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Data Published in the New England Journal of Medicine Demonstrate that Naloxegol Improved Opioid-Induced Constipation in Chronic Pain Patients

SAN FRANCISCO, June 19, 2014 /PRNewswire/ -- Nektar Therapeutics (NASDAQ:NKTR) reported that partner AstraZeneca today announced that the *New England Journal of Medicine (NEJM)* has published results of two pivotal Phase III studies - KODIAC-4 and KODIAC-5 of naloxegol, an investigational treatment for opioid-induced constipation (OIC).

Opioids play an important role in chronic pain relief by binding to mu-receptors in the brain, but they also bind to mu-receptors in the bowel. That is why patients taking opioids for chronic pain can develop OIC. In fact, the incidence of OIC varies and has been reported as high as 81%* in patients taking opioids. Naloxegol, which has the potential to be the first FDA approved once-daily oral treatment for patients with OIC, is a peripherally-acting mu-opioid receptor antagonist (PAMORA) studied in adult patients with chronic non-cancer pain experiencing OIC.

**Primary endpoint data from the KODIAC-4 and -5 studies showed that more OIC patients treated with naloxegol 25 mg had a consistent response of increased spontaneous bowel movements (SBMs) through 12 weeks of treatment compared to placebo [44% vs. 29% (p=0.001 KODIAC-4) and 40% vs. 29% (p=0.021 KODIAC-5)]. The 12.5 mg dose in KODIAC-5 did not show statistical significance for the primary endpoint.

The 25 mg dose also demonstrated a higher response rate through 12 weeks of treatment compared to placebo in patients with laxative inadequate response (LIR), a secondary endpoint. Results for an additional secondary endpoint showed that patients taking naloxegol 25 mg in the KODIAC-4 and KODIAC-5 studies were likely to have a first post-dose spontaneous bowel movement 25-30 hours sooner than placebo, respectively (median six and 12 hours for naloxegol 25 mg compared to 36 and 37 hours for placebo, in studies KODIAC-4 and -5, respectively).

"An estimated 235 million prescriptions for opioids are written in the US each year, of which 20% are for chronic pain. For patients taking prescription opioids for chronic pain, constipation is one of the most common and bothersome side effects, and these patients can experience sub-optimal relief from laxatives," said William Chey, MD, AGAF, FACG, FACP, Professor of Medicine at the University of Michigan Health System. "These results demonstrated the potential for naloxegol, if approved, to be a new treatment option as the studies showed rapid and sustained improvement for these patients, without compromising their pain management over the course of the trials."

The Phase III studies, KODIAC-4 (n=652) and KODIAC-5 (n=700), were 12-week, multicenter, randomised, double blind, placebo-controlled pivotal trials that evaluated 12.5 mg and 25 mg doses of naloxegol, administered once-daily.

Additional results from the KODIAC-4 and KODIAC -5 clinical trials published in *NEJM* included:

- The number of SBMs per week increased with naloxegol 25 mg treatment over 12 weeks, with both studies showing an improvement in treatment effect versus placebo
- Improvements in straining, stool consistency, and frequency of days with complete SBMs were observed with naloxegol 25 mg (both studies)
- The most commonly reported adverse effects with naloxegol were gastrointestinal in origin (abdominal pain, diarrhea, nausea, vomiting, flatulence) and appeared to be dose-ordered, occurring more commonly in the 25 mg group. Most adverse events were mild to moderate in severity and occurred shortly after initiation of naloxegol
- There was 1 major adverse cardiovascular event (MACE) in the 25 mg treatment arm, 1 in the 12.5 mg treatment arm and 2 in the placebo arm

A New Drug Application (NDA) for naloxegol was accepted by the US Food and Drug Administration on 19 November 2013. MOVANTIK™ is the proposed proprietary name for naloxegol. On June 11-12, 2014, the FDA convened the Anesthetic Analgesic Drug Products Advisory Committee (AADPAC) to review the class of peripherally acting opioid receptor antagonists. The Committee voted that the FDA should not require cardiovascular outcomes trials for the PAMORA class of drugs which includes MOVANTIK. Following a clarification of the vote, the majority of the Committee suggested continued post-approval data collection for cardiovascular safety. The Prescription Drug User Fee Act (PDUFA) date set by the FDA for MOVANTIK is September 16, 2014.

MOVANTIK is also under regulatory review with health agencies in the European Union and Canada.

