An SSTR4 agonist: LY3556050/CNTX-0290

Phase 2 'Chronic Pain Master Protocol'

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Financial Disclosure

- No relevant financial disclosures

How we Feel Pain: a piece of the puzzle

- Pathologic states → release of pain mediators→ nociceptor sensitization and firing frequency (McHugh 2000)
- Cellular damage/inflammation further augments nociception

A Solution to Nociceptive Sensitization and Excitability?

- …how can we downregulate nociception?

Somatostatin and Receptors

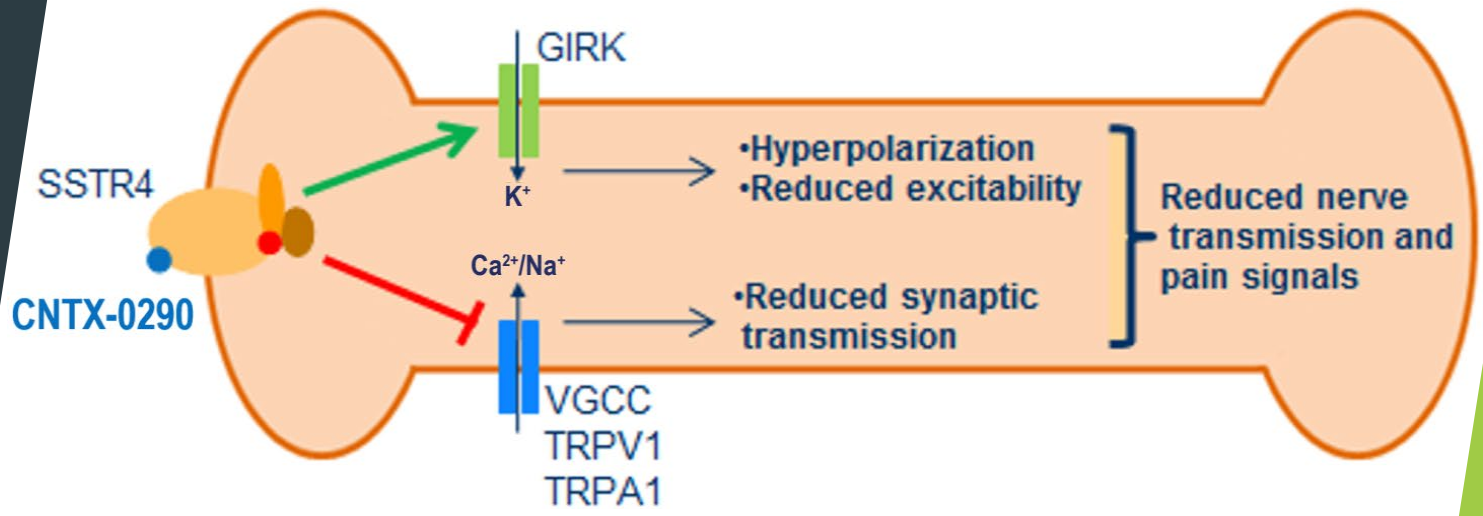
- Somatostatin is an inhibitory neuropeptide
- 5 G-protein coupled receptor subtypes, most of which have endocrine effects

SSTR4 and its Role in Pain

- Somatostatin Receptor 4 (SSTR4) seems to play a role in inflammation and pain transmission without endocrine actions
  - Anti-inflammatory properties in animal models (Elekes 2008)
    - SSTR4 analogue “J-2156” inhibited arthritic pain in rats (Helyes 2006)
  - SSTR4 and δOR exist in a complex and act synergistically (Somvanshi 2014)
  - Somatostatin analogue, octreotide, induced analgesic effects in post-operative, neoplastic pain, headaches, and terminal cancer, where opioids failed (Somvanshi 2014)

SSTR4 and Pain Modulation

- Multiple pathways modulated in the DRG (Jiang 2003, Moore 1998)
  - ⬆ K influx by opening G protein-coupled receptors
  - ⬇ Ca influx by inhibition of voltage-gated channels
  - **Inhibits** transient receptor potential vanilloid-1 and ankyrin-1 channels (ion channels known to play a role in pain)
- Leading to normalization of excitability and reduced synaptic transmission



Stevens, Randall M, et al. Preclincial Poster - Centrexion. https://centrexion.com/wp-content/uploads/2019/09/APS-2019-0290-Preclincial-Poster-Final-3-29-19-Final.pdf.

