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Product Discovery & Development

Cara's no-brainer opioid solution

By Stephen Hansen
Staff Writer

Cara Therapeutics Inc. believes its CR845 kappa opioid agonist will fare better than others because the peptide is too large to cross the blood-brain barrier, meaning it should avoid the side effects and narrow therapeutic windows associated with CNS receptor activation.

The company presented data from a Phase II trial to treat acute post-operative pain earlier this month, showing CR845 met the co-primary endpoint of pain reduction 4-8 hours after dosing.

Standard of care for post-operative pain is multi-modal analgesia, which includes a mu opioid receptor (OPRM1; MOR) agonist such as morphine or fentanyl as the backbone. But because mu opioids activate receptors in the brain, their side effects include nausea, vomiting, sedation, respiratory depression and abuse.

President and CEO Derek Chalmers believes CR845 may reduce the need for morphine and in turn reduce the side effects.

CR845 is a small tetrapeptide that is charged to physiological pH. According to the company, the charge keeps the compound from crossing the BBB, and there is no active uptake of a peptide of its size into the brain. Instead, CR845 acts on kappa receptors on peripheral nerves.

"We essentially have no brain penetration at all; it's entirely peripheral action. It blocks the signal at the site of trauma, which is an advantage to the patient," Chalmers told BioCentury.

He said previous compounds were small organic molecules that had activity in the CNS.

"The issue had been with these early kappa agonists that they had a very narrow therapeutic window," Chalmers said. "From the very beginning we were focused on not only high potency at

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Derek Chalmers, Cara Therapeutics

the target, but producing a chemical class that doesn't enter the brain."

In the double-blind, placebo-controlled, single-dose Phase II trial in 46 patients following laparoscopic-assisted hysterectomy, CR845 significantly reduced pain from 4-8 hours after dosing as measured by pain intensity difference scores vs. placebo ($p < 0.05$).

On the other co-primary endpoint, CR845 also reduced the amount of morphine required by patients by 32% over the 16-hour post-dosing period vs. placebo ($p < 0.05$).

No patients given CR845 vomited, and there was a 72% reduction in the incidence of nausea vs. placebo. Chalmers said there was no evidence of sedation or respiratory depression.

Other compounds targeting the kappa opioid receptor have shown mixed results.

One example is ADL 10-0101 from **Adolor Corp.**, which discontinued development after the compound did not significantly reduce pain scores in three Phase II trials in 2002.

Another kappa opioid agonist has had mixed results. In 2008, all three doses of asimadoline from **Tioga Pharmaceuticals Inc.** missed the primary endpoint of a significant improvement vs. placebo in the percent of months a patient was a responder for adequate relief of pain in a Phase IIb trial to treat irritable bowel syndrome (IBS).

However, while asimadoline didn't meet the primary endpoint for all three subgroups of IBS, it did show significance on the primary endpoint in the two subgroups of diarrhea-predominant IBS (D-IBS) and IBS alternating between diarrhea and constipation (A-IBS). Tioga plans to start a Phase III trial of the compound this quarter (see *BioCentury*, May 26, 2008).

Cara has developed CR845 as an IV formulation for acute
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indications because it is the easiest and cheapest formulation to get into proof of concept quickly. But before it gets into registration trials, Chalmers said, the company hopes to find a partner that can expand development into formulations for chronic indications, such as a subcutaneous, transdermal or oral formulations for inflammatory or neuropathic pain.

This year, Cara plans to start several multidose safety trials. Chalmers said these trials, in addition to the completed Phase II trial, should enable Cara to move CR845 into Phase IIb.

Cara is developing a pipeline of therapeutics for pain that act outside the CNS. Behind CR845 is CR701, which targets the cannabinoid CB1 and CB2 receptors (CNR1 and CNR2) on peripheral nerves. The compound is expected to enter Phase I this year to treat neuropathic pain (see *BioCentury*, Sept. 3, 2007).

COMPANIES AND INSTITUTIONS MENTIONED

Adolor Corp. (NASDAQ:ADLR), Exton, Pa.

Cara Therapeutics Inc., Shelton, Conn.

Tioga Pharmaceuticals Inc., San Diego, Calif.