AMX0035

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

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Clinical Reviewer

Division of Neurology 1

Office of Neuroscience

Food and Drug Administration

AMX0035 (sodium phenylbutyrate (PB) and taurursodiol (TURSO))

FOR THE TREATMENT OF AMYOTROPHIC LATERAL SCLEROSIS (ALS)

CLINICAL OVERVIEW

Drug Product and Dosing Regimen

Drug Product

AMX0035 Powder for Oral Suspension, a fixed dose combination of:
- Sodium Phenylbutyrate (PB): 3 g
- Taurursodiol (TURSO or TUDCA): 1 g

Proposed dosing regimen

Run-in Period:

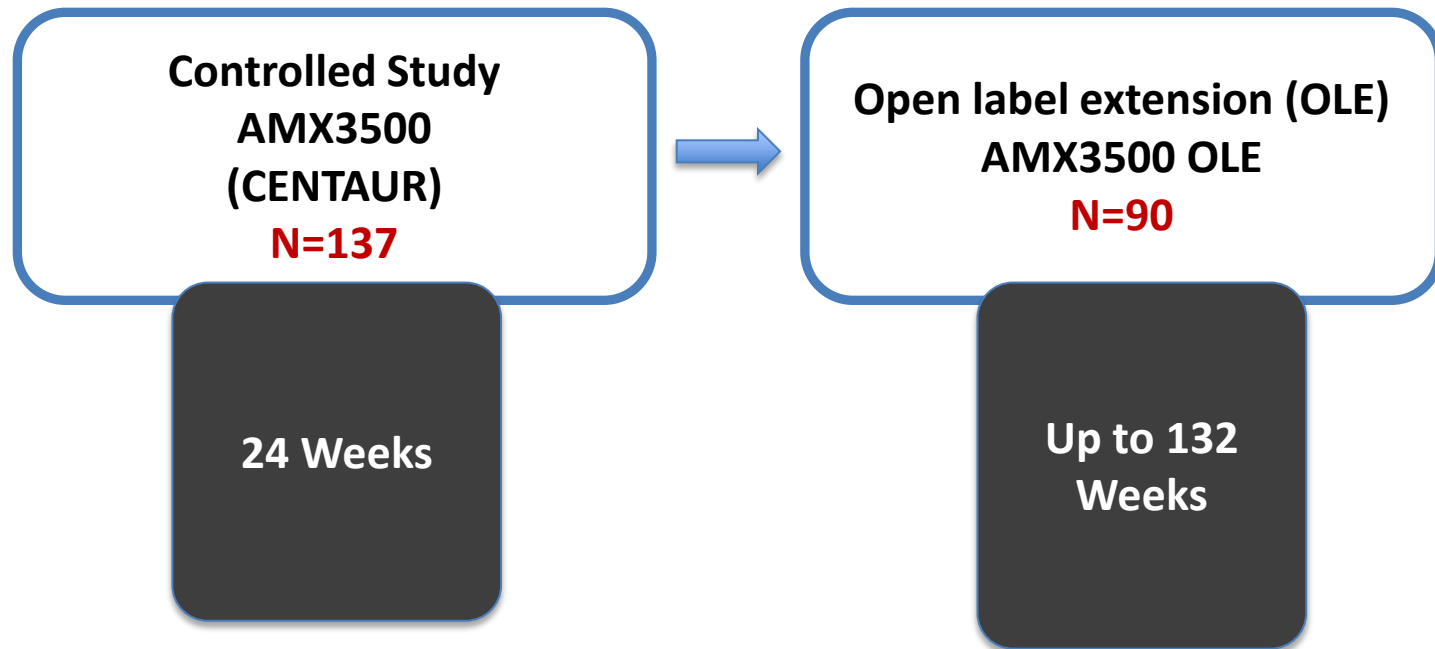1 sachet once daily (OD) for 1-21 days.

Maintenance Dose:

1 sachet twice daily, morning and evening (BID).

