U.S. FOOD & DRUG ADMINISTRATION

AMX0035

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

September 7, 2022

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FDA OVERVIEW

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Background

- NDA for AMX0035 submitted in October 2021
- A single double-blind, placebo-controlled Phase 2 Study (AMX3500 or CENTAUR) in 137 patients with ALS
  - Primary endpoint of the slope of the ALS Functional Rating Scale-Revised (ALSFRS-R) change with a difference of 2.32 points from placebo at 24 weeks (p=0.034)
- An open-label extension study (AMX3500)
  - Post hoc analysis with a nominally significant overall survival benefit (HR=0.64) with longer median OS (23.5 months) observed in patients randomized to AMX0035 than the median OS of patients randomized to placebo (18.7 months) for a difference of 4.8 months

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PCNS Meeting March 30, 2022

- Key Issues discussed at AC
  - Single study
    - Persuasiveness and robustness of evidence from primary endpoint
    - Secondary endpoint results not compelling
    - Issues with randomization and imbalances in concomitant use of riluzole and edaravone
    - Handling of deaths and missing data assumptions in primary analysis
    - Assumption of linearity over time in treatment effect
  - The Agency expressed concerns that the data would not be adequate to serve as a single study providing substantial evidence of effectiveness
  - Persuasiveness of exploratory survival analyses from the open-label extension study and ability to serve as confirmatory evidence

PCNS Voting Question March 30, 2022

- "Do the data from the single randomized, controlled trial and the open-label extension study establish a conclusion that sodium phenylbutyrate/taurursodiol is effective in the treatment of patients with amyotrophic lateral sclerosis (ALS)?"

- 4 votes "Yes"
- 6 votes "No"
- No abstentions

New information as confirmatory evidence

- Following the AC meeting on March 30, 2022, the applicant submitted additional information to contribute to the previously submitted information intended to serve as potential confirmatory evidence to support the treatment benefit seen in the CENTAUR study
  - Responder analysis of the ALSFRS-R in CENTAUR
  - Survival sensitivity analyses from CENTAUR and OLE
    - Survival prediction algorithm from natural history data
    - Rank Preserving Structural Failure Time Model
  - Biomarker data from Phase 2 study in Alzheimer's disease

Statistical Considerations

CENTAUR Trial Statistical Summary
(presented at March 30, 2022 AC)

- "Reliance on a single large multicenter trial to establish effectiveness should generally be limited to situations in which the trial has demonstrated a clinically meaningful and statistically very persuasive effect on mortality, severe or irreversible morbidity..."[1]

- Uncertainty about results from CENTAUR trial (and its Open Label Extension [OLE])
  - –Primary analysis results are not highly persuasive
    - –there was more post-baseline use of riluzole and edaravone in AMX0035 arm
    - -inappropriate handling of deaths and missing data
    - -questionable assumption of linearity over time in treatment effect
  - –Secondary endpoint results not compelling
  - –OLE survival analyses are exploratory

[1]2019 Draft Guidance on Substantial Evidence of Effectiveness https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products

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New Analyses of CENTAUR Survival Data
(post March 30, 2022 AC)

- No new AMX0035 data since the last AC on March 30, 2022
  - – New analyses based on the previously analyzed CENTAUR trial data

- No pre-specified analysis plan
  - – Analyses were planned and conducted after unblinding

- There are numerous analytical choices and assumptions for these analyses that affect the results

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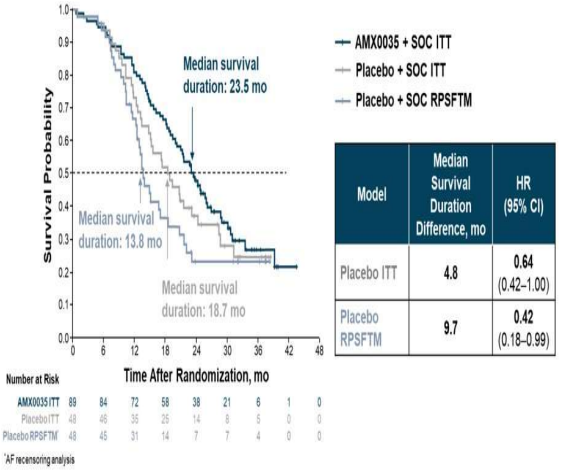
New Post-hoc Survival Analysis
Rank Preserving Structural Failure Time Model (RPSFTM)

