



Q4-2022 RESULTS R&D UPDATE

TREATMENT OF OPIOID USE DISORDER (OUD)

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

- **US Label updates:**
 - *N-methyl-pyrrolidone (NMP) safety*: FDA approval received on August 23, 2022.
 - *Thorough QT (tQT) labelling information*: FDA approved the labeling changes and closed the associated post-marketing requirement (PMR) for SUBOXONE® Film on June 17, 2022.
- **Phase IV studies** aiming at addressing knowledge gaps in the areas of SUBLOCADE rapid induction, benefits of 300 mg maintenance dose, alternate injection sites, long-term recovery outcomes, treatment cessation guidance, impact of SUBLOCADE treatment in the emergency department (ED) environment, comparative effectiveness with other medications for the treatment of OUD, and a platform for data integration/sharing with the scientific and medical communities
- **Long-term collaboration** studies with internationally recognized experts in addiction medicine to understand the long-term outcomes of SUBLOCADE treatment, its differentiation vs. current standard of care, and the journey toward recovery:
 - *RECOVER Long-Term study* with Virginia Tech (Prof. Warren Bickel)
 - *Community Long-Acting Buprenorphine (CoLAB) study* with the National Drug and Alcohol Research Centre (NDARC), UNSW Sydney (Prof. Michael Farrell)
 - Collaboration on *non-fatal overdoses* with Dr. Ken Lee in Canada
 - *Extended-release pharmacotherapy for Opioid Use disorder (EXPO) study* with King's College London (Prof. John Marsden).
- **Real world evidence (RWE)** studies with workstreams clustered into three themes: (1) health disparity including social determinants of health; (2) recovery (transfer of care, patient-centric metrics, treatment pathways, and algorithms of treatment success), and (3) harm reduction (overdose prevention, cost-effectiveness, treatment initiation).
- **Externally sponsored studies (ESS)** with main research areas of interest including (1) high-risk opioid overdose; (2) Criminal Justice System (CJS); (3) rapid initiation in different treatment settings; (4) co-morbidities; (5) long-term efficacy and safety.

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

- Regulatory approvals granted in 11 most-of-the-world countries including Canada, Australia, New Zealand, Israel, Sweden, Finland, Denmark, Norway, Germany, Italy, and Switzerland.
- Pending approval in the UK

SUBOXONE® (BUPRENORPHINE / NALOXONE) FILM:

- Regulatory Approvals granted in 36 most-of-the-world countries including Canada, Israel, all EU Member States (+ UK, Iceland, Norway, and Liechtenstein), Qatar, New Zealand, and United Arab Emirates.
- Filings under review in Kuwait, Kingdom of Saudi Arabia, and Colombia.

TREATMENT OF SCHIZOPHRENIA

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

- Two FDA approvals of Prior Approval Supplement (PAS) in 2022:
 - extension of shelf-life to 36 months and time out of fridge from the current 7 days to 30 days on August 29, 2022
 - alternate injection sites (back of the arm) on December 15, 2022

PIPELINE ACTIVITIES

- **AEF0117 (Cannabinoid-1 [CB1] synthetic Signalling Specific Inhibitor):**
 - Clinical Phase 2B: Central IRB approval and global protocol training achieved on March 30, 2022. First subject first visit May 23, 2022. The estimated Last Subject Last Visit is Q1-2024 with a final CSR in H2-2024.
 - Other: CMC, nonclinical toxicology and clinical workstreams are progressing in parallel as planned.
- **INDV-2000 (Selective Orexin 1 [OX1] receptor antagonist):**
 - SAD study: CSR finalized and published in July 2022.
 - MAD study: First subject dosed on September 14, 2022.

- Other clinical, nonclinical, chemical development, and formulation development activities tracking according to plan.
- **INDV-1000 (GABA_B receptor positive allosteric modulator):**
 - Two lead molecules and potential backups have been chosen for the late lead optimization phase.
 - Ongoing synthesis of the two lead molecules to enable Maximum Tolerated Dose (MTD) / Dose Range Finding (DRF) rat and dog studies.
 - Candidate Selection of lead molecule is expected by end of Q1-2023.

PEER-REVIEWED PUBLICATIONS (2022)

