AMX0035

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

March 30, 2022

Emily Freilich, M.D.
Cross Discipline Team Leader
Office of Neuroscience/Division of Neurology 1

Tristan Massie, Ph.D.
Biostatistics Reviewer
Office of Biostatistics/ Division of Biostatistics 1

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AMX0035 (sodium phenylbutyrate (PB) and taurursodiol (TURSO))
FOR THE TREATMENT OF AMYOTROPHIC LATERAL SCLEROSIS (ALS)

CLINICAL OVERVIEW

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Standards for Determination of Efficacy

- Legal standards to determine if a drug is effective
- Requires "substantial evidence of effectiveness"
- Adequate and well-controlled studies
  - 2 studies
  - Single study plus confirmatory evidence
  - Single, large, and exceptionally persuasive study

Overview

- Unmet need in ALS
- Drug without a highly targeted mechanism of action
- RDBPC study demonstrates positive findings on primary endpoint at 24 weeks
- Survival benefit reported in open-label extension study
- Statistical concerns and study concerns decrease the overall persuasiveness of the results
  - Are the results due to chance alone?
  - Does the drug do what the study says it does?
  - Is more data needed to demonstrate effectiveness?

AMX0035 in ALS

DRUG PRODUCT: AMX0035 Powder for Oral Suspension, a fixed dose combination of

- Sodium Phenylbutyrate (PB): 3 g
- Taurursodiol (TURSO or TUDCA): 1 g

APPLICANT'S PURPORTED MECHANISM OF ACTION:

- Postulated to reduce neuronal death by simultaneous inhibition of "endoplasmic reticulum and mitochondrial stress"

The pathophysiology of ALS is unknown, but likely involves multiple complex processes and pathways. The purported mechanism for AMX0035 is one of the many pathways hypothesized to be involved in the pathophysiology of ALS.

Key Regulatory History

- March 2016 – Initial Pre-IND meeting held
- April 2017 – IND opened
- March 2020 – Type C Meeting
  - Topline results of CENTAUR reviewed
  - Division questioned ability of the study to serve as a single study to demonstrate efficacy and recommended another study
- February 2021 – Type C Meeting
  - Discussed plans for Phase 3 Study (currently ongoing)
- July 2021
  - Division requested the Applicant submit a pre-NDA meeting request
  - Encouraged Applicant to submit the NDA expeditiously to more critically evaluate the survival claims

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CENTAUR STUDY

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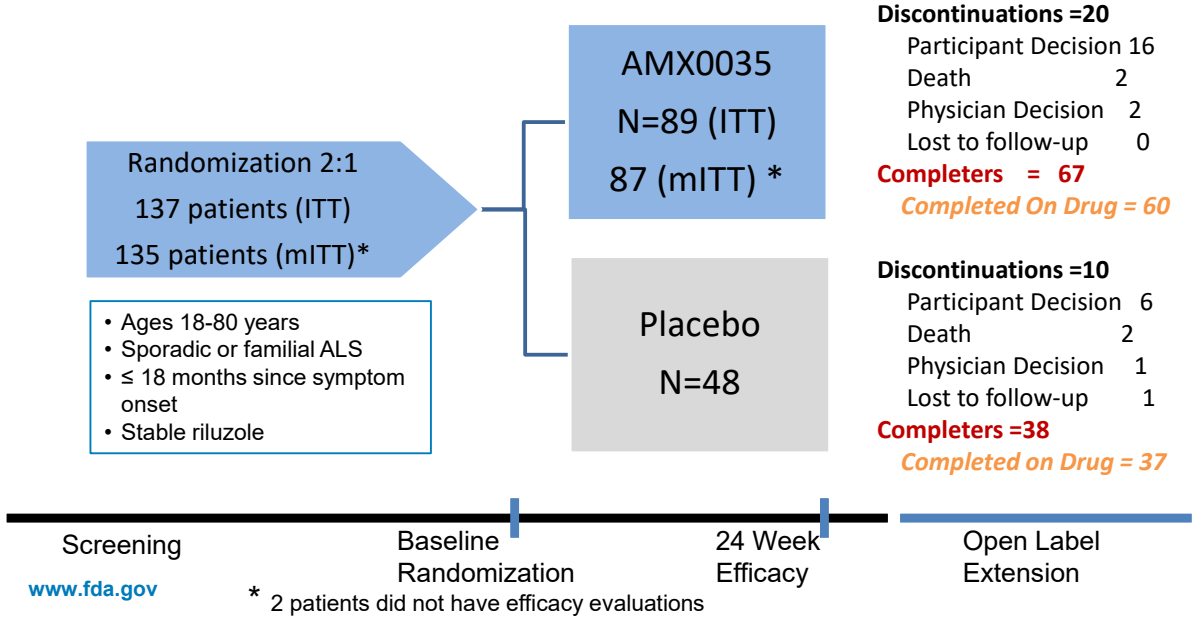
Study AMX3500- CENTAUR



