RBP-6000 Buprenorphine Monthly Depot Phase III Clinical Results

RBP-6000 Investor Event June 29TH, 2017

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

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RBP-6000 IS AN INVESTIGATIONAL PRODUCT THAT HAS NOT BEEN APPROVED BY THE U.S. FOOD AND DRUG ADMINISTRATION FOR SAFETY AND EFFICACY

Today's Agenda

Opening statements

Shaun Thaxter, Chief Executive Officer

Introduction

Christian Heidbreder, Chief Scientific Officer

RBP-6000 Phase III Efficacy & Safety

Susan Learned, Senior VP, Global Clinical Development

Conclusion

Christian Heidbreder, Chief Scientific Officer

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Opening Statements

Shaun Thaxter, Chief Executive Officer

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OUR VISION

For all **patients** around the **world to have access** to **quality treatment** for the chronic relapsing **conditions and co-morbidities of addiction**

Introduction

Christian Heidbreder, Chief Scientific Officer

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RBP-6000 Development Milestones

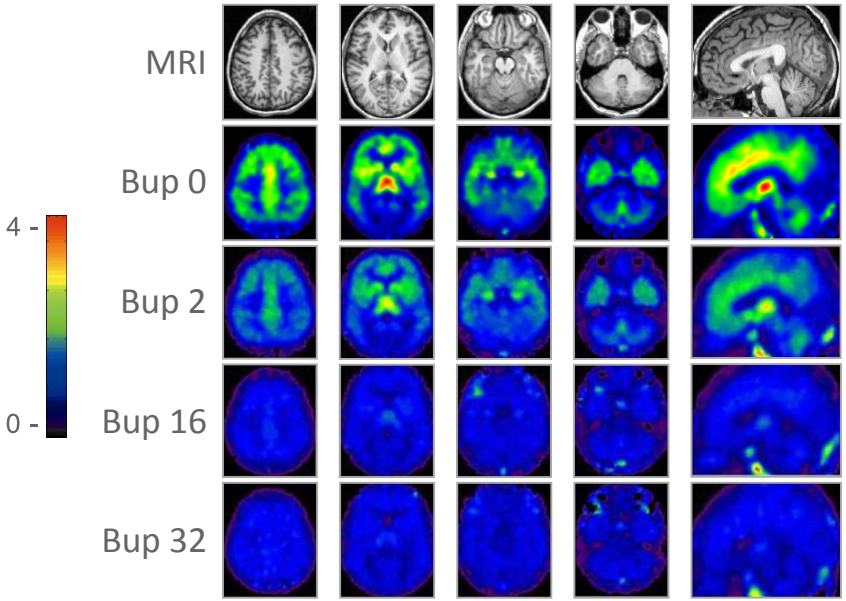
- **Pre-IND submission**: December 18th, 2009
- **Pre-IND meeting with FDA**: April 27th, 2010
- **IND submission**: September 17th, 2010
- **Type C meeting**: May 14th, 2013
- **End-of-Phase II meeting**: September 30th, 2014
- **Pre-NDA meeting**: December 15th, 2016
- **NDA submission**: May 30th, 2017
- **NDA filing by FDA**: July 29th, 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

SUMMARY

- Both dosage regimens of RBP-6000 show statistically significant differences in **percentage abstinence** and **treatment success** vs. placebo.
- Treatment outcomes are consistent across other clinical endpoints including control of **craving** and **withdrawal symptoms**.
- Results from the **exposure-response analyses** predict a relationship between buprenorphine plasma concentration, whole brain mu-opioid receptor occupancy, abstinence, withdrawal and opioid craving.
- Buprenorphine plasma concentration ≥ 2 ng/mL (mu-opioid receptor occupancy ≥ 70%) is the **minimum threshold** to achieve blockade of drug liking and is delivered consistently from the first dose of RBP-6000 treatment across the entire monthly dosing interval.
- The **safety profile** of RBP-6000 is consistent with the known profile of transmucosal buprenorphine, with no unexpected safety findings. Injection site reactions are not treatment-limiting.

