Z944: An oral T-type calcium channel modulator for the treatment of pain

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T-type Calcium Channels: A Novel Target for Pain and Other CNS Disorders

- T-type calcium channels are voltage gated and comprised of three subtypes: Ca\textsubscript{v}3.1, Ca\textsubscript{v}3.2 & Ca\textsubscript{v}3.3
- Expressed in Central and Peripheral Nervous System, including primary afferent, dorsal horn neurons, thalamus and somatosensory cortex
- Contribute to neuronal excitability, synaptic excitation, burst firing and action potential trains, and also lower threshold for action potentials

**Pain Signaling**

**Thalamocortical Connectivity**

- Rodent neuropathic and IBS pain models exhibit increased T-type current density
- Gene knockout or antisense reduces pain in neuropathic, acute and visceral pain models
- T-type channel blockers attenuate neuropathic, inflammatory, acute and visceral pain in animal models

- Thalamocortical dysrhythmia linked to CNS indications, e.g. motor, neuropsychiatric and chronic pain syndromes
- Mutations in T-type channels are found in rodent and human excitability disorders
- Approved anti-convulsants (e.g. ethosuximide, valproate) target T-type channels

Source: Adapted from Zamponi, et al., Brain Res. Reviews. 2009

Source: Adapted from Park, et al., Frontiers Neural Circuits. 2013
Z944 is a Potent, Selective Blocker of T-type Calcium Channels

- Displays enhanced potency for the inactivated state across T-type channels
- Z944 block of Cav3.2 is more pronounced during high-frequency firing
- Z944 has >150-fold selectivity vs. non-T-type voltage-gated ion channels
- Inhibits native neuronal T-type currents and burst firing

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<thead>
<tr>
<th>Channel</th>
<th>IC50 (nM)</th>
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<tr>
<td></td>
<td>30%</td>
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<tr>
<td>Cav3.1 (human, exogenous)</td>
<td>50</td>
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<td>Cav3.2 (human, exogenous)</td>
<td>160</td>
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<td>Cav3.3 (human, exogenous)</td>
<td>110</td>
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<td>N-type (rat, exogenous)</td>
<td>11,000</td>
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<td>L-type cardiac calcium (rat CaV1.2)</td>
<td>32,000</td>
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<td>Cardiac Sodium (human NaV1.5)</td>
<td>100,000</td>
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<tr>
<td>hERG channel (human)</td>
<td>7,800</td>
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Z944 Demonstrates Robust Efficacy in Preclinical Pain Models

- **Z944 increases paw withdrawal thresholds in the CFA model of inflammatory pain**
  - Superior to Naproxen (30 mg/kg) in reversing hyperalgesia

- **Z944 decreases pain behavior in the Formalin model**
  - Decreases flinching during the inflammatory phase in rat Formalin model
  - Decreases licking response in both acute and inflammatory phases in mouse Formalin model

- **Z944 restores baseline pain thresholds in the rat model of butyrate induced visceral pain**
  - Model of IBS visceral pain known to involve CaV3.2 overexpression

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**CFA - Rat**

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<tr>
<th>Vehicle</th>
<th>Z944 3 mg/kg PO</th>
<th>Z944 30 mg/kg PO</th>
<th>Naproxen</th>
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**Formalin - Mouse**

- **Vehicle**
- **Z944 (60 mg/kg ip)**

**Visceral - Rat**

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<tr>
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*** p<0.0001; ** p<0.001 vs. vehicle
One-way ANOVA, Tukey’s post test

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**Paw Withdrawal Threshold (g)**

- Z944 (60 mg/kg PO) vs. Vehicle
- *p<0.001 vs. Vehicle

**Time Spent Licking (s)**

- **Vehicle**
- **Z944 (60 mg/kg ip)**

**Blood Pressure (mm Hg)**

- **Vehicle**
- **Z944 (60 mg/kg PO)**

**Butyr**

- *p<0.001 vs. Butyr
One-way ANOVA; Tukey’s post test
**Z944: Pharmacology Summary**

- **Potent**
  - IC$_{50}$ values of 50-160 nM at human T-type calcium channel subtypes

