Summary Memorandum

Date	September 29, 2022
From	Emily R. Freilich, MD Teresa Buracchio, MD Billy Dunn, MD
Subject	Summary Memorandum
NDA/BLA # and Supplement#	216660
Applicant	Amylyx Pharmaceuticals, Inc.
Date of Submission	October 29, 2021
PDUFA Goal Date	September 29, 2022
Proprietary Name	Relyvrio
Established or Proper Name	Sodium phenylbutyrate and taurursodiol
Dosage Form(s)	3 g/1 g powder-filled sachets for oral suspension
Applicant Proposed Indication(s)/Population(s)	Amyotrophic lateral sclerosis (ALS)
Applicant Proposed Dosing Regimen(s)	Initial dosage: 1 sachet daily for (b) (4) 21 days Maintenance: 1 sachet twice daily
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of amyotrophic lateral sclerosis (ALS) in adult patients
Recommended Dosing Regimen(s) (if applicable)	Initial dosage: 1 packet daily for 21 days Maintenance: 1 packet twice daily

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive and fatal neurodegenerative disease characterized by the death of motor neurons that results in loss of voluntary muscle control, paralysis, and eventually death typically secondary to respiratory failure. Approximately 85-90% of cases of ALS are sporadic, and the remaining 10-15% are familial due to a variety of genetic mutations. The exact pathophysiology of ALS is not well elucidated. The majority of patients die within 3 years of onset of symptoms, and approximately 90% of patients with ALS die within 5 years of symptom onset. Disease course can be heterogeneous, and 10% of patients can live for 5-10 years or longer after diagnosis.

There are two FDA-approved drugs for ALS. Riluzole, approved in 1995, was found to improve early survival; however, measures of muscle function and neurological function did not show benefit. Edaravone was approved in 2017, based on a functional benefit shown on the ALS Functional Rating Scale-Revised (ALSFRS-R). Edaravone is not known to improve survival. In 2022, an oral formulation of edaravone was approved.

The Applicant has provided data from a single randomized, double-blind, placebo-controlled study (AMX3500) and an open-label extension study (AMX3500OLE). In Study AMX3500, 137 patients were randomized 2:1 to receive AMX0035 (N = 89) or placebo (N = 48) for 24 weeks. Study AMX3500 demonstrated a statistically significant mean treatment difference of 2.32 points (p = 0.034) in patients receiving AMX0035 compared to placebo on the prespecified primary endpoint, the ALSFRS-R rate of decline, in the mITT population. However, the prespecified analysis did not account for deaths during the study. There were five deaths during the double-blind treatment period in the mITT population, and seven deaths in the ITT population. Because deaths are typically anticipated to occur during a study of ALS patients, FDA generally recommends a combined analysis of survival and function as the preferred primary analysis method. The Applicant performed a post hoc joint rank analysis of survival and change from baseline in ALSFRS-R on the mITT population, which also had a nominally significant p-value of 0.03, but which did not allow for a missing-at-random assumption for handling missing data. FDA performed an analysis with a missing-at-random assumption for handling missing data, which was felt to be more appropriate, resulting in a p-value = 0.063 for the mITT population and 0.079 for the ITT population. Although strength and respiratory assessments numerically favored AMX0035, no secondary endpoints reached statistical significance. A post hoc analysis of time to death, based on vital status data collected on 136 of the 137 patients originally randomized in Study AMX3500, demonstrated a nominally significant longer median overall survival (p = 0.0475) in patients originally randomized to AMX0035 compared to those originally randomized to placebo.

There are no significant safety signals of concern with AMX0035. During Study AMX3500, there were no differences in fatal or serious adverse events between AMX0035 and placebo. Most of the serious adverse events were complications of the underlying ALS. The percentage of subjects that discontinued due to Treatment Emergent Adverse Events (TEAEs) was higher in the AMX0035 treatment group (20%) compared to placebo (10%) in the double-blind controlled phase of the study. Common TEAEs occurring in more than 5% of AMX0035 patients and at least 5% greater than placebo

mostly belonged to the gastrointestinal SOC, including diarrhea, abdominal pain, nausea, and salivary hypersecretion. Other common TEAEs included dizziness, upper respiratory tract infection, and fatigue.

