RBP-6000 (Extended-Release Buprenorphine) for the Treatment of Opioid Use Disorder

October 31, 2017
Indivior, Inc.
Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
Introduction

Susan Learned, MD, PharmD, PhD
Senior Vice President of Global Medicines Development
Indivior, Inc.
More Than 53,000 Opioid Overdose Deaths Projected in 2017

Synthetic Opioids other than Methadone (N=20,145)
Heroin (N=15,446)
Natural and Semi-Synthetic Opioids (N=14,427)
Methadone (N=3,314)

CDC. Wonder Database.
RBP-6000: Long-Acting Subcutaneous Injection
Administered Monthly by HCP in Health Care Setting

- **ATRIGEL® Delivery System**
  - Biodegradable polymer and solvent create solid depot of buprenorphine
  - Two targeted release phases: rapid achievement of therapeutic levels that are sustained over monthly dosing interval
  - Used in 7 FDA-approved products
- **100 mg and 300 mg dosage strengths**
  - Prefilled syringe, administered subcutaneously
- **Recommended dosing regimen**
  - Two initial monthly 300 mg doses
  - Monthly maintenance doses of 100 mg or 300 mg based on clinical condition of patient
RBP-6000 studied in and intended for patients attempting to recover from OUD
- May or may not have tried Medication Assisted Treatment (MAT) in the past
- Utilized science on relationship between buprenorphine levels, mu-opioid receptor occupancy (µORO), and clinical effects to maximize benefits for patients with OUD

### Overview of RBP-6000 Clinical Development Program

- **First-in-Human (FIH) Study** (20 mg)
- **Single Ascending Dose (SAD) Study** (50, 100, 200 mg)
- **Multiple Ascending Dose (MAD) Study** (50, 100, 200, 300 mg)
- **Molecular Weight (MW) Study** (300 mg)
- **Opioid Blockade (OB) Study** (300 mg)
- **Phase 3 Double-Blind Placebo-Controlled Study** (300/100, 300/300 mg)
- **Phase 3 Long-Term Open-Label Safety Study** (300 mg → Flex dosing)
- **Treatment Extension Study** (Flex dosing)
Key Findings from Development Program

- RBP-6000 designed to maximize benefits of buprenorphine
  - Opioid blockade: ≥ 70-80% μORO achieved with ≥ 2-3 ng/mL buprenorphine plasma concentration
- Two safe and effective dosing regimens
  - 300/100 mg for many patients
  - 300/300 mg for select patients who need higher concentrations
- Significant benefits in abstinence, control of withdrawal symptoms, and reduction in opioid craving
- Safety profile consistent with transmucosal buprenorphine products
  - Exception of anticipated injection site reactions
**RBP-6000 Advances Treatment Options for OUD**

<table>
<thead>
<tr>
<th>Limitations of Current MAT Options</th>
<th>Advancements with RBP-6000</th>
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<tbody>
<tr>
<td>Often requires daily medication adherence</td>
<td>• Monthly dosing removes burden of daily adherence</td>
</tr>
<tr>
<td>Daily medications subject to “drug holidays”</td>
<td>• Long-acting nature would not allow for “drug holidays”</td>
</tr>
<tr>
<td>Daily fluctuations in buprenorphine concentrations</td>
<td>• Delivers consistent buprenorphine concentrations that provide opioid blockade from first dose</td>
</tr>
</tbody>
</table>
| Occasional need for supplemental dosing | • Controls withdrawal symptoms and craving  
• Efficacious in absence of supplemental buprenorphine |
| Subject to diversion, misuse, abuse, and accidental poisoning of children | • Restricted distribution system  
• Administered by health care professional |
Risk Evaluation and Mitigation Strategy (REMS) for Safe and Appropriate Use

Goals of REMS:
• Mitigate risks of diversion, misuse, abuse, and accidental exposure
• Inform prescribers, pharmacists, and patients about RBP-6000:
  • Risks
  • Long-acting formulation
Restricted Distribution System to Ensure RBP-6000 Administered Only by Qualified HCPs

- Goals: ensure product never distributed directly to patient; prevent diversion and IV injection
- Under CSA, every step in distribution chain controlled and monitored by personnel registered with DEA
- Specialty pharmacies and distributors must ensure RBP-6000 is dispensed only to HCPs with DATA-2000 waiver (~40,500 prescribers)
  - Indivior and DEA will each audit specialty pharmacies and distributors
  - DEA will audit prescribing practices of HCPs

CSA = Controlled Substances Act
Co-10

Proposed Indication

RBP-6000 is indicated for the treatment of moderate-to-severe opioid use disorder (OUD) in patients who have undergone induction to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product.

