HYDEXOR™ (CL-108) for the management of acute post-operative pain severe enough to require an opioid analgesic, for a maximum of 3 days, in adults at high risk for nausea and vomiting with hydrocodone-containing products

US Food & Drug Administration
Joint Meeting of the Anesthetic and Analgesic Drug Products and Drug Safety and Risk Management Advisory Committees
November 2, 2020
Introduction: Today’s Purpose

George A. Scott, Jr., JD, MBA
Executive Vice President of Corporate Affairs & Chief Legal Officer
Ólas Pharma, Inc.
Olas Pharma, Inc.: A wholly owned subsidiary of Charleston Laboratories, Inc.

Corporate Headquarters
Jupiter, FL
Why We’re Here Today

- Discuss safety concerns from February 14, 2018 AdCom and steps taken to mitigate said concerns
  - Outline full agreement and alignment between FDA and Ólas pharma
    - Limitations of population, use, setting, and dose
    - HYDEXOR™ specific REMS program
- Need for better management of acute in-patient, post-operative pain severe enough to require an opioid analgesic for adults at high risk for nausea and vomiting with hydrocodone-containing products
Opioid-Induced Nausea and Vomiting (OINV): Common, Burdensome, and Costly

- OINV is common\textsuperscript{1-5}
  - \textasciitilde40\% report nausea and \textasciitilde20\% report vomiting
- OINV associated with significant burden
  - Inadequate pain management and substantial effects on QoL\textsuperscript{6}
  - Nonadherence or discontinuation\textsuperscript{7-9}
  - Post-surgical complications\textsuperscript{6}
  - Economic burden: higher healthcare resource use and reduced productivity\textsuperscript{10}
- Patient reported nausea and vomiting cited as a significant concern at previous pain therapy AdCom\textsuperscript{11}

QoL=quality of life.
**HYDEXOR™: Novel Treatment of an Opioid and Antiemetic**

- No currently approved therapy for OINV
  - Off-label utilization carries own risks
- HYDEXOR provides pain relief to immediate post-operative in-patients with pain severe enough to require an opioid
  - Immediate-release opioid (hydrocodone [HC] 7.5 mg)
  - Non-opioid pain reliever (acetaminophen [APAP] 325 mg)
- HYDEXOR prevents opioid-induced nausea and vomiting in immediate post-operative in-patients at high risk for nausea and vomiting with hydrocodone-containing products
  - Low-dose antiemetic (promethazine [PMZ] 12.5 mg)
HYDEXOR™ Met All NDA Requirements

Clinical Pharmacology
- HYDEXOR demonstrated bioequivalence to RLDs and Norco® (fasted and fed)

Clinical Efficacy
- 2 pivotal, multicenter, randomized, double-blind, placebo- and active-controlled multiple-dose trials in acute pain models (oral surgery and bunionectomy)
  - Met primary and secondary endpoints
  - First reported studies of combination treatment for acute pain and prevention of OINV

Clinical Safety
- >642 patients and subjects were exposed to HYDEXOR
  - 2 pivotal trials and 1 actual use
  - No new safety signals identified

Abuse Liability
- No increased risk of abuse was observed at supratherapeutic doses compared to HC/APAP

RLDs=reference listed drugs.
## Agenda

<table>
<thead>
<tr>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Efficacy and Safety</td>
<td>Bernard P. Schachtel, MD Ólas Pharma, Inc.</td>
</tr>
<tr>
<td>Aligned Proposal to Mitigate Safety Concerns</td>
<td>George A. Scott, Jr., JD, MBA Ólas Pharma, Inc.</td>
</tr>
</tbody>
</table>
Additional Experts and Respondents

G. Paul Bosse III.
President and Chief Executive Officer
Ölas Pharma, Inc.

Tong Joo (TJ) Gan, MD, MBA, MHS, FRCA
Professor and Distinguished Endowed Chair,
Department of Anesthesiology
Renaissance School of Medicine
Stony Brook University
HYDEXOR™: Efficacy

Bernard P. Schachtel, MD
Chief Scientific Officer
Olas Pharma, Inc.
Key Clinical Components of HYDEXOR™ Label and REMS Program

- Identification of patients appropriate for treatment with HYDEXOR
- Importance of patient-reported nausea
- Mitigation of potential adverse events

REMS=Risk Evaluation and Mitigation Services
Study Designs Assess Acute Pain Reduction and Prevention of Opioid-Induced Nausea and Vomiting (OINV)

Co-primary analgesic endpoint
(Summed Pain Intensity Differences)

