# Decoding Regulatory Agency Decisions: The Case of Amylyx's Relyvrio/Albrioza In The US And EU

24 Jul 2024 | **ANALYSIS**

by Francesca Bruce

@ScripFrancesca | francesca.bruce@citeline.com

**Executive Summary**

Relyvrio/Albrioza, Amylyx's ill-fated treatment for amyotrophic lateral sclerosis, was approved for marketing by the US Food and Drug Administration but rejected by the European Medicines Agency. The *Pink Sheet* explores how the two agencies applied the available regulatory flexibilities and the impact of other factors, such as regulatory precedence and patient influence, on decision-making.

EU AND US REGULATORS TOOK DIFFERENT APPROACHES TO REGULATORY FLEXIBILITY WHEN IT CAME TO AMYLYX'S ALS TREATMENT

*Source: SHUTTERSTOCK*

Is the risk of delaying patient access to a desperately needed potential treatment greater than the risk of facilitating access to an ineffective but relatively safe product? How important is regulatory precedence? And how much should patients influence the final outcome?

These are some of the issues that the US Food and Drug Administration took into consideration when it decided whether to apply regulatory flexibility and finally approve Amylyx Pharmaceuticals, Inc.'s amyotrophic lateral sclerosis (ALS) treatment Relyvrio (sodium phenylbutyrate/taurursodiol) despite significant concerns.

In the EU, meanwhile, despite patient support and precedence set by a prior ALS drug approval, the European Medicines Agency refused to award a conditional marketing authorization (CMA) for Albrioza, as the drug is known in the bloc. The CMA pathway is the EMA's version of regulatory flexibility for approving much-needed drugs that are not supported by the usual standard of data required for regular approval.

## Key Takeaways

- Amylyx's Relyvrio/Albrozia for treating amyotrophic lateral sclerosis was refused approval in the EU but was approved in the US before it was withdrawn following poor Phase III study results.
- In the US, a more discretionary approach to flexibility was taken as regulators thought it would be better to deliver a safe but ineffective drug to patients than make them go without a treatment that turned out to be effective.
- There was more pressure from patient activists in the US, and at the FDA, a patient representative took part as a voting member of the advisory committee meeting.

The *Pink Sheet* examines the bumps in the regulatory road travelled by Relyvrio/Albrioza and how far the agencies were able or willing to exercise flexibility in their final decision-making despite similar concerns about the underlying data.

Albrioza (also known as AMX0035) underwent two reviews by the CHMP, the EMA's human medicines committee. This is commonplace when the CHMP initially issues a negative opinion as companies often request a reexamination.

However, the drug also was the subject of two FDA advisory committee meetings during the same review cycle, which is highly unusual. *(See timeline below for key dates.)* Both agencies cited similar concerns regarding primary analysis of the Phase II CENTAUR trial, secondary endpoints and biomarkers, but they reached very different conclusions on approval.

## Endpoints

ALS is a progressive neurodegenerative disease affecting motor neurons in the brain and spinal cord. The condition is fatal with a median survival of approximately two years following diagnosis. Rapid progression of symptoms directly results from degeneration in motor neurons, causing motor function loss, which leads to loss of speech, fine motor skills and mobility.

There is a high unmet need for ALS treatments even though two drugs had already been approved in the US – Covis Pharma's Rilutek (riluzole) and Mitsubishi Tanabe Pharma Corporation's Radicava (edaravone) – when the FDA approved Relyvrio. Only Rilutek had been approved in the EU when the CHMP rejected Amylyx's drug for the second time.

The US and EU marketing applications for Relyvrio/Albrioza were supported by data from the Phase II CENTAUR trial and its open-label extension.

The primary efficacy endpoint of the CENTAUR study was the rate of decline in the total score on the Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised (ALSFRS-R). The total ALSFRS-R scores at week 24 were 29.06 in the Relyvrio/Albrioza arm and 26.73 for the placebo group. The estimated treatment difference of 2.32 was statistically significant (p = 0.034).

