Phase 1 Study of the Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Ascending Doses of the Selective Oral CCR2 Antagonist CNTX-6970 in Healthy Subjects

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INTRODUCTION

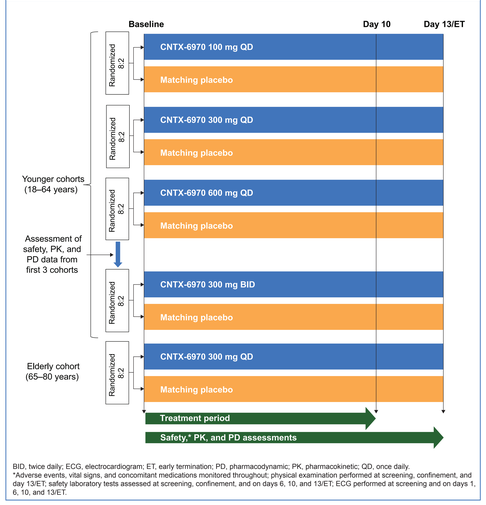
- Chronic inflammatory pain, such as pain associated with osteoarthritis, is a major cause of disability[1-3]
- The chemokine C-C motif receptor 2 (CCR2) and its ligand, monocyte chemoattractant protein-1 (MCP-1), are potentially important mediators of chronic inflammatory pain[4]
  - Inflammatory pain occurs in part due to MCP-1 activation of inflammatory signaling via CCR2 receptors in monocytes and in sensory neurons of the dorsal root ganglia (DRG), and through CCR2-mediated recruitment of macrophages to the DRG[4,5]
  - Peripheral nerve injury has also been shown to trigger pain signaling by inducing the release of MCP-1 in the dorsal horn spinal cord[6]
- CNTX-6970, a potent and selective CCR2 inhibitor, has demonstrated activity in animal models of inflammatory pain in preclinical studies,[7] and a phase 1 single-ascending-dose (SAD) study showed that CNTX-6970 was well tolerated; adverse events (AEs) were predominantly unrelated to CNTX-6970, and no serious AEs occurred[7,8]
- We report safety, pharmacokinetic (PK), and pharmacodynamic (PD) results from a phase 1 multiple-ascending-dose (MAD) study of CNTX-6970 (NCT03787004)

METHODS

Study Design

- An institutional review board at the clinical site approved the study
- Healthy adults aged 18 to 64 years were randomized 8:2 to receive oral CNTX-6970 (100, 300, or 600 mg QD) or placebo, based on findings from the previous SAD study, for 10 days (from day 1 to day 10; **Figure 1**)
  - After assessment of safety, PK, and PD data from the first 3 dose cohorts, the Cohort Review Committee approved enrollment of a 300-mg BID cohort of healthy adults and a 300 mg-QD cohort of healthy elderly subjects (aged 65–80 years); both cohorts were randomized 8:2 to receive oral CNTX-6970 or placebo

Figure 1. CNTX-6970 Multiple-Ascending-Dose Study Design



BID, twice daily; ECG, electrocardiogram; ET, early termination; PD, pharmacodynamic; PK, pharmacokinetic; QD, once daily.
*Adverse events, vital signs, and concomitant medications monitored throughout; physical examination performed at screening, confinement, and day 13/ET; safety laboratory tests assessed at screening, confinement, and on days 6, 10, and 13/ET; ECG performed at screening and on days 1, 6, 10, and 13/ET.

