



Q3-2022 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.
- PMR study (INDV-6000-401): Objectives are threefold: (1) Identify the population of patients who may benefit from the 300 mg/month maintenance regimen; (2) Demonstrate that initiating SUBLOCADE® 300 mg following a single 4 mg dose of transmucosal buprenorphine is well-tolerated with a safety profile similar to that observed with SUBLOCADE® administered as per current FDA label; (3) Assess feasibility of fast 300 mg loading induction for the most vulnerable patients. Achieved number of subjects to allow database lock for interim analysis for rapid induction as per plan.
- Lifecycle Management Plan: Generate further evidence on how to (1) use SUBLOCADE® in fentanyl and synthetic opioids' users; (2) treat subjects with opioid use disorder (OUD) in the criminal justice system to potentially decrease the risk of overdose after release and improve linkage to care, and (3) initiate treatment in the emergency department to potentially decrease the rates of relapse and overdose and facilitate transitions to community-based care. All studies ongoing.
- Collaboration studies:
 - *RECOVER® long-term study*: Extension of RECOVER® 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.¹
 - *Real world Australian experience with SUBLOCADE®*: COLAB study, an open-label, multicentre, single-arm trial of monthly injections of SUBLOCADE® in people with OUD.^{2 3}
 - *Real world Canadian experience with SUBLOCADE®*: Distribution of reported non-fatal overdose events by month & treatment cohort.⁴
 - *EXPO study*: First prospective randomized comparison of SUBLOCADE® with standard of care (SL buprenorphine/naloxone and methadone).

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.
- Waiting for MHRA feedback 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 and Kingdom of Saudi Arabia.
- Filed in Colombia.

¹ 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>

² 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>

³ Andrada E et al. (2022). Retention Rates with Monthly Depot Buprenorphine in General Practice in Melbourne, Australia. *Aust J Gen Pract.* 2022 Jun;51(6):447-451. <https://doi.org/10.31128/AJGP-07-21-6098>

⁴ 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

TREATMENT OF SCHIZOPHRENIA

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

Pre-Approval Submissions to support:

- extension of shelf-life to 36 months and time out of fridge to 1 month: FDA approval granted on August 29, 2022.
- alternate injection site (PDUFA date 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. Last Subject Last Visit expected Q4-2023.
 - 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: Following clinical hold lift on July 27, 2022, MAD study dosed on September 14, 2022.
 - Formulation PK study: Study conduct to begin October 2022.
 - CYP3A4 interaction study: Start-up process in progress.
 - Nonclinical, chemical development, and formulation development activities in parallel 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 (DFR) 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> Epub ahead of print.

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>

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.
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.
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.
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.
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.
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.
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.
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.