IDIOPATHIC PULMONARY FIBROSIS

IPF up and comers look to add on rather than compete

By Brian Orelli, Staff Writer

Esbriet (pirfenidone, Roche Holding AG) and Ofev (nintedanib, Boehringer Ingelheim GmbH) were approved to treat idiopathic pulmonary fibrosis (IPF) by the FDA two years ago – serendipitously on the same day – giving patients in the U.S. their first treatment options for the lung disease. (See *BioWorld Today*, Oct. 17, 2014.)

Since then, both companies have battled for patients. Sales of Esbriet, which Roche got through its buyout of Intermune Inc., increased 45 percent year over year during the first nine months of this year to CHF571 million (US$575 million). The company's report noted that "significant potential still remains in patients with a less advanced form of the disease."

Boehringer Ingelheim, which as a private company doesn't release quarterly sales numbers, is also going after earlier-stage patients, releasing two post-hoc analyses of the pooled data from the phase III trials that supported the approval at last week's Chest annual meeting in Los Angeles.

The first analysis showed a similar reduction in disease progression with Ofev vs. placebo regardless of the patients GAP (gender, age, physiology) stage, a measure used by doctors to predict prognosis in patients with IPF. There was no significant difference between GAP stage I vs. patients at GAP stage II/III. A similar analysis using the composite physiologic index (CPI) showed comparable treatment regardless of whether patients had a higher or lower baseline CPI score.

IF YOU CAN'T BEAT 'EM, JOIN 'EM

Neither Esbriet nor Ofev is a cure for IPF, opening opportunities to develop new medications.

"No one is particularly satisfied with the efficacy and safety profiles of pirfenidone and nintedanib. The drugs are largely succeeding because there is nothing else out there for IPF," Seth Porter, Fibrogen Inc.'s vice president of fibrosis therapeutics, told *BioWorld Insight*.

But rather than compete, companies are looking to combine their drugs with the current standard of care.

Fibrogen is developing pamrevlumab (FG-3019), a monoclonal antibody that targets connective tissue growth factor, a mediator of fibrosis that is up-regulated during wound healing.

In a pilot study, pamrevlumab was able to reverse fibrosis in some IPF patients, which hadn't been seen before. "People have typically assumed once its scarred and the tissue structure is damaged, it cannot be reversed," Porter said, noting that the study was open label without a placebo control.

San Francisco-based Fibrogen started a larger phase II placebo-controlled trial to confirm the initial findings in 2013. But once Esbriet and Ofev were approved in the U.S., enrollment became challenging; Fibrogen was finally able to complete enrollment in June and expects data next year.

Since a phase III trial comparing pamrevlumab head-to-head to placebo would take forever to enroll, Fibrogen is exploring the possibility of combining pamrevlumab with Esbriet or Ofev in a substudy of the ongoing phase II trial. In addition to efficacy, Fibrogen will learn about safety of the combinations, although Porter noted that pamrevlumab has a "remarkably good" safety profile and has even been combined with chemotherapy in a study testing the drug in pancreatic cancer.

The size of the phase III program will largely depend on the magnitude of the efficacy effect vs. placebo in the phase II trial. Depending on how large the trials need to be, Fibrogen may need a partner to complete the program. Porter commented that the company has already seen some interest

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from companies interested in partnering.

Genoa Pharmaceuticals Inc. is developing Aerodone, an inhaled version of pirfenidone to avoid the side effects seen in the oral version of the drug. Because pirfenidone is a low potency drug, large doses have to be given to get a high enough concentration in the lung where it works. But the high dose causes side effects elsewhere, especially gastrointestinal issues.

By dosing directly to the lung, Aerodone avoids "exposure to the blood, therefore getting around the side effect issues associated with the large oral doses," Mark Surber, Genoa's president and CEO, told *BioWorld Insight*. And by avoiding the side effects, it may be possible to deliver a larger dose to the lungs, potentially increasing the efficacy compared to the oral medication.

Genoa's team came together in 2010, but is just now in the final stages of completing its series A funding. IPF trials take awhile to get proof-of-concept data, making it hard to raise money from venture capital.

"It takes a little more money and a little more time than they're willing to invest," Surber said, adding that investors have come to realize there's a "social responsibility to accept these long timelines" and interest has increased because of the continued unmet need.

San Diego-based Genoa plans to start a phase I trial in about a year. Once safety and dosing is established, the phase II program will test Aerodone alone as well as in combination with Ofev. The oral versions of the two drugs aren't used in combination now due to additive side effects, which Genoa hopes to avoid with the inhaled version.

Like Fibrogen, Genoa is already in talks with potential partners. Some are interested in doing a deal after a phase I that shows the drug can be delivered with minimal side effects while other potential suitors are more interested in a deal after proof of concept has been established in a phase II.

"We know what they want and part of our development plan is to target that," Surber said.

PHARMA BUYS IN

Based on recent deals, Fibrogen and Genoa shouldn't have too much trouble finding companies willing to do a deal.

In June, Merck & Co. Inc., of Kenilworth, N.J., bought Afferent Pharmaceuticals Inc. for $500 million up front and a potential for another $750 million if development and commercial goals are met. San Mateo, Calif.-based Afferent's lead compound, AF-219, is an oral drug that acts on overexcited nerves that trigger an unproductive cough. AF-219 is at the phase IIb stage for refractory, chronic cough and in phase II for IPF with cough. (See *BioWorld Today*, June 13, 2016.)

"We spoke to the company, who emphasized that this acquisition was in line with management's desire to bolster the phase II pipeline through business development. Merck suggested that this is one of several potential acquisitions in this vein, and fits in well with their existing primary care business," Evercore ISI analyst Mark Schoenebaum wrote in an e-mail to clients.

Last year, Jerusalem-based Teva Pharmaceutical Industries Ltd. bought Auspex Pharmaceuticals Inc. for roughly $3.2 billion to gain access to SD-809 (deutetrabenazine), which La Jolla, Calif.-based Auspex was developing for IPF among other indications. (See *BioWorld Today*, March 31, 2015.)

In 2012, Biogen Inc. and Stromedix Inc., both of Cambridge, Mass, struck a deal for Stromedix's IPF treatment, STX-100, which had originally been developed by Biogen before Stromedix licensed the drug. Biogen paid $75 million up front, and agreed to pony up another $487.5 million if milestones were met. (See *BioWorld Today*, Feb. 15, 2012.) //