



## RBP-6000 Phase 3 Top Line Results

August 17, 2016

### Indivior Announces Positive Top-line Phase 3 Pivotal Study Results for RBP-6000 Buprenorphine Monthly Depot for the Treatment of Opioid Use Disorder

**This announcement contains inside information.**

**Slough, UK, August 17, 2016** – Indivior PLC (LON: INDV) today announces positive top-line results of the pivotal Phase 3 clinical trial of RBP-6000 buprenorphine monthly depot, an investigational new drug for the treatment of opioid use disorder as part of a complete treatment plan to include counseling and psychosocial support. These results bring the potentially transformational drug one step closer to market, further bolstering the Company's efforts to pioneer life-transforming treatments for people suffering with opioid use disorder. Indivior remains on track to complete the data analysis of this Phase 3 trial as well as the open-label long-term assessment of the safety and tolerability of RBP-6000 by Q1 2017 in line with previous guidance. Subject to satisfactory completion of the analysis and, assuming the U.S. Food and Drug Administration (FDA) review and approval is achieved within the assumed six month Priority Review timeline, it is possible that a marketing authorization could be granted in Q4 2017 per previous guidance.

This development comes at a time when there is intensified focus by the U.S. government and regulators to address the public health epidemic of opioid abuse, addiction and overdose. This was most recently demonstrated by two landmark actions, the Comprehensive Addiction and Recovery Act of 2016 (CARA) legislation and the U.S. Department of Health and Human Services (HHS) final rule, each aimed at increasing access to medication-assisted treatment for addiction.

RBP-6000 is a subcutaneous (SC) long-acting monthly depot injection that delivers a sustained-release formulation of buprenorphine and, if granted marketing authorization (in the U.S.), will provide a new option to help address the unmet treatment needs of patients as they work to regain control of their lives. This new delivery system may benefit multiple types of patients, including those who struggle with the need to take a daily medication and those who face the ongoing risk of relapse due to the chronic, relapsing nature of opioid addiction.

The primary objective of this study was to assess the efficacy of monthly SC injections of RBP-6000 in two dosing regimens containing either 300 mg buprenorphine for six injections, or 300 mg for two injections followed by 100 mg buprenorphine for four injections, compared with placebo over a six-month dosing period in subjects not currently in treatment but seeking medication-assisted treatment for opioid use disorder. In this study, RBP-6000 achieved the primary endpoint of the cumulative distribution function (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 ( $p < 0.0001$  for both dosage regimens vs. placebo). The key secondary endpoint in this study was treatment success defined as any subject with  $\geq 80\%$  of urine samples negative for opioids combined with self-reports negative for illicit opioid use from week 5 through week 24. The secondary endpoint was also achieved for both dosage regimens at  $p < 0.0001$  vs. placebo.

RBP-6000 has previously received Fast Track designation from the FDA. Fast Track designation is granted to facilitate and expedite development and review for drugs that are intended to treat a serious condition and with nonclinical or clinical data that demonstrate the potential to address an unmet medical need. By granting this designation, the FDA agreed that RBP-6000 meets these criteria.

"The treatment of opioid use disorder aims to reduce opioid drug misuse by decreasing cravings and addressing withdrawal symptoms. Treatment involves pharmacological and behavioral therapy, as well as psychosocial support to eventually end illicit drug-taking behavior. Opioid use disorder is an underserved disease and we are pleased to add preliminary clinical evidence that supports the efficacy and safety of RBP-6000 in the treatment of this potentially fatal, chronic disease," said Christian Heidbreder, Ph.D., Chief Scientific Officer of Indivior. "With these compelling Phase 3 data in hand, we are on track to complete the data analysis of this Phase 3 trial as well as the open-label long-term assessment of the safety and tolerability of RBP-6000 by Q1 2017 in line with previous guidance."

