



Q2-2020 R&D UPDATE

TREATMENT OF OPIOID USE DISORDER (OUD)

SUBLOCADE® (BUPRENORPHINE EXTENDED-RELEASE) INJECTION (US)

- Post Marketing Commitments: all approved by the FDA and considered closed.
- Post Marketing Requirement studies: all completed except for one clinical study ongoing and delayed due to the COVID-19 pandemic.
- Lifecycle Evidence Generation & Optimization (LEGO) Studies: These studies are dedicated to (1) understand the root causes of buprenorphine abuse, diversion and misuse; (2) assess how to induce SUBLOCADE treatment in the emergency department environment, and (3) investigate how high plasma concentrations of buprenorphine, consistent with those delivered by the two approved dosing regimens of SUBLOCADE, may reduce the effects of respiratory depression produced by fentanyl. All studies are on track.
- RECOVER™ (REmission from Chronic Opioid use: Studying enVironmental and socioEconomic factors on Recovery) study: 1-year outcomes were published in the Journal of Addiction Medicine (see publication list). The two-year outcomes were presented at the CPDD meeting (see publication list); a peer-reviewed publication is also in preparation. The scope and duration of the RECOVER™ outcomes are being pursued through a partnership with the Virginia Polytechnic Institute and State University (Virginia Tech).

SUBUTEX® PROLONGED-RELEASE SOLUTION FOR INJECTION (ex-US):

- Regulatory approvals: Israel, Sweden, and Finland.
- Under review by local Regulatory Authorities: Denmark, Germany, UK, Italy, France (including Belgium; Czech Republic; Latvia; Luxembourg), Norway and New Zealand.

SUBOXONE® (BUPRENORPHINE / NALOXONE) FILM:

- Regulatory Approvals: Israel, Europe (27 EU member states + United Kingdom, Norway, Iceland, Liechtenstein) and Canada.
- Under review by local Regulatory Authorities: New Zealand and Kuwait.
- Pending regulatory dossier submissions: Kingdom of Saudi Arabia, United Arab Emirates, and Qatar.

TREATMENT OF SCHIZOPHRENIA

PERSERIS™ ONCE MONTHLY RISPERIDONE FOR EXTENDED-RELEASE INJECTABLE SUSPENSION:

- US: Post Marketing Commitment studies on track.
- Canada: Partnership with HLS Therapeutics. The NDS was submitted to Health Canada on November 7, 2019 and was accepted into formal review on January 23, 2020. The Notice of Compliance (NOC) date is November 16, 2020.

EARLY STAGE ASSET DEVELOPMENT (ESAD)

- **INDV-1000 (Selective Orexin 1 [OX1] receptor antagonist):**
 - On September 26, 2019 the National Institutes of Health (NIH) granted Indivior's application entitled "*Clinical Evaluation of C4X3256, a Non-Opioid, Highly-Selective Orexin-1 Receptor Antagonist for the Treatment of Opioid Use Disorder*" pursuant to Funding Opportunity Announcement RFA-DA-19-002 dedicated to the development of medications to prevent and treat opioid use disorder and overdose.

- Our development plans were presented at the first HEAL Investigator Meeting in Bethesda on January 16-17, 2020 (see publication list).
- The Single Ascending Dose (SAD) study was planned to start in April 2020 but was delayed by approximately 3 months due to the COVID-19 pandemic. The first dosing in Man is currently scheduled for August 2020.
- Nonclinical pivotal toxicokinetics and embryofetal studies have been completed.
- **INDV-2000 (GABA_B positive allosteric modulator):**
 - New lead identification and optimization program is ongoing in partnership with Addex Therapeutics.
- **INDV-3000 (Selective dopamine [DA] D3 receptor antagonist):**
 - Preparation of IND-related activities.

