New Study Comparing Effectiveness of Extended-Release Naltrexone to Buprenorphine-Naloxone for Opioid Dependence Published in JAMA Psychiatry

October 18, 2017

— Extended-Release Naltrexone as Effective as Buprenorphine-Naloxone on Retention in Treatment and Reducing Use of Heroin and Other Illicit Opioids in Head-to-Head Comparison Trial —

DUBLIN, Ireland--(BUSINESS WIRE)--Oct. 18, 2017-- Results from the first-ever study directly comparing the effectiveness of once-monthly extended-release naltrexone (VIVITROL®) to daily buprenorphine-naloxone in patients with opioid dependence were published this week in the *Journal of the American Medical Association (JAMA) Psychiatry*. VIVITROL is Alkermes' (NASDAQ: ALKS) once-monthly, non-narcotic medication for the prevention of relapse to opioid dependence, following opioid detoxification.

In the 12-week, open-label, randomized-controlled study, 159 patients with opioid dependence were randomized to treatment with either extended-release naltrexone or buprenorphine-naloxone, following detoxification. In the study, extended-release naltrexone met pre-specified non-inferiority criteria for comparison to buprenorphine-naloxone on all primary endpoints, including retention in treatment, proportion of total number of opioid-negative urine drug tests, and number of days of use of heroin and other illicit opioids. Overall, more patients reported adverse events in the extended-release naltrexone group versus those in the buprenorphine-naloxone group. Ten patients discontinued treatment due to adverse events: four in the extended-release naltrexone group and six in the buprenorphine-naloxone group.

"This study is the first-ever direct comparison of extended-release naltrexone and buprenorphine-naloxone in a randomized-controlled clinical setting. These data showed that treatment with extended-release naltrexone was as effective as buprenorphine-naloxone, the current standard of treatment, in maintaining short-term abstinence from heroin and other illicit opioids," said study lead investigator, Lars Tanum, M.D., Ph.D., Associate Professor, Norwegian Centre for Addiction Research at the University of Oslo, Norway, and Head of Research Unit, Department of R&D in Mental Health Services, Akershus University Hospital, Norway. "In a disease affecting millions of patients, where there is significant suffering and limited choices for treatment, it is encouraging to see an additional proven treatment option for patients struggling with opioid dependence."

"VIVITROL represents Alkermes' commitment to providing medication options to support patient-centered treatment for those afflicted by opioid dependence, a critical and challenging public health issue. The results of this study build upon the substantial body of evidence supporting VIVITROL as an important treatment option," said Elliot Ehrich, M.D., Executive Vice President, Research and Development of Alkermes. "These data underscore that all FDA-approved options for the treatment of opioid dependence should be made available to patients struggling with opioid addiction, and we are encouraged that the research community is actively generating new data designed to help inform this underserved patient population."

The article, titled "The Effectiveness of Injectable Extended-Release Naltrexone vs. Daily Buprenorphine-Naloxone for Opioid Dependence: A Randomized Clinical Non-Inferiority Trial," is available online and will appear in a forthcoming print issue of *JAMA Psychiatry*. All patients who completed this 12-week study were invited to participate in a 36-week, open-label extension study using extended-release naltrexone. This extension portion of the study has been completed, and results are expected to be submitted to a peer-reviewed journal for publication.

Results of Study Published in *JAMA Psychiatry*
The open-label, randomized-controlled study compared the use of extended-release naltrexone to buprenorphine-naloxone in patients with opioid dependence at five urban addiction clinics in Norway. Following detoxification, a total of 159 patients were randomly assigned to either daily sublingual buprenorphine-naloxone, 4 to 24 mg/day (target dose of 16 mg/day), or once-monthly injectable extended-release naltrexone 380 mg for a total of 12 treatment weeks.

