THERAPEUTIC DEVELOPMENT FOR OPIOID USE DISORDER & OVERDOSE PREVENTION AND REVERSAL

Extended Release Formulations for Opioid Use Disorder: A Case Study

Christian Heidbreder, Ph.D.
Chief Scientific Officer, Indivior Inc.

TODAY'S PRESENTATION

Part I: Improving Current Treatment Options for Opioid Use Disorder

Part II: Lessons learned

Part III: From Translational Medicine to Clinical Efficacy & Safety

Part IV: Accelerating the Development of new Treatment Options for OUD: Public/Industry partnership

Our vision is that all patients around the world will have access to quality treatment for the chronic relapsing conditions and co-morbidities of addiction

Part I: Improving Current Treatment Options for Opioid Use Disorder

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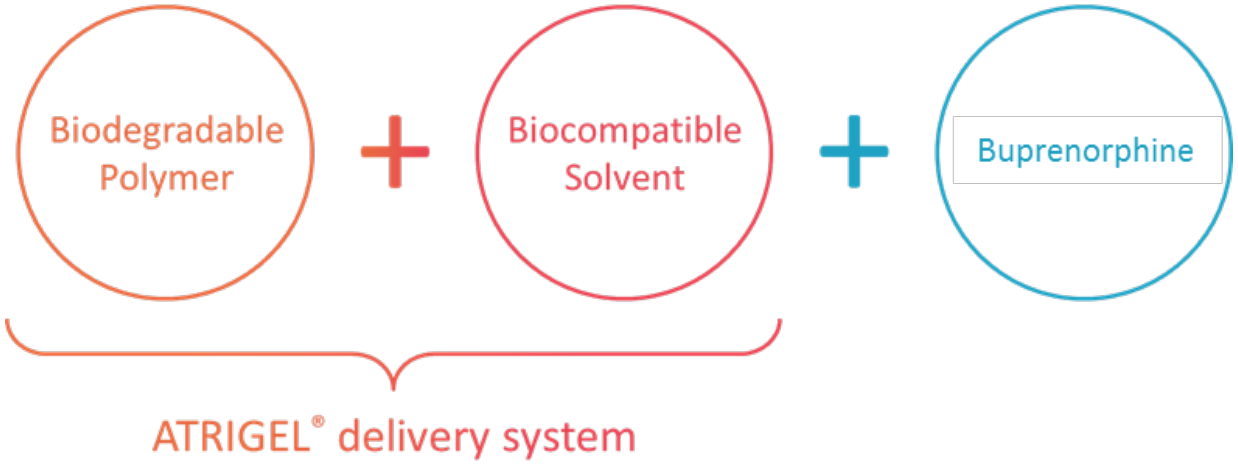
1 LANDSCAPE OF CURRENT MAT VS. NEW OPPORTUNITIES

