PF86

Safety and Pharmacokinetics of Single Ascending Doses of Human Somatostatin Receptor 4 (hSSTR4) Agonist CNTX-0290 in Healthy Subjects

Randall M. Stevens, MD[1]; Kimberly Guedes, RN, BSN[1]; William Kerns, DVM[2]; Kei-Lai Fong, PhD[2]; Michael H. Silverman, MD, FACP[2]; Guangchun Zhou, PhD[3]; Leela Vrishabhendra, MD[3]

[1]Centrexion Therapeutics Corp., Boston, MA, USA; [2]Accellient Partners LLC, Boston, MA; [3]Medpace, Inc., Cincinnati, OH

INTRODUCTION

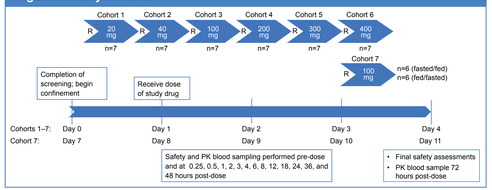
- Chronic pain is often clinically challenging due to difficulty determining its etiology and the occurrence of multiple comorbid painful conditions
- CNTX-0290 is a potent and selective full agonist for the human somatostatin receptor 4 (SSTR4), a novel target for potential pain therapy
- CNTX-0290 is in clinical development as an orally delivered analgesic for chronic pain, and broad analgesia in models of nociceptive and neuropathic pain has been observed in preclinical studies
- We report results from a first-in-human, single ascending dose study conducted to evaluate the safety and pharmacokinetics (PK) of CNTX-0290

METHODS

Study Design

- This study evaluated the safety and PK of CNTX-0290 in healthy subjects (**Figure 1**)
- For each cohort, the first 2 subjects were dosed with blinded study drug; the remaining 5 subjects were dosed at least 48 hours after the sentinel dose, provided no significant safety or tolerability issues were observed
- In cohorts 1–6 (n=7 each), subjects were randomized 6:1 in a double-blind fashion to receive a single dose of CNTX-0290 20, 40, 100, 200, 300, or 400 mg in successive cohorts or placebo in a fasted state
- In cohort 7, 12 subjects received CNTX-0290 100 mg in a randomized (1:1), open-label, 2-period crossover design (fed/fasted)
  - Subjects in cohort 7 underwent 2 dosing periods, with at least 1 week separating the 2 doses

Figure 1. Study Schema



Key Inclusion Criteria

- Healthy male and female volunteers aged 18–45 years (inclusive) based on review of medical history, concomitant medications, physical examination, and clinical laboratory and electrocardiogram evaluations
- Body mass index 18–35 kg/m^2 (inclusive)
- Weight ≥50 kg

Key Exclusion Criteria

- Abnormal findings in the medical examination or laboratory values judged as clinically relevant by the investigator
- Repeated measurement of systolic blood pressure (BP) outside the range of 90–140 mm Hg, diastolic BP outside the range of 50–90 mm Hg, or heart rate outside the range of 50–100 beats per minute
- Evidence of concomitant disease or hepatic, renal, respiratory, cardiovascular, metabolic, immunological, psychiatric, or hormonal disorders
- Evidence of a gastrointestinal disorder that could have interfered with the absorption of orally administered drugs

Pharmacokinetic and Safety Assessments

- Primary objectives included evaluation of PK, dose proportionality, urinary excretion, and safety of single doses of CNTX-0290 in healthy subjects
  - Evaluations included effects of food on CNTX-0290 PK
- The following PK parameters were determined
  - Observed maximum plasma concentration (C_{max})
  - Observed time to reach C_{max} (t_{max})
  - Terminal elimination half-life ($t_{1/2}$)
  - Area under the plasma concentration vs time curve (AUC) from time 0
    - To last quantifiable plasma concentration (AUC_{0-t})
    - Extrapolated to infinity (total exposure; $AUC_{0-\infty}$)
    - To 24 hours post-dose (AUC_{0-24})
  - Apparent plasma clearance (CL/F)
- Dose proportionality was analyzed for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ using a linear regression model applied to log-transformed dose with log-transformed dose as a covariate
- Fraction of study drug excreted in 24- and 48-hour urine for cohort 7 (fe_{0-24} and fe_{0-48})

Prohibited Concomitant Medications

- Use of any prescribed medication within 14 days prior to the first admission and throughout the study (except for hormonal contraception)
- Use of over-the-counter medicinal products (including herbal and dietary supplements) within 7 days prior to the first admission and throughout the study

