



Q2-2022 RESULTS R&D UPDATE

TREATMENT OF OPIOID USE DISORDER (OUD)

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

- US Label updates:
 - *N-methyl-pyrrolidone (NMP) safety:* Proposed label reviewed by FDA and responses sent back to the Agency on April 4, 2022. Feedback from the FDA received on July 6, 2022. Waiting for final approval.
 - *Thorough QT (tQT) labelling information:* The FDA provided (March 31, 2022) a Safety Labelling Change (SLC) notification to harmonize the QTc information in all buprenorphine labels, including SUBLOCADE®. FDA approved the labeling changes and closed the associated post-marketing requirement (PMR) for SUBXONE 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. First subject randomized on December 23, 2021. Interim cut-count of 120-subject for rapid induction on target for Q3-2022.
- 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 in planning phase.
- 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:

- alternate injection site (PDUFA date December 15, 2022)
- extension of shelf-life & time out of fridge (PDUFA date September 06, 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):**
 - FDA clinical hold letter received September 1, 2021, asking Indivior to conduct an additional 28-day repeat-dose toxicology study. FDA's decision was based on non-clinical findings from a separate (not sponsored by Indivior) development program.
 - Complete response to the clinical hold was submitted to the FDA on June 27, 2022.
 - Clinical hold was lifted on July 27, 2022, the Phase 1 multiple ascending dose (MAD) study is expected to start in September 2022.
- **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. PlosOne, Published online January 27, 2022. <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. Farrell 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. 2022 Feb;100:103492. <https://doi.org/10.1016/j.drugpo.2021.103492>
4. Olofsen E. et al. (2022) Modelling Buprenorphine Mitigation of Fentanyl-Induced Respiratory Depression in Chronic Opioid Users and Opioid-Naïve Volunteers. JCI Insight. <https://doi.org/10.1172/jci.insight.156973>
5. 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. Curr Top Behav Neurosci. 2022 May 12. Epub ahead of print. https://doi.org/10.1007/7854_2022_347
6. 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>

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. NCCHC 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.

Next Conferences:

- NCCHC Mental Health, July 31- August 1, 2022, Denver, CO
- American Psychiatric Nurses Association (APNA), October 19-22, 2022, Long Beach, CA
- NCCHC Annual, October 22-26, 2022, Las Vegas, NV