Overall, Study AMX3500 demonstrated a statistically significant treatment benefit of AMX0035 compared to placebo on the prespecified primary endpoint, the rate of decline of ALSFRS-R. In post hoc long-term analyses, an overall survival benefit was observed for those patients who were originally randomized to AMX0035 compared to those originally randomized to placebo. Supplemental post hoc exploratory analyses comparing the overall survival to natural history databases provided consistent results. There are limitations to these findings that result in 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; however, given the serious and life-threatening nature of ALS and the substantial unmet need, this level of uncertainty is acceptable in this instance and consideration of these results in the context of regulatory flexibility is appropriate. Exercising regulatory flexibility, the single study with positive results on a clinically meaningful primary outcome accompanied by confirmatory evidence of an observed survival benefit provides substantial evidence of effectiveness. The benefits of AMX0035 outweigh the risk, as the drug appears well tolerated without any significant safety signals of concern.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Amyotrophic lateral sclerosis (ALS) is a rapidly progressive and fatal neurodegenerative disease characterized by the death of motor neurons that result in loss of voluntary muscle control, paralysis, and eventually death. • 85-90% of cases of ALS are sporadic; the remaining 10-15% are familial. • Approximately 50% of ALS patients die within 3 years from the onset of symptoms and approximately 90% die within 5 years. • The remaining patients may survive 5-10 years or longer from symptom onset. • Death is generally due to complications arising from diaphragmatic failure.	ALS is a serious and life-threatening neurodegenerative disease which causes progressive weakness of all muscles, starting with muscles of voluntary control, ultimately leading to respiratory failure and death.
Current Treatment Options	• There are two FDA-approved drugs for ALS: • Riluzole (Rilutek): Riluzole improved early survival, but measures of muscle function and neurological function did not show benefit. • Edaravone (Radicava): An intravenous injection of riluzole given once daily for 10 days in recurring cycles was demonstrated to have a treatment difference of 2.49 (p=0.0013) on the change from baseline in the ALS Functional Rating Scale-Revised (ALSFRS-R) Total score compared to placebo. • Frequent intravenous administration typically required surgical catheter placement. • Oral edaravone (Radicava ORS) was approved in May 2022.	Although riluzole and edaravone have demonstrated benefits for ALS, the disease remains progressive and fatal despite these available therapies. There is an urgent unmet medical need for new treatments for individuals with ALS.
Benefit	• The Applicant conducted a single, randomized, double-blind, placebo-controlled phase 2 study for 24 weeks (AMX3500), followed by an open-label extension study for 132 weeks (AMX3500OLE). • Study AMX3500 demonstrated a statistically significant mean treatment difference of 2.32 points (p = 0.034) in patients receiving AMX0035 compared to placebo on the prespecified, primary endpoint, ALSFRS-R rate of decline, in the mITT population. • A joint rank analysis with combined assessment of survival and function, as analyzed by the Applicant, had a p-value of 0.03. The FDA statistical reviewer concluded that a more appropriate analysis with a missing-at-random assumption for handling missing data has a p-value of 0.063 for the	Study AMX3500 demonstrated a statistically significant, although not exceptionally persuasive, treatment benefit of AMX0035 compared to placebo on the prespecified primary endpoint, the rate of decline of ALSFRS-R, indicating a slowing of disease progression. Exploratory analyses of overall survival demonstrated a nominally statistically significant survival benefit for those patients who were originally randomized to AMX0035 compared to those originally randomized to placebo. Overall, the single positive study accompanied by confirmatory evidence of a survival benefit

