Indivior R&D Day

New York City, USA
December 9th, 2015

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

INDIVIOR
Focus on you.

Forward-looking statements

This presentation contains forward-looking statements. We may, in some cases, use terms such as "predicts," "believes," "potential," "proposed," "continue," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should" or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. Forward-looking statements include, among other things, statements regarding our financial guidance for 2015 and our medium- and long-term growth outlook, our operational goals, our product development pipeline and statements regarding ongoing litigation.

Various factors may cause differences between Indivior's expectations and actual results, including: factors affecting sales of Suboxone Tablet, Suboxone Film, Subutex Tablet and any future products; the outcome of research and development activities; decisions by regulatory authorities regarding the Indivior Group's drug applications; the speed with which regulatory authorizations, pricing approvals and product launches may be achieved; the outcome of post-approval clinical trials; competitive developments; difficulties or delays in manufacturing; the impact of existing and future legislation and regulatory provisions on product exclusivity; trends toward managed care and healthcare cost containment; legislation or regulatory action affecting pharmaceutical product pricing, reimbursement or access; claims and concerns that may arise regarding the safety or efficacy of the Indivior Group's products and product candidates; risks related to legal proceedings; the Indivior Group's ability to protect its patents and other intellectual property; the outcome of the Suboxone Film patent litigation relating to the ongoing ANDA lawsuits; changes in governmental laws and regulations; issues related to the outsourcing of certain operational and staff functions to third parties; uncertainties related to general economic, political, business, industry, regulatory and market conditions; and the impact of acquisitions, divestitures, restructurings, internal reorganizations, product recalls and withdrawals and other unusual items.

Any forward-looking statements that we make in this presentation speak only as of the date of this presentation. We assume no obligation to update our forward-looking statements whether as a result of new information, future events or otherwise, after the date of this presentation.

INDIVIOR R&D DAY

WELCOME - INDIVIOR 2016 FINANCIAL OUTLOOK

Shaun Thaxter, *Chief Executive Officer*

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Intranasal Naloxone for Opioid Overdose Treatment

History (US)

- Fast-Track Designation granted Jul 7th, 2014
- Pre-NDA meeting Nov 13th, 2014
- NDA submission #205678 on May 29th, 2015
- FDA Meeting on Naloxone Access on Jul 1st, 2015
- Priority Review granted on Jul 28th, 2015 with a PDUFA date of Nov 29th, 2015
- No Advisory Board; CMC questions; no clinical questions
- Carton/packaging and USPI changes discussions Oct 15th, 2015
- Request from FDA to list Indivior's device on FDA website for Combination products
- FDA approval of Adapt Pharma's Narcan (Naloxone Hydrochloride) Nasal Spray on Nov 19th, 2015
- FDA non-approval letter received on Nov 23rd, 2015

Next steps

US:

- Under evaluation

Canada:

- Pre-NDS meeting with Health Canada on Oct 22nd, 2015

France:

- Temporary Authorization for Use (ATU) dossier filed on Jun 17th, 2015.
- ATU approved by ANSM on Nov 5th, 2015

Europe:

- EMA's CHMP confirmed (Jul 6th, 2015) naloxone nasal spray is eligible for submission via the centralized route in the EU
- Meeting with MHRA on Dec 14th, 2015

Financial Guidance for 2016

	2015 Indivior Guidance	2016 Indivior Guidance	2016 Analyst Consensus	Range of Consensus
Net Revenue $m	**990-1010**	**945-975**	894	860-900
Operating Margin %		**>30%**	30%	27%-35%
Net Income $m*	**215-225**	**155-180**	166	140-180

- **No material change in current market conditions;**
  - ✓ no deterioration in generic tablet pricing;
  - ✓ limited impact of branded competition
  - ✓ no generic film entry in 2016.
  - ✓ modest loss of US share due to formulary changes & managed Medicaid accounts lost in 2015

- **Reinvestment of >$35m of the gross profit above original assumptions in driving innovations:-**
  - ✓ Buprenorphine Monthly Depot

At constant exchange rates (to estimated 2015 averages)

*Excluding Exceptionals

Why invest an extra $35m plus?

We can now afford to invest more

- Revenue, profit and cash flow above our earlier expectations
- But we believe we will protect the bottom line by releasing investment through the year

Builds the potential of our pipeline for better start on launch

- Intention is to deliver the sales and profit potential of the pipeline
- Exploits our leadership over competition – building on our leadership position

Invests in our core business and supported by our core skillset

- We have already demonstrated that we know how to develop these markets
- Allows us to invest in pre-commercialisation and infrastructure build

We believe this is the best kind of investment we can make in our future

Reinvestment - Buprenorphine Monthly Depot

Pre-launch activities

- Policy & stakeholder education
- Medical Education
- Publications

- Market Research
- Additional health policy advisers
- Additional field medical personnel

Reinvestment – R&D Pipeline Advancing

Buprenorphine Monthly Depot

- Topline results (TLFs) of Phase 3 Efficacy & Safety clinical trial (RB-US-13-0001)
- Submission of pre-NDA package to FDA
- HEOR study interim analysis results

Risperidone Monthly Depot

- Final Human Factor Study Report
- Topline results (Interim analysis TLFs for inclusion in the NDA) of Phase 3 Open Label Safety clinical trial (RB-US-13-0005)

So what do we hope you will learn today?

Patient experience

- What is addiction from a patient perspective?
- What do patients say about the difficulty of treatment for addiction?
- What are the unmet medical needs from a patient perspective?
- What does successful treatment look like for patients?

Indivior's focus

- What is Indivior doing to address these unmet needs and generate new, successful treatment options?
- How is Indivior contributing to successful development of treatment?
- Why is Indivior's pipeline exciting from a patient perspective?

INDIVIOR R&D DAY

OUTLINE OF THE DAY

Christian Heidbreder, Ph.D., *Chief Scientific Officer*

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R&D Day Agenda & Outline

Time (EST)	Topic	Presenter
7:30 AM - 8:00 AM		Coffee – Get Together
8:00 AM - 8:15 AM	Welcome & Indivior 2016 financial outlook	**Shaun Thaxter**, *Chief Executive Officer*
8:15 AM - 8:45 AM	- Outline of the day - R&D strategy & capabilities	**Dr. Christian Heidbreder**, *Chief Scientific Officer*
8:45 AM - 9:45 AM	**Opioid Use Disorder**: - History of Buprenorphine - Patient journey - Unmet medical needs	**Dr. Paul Fudala**, *Senior Fellow Clinical Science* **Dr. Tim Baxter**, *Chief Medical Officer* **Dr. Walter Ling**, *Professor of Psychiatry and Director of Integrated Substance Abuse Programs (ISAP) at UCLA*
9:45 AM - 10:00 AM		Break
10:00 AM - 10:30 AM	Introduction to the Opioid Blockade concept and clinical significance	**Dr. Mark Greenwald**, *Professor and Director, Substance Abuse Research Division, Department of Psychiatry and Behavioral Neuroscience, Wayne State University School of Medicine*
10:30 AM - 11:00 AM	Introduction to the ATRIGEL drug delivery platform	**Dr. Rick Norton**, *Director Formulation Development*
11:00 AM - 11:30 AM	**RBP-6000**: Opioid blockade study outcome & current status of Phase 3 pivotal trial	**Dr. Susan Learned**, *SVP Global Clinical Development* **Dr. Amit Vijapura**, *Board Certified Psychiatrist & Diplomate of the American Board of Addiction Medicine (ABAM). Medical director and owner of Vijapura Behavioral Health in Jacksonville, Florida*
11:30 AM - 12:15 PM	**Indivior Strategic Pipeline: Latest Status** - Existing Product Development (EPD) - New Product Development (NPD) - Early Stage Asset Development (ESAD)	**Dr. Christian Heidbreder**, *Chief Scientific Officer*
12:15 PM - 1:00 PM		Conclusions and Q&A

INDIVIOR R&D DAY

R&D STRATEGY & CAPABILITIES

Christian Heidbreder, Ph.D., *Chief Scientific Officer*

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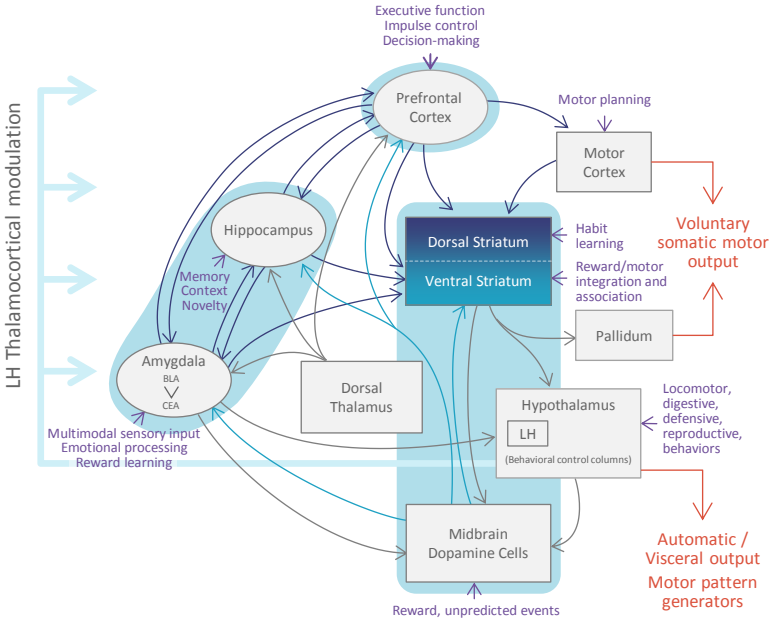
What are the challenges in addiction neuroscience?



Understanding addiction as the result of long-term molecular & cellular adaptations in key neural networks

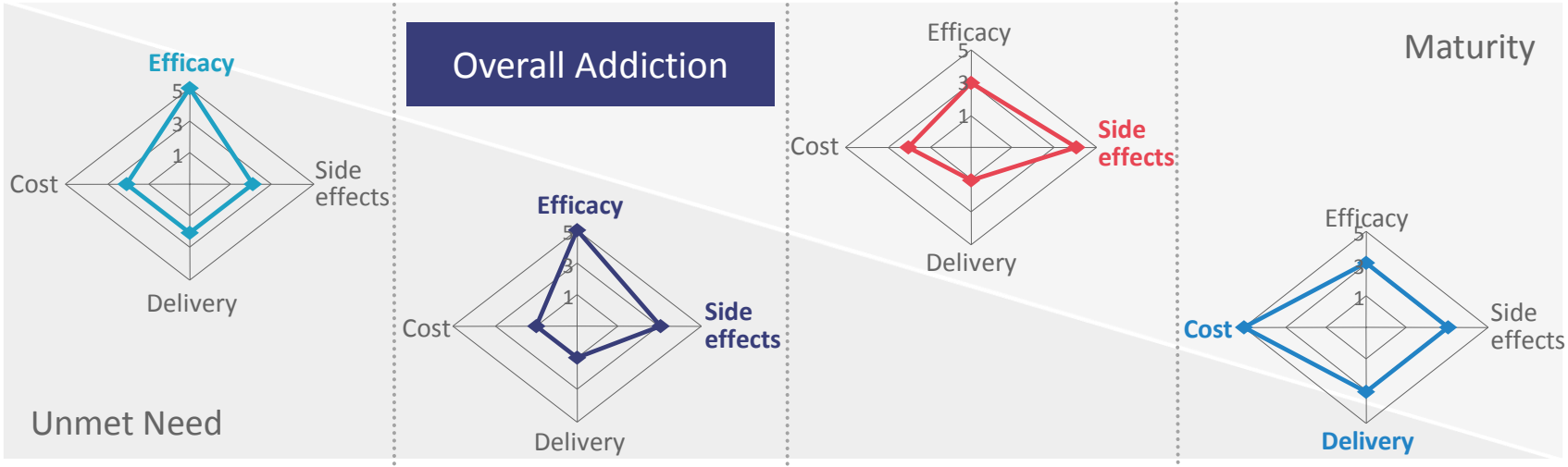
- **Learning & memory** are impaired
- Resisting **repetitive, maladaptive** behaviors is failing
- Aspects of **decision-making** are compromised
- **Reward prediction** is biased
- **Motivation** is altered

The "ideal" drug candidate would:

- **Inhibit the reinforcing properties** of drugs and associated cues
- **Reinstate the mechanisms of control** by the PFC over the VTA-NAc
- Relieve physical and motivational **withdrawal symptoms**
- **Prevent relapse** in response to drug priming, environmental cues (context), and stress
- Have an **impact on the negative reinforcement** generated by the stress neural circuit (extended amygdala)

Source: Modified from Kelley AE, Memory and addiction: shared neural circuitry and molecular mechanisms. Neuron. 2004 Sep 30;44(1):161-79. DOI: http://dx.doi.org/10.1016/j.neuron.2004.09.016

R&D strategy to address challenges in addiction medicine



Type A
New disease area
High unmet needs
Stimulant Use Disorder
Cannabis Use Disorder

Type B
Low disease maturity
High unmet needs
Alcohol Use Disorder

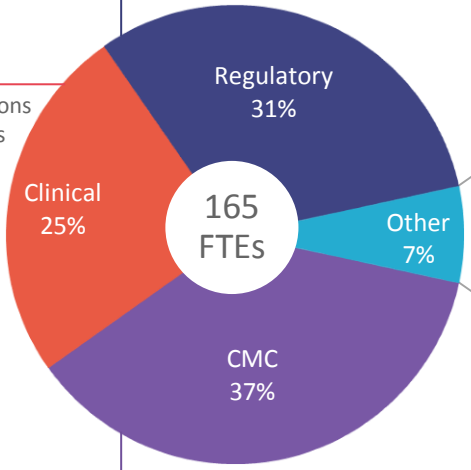
Type C
Relative maturity
Some unmet needs
Opioid Use Disorder

Type D
Mature disease area
No unmet needs

Building an R&D organization fit for purpose

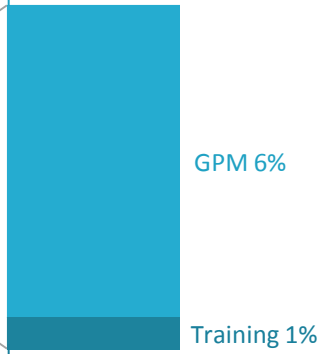
- Regulatory Strategy
- Regulatory Operations
- Regulatory Affairs NA; EU; Australasia

- Clinical Operations
- Clinical Sciences
- HEOR

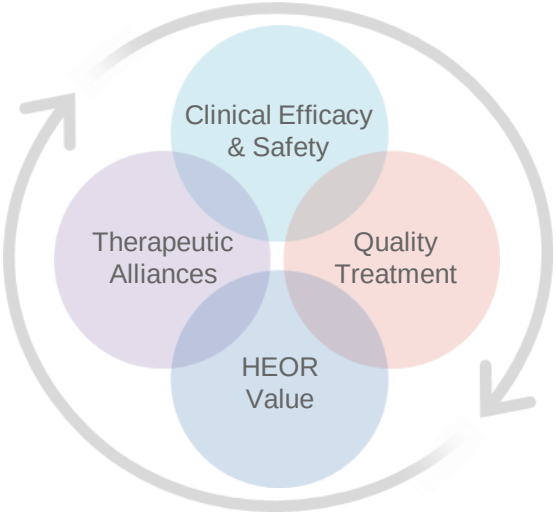


- Formulation Development
- Analytical Development
- Process Development
- Chemical Development

- Global Program Management
- Financial planning
- Timelines
- KPIs



- Onboarding
- Development
- Retain Talents



Delivering major milestones across functions

Clinical

- **10 programs** in development
- **Unprecedented number of ongoing trials:**
  - 2 Phase 1 trials
  - 2 Phase 2 trials
  - 4 Phase 3 trials
  - 1 Phase 4 study
  - 5 prospective HEOR studies
- **Well-positioned to deliver on KPI expectations**

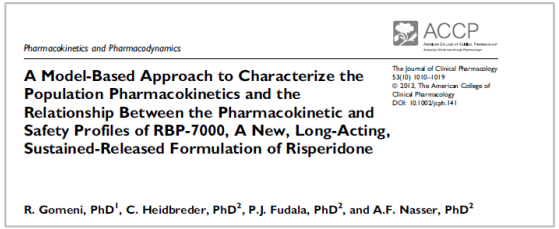
Regulatory

- **Suboxone sublingual film:**
  - 2/8mg FDA approval Aug ’10; TGA approval Feb ’11; Malaysia approval Jul ‘13
  - 4/12mg FDA approval Aug ’12; TGA approval May ‘14
  - 2/4/8/12mg induction indication FDA approval Apr ’14; buccal indication FDA approval Sep ‘15
- **Intranasal naloxone:**
  - France: ATU approved in Nov ‘15
- **RBP-8000:**
  - Breakthrough Therapy Designation granted by FDA Oct ‘14

CMC

- **Pillar 1: Internal non-GMP capability (Innovation)**
  - Formulation research & innovation lab
  - Analytical research lab
  - Chemistry research lab (Hull) & non-clinical lab (Ft Collins)
- **Pillar 2: Internal GMP capability (Pilot Scale Manufacturing)**
  - Pilot plant manufacturing unit
  - Analytical development lab
  - ICH stability
- **Pillar 3: Technology Transfer**
  - Management of 3rd party CMO
  - Formal hand over of ownership to Indivior supply

Recognized for scientific excellence



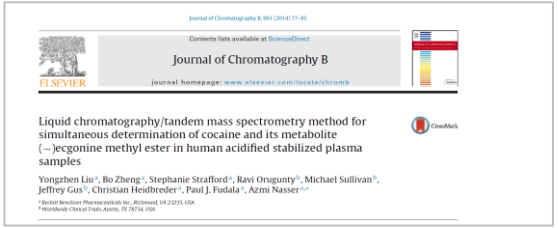
Pharmacokinetics and Pharmacodynamics

ACCP

A Model-Based Approach to Characterize the Population Pharmacokinetics and the Relationship Between the Pharmacokinetic and Safety Profiles of RBP-7000, A New, Long-Acting, Sustained-Released Formulation of Risperidone

The Journal of Clinical Pharmacology 53(10) 1010–1019 © 2013, The American College of Clinical Pharmacology DOI: 10.1002/jcph.141