Brain μ-OPIOID RECEPTORS (μOR) ARE RELEVANT TO TREATING OUD

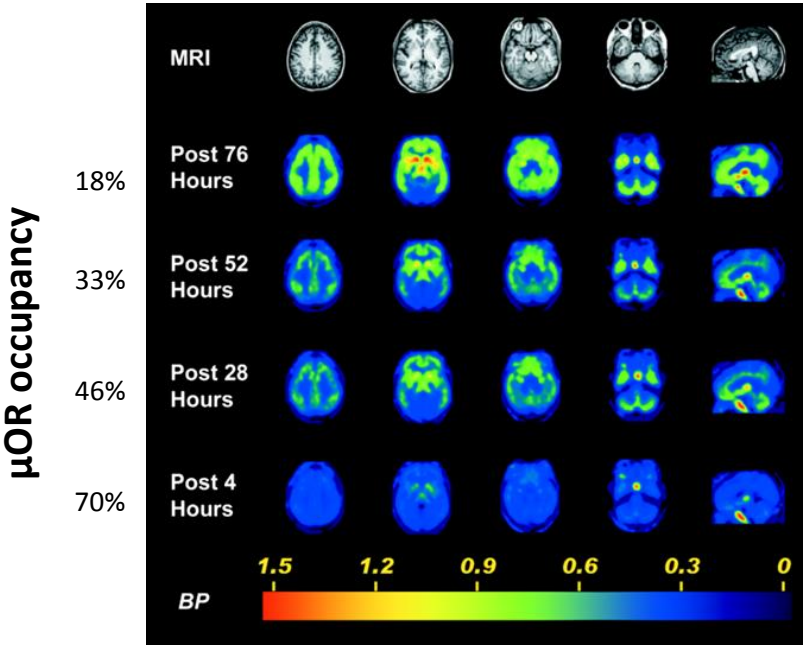


- [11C]Carfentanil PET has been successfully used to reliably measure *in vivo* brain μOR availability following buprenorphine administration in opioid-dependent patients.
- **At least 70% brain μ-opioid receptor (μOR) occupancy** by buprenorphine is required to block the subjective drug-liking effect (opioid blockade) of full agonist-induced responses. An analysis of brain μOR occupancy and buprenorphine plasma concentrations demonstrated that **opioid blockade requires buprenorphine plasma concentrations of ≥2 ng/mL**

Parametric images of brain μOR availability as assessed by [11C]Carfentanil PET from a representative opioid-dependent volunteer during daily maintenance with placebo or buprenorphine 2-32 mg. Anatomical MRI images are shown on top. Placebo images show μOR availability, whereas buprenorphine 32 mg significantly decreased μOR availability by >94%.

Adapted from: Greenwald MK, Johanson CE, Moody DE, Woods JH, Kilbourn MR, Koeppe RA, Schuster CR, Zubieta JK (2003) Effects of Buprenorphine Maintenance Dose on Mu-Opioid Receptor Availability, Plasma Concentrations, and Antagonist Blockade in Heroin-Dependent Volunteers Neuropsychopharmacology 28: 2000-2009.

PHARMACODYNAMIC ACTION OF BUPRENORPHINE DECREASES WITH A DECREASE IN PLASMA CONCENTRATIONS & BRAIN μOR OCCUPANCY



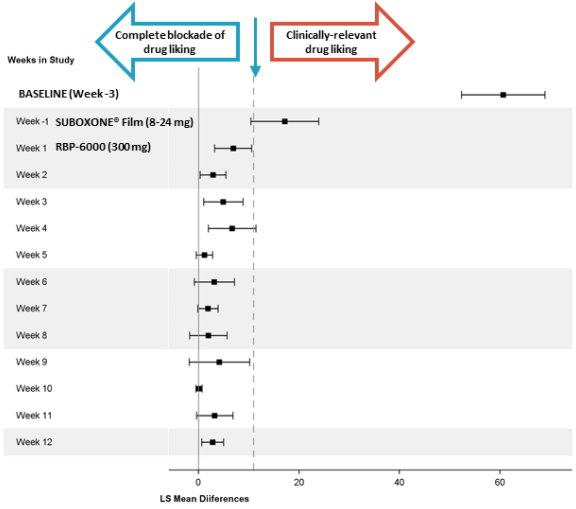
- Acute sublingual (SL) buprenorphine duration of pharmacodynamic action (*estimated by abstinence, suppression of withdrawal and craving, and blockade of the effects of an opioid agonist such as hydromorphone*) decreases over time and is highly correlated with plasma concentrations of buprenorphine and μOR occupancy.
- Agonist symptoms produced by hydromorphone were blocked at 4 hours after acute SL BUP 16 mg, but recovered increasingly as time elapsed together with withdrawal symptoms and craving as plasma concentrations of buprenorphine and μOR occupancy progressively decreased.

Parametric images of brain μOR availability as assessed by [11C]Carfentanil PET from a representative opioid-dependent volunteer at different times (4, 28, 52, and 76 hours) after the sublingual administration of a maintenance dose of buprenorphine 16 mg. Anatomical MRI images are shown on top. Images show a clear time-dependent increase in μOR availability (i.e., a decrease in μOR occupancy) post-buprenorphine administration that was associated with a progressive increase in withdrawal symptoms, cravings and agonist effects produced by an opioid agonist.

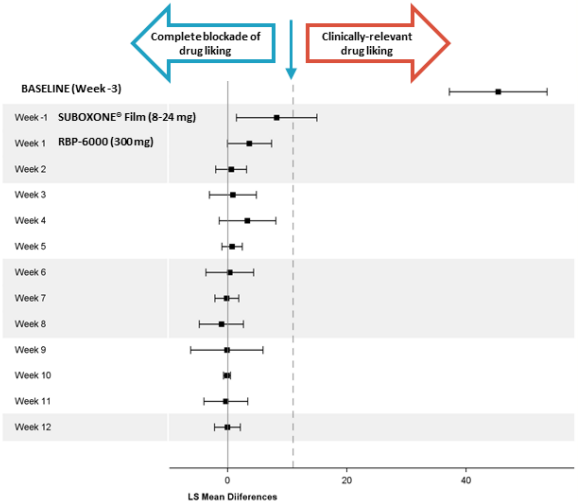
Adapted from: Greenwald MK, Johanson CE, Bueller J, Chang Y, Moody DE, Kilbourn MR, Koeppe RA, Zubieta JK (2007) Buprenorphine duration of action: Mu-opioid receptor availability, pharmacokinetic and behavioral indices. Biological Psychiatry 61: 101-110.

