EMERGING COMPANY PROFILE

ORAL ROUTE FOR HAE

By Mary Romeo, Staff Writer

The team behind Firazyr icatibant has reunited to develop an oral version of the drug that could give hereditary angioedema patients the alternative to injectables they've been asking for.

Pharvaris B.V. brings together team members responsible for developing Firazyr at Jerini AG with veterans of rare disease company Prosensa Holding N.V. to develop a compound that could improve ease of use for HAE patients by treating the disease both prophylactically and on-demand. All six marketed HAE drugs require parenteral delivery. None act as both a prophylactic and a therapy for acute attacks. Five act by replacing the C1 esterase inhibitor or inhibiting KLKB1, while Shire plc's Firazyr is a BDKRB2 antagonist.

At an FDA Patient-Focused Drug Development meeting on HAE last year, 29% of patients ranked route of administration as the most important consideration in a new therapeutic, followed by 27% who said access to treatment and 16% who said frequency of administration.

To create lead compound PHA121, Pharvaris used chemical synthesis to create a compound based on the BDKRB2 antagonist behind Firazyr. HAE is caused by insufficient levels or dysfunctional C1 esterase, which normally suppresses activation of the complement system. The resulting overstimulation activates KLKB1, leading to increased levels of bradykinin, which then acts through its GPCR B2 receptor to cause angioedema in cells.

"The B2 receptor mediates all signs and symptoms of the disease," said CSO and COO Jochen Knolle, who developed Firazyr while CSO at Jerini. Other therapies attempt to interfere with the disease in two ways — either by substituting the missing complement protein or preventing development of bradykinin by targeting KLKB1. However, "plasma kallikrein has other functions in other pathways, so it is not as specific as targeting the bradykinin receptor itself," Knolle said.

While Firazyr can be self-administered, Knolle said the compound's short half-life prevents prophylactic use, and many patients experience injection site reactions and pain. "We created a completely new molecule that was better than icatibant," said CEO Berndt Modig, who was CFO at Jerini and Prosensa.

Pharvaris has unpublished preclinical studies showing PHA121 was 60 times more potent than Firazyr against BDKRB2, had onset within one hour, and "very promising oral bioavailability," said Knolle. It plans to start a Phase I trial this year, and has IND-enabling safety and toxicology studies ongoing.

"We can stop the effect of bradykinin in animals less than an hour after oral dosing, so we expect it to work similarly to icatibant. We can also intervene in a prophylactic way due to specificity of the pathway," CBO Morgan Conn said.

Two other oral HAE therapies are in the clinic. BioCryst Pharmaceuticals Inc.'s BCX7353 is a second-generation kallikrein inhibitor in Phase III testing to prevent HAE. BioCryst reported BCX7353 significantly reduced the frequency of HAE attacks in the APeX-1 Phase II trial.

Knolle said BCX7353 has a slow onset of buildup in the system of up to a week, which would limit its on-demand use. In addition, patients reported GI side effects including abdominal pain at the high dose in the Phase II trial. BioCryst CFO Thomas Staab said that while GI AEs did occur at high doses in Phase II testing, the company doesn't view GI side effects as a problem in the product profile or as a negative compared to competitors.

KalVista Pharmaceuticals Inc. is developing a portfolio of kallikrein inhibitors to prevent and treat HAE. Its most advanced, KVD818, is in Phase I testing to prevent HAE. Knolle declined to comment on the compound, citing unfamiliarity. /

PHARVARIS B.V., Leiden, the Netherlands
Technology: Oral bradykinin B2 receptor antagonist to treat hereditary angioedema
Disease focus: Inflammation
Clinical status: Preclinical
Founded: 2015 by Berndt Modig, Jochen Knolle, Jens Schneider-Mergener, Hans Schikan, Luc Dochez and Anne Lesage
University collaborators: Charite - Universitaetsmedizin Berlin, Johannes Gutenberg University Mainz, Ludwig Maximilians University of Munich, Universite Laval, University of Milan
Corporate partners: None
Number of employees: 7
Funds raised: €15 million ($17.6 million)
Investors: Kurma Partners and Life Science Partners
CEO: Berndt Modig
Patents: None issued

COMPANIES AND INSTITUTIONS MENTIONED

BioCryst Pharmaceuticals Inc. (NASDAQ:BCRX), Durham, N.C.
KalVista Pharmaceuticals Inc. (NASDAQ:KALV), Cambridge, Mass.
Pharvaris B.V., Leiden, the Netherlands
Shire plc (LSE:SHP; NASDAQ:SHPG), Dublin, Ireland

TARGETS

BDKRB2 (BR2) - Bradykinin B2 receptor
Complement 1 (C1) esterase
KLKB1 - Plasma kallikrein