R. Gomeni, PhD[1], C. Heidbreder, PhD[2], P.J. Fudala, PhD[2], and A.F. Nasser, PhD[2]



Journal of Chromatography B, 961 (2014) 77–85

Contents lists available at ScienceDirect

Journal of Chromatography B

journal homepage: www.elsevier.com/locate/chromb

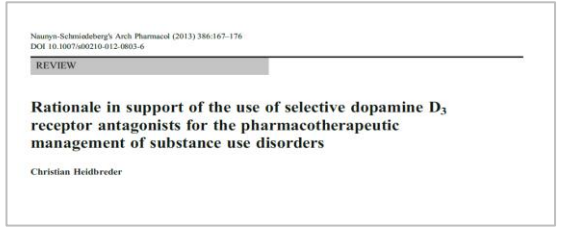
ELSEVIER

CrossMark

Liquid chromatography/tandem mass spectrometry method for simultaneous determination of cocaine and its metabolite (−)ecgonine methyl ester in human acidified stabilized plasma samples

Yongzhen Liu[a], Bo Zheng[a], Stephanie Strafford[a], Ravi Orugunty[b], Michael Sullivan[b], Jeffrey Gus[b], Christian Heidbreder[a], Paul J. Fudala[a], Azmi Nasser[a,b]

[a] Reckitt Benckiser Pharmaceuticals Inc., Richmond, VA 23235, USA
[b] Worldwide Clinical Trials, Austin, TX 78754, USA

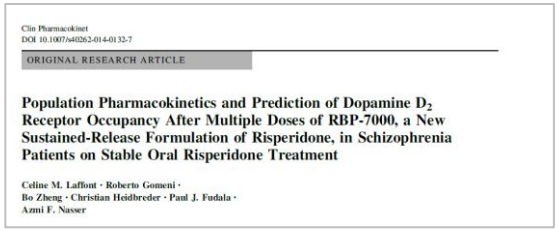


Naunyn-Schmiedeberg's Arch Pharmacol (2013) 386:167–176
DOI 10.1007/s00210-012-0803-6

REVIEW

Rationale in support of the use of selective dopamine D_3 receptor antagonists for the pharmacotherapeutic management of substance use disorders

Christian Heidbreder

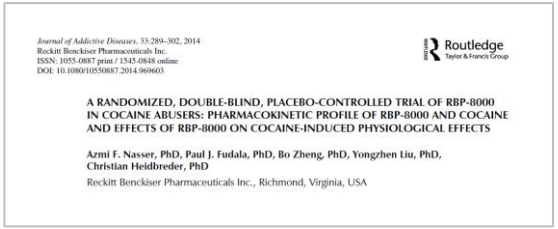


Clin Pharmacokinet
DOI 10.1007/s40262-014-0132-7

ORIGINAL RESEARCH ARTICLE

Population Pharmacokinetics and Prediction of Dopamine D_2 Receptor Occupancy After Multiple Doses of RBP-7000, a New Sustained-Release Formulation of Risperidone, in Schizophrenia Patients on Stable Oral Risperidone Treatment

Celine M. Laffont · Roberto Gomeni · Bo Zheng · Christian Heidbreder · Paul J. Fudala · Azmi F. Nasser



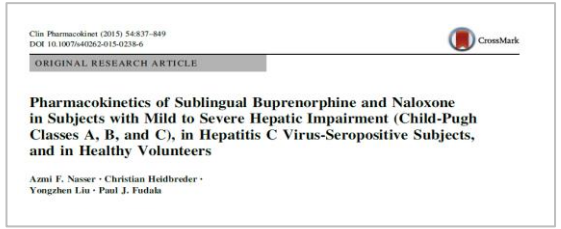
Journal of Addictive Diseases, 33:289–302, 2014
Reckitt Benckiser Pharmaceuticals Inc.
ISSN: 1055-0887 print / 1545-0848 online
DOI: 10.1080/10550887.2014.969603

Routledge Taylor & Francis Group

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF RBP-8000 IN COCAINE ABUSERS: PHARMACOKINETIC PROFILE OF RBP-8000 AND COCAINE AND EFFECTS OF RBP-8000 ON COCAINE-INDUCED PHYSIOLOGICAL EFFECTS

Azmi F. Nasser, PhD, Paul J. Fudala, PhD, Bo Zheng, PhD, Yongzhen Liu, PhD, Christian Heidbreder, PhD

Reckitt Benckiser Pharmaceuticals Inc., Richmond, Virginia, USA



Clin Pharmacokinet (2015) 54:837–849
DOI 10.1007/s40262-015-0238-6

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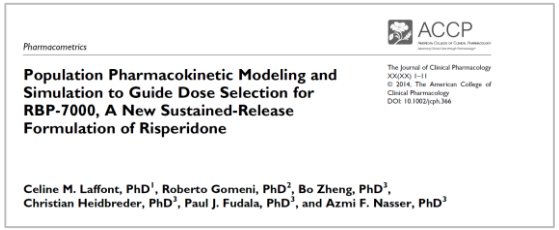
ORIGINAL RESEARCH ARTICLE

Pharmacokinetics of Sublingual Buprenorphine and Naloxone in Subjects with Mild to Severe Hepatic Impairment (Child-Pugh Classes A, B, and C), in Hepatitis C Virus-Seropositive Subjects, and in Healthy Volunteers

Azmi F. Nasser · Christian Heidbreder · Yongzhen Liu · Paul J. Fudala



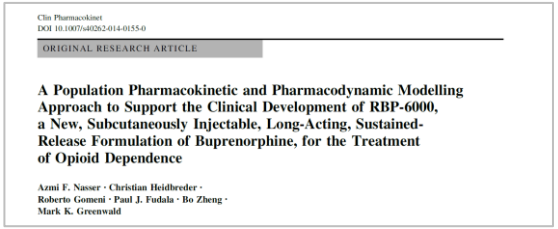
Pharmacometrics

ACCP

Population Pharmacokinetic Modeling and Simulation to Guide Dose Selection for RBP-7000, A New Sustained-Release Formulation of Risperidone

The Journal of Clinical Pharmacology XX(XX) 1–11 © 2014, The American College of Clinical Pharmacology DOI: 10.1002/jcph.366

Celine M. Laffont, PhD[1], Roberto Gomeni, PhD[2], Bo Zheng, PhD[3], Christian Heidbreder, PhD[3], Paul J. Fudala, PhD[3], and Azmi F. Nasser, PhD[3]



Clin Pharmacokinet
DOI 10.1007/s40262-014-0155-0

ORIGINAL RESEARCH ARTICLE

A Population Pharmacokinetic and Pharmacodynamic Modelling Approach to Support the Clinical Development of RBP-6000, a New, Subcutaneously Injectable, Long-Acting, Sustained-Release Formulation of Buprenorphine, for the Treatment of Opioid Dependence

Azmi F. Nasser · Christian Heidbreder · Roberto Gomeni · Paul J. Fudala · Bo Zheng · Mark K. Greenwald

Sponsoring scientific excellence

Nature "Outlook Addiction", a supplement section within the regular edition of the journal Nature:
http://www.nature.com/nature/outlook/addiction

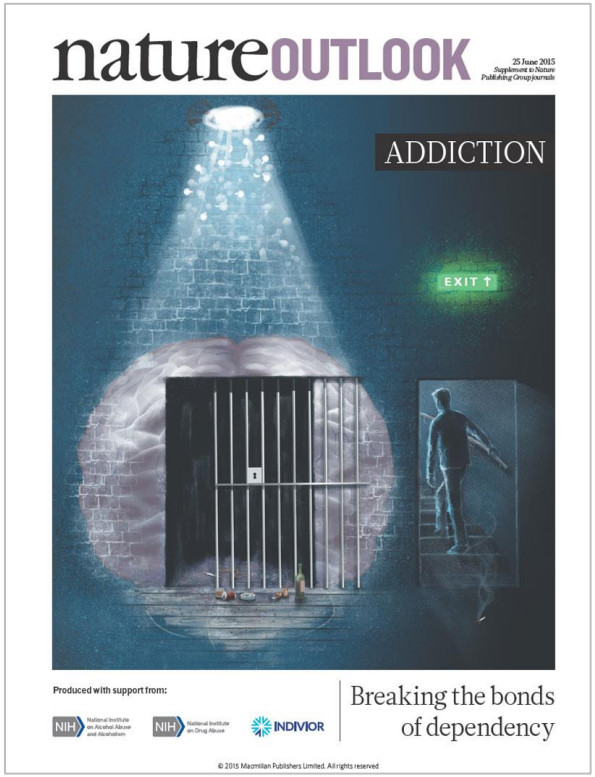
Indivior's White Paper:
http://www.nature.com/nature/outlook/addiction/pdf/Indivior.pdf

INDIVIOR

NIH National Institute on Drug Abuse
The Science of Drug Abuse & Addiction

NIH National Institute on Alcohol Abuse and Alcoholism

NIH…Turning Discovery Into Health®



Building a new Centre of Excellence in Hull, UK

Source: Boulting Environmental Services (BES), Manchester, UK

Enabling Indivior's vision & mission

Disease understanding

Translate scientific knowledge into new opportunities

Pharmacoeconomics

Prospective HEOR plans in Indivior's pivotal phase III trials respond to payers' focus on actual medical and financial benefits for patients

Pharmacogenetics

Pharmacogenetics plans in Indivior's pivotal phase III trials respond to a vision for addressing patients' unmet needs

Therapeutic alliances

Long-term strategic alliances with NIDA, NIAAA, and KOLs enable Indivior to be at the forefront of new treatment options for patients

INDIVIOR R&D DAY

OPIOID USE DISORDER

Paul J. Fudala, Ph.D, R.Ph., *Senior Fellow Clinical Sciences*
Walter Ling, M.D., *Professor & Founding Director of UCLA's Integrated Substance Abuse Programs*
Tim Baxter, M.D., *Chief Medical Officer*

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Paul J. Fudala, Ph.D, R.Ph.

Dr. Fudala is a pharmacist and toxicologist by training

- Initially worked as a **community and hospital pharmacist**, including as a commissioned officer in the USPHS on the Pine Ridge Indian Reservation in SD
- Earned **doctorate degree** at the University of Kentucky; mainly conducted research on behavioral pharmacology/toxicology of nicotine
  - First to demonstrate/publish on the rewarding effects of nicotine in the CPP paradigm
- 4 years at the **ARC in Baltimore** starting in 1987; 1 as **post-doctoral fellow** and then 3 as **Deputy Chief of Research Support Branch** and later **Acting Head of Clinical Trials Laboratory**
  - Conducted clinical research in various addiction-related areas; conducted/published along with Drs. Ed Johnson and Jerome Jaffe a buprenorphine/methadone comparison study that was pivotal with regards to FDA approval of SUBUTEX and SUBOXONE tablets
- 14 years at **UPENN Dept. of Psychiatry and Philadelphia VAMC** beginning in 1991; for most of those years chaired an interagency medication development effort between NIDA and the VA; focused primarily on developing new treatments for opioid and cocaine addiction
  - Study Chairman on the final trial that supported FDA approval of LAAM and, along with Dr. Peter Bridge from NIDA, was Co-Chairman on another of the 3 pivotal trials that led to FDA approval of SUBUTEX and SUBOXONE tablets
- Joined **RBP Pharma** (now Indivior) in August, 2005
  - Held various Director and Global Director positions; currently Senior Fellow, Clinical Science
  - Lead the clinical development effort for SUBOXONE sublingual film and has been involved in almost all EPD/NPD projects

Prof Walter Ling, MD

Prof Ling is board certified both in neurology and in psychiatry

- Based in Los Angeles, he is a physician who is active both in **research and in clinical practice**
- Prof Ling is and has been consistently listed in the **Best Doctors in America**, **Best Doctors in the West** and **Best Doctors in Los Angeles**
- He is **Professor and Founding Director of UCLA's Integrated Substance Abuse Programs**, one of the premier addiction research organizations worldwide
- Involved in **treating opioid addiction since the introduction of methadone treatment in this country** and he received his first grant from Jerry Jaffe, our first Drug Czar under president Nixon
- Prof Ling has been a **continuous grantee researcher of NIDA** since its inception in the 70s and he has conducted most of the pivotal clinical trials of buprenorphine that provided data for its approval by the FDA

INDIVIOR R&D DAY

RBP-6000 – A ONCE-MONTHLY SUSTAINED RELEASE FORMULATION OF BUPRENORPHINE FOR THE TREATMENT OF OPIOID USE DISORDER

Dr. Mark K. Greenwald, Ph.D.
Dr. Rick Norton, Ph.D.
Dr. Susan Learned, M.D., Pharm.D., Ph.D.
Dr. Amit Vijapura, M.D.

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

INDIVIOR R&D DAY

INTRODUCTION TO THE OPIOID BLOCKADE CONCEPT & CLINICAL SIGNIFICANCE

Dr. Mark K. Greenwald, Ph.D.

Professor, Associate Chair for Research, and Director of the Substance Abuse Research Division
Department of Psychiatry and Behavioral Neurosciences & Department of Pharmacy Practice

Wayne State University, Detroit, MI, USA

INDIVIOR

Objectives

Introduce opioid blockade concept

Highlight mu-opioid receptor (μOR) actions of buprenorphine (BUP) as the critical target

Clinical significance

Review landmark studies that examined two major functional outcomes of varying μOR occupancy and BUP plasma concentrations in opioid-dependent volunteers maintained on the BUP sublingual tablet

- BUP-induced suppression of withdrawal signs/symptoms while the subject is abstaining from other opioid use (“withdrawal suppression”)
- BUP-induced attenuation of agonist effects from experimental opioid challenges (“opioid blockade”)

Discuss implications for optimal dosing levels of RBP-6000

PK/PD model (from BUP tablet studies) to predict plasma (and, by inference, brain) levels of sustained release BUP needed to induce opioid withdrawal suppression AND blockade

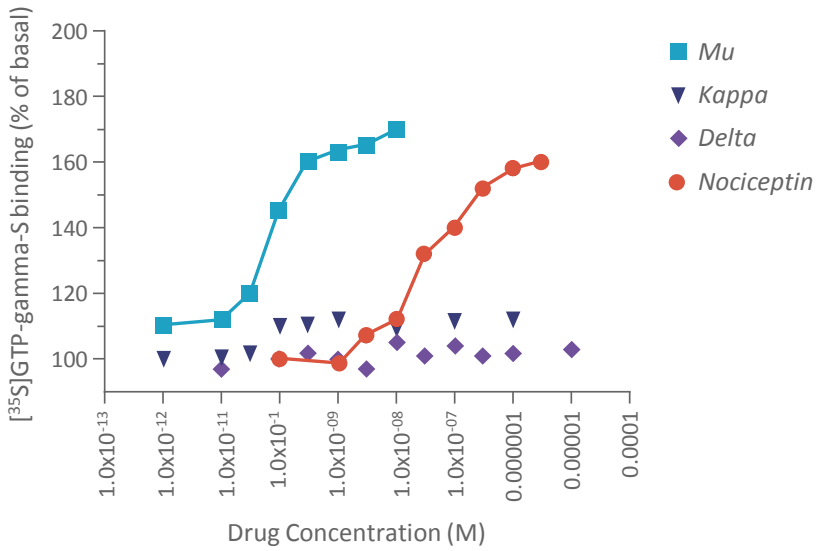
BUP activates Mu-Opioid receptors at physiologically relevant concentrations

BUP is a **partial agonist at µORs** but across a wide dose range it does not activate *kappa* or *delta* opioid receptors (where it is an antagonist).

There is no convincing evidence to date that BUP antagonism at *kappa* or *delta* receptors mediates its clinical efficacy for treating opioid use disorder.

BUP-induced intracellular activation is ≈1000 x more potent at µORs than at nociceptin receptors, which are probably not relevant to BUP effects at clinically relevant doses.

Thus, BUP effects are essentially attributable to its partial agonist effects at the µOR.



Adapted from Huang P, Kehner GB, Cowan A, Liu-Chen L-Y (2001) Comparison of pharmacological activities of buprenorphine and norbuprenorphine: norbuprenorphine is a potent opioid agonist. JPET 297(2): 688-695. PMID: 11303059

Do medication plasma concentrations and brain receptor occupancy closely correlate?

Medication plasma levels have sometimes been assumed as a **proxy for CNS receptor concentration**, but this assumption may not universally hold true.

Need to consider:

Dosing regimen

Acute vs. chronic daily vs. sustained release

Medication characteristics

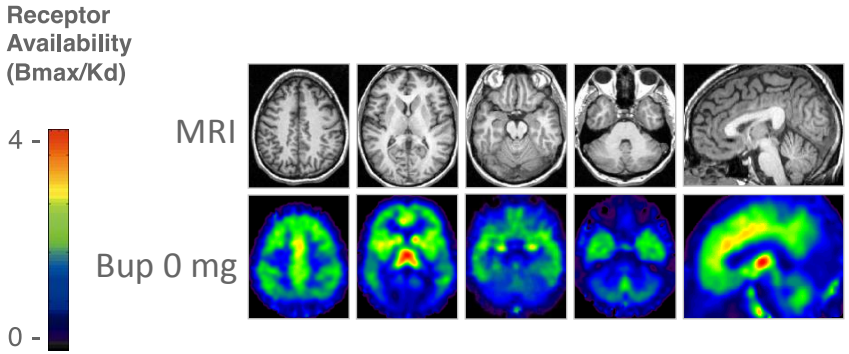
e.g., affinity, half-life, biodistribution

Also, it's not known whether plasma level corresponds to effective concentrations at specific CNS anatomical sites that mediate signs/symptoms of the disorder

µOR occupancy measurement during Buprenorphine exposure

Use PET imaging and [^{11}C]-carfentanil to estimate µOR "occupancy" *in vivo*

- This radiotracer (administered at sub-pharmacological doses) is very selective, and has high affinity, for µORs
- **Method:** Infuse the tracer after a known BUP dose (and time since dose) to examine competitive binding between BUP and the tracer
  - Think of carfentanil just like any other opioid drug
- Co-register each PET image to the subject's MRI scan to localize brain regions of interest that are involved in addictive behaviors (relative to a control region without µORs, occipital cortex)
- ***Caveat*:** Technical term is receptor "availability" (non-displaceable binding potential, BP_{ND}) = 100% *minus* the percentage of receptors occupied by BUP. Occupancy is the *complement* of availability.
  - Gas-tank analogy (full/occupied vs. empty/available)



