Evaluate Vantage

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Event – High-risk heart disease play nears readout for Glaxo

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The sector will soon know whether it was worth the hundreds of millions of dollars GlaxoSmithKline gambled to put its heart disease candidate darapladib into phase III trials after missing primary endpoints in phase II. Two massive studies, totalling nearly 30,000 patients, are expected to report data in the next 12 months or so, testing whether inhibition of lipoprotein-associated phospholipase-A2 (Lp-PLA2) can delay cardiovascular events.

Glaxo had little but pipeline success in the first half of 2013, but the second half is turning a less positive, and few are betting that darapladib will turn the momentum back. However, if the pill succeeds it should give a lift to the group's shares, not to mention open the door to new trials in combination with statins and other established lipid-lowering drugs, potentially expanding its market.

Company	GlaxoSmithKline
Product	Tyrisa (darapladib)
Market cap	$119.2bn
Product NPV	$451m
% of market cap	0%
Event type	Phase III results
Date	Q4 2013

HGSI delivers

Darapladib has the proposed brand name Tyrisa, and was originally licensed from Human Genome Sciences. Glaxo took on full commercialisation risk when it bought out the Maryland-based company for $3.6bn in 2012 (*Game of hardball wins Human Genome for Glaxo, July 17, 2012*). A second Lp-PLA2 from that partnership was rilapladib, although this appears to have been shelved after completing phase II trials in atherosclerosis and Alzheimer's disease.

A scan of the pipeline in the Lp-PLA2 class shows that all five of the compounds that ever entered the clinic emerged from the Glaxo-Human Genome Sciences partnership – GSK2647544 remains in phase I trials in Alzheimer's – so the coming phase III data will reveal whether this is a productive mechanism in cardiovascular disease. Those handicapping the results should not be encouraged by the failure of the related drug varespladib, a secretory phospholipase A2 inhibitor (*Anthera shares fall on failure of heart drug, March 12, 2012*).

Lp-PLA2 is an enzyme important to lipid metabolism and inflammation that circulates with lipoprotein molecules. When carried into arterial walls with low-density lipoprotein as atherosclerosis progresses, Lp-PLA2 stimulates macrophage activity, which can cause ruptures that release thrombogenic agents that can cause heart attacks.

The key phase II trial failed to show, after 12 months of treatment, that the agent reduced high-sensitivity C-reactive protein, a biomarker for cardiovascular disease, and plaque deformability, an indicator of susceptibility towards rupture; these were the two primary endpoints.

On a secondary endpoint, darapladib was able to show that it could arrest the growth of the necrotic core of atherosclerotic plaques, an area vulnerable to rupture, compared with placebo. This trial was conducted in 300 patients who had already undergone coronary interventions or diagnostic catheterisation.

Glaxo was encouraged enough by the win on the secondary endpoint to take darapladib into very expensive

and lengthy phase III studies.

Year-end bonus or bust

The two phase III trials are event-driven, and it is not clear when they will report data. In Glaxo's second-quarter earnings call, chief executive Andrew Witty said the first data should be disclosed by the end of 2013.

The first to enrol patients was Stability, which began in 2008, a test in 15,000 coronary heart disease patients to determine whether darapladib can delay the time to the first occurrence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. The second, Solid-Timi 52, began in 2009, with a goal of enrolling 13,000 acute coronary syndrome patients and measuring the same endpoint.

Analysts have largely discounted the possibility that darapladib will return with positive data – Societe Generale points to an inability to extrapolate the limited phase II data and the relevance of the biomarkers used in phase II to outcomes as reasons to make no forecast for now. The more generous analysts hardly foresee a blockbuster: Deutsche Bank forecasts £505m ($806m) in 2017 sales, and Bank of America-Merrill Lynch £389m.

On the other hand, the SocGen analysts write that a win on outcomes data should make darapladib an approvable product that can be expanded to other settings, such as in combination therapy with statins or triglyceride-lowering drugs. "In our view, positive data would probably mean a re-evaluation of GSK's strategy (for investors), since GSK would potentially have a large and commercially meaningful cardiovascular drug," writes their analyst Stephen McGarry.

Daraplapib is a long shot, however, and a costly one at that.

Trial	Population	ID
Stability	15,000 coronary heart disease patients	NCT00799903
Solid-Timi 52	13,000 acute coronary syndrome patients	NCT01000727

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