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CITELINE REGULATORY

09 Aug 2023 | **News**

Regulators Still To Get To Grips With Neurodegenerative Outcome Measures

by Francesca Bruce

Outcomes measures in the neurodegenerative disease space are not yet well understood by regulators, according to Amylyx, which recently received a negative opinion from the EMA for its amyotrophic lateral sclerosis drug, Albrioza.

Following a negative opinion from the EMA's human medicines committee, the CHMP, for its orphan drug Albrioza (sodium phenylbutyrate/ursodoxicoltaurine) for amyotrophic lateral sclerosis (ALS), *Amylyx Pharmaceuticals, Inc.* told the *Pink Sheet* that regulators do not yet fully understand the best outcomes measures for neurodegenerative diseases.

Justin Klee and Joshua Cohen, co-CEOs of Amylyx, said that while experts were aligned on the best way to measure disease, regulators were still wrestling with challenging questions relating to outcomes in the treatment.

Albrioza, an orphan drug, is an oral, fixed-dose combination therapy for treating ALS. The CHMP issued a negative opinion on the drug in June. (Also see "*Amylyx To Appeal Against EMA Rejection Of ALS Drug Albrioza*" - Pink Sheet, 23 Jun, 2023.) It said that "the main study did not show convincingly that Albrioza was effective in slowing down the worsening of the disease." It also said that survival data were not reliable "given the way the data were collected and analyzed." Amylyx disagreed with the opinion and has filed for a re-examination, which is likely to take around four months.

Amylyx's marketing authorization submission for Albrioza was based on the CENTAUR Phase II trial and confirmatory evidence. The study met its pre-specified primary endpoint, which was a statistically significant change on the Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised (ALSFRS-R) at 24 weeks. It achieved a 2.32 point difference at 24 weeks, equating to a rate of decline that was 25.3% less in patients randomized to AMX0035 versus placebo.

Cohen and Klee declined to comment on the CHMP's reasoning but said that important conversations on outcome measures among regulators and reimbursement authorities were yet to take place in the neurodegenerative diseases space.

Cohen noted that ALSFRS-R as an outcome measure in this area was new. He pointed out that just one other treatment has been approved for ALS in the EU: riluzole, which was authorized some 25 years ago.

Trials underpinning that authorization looked at the product's effect on mortality. The studies did not meet pre-specified primary outcomes, but "showed promise," with two to three months' added survival, which is why the drug was approved, said Cohen. The EMA noted at the time that treatment with riluzole did not demonstrate a positive effect on functional symptoms of the disease while the magnitude of the effect on survival was modest.

Since the approval of riluzole, the ALSFRS-R has become the "gold standard" for measuring functional progressions in the disease. However, it is a new measure for the agency to consider and there is no precedent to refer to, said Klee.

Although the expert community is aligned on how to measure neurodegenerative diseases like ALS, the conversations have not yet happened with regulatory or reimbursement bodies because effective treatments have not yet been available, commented Klee.

Meanwhile, in other disease areas such as oncology there are very clear methodologies and precedents around outcomes, such as overall survival and progression-free survival, because effective treatments in oncology have been coming to the market for a long time, said Klee. Conversations have therefore already taken place among developers, key opinion leaders, patients, regulators, reimbursement authorities and the general public about how to approach cancer and what meaningful outcome measures should be used.

US

In the US, the FDA approved the drug as Relyvrio in 2022 based on the Phase II CENTAUR trial and confirmatory evidence. However, the path to authorization was winding, including two advisory committee meetings, which Klee noted was "certainly unusual." The FDA's summary review noted that there remained some uncertainty regarding the effectiveness of the product but that this uncertainty was acceptable given the serious and life-threatening nature of ALS and the substantial unmet need. (Also see "*Regulatory Flexibility: US FDA Approves Amylyx's Relyvrio For ALS Despite 'Degree Of Residual Uncertainty'*" - Pink Sheet, 29 Sep, 2022.)

Following the first advisory committee meeting, the FDA noted that the ALSFRS-R was an appropriate primary endpoint of the study. However, it said that the review division typically recommends a joint-rank analysis of the ALSFRS-R change from baseline and mortality as the

primary analysis in ALS.

“Functional endpoints can be confounded by loss of data because of patient deaths, which is why FDA recommends an analysis method that combines survival and function into a single overall measure in ALS, such as the joint-rank test,” the agency said. (Also see "*Amylyx’s ALS Drug Brings Questions On Efficacy Data Robustness To US FDA Panel*" - Pink Sheet, 28 Mar, 2022.)

EMA Re-examination

The CHMP’s re-examination will be based on the same data package, but a new rapporteur and co-rapporteur will be appointed, which the two executives said would essentially bring a fresh pair of eyes. “We are optimistic, but of course we don’t know what their opinion will be,” said Cohen.

If the re-examination yields the same outcome, the company will likely refile based on the Phase III Phoenix study. said Klee. Topline data from this study are expected in mid-2024 and overall survival data are due in 2025.