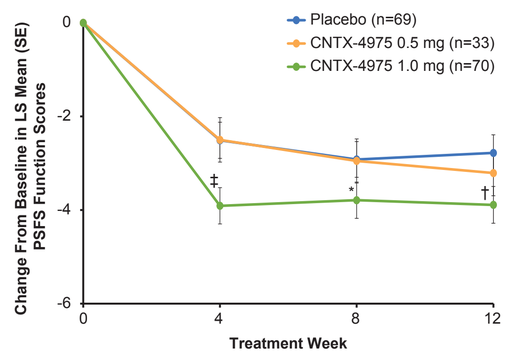


*P<0.01, CNTX-4975 versus placebo.
ANCOVA, analysis of covariance; AUC, area under the curve; LS, least squares; mITT, modified intent to treat; SE, standard error; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Average Functional Outcomes Assessed Using the Modified PSFS, mITT Population

- Mean baseline modified PSFS function scores, which can range from 0 to 10, were 8.00 for placebo, 7.86 for CNTX-4975 0.5 mg, and 7.70 for CNTX-4975 1.0 mg
- Statistically significant improvements in functional outcomes based on LS mean changes in PSFS scores were observed for CNTX-4975 1.0 mg versus placebo by week 4, and these improvements in function were stable through 12 weeks (**Figure 5**)
- At week 12, the LSMD (SE) versus placebo was −0.43 (0.51; *P*=0.40) for CNTX-4975 0.5 mg and −1.12 (0.41; *P*=0.007) for CNTX-4975 1.0 mg

Figure 5. Change From Baseline in LS Mean (SE) Modified PSFS Scores[a], MMRM Analysis, mITT Population



[a]Modified PSFS scores range from 0–10, with higher values indicating worse functioning.
*P<0.05, †P<0.01, ‡P<0.001, CNTX-4975 versus placebo.
LS, least squares; mITT, modified intent to treat; MMRM, mixed model for repeated measures; PSFS, Patient Specific Function Scale; SE, standard error.

Safety at 24 Weeks

- Pharmacokinetic studies have shown that intra-articular injection of CNTX-4975 has a short half-life (0.25–3 hours), and systemic exposure is undetectable within 24 hours
- The safety population included 175 subjects (placebo, n=70; CNTX-4975 0.5 mg, n=34; CNTX-4975 1.0 mg, n=71)
- TEAEs were reported by 30% (placebo), 47% (CNTX-4975 0.5 mg), and 30% (CNTX-4975 1.0 mg) of subjects
- The most commonly reported TEAEs (incidence >5%) were arthralgia for placebo (5.7%) and CNTX-4975 1.0 mg (7.0%), and joint effusion (8.8%), arthralgia (8.8%), upper respiratory tract infection (5.9%), OA (5.9%), and hepatic enzyme increase (5.9%) for CNTX-4975 0.5 mg
- All TEAEs were mild or moderate and most TEAEs were not considered related to study treatment (**Table 3**)
- No serious treatment-related TEAEs were reported
- No subjects discontinued from the study due to TEAEs and no deaths occurred during the study
- Among the laboratory abnormalities observed, most were associated with comorbid conditions

Table 3. Overview of TEAEs Through Week 24, Safety Population

	Placebo (n=70)	CNTX-4975 0.5 mg (n=34)	CNTX-4975 1.0 mg (n=71)
Subjects with ≥1 TEAE, n (%)	21 (30.0)	16 (47.1)	21 (29.6)
Subjects with ≥1 TEAE by severity, n (%)			
Mild	13 (18.6)	10 (29.4)	14 (19.7)
Moderate	8 (11.4)	6 (17.6)	7 (9.9)
Severe	0	0	0
Subjects with ≥1 TEAE by relationship, n (%)			
Unrelated	20 (28.6)	12 (35.3)	17 (23.9)
Not likely related	1 (1.4)	2 (5.9)	2 (2.8)
Possibly related	0	1 (2.9)	1 (1.4)
Probably related	0	1 (2.9)	1 (1.4)

TEAE, treatment-emergent adverse event.

CONCLUSIONS

- A single intra-articular injection of CNTX-4975 1.0 mg provided statistically significant improvements in pain with walking for subjects with moderate to severe knee pain associated with OA, including when accounting for the use of rescue medications
- CNTX-4975 1.0 mg significantly improved functional outcomes and the ability for subjects to perform important daily activities compared with placebo
- The safety profile of CNTX-4975 1.0 mg was generally comparable to placebo for up to 24 weeks
- These results support the continued development of CNTX-4975 1.0 mg for treatment of subjects with moderate to severe knee pain associated with OA

REFERENCES

1. Felson DT. *Arthritis Res Ther.* 2009;11:203.
2. Neogi T. *Osteoarthritis Cartilage.* 2013;21:1145-53.
3. Wang H, et al. *Sci Rep.* 2016;6:39672.
4. Hunter DJ, et al. *Rheum Dis Clin North Am.* 2008;34:623-43.
5. Antman EM, et al. *Circulation.* 2007;115:1634-42.
6. Veronese N, et al. *Arthritis Rheumatol.* 2016;68:1136-44.
7. Kearney PM, et al. *BMJ.* 2006;332:1302-8.
8. da Costa BR, et al. *Cochrane Database Systematic Rev.* 2014(9):Cd003115.

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