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Nektar Announces Topline Data from Human Abuse Potential Study for NKTR-181, a First-in-Class Investigational Opioid to Treat Chronic Pain

NKTR-181 shows significantly less abuse potential compared to oxycodone
Analyst Conference Call and Webcast Today at 5:45 a.m. PDT/8:45 a.m. EDT

SAN FRANCISCO, July 18, 2017 /PRNewswire/ -- Nektar Therapeutics (NASDAQ: NKTR) announced positive topline results from an oral Human Abuse Potential (HAP) study of NKTR-181, a first-in-class opioid analgesic. NKTR-181 is a new chemical entity (NCE) that is the first full mu-opioid agonist molecule designed to provide potent pain relief without the high levels of euphoria that can lead to abuse and addiction with standard opioids.[1] NKTR-181 is the first analgesic opioid molecule to exhibit reduction in specific CNS-mediated side effects, like euphoria, through the strategic alteration of brain-entry kinetics. The U.S. Food and Drug Administration (FDA) has granted the investigational medicine NKTR-181 Fast Track designation for the treatment of moderate to severe chronic pain.

The NKTR-181 HAP study was designed to confirm and assess the relative oral abuse potential of NKTR-181 at its maximum analgesic or therapeutic dose (400 mg) and at a supratherapeutic dose (3 times to 12 times greater than its analgesic dose range of 100 mg to 400 mg) compared to common therapeutic doses of a Schedule II opioid, oxycodone.

"Today's opioid abuse epidemic has created a pressing need for a better pain medicine that does not possess the euphorigenic qualities of conventional opioids," said Ivan Gergel, MD, Senior Vice President and Chief Medical Officer of Nektar. "It is clear from our new study results that NKTR-181 is highly differentiated in this respect from oxycodone, which is a choice drug of abuse. Further, and critically important in the context of this public health emergency, NKTR-181's less rewarding properties and strong analgesia are inherent to its novel molecular structure and independent of any abuse-deterrent formulation. Many patients do not receive adequate pain relief because they fear taking conventional opioids, including abuse-deterrent formulations, because of their potential for abuse and addiction. We believe NKTR-181 is a transformational pain medicine that should significantly advance the treatment of chronic pain and could be a fundamental building block in the fight against prescription opioid abuse. We are committed to bringing this new pain treatment to patients and physicians as quickly as possible."

Opioids act on specific receptors in the brain to provide pain relief, but they also target the dopamine reward system in the brain to produce euphoria and other psychoactive effects, which leads to addiction and abuse.[1] Brain imaging studies have shown that the faster a euphorigenic drug enters and leaves the brain, the stronger are its reinforcing effects.[2] In 2014, nearly 2 million Americans either abused or were dependent on prescription opioid pain relievers.[3] Opioid abuse is a growing epidemic in the U.S., with one in five Americans who say they have a family member who has been addicted to prescription painkillers.[4]

"Getting very high, very fast, is a mark of conventional high-risk, abused opioids," said Jack Henningfield, PhD, vice president at Pinney Associates and adjunct professor at The Johns Hopkins University School of Medicine. "NKTR-181 represents a meaningful advance in the treatment of pain as the first opioid analgesic with inherent brain-entry kinetics that avoids this addictive quality of traditional opioids. This prevents the rapid 'rush' that abusers seek during the critical period immediately after dosing. Importantly, these properties of NKTR-181 are inherent to its molecular structure and are not changed through tampering or route of administration."

In March 2017, NKTR-181 completed a Phase 3 efficacy trial (SUMMIT-07) in 610 patients with moderate to severe chronic low back pain who were new to opioid therapy (opioid-naïve). SUMMIT-07 evaluated four analgesic doses of NKTR-181 (100 mg, 200 mg, 300 mg and 400 mg). Patients in the trial achieved an average pain score reduction of over 65% (from 6.73 at screening to 2.32 at randomization) during the dose titration period. The primary efficacy endpoint of the study demonstrated significantly improved chronic back pain relief with NKTR-181 compared to placebo (p=0.0019). Key secondary endpoints of the study also achieved high statistical significance. The study demonstrated that NKTR-181 had a favorable safety profile and was well tolerated.

HAP Study Design and Objectives

HAP studies are clinical studies that help assess the relative abuse potential of a medicine. The NKTR-181 HAP study was a randomized, double-blind, placebo-controlled, six-sequence crossover study evaluating the relative oral abuse potential of NKTR-181 relative to the Schedule II opioid oxycodone in healthy non-dependent recreational drug users experienced in the oral abuse of opioids who can identify drug effects that are relevant to abuse risk assessment. Subjects (n=54) were randomized to one of six test sequences, in each of which they received a single dose of one of the six study drugs:

- NKTR-181 400 mg (highest efficacious dose established in the Phase 3 efficacy trial);
- NKTR-181 600 mg (a dose of 1.5 to 6 times greater than the efficacious dose range established in the Phase 3 efficacy trial);
- NKTR-181 1200 mg (a supratherapeutic dose of 3 to 12 times greater than the efficacious dose range of 100 mg to 400 mg established in the Phase 3 efficacy trial);
- Moderate therapeutic dose of oxycodone at 40 mg
- High therapeutic dose of oxycodone at 60 mg

There was a five-day washout period between each treatment. NKTR-181 doses and its matching placebo were administered as oral tablets. Oxycodone HCl doses were administered as over-encapsulated oral tablets.