"We believe that RBP-6000 can potentially transform the treatment of opioid dependence, if approved, by possibly reducing patients' treatment administration days from 365 a year to 12. RBP-6000 was designed to offer physicians the potential for increased certainty of treatment adherence, and developed with the desire to help mitigate abuse, misuse and diversion of medication," said Shaun Thaxter, Chief Executive Officer of Indivior. "We look forward to working with the FDA to bring this important new therapy to patients living with opioid use disorder."

"The development of RBP-6000 further builds on Indivior's commitment to expand and strengthen our addiction portfolio, most

recently demonstrated with Suboxone® Film which has achieved a 61% share of the U.S. market as of 30 June 2016,” Shaun Thaxter continued. “This market leadership is testament to Indivior’s ability to leverage the insights and experience of opinion leaders, healthcare professionals, patients and other stakeholders in developing innovative medical treatments for opioid use disorder.”

### **RBP-6000 Study Overview**

This was a multicenter, randomized, double-blind, placebo-controlled study, which randomized 489 subjects with moderate or severe opioid use disorder (based on criteria from the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders [DSM–5; American Psychiatric Association, 2013])<sup>1</sup> who were not currently in treatment but seeking medication-assisted treatment for opioid use disorder. Subjects were initially inducted onto SUBOXONE® (buprenorphine/naloxone) sublingual film for 3 days according to the SUBOXONE® sublingual film prescribing information in order to prevent withdrawal from opiates and to ensure lack of allergy to buprenorphine. The subjects then completed a 4- to 11-day SUBOXONE® sublingual film dose adjustment (SUBOXONE® doses ranging from 8 mg to 24 mg). Once subjects met the randomization criteria of no significant opioid craving ( $\leq 20$  mm on the Opioid Craving Visual Analog Scale [VAS]) or withdrawal (a score of  $\leq 12$  on the Clinical Opiate Withdrawal Scale [COWS]) after at least 7 days of SUBOXONE® sublingual film therapy, they were randomized to either 1 of 2 dose regimens of RBP-6000 or placebo of the equivalent volume in 6 SC injections separated by 28 days. Subjects randomized to receive dose regimen #1 of RBP-6000 received 1 injection of 300 mg RBP-6000 on Day 1 and then every 28 ( $\pm 2$ ) days thereafter. Subjects randomized to receive dose regimen #2 of RBP-6000 received 1 injection of 300 mg RBP-6000 on Day 1 and Day 29 ( $\pm 2$  days), which were then followed by 4 injections (once every 28  $\pm 2$  days) of 100 mg of RBP-6000.

RBP-6000 was generally well tolerated in this study. Available safety findings suggest that 2.8% of subjects on RBP-6000 (both dosage regimens combined) experienced a serious treatment-emergent adverse event (TEAE) compared with 5.1% of subjects on placebo. There were no related serious TEAEs across groups. 7.2% of subjects on RBP-6000 (both dosage regimens combined) experienced a severe TEAE compared with 4.0% of subjects on placebo. 4.6% of subjects on RBP-6000 (both dosage regimens combined) discontinued treatment due to TEAEs compared with 2.0% of subjects on placebo.

### **About RBP-6000**

RBP-6000 is an investigational buprenorphine sustained-release formulation using our ATRIGEL® delivery system, which consists of a polymeric solution of a biodegradable poly-(DL-lactide-co-glycolide) co-polymer dissolved in N-methyl pyrrolidone (NMP), a water-miscible biocompatible solvent. After SC injection, NMP diffuses out of the polymer matrix and the polymer precipitates, trapping the drug inside and forming an amorphous solid depot in situ. The depot releases buprenorphine over a one-month period by diffusion as the polymer biodegrades.

### **About Opioid Use Disorder**

According to the DSM–5, opioid use disorder is characterized by signs and symptoms that reflect compulsive, prolonged self-administration of opioid substances that are used for no legitimate medical purpose or, if another medical condition is present that requires opioid treatment, they are used in doses greatly in excess of the amount needed for that medical condition.

