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Investment highlights

First-in-Class Dimer Therapeutics
- Proprietary dimer platform technology
- NCE and NME dimer therapeutics
  - Dimers synthesized with proven mechanisms of action
  - Designed for superior efficacy and safety
- Global IP footprint; no royalties, no milestones

Best-in-Class Therapeutics
- ORP-101, a peripherally-acting buprenorphine dimer for treating IBS-D
  - Fast Track designation from FDA
  - Designed for superior visceral pain relief, GI motility control, and safety
  - No risk of pancreatitis or CNS effects observed to date
  - Phase 2 protocol accepted by FDA, approved by IRB, ready to begin enrollment
- ORP-105, an oral acetaminophen dimer for moderate to severe pain
  - Non-addictive Tx designed to replace opioids as a first-line pain therapy
  - No risk of hepatotoxicity in preclinical testing
- ORP-110, non-depletery CFTR potentiator

Robust Pipeline
- Dimer therapeutics pipeline allows for future development/licensing opportunities

Extensive Experience
- Team with successful track record in fund raising, drug development, strategic exits
- $43M Series A with NEA, Takeda, Pappas, FOs Ernie Mario & Allen Chao
First-in-class dimer therapeutics, proven MOA

- Chemically and metabolically stable
- Receptor pharmacology similar to the parent
- Distribution different from the parent
# Robust pipeline of dimer therapeutics

<table>
<thead>
<tr>
<th>ORP-101</th>
<th>ORP-105</th>
<th>ORP-110</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Optimization</strong></td>
<td><strong>Pre-IND</strong></td>
<td><strong>Phase 1</strong></td>
</tr>
<tr>
<td><strong>Phase 2</strong></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>ORP-101</th>
<th>Irritable bowel syndrome-diarrhea (IBS-D)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Metabolically-stable, peripheral partial ( \mu ) opioid agonist receptor and ( \kappa ) opioid antagonist for treatment of IBS-D</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>ORP-105</th>
<th>Moderate to severe pain</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Metabolically-stable, potent, non-addictive acetaminophen-derived analgesic that does not form the liver-toxic metabolite</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>ORP-110</th>
<th>Cystic fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Metabolically-stable, non-depletory cystic fibrosis transmembrane regulator potentiator</td>
</tr>
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</table>
## On-shelf dimer assets for future early out-licensing opportunities

<table>
<thead>
<tr>
<th>Dimer</th>
<th>Parent</th>
<th>MOA</th>
<th>Potential Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORP-102</td>
<td>Naloxone</td>
<td>Inverse $\mu$-agonist (full $\mu$ antagonist)</td>
<td>OBD; Opioid &amp; alcohol addiction; chronic pruritis (also for naltrexone)</td>
</tr>
<tr>
<td>ORP-103</td>
<td>Desvenlafaxine</td>
<td>SNRI-reuptake inhibitor</td>
<td>Gastroparesis; palliative CNS</td>
</tr>
<tr>
<td>ORP-104</td>
<td>Albuterol</td>
<td>$\beta_2$-agonist</td>
<td>Oral treatment for respiratory disorders</td>
</tr>
<tr>
<td>ORP-106</td>
<td>Naltrexone</td>
<td>Inverse $\mu$-agonist</td>
<td>Opioid &amp; alcohol addiction</td>
</tr>
</tbody>
</table>
Global intellectual property footprint

Patents: 53 allowed and 49 in prosecution

Lead IP strategist Tom Kiley; attorney Bill Kezer

Patent Expiration (not including PTE):
- ORP-101: 4/27/2035
- ORP-105: 4/27/2035
ORP-101
IBS-D
IBS-D is a chronic and debilitating condition
- Abdominal pain due to visceral hypersensitivity (neuropathic)
- Frequent diarrhea
- Patients w/o gallbladders at highest risk of pancreatitis