- **State-dependent**
  - 2.5-4 fold more potent for the inactivated state vs. the closed (resting) state

- **Selective**
  - >150 fold less potent at N-type, L-type, hERG and cardiac sodium channels

- **Effective**
  - Significant reduction in hyperalgesia in rodent inflammatory and visceral pain models

- **Drug-like**
  - Soluble, orally bioavailable with excellent pharmaceutical properties

- **Acceptable safety profile**
  - Non-clinical toxicology program supports human studies of up to 28-days dosing
• A Phase 1, double-blind, placebo-controlled study to determine the safety, tolerability and pharmacokinetics of oral Z944 in healthy male subjects in the fed and fasted states

• Phase 1 complete (SAD / MAD) using immediate release formulation
  • Dose proportional pharmacokinetics with good pharmaceutical properties
  • Safe and well tolerated, mild and expected CNS side effects observed, no serious adverse events
  • Maximum tolerated dose identified
  • Exposure similar to preclinical doses where efficacy was achieved

• Supported advancement of Z944 into Phase 1b experimental model of pain
• Phase 1b experimental pain study with Z944
  • Utilized state-of-the-art experimental clinical model measuring Laser-Evoked Potentials (LEP) following administration of capsaicin or exposure to UV light
  • Designed to efficiently provide objective and subjective data on a drug’s ability and modulate neuropathic pain signaling
  • Enables informed decision-making to determine next steps for further clinical study
  • Many currently approved and emerging pain drugs have been tested using the LEP model

Objective LEP results highly correlative with subjective VAS outcomes
Z944-102 LEP study overview

- Double-Blind, Placebo-Controlled, Split Single-Dose, Randomized Crossover Study of the Analgesic/Anti-Hyperalgesic Properties of Z944 in Healthy Volunteers as Measured by Laser Evoked Potentials
  - 20, 40 and 80 mg doses split in 4 administrations every 2 hours vs. placebo
  - 4-period randomized cross-over design

- Primary Endpoint
  - Overall peak-to-peak (PtP) amplitude of laser evoked potentials (LEPs) from capsaicin-irritated skin (a model of neuropathic pain)

- Key Secondary Endpoints
  - PtP amplitude of LEPs from UV-irritated skin (a model of inflammatory pain)
  - Subjective pain using an electronic 100-mm visual analog scale (VAS)
  - Subjective “alertness”, “hand-eye coordination” and “drug liking” using VAS
  - Peripheral and central component amplitudes of LEPs from both skin type areas
  - PK/PD evaluation
Z944 reduces peak-to-peak amplitudes in neuropathic (capsaicin) and inflammatory (UV) pain models

- Statistically significant responses observed at all dose levels

Z944 reduces subjective VAS pain scores in both neuropathic and inflammatory pain models

- At some doses, statistically significant response observed in the neuropathic pain model while inflammatory pain model trended towards significance

Adverse events were generally mild to moderate and no serious adverse events occurred

- Adverse events were primarily central nervous system related
Z944: A T-type Calcium Channel Modulator

- **Reported Positive Phase 1b data in Clinical Pain Model**
  - Efficacy signals observed in inflammatory and neuropathic pain clinical models
  - The first T-type calcium channel modulator to demonstrate clinical translation in pain
  - Results are indicative of Z944’s potential activity in modulating pain signaling

- **Completed Phase 1 SAD and MAD clinical development**
  - Human exposures cover efficacy levels in animal pain models
  - Generally well tolerated with predominantly mild side effects
  - Side effect profile confirms CNS exposure

- **Good pharmaceutical properties**
  - Rapid absorption, dose proportional pharmacokinetics and half life supporting once to twice daily dosing
  - Modified release formulation prototypes developed to smooth out peak exposure levels

- **Strong Intellectual Property**
  - Two issued U.S. patents provide exclusivity until at least 2029

- **Next steps for Z944:**
  - Evaluate modified release formulation in healthy volunteers
  - Initiate Phase 2 studies in an appropriate pain indication in the US in late 2014
Thank You