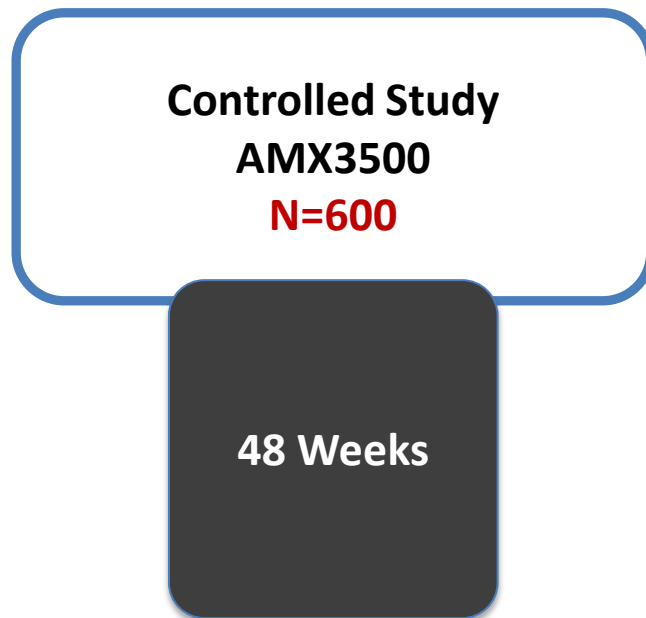# Applicant's Purported Mechanism of Action for AMX0035 in ALS

FDA

- Phenylbutyrate is proposed to ameliorate endoplasmic reticulum stress through upregulation of chaperone proteins.

- Taurursodiol (TURSO or TUDCA) is proposed to ameliorate mitochondrial stress by reducing mitochondrial permeability and increasing the apoptotic threshold of the cell.

- Combination product AMX0035 is postulated to have a synergistic effect that can 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.

Single Controlled Study and its Extension

FDA

Controlled Study
AMX3500
(CENTAUR)
N=137

24 Weeks

Open label extension (OLE)
AMX3500 OLE
N=90

Up to 132 Weeks

Phase 3 Pivotal Study A34-004 Ongoing

FDA
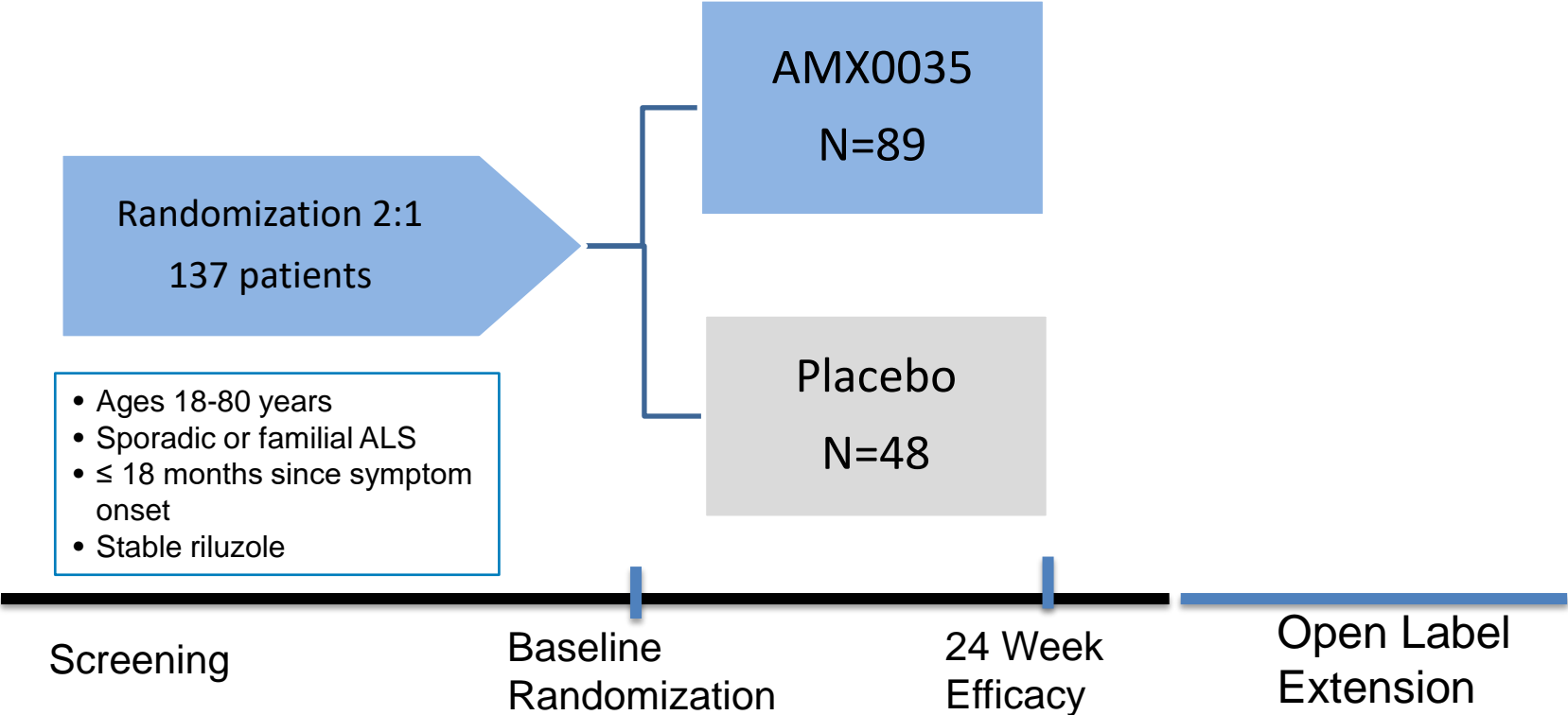
Controlled Study
AMX3500
N=600

48 Weeks

Full results
anticipated
2024

AMX3500
CENTAUR

Study AMX3500 (CENTAUR)

