Study on Extended-Release Naltrexone in Opioid-Dependent Patients Involved in Criminal Justice System Published in the New England Journal of Medicine

March 31, 2016

— Investigator-Led Study Showed Treatment With Extended-Release Naltrexone Reduced Relapse Rates and Demonstrated Longer Median Time to Relapse to Opioid Dependence During Six-Month Treatment Period —

— Current VIVITROL® Use in Criminal Justice Setting Highlights Importance of Medication Along With Continuity of Care, Including Community-Based Addiction Recovery Support —

DUBLIN, Ireland--(BUSINESS WIRE)--Mar. 31, 2016-- Results from a study published this week in the *New England Journal of Medicine* (*NEJM*) demonstrated the utility of extended-release naltrexone (VIVITROL®) in individuals involved in the criminal justice system. VIVITROL is Alkermes' (NASDAQ: ALKS) once-monthly, non-narcotic medication for the prevention of relapse to opioid dependence, following opioid detoxification. The open-label, randomized, controlled, effectiveness trial compared six monthly injections of extended-release naltrexone with usual treatment (brief counseling and referrals for community treatment programs, including the option of agonist therapies) for the prevention of opioid relapse among criminal justice offenders. In the study, extended-release naltrexone showed a statistically significant reduction in relapse rates ($p<0.001$) and, for those who relapsed, a significantly longer median time to relapse compared with the usual-treatment group in the six-month treatment period ($p<0.001$). Overall, more participants reported adverse events in the extended-release naltrexone group versus those in the usual-treatment group, whereas the rate of serious adverse events was significantly lower in the extended-release naltrexone group, compared with the usual-treatment group ($p=0.006$).

Reflective of the growing public health concern of opioid addiction and its impact on the criminal justice system, the study, entitled "Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders,"[1] was sponsored by the National Institute on Drug Abuse (NIDA) and was led by 17 clinical researchers and addiction specialists throughout the U.S. The study's lead author is Joshua D. Lee, M.D., M.Sc., associate professor in the departments of Population Health and Medicine at NYU Langone Medical Center, and the senior author is Charles O'Brien, M.D., Ph.D., vice chair of Psychiatry at the Perelman School of Medicine at the University of Pennsylvania and founding director of Penn's Center for Studies of Addiction.

Approximately one-third of heroin users pass through correctional facilities annually in the U.S.[2] Nearly 65 percent of the 2.3 million U.S. prison inmates meet the medical criteria for substance abuse or addiction, yet only 11 percent receive treatment during their incarceration.[3] In addition, more than half of those on parole or probation continue to go untreated.[4]

"The opioid epidemic has put a growing strain on our criminal justice system where individuals struggling with opioid addiction are in need of treatment. Since our prisons and criminal justice system are among the largest providers of addiction services in the country, it is critical that we expand the range of medication treatment options available to this population and connect people to community-based treatment programs," commented Sheriff James M. Cummings of Barnstable County, Mass. "In Barnstable, we've had success with VIVITROL as an important component of our program, which also includes counseling and other support services essential for individuals to successfully recover and re-enter the community. VIVITROL may play an important role in the criminal justice system, as it is a long-acting, non-narcotic, non-addictive opioid antagonist with no known abuse or diversion potential."

This NIDA-sponsored study began in 2009, prior to the approval of extended-release naltrexone for the treatment of opioid dependence. Consequently, as noted by the authors, extended-release naltrexone was not widely available to the public sector community during the treatment period. Today, extended-release naltrexone is being used in the criminal justice setting in more than 100 pilot programs throughout 30 states, including drug court, criminal justice re-entry, legislative and public health initiatives. Each of these programs is designed with various medication treatment parameters, psychosocial support and differing scopes of surrounding community support services.

"It is encouraging to see data showing, in comparison with a traditional treatment approach, VIVITROL helped to reduce relapse to opioid dependence and protected against overdoses in this patient population. It is also reassuring to see that the frequency of overdoses in patients treated with VIVITROL did not increase after the medication was discontinued," stated Adam Bisaga, M.D., Professor of Psychiatry at the Columbia University Medical Center. "Opioid dependence is a chronic disease that requires an individualized treatment plan, including psychosocial treatments and a medication support, along with monitoring that should extend over the long term to assure the best possible clinical outcome."