RBP-6000 should be used as part of a complete treatment program that includes counseling and psychosocial support.
## Agenda

<table>
<thead>
<tr>
<th>Topic</th>
<th>Speaker</th>
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<tbody>
<tr>
<td>Need for Improvements in the Treatment of Opioid Use Disorder</td>
<td><strong>Brent Boyett, DO, DMD</strong>&lt;br&gt;Boyett Health Services, Inc.</td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
<td><strong>Celine Laffont, PhD</strong>&lt;br&gt;Director, Quantitative Clinical Pharmacology&lt;br&gt;Indivior, Inc.</td>
</tr>
<tr>
<td>Efficacy</td>
<td><strong>Barbara Haight, PharmD</strong>&lt;br&gt;Medicines Development Leader, RBP-6000&lt;br&gt;Indivior, Inc.</td>
</tr>
<tr>
<td>Safety</td>
<td><strong>Anne Andorn, MD</strong>&lt;br&gt;Head, Late Stage Global Clinical Development&lt;br&gt;Indivior, Inc.</td>
</tr>
<tr>
<td>Clinical Perspective</td>
<td><strong>Eric C. Strain, MD</strong>&lt;br&gt;Director, Johns Hopkins Center for Substance Abuse Treatment and Research, Johns Hopkins University</td>
</tr>
<tr>
<td>Field</td>
<td>Expert</td>
</tr>
<tr>
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<tr>
<td>Statistics</td>
<td>Jason Connor, PhD</td>
</tr>
<tr>
<td>Epidemiology / REMS</td>
<td>Howard Chilcoat, ScD, MHS</td>
</tr>
<tr>
<td>Toxicology</td>
<td>Rosonald Bell, PhD</td>
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</tbody>
</table>
Need for Improvements in the Treatment of Opioid Use Disorder

Brent Boyett, DO, DMD
Boyett Health Services, Inc.
Hamilton, Alabama
Rapidly Escalating Epidemic of Illicit Opioid Use in the United States

- ~1.8 million with prescription pain reliever use disorder
- ~630,000 with heroin use disorder
- Patients with OUD have 14x higher mortality than general population
- Opioid overdose deaths quadrupled from 2000-2016
  - > 50,000 people died from opioid-related deaths last year
    - As many deaths as from AIDS at peak of epidemic
- Injecting drug users at serious risk for HIV and hepatitis C

Opioid Use Disorder is Chronic Disease With High Risk of Fatal Consequences

- OUD characterized by repeated, compulsive use of opioids
  - Despite social, psychological, and physical consequences
- Pathologically pursue reward or relief by substance use\(^1\)
- Similar to other chronic, relapsing conditions\(^2\)
  - Periods of exacerbation and periods of remission
- Long-term management challenging, adherence often incomplete
- Can take time to extinguish long-standing behaviors, achieve abstinence

Goals of MAT

- Achieve abstinence
- Prevent overdose, death
  - Treatment reduces risk of mortality by 2.4 times
- Return to normal living

## Available Medications Offer Different Approaches for Patients with Opioid Use Disorder

<table>
<thead>
<tr>
<th>Category</th>
<th>Naltrexone</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>μ-opioid antagonist</td>
<td>Daily or monthly</td>
<td>Daily</td>
<td>Daily or every 6 months</td>
</tr>
<tr>
<td>Frequency of Administration</td>
<td>Reduces risk of relapse following abstinence</td>
<td>Reduces opioid withdrawal and craving</td>
<td>Reduces opioid withdrawal and craving</td>
</tr>
<tr>
<td>Clinical Uses</td>
<td>Does not control withdrawal symptoms</td>
<td>Patients often have to receive daily dose at certified clinic</td>
<td>Transmucosal can be diverted, requires daily adherence</td>
</tr>
</tbody>
</table>
Take-Home Buprenorphine Subject to Diversion, Misuse, Abuse, and Accidental Poisoning of Children

- Patients share, sell, trade medication
- In 2013, 33% entering opioid treatment reported use of diverted buprenorphine in last month\(^1\)
- “Bridge” between periods of illicit opioid use
- Accidental poisoning in children is public health concern\(^2\)
  - > 8100 ER visits for children < 6 years old for ingesting buprenorphine from 2008-2016
  - Three-quarters involved children 1-2 years old

2. MMWR 2016;65:1148-1149.
Nonadherence to Daily Buprenorphine Dosing Leaves Patients Vulnerable to Relapse

- Adherence to daily medication regimen often a challenge
  - Human error
  - Lost or stolen
  - Dose splitting, treatment holidays
- 10 times greater likelihood of relapse when daily buprenorphine adherence drops below 80%\(^1\)

Need for New Treatment Option to Address Seriousness and Complexities of OUD

- New buprenorphine treatment options could make meaningful difference
  - Reduce risk of diversion, misuse, abuse, and accidental pediatric poisoning
  - Remove burden of daily medication adherence to improve outcomes and enhance retention in treatment
  - Assures compliance, removing ability to take “drug holidays”
Clinical Pharmacology

Celine Laffont, PhD
Director, Quantitative Clinical Pharmacology
Indivior, Inc.
Effect of μ-Opioid Receptor Occupancy (μORO) on Withdrawal Suppression and Blockade of Opioid Subjective Effects

- Reinforcing Effect
- Analgesic Effect
- Withdrawal Suppression
- Opioid Blockade

Individuals abusing high doses of opioids may require higher concentrations for opioid blockade*