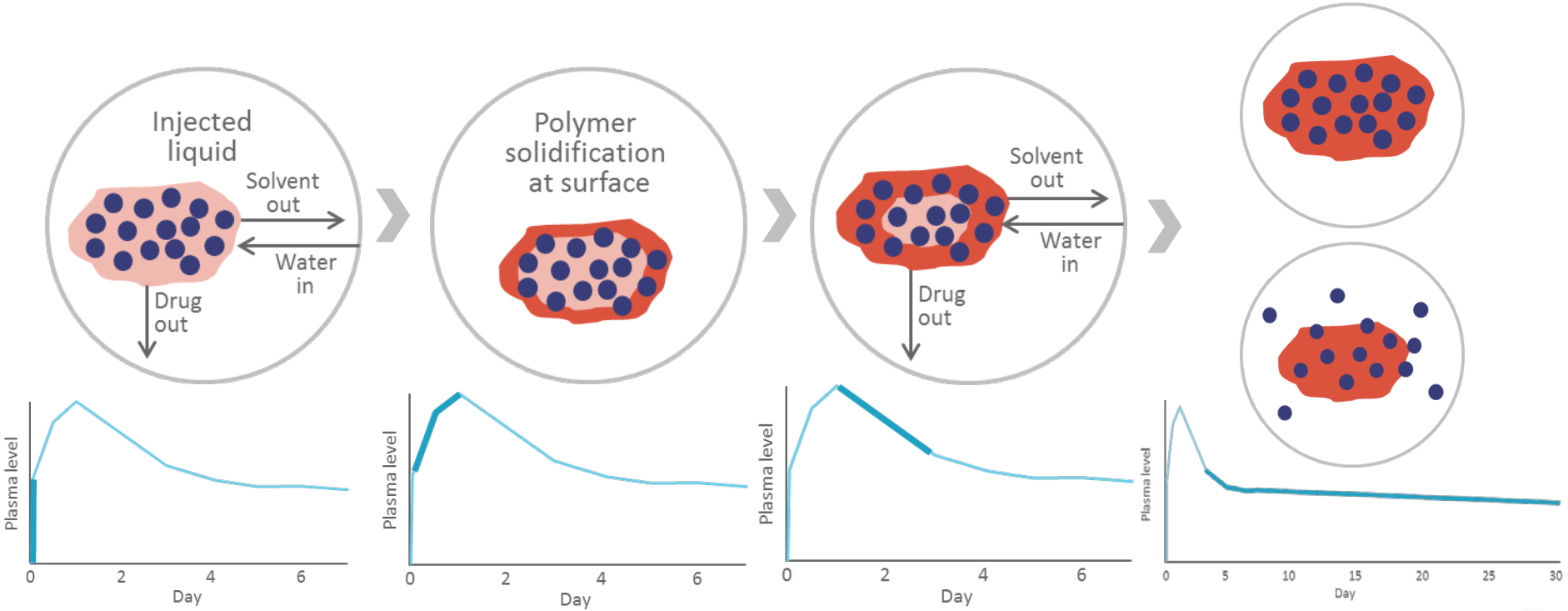
Current MAT Options	Objectives of extended-release (ER) formulations of buprenorphine
Require daily medication adherence	▪ Monthly or longer dosing interval to remove burden of daily adherence
Potential sub-therapeutic buprenorphine level at end of dosing interval & occasional need for supplemental dosing	▪ Deliver therapeutic buprenorphine level and effective opioid blockade from first dose ▪ Control of withdrawal symptoms and craving
Potential diversion, misuse, abuse and accidental exposure	▪ Restricted distribution scheme ▪ Administered by health care professional

2 DEVELOPING EXTENDED-RELEASE BUPRENORPHINE: OUR EXPERIENCE WITH ATRIGEL® DRUG DELIVERY PLATFORM

- ✓ **Used in 7 other FDA-approved drug products**
- ✓ **Biodegradable depot of buprenorphine**
- ✓ **Prefilled syringe, administered subcutaneously**



3 DEVELOPING EXTENDED-RELEASE BUPRENORPHINE: RELEASE PROFILE CONCEPT



Balance of diffusion and polymer degradation needed to obtain desired release rate and pharmacokinetics

