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Nektar Announces Start of Enrollment in Phase 2 Study of NKTR-181, a Novel Opioid Analgesic Molecule, for Treatment of Chronic Pain

SAN FRANCISCO, July 24, 2012 /PRNewswire/ -- Nektar Therapeutics (NASDAQ: NKTR) announced today that the first patient has been enrolled in a Phase 2 clinical study of NKTR-181, a new, first-of-its-kind, opioid analgesic candidate. NKTR-181 is a novel mu-opioid agonist molecule designed to have a slow rate of entry into the brain to reduce the attractiveness of the molecule as a target of abuse and to reduce other CNS-mediated side effects, such as sedation and respiratory depression. The Phase 2 study will utilize a double-blind, placebo-controlled, randomized withdrawal study design to assess the efficacy, safety and tolerability of NKTR-181 in patients with moderate to severe chronic pain from osteoarthritis of the knee. Approximately 200 patients will be randomized to receive either NKTR-181 or placebo in the study.

"We are extremely pleased to be part of this Phase 2 clinical study of NKTR-181 in chronic pain patients," said Jeffrey Gudin, MD, Director of Pain Management and Palliative Care, Englewood Hospital & Medical Center and Clinical Instructor of Anesthesiology at Mt. Sinai School of Medicine. "NKTR-181 exhibited highly differentiated properties in its Phase 1 development, which include slow penetration across the blood-brain barrier into the CNS. This slow rate of entry may allow us to effectively address pain while reducing some of the most troubling opioid CNS effects such as euphoria, sedation, and respiratory depression. NKTR-181 represents a potential paradigm shift in the way we think about opioid analgesia."

NKTR-181 is an NCE (new chemical entity) which was created using Nektar's proprietary small molecule polymer conjugate technology and its potential differentiating properties are inherent to the design of the new molecule. As a new molecular structure, NTKR-181 does not rely on a formulation approach, which is a common method that has been used with opioid drugs in order to attempt to block their conversion into abusable forms of an opioid. Phase 1 studies demonstrated that NKTR-181 produced sustained and dose-dependent analgesic responses in healthy volunteers, a slower rate of CNS entry as measured by pupillometry, or contraction of the pupils, and an excellent tolerability profile. NKTR-181's Phase 1 clinical development program evaluated the molecule in approximately 180 healthy volunteers.

"As a new mu-opioid analgesic molecule, NKTR-181 has the potential to transform the treatment of chronic pain by using a molecular approach to reduce the risk of traditional opioid therapy while preserving its analgesic benefit," said Robert Medve, MD, the company's Senior Vice President and Chief Medical Officer. "We are excited to be advancing this molecule into Phase 2 testing in chronic pain patients."

The NKTR-181 Phase 2 study uses a randomized withdrawal design, which includes a baseline period and a drug titration period followed by a randomized, placebo-controlled, double-blind phase of the study. The primary endpoint of the study will be the average change in a patient's pain score from baseline to the end of the double-blind, randomized treatment period. The study will enroll opioid-naive patients with osteoarthritis of the knee who are not getting adequate pain relief from their current non-opioid pain medication. Patients who qualify during the baseline period will enter a titration phase, during which they will be titrated on NKTR-181 tablets administered orally twice-daily until a dose is reached that provides a reduction of at least 20% in the patient's pain score as compared to the patient's own baseline. Patients that achieve this level of analgesia will then be randomized on a 1:1 basis to either continue to receive their analgesic dose of NKTR-181 or to receive placebo for up to 25 days. Secondary endpoints of the study include quality-of-life assessment, sleep and motor activity scoring, as well as tolerability endpoints.

The company is also planning a separate human abuse liability study for NKTR-181 as part of Phase 2 development for the compound. This study will measure liking scores for NKTR-181 as compared to an active opioid in approximately 20 recreational drug users.