Approved therapies have limited efficacy, significant safety concerns

>28M IBS-D patients need better treatments

Chronic Condition

Highest GI Specialist Care Burden

Over 3M IBS-D Patients Had Their Gallbladder Removed

>28M IBS-D patients need better treatments
IBS-D remains a multi-billion-dollar opportunity
Current treatments have limited efficacy and serious risks

<table>
<thead>
<tr>
<th>Xifaxan (rifaximin, antibiotic)</th>
<th>Viberzi (eluxadoline, full μ-agonist)</th>
</tr>
</thead>
<tbody>
<tr>
<td>~$1.5B+ annual sales, increased by 22% last year</td>
<td>Allergan acquired for $1.1B upfront in 2014, $360M CVR</td>
</tr>
<tr>
<td>&gt;60% relapse rate – treatment limited to 2 weeks in order to reduce development of drug-resistant bacteria</td>
<td>$500M peak estimates</td>
</tr>
<tr>
<td>No reproducible effect on GI motility</td>
<td>15 deaths and 261 cases of serious pancreatitis²</td>
</tr>
<tr>
<td>Response rate¹ of patients treated:</td>
<td>Not effective on IBS-D abdominal pain</td>
</tr>
<tr>
<td>• 38% Xifaxan; 31% Placebo</td>
<td>• Response rate³ of patients treated:</td>
</tr>
<tr>
<td></td>
<td>• 29% Viberzi; 19% Placebo</td>
</tr>
</tbody>
</table>

>60% of Patients Treated for IBS-D Do Not Respond to Current Approved Treatments

¹ Package insert. Combined response rate defined as abdominal pain and stool consistency; ² events reported to FDA (FAERs database); may not be all inclusive³ Package insert. Response defined as simultaneous improvement in daily worst abdominal pain score by ≥30% compared to baseline weekly average and a reduction in the BSS to <5 on at least 50% of the days within a 12-week time interval

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ORP-101: A partial μ agonist/full κ antagonist designed to be superior to current treatment options

- **Dual Receptor**: Partial μ agonism for motility control and κ antagonism for pain control
- **Controls Abdominal Pain**: Potent anti-hyperalgesic; peripheral blockade of dynorphin (κ agonist)
- **No Pancreatitis Risk**: Avoids sphincter of Oddi dysfunction by relaxing it
- **No Risk of Abuse**: Does not cross the blood brain barrier
- **Low Rx-Rx Risk**: Metabolically stable: Drug-drug interaction risk low
Phase 1 healthy subject data: ORP-101 was safe and well tolerated without any opioid-like CNS effect.

High Plasma Concentrations after Oral Dose +/- SE (ng/mL)

- GI Distribution Maximizes ORP-101’s Therapeutic Potential

No Change in Pupillary Diameter after Oral Dose (mm)

- Lack of CNS Effect Mitigates Risk of Abuse
ORP-101 Phase 2 study: Adaptive 12-week trial design with 320 patients

**Study Design**
- Fully adaptive with randomization re-allocation based on 2 interim analyses

**Interim Analyses**
- Futility check and reallocation upon enrollment of 200 and 260 patients

**Dose Regimen**
- ORP-101 once-daily 50 or 100 mg dose or placebo

**Topline Data**
- Topline data available Q1 2021
ORP-105
Moderate to Severe Pain
Chronic pain costs US over $600B per year

100M+ Pain Patients in U.S.¹

Opioids
$7B Revenues²

Acetaminophen
$3B+ Revenues³

Addiction & Overdose

Liver Failure

Patients need non-addictive, efficacious, and safer analgesics

Sources: ¹ Institute of Medicine of The National Academies
² Annually in U.S. by 2021; Cowen November 2017.
³ Annually in U.S. in 2016, 30% Tylenol; Cowen November 2017.
APAP hepatotoxicity due to unconjugated NAPQI metabolite
### ORP-105: Potential to be the best-in-class pain treatment