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* 2 patients did not have efficacy evaluations

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Clinical Endpoints: CENTAUR

Primary

- Rate (slope) of Decline in ALS Function Rating Scale-Revised (ALSFRS-R) at Week 24
  - ALSFRS-R has 4 domains with 3 questions each
  - Higher scores indicate better performance

Secondary

- Rate of change in Accurate Test for Limb Isometric Strength (ATLIS) at Week 24
- Rate of change in plasma neurofilament heavy chain at Week 24
- Rate of change from baseline in Slow Vital Capacity (SVC) at Week 24
- Survival (death, tracheostomy, permanent assisted ventilation, hospitalization) at Week 24

No imbalance in baseline demographic characteristics (ITT)

Baseline Demographics	Placebo (N=48) n (%)	AMX0035 (N=89) n (%)
Sex		
Male	32 (67)	61 (69)
Female	16 (33)	28 (32)
Age		
Mean years (SD)	57.3 (8)	57.9 (11)
Median (years)	57.5	60
Min, max (years)	36, 79	31, 79
Age Group		
< 65 years	41 (86)	64 (72)
≥ 65 years	7 (15)	25 (28)
Race		
White	46 (96)	84 (94)
Black or African American	1 (2)	2 (2)
Asian	1 (2)	2 (2)
Other	0	1 (1)

A few imbalances in baseline disease characteristics (ITT)

Baseline Disease Characteristics	Placebo (N=48)	AMX0035 (N=89)
ALS Onset Location n (%)		
Brain Stem	10 (21%)	**26 (29%)**
Limb	**38 (79%)**	61 (69%)
Respiratory System	0	1 (1)
Multiple	0	1 (1)
Family History of ALS n (%)		
Yes	**7 (15%)**	9 (10%)
Unknown	3 (6%)	2 (2%)
Use of Riluzole or Edavarone n (%)		
Yes	**42 (88%)**	64 (72%)
Use of Riluzole n (%)		
Yes	**37 (77%)**	60 (67%)
Use of Edavarone n (%)		
Yes	**24 (50%)**	23(26%)
Baseline ATLIS		
Mean (SD)	53.9 (21)	**56.8 (20)**

- Patients in the treatment arm had a better baseline ATLIS score.
- Relationship of family history to disease prognosis is unclear; impact of baseline difference in family history is uncertain.