4 DESIGNING & PLANNING A DRUG DEVELOPMENT PLAN: A CASE STUDY WITH RBP-6000

2009

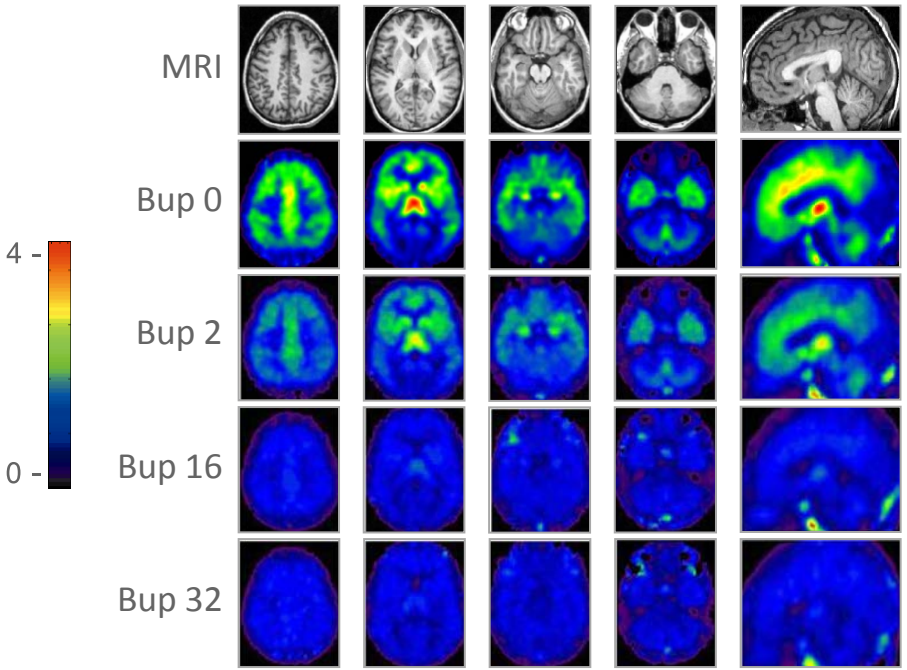
- **Pre-IND submission**: Dec 18th, 2009
- **Pre-IND meeting with FDA**: Apr 27th, 2010
- **IND submission**: Sep 17th, 2010
- **Type C meeting**: May 14th, 2013
- **End-of-Phase II meeting**: Sep 30th, 2014
- **Pre-NDA meeting**: Dec 15th, 2016
- **NDA submission**: May 30th, 2017
- **NDA filing and PDUFA Priority Review Designation by FDA**: Jul 29th, 2017
- **Advisory Committee**: Oct 31st, 2017
- **PDUFA date**: Nov 30th, 2017

2017

- **First-in-Man** study (20 mg)
- **Single Ascending Dose (SAD)** study (50, 100, 200 mg)
- **Multiple Ascending Dose (MAD)** study (50, 100, 200, 300 mg)
- **Opioid blockade** study
- **Phase III double-blind** placebo-controlled study
- **Phase III open label** long-term safety extension study

Part II: Lessons Learned

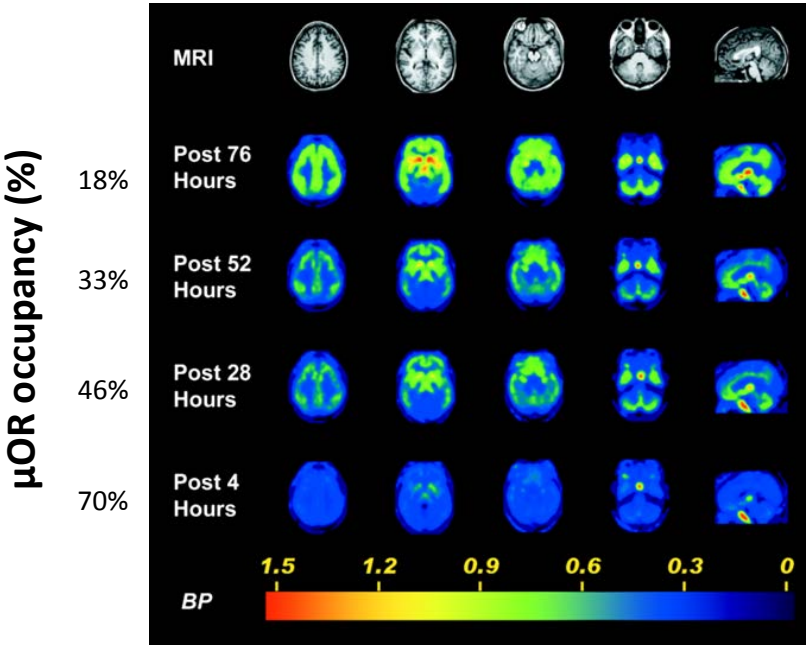
1 AT LEAST 70% BRAIN μ-OPIOID RECEPTOR OCCUPANCY (μORO) BY BUPRENORPHINE IS REQUIRED FOR OPIOID BLOCKADE



Adapted from: Greenwald MK et al. (2003) Neuropsychopharmacology 28: 2000-2009.