- Placebo patients cross over to AMX0035, by design, in the OLE phase
- Non-completers from double-blind phase were ineligible for OLE but were included in the analysis
- RPSFTM reduces hazard ratio estimate, but with decreased precision and upper bound of confidence interval is the same



Model	Median Survival Duration Difference, mo	HR (95% CI)
Placebo ITT	4.8	0.64 (0.42–1.00)
Placebo RPSFTM	9.7	0.42 (0.18–0.99)

*Analysis based on March 2021 event cutoff data

Rank Preserving Structural Failure Time Model (RPSFTM) Limitations

- RPSFTM is heavily dependent on untestable assumptions, such as
  - Survival time benefit is proportional to time on drug
  - Same proportionality for placebo after switching to AMX0035 in OLE
- RPSFTM analysis models survival of placebo patients had they never switched to AMX0035
- Placebo patients who switched to AMX0035 are different than those who did not switch, but model assumes they are the same.
  - Mean baseline ALSFRS-R* is 3.7 points higher for double-blind period placebo completers than placebo dropouts

* ALS Functional Rating Scale – Revised Version

Rank Preserving Structural Failure Time Model (RPSFTM) Limitations

- Applicant's reference methodological article[1] indicates the new analysis may be biased in favor of drug
  - "We found that analyses which re-censored usually produced negative bias (i.e. underestimating control group restricted mean survival and overestimating the treatment effect)"[1]
  - "The increased switching proportion had an important impact, leading to increased bias, with the relative effect on the different adjustment methods dependent on the size of treatment effect."[1]
    - 71% of placebo patients switched to AMX0035 in OLE
  - Recommends complementary analysis to assess the bias of the analysis
- According to Applicant's reference article[2] on CENTAUR analysis,

"AF [acceleration factor] could not be estimated in assessments of on-treatment RPSFTM without applying recensoring".

[1]Latimer et. al. 2019 https://pubmed.ncbi.nlm.nih.gov/29940824/
[2]Paganoni et. al. 2022 doi: 10.1002/mus.27569 https://pubmed.ncbi.nlm.nih.gov/35508892/

New Post-Hoc Comparisons to External Data

1. Compared survival in CENTAUR OLE to prediction based on model developed by ENCALS*
   - Model based on European patients from 1992 to 2016
2. Compared survival in CENTAUR OLE to matched patients from PRO-ACT**
   - PRO-ACT contains patients from ALS clinical trials from 1990-2010
   - Based on propensity score matching of CENTAUR patients to PRO-ACT patients

*ENCALS is European Network for the Cure of ALS
**PRO-ACT is Pooled Resource Open-Access ALS Clinical Trial Database

New Post-hoc Comparisons to External Data Limitations

- Non-randomized comparison without a common treatment protocol or a prespecified analysis plan
  - Patients in CENTAUR may differ from those in ENCALS and PRO-ACT cohorts
    - Patients may differ in the measurement of prognostic factors (stage/severity of disease)
    - Patients may differ in unmeasured prognostic factors
    - Patients may have received different supportive care and available therapies

New Post-hoc Comparisons to External Data Limitations

- PRO-ACT analysis:
  - Propensity score matched analysis involves numerous analysis choices, which were not prespecified
  - Only 74 of 89 CENTAUR patients randomized to AMX0035 were matched, which may create bias
- Both ENCALS and PRO-ACT analyses were post-hoc, unblinded analyses
  - Ideally, analysis plans would have been in place before the conduct of the CENTAUR trial