- 50-60% μORO (BUP ≥ 1 ng/mL)
- ≥ 70-80% μORO (BUP ≥ 2-3 ng/mL)

Two Studies Evaluated Relationship Between Buprenorphine Concentration and Pharmacodynamic Effects

- **Greenwald et al, 2003**
  - 32 mg, 16 mg, 2 mg sublingual (SL) buprenorphine and placebo
  - PET scans at 4 hours post-dose

- **Greenwald et al, 2007**
  - 16 mg SL buprenorphine
  - PET scans 4, 28, 52, and 76 hours after last dose

- Both studies administered hydromorphone challenges to assess ability of buprenorphine to block effects of μ-opioid full agonist

PET Scans Illustrate Effect of Increasing Buprenorphine Exposure on \( \mu \)ORO

PET Scan Results at Various Doses

(Greenwald et al, 2003)

Relationship Between Buprenorphine Concentration, Brain μORO, and Pharmacodynamics

Pharmacodynamic Results

At least 70% receptor occupancy needed to achieve both:

- Suppression of subjective effects of a μ-opioid full agonist (hydromorphone)
- Suppression of withdrawal symptoms
Multiple Ascending Dose (MAD) study assessed 4 doses of RBP-6000 (50, 100, 200, and 300 mg)

Evaluated ability of doses to achieve average target of 2 ng/mL at:
- First dose
- Steady-state

300 mg dose
- Reaches average target of 2 ng/mL buprenorphine after first dose
- Achieves average concentration of 5-6 ng/mL at steady-state

100 mg dose
- Reaches average target of 2 ng/mL buprenorphine at steady-state
- 2 initial doses of 300 mg reach average target levels more quickly
Opioid Blockade Study

Designed to assess ability of RBP-6000 to block subjective effects of μ-opioid full agonist
Opioid Blockade Study Designed to Assess Ability of RBP-6000 to Block Subjective Effects of $\mu$-Opioid Full Agonist

Randomization 1st Injection 2nd Injection

Screening Run-in (SUBOXONE) 1 2 3 4 5 6 7 8 9 10 11 12

Weeks

Challenges (IM injections):

- SUBOXONE
- RBP-6000 300 mg
- Placebo
- Hydromorphone 6 mg
- Hydromorphone 18 mg

N = 39 non-treatment-seeking, opioid-dependent subjects
Mean Buprenorphine Plasma Concentrations from Opioid Blockade Study

Mean Buprenorphine Plasma Concentration (ng/mL) [SD]

Time (Weeks)

Run-in 1 2 3 4 5 6 7 8 9 10 11 12

SUBOXONE RBP-6000 Dose
RBP-6000 300 mg Blocked Opioid Subjective Effects

LS Mean Drug Liking VAS Score [95% CI]

Time (Weeks)
Summary of Clinical Pharmacology

- RBP-6000 designed based on totality of data to maximize the benefits of buprenorphine for patients with OUD
- Clinical pharmacology program led to dosing regimens for Phase 3

<table>
<thead>
<tr>
<th>Doses</th>
<th>300/100 mg</th>
<th>300/300 mg</th>
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</thead>
<tbody>
<tr>
<td>Two Initial Doses</td>
<td>300 mg provides opioid blockade from first dose</td>
<td></td>
</tr>
<tr>
<td>Subsequent Maintenance Doses</td>
<td>100 mg would maintain average target concentrations (2-3 ng/mL)</td>
<td>300 mg would provide average levels of 5-6 ng/mL at steady-state</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exposures needed for certain patients, e.g., using high doses of opioids</td>
</tr>
</tbody>
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Efficacy

Barbara Haight, PharmD
Medicines Development Leader, RBP-6000
Indivior, Inc.
Design of Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Study

Run-in Period

<table>
<thead>
<tr>
<th>Screening (2 weeks)</th>
<th>3 Day Induction (SUBOXONE)</th>
<th>4-11 Day Dose Stabilization (SUBOXONE)</th>
<th>Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>300 mg RBP-6000 (Doses 1-6) + IDC</td>
<td>300 mg RBP-6000 (Doses 1-2) + IDC</td>
<td>300 mg Placebo (Doses 1-6) + IDC</td>
<td>300 mg Placebo (Doses 1-2) + IDC</td>
</tr>
</tbody>
</table>

Treatment Period
(24 weeks)

SC dose every 28 ± 2 days

- Optional Open-Label Safety Study

- Supplemental buprenorphine not permitted after randomization

IDC = individual drug counseling
Key Inclusion and Exclusion Criteria

Key Inclusion Criteria:
- Age 18-65 years
- Moderate or severe OUD
- Seeking MAT
- No MAT for OUD within 90 days

Key Exclusion Criteria:
- Other diagnosis requiring prescription opioids
- Recent history of suicidality
- Significant medical problems
Primary Efficacy Endpoint: Percentage Abstinence from Illicit Opioids