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

- ALSFRS-R is an acceptable primary endpoint to measure functional change in ALS.
  - Functional endpoints can be confounded by loss of data due to patient deaths
  - FDA recommends use of an analysis method that combines survival and function into a single overall measure, such as the joint rank test.
- Do not agree with rate of decline analysis because it assumes linearity over time, which is not established.
- Analysis concerns will be discussed further in the Statistical presentation

Clinical Endpoints: CENTAUR

FDA

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

- Secondary endpoints were also analyzed using the primary slope model.
- ATLIS can give Total, Upper Extremity, or Lower Extremity ATLIS scores. It was not specified in the Statistical Analysis Plan which of these would be the key secondary endpoint.
- pNF-H is a potential biomarker of neuronal degeneration and neuronal axonal injury.

Clinical Endpoints: CENTAUR

FDA

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

- SVC is a measure of respiratory function in ALS.

- FDA does not agree with the inclusion of tracheostomy and hospitalization in the definition of survival as there is variability in the time to hospitalization or when a tracheostomy is placed due to differences in standard of care by treating physicians and patient preference, and tracheostomies may also be placed for the management of secretions.

Key Regulatory History related to Efficacy Analyses

1st ALS patient enrolled 2017

Last ALS patient enrolled 9/2019

Pre-IND **3/2016**	• FDA recommended Joint Rank Analyses of ALSFRS-R
SAP **3/2019**	• Applicant proposed slope analyses of ALSFRS-R • FDA recommended Joint Rank Analyses of ALSFRS-R • Recommended a backup analysis if change in ALSFRS-R is non-linear over time
Type C **3/2020**	• FDA stated Joint Rank most appropriate analysis • On face CENTAUR results not adequate for single trial approval
New SAP **4/2020**	• New "supplementary" SAP for additional post hoc survival analyses
Type C **2/2021**	• FDA reiterated the recommendation for a Phase 3 study despite encouraging results of CENTAUR • Applicant planned to conduct Phase 3 Study A34-004 • Discussed possible option for interim analysis to demonstrate efficacy
7/2021	• Pre-NDA meeting

Clinical Efficacy Results
CENTAUR

Study AMX3500 Disposition

Randomization 2:1

137 patients (ITT)

135 patients (mITT)*
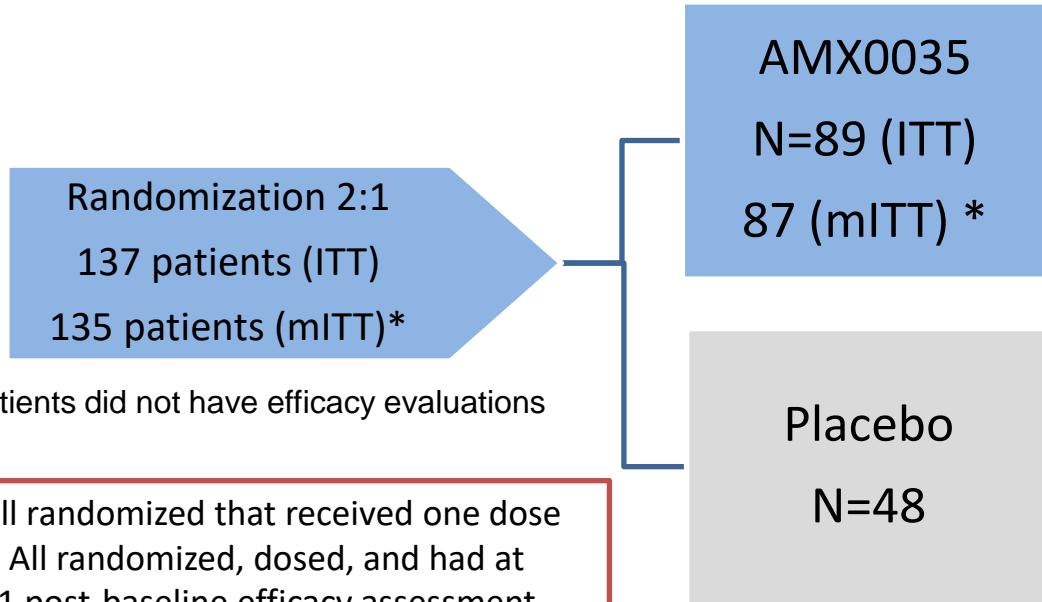
* 2 patients did not have efficacy evaluations