Note: No clinically meaningful difference between groups in other disease characteristics including Time since symptom onset and ALS diagnosis, rate of ALSFRS-R decline, baseline ALSFRS-R, SVC

Issues during Study Conduct

- There was a randomization implementation problem such that the first 18 patients (13% of the overall sample size) were assigned to the drug arm in a row, reportedly due to a shipping problem resulting in unavailability of placebo doses.
- Imbalances in edaravone initiation during the study (post-baseline)
- Potential for unblinding due to gastrointestinal adverse events and bitter taste of the drug

Efficacy Results at Week 24 - CENTAUR

Primary Endpoint:

- Applicant reports statistically significant mean treatment difference of 2.32 points for AMX0035 compared to placebo on the ALSFRS-R rate of decline (p = 0.034)

Secondary Endpoints (ATLIS):

- Applicant reports non-significant difference of 2.8 percentage points on TOTAL ATLIS for AMX0035 compared to placebo (p = 0.1129)

Exploration of ATLIS Endpoint

	ATLIS Scores at Baseline (Mean (SD))		Results (Rate of Decline)	
	Placebo	AMX0035	Treatment Diff. Week 24	P-value
Total ATLIS	53.9 (20.9)	56.8 (20.0)	2.8	0.1129
Components of ATLIS				
Upper ATLIS	51.4 (25.2)	54.7 (24.2)	4.3	0.0420
Lower ATLIS	57.1 (25.8)	57.6 (24.8)	2.1	0.3424

Limited Support from Other Secondary Endpoints

- pNF-H
  - No significant differences between AMX0035 and placebo for rate of change from baseline (p = 0.26)
  - pNHF-H decreased more in the placebo arm
- SVC
  - Non-significant treatment difference of 5% compared to placebo (p = 0.076)
- Composite survival
  - No survival benefit at 24 weeks

Summary of Concerns - CENTAUR

- Small trial
- Baseline imbalances
- Issues during study conduct
- Result on primary endpoint is not highly persuasive, without significant support from secondary endpoints
- No survival benefit at 24 weeks
- Appropriateness of statistical methods for efficacy analyses

AMX3500 OLE

34% Percent of Patients Did Not Enroll in the OLE

	Randomized to Placebo (RP) Group N = 48 n (%)	Randomized to Amylyx (RA) Group N = 89 n (%)	Total N= 137 n (%)
Completed 24-weeks in CENTAUR	38 (79)	67 (75)	105 (77)
Enrolled in OLE	34 (71)	56 (63)	90 (66)
Discontinued OLE (% of OLE) Participant Decision Physician Decision Sponsor Decision Death Lost to follow up	34 (100) 18 1 4 11 0	54 (96) 33 3 7 8 3	88 (98) 51 4 11 19 3
Completed **132 weeks** of OLE	**0**	**2**	**2**
Completed **48 weeks** of OLE (% of total)	19 (40)	36 (40)	55 (40)

Efficacy Analyses on Open-Label Extension Extended Slope Analysis At Week 48

- Applicant reports a statistically significant extended slope analysis at Week 48 for those randomized to AMX0035 (RA group) compared to those randomized to Placebo (RP) for **ALSFRS-R, Upper ATLIS,** and **SVC**

OLE Efficacy Analysis Limitations

- 34% non-participation in OLE, significant drop-outs during study
  - 56 AMX0035-treated subjects and 34 placebo subjects enrolled
  - 40% remained at Week 48 (36 patients in RA and 19 patients in RP)
- There was no indication in the protocol that the blind was to be maintained
  - Potential unblinding to treatment received
- Deaths are ignored in the slope analysis

Applicant's Composite Survival Analyses Up to Week 132 (March 1, 2021, data cutoff)

- Applicant reports a statistically significant increase in the **composite** time to survival events (including death, tracheostomy, PAV, hospitalization) in the RA group compared to RP group in the mITT population

Composite Survival Limitations

- 34% non-participation in OLE, significant drop-outs
- Limitations of including tracheostomy and hospitalization data
- No information on clinical care of patients after study discontinuation
- Several vitals status sweeps after initial September 2019 survival analysis
- Deaths that occur after the final cutoff date change the analysis

Post Hoc Survival Analysis

- Applicant reports statistically significant survival benefit on Time to Death only analysis (median difference=4.8 months, HR=0.644, p=0.0475)

Survival Analysis Limitations Decrease Persuasiveness of the Results

- Small study with baseline disease imbalances, p-value is nominal and not highly persuasive
- Timing of the analyses was not prespecified in the initial SAP
  - Results differed based on the cutoff date; apparent survival benefit decreased between July 2020 and March 2021
  - March 1, 2021- 70% patients randomized to drug had died compared to 73% patients randomized to placebo
- No apparent correlation between exposure and survival

Is Applicant's reported survival benefit a true effect of the drug or due to chance alone and/or underlying disease heterogeneity?