In the most recent report from the National Survey on Drug Use and Health (NSDUH, 2014)<sup>2</sup>, 4.3 million Americans engaged in non-medical use of prescription painkillers including opioids in the last month. Approximately 1.9 million Americans met criteria for prescription painkillers use disorder based on their use of prescription painkillers in the past year. In addition, 1.4 million people used prescription painkillers non-medically for the first time in the past year. The same report suggested that 4.8 million people have used heroin at some point in their lives with 212,000 people aged 12 or older using heroin for the first time within the past 12 months. Approximately 435,000 people were regular (past-month) users of heroin.

Perhaps most concerning, deaths from overdose of opioid analgesics (including opioids, methadone and other synthetic narcotics) showed a 4.7-fold increase from 5,528 to 18,893 deaths between 2001 and 2014. Similarly, heroin-related overdose fatalities showed a 5.4-fold increase during this same period, from 1,779 deaths in 2001 to 10,574 in 2014.<sup>3</sup>

The U.S. government recently took landmark actions to address this public health crisis; the Comprehensive Addiction and Recovery Act of 2016 (CARA) was recently signed into law, creating new grant opportunities for prevention, education, law enforcement, treatment options, recovery, and veterans’ programs. Further, it authorizes nurse practitioners and physician assistants, under state law and after 24hrs of training, to prescribe Schedule III, IV and V medications to patients with opioid use disorder. CARA, combined with the U.S. Department of Health and Human Services (HHS)/Substance Abuse and Mental Health Services Administration (SAMHSA)’s final regulation increasing the cap on the number of patients that a qualified physician may treat from 100 to 275, signals a strong federal response to the nation’s opioid epidemic.

### **About Indivior**

Indivior is a global specialty pharmaceutical company with a 20-year legacy of leadership in patient advocacy, health policy and evidence-based best practice models that have revolutionized modern addiction treatment. The name is the fusion of the words individual and endeavour, and the tagline “Focus on you” makes the company’s commitment clear. Indivior is dedicated to transforming addiction from a global human crisis to a recognized and treated chronic disease. Building on its robust, global opioid dependence portfolio featuring SUBOXONE® (buprenorphine and naloxone) Sublingual Film (CIII), SUBOXONE® (buprenorphine and naloxone) Sublingual Tablet, and SUBUTEX® (buprenorphine) Sublingual Tablet, Indivior has a strong pipeline of product candidates designed to both expand on its heritage in this category and address other chronic diseases of addiction – including

opiate overdose, alcohol use disorders and cocaine intoxication. It also is pursuing novel product candidates in related mental health disorders such as schizophrenia. Headquartered in the United States in Richmond, VA, Indivior employs more than 900 individuals globally and its portfolio is available in over 40 countries worldwide. Visit [www.Indivior.com](http://www.Indivior.com) to learn more.

## **IMPORTANT SAFETY INFORMATION**

### **Indication**

SUBOXONE® (buprenorphine and naloxone) Sublingual Film (CIII) is a prescription medicine indicated for treatment of opioid dependence and should be used as part of a complete treatment plan to include counseling and psychosocial support.

**Treatment should be initiated under the direction of physicians qualified under the Drug Addiction Treatment Act.**

### **Important Safety Information**

Do not take SUBOXONE Film if you are allergic to buprenorphine or naloxone as serious negative effects, including anaphylactic shock, have been reported.

SUBOXONE Film can be abused in a manner similar to other opioids, legal or illicit.

SUBOXONE Film contains buprenorphine, an opioid that can cause physical dependence with chronic use. Physical dependence is not the same as addiction. Your doctor can tell you more about the difference between physical dependence and drug addiction. Do not stop taking SUBOXONE Film suddenly without talking to your doctor. You could become sick with uncomfortable withdrawal symptoms because your body has become used to this medicine.