Key Inclusion Criteria

- Adults 18 to 80 years of age in good general health based on a complete medical history, including physical examination, vital signs, 12-lead electrocardiogram (ECG), and clinical laboratory assessments
- Body mass index 18 to 35 kg/m^2 and weight ≥50 kg
- CYP2C9 extensive or intermediate metabolizers

Key Exclusion Criteria

- History of cardiac disease or history of or current cancer (except excised/cured basal cell carcinoma)
- Psychiatric condition requiring active treatment; diabetes/other active endocrinopathy; gastrointestinal disorder that may interfere with absorption of orally administered drugs; asthma/other severe respiratory disease requiring daily prescription medicine or prior emergency room visits/hospitalization; systemic infection requiring antibiotic, antifungal, antiparasitic, or antiviral medication; immunologic disorder; or any organ system disease that, in the investigator's opinion, precluded study participation
- Clinically significant ECG abnormality, based on investigator's judgment or prespecified parameters
- Heart rate (HR) outside the range of 50 to 100 beats per minute, systolic blood pressure (BP) outside the range of 90 to 140 mmHg, or diastolic BP outside the range of 50 to 90 mmHg at screening or on day 0
- Hemoglobin level below the lower limit of normal; serum creatinine level above the upper limit of normal (ULN); or abnormal elevation of alanine aminotransferase, aspartate aminotransferase, or total serum bilirubin (above 1.2 of ULN) at screening or on day 0
- Use of prescription medications (except hormonal contraceptives) within 30 days of study or during the study; use of over-the-counter medicinal products (except for occasional use of acetaminophen or nonsteroidal anti-inflammatory drugs, calcium, or vitamin D) within 14 days of study or during the study; use of a known CYP2D9 inhibitor within 14 days of dosing; allergy injections within 7 days prior to screening or during the study; immunization within 30 days of screening; previous or current use of human growth hormone, octreotide, antidiabetic medication, thyroid suppressors or supplements; or osteopenia or osteoporosis medications (other than calcium and vitamin D supplements)

Safety Assessments

- Safety assessments included monitoring of treatment-emergent AEs (TEAEs), changes in vital signs, physical examinations, clinical laboratory tests (including absolute monocyte counts), and ECG findings
  - TEAEs, including severity, seriousness, and relationship to study drug, and vital signs were recorded throughout the study
  - Laboratory tests and ECG were assessed at screening; at confinement/day 0 (laboratory tests only); on days 1 (ECG only), 6, and 10 of treatment; and on day 13/early termination (ET)
  - Physical examination was performed prior to treatment and on day 13/ET

Pharmacokinetic Assessments

- PK parameters evaluated as secondary endpoints included
  - Maximum plasma concentration (C_{max}) after a single oral dose of CNTX-6970
  - Area under the concentration-time curve of CNTX-6970 in plasma over time (interval from baseline extrapolated to infinity [$AUC_{0-\infty}$])
- Other PK parameters assessed included
  - Interval from baseline to 12 hours or to 24 hours (AUC_{0-12} and AUC_{0-24}), for the BID and QD cohorts, respectively
  - Time from dosing to maximum measured concentration (t_{max})
  - Terminal half-life in plasma ($t_{1/2}$)
  - Total/apparent clearance of CNTX-6970 in plasma after extravascular administration (CL/F)
- PK variables calculated on day 1 were compared with those calculated on day 10

Biomarker Assessments

- Absolute monocyte counts were monitored throughout the study in whole blood samples (collected predose and at 1, 2, and 4 hours postdose on days 1, 5, and 10; and at 24, 48, and 72 hours postdose on days 11–13/ET)
- Percentage inhibition of binding of fluorescence-labeled MCP-1 and RANTES (regulated on activation, normal T cell expressed and secreted) ligands to CCR2 and chemokine C-C motif receptor 5 (CCR5), respectively, in whole human blood (collected before and after [1, 2, 3, 4, and 6 hours] drug administration on days 1 and 10, before and after [1 hour] drug administration on days 2–9, and at 24, 48, and 72 hours postdose on days 11–13)
- Correlations between plasma concentrations and receptor binding were examined

Statistical Analysis

- The safety population included all subjects who received any study drug; data were reported using descriptive statistics
- The PK population included all subjects who received study drug, had no major deviations, and had at least 1 interpretable primary PK concentration value
  - PK parameters were summarized using descriptive statistics, and dose-normalized PK parameters were calculated using standard noncompartmental methods
  - For C_{max}, $AUC_{0-\infty}$, and AUC_{0-24}, dose proportionality was analyzed using a power model applied to natural log-transformed data
- The PD population included all subjects who received study drug, had no major deviations, and had at least 1 interpretable PD data value
  - Biomarker data were analyzed graphically and descriptively

RESULTS

Subject Disposition and Baseline Characteristics

- A total of 50 randomized subjects (younger cohorts: 100 mg QD, n=8; 300 mg QD, n=8; 600 mg QD, n=8; 300 mg BID, n=8; pooled placebo, n=8; elderly cohort: 300 mg QD, n=8; placebo, n=2) were included in safety, PK, and PD analyses
  - Three subjects discontinued early from the study: 1 subject each in the younger cohort (600 mg QD) and elderly cohort (placebo) discontinued due to withdrawn consent; and 1 subject in the 300-mg BID cohort discontinued due to other reasons (≥50% decrease in monocyte count from baseline to <0.2 x 103/µL on 2 consecutive days as prespecified in protocol)
- Demographics and baseline characteristics are shown in **Table 1**

Table 1. Demographics and Baseline Characteristics

	Younger Cohorts					Elderly Cohort	
Parameter	CNTX-6970 100 mg QD (n=8)	CNTX-6970 300 mg QD (n=8)	CNTX-6970 600 mg QD (n=8)	CNTX-6970 300 mg BID (n=8)	Pooled Placebo (n=8)	CNTX-6970 300 mg QD (n=8)	Placebo (n=2)
Age, mean (SD), years	48.0 (8.6)	39.5 (11.2)	41.8 (15.1)	41.9 (13.0)	43.9 (10.7)	69.3 (3.7)	68.0 (2.8)
Male, n (%)	4 (50.0)	5 (62.5)	4 (50.0)	2 (25.0)	4 (50.0)	6 (75.0)	0
White, n (%)	5 (62.5)	3 (37.5)	3 (37.5)	4 (50.0)	3 (37.5)	7 (87.5)	2 (100.0)
Not Hispanic or Latino, n (%)	8 (100.0)	7 (87.5)	6 (75.0)	7 (87.5)	7 (87.5)	7 (87.5)	2 (100.0)
Weight, mean (SD), kg	73.9 (17.4)	78.3 (17.9)	73.3 (11.9)	75.5 (6.8)	78.0 (10.9)	76.2 (12.8)	61.0 (0.0)
BMI, mean (SD), kg/m^2	25.4 (3.5)	27.3 (4.7)	26.3 (4.4)	27.4 (3.0)	26.9 (2.4)	25.7 (3.4)	24.3 (1.6)

BID, twice daily; BMI, body mass index; QD, once daily; SD, standard deviation.

Safety

- A summary of AEs is presented in **Table 2**
  - TEAEs, all mild, occurred in 6 subjects across cohorts
    - In the younger cohorts, dizziness (300 mg QD), headache (300 mg BID), dermatitis contact (placebo), and orthostatic hypotension (placebo) were reported (n=1 each)
    - In the elderly cohort, 1 subject experienced worsening of benign prostatic hyperplasia and hematochezia (300 mg QD), and 1 subject reported constipation and nausea (placebo)

Table 2. Summary of Subjects Experiencing TEAEs

	Younger Cohorts					Elderly Cohort	
TEAE, n (%)	CNTX-6970 100 mg QD (n=8)	CNTX-6970 300 mg QD (n=8)	CNTX-6970 600 mg QD (n=8)	CNTX-6970 300 mg BID (n=8)	Pooled Placebo (n=8)	CNTX-6970 300 mg QD (n=8)	Placebo (n=2)
Any TEAE	0	1 (12.5)	0	1 (12.5)	2 (25.0)	1 (12.5)	1 (50.0)
Severe TEAEs	0	0	0	0	0	0	0
Investigator-defined drug-related TEAEs	0	0	0	1 (12.5)	1 (12.5)	0	0

Percentages were calculated using the total number of subjects in each treatment group as the denominator.
A subject may be counted in ≥1 category.
BID, twice daily; QD, once daily; TEAE, treatment-emergent adverse event.

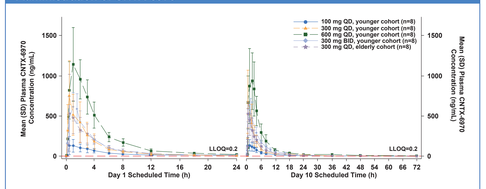
- Two TEAEs (headache [300 mg BID] and orthostatic hypotension [placebo]), both occurring in the younger cohorts, were considered related to study drug
- There were no serious AEs or AEs leading to discontinuation or death
- No other clinically significant findings were observed with regard to vital signs, physical examinations, clinical laboratory tests, or ECG findings

Pharmacokinetics

Pharmacokinetic Parameters

- PK parameters on days 1 and 10 following oral administration are presented in **Figure 2** and **Table 3**
  - CNTX-6970 was rapidly absorbed, with median t_{max} values between 0.5 and 1.5 hours on day 1 and between 0.5 and 1.0 hour on day 10 across dose groups
  - On day 1, mean $t_{1/2}$ ranged from 3.6 to 8.8 hours, and geometric mean $t_{1/2}$ ranged from 3.5 to 8.7 hours
- Exposure (C_{max} and AUC_{0-24}) was similar on day 1 compared with day 10 for each dose group (**Table 3**)
- Steady-state was reached on day 2 with repeated QD or BID dosing

Figure 2. Geometric Mean Plasma Concentration Over Time After Oral Administration of CNTX-6970



Concentrations with actual time outside of the scheduled collection window were not included in the summary but were still used in the calculation of PK parameters.
Lower limit of quantitation for CNTX-6970 is 0.2 ng/mL.
BID, twice daily; LLOQ, lower limit of quantitation; PK, pharmacokinetic(s); QD, once daily; SD, standard deviation.

Table 3. Selected Pharmacokinetic Plasma Parameters After Oral Administration of CNTX-6970

	Younger Cohorts				Elderly Cohort
Pharmacokinetic Parameter	CNTX-6970 100 mg QD (n=8)	CNTX-6970 300 mg QD (n=8)	CNTX-6970 600 mg QD (n=8)	CNTX-6970 300 mg BID (n=8)	CNTX-6970 300 mg QD (n=8)
AUC_{0-24}, h•ng/mL					
Day 1*	615.4 (45.7)	2023.1 (44.2)	4979.2 (28.2)	2044.5 (35.2)	2146.4 (36.8)
Day 10*	704.6 (43.2)	2075.0 (31.8)	4987.4 (31.0)	2686.8 (34.6)	2198.4 (33.8)
$AUC_{0-\infty}$, h•ng/mL					
Day 1	669.2 (44.3)	2096.5 (43.2)	5161.8 (27.6)	2186.0 (35.4)	2309.8 (37.0)
C_{max}, ng/mL					
Day 1	138.3 (61.8)	680.2 (63.4)	1126.6 (35.1)	640.4 (34.6)	541.8 (63.0)
Day 10	166.0 (39.5)	706.9 (45.2)	1051.5 (41.9)	659.9 (50.2)	524.6 (61.1)
t_{max}, h					
Day 1	1.0 (0.5–3.0)	0.5 (0.5–2.0)	1.0 (0.5–2.0)	1.5 (0.5–1.5)	1.0 (0.5–1.0)
Day 10	0.75 (0.5–3.0)	0.5 (0.5–2.0)	1.0 (0.5–3.0)	1.0 (0.5–1.0)	0.5 (0.5–4.0)
$t_{1/2}$, h					
Day 1	8.70 (16.7)	6.72 (16.5)	6.46 (14.7)	3.51 (16.7)	8.40 (15.6)
CL/F, L/h					
Day 1	149.4 (44.3)	143.1 (43.2)	116.2 (27.6)	137.2 (35.4)	129.9 (37.0)

Data presented as geometric mean (geometric coefficient of variation) except t_{max}, which is presented as median (range).
*For the BID dosing regimen, data shown are for AUC_{0-12}.
AUC, area under the curve; BID, twice daily; CL/F, apparent plasma clearance; C_{max}, maximum plasma concentration; QD, once daily; $t_{1/2}$, half-life; t_{max}, time from dosing to maximum plasma concentration.