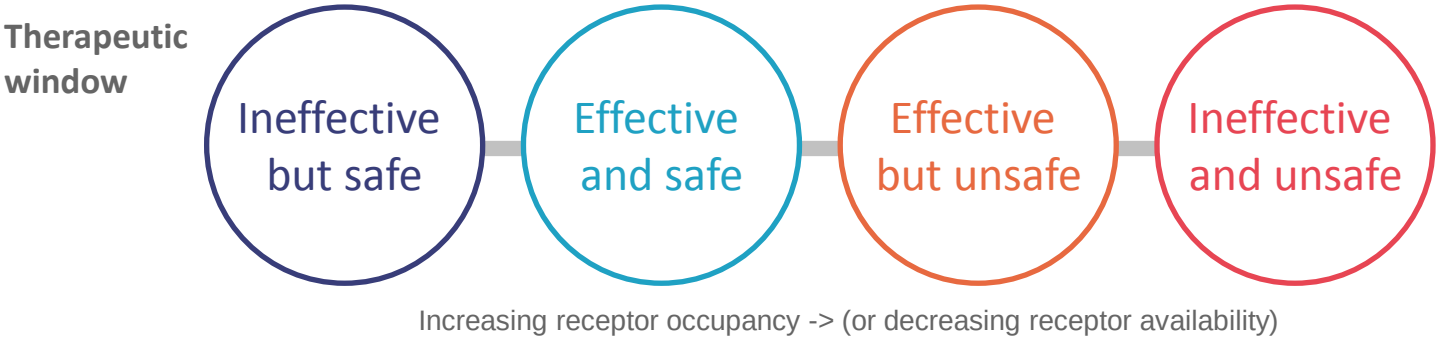
Greenwald MK, Johanson CE, Moody DE, Woods JH, Kilbourn MR, Koeppe RA, Schuster CR, Zubieta JK (2003) Effects of buprenorphine maintenance dose on mu-opioid receptor binding potential, plasma concentration, and antagonist blockade in heroin-dependent volunteers. Neuropsychopharmacology 28: 2000-2009. PMID: 12902992; DOI: 10.1038/sj.npp.1300251

Practical application of receptor theory to medication development

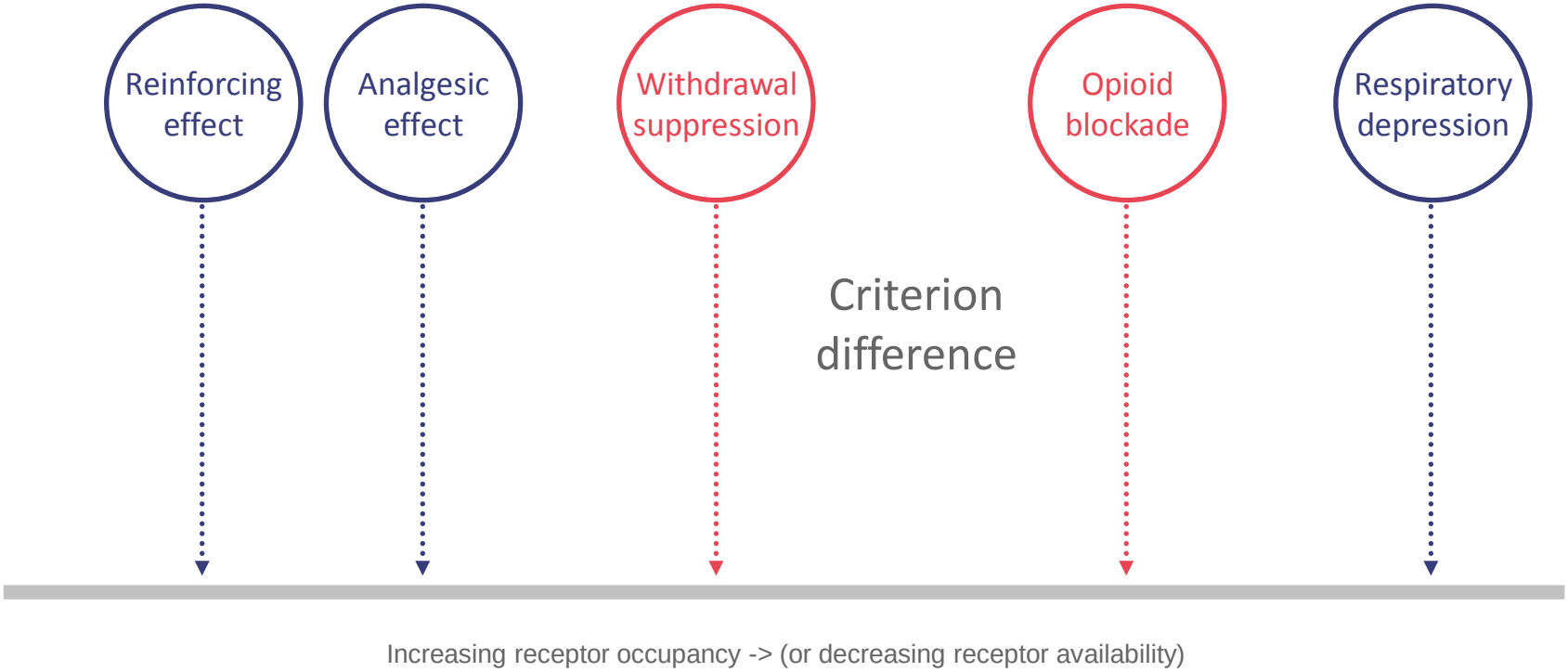
Target for treating opioid use disorder is the *mu*-opioid receptor (μOR), regardless of whether the medication is an agonist (buprenorphine, methadone) or antagonist (naltrexone)

- μOR is implicated in the reinforcing and physical dependence related effects of major opioids including heroin and FDA-approved analgesics
- All FDA-approved medications for treating opioid use disorder act primarily at the μOR

With addiction medicines such as BUP, we are looking to maximize efficacy and minimize side effects within a 'therapeutic window' along a continuum (mediated by μOR occupancy), but need to be clear regarding *which* efficacy measures



Theoretical ordering of μOR requirements for differing behavioral tests



Research objective/strategy

Use multi-dimensional assessments to characterize relationships between *μOR* occupancy (PET and [^{11}C]-Carfentanil), plasma BUP concentrations, and clinically relevant outcomes esp. opioid withdrawal suppression and opioid blockade

In two related studies, used complementary experimental strategies to manipulate μOR occupancy in heroin-dependent, buprenorphine (BUP; Subutex) tablet-maintained subjects

- ✓ **Study 1 – Greenwald et al. 2003**
  Vary maintenance dose (on different weeks) – Scan at the same post-dose time (4 hours, close to peak effect)
- ✓ **Study 2 – Greenwald et al. 2007**
  Omit maintenance dose (over several days) – Scan at different post-dose times

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 binding potential, plasma concentration, and antagonist blockade in heroin-dependent volunteers. Neuropsychopharmacology 28: 2000-2009. PMID: 12902992; DOI: 10.1038/sj.npp.1300251

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. PMID: 16950210; DOI: 10.1016/j.biopsych.2006.04.043

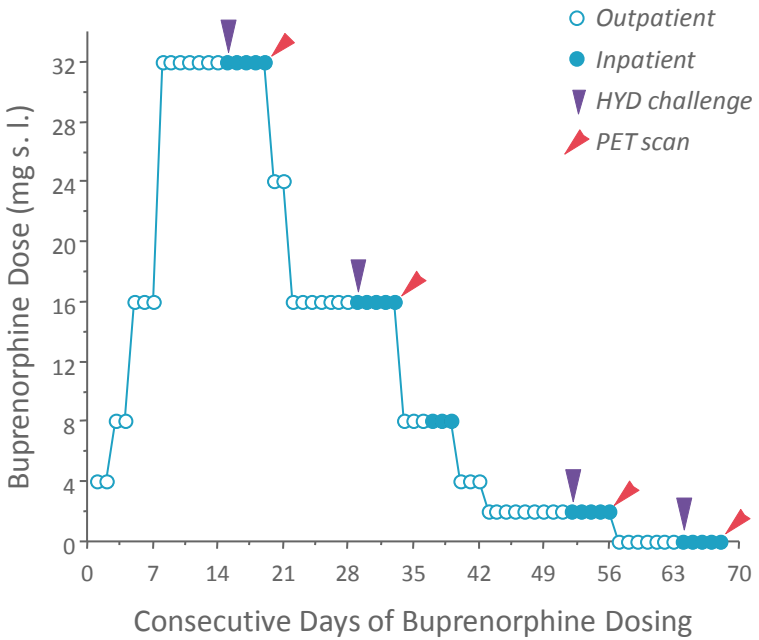
Study 1:
Methods

Each subject maintained on **descending series of daily BUP (Subutex) tablet doses**: 32-mg, 16-mg, 2-mg and then placebo (detoxification) across successive weeks.

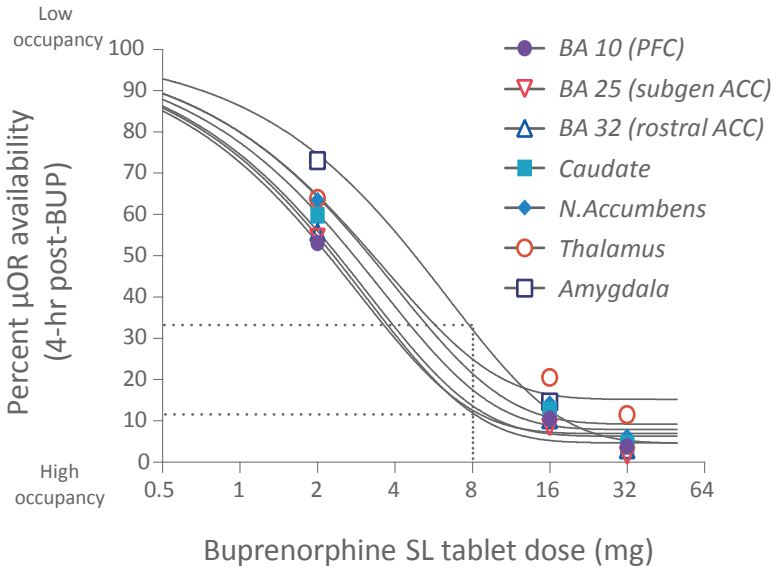
Outpatient weeks (stabilization) alternated with inpatient weeks (testing). **Inpatient stays and urine testing** ensured no additional drug use that would interfere with measurements.

[^{11}C]-Carfentanil PET scans, BUP plasma levels (24-hour PK), **opioid symptom measures, and hydromorphone 24-mg IM challenge to test opioid blockade** at each BUP maintenance dose level (4 hours after the daily dose) on each of the 4 experimental weeks.

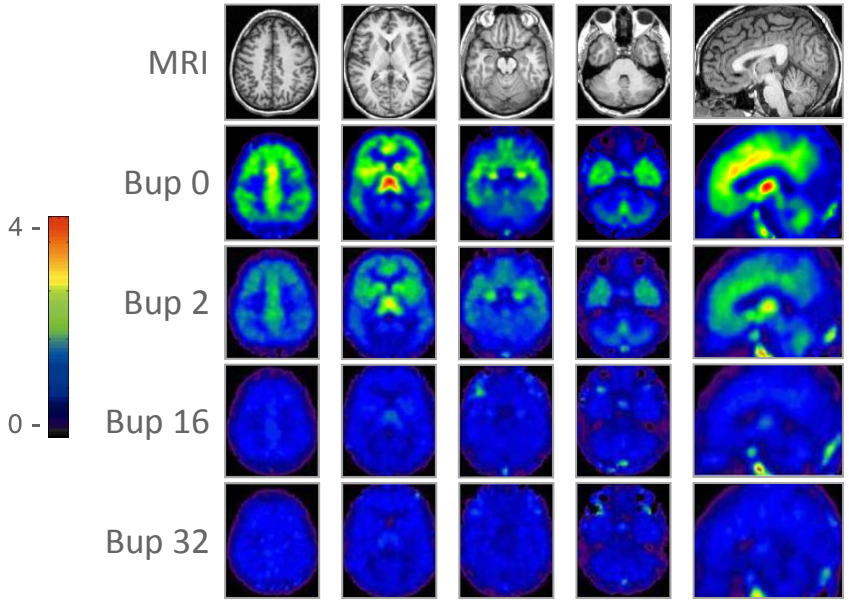
Study 1 protocol timeline



Study 1:
Buprenorphine dose-effect on µOR availability

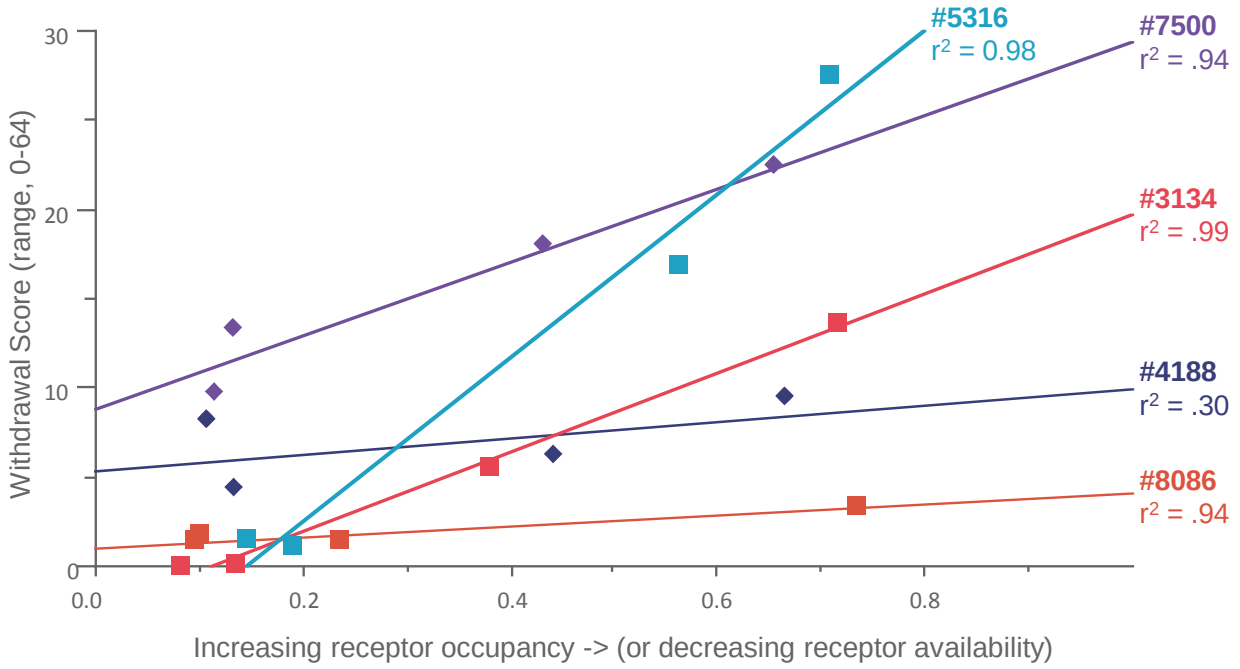


Greenwald MK et al. (2014) Drug and Alcohol Dependence 144: 1-11. DOI: 10.1016/j.drugalcdep.2014.07.035



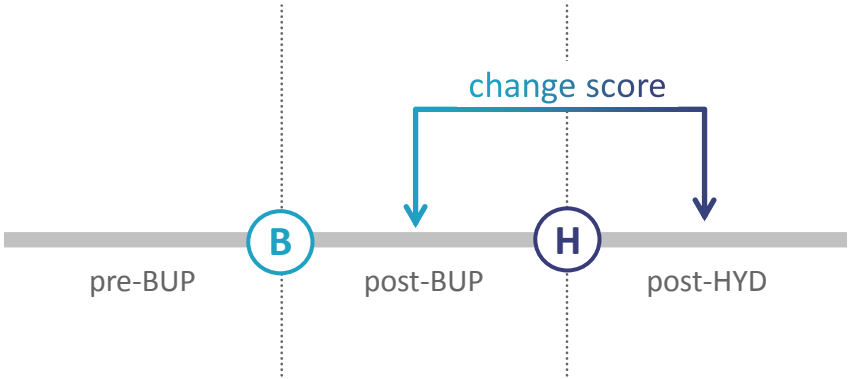
Greenwald MK, Johanson CE, Moody DE, Woods JH, Kilbourn MR, Koeppe RA, Schuster CR, Zubieta JK (2003) Neuropsychopharmacology 28: 2000-2009. DOI:10.1038/sj.npp.1300251

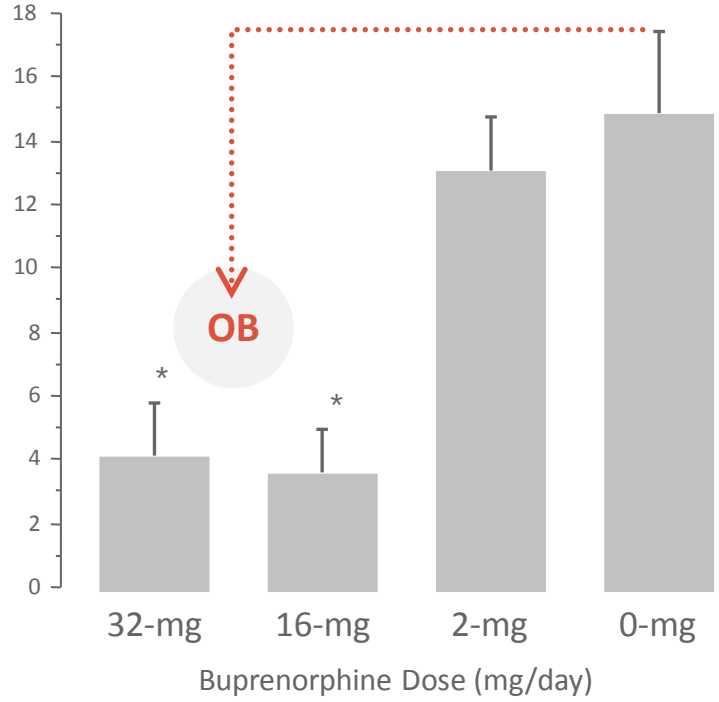
Study 1:
Global-brain μOR availability predicts withdrawal suppression



Greenwald MK (2006) Human experimental therapeutic models in opioid dependence: translational research advances and implications. In: McKenna CR (Ed.), Trends in Substance Abuse Research, pp. 1-55. New York: Nova Science Publishers, Inc.