ITT: All randomized that received one dose
mITT: All randomized, dosed, and had at
least 1 post-baseline efficacy assessment

AMX0035

N=89 (ITT)

87 (mITT) *

Discontinuations =20
Participant Decision 16
Death   2
Physician Decision   2
Lost to follow-up   0
Completers   = 67
Completed On Drug = 60

Placebo

N=48

Discontinuations =10
Participant Decision   6
Death   2
Physician Decision   1
Lost to follow-up   1
Completers =38
Completed on Drug = 37

No imbalance in baseline demographic characteristics (ITT)

FDA

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)

FDA

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)**

- Higher percentages shown in red favor treatment arm.
- Clinical relevance of difference in family history is unclear

Note: No clinically meaningful difference between groups in other disease characteristics that include- 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

Applicant's Primary Efficacy Analysis on ALSFRS-R at Week 24

- The Applicant reports a statistically significant mean treatment difference of 2.32 points in favor of AMX0035 (p = 0.034) on the **ALSFRS-R rate of decline** between the treatment arm and placebo in the mITT population (N=135)

- Applicant's primary slope analysis assumes linearity of ALSFRS-R over time, which is not established.
- Primary analysis ignores deaths that occurred during the study.
- Applicant's analysis is on the mITT population, which excludes two deaths on treatment.
- There is considerable missing data on alive patients at week 24 assessment.
- Details of these will be discussed in the FDA Statistics presentation.

Limited Support from Secondary Endpoint ATLIS

	ATLIS Scores at Baseline (Mean (SD))		Results (Rate of decline)	
	Placebo	**AMX0035**	**Treatment Difference Week 24**	**P-value**
Total ATLIS	53.9 (20.9)	56.8 (20.0)	2.8	0.1129
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

- The SAP did not pre-specify which ATLIS score would be analyzed first.
- There are imbalances in the Total ATLIS Score at baseline, driven by imbalance in the Upper ATLIS that favored the AMX0035 group.
- These baseline differences could lead to proportional slower decline in the AMX0035 group.

Limited Support from Other Secondary Endpoints

- There was a statistically non-significant treatment difference (p=0.260) of 32.7 pg/mL in favor of placebo for the **rate of decline in pNF-H**

- There was a statistically non-significant treatment difference (p=0.076) of 5% in favor of AMX0035 for **rate of decline in SVC**

- No **survival benefit** in the first 24 weeks

- These endpoints were also slope analyses and assume linearity in change and therefore have similar concerns as the primary endpoint.
- The change observed in the rate of decline in pNF-H favored placebo.
- The small numerical trend in rate of decline in SVC in favor of AMX0035 is not statistically significant and is not consistent with a clinically meaningful change in SVC.