1. Moss LM et al. (2022) Effect of sustained high buprenorphine plasma concentrations on fentanyl-induced respiratory depression: A placebo-controlled crossover study in healthy volunteers and opioid-tolerant patients. PLoS ONE 17(1): e0256752. <https://doi.org/10.1371/journal.pone.0256752>
2. Craft W et al. (2022) Recovery from opioid use disorder: a 4-year post-clinical trial outcomes study. Drug Alcohol Depend. Mar 9;234:109389. <https://doi.org/10.1016/j.drugalcdep.2022.109389>
3. Olofsen E. et al. (2022) Modelling Buprenorphine Mitigation of Fentanyl-Induced Respiratory Depression in Chronic Opioid Users and Opioid-Naïve Volunteers. JCI Insight; 7(9):e156973. <https://doi.org/10.1172/jci.insight.156973>
4. Newman AH, Xi ZX, Heidbreder C (2022) Current Perspectives on Selective Dopamine D3 Receptor Antagonists/Partial Agonists as Pharmacotherapeutics for Opioid and Psychostimulant Use Disorders. In: Current Topics in Behavioral Neurosciences. Springer, Berlin, Heidelberg. https://doi.org/10.1007/7854_2022_347
5. Andrada E et al. (2022). Retention Rates with Monthly Depot Buprenorphine in General Practice in Melbourne, Australia. Aust J Gen Pract. 2 Jun;51(6):447-451. <https://doi.org/10.31128/AJGP-07-21-6098>
6. Treloar et al. (2022) Can a new formulation of opiate agonist treatment alter stigma? Place, time and things in the experience of extended-release buprenorphine depot. Int J Drug Policy. Sept;107:103788. <https://doi.org/10.1016/j.drugpo.2022.103788>
7. Boyett B et al. (2022) Continued Post-Trial Benefits of Buprenorphine Extended Release: RECOVER Study Findings. J Addict Med. 16 Sept. <https://doi.org/10.1097/ADM.0000000000001070>
8. Hassman H et al. (2022) Open-label, Rapid Initiation Study for Extended-Release Buprenorphine Subcutaneous Injection. Am J Drug Alcohol Abuse. 24 Aug:1-10. <https://doi.org/10.1080/00952990.2022.2106574>
9. Mullen W et al. (2022) The Introduction of a Novel Formulation of Buprenorphine into Organized Health Systems. Drug Alcohol Depend Rep. 26 Aug:100090. <https://doi.org/10.1016/j.dadr.2022.100090>
10. Keith DR et al. (2022) Struggling with recovery from opioids: Who is at risk during COVID-19? J Addict Med. 18 Oct. <https://doi.org/10.1097/ADM.0000000000001096>
11. Lunacsek O. et al. (2022) Impact of Medications for Opioid Use Disorder on Healthcare Resource Utilization and Costs for Patients Served by a State Medicaid Program. Curr Med Res Opin.19 Oct. <https://doi.org/10.52845/CMRO/2022/5-10-2>
12. Laffont C et al. (2022) Buprenorphine Exposure Levels to Optimize Treatment Outcomes in Opioid Use Disorder. Front Pharmacol. 18 Nov. <https://doi.org/10.3389/fphar.2022.1052113>

CONFERENCE ABSTRACTS (2022)

1. Abdel-Sattar M et al. (2022) Provider and Payer Perspectives on the Impact of the COVID-19 Pandemic on Patients With Opioid Use Disorder in the United States: Multi-Stakeholder In-Depth Interviews, AMSUS (The Society of Federal Health Professionals), February 7-10, 2022 (Virtual February 22-25).
2. Carey J et al. (2022) The Identification of Naloxone Related Degradants in Drug Product, 38th SCI Process Development Symposium, Society of Chemical Industry (SCI), March 30 – 31, 2022, London, UK.
3. Rutrick D et al. (2022) Long-Term Treatment Benefit of BUP-XR for Patients Struggling to Abstain from Opioid, American Society of Addiction Medicine (ASAM), March 31-April 3, 2022, Hollywood, FL.
4. Heidbreder C, Young M (2022) Clinical Evaluation of INDV-2000 (C4X3256), a Non-Opioid, Highly Selective Orexin-1 Receptor Antagonist for the Treatment of Opioid Use Disorder. Third Annual NIH HEAL Initiative Investigator Meeting April 11-12, Virtual.
5. Gaiazov S et al. (2022) Recognizing the Role of Socioeconomic Geography in the Distribution of Waivered Providers. NCCCHC Spring, April 9-12, 2022, Atlanta, GA.

