



Q3-2021 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.
- US Label updates:
 - Buprenorphine-Fentanyl interaction study: Approved by the FDA May 17, 2021.
 - Transition to SUBLOCADE from transmucosal (TM) buprenorphine: Approved by the FDA May 11, 2021.
 - N-methyl-pyrrolidone (NMP) safety: Under review by the FDA.
- Post Marketing Requirement study: Rapid induction of OUD treatment with SUBLOCADE and characterization of patients who may benefit from the highest maintenance dose (300 mg) of SUBLOCADE. First site activation started October 7, 2021.
- RECOVER Long-Term study: First wave of assessments completed. The average follow-up time for participants was 4.2 years since enrolment in the RECOVER study. The majority of participants reported abstinence from opioids since the last RECOVER study assessment (55%) and in the past 30 days (69%). Participants reported low levels of depression and psychological distress.

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

- Regulatory approvals: Canada (November 21, 2018), Australia (July 17, 2019), Israel (February 13, 2020), Sweden (April 15, 2020), Finland (July 10, 2020), New Zealand (November 3, 2020), Denmark (December 21, 2020), Germany (April 29, 2021), Italy (May 17, 2021), and Norway (August 3, 2021).
- Under review by local Regulatory Authorities: UK.

SUBOXONE® (BUPRENORPHINE / NALOXONE) FILM:

- Regulatory Approvals: Israel (April 7, 2020), Europe (27 EU member states + United Kingdom, Norway, Iceland, Liechtenstein - July 3, 2020), Canada (July 17, 2020), Qatar (October 3, 2021).
- Under review by local Regulatory Authorities: New Zealand, Kuwait, and United Arab Emirates.
- Submission: Dossier submitted to Kingdom of Saudi Arabia's Regulatory Agency on September 14, 2021.

TREATMENT OF SCHIZOPHRENIA

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

- US: PMC 3451-2 (fill-weight change to support delivered mass for 90 mg strength): Approved by the FDA on March 31, 2021; PMC 3451-1 (clinical efficacy & safety of PERSERIS® 180 mg (2 x 90 mg) and alternate injection site): Submission February 12, 2021 with PDUFA date of December 12, 2021.
- Canada: Regulatory approval on November 19, 2020 (partnership with HLS Therapeutics).

EARLY STAGE ASSET DEVELOPMENT (ESAD)

- **INDV-2000 (Selective Orexin 1 [OX1] receptor antagonist):**
 - Phase 1 Single Ascending Dose (SAD) study has completed and shows encouraging safety and pharmacokinetics in healthy volunteers. The final Clinical Study Report is expected by the end of Q4-2021.
 - FDA clinical hold letter received September 1, 2021, asking Indivior to conduct an additional 28-day repeat-dose toxicology study. FDA's decision is based on non-clinical findings from a separate (not sponsored by Indivior) development program. Non-clinical study planning underway. MAD study in planning phase and pending outcome of non-clinical toxicology study.
- **INDV-1000 (GABA_B positive allosteric modulator):**
 - New lead identification and optimization program is ongoing in partnership with Addex Therapeutics.
 - Two lead molecules and potential backups have been chosen for the late lead optimization phase.

▪ **AEF0117 (CB1 synthetic Signalling Specific Inhibitor):**

- Strategic collaboration with Aelis Farma announced June 8, 2021.
- First Individior-Aelis Joint Steering Committee (JSC) held on July 19, 2021.
- Phase 2B protocol finalized; agreement on nonclinical studies required prior to Phase 2B and prior to Phase 3; agreement on CMC strategy.

PEER-REVIEWED PUBLICATIONS (2021)

1. Le Moigne A et al. (2021) Reanalysis of a phase 3 trial of a monthly extended-release risperidone injection for the treatment of acute schizophrenia. *J Clin Psychopharmacol*, 41(1): 76-77. <https://doi.org/10.1097/JCP.0000000000001319>
2. Kranzler HR et al. (2021) Moderation by a Delta-Opioid Receptor Gene Polymorphism of the Therapeutic Effect of Extended-Release Buprenorphine in Opioid Use Disorder. *Int. J. Neuropsychopharm.*, 24(2): 89-96. <https://doi.org/10.1093/ijnp/pyaa069>
3. Monico LB et al. (2021) Exploring non-prescribed use of buprenorphine in the criminal justice system through qualitative interviews among individuals recently released from incarceration. *J. Subst. Abuse Treat.*, 123:108267. <https://doi.org/10.1016/j.jsat.2020.108267>
4. Allsop G et al. (2021) Process Development Towards a Pro-Drug of R-Baclofen. *Org. Process Res. Dev.*, 25(1): 136–147. <https://pubs.acs.org/doi/10.1021/acs.oprd.0c00491>
5. Kharidia J et al. (2021) Quantitative Prediction of the Systemic Exposure to Buprenorphine Extended-Release Monthly Injection Following Co-administration of Strong CYP3A4 Inhibitors/Inducers. *Clin. Pharmacol. Drug Dev.*, Epub ahead of print <http://doi.org/10.1002/cpdd.934>
6. Jones AK et al. (2021) Population Pharmacokinetics of a Monthly Buprenorphine Depot Injection for the Treatment of Opioid Use Disorder: A Combined Analysis of Phase II and Phase III Trials. *Clin Pharmacokinetics*, 60(4):527-540. <http://doi.org/10.1007/s40262-020-00957-0>
7. Algera MH et al. (2021) Tolerance to opioid-induced respiratory depression in chronic high-dose opioid users: a model-based comparison with opioid-naïve individuals. *Clin. Pharmacol. Ther.* 109(3):637-645. <https://doi.org/10.1002/cpt.2027>
8. Wiest K et al. (2020) RBP-6000: a rationally designed prolonged-release buprenorphine formulation. *Heroin Addiction and Related Clinical Problems (HARCP)*. Published Ahead of Print, January 18, 2021.
9. Lintzeris N et al. (2021) Strategies for transfer between buprenorphine and methadone for medication-assisted treatment for opioid use disorders and associated outcomes: a systematic review. *J Addict Med*, e-published https://journals.lww.com/journaladdictionmedicine/Abstract/9000/Strategies_for_Transfer_From_Methadone_to.99047.aspx
10. Hill D et al. (2021) Clinical Case Conference: Strategies for Transferring from Methadone to Buprenorphine. *J Addict Med*, Epub ahead of print: *J Addict Med*. Apr 14. <http://doi.org/10.1097/ADM.0000000000000854>
11. Gryczynski J et al. (2021) Use of non-prescribed buprenorphine in the criminal justice system: Perspectives of individuals recently released from incarceration. *J. Subst. Abuse Treat.*, e-published [https://www.journalofsubstanceabusetreatment.com/article/S0740-5472\(21\)00075-1/fulltext](https://www.journalofsubstanceabusetreatment.com/article/S0740-5472(21)00075-1/fulltext)
12. Le Moigne A et al. (2021) PANSS Individual Item and Marder Dimension Analyses from a Pivotal Trial of RBP-7000 (Monthly Extended-Release Risperidone) In Schizophrenic Patients. *J. Clin. Psychiatry*, Manuscript accepted July 7.
13. Moss LM et al. (2021) Effect of Sustained High Buprenorphine Plasma Concentrations on Fentanyl-Induced Respiratory Depression: A Placebo-Controlled Crossover Study. *PlosOne*, Manuscript accepted August 16, 2021.
14. Boyett B et al. (2021) Assessment of Craving in opioid Use Disorder: Psychometric Evaluation and Predictive Validity of the Opioid Craving VAS. *Drug & Alcohol Dependence*, Manuscript accepted August 30, 2021.

CONFERENCE ABSTRACTS (2021)

1. Andrada E et al. (2021) Depot buprenorphine: patient characteristics and treatment retention in a general practice setting in Victoria, Australia. *International Medicine in Addiction (IMIA)*, February 25-28, 2021.