- Primary endpoint: percentage abstinence from Week 5 through 24
  - Abstinence: urine samples negative for opioids with self-reports negative for illicit opioid use (TLFB interview)
  - Urine drug screen (UDS) and self-reports collected weekly
- First 4 weeks of Treatment Period designated as “grace period”
- Missing UDS or self-report (due to missed visits or early discontinuation) considered positive for opioids

TLFB = Timeline Followback
Analysis Populations and Statistical Considerations

- Efficacy data analyzed using Full Analysis Set
  - Intention-to-treat (ITT) analysis of all randomized subjects
- In agreement with FDA, 1 site (15 subjects) removed from efficacy analyses (compliance issues), but included in safety analyses
Disposition of All Screened Subjects

Screened
N=1187

Failed Screening
n=522

Run-in Failure
n=161

Randomized
n=504

RBP-6000 300/300 mg
n=201

Lost to follow-up 23 (11.4%)
Withdrew consent 21 (10.4%)
Other 8 (4.0%)
Lack of efficacy 5 (2.5%)
Adverse event 10 (5.0%)
Protocol deviation 5 (2.5%)
Completed n=129 (64.2%)

RBP-6000 300/100 mg
n=203

Lost to follow-up 26 (12.8%)
Withdrew consent 20 (9.9%)
Other 21 (10.4%)
Lack of efficacy 3 (1.5%)
Adverse event 6 (3.0%)
Protocol deviation 2 (1.0%)
Completed n=125 (61.6%)

Placebo
n=100

Lost to follow-up 12 (12.0%)
Withdrew consent 18 (18.0%)
Other 16 (16.0%)
Lack of efficacy 18 (18.0%)
Adverse event 2 (2.0%)
Protocol deviation 0 (0.0%)
Completed n=34 (34.0%)
## Treatment Groups Balanced on Demographic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>RBP-6000 300/300 mg</th>
<th>RBP-6000 300/100 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N=201</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years (mean, range)</td>
<td>39 (19-64)</td>
<td>40 (20-64)</td>
<td>39 (20-63)</td>
</tr>
<tr>
<td>Male, %</td>
<td>67</td>
<td>66</td>
<td>65</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>71</td>
<td>68</td>
<td>78</td>
</tr>
<tr>
<td>Black or African American</td>
<td>28</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>&lt;1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Multiple</td>
<td>&lt;1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hispanic or Latino Ethnicity, %</td>
<td>9</td>
<td>6</td>
<td>10</td>
</tr>
</tbody>
</table>
## History of Opioid Use at Baseline

<table>
<thead>
<tr>
<th></th>
<th>RBP-6000 300/300 mg N=201</th>
<th>RBP-6000 300/100 mg N=203</th>
<th>Placebo N=100</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severity of OUD, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>34</td>
<td>26</td>
<td>32</td>
</tr>
<tr>
<td>Severe</td>
<td>66</td>
<td>74</td>
<td>68</td>
</tr>
<tr>
<td><strong>Duration of Opioid Use, years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>11 (9)</td>
<td>12 (10)</td>
<td>11 (9)</td>
</tr>
<tr>
<td><strong>Users by Injectable Route, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injecting Users</td>
<td>41</td>
<td>43</td>
<td>51</td>
</tr>
<tr>
<td>Non-injecting Users</td>
<td>59</td>
<td>57</td>
<td>49</td>
</tr>
</tbody>
</table>
RBP-6000 PK in Phase 3 Double-Blind Study

Mean Buprenorphine Plasma Concentration (ng/mL) [SD]

Observed Data – Double-blind Study
Primary and Key Secondary Endpoints Met: Significantly Higher Percentage Abstinence with RBP-6000

- RBP-6000 300/300 mg
- RBP-6000 300/100 mg
- Placebo

Percentage of Weeks Abstinent

- 80-100%
- 60% to <80%
- 40% to <60%
- 20% to <40%
- 1% to <20%
- 0%

P < 0.0001 for both RBP-6000 groups vs. Placebo

Full Analysis Set
Consistent Abstinence Rates Over Time

Subjects Abstinent (%)
[95% CI]

Time (Weeks)

RBP-6000 300/300 mg
RBP-6000 300/100 mg
Placebo

Full Analysis Set
RBP-6000 Provided Control of Opioid Craving and Withdrawal Symptoms

- MMRM models determined time-averaged responder estimates

<table>
<thead>
<tr>
<th>Secondary Endpoint</th>
<th>RBP-6000 300/300 mg</th>
<th>RBP-6000 300/100 mg</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Control of Opioid Craving (≤ 5 mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Responders</td>
<td>81%</td>
<td>81%</td>
<td>48%</td>
</tr>
<tr>
<td>95% CI</td>
<td>77-84</td>
<td>77-84</td>
<td>41-56</td>
</tr>
<tr>
<td>Control of Withdrawal (COWS ≤ 12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Responders</td>
<td>99%</td>
<td>99%</td>
<td>97%</td>
</tr>
<tr>
<td>95% CI</td>
<td>99-100</td>
<td>99-100</td>
<td>96-98</td>
</tr>
</tbody>
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- > 90% of placebo subjects tested positive for illicit opioids throughout study