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	mITT population and 0.079 for the ITT population. • Although strength and respiratory assessments numerically favored AMX0035, no secondary endpoints reached statistical significance. The secondary biomarker, pNF-H, did not improve compared to placebo. • An exploratory analysis of survival, based on a time to death alone analysis of 136 of the original 137 patients originally randomized in Study AMX3500, demonstrated a nominally significant survival benefit, p = 0.0475.	provides substantial evidence of effectiveness.
Risk and Risk Management	• There were no differences in fatal or serious adverse events between AMX0035 and placebo. Most of the serious adverse events were complications of the underlying ALS. • The percentage of subjects that discontinued due to Treatment Emergent Adverse Events (TEAEs) was higher in the AMX0035 treatment group (20%) compared to placebo (10%) in the double-blind controlled phase of the study. • Common TEAEs occurring in more than 5% of AMX0035 patients and at least 5% greater than placebo mostly belonged to the gastrointestinal SOC, including diarrhea, abdominal pain, nausea, and salivary hypersecretion. Other common TEAEs included dizziness, upper respiratory tract infection, and fatigue. • There were no significant differences in laboratory abnormalities or vital signs between AMX0035 and placebo subjects. • QT evaluation was only able to exclude large effects (>20 msec).	There were no significant safety signals of concern with use of AMX0035. The most common TEAES include diarrhea, abdominal pain, nausea, upper respiratory tract infection, fatigue, salivary hypersecretion, and dizziness. Risk management can be achieved through the recommendations in the product labeling and routine postmarketing surveillance.

2. Background

This application under review is for AMX0035, a fixed-dose combination of sodium phenylbutyrate and taurursodiol, for the treatment of amyotrophic lateral sclerosis (ALS). AMX0035 is a powder for oral suspension composed of 3 g of sodium phenylbutyrate and 1 g of taurursodiol.

Sodium phenylbutyrate is approved in the United States as BUPHENYL for adjunctive therapy in treatment of patients with urea cycle disorders at doses of 9.9-13 g/m^2 given three to six times daily. A prodrug of phenylbutyrate, glycerol phenylbutyrate, is approved as RAVICTI, in the management of urea cycle disorders at doses up to 19 g given three times daily. Taurursodiol is a bile acid found in large amounts in bears, and is approved in Italy, China, and Turkey for the treatment of disorders of bile production. A metabolite of taurursodiol, ursodiol (UDCA), is approved in the United States for the treatment of primary biliary cirrhosis at total daily doses of 13-15 mg/kg.

The Applicant has an ongoing Phase 3 trial (A35-004) that will enroll approximately 600 subjects at over 70 sites in the US and Europe. It is expected to complete in late 2023 or early 2024 with results available shortly thereafter.

ALS is a rapidly progressive and fatal neurodegenerative disease that primarily affects motor neurons in the cerebral motor cortex, brainstem, and spinal cord, leading to loss of voluntary movement and the development of difficulty in swallowing, speaking, and breathing, ultimately leading to death. ALS patients can present with weakness and muscle atrophy in different areas of the body, with about 75 percent of patients first experiencing weakness in their limbs, and about 25 percent of patients presenting with difficulty swallowing and/or speaking (bulbar-onset ALS). Respiratory muscles are also affected, leading to respiratory failure and death of most patients within 3 to 5 years from the onset of symptoms. Approximately 10 percent of ALS patients survive for 5-10 years or longer after diagnosis. Shorter survival may be associated with older age at onset, bulbar-onset, and faster rate of respiratory dysfunction. ALS is a heterogeneous disease, but all forms of the disease share the defining features of degeneration of both upper and lower motor neurons. ALS is also considered a multisystem neurodegenerative disorder that can include cognitive and behavioral changes in addition to muscle weakness.

The incidence of ALS is 2 per 100,000 per year, with approximately 6,000 new cases per year in the U.S. The estimated prevalence in the U.S. is 5 per 100,000 population, with approximately 16,000 cases. ALS most frequently affects people between 40 and 70 years of age (median age 55). Most cases of ALS are sporadic with no known cause or inheritance pattern. Five to ten percent of ALS cases are familial and are associated with approximately 50 different identified genes. Familial ALS generally has a 10-year earlier onset than sporadic ALS.

