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Study 'ready to go'

Aiming at Soliris, Apellis loads for PNH phase III with $60M series E

By Marie Powers, News Editor

Apellis Pharmaceuticals Inc. extended its string of financings with a $60 million series E preferred stock round led by Sectoral Asset Management that included new investors Sofinnova, Vivo Capital, F-Prime Capital Partners, investment funds advised by Clough Capital Partners LP and Venbio Select. Existing investors Morningside Ventures, Cormorant Asset Management, Venbio Global Strategic Fund and Epidarex Capital also participated in the financing.

In conjunction with the financing, Maha Katabi, private equity partner at Sectoral Asset Management, is set to join the Apellis board, chaired by Morningside co-founder Gerald Chan.

The raise represents the largest to date for the Louisville, Ky.-based company, topping last year's $47 million series D. Late in 2015, Apellis considered a run at the public markets to fund development of its lead program, APL-2, but the timing was "unfortunate," according to Cedric Francois, co-founder, president and CEO, with the company's S-1 dropping at about the same time the markets were doing the same.

Still, Apellis, founded in 2009, has had little trouble securing the funds to keep moving forward, raising $92 million prior to the series E.

"The real purpose of this round was to broaden our existing syndicate by bringing in investors that can help us take this company to the next level," Francois told *BioWorld*.

The round, which came together in less than three months, positions Apellis to move its complement C3 inhibitor into a phase III program in paroxysmal nocturnal hemoglobinuria (PNH) and to advance studies in other indications.

A synthetic cyclic peptide conjugated to a polyethylene glycol polymer that binds specifically to C3 and C3b, APL-2 blocks all three pathways of complement activation (classical, lectin and alternative) with a particularly high potency against the alternative pathway.

In December 2016, Apellis disclosed interim results from two phase Ib open-label, dose-escalation trials of the self-injected APL-2, reporting that the drug reduced the breakdown of red blood cells in patients when given daily as a monotherapy or as an add-on to standard-of-care therapy, the intravenous Soliris (eculizumab) from Alexion Pharmaceuticals Inc., of Cheshire, Conn.

At the time of the report, 15 patients dosed across the two trials had completed a month of dosing, and five had completed more than three months of treatment. With APL-2 (270 mg) as a monotherapy, three of three PNH patients achieved a reduction in levels of the biomarker lactate dehydrogenase (LDH) to below the standard for control in PNH (500 U/L). With APL-2 (270 mg) as a Soliris add-on, six of six previously transfusion-dependent PNH patients did not require transfusions during the study, and five of six achieved hemoglobin levels within the normal range for healthy people.

"We might be on to something," Francois said at the time. (See *BioWorld Today*, Dec. 5, 2016.)

The phase III program will help to advance that thesis by confirming whether inhibition of C3 offers advantages over drugs like Soliris, which targets complement C5. Apellis plans to begin enrolling the first phase III in PNH in the fourth quarter, "where, ultimately, the goal will be to find out if APL-2 can be superior to Soliris in its mechanism of action," Francois said.

'Everything still belongs to us'

The premise is promising. All three activation pathways of the complement system converge on C3, leading to three principal effects: opsonization, inflammation and the membrane attack complex formation. When C3 is activated, C3 fragments, such as C3b, tag cell surfaces in the opsonization process, marking the cells for removal from tissues or the bloodstream. Two other fragments, C3a and C5a, also are released, contributing to inflammation. As the final step in complement activation, the membrane attack complex forms on cell surfaces, piercing holes and causing cells to rupture.

The company's therapeutic candidates act against the complement system at the level of C3 to block the effects of the complement cascade, regardless of the activation pathway. In PNH, caused by the presence of mutant stem cells in the bone marrow that lack fundamental proteins to protect against complement activation, APL-2 prevents the formation of the membrane attack complex and may also prevent subsequent activation of platelets and intravascular hemolysis – the main causes of thrombosis, which is the leading cause of mortality in PNH. Because APL-2 also prevents the formation of the membrane attack complex and C3b opsonization, the agent also may affect intravascular and extravascular hemolysis and, thus, reduce anemia and transfusion dependency in patients with PNH.

Soliris, which inhibits C5, also prevents the formation of

the membrane attack complex, blood clot formation and intravascular hemolysis, but more than half of patients with PNH treated with the drug continue to have low hemoglobin levels, possibly due to its inability to control extravascular hemolysis, Francois said.

"Soliris is a fantastic product, but most of these patients still have anemia," he said. "We have lots of evidence to show that that's primarily related to upstream complement activation at the level of C3. Our first phase III clinical trial will allow us to show that, with C3 inhibition, we can improve the condition of those patients."

With input from the FDA, design of that study is "ready to go," he added. The multinational trial is expected to enroll approximately 60 individuals with PNH, with top-line data anticipated in 2019.

The company expects to conduct a second phase III that will compare APL-2 as a monotherapy against Soliris in patients with PNH. The phase III program was designed to pursue global regulatory filings, according to Francois, who previously co-founded the complement C3 specialist Potentia Pharmaceuticals Inc., which Apellis acquired in 2014. (See *BioWorld Today*, Sept. 12, 2008.)

The systemic treatment of rare diseases, beginning with PNH, represents just the first of three "cornerstones" for Apellis, Francois said. In ophthalmology, Apellis is studying APL-2, injected locally, to treat geographic atrophy, the advanced dry form of age-related macular degeneration (AMD). Data from a phase II study – designed to mimic the phase Ib/II Mahalo study of Roche Holding AG/Genentech Inc. agent, lampalizumab (RG-7417), in the same indication – are "imminent," according to Francois.

"Again, we want to take advantage of this unique mechanism of action and the broad inhibition that you get with this agent to see if we have a solution for this currently untreatable disease," he said.

The company also is awaiting data this year from a phase I study of APL-2 in autoimmune hemolytic anemia.

Apellis originally licensed the C3 inhibitor technology for exclusive use from the University of Pennsylvania before making "significant and essential improvements to the base molecules," Francois said. With its third cornerstone – a set of preclinical and early clinical assets also targeting the complement pathway and C3, in particular – Apellis has moved well beyond the foundational intellectual property. The company sees opportunities for its early stage pipeline to offer improved therapies in complement-mediated indications, but it's also exploring "the cross-talk between complement and adaptive immunity," Francois added, with the potential to show disease-modifying properties against certain targets.

Although specific indications have not been disclosed, the company's preclinical efforts are broadly focused on cancer immunotherapy.

Apellis seems primed, when the timing is right, to revisit plans for an IPO. In the meantime, partnering discussions are already underway to position the company to move quickly into bigger trials in broader indications.

"We are entirely unencumbered. Everything still belongs to us," Francois said, noting that the 30-person firm has nevertheless "carefully crafted" a strategy that offers maximum optionality.

"We are, for now, a rare disease company, with our systemic programs having shown great early clinical promise," he said. "But, in the background we have this large, 240-patient clinical trial [in AMD] that is going to read out in the very, very near future. Should that trial be positive, we have an opportunity to start thinking more broadly outside of rare diseases." ♦