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Protalix nears planned BLA filing for new Fabry disease therapy

By Michael Fitzhugh, News Editor

Israel's Protalix Biotherapeutics Inc., the first company to gain FDA approval for a protein therapy produced by plant cell cultures in 2012, has moved one step closer to seeking FDA approval for a second such product with new phase III data supporting its experimental therapy for Fabry disease. New 12-month results from the ongoing Bridge study, evaluating a switch to the company's pegunigalsidase alfa from Takeda Pharmaceutical Co. Ltd.'s Replagal (agalsidase alfa), found clinical goals met and improvements in kidney function for patients moved to the Protalix drug. Now, assuming all goes well, a BLA filing is planned for March or April of 2020, Protalix's president and CEO, Dror Bashan, told *BioWorld*.

Dror Bashan, president and CEO, Protalix Biotherapeutics Inc.

Though under threat of de-listing from the NYSE – a temporary state for most biotechs encountering it – Protalix shares (NYSE:PLX) spiked Thursday, rising 74% to 32 cents.

The company's upcoming bid for accelerated approval from the FDA will rely foremost on data from completed phase I/II trials of pegunigalsidase alfa, but also on safety data from the ongoing phase III Bridge study. Should it win FDA approval, final two-year results of a separate phase III study, Balance, comparing it head-to-head vs. Sanofi SA's Fabrazyme (agalsidase beta), would be used to support conversion of the potential FDA approval to regular vs. accelerated status.

Along the way, interim one-year data from Balance and the results of the Bridge study will be used to support filing of an MAA with the EMA. Outcomes from a third and final phase III study, called Bright, may support a less-frequent dosing regimen for pegunigalsidase alfa in patients with mild disease.

As it moves ahead, Protalix is working closely with partner Chiesi Farmaceutici SpA, which is in the midst of building up its rare disease business, partly through a focus on lysosomal storage disorders such as Fabry. Parma, Italy-based Chiesi paid Protalix $25 million up front in October for ex-U.S. rights to the drug and a further $25 million in 2018 for U.S. rights, deals that carry both limited coverage of development costs for the therapy and up to $320 million and $760 million, respectively, in regulatory and commercial milestone commitments.

Bridge to better kidney function

Pegunigalsidase alfa is a modified version of the recombinant human alpha-GAL-A protein, the key element that people with Fabry disease lack. Fabry is a progressive disorder caused by an inherited deficiency of the enzyme alpha galactosidase A. The enzyme is necessary for the breakdown of the lipid globotriaosylceramide, often abbreviated as GB-3. It occurs in about one person per 40,000. As patients with Fabry grow older, damage to their blood vessels from the disorder can lead to reduced kidney function and, in the case of kidney failure, the need for dialysis or kidney transplant.

In the 12-month interim data from Bridge, Protalix shared results from the first 16 of 22 adults enrolled in the study, all of whom showed a mean improvement in kidney function when switched from Replagal to pegunigalsidase alfa.

All of the participants with progressing disease, those with an estimated Glomerular Filtration Rate (eGFR) slope between -5 and -3 mL/min/1.73 m2/year, and 66.7% in the fast progressing group, with an eGFR slope < -5 mL/min/1.73 m2/year, achieved the proposed therapeutic goals of the study after switching to pegunigalsidase alfa. The majority of the patients who completed the study also rolled over to a long-term extension study, continuing to be treated with pegunigalsidase alfa, Protalix said.

"The outcomes are very, very good," Bashan said, noting that eGFR measurements are reflective of each patient's clinical situation. Should the Balance study show superiority for pegunigalsidase alfa compared to Fabrazyme, he said, it could potentially show an ability to significantly delay the time to dialysis for Fabry patients.

Challenges ahead

Should it gain approval, the challenges Protalix and Chiesi will face vary by market. Sanofi's Fabrazyme is approved in both the U.S. and the EU, while Takeda's Replagal is only approved in the EU. Both are entrenched enzyme replacement therapies for Fabry disease, having been available for more than 10 years in those key markets, according to Cortellis. European patients with eligible mutations have a further treatment option in Amicus Therapeutics Inc.'s Galafold (migalastat), which is approved in Europe with both cardiac and renal benefit claims on its label. Another investigational medicine, Sanofi's venglustat, has advanced to phase II trials.

Sales of Fabrazyme hit $891 million in 2018 and are projected to continue climbing, though a biosimilar version of the medicine, JR-051 (JCR Pharmaceuticals Co. Ltd. and Glaxosmithkline plc), has been approved in Japan. Revenue from Replagal reached $596 million in 2018, but is expected to fall following the expiration of orphan exclusivity. Sales of Galafold were $91 million in 2018.

If anything, with Chiesi, Protalix is likely to fare far better than it has with partner Pfizer Inc., to which it licensed its first commercial product, taliglucerase alfa for the treatment of Gaucher disease, outside Brazil. Pfizer sells the therapy as Elelyso, but has thus far failed to secure meaningful market share for it vs. the standard of care, Sanofi's Cerezyme (imiglucerase). Protalix, which markets taliglucerase alfa inside Brazil as alfataliglicerase, expects revenue to grow there, reaching about $9 million this year.

Room to grow

No matter the outcomes, the Carmiel, Israel-based company retains a special place as one of the few companies that have pioneered the manufacturing of its products in plant cells, using its patented Procellex protein expression system. Pegunigalsidase alfa is expressed by tobacco plant cell, while other carrot, celery, ginger and horseradish plant cells have been used, too.

"In the next 12 to 18 months, we have some very interesting data points ahead. If all goes well, we'll get [FDA] approval at the end of next year," Bashan said. "With regard to Fabry, there is a lot of optimism." ♦