There is no cure for ALS. There are two FDA-approved therapies for the treatment of ALS. Riluzole was approved in 1995, although the two studies failed to demonstrate statistical significance on the prespecified primary analyses of survival and also failed to demonstrate

benefit on various secondary outcomes of function. Additional, alternative, post hoc analyses conducted by the FDA were able to demonstrate an ability of riluzole to prolong survival by about 3 months and extend the time before ventilatory support was needed to support approval. Edaravone was approved in 2017 based on a single, non-US study of 137 patients in Japan, which demonstrated a 33% reduction in the rate of functional decline over 24 weeks of treatment, compared to placebo, in patients who were within 2 years of ALS diagnosis. The persuasiveness of the primary outcome was strong with sensitivity analyses providing additional strong support for the primary analysis, allowing it to serve as a single study supporting approval. There are no data on survival benefit with edaravone. Although these therapies provide some benefit, there is a continued and substantial unmet need for new treatments for patients living with ALS.

This application provides efficacy and safety data from a single clinical study, Study AMX3500, and the long-term, open-label, extension study (AMX3500OLE). Study AMX3500 is a randomized, double-blind, placebo-controlled study for 24 weeks intended to serve as the basis for the conclusion that AMX0035 is effective for the treatment of ALS. Confirmatory evidence is proposed by the Applicant to come from additional post hoc analyses of clinical endpoints and benefit from AMX3500OLE and survival analyses based on a vital status sweep that was conducted for all subjects who were enrolled in Study AMX3500.

The regulatory history for AMX0035 is detailed in Dr. Veneeta Tandon's clinical review.

3. Product Quality

The Office of Pharmaceutical Quality (OPQ) Review team assessed this application with respect to Chemistry, Manufacturing, and Controls (CMC). The technical lead for this application was Dr. Martha Heimann (see OPQ review for a list of the entire team that was involved with the review of this application).

The OPQ team found the quality assessment adequate for the drug substance and the drug product. CMC information for sodium phenylbutyrate is cross-referenced to DMF (b) (4), and for taurursodiol is cross-referenced to DMF (b) (4). Both were found to be adequate. The information submitted to the NDA is consistent with the referenced DMFs. The drug product formulation is packaged in a single dose laminate packet and is to be reconstituted in 8 ounces of water with vigorous stirring and taken within one hour. It is noted that during product development, three different formulations were manufactured, with Formulation 3 being (b) (4) as the to-be-marketed formulation. In a pre-NDA meeting held on March 11, 2020, an agreement was made to (b) (4) However, dissolution testing was used to bridge the formulations throughout product development (see Clinical Pharmacology Review).

The Applicant provided in-use stability data to support the compatibility of the drug product with water and in-use period. The proposed specification includes appropriate tests for an oral dosage form and justification for tests omitted from the specification. The Applicant proposed

a shelf life of (b) (4) months; however, the maximum shelf life that can be granted based on the data provided is 12 months.

Manufacturing, biopharmaceutics, microbiology, and environmental assessments were reviewed and determined to be adequate with no deficiencies identified. OPQ recommends approval of this NDA from a quality perspective.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application was Dr. David Carbone, with Dr. Lois Freed performing the secondary review. Please see Dr. Carbone's Pharmacology/Toxicology Review for a full review of the nonclinical considerations for this application. The key findings are summarized below.

The Applicant conducted in vitro primary pharmacology studies in cyclid models of mitochondrial disease and cell culture models of hydrogen peroxide and glutamate toxicity, and claims that these studies demonstrate (b) (4) However, Dr. Carbone notes that such claims are not supported by the data, which are inconsistent. An additional study in SOD1G93A transgenic mouse model of ALS showed that twice daily oral administration of 100 mg/kg PB and 200 mg/kg TUDCA had no effects on the lifespan or markers of disease progression.

