A NOVEL PARTIAL M AGONIST K ANTAGONIST FOR THE TREATMENT OF IBS-D WITHOUT THE RISK OF PANCREATITIS/SPHINCTER OF ODDI SPASM

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The treatment of IBS remains challenging

Existing products marketed to treat IBS-D have significant limitations

- Lotronex – (alosetron, 5-HT3 inhibitor)
  - Serious risk of ischemic colitis risk (black box)

- Xifaxan (rifaximin, antibiotic)
  - Short term treatment with poor and variable response

- Viberzi (eluxadoline, mu agonist)

40% increase in pancreatobiliary AEs between Oct ‘16 and Jan ‘17
Aims

• To develop a peripherally restricted μ agonist that is devoid of pancreatobiliary and other gastrointestinal adverse effects

• To test its pharmacological effects in pre-clinical models
Not all opioids cause sphincter of Oddi spasm: a case for buprenorphine

<table>
<thead>
<tr>
<th>FEATURES</th>
<th>BEFORE</th>
<th>AFTER</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenal pressure mmHg</td>
<td>7.5</td>
<td>8.1</td>
<td>&gt;0.1 NS</td>
</tr>
<tr>
<td>SO basal pressure mmHg</td>
<td>18.1</td>
<td>16.5</td>
<td>&gt;0.2 NS</td>
</tr>
<tr>
<td>Duration of SO waves S</td>
<td>3.3</td>
<td>3</td>
<td>&gt;0.1 NS</td>
</tr>
<tr>
<td>Amplitude of SO waves cpm</td>
<td>58.3</td>
<td>30.4</td>
<td>&lt; 0.0005 S</td>
</tr>
<tr>
<td>Frequency of SO waves cpm</td>
<td>8.4</td>
<td>9</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Cholodecal pressure mmHg</td>
<td>11.3</td>
<td>10.8</td>
<td>&gt;0.2</td>
</tr>
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ORP-101: A novel peripherally restricted opioid agonist

Dimer of buprenorphine

STABLE AND SAFE LINKER
ORP-101: Receptor pharmacology

Affinity constants

<table>
<thead>
<tr>
<th>Opioid Receptor</th>
<th>ORP-101 Ki (nM)</th>
<th>Buprenorphine Ki (nM)</th>
<th>Morphine Ki (nM)</th>
<th>Eluxadoline Ki (nM)</th>
<th>Loperamide Ki (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>µOR</td>
<td>1.27</td>
<td>0.9</td>
<td>4.55</td>
<td>1.3</td>
<td>3.3</td>
</tr>
<tr>
<td>δOR</td>
<td>2.8</td>
<td>3.7</td>
<td>217</td>
<td>1.7</td>
<td>48</td>
</tr>
<tr>
<td>κOR</td>
<td>2.2</td>
<td>0.7</td>
<td>26.9</td>
<td>55</td>
<td>1600</td>
</tr>
</tbody>
</table>

1. ORP-101 and buprenorphine data from Caliper study for OrphoMed
2. Eluxadoline from Furiex investor presentation
3. Rest from Opiophile.org website
ORP-101: Insignificant systemic exposure after oral administration in mice

Oral BA less than 1% in mice (n = 36)
ORP-101

EFFICACY STUDIES IN PRECLINICAL MODELS
ORP-101 decreases fecal output in stressed mice model

Dose dependent decrease in Fecal Pellet Count (n = 50 mice)

EFFICACY LIKELY DUE TO PARACELLULAR TRANSPORTATION TO SUBMUCOUS PLEXUS
**ORP-101 simultaneously attenuates GI motility and abdominal pain**

**ORP-101 TREATMENT EFFECT ON ABDOMINAL PAIN AFTER COLONIC MUSTARD OIL**

<table>
<thead>
<tr>
<th>Day</th>
<th>Percent reduction in pain behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1200</td>
</tr>
<tr>
<td>3</td>
<td>1000</td>
</tr>
<tr>
<td>7</td>
<td>800</td>
</tr>
</tbody>
</table>

- **Vehicle control**
- **ORP-101 40 mg/kg**

**p = 0.07 vs. vehicle control**

**p = 0.01 vs. vehicle control**

**p = 0.02 vs. vehicle control**

**Abdominal behaviors** = average of abdominal licking or hunching the first 2.5 hours after treatment.

**ORP-101 TREATMENT EFFECT ON FECAL OUTPUT AFTER COLONIC MUSTARD OIL**

- **Vehicle Control**
- **Mustard Oil (MO)**
- **MO+PO ORP-101 40mg/kg**

**p < 0.05 vs. Vehicle Control & MO**

**p < 0.05 vs. Vehicle Control & MO**
ORP-101 also attenuated hyperalgesic abdominal pain in a mouse model of IBS

Visceromotor Reflex (EMG activity expressed as % over average baseline for each group)

mm Hg of colorectal distension pressure

p = 0.017

p = 0.03
OTHER PHARMACODYNAMIC EFFECTS ON THE GI TRACT
ORP-101 effect on sphincter of Oddi was studied in vivo using manometric system in guinea pigs.
Comparison of ELX and ORP-101 on resting SO pressure

Sphincter of Oddi pressure (% of baseline)

Time after infusion (min)

Eluxadoline 5mpk IV

p = 0.002 (2-way ANOVA, n = 4)

ORP-101 5mpk IV
Comparison of ELX and ORP-101 on Biliary Dynamics

Gallbladder weight (with bile)

- Saline
- ORP101 50 mpk
- ELX 50 mpk

p = 0.01
p = NS
p = 0.04

Retained bile weight

- Saline
- ORP101 50 mpk
- ELX 50 mpk

p = 0.01
p = NS
p = 0.05
Comparison of ELX and ORP-101 on Gastric Emptying

Liquid gastric emptying (% of dye ingested)

- **Saline**
- **ORP-101 50 mpk**
- **ELX 50 mpk**

Statistical significance:
- p = 0.04
- p = NS
- p = 0.04
Conclusions

- ORP-101 is a novel peripherally restricted partial μ agonist and full κ antagonist
- ORP-101 is effective in slowing transit in pre-clinical models
- Unlike eluxadoline, ORP-101:
  - Relaxes the sphincter of Oddi and does not cause biliary stasis
  - Does not impair gastric emptying
- ORP-101 is more effective than eluxadoline in colonic hyperalgesia in a preclinical model of IBS
- ORP101 therefore has the potential to be safer and more effective treatment relative to currently approved prescription IBS-D drugs