HYDEXOR™  Norco®  Placebo

Co-primary OINV endpoint
(Occurrence of vomiting and/or use of anti-emetic)
Met Co-Primary Analgesic Endpoint
Studies 002 and 003, ITT Population

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Study 002</th>
<th>Study 003</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYDEXOR™ n=211</td>
<td>16.2 ± 3.5</td>
<td>118.4 ± 5.3</td>
</tr>
<tr>
<td>Norco® n=205</td>
<td>14.6</td>
<td>107.0 ± 7.5</td>
</tr>
<tr>
<td>Placebo n=50</td>
<td>3.5</td>
<td>53.1 ± 7.5</td>
</tr>
</tbody>
</table>

1Pain intensity measured on a 0-3 categorical scale
2Pain intensity measured on a 0-10 numerical rating scale

Study 002 p<0.001
Study 003 p<0.001
Met Co-Primary OINV Endpoint
Studies 002 and 003, ITT Population

Study 002

- Patients with OINV\(^1\) over 24 hours, %
  - HYDEXOR\(^{TM}\) n=211: 11
  - Norco\(^\circledast\) n=205: 32
  - Placebo n=50: 0

64% relative risk reduction

p<0.001

Study 003

- Patients with OINV\(^1\) over 48 hours, %
  - HYDEXOR n=252: 12
  - Norco n=250: 45
  - Placebo n=50: 6

74% relative risk reduction

p<0.001

\(^1\)OINV: occurrence of vomiting and/or use of anti-emetic
Bernard P. Schachtel, MD
Chief Scientific Officer
Ólas Pharma, Inc.
Intensity of Nausea and Frequency of Vomiting Over 24 Hours
Study 002, ITT Population

Intensity of nausea over 24 hours\(^1\)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Summed Intensity of Nausea over 24 hr (±SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYDEXOR™</td>
<td>20.1</td>
</tr>
<tr>
<td>Norco®</td>
<td>47.2</td>
</tr>
<tr>
<td>Placebo</td>
<td>8.8</td>
</tr>
</tbody>
</table>

\(^1\)Nausea intensity measured on a 0-10 numerical rating scale

Frequency of vomiting over 24 hours\(^2\)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Frequency of Vomiting over 24 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYDEXOR™</td>
<td>0.7</td>
</tr>
<tr>
<td>Norco®</td>
<td>2.4</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.5</td>
</tr>
</tbody>
</table>

\(^2\)Number of episodes of vomiting

p<0.001
Intensity of Nausea Over 48 Hours
Study 003, ITT Population

![Bar chart showing the intensity of nausea over 48 hours for HYDEXOR™ (n=252), Norco® (n=250), and Placebo (n=50).]

- **HYDEXOR™**
  - Mean summed intensity of nausea over 48 hr (±SE): 16.96
  - n=252

- **Norco®**
  - Mean summed intensity of nausea over 48 hr (±SE): 64.36
  - n=250

- **Placebo**
  - Mean summed intensity of nausea over 48 hr (±SE): 15.65
  - n=50

*p<0.001

Intensity of nausea over 48 hours

Source: CLCT-003 CSR Figure 14.2.6.2

1Nausea intensity measured on a 0-10 numerical rating scale
Relationship Between Nausea and Use of an Antiemetic

Figure 6. Antiemetic Use vs. NIS Score (CLCT-003)

Source: November 2, 2020 FDA HYDEXOR Briefing Document
Patients with Emetic Episodes (Retching or Vomiting) Over 48 hours
Studies 003, ITT Population

p<0.001
63% relative risk reduction
## OINV Endpoints Over 3 Days
### Study 003, ITT Population

### Norco Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Number of Doses of Study Drug</th>
<th>Patients with Nausea n (%)</th>
<th>Patients with Vomiting n (%)</th>
<th>Patients with Retching n (%)</th>
<th>Patients with Rescue Anti-Emetic Use n (%)</th>
<th>Patients with Moderate/Severe Nausea n (%)</th>
<th>Patients with OINV (3-component) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norco (n=250)</td>
<td>12.5</td>
<td>208 (83.2%)</td>
<td>61 (24.4%)</td>
<td>72 (28.8%)</td>
<td>114 (45.6%)</td>
<td>208 (83.2%)</td>
<td>129 (51.6%)</td>
</tr>
</tbody>
</table>

