OP0166 RADIOGRAPHIC OUTCOMES FROM A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2 STUDY OF A NOVEL, INTRA-ARTICULAR, INJECTABLE, WNT PATHWAY INHIBITOR (SM04690) IN THE TREATMENT OF OSTEOARTHRITIS OF THE KNEE: WEEK 26 INTERIM ANALYSIS

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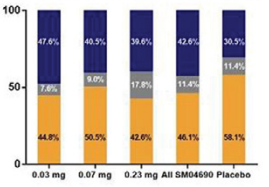
Background: Knee osteoarthritis (OA) is characterized by pain, functional impairment, and joint space narrowing due to degradation of articular cartilage and bone remodeling. The Wnt pathway plays a central role in the formation of joint tissues, and altered Wnt signaling has been associated with cartilage loss in preclinical studies. SM04690 is a small molecule Wnt pathway inhibitor in development as a disease modifying OA drug (DMOAD) and administered as an intra-articular (IA) knee injection. A phase 2, multicenter, 52-week, single-dose, randomized controlled trial of SM04690 is ongoing in subjects with moderate to severe knee OA. Radiographic results from an interim analysis at 26 weeks are reported.
Objectives: To evaluate the safety and efficacy of SM04690 IA injection for the treatment of OA.
Methods: Subjects were randomized to receive a single, 2 mL, IA injection of 0.03 mg, 0.07 mg, 0.23 mg SM04690 or placebo into the target knee on Treatment Day 1. Safety, tolerability and efficacy outcomes were assessed at Weeks 4, 13 and 26. Target knee radiographs were taken at baseline and Week 26; change in medial joint space width (mJSW) was analyzed using an intention-to-treat analysis of covariance (ANCOVA) adjusting for baseline mJSW.
Results: 455 subjects (average age 60.3 [±8.7] years, 268 [58.9%] female, mean BMI 29.9 [±4.6] kg/m^2, 293 [64.4%] Kellgren-Lawrence Grade 3, 291 [64.0%] bilateral OA) were enrolled. At Week 26, 8 serious adverse events (SAEs) in 7 subjects were reported; these were deemed unrelated to drug by the investigators. Mean mJSW change from baseline was -0.22 [±0.64] mm in placebo cohort (table 1). Compared to placebo, mean mJSW change from baseline was -0.07 [±0.62] mm in the 0.03 mg (p=0.069), -0.16 [±0.95] mm in 0.07 mg (p=0.489), and -0.03 [±0.59] mm in 0.23 mg (p=0.019) cohorts, respectively. Increase in mean mJSW was observed in 50 (47.6%) subjects in 0.03 mg, 45 (40.5%) subjects in 0.07 mg, 40 (39.6%) subjects in 0.23 mg and 32 (30.5%) subjects in placebo cohorts, respectively (figure 1). Odds of mJSW improvement, defined as change in mJSW >0, were increased 107% in 0.03 mg cohort compared to placebo (OR=2.1, 95% CI [1.2, 3.7], p=0.011), and odds of mJSW improvement were increased 69% for all SM04690 doses combined compared to placebo (OR=1.7, 95% CI [1.1, 2.7], P=0.029). Additionally, in *a priori* subanalyses, each treatment cohort, and all SM04690 doses combined, had higher probability of improving mJSW in the unilateral OA subgroup, with a 420% increase in odds of JSW response compared to placebo (all SM04690 groups combined OR=5.2, 95% CI [2.1, 12.8], p<0.001).

Table 1. Medial joint space width at baseline and week 26

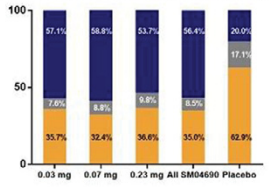
	0.03 mg	0.07 mg	0.23 mg	All SM04690	Placebo
N	111	117	109	337	116
Baseline (mm) [Mean (SD)]	3.41 (1.28)	3.45 (1.11)	3.08 (1.26)	3.34 (1.24)	3.33 (1.36)
Week 26 (mm) [Mean (SD)]					
Actual	3.38 (1.38)	3.30 (1.40)	3.06 (1.38)	3.25 (1.39)	3.10 (1.52)
Change from baseline	-0.07 (0.62)*	-0.16 (0.95)	-0.03 (0.59)**	-0.09 (0.74)	-0.22 (0.64)

*0.03 mg vs PBO, p=0.069; **0.23 mg vs PBO, p=0.019

Figure 1. JSW Change at 26 weeks: All subjects



JSW Change at 26 weeks: Unilateral subjects



Conclusions: Radiographic outcomes from this interim analysis demonstrated that treatment with SM04690 maintained or increased JSW compared to placebo. These data support the continued development of SM04690 as a potential DMOAD for the treatment of knee OA. Further studies are ongoing.