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

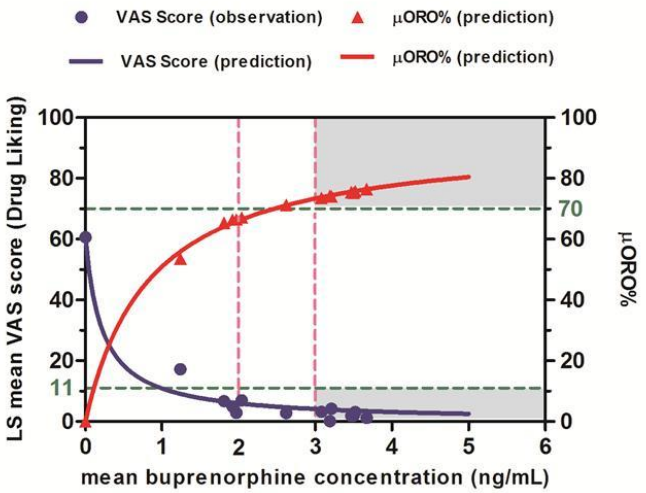
RBP-6000 300mg vs. Hydromorphone 18mg



RBP-6000 300mg vs. Hydromorphone 6mg



Plot of mean difference and 95% confidence interval for "Drug Liking" VAS score. Comparison of placebo vs. 18 mg (*left panel*) and 6 mg (*right panel*) hydromorphone. Blockade was achieved for weeks on study if plots wholly lies left of non-inferiority bound (dashed line).



Modeling of the relationship between plasma concentrations of buprenorphine, drug liking VAS, and predicted whole brain µOR occupancy.

Nasser AF, Greenwald MK, Vince B, Fudala PJ, Twumasi-Ankrah P, Liu Y, Jones JP III, Heidbreder C (2016) Sustained-Release Buprenorphine (RBP-6000) Blocks the Effects of Opioid Challenge with Hydromorphone in Subjects with Opioid Use Disorder. J Clin Psychopharmacol. 36(1):18-26.

Phase III Clinical Efficacy & Safety Trial

Susan Learned, Senior VP Global Clinical Development

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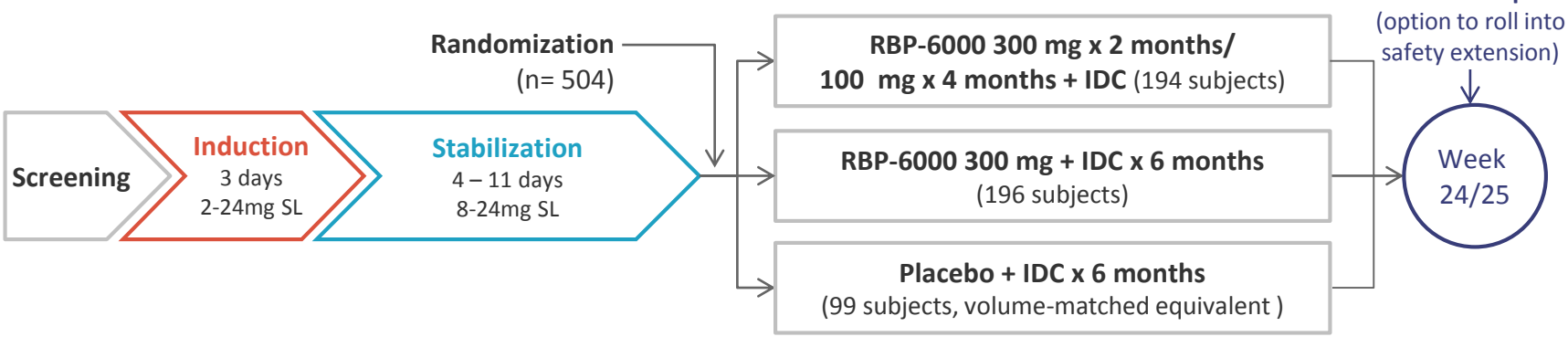
PHASE III EFFICACY & SAFETY STUDY (RB-US-13-0001)

Title	A Randomized, Double-blind, Placebo-Controlled, Multicenter Study to Assess the Efficacy, Safety, and Tolerability of Multiple Subcutaneous Injections of RBP-6000 [100 mg and 300 mg] Over 24 Weeks in Treatment-Seeking Subjects with Opioid Use Disorder
Study Phase	Phase III
Design	Multi-center, Multi-dose, Randomized, Double-blind, Placebo-controlled, 24-week efficacy, safety, and tolerability study
# of patients	N = 504
Primary endpoints	Abstinence Rate (CDF of the % of urine samples combined with self-reports negative for illicit opioid use collected from Week 5 through Week 24). Key Secondary: Responder analysis (defined as ≥80% abstinent rate)
Status	Complete
NCT ref.	NCT02357901

RBP-6000: PHASE III STUDY (RB-US-13-0001) DESIGN

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.

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.

