

Indivior R&D Update Half-Year Results July 31st, 2019

R&D / Pipeline Update

Treatment of Opioid Use Disorder (OUD)

SUBLOCADE™ (BUPRENORPHINE EXTENDED-RELEASE) INJECTION:

- In the US:
 - All Post Marketing Requirement (PMR) and Commitment (PMC) studies are on track.
 - Lifecycle Evidence Generation & Optimization (LEGO) Studies: These studies are dedicated to (1) understand the use of diverted buprenorphine (see our publication list); (2) study the effects of SUBLOCADE™ in the emergency room environment to potentially prevent repeated opioid overdoses and potentially change standards of care, and (3) investigate how high plasma concentrations of buprenorphine, consistent with those delivered by the two approved dosing regimens of SUBLOCADE™, could potentially block the effects of respiratory depression produced by fentanyl that has been increasingly and directly related to drug overdose deaths in the United States. All studies are on track.
 - RECOVER™ Study (REmission from Chronic Opioid use: studying enVironmental and socioEconomic factors on Recovery): This is a study collecting up to 24-month longitudinal data encompassing demographics, drug use, drug treatment, family relationships, quality of life, mental and physical health, health-care utilization, crime, housing, employment, and urine drug screening (see our publication list). The 12-month longitudinal analysis findings were presented at various conferences; the 24-month final report is on track for December 2019.
- Ex-US Regulatory Activities:
 - Canada: SUBLOCADE™ approval on November 21, 2018
 - Australia: SUBLOCADE™ approval on July 17, 2019
 - SUBLOCADE™ / SUBUTEX XR ex-US regulatory filings: Filings were made in Israel (July 2018), New Zealand (September 2018) and Europe (November 2018). Reviews by local Regulatory Authorities are ongoing.

SUBOXONE® (buprenorphine / naloxone) Film:

- Israel: Submission on September 3, 2018. Regulatory Authority review is ongoing.
- Canada: Supplemental New Drug Submission (SNDS) filed June 27, 2019. Regulatory Authority review is ongoing.
- Europe: Market Authorisation Application (MAA – Centralized Procedure) submitted March 8, 2019 and validated on March 28, 2019. Regulatory Authority review is ongoing.

SUBOXONE® (buprenorphine / naloxone) Tablet:

- On September 11, 2018, the Chinese National Medical Products Administration (NMPA) approved SUBOXONE® Sublingual Tablets for the treatment of opioid use disorder.
- On February 4, 2019, Indivior announced a definitive agreement to divest the rights related to SUBOXONE® Sublingual Tablets (Sai Bo Song™) in China to Zhejiang Pukang Biotechnology Co., Ltd. (Pukang). The agreement is subject to various closing conditions and is anticipated to close

Treatment of Schizophrenia

PERSERIS™ (formerly RBP-7000), Monthly Long-Acting Risperidone Injection:

- FDA approval on July 27, 2018.
- PMC studies are on track.

Early Stage Asset Development (ESAD)

- **GABA_B positive allosteric modulator:**
 - New lead identification and optimization program in partnership with ADDEX Therapeutics.

- **C4X3256 (Selective Orexin 1 (OX1) receptor antagonist):**
 - Finalization of FTIH protocol, Investigators Brochure, Investigational Medicinal Product Dossier.
- **APV202701A (Selective dopamine [DA] D3 receptor antagonist):**
 - Initiation of IND dossier preparation.

Peer-Reviewed Publications (2019)

