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Product Discovery & Development

Slow is good

By Michael Flanagan
Senior Writer

Nektar Therapeutics now has proof of mechanism for its small molecule polymer conjugates in a new therapeutic area: pain. Last week, the company presented Phase I data showing its novel mu opioid receptor agonist construct is safe and produces the expected delays in analgesia that Nektar hopes could reduce both side effects and the potential for abuse.

Opioid abuse and dependence are thought to be reinforced by the temporal association between a drug's administration and its euphoric effects. Separating the two is believed to make an agent unappealing to the recreational abuser, CMO Robert Medve told BioCentury.

From a pharmacological perspective, Medve said the higher a compound's peak concentration (Cmax) compared to the time it takes to achieve Cmax (Tmax), the more attractive a drug is for abuse. He referred to this equation as "the abuse quotient."

Medve said slowing the rate at which an opioid enters the CNS could also lead to a better safety profile by decreasing the risk of sedation and respiratory depression.

NKTR-181 comprises an internally designed mu opioid receptor agonist covalently linked to a polymer that changes the compound's physicochemical properties to control distribution across the blood-brain barrier.

Down-shifting penetration into the brain can be done either by making a compound larger or modifying its polarity, or both. Medve declined to discuss the technical details of NKTR-181's design.

Last week's data came from preclinical studies and the first of two Phase I trials.

In two groups of rats, one given the option of self-administering a food pellet or oxycodone and the other a food pellet or NKTR-181, Nektar's compound showed lower abuse liability. There was no difference between NKTR-181 and saline even at doses up to 100-fold higher than that of oxycodone.

On safety, NKTR-181 showed substantial differentiation from oxycodone on the rats' motor ability, a measure of sedation, as well as respiratory effects.

In a separate poster, Nektar reported results from a single ascending-dose Phase I trial in 105 healthy volunteers.

Medve said oral NKTR-181 was well tolerated, had a wide therapeutic index with dose-linear pharmacokinetics, and a 12-hour half-life that should support twice-daily dosing. Transient cases of mild

dizziness and nausea, which are characteristic of an opioid, were reported at the highest dose (500 mg).

Based on pupillometry data, a measure of an opioid's effect in the CNS, NKTR-181 does not enter the brain quickly. Indeed, while the compound's Tmax was achieved after 2-4 hours, the maximal analgesic effect (Emax) did not occur until after 4-6 hours.

In contrast, Medve noted, "if you take highly abused drugs like cocaine, nicotine and oxycodone, they all rush very quickly into the brain, immediately releasing secondary messengers like dopamine, which reinforces the behavior."

FDA has emphasized that drug developers need to focus on

"If you take highly abused drugs like cocaine, nicotine and oxycodone, they all rush very quickly into the brain."

Robert Medve, Nektar Therapeutics

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decreasing their potential for abuse and misuse. In April, the agency said it would require a classwide REMS for all long-acting and extended-release opioids that will provide educational programs and materials for prescribers and patients to counteract misuse, abuse and accidental overdose.

Medve noted that many of the efforts to develop abuse-resistant opioids involve sustained-release formulations of morphine or oxycodone with something added to deter abuse.

Examples include two **Pfizer Inc.** products: Embeda morphine/naltrexone and Oxecta oxycodone/niacin.

Embeda is an extended-release formulation of morphine that includes a sequestered pellet core of naltrexone, an opioid receptor antagonist.

Oxecta, which utilizes Aversion abuse-deterrent technology from **Acura Pharmaceuticals Inc.**, was initially panned by an FDA advisory committee last year, but approved in June after Pfizer removed the niacin component.

Medve noted there are methods for defeating many of the tamper-resistant technologies.

Nektar's scientists have tried both laboratory and "street" methods for crushing, melting or otherwise trying to liberate the opioid in order to accelerate the analgesic effects of NKTR-181. "So far we haven't been able to do it without denaturing the entire opioid," he said.

Nektar this month began a multiple ascending-dose Phase I trial that should be completed by year end. A Phase II trial in patients with either osteoarthritis (OA) or low back pain is slated to begin in mid-2012.

Nektar partnered its most advanced polymer conjugate compound with **AstraZeneca plc** in 2009 for \$125 million up front. In March, the pharma began a Phase III trial of NKTR-118, a conjugated polymer form of the opioid antagonist naloxol to treat opioid-induced constipation (OIC).

Nektar's lead internal program is NKTR-102, a conjugated polymer form of a topoisomerase I (TOPI) inhibitor. It is in Phase II testing for ovarian, breast and colorectal cancers.

COMPANIES AND INSTITUTIONS MENTIONED

Acura Pharmaceuticals Inc. (NASDAQ:ACUR), Palatine, Ill.

AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.

Nektar Therapeutics (NASDAQ:NKTR), San Francisco, Calif.

Pfizer Inc. (NYSE:PFE), New York, N.Y.