Preclinical Trials: Potency and Selectivity

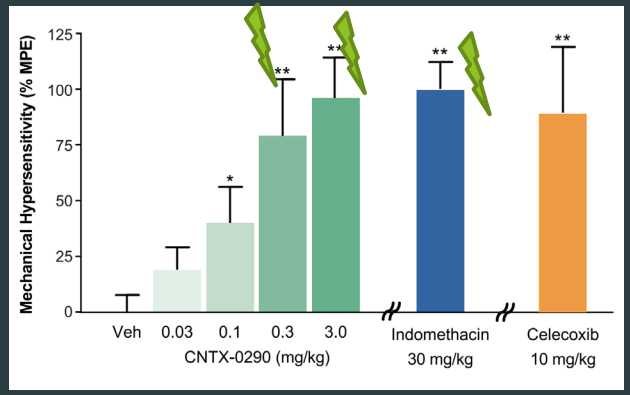
- In vitro studies compared selectivity amongst humans vs. rats. Cynomolgus monkeys
- Significantly selective for hSSTR4 agonism (Ki=41 nM; hSSTR 1, 2, 3, and 5 Ki >10,000 nM)
- hSSTR4 potency was significant (EC50=2.6 nM)

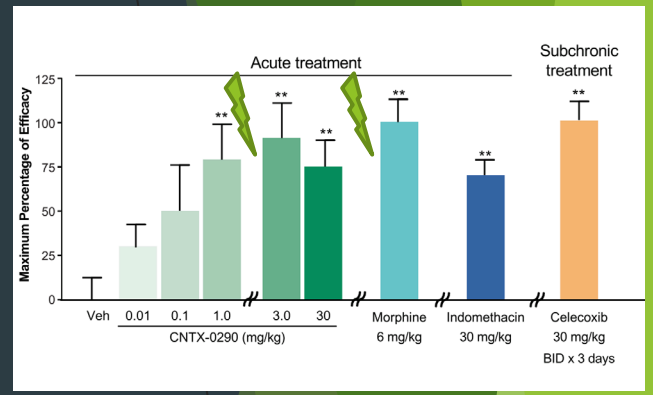
	Human	Rat	Cynomolgus Monkeys
Ki,[a] nM	<50	<80	<10
EC_{50},[b] nM	<10	<80	<10

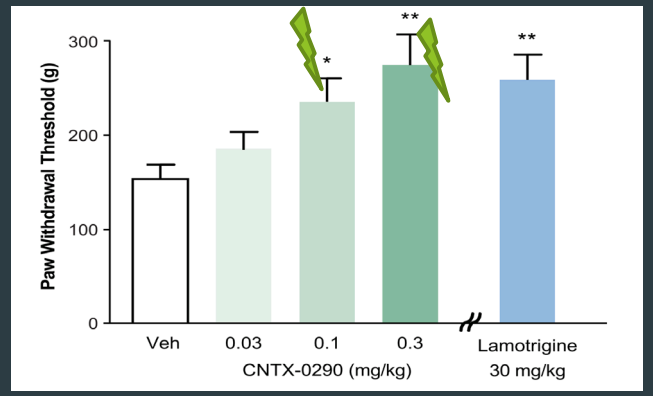
cAMP, cyclic adenosine monophosphate; EC_{50}, half-maximal effective concentration; Ki, inhibitory constant.
[a]Receptor-binding site.
[b]cAMP assay.