- **At least 70% brain μ-opioid receptor (μOR) occupancy** by buprenorphine is required to block the subjective drug-liking effect (opioid blockade) of full agonist-induced responses.
- An analysis of brain μOR occupancy and buprenorphine plasma concentration demonstrated that **opioid blockade requires buprenorphine plasma concentrations of ≥2 ng/mL**

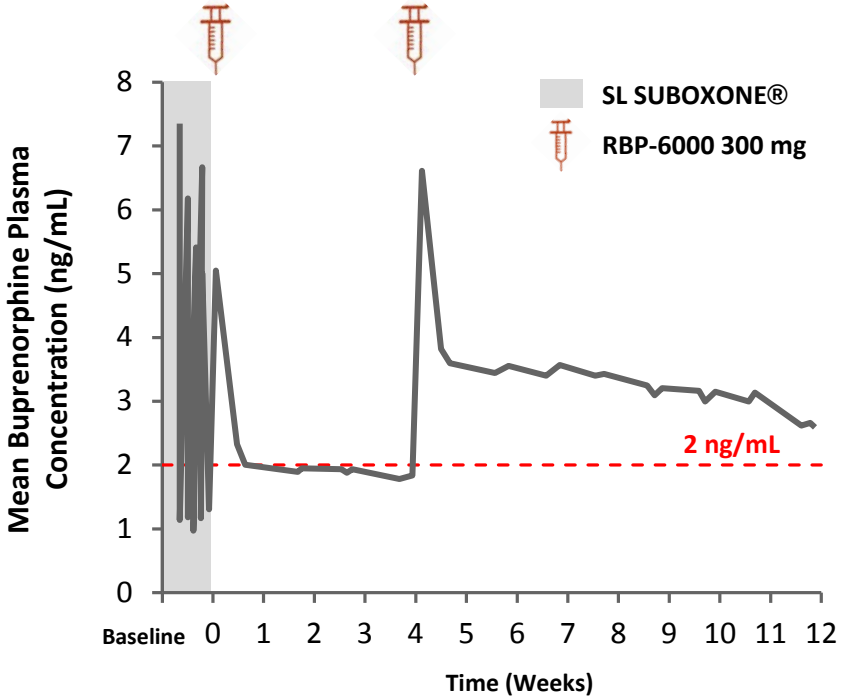
2 PHARMACODYNAMIC ACTION OF BUPRENORPHINE DECREASES WITH A DECREASE IN PLASMA CONCENTRATIONS & μORO