Primary Outcomes: Data from the study showed that extended-release naltrexone was non-inferior to buprenorphine-naloxone on all primary endpoints, including retention in treatment ($p=0.04$), group proportion of total number of opioid-negative urine drug tests ($p<0.001$), days of heroin use ($p<0.001$) and days of other illicit opioids use ($p<0.001$). Extended-release naltrexone patients used significantly less heroin at all timepoints (Week 4 $p=0.001$, Week 8 $p<0.001$, Week 12 $p=0.003$) and significantly less other illicit opioids at Week 4 ($p=0.004$) and Week 8 ($p=0.007$) than patients in the buprenorphine-naloxone treatment group.

Secondary Outcomes: At all timepoints in the study, extended-release naltrexone patients reported significantly less heroin craving and thoughts about heroin than buprenorphine-naloxone patients. Satisfaction with treatment and willingness to recommend their treatment to others was significantly higher among extended-release naltrexone patients. Life satisfaction was significantly higher among extended-release naltrexone patients at Weeks 4 and 8. Mental health, as assessed by the Hopkins Symptom Checklist-25 of anxiety and depression, showed no significant differences between the two treatment groups. There were no significant differences found between the extended-release naltrexone and buprenorphine-naloxone treatment groups in days of non-opioid illicit substance use.

Overall, 66% of patients completed the study, with a mean time of retention on treatment of 69.3 days for the extended-release naltrexone group and 63.7 days for the buprenorphine-naloxone group. More patients reported adverse events in the extended-release naltrexone group versus those in the buprenorphine-naloxone group (69.0% vs. 34.7%). A number of events in the extended-release naltrexone group, and to a lesser degree in the buprenorphine-naloxone group, were related to induced or experienced withdrawal symptoms, which the study investigators attribute largely to insufficient opioid detoxification. A change to the detoxification strategy was made during the first year of the study, which reduced the number of new adverse events related to induction of treatment. There were nine serious adverse events in the study, six in the extended-release naltrexone group and three in the buprenorphine-naloxone group; however, none were considered directly related to the given treatment. There was one reported opioid overdose in the buprenorphine-naloxone treatment group, and no deaths were observed in the study.

Limitations of the study, as noted by the study investigators, include lack of blinding between treatment arms, and the possibility that the patient

population in the study may have been motivated to receive the novel antagonist treatment of extended-release naltrexone, which is unavailable in Norway.

Funding for the head-to-head comparison study was provided by unrestricted grants from the Research Council of Norway and the Western Norway Regional Health Authority. Financial support was also received from the Norwegian Centre for Addiction Research, University of Oslo, and from Akershus University Hospital.

Alkermes did not have access to trial data or editorial control of any publication related to the trial. Alkermes contributed extended-release naltrexone in kind through an investigator-initiated trial contract.

About Opioid Dependence
A chronic brain disease, opioid dependence is characterized by cognitive, behavioral and physiological symptoms in which an individual continues to use opioids despite significant harm to oneself and others.[1] The use of heroin, an illegal opioid drug, and the non-medical use of FDA-approved opioid analgesics, including prescription pain relievers, represents a growing public health problem in the U.S. According to the 2016 U.S. National Survey on Drug Use and Health, nearly 2 million people aged 18 or older had an opioid use disorder.[2]

About VIVITROL®
VIVITROL (naltrexone for extended-release injectable suspension) is a once-monthly medication for the treatment of alcohol dependence as well as for the prevention of relapse to opioid dependence, following opioid detoxification. VIVITROL is a non-narcotic, non-addictive, once-monthly medication approved for the treatment of opioid dependence. Treatment with VIVITROL should be part of a comprehensive management program that includes psychosocial support.

IMPORTANT SAFETY INFORMATION

INDICATIONS

VIVITROL is indicated for:

- Treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with VIVITROL. Patients should not be actively drinking at the time of initial VIVITROL administration.
- Prevention of relapse to opioid dependence, following opioid detoxification.
- VIVITROL should be part of a comprehensive management program that includes psychosocial support.

