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MARKET WATCH

Upcoming market catalysts in Q2 2013

Notable market catalysts expected in the second quarter of 2013 include initial Phase III results for SAR302503 in myelofibrosis and first data from the Phase III rheumatoid arthritis programme for fostamatinib. A decision from the US Food and Drug Administration (FDA) is also expected in June for two melanoma compounds developed by GlaxoSmithKline: dabrafenib and trametinib.

The establishment of Janus kinase 2 (JAK2) as a validated target for myelofibrosis — through the approval of ruxolitinib (Jakafi; Incyte/Novartis) in 2011 — has propelled the rapid development of other JAK inhibitors for the treatment of myeloproliferative disorders. Sanofi gained the JAK2 inhibitor SAR302503 through its acquisition of TargeGen in 2010 and has since advanced it into Phase III development for myelofibrosis. Based on Phase II results in which SAR302503 provided clinically meaningful reductions in splenomegaly and improvements in disease-related symptoms, the Phase III JAKARTA study was initiated. The trial is similarly designed with reduction in spleen volume as the primary end point, and symptom improvement, overall survival and progression-free survival as secondary end points. Positive results from JAKARTA could support a regulatory filing in myelofibrosis and offer potential competition for Jakafi — the only FDA-approved drug for this indication. Phase II studies of SAR302503 in the related diseases polycythaemia vera and essential thrombocythaemia are also underway.

Representing a novel therapeutic approach for rheumatoid arthritis, fostamatinib (developed by AstraZeneca) is the first oral spleen tyrosine kinase (SYK) inhibitor to progress to Phase III development. In a Phase IIb study, fostamatinib resulted in statistically significant changes in the DAS28 score (a measure of disease activity) against placebo but failed to be superior to adalimumab (Humira; AbbVie), a widely used monoclonal antibody that targets tumour necrosis factor (TNF). Although a commercial setback, this head-to-head failure should not hurt the chances of regulatory approval. The pivotal OSKIRA programme focuses on three trials controlled with placebo rather than an active comparator. Furthermore, fostamatinib presents an advantage of oral dosing over the various injectable agents crowding the rheumatoid arthritis market, such as adalimumab and other anti-TNF biologics. If the anticipated OSKIRA data are favourable, fostamatinib could provide an effective alternative for patients who respond inadequately to oral disease-modifying anti-rheumatic drugs such as methotrexate, or to anti-TNF therapies.

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The FDA is reviewing dabrafenib and trametinib as single-agent therapies for *BRAF*^{V600} mutation-positive metastatic melanoma, and both decisions are expected by 3 June 2013. Dabrafenib could become the second approved drug to inhibit BRAF, following the approval of vemurafenib (Zelboraf; Roche) in 2011. In Phase III trials, dabrafenib improved progression-free survival when compared to chemotherapy. Trametinib, the most advanced inhibitor of MAPK/ERK kinase (MEK), a downstream target in the BRAF signalling pathway, also showed significant improvements in progression-free survival, as well as overall survival, in a Phase III trial comparing it with chemotherapy. A Phase III programme evaluating dabrafenib and trametinib as a combination therapy is underway. Potential advantages of combined BRAF and MEK inhibition include reduced side effects and a delay in drug resistance, which has been observed in a subset of patients with melanoma taking BRAF inhibitors. So, although there have been recent breakthroughs for metastatic melanoma with ipilimumab (Yervoy; Bristol-Myers Squibb) and vemurafenib, dabrafenib and trametinib may represent valuable additions to the market.

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