Summary of Clinical Efficacy Concerns
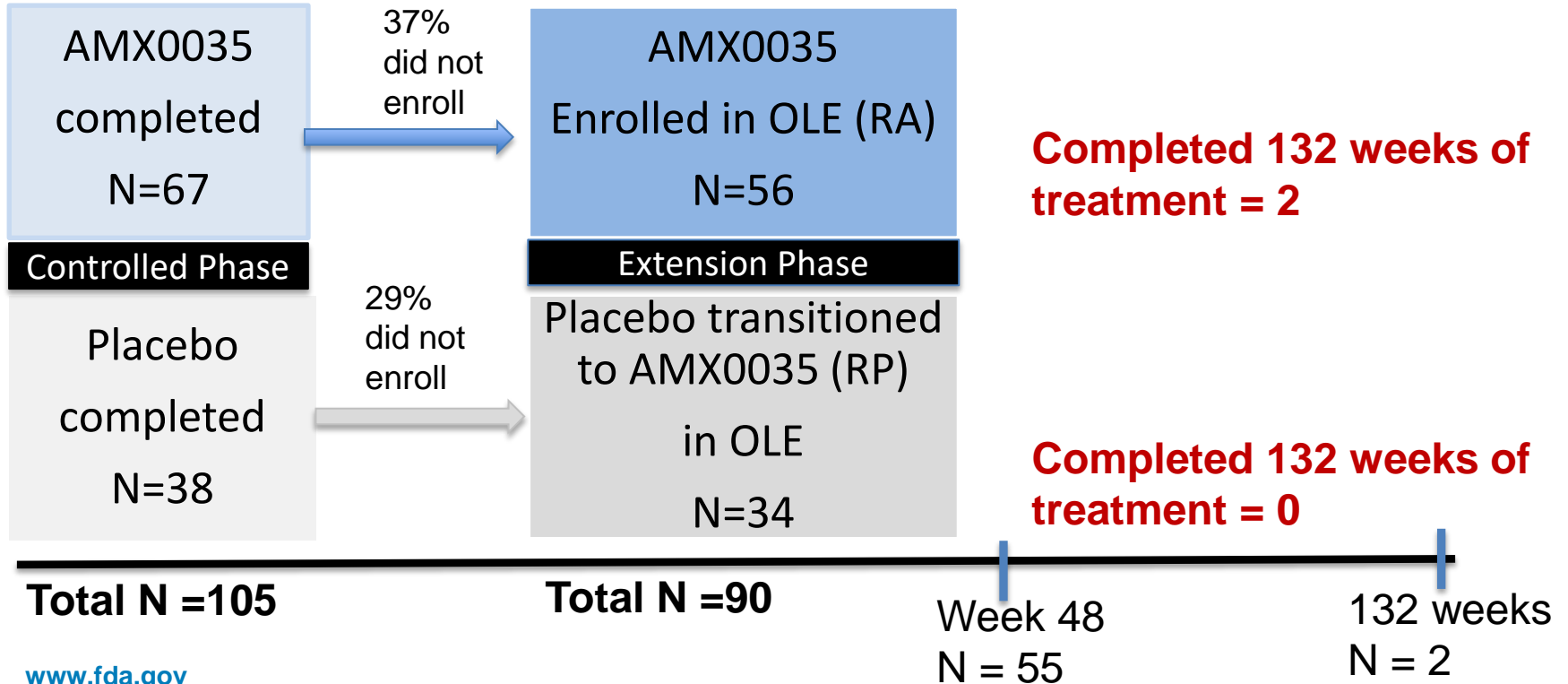## CENTAUR

- Modest results on primary endpoint with limited support from any secondary endpoints
- No survival benefit at 24 weeks
- Appropriateness of Applicant's primary efficacy analysis (i.e., slope analysis)
- Baseline imbalances in disease characteristics
- Issues during study conduct
  - Randomization implementation problem
  - Imbalances in edaravone initiation during the study (post baseline)
  - Potential for unblinding due to gastrointestinal adverse events and bitter taste of the drug

AMX3500 OLE

Only 66 % of total patients enrolled in extension AMX3500OLE

AMX0035 completed N=67	37% did not enroll →	AMX0035 Enrolled in OLE (RA) N=56
Controlled Phase		**Extension Phase**
Placebo completed N=38	29% did not enroll →	Placebo transitioned to AMX0035 (RP) in OLE N=34

Completed 132 weeks of treatment = 2

Completed 132 weeks of treatment = 0

Total N =105   Total N =90

Week 48
N = 55

132 weeks
N = 2

OLE Disposition

	RP Group	RA Group	Total In OLE
Completed 24-week controlled phase	38	67	105
Enrolled in OLE	34	56	90
Discontinued OLE	34	54	88
Participant Decision	18	33	51
Physician Decision	1	3	4
Sponsor Decision	4	7	11
Death	11	8	19
Lost to follow up	0	3	3
Completed 132 weeks of OLE	0	2	2
Completed 48 weeks of OLE	19	36	55

Clinical Endpoints: AMX3500 OLE

FDA

Primary	• Safety
Secondary	• Rate of change in ALSFRS-R at Week 48 • Survival (death, tracheostomy, permanent assisted ventilation, hospitalization) • Rate of change ATLIS At week 48 • Rate of change SVC at Week 48

Clinical Efficacy Results
AMX3500 OLE

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

- Applicant reports a statistically significant extended slope analysis in favor of those randomized to AMX0035 group (RA group) (p=0.0239)

> - Difficult to interpret open-label efficacy data up to Week 48 for the following reasons:
>   - Only 66% of the subjects enrolled in OLE (56 AMX0035-treated subjects and 34 placebo subjects enrolled)
>   - Higher non-participation in the OLE in AMX0035 group
>   - There was no indication in the protocol that the blind was to be maintained
>   - Potential unblinding to treatment received because of GI AEs and bitter taste
>   - Additional discontinuation during the open-label phase: 40% remained at Week 48
>   - Deaths are ignored in the slope analysis

Efficacy Analyses including Open-Label Extension
Upper ATLIS and SVC Extended Slope Analysis At Week 48

- Applicant reports a statistically significant extended slope analysis in favor of those randomized to AMX0035 group (RA group) for upper ATLIS and SVC (p=0.029 and 0.0372, respectively)

  - Similar concerns regarding interpretability of open-label extended slope analysis at Week 48 as that for ALSFRS-R

Efficacy Analyses including Open-Label Extension Survival Analyses

- Overall survival analyses from initial randomization compares:
  - Patients randomized to AMX0035 (RA group)
  - Patients randomized to placebo (RP group)

- Applicant's pre-specified survival analysis included a **composite** time to survival event analysis including death, tracheostomy, Permanent Assisted Ventilation (PAV), hospitalization

- Additional post hoc survival analysis including **time to death alone** was also performed.