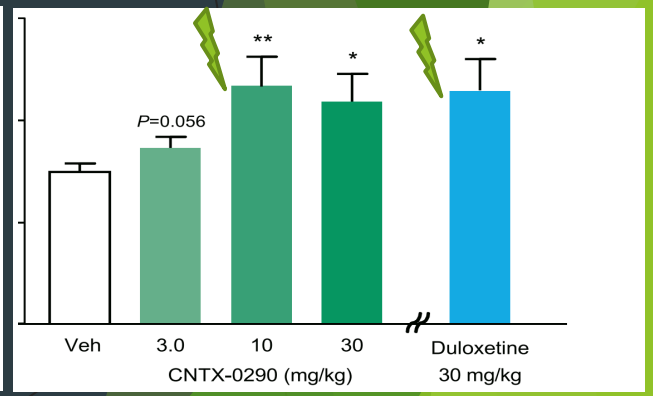
Preclinical Trials: Pain in Rat Models

- Inflammatory Pain:
  - Mycobacterium-induced inflammation
  - Max effective dose (3mg/kg) comparable to indomethacin 30mg/kg and celecoxib 10mg/kg
- Osteoarthritic Pain:
  - Monosodium iodoacetate-induced joint destruction
  - 3mg/kg comparable to morphine and reversed WB deficit after 2 hours
- Mononeuropathy:
  - Partial nerve ligation
  - 0.3mg/kg comparable to lamotrigine 30mg/kg
- Diabetic Peripheral Neuropathy:
  - Streptozotocin-induced insulin deficiency
  - 10mg/kg comparable to duloxetine 30mg/kg









Preclinical Effect of Repeat Exposure in Rats

- Performed in the PNL model, administered BID for 5 days, compared with single-dosing treatment
  - No evidence of tachyphylaxis
  - Efficacy was comparable to single-treatment group

Preclinical Investigation into Adverse Effects in Rats

- Hormonal Regulation:
  - Somatostatin inhibits hormones such as growth hormone and insulin
  - CNTX-0290 did not significantly alter growth hormone release nor glucose levels compared to octreotide
- CNS-related events
  - No CNS-related side effects observed with standard of care therapies e.g. pregabalin and duloxetine

6 Total Clinical Trials

- Phase 1
  - Health Participants
  - Repeated Doses in Healthy Participants
  - Effect on Metformin in Health Participants

- Phase 2 ‘Chronic Pain Master Protocol’
  - Knee Osteoarthritis
  - Chronic Low Back Pain
  - Diabetic Peripheral Neuropathy

Phase I: Healthy Participants

- Double-blinded RCT
- 34 participants
- LY3556050 vs. placebo for 31 days
- Followed for 9 weeks
- Primary outcomes: # of participants with Serious Adverse Events (SAE)
- Secondary outcomes: pharmacokinetics/concentration-related
- Results not yet published, presumed favorable risk/benefit ratio with no significant number of SAEs based on FDA approval

Phase I: Dosing in Healthy Participants

- RCT
- Part 1 (open-label): single dose of LY3556050 vs. placebo for 5 days
- Part 2 (double-blinded): multiple ascending doses vs. placebo 14 days
- 106 participants
- Followed for 30 days
- Primary outcomes: SAEs and pharmacokinetics/concentration
- Results not yet published, presumed favorable risk/benefit ratio with no significant number of SAEs based on FDA approval

