Data from Phase 1 Study of NKTR-181 Demonstrate Proof-of-Concept for Nektar's Novel Opioid Analgesic Candidate

Interim data analysis shows NKTR-181 achieved long-acting PK profile with analgesic response and excellent safety profile

SAN FRANCISCO, June 7, 2011 /PRNewswire/ -- Nektar Therapeutics (NASDAQ:NKTR) announced today positive interim data from an ongoing single-dose Phase 1 clinical trial evaluating NKTR-181, the company's novel mu-opioid analgesic candidate. Interim study results show that the molecule achieved its study objectives with an extended PK profile, slow entry into the CNS, and analgesic response. This interim data also show that the drug candidate exhibits an excellent safety and tolerability profile with no dose-limiting tolerability issues observed in the study to-date.

NKTR-181, a novel mu-opioid analgesic investigational drug candidate, was created using Nektar's small molecule polymer conjugate technology. With slower entry into the CNS when compared to historical oxycodone data, NKTR-181 has the potential to greatly reduce the euphoria that underlies opioid abuse liability and dependence, as well as the serious CNS-related side-effects of respiratory depression and sedation. The unique molecular design of the polymer drug conjugate also prevents conversion of NKTR-181 into a rapidly-acting, more abusable opioid.

"NKTR-181 is an exciting development in pain management research," said Lynn R. Webster, MD, Medical Director of Lifetree Clinical Research. "New therapeutics to manage chronic pain without the serious risks associated with existing opioids are desperately needed. A novel opioid therapy, such as NKTR-181, with lower potential for abuse liability and fewer CNS-related side effects than existing opioids provides great promise for pain practitioners looking for safer, more effective pain management. The profile and properties observed with NKTR-181 in the clinic are highly interesting because these properties are inherent to the molecule's novel structure, which represents a significant potential advance over existing long-acting opioid drugs, which are typically simply re-formulations of many traditional opioids."

Interim pharmacokinetic (PK) data from the Phase 1 study show that single doses of NKTR-181 achieved a dose-linear PK profile and the plasma half-life is greater than 10 hours across all five dose cohorts tested to-date, which includes 75 healthy subjects. NKTR-181 also displayed good oral bioavailability with rapid absorption, and its plasma half-life supports its potential to be dosed on a once-daily (QD) or twice-daily (BID) schedule. Short-acting opioid therapies, such as oxycodone, exhibit half-lives of approximately 3.5 hours, and extended release formulations, such as Oxycontin®, exhibit plasma half-lives of approximately 8 hours.(1)

Additional interim data from the study show that NKTR-181 exhibits pharmacological activity in humans. The study found that NKTR-181 elicited an analgesic response in a cold pressor test, an experimental model of pain used to measure CNS analgesic response in healthy subjects. Preliminary pupillometry data demonstrate that although NKTR-181 is rapidly absorbed and is detected in plasma within 15 minutes, its centrally-mediated opioid effects appear slowly, consistent with slowed entry of the molecule into the CNS.

"NKTR-181 shows linear kinetics, dose proportionality and a half-life following oral administration that should allow once or twice daily dosing," said Robert Medve, MD, Vice President of Development and Clinical Head of the NKTR-181 Program at Nektar Therapeutics. "The results we've seen to date with NKTR-181 in the clinic add to our excitement over the potential of this novel analgesic candidate and the role it could play in treating chronic pain while addressing the risks associated with existing opioids. The data from this first Phase 1 study to-date support continued rapid development of NKTR-181. We look forward to initiating the multi-dose Phase 1 study in the second half of 2011."

About the Single-Dose Phase 1 Study

The Phase 1 study is assessing the pharmacokinetics, pharmacology, safety and efficacy of single doses of NKTR-181 in approximately 125 healthy subjects. The primary objective of the Phase 1 trial is to establish the effective analgesic dose range of NKTR-181 associated with minimal CNS side effects. The study is being conducted in the U.S. and is currently ongoing. Final data from the NKTR-181 single-dose Phase 1 study are planned to be presented at an upcoming medical meeting.

About NKTR-181

NKTR-181 is a novel mu-opioid analgesic investigational drug candidate created using Nektar's small molecule polymer conjugate technology. In preclinical studies, NKTR-181 exhibits a reduced rate of entry into the central nervous system (CNS) providing effective pain relief with fewer CNS-related side effects, such as euphoria, sedation and respiratory depression. The unique molecular design of the polymer conjugate also prevents conversion of NKTR-181 into free opioids or an abusable form of an opioid. As a result, NKTR-181 has the potential to be a highly effective analgesic with a favorable safety profile and reduced potential for abuse, misuse and diversion.

