

Product Development

Down-sizing the high

Since agonizing gamma-aminobutyric acid receptors has been shown to decrease dopamine in the brain, GABA receptors are a target for therapeutics to treat substance abuse. However, compounds that directly agonize the receptors have drawbacks that include dependence and tolerance. Catalyst Pharmaceutical Partners Inc. is looking to sidestep these issues by targeting the enzyme that breaks down GABA.

Last week, the company began Phase II testing of its CPP-109 vigabatrin, a GABA transaminase (GABA-T) inhibitor, to treat cocaine addiction.

GABA is a neurotransmitter that inhibits the release of dopamine, the substance that causes the exaggerated sense of pleasure associated with drug abuse. By inhibiting GABA-T, CPP-109 enables GABA to perform its role.

According to Catalyst (CPRX, Coral Gables, Fla.), CPP-109 irreversibly binds GABA-T and permanently inactivates the enzyme, so that low doses could have long-lasting effects. By contrast, GABA receptor agonists require multiple high doses per day.

CPRX also said CPP-109 does not block natural rewarding pleasures that are activity dependent, such as exercising or eating. The compound only blocks psychostimulant-induced increases in dopamine burst firing and food-induced dopamine burst firing in obese subjects. Natural rewards, which increase tonic cell firing, remain untouched by CPP-109.

"Since we are using an enzymatic approach, we don't have to worry about the addictive liability and withdrawal typically associated with molecules that target specific receptors," said Stephen Dewey, senior chemist at Brookhaven National Labora-

tory and chairman of CPRX's scientific advisory board.

"There are numerous companies working on treating cocaine addiction because there remains a large, unmet clinical need," he added. "Last year, about 700,000 patients sought treatment for cocaine addiction."

According to the company there are no products approved in the U.S. for cocaine addiction. The only compound being examined for cocaine addiction is baclofen, a GABA agonist approved in the 1970s for spasticity, according to Dewey.

Indeed, sanofi-aventis Group (Euronext:SAN; SNY, Paris, France) markets vigabatrin as Sabril outside of North America for adult epilepsy and infantile spasms. In 1998, Brookhaven researchers and colleagues published in *Synapse* the finding that a high, acute dose of vigabatrin can prevent the rise in brain dopamine levels and the conditioning behavior seen

with nicotine administration in rats.

Dewey told BioCentury that two small, open-label studies in Mexico in patients addicted to cocaine or methamphetamine suggested clinical efficacy and showed that vigabatrin was safe.

The results were published in 2003 and 2005 in *Synapse*. The first study showed that there was a significant difference in the consecutive drug-free days among patients who completed the trial versus those who did not ($p < 0.0001$). In the 2005 study assessing safety of vigabatrin, 18 of the 30 subjects completed the nine-week study and of those 16 tested negative for methamphetamine and cocaine during the last six weeks of the trial.

In 2002, CPRX received an exclusive worldwide license from Brookhaven for nine patents and five patents pending in the U.S.



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for all rights to use or sell vigabatrin to treat addiction to cocaine, methamphetamine, prescription pain medications, heroin, nicotine and other addictive drugs. The license also includes rights to foreign patents or patents pending in more than 30 countries.

Last week, CPRX started a Phase II trial of CPP-109 in 180 patients who will be treated for 12 weeks. The primary endpoint is the proportion of patients who are cocaine-free during their last two weeks of treatment. Patients will be followed for another 12 weeks. Top-line data are expected next summer, with Phase III testing slated to begin immediately thereafter. The compound has Fast Track designation for the indication.

CPRX had \$19.1 million in cash at March 31, which the company said is enough to run Phase II and Phase III testing of CPP-109 in cocaine addiction. Since vigabatrin was never approved in the U.S., the company will be submitting an NDA to FDA.

Pending Phase III results, the company plans to pursue other substance dependencies, which may include alcohol, nicotine, inhalants and prescription opiates.

CPRX also is exploring the feasibility of a small pilot study of CPP-109 for obesity in the fall.

Patrick McEnany, chairman, president and CEO, said the company may look to in-license other compounds and seek partnerships for CPP-109. — *Urooj Mujtaba*