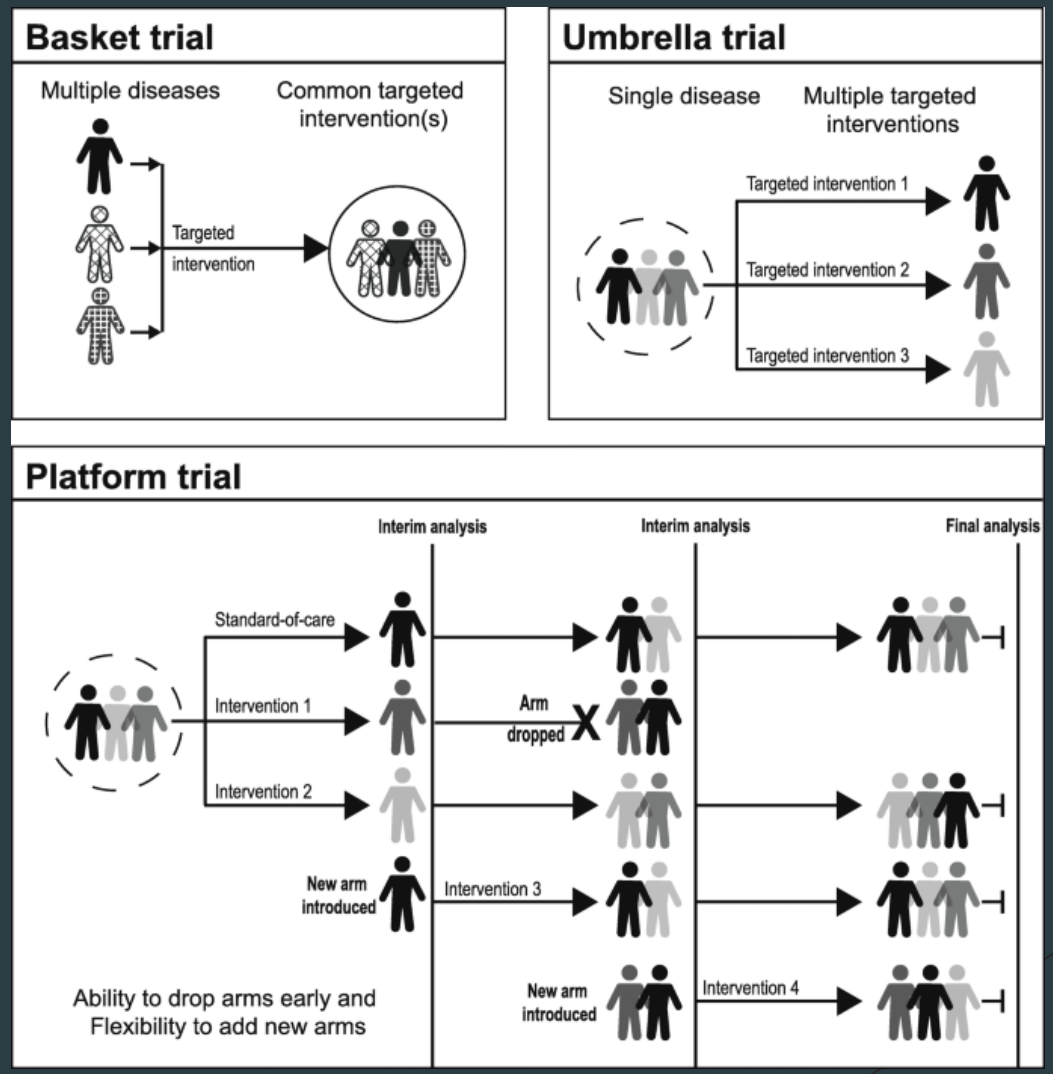
Phase I: Effect on Metformin

- Evaluate Metformin concentration and excretion in combination with LY3556050 in healthy participants
- Open-label non-RCT
- Estimated 18 participants
- Not yet recruiting, approved November 14, 2022

What is a Master Protocol?

- Tests multiple therapies for one indication, one therapy for multiple indications, or both in a standard protocol
- Allow for discontinuation or addition of treatment arms
- 'Borrows' information between study arms to reduce sample size
- May improve the efficiency of drug development through statistical advances and operational efficiencies

Master Protocol



‘Chronic Pain Master Protocol’

- FDA has accepted LY3556050’s master protocol for chronic pain
  - Knee OA
  - Chronic Low Back Pain
  - Diabetic Peripheral Neuropathy

Chronic Pain Master Protocol: Knee Osteoarthritis

- Double-blinded RCT
- LY3556050 vs. placebo (undisclosed treatment duration)
- 202 participants
- Followed up to 8 weeks
- Primary outcomes: Pain severity
- Secondary outcomes: quality of life, functionality, sleep-related
- Data not yet published

Chronic Pain Master Protocol: Chronic Low Back Pain

- Double-blinded RCT
- LY3556050 vs. placebo (undisclosed treatment duration)
- 153 participants
- Followed up to 8 weeks
- Primary outcomes: Pain severity
- Secondary outcomes: quality of life, functionality, sleep-related
- Data not yet published

Chronic Pain Master Protocol: Diabetic Peripheral Neuropathy

- Terminated (slow to enroll, and the sponsor made a business decision to terminate the trial earlier than planned)

What's Next?

- Awaiting results of Phase 2 trials
- Further research is warranted regarding the mechanism and pharmacology regarding SSRT4 and its role in pain

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