Summary

- New analyses of CENTAUR data do not provide a statistically persuasive effect on mortality
  - No new AMX0035 data since last AC meeting, only new analyses of existing data from CENTAUR
  - Analyses were planned and conducted after unblinding
  - There are numerous analytical choices and assumptions for these analyses that affect the results
  - The unplanned analyses are exploratory and have limitations

Biomarker Data

Phase 2 study in Alzheimer's disease (AD)

- Study AMX-8000 (PEGASUS) was a 24-week, randomized, double-blind, placebo-controlled multi-center trial to assess the effects of AMX0035 in adults with dementia or mild cognitive impairment due to AD
- The study enrolled 95 patients, with 51 patients on AMX0035, and 44 patients on placebo
- The primary objective of the study was to assess the safety and tolerability of AMX0035 in the study population
- No differences were seen in the exploratory efficacy outcomes of cognition, function, and imaging measures, or a composite of all three
- Assessed 18 exploratory CSF biomarkers that were felt to be core AD biomarkers or targets of the presumed mechanism of action of AMX0035

CSF biomarkers from PEGASUS study AD

Biomarker	AMX0035	Placebo	LSMEAN Difference (95% CI)	p-value
Neurodegeneration				
Total Tau*(pg/mL)	-64.93	8.82	-73.74 (-106.84, -40.65)	<0.0001
Phosphorylated Tau* (pg/mL)	-14.63	-0.27	-14.36 (-21.51, -7.21)	0.0002
FABP3 (pg/mL)	-344.62	102.90	-447.52 (-684.59, -210.45)	0.0004
NfL (pg/mL)	169.48	63.61	105.87 (-119.74, 331.47)	0.35
Synaptic Function				
Neurogranin (pg/mL)	-81.19	-8.34	-72.85 (-220.82, -34.89)	0.0003
Inflammation				
YKL-40 (pg/mL)	-14635.39	1507.88	-16143.27 (-26995.89, -5290.65)	0.004
IL-15 (pg/mL)	-0.02	0.25	-0.28 (-0.49, -0.06)	0.01
IL-6 (pg/mL)	644.38	565.93	78.45 (-1042.5, 1199.40)	0.89
IL-8 (pg/mL)	1.54	1.17	0.37 (-4.37, 5.11)	0.88
GFAP (pg/mL)	821.68	488.15	333.53 (-2080.17, 2747.22)	0.78
MCP-1 (pg/mL)	-1.97	-0.79	-1.18 (-21.15, 18.79)	0.91
Core AD Pathology				
AB_{42}/AB_{40} ratio	0.0039	-0.0051	0.0090 (0.0029, 0.0151)	0.005
AB_{42} (pg/mL)	-8.09	-41.46	33.37 (-38.37, 105.11)	0.36
AB_{40} (pg/mL)	-752.7	-754.81	2.11 (-1007.67, 1011.88)	1.0
Metabolism/Oxidative Stress				
8-OHdG (pg/mL)	0.31	-0.13	0.44 (0.13, 0.74)	0.006
24=OHC (pg/mL)	-0.20	-0.07	-0.13 (-0.67, 0.41)	0.63
Leptin (pg/mL)	0.45	4.53	-4.09 (-25.71, 17.54)	0.71
sIR (pg/mL)	-0.04	-0.19	0.15 (-0.25, 0.55)	0.47
Neurovascular				
MMP-10 (pg/mL)	-3.13	-0.92	-2.21 (-8.5, 4.1)	0.48

- Biomarkers with nominally significant differences between the treatment arms were total tau, p-tau, neurogranin, YKL-40, FABP3, IL-15, 8-OHdG, and the $A\beta_{42}/A\beta_{40}$ ratio
- The Applicant proposes that improvement in select CSF biomarkers in the PEGASUS study may support the mechanistic activity of AMX0035 in the central nervous system (CNS)