The study evaluated effects that are predictive of abuse potential with opioids for all doses in the study. The HAP trial was powered to detect a relative peak (Emax*) drug liking score difference between oxycodone at 60 mg and NKTR-181 at 1,200 mg. Liking was based on a subject-reported 100-point bipolar liking/disliking visual analog scale (VAS), which is a standard measure of abuse potential in HAP studies. Key secondary endpoints were Area Under Effect for Drug Liking in the first 1, 2 and 3 hours after dosing as well as retrospective subject-reported unipolar VAS ratings for Drug High and bipolar VAS ratings for Take Drug Again.

Topline Results

Primary Endpoint of Drug Liking:

- NKTR-181 400 mg had a significantly lower rating of peak (Emax) liking compared to oxycodone 40 mg (62.0 vs. 76.6, $p < 0.0001$).
- NKTR-181 400 mg had a significantly lower rating of peak (Emax) liking compared to oxycodone 60 mg (62.0 vs. 81.5, $p < 0.0001$).
- NKTR-181 600 mg had a significantly lower rating of peak (Emax) liking compared to oxycodone 40 mg (67.9 vs. 76.6, $p < 0.0001$).
- NKTR-181 600 mg had a significantly lower rating of peak (Emax) liking compared to oxycodone 60 mg (67.9 vs. 81.5, $p < 0.0001$).
- NKTR-181 1200 mg had a significantly lower rating of peak (Emax) drug liking compared to oxycodone 60 mg (76.7 vs. 81.5, $p=0.0071$). This dose was not statistically different from oxycodone 40 mg.

The peak liking score for NKTR-181 400 mg oral tablet in this study confirmed the same peak liking score for NKTR-181 400 mg oral solution evaluated in the company's prior HAP study (62.0 vs 62.3**).

Secondary Endpoint of Area Under Effect (AUE) for Drug Liking Following Dosing (0-1 Hours, 0-2 Hours, 0-3 Hours):

- NKTR-181 400 mg had significantly lower AUE for all timepoints compared to both oxycodone 40 mg and 60 mg ($p < 0.0001$).
- NKTR-181 600 mg had significantly lower AUE for all timepoints compared to both oxycodone 40 mg and 60 mg ($p < 0.0001$).
- NKTR-181 1200 mg had significantly lower AUE for all timepoints compared to both oxycodone 40 mg and 60 mg. For AUE (0-1 Hours), $p=0.0002$ and $p < 0.0001$, respectively; for AUE 0-2 Hours, $p=0.001$ and $p < 0.0001$, respectively; for AUE 0-3 Hours, $p=0.0396$ and $p=0.0003$, respectively).

Secondary Endpoint of Drug High:

- NKTR-181 400 mg had significantly lower ratings of peak (Emax) Drug High compared to both oxycodone 40 mg and 60 mg ($p < 0.0001$).
- NKTR-181 600 mg had significantly lower ratings of peak (Emax) Drug High compared to both oxycodone 40 mg and 60 mg ($p < 0.0001$).
- NKTR-181 1200 mg had a significantly lower rating of peak (Emax) Drug High compared to 60 mg oxycodone ($p=0.0071$).

The peak Drug High score for NKTR-181 400 mg oral tablet in this study confirmed the peak Drug High score in the first

HAP trial, which evaluated 400 mg NKTR-181 as an oral solution (21.3 vs 22.59**).

Secondary Endpoint of Take Drug Again:

- NKTR-181 400 mg had significantly lower ratings of peak (Emax) Take Drug Again compared to the 40 mg and 60 mg oxycodone ($p < 0.0001$).
- NKTR-181 600 mg had significantly lower ratings of peak (Emax) Take Drug Again compared to the 40 mg and 60 mg oxycodone ($p=0.0004$ and $p < 0.0001$, respectively).
- NKTR-181 1200 mg had a significantly lower rating of peak Take Drug Again compared to 60 mg oxycodone ($p=0.011$).

Full data from the NKTR-181 HAP study will be presented at a future medical meeting.

