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MARKET WATCH

Upcoming catalysts in Q3 2018

Upcoming market catalysts in the third quarter of 2018 include US approval decisions for three first-in-class therapies with orphan status. Regulatory applications for migalastat (developed by Amicus) for Fabry disease, ivosidenib (developed by Agios) for acute myeloid leukaemia (AML) and ALIS (amikacin liposome inhalation suspension, developed by Insmed) for nontuberculous mycobacteria (NTM) lung disease are all currently under priority review by the FDA. These novel drugs represent new or differentiated treatment options that will fulfil a significant unmet medical need if approved.

The FDA Prescription Drug User Fee Act (PDUFA) decision date for migalastat is 13 August. Migalastat is intended to treat Fabry disease in patients 16 years or older who have amenable genetic mutations. This rare genetic disease is caused by deficiency of the α-galactosidase A enzyme, which degrades specific lipids in lysosomes that would otherwise accumulate and cause irreversible organ damage. Migalastat is designed as a chaperone therapy to stabilize certain mutant enzymes to facilitate normal trafficking to lysosomes, thereby reducing lysosomal substrate accumulation. In addition to this unique mechanism, migalastat is available orally, which is an advantage over the established enzyme replacement therapy Fabrazyme (agalsidase alfa, marketed by Sanofi), the only Fabry disease treatment to be approved by the FDA since 2003. Migalastat is already approved in the European Union, Japan and other markets, including Australia and Canada. If approved, migalastat is anticipated to have a strong market impact in the United States, and Amicus expects its migalastat global revenue from 2017 to double this year.

Ivosidenib, a small-molecule inhibitor of isocitrate dehydrogenase 1 (IDH1), has a PDUFA date of 21 August. An approval would bring the first targeted treatment to relapsed or refractory AML patients who have an IDH1 mutation. The mutant enzyme IDH1 is found in various tumour types, including gliomas, sarcomas and haematological malignancies such as AML. Although IDH1 mutations are estimated to occur in only 6–10% of AML patients, they are associated with poor disease prognosis. Clinical data supporting the application demonstrate an overall response rate of 41.6%, with durable remission rates (30.4% of patients had a complete remission or complete remission with haematological recovery, including 21.6% who had a complete remission), as well as favourable transfusion independence rates that were achieved across multiple response categories. These results validate the benefit of targeting IDH1, establishing ivosidenib as a new approach to the treatment of AML that could be paradigm-shifting. For the 8–19% of AML patients who carry IDH2 mutations, Agios has already introduced a new treatment paradigm with the IDH2 inhibitor enasidenib (Idhifa), which was approved by the FDA last year. Both drugs highlight the company's rapidly developed portfolio of compounds that target cancer cell metabolism.

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The FDA will decide on the application for ALIS by 28 September. The once-daily formulation of amikacin could potentially be the first approved inhaled therapy for adults with NTM lung disease caused by *Mycobacterium avium* complex (MAC). NTM enters the lungs through the environment and could cause an infection leading to permanent lung damage and increased rates of mortality. Through Insmed's proprietary liposomal technology, ALIS delivers amikacin directly to the infected cells to eradicate the bacteria. A registration study testing ALIS added to guideline-based therapy (GBT) against GBT alone met its primary end point of patients achieving culture conversion at 6 months (29% versus 9%, $P < 0.0001$). Additionally, GBT took approximately 30% longer to convert, demonstrating that ALIS is not only more effective but faster. Having received orphan, breakthrough therapy, fast-track and qualified infectious disease product designations, the FDA clearly recognizes the need for patient access in this space where no approved therapies exist, and regulatory approval is imminent.

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