MMRM = Mixed Model for Repeated Measures
Role of 300 mg Maintenance Dose for Select Patients

- Scientific Literature
- RBP-6000 Exposure-Response (> 11,000 PK samples)
- RBP-6000 Clinical Outcomes
Scientific Literature Supports That Select Patients Require Higher Buprenorphine Doses

- **Bickel and Amass, 1995**
  - Developed buprenorphine treatment guidelines based on drug consumption
  - Patients using high doses of illicit opioids required higher buprenorphine doses to abstain

- **Comer et al, 2005**
  - Heroin-dependent subjects required higher (32 mg buprenorphine or ~90% μORO) to reduce liking and self-administration

- **Greenwald et al, 2014**
  - Review of published data concluded that users of high doses of illicit opioids require higher buprenorphine doses and >90% μORO

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Injecting Drug Users Required Higher Buprenorphine Plasma Concentrations to Maximize Abstinence Probability of Abstinence (%) [95% CI]

11,362 PK Samples from Phase 3 Double-blind Study

- Average concentration of 100 mg maintenance dose
- Average concentration of 300 mg maintenance dose
Consistency Between PK and PD for 300 mg Maintenance Dose Among Injecting Users

**Pharmacokinetics of Injecting Users**

- 300/300 mg
- 300/100 mg

**Pharmacodynamics of Injecting Users**

Relative Risk of Abstinence at Week 24: 1.7 (95% CI: 1.2 - 2.4)

Mean Buprenorphine Plasma Concentration (ng/mL)

Subjects Abstinent (%)

- First Maintenance Dose

Full Analysis Set
Phase 3 Long-Term Safety Study

Interim Analysis
Interim Analysis of Maintenance of Efficacy in Phase 3 Long-Term Safety Study

- **De-novo subjects (N=412)**
  - Did not participate in Phase 3 double-blind study
  - 48-week treatment phase
  - 12 injections of RBP-6000

- **Roll-over subjects (N=257)**
  - Participated in Phase 3 double-blind study (RBP-6000 or placebo groups)
  - 24-week treatment phase
  - 6 injections of RBP-6000

- All subjects received initial dose of 300 mg
  - Flex dosing thereafter (100 or 300 mg) at investigator’s discretion
RBP-6000 300 mg Dose Reaches Steady-State After Six Monthly Injections

Roll-over subjects who received 12 consecutive 300 mg doses.
Roll-Over Subjects Show Maintenance of Efficacy Through 12 Monthly Doses

Subjects Abstinent (%)

- **300/300 mg (roll-over)**
- **300/100 mg (roll-over)**

<table>
<thead>
<tr>
<th>Time (Weeks)</th>
<th>Subjects Abstinent (%)</th>
</tr>
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<tbody>
<tr>
<td>24</td>
<td>All Subjects (Flex Dosing)</td>
</tr>
<tr>
<td>28</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td></td>
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<tr>
<td>40</td>
<td></td>
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<tr>
<td>44</td>
<td></td>
</tr>
<tr>
<td>48</td>
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</tbody>
</table>

Subjects censored after last visit. Missed visits prior to last visit considered positive for opioids.

RBP-6000 300/300 mg 113 112 112 110 113 109 109 101 94 87 66 56
RBP-6000 300/100 mg 112 112 111 111 111 110 107 109 108 104 92 81 65
Summary of RBP-6000 Efficacy

- Both RBP-6000 dosage regimens superior to placebo in percentage abstinence on primary and secondary endpoints
- RBP-6000 effectively controlled opioid craving and withdrawal symptoms
- Totality of results support monthly dosing recommendations
  - Two initial 300 mg doses for all patients
  - 100 mg or 300 mg maintenance dose based on clinical condition
- Consistency between literature, exposure-response modeling, and clinical outcomes support 300 mg maintenance dose for select patients
- Abstinence rates maintained through 12 monthly doses
Safety

Anne Andorn, MD
Head, Late Stage Global Clinical Development
Indivior, Inc.
### RBP-6000 Exposure in Phase 3 Program

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Number of Subjects Exposed</th>
<th>Phase 3 Double-Blind Study</th>
<th>Phase 3 Long-Term Safety Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Exposures in Phase 3</td>
<td>848 (138 with 12 doses)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBP-6000 300/300 mg</td>
<td>201</td>
<td></td>
<td>113 (roll-over)</td>
</tr>
<tr>
<td>RBP-6000 300/100 mg</td>
<td>203</td>
<td></td>
<td>112 (roll-over)</td>
</tr>
<tr>
<td>Placebo</td>
<td>-</td>
<td></td>
<td>32 (roll-over)</td>
</tr>
<tr>
<td>De-novo</td>
<td>-</td>
<td></td>
<td>412</td>
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- Subjects in long-term safety study administered 300 mg as first dose
  - Flex dosing (300 mg or 100 mg) thereafter
# Overall Summary of Safety in Phase 3 Studies

