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New data underscore benefits of idebenone in DMD as Biomarin pulls drisapersen MAA

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DUBLIN – Even as Biomarin Pharmaceutical Inc.'s dwindling hopes for its exon-skipping pipeline in Duchenne muscular dystrophy (DMD) turned to ash this week, with the withdrawal of its marketing authorization application (MAA) for drisapersen from the EMA, there was also some positive news for DMD patients and their families. Santhera Pharmaceuticals AG released additional clinical data from its Delos phase III study of Raxone (idebenone) in Duchenne muscular dystrophy (DMD), which showed that the drug's ability to slow the rate of decline of respiratory function over one year converted into a range of clinical benefits.

The new analysis forms part of its recently completed regulatory filing in Europe and its planned filing in the U.S. The Liestal, Switzerland-based company filed for approval in DMD in Europe Tuesday, as a type II variation to its existing approval for treating visual impairment in Leber's hereditary optic neuropathy. If the FDA is agreeable, it could complete a rolling new drug application during the third quarter of 2016 – although that depends on the outcome of a meeting in late July.

The primary endpoint of the Delos trial, which recruited 64 DMD patients who were not on concomitant glucocorticoid therapy, was the alteration in lung function over the one-year trial, as measured by the percentage change from baseline to week 52 in peak expiratory flow (PEF) for each patient. PEF for those in the drug treatment group declined by an average 2.57 percent, whereas it declined by an average 8.84 percent for those in the control group. (See *BioWorld Today*, May 14, 2014.)

The new analysis illustrates the clinical outcomes in terms of fewer bronchopulmonary adverse events (BAEs) – that were associated with slowing the rate of decline in lung function. Six of 31 patients on the drug had a total of seven BAEs, whereas 17 of 33 patients on placebo did. They were also of shorter duration – a total of 82 days for the idebenone-treated group vs. 222 days for those on placebo. The two groups also differed in their use of antibiotics to treat BAEs. Seven of those in the

drug treatment group reported antibiotic use over 65 days, whereas 13 patients in the control group used antibiotics over 105 days.

"These are hard endpoints, and they substantiate the functional measures that were the primary and secondary endpoints of the Delos trial," Santhera CEO Thomas Meier told *BioWorld Today*. Four patients in the control group were hospitalized due to BAEs, whereas just one in the treatment arm was. "It's a small n, but hospitalization is a very hard endpoint," he said.

The new data, published online in *Neuromuscular Disorders*, constitute an obvious efficacy signal, but they were only prospectively included in the Delos protocol as part of the safety analysis. The protocol for the forthcoming phase III Sideros trial, which will recruit 260 DMD patients who are also on concomitant glucocorticoid therapy, will take account of the findings. "In the new trial, the endpoints are being prospectively planned as efficacy outcomes," Meier said.

Glucocorticoid therapy has been widely used in DMD for several decades as it delays the loss of ambulation and the need for respiratory support. About 40 percent stop the therapy, however, due to side effects, including weight gain that follows loss of ambulation. The Sideros trial, which is due to start later this year, with an estimated read-out in late 2019, will evaluate idebenone's efficacy in patients that continue to receive glucocorticoids. It will also serve as a confirmatory trial, although whether or not the company needs to complete it before it can file an NDA is not yet clear. The upcoming FDA meeting will clarify whether it can proceed to file for conditional approval under the subpart H pathway. "If there is a 'yes, go ahead,' we would anticipate we would start a rolling NDA because of the fast-track designation we have and that would take approximately three months. We would also be eligible for priority review," Meier said.

Shares in Santhera (ZURICH:SANN) gained almost 10 percent Wednesday to close at CHF82 (US$82.93).

Meanwhile, Rafael, Calif.-based Biomarin's withdrawal of its application for approval of drisapersen in Europe was "no surprise," noted RBC Capital Markets analyst Michael Yee, and the news would have no impact on its investment model. The FDA had already declined to approve the same drug in January – and Biomarin has now terminated development of several other earlier stage exon-skipping drugs directed at different mutations in dystrophin, the absence of which causes DMD. The company said it will continue to explore next-generation oligonucleotides, but its $680 million acquisition in late 2014 of Leiden, the Netherlands-based Prosensa Holding BV, is now looking like an expensive mistake. Sarepta Therapeutics Inc., of Cambridge, Mass., is still in the game – just. The FDA pushed back its May 26 PDUFA date for eteplirsen and has yet to indicate when it will issue a decision.