Study 1:
Higher-dose BUP produces significant opioid blockade (OB)





Adapted from Greenwald MK, et al. (2003) Effects of buprenorphine maintenance dose on mu-opioid receptor binding potential, plasma concentration, and antagonist blockade in heroin-dependent volunteers. Neuropsychopharmacology 28: 2000-2009. PMID: 12902992; DOI: 10.1038/sj.npp.1300251

Study 2:
Vary time since Buprenorphine dose

Aims

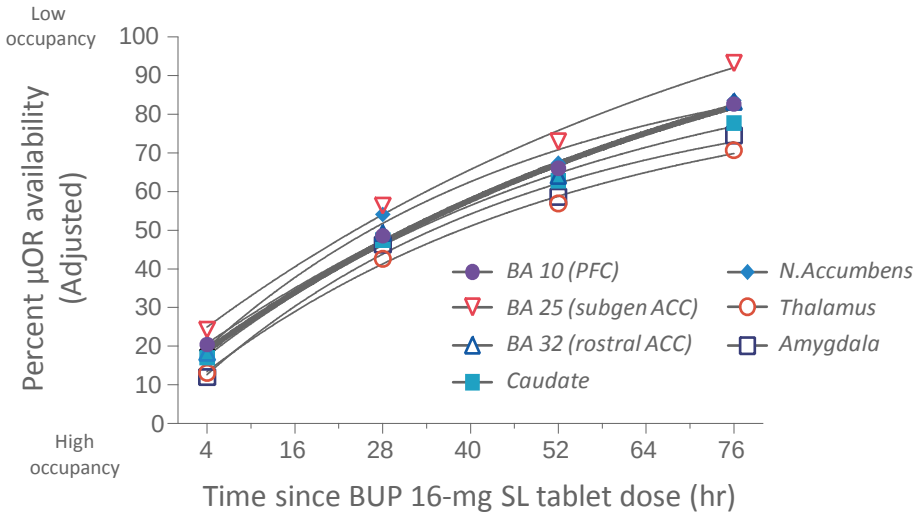
Determine if µOR availability differs at 4, 28, 52 and 76 hours after **omitting BUP maintenance dose** (16 mg Subutex)

Do post-BUP time-related variations in µOR availability correlate with BUP plasma levels, opioid withdrawal symptoms, and the ability of BUP to block effects of hydromorphone?

Method

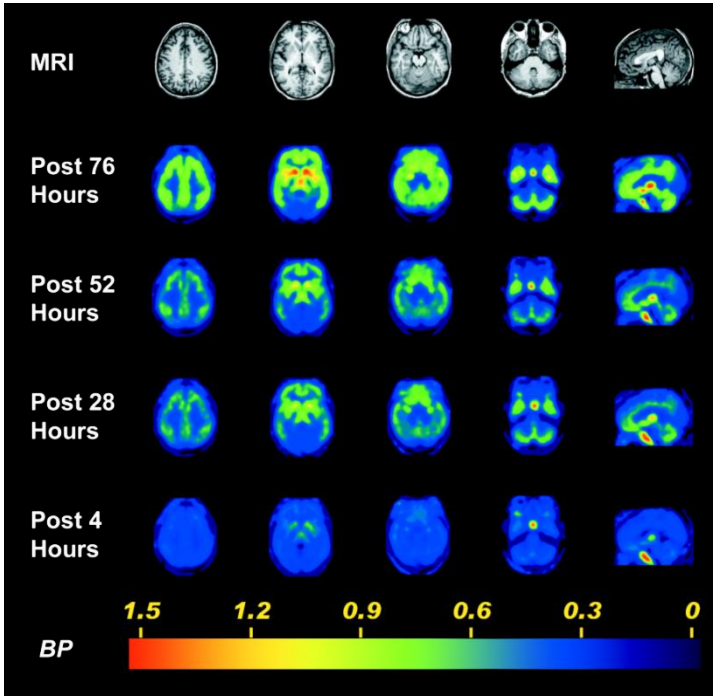
Each volunteer (n=10 completed) was tested in **all 4 conditions**, thereby serving as his/her own control

Study 2:
µOR availability across post-BUP time and brain regions



Greenwald MK, Comer SD, Fiellin DA (2014) Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. Drug and Alcohol Dependence 144: 1-11. PMID: 25179217; DOI: 10.1016/j.drugalcdep.2014.07.035

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. PMID: 16950210; DOI: 10.1016/j.biopsych.2006.04.043



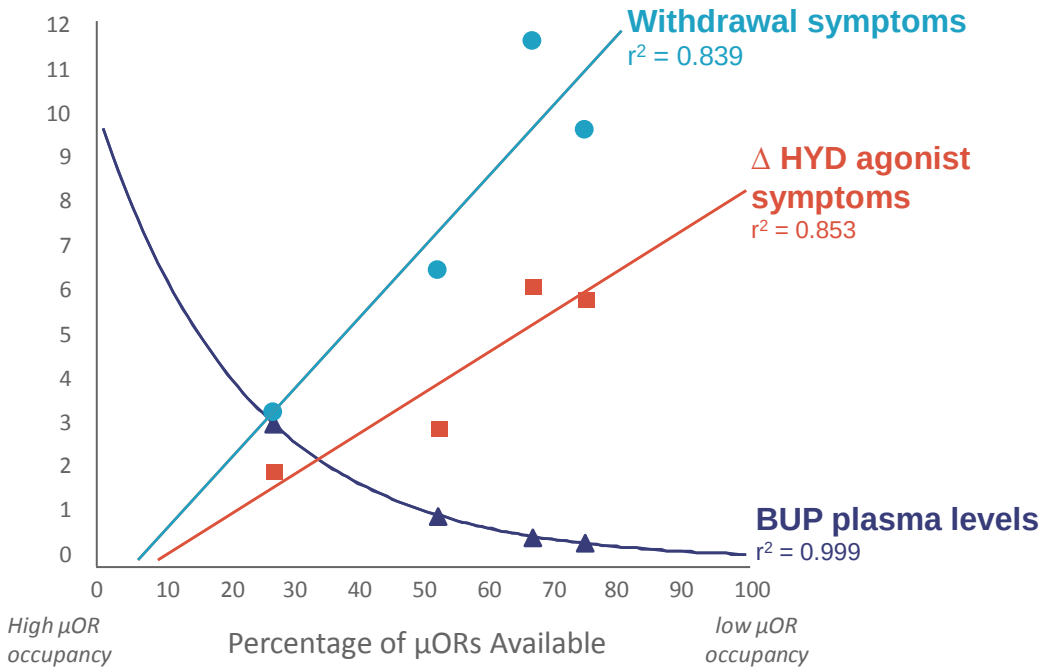
Study 2:
Relationships of μOR occupancy to plasma, withdrawal and blockade

Outcome measure

Plasma level
(ng/ml);

Opioid Withdrawal symptoms
(0-64 scale),

or change in Agonist Symptoms
(blockade)



Adapted from Greenwald MK, et al. (2007) Buprenorphine duration of action: Mu-opioid receptor availability, pharmacokinetic and behavioral indices. Biological Psychiatry 61: 101-110. PMID: 16950210; DOI: 10.1016/j.biopsych.2006.04.043

Conclusions

μOR occupancy is non-linearly related to BUP plasma concentrations

Significant relationship observed for each individual subject

μOR occupancy is linearly related to withdrawal suppression and blockade

- In these physically dependent individuals, average μOR occupancy of ≈50% is effective for withdrawal suppression; associated with plasma levels > 1 ng/mL (and, generally speaking, BUP tablet doses > 4 mg/day)
- Estimating μOR occupancy requirement for opioid blockade partly depends on methodological differences (HYD bolus in Study 1, whereas cumulative in Study 2); however, data suggest μOR occupancy requirement for blockade is ≈80%, which is higher than for withdrawal suppression; associated with plasma levels > 3 ng/mL (and, generally speaking, BUP tablet doses > 16 mg/day)

Time-related variation in these BUP effects should be minimized with a sustained-release formulation

Greenwald MK, Comer SD, Fiellin DA (2014) Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. Drug and Alcohol Dependence 144: 1-11. PMID: 25179217; DOI: 10.1016/j.drugalcdep.2014.07.035

Summary and "lessons learned" for planning RBP-6000 clinical trials

- BUP tablet maintenance produces dose- and time-dependent increases in µOR occupancy that closely correlate with its plasma concentrations as well as opioid withdrawal suppression and opioid blockade

- Opioid blockade is a "taller order": this behavioral criterion requires more µOR occupancy than opioid withdrawal suppression; need to pay careful attention to this difference because it will predict efficacy in long-term treatment
  - ✓ "opioid blockade" = "the absence of reactivity to (physiological or abuse-related subjective effects) or responding for (reinforcing effects) an opioid agonist, when statistically compared to placebo", and we noted that "most practitioners and policymakers typically intend this desired blockade effect should be evident in most patients to be clinically meaningful and relevant to guidelines or dosing limits". We also concluded that "opioid blockade (more so than withdrawal suppression) should be the primary criterion guiding BUP maintenance dose" (Greenwald et al. 2014, p.8).

- Sustained-release RBP-6000 at 300-mg seems very likely to produce the target plasma level and µOR occupancy requirements that should be effective for withdrawal suppression and blockade

Greenwald MK, Comer SD, Fiellin DA (2014) Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. Drug and Alcohol Dependence 144: 1-11. PMID: 25179217; DOI: 10.1016/j.drugalcdep.2014.07.035

INDIVIOR R&D DAY

INTRODUCTION TO ATRIGEL®

Dr. Rick Norton, Ph.D.

Director, Formulation Development, Indivior Inc.

INDIVIOR

Outline

ATRIGEL® drug delivery platform

- Patient's point of view
- Underlying science

RBP-6000 for opioid use disorder

ATRIGEL is a registered trademark of Tolmar Therapeutics, Inc.

ATRIGEL® drug delivery platform: Patient's point of view

Long acting injectable

One injection per month (typically)

Compliance/ Confidence

Subcutaneous injection in abdomen

Biodegradable - no removal required

ATRIGEL® drug delivery platform: Established products

ELIGARD

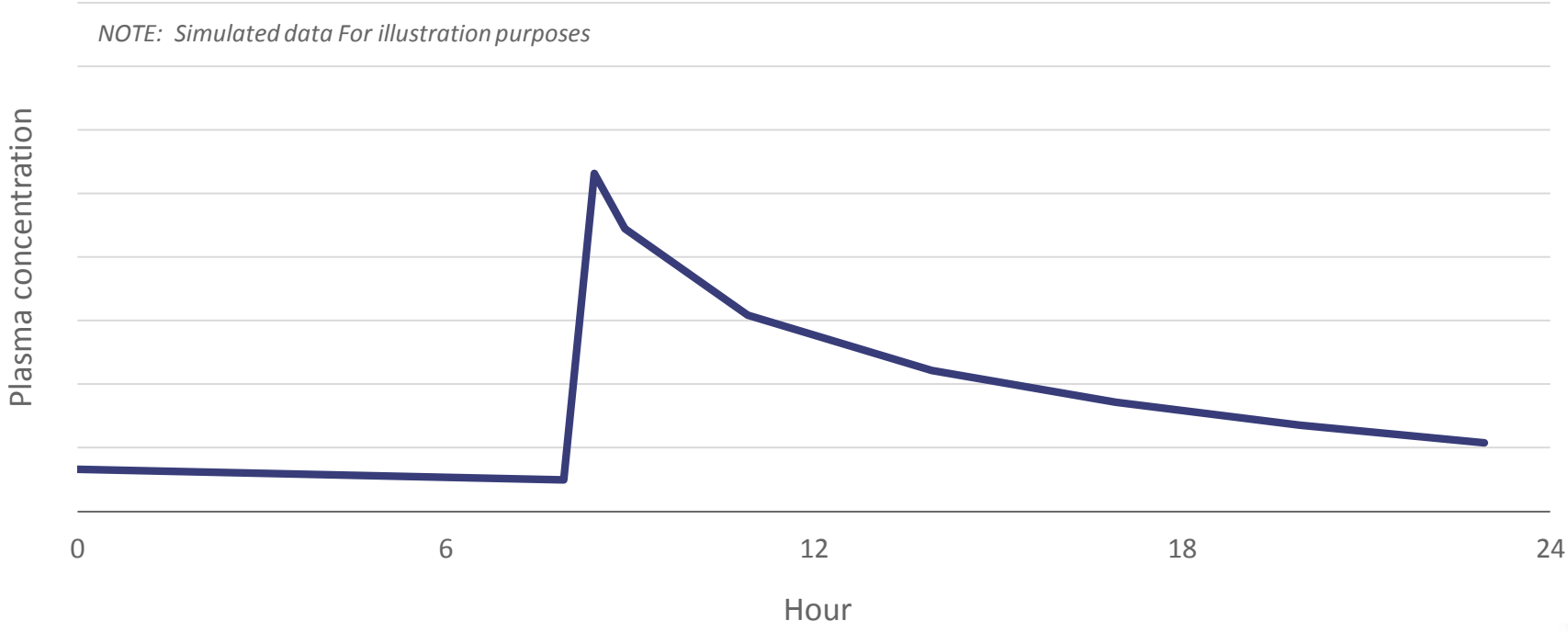
Available in 1, 3, 4 and 6 month dosages

Subcutaneous doses for controlled release of leuprolide acetate

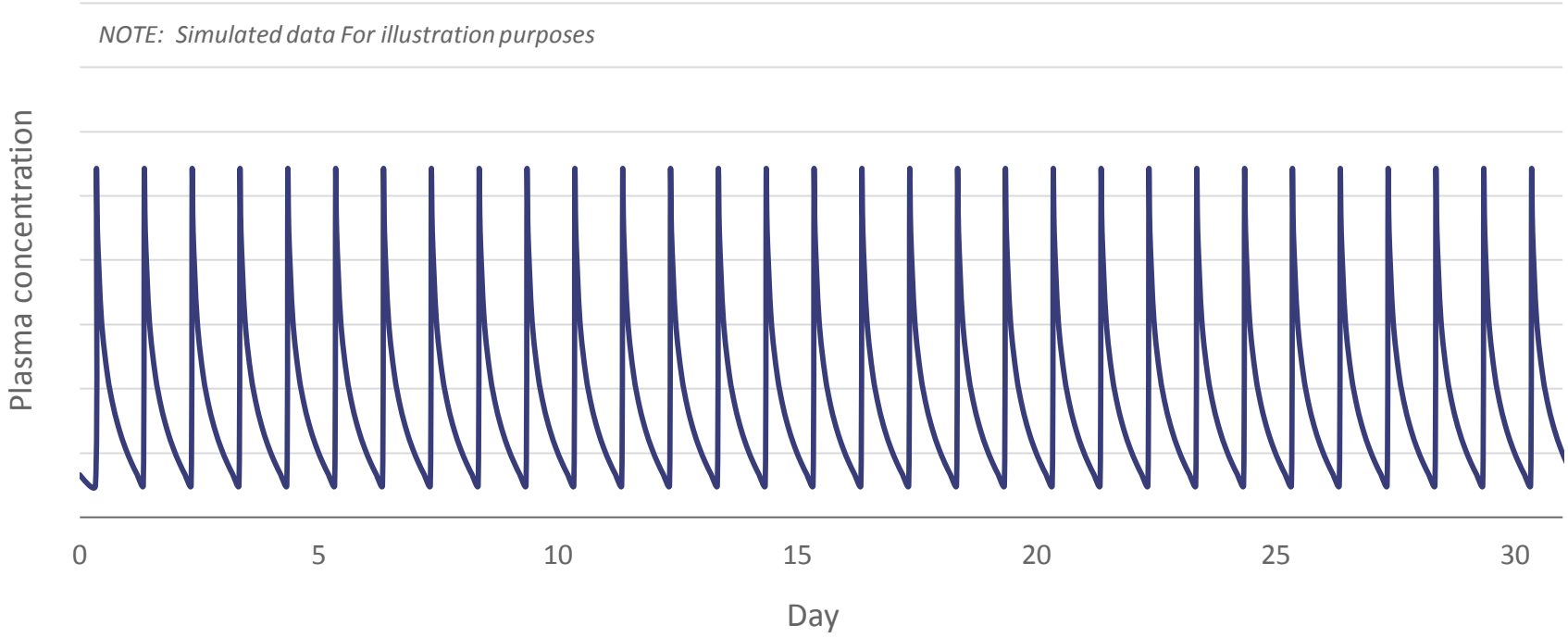
Currently marketed in 67 countries

Source – May 18, 2015 Tolmar Press Release (Business Wire)

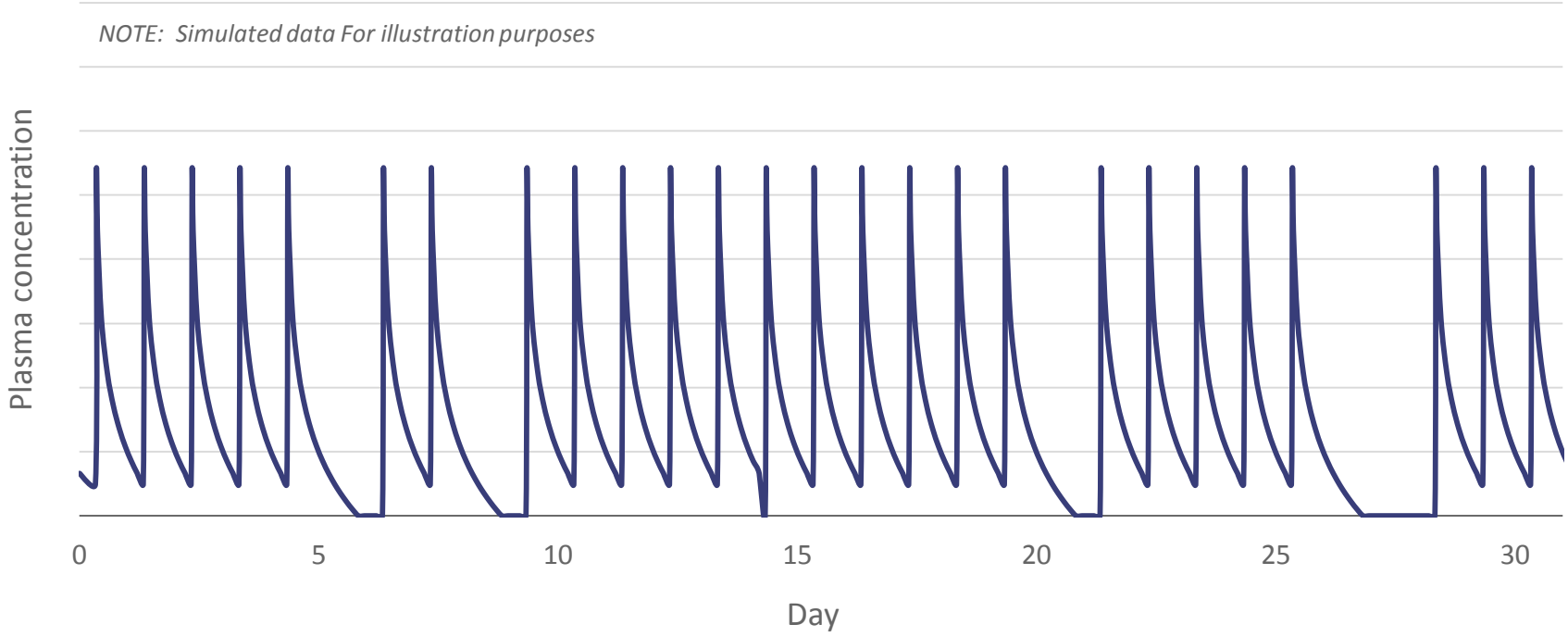
Plasma levels:
Typical daily dosing - illustration