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<thead>
<tr>
<th>Treatment-Emergent Adverse Event, %</th>
<th>Phase 3 Double-Blind Study</th>
<th>Phase 3 Long-Term Safety Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RBP-6000 300/300 mg N=201</td>
<td>RBP-6000 300/100 mg N=203</td>
</tr>
<tr>
<td>Any TEAE</td>
<td>66.7</td>
<td>76.4</td>
</tr>
<tr>
<td>TEAE leading to discontinuation</td>
<td>5.0</td>
<td>3.4</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>3.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Severe TEAE</td>
<td>6.5</td>
<td>7.4</td>
</tr>
<tr>
<td>Death</td>
<td>0.5*</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RBP-6000 De-novo N=412</td>
<td>RBP-6000 Roll-over N=257</td>
</tr>
<tr>
<td></td>
<td>70.6</td>
<td>54.9</td>
</tr>
<tr>
<td></td>
<td>2.7</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>4.1</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>8.5</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
* Homicide
Injection Site TEAEs in Phase 3 Studies

- Most common injection site TEAEs: pain, pruritus, erythema, and induration
- No injection site SAEs
- 99% of TEAEs were mild or moderate
- < 1% of subjects discontinued for injection site TEAE
Hepatic Enzyme Elevations Consistent with Known Safety Profile of Buprenorphine

<table>
<thead>
<tr>
<th>Liver Enzyme Elevation, %</th>
<th>Phase 3 Double-Blind Study</th>
<th>Phase 3 Long-Term Safety Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RBP-6000 300/300 mg (N=201)</td>
<td>RBP-6000 300/100 mg (N=203)</td>
</tr>
<tr>
<td>ALT &amp; AST at same visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 3× ULN to &lt; 5× ULN</td>
<td>3.0</td>
<td>1.5</td>
</tr>
<tr>
<td>≥ 5× ULN to &lt; 8× ULN</td>
<td>2.5</td>
<td>1.5</td>
</tr>
<tr>
<td>≥ 8× ULN</td>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Total Bilirubin &gt; 2× ULN</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>ALT or AST &gt; 3× ULN + Bilirubin &gt; 2× ULN (Hy’s Law)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
# Treatment Decisions Based on Liver Chemistry Elevations

<table>
<thead>
<tr>
<th>Treatment Decisions for Liver Chemistry Elevation, %</th>
<th>Phase 3 Double-Blind Study</th>
<th>Phase 3 Long-Term Safety Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RBP-6000 300/300 mg N=201</td>
<td>RBP-6000 De-novo N=412</td>
</tr>
<tr>
<td></td>
<td>RBP-6000 300/100 mg N=203</td>
<td>RBP-6000 Roll-over N=257</td>
</tr>
<tr>
<td></td>
<td>Placebo N=100</td>
<td></td>
</tr>
<tr>
<td>Discontinuation</td>
<td>1.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Dose Reduction</td>
<td>-</td>
<td>2.4</td>
</tr>
</tbody>
</table>

|                                                     | 1.2                         |                                |
# RBP-6000 Hepatic Safety Profile Similar to SUBOXONE

<table>
<thead>
<tr>
<th>Liver Enzyme Elevation, %</th>
<th>Phase 3 Double-Blind Study</th>
<th>NIDA Study&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RBP-6000 300/300 mg N=201</td>
<td>RBP-6000 300/100 mg N=203</td>
</tr>
<tr>
<td>ALT &amp; AST at same visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 3× ULN to &lt; 5× ULN</td>
<td>3.0</td>
<td>1.5</td>
</tr>
<tr>
<td>≥ 5× ULN to &lt; 10× ULN</td>
<td>2.5</td>
<td>1.5</td>
</tr>
<tr>
<td>≥ 10× ULN</td>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Total Bilirubin &gt; 2× ULN</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

1. NIDA CTN-0027 Final Report (mean dose 22 mg; median 24 mg).
RBP-6000 Hepatic Safety Conclusions

- OUD patient population at high risk for pre-existing liver disease (e.g., Hepatitis B, C, D; HIV; alcohol-induced)
- Hepatic safety profile of RBP-6000 similar to SUBOXONE
- Current SUBOXONE label and proposed RBP-6000 label address these issues by recommending:
  - Liver chemistry at baseline
  - Periodic monitoring
  - Investigation of etiology if liver chemistry values rise
  - Not for patients with severe hepatic impairment
Ph3OL Flex Dosing: Most Dose Reductions Due to Investigator or Subject Request

- Ph3OL study allowed for flex dosing after initial 300 mg dose
  - Ph3DB results not available during Ph3OL study
- 463 (70%) subjects remained on 300 mg
- 201 (30%) subjects had dose reduced to 100 mg at some time
  - 140 – investigator thought subject was doing well or at subject request
  - 12 – investigator discretion
  - 49 – adverse events
    - 16 for sedation – all resolved
    - 13 for liver chemistry elevations – 12 resolved, 1 pregnant & withdrawn
    - 5 for constipation – all resolved
Two Elective Depot Removals Across All Studies

