Abuse Potential Assessment of Novel Opioid Analogic NKTR-181: Implications for Labeling and Scheduling

INTRODUCTION

The FDA has acknowledged the need to positivity and proactively address the problem of prescription opioid abuse and recently provided Draft Guidance (Guidance for Industry Abuse-Deterrent Opioids Evaluation and Labeling, January 2012) (1) that seeks to not only establish standards for the development of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 nonmedical use repeatedly or even eventually. It is, consequently, for the positive psychotropic effects it produces. These drugs are characterized by central nervous system (CNS) effects, in particular psychoactive effects including sedation, euphoria, perceptual and other cognitive activity, in particular psychoactive effects. Drugs with abuse potential often (but not always) produce psychosocial dependence and may lead to the disorder of addiction.

Assessment of the abuse potential of a new drug is based on a composite analysis of chemical, pharmaceutical, 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.

Human abuse liability (HAL) assessment is typically conducted by comparing an investigational drug to a known drug of abuse and to placebo. NKTR-181 is a new molecule designed to have a reduced rate and extent of entry into the CNS, with the intent of preserving analgesic effectiveness while reducing CNS (including centrally-mediated pain) side effects. NKTR-181 provides reduced CNS-related effects, including reduced withdrawal symptom scores in rodents, when compared to placebo.

NKTR-181 is not subject to physical manipulation and was administered as an oral solution in this HAL study. NKTR-181 is not readily manipulated into a more abusable substance. The results suggest that NKTR-181 is not readily manipulated into a more abusable substance.

REFERENCES

1) FDA Guidance for Industry Abuse-Deterrent Opioids Evaluation and Labeling, January 2013
2) FDA Guidance for Industry Assessment of Abuse Potential of Drugs – January 2010

Outlook Concerning Scheduling and Tiered Labeling

• Preliminary and clinical results to-date suggest that a scheduling recommendation less restrictive than CII is a plausible outcome for NKTR-181.
• Tiered labeling appears highly likely if the findings to date are sufficiently replicated and extended.
• The recent Draft FDA Guidance for Industry (Abuse-Deterrent Opioids Evaluation and Labeling) recognizes the need for safer opioids designed to reduce abuse through their chemical structure. Such molecules have been described with re-formulations of the drugs 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.

Nektar NKTR-181: On the Path to Less Restrictive Scheduling and Tiered Labeling?

NKTR-181: New Mu Opioid Analogic Molecule 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 not subject to physical manipulation and was administered as an oral solution in this HAL study.
• As a mu-agonist opioid molecule, NKTR-181 is by default placed in Schedule II of the CSA during development.
• The recent Draft FDA Guidance for Industry Abuse-Deterrent Opioids Evaluation and Labeling recognizes the need for safer opioids designed to reduce abuse through their 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.

In Vitro Manipulation and Extraction Studies

• 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.
• Traditional temper resistance is common for substances known to be difficult to dissolve (e.g. extraction) into immediate-release forms of the current opioids. 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 a wide variety of chemical (conventional and household agents) 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.

Preclinical Positioning and Clinical Pathway

In Vitro

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

Factor

Key Findings

1. Physical manipulation

NKTR-181 is not subject to physical manipulation and was administered as an oral solution in this HAL study.

2. Pharmacology

NKTR-181 has been subjected to a wide variety of chemical (conventional and household agents) 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.

3. Chemical stability

NKTR-181 is not subject to physical manipulation and was administered as an oral solution in this HAL study.

4. Potent analgesic activity

NKTR-181 demonstrated slow rate of CNS entry and analgesic response compared to plasma PK data. The study consisted of a Screening Period – 3 days) and an observation period (3 days).

5. Compounds

In Vitro

Single doses of NKTR 181 (100 mg, 200 mg and 400 mg administered as an oral solution) were compared with a 40 mg dose of oxycodone and with placebo. The study consisted of a Screening Period – 3 days) and an observation period (3 days).

6. Public health implications

Outlook Concerning Scheduling and Tiered Labeling

• Preliminary and clinical results to-date suggest that a scheduling recommendation less restrictive than CII is a plausible outcome for NKTR-181.
• Tiered labeling appears highly likely if the findings to date are sufficiently replicated and extended.
• The recent Draft FDA Guidance for Industry (Abuse-Deterrent Opioids Evaluation and Labeling) recognizes the need for safer opioids designed to reduce abuse through their chemical structure. Such molecules have been described with re-formulations of the drugs 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.

NKTR-181: New Mu Opioid Analogic Molecule for Chronic Pain Intended to Deter Abuse and Reduce CNS Side Effects

• NKTR-181 is not subject to physical manipulation and was administered as an oral solution in this HAL study.
• NKTR-181 is a mu-agonist opioid molecule, NKTR-181 is by default placed in Schedule II of the CSA during development.
• The recent Draft FDA Guidance for Industry Abuse-Deterrent Opioids Evaluation and Labeling recognizes the need for safer opioids designed to reduce abuse through their 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.

PRELIMINARY 8-FACTOR ANALYSIS

• Preliminary and clinical results to-date suggest that a scheduling recommendation less restrictive than CII is a plausible outcome for NKTR-181.
• Tiered labeling appears highly likely if the findings to date are sufficiently replicated and extended.
• The recent Draft FDA Guidance for Industry (Abuse-Deterrent Opioids Evaluation and Labeling) recognizes the need for safer opioids designed to reduce abuse through their chemical structure. Such molecules have been described with re-formulations of the drugs 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.

PRELIMINARY 8-FACTOR ANALYSIS

• Preliminary and clinical results to-date suggest that a scheduling recommendation less restrictive than CII is a plausible outcome for NKTR-181.
• Tiered labeling appears highly likely if the findings to date are sufficiently replicated and extended.
• The recent Draft FDA Guidance for Industry (Abuse-Deterrent Opioids Evaluation and Labeling) recognizes the need for safer opioids designed to reduce abuse through their chemical structure. Such molecules have been described with re-formulations of the drugs 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.