Pain is one of the most common reasons people seek medical treatment.[5] A study published in the American Pain Society's *The Journal of Pain* in October 2014 estimated that 19 percent of the U.S. population, or 39 million people, suffer from some type of persistent pain.[6] In 2015, there were nearly 22,000 deaths involving prescription opioids in the U.S.[7] The health care utilization consequences are also significant; for every one death from prescription opioids, it is estimated that there are 10 treatment admissions for abuse, 32 emergency room visits for misuse or abuse, 130 people who are dependent, and 825 people who report non-medical use of these drugs.[8]

Conference Call and Webcast Information
Nektar will host a conference call and webcast presentation today, July 18, 2017 at 8:45 a.m. Eastern Daylight Time to discuss the study results. The call can be accessed by dialing (877) 881-2183 (U.S.) or (970) 315-0453 (international), and entering passcode 56389932. To access the live webcast, or the subsequent archived recording, visit the Investors section of the Nektar website at www.nektar.com. The webcast will be available for replay on Nektar's website for two weeks following the call.

About NKTR-181
NKTR-181 is the first long-acting, selective mu-opioid agonist designed to provide potent pain relief without the inherent high levels of euphoria which lead to abuse and addiction with standard opioids. The novel molecular structure of NKTR-181 is designed to have low permeability across the blood-brain barrier in order to slow its rate of entry into the brain and attenuate the dopamine release that underlies euphoria. NKTR-181 is the first opioid molecule to exhibit reduction in specific CNS-mediated side effects, like euphoria, through the strategic alteration of brain-entry kinetics. In addition, NKTR-181 is designed with an inherent 12-hour elimination half-life to enable twice-daily dosing with continuous pain control. NKTR-181 is an investigational medicine and has not been approved by the FDA or any other regulatory agencies.

Current and past strategies of abuse deterrence to address the addictive qualities of standard opioids rely on formulations alone. However, all abuse-deterrent formulations are pre-cursors to highly euphorigenic rapid-acting opioids, which can liberated through tampering. The National Survey on Drug Use and Health (NSDUH) indicated that 16.0 million people in the U.S. reported using oxycodone products non-medically in their lifetime in 2012.

Preclinical and clinical data show that the inherent properties of NKTR-181 reduce its rate of entry into the brain compared to standard mu opioids, regardless of route of administration.[9]

About Nektar Therapeutics
Nektar Therapeutics is a research-based biopharmaceutical company whose mission is to discover and develop innovative medicines to address the unmet medical needs of patients. Our R&D pipeline of new investigational medicines includes treatments for cancer, auto-immune disease and chronic pain. We leverage Nektar's proprietary and proven chemistry platform in the discovery and design of our new therapeutic candidates. 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 which can be identified by words such as: "plan," "expect," "may," "will," "believe," "can," "should," "could" and similar references to future periods. Examples of forward-looking statements include, among others, statements we make regarding the potential therapeutic benefit of NKTR-181 for treating patients with pain, the potential importance of NKTR-181's development in the area of new pain medicines, the risks of opioid abuse resulting from use of NKTR-181, as well as from new and existing pain medicines, future development plans for NKTR-181 (including, but not limited to, future clinical development plans and future regulatory filings seeking regulatory approval for NKTR-181), the potential timeframe for commercial availability of NKTR-181, and certain other statements regarding the prospects and potential of NKTR-181 specifically, and Nektar's business and technology platform generally. 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) challenges and uncertainties inherent in pharmaceutical research and development, including the uncertainty of future clinical and regulatory success, where the risk of failure remains high and failure can unexpectedly occur at any stage prior to regulatory approval due to lack of sufficient efficacy, safety considerations or other factors; (ii) the regulatory pathway to review and approve NKTR-181 for use in patients, even with a Fast Track designation by the FDA, is subject to substantial uncertainty; (iii) regulations concerning and controlling the access to opioid-based pharmaceuticals are strict and there is no guarantee which scheduling category will apply to NKTR-181 if regulatory approval is achieved; (iv) the partnering process for NKTR-181 is at an early stage and there is therefore substantial uncertainty as to the timing and terms of a potential partnership, or the success of our partnering efforts; (v) drug manufacturing challenges which can delay or render unavailable sufficient supplies of NKTR-181; (vi) changing standards of care and new regulations (including, but not limited to, standards and regulations related to health care cost containment) can affect the use NKTR-181 and commercial success following a regulatory approval; (vii) Nektar's patent applications for NKTR-181 may not issue in one or more jurisdictions, patents that have issued may not be enforceable, or additional intellectual property licenses from third parties may be required in the future; (viii) the outcome of any existing or future intellectual property or other litigation related to Nektar's proprietary product candidates, including, without limitation, NKTR-181, is unpredictable and could have a material adverse effect on our business; and (ix) certain other important risks and uncertainties set forth in Nektar's Quarterly Report on Form 10-Q for the quarter ended March 31, 2017 filed with the Securities and Exchange Commission on May 10, 2017. 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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** Emax equal to Maximum Effect (at all timepoints)*
*** Webster et al.; Human Abuse Potential of the New Opioid Analgesic Molecule NKTR-181 Compared with Oxycodone. Pain Med 2017 pnw344. doi: 10.1093/pm/pnw344*

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