First-in-Class Dimer Therapeutics to Bring Relief to Patients with Gastrointestinal Disorders
Investment Highlights

### First-in-Class Therapeutics
- Proprietary dimer platform technology
- NCE and NME dimer therapeutics
  - Proven mechanisms of action
  - Designed for superior efficacy and safety
- Portfolio of multiple patents issued, no royalties or milestone payments

### ORP-101, Best-in-Class IBS-D Therapy
- Lead asset ORP-101, a non-CNS buprenorphine dimer
- Designed to be the best-in-class IBS-D therapy
  - >28M patients in U.S. and EU
  - >60% of patients do not respond to currently approved therapies
- Data demonstrate: Superior abdominal pain relief, GI motility control, safety, without risk of pancreatitis & CNS effect (no abuse potential)

### Robust Pipeline
- Dimer therapeutics pipeline allows additional opportunities

### Resourced for Success
- Team with successful track record in drug development for GI disorders
- $39M Series A with NEA, Takeda Ventures, Pappas Capital, Relativity HC
- Funded through Phase 2 data for ORP-101
First-in-Class Dimer Therapeutics, Proven MOA

- Unbreakable link (chemically and metabolically stable)
- Same pharmacology as the parent
- Distribution profile is different from the parent

Drug \[\rightarrow\] Linker \[\rightarrow\] Dimer

The Linker
>28M IBS-D Patients, Urgent Need for Better Treatments

- IBS-D is a chronic and debilitating condition
  - Abdominal pain due to visceral hypersensitivity (neuropathic)
  - Frequent diarrhea
  - Only 30% consult a physician
- Approved therapies have limited efficacy, significant safety concerns
IBS-D Medicines: Limited Efficacy, Serious Risks

Xifaxan (rifamixim, antibiotic)

- To reduce development of drug-resistant bacteria, treatment limited to 2 weeks, >60% relapse rate
- Irreproducible effect on GI motility
- Response rate\(^1\) of patients treated:
  - 38% Xifaxan; 31% Placebo

Viberzi (eluxadoline, full \(\mu\)-agonist)

- DEA schedule IV, potential for abuse; 120 cases of serious pancreatitis, including deaths (as of 3/17)
- Not effective on IBS-D abdominal pain
- Response rate\(^2\) of patients treated:
  - 29% Viberzi; 19% Placebo

>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; \(2\) Package insert. Composite response rate over 26 weeks defined as simultaneous improvement in the daily worst abdominal pain score by \(\geq 30\%\) 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.
Eluxadoline: Many AEs, 10x Risk of Pancreatitis

Adverse Events$^1$
(January 2016 – January 2017)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Pain</td>
<td>289</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>139</td>
</tr>
<tr>
<td>SOD</td>
<td>56</td>
</tr>
<tr>
<td>Ischemic Colitis</td>
<td>10</td>
</tr>
<tr>
<td>Deaths</td>
<td>6</td>
</tr>
</tbody>
</table>

198 Events per 100,000 Eluxadoline vs. 17 Events per 100,000 U.S. Incidence$^2$

$^1$FDA – AERS; $^2$NIDDK
ORP-101: A Partial $\mu$ agonist Full $\kappa$ Antagonist Designed to Be Superior

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual Receptor</td>
<td>Partial $\mu$ agonism for motility control and $\kappa$ antagonism for pain control</td>
</tr>
<tr>
<td>Controls Abdominal Pain</td>
<td>Potent anti-hyperalgesic; peripheral blockade of dynorphin ($\kappa$ agonist)</td>
</tr>
<tr>
<td>No Pancreatitis Risk</td>
<td>Avoids sphincter of Oddi dysfunction by relaxing it</td>
</tr>
<tr>
<td>Low Rx-Rx Risk</td>
<td>Low probability of interaction with co-administered drugs in IBS-D patients</td>
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<tr>
<td>No Risk of Abuse</td>
<td>Does not cross the blood brain barrier</td>
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</table>
ORP-101: Control of GI Motility is Dose Dependent

