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EMA And FDA Compared – The Case Of Minoryx's Leriglitazone

by Francesca Bruce

The EMA offers more flexibility than the US FDA when it comes to missed primary endpoints in certain circumstances, meaning a potentially quicker route to authorization in the EU.

Spanish biotech firm *Minoryx Therapeutics* hopes a newly approved Phase III trial will lead to the US approval of its orphan drug leriglitazone for X-linked adrenoleukodystrophy (X-ALD) in 2026 at the earliest.

Meanwhile, the European Medicine Agency's review of the drug is well under way, with a decision on marketing authorization expected at the end of 2023 or the beginning of 2024. The *Pink Sheet* took a look at the different approaches to approval in the two markets and how missed primary endpoints and a lack of natural history data have impacted the route to authorization.

In June, the FDA gave Minoryx the go-ahead to initiate the Phase III CALYX trial of leriglitazone for treating X-ALD patients with cerebral adrenoleukodystrophy (cALD). The study is intended to lead to full approval in 2026, although the timeline could be longer. If the first efficacy readout for the study at 18 months does not show efficacy, there will be a second readout at a later date, followed by a third if necessary.

Key Takeaways

- The EMA offers a more flexible approach than the FDA when primary endpoints are missed for orphan products where there has been little natural history data of the disease to inform trial design.
- The review of leriglitazone is more advanced in Europe than in the US.

By contrast, in the EU, a review of the company's marketing authorization application by the EMA's committee for human medicinal

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products (CHMP) began in September 2022 . The process is ongoing and the company is waiting for the next round of comments from the committee, said Marc Martinell, CEO of Minoryx, in an interview with the Pink Sheet. He expects an EU decision on authorization at the end of 2023, or the beginning of 2024 if the CHMP has any "unforeseen requirements". CALYX will have little bearing on the decision as the EU submission is based on the results of an earlier trial.

- Leriglitazone could be offered a conditional marketing authorization in the EU.

Endpoints

"There have always been some important differences in the development on both sides of the Atlantic and in the way the FDA and EMA have seen the product and what they have been requesting," said Martinell.

One notable difference has been the EMA's flexibility with regard to missed primary endpoints for a treatment for a rare disease with little natural history data available to inform trial design.

"When you move into the zone of results with a missed primary endpoint, that is when the differences between regulators become more pronounced... In Europe you may have more of a global picture perspective... whereas in the US, you are more tied by the primary endpoints," Martinell commented.

In the EU, the marketing authorization application for leriglitazone is based on the Phase II/III ADVANCE trial, a two-year double blind placebo controlled study that aimed to evaluate the efficacy of leriglitazone on the progression of adrenomyeloneuropathy (AMN) in male patients, determined by a motor function test. The study missed its primary endpoint in the overall population, which was a change from baseline in the 6-minute walk test.

Despite missing the primary endpoint, the study did yield "important results in other endpoints," said Martinell. It showed that leriglitazone reduced the progression of cerebral lesions and incidence of cALD and the progression of myelopathy symptoms, including balance deterioration.

The Disease.

X-ALD is an orphan neurodegenerative disease with a global incidence of approximately 6.2/100,000 live births and which is characterized by demyelinating brain lesions. The lesions rapidly progress and lead

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"The reason why we missed the primary endpoint was essentially because of the lack of the proper understanding of the natural history of this disease," Martinell observed. "When we were starting, very little was known about X-ALD and particularly AMN, the chronic component of the disease affecting the spinal cord. This was the target population under the study."

"The EMA recognized this sometime ago when we were discussing the study design," he said, adding that there were discussions on how to present the data in a pre-submission meeting.

Now there is more natural history data available and a better understanding about the disease progression. "There is a phase of disease when patients progress a lot on that endpoint and a phase where they do not," Martinell noted. Analysis of patients in the early phase of the disease versus those in later stage disease showed that there is an important effect on the early stage group with regard to the primary endpoint. According to Martinell, the company has been able to set this out to the EMA. "This is the kind of consideration we describe in the file."

to acute neurological decline and death. They also produce severe symptoms, including loss of voluntary movements, inability to swallow, loss of communication, cortical blindness and total incontinence and death, with a mean survival of three to four years.

Adrenomyeloneuropathy (AMN) and cerebral adrenoleukodystrophy (cALD) are the most common phenotypes. AMN, the chronic form of the disease, affects patients at adulthood and is characterized by progressive spastic paraparesis, sensory dysfunction and incontinence. AMN patients are also at risk of developing progressive cerebral lesions. cALD mostly affects males, and onset is typically between the age of four and eight. If untreated cALD progresses quickly and leads to permanent disability and death within two to four years.

Meanwhile, in the US the company had anticipated that another trial would be necessary. The FDA wanted a larger sample size of patients and a study with primary endpoints that definitively showed clinical benefit, said Martinell. The FDA-approved CALYX Phase III trial is designed to satisfy these requests and is enrolling 40 male X-ALD patients with progressive cALD defined by the presence of gadolinium-enhancing brain lesions. The primary endpoint of the placebo controlled trial is time to death or bedridden with permanent ventilatory support.

CMA V Accelerated Approval

Another important difference between the two regulatory systems is that in the EU there is the possibility of receiving conditional marketing authorization (CMA). "You don't have the equivalent in the US. You have accelerated approval. That can change things and be why you may end up in different situations on both sides [of the Atlantic]."

In the EU products are eligible for a CMA if they are intended to treat or prevent a seriously debilitating or life threatening disease. They must serve an unmet need and have a positive benefit-risk profile. When a CMA has been granted, the authorization holder must fulfill certain obligations, such as completing ongoing studies, starting new studies or collecting additional data to confirm the medicine's positive benefit-risk profile. Martinell did not rule out the possibility of a conditional marketing authorization for leriglitazone in the EU.

In the US, the accelerated approval pathway allows for earlier authorization of drugs that fulfill an unmet need and treat serious conditions based on a surrogate endpoint. Companies are then expected to conduct further studies to confirm the expected clinical benefit.

CALYX is intended to lead to full approval straightaway as the primary endpoint is on survival, said Martinell, though he acknowledged the accelerated approval pathway could be a possibility if primary endpoints are not hit.

PIP

A third difference between the two markets is the requirement that in the EU the company must produce a pediatric investigation plan (PIP) detailing clinical studies to be conducted in children, unless a waiver is granted.

As part of its EMA-approved PIP, Minoryx is conducting the NEXUS study in 20 boys between two and 12 years old with cALD with brain lesions with or without gadolinium enhancement. The primary endpoint is the proportion of patients with clinically and radiologically arrested disease at week 96. Interim results included in the EU filing for leriglitazone show that all evaluable patients were clinically stable with radiologically demonstrated disease arrest or lesion growth stabilization after 24 weeks.