RBP-6000 Clinical Efficacy

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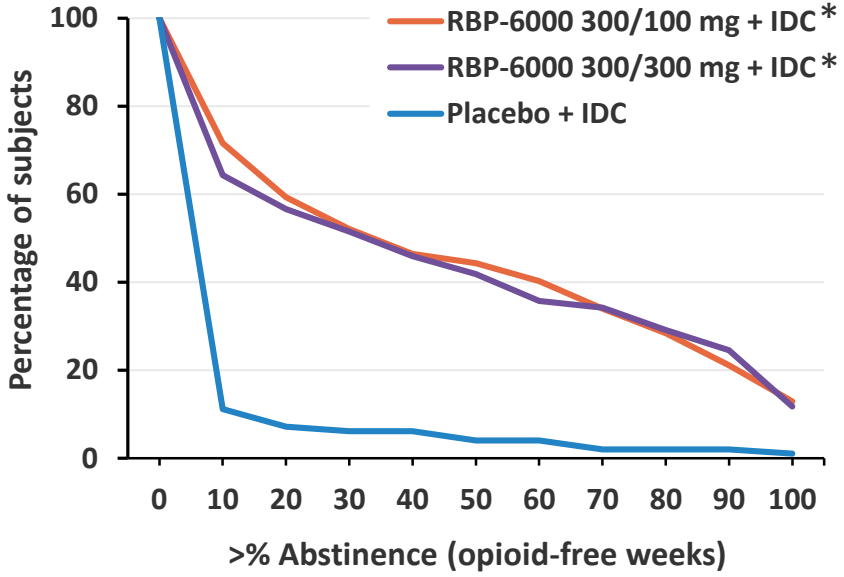
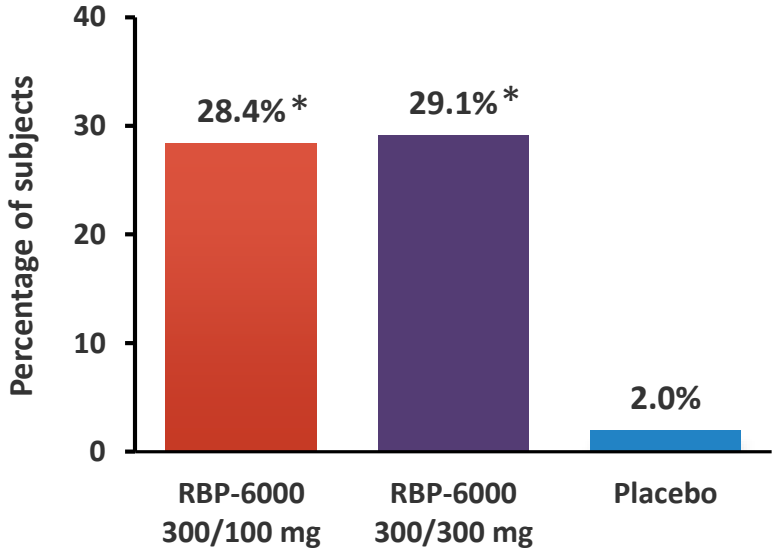
RBP-6000: Primary & Secondary Endpoints

Primary: CDF of % urine samples negative for opioids + negative self-reports of illicit opioid use (Weeks 5 to 24)



Key secondary: ≥80% of urine samples negative for opioids + negative self-reports of illicit opioid use (Weeks 5 to 24)