CSF biomarkers in AD

- No clear or consistent relationship between the biomarkers that had nominally significant findings and those that did not to suggest a true treatment effect on nervous system inflammation or neuronal degeneration
- Relevance of AD findings to ALS is unclear
- Assessment of 18 exploratory biomarkers was not adjusted for multiplicity
- No clear evidence of a potential for clinical benefit in patients with ALS

Regulatory Considerations

Regulatory standards for effectiveness

- *Substantial evidence of effectiveness* is the legal standard to establish the effectiveness of a drug for approval
- Required for all diseases, regardless of seriousness of the disease or availability of other therapies
- *Substantial evidence* is defined in section 505(d) of the Food, Drug and Cosmetic Act as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

Two studies

- The usual requirement is for at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness
- Reflects the need for independent substantiation of experimental results
- Independent substantiation of a favorable result protects against the possibility that a chance occurrence in a single study will lead to an erroneous conclusion that a treatment is effective

Single study

- Reliance on a single trial to establish effectiveness should generally be limited to situations in which an adequate and well-controlled trial has demonstrated a clinically meaningful and statistically very persuasive effect on mortality, severe or irreversible morbidity, or prevention of a disease with potentially serious outcome, and confirmation of the result in a second trial would be impracticable or unethical
- In other words, the single trial provides evidence that is similarly persuasive to that which might result from two separate trials taken together

Single study

- Characteristics of a single adequate and well-controlled study that could make the study adequate support for an effectiveness claim include:
  - Large multicenter study
  - Consistency across study subsets
  - Multiple studies in a single study
  - Multiple endpoints involving different events
  - Statistically very persuasive finding

Single study plus confirmatory evidence

- Under certain circumstances, FDA can also conclude that one adequate and well-controlled clinical investigation plus confirmatory evidence is sufficient to establish effectiveness
- In this situation, the confirmatory evidence would serve to provide independent substantiation of the results of the single study

Single study plus confirmatory evidence

- The Agency will consider the following factors when determining whether it is appropriate to rely on a single study with confirmatory evidence
  - The persuasiveness of the single trial
  - The robustness of the confirmatory evidence
  - The seriousness of the disease and whether there is an unmet need
  - The size of the patient population
  - Whether it is ethical and practicable to conduct more than one adequate and well-controlled clinical investigation

Examples of confirmatory evidence

- Data from adequate and well-controlled clinical studies that demonstrate the effectiveness of the drug in a closely related approved indication
- Data that provide strong mechanistic support of the drug in the pathophysiology of the disease
- Data from a well-documented natural history of the disease can potentially reinforce very persuasive and compelling results from a single AWC study.
- Scientific knowledge about the effectiveness of other drugs in the same pharmacological class

Approval pathways

- Traditional Approval
  - Substantial evidence of effectiveness demonstrated on a clinically meaningful endpoint (e.g., how a patient feels, functions, or survives)
- Accelerated Approval
  - Substantial evidence of effectiveness demonstrated on an endpoint that is not itself a direct measure of the clinical benefit of interest but is instead reasonably likely to predict that clinical benefit
  - Subsequent confirmation of clinical benefit is required
  - May be considered for considered for serious or life-threatening diseases with an unmet need
  - Importantly, the evidentiary requirements for accelerated approval are not lower than for traditional approval; substantial evidence of effectiveness is required

Accelerated Approval vs. "Conditional Approval"

- Some regulatory authorities have a "conditional approval" marketing authorization pathway that may be confused with accelerated approval
- Both accelerated approval and conditional approval pathways are intended to expedite therapies that address an unmet need
- Both require confirmation of benefit
- Conditional approval pathways generally allow for marketing authorization based on an overall assessment of "positive benefit-risk" or "promising clinical evidence"; these pathways do not require the equivalent of substantial evidence of effectiveness

https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation
https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/notice-compliance-conditions.html

Unmet Medical Need in ALS

- Unmet medical need refers to a condition whose treatment is not addressed adequately by available therapy
- ALS is a serious and devastating disease with substantial unmet need
- Although there are two approved therapies, ALS remains a progressive and fatal disease
- FDA is highly sensitive to the urgent need for safe and effective therapies for ALS

Regulatory Flexibility

Our regulations allow for the application of regulatory flexibility in life-threatening and severely-debilitating illnesses.

