Preclinical Evaluation of Human Somatostatin Receptor 4 (hSSTR4) Agonist CNTX-0290 for Mixed Pain Conditions

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INTRODUCTION

- Various mediators released during pathological pain states contribute to the sensitization and hyperexcitability of nociceptive neurons[1]
- Stimulation of somatostatin receptor 4 (SSTR4) inhibits nociception in animals, and SSTR4 knockout mice have heightened responses to painful stimuli compared with wild-type mice
- SSTR4 agonists can induce normalization of neuronal excitability, reducing inflammatory and neuropathic pain,[2] and are a novel target for pain therapy
- CNTX-0290 is a human SSTR4 (hSSTR4) agonist under development as an oral analgesic for nociceptive and non-nociceptive pain

MECHANISM OF ACTION

- Somatostatin is an inhibitory neuropeptide that acts via 5 receptor subtypes (SSTR1–5)[3]
- While most SSTR subtypes are involved in homeostatic hormone regulation, SSTR4 appears to have a functional role in modulating sensory nerve transmission
- SSTR4 has been shown to be localized to axons and cell bodies of dorsal root ganglia neurons in rats, cynomolgus monkeys, and humans
- SSTR4 controls nociceptive transmission by modulating multiple pathways in dorsal root ganglia neurons (**Figure 1A**):
  - Enhances potassium currents by opening G protein–coupled, inwardly rectifying potassium channels
  - Decreases calcium currents by inhibition of voltage-gated calcium channels
  - Inhibits transient receptor potential vanilloid-1 and ankyrin-1 channels
- CNTX-0290 activates the SSTR4 receptor, leading to normalization of excitability and reduction of synaptic transmission (**Figure 1B**)

Figure 1. Mechanism of Action of CNTX-0290

A. Regulatory Role of SSTR4 in Pain Pathways

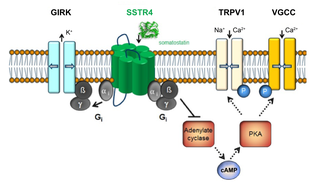
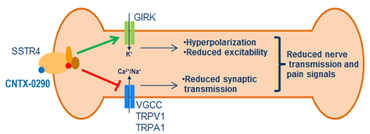


Figure 1. Mechanism of Action of CNTX-0290 (cont'd)

B. Mechanism of Action of CNTX-0290



Ca^{2+}, calcium; cAMP, cyclic adenosine monophosphate; Gi, inhibitory G protein complex, comprising α, β, and γ subunits; GIRK, G protein–coupled inwardly rectifying potassium channel; K^+, potassium; Na^+, sodium; PKA, protein kinase A; SSTR4, somatostatin receptor 4; TRPA1, transient receptor potential ankyrin 1; TRPV1, transient receptor potential vanilloid 1; VGCC, voltage-gated calcium channel.

PRECLINICAL STUDIES

In Vitro Potency and Selectivity

- CNTX-0290 demonstrated potent and selective agonism for the hSSTR4 receptor
  - Moderate species selectivity was identified for human vs homologues of rat (1.5-fold) and cynomolgus monkey (5-fold) receptors (**Table 1**)
  - The affinity of CNTX-0290 for hSSTR1, 2, 3, and 5 and toward a panel of 97 peripheral and central targets is >10,000 nM, indicating a favorable selectivity profile

Table 1. CNTX-0290 SSTR4 In Vitro Binding Pharmacology

	Human	Rat	Cynomolgus Monkeys
Ki,[a] nM	<50	<80	<10
EC_{50},[b] nM	<10	<80	<10

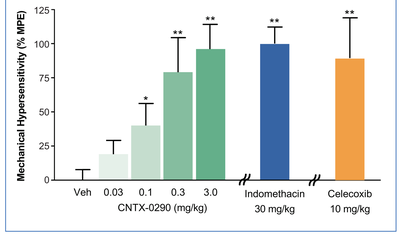
cAMP, cyclic adenosine monophosphate; EC_{50}, half-maximal effective concentration; Ki, inhibitory constant.
[a]Receptor-binding site.
[b]cAMP assay.

Analgesic Activity

Complete Freund's Adjuvant Model: Inflammatory Pain

- Efficacy of CNTX-0290 0.03 to 3 mg/kg vs vehicle 2 hours after oral administration was compared with indomethacin 30 mg/kg and celecoxib 10 mg/kg, and minimal effective dose (MED) was determined
- CNTX-0290 showed dose-dependent antinociceptive effects (**Figure 2**)
  - Maximum efficacy, comparable to indomethacin and celecoxib, was achieved at 3 mg/kg
  - MED was 0.1 mg/kg, corresponding to a minimal effective concentration (MEC) of 32 nM
  - Efficacy was observed up to 24 hours

Figure 2. CNTX-0290 Dose Response in the Rat CFA Model of Inflammatory Pain

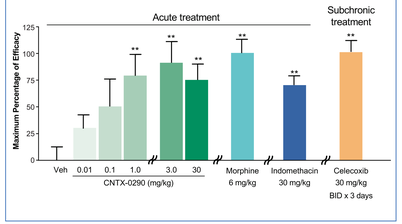


CFA, complete Freund's adjuvant; MPE, maximum percentage of efficacy; SEM, standard error of the mean; Veh, vehicle. Data are mean ± SEM of 10–12 rats per group.
*P<0.05; **P<0.01 vs vehicle.