Results of Study Published in *NEJM*

The study compared the use of extended-release naltrexone versus usual treatment in more than 300 criminal justice offenders at five sites.[5] During the six-month treatment period of the open-label study, participants were randomized to two arms: one receiving extended-release naltrexone once monthly and the other receiving usual treatment (brief counseling and referrals for community treatment programs, including the option of agonist therapies) without extended-release naltrexone. The lead investigators of the study made an independent determination to select a six-month treatment period for study participants, followed by discontinuation of extended-release naltrexone in the treatment group and provision of referrals to local community treatment programs to all study participants. In addition to referrals, participants received brief counseling and the option of agonist therapies. Thirty-seven percent of the usual-treatment group pursued agonist treatments, primarily after resumed illicit opioid use and relapse, during the trial.

Data from the study showed that the median time to relapse, the primary endpoint, was more than two times longer, among those who relapsed, in participants randomized to extended-release naltrexone, compared with usual treatment ($p<0.001$). The usual-treatment group experienced nearly 50 percent more relapse events than the extended-release naltrexone group ($p<0.001$) during the treatment period. An opioid-relapse event was defined as 10 or more days of opioid use in a 28-day period as assessed by self-report or by testing urine toxicology samples obtained every two weeks; a

positive or missing sample was computed as five days of opioid use. Sixty-one percent of patients in the extended-release naltrexone group participated in all six injections during the treatment period. While the study was not powered to show statistical significance for the secondary endpoint of days of reincarceration, substantially fewer (37%) days of reincarceration were reported in the extended-release naltrexone group.

Participants were followed for a total of 78 weeks. Three follow-up visits occurred during the year following the six-month treatment period, beginning at Week 27 and at six-month intervals for both arms. Opioid-use prevention effects waned after discontinuation of treatment. As noted by the authors in the study, symptoms of opioid-use disorder are more likely to recur with the discontinuation of effective pharmacotherapy as with other chronic diseases.

Overall, more participants reported adverse events in the extended-release naltrexone group versus those in the usual-treatment group. The most common adverse events (≥ 10%) related to extended-release naltrexone were injection-site reaction, headache and gastrointestinal upset. Significantly fewer serious adverse events occurred with extended-release naltrexone, compared with the usual-treatment group. There were no overdose events observed in the extended-release naltrexone group in the 78-week period compared with seven overdose events, including three deaths, in the usual-treatment group.

Alkermes did not have editorial control or access to trial data. The company contributed VIVITROL 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.[6] 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 2014 U.S. National Survey on Drug Use and Health, an estimated 2.3 million people aged 18 or older were dependent on pain relievers or heroin in the U.S.[7]

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 the first and only 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

WHAT IS VIVITROL®?

VIVITROL (naltrexone for extended-release injectable suspension) is a prescription injectable medicine used to:

- Treat alcohol dependence. You should stop drinking before starting VIVITROL.
- Prevent relapse to opioid dependence **after** opioid detox. You must stop taking opioids or other opioid-containing medications before starting VIVITROL.

VIVITROL must be used with other alcohol or drug recovery programs such as counseling.

VIVITROL may not work for everyone and has not been studied in children.

DO NOT TAKE VIVITROL IF YOU:

- Are still using or still have any symptoms of physical withdrawal due to dependence on opioid street drugs or opioid-containing medicines.
- Have opioid withdrawal symptoms.
- Are allergic to naltrexone or any of the ingredients in VIVITROL or the liquid used to mix VIVITROL.

See the Medication Guide for more information about opioid withdrawal and the ingredients in VIVITROL and the liquid used to mix it.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT VIVITROL?

VIVITROL can cause serious side effects, including:

RISK OF OPIOID OVERDOSE

Using opioids, even in amounts that you used before VIVITROL treatment, can lead to accidental overdose, serious injury, coma or death. To avoid accidental overdose:

- **Do not** take large amounts of opioids or try to overcome the opioid-blocking effects of VIVITROL.
- Do not use opioids in amounts that you used before VIVITROL treatment. You may even be more sensitive to **lower** amounts of opioids:
    - After detox.
    - When your next VIVITROL dose is due.
    - If you miss a dose of VIVITROL.
    - After you stop VIVITROL treatment.

Get emergency medical help right away if you have trouble breathing; become very drowsy with slowed breathing; have slow, shallow breathing; feel faint, dizzy, confused; or have other unusual symptoms.

