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Merck KGaA Overcomes Ukraine Disruption To Keep MS Frontrunner On Track

FDA Has Approved Trial Adaptations

by Andrew McConaghie

The German group is optimistic evobrutinib can be a blockbuster in multiple sclerosis and has adapted its pivotal trial to cope with disruption caused by the war in Ukraine.

Merck KGaA is still on track to produce Phase III results from its multiple sclerosis drug evobrutinib in late 2023, which would keep it ahead of a crowded field of Bruton's tyrosine kinase (BTK) inhibitor pipeline competitors.

The drug is also the most advanced candidate in its pipeline and carries with it the hopes of the German company's near-term growth ambitions. But the company has had to think fast in the face of disruption caused by the ongoing Russian invasion of Ukraine, where many of the trial's patients were enrolled.

Speaking at a capital markets day meeting on 6 October, Merck's pharma chief Peter Guenter expressed confidence in the late 2023 timing of the readout, despite the huge upheaval caused by war in Ukraine.

That would then allow it to file in early 2024, and potentially set Merck up for a first-to-market launch within a year.

The company's Phase III EVOLUTION RMS clinical trial program is evaluating evobrutinib, a BTK inhibitor in patients with relapsing MS.

The global randomized study has over 700 recruitment sites worldwide, with 16 of these in

Ukraine. These include regions in the south and east of the country which have become frontlines in the conflict and occupied by Russia, including cities such as Kharkiv and Odessa.

PETER GUENTER

"We have faced significant headwinds with the Ukraine situation," said Guenter. "0ur teams have been able to do a fantastic job in keeping the integrity of the data but not only that, changing the protocol to be an event-driven protocol."

The study, which began enrolling in 2020, compares evobrutinib with *Sanofi*'s Aubagio (teriflunomide) in participants with relapsing MS and its primary endpoint is the annualized relapse rate (AAR).

Updates to the protocol include extending the original timeframe from 96 weeks to 156 weeks and the company has agreed with the US Food and Drug Administration to switch to an event-driven rather than timeframe-based protocol. It is hoped this will maintain the integrity of the trial and also help avoid a delay to the readout.

Changes to the number of MRI tests required in the study have also been agreed, moving from regular scans to monitor for characteristic brain lesions to "all available" scans. However Merck said these changes reflected more flexible approaches to MS trials rather than any scarcity of MRI scans.

Following Russia's invasion in late February, Merck has also decided to add extra patients outside of the affected counties, with recruitment now underway.

"Look, [the Russia-Ukraine situation] has been a rollercoaster. We've managed and we're very confident about the data," added Merck's R&D leader Danny Bar-Zohar.

"We recently had a very good dialogue with FDA regarding the quality of the data that comes from there and we are strongly committed to the readout before the end of next year."

How Will Evobrutinib Challenge Current MS Leaders?

MS is one of the German company's key franchises, with first Rebif (interferon beta-1a) and more recently Mavenclad (cladribine) being major players in the field.

However new products have raised the bar in MS in recent years in terms of minimizing relapses in patients, most notably Roche's market leader Ocrevus (ocrelizumab). The latter demonstrated

an AAR of 0.156/0.155 in its pivotal OPERA studies, versus 0.292/0.290 in Rebif, a low relapse rate which new market entrants will find hard to beat.

Given that evobrutinib's EVOLUTION RMS study is a head-to-head with the older Aubagio study, Merck will not have immediate firepower on ARR efficacy against Ocrevus.

However, Bar-Zohar sees evobrutinib having the potential to demonstrate efficacy in other serious aspects of the progressive disease not addressed by these drugs.

"It's very clear that beyond the relapse rate of 0.1, there is not so much to add. But there is much to add in progression that is not related to relapses; fatigue, loss of your occupation, cognitive decline."

BTK Inhibitors Are The Next Big Race In MS

By Jessica Merrill

09 Jun 2022
BTK inhibitors are in late-stage development for multiple sclerosis, with Merck KgAA and Sanofi in the lead and Roche and Novartis close behind.

Read the full article here

He said evobrutinib was likely to show efficacy against this "smoldering inflammation" because as a brain penetrant drug, it reaches the microglia and B cells inside the central nervous system which cause these problems. The drug has already amassed data on these targets in its Phase II study, as well as against slowly expanding lesions and neurofilaments, two early indicators of disease progression.

Merck will also be looking for safety advantages over Ocrevus and *Novartis*'s fellow CD20-targeting antibody Kesimpta (ofatumumab). While both are high efficacy therapies, they also come with side effects such as higher risk of infection or malignancy.

Evobrutinib is taken as a twice-daily pill, a convenient oral formulation which the company hopes will be more attractive that Ocrevus. The Roche therapy is administered every six months via intravenous, though the company is developing a subcutaneous version.

Sanofi Not Far Behind

Merck is aware that it is in a race to be first to market with its candidate. Close behind is Sanofi with its rival BTK inhibitor tolebrutinib. Its GEMINI I and GEMINI II studies are now fully enrolled and on track for a 2024 submission to the FDA.

Sanofi's drug has been subject to a safety scare, however. Separate trials in progressive MS and myasthenia gravis were placed on hold by the FDA in August, following a small number of drug

induced liver injury, though the company stressed its RMS study was unaffected.

Meanwhile, *Roche* has its own BTK inhibitor in the pipeline, fenebrutinib, which is expected to have its pivotal readout in 2025 data, and Novartis is a little further behind with remibrutinib.

For Merck, evobrutinib is one of two Phase III candidates which it believes have blockbuster potential, the other being xevinapant, an IAP inhibitor drug for squamous cell carcinoma of the head and neck. (Also see "*Merck KGaA Bags Exclusive Rights To Develop, Sell Debiopharm's Xevinapant*" - Scrip, 1 Mar, 2021.)

Guenter said the company was now "in full pre-launch mode" as it gears up to take on the bigger pharma companies now dominating the market.

Please note this article was amended on 7 October to show that the MRI scan protocol update was in line with clinical trial practices, and was not a reflection of the war in Ukraine.