Clinical Safety

Overall Exposure on AMX0035

Overall, 137 patients (including placebo patients) provided safety data in combined controlled and open label extension phase

Duration	Number of Patients On Active Treatment
≥ 6 months	75
>1 year	43
> 1.5 years	23
>2 years	13

Safety Summary - CENTAUR

- No significant safety concerns with AMX0035 at proposed dose.
- No difference in fatal or serious adverse events (SAEs) between AMX0035 and placebo
  - Deaths and SAEs were mostly related to disease progression
- Discontinuations higher in AMX0035 group (20%) compared to placebo (10%)
- **Common Adverse Events (AEs)** belonged to the Gastrointestinal System Organ Class (including diarrhea, abdominal pain, nausea, salivary hypersecretion).
  - Others common AEs included dizziness, disease progression, respiratory tract infection, fatigue, and dyspnea.
- No differences in laboratory abnormalities, vital signs, electrocardiograms, QTc, suicidality between AMX0035 and placebo-treated participants.

Statistical Presentation

Summary

- Single trial to establish effectiveness should demonstrate a "clinically meaningful and statistically very persuasive effect" [1]
  - Also, "close scrutiny of trial conduct, including, for example, completeness of follow-up, methods of analysis, imputation of missing data, evaluation of trial endpoints, is critical" [1]
- Uncertainty about results from the single trial (and its open-label extension) of AMX0035
- Division advised another phase 3 study needed (3/2020 and 2/2021 meetings)

[1] FDA Guidance *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products*

Study AMX3500 Design

- Multi-center, randomized, double-blind, placebo-controlled, superiority study with open-label extension(OLE) in adult patients with ALS
- Two treatment groups:
  - AMX0035 (sodium phenylbutyrate and taurursodiol)
  - placebo
- 2:1 randomization
- Key efficacy outcomes collected at Weeks 3, 6, 9, 12, 15, 18, and 24
- Primary Endpoint: ALS Functional Score Rating Scale-Revised (ALSFRS-R) at Week 24

Key Issues

- Single study
- Persuasiveness and Robustness of Evidence from primary endpoint
  - p=0.034, Week 24 mean difference of 2.32 points [48 point ALS Functional Rating Scale]
  - 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
- Secondary endpoint results not compelling
- Persuasiveness of OLE exploratory survival analyses

Analysis Methods

- Intention to treat (ITT) population: all randomized patients who received at least one dose of study drug
- Modified intention to treat (mITT) population: all randomized patients who received at least one dose of study drug and had at least one post-baseline ALSFRS-R assessment
- Primary analysis: ALSFRS-R analyzed by a mixed model for repeated measures (MMRM) with ALSFRS-R linearity (slope) assumption in the mITT population
  - Fixed effects: intercept, week (slope), and pre-randomization slope-by-week, age-by-week, and treatment group-by-week interactions
  - Random (adjustments) to intercept and slope for individual patients
  - Assumed missing at random (including for deaths)

Timeline of Key Events

- March 6, 2019: FDA comments on Statistical Analysis Plan (SAP) sent to Applicant
- October 15, 2019: Revised, final SAP submitted by Applicant
- November 5, 2019: Final separate SAP for OLE submitted by Applicant
- November 26, 2019: Reported date of unblinding of double-blind period
- December 16, 2019: Press release citing positive double-blind results
- March 12, 2020: Type C meeting (including survival analysis of double-blind and OLE data through September 25, 2019)
- April 1, 2020: Submission of supplemental OLE survival SAP dated March 27, 2020
- March 1, 2021: Survival status sweep informing current OLE survival analyses