SUBOXONE Film can cause serious life-threatening breathing problems, overdose and death, particularly when taken by the intravenous (IV) route in combination with benzodiazepines or other medications that act on the nervous system (ie, sedatives, tranquilizers, or alcohol). It is extremely dangerous to take nonprescribed benzodiazepines or other medications that act on the nervous system while taking SUBOXONE Film.

You should not drink alcohol while taking SUBOXONE Film, as this can lead to loss of consciousness or even death.

Death has been reported in those who are not opioid dependent.

Your doctor may monitor liver function before and during treatment.

SUBOXONE Film is not recommended in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. However, SUBOXONE Film may be used with caution for maintenance treatment in patients with moderate hepatic impairment who have initiated treatment on a buprenorphine product without naloxone.

Keep SUBOXONE Film out of the sight and reach of children. Accidental or deliberate ingestion of SUBOXONE Film by a child can cause severe breathing problems and death.

Do not take SUBOXONE Film before the effects of other opioids (eg, heroin, hydrocodone, methadone, morphine, oxycodone) have subsided as you may experience withdrawal symptoms.

Injecting the SUBOXONE Film product may cause serious withdrawal symptoms such as pain, cramps, vomiting, diarrhea, anxiety, sleep problems, and cravings.

Before taking SUBOXONE Film, tell your doctor if you are pregnant or plan to become pregnant. If you are pregnant or become pregnant while taking SUBOXONE Film, alert your doctor immediately and you should report it using the contact information provided below.\*

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy, whether that use is medically-authorized or illicit. Unlike opioid withdrawal syndrome in adults, NOWS may be life-threatening if not recognized and treated in the neonate. Healthcare professionals should observe newborns for signs of NOWS and manage accordingly.

Before taking SUBOXONE Film, talk to your doctor if you are breastfeeding or plan to breastfeed your baby. The active ingredients of SUBOXONE Film can pass into your breast milk. You and your doctor should consider the development and health benefits of breastfeeding along with your clinical need for SUBOXONE Film and should also consider any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

Do not drive, operate heavy machinery, or perform any other dangerous activities until you know how SUBOXONE Film affects you. Buprenorphine in SUBOXONE Film can cause drowsiness and slow reaction times during dose-adjustment periods.

Common side effects of SUBOXONE Film include nausea, vomiting, drug withdrawal syndrome, headache, sweating, numb mouth, constipation, painful tongue, redness of the mouth, intoxication (feeling lightheaded or drunk), disturbance in attention, irregular heartbeat, decrease in sleep, blurred vision, back pain, fainting, dizziness, and sleepiness.

This is not a complete list of potential adverse events associated with SUBOXONE Film. Please see full Prescribing Information for a complete list.

\*To report negative side effects associated with taking SUBOXONE Film, please call 1-877-782-6966. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call 1-800-FDA-1088.

For more information about SUBOXONE Film, SUBOXONE® (buprenorphine and naloxone) Sublingual Tablets (CIII), or SUBUTEX® (buprenorphine) Sublingual Tablets (CIII), please see the respective full Prescribing Information and Medication Guide at [www.suboxoneREMS.com](http://www.suboxoneREMS.com).

### **Forward-Looking Statements**

This press release 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 statements regarding our intentions, beliefs, projections, outlook, analyses or current expectations.

Various factors may cause differences between Indivior’s expectations and actual results, including: factors affecting sales of Indivior products 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 patent litigation relating to 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 press release speak only as of the date of this press release. 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 press release.

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### **REFERENCES**

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<sup>2</sup> Center for Behavioral Health Statistics and Quality (2015). Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health (HHS Publication No. SMA 15-4927, NSDUH Series H-50). Retrieved from <http://www.samhsa.gov/data/>

<sup>3</sup> National Institute on Drug Abuse. Overdose death rates: national overdose deaths from select prescription and illicit drugs.

Updated December 2015. <http://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates>