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Emerging Company Profile

CoLucid: Safety in the CNS

By Jesse Beckstein
Staff Writer

CoLucid Pharmaceuticals Inc. is developing two CNS programs aimed at matching or beating the efficacy of approved drugs while besting their side effect profiles. The company has a migraine compound with a novel mechanism of action that it believes will have better efficacy than triptans without their risks. Similarly, CoLucid's stigmine platform for development of bifunctional compounds that hit two CNS targets in succession offers a new approach to delivering approved therapeutics to the brain to retain the efficacy of delivering each separately, but with fewer side effects.

Triptans, the leading class of marketed migraine drugs, target serotonin (5-HT_{1B/1D}) receptors, alleviating pain by indirectly binding to these receptors on trigeminal neurons and on cerebral blood vessels, causing vasoconstriction. This mechanism limits their use in patients with underlying cardiac risk because the receptors also exist on coronary arteries, which can lead to serious adverse events, including myocardial infarction (MI).

CoLucid's COL-144 is a neurally acting anti-migraine agent (NAAMA) that selectively targets the serotonin (5-HT_{1F}) receptor in the trigeminal nerve pathway. Binding these receptors inhibits the activation of nociceptive neurons in the trigeminal nucleus caudalis, thus blocking nociceptive transmission to the brain. The compound completely avoids vasoconstrictive activity, as 5-HT_{1F} receptors are not present on cerebral blood vessels or coronary arteries.

According to President and CEO James White, in a Phase II trial in about 130 patients, intravenous COL-144 demonstrated efficacy in acute treatment of mi-

CoLucid Pharmaceuticals Inc.

Indianapolis, Ind.

Technology: Neurally acting anti-migraine agent (NAAMA), conjugated stigmine platform for CNS drug discovery

Disease focus: Neurology

Clinical status: Phase II

Founded: 2005 by Pappas Ventures

University collaborators: Undisclosed

Corporate partners: None

Number of employees: 10 FTEs

Funds raised: \$41.5 million

Investors: Pappas Ventures; Domain Associates; Care Capital; Pearl Street Venture Funds; Triathlon Medical Ventures

CEO: James White

Patents: Undisclosed

graine comparable to historical data on triptans.

The adaptive trial was designed to find the dose of COL-144 that would produce the 60% maximal response rate seen two hours after dosing with triptans. The study did not look at doses of COL-144 that might produce greater response rates. The company plans to present the Phase II data at the European Headache and Migraine Trust International Congress in September.

Based on these results, and to develop a competitive product, CoLucid designed an oral formulation of COL-144, which recently completed a Phase I trial.

The data have yet to be unblinded, but White said that even with the placebo group included, the safety profile looks

cleaner than that of the IV formulation. To date, no triptan-like CV adverse events have occurred in any studies of either formulation of COL-144.

The company plans to begin a Phase II trial of oral COL-144 in 1Q09 that will test higher doses than those used in the Phase II IV trial. CoLucid is no longer developing the IV formulation.

"We believe that with our knowledge of COL-144 to date, there is a real opportunity to see superior efficacy to triptans without the cardiovascular risk," said White.

COL-144 was in-licensed from **Eli Lilly and Co.** in 2005. The pharma discontinued another selective 5-HT_{1F} antagonist, LY334370, prior to Phase III due to unforeseen liver toxicity in dogs. White said CoLucid has not seen the problem in toxicology studies of COL-144, which is a third-generation molecule from the same program as LY334370, but with a different chemical structure.

In addition to COL-144, CoLucid has a conjugated stigmine platform that enables rapid synthesis of bifunctional compounds that inhibit a key CNS target initially and subsequently release a second active CNS drug against another target. The company is using the approach to link approved drugs.

Using this platform, CoLucid has built a library of linked drugs that may be useful to treat CNS disorders including sleep/wake disorders, chronic pain, Alzheimer's disease (AD) and psychiatric disorders.

Preclinical studies have shown that these constructs have efficacy comparable to drugs against each target delivered separately, but with fewer side effects.

The lead compound is COL-204, which is expected to begin Phase I trials in 1H09

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for wake promotion. According to the company, the compound has shown positive wake-promoting effects in multiple animal models, without side effects of approved drugs, such as rebound hypersomnolence and addiction potential.

White said the stigmine platform may have potential for delivering other kinds of drugs to the CNS, including oncolytic, anti-inflammatory, antibiotic and antiviral drugs that don't currently penetrate the brain effectively. CoLucid may license or partner subsets of the stigmine portfolio by indication.

The company also is talking to potential partners for Phase III development of COL-144; however, White told BioCentury CoLucid may decide to raise additional funds to run the trial itself.

CoLucid raised \$25 million in a series B round in July and has now raised a total of \$41.5 million. White said the company expects the cash to last up to Phase III testing for COL-144 and to fund Phase I testing of two NCEs from the stigmine platform.

The stigmine platform was acquired in 2005 from Sention Inc., which is no longer in business.

COMPANIES AND INSTITUTIONS MENTIONED

CoLucid Pharmaceuticals Inc., Indianapolis, Ind.

Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.

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