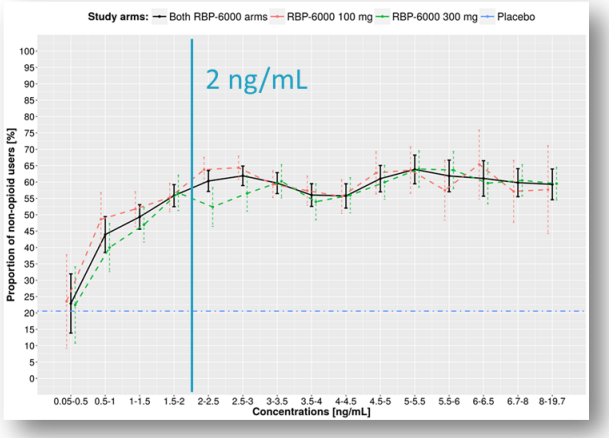


*P<0.0001 vs. placebo

RBP-6000: Primary/Secondary Endpoints & Exposure-Response

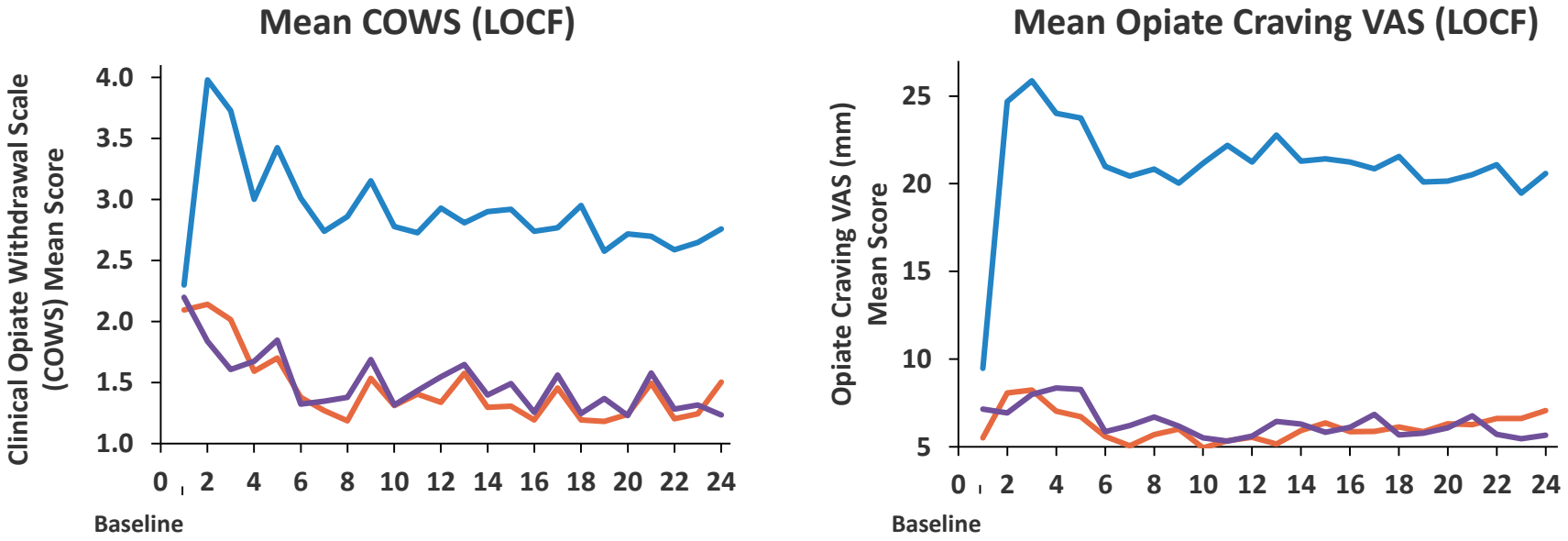
	RBP-6000 300mg/100mg	RBP-6000 300mg/300mg	Placebo
Percentage Abstinent Weeks			
Mean (SD)	**42.7% (38.50%)**	**41.3% (39.66%)**	**5.0% (16.98%)**
p-value	< 0.0001	< 0.0001	-
≥ 80% Abstinent Weeks (Responder)			
Treatment Success*	**28.4%**	**29.1%**	**2.0%**
p-value	< 0.0001	< 0.0001	-

**Treatment success was defined as any subject with ≥ 80% of urine samples negative for opioids combined with self-reports negative for illicit opioid use between Week 5 and Week 24.*



- 64% and 61% of patients completed therapy over the course of study in each of the RBP-6000 arms (300 mg/300 mg and 300 mg/100 mg, respectively) vs. 33.3% for patients taking placebo.
- 47% of patients on 300 mg/300 mg dosing regimen were drug free in the last four weeks of the 6-month study
- An exposure-response relationship confirmed the 2ng/mL threshold to deliver significant levels of abstinence

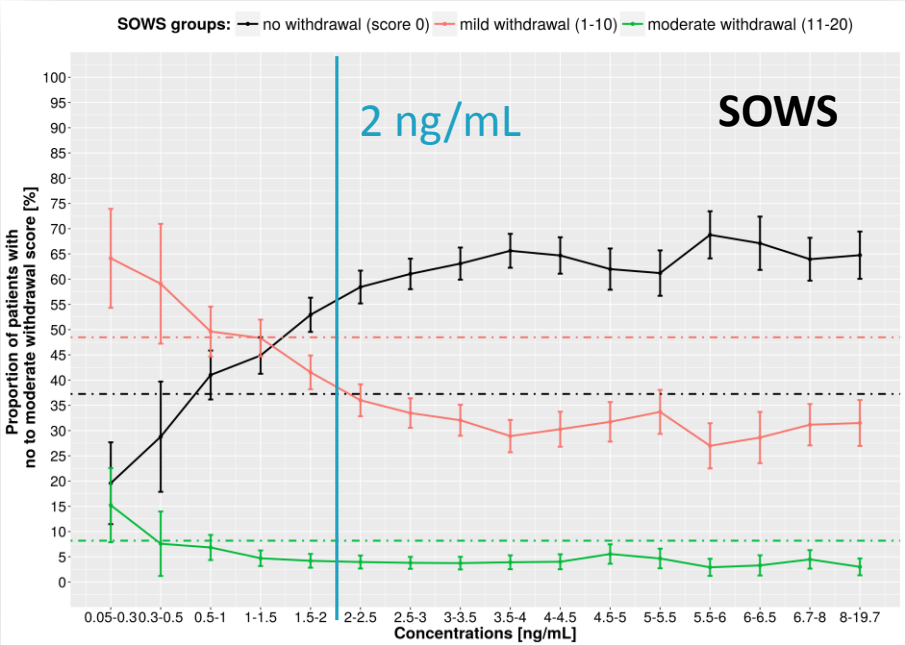
Clinical Opiate Withdrawal Scale (COWS) + Craving VAS