1. Ling W, Nadipelli V, Ronquest N, Albright V, Aldridge A, Learned S, Mehra V, Heidbreder C (2019) Remission from Chronic Opioid Use—Studying Environmental and Socio-economic Factors on Recovery (RECOVER): study design and participant characteristics. *Contemp Clin Trials*, 76: 93-103. <https://doi.org/10.1016/j.cct.2018.11.015>
2. Haight BR, Learned SM, Laffont CM, Fudala PJ, Zhao Y, Garofalo AS, Greenwald MK, Nadipelli VR, Ling W, Heidbreder C (2019) Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled trial. *The Lancet*, 393 (10173): 778-790. [https://doi.org/10.1016/S0140-6736\(18\)32259-1](https://doi.org/10.1016/S0140-6736(18)32259-1)
3. Ling W, Nadipelli VR, Solem CT, Ronquest NA, Yeh Y-C, Learned SM, Mehra V, Heidbreder C (2019) Life-activity Outcomes in Participants of a Buprenorphine Monthly Depot (BUP-XR) Double-blind, Placebo-controlled, Multicenter, Phase 3 Study. *J. Addiction Med.*, Electronic Publication ahead of Print, March 4. <https://doi.org/10.1097/ADM.0000000000000517>.
4. Schmith VD, Curd L, Lohmer LRL, Laffont CM, Andorn A, Young, MA (2019) Evaluation of the effects of a monthly buprenorphine depot subcutaneous injection on qt interval during treatment for opioid use disorder. *Clin Pharmacol Ther*, Epub 2019 Apr 8. <https://doi.org/10.1002/cpt.1406>
5. Berrell SL, Stephen J. Byard SJ, John S. Carey JS, Antonio Codina A, J. Alf Davis JA, Katherine Filer K, Alasdair Garnett A, Robin Marshall R, Martin SJ, Mykytiuk J, Northen J, Pandya U, Reid G, Smyth C, Watson (2019) Process Development toward a Pro-Drug of Buprenorphine. *Organic Proc Res & Dev*, 23(5): 762-770. <https://pubs.acs.org/doi/10.1021/acs.oprd.9b00025>
6. Carey JS and McCann E (2019) Lipase-Catalyzed Regioselective Ester Hydrolysis as a Key Step in an Alternative Synthesis of a Buprenorphine Pro-Drug. *Organic Process Res & Dev*, 23(5): 771-774. <https://pubs.acs.org/doi/pdf/10.1021/acs.oprd.9b00026>
7. Ling W, Nadipelli VR, Solem CT, Farabee D, Ronquest NA, Perrochet B, Learned SM, Deshpande CG, Heidbreder C (2019) Measuring recovery in OUD: clinical utility and psychometric properties of the treatment effectiveness assessment. *Subst Abuse Rehabil*, Epub 5 June 2019 Vol. 10 Pages 13—21. <https://doi.org/10.2147/SAR.S198361>
8. Dong R, Wang H, Lang L, Gray F, Liu Y, Laffont C, Young M, Jiang J, Liu Z, Learned SM (2019) Pharmacokinetics of sublingual buprenorphine tablets following single and multiple doses in Chinese participants with and without opioid use disorder. *Drugs in R&D*, Epub 2019 Jun 13. <https://doi.org/10.1007/s40268-019-0277-9>
9. Chilcoat HD, Amick HR, Sherwood, MR, Dunn KE (2019) Buprenorphine in the United States: motives for abuse, misuse, and diversion. *J Subst Abuse Treat*, Epub 2019 <https://doi.org/10.1016/j.jsat.2019.07.005>.
10. Dhanda R, Varghese D, Nadipelli VR, Fava M, Joshi N, Solem C, Graham J, Learned SM, Heidbreder C (2019) Patient-reported outcomes in schizophrenia patients treated with once-monthly extended-release risperidone in a long-term clinical study. *Patient Preference & Adherence*, 2019(13):1037-1050.

Conference Abstracts (2019)

1. Nadipelli, V.R., Solem, C.T., Ronquest, N.A., Yeh, Y.-C., Heidbreder, C., Learned, S.M., Mehra, V. (2019) Impact of RBP-6000 on Patient-reported Outcomes in Patients with Opioid Use Disorder: Results of a

