



# Q3-2020 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 scheduled to start Q4-2020.
- 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, 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, Kuwait, Qatar and United Arab Emirates.
- Pending regulatory dossier submissions: Kingdom of Saudi Arabia.

## 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-2000 (Selective Orexin 1 [OX1] receptor antagonist):**
  - The Single Ascending Dose (SAD) study is ongoing. The first subject was dosed on July 28, 2020.
  - Nonclinical pivotal toxicokinetics and embryofetal studies have been completed.
- **INDV-1000 (GABA<sub>B</sub> 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, Nadipelli VR, Solem CT, Ronquest NA, Yeh YC, Learned SM, Mehra V, Heidbreder C. (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, Nadipelli VR, Aldridge A, Ronquest N Solem C, Chilcoat H, Albright V, Johnson C, Learned SM, Mehra V, Heidbreder C (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, Haight B, Shinde S, Fudala P, Zhao S, Heidbreder C, Learned S, Fox NL, Nadipelli VR, Hassman D, Rutrick D (2020) Treating opioid use disorder with a monthly subcutaneous buprenorphine depot injection: 12-month safety, tolerability, and efficacy analysis. *J Clin Psychopharmacol*, May/June 2020;40(3):231-239. <https://doi.org/10.1097/JCP.0000000000001195>
4. Alho H, Dematteis M, Lembo D, Maremmanni I, Roncero C, Somaini L (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, Vogelmann T, Trümper D, Scherbaum N (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, Byrne M, Lintzeris N, Nielsen S, Grebely J, Degenhardt L, Shahbazi J, Shanahan M, Lancaster K, Dore G, Ali R, Farrell M; CoLAB study team (2020). Open-label, multicentre, single-arm trial of monthly injections of depot buprenorphine in people with opioid dependence: protocol for the CoLAB study. *BMJ Open*, 10(7): e034389. <https://doi.org/10.1136/bmjopen-2019-034389>
7. Algera MH, Olofsen E, Moss L, Dobbins RL, Niesters M, van Velzen M, Groeneveld GJ, Heuberger J, Laffont CM, Dahan A (2020) Tolerance to Opioid-Induced Respiratory Depression in Chronic High-Dose Opioid Users: A Model-Based Comparison with Opioid-Naïve Individuals. *Clin Pharmacol Ther.* 2020 Aug 31. <https://doi.org/10.1002/cpt.2027>
8. Le Moigne A, Fava M, Csernansky J, Newcomer C, Graham J (2020). Reanalysis of a phase 3 trial of a monthly extended-release risperidone injection for the treatment of acute schizophrenia. *J Clin Psychopharmacol*, In Press.
9. Kranzler HR, Lynch K, Crist R, Hartwel E, Le Moigne A, Laffont CM, Andorn AC (2020) Moderation by a Delta-Opioid Receptor Gene Polymorphism of the Therapeutic Effect of Extended-Release Buprenorphine in Opioid Use Disorder. *Int J Neuropsychopharm*, In Press.
10. Jones AK, Ngaimisi E, Gopalakrishnan M, Young MA, Laffont CM (2020) Population Pharmacokinetics of a Monthly Buprenorphine Depot Injection for the Treatment of Opioid Use Disorder: A Combined Analysis of Phase 2 and Phase 3 Trials. *Clin Pharmacokin*, 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 51<sup>st</sup> 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 51<sup>st</sup> Annual Conference of the American Society of Addiction Medicine (ASAM). April 3-4, 2020.
5. Chilcoat H, DeVeaugh-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, DeVeaugh-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.
12. Casale N, Mullen W, Heidbreder C (2020) Variations in DEA Waivered Provider Utilization of Buprenorphine for Opioid Use Disorder (OUD). Academy of Managed Care Pharmacy (AMCP) Nexus 2020, October 19-23, 2020.
13. Farah M, Fox NL, Laffont CM, Zhao S, Gray F, Andorn A, Learned S, Heidbreder C (2020) Risk-Adjusted Abstinence Rates are Higher with Greater Buprenorphine Plasma Exposure Among Patients Who Inject Opioids. 14e Congrès International d'Addictologie de l'ALBATROS, October 27-29, 2020.
14. Algera MH, Olofsen E, Moss L, Dobbins RL, Niesters M, van Velzen M, Groeneveld GJ, Heuberger J, Laffont CM, Dahan A (2020) Modelling of Tolerance to Opioid-induced Respiratory Depression in Chronic High-dose Opioid Users versus Opioid-naïve Individuals. Eleventh American Conference on Pharmacometrics (ACoP11), November 9-13, 2020.
15. Boyett B, Nadipelli VR, Solem CT, Chilcoat H, Ling W (2020) Outcomes after Discontinuation of Buprenorphine Extended-Release (BUP-XR): 18 Months Later. ISAM – CSAM 2020 Scientific Conference and Annual Meeting, November 12-14, 2020.
16. Mullen W, Casale N, Gadbois B, Heidbreder C (2020) Past-Year Distribution Patterns of Buprenorphine Extended Release (BUP-XR) Within Organized Health Systems (OHS). 129th AMSUS Annual Meeting, The Society of Federal Health Professionals, December 6-10, 2020.