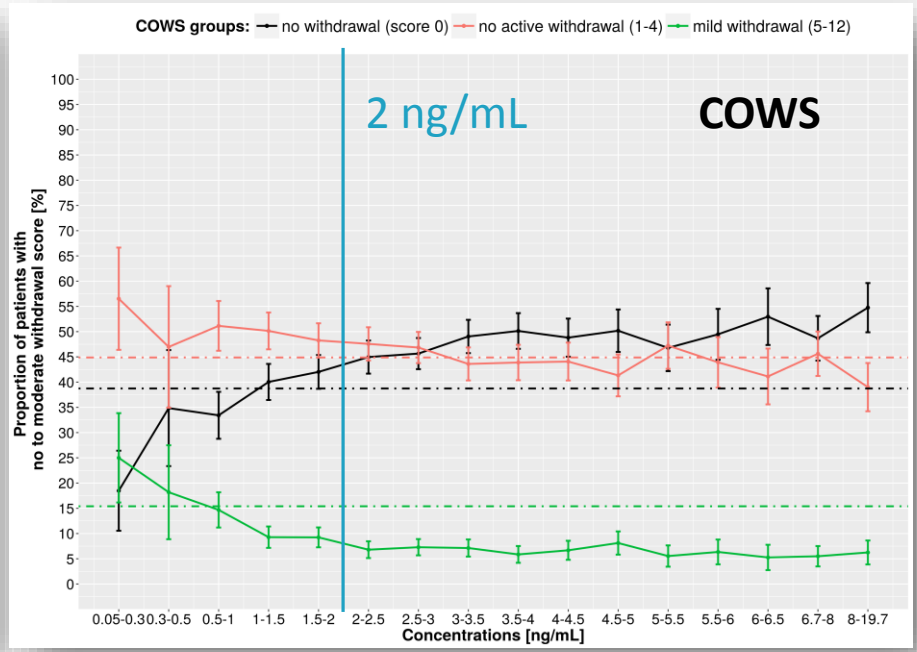


RBP-6000: Secondary Endpoints Summary

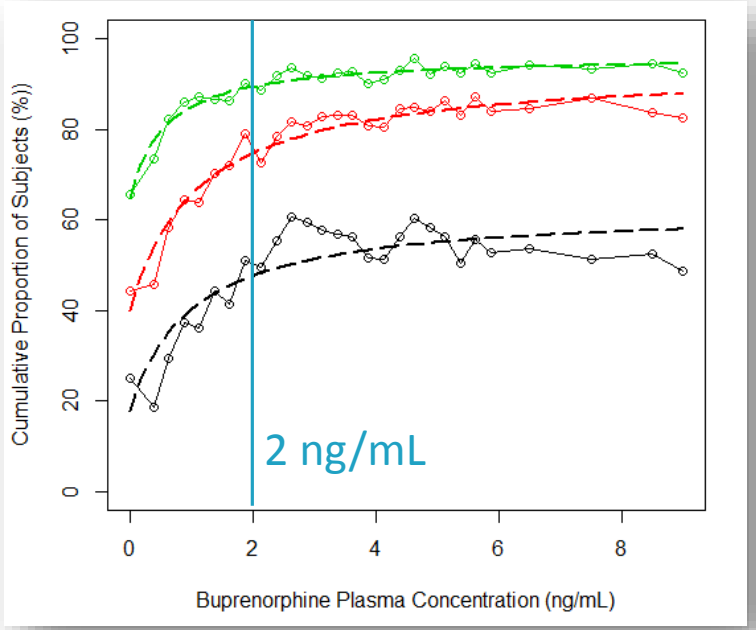
	RBP-6000 (300mg/100mg + IDC) vs. placebo + IDC (N=194)	RBP-6000 (300mg/300mg + IDC) vs. placebo + IDC (N=196)
Secondary Efficacy Endpoints		
Opioid Craving Visual Analog Scale Scores (VAS)		
Difference in LS means (SE)	-9.4 (2.62)	-12.4 (2.61)
95% CI	-14.56, -4.30	-17.51, -7.28
p-value	0.0003	0.0101
Clinical Opiate Withdrawal Scale (COWS)		
Difference in LS means (SE)	-0.4 (0.38)	-1.0 (0.38)
95% CI	-1.13, 0.36	-1.72, -0.23
p-value	0.3143	0.0101
Subjective Opiate Withdrawal Scale (SOWS)		
Difference in LS means (SE)	-1.6 (0.87)	-2.6 (0.87)
95% CI	-3.29, 0.14	-4.32, -0.90
p-value	0.0726	0.0028