- Randomized, Placebo-controlled, Phase 3 Study. AMCP Managed Care & Specialty Pharmacy Annual Meeting, March 25-28, San Diego, CA.
2. Andorn, A., Haight, B., Greenwald, M.K., Zhao, S., Fox, N.L., Heidbreder, C., Learned, S.M. (2019) Higher Abstinence Rates with Greater Buprenorphine Exposure Among Patients Who Inject Opioids. AMCP Managed Care & Specialty Pharmacy Annual Meeting, March 25-28, San Diego, CA.
 3. Thompson, S., Andorn, A., Nadipelli, V.R., Graham, J., De Veugh-Geiss, A., Learned, S.M., Heidbreder, C. (2019) The Budget Impact of PERSERIS™: A Once-Monthly Long-Acting Injectable (LAI) Antipsychotic in Patients with Schizophrenia. AMCP Managed Care & Specialty Pharmacy Annual Meeting, March 25-28, San Diego, CA.
 4. Thompson, S., Andorn, A., Nadipelli, V.R., Graham, J., De Veugh-Geiss, A., Learned, S.M., Heidbreder, C. (2019) The Cost-Effectiveness of PERSERIS™: A Once-Monthly Long-Acting Injectable Antipsychotic in Patients with Schizophrenia. AMCP Managed Care & Specialty Pharmacy Annual Meeting, March 25-28, San Diego, CA.
 5. Ling, W., Nadipelli, V.R., Ronquest, N., Aldridge, C.T., Solem, N., Peiper, S., Learned, S.M., Heidbreder, C. (2019) Recovery from OUD Following Monthly Extended-Release Buprenorphine Treatment: 12-Month Longitudinal Outcomes. 50th Annual Meeting of the American Society of Addiction Medicine (ASAM), April 4-7, Orlando, FL.
 6. Wiest K, van Velzen M, Algera H, Moss L, Dobbins R. (2019) High therapeutic buprenorphine levels reduce IV fentanyl respiratory depression. Annual Meeting of the American Society of Addiction Medicine (ASAM), April 4-7, Orlando, FL.
 7. Andorn A, Boyett B, Shinde S, Fox NL, Zhao Y, Learned SM (2019) Long-term RBP-6000, sustained-release buprenorphine for moderate-to-severe OUD. Annual Meeting of the American Society of Addiction Medicine (ASAM), April 4-7, Orlando, FL.
 8. Wiest K, Andorn A, Fox NL, Learned S, Zhao Y, Gray F (2019) Abstinence response to 300mg vs 100mg RBP-6000 among opioid injection users. Annual Meeting of the American Society of Addiction Medicine (ASAM), April 4-7, Orlando, FL.
 9. Andorn A, Graham J, Fava M., Csernansky J, Newcomer JW, Walling, D., Shinde S, Muma G, Heidbreder C, (2019) Efficacy of Monthly Extended-release Risperidone Injections (RBP-7000) for the Treatment of Schizophrenia: An Analysis of Individual PANSS Items. Congress of the Schizophrenia International Society's (SIRS), April 10-14, Orlando, FL.
 10. Andorn A, Graham J, Csernansky J, Newcomer JW, Shinde S, Muma G, Heidbreder C, Fava M. (2019) Efficacy of Monthly Extended-release Risperidone Injections (RBP-7000) for the Treatment of Schizophrenia: Comparison of Two Analyses. 172nd Annual Meeting of the American Psychiatric Association (APA), May 18-22, San Francisco, CA.
 11. Andorn A, Boyett B, Shinde S, Fox NL, Zhao S, Learned S (2019). 18-month Safety and Efficacy of RBP-6000 Extended-release Buprenorphine for OUD. ALBATROS - 13th Congrès International d'Addictologie (ALBATROS), June 5-7, 2019, Paris, France.
 12. Fox N.L., Laffont C.M., Zhao S., Gray F., Andorn, A., Learned, S.M., Heidbreder, C. (2019) Risk-Adjusted Abstinence Rates are Higher with Greater Buprenorphine Plasma Exposure Among Patients Who Inject Opioids. 81st Annual Scientific Meeting of the College on Problems of Drug Dependence (CPDD), June 15-19, San Antonio, TX.
 13. Ling W., Nadipelli V.R., Ronquest N., Aldridge C.T., Solem N., Peiper S., Learned S.M., Heidbreder C. (2019) How Long Should Pharmacotherapy Last for the Treatment of Opioid Use Disorder? Evidence from a 12-Month Observational Study. 81st Annual Scientific Meeting of the College on Problems of Drug Dependence (CPDD), June 15-19, San Antonio, TX.
 14. Chilcoat H.D., Amick H.R., Sherwood M.R., Dunn K.E. (2019) Buprenorphine in the United States: motives for misuse, abuse, and diversion. 81st Annual Scientific Meeting of the College on Problems of Drug Dependence (CPDD), June 15-19, San Antonio, TX.

15. DeVeough-Geiss A.M., Chilcoat H.M. (2019) Buprenorphine use and misuse among those with opioid use disorders with and without recent treatment. 81st Annual Scientific Meeting of the College on Problems of Drug Dependence (CPDD), June 15-19, San Antonio, TX.
16. Moss L.M., Algera M.H, van Velzen M, Heuberger J, Strafford S, Gray F, Dobbins R, Dahan A, Groeneveld G. (2019) High therapeutic buprenorphine levels reduce IV fentanyl respiratory depression. Nederlandse Vereniging voor Toxicologie (NVT) - 2019 Annual Meeting, June 12-13, Ede, Netherlands.
17. Roncero C, Dorado ML, Orengo T, Ortega RL, Palma-Álvarez RF, Yébenes M, Ordovás M, Grau-López L. (2019) Direct healthcare costs for the management of patients with Opioid Use Disorder treated with methadone and buprenorphine/naloxone in Real-World setting in Spain. COSTEDOPIA Study. World Association on Dual Disorders (WADD) - 3rd World Congress, June 19-22, Madrid, Spain.
18. Simmel B, Ling W, Nadipelli V, Ronquest N, Aldridge A, Solem C, Peiper N, Learned S, Heidbreder C. (2019) Recovery from OUD Post Monthly Buprenorphine-XR Treatment: 12-Month Longitudinal Outcomes. Interdisziplinärer Kongress für Suchtmedizin -20th (IKS), July 4-6, Munich, Germany.
19. Simmel B, Andorn A, Boyett B, Shinde S, Fox NL, Zhao Y, Learned S. (2019) Recovery from OUD Post Monthly Buprenorphine-XR Treatment: 18-month Safety and Efficacy of RBP-6000 Extended-release buprenorphine for OUD. Interdisziplinärer Kongress für Suchtmedizin -20th (IKS), July 4-6, Munich, Germany