- No depot removals in Phase 3 studies
- 1 subject in opioid blockade study
  - Depot removed after withdrawing consent
- 1 subject in single-dose molecular weight study
  - Depot removed due to SAE (abnormal LFT)
    - Subject tested positive for new onset hepatitis C 18 days after first abnormal LFT
    - Abnormal LFT recovered and resolved
- No complications following depot removal for either subject
Summary of RBP-6000 Safety

- Safety of RBP-6000 evaluated extensively
  - 1048 total subjects
  - 848 subjects in Phase 3, with up to 12 monthly doses
- Safety profile similar to transmucosal buprenorphine with exception of anticipated injection site reactions
  - Known risks for elevations in liver chemistry
- Injection site reactions generally mild or moderate, self-limiting, and led to treatment discontinuation in < 1%
- Safety profiles of 300/100 and 300/300 mg regimens generally similar
  - Injection site reactions and liver chemistry elevations occurred at higher frequency with 300/300 mg
Clinical Perspective

Eric C. Strain, MD
Director, Johns Hopkins Center for Substance Abuse Treatment and Research
Executive Vice Chair for Psychiatry, Johns Hopkins Bayview Medical Center
Benefit-Risk Analysis of RBP-6000

**Patient Benefits**
- Convenience of monthly vs. daily dosing
- Reduces adherence burden
- Ensures compliance (no “drug holidays”)
- Opioid blockade from first dose
- Benefits without supplemental buprenorphine

**Public Health Benefits**
- Restricted distribution and administration only by HCPs reduces risk of diversion
- Depot formulation reduces risks of misuse
- Eliminates accidental pediatric exposures

**Patient Risks**
- Safety profile similar to currently-approved transmucosal buprenorphine products
- Injection site reactions
- Cannot immediately discontinue treatment
- Depot may require surgical removal if treatment needs to be discontinued

**Public Health Risks**
- If RBP-6000 could be diverted:
  - Abuse potential of buprenorphine
  - Risks associated with IV injection
Two current buprenorphine treatment options for OUD

1. Transmucosal buprenorphine (e.g., SUBOXONE, other forms)
   - *Daily* administration
   - Wide dose range (2-32 mg buprenorphine used in clinical practice)

2. Subdermal implant (PROBUPHINE)
   - *6-month* administration
   - For patients clinically stable on low-moderate dose (≤ 8 mg) of transmucosal buprenorphine

If approved, RBP-6000 would offer a *monthly* treatment option
   - Addresses a need in continuum of buprenorphine products
RBP-6000 Offers New Treatment Option for Patients with OUD

- Considering when to use RBP-6000:
  - Concern about diversion or misuse
  - Concern about adherence or compliance
  - At risk for “drug holidays”
  - Children in the home
  - Clinically stable patients who need long-term buprenorphine treatment
RBP-6000 Dosing Regimens Provide Flexibility to Individualize Patient Care

- Both dosing regimens safe and effective
- Choice of maintenance dose based on history and clinical condition
- 100 mg maintenance dose appropriate for many patients
- 300 mg maintenance dose for select patients
  - Need higher buprenorphine concentrations to maximize abstinence and retention in treatment
  - Balancing injection site reactions and LFT elevations against risks of continued illicit opioid use
RBP-6000 (Extended-Release Buprenorphine) for the Treatment of Opioid Use Disorder

October 31, 2017
Indivior, Inc.
Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
BACK-UP SLIDES SHOWN ONSCREEN
Exposure-Response for Abstinence Modeling vs Observations for Injectable vs Non-injectable Route

Observations

Model

% Subjects Abstinent [95% CI]

Injectable Route

Non-Injectable Route

Predicted % of Subjects Abstinent

Buprenorphine concentration (ng/mL)

Buprenorphine concentration (ng/mL)
Higher Rate of Abstinence at End of Study with 300/300 mg Regimen among Injecting Users

![Graph showing subjects abstinent last 4 weeks (%)]

- Injecting Drug Users:
  - RBP-6000 300/300 mg: 34% (N=80) ± 28% (N=84)
  - RBP-6000 300/100 mg: 18% (N=84)

- Non-injecting Drug Users:
  - RBP-6000 300/300 mg: 28% (N=115) ± 28% (N=110)
## Most Common Reasons for Screen Failures

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>212 (41)</td>
<td>Use of barbiturates, benzodiazepines, methadone, or buprenorphine (within past 30 days prior to informed consent) or positive UDS result at screening</td>
</tr>
<tr>
<td>91 (17)</td>
<td>Unable to comply fully with study requirements (Based on opinion of Investigator or medically responsible physician)</td>
</tr>
<tr>
<td>55 (11)</td>
<td>Total bilirubin $\geq 1.5x$ ULN, ALT $\geq 3x$ ULN, AST $\geq 3x$ ULN, serum creatinine $&gt; 2x$ ULN, lipase $&gt; 3x$ ULN, or amylase $&gt; 3x$ ULN</td>
</tr>
<tr>
<td>58 (11)</td>
<td>Willing to adhere to study procedures and provide informed consent prior to study start</td>
</tr>
<tr>
<td>30 (5)</td>
<td>Missing</td>
</tr>
<tr>
<td>13 (2.5)</td>
<td>Current substance use disorder, as defined by DSM-5 criteria, with regard to any substances other than opioids, cocaine, cannabis, tobacco, or alcohol</td>
</tr>
<tr>
<td>13 (2.5)</td>
<td>Uncontrolled medical or psychiatric illness that, may place subject at risk or interfere with outcome measures or ability to participate in study</td>
</tr>
</tbody>
</table>
RBP-6000 Should be Injected in Abdominal Region and Site Should be Rotated Within That Region
Greater Retention of Subjects Over Time in RBP-6000 Groups
## Use of Other Substances Did Not Increase During Phase 3 Double-Blind Study