PEER-REVIEWED PUBLICATIONS (2020)

1. Ling W et al. (2020) Effects of Monthly Buprenorphine Extended-Release Injections on Patient-Centered Outcomes: A Long-Term Study. *J Subst Abuse Treat.* 110:1-8. <https://doi.org/10.1016/j.jsat.2019.11.004>
2. Ling W et al. (2020) Recovery From Opioid Use Disorder (OUD) After Monthly Long-acting Buprenorphine Treatment: 12-Month Longitudinal Outcomes From RECOVER, an Observational Study. *J Addict Med*, Epub 13 March 2020. <https://doi.org/10.1097/ADM.0000000000000647>
3. Andorn A et al. (2020) Treating opioid use disorder with a monthly subcutaneous buprenorphine depot injection: 12-month safety, tolerability, and efficacy analysis. *J Clin Psychopharmacol*, May/Jun 2020;40(3):231-239. <https://doi.org/10.1097/JCP.0000000000001195>
4. Alho H et al. (2020) Opioid-related deaths in Europe: Strategies for a comprehensive approach to address a major public health concern. *Int J of Drug Pol*, 76:1-10. <https://doi.org/10.1016/j.drugpo.2019.102616>
5. Reimer J et al. (2020) Impact of Buprenorphine Dosage on the Occurrence of Relapses in Patients with Opioid Dependence. *Eur Addict Res*, 26:77–84. <https://doi.org/10.1159/000505294>
6. Larance B et al. (2020). An open-label, multicentre, single-arm trial of monthly injections of depot buprenorphine in people with opioid dependence: Protocol for the CoLAB study. *BMJ Open*, In press

CONFERENCE ABSTRACTS (2020)

1. Heidbreder C et al. (2020) Clinical Evaluation of C4X3256, a Non-Opioid, Highly selective Orexin 1 Receptor Antagonist for the Treatment of Opioid Use Disorder. NIH HEAL Initiative Investigator’s Meeting, Jan 16-17, 2020, Bethesda, MD.
2. Howgate EM et al. (2020) Quantitative Prediction of the Systemic Exposure to RBP-6000 (Buprenorphine Extended-Release) Following Co-administration of Strong CYP3A4 Inhibitors/Inducers. American Society for Clinical Pharmacology & Therapeutics (ASCPT), Mar 17-21, Houston, TX. *Clinical Pharmacology and Therapeutics*, 107 (Suppl 1): S99.
3. Shinde S et al. (2020) One-Year Hepatic Safety with Buprenorphine Extended-Release for Moderate-to-Severe OUD. Proceedings of the 51st Annual Conference of the American Society of Addiction Medicine (ASAM). April 3-4, 2020.
4. Boyett B et al. (2020) Outcomes After Discontinuation of Buprenorphine Extended release: 18 Months Later. Proceedings of the 51st Annual Conference of the American Society of Addiction Medicine (ASAM). April 3-4, 2020.

5. Chilcoat H, DeVeough-Geiss A (2020) Trends in buprenorphine abuse, misuse, and diversion: Results from three US national data sources. The College on Problems of Drug Dependence (CPDD). June 22 – 24, 2020.
6. Ling W et al. (2020) Characterizing Patient Outcomes After Treatment: Results of the RECOVER 24-Month Observational Study. The College on Problems of Drug Dependence (CPDD). June 22-24, 2020.
7. Gryczynski J et al. (2020) Use of non-prescribed buprenorphine during incarceration: Perspectives of former inmates. The College on Problems of Drug Dependence (CPDD). June 22-24, 2020.
8. Sharma A et al. (2020) Correlates of non-prescribed buprenorphine use during incarceration and in community settings. The College on Problems of Drug Dependence (CPDD). June 22-24, 2020.
9. Chilcoat H, DeVeough-Geiss A (2020) Substance Use and Behavioral Problems Among Methamphetamine Users. The College on Problems of Drug Dependence (CPDD). June 22-24, 2020.
10. Monico L et al. (2020) Exploring non-prescribed use of buprenorphine in the criminal justice system through qualitative interviews among individuals recently released from incarceration. The College on Problems of Drug Dependence (CPDD). June 22-24, 2020.
11. McDonald MJ et al. (2020) Buprenorphine Misuse Among Drug Users in Rural Kentucky. The College on Problems of Drug Dependence (CPDD). June 22-24, 2020.