Dose Proportionality of CNTX-6970 Pharmacokinetic Parameters

- CNTX-6970 demonstrated dose-proportional PK on day 1 and day 10 for C_{max}, $AUC_{0-\infty}$, and AUC_{0-24} from 100 mg to 600 mg (**Table 4**)
- PK parameters indicated that exposure was higher in females versus males and in elderly versus younger subjects

Table 4. Dose Proportionality of CNTX-6970 Pharmacokinetic Parameters After Oral Administration

	Day 1 Younger Cohort CNTX-6970 100–600 mg QD (n=24)	Day 10 Younger Cohort CNTX-6970 100–600 mg QD (n=24)
Parameter	Slope β (90% CI)	Slope β (90% CI)
AUC_{0-24}	1.16 (0.98–1.34)	1.08 (0.91–1.25)
$AUC_{0-\infty}$	1.13 (0.95–1.31)	NA
C_{max}	1.20 (0.98–1.43)	1.08 (0.87–1.28)

AUC, area under the curve; β, slope parameter; C_{max}, maximum plasma concentration; NA, not available; QD, once daily.

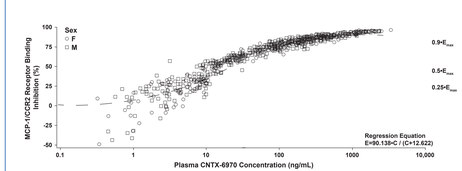
Monocyte Counts

- In younger subjects, a trend toward decreased monocyte counts (generally within normal limits) was observed only at 4 hours postdose; this decrease was transient and not clinically significant
- There were no evident trends in monocyte counts among elderly subjects

CNTX-6970 Inhibition of Ligand Binding to CCR2 and CCR5

- CNTX-6970 resulted in dose-dependent inhibition of MCP-1 ligand binding to CCR2 receptors (**Figure 3**)
  - Inhibition of CCR2 receptor binding was generally similar between males and females, with a gender difference noted for the placebo and 100 mg QD cohorts
  - Inhibition of ligand binding to CCR2 was greater in elderly subjects (300 mg QD) versus younger subjects receiving the same dose
- CNTX-6970 inhibited binding of MCP-1 to CCR2 in a concentration-dependent manner (**Figure 3**)

Figure 3. Pharmacokinetic/Pharmacodynamic Correlation Between CNTX-6970 Plasma Concentration and Percent Inhibition of CCR2



C, concentration; CCR, chemokine receptor; E, effect; E_{max}, maximum observed pharmacodynamic effect from modeling; F, female; M, male; MCP, monocyte chemoattractant protein.

- Data for inhibition of RANTES ligand binding to CCR5 receptor were inconclusive

CONCLUSIONS

- There were no serious AEs or AEs leading to discontinuation with CNTX-6970 across the full dose range (100–600 mg) in healthy male and female subjects and in elderly subjects (300 mg)
- CNTX-6970 exhibited a favorable PK profile and dose proportionality in C_{max}, $AUC_{0-\infty}$, and AUC_{0-24} values on days 1 and 10
- CNTX-6970 inhibited CCR2 receptor binding to the MCP-1 ligand in a dose- and concentration-dependent manner
- These findings support the continued clinical development of CNTX-6970

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DISCLOSURES

This study was sponsored by Centrexion Therapeutics Corp., Boston, MA. Randall M. Stevens, Kimberly Guedes, and Nilam Mistry are employees of Centrexion Therapeutics Corp. and own stock/stock options in that company. Michael H. Silverman is a consultant for Centrexion Therapeutics Corp. Lukasz Biernat is an employee of Medpace Inc.