6. Gaiazov et al. (2022) Recognizing the Role of Socioeconomic Geography in the Distribution of Waivered Providers. The College of Psychiatric and Neurologic Pharmacists (CPNP), April 24-27, San Antonio, TX. Encore presentation.
7. Gaiazov S et al. (2022) Mental Health and its relationship to Economic Stability, Education, Health and Treatment Facilities: A State-level analysis. American Psychiatric Association (APA), May 21-25, New Orleans, LO.
8. Partanen M et al. (2022). Early experience of buprenorphine long-acting injection in Finland: a retrospective cohort study. EUROPAD, May 20-22, 2022, Pisa Italy.
9. McLaughlin T et al. (2022) Impact Of Changes In Utilization Management Programs (UMP) On The Use Of Medications For Opioid Use Disorder (MOUD) And Outcomes In Opioid Use Disorder (OUD) Patients Served By A State Medicaid Program. USPHS (United States Public Health Services), May 23-27 Phoenix, AZ.
10. Rutrick D et al. (2022) Long-Term Treatment Benefit of BUP-XR for Patients Struggling to Abstain from Opioid, ALBATROS International Congress of Addictology, June 7-9, 2022, Paris, France. Encore presentation.
11. Dobbins R. et al. (2022) First in Human Trial of the Non-Opioid Selective Orexin-1 Antagonist INDV-2000 in Healthy Volunteers. The College on Problems of Drug Dependence (CPDD) 84th Annual Scientific Meeting, June 11-15, 2022, Minneapolis, MN.
12. Laffont CM et al. (2022) Modelling buprenorphine mitigation of fentanyl-induced respiratory depression. The College on Problems of Drug Dependence (CPDD) 84th Annual Scientific Meeting, June 11-15, 2022, Minneapolis, MN.
13. Goslow et al. (2022) Buprenorphine misuse in opioid use disorders: subgroups, motivations, and opioid demand. The College on Problems of Drug Dependence (CPDD) 84th Annual Scientific Meeting, June 11-15, 2022, Minneapolis, MN.
14. Gray et al. (2022) Transition of patients established on long-term transmucosal buprenorphine treatment to monthly buprenorphine injection. The College on Problems of Drug Dependence (CPDD) 84th Annual Scientific Meeting, June 11-15, 2022, Minneapolis, MN.
15. Craft W. et al. (2022) Pain in recovery from OUD: the importance of acute & chronic pain. The College on Problems of Drug Dependence (CPDD) 84th Annual Scientific Meeting, June 11-15, 2022, Minneapolis, MN.
16. Tegge A. et al. (2022) Long-term recovery from opioid use disorder: identification of recovery subgroups and their association with opioid use, treatment, and quality of life. The College on Problems of Drug Dependence (CPDD) 84th Annual Scientific Meeting, June 11-15, 2022, Minneapolis, MN.
17. Miller E. et al. (2022) Opioid use disorder (OUD) and treatment for opioid problems among OUD symptom subtypes. The College on Problems of Drug Dependence (CPDD) 84th Annual Scientific Meeting, June 11-15, 2022, Minneapolis, MN.
18. Lunacsek O et al. (2022). Impact of Changes in Utilization Management Programs on the Use of Medications for Opioid Use Disorder and Outcomes in Opioid Use Disorder Patients Served by a State Medicaid Program. SAMPA, June 25-28, 2022, Columbia, SC.
19. Gaiazov S et al. (2022) Mental Health and its relationship to Economic Stability, Education, Health and Treatment Facilities. NCCHC Mental Health, July 31- August 1, 2022, Denver, CO.
20. Weist K et al. (2022) High Plasma Buprenorphine Concentrations Decrease Respiratory Effects of Intravenous Fentanyl. NORDIC Opioid Symposium, Sept 22-23, Uppsala, Sweden.
21. Rutrick D et al. (2022) Long-Term Treatment with BUP-XR in Patients Struggling to Abstain from Opioids. FeDerSerd, Sept 28-20, Rome, Italy. Encore presentation.
22. Lee K et al. (2022) Real-World Evidence for Impact of OAT on Non-Fatal Overdose in Patients with OUD during the COVID-19 Pandemic. International Society of Addiction Medicine (ISAM), October 4-7, 2022, Valletta, Malta.
23. Tegge A. et al. (2022) Long-term recovery from opioid use disorder: identification of recovery subgroups and their association with opioid use, treatment, and quality of life. Australian Professional Society on Alcohol and other Drugs (APSAD), October 9-12, 2022, Darwin, Australia. Encore presentation.
24. Rutrick D et al. (2022) Long-Term Treatment Benefit of BUP-XR for Patients Struggling to Abstain from Opioid, Australian Professional Society on Alcohol and other Drugs (APSAD), October 9-12, 2022, Darwin, Australia. Encore presentation.
25. Halpern R et al (2022) Analysis of Treatment Paths Among Patients After an Acute Opioid Related Event. AMCP-Nexus, October 11-14, 2022, National Harbor, MD. Encore presentation.
26. Halpern et al. (2022) Assessment of Treatment Paths for OUD Patients After an Acute OUD Event. American Psychiatric Nurses Association (APNA), October 19-22, 2022, Long Beach, CA.
27. Wolfe C et al. (2022). Current State of Medications for Opioid Use Disorder in U.S. Correctional Facilities: A Proposal. NCCHC Annual, October 22-26, 2022, Las Vegas, NV.

28. Lee K et al. (2022) Real-World Evidence for Impact of OAT on Non-Fatal Overdose in Patients with OUD during the COVID-19 Pandemic. Canadian Society of Addiction Medicine (CSAM), November 3-5, 2022, Saskatoon, Canada. Encore presentation.
29. Laffont C et al. (2022) Modelling buprenorphine mitigation of fentanyl-induced respiratory depression. Canadian Society of Addiction Medicine (CSAM), November 3-5, 2022, Saskatoon, Canada. Encore presentation.
30. Gray et al. (2022) Transition of patients established on long-term transmucosal buprenorphine treatment to monthly buprenorphine injection. Canadian Society of Addiction Medicine (CSAM), November 3-5, 2022, Saskatoon, Canada. Encore presentation.
31. Rutrick et al (2022) Long-Term Treatment with BUP-XR in Patients Struggling to Abstain from Opioids. Canadian Society of Addiction Medicine (CSAM), November 3-5, 2022, Saskatoon, Canada. Encore presentation.
32. Rutrick et al (2022) Long-Term Treatment with BUP-XR in Patients Struggling to Abstain from Opioids. Italian Society of Addiction Disease (SIPaD), November 10-11, 2022, Rome, Italy. Encore presentation.