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04 Apr 2024 | **Analysis**

Amylyx's Relyvrio Withdrawal May Trigger More Public Pledges Based On Confirmatory Trial Data

by Sue Sutter

Company makes good on vow at a September 2022 advisory committee meeting to withdraw the ALS drug if the PHOENIX trial failed. That pledge served as a backstop to FDA's approval decision based on a single study and created a level of sponsor accountability that often is missing when postmarketing studies fail.

Some may question whether the US Food and Drug Administration will be less willing to exercise regulatory flexibility for diseases with high unmet need following *Amylyx Pharmaceuticals, Inc.*'s decision to withdraw the amyotrophic lateral sclerosis drug Relyvrio due to a failed Phase III trial.

Perhaps a better question to ask, however, is whether senior FDA staff and external experts will be more likely to extract a public withdrawal commitment from sponsors when efficacy data rest on the edge of approvability.

On 4 April, Amylyx announced it had started the process of withdrawing Relyvrio (sodium phenylbutyrate/taurursodiol) from the US and Canada, where the drug is branded as Albrioza, based on results from the Phase III PHOENIX trial, which failed to hit its primary and secondary endpoints.

Key Takeaways

The company said Relyvrio/Albrioza will no longer be available for new patients effective immediately. Patients currently on therapy in the US and Canada who, in consultation with their physician, wish to stay on treatment can be transitioned to a free drug program under expanded access, Amylyx

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said.

"While this is a difficult moment for the ALS community, we reached this path forward in partnership with the stakeholders who will be impacted and in line with our steadfast commitment to people living with ALS and other neurodegenerative diseases," co-CEOs Joshua Cohen and Justin Klee said. "The decision to remove Relyvrio/Albrioza from the market and provide therapy free of charge for those who wish to continue was informed by the PHOENIX trial results, engagement with regulatory authorities, and discussions with the ALS community."

- Amylyx has started the withdrawal process for Relyvrio due to failure of the PHOENIX trial, making good on its pledge at a September 2022 US FDA advisory committee meeting.
- Although not legally binding, Amylyx's pledge created a degree of public accountability that often seems to be lacking when marketed drugs fail subsequent studies.
- Future sponsors may face pressure from FDA staff or advisory committee members to publicly declare their plans in the event a confirmatory trial fails.

Approximately 3,900 US patients were taking Relyvrio in the 2023 fourth quarter, the company told the *Pink Sheet*. The drug launched at a wholesale acquisition cost of about $158,000 for the first year.

Extraordinary Regulatory Journey

Amylyx's withdrawal announcement came 18 months after Relyvrio received regular approval from the FDA on the basis of a single, positive Phase II study, along with confirmatory evidence of benefit on long-term survival in the study's open-label extension. (Also see "*Regulatory Flexibility: US FDA Approves Amylyx's Relyvrio For ALS Despite 'Degree Of Residual Uncertainty'*" - Pink Sheet, 29 Sep, 2022.)

Despite internal disagreement on the FDA review team, the agency determined the data collectively demonstrated substantial evidence of effectiveness, although with "a degree of residual uncertainty," and that regulatory flexibility was warranted given the serious and life-threatening nature of ALS and the substantial unmet need. (Also see "*Amylyx's Relyvrio: US FDA Review Shows Regulatory Flexibility Can Come In Many Forms*" - Pink Sheet, 9 Nov, 2022.)

Relyvrio's regulatory path has been extraordinary in a number of ways.

The new drug application had two advisory committee meetings in the same review cycle. At the second meeting in September 2022, Billy Dunn, then-director of the FDA's Office of Neuroscience, made the case for regulatory flexibility and urged Amylyx to publicly state that if

PHOENIX were not successful, it would withdraw the drug (then known as AMX0035) from the US market.

Amylyx's Klee responded that if PHOENIX failed, the company would do what is right for patients, "which includes voluntarily removing the product from the market."

This pledge was put to the test in early March 2024 when Amylyx announced that PHOENIX failed to demonstrate statistical significance on its primary endpoint of change from baseline in the Amyotrophic Lateral Sclerosis Function Rating Scale-Revised at week 48, or on secondary endpoints. (Also see "*Amylyx's ALS Drug Relyvrio Fails In PHOENIX Confirmatory Study, Setting Up Withdrawal Question*" - Pink Sheet, 8 Mar, 2024.)

At that time, the company said it would engage with regulatory authorities and the broader ALS community to discuss the results within the next eight weeks and make informed decisions, which may include voluntary withdrawal.

