Evaluate Vantage

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Marinus finds a path forward in rare epilepsies

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Marinus celebrates pivotal trial success with ganaxolone, but a quick approval could depend on lenient regulators.

Marinus Pharmaceuticals might have missed out on the big prize for its sole project, ganaxolone. But a year after the Gaba modulator crashed out in post-partum depression, the group's decision to switch focus to rare epilepsies looks like a good move.

The company's stock climbed 85%, albeit from a low base, on news of a pivotal trial success in CDKL5 deficiency disorder (CDD). But with several red flags – including a very low placebo response and missed secondary endpoints – regulators might at least want a confirmatory trial before giving ganaxolone the green light.

Marinus, meanwhile, is optimistic about its chances of getting a quick approval: on the strength of the Marigold trial results it plans to file oral ganaxolone with the US FDA in mid-2021, and with Europe's EMA by the third quarter of next year.

The group's hopes are no doubt fuelled by the fact there are no approved drugs for CDD, a genetic disorder characterised by severe epilepsy and developmental delay. It affects around 5,000 patients apiece in the US and Europe, Marinus estimates.

This market might not be huge but it could still make a difference for a company the size of Marinus: Leerink analysts estimate that if 1,000 CDD patients receive ganaxolone at $100,000 per year, it would make a peak sales opportunity of $100m.

Perhaps more importantly the Marigold data could bode well for ganaxolone's chances in the other rare epilepsies in which it is being developed, including tuberous sclerosis, where GW Pharmaceuticals' Epidiolex was recently approved.

And approval in CDD should net Marius a priority review voucher; although the value of these is not what it once was, it could provide a useful source of funds.

Marigold blooms?

Marigold's primary endpoint was change in 28-day seizure frequency, and it hit this, with ganaxolone showing a median 32% reduction versus a 4% reduction with placebo. This was statistically significant with a p value of 0.002.

However, ganaxolone was flattered by the low placebo response – Marinus had been expecting a 10-20% reduction in the placebo group.

Another reason for caution is that Marigold did not meet its predefined secondary endpoints. The company's chief medical officer, Joe Hulihan, said during a conference call to discuss the data that the study had been powered for the primary endpoint rather than the secondaries.

Marinus claimed the trial did meet significance on "exploratory" secondary endpoints including caregiver global impression of change in seizure intensity/duration; however, if this is an exploratory endpoint it cannot, by definition, be statistically significant.

Overall, these issues might not scupper ganaxolone's chances in a disease where the unmet need is so high. Patients in Marigold had a median of 50 or more seizures per month at baseline and had failed, on average, seven anti-epilepsy drugs.

However, the FDA might require Marinus to carry out another pivotal trial – Reata Pharmaceuticals was recently hit with such a request for omaveloxolone, which it is developing for Friedreich's ataxia, a rare neurological disease with no approved therapies.

Success in other rare epilepsies would make for a stronger story, but at least Marinus's prospects look a lot rosier than they did last year.

Life after depression – ongoing trials of ganaxolone

Setting	Formulation	Trial name	Trial ID	Note
CDKL5 deficiency disorder	Oral	Marigold	NCT03572933	Hit primary endpoint
Status epilepticus	IV	Raise	NCT04391569	Not yet recruiting
PCDH-19-related epilepsy	Oral	Violet	NCT03865732	Data due H1 2021
Tuberous sclerosis	Oral	-	NCT04285346	Data due mid-2021

Source: EvaluatePharma, clinicaltrials.gov.