2. Halpern R et al. (2021) Characteristics, Health Care Utilization, and Treatment Patterns Among Patients Initiating Therapy on SUBLOCADE (BUP-XR) for Opioid Dependence: A Retrospective Claims Data Analysis. Academy of Managed Care Pharmacy (AMCP), April 13-16, 2021.
3. Mullen W et al. (2021) Past-Year Distribution Patterns of BUP-XR Within Organized Health Systems, Academy of Managed Care Pharmacy (AMCP), April 13-16, 2021.
4. Mullen W et al. (2021) Access to Medications for Opioid Use Disorder Within Integrated Healthcare Systems: Barriers and Potential Solutions. Annual Virtual Meeting of the College of Psychiatric and Neurologic Pharmacists (CPNP), April 19-23, 2021.
5. Abdel-Sattar M et al. (2021) Impact of COVID-19 on OUD Management and MOUD Access in the US. Annual Virtual Meeting of the American Society of Addiction Medicine (ASAM), April 22-24, 2021.
6. Gryczynski J et al. (2021) Use of non-prescribed buprenorphine during incarceration: Perspectives of former inmates, National Commission on Correctional Health Care (NCCHC) Spring Conference, April 24-27, 2021.
7. Mullen W et al. (2021) Variations in DEA Waivered Provider Utilization of Buprenorphine for the Treatment Opioid Use Disorder (OUD) National Commission on Correctional Health Care (NCCHC) Spring Conference, April 24-27, 2021.
8. Walling D et al. (2021) RBP-7000 Monthly Risperidone Injection (180 mg) Following Switch from Daily Oral Risperidone (6 mg) in Stable Schizophrenic Patients, American Psychiatric Association, (APA) May 1-3.
9. Walling D et al. (2021) Alternate Injection Site (Back of Upper Arm) for Monthly Long-acting Risperidone Injections of RBP-7000, American Psychiatric Association, (APA) May 1-3.
10. Wiest K et al. (2021) Initiating Monthly Buprenorphine Injection After Single Dose of Sublingual Buprenorphine. 83rd Annual Scientific Virtual Meeting of the College on Problems of Drug Dependence (CPDD), June 21-24, 2021.
11. Wiest K et al. (2021) Examining the benefit of RBP-6000 300mg versus 100mg maintenance dose in opioid injectors. 83rd Annual Scientific Virtual Meeting of the College on Problems of Drug Dependence (CPDD), June 21-24, 2021.
12. Farrell M et al. (2021) An open-label, multicenter, single-arm trial of monthly injections of extended-release buprenorphine in people with opioid use disorder: the CoLAB (Community Long-Acting Buprenorphine) study. 83rd Annual Scientific Virtual Meeting of the College on Problems of Drug Dependence (CPDD), June 21-24, 2021.
13. Black JC et al. (2021) Mortality of Buprenorphine and Methadone in the United States 2010-2017. 83rd Annual Scientific Virtual Meeting of the College on Problems of Drug Dependence (CPDD), June 21-24, 2021.
14. Keith DR et al. (2021). Struggling with recovery from opioids: Who is at risk during COVID-19? 83rd Annual Scientific Virtual Meeting of the College on Problems of Drug Dependence (CPDD), June 21-24, 2021.
15. Abdel-Sattar M et al. (2021) Impact of COVID-19 on OUD Management and MOUD Access in the US, NCCHC (Annual Correctional Mental Health Care Conference), July 20-21, 2021.
16. Sreetharan A, Johnston L (2021) Geographic distribution and community pharmacy involvement in SUBLOCADE® (long-acting buprenorphine injection) uptake in the first 6 months after launch, PSA (Pharm Society of Australia), July 30-August 1, 2021.
17. Mullen W et al. (2021) Access to Medications for Opioid Use Disorder Within Integrated Healthcare Systems: Barriers and Potential Solutions. American Psychiatric Nurses Association (APNA), October 13-16, 2021.
18. Mariani J et al. (2021) Rapid Initiation of Extended-Release Buprenorphine in Patients using Fentanyl and Fentanyl Analogs. Canadian Society of Addiction Medicine (CSAM), October 21-23, 2021.
19. Wiest et al. (2021) Examining the benefit of RBP-6000 300mg versus 100mg maintenance dose in opioid injectors, CSAM, October 21-23, 2021.
20. Keith et al. (2021) Struggling with recovery from opioids: Who is at risk during COVID-19? CSAM, October 21-23, 2021.
21. Wiest et al. (2021) Initiating Monthly Buprenorphine Injection After Single Dose of Sublingual Buprenorphine, CSAM, October 21-23, 2021.
22. Lee et al. (2021) Real-World Evidence for the Management of Opioid Use Disorder (OUD) During COVID-19 pandemic for patients receiving Opioid Agonist Treatment (OAT), CSAM, October 21-23, 2021.
23. Mullen W et al. (2021) Factors impacting MOUD treatment decisions in criminal justice-involved populations. National Conference on Correctional Health Care (NCCHC) October 30-November 3, 2021.

24. Boyett et al. (2021) Assessment of a single-item Opioid Craving Visual Analog Scale (OC-VAS) in patients with opioid use disorder, APSAD, Hobart, Australia, November 7-10, 2021.
25. Olofsen E et al. (2021) Modelling Buprenorphine Effect on Fentanyl-induced Respiratory Depression in Opioid-naïve and Opioid-tolerant Subjects. ACoP (Amer Conf Pharmacometrics), November 8-12, 2021.
26. Mariani et al. (2021) Rapid Initiation of Extended-Release Buprenorphine in Patients Using Fentanyl and Fentanyl Analogs, Albatros, Paris, France, December 7-9, 2021.
27. Wiest et al. (2021) Examining efficacy and safety of extended-release buprenorphine in subgroups of subjects with moderate to severe opioid use disorder, Albatros, Paris, France, December 7-9, 2021.