

## News Release

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### **NKTR-118 Shows Substantial Oral Bioavailability and Extended Half-Life In Phase 1 Clinical Data Presented at American Pain Society Meeting**

**San Carlos, Calif., May 7, 2008** – New Phase 1 clinical trial results for NKTR-118 (oral PEG-naloxol) were presented by Nektar Therapeutics (Nasdaq: NKTR) this week at the Annual Meeting of the American Pain Society (APS) in Tampa, Florida. In this multiple-dose Phase 1 study, oral NKTR-118 was shown to have substantial oral bioavailability with rapid absorption and an extended half-life that is up to ten times the known half-life of unPEGylated naloxone.

NKTR-118 is Nektar's proprietary peripheral opioid antagonist candidate currently in a Phase 2 trial in patients with opioid-induced bowel dysfunction (OBD), including opioid-induced constipation. Nektar's advanced small molecule PEGylation technology has been shown to reduce NKTR-118's penetration across the blood-brain barrier, an important potential advance for this and many other potential therapies.

"For the first time, it has now been shown that Nektar's proprietary PEGylation technology can be used to enhance oral bioavailability for a small molecule drug," said Timothy A. Riley, Ph.D., Vice President of PEGylation Research at Nektar. "In addition, this PEGylated drug exhibited an exceptionally long half-life of eleven hours, enabling a once-daily dosing regimen for NKTR-118 as an oral therapy."

NKTR-118 was also shown to be safe and generally well-tolerated at doses up to 250 mg twice daily, with no serious or severe adverse events. The pharmacokinetics of NKTR-118 were dose-proportional and the observed terminal half-life of the drug was approximately eleven hours, independent of dose. This compares to a known half-life of between 45 and 100 minutes for naloxone.<sup>1</sup> At all dose levels, NKTR-118 was rapidly absorbed after oral administration, as evidenced by a steep increase of plasma NKTR-118 concentration. Plasma concentrations of NKTR-118-glucuronide were approximately 100-fold less than plasma NKTR-118 concentrations. Studies have shown that the bioavailability of oral naloxone is limited by first-pass metabolism of naloxone.<sup>1</sup>

"The prevalence and impact of opioid-bowel dysfunction among chronic pain patients are underestimated today," said Sunil J. Panchal, M.D., President of the National Institute of Pain and the Coalition for Pain Education (COPE) Foundation. "The condition can have a serious deleterious impact on a patient's quality of life and can also limit chronic pain management treatments. There is a clear need for an oral therapy that targets the underlying cause of OBD while preserving the desired analgesic effects of opioid treatment."

## **About the Phase 1 Clinical Trial**

The primary objective of this Phase 1 multi-dose, double-blind, randomized, placebo-controlled study was to evaluate the safety and tolerability of multiple doses of oral NKTR-118 in healthy human subjects not receiving opioid therapy. A total of 32 subjects enrolled in the trial. The secondary objective of the trial was to evaluate the pharmacokinetics of oral NKTR-118 and its metabolite (NKTR-118 glucuronide) following twice-daily oral administration for seven days. Escalating doses up to 250 mg twice daily were studied. Subjects were randomized 3:1 to NKTR-118 or placebo twice daily (every 12 hours) for seven days, with a single dose on the eighth day.

## **Prior Clinical Study Results for NKTR-118**

Nektar previously presented results from a proof-of-principle, single-dose Phase 1 study at the American College of Clinical Pharmacology Meeting (ACCP) conference in September of 2007. In this proof-of-principle study, single oral doses of NKTR-118 antagonized morphine-induced delay in gastrointestinal transit time demonstrating the potential of the drug to relieve constipation. Further, no diminution of morphine-induced miosis, a CNS effect, was observed at single oral doses of NKTR-118 of 125 mg or less. In addition, NKTR-118 at single doses up to 1,000 mg was well-tolerated. The drug was rapidly absorbed with dose-proportional pharmacokinetics over the 8-1,000 mg dose range.