Correspondence on Analysis Plan

- Notable FDA comments on SAP:
  - Need to specify estimand and how to handle intercurrent events such as death, with recommendation for joint rank analysis of function and survival
  - Importance of backup/sensitivity analyses for missing data and linearity assumptions
- Applicant provided responses to these comments on August 26, 2019 (including lack of agreement with joint rank analysis as the primary) and a revised SAP on October 15, 2019

Randomization Implementation Issue

- Randomization implementation problem identified:
  - First 18 patients all received drug, reportedly due to shipping problem resulting in unavailability of placebo doses
- Unblinded DMC statistician noticed this and made changes to adjust
- Subsequent 9 patients all received placebo
- Applicant reports as-treated results for those affected by shipping issue, not as-randomized results

Imbalances in Use of Edaravone and Riluzole

- Use of treatments at baseline (prior to or at study entry):
  - Greater proportion of placebo on edaravone at or prior to study entry compared to AMX0035 patients (50% vs. 25%)
  - Greater proportion of placebo on riluzole at or prior to study entry compared to AMX0035 patients (77% vs. 68%)
- Initiation of treatments post-baseline:
  - Greater proportion of patients on drug vs. placebo (16% vs. 4%) initiated edaravone or riluzole. This may affect interpretation of results.

Handling Deaths

- Primary analysis did not account for deaths
  - Potential bias due to 7 deaths by 24 weeks: 2 (4.2%) on placebo and 5 (5.6%) on drug
  - More appropriate to combine survival and function, considering death as unfavorable outcome, such as with a joint rank analysis
- mITT population excluded patients without post-baseline visits
  - Potential bias due to excluding 2 deaths on drug (occurring prior to post-baseline visits)
  - Sensitivity analyses in ITT population are important

Handling Missing Data

- Considerable missing data: 8 (17.4%) on placebo and 15 (17.9%) on drug who survived but had missing Week 24 ALSFRS-R scores
- Primary analysis relied on missing-at-random (MAR) assumption for missing data
- Applicant's sensitivity joint rank analysis relied on last observation carried forward (LOCF)
  - LOCF relies on unrealistic assumption of no worsening after dropout and does not appropriately capture statistical uncertainty in missing values
  - FDA used MAR multiple imputation approach
  - Even MAR assumption is strong and unverifiable

Joint Rank Analysis Results

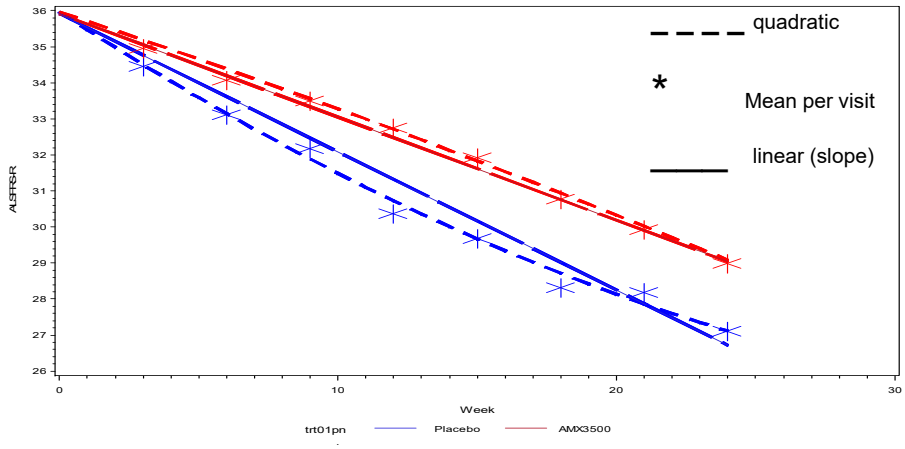
- FDA analysis incorporating deaths via joint rank test provides less persuasive evidence

