INTRODUCTION
The FDA has acknowledged the need to positively and proactively address the problem of prescription opioid abuse and has recently provided Draft Guidance (guidance for Industry: Abuse-Deterrent Opioid Evaluation and Labeling, January 2013) that seeks to not only establish standards for the development of abuse-deterrent products, but to provide incentive to develop these products by offering differentiated labeling claims for products that are able to meet the standards described in the Guidance. Abuse potential refers to the likelihood that a drug is attractive for use for nonmedical purposes repeatedly or even sporadically, for the positive psychotropic effects that produces. These drugs are characterized by central nervous system (CNS) activity, in particular pain modulation (including sedation, euphoria, perceptual and other cognitive effects, hallucinations, and mood changes). Drugs with abuse potential often (but not always) produce psychic or physiological dependence and may lead to the disorder of addiction. (1)

Assessment of the abuse potential of a new drug is based on a composite analysis of preclinical pharmacokinetics, pharmacology, and clinical data, and the potential public health risk that the drug presents. Data from human abuse potential studies is an important factor in the development of product labeling and drug scheduling recommendations. (1)

Human abuse liability (HAL) assessment is typically conducted by comparing an investigational drug to a known drug of abuse and to placebo (1).

NKTR-181 is NKTR-181 is a new molecule designed to have a reduced rate and extent of entry into the CNS, with the intent to reduce its abuse potential compared to its comparator.

Clinical Data
The study described here is a single-center, randomized, double-blind, placebo-controlled, multi-period crossover study to assess the abuse potential of the investigational new molecule NKTR-181 in non-dependent, recreational opioid users.

NKTR-181 is a new opioid analgesic which has been engineered using Nektar’s advanced polymer technology platform. NKTR-181 is not a prodrug or a reformulation of a marketed opioid. To date, there is no known chemical or physical method to alter NKTR-181 to generate an active opioid that would increase its rate of entry into the CNS. Despite NKTR-181’s rapid absorption into plasma, its onset and peak CNS effects are substantially slower compared to prototypic CII opioids.

NKTR-181 is a unique new chemical entity (NCE) specifically designed to reduce the rate of CNS entry: the clinical profile, including liking scores similar to placebo, are intrinsic to the molecule and not dependent upon a formulation. (1)

Traditional tamper-resistant techniques are commonly subject to conversion (e.g. extraction) into immediate-release forms of the current opioids. Traditional abuse-deterrent technologies are not designed to reduce the abuse potential of a new drug. NKTR-181 is not subject to physical manipulation and was administered as an oral solution in this HAL study.

NKTR-181 has been subjected to the combined effects of conventional (chemical and household agent) and temperature conditions in an attempt to convert the molecule to an abusable opioid. The results suggested that NKTR-181 is not readily manipulated into a more abusable substance.

In Vitro Manipulation and Extraction Studies
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Nektar NKTR-181: On the Path to Less Restrictive Scheduling and Tiered Labeling?
Nektar NKTR-181: New Opioid Analgesic Molecular for Chronic Pain Intended to Deter Abuse and Reduce CNS Side Effects by Reducing the Rate and Extent of Entry into the CNS

• NKTR-181 is a novel mu opioid molecule designed to treat chronic pain but have lower abuse potential than prototypic Schedule II opioid.

• As a mu-agonist opioid molecule, NKTR-181 is by default placed in Schedule II of the CSA during development.

• The regulatory and scientific path to less restrictive scheduling may be defined by NKTR-181 development.

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Preliminary 8-Factor Analysis

Summary and Status of NKTR-181 as a Potential Candidate for Scheduling Less Restrictive than CII and for a Tiered Label

• Known Abuse Potential: NKTR-181 is a new, unique mu opioid molecule that may be scheduled less restrictively than Schedule II or III opioids.

• Tiered labeling appears likely if the findings to date are sufficiently replicated and extended.

• The recent Draft FDA Guidance for Industry (Abuse-Deterrent Opioid Evaluation and Labeling) recognizes the need for safer opioids designed to deter abuse rather than simply reduce severity of the opioid epidemic. Current experience in the field has been with re-formulations that are highly abused, hence the draft guidance does not provide specific consideration of new molecules with reduced abuse potential specifically engineered into the chemical structure. Since physical manipulation is not relevant in this setting, a new molecule with reduced abuse potential that is not subject to degradation or transformation of the chemical bonds to yield an abusable opioid may warrant an additional tier in the draft FDA guidance.