## **Data Presentations for NKTR-118**

The poster presentation made this week at the APS Meeting, as well previous data presentations for NKTR-118, can be found on Nektar's website at <http://www.nektar.com/wt/page/nktr118media>

*APS Poster #210: "Results from a Phase 1, Double-Blind, Randomized, Placebo-Controlled, Multiple-Dose Study Evaluating the Safety, Tolerability and Pharmacokinetics of Oral Doses of NKTR-118 (PEG-Naloxol)"*

## **About NKTR-118**

Oral NKTR-118 is currently in a Phase 2 study to evaluate the efficacy, safety and tolerability of once-daily doses in patients with opioid-induced constipation (OIC). The investigational drug combines Nektar's advanced small molecule PEGylation technology platform with naloxol, a derivative of the opioid-antagonist drug, naloxone. In a Phase 1 clinical study, Nektar's PEGylation technology has been shown to reduce penetration of oral NKTR-118 across the blood-brain barrier, an important potential advance for this and possibly many other small molecule therapies.

The antagonist NKTR-118 targets mu-opioid receptors within the enteric nervous system, which mediate OBD, a symptom complex resulting from opioid use that encompasses constipation, bloating, abdominal cramping, and gastroesophageal reflux. Constipation is the hallmark of this syndrome, and is generally its most prominent component. Many studies indicate that a high percentage of patients receiving opioids are likely to experience significant constipation and other symptoms of OBD. According

to IMS Health, about 230 million prescriptions were written for opioids in 2007 in the United States, alone.

Currently, there are no specific oral drugs approved that are indicated to treat OIC. Stool softeners or laxatives may be ineffective for many patients with OIC and they are often associated with side effects like diarrhea and stomach cramps. OBD and OIC can significantly impact quality of life and increase healthcare utilization. A meta-analysis of available randomized, placebo-controlled trials of non-cancer patients receiving opioids for moderate-to-severe pain revealed that constipation is one of the most common opioid-related side effects.<sup>2</sup>

### **Nektar PEGylation Platform**

Nektar PEGylation technology can enhance the properties of therapeutic agents by increasing drug circulation time in the bloodstream, decreasing immunogenicity and dosing frequency, increasing bioavailability and improving drug solubility and stability. It can also be used to modify pharmaceutical agents to preferentially target certain systems within the body and reduce penetration of drug across the blood-brain barrier. It is a technique in which non-toxic polyethylene glycol (PEG) polymers are attached to therapeutic agents, and it is applicable to most major drug classes, including proteins, peptides, antibody fragments, small molecules, and other drugs.

Nektar PEGylation technology is also used in eight additional approved partnered products in the U.S. or Europe today, including UCB's Cimzia for Crohn's disease, Roche's PEGASYS® for hepatitis C and Amgen's Neulasta® for neutropenia.

### **About Nektar**

Nektar Therapeutics is a biopharmaceutical company that develops and enables differentiated therapeutics with its industry-leading PEGylation and pulmonary drug development platforms. Nektar's technology and drug development expertise have enabled nine approved products for partners, which include leading biopharmaceutical companies. Nektar is also developing a robust pipeline of its own high-value therapeutics that addresses unmet medical needs by leveraging and expanding its technology platforms to improve known molecules.

This press release contains forward-looking statements regarding the potential of the company's PEGylation technology platform and NKTR-118. These forward-looking statements involve important risks and uncertainties, including but not limited to: (i) preclinical testing and clinical trials for NKTR-118 are long, expensive and uncertain processes, (ii) because the NKTR-118 product development program is in the early phases of clinical development, the risk of failure is high and can occur at any stage of development, (iii) the company may fail to obtain regulatory approval of NKTR-118, (iv) potential competition from approved drugs or drugs under development that may be safe and effective for the same indication as that targeted by NKTR-118, and (v) the company's patent applications for NKTR-118 may fail to issue; patents that have issued may not be enforceable; or unanticipated intellectual property licenses from third parties may be required in the future. Other important risks and uncertainties are detailed in the company's reports and other filings with the SEC; including its most recent Annual Report on Form 10-K and Quarterly Report on Form 10-Q. Actual results could differ

materially from the forward-looking statements contained in this press release. The company undertakes no obligation to update forward-looking statements, whether as a result of new information, future events, or otherwise. No information regarding or presented at the scientific meetings referred to above (or contained at the Internet links provided herein) is intended to be incorporated by reference in this press release.

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- 1 Handel K, Schauben J, Salmone F, Naloxone. *Annals of Emergency Medicine* 1993; 12.7; 438-51
- 2 Kalso et al., Opioids in chronic non-cancer pain; systematic review of efficacy and safety.

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