Analysis Source	Population	Missing Data Handling for Survivors	Difference in Mean Rank	Standard Error of Difference	P-value
Applicant	MITT	LOCF	13.85	6.61	0.0381
FDA	ITT	MAR Multiple Imputation	12.00	6.82	0.0785

Notes: Applicant's implementation also ranked covariates, which was not prespecified
Applicant's alternative prespecified sensitivity analysis for deaths (left censored slope analysis) is problematic

Sensitivity to Linearity Assumption

- Quadratic and mean-per-visit models and residual plots suggest potential non-linearity and optimistic bias at Week 24 in slope model



Sensitivity to Linearity Assumption

- Sensitivity analyses allowing for non-linearity provide less favorable results

Sensitivity Analysis Description	Week 24 Mean Treatment Difference	Standard Error	P-value
Applicant's Reported Backup Quadratic Model	2.28	1.10	0.0385
Applicant's Pre-specified Backup Quadratic Model	1.68	1.06	0.1134
FDA Exploratory Quadratic Model (allowing quadratic term to vary by treatment)	1.97	1.06	0.0644
FDA Exploratory Mean-per-Visit MMRM (non-linear compatible)	1.86	1.04	0.0749

Secondary Endpoint Results

- Secondary endpoint results not compelling
  - ATLIS has multiple components and Applicant was not clear on priority in SAP
    - Only Upper ATLIS score was nominally significant (unadjusted p=0.0420)
    - Total score usually given highest priority when there are subcomponents
  - SVC
  - Biomarker pNF-H
  - Composite survival endpoint

} not significant

Categorical Outcome	Estimated Percentage of Event (SE)		Hazard Ratio: Active vs. Placebo (95% CI)	P-Value
	AMX0035 + SOC	Placebo + SOC		
Death, Death Equivalent, or Hospitalization	19.2 (4.20)	31.0 (6.78)	0.575 (0.290, 1.152)	0.1122
Death or Death Equivalent	2.8 (1.69)	4.4 (3.02)	0.632 (0.110, 3.924)	0.5960
Hospitalization	17.4 (4.07)	27.7 (6.50)	0.590 (0.286, 1.234)	0.1530
Death Events Only	2.6 (1.65)	2.6 (2.28)	1.016 (0.151, 9.753)	0.9873

Abbreviations: CI = confidence interval; mITT = modified Intent-to-Treat population; SE = standard error; SOC = standard of care.

OLE Analysis Plan

- Efficacy outcomes included:
  - ALSFRS-R rate of decline
  - Composite survival endpoint of time to first hospitalization, tracheostomy, or death
  - Upper and lower ATLIS scores rate of decline
  - Rate of progression on ALSFRS-R subdomains
  - Rate of progression on total ATLIS score
- Time to death alone not included in list of efficacy outcomes
- Analysis of time to death alone included in description of analyses of components of composite survival endpoint, not given priority relative to other two components or composite itself
- Composite survival endpoint analysis based on Cox proportional hazards regression with age and pre-randomization slope as covariates