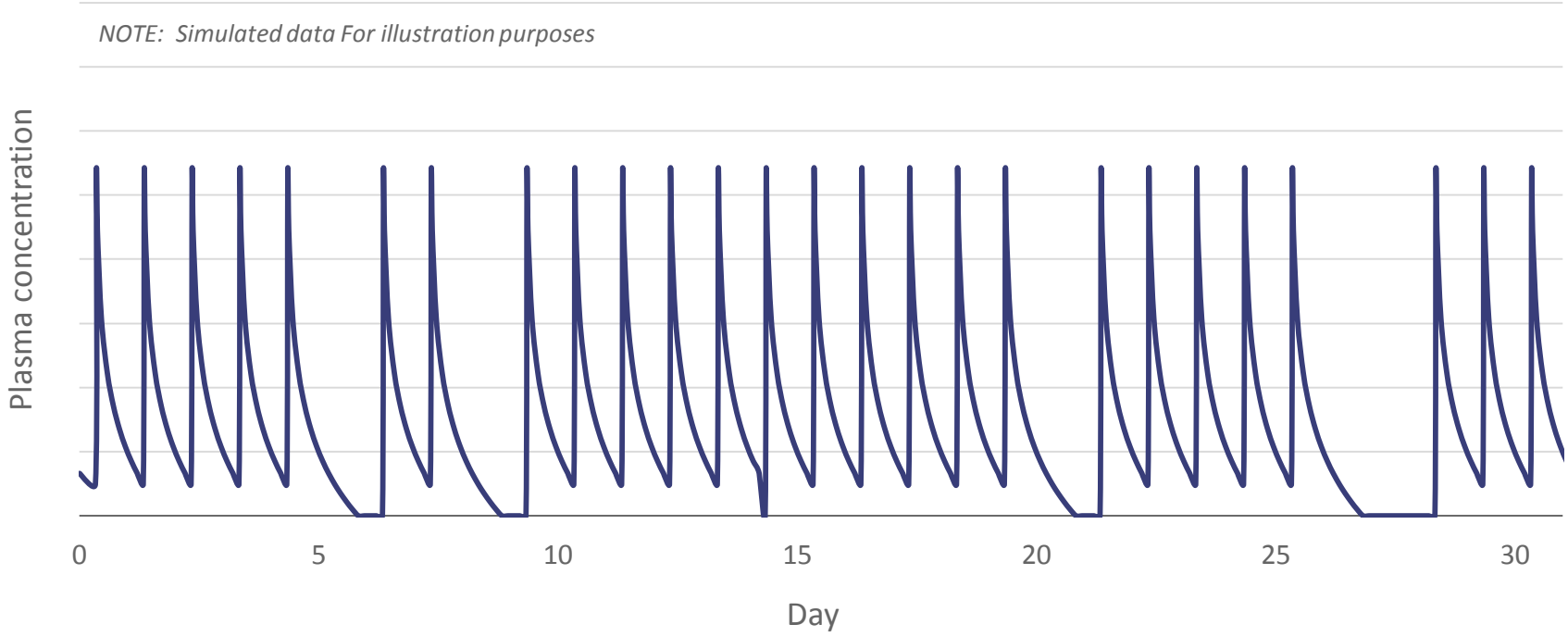
Plasma levels:
Month of daily dosing - illustration



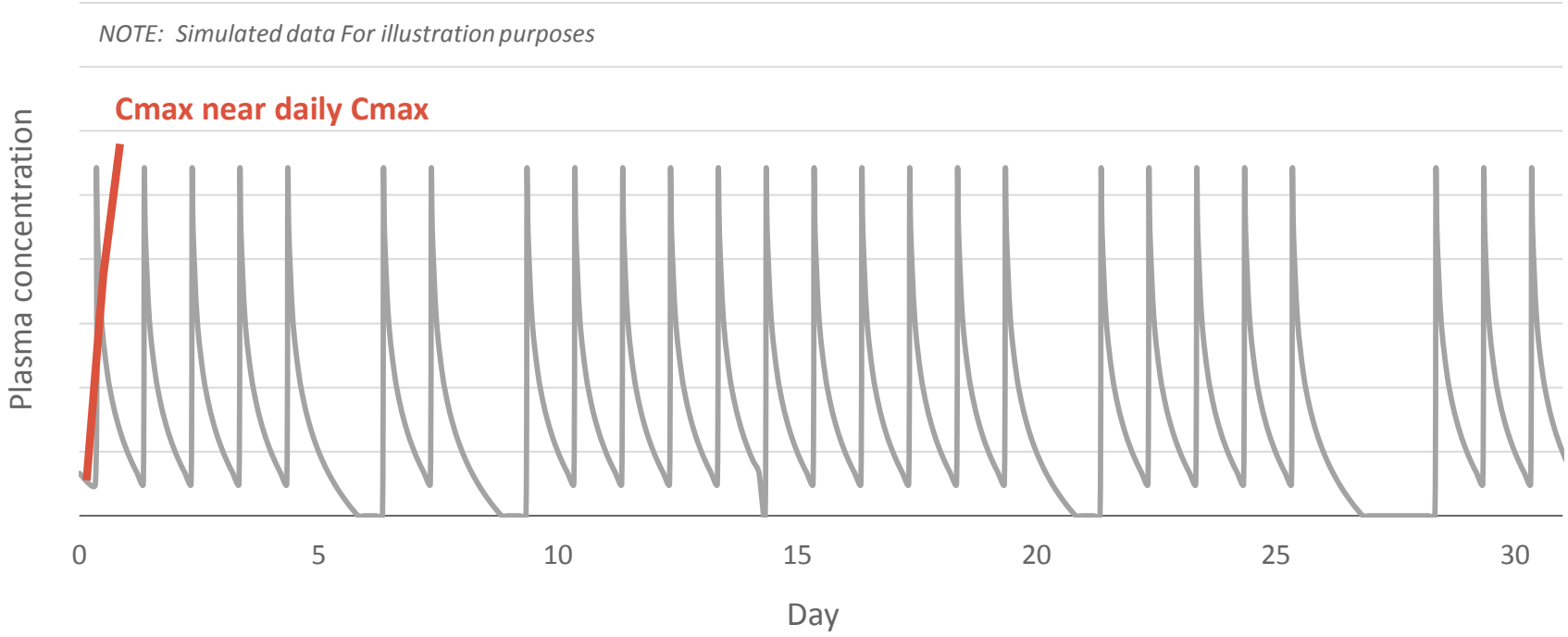
Plasma levels:
Lack of compliance - illustration



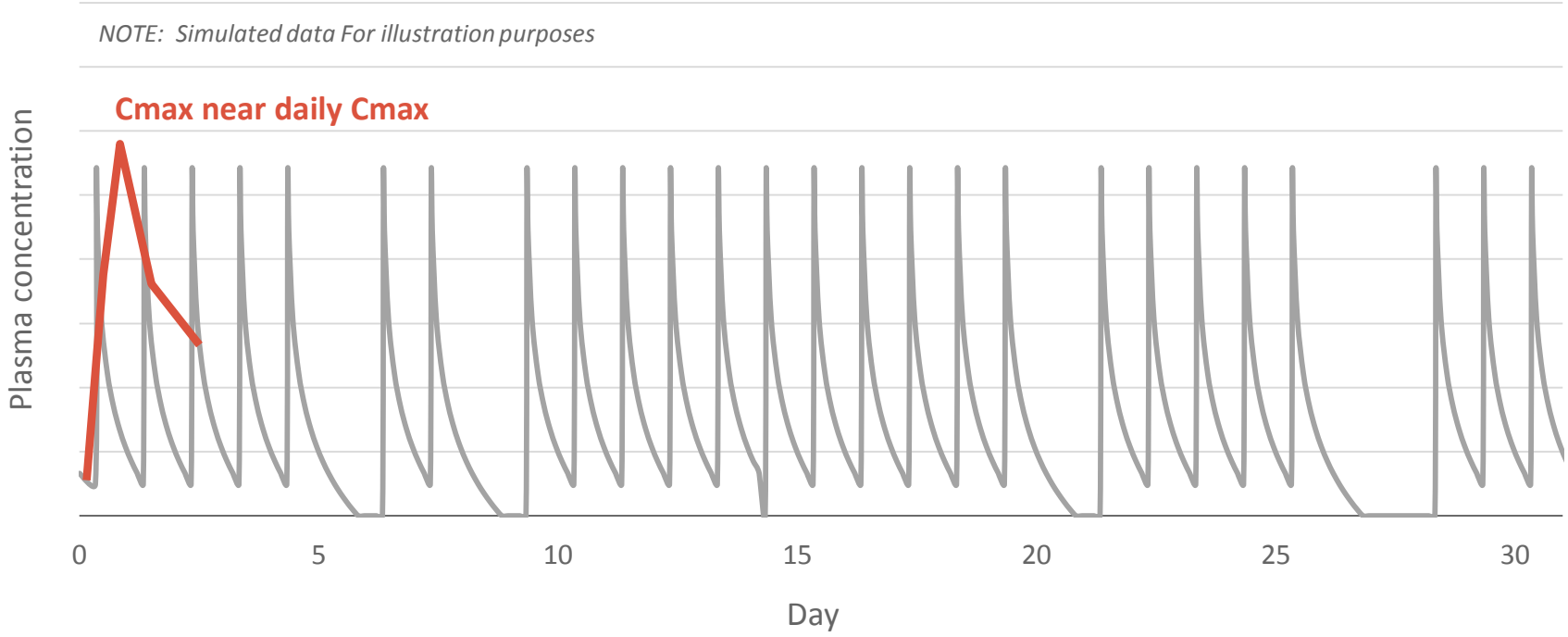
Plasma levels:
Compare with ATRIGEL® depot - idealized illustration



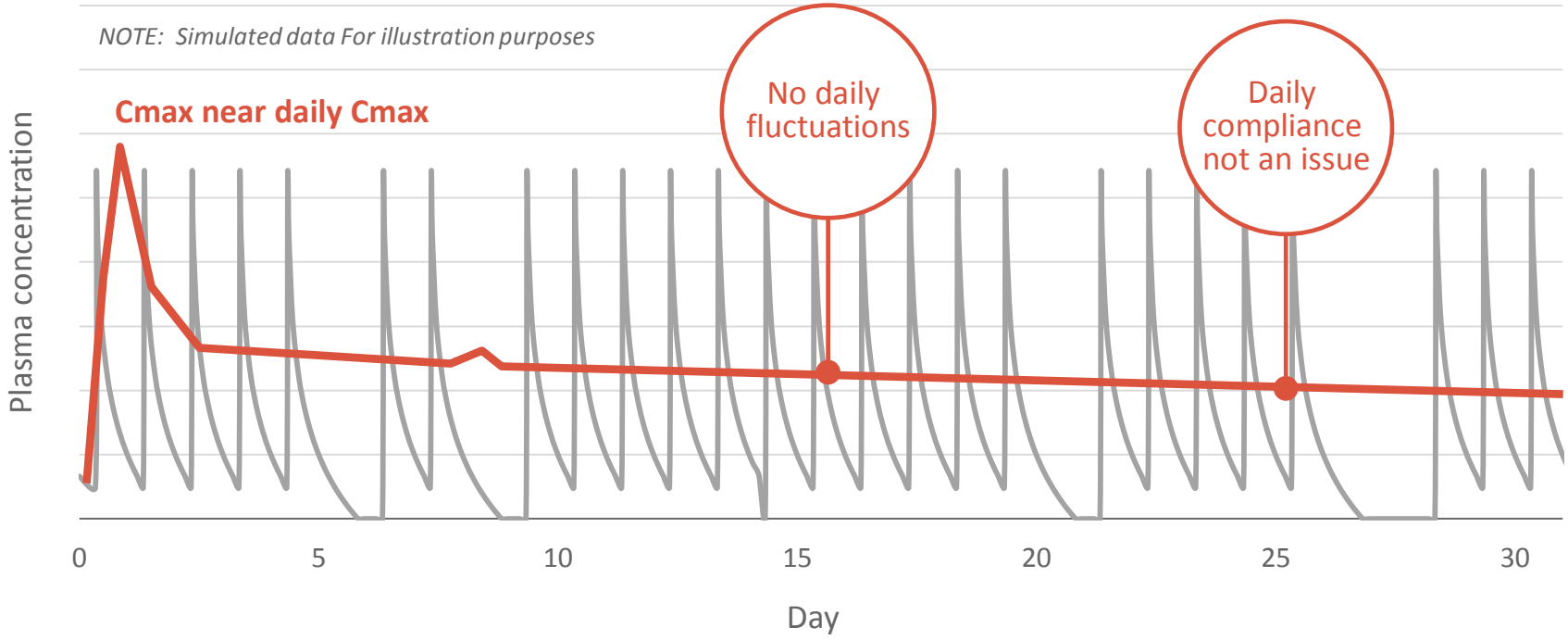
Plasma levels:
Compare with ATRIGEL® depot - idealized illustration



Plasma levels:
Compare with ATRIGEL® depot - idealized illustration



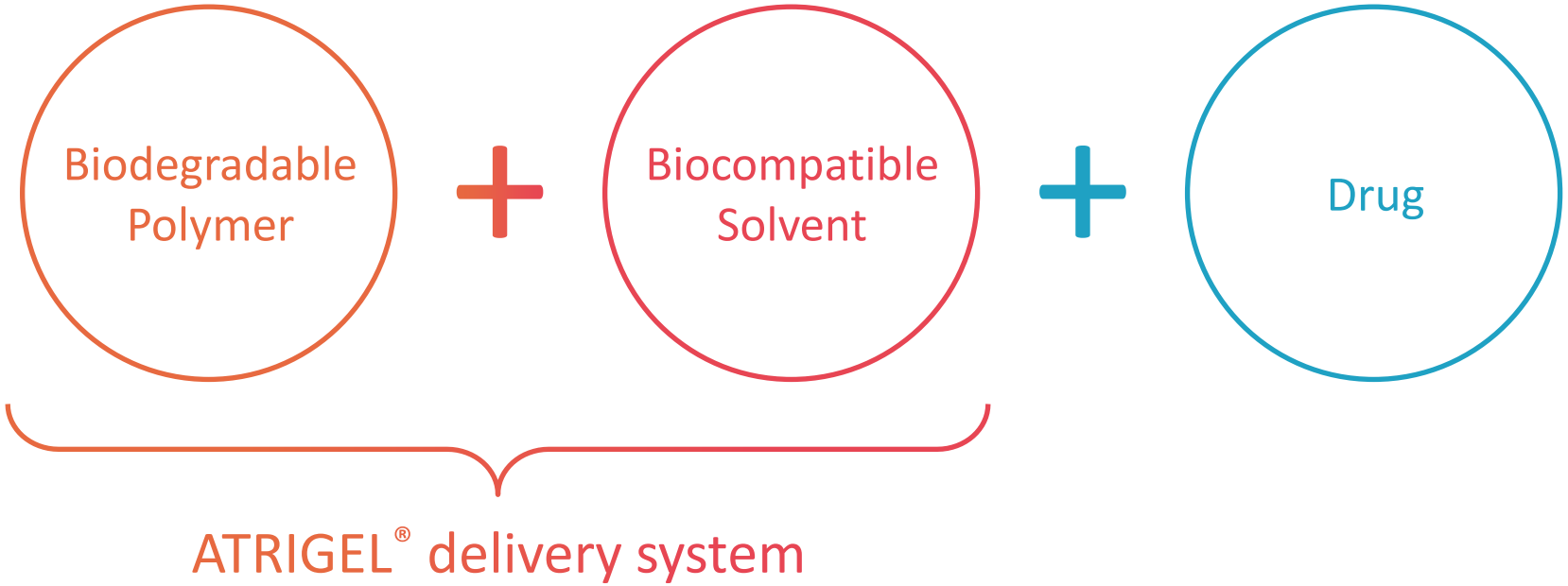
Plasma levels:
Compare with ATRIGEL® depot - idealized illustration



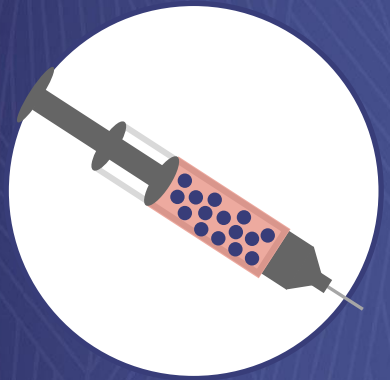
ATRIGEL® drug delivery platform:

Underlying science

ATRIGEL® components

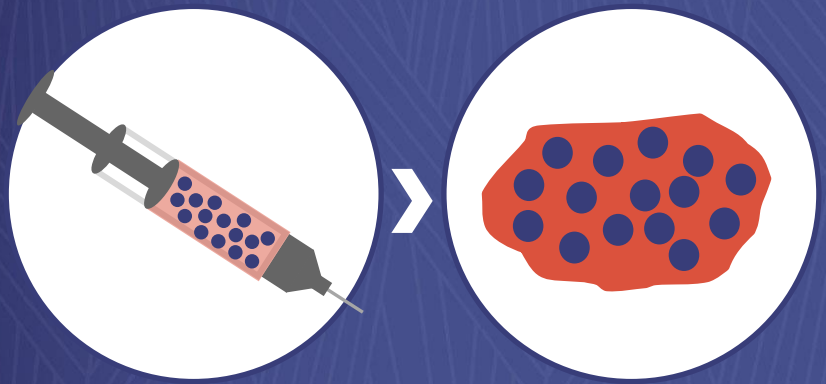


How does it work?



Injected
as a liquid

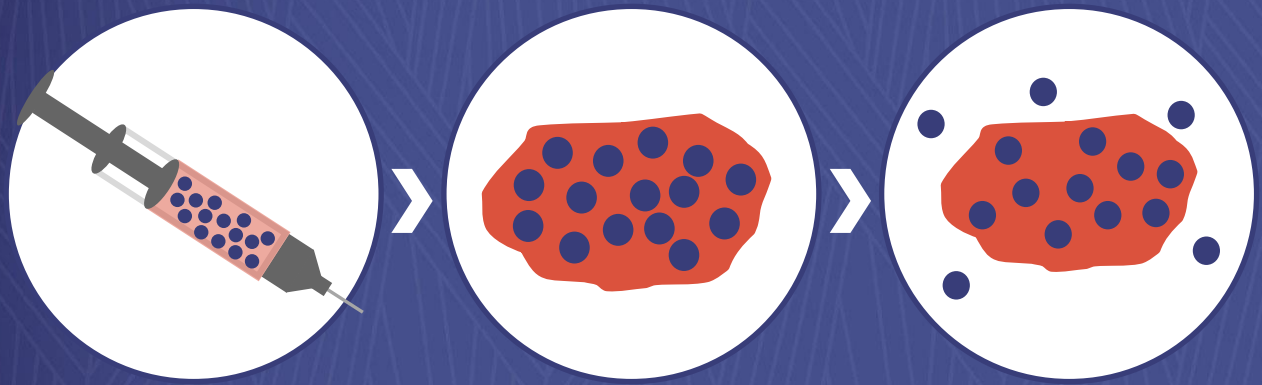
How does it work?



