



The Lancet Publishes Phase 3 Results Demonstrating Efficacy, Safety and Tolerability of SUBLOCADE™ (Buprenorphine Extended-Release) Injection for Subcutaneous Use (CIII) in Patients with Moderate to Severe Opioid Use Disorder (OUD)

SUBLOCADE – the first FDA-approved monthly injectable buprenorphine treatment for OUD – met primary and key secondary endpoints in the 24-week pivotal trial

Slough, UK and Richmond, VA, 19 February, 2019 – Indivior PLC (LON: INDV) today announced that data from its pivotal phase 3 clinical trial evaluating the efficacy, safety and tolerability of SUBLOCADE™ (buprenorphine extended-release) injection for subcutaneous use (CIII), were published by *The Lancet*. The 24-week trial met its primary and key secondary endpoints for both the 300/300 mg and 300/100 mg dosage regimens of SUBLOCADE, which demonstrated clinically and statistically significant differences in percentage abstinence from opioid use based on negative urine samples and self-reports of illicit drug use as well as treatment success defined as participants with $\geq 80\%$ opioid abstinence during weeks 5-24, compared to placebo¹.

“Findings show that SUBLOCADE administered by healthcare providers delivered sustained buprenorphine exposure for the entire monthly period while increasing abstinence rates and controlling craving and withdrawal symptoms for patients in this pivotal trial, compared to placebo. This represents an effective option in the treatment of opioid use disorder,” said Christian Heidbreder, Ph.D., Chief Scientific Officer of Indivior. “We are proud of the potential impact that these data represent for patients on their path to recovery from opioid use disorder and our continuing efforts to partner with the treatment community.”

The manuscript, published on February 18, 2019 in *The Lancet*, is titled “Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial.” This phase 3 study served as one of the key studies from the clinical development program that supported the U.S. Food and Drug Administration (FDA) approval of SUBLOCADE in November 2017.

“Opioid use disorder is a chronic condition, with many barriers to recovery, including withdrawal symptoms, cravings and potential for relapse,” said Walter Ling, M.D., Professor Emeritus of Psychiatry and Founding Director of the Integrated Substance Abuse Programs (ISAP), University of California, Los

Angeles. “These data show SUBLOCADE can be effective in maintaining control of some barriers, making it an important treatment option for patients with moderate to severe opioid use disorder.”

In the phase 3 trial, a total of 504 treatment-seeking adults with moderate or severe OUD were randomised to monthly SUBLOCADE 300/300 mg (6×300 mg injections), SUBLOCADE 300/100 mg (2×300 mg injections + 4×100 mg injections) or placebo (6× placebo injections) for 24 weeks and received weekly individual drug counselling¹. No supplemental buprenorphine was allowed¹. Withdrawal and craving symptoms were partially clinically controlled with buprenorphine/naloxone sublingual film prior to the first injection of SUBLOCADE¹. The primary efficacy endpoint was percentage abstinence from opioid use, based on negative urine samples and self-reports of illicit drug use at Weeks 5-24¹. The key secondary efficacy endpoint was treatment success, as defined by participants with ≥80% opioid abstinence during weeks 5-24¹. Other secondary efficacy endpoints included opioid craving and withdrawal¹.

The results showed that SUBLOCADE met the primary efficacy endpoint, with both dosage regimens demonstrating mean percentage abstinence rates significantly higher than those of the placebo group (300/300 mg: 41.3% and 300/100 mg: 42.7% compared with 5.0% for placebo, $P < 0.0001$)¹. Both SUBLOCADE dosage regimens also met the key secondary endpoint for treatment success (300/300 mg: 29.1%; 300/100 mg: 28.4%; placebo: 2.0%, $P < 0.0001$)¹. In addition, mean withdrawal and craving scores in both SUBLOCADE groups remained relatively constant and were consistently lower than those observed in the placebo group¹. Retention was nearly twice as high with SUBLOCADE compared to placebo, and no compensatory non-opioid drug use (e.g., amphetamine and methamphetamine, barbiturates, benzodiazepines, cocaine, cannabinoids and phencyclidine) was observed during SUBLOCADE treatment¹. Furthermore, increased medication satisfaction was found among participants treated with SUBLOCADE compared to placebo¹.