CONTRAINDICATIONS

VIVITROL is contraindicated in patients:

- Receiving opioid analgesics
- With current physiologic opioid dependence
- In acute opioid withdrawal
- Who have failed the naloxone challenge test or have a positive urine screen for opioids
- Who have exhibited hypersensitivity to naltrexone, polylactide-co-glycolide (PLG), carboxymethylcellulose, or any other components of the diluent

WARNINGS AND PRECAUTIONS

Vulnerability to Opioid Overdose:

- After opioid detoxification, patients are likely to have a reduced tolerance to opioids. VIVITROL blocks the effects of exogenous opioids for approximately 28 days after administration. As the blockade wanes and eventually dissipates completely, use of previously tolerated doses of opioids could result in potentially life-threatening opioid intoxication (respiratory compromise or arrest, circulatory collapse, etc.).
- Cases of opioid overdose with fatal outcomes have been reported in patients who used opioids at the end of a dosing interval, after missing a scheduled dose, or after discontinuing treatment. Patients and caregivers should be told of this increased sensitivity to opioids and the risk of overdose.
- Although VIVITROL is a potent antagonist with a prolonged pharmacological effect, the blockade produced by VIVITROL is surmountable. The plasma concentration of exogenous opioids attained immediately following their acute administration may be sufficient to overcome the competitive receptor blockade. This poses a potential risk to individuals who attempt, on their own, to overcome the blockade by administering large amounts of exogenous opioids.
- Any attempt by a patient to overcome the VIVITROL blockade by taking opioids may lead to fatal overdose. Patients should be told of the serious consequences of trying to overcome the opioid blockade.

Injection Site Reactions:

- VIVITROL injections may be followed by pain, tenderness, induration, swelling, erythema, bruising, or pruritus; however, in some cases injection site reactions may be very severe.
- Injection site reactions not improving may require prompt medical attention, including, in some cases, surgical intervention.
- Inadvertent subcutaneous/adipose layer injection of VIVITROL may increase the likelihood of severe injection site

reactions.
- Select proper needle size for patient body habitus, and use only the needles provided in the carton.
- Patients should be informed that any concerning injection site reactions should be brought to the attention of their healthcare provider.

Precipitation of Opioid Withdrawal:

- When withdrawal is precipitated abruptly by administration of an opioid antagonist to an opioid-dependent patient, the resulting withdrawal syndrome can be severe. Some cases of withdrawal symptoms have been severe enough to require hospitalization, and in some cases, management in the ICU.
- To prevent occurrence of precipitated withdrawal, opioid-dependent patients, including those being treated for alcohol dependence, should be opioid-free (including tramadol) before starting VIVITROL treatment:
- An opioid-free interval of a minimum of 7–10 days is recommended for patients previously dependent on short-acting opioids.
- Patients transitioning from buprenorphine or methadone may be vulnerable to precipitated withdrawal for as long as two weeks.
- If a more rapid transition from agonist to antagonist therapy is deemed necessary and appropriate by the healthcare provider, monitor the patient closely in an appropriate medical setting where precipitated withdrawal can be managed.
- Patients should be made aware of the risk associated with precipitated withdrawal and be encouraged to give an accurate account of last opioid use.

Hepatotoxicity:

- Cases of hepatitis and clinically significant liver dysfunction have been observed in association with VIVITROL. Warn patients of the risk of hepatic injury; advise them to seek help if experiencing symptoms of acute hepatitis. Discontinue use of VIVITROL in patients who exhibit acute hepatitis symptoms.

Depression and Suicidality:

- Alcohol- and opioid-dependent patients taking VIVITROL should be monitored for depression or suicidal thoughts. Alert families and caregivers to monitor and report the emergence of symptoms of depression or suicidality.

When Reversal of VIVITROL Blockade Is Required for Pain Management:

- For VIVITROL patients in emergency situations, suggestions for pain management include regional analgesia or use of non-opioid analgesics. If opioid therapy is required to reverse the VIVITROL blockade, patients should be closely monitored by trained personnel in a setting staffed and equipped for CPR.