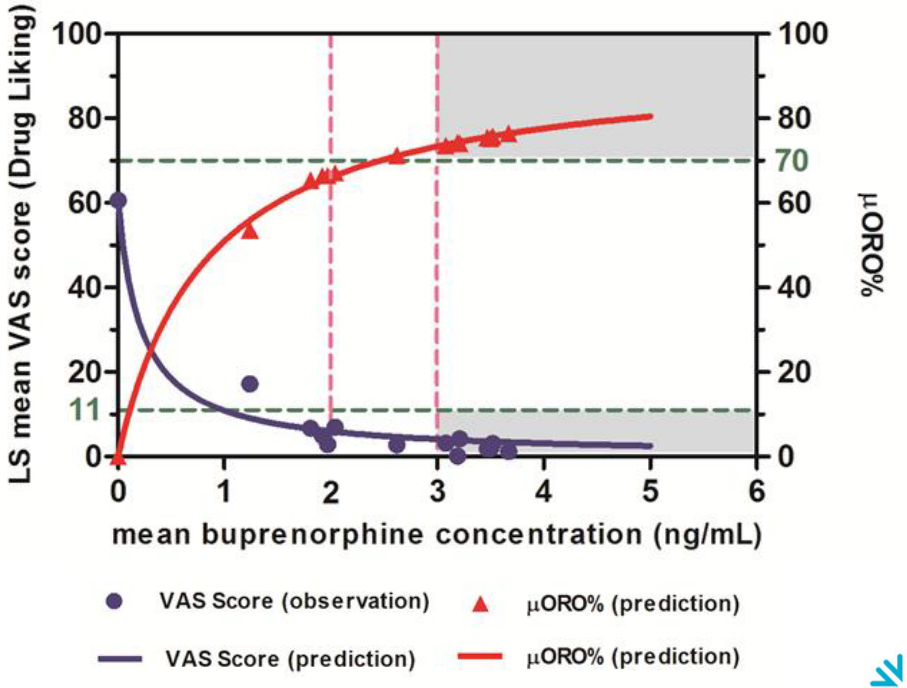


Adapted from: Greenwald MK et al. (2007) Biological Psychiatry 61: 101-110.

- Pharmacodynamic action (*estimated by abstinence, suppression of withdrawal and craving, and blockade of the effects of an opioid agonist such as hydromorphone*) of acute sublingual (SL) buprenorphine decreases over time and is **highly correlated with plasma concentrations of buprenorphine (≥ 2 ng/mL) and μOR occupancy (> 70%).**

3 BUPRENORPHINE PLASMA LEVEL ≥ 2NG/ML (≥ 70% μOR) IS THE MINIMUM THRESHOLD TO ACHIEVE BLOCKADE OF DRUG LIKING





Nasser AF et al. (2016) J Clin Psychopharmacol. 36(1):18-26.

Part III: Translating Opioid Blockade Data Into Clinical Efficacy & Safety

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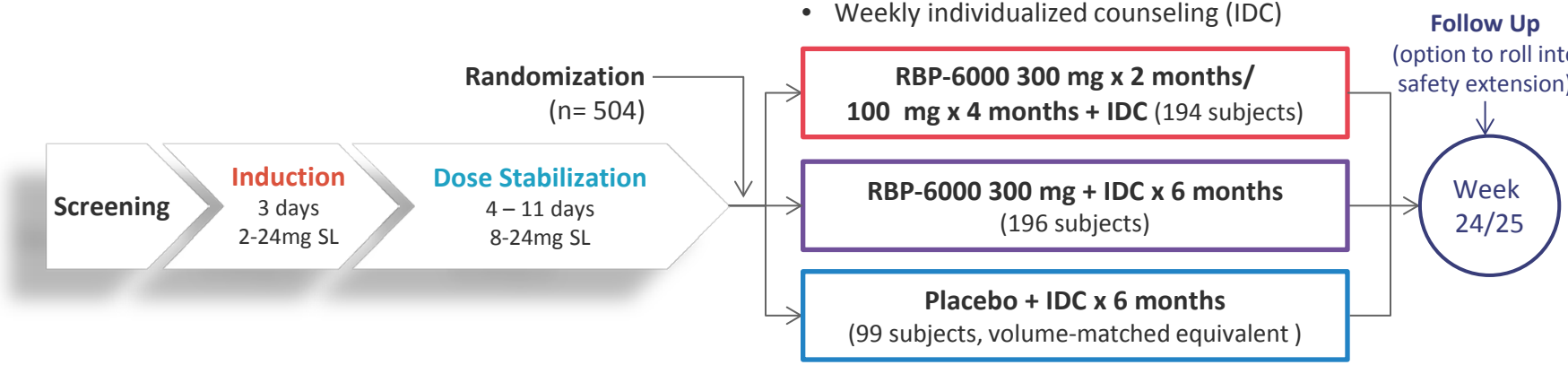
1 DESIGNING A PHASE III CLINICAL TRIAL (RB-US-13-0001) TO ADDRESS EFFICACY & SAFETY

Treatment Period:

- 6 double-blind subcutaneous injections
- Weekly urine drug screens and self-reports
- Weekly individualized counseling (IDC)



Primary endpoint:

The CDF (Cumulative Distribution Function) of the % of urine samples negative for opioids combined with self-reports negative for illicit opioid use collected from Week 5 through Week 24. Urine drug screen (UDS) and self-reports collected weekly

Key Secondary Endpoint:

Treatment success, defined as any subject with ≥80% of urine samples negative for opioids combined with self-reports negative for illicit opioid use between Week 5-24. Missing UDS or self-report considered positive for opioids

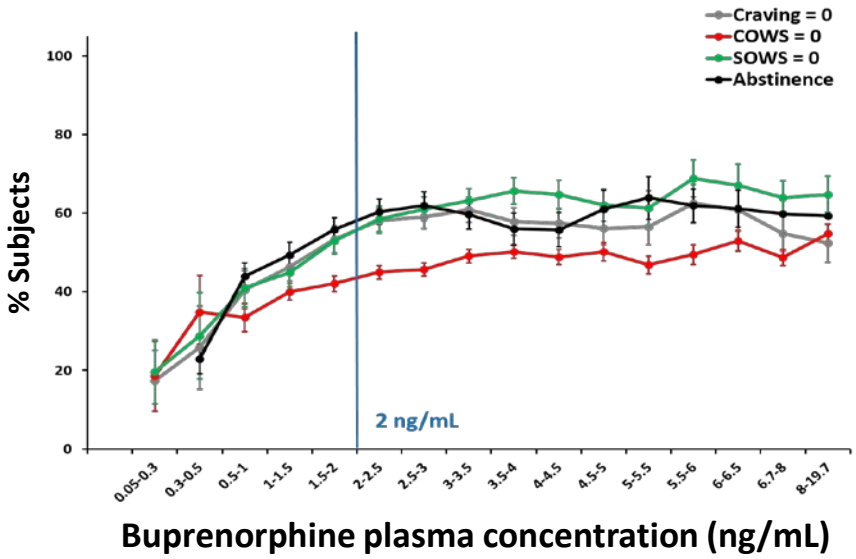
2 DEMONSTRATING CLINICAL EFFICACY: PRIMARY & SECONDARY ENDPOINTS (WEEKS 5 - 24)

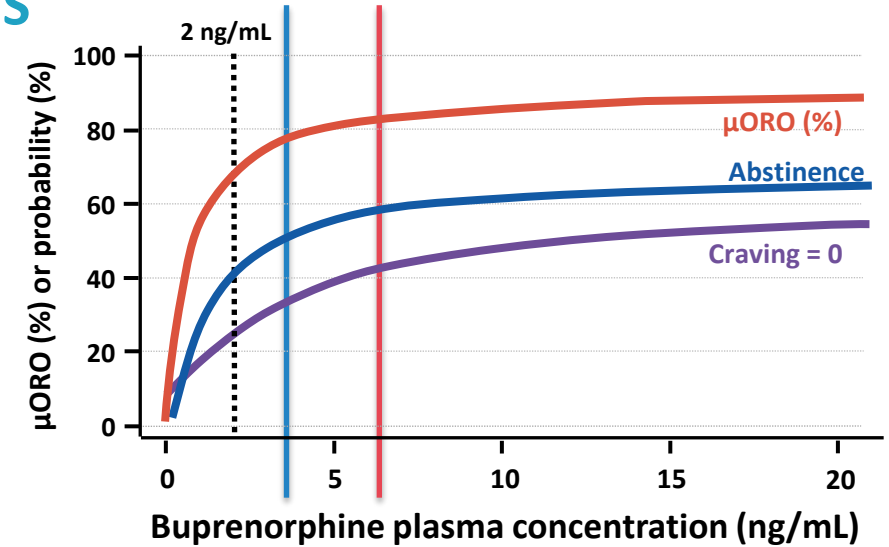
	RBP-6000 300mg/100mg	RBP-6000 300mg/300mg	Placebo
% Abstinent Weeks			
Mean (SD)	**42.7% (38.50%)**	**41.3% (39.66%)**	**5.0% (16.98%)**
p-value	< 0.0001	< 0.0001	-
≥ 80% Abstinent Weeks (Responder)			
Treatment Success	**28.4%**	**29.1%**	**2.0%**
p-value	< 0.0001	< 0.0001	-