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OP0167 EFFICACY AND SAFETY OF CNTX-4975 IN SUBJECTS WITH MODERATE TO SEVERE OSTEOARTHRITIS KNEE PAIN: 24-WEEK, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-RANGING STUDY

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Background: Osteoarthritis causes joint pain, stiffness, and reduced function, leading to disability. CNTX-4975, a highly purified, synthetic *trans*-capsaicin, targets the transient receptor potential vanilloid 1, producing analgesia via reversible deactivation of end terminals of primary afferent pain fibers within the joint and capsule.
Objectives: This 24-week dose-ranging study evaluated CNTX-4975 efficacy and safety in subjects with chronic, moderate to severe osteoarthritis-associated knee pain.
Methods: Subjects aged 45–80 years with chronic knee osteoarthritis, stable moderate to severe knee pain, and intolerability to oral or intra-articular analgesics were randomized to a single injection of placebo, CNTX-4975 0.5 mg, or CNTX-4975 1.0 mg. The primary efficacy endpoint was the area under the curve (AUC) for change from baseline in daily Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) A1 score through week 12. Least squares mean differences (LSMD) for CNTX-4975 vs placebo were calculated for the primary endpoint and the average weekly AUC WOMAC A1 scores using analysis of covariance. Additional efficacy endpoints, mean change from baseline in weekly WOMAC A1 score, WOMAC B stiffness subscale, and WOMAC C physical function subscale through week 24, were analyzed using a mixed model for repeated measures (MMRM). Statistical tests were 2-sided (alpha, P=0.10). Safety assessments included treatment-emergent adverse events (TEAEs).
Results: Efficacy was evaluated in 172 subjects (placebo, n=69; CNTX-4975 0.5 mg, n=33; CNTX-4975 1.0 mg, n=70). Mean WOMAC A1 pain scores at baseline were 7.4 (placebo), 7.2 (CNTX-4975 0.5 mg), and 7.2 (CNTX-4975 1.0 mg). In the primary efficacy analysis, significant improvements vs placebo in WOMAC A1 scores were observed at week 12 with CNTX-4975 0.5 mg (LSMD: –0.8; P=0.07) and CTNX-4975 1.0 mg (LSMD: –1.6; P<0.0001). Significant improvements vs placebo were also observed at week 24 with CNTX-4975 1.0 mg (LSMD: –1.35; P=0.0002). In the MMRM analysis, significant improvements in WOMAC A1 scores vs placebo were demonstrated with CNTX-4975 0.5 mg at week 12 (LSMD: –0.9; P=0.087) but not week 24 (LSMD: –0.5; P=0.41), and with CNTX-4975 1.0 mg at weeks 12 (LSMD: –1.5; P=0.0003) and 24 (LSMD: –0.9; P=0.067). CNTX-4975 1.0 mg significantly improved WOMAC B (LSMD: –2.5; P=0.0013) and WOMAC C scores vs placebo (LSMD: –18.3; P=0.004) at week 12. Numerically greater improvements were observed in WOMAC B and C at week 24, but differences were not significant (WOMAC B LSMD: –1.2; P=0.14; WOMAC C LSMD: –7.2; P=0.28). In the safety population, the incidence of TEAEs was 30% for placebo or CNTX-4975 1.0 mg, and 47% for CNTX-4975 0.5 mg at week 24. Most TEAEs were considered unrelated to study treatment. Arthralgia was the most common TEAE with CNTX-4975 1.0 mg (placebo, 5.7%; CNTX-4975 1.0 mg, 7.0%).
Conclusions: A single injection of CNTX-4975 1.0 mg improved pain with walking, knee stiffness, and physical function, and was well tolerated in subjects with moderate to severe osteoarthritis-associated knee pain.

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