This is the first published study to translate the original observations which suggested that ≥70%-80% brain mu-opioid receptor occupancy associated with buprenorphine plasma concentrations of ≥2-3 ng/mL is required to block subjective drug-liking of exogenous opioid, into statistically significant clinical efficacy¹.

The safety profile of SUBLOCADE was consistent with other buprenorphine products for OUD treatment except for injection-site reactions, which were mostly mild and not treatment-limiting¹. The most common adverse events were headache, constipation, nausea and injection-site pruritus¹.

More information about this study can be found online on The Lancet website [here](#).

About SUBLOCADE™

SUBLOCADE is approved by the U.S. Food and Drug Administration (FDA) for the treatment of moderate to severe OUD in adult patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of seven days². It should be administered only by healthcare providers and should be used as part of a complete treatment program that includes counseling and psychosocial support². The overall safety profile for SUBLOCADE, given by a healthcare provider in clinical trials, was consistent with the known safety profile of transmucosal buprenorphine, except for injection site reactions². Adverse reactions commonly associated with SUBLOCADE (in ≥5% of subjects) were constipation, headache, nausea, injection site pruritus, vomiting, increased hepatic enzymes, fatigue, and injection site pain. Injection site reactions were reported in 16.5

percent of patients in phase 3 studies². Most of the injection site adverse reactions (ADRs) were of mild to moderate severity². None of the injection site reactions were serious and one led to study treatment discontinuation².

SUBLOCADE has a BOXED WARNING and is available through restricted distribution under the SUBLOCADE Risk Evaluation and Mitigation Strategy (REMS) Program². Pursuant to the SUBLOCADE REMS, all healthcare settings and pharmacies that order and dispense SUBLOCADE must be certified and establish processes and procedures to verify the medication is dispensed directly to a healthcare provider for administration by a healthcare provider and is not dispensed directly to the patient². Moreover, certified healthcare settings and pharmacies must not distribute, transfer, loan or sell SUBLOCADE².

INDICATION AND USAGE

SUBLOCADE is indicated for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by a dose adjustment period for a minimum of seven days.

SUBLOCADE should be used as part of a complete treatment program that includes counseling and psychosocial support.

IMPORTANT SAFETY INFORMATION

**WARNING: RISK OF SERIOUS HARM OR DEATH WITH INTRAVENOUS ADMINISTRATION;
SUBLOCADE RISK EVALUATION AND MITIGATION STRATEGY**

- **Serious harm or death could result if administered intravenously. SUBLOCADE forms a solid mass upon contact with bodily fluids and may cause occlusion, local tissue damage, and thrombo-embolic events, including life threatening pulmonary emboli, if administered intravenously.**
- **Because of the risk of serious harm or death that could result from intravenous self-administration, SUBLOCADE is only available through a restricted program called the SUBLOCADE REMS Program. Healthcare settings and pharmacies that order and dispense SUBLOCADE must be certified in this program and comply with the REMS requirements.**

Prescription use of this product is limited under the Drug Addiction Treatment Act.

CONTRAINDICATIONS

SUBLOCADE should not be administered to patients who have been shown to be hypersensitive to buprenorphine or any component of the ATRIGEL[®] delivery system.

WARNINGS AND PRECAUTIONS

Addiction, Abuse, and Misuse: SUBLOCADE contains buprenorphine, a Schedule III controlled substance that can be abused in a manner similar to other opioids. Monitor patients for conditions indicative of diversion or progression of opioid dependence and addictive behaviors.

Respiratory Depression: Life threatening respiratory depression and death have occurred in association with buprenorphine. Warn patients of the potential danger of self-administration of benzodiazepines or other CNS depressants while under treatment with SUBLOCADE.

Neonatal Opioid Withdrawal Syndrome: Neonatal opioid withdrawal syndrome is an expected and treatable outcome of prolonged use of opioids during pregnancy.

Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid.

Risk of Opioid Withdrawal With Abrupt Discontinuation: If treatment with SUBLOCADE is discontinued, monitor patients for several months for withdrawal and treat appropriately.

Risk of Hepatitis, Hepatic Events: Monitor liver function tests prior to and during treatment.

Risk of Withdrawal in Patients Dependent on Full Agonist Opioids: Verify that patient is clinically stable on transmucosal buprenorphine before injecting SUBLOCADE.

Treatment of Emergent Acute Pain: Treat pain with a non-opioid analgesic whenever possible. If opioid therapy is required, monitor patients closely because higher doses may be required for analgesic effect.