Monosodium Iodoacetate Model: Osteoarthritis Pain

- In the monosodium iodoacetate model, weight-bearing deficit was assessed following oral administration of CNTX-0290 0.01 to 30 mg/kg
- CNTX-0290 1 to 30 mg/kg significantly reversed weight-bearing deficit 2 hours after dosing compared with vehicle
  - At 3 and 30 mg/kg, CNTX-0290 efficacy was comparable to morphine (**Figure 3**)
  - Celecoxib showed efficacy only after subchronic treatment
- Efficacy was observed up to 24 hours

Figure 3. CNTX-0290 Efficacy in the Rat MIA Model of Osteoarthritis Pain



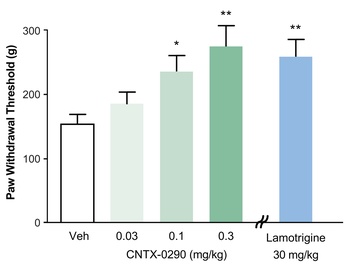
BID, twice daily; MIA, monosodium iodoacetate; SEM, standard error of the mean; Veh, vehicle. Data are mean ± SEM of 10–11 rats per group.
**P<0.01 vs vehicle.

Partial Nerve Ligation Model: Mononeuropathic Pain

Analgesic Efficacy

- Paw withdrawal threshold was determined for oral CNTX-0290 0.03 to 0.3 mg/kg vs vehicle, with lamotrigine 30 mg/kg serving as a positive control
- Maximum efficacy 2 hours after CNTX-0290 administration was achieved at 0.3 mg/kg and was comparable to lamotrigine (**Figure 4**)
  - MED=0.1 mg/kg, corresponding to MEC=25 nM

Figure 4. CNTX-0290 Efficacy in the Rat PNL Model of Mononeuropathic Pain



g, grams; PNL, partial nerve ligation; SEM, standard error of the mean; Veh, vehicle. Data are mean ± SEM of 10 rats per dose group.
*P<0.05; **P<0.01 vs vehicle.

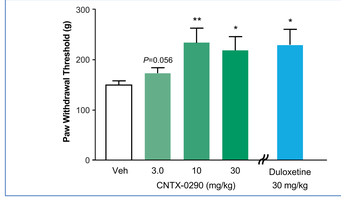
Effect of Repeated Exposure

- Receptor desensitization and loss of function after repeated exposures were investigated in the same model
- CNTX-0290 was dosed twice daily for 5 days and pain threshold was assessed at the end of treatment and compared with single-dosing treatment
- No evidence of tachyphylaxis was identified; CNTX-0290 maintained efficacy in the same magnitude range as the single-treatment group

Streptozotocin-Induced Diabetic Peripheral Polyneuropathic Pain Model

- The effect of oral CNTX-0290 10 and 30 mg/kg on diabetic polyneuropathy was assessed using the streptozotocin model and compared with the positive control duloxetine 30 mg/kg
- In a dose-dependent manner, CNTX-0290 significantly increased paw withdrawal threshold vs vehicle (**Figure 5**), with an effect comparable to duloxetine 30 mg/kg

Figure 5. CNTX-0290 Efficacy in the STZ Rat Model of Diabetic Neuropathy



g, grams; SEM, standard error of the mean; STZ, streptozotocin; Veh, vehicle. Data are mean ± SEM of 12 rats per dose group.
*P<0.05; **P<0.01 vs vehicle.

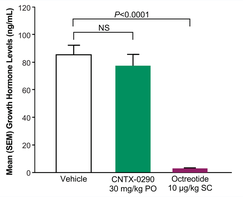
SAFETY

- Safety pharmacology studies were conducted in rats and cynomolgus monkeys
  - Cynomolgus monkey is the proposed nonrodent species for toxicology studies as SSTR4 is not expressed in dogs, pigs, and guinea pigs

Hormonal Regulation

- Somatostatin inhibits secretion of hormones such as growth hormone and insulin
- Octreotide exerts pharmacologic actions similar to somatostatin, and is a more potent inhibitor of growth hormone and insulin
  - Data suggest that octreotide is a SSTR1, 2, 3, and 5 agonist, indicating that its effect on glucose metabolism may not be related to SSTR4
- The effects of CNTX-0290 on growth hormone and glucose tolerance were evaluated
- CNTX-0290 did not significantly alter growth hormone release
  - Growth hormone release was significantly inhibited by octreotide (**Figure 6**)

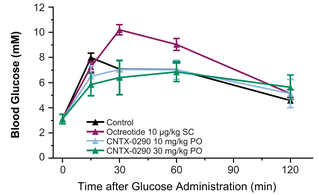
Figure 6. Effect of CNTX-0290 on Growth Hormone Release



NS, not significant; PO, orally; SC, subcutaneously; SEM, standard error of the mean.

- CNTX-0290 did not affect glucose tolerance (**Figure 7**), while octreotide significantly increased glucose levels

Figure 7. Effect of CNTX-0290 on Glucose Levels



PO, orally; SC, subcutaneously.

Central Nervous System Activity

- CNTX-0290 was not associated with central nervous system side effects observed with standard of care therapies pregabalin and duloxetine

CONCLUSIONS

- CNTX-0290 is a potent, selective full agonist for hSSTR4
- CNTX-0290 has broad analgesic efficacy in animal models of nociceptive and neuropathic pain, demonstrating the potential to treat mixed pain conditions
- CNTX-0290 did not adversely affect growth hormone release, glucose tolerance, or central nervous system activity

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