CLE-400 - a potent alpha-2 adrenergic receptor agonist for the treatment of chronic itch

Dr. Johanna Schumann

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Authors and Disclosures

Johanna Schumann, PhD¹
Elanite Caspi, PhD¹
Orna Goren, PhD¹
Elena Kagan¹

¹Clexio Biosciences, 17 Yegi’a Kapaim St., Petach Tikva, Israel

All authors are employees of Clexio Biosciences
CLE-400: A Novel, Non-Opioid Topical Treatment for Chronic Pruritus

• A New Molecule for Pruritus: CLE-400 is a new investigational drug that has not been approved for commercial distribution. CLE-400 is an aqueous gel of detomidine, a potent α2-adrenergic agonist activating additional potentially therapeutically relevant targets (SST4, H4).
  • Detomidine is approved as a systemic medication for veterinary use. Never developed for human.

• Targeting α2-adrenergic receptors peripherally
  • Systemically administered α2-adrenergic agonists have shown anti-pruritic effect in preclinical model. But limited use to invasive RoA and systemic AEs
  • Clexio’s Immunohistochemistry studies demonstrated that α2-ARs, H4R and SST4R are expressed in pig skin.
  • Activation of α2 receptors could produce anti-pruritic effects by inhibiting the excitability and neural signaling from the peripheral nociceptors/pruriceptors (C-fibers) to the brain

• The technology: CLE-400 gel formulation was developed to deliver high dermal concentrations over an extended period of time (depot effect in the skin) while maintaining limited systemic exposure
Pruritus (itch) is a common and distressing symptom of several dermatological and non-dermatological conditions. Pruritus may result in sleeplessness, inability to work, aggression, anxiety, depression and low quality of life.

23-44 million Americans are estimated to suffer from chronic pruritus due to cutaneous or systemic conditions.¹

No FDA-approved treatment and limited research, especially on neuropathic itch.

Pathophysiological sub-types:
- Dermatological, Systemic, Psychogenic
- Neuropathic (BRP, NP, Post-burn...)

CLE-400: novel topical treatment for Chronic Pruritus

Safe and efficacious treatment options are limited for the treatment of chronic itch.

CLE-400 has a potential to become first topical treatment given the lack of approved therapies and great unmet need.

¹ Mollanazar, Nicholas K., Savannah Dean Koch, and Gil Yosipovitch. "Epidemiology of chronic pruritus: where have we been and where are we going?." Current Dermatology Reports 4.1 (2015): 20-29
# Detomidine: a Potent α2-Adrenergic Receptor Agonist

- Clexio conducted binding and functional assays with Detomidine against a wide range of molecular targets (G-protein coupled receptors, ion channels, transporters, enzymes) in order to better understand its MOA.

- Detomidine has been confirmed to potently activate α2A adrenergic receptors in vitro.

- Clexio also discovered that detomidine activates 2 secondary targets, histamine 4 (H4) and somatostatin 4 (sst4) receptors.

- Detomidine’s targets have been shown to be expressed in the skin.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Source</th>
<th>Activity</th>
<th>Detection method (Incubation)</th>
<th>Measured Component</th>
<th>Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>α2A adrenergic</td>
<td>human recombinant (RBL cells)</td>
<td>agonist</td>
<td>Fluorimetry (RT)</td>
<td>intracellular [Ca2+]</td>
<td>EC_{50} ~24 nM</td>
</tr>
<tr>
<td>Histamine H4</td>
<td>human recombinant (HEK-293 cells)</td>
<td>(partial) agonist</td>
<td>Cellular dielectric spectroscopy (28°C)</td>
<td>Impedance</td>
<td>EC_{50} ~5μM</td>
</tr>
<tr>
<td>Somatostatin 4 sst4</td>
<td>human recombinant (CHO cells)</td>
<td>agonist</td>
<td>HTRF* (37°C)</td>
<td>cAMP</td>
<td>EC_{50} ~7μM</td>
</tr>
</tbody>
</table>

*Homogeneous Time Resolved Fluorescence*  

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**CLE-400 Shows Robust Efficacy in a Mice Chloroquine-induced Pruritus Model**

**Total scratching events over 15 min (0-15 min).****P < 0.0001 compared to vehicle-treated group. N=7-8 per group. One-way ANOVA with Fisher’s LSD test.

Positive control, U-50,488, was injected IP and is known to be a short-acting antipruritic agent (lasting for ~15 to 30 min)

**Topical application of CLE-400 significantly suppressed and almost completed blocked chloroquine-induced scratching behaviors at all dose levels**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Group Size</th>
<th>Frequency of dosing</th>
<th>Dose Level</th>
<th>Route</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLE-400 Placebo</td>
<td>8 CD-1 mice (4 Males + 4 Females)</td>
<td>Once daily for 5 days prior to induction (Day 5), with the 5th application 30 min prior to chloroquine challenge**</td>
<td>Topical 75 µL/cm² over 2 cm² (total of 150 µL)</td>
<td>Dermal</td>
<td>On day 5: Number of scratching events recorded for 30 min post-chloroquine induction (0-30min, at 5-min bins) and scored in a blinded fashion</td>
</tr>
<tr>
<td>CLE-400 0.1%</td>
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<tr>
<td>CLE-400 0.33%</td>
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<tr>
<td>CLE-400 1%</td>
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</tr>
<tr>
<td>Positive control</td>
<td>U-50,488*</td>
<td>Single Dose on Day 5, 30 min prior to chloroquine challenge</td>
<td>3 mg/kg</td>
<td>IP</td>
<td></td>
</tr>
</tbody>
</table>

*U-50,488, a kappa opioid receptor agonist, administered intraperitoneally 30 min prior to chloroquine, significantly attenuated scratching, confirming the validity of the model.

**Chloroquine (0.4 mg/animal) was injected subcutaneously into the right shoulder area at time 0 on Day 5**
CLE-400: results and conclusions

- Detomidine has been confirmed to potently activate $\alpha_2A$ adrenergic receptors \textit{in vitro}, with additional modalities that might contribute to CLE-400 efficacy, presenting a possible multi-modal MOA.

- Main and secondary targets of detomidine have been shown to be expressed in the skin, strengthening the proposition of local activity of CLE-400.

- Topical administration of CLE-400 demonstrated robust pharmacological effect in a mouse model of pruritus.

- CLE-400 is generally well tolerated locally and systemically in efficacy and safety/toxicology studies.

- FIH SAD study was completed successfully, 3 doses tested. MAD study is ongoing.
You are welcome to contact us

Johanna.schumann@clexio.com
david.dangoor@clexio.com