"The Food and Drug Administration (FDA) has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated."

21 CFR 312.80 Subpart E Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses

Regulatory Flexibility

- 2019 FDA Draft Guidance, "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products," discusses that certain situations, such as when a disease is rare or the disease is life-threatening or severely debilitating with an unmet medical need, may warrant additional flexibility
- "…in certain settings, a somewhat greater risk (compared to placebo-controlled or other randomized superiority trials) of false positive conclusions – and therefore less certainty about effectiveness – may be acceptable, when balanced against the risk of rejecting or delaying the marketing of an effective therapy, (…) for an unmet medical need."

Examples of regulatory flexibility

- Alternate trial designs to randomized, double-blind, placebo-controlled studies
- Use of surrogate or intermediate clinical endpoints for accelerated approval
- Flexibility on p-value
- Number of trials to establish effectiveness

Regulatory flexibility in ALS

- Riluzole (Rilutek) approved in 1995
  - Approval based on two "failed" studies (p-values of 0.12 and 0.076 on pre-specified analysis); Agency used an exploratory post hoc alternative statistical test, with nominally significant results
- Edaravone (Radicava) approved in 2017 (IV) and 2022 (oral)
  - Approval based on a single study conducted in Japan
  - Persuasive results with strong p-value (p=0.0013); supportive trends on secondary endpoints
  - Multicenter study; no single site responsible for treatment effects
  - Consistency across subsets of patients

Ongoing Phase 3 Trial of AMX0035 in ALS

- Study A35-004 (PHOENIX) (NCT05021536)
- Phase 3, 48-week, randomized, double-blind, placebo-controlled trial of AMX0035 in patients with ALS
- Planned to assess 600 subjects at over 70 sites in US and Europe
- Primary endpoint is a joint analysis of survival and function, as measured by the ALSFRS-R
- Anticipated completion in late 2023; results in late 2023 or early 2024

Expanded access with AMX0035

- Expanded access (also referred to as “compassionate use”) is a potential pathway for patients with a serious or immediately life-threatening disease or condition to gain access to an investigational medical product for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available
- The applicant has initiated an expanded access program in the US, Study A35-006, to allow for access for AMX0035 for eligible adults with ALS with symptoms for at least 3 years and who are not eligible to participate in clinical trials (ClinicalTrials.gov Identifier: NCT05286372)

Summary

- Single positive trial
  - Although not exceptionally persuasive, did succeed on its primary endpoint
- Proposed confirmatory evidence of a survival benefit and biomarker effects
  - Post hoc survival analyses are nominally positive, but exploratory
    - May be impacted by baseline imbalances and small sample size
  - Unclear relevance of exploratory biomarker endpoints in AD to ALS
- Phase 3 study in ALS is ongoing and expected to be completed in late 2023/early 2024
- ALS is a serious and fatal disease with substantial unmet need and consideration of regulatory flexibility is appropriate

Discussion/Question for the Committee

- DISCUSSION: Discuss the strength of the currently available data regarding the effectiveness of sodium phenylbutyrate/taurursodiol (AMX0035), to include the new information submitted and the information presented at the March 30, 2022, PCNS meeting. The discussion may include considerations regarding the unmet need in amyotrophic lateral sclerosis (ALS), the status of the ongoing Phase 3 trial, and the seriousness of ALS.

- VOTE: Considering the new information submitted and the information presented at the March 30, 2022, PCNS meeting, is the available evidence of effectiveness sufficient to support approval of sodium phenylbutyrate/taurursodiol (AMX0035) for the treatment of patients with ALS? In addition to the prior and new evidence presented, you may take into account in your vote the unmet need in ALS, the status of the ongoing Phase 3 trial, and the seriousness of ALS.

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