Secondary endpoints were:

- Accurate Test of Limb Isometric Strength (ATLIS) – a new strength measurement device that Amylyx used for the first time in an interventional study, according to a joint FDA/sponsor advisory committee briefing document;
- Levels of plasma neurofilament heavy chain (pNF-H) – a biomarker that at the time of the study was thought to be a potential marker of neuronal degeneration;
- Slow Vital Capacity (SVC) – the preferred method of ALS centers of excellence for measuring pulmonary capacity; and
- Survival, measured as the rate of deaths, hospitalizations, and tracheostomies.

### The Relyvrio/Albrioza Regulatory Journies, A Timeline

**Sep 2017:** FDA grants AMX0035 orphan drug designation for ALS

**Nov 2021:** Amylyx submits new drug application for AMX0035

**Mar 2022:** First FDA advisory committee meeting votes against AMX0035

**Jun 2022:** PDUFA date extended to 29 September after additional data analyses were submitted for the product

**Sep 2022:** Second advisory committee meeting votes in favor of approval

**Sep 2022:** FDA approves Relyvrio

**Apr 2024:** Amylyx announce Relyvrio's withdrawal following negative Phase III trial results

**Apr 2020:** EMA grants AMX0035 orphan designation for ALS

**Jan 2022:** Amylyx submits marketing authorization application

**Jun 2023:** CHMP issues first negative opinion and Amylyx announces it will seek a reexamination of the opinion

**Oct 2023** CHMP issues second negative opinion after reexamining its June opinion

**Jan 2024:** European Commission refuses marketing authorization

In the open-label extension of CENTAUR, patients originally randomized to Relyvrio/Albrioza showed sustained benefit of treatment across ALSFRS-R, ATLIS and SVC over 48 weeks, the company said.

In the US, six out of 10 members of the FDA's Peripheral and Central Nervous System Drugs Advisory Committee voted against approving the drug in March 2022, saying that the agency should wait for the results of the Phase III PHOENIX trial. (Also see "Amylyx's ALS Drug Should Wait For Phase III Results, US FDA Panel Says" - Pink Sheet, 30 Mar, 2022.).

At a second meeting the following September, the committee voted in favor of approval, despite the FDA's briefing document indicating that additional analyses and biomarker data did not give the confirmatory evidence required to satisfy evidentiary requirements.

In the EU, meanwhile, the CHMP twice declined to give a positive opinion on the drug. (Also see "Amylyx To Appeal Against EMA Rejection Of ALS Drug Albrioza" - Pink Sheet, 23 Jun, 2023.) (Also see "Bad News For Amylyx As EMA Upholds Rejection Of ALS Drug Albrioza" - Pink Sheet, 13 Oct, 2023.)

## Regulatory Concerns In A Nutshell

### Phase II CENTAUR Study Raised Red Flags

With regard to the analysis of the CENTAUR primary endpoints, the US Food and Drug Administration and the European Medicines Agency shared some similar concerns.

For example, both were unhappy that the primary analysis (slope analysis) assumed linearity of ALSFRS-R overtime. The FDA commented that linearity of ALSFRS-R over time had not been established, while the EMA's human medicines committee, the CHMP, said it exaggerated disease effect.

The agencies were also concerned that the analysis was conducted in the modified intent-to-treat population and excluded two patients from the experimental arm who died while taking Relyvrio/Albrioza but who did not have post-baseline ASLFRS-R measurements. Both agreed this could introduce bias.

Both agencies were concerned that the analysis ignored loss of patient data due to deaths, which the CHMP said could confound functional endpoints. The FDA added that it preferred an analysis method, such as joint-rank analysis that combines survival and function into a single overall measure.

Both agencies highlighted other issues too. For example, the FDA said that a higher number of patients in the Relyvrio arm started on FDA-approved ALS drugs, edaravone or riluzole, after baseline compared to the placebo arm. "These concomitant ALS treatment intercurrent events are difficult to correct for, and the primary analysis inclusion of data after these intercurrent events could have confounded the test for treatment effect."

