

BIOBUSINESS BRIEFS

DEAL WATCH

Nektar in US\$1.5 billion licensing deal with AstraZeneca

Nektar Therapeutics — a company focused on drug development based on advanced polymer conjugate technology — has announced a licensing deal with AstraZeneca for two compounds to combat opioid-induced constipation. Under the deal, Nektar will receive an upfront payment of US\$125 million and up to a total of \$1.4 billion in milestone payments. AstraZeneca will be responsible for the development of both compounds, including Phase III trials for the most advanced compound, NKTR-118.

According to David Rowbotham, Professor of Anaesthesia and Pain Management at the University of Leicester, UK, “There is a very real need to stop the constipation that is associated with the chronic use of opioids, since current treatments [such as laxatives] have mixed efficacy.”

Opioid analgesics, such as morphine, are agonists at opioid receptors in the central nervous system (CNS), which mediate analgesia, and at opioid receptors in the peripheral nervous system, which are responsible for side effects such as constipation. NKTR-118 is a PEGylated

derivative of the opioid antagonist naloxol that has a restricted ability to cross the blood–brain barrier. In this way, it antagonizes the peripherally mediated constipation induced by long-term opioid use, while the centrally mediated analgesia is maintained. PEGylation of naloxol also reduces first-pass metabolism.

“When opioids are used chronically, patients become tolerant to most of the side effects — except constipation, which is very distressing and often limits the amount of analgesia that you can get from opioids,” Rowbotham says.

Indeed, as Jonathan Moss, Professor of Anesthesia and Critical Care at the University of Chicago, USA, highlights, “Opioid-induced constipation often limits pain control, and in some cases patients may actually prefer pain to severe constipation.”

In a Phase II trial of 208 patients who were receiving morphine for moderate to severe pain, oral administration of NKTR-118 resulted in a significant increase in spontaneous bowel movements (SBMs). Patients receiving 25 mg of NKTR-118 experienced an average of 5.1 SBMs during the first week of treatment, compared

with 1.5 at baseline, and patients on 50 mg had 5.7 SBMs, compared with 1.6 baseline. These increases were maintained over a 4-week treatment period and, importantly, there was no reversal of analgesia.

NKTR-119 is a co-formulation of NKTR-118 and an opioid analgesic, but is not yet in clinical trials. As Rowbotham notes, “At this early stage it is difficult to assess how useful this combination would be, since the dose requirement for each drug may differ.”

Two opioid antagonists that have restricted access to the CNS are on the market, but their use is currently limited to certain patient populations. Alvimopan (Entereg; Adolor/GlaxoSmithKline) is licensed for short-term use for the treatment of post-operative ileus in an in-patient setting. Methylnaltrexone (Relistor; Wyeth/Progenics) is approved as a subcutaneous therapy for opioid-induced constipation in patients with advanced illness. As Moss concludes, “An oral formulation would be beneficial in palliative-care settings, and also in patients with severe chronic non-cancer pain.”

