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Chief Scientific Officer

Chief Scientific Officer Update for 2021

In 2021, our Research & Development (R&D) organization supported SUBLOCADE® for the treatment of opioid use disorder (OUD) through a broad range of lifecycle management studies. For example, a new US label update was approved by the FDA based on the outcome of an open-label, cross-over study showing that treatment-relevant plasma concentrations of buprenorphine significantly decreased respiratory depression and resultant apnea (cessation of breathing) induced by escalating doses of fentanyl. We further pursued our collaboration with Virginia Polytechnic Institute and State University to extend our Remission from Chronic Opioid Use-Studying Environmental and SocioEconomic Factors on Recovery (RECOVER® long-term study) to provide a multidimensional (e.g., substance use, psychosocial and physiological outcomes, temporal reward preference) understanding of recovery from OUD at an average of 4.2 years post-participation in SUBLOCADE® pivotal Phase 3 clinical trial. A pilot proof-of-concept study supported by our Externally Sponsored Studies (ESS) Program also showed that SUBLOCADE® treatment was acceptable to most criminal justice-involved adult participants with OUD, making it a feasible option in the setting of a large jail opioid treatment program.¹ Another pilot study evaluating the effectiveness of SUBLOCADE® in Veterans Health Administrations (VHA) facilities for complex treatment-resistant patients with high mortality risk showed that retention with SUBLOCADE® treatment was associated with a reduction in emergency department (ED) visits, days of hospitalization, non-prescribed opioid use, and homelessness.²

Regulatory approval of SUBLOCADE® outside of the US has now been granted in 10 countries including Canada, Australia, New Zealand, Israel, Sweden, Finland, Denmark, Norway, Germany, and Italy. In Canada, Alberta's government announced that it is the first province to fully cover the cost of SUBLOCADE®.³ In Australia, an open-label real-world community-based services study⁴ led by researchers at the National Drug

Imagining a better future for patients

According to the United Nations,¹ approximately 275 million people globally have used drugs in the past year. The burden of disease caused by drug use continues to increase. In 2019, 18 million years of healthy life were lost due to substance use disorder (SUD), and opioid use disorder (OUD) accounted for 70 percent of the total.¹ Unfortunately, the COVID-19 pandemic has intensified substance misuse: the decrease in health services, limited access to medical care and increased access to highly potent synthetic opioids such as fentanyl and illicit fentanyl analogs has been complemented by an increased supply of methamphetamine, resulting in more than 100,000 drug overdose deaths in the United States.¹

The unprecedented magnitude and dynamic nature of the global SUD crisis worsened by the COVID-19 pandemic requires evidence that comprehensive treatment strategies lead to better outcomes that ultimately offset medical costs associated with SUD, and costs of incarceration, shelter, and welfare when these burdensome conditions are untreated. In 2021, our science was disseminated through 15 peer-reviewed publications and 37 conference presentations around the globe to further characterize the process of recovery, identify factors that promote or hinder treatment success, and develop new treatment strategies for SUD.

¹ United Nations World Drug Report 2021

¹ Lee JD et al. (2021) Comparison of treatment retention of adults with opioid addiction managed with extended-release buprenorphine vs daily sublingual buprenorphine-naloxone at time of release from jail. *JAMA Netw Open*, 4(9):e2123032.

<https://doi.org/10.1001/jamanetworkopen.2021.23032>

² Cotton AJ et al. (2021) Extended-release buprenorphine outcomes among treatment resistant veterans, *Am J Drug Alcohol Abuse*, 1-4, <https://doi.org/10.1080/00952990.2021.1992773>

³ <https://www.alberta.ca/release.cfm?xID=80578125DD79B-F2C1-83AF-C359561FDF962FFE>

⁴ Farrell M et al. (2022) Outcomes of a single-arm implementation trial of extended-release subcutaneous buprenorphine depot injections in people with opioid dependence. *Int J Drug Policy*, 100: 103492. <https://doi.org/10.1016/j.drugpo.2021.103492>

and Alcohol Research Centre (NDARC) showed that SUBLOCADE® treatment led to declines in heroin use, non-prescribed opioid use, and injecting drug use. Improvements in quality of life, participation in employment, and treatment satisfaction measures were also observed.

We geographically expanded our SUBOXONE® film franchise by securing regulatory approvals in Canada, Israel, all EU Member States (+ UK, Iceland, Norway, and Liechtenstein), New Zealand, and Qatar. Regulatory review has been completed in United Arab Emirates, and is ongoing in Kuwait, and the Kingdom of Saudi Arabia.

The United Nations recently estimated that roughly 200 million people had used cannabis in 2019, which represents 4% of the global population.¹ The number of cannabis users globally has increased by nearly 18% over the past decade.¹ In the US alone, there were nearly 50 million past year cannabis users among people aged 12 or older in 2020.⁵ Numerous studies have shown that there is a short- and long-term cerebral toxicity of cannabis, marked mainly by cognitive, addictive and psychotomimetic effects linked to the duration, frequency, dose, and age at onset of cannabis use.¹ We are, therefore, eager to expand our pipeline toward Cannabis Use Disorder (CUD) with the announcement of a strategic collaboration with Aelis Farma, a private biotechnology company based in Bordeaux, France. The collaboration includes an exclusive option and license agreement for the global rights to AEF0117, Aelis' first-in-class synthetic Signaling Specific inhibitor (SSi) engineered to inhibit the cannabinoid type 1 (CB1) receptor (CB1-SSi). In clinical Phase 1 and Phase 2A studies, AEF0117 showed promising safety, tolerability, and efficacy signals in subjects with CUD. A Phase 2B proof of concept study protocol that will be coordinated by Prof. Frances Levin at Columbia University, is planned to start at the end of Q1-2022.

