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Gilead Sciences pads its NASH stash with potential $1.2B Nimbus Therapeutics deal

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Gilead Sciences [2] Inc. made a long-awaited M&A move with a deal to acquire Nimbus Apollo Inc., a wholly owned subsidiary of Nimbus Therapeutics [3], for $400 million up front and $800 million in development-related milestone payments.

Gilead, of Foster City, Calif., gains the lead acetyl-coA carboxylase (ACC) inhibitor program at Nimbus, including a phase II-ready and preclinical allosteric ACC inhibitors aimed at treating non-alcoholic steatohepatitis (NASH), hepatocellular carcinoma (HCC) and other metabolic and liver diseases.

In February, the lead compound, NDI-010976 [4], was granted fast track designation by the FDA. Phase I data are scheduled to be presented next month during an oral session at the International Liver Congress 2016, the annual meeting of the European Association for the Study of the Liver, in Barcelona. NDI-010976 was expected to move into a phase II study in NASH in the first half of this year.

A second ACC inhibitor, ND-654 [5], is preparing to move into investigational new drug-enabling studies to treat HCC.

Founded in 2009 as Nimbus Discovery LLC, Cambridge, Mass.-based Nimbus is structured as a series of independent C corporations, each of which houses a distinct R&D program with a singular focus. The company gained momentum in 2011 when its computational drug discovery model attracted high-profile investor and philanthropist Bill Gates, co-founder of Microsoft Corp. Gates had committed $10 million to Schrödinger LLC, a 25-year-old Columbia University spinout that offers a range of informatics and drug discovery software to the biotech and pharmaceutical industries. Schrödinger had participated in the Atlas Ventures-led launch of Nimbus, and the companies continue to work closely to translate Schrödinger's computational chemistry and software solutions into therapeutic applications. (See *BioWorld Today*, March 28, 2011.)

NASH has become one of the hottest targets in therapeutic development, with nearly four dozen compounds in mid- to late-stage development and dozens more in discovery or early stage studies, according to Thomson Reuters Cortellis Competitive Intelligence.

Within its considerable portfolio of assets targeting liver disease – including the approved hepatitis C virus blockbusters, Sovaldi (sofosbuvir) and Harvoni (ledipasvir/sofosbuvir), and its hepatitis B virus drug, Viread (tenofovir disoproxil fumarate) – Gilead is advancing several NASH compounds. Simtuzumab, a lysyl oxidase homolog 2 inhibitor, is in phase II development, according to Cortellis, along with GS-4997, an apoptosis signal-regulating kinase, or ASK-1 inhibitor, which the company is investigating alone and in combination with simtuzumab. Gilead also has GS-9674, a farnesoid X receptor agonist.

The Nimbus ACC inhibitors give Gilead additional shots on goal by targeting a central cause of NASH: seeking to reduce aberrant lipid-derived signaling that can result in steatosis, inflammation and fibrosis.

ACC is an enzyme with two isoforms, ACC1 and ACC2, involved in the synthesis of endogenous fatty acids and the regulation of beta-oxidation – the process by which fatty acids are broken down at a cellular level. Inhibitors of ACC, thus, have the potential to prevent production of new lipids within the liver and stimulate their break down. In animal models of fatty liver, Nimbus showed that ACC inhibition reduces hepatic fat content, inflammation and fibrosis. Lead asset, NDI-010976, is a potent, liver-targeted, allosteric inhibitor of both ACC isoforms.

Past industry attempts to inhibit ACC mostly failed due to inherent challenges posed by the target binding site and poor drug-like qualities of the molecules in development, according to Nimbus CEO Don Nicholson, who said the company "made a fundamental decision four or five years ago that NASH would crack wide open" – a prediction now coming to pass, with prevalence of the disease last year estimated at 3 percent to 5 percent of the U.S. population, or up to 15 million people.

Other candidates targeting NASH are largely "repurposed" from other fields, including diabetes and inflammatory conditions, Nicholson said, and each targets only one piece of the NASH puzzle. Nimbus, in contrast, solved the challenge of addressing all three elements of the disease by targeting a domain of ACC where a natural product ACC inhibitor known as soraphen A was shown to bind to the enzyme and neutralize its activity.