### HYDEXOR™ Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Number of Doses of Study Drug</th>
<th>Patients with Nausea n (%)</th>
<th>Patients with Vomiting n (%)</th>
<th>Patients with Retching n (%)</th>
<th>Patients with Rescue Anti-Emetic Use n (%)</th>
<th>Patients with Moderate/Severe Nausea n (%)</th>
<th>Patients with OINV (3-component) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYDEXOR (n=252)</td>
<td>12.8</td>
<td>161 (63.9%)</td>
<td>20 (7.9%)</td>
<td>42 (16.7%)</td>
<td>34 (13.5%)</td>
<td>161 (63.9%)</td>
<td>72 (28.6%)</td>
</tr>
</tbody>
</table>
Bernard P. Schachtel, MD
Chief Scientific Officer
Ólas Pharma, Inc.

HYDEXOR™: Safety
## Safety of HYDEXOR™
### Phase 3 Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Purpose</th>
<th>n</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>002</td>
<td>Evaluate safety and efficacy</td>
<td>466</td>
<td>Post-oral surgery</td>
</tr>
<tr>
<td>003</td>
<td>Evaluate safety and efficacy</td>
<td>552</td>
<td>Post-Bunionectomy</td>
</tr>
<tr>
<td>006</td>
<td>Evaluate safety in actual use</td>
<td>179</td>
<td>Acute osteoarthritis (flare)</td>
</tr>
</tbody>
</table>

- 642 HYDEXOR-treated patients
Adverse Event Collection
Studies 002 and 003

- Nausea and vomiting (assessed as efficacy measures)
- 9 other common opioid side effects
- All other AEs voluntarily reported by patients
Incidence and Severity of Drowsiness Over 3 Days
Study 003, ITT Population

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Number of Doses of Study Drug</th>
<th>Patients with Drowsiness n (%)</th>
<th>Severity of Drowsiness(^1) Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYDEXOR™  (n=252)</td>
<td>12.8</td>
<td>231 (91.7%)</td>
<td>3.91 (2.535)</td>
</tr>
<tr>
<td>Norco      (n=250)</td>
<td>12.5</td>
<td>214 (85.6%)</td>
<td>2.58 (2.141)</td>
</tr>
<tr>
<td>Placebo    (n=50)</td>
<td>12.4</td>
<td>27 (54.0%)</td>
<td>1.28 (1.917)</td>
</tr>
</tbody>
</table>

\(^1\)Drowsiness severity measured on a 0-10 numerical rating scale
HYDEXOR™ Safety Summary

- HYDEXOR well-tolerated
- AEs were mostly mild or moderate in intensity and limited in duration
- No study-drug interruption or discontinuation
- No clinically significant sequelae
  - No falls observed in clinical program related to study drug
  - Incidence and severity (e.g., drowsiness) dose-related
- All resolved without recurrence while continuing study medication
- Three SAEs noted among 1,197 patients\(^1\) – none related to study medication
  - No respiratory depression
- No new safety signals: predictable and manageable safety profile

SAE=serious adverse event; AE=Adverse Event; 1. All patients in studies 002, 003, and 006
Proposed Label and Specific REMS Mitigates Safety Concerns

- Administered only to post-operative, in-patient adults
  - At high risk of nausea and vomiting from hydrocodone-containing products
- Used only in certified, medically supervised healthcare settings
- Administration of HYDEXOR™ limited to 3 days
- Maximum of 5 doses per day
- Up to maximum of 15 tablets dispensed per patient
- For use only when non-sedating alternatives not tolerated or effective
- Product-specific REMS program
Bernard P. Schachtel, MD
Chief Scientific Officer
Õlas Pharma, Inc.
HYDEXOR™: Aligned Proposal to Mitigate Safety Concerns

George A. Scott, Jr., JD, MBA
Executive Vice President of Corporate Affairs & Chief Legal Officer
Ólas Pharma, Inc.
HYDEXOR™: February 2018 AdCom Combined Proposed Indication

- Short-term (generally less than 14 days) management of acute pain severe enough to require an opioid analgesic while preventing opioid-induced nausea and vomiting (OINV) in patients expected to be prone to nausea and vomiting
HYDEXOR™: Agency Clarifications of Complete Response Letter (CRL)

- Effectiveness with every patient and every dose is not the standard for approval

- No regulatory requirement to show majority of patients need anti-emetic
Patient Reported Nausea and Vomiting Considerations

- **2-Component**
  - Occurrence of vomiting
  - Use of rescue antiemetic

- **3-Component**
  - Occurrence of vomiting
  - Use of rescue antiemetic
  - Presence of moderate or severe nausea
  - ~40% report nausea and ~20% report vomiting