RBP-6000: 2NG/ML THRESHOLD & WITHDRAWAL REDUCTION





RBP-6000: 2NG/ML THRESHOLD & CRAVING REDUCTION

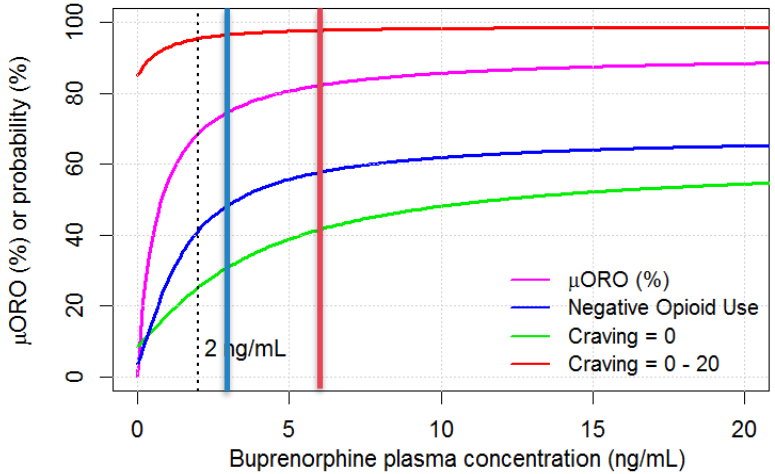


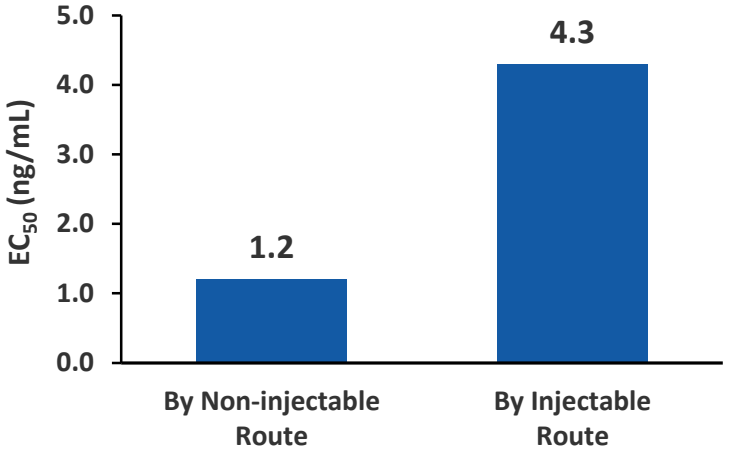
Craving ≤ 20

Craving ≤ 5

Craving = 0

Association Between Plasma Concentrations of Buprenorphine, Predicted μOR Occupancy & Clinical Endpoints





Dose Group	N	C_{min} (ng/mL)	C_{max} (ng/mL)	C_{avg} (ng/mL)	μORO (%)*
300 mg/100 mg	194	2.74	4.11	3.14	75
300 mg/300 mg	196	5.11	8.68	6.32	83

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

Abstinence Rate (Day 169) in Users by Injectable Route	
300 mg /100 mg	53%
300 mg/300 mg	69%