Public Pledge Created Accountability

Although not legally binding, Amylyx's pledge at the September 2022 adcomm and in subsequent comments created a degree of public accountability – to the patient community, investors and the FDA – that often seems to be lacking when marketed drugs fail subsequent studies.

The FDA has endured three cases in which a sponsor has objected to withdrawal of an accelerated approval product or indication due to lack of efficacy or safety concerns in confirmatory studies. Those disputes have dragged on for months and even years. (Also see "*Oncopeptides' Pepaxto Withdrawal Speeds Through In 7 Months Under Expedited Procedures*" - Pink Sheet, 23 Feb, 2024.)

Following FDA Commissioner Margaret Hamburg's November 2011 decision ordering the withdrawal of the breast cancer claim for *Genentech, Inc.* 's Avastin (bevacizumab), some oncology drug sponsors were pressed at advisory committee meetings to commit to withdrawing their drugs if confirmatory trials required under accelerated approval failed. (Also see "*"Not Another Avastin," FDA Panel Warns Genentech At Perjeta Review*" - Pink Sheet, 16 Sep, 2013.) (Also see "*AstraZeneca Takes "Anti-Avastin" Pledge On Accelerated Approval Withdrawal*" - Pink Sheet, 30 Jun, 2014.)

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In some cases, accelerated approval drugs remain on the market years or decades after approval despite unsuccessful confirmatory trials or sponsors' failure to conduct the studies in a timely fashion. (Also see "*Accelerated Approval Withdrawals: Will Non-Oncology Indications Stop 'Dangling' In 2024?*" - Pink Sheet, 30 Jan, 2024.)

Since the endpoint in Amylyx's Phase II CENTAUR trial was a functional scale, accelerated approval based on a surrogate was not a consideration. Thus, the FDA could not require that the company complete the ongoing PHOENIX trial as a confirmatory study under accelerated approval, and it would not have been able to apply the expedited withdrawal procedures applicable to accelerated approval drugs.

PHOENIX was required as a condition of the drug's approval in Canada. The company's pledge at the second adcomm that it would allow Relyvrio's US approval to rise or fall on the PHOENIX results helped persuade some members of that expert panel that approval was warranted even before the Phase III trial read out. (Also see "*Second Time's The Charm: Amylyx's ALS Drug Wins US FDA Panel Nod*" - Pink Sheet, 7 Sep, 2022.)

It also meant the agency would not have to try to leverage a little used, but likely cumbersome, regulatory provision to withdraw regular approval of a new drug for lack of substantial evidence of effectiveness. (Also see "*Amylyx's ALS Pledge Vs. FDA's Obscure Withdrawal Authority: Which Holds More Power?*" - Pink Sheet, 16 Sep, 2022.)

Are More Pledges Coming?

Ultimately, Amylyx's pledge helped bolster the case for approval, albeit with a nonbinding backstop. The sponsor did indeed follow through on its promise, seemingly without an extended period of wrangling with the FDA.

As a result, Amylyx appears to be coming out of this experience with its reputation and goodwill with the FDA and the ALS community relatively intact.

"We appreciate that Amylyx fulfilled their commitment to complete their Phase III clinical trial and share the results," the FDA told the *Pink Sheet*. "The FDA shares the disappointment of the ALS community at the news that the Phase III study for Relyvrio failed to meet its primary and

secondary endpoints."

The agency said it recognizes the need for new therapies for ALS. "In particular, we recognize importance of using a science-based approach that incorporates consideration of patient perspectives in its evaluation of the benefits and risks of this therapy. It is vital the FDA use the tools at its disposal to help make more safe and effective treatments available while ensuring public health is protected."

The prominence of Amylyx's pledge, which made headlines, and the impact it had on the advisory committee proceedings suggests future sponsors will be pressed for a withdrawal promise if the robustness of efficacy data are in question.

> ***"I don't love the idea of FDA relying on these sorts of comments at advisory committee meetings going forward – they can be too vague, leaving too many loose ends for companies to wiggle out of later, even as they might sway advisory committee votes." – U-Penn's Holly Fernandez Lynch***

"It is reasonable to expect that in the future the FDA or committee members will question sponsors regarding their intent to withdraw a product from the market if the product efficacy profile is based in part on an ongoing trial," said Jim DiBiasi, co-founder of 3D Communications, which prepares sponsors for adcomms. "This is especially true where the FDA is exercising regulatory flexibility to bring much needed treatments to patients for deadly diseases."