Norco Patients (Study 003, ITT Population)

<table>
<thead>
<tr>
<th>Treatment Period</th>
<th>Patients with Nausea n (%)</th>
<th>Patients with Moderate/Severe Nausea n (%)</th>
<th>Patients with OINV (3-component) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over 3 Days</td>
<td>208 (83.2%)</td>
<td>129 (51.6%)</td>
<td>140 (56.0%)</td>
</tr>
</tbody>
</table>

Patient Reported Nausea and Vomiting Considerations

“...efficacy was established with both the 2-component and 3-component endpoints,... there is validity in accepting the analyses based on the NIS as supportive evidence that a significant proportion of patients experienced symptoms that could merit treatment with an anti-emetic.”

Mary Thanh Hai, MD
FDA 2020 HYDEXOR Briefing Document
HYDEXOR™: February 2018 AdCom Concerns

- Commercial
  - Not within focus of AdCom
    • Labeling and REMS mitigate most commercial concerns

- CNS Depression
  - Labeling and REMS mitigate safety concerns

- Abuse/Misuse
  - Labeling and REMS mitigate abuse potential

REMS=Risk Evaluation and Mitigation Services
## HYDEXOR™: February 2018 AdCom Concern and Mitigation

### Commercial

<table>
<thead>
<tr>
<th>Commercial/Clinical Concerns</th>
<th>Response and Mitigation Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Reduced dosing flexibility with fixed-dose</td>
<td>● Commercialization not the focus of AdCom</td>
</tr>
<tr>
<td>● Packaging could encourage patients to finish Rx</td>
<td>● Promethazine addresses pathophysiology of OINV</td>
</tr>
<tr>
<td>● Promethazine not the favored antiemetic by committee members</td>
<td>– Safe, well-understood, highly utilized antiemetic agent effective at addressing nausea</td>
</tr>
<tr>
<td>● Potential CYP-2D6 implications for ‘fast metabolizers’</td>
<td>– 12.5 mg lowest approved oral dose</td>
</tr>
<tr>
<td>● Which pain specialties would make up sales targets</td>
<td>● Revised labeling and REMS</td>
</tr>
<tr>
<td></td>
<td>– Use in monitored in-patient setting only</td>
</tr>
<tr>
<td></td>
<td>– Limited to 5 tablets per day/maximum of 3 days</td>
</tr>
</tbody>
</table>
**HYDEXOR™: February 2018 AdCom Concern and Mitigation**

**CNS Depression**

<table>
<thead>
<tr>
<th>Risks of combining CNS depressants</th>
<th>Response and Mitigation Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Respiratory depression</td>
<td>● HYDEXOR safety in clinical trials</td>
</tr>
<tr>
<td>● Increased sedation (drowsiness)</td>
<td>– No new safety concerns identified</td>
</tr>
<tr>
<td>● Risk of falls</td>
<td>– No falls related to study drug</td>
</tr>
<tr>
<td>● Promethazine taken when patient may not need it with ‘every dose’</td>
<td>– No respiratory depression</td>
</tr>
<tr>
<td>● Length of therapy could increase exposure to promethazine when not needed</td>
<td>● Revised labeling and specific REMS</td>
</tr>
<tr>
<td></td>
<td>– Immediate post-operative monitored in-patient at high risk for OINV</td>
</tr>
<tr>
<td></td>
<td>– Certified, medically supervised healthcare settings with fall prevention protocols</td>
</tr>
<tr>
<td></td>
<td>– Limited to 5 tablets per day/maximum of 3 days</td>
</tr>
</tbody>
</table>
## HYDEXOR™: February 2018 AdCom Concern and Mitigation

### Abuse/Misuse

<table>
<thead>
<tr>
<th>Abuse/Misuse</th>
<th>Response and Mitigation Strategy</th>
</tr>
</thead>
</table>
| - Ability to take more than recommended dose in retail setting | - HYDEXOR Human Abuse Liability Study
| - No ADT (purple drank) | - No difference in abuse potential between HYDEXOR and active control
| - Promethazine making opioid more tolerable for abusers | - No respiratory depression
| - Post-surgical patient population in studies | - HYDEXOR clinical data showed no evidence of abuse, misuse, or diversion
|   - Available to non-surgical pain patients | - Revised labeling and specific REMS
|   |   - Immediate post-operative monitored in-patient at high risk for OINV
|   |   - Certified, medically supervised healthcare settings with fall prevention protocols
|   |   - Limited to 5 tablets per day/maximum of 3 days
|   |   - No retail prescribing or availability |
HYDEXOR™: Patient Journey and Responsible Use

