Evaluate Vantage

October 19, 2018

Upcoming events – Takeda awaits dengue data and Regenxbio needs more heartening results

Elizabeth Cairns

Takeda will soon report phase III results with its dengue fever vaccine, while Regenxbio needs an improvement with its cholesterol-lowering gene therapy candidate, RGX-501.

Welcome to your weekly digest of upcoming events. It was nearly a year ago that use of Sanofi's Dengvaxia was found to cause more severe disease in previously uninfected vaccine recipients who went on to contract dengue than in those who had had a bout of the fever before they were vaccinated. This caused its restriction to patients who had already been infected, hitting revenues hard.

Sanofi's closest competitor here, Takeda, will soon find out whether it will be able to capitalise on the French group's misfortune. The huge phase III trial of TAK-003, Takeda's dengue vaccine candidate, is expected to report by the end of the year. The Tides study has enrolled 20,100 healthy people who underwent two subcutaneous injections of 0.5ml of '003, the second dose being administered three months after the first.

According to Takeda the Tides study aims to prove the utility of TAK-003 regardless of recipients' previous dengue exposure – a crucial point given Dengvaxia's fate. The inclusion and exclusion criteria of Tides as listed on clinicaltrials.gov make no mention of prior dengue infection.

The study is being conducted in three parts. Part 1 evaluates vaccine efficacy and will last 15 months. Part 2 will look at efficacy over an additional six months and part 3 evaluates long-term safety over three more years by following participants for side-effects.

Part 1 is the trial's primary endpoint and it is these data that will emerge in the coming weeks. Derek Wallace, head of Takeda's global dengue programme, told *Vantage* last year that at this point the company will have data on TAK-003's efficacy against individual serotypes – it is designed to work against all four variants of the virus – and efficacy according to baseline status.

Dengvaxia was approved based on a trial in 20,869 healthy children which had an efficacy rate of 60.8% in the per-protocol population and serotype-specific vaccine efficacy of 50.3% for serotype 1, 42.3% for serotype 2, 74.0% for serotype 3, and 77.7% for serotype 4.

This will give Takeda something to aim for, though of course avoiding a similar exacerbatory effect to Dengvaxia's in the longer term will be vital.

By coincidence, Dengvaxia received a positive opinion today from the CHMP recommending its use in patients who have had a prior infection. But it remains a cautionary tale. As recently as February 2017 the sellside forecast blockbuster sales, according to *EvaluatePharma*'s archived data, but current forecasts have it selling just $4m in 2024. TAK-003 is forecast to do $201m of business in 2024.

Regenxbio takes heart

Meanwhile, more data are due this quarter from a phase I/II trial of Regenxbio's RGX-501, a gene therapy being tested in patients with homozygous familial hypercholesterolemia (HoFH). An update in August raised questions over the project's therapeutic window, and there are also doubts about its commercial opportunity.

RGX-501 aims to deliver the low-density lipoprotein receptor gene, which is mutated in patients with HoFH, leading to very high cholesterol levels and life-threatening coronary artery disease. LDL-lowering drugs such as PCSK9 inhibitors are already used, but there is no cure.

The primary endpoint of the open-label study of RGX-501 is safety and the key efficacy outcome is LDL cholesterol reduction at 12 weeks. The trial is funded by Regenxbio but is being carried out at the University of Pennsylvania.

Regenxbio's August update concerned six patients treated with RGX-501 dosed at either $2.5x10^{12}$ vector genomes/kg or $7.5x10^{12}$ vg/kg.

Worryingly, all three patients in the high-dose cohort had an increase in liver enzymes – something that has also been seen with other AAV vector-based gene therapies. The affected patients in Regenxbio's trial were treated with steroids, which brought liver enzyme levels down but hampered the measurement of LDL-C, according to the company.

Meanwhile, the low-dose group did not show a clinically meaningful reduction in LDL-C. More data from both cohorts are due to be presented this quarter at a scientific meeting.

Regenxbio hopes to tinker with the trial in light of the interim data, changing it to include steroid prophylaxis and the measurement of LDL cholesterol at a later time point, by which time steroid therapy would have finished. The group also hopes to include more patients in the current high-dose group and to enrol a third dose cohort. The company should provide an update on its plans this quarter.

Even if RGX-501 works, there are questions about the size of its potential market, with estimates of the number of US HoFH patients ranging from a few hundred to 2,000, Evercore ISI analysts noted. And expanding into less serious cholesterol-lowering indications looks unlikely, particularly if safety worries are not assuaged.

Also this quarter, Regenxbio is expecting more data with its wet age-related macular degeneration gene therapy project, RGX-314 (*Why Regenxbio's eye gene therapy would have to be the cheapest yet, August 13, 2018*).