Both agencies declared that secondary efficacy endpoints failed to support any primary endpoint benefit. Neither agency deemed the open-label extension of the CENTAUR trial to be satisfactory.

## Additional Analyses

Ahead of the FDA's September advisory committee meeting, Amylyx submitted additional analyses of individual responses and survival data from the CENTAUR trial, along with biomarker data from a recently completed Phase II trial in Alzheimer's disease. However, an FDA briefing document released before the panel review indicated that the additional input did not satisfy the substantial evidence of effectiveness standards when relying upon a single adequate, well-controlled trial.

The biomarker data was also found to be wanting. For example Amylyx submitted biomarker data to the FDA from the Phase II PEGASUS trial in Alzheimer's disease, asserting that improvement in select cerebrospinal fluid (CSF) biomarkers supports the mechanistic activity of the product in the central nervous system. Relyvrio had beneficial effects on CSF total tau, p-tau 181 and YKL-40, which have also been shown to be elevated in patients with ALS. However, the FDA said the biomarker data were unconvincing and that their relevance to ALS was unclear.

In the EU, meanwhile, the re-examination process by the CHMP involved looking at three additional placebo crossover survival analyses. However, the CHMP concluded that they were "post hoc comparisons with essentially no details how these comparisons were performed. Thus, their value is of limited importance. The use of external data is not considered to add any valuable information to this randomized trial," according to the European Public Assessment Report for Albrioza.

## Regulatory Flexibility

In both jurisdictions, regulatory flexibility was in play to allow health authorities more leeway when it came to the uncertainty regarding Relyvrio/Albrioza's clinical effectiveness.

In Europe, Amylyx opted to apply for a CMA. Through the CMA pathway, the EMA is able to offer regulatory flexibility for promising drugs that treat areas of unmet need but lack adequate effectiveness data for a full approval. To win a CMA, the following criteria must be met:

- A positive benefit-risk balance.
- Likelihood that the applicant will be able to provide comprehensive data following CMA.
- The product addresses unmet needs.
- Benefits to public health of immediate availability outweigh the risks inherent in the need for additional data.

Amylyx filed for a CMA on the basis of results from the CENTAUR study with the promise of confirmatory findings from PHOENIX. However, the CHMP turned down the drug for a CMA twice, asserting that "efficacy has not been established in a robust and compelling way and thus the benefit-risk balance is negative."

The committee was unable to apply the flexibility afforded by a CMA while results of the Phase III trial were pending because the evidentiary concerns were too great. "Albrioza received a negative opinion because the benefit-risk balance was considered negative. The CHMP did not find the positive findings from the CENTAUR trial as a valid estimate of efficacy," the EMA told the *Pink Sheet*.

In the US, meanwhile, a more discretionary approach to regulatory flexibility was possible. Relyvrio was approved under the FDA's traditional pathway in September 2022, though not without difficulty.

The drug did not qualify for the agency's accelerated approval pathway – another tool that makes allowances for uncertainty – because the development focused on the ALSFRS-R rather than a surrogate endpoint, such as biomarkers that were assessed as secondary endpoints. This meant that the FDA had no authority to require a confirmatory follow-up trial.

In voting against the drug's approval, the first FDA advisory committee cited a range of concerns, including flawed analysis of primary endpoints and a lack of secondary endpoint support for the primary analysis. *(See In A Nutshell box above for details on regulatory concerns.)* The company subsequently submitted further analyses as confirmatory evidence to support the findings of CENTAUR and address the concerns. A second advisory committee meeting was scheduled, and the FDA action date was extended by three months.

Full US approval for Relyvrio was eventually granted despite limitations to the findings that led to a "degree of residual uncertainty about the evidence of effectiveness that exceeds that which might typically remain following a conclusion that substantial evidence of effectiveness has been demonstrated," the FDA said in its summary review.