Dr. Carbone summarizes the pharmacokinetic studies in plasma and CSF in rats administered PB (mg/kg) and TUDCA (mg/kg) in combinations of 50/50, 100/100, and 300/300. In CSF, PB was only detected at quantifiable levels following the high dose, at which point the CSF C_{max} and AUC were approximately 28% and 19% those in plasma. TUDCA CSF levels were below the limits of quantification at all doses. Dr. Carbone's review also summarizes the ADME data, collected in a single distribution and excretion mass balance study of orally administered PB/TUDCA in rat. A mass balance study in humans has not been conducted in AMX0035; therefore, it is unknown whether there are any major circulating human metabolites that would warrant testing in nonclinical studies.

The pivotal general toxicology studies with AMX0035 included daily oral dosing in rat and minipig, for 26 or 39 weeks, respectively, with no notable toxicity in either species. PB and TUDCA were also individually assessed in Ames and in vitro chromosomal aberration assays and were negative. AMX0035 was also found to be negative in an in vivo micronucleus assay in CD1 mice up to 2000 mg/kg. There were no adverse findings following oral administration of AMX0035 in a fertility study in rat, embryofetal development studies in CD1 mice and SD rats, and a pre- and post-natal development studies in SD rats at doses up to 1500 mg/kg (750 mg/kg BID). Carcinogenicity studies are to be conducted as post-marketing requirements, as previously agreed upon with the Applicant.

Dr. Carbone concludes that the nonclinical data support approval of AMX0035.

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was written by Dr. Xioahan Ciao (primary reviewer) and Dr. Bilal Abuasal (clinical pharmacology team leader). Overall, OCP did not find any clinical pharmacology issues that preclude approval.

OCP notes the following key review issues:

- There is limited clinical pharmacology information that can be used to assess the pivotal or supportive evidence of effectiveness. Definitive conclusions were not possible based on the available biomarker data, and exposure-response analyses were not possible because of the lack of exposure data of one of the components of AMX0035 from Study AMX3500.
- The general dosing instructions are to dose once daily for the first 3 weeks and increase the dose to twice daily subsequently. Each sachet contains 3 g of phenylbutyrate and 1 g of TUDCA, and should be mixed with water and administered orally or via feeding tube before a meal or snack.
- No dose adjustments are needed for the following intrinsic factors: mild hepatic impairment and mild renal impairment.
- Use should be avoided in moderate and severe hepatic impairment and moderate and severe renal impairment.
- Use should be avoided for the following extrinsic factors: concomitant use with substrates of CYP1A2, CYP2C8, CYP2B6, and CYP3A4, in which a small change in substrate plasma concentration may lead to serious toxicities or loss of efficacy, concomitant use with transporter inhibitors of OATP1B3, concomitant use with substrates of OAT1, BCRP, and P-gP, and concomitant use with bile acid sequestering agents, inhibitors of bile acid transporters, probenecid, and hDAC inhibitors.
- Although the clinical formulation was different from the to-be-marketed formulation, the dissolution data support the bridging of the formulations (refer to the Integrated Quality Review for further information).

The OCP team recommends additional studies as post-marketing requirements (see *Section 13 Postmarketing Recommendations*).

The Interdisciplinary Review Team for Cardiac Safety Studies also conducted a QT Study Review for this Application. The IRT team notes that the Applicant measured ECGs in 2 clinical studies, neither of which were adequate as a substitute for a thorough QT study. However, study A35-002 was acceptable to exclude large mean increases (i.e., > 20 msec) in the QTc interval at the therapeutic dose level. Potential effects of parent drugs and metabolites on QTc at higher exposures are unknown. The IRT was reluctant to draw conclusions on lack of an effect in the absence of positive control or large exposure margin, or an integrated nonclinical safety assessment.