Injected
as a liquid

Solidifies in the
subcutaneous space

How does it work?

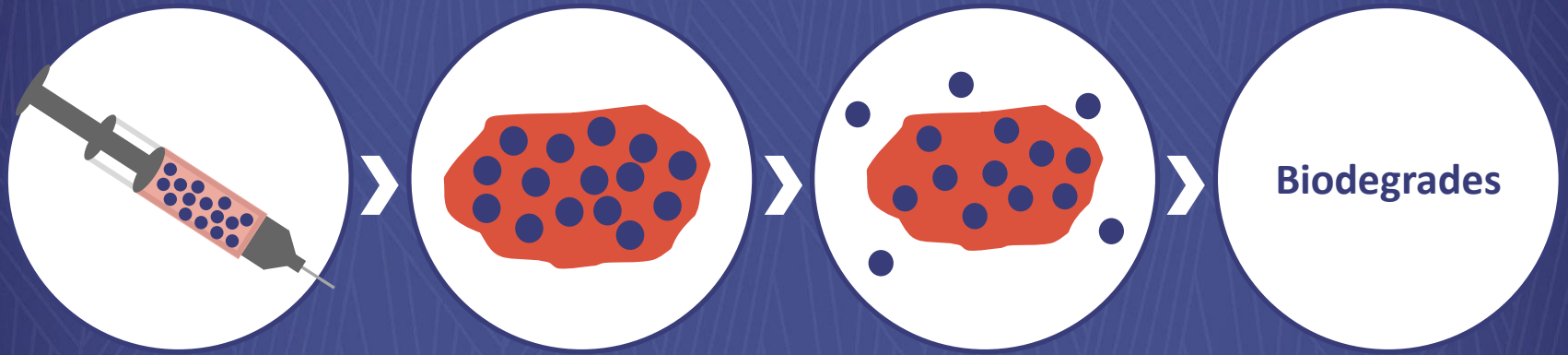


Injected as a liquid

Solidifies in the subcutaneous space

Releases drug into the body

How does it work?

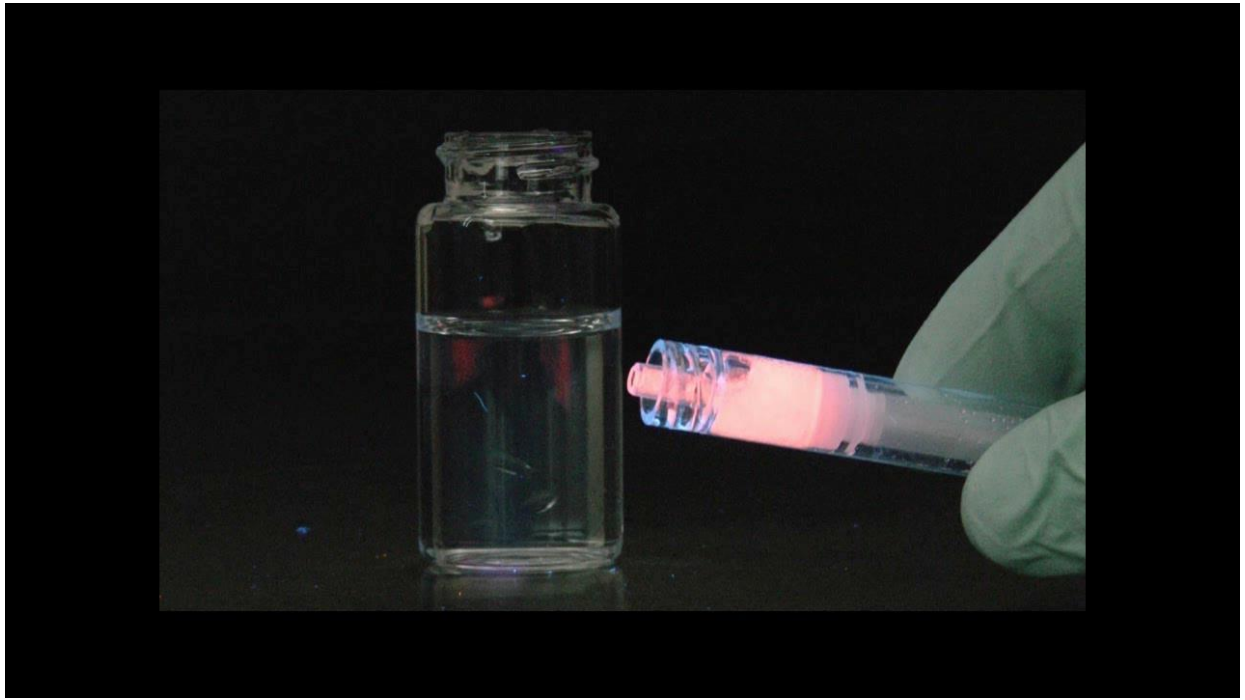


Injected as a liquid

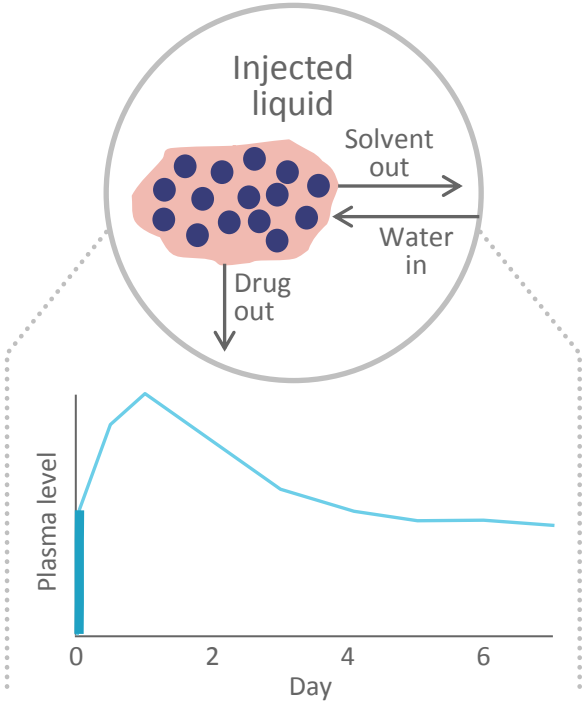
Solidifies in the subcutaneous space

Releases drug into the body

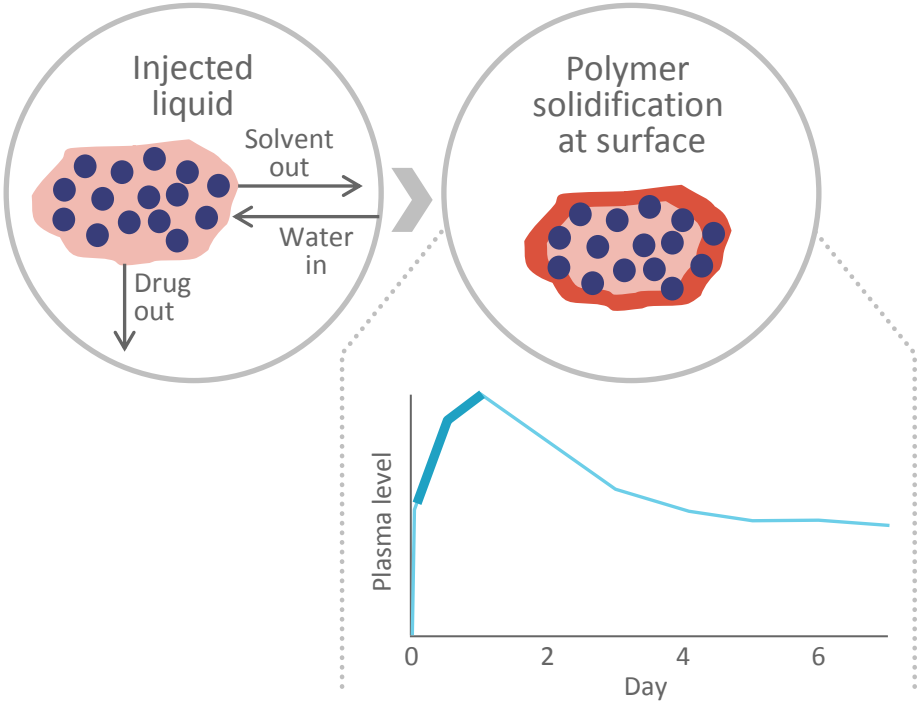
Solidification demonstration



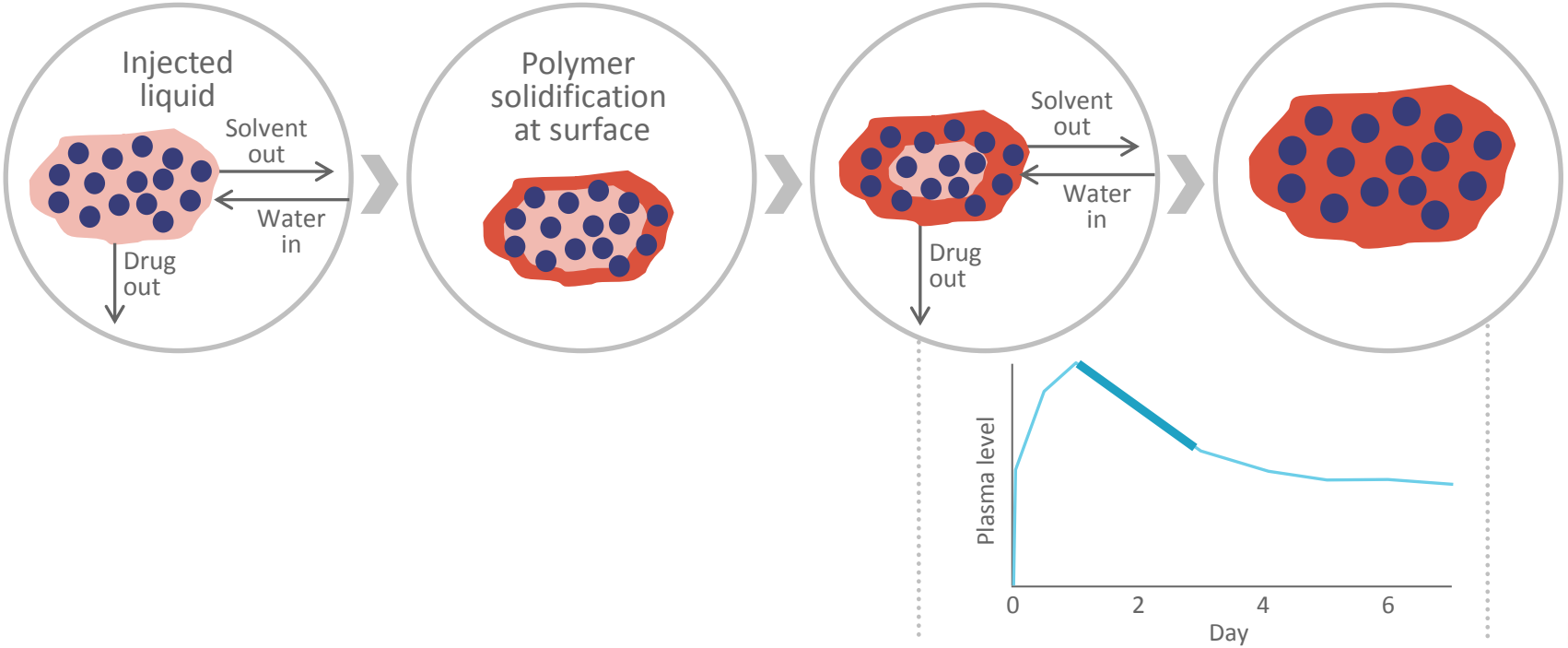
How does it work?
Solidification



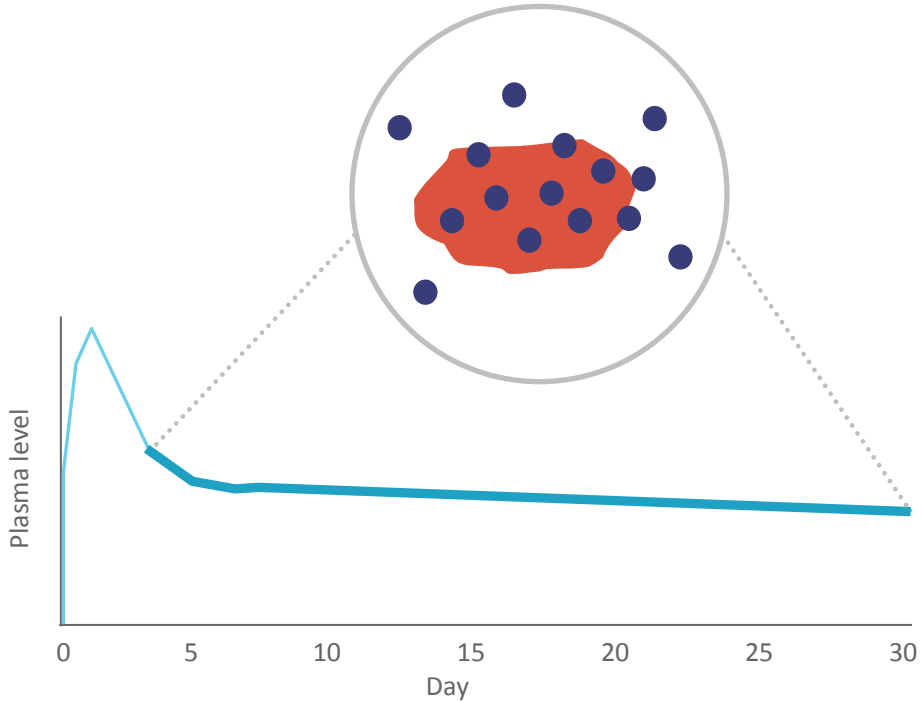
How does it work?
Solidification



How does it work?
Solidification



How does it work?
Drug release



- Diffusion
- Polymer Degradation – lowers barrier to diffusion over time
- Balance of diffusion and polymer degradation needed to get desired release rate and pharmacokinetics

Why does it work?

Biocompatible solvent

In addition to all the safety requirements

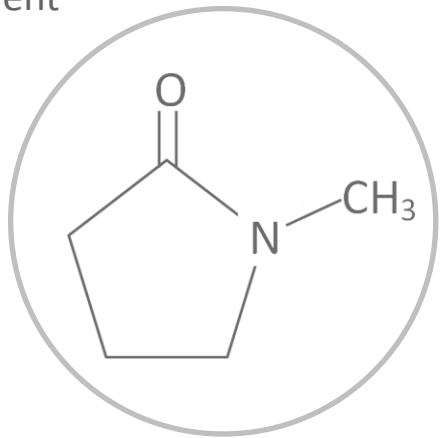
- Good solvent for the polymer
- Water miscible

N-methyl-pyrrolidone (NMP)

Used in all ATRIGEL® products to date

Great polymer solvent

Quickly dissipates into the body



Why does it work?

Biodegradable polymer

In addition to biodegradable

- Biocompatible
- Water insoluble
- Customizable structure

Poly(lactide-co-glycolide) family of polymers

Used in all ATRIGEL® products to date

Used in wide range of drug delivery systems and medical devices

Solid safety record

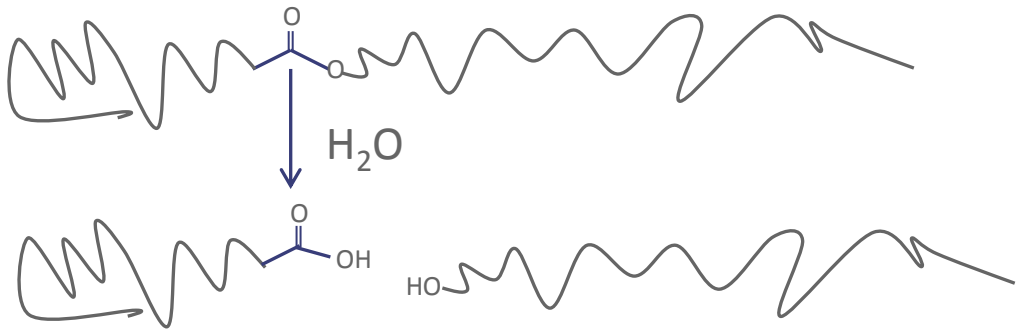
Breaks down to lactic and glycolic acids

Customizable structure

Polymer degradation

Degradation of Poly(lactide-co-glycolide) polymers

- Hydrolysis of ester bonds
- Molecular weight drops due to random chain scission
- Low molecular weight fragments are water soluble
- Eventually lactic and glycolic acid



Introduction to RBP-6000

U.S. patents

- 8,921,387
- 8,975,270

International patents

- U.K. GB2513267
- Australia 2011263478
- New Zealand 604026
- South Africa 2012/09233

Various patent applications pending

Introduction to RBP-6000

Solution of Buprenorphine in ATRIGEL® delivery system

Syringe

Ready to Inject

Refrigerated; 7 days at room temperature

Dosage strengths

100 mg (0.5 mL injection)

300 mg (1.5 mL injection)

Indivior R&D Day

RBP-6000: Clinical development

The pathway to where we are today

Dr. Susan Learned, M.D., Pharm.D., Ph.D.

Senior Vice-President, Global Clinical Development, Indivior Inc.

INDIVIOR

RBP-6000 - US clinical development program

First-in-man study

(20 mg)

Single Ascending Dose study

(50, 100, and 200 mg)

Multiple Ascending Dose study

(50, 100, 200, and 300 mg)

Opioid blockade study

Double blind, PC phase 3 study

Open label extended safety study

OUD treatment paradigm shift

FDA Type C meeting:

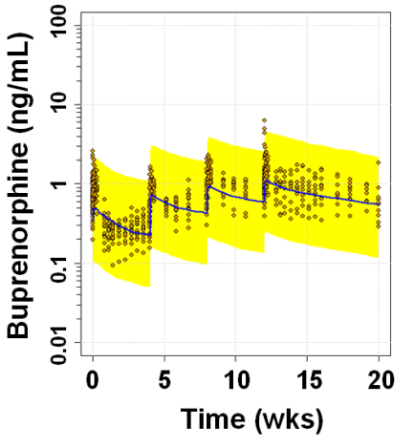
Target a dose that will **fully block** opioid agonist effects in Phase 3 trial

Hypotheses testing:

- Based on PD analysis, an average buprenorphine plasma level of 2-3 ng/mL will produce ~70% μ receptor occupancy (confirm in Phase 2 MAD study)
- Obtain these levels from the first SC injection (avoid SL rescue medication in Phase 3; block effects of illicit opioid use)
- Perform preliminary assumptions testing by using clinical data from Greenwald et al.
- Conduct an opioid blockade study to confirm the assumptions

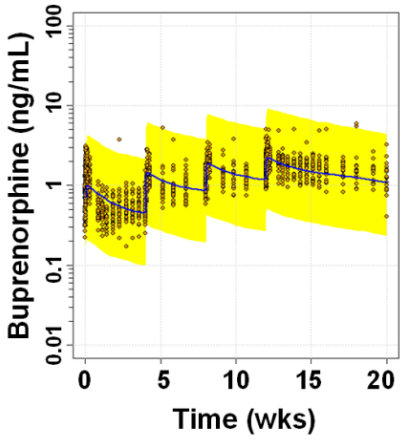
Q#1: What is the PK profile of RBP-6000 in a Multiple Ascending Dose (MAD) study?