Eosinophilic Pneumonia:

- Cases of eosinophilic pneumonia requiring hospitalization have been reported. Warn patients of the risk of eosinophilic pneumonia and to seek medical attention if they develop symptoms of pneumonia.

Hypersensitivity Reactions:

- Patients should be warned of the risk of hypersensitivity reactions, including anaphylaxis.

Intramuscular Injections:

- As with any IM injection, VIVITROL should be administered with caution to patients with thrombocytopenia or any coagulation disorder.

Alcohol Withdrawal:

- Use of VIVITROL does not eliminate nor diminish alcohol withdrawal symptoms.

ADVERSE REACTIONS

- Serious adverse reactions that may be associated with VIVITROL therapy in clinical use include severe injection site reactions, eosinophilic pneumonia, serious allergic reactions, unintended precipitation of opioid withdrawal, accidental opioid overdose, and depression and suicidality.
- The adverse events seen most frequently in association with VIVITROL therapy for alcohol dependence (ie, those occurring in ≥5% and at least twice as frequently with VIVITROL than placebo) include nausea, vomiting, injection site reactions (including induration, pruritus, nodules, and swelling), muscle cramps, dizziness or syncope, somnolence or sedation, anorexia, decreased appetite or other appetite disorders.
- The adverse events seen most frequently in association with VIVITROL in opioid-dependent patients (ie, those occurring in

≥2% and at least twice as frequently with VIVITROL than placebo) were hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache.

You are encouraged to report side effects to the FDA.

Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see Full Prescribing Information **for VIVITROL.**

About Alkermes

Alkermes plc is a fully integrated, global biopharmaceutical company developing innovative medicines for the treatment of central nervous system (CNS) diseases. The company has a diversified commercial product portfolio and a substantial clinical pipeline of product candidates for chronic diseases that include schizophrenia, depression, addiction and multiple sclerosis. Headquartered in Dublin, Ireland, Alkermes plc has an R&D center in Waltham, Massachusetts; a research and manufacturing facility in Athlone, Ireland; and a manufacturing facility in Wilmington, Ohio. For more information, please visit Alkermes' website at www.alkermes.com.

Note Regarding Forward-Looking Statements

Certain statements set forth in this press release constitute "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, but not limited to, statements concerning the potential therapeutic and commercial value of VIVITROL. The company cautions that forward-looking statements are inherently uncertain. Although the company believes that such statements are based on reasonable assumptions within the bounds of its knowledge of its business and operations, the forward-looking statements are neither promises nor guarantees and they are necessarily subject to a high degree of uncertainty and risk. Actual performance and results may differ materially from those expressed or implied in the forward-looking statements due to various risks and uncertainties. These risks and uncertainties include, among others: whether clinical results for VIVITROL will be predictive of future clinical study results or commercial success; and those risks and uncertainties described under the heading "Risk Factors" in the company's Annual Report on Form 10-K for the year ended Dec. 31, 2016 and Quarterly Reports on Form 10-Q for the quarters ended March 31, 2017 and June 30, 2017 and in subsequent filings made by the company with the U.S. Securities and Exchange Commission (SEC), which are available on the SEC's website at www.sec.gov. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. Except as required by law, the company disclaims any intention or responsibility for updating or revising any forward-looking statements contained in this press release.

VIVITROL® is a registered trademark of Alkermes, Inc.

[1] DSM-IV-TR, American Psychiatric Association.

[2] SAMHSA. *Behavioral Health Trends in the United States: Results from the 2016 National Survey on Drug Use and Health*.

View source version on businesswire.com: http://www.businesswire.com/news/home/20171018006067/en/

Source: Alkermes plc

Alkermes Contacts:
For Investors:
Eva Stroynowski, +1 781-609-6823
or
Sandy Coombs, +1 781-609-6377
or
For Media:
Matthew Henson, +1 781-609-6637