RBP-6000 Clinical Safety

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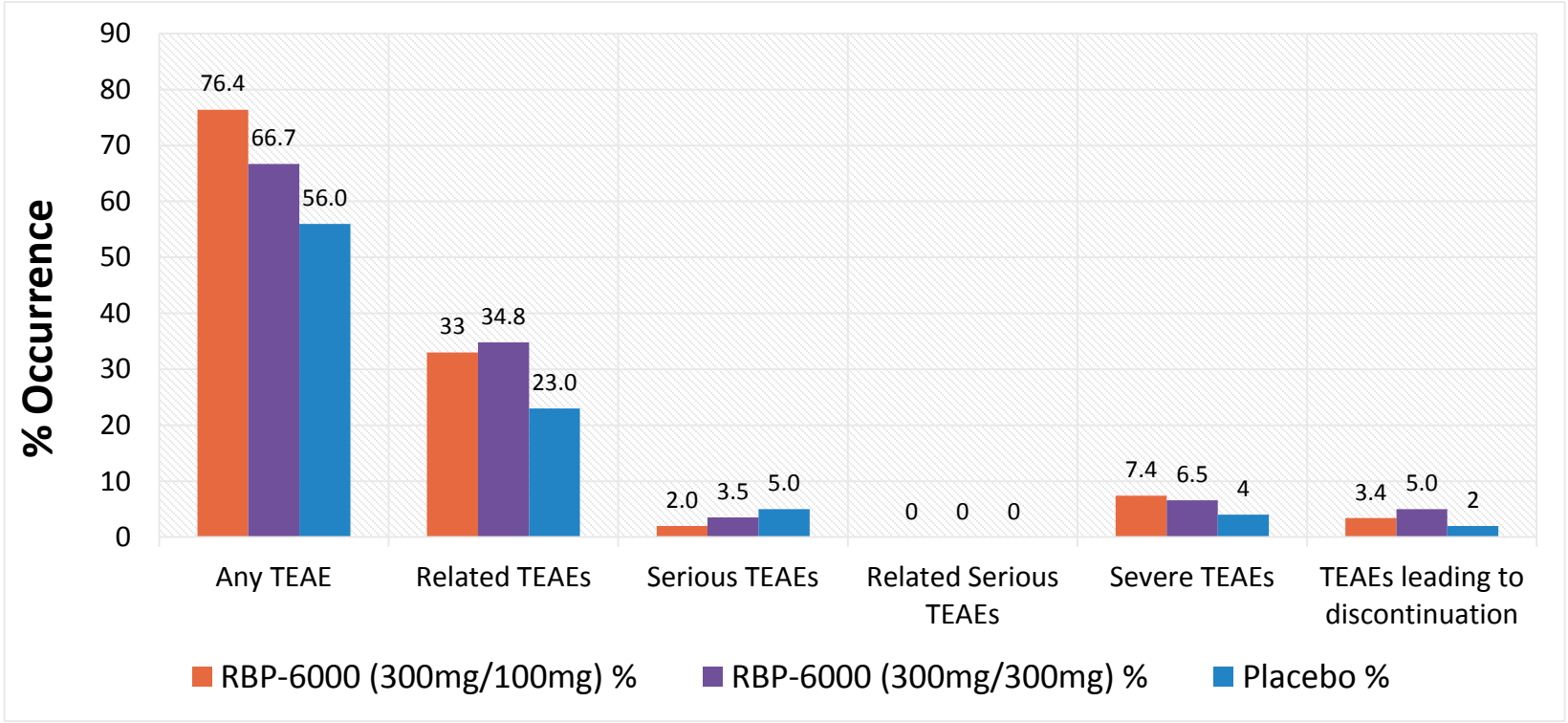
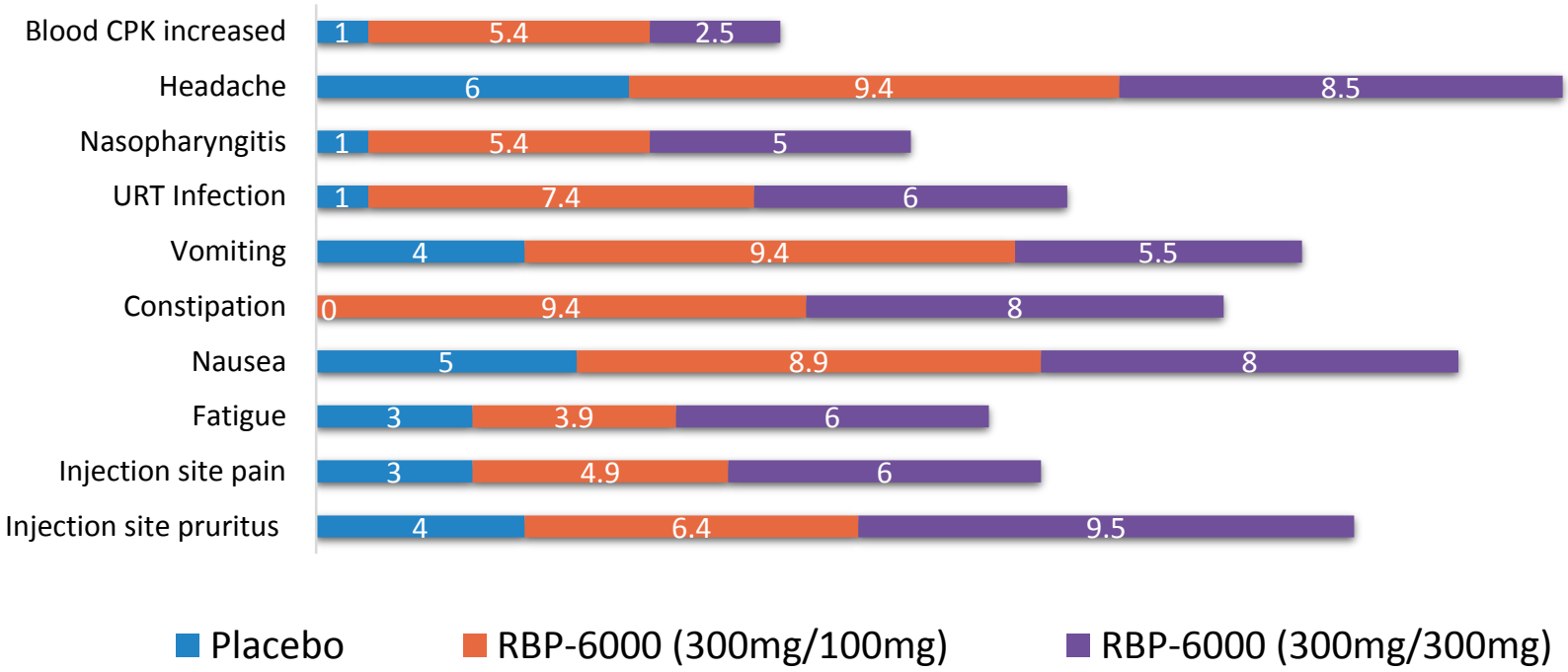
RBP-6000: Safety Profile Phase III Efficacy & Safety



RBP-6000: Safety Profile Phase III Efficacy & Safety



TEAEs occurring in ≥ 5% in any treatment group and more frequently in RBP-6000 group than in placebo group

Conclusion

Christian Heidbreder, Chief Scientific Officer

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SUMMARY

- Both dosage regimens of RBP-6000 showed statistically significant differences in **percentage abstinence** and **treatment success** vs. placebo.
- Treatment outcomes were consistent across other clinical endpoints including control of **craving** and **withdrawal symptoms**.
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POST-CPDD CONFERENCES 2017

Conference	Where?	When?	What?
American Conference on Pharmacometrics (ACoP)	Fort Lauderdale, FL	Oct 15th-18th	Phase III PK/PD/RO model
Canadian Society of Addiction Medicine (CSAM)	Niagara Falls, ON	Oct 19th-21st	Phase III efficacy & safety results (Encore session)
Association for Medical Education & Research in Substance Abuse (AMERSA)	Washington, DC	Nov 2nd-4th	Phase III health economics & outcomes research (HEOR) endpoints
American College of Neuropsychopharmacology (ACNP)	Palm Springs, CA	Dec 3rd-7th	Phase III efficacy & safety + PK/PD/RO model
American Academy of Addiction Psychiatry (AAAP)	San Diego, CA	Dec 7th-10th	Phase 3 predictors of dropout

THANK YOU

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