Statistical Analysis

- The PK population included all subjects who received CNTX-0290 study drug, had no major deviations, and for whom ≥1 primary PK variable could be determined and was interpretable
- Data were summarized by treatment using descriptive statistics (number of subjects, mean, median, standard deviation [SD], coefficient of variation [CV], minimum, maximum, geometric mean [GM], and GM CV) for continuous variables and summarized by treatment using frequencies and percentages for categorical variables
- Food effect evaluation used an analysis of variance model performed on ln-transformed values (fed vs fasted)
- Urinary excretion was reported as the amount of study drug recovered in 24 and 48 hours, and the percentage of the dose administered
- Safety analyses were reported using descriptive statistics and included all subjects who received ≥1 dose of study drug

RESULTS

Subject Disposition and Baseline Characteristics

- A total of 54 subjects were enrolled (**Table 1**)
  - Cohorts 1–6: 36 subjects randomized to receive CNTX-0290 and 6 randomized to receive placebo
  - Cohort 7: 12 subjects randomized
  - 48 subjects comprised the PK population
- All subjects completed the study

Table 1. Demographics and Baseline Characteristics

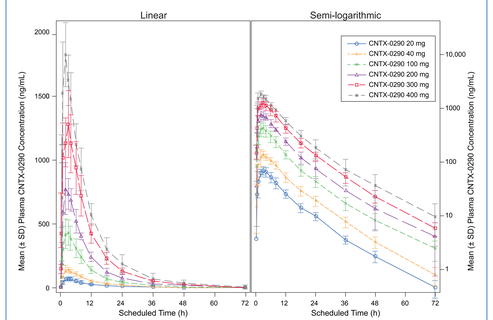
Parameter	Cohorts 1–6, CNTX-0290 (n=36)	Cohort 7 (n=12)
Age, mean (SD), y	32 (6.8)	34 (6.3)
Sex, n (%)		
Female	18 (50)	6 (50)
Male	18 (50)	6 (50)
Race, n (%)		
Black/African American	21 (58)	6 (50)
White	14 (39)	3 (25)
Ethnicity, n (%)		
Not Hispanic or Latino	35 (97)	12 (100)
Hispanic or Latino	1 (3)	0
Weight, mean (SD), kg	81 (11.7)	80 (16.3)
BMI, mean (SD), kg/m^2	28 (3.2)	27 (4.6)

Pharmacokinetic Parameters

Cohorts 1–6

- Following a single dose of CNTX-0290 20–400 mg to healthy subjects, C_{max} was reached at a median time range of 2–3 hours post-dose and then declined in a biphasic fashion, with an apparent $t_{1/2}$ of 10.9–12.6 hours (**Table 2**)
  - Mean plasma CNTX-0290 concentrations throughout the 72-hour post-dose time course are shown in **Figure 2**

Figure 2. Mean Plasma CNTX-0290 Concentrations by Treatment Dose in Cohorts 1–6, PK Population



- Geometric means for C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, and AUC_{0-24} increased with dose (**Table 2**)

Table 2. Summary of PK Parameters for CNTX-0290 by Dose, PK Population

Parameter	Cohort 1 (n=6)	Cohort 2 (n=6)	Cohort 3 (n=6)	Cohort 4 (n=6)	Cohort 5 (n=6)	Cohort 6 (n=6)
C_{max}, ng/mL	70.8 (16.7)	142.7 (17.9)	454.0 (19.0)	827.2 (20.6)	1297.5 (21.2)	1826.11 (12.6)
AUC_{0-t}, h•ng/mL	854.5 (16.8)	1717.2 (14.0)	4789.5 (16.1)	8360.0 (11.1)	14,316.4 (20.5)	19,393.6 (19.1)
$AUC_{0-\infty}$, h•ng/mL	862.5 (17.0)	1729.8 (14.2)	4833.6 (16.2)	8432.9 (11.8)	14,410.6 (20.6)	19,554.7 (19.5)
AUC_{0-24}, h•ng/mL	728.0 (17.4)	1467.9 (12.7)	4194.4 (16.4)	7344.2 (8.5)	12,589.5 (20.5)	16,960.1 (15.7)
t_{max}, h	3.0 (1.1, 4.0)	2.0 (2.0, 2.4)	2.0 (1.0, 3.0)	2.0 (1.0, 4.0)	3.0 (1.0, 3.0)	2.0 (1.0, 3.0)
$t_{1/2}$, h	12.0 (12.8)	10.9 (8.9)	12.6 (13.3)	11.5 (23.4)	11.4 (9.3)	11.8 (18.6)
CL/F, L/h	23.2 (17.0)	23.1 (14.2)	20.7 (16.2)	23.7 (11.8)	20.8 (20.6)	20.5 (19.5)

Data presented as geometric mean (CV%) except for t_{max}, which is shown as median (min, max).
Geometric CV%=100 × (exp(SD^2) − 1)$^{0.5}$, where SD was the SD of the logarithm-transformed data.