Given the proposed indication of ALS, the exclusion of only large QT effects is acceptable. However, if AMX0035 is considered for any use in additional indications in the future, a thorough QT study (TQT) would be recommended at that time.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Dr. Veneeta Tandon was the clinical reviewer for this application. Dr. Tristan Massie was the biometrics reviewer, and Dr. Kun Jin was the biometrics team leader for this application. Please refer to the combined clinical and statistical review for additional details on the efficacy analyses outlined below. The limitations of the effectiveness data described in the combined clinical and statistical review by Drs. Tandon and Massie are acknowledged and have been carefully considered. As further detailed below, we conclude that the Applicant has submitted sufficient data to support the approval of AMX0035 for the treatment of ALS based on the results of a single adequate and well-controlled investigation accompanied by confirmatory evidence.

The Applicant conducted a single clinical trial, Study AMX3500, or CENTAUR, which serves as the primary basis for assessing effectiveness of the drug, with additional analyses coming from the long-term, open-label, extension study, AMX3500OLE, and from post hoc long-term survival analyses.

Study AMX3500 (CENTAUR)
Study AMX3500 was a Phase 2 randomized, double-blind, placebo-controlled study that randomized patients 2:1 to AMX0035 or placebo for 24 weeks. Patients received 1 sachet daily for 3 weeks, and then increased to 1 sachet twice daily orally, or via feeding tube, as tolerated. Patients were then allowed to participate in an optional, open-label extension study (AMX3500OLE) which followed patients on drug for up to 132 weeks. The OLE study was primarily intended for evaluation of long-term safety.

The inclusion/exclusion criteria for Study AMX3500 included adult patients with definite diagnosis of ALS as defined by the revised El Escorial criteria, who were less than or equal to18 months from symptom onset and had a slow vital capacity (SVC) of greater than 60% of the predicted value for gender, height, and age. Patients were allowed to be on stable doses of riluzole. Edaravone was approved in 2017, following initiation of Study AMX3500, and subsequently patients were allowed to initiate edaravone during the study or be on stable doses at the time of enrollment.

A bittering agent was added to the placebo to reduce the risks of unblinding due to a bitter taste of the drug when swallowed. Patients were instructed to add the contents of a sachet into a cup and add 8 ounces of water and shake vigorously.

Efficacy Endpoints
The primary efficacy endpoint for Study AMX3500 was the rate of decline (slope) of the total ALSFRS-R score. The ALSFRS-R is a measure of clinical function that has been correlated with quality of life and survival in patients with ALS. The ALSFRS-R has been widely used in

clinical studies in ALS, and it is considered a clinically relevant measure of functional change in ALS.

The ALSFRS-R is an ordinal rating scale of 12 functional activities relevant to ALS across four functional domains (bulbar, fine motor, gross motor, and breathing). Each domain is comprised of 3 questions rated on an ordinal scale of 0-4, with higher scores indicating better performance and the maximum score is 48 points. The ALSFRS-R domains are outlined below:

1. Bulbar
    a. Speech
    b. Salivation
    c. Swallowing
2. Fine Motor
    a. Handwriting
    b. Cutting Food/Handling Utensils
    c. Dressing and Hygiene
3. Gross Motor
    a. Turning in Bed
    b. Walking
    c. Climbing Stairs
4. Breathing
    a. Dyspnea
    b. Orthopnea
    c. Respiratory Insufficiency

The secondary endpoints for Study AMX3500 included a measure of strength using a new device, the Accurate Test of Limb Isometric Strength (ATLIS), levels of a biomarker of neuronal degeneration, plasma neurofilament heavy chain (pNF-H), slow vital capacity (SVC), and survival measured as the combined rate of deaths, hospitalizations, and tracheostomies.

Strength, as measure by the ATLIS, is acceptable as a secondary endpoint that is relevant to the disease and capable of providing support for the primary endpoint. We note that the protocol did not prespecify which component of the ATLIS (i.e., total, upper extremity, and lower extremity) would be the key secondary endpoint in the hierarchy. Because it was not specified, the total ATLIS was presumed to be the key secondary endpoint, with additional exploratory analyses of the individual components.