SEVERE REACTIONS AT THE INJECTION SITE

VIVITROL may cause severe injection site reactions, including tissue death. Some injection site reactions have required surgery. Call your doctor right away if you notice any of the following at your injection site:

- Intense pain
- The area feels hard
- Swelling
- Lumps
- Blisters
- An open wound
- A dark scab

Tell your doctor about any injection site reaction that concerns you, gets worse overtime or does not get better by two weeks after the injection.

SUDDEN OPIOID WITHDRAWAL

To avoid sudden opioid withdrawal, you must stop taking any opioids or opioid-containing medications, including buprenorphine or methadone, **for at least 7 to 14 days** before starting VIVITROL. If your doctor decides that you don't need to complete detox first, he or she may give you VIVITROL in a medical facility that can treat sudden opioid withdrawal.

Sudden opioid withdrawal can be severe and may require hospitalization.

LIVER DAMAGE OR HEPATITIS

Naltrexone, the active ingredient in VIVITROL, can cause liver damage or hepatitis. Tell your doctor if you have any of the following symptoms of liver problems during VIVITROL treatment:

- Stomach area pain lasting more than a few days
- Yellowing of the whites of your eyes
- Dark urine
- Tiredness

OTHER POSSIBLE SIDE EFFECTS

VIVITROL can cause other serious side effects, such as:

- **Depressed mood –** Sometimes this leads to suicide or suicidal thoughts and behavior. Tell those closest to you that you are taking VIVITROL. You or those closest to you should call your doctor right away if you become depressed or have any new or worsening depression symptoms.
- **Allergic pneumonia –** Tell your healthcare provider if you have shortness of breath, wheezing or a cough that doesn't go away.
- **Serious allergic reactions –** Get medical help immediately if you have a skin rash; swelling of your face, eyes, mouth or tongue; trouble breathing or wheezing; chest pain; or are feeling dizzy or faint.

Common side effects of VIVITROL include nausea, tiredness, headache, dizziness, vomiting, decreased appetite, painful joints, and muscle cramps; in addition, common side effects in people taking VIVITROL for opioid dependence also include cold symptoms, trouble sleeping and toothache.

These are not all of the side effects of VIVITROL. For more information, ask your healthcare provider. Tell your doctor right away if you have any side effect that does not go away. See the Medication Guide for more information.

Call your doctor for medical advice about any side effects. You are encouraged to report negative side effects to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

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: successful outcomes using VIVITROL in the criminal justice system; and the growth of opioid dependence as a disease and public health problem. 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 VIVITROL will continue to be utilized in the criminal justice system; whether the outcomes from the use of VIVITROL in the criminal justice system will be positive; whether opioid dependence will

continue to grow as a public health and criminal justice problem; and those risks described in the Alkermes plc Annual Report on Form 10-K for the fiscal year ended Dec. 31, 2015, and in other 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. The information contained in this press release is provided by the company as of the date hereof, and, except as required by law, the company disclaims any intention or responsibility for updating or revising any forward-looking information contained in this press release.

VIVITROL® is a registered trademark of Alkermes, Inc.

[1] Lee, J. et al. Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders. The *New England Journal of Medicine.* 2016, 374: 1232-1242.

[2] Boutwell, A. et al. Arrested on heroin: a national opportunity. *Journal of Opioid Management*. 2007, 3: 328–332.

[3] CASAColumbia. *Behind Bars II: Substance Abuse and America's Prison Population* . Accessed on March 30, 2016 from http://www.centeronaddiction.org/download/file/fid/487.

[4] Legal Action Center. *Confronting an Epidemic: The Case for Eliminating Barriers to Medication Assisted Treatment of Heroin and Opioid Addiction*. Accessed on March 30, 2016 from http://lac.org/wp-content/uploads/2014/07/LAC-The-Case-for-Eliminating-Barriers-to-Medication-Assisted-Treatment.pdf.

[5] University of Pennsylvania (Philadelphia), New York University School of Medicine and Bellevue Hospital Center (New York), Rhode Island Hospital and Brown University (Providence, Rhode Island), Columbia University Medical Center (New York), and Friends Research Institute (Baltimore).

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

[7] SAMHSA. *Behavioral Health Trends in the United States: Results from the 2014 National Survey on Drug Use and Health*. Accessed on March 30, 2016 from http://www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf.

View source version on businesswire.com: http://www.businesswire.com/news/home/20160331005357/en/

Source: Alkermes plc

Alkermes Contacts:
For Investors:
Sandra Coombs, +1 781-609-6377
or
For Media:
Jennifer Snyder, +1 781-609-6166