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 (Difference=4.8 months, HR=0.62, p=0.0196)

- Applicant reports this analysis as a prespecified analysis
- Survival analyses were done after multiple data cutoff dates:
  - 25 September 2019
  - 29 February 2020
  - 20 July 2020
  - 01 March 2021
- Professional firm, Omnitrace, was contracted to conduct a search based on subject's family, clinic notes, CDC national death index, social security index

Composite Survival Analysis Limitations

- There were number of dropouts during OLE, in addition to 34% non-participation
- Limitations of including tracheostomy and hospitalization data
  - Subjectivity due to physician and patient preference
  - Not systematically collected in OLE
  - May have had missing data on tracheostomy and hospitalizations after subject terminated from the study (not captured in vital status sweeps)
- 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

Summary of Clinical Efficacy Concerns
Open Label Extension AMX0035 OLE

- Only 66% of the subjects enrolled in OLE

- Additional dropouts during the course of the OLE study

- Additional deaths during the study were not accounted for in the functional analyses on ALSFRS-R, ATLIS, SVC that were similar to the primary linear slope analyses

- This renders it difficult to interpret the efficacy data on ALSFRS-R, ATLIS, SVC including the composite survival analyses

Post-hoc Survival Analysis including Time to Death Only

- Applicant reports statistically significant survival benefit on a supplemental time to death only analysis
    - median difference=4.8 months, HR=0.644, p=0.0475 in the ITT population
    - median difference=4.8 months, HR=0.62, p=0.0324 in the mITT population

> - The Applicant reports the p-values from the Cox proportional hazard model instead of the pre-specified likelihood ratio test which gives a larger p-value
> - Details will be discussed in the FDA Statistical presentation.

Limitations of Survival Analysis

- Small study
- Baseline disease imbalances in the treatment groups
- Limited enrollment in open-label extension
- Time to death/survival was not prespecified
- Borderline significant p-value

- Is survival benefit due to treatment or due to chance alone/underlying disease heterogeneity?

Evidence of Effectiveness Based on Single Study are Not Compelling

- Results of CENTAUR not persuasive for establishment of efficacy based on a single study
  - Small, Phase 2 study
  - Results of primary endpoint are not robust
  - The secondary endpoint results are not generally supportive of the primary endpoint

- The AMX3500 OLE results, including survival, are not persuasive
  - Does not provide compelling evidence of efficacy

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 between AMX0035 and placebo
  - There were 7 Fatal TEAEs:
    - All deaths were disease progression-related (respiratory failure/arrest)
  - Serious TEAEs occurred more frequently in the placebo group:
    - All related to ALS, treatment procedure (port-a-cath, g-tube), or falls due to disease progression
- Discontinuations higher in AMX0035 group (20%) compared to placebo (10%)
  - Driven by diarrhea, abdominal pain, nausea, and dysgeusia in the AMX0035 group

Safety Summary

- **Common TEAEs** belonged to the Gastrointestinal System Organ Class (including diarrhea, abdominal pain, nausea, salivary hypersecretion). Others common TEAEs included dizziness, disease progression, respiratory tract infection, fatigue, and dyspnea.
  - increase in gastrointestinal (GI) adverse events during the initial 3 weeks of treatment
    - raises concern for the potential for unblinding of patients

- There were no differences in laboratory abnormalities, vital signs electrocardiograms, QTc, suicidality between AMX0035 and placebo-treated participants.