The ability of pNF-H to assess effectiveness of drugs is not established, and the clinical significance of a change in pNF-H is unclear. In general, it may be hypothesized that a therapy that shows benefit in the treatment of ALS might also decrease pNF-H levels, if the drug had an effect on the neurodegeneration of the disease.

Because decline in respiratory function is a direct result of the known pathophysiology of the disease, demonstration of a treatment benefit on respiratory endpoints may also provide

support for a finding of effectiveness on the primary functional endpoint. SVC is an appropriate outcome measure of respiratory function in patients with ALS.

Survival is an important endpoint to assess in ALS clinical trials. A well-defined assessment of permanent assisted ventilation is important to include in studies to assist in the interpretation and analysis of survival; however, the Division does not agree with inclusion of tracheostomy or hospitalizations in the definition of survival, as there is considerable variation in clinical practice as to when to hospitalize a patient or perform a tracheostomy. Differences in standard of care by treating physicians, as well as patient preference and comfort, may influence these outcomes. For example, tracheostomies may be placed for the management of secretions, or they may be performed earlier in the disease course prior to the onset of acute respiratory insufficiency/failure in anticipation of future need for ventilatory support. The Division currently advises sponsors against such survival definitions.

Statistical Analysis

The primary efficacy endpoint is the rate of decline (slope) in the ALSFRS-R over time. The placebo and AMX0035 arms were compared by a shared-baseline, linear mixed effects analysis. FDA has traditionally had concerns with the use of a slope analysis because of questions regarding the assumptions of linearity of the ALSFRS-R over time. With such an approach, sensitivity analyses allowing for non-linearity are important.

The Applicant reported that historical analyses have shown ALS to be a disease with linear progression over time. However, the Applicant also noted that linearity could not be assumed at this point for the study given the unknown effect of the treatment, and therefore, to confirm linearity, the primary analysis model would be modified to include quadratic terms for time. If the quadratic terms for time were not significant (p-value > 0.10) then linearity would be assumed, and the linear primary model would be used for the primary analysis. If any one of the interaction terms is significant (p-value < 0.10), then the quadratic version of the model would be used.

FDA typically recommends the use of a combined analysis of function and survival, such as the joint rank analysis of the ALSFRS-R, as the primary analysis in ALS. FDA has long indicated that deaths may cause bias if ignored in the primary analysis since some deaths are expected in the double-blind period. Missing data as a result of death are not missing at random, and therefore not appropriate to impute data after death. The advice to use a combined analysis of function and survival, such as a joint rank analysis, was provided to the Applicant at the pre-IND meeting and in an advice email after review of the SAP in March 2019. A joint rank analysis was later conducted by the Applicant as a post hoc analysis.