George A. Scott, Jr., JD, MBA
Executive Vice President of Corporate Affairs & Chief Legal Officer
Ólas Pharma, Inc.
HYDEXOR™ Patient Journey: Improved Post-Surgical Pain Management

HYDEXOR utilization will be limited to the in-patient immediate post-surgical setting for up to 3 days.
Proposed indication

- For the management of acute post-operative pain severe enough to require an opioid analgesic, for a maximum of 3 days, in adults at high risk for nausea and vomiting with hydrocodone-containing products

- used only when non-sedating alternatives are either not tolerated or ineffective

Setting

- Certified, medically supervised healthcare settings, such as hospitals and surgical centers

Dosage

- One tablet every 4 to 6 hours as needed for pain; the total daily dosage should not exceed 5 tablets
The AdCom Process Worked as Intended

- November 2020 AdCom is result of agreed approach to mitigate concerns
  - 2018 AdCom raised concerns
  - 2018-2020 Ōlas and FDA worked towards aligned strategy
- HYDEXOR:
  - Label restrictions
    - Post-operative in-patient
    - High risk for nausea and vomiting with hydrocodone products
    - Only when non-sedating alternatives are not effective/tolerated
    - Certified medical facility w/fall prevention protocol
    - Limited to 3 days or less and no more than 5 tablets per day
  - Product specific REMS program

REMS=Risk Evaluation and Mitigation Services
Favorable Benefit-Risk Assessment for HYDEXOR™

- **Unmet need: OINV creates significant burdens**
  - Patient recovery
  - Clinical outcomes
  - Economic impact

- **Demonstrated efficacy**
  - Significant relief of pain compared to placebo
  - 64% to 74% reduction in risk of OINV compared to Norco®
  - Consistent and durable results

- **No new safety concerns**
  - Increased risk of drowsiness observed (addressed in label and REMS)

- **Commitment to responsible use**
  - REMS and labeling
  - Limited dosing and duration
  - Limited to post-operative in-patient
  - Limited to certified healthcare facility
  - No retail distribution

APAP=acetaminophen; HC=hydrocodone; OINV=opioid-induced nausea and vomiting; REMS=Risk Evaluation and Mitigation Strategy.
Back Up Slides Shown by Ólas Pharma, Inc.

US Food & Drug Administration
Joint Meeting of the Anesthetic and Analgesic Drug Products and Drug Safety and Risk Management Advisory Committees
November 2, 2020
Presence of Immediate PONV Similar Across Treatment Groups at Baseline
Studies 002 and 003

**Study 002**

- HYDEXOR™ (n=211)
- Norco® (n=205)
- Placebo (n=50)

- Patients, %

<table>
<thead>
<tr>
<th>Group</th>
<th>Study 002</th>
<th>Study 003</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYDEXOR™</td>
<td>51.0</td>
<td>28.6</td>
</tr>
<tr>
<td>Norco®</td>
<td>49.0</td>
<td>27.6</td>
</tr>
<tr>
<td>Placebo</td>
<td>58.0</td>
<td>22.0</td>
</tr>
</tbody>
</table>

**Study 003**

- HYDEXOR (n=252)
- Norco (n=250)
- Placebo (n=50)

- Patients, %

Study 002 PONV defined as NIS >0 or VFS >0. Study 003 defined as NIS >0 and RVI >2.
Patients Without Immediate PONV at Baseline Were Still at Risk for OINV
Studies 002 and 003

Study 002

Study 003

Study 002 PONV defined as NIS >0 or VFS >0. Study 003 defined as NIS >0 and RVI >2.
Patients With Immediate PONV at Baseline Were Still at Risk for OINV Studies 002 and 003

Study 002

- HYDEXOR™ (n=107)
- Norco® (n=101)
- Placebo (n=29)

<table>
<thead>
<tr>
<th>Group</th>
<th>Study 002</th>
<th>Study 003</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYDEXOR™</td>
<td>14.0%</td>
<td>17.4%</td>
</tr>
<tr>
<td>Norco®</td>
<td>32.7%</td>
<td>55.2%</td>
</tr>
<tr>
<td>Placebo</td>
<td>3.5%</td>
<td>9.1%</td>
</tr>
</tbody>
</table>

Study 002 PONV defined as NIS >0 or VFS >0. Study 003 defined as NIS >0 and RVI >2.