Stress-Induced Diarrhea Model

Cumulative 2 Hour Pellets

N = 50

Dose (mg/kg)

0 5 10 15 20 25 30 35 40 45 50

Human Therapeutic Dose expected to be between 10-50 mg

Human Equivalent Dose = 250mg
ORP-101 Relieves Abdominal Pain in IBS-D Murine Models

Neuropharmacology

Acetic Acid Neonatal IBS-D Mouse Model

Relieves Pain by Blocking Peripheral Dynorphin (K Agonist)

ORP-101: Relaxes Sphincter of Oddi, Mitigates Risk of Pancreatitis

Guinea Pig Manometry Study

Sphincter of Oddi

Gallbladder Volume Study

SoO (Common Duct) Pressure (% CFB)

Time after Infusion (Minutes)

Eluxadoline 5 mpk IV

ORP-101 5 mpk IV

p = 0.002
n = 10

SoO = Sphincter of Oddi; % CFB = % change from baseline
Clinical and Preclinical Data Show ORP-101 Has No CNS Opiate Effect

Lack of CNS Effect Mitigates Risk of Abuse
ORP-101: Projected to be Leading IBS-D Therapy

Market Share
24 Months Post Viberzi Launch

Projected Market Share
24 Months Post ORP-101 Launch

% of IBS-D Patients

- Anti-spasmodics: 41%
- OTC: 31%
- Xifaxan: 21%
- Viberzi: 10%
- Lotronex: 8%

ORP-101: Projected to be Leading IBS-D Therapy

Projected Market Share
24 Months Post ORP-101 Launch

- ORP-101: 35%
- Anti-spasmodics: 31%
- OTC: 31%
- Xifaxan: 19%
- Viberzi: 4%
- Lotronex: 6%

>$3B Peak Sales Projected for Currently Approved Therapies

Source: Independent survey of 34 gastroenterologists, totals exceed 100% due to combination therapies
Pipeline of Promising Dimer Therapeutics

<table>
<thead>
<tr>
<th>Candidate Nomination</th>
<th>Development</th>
<th>Phase 1</th>
<th>Phase 2</th>
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<tbody>
<tr>
<td>ORP-101 IBS-D</td>
<td>Metabolically stable, peripheral partial agonist of the μ opioid receptor and antagonist of the κ opioid receptor that is designed to mitigate colonic hypersensitivity due to intestinal hyperalgesia and associated motility dysfunction in IBS-D.</td>
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<tr>
<td>ORP-105 Liver-Safe Analgesic</td>
<td>Metabolically stable, potent, non-opioid analgesic that targets the same receptors as acetaminophen but does not form metabolites that cause liver injury.</td>
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<tr>
<td>ORP-102 Opioid Bowel Disorder</td>
<td>Metabolically stable, non-systemic full antagonist of the μ opioid receptor designed to mitigate abdominal distress following chronic use.</td>
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<tr>
<td>ORP-103 Gastroparesis</td>
<td>Metabolically stable, modulator of intestinal serotonin and norepinephrine to address intestinal motility disorders.</td>
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Poised to Become Leading GI Therapeutics Company Based on Dimer Platform

<table>
<thead>
<tr>
<th>Leadership</th>
<th>Lead Asset</th>
<th>Platform &amp; Pipeline</th>
<th>Funding</th>
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<tr>
<td>Experienced team</td>
<td>ORP-101, potential best-in-class therapy for IBS-D</td>
<td>ORP-105 IND planned 2018</td>
<td>$39M Series A</td>
</tr>
<tr>
<td>GI drug development expertise</td>
<td>Proven MOA derisks molecule</td>
<td>Robust pipeline with significant potential</td>
<td>Interest from top-tier institutional and strategic investors, partners</td>
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<td>Track record of drug approvals</td>
<td>P1 data 1H18</td>
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<td>P2 trial initiated 2H18</td>
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<td>Multi $B market opportunity for efficacious, safe therapy</td>
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Trulance® (plecanatide)

Viberzi® (eluxadoline) tablets

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Q&A

BRINGING RELIEF TO PATIENTS WITH GASTROINTESTINAL DISORDERS

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