<table>
<thead>
<tr>
<th>Substance, %</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Baseline</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RBP-6000 300/300 mg N=194</td>
<td>RBP-6000 300/100 mg N=196</td>
<td>Placebo N=99</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphetamines</td>
<td>15</td>
<td>7 – 12</td>
<td>25</td>
<td>11 – 22</td>
<td>19</td>
<td>5 – 19</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>1</td>
<td>0 – 2</td>
<td>2</td>
<td>0 – 2</td>
<td>0</td>
<td>0 – 3</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>10</td>
<td>3 – 9</td>
<td>12</td>
<td>3 – 10</td>
<td>13</td>
<td>3 – 20</td>
</tr>
<tr>
<td>Cocaine</td>
<td>40</td>
<td>27 – 39</td>
<td>47</td>
<td>25 – 33</td>
<td>42</td>
<td>20 – 45</td>
</tr>
<tr>
<td>Phencyclidine</td>
<td>1</td>
<td>1 – 4</td>
<td>0</td>
<td>0 – 2</td>
<td>1</td>
<td>0 – 6</td>
</tr>
</tbody>
</table>

Follow-up use is shown as the range of observed values over follow-up. Use defined as positive UDS, positive self-report on TLFB, or concomitant medication.
EMIT II Plus Opiate Assay & EMIT II Plus Methadone Assay*
  ▪ Competition between drug in specimen and labelled drug
DRL Oxycodone Assay*
  ▪ Specific antibodies to detect oxycodone and oxymorphone
CEDIA Buprenorphine Assay
  ▪ Competition between drug in specimen and conjugated drug

*Positive for opiate, methadone, or oxycodone prompted confirmation by GC/MS
Clinical Courses Differed Between RBP-6000 and Placebo Groups

RBP-6000 300/300 mg (N=196)
RBP-6000 300/100 mg (N=194)
Placebo (N=99)

Week

Missing
Opioid Positive
Opioid Negative

Patient
Label: Use of RBP-6000 in Pregnant Patients

- The data on use of buprenorphine in pregnancy, are limited and do not indicate an increased risk of major malformations specifically due to buprenorphine exposure.
- RBP-6000 should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. This risks should be balanced against the risk of untreated opioid addiction which often results in continued or relapsing illicit opioid use and is associated with poor pregnancy outcomes.
- Prescribers should discuss the importance of management of opioid addiction throughout pregnancy.
RBP-6000 Program: Pregnancy Summary

- Total 21 pregnancies
  - 6 live births (5 pregnancies)
  - 11 cases outcome is unknown
  - 1 spontaneous and 4 elective abortion
  - 1 neonate treated for NAS
  - No reports of neonatal defects
Restricted Distribution System for RBP-6000

Indivior Manufacturer

Specialty Pharmacy (SP) or Specialty Distributor (SD) purchases product from manufacturer

Specialty Pharmacy

SP sends directly to DATA-2000-waivered HCP

--OR--

Healthcare Setting

Healthcare setting (e.g., OTP, hospital pharmacy) purchases product from SD and distributes only to DATA-2000-waivered HCP in that setting

HCP
Higher Rate of Abstinence at End of Study with 300 mg Maintenance Dose among Injecting Users

Pharmacodynamics of Injecting Users

- First Maintenance Dose
- Relative Risk of Abstinence at Week 24: 1.7 (95% CI: 1.2 - 2.4)
- 300/300 mg: 54%
- 300/100 mg: 32%

Pharmacodynamics of Non-injecting Users

- First Maintenance Dose
- Relative Risk of Abstinence at Week 24: 1.1 (95% CI: 0.8 – 1.4)
- 300/300 mg: 40%
- 300/100 mg: 40%
Higher Abstinence in Last 4 Weeks of Study with 300/300 mg Among Injecting Drug Users

Subjects Abstinent for Weeks 21-24 (%)

<table>
<thead>
<tr>
<th></th>
<th>Abstinent (95% CI)</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injecting Drug</td>
<td>34% (30/90)</td>
<td>1.9</td>
<td>1.1 - 3.3</td>
</tr>
<tr>
<td>Users</td>
<td></td>
<td>1.0</td>
<td>0.6 - 1.5</td>
</tr>
<tr>
<td>Non-injecting</td>
<td>28% (24/86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Users</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Completers – Double-blind Study