Safety Summary OLE

- **Common TEAEs** in the OLE were similar to those seen in the double-blind treatment period
- Deaths and SAEs were related to complications of underlying ALS or disease progression
- 44% of patients who switched to drug from placebo discontinued due to AEs
 - also indicates potential for unblinding to original treatment

Common TEAEs in > 5% of AMX0035 Treated Subjects and >1% Difference Compared to Placebo

Preferred Terms	Placebo (N = 48)	AMX0035 (N = 89)
Total Subjects with any Adverse Events	46 (96%)	86 (97%)
Diarrhea	9 (19%)	22 (25%)
Abdominal pain	6 (13%)	19 (21%)
Nausea	6 (13%)	16 (18%)
Respiratory tract infection	5 (10%)	16 (18%)
Fatigue	3 (6%)	11 (12%)
Dyspnea	4 (8%)	10 (11%)
Salivary hypersecretion	1 (2%)	10 (11%)
Dizziness	2 (4%)	9 (10%)
Decreased appetite	2 (4%)	7 (8%)
Dysarthria	2 (4%)	7 (8%)
Proteinuria	2 (4%)	6 (7%)
Arthralgia	2 (4%)	5 (6%)
Weight decreased	1 (2%)	5 (6%)

Higher Incidence of Gastrointestinal AEs in AMX0035 Arm in the first 3 weeks of Treatment
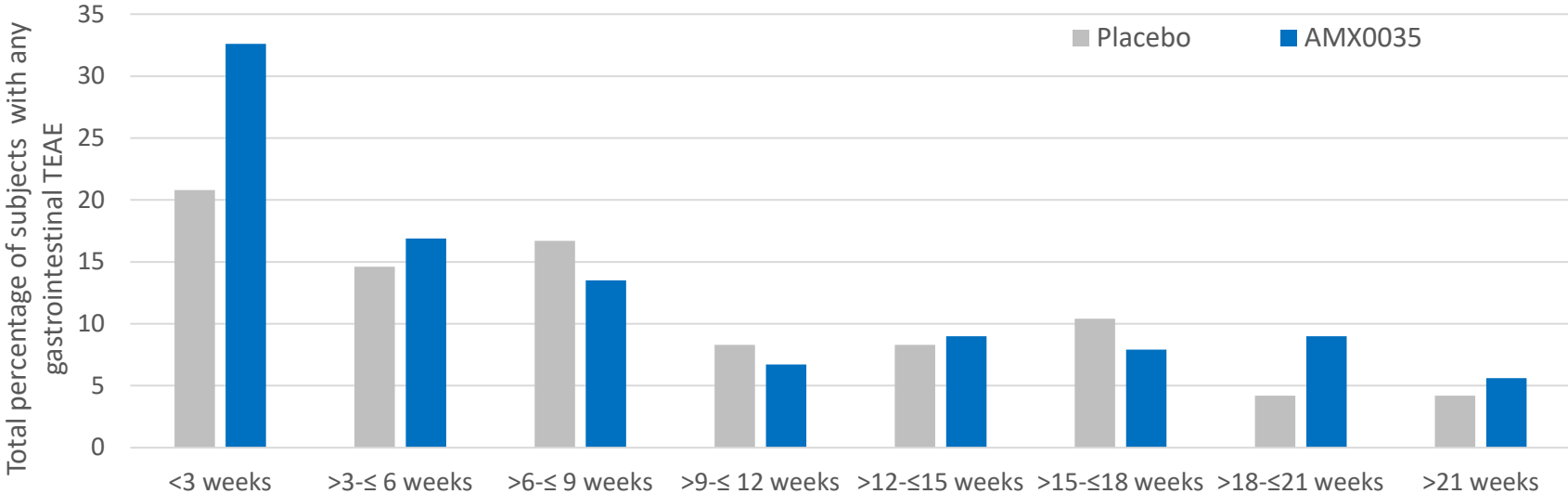
This raises concern for the potential for unblinding of patients during the study, as well as upon transition to the open-label phase of the study.

Thank you!

NDA 216660

Product: Sodium Phenylbutyrate and Taurursodiol
Indication: Treatment of Patients with ALS
Applicant: Amylyx
Received: 10/29/2021

Statistical Review Team: Tristan Massie, Kun Jin
Clinical Review Team: Veneeta Tandon, Emily Freilich