Dose Proportionality of CNTX-0290 Pharmacokinetic Parameters

- Dose proportionality existed across the 20- to 300-mg dose range
  - There was no dose proportionality for all cohorts; therefore, cohort 6 (highest dose level) was excluded from the analysis to determine the dose range in which dose proportionality existed
  - Estimated slopes (90% CI) across the 20- to 300-mg range are shown in **Table 3**
    - 90% CIs for AUCs contained 1, indicating dose proportionality
    - 90% CI for C_{max} did not contain 1, showing slight deviation from dose proportionality

Table 3. Dose Proportionality of CNTX-0290

	CNTX-0290, 20–300 mg (n=30)	
Parameter	Slope Estimate (SE)	90% CI
AUC_{0-t}, h•ng/mL	1.03 (0.029)	0.98, 1.08
$AUC_{0-\infty}$, h•ng/mL	1.03 (0.029)	0.98, 1.08
C_{max}, ng/mL	1.08 (0.035)	1.02, 1.14

Evaluation of the Effects of Food on CNTX-0290 Pharmacokinetics

- Mean plasma concentrations for cohort 7 are shown by food status in **Figure 3**, and the summary of PK parameters is shown in **Table 4**

Figure 3. Mean Plasma Concentrations by Food Status in Cohort 7, PK Population

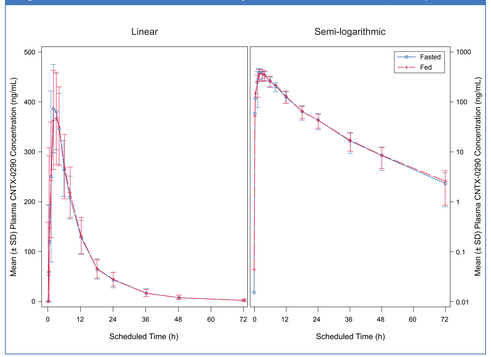


Table 4. Summary of PK Parameters by Food Status in Cohort 7

Parameter	Fasted (n=12)	Fed (n=12)	Fed vs Fasted, Geometric Mean Ratio (90% CI)
C_{max}, ng/mL	404.0 (23.2)	426.32 (21.3)	105.52 (95.72, 116.32)
AUC_{0-t}, h•ng/mL	4358.6 (22.3)	4333.6 (20.5)	99.43 (97.29, 101.61)
$AUC_{0-\infty}$, h•ng/mL	4406.4 (22.5)	4375.1 (20.8)	99.29 (97.18, 101.45)
AUC_{0-24}, h•ng/mL	3770.9 (20.9)	3756.6 (18.5)	—
t_{max}, h	2.0 (0.5, 4.0)	2.5 (0.5, 4.0)	—
$t_{1/2}$, h	12.7 (18.8)	12.4 (17.8)	—
CL/F, L/h	22.7 (22.5)	22.9 (20.8)	—
fe_{0-24}	39.2 (18.8)	40.4 (15.0)	—
fe_{0-48}	43.7 (16.6)	45.0 (14.2)	—

Data presented as geometric mean (CV%) except for t_{max}, which is shown as median (min, max).
Geometric CV% = 100 × (exp(SD^2) − 1)$^{0.5}$, where SD was the SD of the logarithm-transformed data.

- For the ratios of geometric means (90% CI) for the fed vs fasted state, all CIs fell within the prespecified 80% to 125% bounds, indicating that there was no food effect on plasma CNTX-0290 PK parameters
- At 24 hours, 39% and 40% of the administered oral dose of CNTX-0290 was excreted unchanged in urine for the fed and fasted states, respectively
  - At 48 hours, 44% and 45% of the administered dose was excreted unchanged

Safety

- Three subjects receiving CNTX-0290 reported treatment-emergent adverse events, all mild and unrelated to treatment
  - One subject (16.7%) in cohort 3 reported temporomandibular joint syndrome
  - One subject (16.7%) in cohort 4 reported tension headache
  - One subject (8.3%) in fasted cohort 7 reported dry eyes and nausea
- There were no serious adverse events, adverse events that led to discontinuation of study drug, or adverse events that led to death

CONCLUSIONS

- In healthy adults, CNTX-0290 exhibited dose proportionality across the 20- to 300-mg range for AUC_{0-t} and $AUC_{0-\infty}$, but not C_{max}
- There was no effect of food on plasma CNTX-0290 PK parameters
- CNTX-0290 20–400 mg was well tolerated in healthy male and female subjects

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