"The FDA's commitment to providing regulatory flexibility for rare and life-threatening diseases in hand with sponsor's commitment to doing what is best for patients are prime examples of the system working, and a clear indicator that advisory committees provide a critical forum for the American public to build trust in their health care system," DiBiasi said.

Holly Fernandez Lynch, assistant professor of medical ethics and health policy at the University of Pennsylvania, said she was relieved to see Amylyx move so quickly to voluntary withdrawal. However, Lynch said she would prefer to see the FDA leverage its full statutory authority rather than rely on companies to fulfill promises made at public meetings.

What Amylyx told Dunn at the September 2022 adcomm "wasn't a legally binding promise, so I don't love the idea of FDA relying on these sorts of comments at advisory committee meetings

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going forward – they can be too vague, leaving too many loose ends for companies to wiggle out of later, even as they might sway advisory committee votes," Lynch said.

"What FDA should do instead, when it wants to grant early approvals in the face of promising but uncertain evidence, is impose postmarketing requirements with very clear terms about what needs to be demonstrated in order for the drug to stay on the market," Lynch said. "That's akin to what FDA does with accelerated approvals, although even there we see a lot of leeway for drugs being allowed to remain on the market even when the confirmatory studies don't clearly demonstrate benefit."

Lynch was the lead author on a June 2023 paper in JAMA Health Forum that urged the FDA to draw on the Food, Drug, and Cosmetic Act's broad language and independently extend its core accelerated approval authorities – required postmarketing efficacy studies and expedited withdrawal procedures – to any drugs approved with substantial residual uncertainty about benefit, such as those supported by a single pivotal trial.

Amylyx Resets As A Clinical-Stage Company, Withdrawing Relyvrio

By Jessica Merrill

04 Apr 2024
The ALS treatment Relyvrio was removed from the market as expected following a Phase III trial failure.

Read the full article here

"As I've argued with colleagues, FDA has the authority to do this now, i.e., demand PMRs for efficacy outside accelerated approval, they just need to start applying that authority," she said.

"Overall, I think Amylyx handled everything but Relyvrio's price in an exemplary fashion," Lynch said, adding that she is glad the company is continuing to pursue ALS research.

Amylyx is studying AMX0114, an antisense oligonucleotide targeting calpain-2, in ALS. It also has AMX0035 in late-stage trials for Wolfram syndrome and progressive supranuclear palsy. *(See sidebar for related story.)*

A Failed Drug, But A System That Worked

Amylyx also won plaudits from patient advocacy organizations, which continue to make the case for FDA regulatory flexibility on potential ALS treatments.

"We commend Amylyx for pulling Relyvrio off the market, while still ensuring that people living with ALS can access the drug if they believe it is helping them," the ALS Association posted on X (formerly Twitter).

“ALS is a fatal and heterogenous disease with few treatment options, and creative solutions are needed. We believe the example of Relyvrio shows how the system can work. FDA approved Relyvrio based on solid safety data and positive efficacy data from a Phase II trial on function and survival. Safe and potentially effective treatments can be made accessible rapidly until further research can confirm their efficacy,” the group said.

“We believe the example of Relyvrio shows how the system can work. FDA approved Relyvrio based on solid safety data and positive efficacy data from a Phase II trial on function and survival. Safe and potentially effective treatments can be made accessible rapidly until further research can confirm their efficacy.” – ALS Association

“There are more than 40 more potential treatments in the pipeline and we are focused on trying to advance the safe and effective ones as quickly as possible.”

In a series of posts on X, the advocacy group I AM ALS commended the company “for working with the community to make a very difficult decision.”

“I AM ALS also extends our gratitude to the FDA for their flexibility and recognition of the complexities surrounding ALS. We must ensure that companies have the regulatory flexibility to navigate the challenging landscape of ALS research and development.”

However, not everybody views the FDA’s use of regulatory flexibility for Relyvrio as prudent.

Caleb Alexander, professor of epidemiology and medicine at Johns Hopkins, voted against approval at both Relyvrio adcomms. At the second meeting, he noted that whether or not the agency can ultimately pull a product from the market is no substitute for the evidentiary thresholds required for approval.

When asked to comment following Amylyx’s withdrawal announcement, Alexander said: “This was an unusual case from the start, and it illustrates the value of the FDA’s usually strenuous process to ensure that approved products meet the standards established by law and regulation.”