Nektar Announces Positive Clinical Data from Second Phase 1 Clinical Study of NKTR-181, a Novel Opioid Analgesic Molecule to Treat Chronic Pain

NKTR-181 Exhibits Sustained and Dose-Dependent Analgesic Effect, Reduced Rate of Entry into the CNS and Wide Therapeutic Window

SAN FRANCISCO, Dec. 13, 2011 /PRNewswire/ -- Nektar Therapeutics (Nasdaq: NKTR) today announced positive data from a Phase 1 clinical study of NKTR-181 evaluating multiple ascending oral doses of NKTR-181 over an 8-day treatment period in healthy subjects. NKTR-181 is Nektar's new oral opioid analgesic candidate designed to address the abuse liability and serious central nervous system (CNS) side effects associated with current opioid therapies. In this multiple dose Phase 1 study, NKTR-181 exhibited a sustained analgesic response, supporting its development as a twice-daily oral tablet for the treatment of chronic pain conditions. Pupillometry data from the study demonstrated that NKTR-181's centrally-mediated opioid effects are dose-dependent and that the molecule enters the brain slowly, which could reduce the euphoria and other CNS side effects that are associated with current opioids. NKTR-181 was also well-tolerated over the entire 8-day dosing period in the study at all doses evaluated.

NKTR-181 is a novel mu-opioid agonist molecule created using Nektar's proprietary polymer conjugate technology and its differentiating properties are inherent to the design of the new molecule. As a new molecular structure, NKTR-181 is unique in that it does not rely on a formulation approach to prevent its conversion into a more abusable form of an opioid.

"NKTR-181 is emerging as an exciting new development in the treatment of chronic pain," said Lynn R. Webster, MD, Medical Director of Lifetree Clinical Research. "The positive findings from both of the Phase 1 studies for NKTR-181 demonstrate that NKTR-181 has a unique and highly attractive therapeutic profile that is inherent to its new molecular structure. As a novel opioid that could provide sustained analgesia with less CNS side effects and euphoria than existing opioids, NKTR-181 provides great promise for pain practitioners and for patients."

In the Phase 1 multiple ascending dose study, NKTR-181 produced a dose-dependent and sustained analgesic response in a model of pain used in healthy subjects to measure central analgesic activity. NKTR-181 exhibited predictable dose-linear pharmacokinetics across all dose levels with an average half-life of approximately 12 hours and no evidence of pharmacological tolerance over the 8 days of twice-daily dosing. The sustained central response, analgesic effect and safety profile over a 12-hour period supports a twice-daily (BID) dosing schedule.

Full results and data from this multiple ascending dose Phase 1 study of NKTR-181 have been accepted for presentation at the 2012 American Academy of Pain Medicine's 28th Annual Meeting to be held February 23 — 26, 2012.

"These exciting clinical results underscore our enthusiasm for advancing NKTR-181 into Phase 2 development in chronic pain patients," said Robert Medve, MD, Chief Medical Officer at Nektar Therapeutics. "As a new mu-opioid analgesic molecule that does not rely on a formulation approach, NKTR-181 has the potential to transform the treatment of chronic pain by providing effective pain relief with less CNS-related side effects than traditional opioid therapies. Our clinical results to-date suggest that NKTR-181 exhibits a continuous analgesic effect over a 12-hour period, with a slower rate of entry into the CNS, which could greatly reduce its potential dangerous CNS-related side effects and the euphoria that leads to abuse of traditional opioids. We look forward to initiating our Phase 2 clinical study of NKTR-181 in mid-2012."

Chronic pain conditions, such as osteoarthritis, back pain and cancer pain, affect at least 126 million adults in the U.S. annually and contribute to over $100 billion a year in lost productivity.(1)

About the NKTR-181 Phase 1 Multiple Ascending Dose Study

The Phase 1 multiple ascending dose study of NKTR-181 was conducted in the U.S. at Lifetree Clinical Research. The study enrolled a total of 60 healthy subjects over an eight-day treatment period. Four dose cohorts were evaluated with 12 subjects in each dose cohort (100, 200, 300 and 400 mg). Subjects in each cohort received oral doses of NKTR-181 (n=12) or placebo (n=3) following an overnight fast. Pharmacokinetics were determined through serial blood and urine samples. Serial opioid pharmacodynamic tests included a cold pressor test for analgesia and pupillometry as an indicator of the onset and duration of

opioid effect. NKTR-181 was generally well-tolerated at all dose levels in the study: most adverse events were mild and no serious adverse events were reported. Most frequent adverse events observed at the highest doses tested were consistent with AEs characteristic of an opioid agonist, such as constipation, headache and nausea.

The multiple ascending dose study is the second study in the Phase 1 clinical program for NKTR-181. Positive results from the first Phase 1 study, which was a single ascending dose trial in 110 healthy subjects, were presented at the American Academy of Pain Management (AAPM) Annual Meeting in September 2011.

NKTR-181 is currently being prepared for Phase 2 development in chronic pain patients in mid-2012.

About NKTR-181

NKTR-181 is a novel mu-opioid analgesic investigational drug candidate created using Nektar's advanced small molecule polymer conjugate technology. The unique molecular design of the polymer conjugate is designed to prevent conversion of NKTR-181 into a more abusable form of an opioid. With slower entry into the CNS when compared to published oxycodone data, NKTR-181 has the potential to greatly reduce the euphoria that underlies opioid abuse liability and dependence. In addition, NKTR-181 is intended to reduce the other serious CNS-related side effects such as respiratory depression and sedation which are associated with current opioid therapies.

About Opioids and Pain Management

Pain is the most common symptom for which patients seek medical attention.(1) 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 conditions, such as osteoarthritis, back pain and cancer pain, affect at least 126 million adults in the U.S. annually and contribute to over $100 billion a year in direct health-care expenditures and lost work time.(1) 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.(2,3) 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.(4) 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.(5)

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 seven 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 currently 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.

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*.

This press release contains forward-looking statements that reflect Nektar's current views as to the therapeutic potential of NKTR-181, 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 statements regarding the potential therapeutic potential of NKTR-181 are based on preclinical data and data from both Phase 1 clinical studies and future clinical studies may not confirm one or more of these potential therapeutic benefits; (ii) although Nektar has conducted various experiments using laboratory and home-based chemistry techniques that have so far been unable to convert NKTR-181 into a rapidly-acting, more abusable opioid, there is a risk that an alternative chemistry technique or process may be discovered in the future that would enable the conversion of NKTR-181 into a more abusable opioid; (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 development; (iv) the U.S. Food and Drug Administration and other regulatory agencies could impose significant risk mitigation requirements that hamper market acceptance of NKTR-181, even if approved for commercialization; (v) 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; (vi) patents may not issue from Nektar's patent applications for NKTR-181, patents that have issued may not be enforceable, or additional intellectual property licenses from third parties may be required; and (vii) 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 September 30, 2011, filed on November 4, 2011. Nektar undertakes no obligation to update forward-looking statements, whether as a result of new information, future events or otherwise.

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(1) 2011 National Academy of Sciences. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education and Research, 2010 Decision Resources, and Harstall, C. How prevalent is chronic pain? *Pain Clinical Updates* X, 1—4 (2003).

(2) IMS, NSP, NPA and Defined Health 2010 Estimates.

(3) Melnikova, I, Pain Market, *Nature Reviews Drug Discovery*, Volume 9, 589-90 (August 2010).

(4) 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.

(5) *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