About Opioids and Pain Management

Pain is one of the most common reasons people seek medical treatment.[1] The American Pain Society estimates that 35.5 percent of the U.S. population, or 105 million people, suffer from chronic pain in the United States. 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 healthcare expenditures and lost work time.[1] Opioids are considered the most effective therapeutic option for pain, with sales exceeding over $10 billion a year in the U.S. alone.[2,3] However, opioids can cause serious side effects such as respiratory depression and sedation and have the potential for addiction, abuse and misuse. In 2010, the Centers for Disease Control and Prevention reported that emergency room visits for non-medical use of opioid analgesics

increased 111 percent over a five-year period.[4]

About Nektar

Nektar Therapeutics is a biopharmaceutical company developing novel therapeutics based on its PEGylation and advanced polymer conjugation technology platforms. Nektar has a robust R&D pipeline of potentially high-value therapeutics in oncology, pain and other therapeutic areas. In the area of pain, Nektar has an exclusive worldwide license agreement with AstraZeneca for naloxegol (NKTR-118), an investigational drug candidate, which is being evaluated in Phase 3 clinical studies as a once-daily, oral tablet for the treatment of opioid-induced constipation. This agreement also includes NKTR-119, an earlier stage development program that is a co-formulation of naloxegol and an opioid. NKTR-181, a novel mu-opioid analgesic candidate for chronic pain conditions, is in Phase 2 development in osteoarthritis patients with chronic knee pain. NKTR-192, a novel mu-opioid analgesic in development to treat acute pain is in Phase 1 clinical development. In oncology, etirinotecan pegol (NKTR-102) is being evaluated in a Phase 3 clinical study (the BEACON study) for the treatment of metastatic breast cancer and is also in Phase 2 studies for the treatment of ovarian and colorectal cancers.

Nektar's technology has enabled eight approved products in the U.S. or Europe through partnerships with leading biopharmaceutical companies, including Affymax's OMONTYS® for anemia, UCB's Cimzia® for Crohn's disease and rheumatoid arthritis, Roche's PEGASYS® for hepatitis C and Amgen's Neulasta® for neutropenia. Additional development-stage products that leverage Nektar's proprietary technology platform include Baxter's BAX 855, a long-acting PEGylated rFVIII program, which is in Phase 1 clinical development.

Nektar is headquartered in San Francisco, California, with additional 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.

Forward-Looking Statements

This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements can be identified by words such as: "anticipate," "intend," "plan," "expect," "believe," "should," "could," "potential," "may" and similar references to future periods. Examples of forward-looking statements include our current views as to the potential of NKTR-181 as a new approach to opioid analgesia and pain therapy; the potential of NKTR-181 to be less attractive as a target of user abuse than standard opioid therapies; the potential of NKTR-181 to exhibit reduced CNS-related side effects associated with standard opioid therapies; our plan to commence a separate human abuse liability study for NKTR-181 as part of Phase 2 development for the compound; the value of our polymer conjugate technology platform; and the potential of certain of our other drug candidates and those of our collaboration partners. Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based only on our current beliefs, expectations, observations and assumptions regarding the potential of our business, drug candidates and our technology. Because forward-looking statements relate to the future, they are subject to inherent uncertainties, risks and changes in circumstances that are difficult to predict and many of which are outside of our control. Our actual results may differ materially from those indicated in the forward-looking statements. Therefore, you should not rely on any of these forward-looking statements. Important factors that could cause our actual results to differ materially from those indicated in the forward-looking statements include, among others: (i) the statements regarding the therapeutic potential of NKTR-181 are based on preclinical data and data from completed Phase 1 clinical studies and future clinical studies may not confirm these potential therapeutic benefits; (ii) although we have conducted various experiments using laboratory and home-based chemistry techniques that have so far been unable to convert NKTR-181 into a rapid-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 the earlier stages of 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 health authorities could impose significant risk mitigation requirements that hamper the commercial potential of NKTR-181, even if this drug candidate receives regulatory approval; (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 our 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 our proprietary drug candidates. Other important risks and uncertainties are detailed in our reports and other filings with the Securities and Exchange Commission ("SEC"), including without limitation, those risks and uncertainties set forth in our Form 10-Q for the quarter ended March 31, 2012, filed with the SEC on May 4, 2012. We undertake no obligation to update any forward-looking statement, whether written or oral, that may be made from time to time, whether as a result of new information, future developments 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) *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).

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