47% of patients on 300 mg/300 mg dosing regimen were drug free in the last 4 weeks of the 6-month study

Secondary Endpoint	LS Mean Difference vs Placebo (95% CI)	p-value
Opioid Craving VAS (0 – 100 mm scale)		
300/300 mg vs placebo	-12.4 (-17.5, -7.3)	< 0.0001
300/100 mg vs placebo	-9.4 (-14.6, -4.3)	0.0003
COWS (0 – 48 scale)		
300/300 mg vs placebo	-1.0 (-1.7, -0.2)	0.010
300/100 mg vs placebo	-0.4 (-1.1, 0.4)	0.31
SOWS (0 – 64 scale)		
300/300 mg vs placebo	-2.6 (-4.3, -0.9)	0.003
300/100 mg vs placebo	-1.6 (-3.3, 0.1)	0.072

3 DEMONSTRATING CLINICAL EFFICACY: EXPOSURE-RESPONSE ANALYSIS





Dose Group	N	C_{avg} (ng/mL)	µORO (%)*
300 mg/100 mg	194	3.14	75
300 mg/300 mg	196	6.32	83

* Predicted whole brain µ-Opioid Receptor Occupancy corresponding to C_{avg}

4 DEMONSTRATING CLINICAL SAFETY

Occurrence (%)	Placebo + IDC (n=100)	RBP-6000 300/100 mg + IDC (n=203)	RBP-6000 300/300 mg + IDC (n=201)
Any TEAE	56.0	76.4	66.7
Serious TEAE	5.0	2.0	3.5
TEAE leading to discontinuation	2.0	3.4	5.0
Any injection site TEAE	9.0	13.8	18.9
Serious injection site TEAE	0	0	0
Injection site TEAE leading to discontinuation	0	0	0.5

- 1048 total exposures
- 848 exposures in Phase 3 with up to 12 monthly doses
- Safety profile consistent with transmucosal buprenorphine-containing products with exception of anticipated injection site reactions
- Injection site reactions generally mild to moderate and self-limiting, and led to treatment discontinuation in < 1%

Accelerating the Development of new Treatment Options for OUD: Public/Industry Partnership

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1 AREAS OF FOCUS: PUBLIC/INDUSTRY PARTNERSHIP

- **ER buprenorphine formulation to prevent opioid overdose?**
- **ER buprenorphine formulation in patient sub-populations?**
- **Impact of ER buprenorphine formulation on patient outcomes?**
  - ✓ improvement in health status and health-related quality of life
  - ✓ medication satisfaction
  - ✓ decreased health care resource utilization
  - ✓ improvement in employment status and health insurance
  - ✓ decreases in comorbid drug use and psychiatric associations
- **Craving research?**

2 AREAS OF FOCUS: PUBLIC/INDUSTRY PARTNERSHIP

- **Biomarkers for patient stratification and as endpoints for clinical trials?**
  - ✓ Clinical phenotyping and identification of common genetic variants
  - ✓ Small clinical trials of homogeneous populations to establish PoC
- **DMPK/DDI?**
  - ✓ Demonstrate early that therapeutic levels of a drug can be reliably delivered to the brain
  - ✓ Demonstrate that, at those levels, the drug binds its target and modifies the disease pathway in the desired directions
- **“Combinatorial” approaches to treatments?**
  - ✓ E.g., combination of drugs, behavioral therapies and psychotherapies, or devices

3 AREAS OF FOCUS: PUBLIC/INDUSTRY PARTNERSHIP

- **Reliability and reproducibility of published data?**
  - ✓ Preclinical studies to have rigorous standards, similar to clinical trials, ensuring sound research design and credible statistical analyses for successful translational medicine.
  - ✓ Overrepresentation of positive data in the published literature and corresponding underrepresentation of negative data.
- **Data sharing?**
  - ✓ Success cannot be achieved independently.
  - ✓ Fight high-risk target aversion.
- **Collaborations and cross-training with disciplines outside the neurosciences?**
  - ✓ E.g., engineering, chemistry, physics, and mathematics.

THANK YOU

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