'IT'S BUSINESS AS USUAL TODAY FOR NIMBUS'

Nimbus and Gilead began talking some time ago, "although the starting point, very oddly, was that Gilead was interested in one of our other programs," Nicholson recalled. Nimbus tried unsuccessfully to meet with the big biopharma at an annual J.P. Morgan Healthcare Conference and when the two finally connected, "we told them they were looking at the wrong program," Nicholson told *BioWorld Today*. "With their heritage in liver disease, we thought they should be looking at ACC."

At the time, Nimbus was prepared to take its lead program deep into development and wasn't actively seeking a partner or suitor. But once Gilead turned its attention to the

assets housed in Nimbus Apollo, "we really felt Gilead would be a fabulous company to advance this program all the way to an approved therapy," Nicholson said.

Nimbus scientists had built the ACC program from the ground up, using their own proprietary playbook, in the days before NASH agents became a hot commodity, "and Gilead got that," he added. As opposed to some big biopharmas still chewing on their approach to NASH, Gilead was ready to move.

J.P. Morgan analyst Cory Kasimov agreed the deal made sense for Gilead and would muffle, though not silence, voices calling for the company to step up its M&A activity.

"Given the overwhelming focus for GILD has been on M&A, we are incrementally encouraged to see progress on this front, though we highly doubt this acquisition will put the M&A question to rest, "he wrote in an email following disclosure of the deal. Although the Nimbus program "fits well with GILD's existing pipeline given its focus on NASH and oncology," he added, "it is a relatively small deal and earlier stage."

The Nimbus deal "exemplifies GILD's committed focus towards expanding in liver disease and fibrosis and an eye for potential combos with existing pipeline programs," Jefferies LLC analyst Brian Abrahams agreed in a flash note. "While GILD's continued pursuit to explore multiple mechanisms in NASH suggest more of a string of pearls [business development] strategy, a $400M up-front is not material for GILD and would not preclude something more transformative this year."

Gilead got more good news Monday with the FDA approval of Descovy (emtricitabine 200 mg/tenofovir alafenamide 25 mg, or F/TAF), a fixed-dose combination indicated for use in conjunction with other antiretroviral agents to treat HIV-1 infection in adults and pediatric patients 12 and older. Descovy is not indicated for use as pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 in adults at high risk.

Approval came with a boxed warning about the risks of lactic acidosis/severe hepatomegaly with steatosis and of post-treatment acute exacerbation of hepatitis B. Nevertheless, the therapy added another HIV treatment backbone to Gilead's already considerable HIV arsenal.

Gilead's shares (NASDAQ:GILD) closed Monday at $94.24 for a gain of 12 cents.

BUSINESS AS USUAL

Upon completion of the acquisition, Nimbus Apollo will become a wholly owned subsidiary of Gilead, which assumed sole responsibility for future development and commercialization of NDI-010976 and other ACC inhibitors. Nimbus Therapeutics retained ownership of its other R&D subsidiaries.

Although Nimbus hands over its intellectual property and related data for the ACC program and has a transition agreement with Gilead, the C Corp. structure enables the company to walk away from the deal otherwise intact.

"We're able to continue to operationalize the company even though we're selling our lead asset," Nicholson said. "As opposed to some of my colleagues, who have had to move on after a transaction like this, it's business as usual today for Nimbus."

With 20 full-time employees and dozens of contractors, the company has been focused in recent months mainly on closing the deal with Gilead. Attention now turns to creating "Nimbus 2.0," according to Nicholson, who said the spotlight will stay mainly on programs in oncology, immunology and fungicides already up and running in Nimbus units. Those areas offer vast opportunities individually and in combination, he noted, citing immuno-oncology as one example.

The company has an exclusive global license agreement with Genentech, a unit of Roche AG, of Basel, Switzerland, to discover and develop small-molecule inhibitors of interleukin-1 receptor-associated kinase 4, or IRAK4, and a research collaboration and option agreement with Monsanto Co., of St. Louis, to develop broad-spectrum fungicides to control plant diseases and promote overall plant health.

But Nimbus was founded with an agnostic view toward therapeutic classes, said Nicholson, who joined Nimbus in 2014 after a 25-year career with Merck & Co. Inc., that culminated in his position as worldwide discovery head for the respiratory and immunology franchise in Kenilworth, N.J.

"Although we will bias ourselves toward the three therapeutic areas in our existing pipeline, we wouldn't want to rule out other options if opportunities present themselves," he said. "We want to evolve programs like the one we sold to Gilead, but we also want to build a company and take candidates to registration studies and beyond. We have enough of a portfolio – mostly undisclosed – to do both. We're just looking for the right blend to achieve that goal."