50 mg



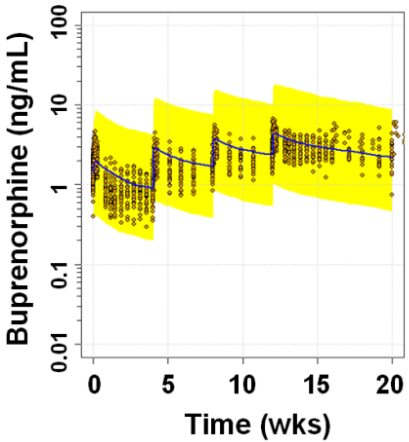
SS C_{avg} = 0.96 ng/mL

100 mg



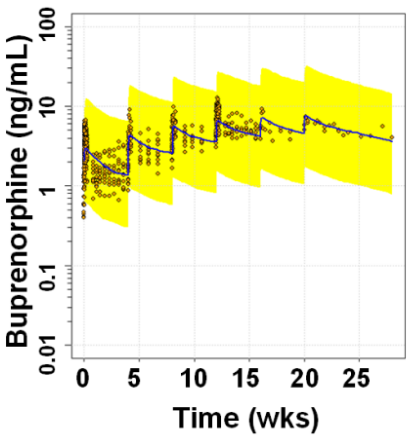
SS C_{avg} = 1.66 ng/mL

200 mg



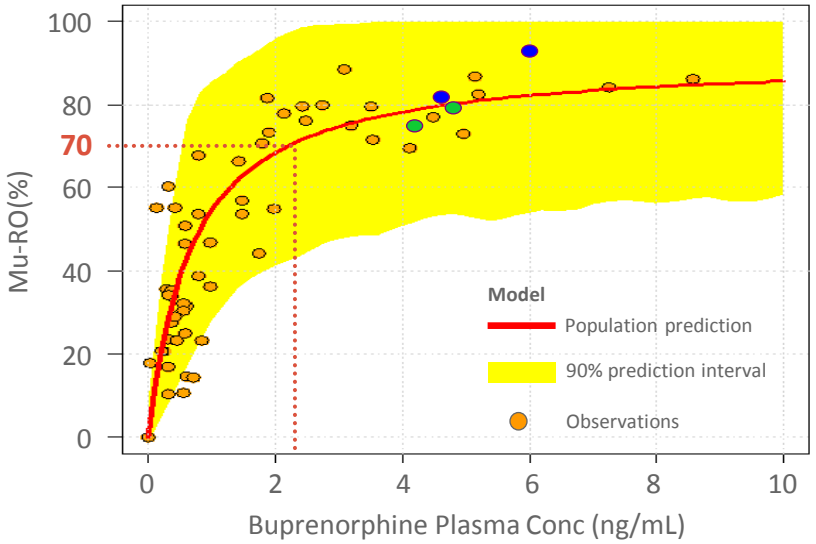
SS C_{avg} = 2.8 ng/mL

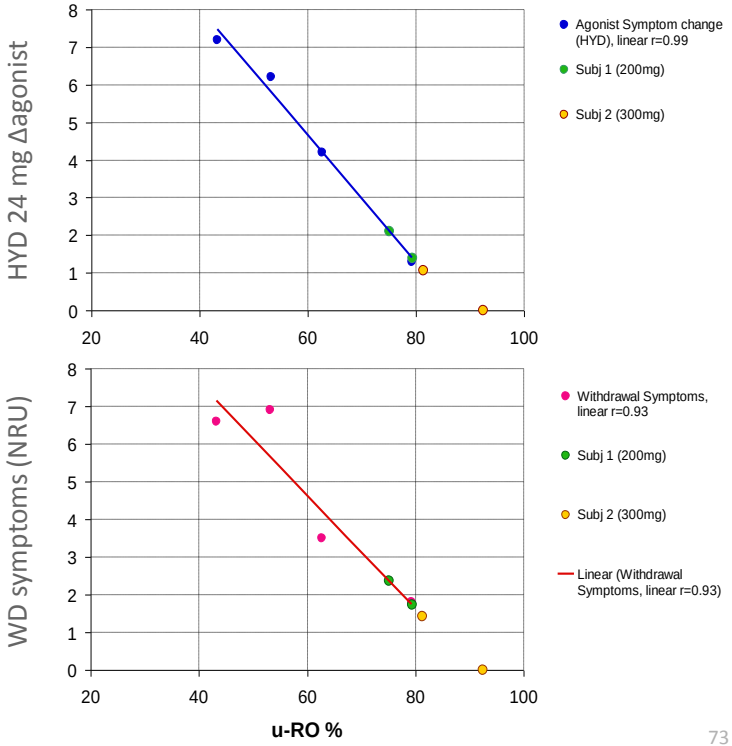
300 mg



SS C_{avg} = 5.12 ng/mL

Q#2: What is the PK/RO relationship & predictions of opioid blockade with RBP-6000 (200 mg & 300 mg)?





200mg: 2-3ng/mL / 75-80% RO
300mg: 4-7ng/mL / 81-92% RO

RBP-6000: Opioid blockade study

Title

A Multiple-Dose study of blockade of subjective opioid effects, plasma levels, and safety of subcutaneous injections of depot Buprenorphine (RBP-6000) in subjects with opioid use disorder

Patient population

39 opioid-dependent males and females; not treatment-seeking

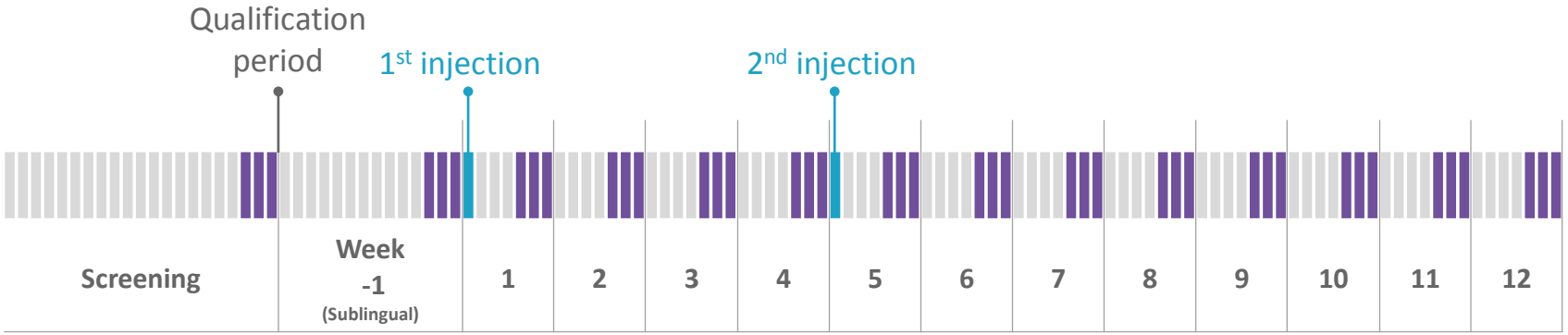
Dosing level for all subjects

0 mg hydromorphone challenges after 300 mg RBP-6000

6 mg hydromorphone challenges after 300 mg RBP-6000

18 mg hydromorphone challenges after 300 mg RBP-6000

Opioid blockade study design



RBP-6000 injection days

Hydromorphone challenge days
(5th, 6th, and 7th day of each week)

RBP-6000: Opioid blockade study – outcome measures

Subjective Effects (VAS Scores)

- Drug Liking (Primary outcome measure)
- Any Drug Effect
- Good Drug Effect
- Bad Drug Effect
- High
- Sedation
- 30(±5) before and 15, 30, 45, 60, 75, 90, 120, 150, 180, 210, 240, 270, and 300(±5) minutes after HM challenge

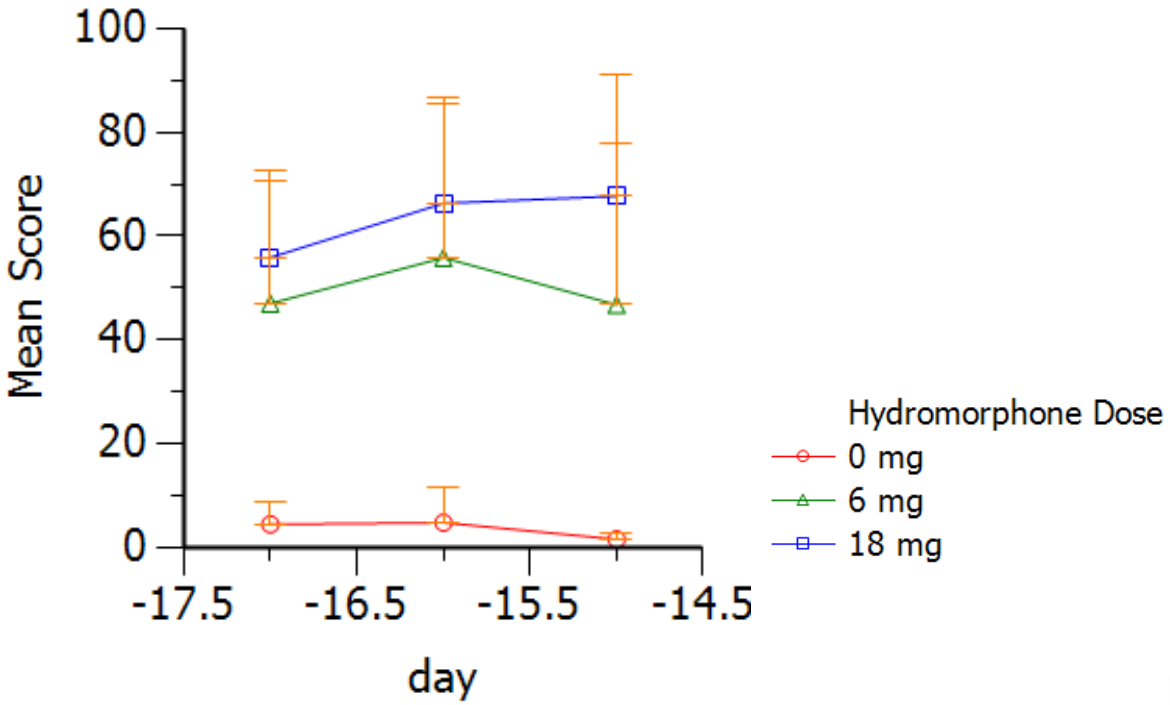
Reinforcing Effects

- No earlier than 5 hours after HM challenge
- Choose the amount of HM dosed that day or money in progressive ratio schedule
- HM break point value:
  - Highest Level of HM Units Earned

Q#3: Can we confirm the PD predictions with the opioid blockade study?

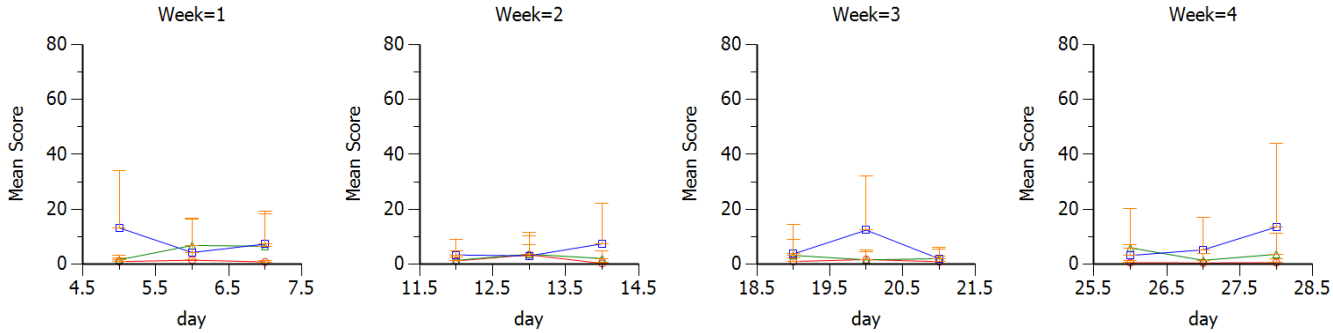
Opioid blockade study:

Drug liking – baseline scores

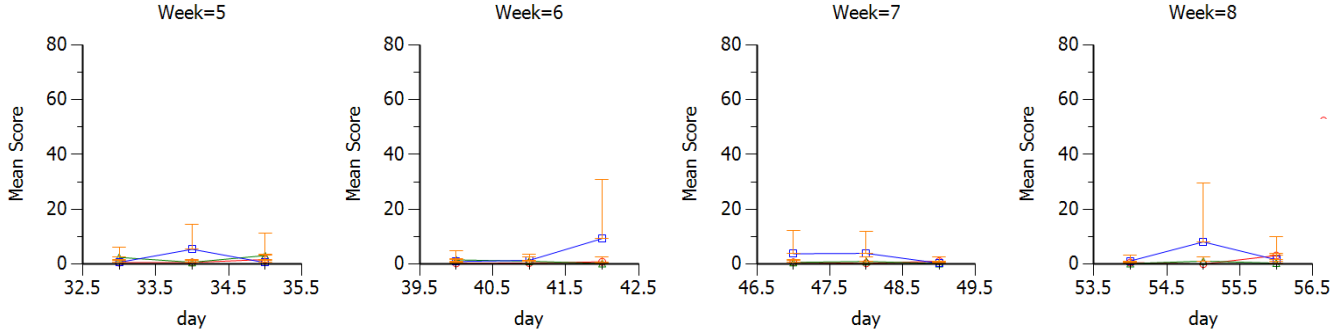


Q#3: Can we confirm the PD predictions with the opioid blockade study?

Opioid blockade study:
Drug liking – RBP-6000
month 1



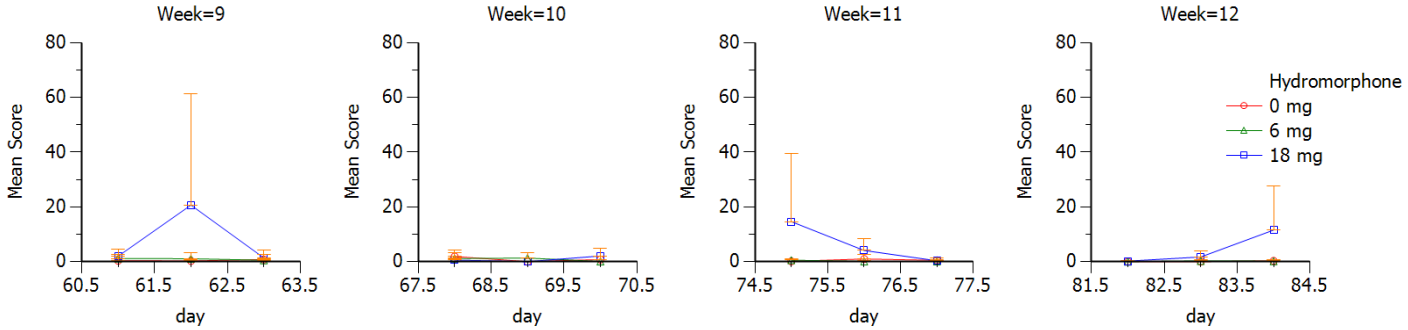
Opioid blockade study:
Drug liking – RBP-6000
month 2



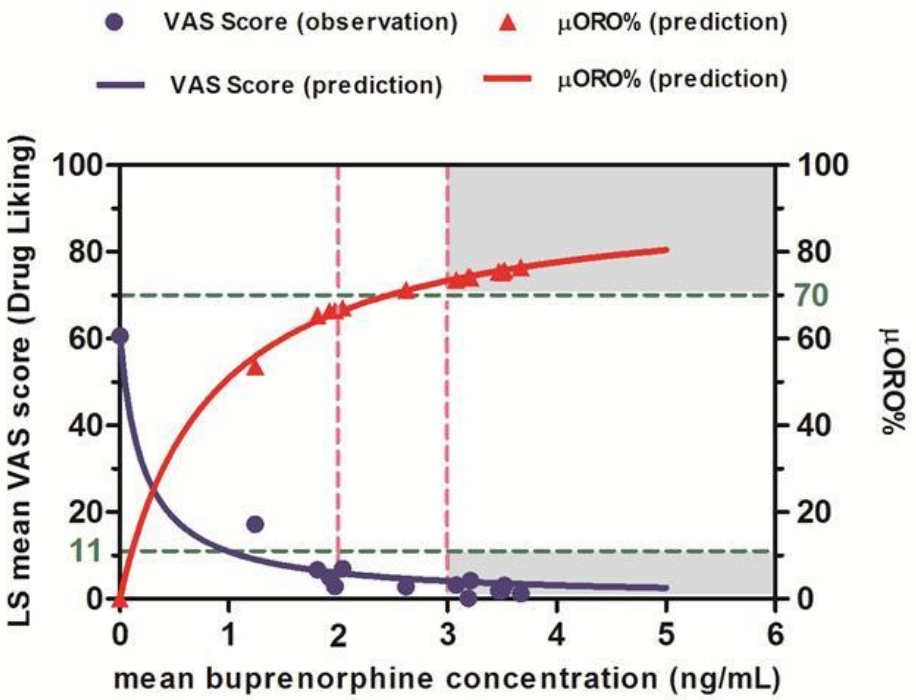
Hydromorphone
0 mg
6 mg
18 mg

Q#3: Can we confirm the PD predictions with the opioid blockade study?