With the support of an NIH grant entitled "*Clinical Evaluation of C4X3256, a Non-Opioid, Highly-Selective Orexin-1 Receptor Antagonist for the Treatment of Opioid Use Disorder*" we completed our Phase 1 INDV-2000-101 single ascending dose (SAD) study and pursued drug substance and drug product development work. Finally, our collaboration with Addex Therapeutics for the lead optimization of INDV-1000 (GABA-B positive allosteric modulator (PAM) for Alcohol Use Disorder (AUD) led to major achievements with the ongoing characterization of two lead molecules.

⁵ Substance Abuse and Mental Health Services Administration. (2021). Key substance use and mental health indicators in the United States: Results from the 2020 National Survey on Drug Use and Health (HHS Publication No. PEP21-07-01-003, NSDUH Series H-56). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration.

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. Manuscript accepted July 7, published *J. Clin. Psychiatry* 2021; 82(5):21m13906. <https://www.psychiatrist.com/read-pdf/37024/>
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. Pre-proofs: <https://www.sciencedirect.com/science/article/pii/S0376871621005524>
15. Brailey-Partridge J et al. (2021) Synthesis of 1-Chloronaloxone and 2-Chloronaloxone. *Org. Process Res. Dev.* 2021, 25, 11, 2502–2507. <https://doi.org/10.1021/acs.oprd.1c00288>

Published 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. Gray F., Sublocade®, From the Clinic into the Real World, ATHS, October 19-22, 2021, Biarritz, France.
19. 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.
20. Wiest et al. (2021) Examining the benefit of RBP-6000 300mg versus 100mg maintenance dose in opioid injectors, CSAM, October 21-23, 2021.
21. Keith et al. (2021) Struggling with recovery from opioids: Who is at risk during COVID-19? CSAM, October 21-23, 2021.
22. Wiest et al. (2021) Initiating Monthly Buprenorphine Injection After Single Dose of Sublingual Buprenorphine, CSAM, October 21-23, 2021.
23. 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.
24. Walling D et al. (2021) RBP-7000 monthly risperidone injection (180 mg) following switch from daily oral risperidone (6 mg) in stable schizophrenic patients, US Psych 2021, San Antonio, TX, Oct 29-Nov 1 2021.
25. Walling D et al. (2021) Alternate injection site (back of upper arm) for monthly long-acting risperidone injections of RBP-7000. US Psych 2021, San Antonio, TX, Oct 29-Nov 1 2021.
26. 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.
27. Patient-relevant therapy outcomes in the routine treatment of opioid-dependent patients in Germany with Suboxone® Sublingual Film [PROFIL], DGS Berlin, Nov 5-11 2021, Germany,
28. Boyett et al. (2021) Assessment of a single-item Opioid Craving Visual Analog Scale (OC-VAS) in patients with opioid use disorder, Australasian Professional Society on Alcohol and other Drugs (APSAD), Hobart, Australia, November 7-10, 2021.
29. 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.
30. Lee K et al. (2021) Real-World Evidence for the Management of Opioid Use Disorder (OUD) During COVID-19 pandemic for Patients Treated with Opioid Agonist Treatment (OAT), International Society of Addiction Medicine (ISAM), Virtual, November 19-21, 2021.
31. Grover P. et al. (2021) Understanding Real-World Treatment Patterns in Opioid Use Disorder (OUD): Clinical Practice Versus Treatment Guidelines, International Society of Addiction Medicine (ISAM), Virtual, November 19-21, 2021.
32. Rutrick et al (2021) Long -Term Efficacy and Safety of SUBLOCADE®, a Monthly Subcutaneous Buprenorphine Depot Injections for Opioid Use Disorder, International Society of Addiction Medicine (ISAM), Virtual, November 19-21, 2021.
33. Wiest et al. (2021) Initiating Monthly Buprenorphine Injection After Single Dose of Sublingual Buprenorphine, International Society of Addiction Medicine (ISAM), Virtual, November 19-21, 2021.
34. Wiest et al. (2021) Examining the benefit of RBP-6000 300mg versus 100mg maintenance dose in opioid injectors, International Society of Addiction Medicine (ISAM), Virtual, November 19-21, 2021.
35. Mariani et al. (2021) Rapid Initiation of Extended-Release Buprenorphine in Patients Using Fentanyl and Fentanyl Analogs, Albatros, Paris, France, December 7-9, 2021.
36. 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.

37. Gaiazov, S et al (2021) Recognizing the Role of Socioeconomic Geography in the Distribution of Waivered Providers, 32nd Annual Meeting and Scientific Symposium of the American Academy of Addiction Psychiatry (AAAP), December 9-12, 2021.

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