However, because of the "serious and life-threatening nature of ALS and the substantial unmet need," the FDA deemed the level of uncertainty as acceptable and that "consideration of these results in the context of regulatory flexibility [was] appropriate."

At the second advisory committee meeting in September 2022, Billy Dunn, the then-director of the FDA's Office of Neuroscience, made a plea for regulatory flexibility to be applied. (Also see "Tolerating False Positives: Amylyx, FDA, And The Legal Case For Broad Regulatory Flexibility" - Pink Sheet, 8 Sep, 2022.). Crucially, Dunn also called on Amylyx to withdraw the drug if the PHONEIX trial were to fail. The company said at the meeting that it would, and repeated the pledge in subsequent statements.

> Dunn cited Code of Federal Regulations, Title 21, Section 312.80 (21 CFR 312.80), which discusses the need for flexibility in applying regulatory standards of safety and effectiveness to new therapies intended to treat patients with life-threatening and severely debilitating illnesses, particularly when there are no alternatives. "This makes it abundantly clear that for these serious diseases, like ALS and so many other neurological conditions, the maximum degree of regulatory flexibility, 'the broadest flexibility in applying the statutory standards' is operational," Dunn said.
>
> It would be better to make a type 1 error in backing a false positive than a type II error, when a false negative occurs, Dunn said. He explained it was preferable to approve a drug that turns out to be safe but ineffective than force patients to go without a treatment that turned out to be effective. He also pointed out that under 21 CFR 312.80, the FDA has the authority to withdraw the drug in case of a type I error.

## Regulatory Precedence

Regulatory precedence and the approval of other ALS treatments also were considered in both the EU and US, though to differing degrees.

In the US, Dunn pointed to the FDA's history of flexibility when it comes to ALS treatments.

Rilutek was approved in 1995 based on two trials that assessed survival in which the drug failed to show a statistically significant difference using the prespecified statistical analysis method (p=0.12 and 0.076). After using a "more appropriate statistical analysis method for these trials … both studies were found to demonstrate statistically significant effects on survival (p=0.05 for both studies)," said the 7 September 2022 FDA briefing document.

Radicava was approved for the treatment of ALS in 2017 based on a single six-month, randomized, double-blind, placebo-controlled trial conducted in 137 Japanese patients who were living independently. Results were corroborated by an FDA analysis.

"Although every drug development program is distinct and must be considered individually, this history of the application of regulatory flexibility in ALS is a relevant precedent for both ALS and other neurological diseases and should be taken into account when considering the evidence supporting the AMX0035 application," said the September FDA briefing document.

Meanwhile, in Europe Amylyx also asserted that the European Public Assessment Report for the only drug approved for ALS at the time, Rilutek, could serve as "as a matter of consistency in regulatory decision-making."

This EPAR said: "Riluzole has been demonstrated to extend survival in two studies conducted in patients with ALS, but not in a third trial. Survival was the main efficacy criteria and was considered as a strong outcome measure. The failure to find any effect on functional end-points does not affect the reliability of the survival results."

But the CHMP pointed out that Rilutek was approved in 1996 and that the EPAR should be interpreted in its context.

## Outside Influence?

Pressure to approve Relyvrio in the US came from a number of sources, including members of the House of Representatives, which urged the FDA to use flexibility to approve ALS drugs as it had for oncology products. (Also see "More Action, Less Plan? House Keeps Pressure On US FDA Over ALS Drugs" - Pink Sheet, 25 Jul, 2022.)

There was also pressure from patient activists. The ALS Association launched a petition in 2020 calling on the FDA to approve Relyvrio as quickly as possible following publication of the CENTAUR trial results in the *New England Journal of Medicine*.

> *"In the US, patient 'activism' (direct confrontation) is more common than in EU, where we at EUpALS stand for patient 'advocacy' calling for a constructive dialogue between all stakeholders in the clinical development process." - EUpALS*

Although there was external support for the drug in the EU, campaigning was less vociferous, and the EMA was not exposed to the same amount of pressure from politicians or patients that the FDA experienced. According to the European ALS patient group EUpALS, "there is some kind of cultural difference in the way that most patients bring their message at both sides of the Atlantic Ocean."