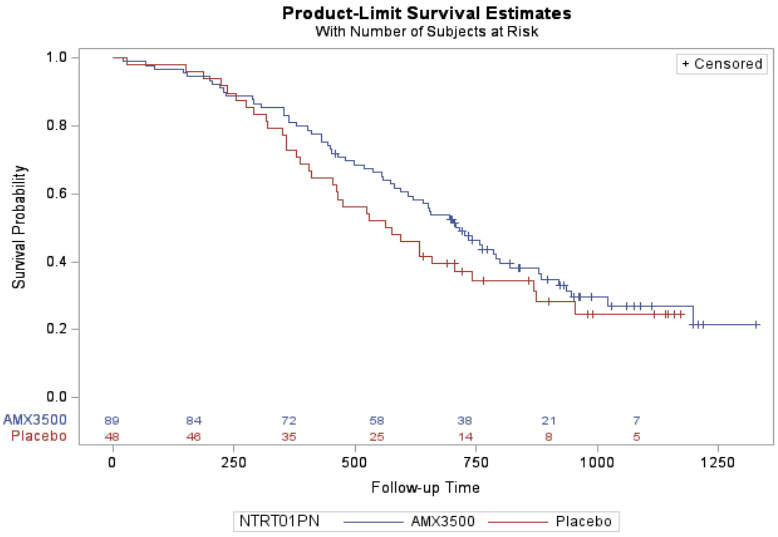
OLE Results for Non-Survival Endpoints

- Results for all endpoints except death difficult to interpret due to substantial dropout and missing data and many deaths
  - Only 66% of patients entered OLE
  - Only ~40% have Week 48 ALSFRS-R measurements
  - 15-20% mortality by Week 48

Supplemental OLE SAP for Survival

- Focus on time to death alone and submission of supplemental OLE SAP for survival occurred after unblinding of double-blind period and preliminary survival analyses of data from the double-blind and OLE period through September 25, 2019
- Supplemental SAP specified Cox proportional hazards regression with age, baseline ALSFRS-R, and pre-randomization slope as covariates

OLE Time to Death Alone Results



- Using supplemental SAP methods:
  - hazard ratio: 0.64 (95% CI: 0.42, 1.00)
  - nominal p = 0.0518

OLE Time to Death Alone Results

- Results are not persuasive
  - Analyses are exploratory
    - OLE periods typically focus on safety
    - Time to death alone not included in planned OLE endpoint hierarchy
    - Focus on death alone and submission of supplemental OLE survival SAP occurred after unblinding of double-blind period and preliminary survival analysis
    - Multiple survival data sweeps
  - No evidence of effect on death or composite survival endpoint in double-blind period
  - Evidence not compelling: nominal p-value ~ 0.05 based on supplemental SAP methods

Applicant's Post-hoc Bayesian Analysis

- FDA has concerns and believes analysis is inappropriate and misleading
  - Analysis is post hoc with emphasis on selected set of endpoints determined after seeing the trial results (e.g., biomarker endpoint was higher in hierarchy than survival but is omitted)
  - No plan to collectively examine these selected endpoints
  - Calculated "error" decreases as more endpoints are added, even if estimated treatment effect for an added endpoint is zero or in wrong direction
  - Analysis does not give primary endpoint due prominence and also may not capture false positives among other endpoints prespecified for testing
  - Calculation is inadequate for quantifying strength of evidence, as this depends on many factors, such as clinical relevance of endpoints and effects, quality of trial conduct, sensitivity to violations in assumptions or limitations of data

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Concluding Remarks

- Single trial to establish effectiveness should demonstrate a clinically meaningful and statistically very persuasive effect
- Uncertainty about results from single trial (and its OLE) that evaluated AMX0035
  - Primary analysis results not highly persuasive
  - Issues with randomization, imbalances in use of riluzole and edaravone, handling of deaths and missing data, assumption of linearity over time in treatment effect
  - Sensitivity analysis results less favorable in some cases and cannot address all issues
  - Secondary endpoint results not compelling
  - OLE survival analyses exploratory

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Focus of Discussion

Phase 3 Pivotal Study Ongoing

- 48-week double-blind, placebo-controlled study in 600 patients
  - Primary endpoint is a joint analysis of survival and function, as measured by the ALSFRS-R
- Results anticipated in late 2023/early 2024

- How does this study fit in with the existing evidence?
- What is the impact of a positive or negative outcome in this study?

Question to the Committee

VOTE: 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 ALS?

- If you voted "no", please discuss what additional information you would consider necessary to establish a conclusion that sodium phenylbutyrate/taurursodiol is effective in the treatment of patients with ALS.

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