Opioid blockade study:
Drug liking – RBP-6000
month 3

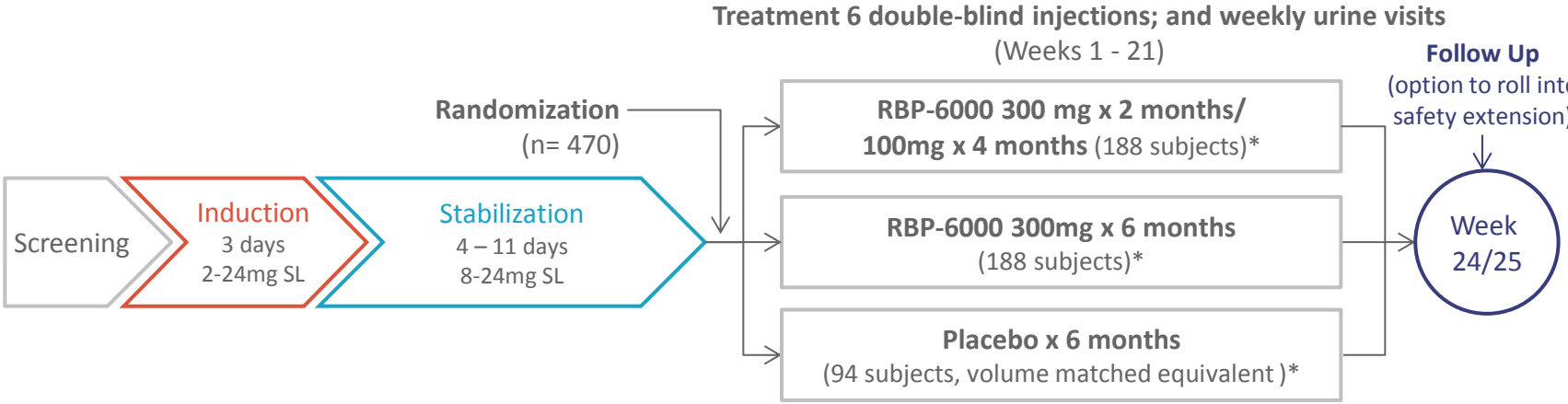


RBP-6000: PK/PD/RO relationship



- The PK profile of RBP-6000 was derived after single and multiple ascending dose studies
- A PK/RO model was established and validated with data from the MAD study
- The "opioid blockade" hypothesis was tested clinically
- The outcome of the "opioid blockade" study was used to support the design of the pivotal Phase 3 trial

RBP-6000: Phase 3 study design



Randomized, double-blind, placebo-controlled study

Primary endpoint:
The CDF of the percentage of urine samples negative for opioids combined with self-reports negative for illicit opioid use collected from Week 5 through Week 24.

Secondary endpoints:
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 17-24.

**All randomized subjects receive the following taper doses: Day 1: 6 mg; Day 2: 4 mg; Day 3: 4 mg; Day 4: 2 mg; Day 5: 2 mg*

INDIVIOR R&D DAY

UPDATE ON PHASE 3 PIVOTAL TRIAL WITH RBP-6000

Dr. Amit Vijapura, M.D.

INDIVIOR

Dr. Amit Vijapura, M.D.

Dr. Vijapura is a medical specialist with board certification in Psychiatry & Addiction Medicine based in Jacksonville, Florida in private practice for the last 25 years.

He is running a clinical research site with three research coordinators. He has been involved in clinical research for opioid dependence for the last 10 years and has completed many different Phase II and Phase III studies for this condition.

He is a Principal Investigator of RB - US 0001 and 0003 studies.

His private practice has many opioid-dependent patients. He is able to utilize all available FDA approved products to treat his patients.

He is also involved in teaching at the local, regional, and national level for different diseases and pharmaceutical products, teaching medical students and resident physicians.

Experience treating OUD patients with RBP-6000 in ongoing clinical trials

01 Dealing with non-compliance, diversion in office-based treatment

02 Experience with depot Buprenorphine studies

03 Clinical trials:

1. **RB-US 0001**
   (Total subjects = 34);
2. **RB-US 0003**
   (Current subjects = 23, and enrolling)

04 Patient experience during research

05 Physician experience during research

06 Verbal testimonial from subjects

07 As a clinician if depot Buprenorphine gets FDA approval in future how it will change treatment paradigm for doctors and patients

INDIVIOR R&D DAY

R&D STRATEGIC PIPELINE UPDATE

Christian Heidbreder, Ph.D., *Chief Scientific Officer*

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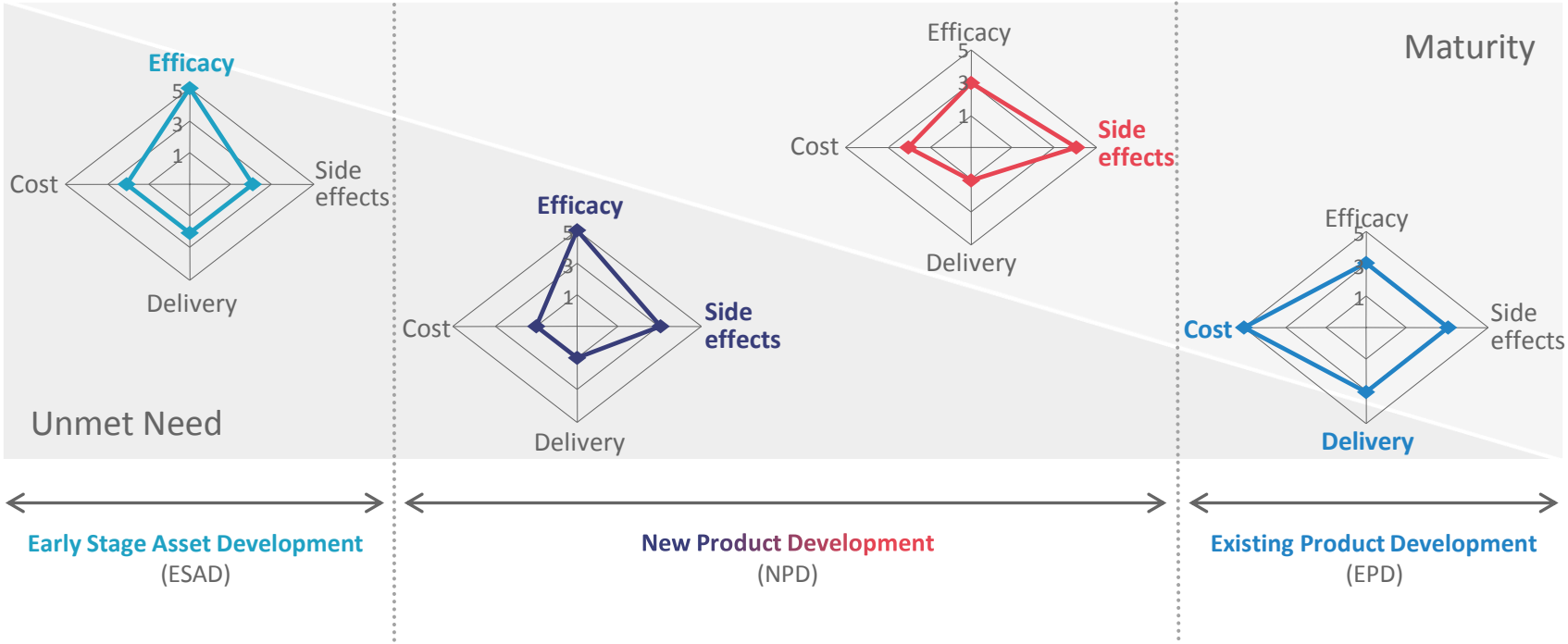
Our vision is that all patients around the world will have unrestricted access to quality treatment services for the chronic relapsing conditions and co-morbidities of addiction

R&D strategy to address challenges in addiction medicine



Existing Product Development (EPD)

Overview & latest update

Suboxone® Tablet

Target	Objective	Status
USA/Global	Changes to the pregnancy and nursing mothers sections of the labeling for all buprenorphine products [1]	• Briefing Book submitted to FDA Jun 19th, 2014; feedback received Sep 12th, 2014 • sNDA successfully submitted to the FDA on May 15th, 2015 • Approval expected in May 2016
Europe	Additional dosage strength 16 mg/4 mg	• Completion of clinical PK studies (RB-UK-12-0007 & RB-UK-12-0008) • Dossier submitted to EMA Sep 1st, 2014 • Response from EMA received on Sep 4th, 2015. • Approval of Suboxone 16mg/4mg strength in the EU received on Nov 16th, 2015
China	Clinical efficacy & safety	• **RB-CN-10-0012:** SAD[2] PK Study in Chinese Subjects; final CSR Aug 25th, 2014. • **RB-CN-10-0013:** Efficacy study on track for Last Patient last Visit by Dec 31st, 2015 • **RB-CN-10-0015:** MD[3] study on track for Last Patient last Visit by Dec 31st, 2015

(1) Jones HE et al. N Engl J Med. 2010 Dec 9;363(24):2320-31. doi: 10.1056/NEJMoa1005359
(2) SAD = Single Ascending Dose
(3) MD = Multiple Dose

Suboxone® Film

Target	Objective	Status
USA	Buccal indication	• PDUFA date Feb 21st, 2015 • FDA approval on Sep 22nd, 2015
	Phase IV Commitment Hepatic	• Published in *Clin Pharmacokinet. 2015 Aug;54(8):837-49.* http://dx.doi.org/10.1007/s40262-015-0238-6
	Phase IV Commitment tQT*	• Clinical Study Protocol successfully sent to the FDA on May 12th, 2015 • FDA feedback received on Jul 27th, 2015 • Final tQT CSP (RB-US-11-0019) submitted to FDA on Oct 5th, 2015.
EU CAN GLOBAL	Film reformulation	• Final Clinical Study Report (RB-US-14-0002) on Aug 17th, 2015 • Project delayed as the prototype formulation for EU has not met its specified bio-equivalency to the EU/Rest of World Suboxone® Tablet formulation
CHINA	Clinical efficacy & safety	• Clinical Trial Application approved by the Chinese *Center for Drug Evaluation* (CDE) at SFDA

** tQT = Thorough QTc prolongation*

New Product Development (NPD)

Overview & latest update

New Product Development: Opioid use disorder

Product	Status
RBP-6000: Buprenorphine once monthly in Atrigel® 	**US:** • **Phase III Efficacy study (RB-US-13-0001):** LPI achieved on Nov 17th, 2015. • **Phase III Safety extension study (RB-US-13-0003):** Screening and enrollment ongoing. • **US Patent No. 8,975,270** was issued Mar 10th, 2015 with an expiration date of Sep 5th, 2031. The '270 patent will be the second listable patent in the Orange Book upon FDA approval of the product. • Four major **Health Economics & Outcomes Research projects** currently ongoing. **EU:** • Optimization of European Clinical Study Protocol to leverage RB-US-13-0001 and RB-US-13-0003 trials translates into possible changes in current approval date (2018) in Europe. Final European CSP will be confirmed by Q3-2016 for implementation in Q4-2016.
RBP-6300: Buprenorphine Hemiadipate in Encap's Abusolve 	• MHRA approved CTA on Aug 28th, 2015. • **PK Study in Man (RB-EU-14-0001):** First Patient In on Sep 30th, 2015. • **US/EU:** A Phase 2 dose-ranging study following the pivotal PK study in Man will most probably be required before committing to a pivotal Phase 3 trial, which will translate into possible changes in current approval date (2018) in Europe. Remaining development plans and associated timelines will be confirmed following outcome of pivotal PK study in Q2-2016.

New Product Development:
Rescue medications for drug overdose

Product	Status
Naloxone intranasal spray *for treatment of opioid overdose* 	**US:** **Under evaluation** **Canada:** Pre-NDS meeting with Health Canada on Oct 22nd, 2015 **France:** Temporary Authorization for Use (ATU) dossier filed on Jun 17th, 2015. ATU approved by ANSM on Nov 5th, 2015 **Europe:** EMA's CHMP confirmed (Jul 6th, 2015) naloxone nasal spray is eligible for submission via the centralized route in the EU
RBP-8000: *Cocaine esterase for treatment of cocaine intoxication*	• Breakthrough Therapy Designation granted Oct 17th, 2014 • Briefing Pack submission to FDA Feb 6th, 2015 • Type B meeting with the FDA successfully held on May 7th, 2015 • Clinical development and manufacturing plans currently re-assessed according to FDA requirements in the context of Breakthrough Therapy Designation. Second Type B meeting with the FDA to be held by Dec 31st, 2015

New Product Development: Alcohol use disorder

Product	Status
Arbaclofen Placarbil	• Pre-IND meeting with FDA Jan 29th, 2015 • IND submission: Jun 26th, 2015 • *RB-US-14-0001:* A randomized, double-blind, placebo-controlled, Dose escalation study to determine the Maximum Tolerated Dose (MTD) of Arbaclofen Placarbil (AP) in subjects with Alcohol Use Disorder (AUD); First patient screened on Sep 15th, 2015


Alcoholism:
Developing Drugs for Treatment
Guidance for Industry
DRAFT GUIDANCE

Primary endpoints:

Efficacy should be expressed by change to baseline in total consumption of alcohol (per month, presented as amount of pure alcohol in grams per day) as well as by reduction in number of Heavy Drinking Days (HDD defined as more than 56 grams of pure alcohol in men and 42 grams in women). A clinically relevant difference compared to placebo should be demonstrated.

Secondary endpoints:

Efficacy should be evaluated in terms of responders, reflecting an expected significant improved health outcome on an individual patient level (e.g., % subjects with a 50%, 70% and 90% reduction in alcohol consumption and % patients achieving maintained abstinence or % subjects with a significant categorical shift in WHO risk levels of drinking.

Source: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm433618.pdf

New Product Development: Psychiatric co-morbidities

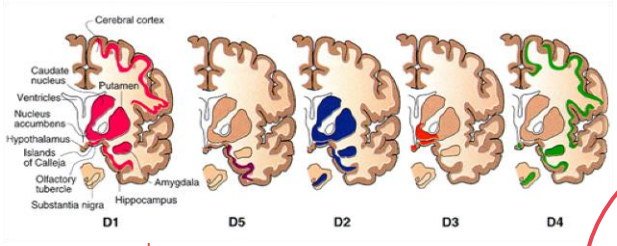
Product	Status
RBP-7000: Risperidone once monthly in Atrigel® 	• **Phase 3 pivotal efficacy study (RB-US-09-0010):** Completed; Preliminary data from pivotal Phase III Efficacy study were published on May 5th, 2015 • **Phase 3 long-term safety study (RB-US-13-0005):** Enrolment ongoing • **US Application No. 14/490,034 and US Application No. 14/490,082:** Notices of Allowance have been received on Sep 25th; US patents granted in Nov; these patents will be listable in the Orange Book

Early Stage Asset Development (ESAD)

Overview &
latest update

Selective dopamine D3 receptor antagonists for the treatment of Stimulant Use Disorder

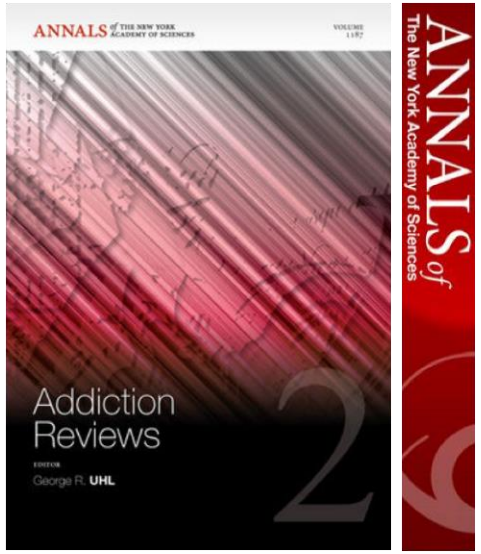
D_3 receptors are located on a pathway known to modulate reward-related mechanisms



D_3 receptors are over-expressed in brain tissues from **human addicts**

D_3 receptors are over-expressed in brain tissues from **animal disease models**

Would a selective DA D_3 receptor antagonist show efficacy in the treatment of stimulant addiction?



ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: *Addiction Reviews 2*

Current perspectives on selective dopamine D_3 receptor antagonists as pharmacotherapeutics for addictions and related disorders

Christian A. Heidbreder[1] and Amy H. Newman[2]
[1]Reckitt Benckiser Pharmaceuticals, Global Research & Development, Richmond, Virginia, USA. [2]National Institute on Drug Abuse, Medicinal Chemistry Section, Intramural Research Program, Baltimore, Maryland, USA
Address for correspondence: Christian A. Heidbreder, Reckitt Benckiser Pharmaceuticals, Global Research & Development, 10710 Midlothian Turnpike, Ste. 430, Richmond, VA 23235. Voice: 804-594-4456; fax: 804-379-1215. christian.heidbreder@reckittbenckiser.com

Source: Heidbreder CA, Newman AH (2010) Current perspectives on selective dopamine D_3 receptor antagonists as pharmacotherapeutics for addictions and related disorders. Ann. N.Y. Acad. Sci., 1187:4-34.
http://dx.doi.org/10.1111/j.1749-6632.2009.05149.x

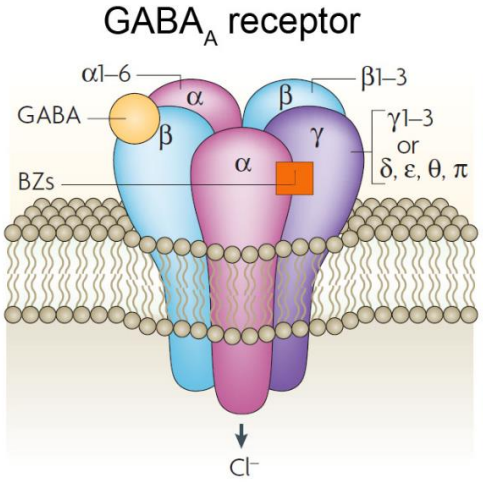
Positive Allosteric Modulator of GABA-A receptors for the treatment of Alcohol Use Disorder

The GABA-A receptor is a complex pentameric (five subunit) protein which is composed of particular combinations of α (1–6), β (1–3), γ (1–3), δ, ε, and θ subunits.

The presence of the δ subunit-containing GABA-A generates a receptor that is not responsive to benzodiazepines, *but that is significantly more sensitive to ethanol* than GABA-A receptors containing the γ subunit (the subunit which is necessary for the actions of benzodiazepines).

Lohocla Research Corporation, a company established in 1983 in Chicago by Dr. Boris Tabakoff, has developed a positive allosteric modulator (PAM) at GABA-A receptors of particular subunit compositions.

Indivior is sponsoring a 5-year National Institute on Alcohol Abuse and Alcoholism (NIAAA) grant (NIAAA PAR 15-154) that was approved for a total of a $6.5 million.



Source: Jacob TC, Moss SJ, Jurd R. GABA(A) receptor trafficking and its role in the dynamic modulation of neuronal inhibition. Nat. Rev. Neurosci. 2008 May;9(5):331-43. DOI: 10.1038/nrn2370

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Q&A SESSION

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