ADVERSE REACTIONS

Adverse reactions commonly associated with SUBLOCADE (in ≥5% of subjects) were constipation, headache, nausea, injection site pruritus, vomiting, increased hepatic enzymes, fatigue, and injection site pain.

For further product information, see full [Prescribing Information](#) including BOXED WARNING and [Medication Guide](#) at www.SUBLOCADE.com.

About Opioid Use Disorder (OUD)

Opioid use disorder (OUD), sometimes referred to as opioid addiction, is a chronic disease². According to DSM-5, “OUD is characterized by signs and symptoms that reflect compulsive, prolonged self-administration of opioid substances that are used for no legitimate medical purpose or, if another medical condition is present that requires opioid treatment, they are used in doses greatly in excess of the amount needed for that medical condition³.”

Based on 2016 data from the National Survey on Drug Use and Health report, approximately 11.8 million Americans (age 12+ years) engaged in misuse of opioids in the past year⁴. From 1999 to 2016, the rate of deadly prescription opioid overdoses increased five-fold⁵. In 2016, an average of 115 people died of opioid overdose each day in the United States⁶. In addition, in 2016, 948,000 Americans (age 12+ years) used heroin and approximately 626,000 Americans (age 12+ years) had a heroin use disorder⁴. In 2016, opioids accounted for more than 70 percent of the disease burden associated with drug use disorders worldwide⁷.

About Indivior

Indivior is a global specialty pharmaceutical company with a 20-year legacy of leadership in patient advocacy and health policy while providing education on evidence-based treatment models that have revolutionized modern addiction treatment. Our vision is for all patients around the world to have access to evidence-based treatment for the chronic conditions and co-occurring disorders of addiction. The name is the fusion of the words individual and endeavor, and the tagline “Focus on you” makes the

Company's commitment clear. Indivior is dedicated to transforming addiction from a global human crisis to a recognized and treated chronic disease. Building on its global portfolio of opioid dependence treatments, Indivior has a strong pipeline of product candidates designed to both expand on its heritage in this category and address other chronic conditions and co-occurring disorders of addiction, including alcohol use disorder and schizophrenia. Headquartered in the United States in Richmond, VA, Indivior employs more than 900 individuals globally and its portfolio of products is available in over 40 countries worldwide. Visit www.indivior.com to learn more.

Forward-Looking Statements

This press release contains certain statements that are forward-looking and which should be considered, amongst other statutory provisions, in light of the safe harbor provisions of the United States Private Securities Litigation Reform Act of 1995. By their nature, forward-looking statements involve risk and uncertainty as they relate to events or circumstances that may or may not occur in the future. Actual results may differ materially from those expressed or implied in such statements because they relate to future events. Forward-looking statements include, among other things, statements regarding the Indivior Group's financial guidance for 2018 and its medium- and long-term growth outlook, its operational goals, its product development pipeline and statements regarding ongoing litigation.

Various factors may cause differences between Indivior's expectations and actual results, including: factors affecting sales of Indivior Group's products; the outcome of research and development activities; decisions by regulatory authorities regarding the Indivior Group's drug applications; the speed with which regulatory authorizations, pricing approvals and product launches may be achieved; the outcome of post-approval clinical trials; competitive developments; difficulties or delays in manufacturing; the impact of existing and future legislation and regulatory provisions on product exclusivity; trends toward managed care and healthcare cost containment; legislation or regulatory action affecting pharmaceutical product pricing, reimbursement or access; claims and concerns that may arise regarding the safety or efficacy of the Indivior Group's products and product candidates; risks related to legal proceedings, including the ongoing investigative and antitrust litigation matters; the Indivior Group's ability to protect its patents and other intellectual property; the outcome of patent infringement litigation relating to Indivior Group's products, including the ongoing ANDA lawsuits; changes in governmental laws and regulations; issues related to the outsourcing of certain operational and staff functions to third parties; uncertainties related to general economic, political, business, industry, regulatory and market conditions; and the impact of acquisitions, divestitures, restructurings, internal reorganizations, product recalls and withdrawals and other unusual items.

This press release does not constitute an offer to sell or the solicitation of an offer to subscribe for or otherwise acquire or dispose of shares in the Company to any person in any jurisdiction to whom it is unlawful to make such offer or solicitation.

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