"In the US, patient 'activism' (direct confrontation) is more common than in EU, where we at EUpALS stand for patient 'advocacy' calling for a constructive dialogue between all stakeholders in the clinical development process," the association told the *Pink Sheet*.

"The FDA has the statutory authority to be flexible when reviewing drugs that meet criteria for safety and show promise for people with terminal diseases," the association said. "This authority, combined with the ALS community's expressed willingness to accept risk for potential treatment benefit, should compel the FDA to work quickly and cooperatively with Amylyx to make AMX0035 available to the entire ALS community without delay."

The ALS Association also submitted letters to the FDA signed by ALS specialist clinicians, while ALS advocates sent over 1,100 comments to the second FDA advisory committee and almost 10,000 emails to the FDA urging for approval of AMX0035.

Although there was external support for the drug in the EU, campaigning was less vociferous, and the EMA was not exposed to the same amount of pressure from politicians or patients that the FDA experienced. According to the European ALS patient group EUpALS, "there is some kind of cultural difference in the way that most patients bring their message at both sides of the Atlantic Ocean."

"In the US, patient 'activism' (direct confrontation) is more common than in EU, where we at EUpALS stand for patient 'advocacy' calling for a constructive dialogue between all stakeholders in the clinical development process," the association told the *Pink Sheet*.

## Patient Involvement

Nevertheless, both regulators said the patient voice had an important role to play during the regulatory processes. That said, the opportunities for providing input in the regulatory processes are different, with US patients perhaps having a stronger voice.

Patients were involved in the CHMP process through early dialogue with patient organizations, in line with CHMP methodology that recommends consulting with organizations on day one of the evaluation process for the marketing application, the agency said.

There was further dialogue at day 120 of the process, and patient representatives were also invited to take part in a scientific advisory group, which is convened to answer specific questions from the CHMP. Patients also took part in the oral explanation meeting that the CHMP held for Amylyx to address its questions.

The EMA maintains that it has "a longstanding and very good working relationship with ALS patient organizations, and consistently involves them in relevant regulatory procedures."

Patient input on drug development and marketing authorization assessments are crucial for understanding certain aspects, the EMA said, such as the willingness to take risks, feasibility of proposed additional risk minimization measures, and the clinical relevance of efficacy measures if used properly, for example, to validate outcomes. "However, the input does not substitute the results from a clinical trial, or the assessment of the trial results," the EMA said.

Meanwhile, in the US patient representatives take part as actual voting members for marketing applications that go to an advisory committee meeting. Notably, the patient representative taking part in the advisory committee meetings for Relyvrio voted twice in support of approval.

"Patients also provide comments as part of the open public comment portion of the advisory committee meeting," the FDA told the *Pink Sheet*. "In addition, patient and patient representatives participate in FDA meetings with sponsors when they are invited by sponsors to participate in the meeting."

The FDA added that it "has been very engaged with the ALS community and will continue to remain engaged moving forward."

Amylyx declined to comment on the FDA or EMA regulatory procedures but noted that ALS is a global disease with no borders. "There is a universal urgency and need for new, effective treatment options. We have been inspired by advocacy efforts around the world to change the status quo and improve outcomes for these communities," the company told the *Pink Sheet*.

The company went on to defend the CENTAUR study, which it said was "conducted with scientific rigor in collaboration with leading experts in ALS" and was "clearly successful." The trial demonstrated for the first time a slowing of disease progression, maintenance of functional independence, and an extension of overall survival in the same trial.

"PHOENIX did not confirm these benefits, which underscores that we still have a lot to learn about ALS as a heterogeneous disease. We are confident that the results of our trials will continue to push the needle forward in terms of research and innovation in ALS and other neurodegenerative diseases," Amylyx said.

Source: **The Pink Sheet – Citeline Regulatory**