About Opioids and Pain Management

Pain is the most common symptom for which patients seek medical attention.(2) According to the American Pain Society, the prevalence of chronic pain in the United States is estimated to be 35.5% or 105 million people. Chronic pain costs more than $100 billion per year in direct health-care expenditures and lost work time. Opioids are considered to be the most effective therapeutic option for pain and have over $10 billion a year in sales in the U.S. alone.(3),(4) However, opioids cause significant problems for physicians and patients because of their serious side effects such as respiratory depression and sedation, as well as the risks they pose for addiction, abuse, misuse, and diversion. The U.S. Food and Drug Administration has cited prescription opioid analgesics as being at the center of a major public health crisis of addiction, misuse, abuse, overdose and death.(5) A 2010 recent report from the Center for Disease Control and Prevention (CDC) notes that emergency room visits tied to the abuse of prescription painkillers is at an all-time high, having increased 111 percent over a five-year period.(6)

About Nektar

Nektar Therapeutics is a biopharmaceutical company developing novel therapeutics based on its PEGylation and advanced polymer conjugation technology platforms. Nektar's technology and drug development expertise have enabled nine approved products in the U.S. or Europe for leading biopharmaceutical company partners, including UCB's Cimzia(R) for Crohn's disease and rheumatoid arthritis, Roche's PEGASYS(R) for hepatitis C and Amgen's Neulasta(R) for neutropenia.

Nektar has created a robust pipeline of potentially high-value therapeutics to address unmet medical needs by leveraging and expanding its technology platforms to improve and enable molecules. In addition to the releasable polymer technology, Nektar is the first company to create a permanent small molecule-polymer conjugate with enhanced oral bioavailability and restricted entry into the CNS. Nektar is conducting clinical and preclinical programs in oncology, pain and other therapeutic areas. Nektar has an exclusive worldwide license agreement with AstraZeneca for its oral NKTR-118 program to treat opioid-induced constipation and its NKTR-119 program for the treatment of pain without constipation side effects. NKTR-102 is being evaluated in Phase 2 clinical studies for the treatment of ovarian, breast and colorectal cancers. NKTR-105 is in a Phase 1 clinical study in cancer patients with refractory solid tumors.

Nektar is headquartered in San Francisco, California, with additional R&D operations in Huntsville, Alabama and Hyderabad, India. Further information about the company and its drug development programs and capabilities may be found online at http://www.nektar.com.

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This press release contains forward-looking statements that reflect Nektar's current views as to the therapeutic potential of NKTR-181, observations based on the preliminary interim data from the first NKTR-181 Phase 1 clinical study, the value of Nektar's polymer conjugate technology platform, and the potential for certain of Nektar's other drug candidates. These forward-looking statements involve substantial risks and uncertainties including but not limited to one or more of the following: (i) the preliminary interim Phase 1 clinical study data for NKTR-181 and observations described in this press release are based on results to date from an ongoing study and there is a risk that future clinical results from the Phase 1 study may not confirm one or more of these results and observations; (ii) although Nektar has conducted various experiments using laboratory and home-based chemistry techniques that have been unable to convert NKTR-181 into a rapidly-acting, more abusable opioid, there can be no assurance that an alternative chemistry technique or process to convert NKTR-181 into a more abusable opioid may be discovered; (iii) NKTR-181 is in early stage clinical development and could fail at any time due to numerous unpredictable and significant risks related to safety, efficacy and other important findings that can negatively impact clinical studies; (iv) scientific discovery of new medical breakthroughs is an inherently uncertain process and the future success of the application of Nektar's technology platform to potential new drug candidates such as NKTR-181 is therefore very uncertain and unpredictable and could unexpectedly fail at any time; (v) Nektar's patent applications for NKTR-181 may not issue, patents that have issued may not be enforceable, or additional intellectual property licenses from third parties may be required; and (vi)

the outcome of any existing or future intellectual property or other litigation related to Nektar's proprietary drug candidates including without limitation NKTR-181. Other important risks and uncertainties are detailed in Nektar's reports and other filings with the Securities and Exchange Commission, including without limitation, those risks and uncertainties set forth in Nektar's Form 10-Q for the quarter ended March 31, 2011, filed on April 29, 2011. Nektar undertakes no obligation to update forward-looking statements, whether as a result of new information, future events or otherwise.

References:

(1) Mandema et al., 1996
(2) Harstall, C. How prevalent is chronic pain? *Pain Clinical Updates* X, 1—4 (2003).
(3) IMS, NSP, NPA and Defined Health 2010 Estimates.
(4) Melnikova, I, Pain Market, *Nature Reviews Drug Discovery*, Volume 9, 589-90 (August 2010).
(5) Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, "*Risk Evaluation and Mitigation Strategies (REMS) for Extended-Release and Long-Acting Opioid Analgesics*", July 23-4, 2010.
(6) Morbidity and Mortality Weekly Report (MMWR), Emergency Department Visits Involving Nonmedical Use of Selected Prescription Drugs — United States, 2004—2008, 59(23);705-709 (June 2010).

SOURCE Nektar Therapeutics