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-addictive?</td>
<td>Yes</td>
</tr>
<tr>
<td>Efficacy &gt; APAP?</td>
<td>Yes</td>
</tr>
<tr>
<td>First-line alternative to opioids?</td>
<td>Yes</td>
</tr>
<tr>
<td>Dose up-titration for severe pain?</td>
<td>Yes</td>
</tr>
<tr>
<td>Hepatotoxic NAPQI formation?</td>
<td>No</td>
</tr>
</tbody>
</table>

1 In rodent pain model
ORP-105: Efficacy similar to morphine and no injury to liver in rodent studies

**Analgesic Study**

- Rat Paw Formalin Pain Model
  - Licking time (seconds)
  - Vehicle, Acetaminophen 200mpk, Morphine 5mpk, ORP-105 200mpk, ORP-105 400mpk
  - ***P<0.0001 vs Vehicle

**Liver Safety (Transaminases) Study**

- Mouse Liver Injury Model
  - Liver Enzymes
  - Vehicle, Acetaminophen 300 mpk, Acetaminophen 400 mpk, ORP-105 300 mpk, ORP-105 400 mpk
  - APAP: 10x spike in transaminases
  - ORP-105: No spike in transaminases
  - *p<0.05 vs Vehicle
  - **p<0.001
ORP-110
CFTR Potentiator
Ivacaftor transformed cystic fibrosis patients’ lives

<table>
<thead>
<tr>
<th><strong>Ivacaftor</strong> (Kalydeco®)</th>
<th>- CFTR potentiator benefits primarily cystic fibrosis patients with gating and conduction mutation (2018 revenues ~$1B)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ivacaftor Lumacaftor</strong> (Orkambi®)</td>
<td>- Lumacaftor primarily functions as a chaperone to CFTR protein in patients with two copies of F508 deletion (~$1.3B)</td>
</tr>
<tr>
<td><strong>Ivacaftor Tezacaftor</strong> (Symdeko®)</td>
<td>- Benefits patients with two copies of F508 deletion (~ 10% improvement) and some splice and missense mutations (~$0.8B)</td>
</tr>
<tr>
<td><strong>Ivacaftor Tezacaftor Elexacaftor</strong> (Trikafta®)</td>
<td>- Benefits patients with two copies of F508 deletion and also patients who benefit from Symdeko and Orkambi (new launch)</td>
</tr>
</tbody>
</table>

Without a potentiator, CFTR combination components have negligible efficacy
ORP-110 potentiatior response within 20% of positive control and without depletory effect (Ussing chamber)

ORP-110 CFTR Concentration-Response

Positive Control CFTR Concentration-Response

Solubility 0.1µM (pH 7.5)

Solubility 7.9µM (pH 7.5)
Advancing novel dimer therapies targeting urgent unmet needs

<table>
<thead>
<tr>
<th>Leadership</th>
<th>ORP-101</th>
<th>ORP-105 &amp; 110</th>
<th>Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Experienced team</td>
<td>▪ Best-in-class potential in IBS-D</td>
<td>▪ ORP-105 IND-enabling studies ongoing</td>
<td>▪ $43M Series A</td>
</tr>
<tr>
<td>▪ Broad drug development expertise</td>
<td>▪ Clear regulatory path to de-risk molecule</td>
<td>▪ ORP-110 in formulation optimization stage</td>
<td>▪ Additional ~$4M in other financial vehicles</td>
</tr>
<tr>
<td>▪ Track record of drug approvals and exits</td>
<td>▪ FDA Fast Track</td>
<td>▪ Phase 2 trial initiated mid-2019</td>
<td>▪ Potential to partner ORP-101 with Phase 2 topline</td>
</tr>
<tr>
<td></td>
<td>▪ Phase 1 data support advancing to Phase 2</td>
<td>▪ Multi $B market potential</td>
<td>▪ ORP-105 and 110 evaluating funding options</td>
</tr>
</tbody>
</table>

Movantik® is a trademark of AztraZeneca. Viberzi is a trademark of Allergan