Peripheral and Central Nervous System Advisory Committee Meeting
March 30, 2022

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
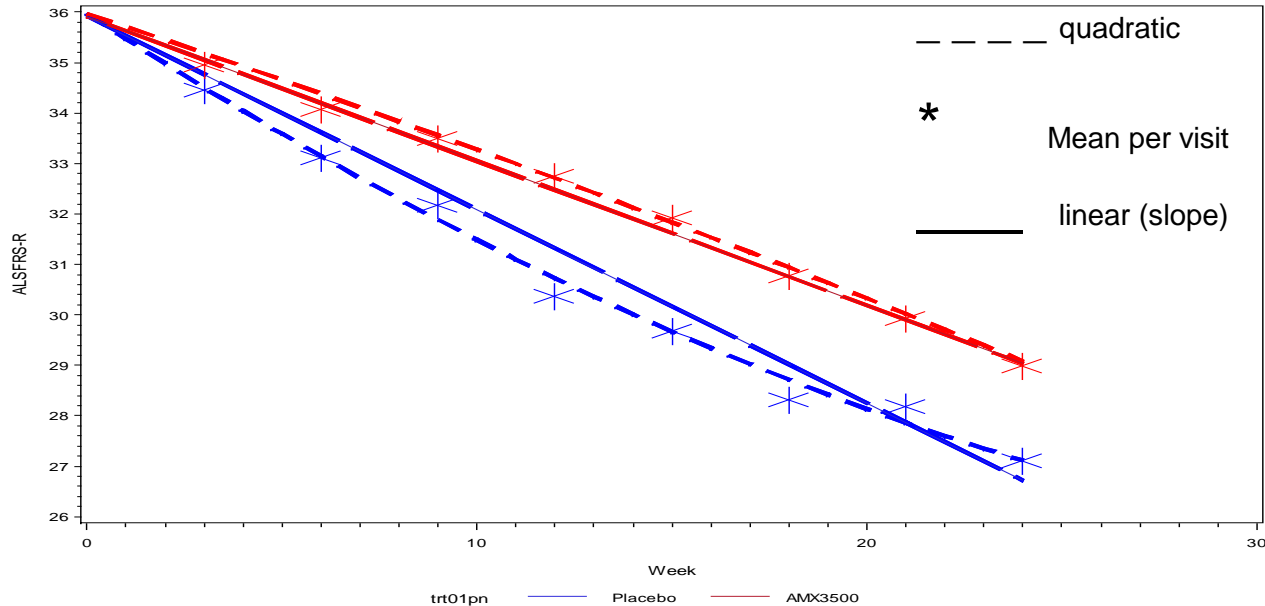
Sensitivity to Linearity Assumption

- 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 — not significant
  - Composite survival endpoint

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

Product-Limit Survival Estimates
With Number of Subjects at Risk
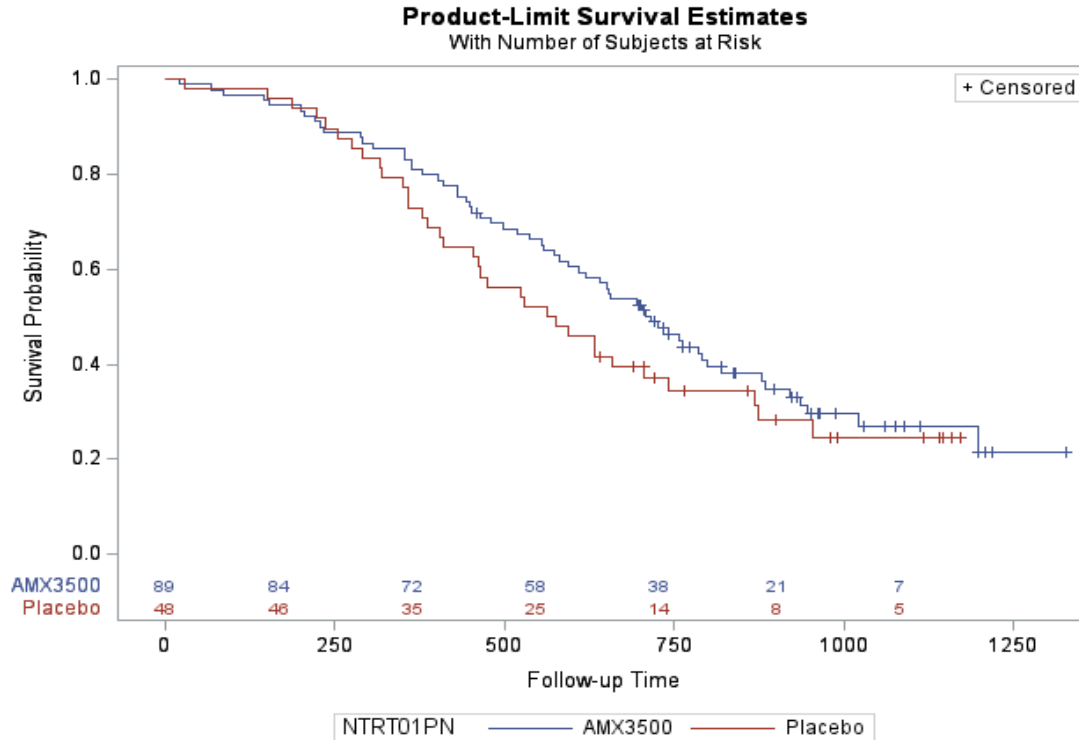
- Using supplemental SAP methods:
  - hazard ratio: 0.64 (95% CI: 0.42, 1.00)
  - nominal p = 0.0518

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

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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