About naloxegol
Naloxegol is an investigational peripherally-acting mu-opioid receptor antagonist (PAMORA), which has been specifically designed for the treatment of opioid-induced constipation, a condition caused by prescription opioid pain medicines. In the Phase III clinical studies, naloxegol was administered as a once-daily tablet and is designed to block the binding of opioids to the opioid receptors in the gastrointestinal (GI) tract without impacting the opioid receptors in the brain.

Naloxegol is part of the exclusive worldwide license agreement announced in September 2009, between AstraZeneca and Nektar Therapeutics. Naloxegol was developed using Nektar's proprietary oral small molecule polymer conjugate technology.

About Opioid-Induced Constipation
Opioids play an important role in chronic pain relief by binding mu-receptors in the brain. But they also bind mu-receptors in the bowel. That is why patients taking opioids for chronic pain can develop opioid-induced constipation (OIC). In fact, the incidence of OIC varies and has been reported as high as 81%* in patients taking opioids.

**Published estimates of the incidence of OIC in patients receiving opioids for chronic pain vary due to differences in the studies conducted (eg, study design, definition of constipation, opioids used). Meta-analyses of randomized controlled trials suggest that 15%-41% of these patients develop OIC, while observational and survey based studies suggest that 37%-81% develop OIC.*

***The primary endpoint in both trials was percentage of OIC responders, versus placebo, over 12 weeks of treatment.*

About Nektar
Nektar Therapeutics (NASDAQ: NKTR) 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 pain, oncology 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 has been filed for regulatory approvals in the U.S., Europe and Canada 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 molecule for chronic pain conditions, has completed Phase 2 development in osteoarthritis patients with chronic knee pain. NKTR-171, a new sodium channel blocker being developed as an oral therapy for the treatment of peripheral neuropathic 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, colorectal, lung and brain cancers. In anti-infectives, Amikacin Inhale is in Phase 3 studies conducted by Bayer Healthcare as an adjunctive treatment for intubated and mechanically ventilated patients with Gram-negative pneumonia. 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 3 clinical development for patients with hemophilia A.

Nektar's technology has enabled eight approved products in the U.S. or Europe through partnerships with leading biopharmaceutical companies, including UCB's Cimzia® for Crohn's disease and rheumatoid arthritis, Roche's PEGASYS® for hepatitis C and Amgen's Neulasta® for neutropenia.

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.

Cautionary Note Regarding 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," "may," "will" and similar references to future periods. Examples of forward-looking statements include, among others, statements we make regarding the therapeutic potential for MOVANTIKTM (naloxegol), the regulatory process and outcomes for MOVANTIK, and the value and potential of our technology and research and development pipeline. Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based only on our current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, anticipated events and trends, the economy and other future conditions. 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 voting and recommendations from the AADPAC are advisory only and not binding on the FDA; (ii) upcoming FDA determinations made in the MOVANTIKTM new drug

application review process will have a significant impact on the Company's financial position based on significant regulatory and launch milestone opportunities and a potential repayment obligation by the Company to AstraZeneca as described in our most recent Quarterly Report on Form 10-Q filed with the SEC on May 8, 2014 (the "Form 10-Q") and the Current Report on Form 8-K filed with the SEC on August 8, 2013; (iii) our drug candidates and those of our collaboration partners are in various stages of clinical development and the risk of failure is high and can unexpectedly occur at any stage prior to regulatory approval for numerous reasons including safety and efficacy findings even after positive findings in previous preclinical and clinical studies; (iv) the timing of the commencement or end of clinical trials and the commercial launch of our drug candidates may be delayed or unsuccessful due to regulatory delays, slower than anticipated patient enrollment, manufacturing challenges, changing standards of care, evolving regulatory requirements, clinical trial design, clinical outcomes, competitive factors, or delay or failure in ultimately obtaining regulatory approval in one or more important markets; (v) acceptance, review and approval decisions for new drug applications by health authorities is an uncertain and evolving process and health authorities retain significant discretion at all stages of the regulatory review and approval decision process; (vi) scientific discovery of new medical breakthroughs is an inherently uncertain process and the future success of the application of our technology platform to potential new drug candidates is therefore highly uncertain and unpredictable and one or more research and development programs could fail; and (vii) certain other important risks and uncertainties set forth in our Form 10-Q. Any forward-looking statement made by us in this press release is based only on information currently available to us and speaks only as of the date on which it is made. 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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