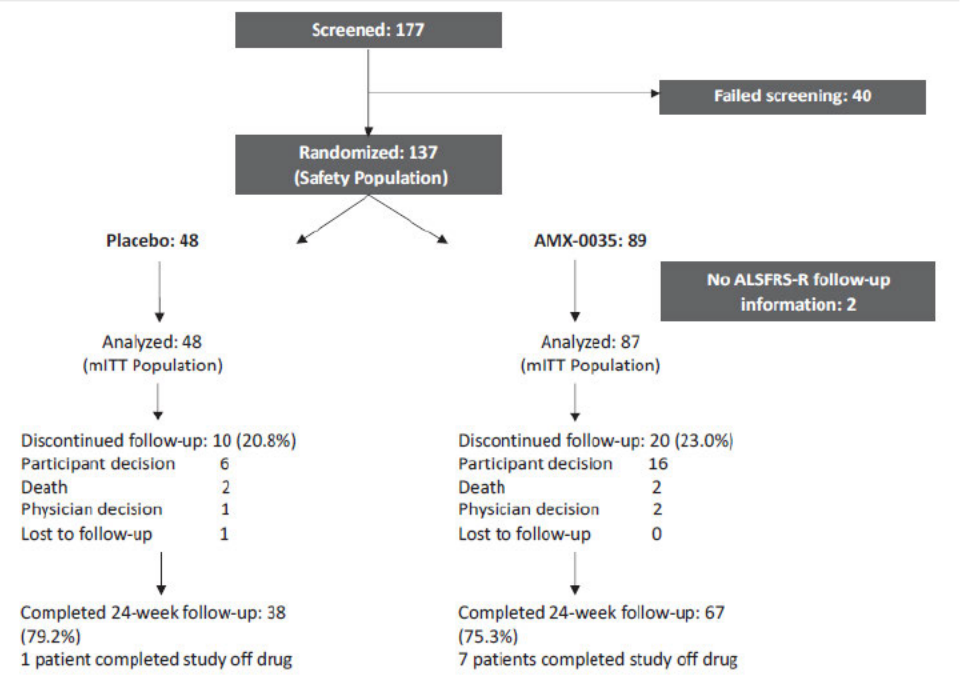
As described in Dr. Massie's review, all continuous primary, secondary, and exploratory efficacy measures were to use the same statistical model and were to be presented in hierarchical order. Covariates of age, rate of disease progression prior to entering the trial (del-FS) and change of the efficacy outcome being measured (if other than ALSFRS-R) interacting with time were to be included in the analysis. The analyses of the secondary endpoints have the same concerns as the primary analysis of not incorporating deaths. The use of a joint rank analysis would be applicable to these endpoints as well.

Results

A total of 177 subjects were screened for study participation and of these, 137 were randomized 2:1, with 89 subjects receiving treatment with AMX0035 and 48 subjects receiving placebo. Of the 137 subjects, 105 (76.6%) completed the 24-week double-blind study, with only 97 of them completing the study on drug. There were 8 subjects (7 on drug and 1 on placebo) who completed the 24-week period but had discontinued study medication earlier. The discontinuations were balanced across the group with 10 (20.8%) and 22 (24.7%) of the placebo and AMX0035 groups discontinuing early, respectively. The mITT population includes all patients who received drug and had post-baseline ALSFRS-R evaluations, which excludes 2 patients in the treatment arm who received drug and discontinued early prior to the initial post-baseline assessment. Both patients died shortly after discontinuation of treatment and are included in the ITT population.

The below figure details the disposition of the patients in the study:

Figure 1 Subject Disposition in Study AMX3500



Note: Death = death or death equivalent (includes tracheostomy or PAV). Some deaths were recorded after patient withdrawal from trial and are not accounted in reason for discontinuation.

Source: Figure 3, CSR Study AMX3500

There were a large number of treatment discontinuations in the study. Most patients discontinued secondary to "participant decision", some of which were also related to adverse events.

As indicated above, the active drug contains a bitter taste and causes transient gastrointestinal symptoms (i.e., diarrhea, abdominal pain), which were reported most frequently in the first three weeks after initiation. Although bittering agent was added to mask the placebo in the double-blind treatment period, there were still a number of patients who discontinued early in

the study (20% in the first 12 weeks), potentially due to the bitter taste and/or the GI symptoms. Diarrhea and bitter taste were described in the informed consent as possible adverse reactions with AMX0035. This had the potential to alert patients to these symptoms and could have led to functional unblinding.

The following table (Table 1) details the subjects that died during the study.

Table 1 Details of Subjects that Died During Study AMX3500

Subject ID (b) (6)	Treatment	Study Discontinuation By subject	Withdrawal day	Death day
AMX3500	AMX0035	Disease progression	77	86
AMX3500	AMX0035			145
AMX3500	AMX0035			153
AMX3500	AMX0035	Adverse Event	33	69
AMX3500	AMX0035			22
AMX3500	Placebo	Disease progression	27	29
AMX3500	Placebo			152

5 of these patients were on either Riluzole or edaravone

*not included in mITT population because of no post-baseline efficacy assessment

Source: Dr. Tandon's clinical review

There were also a high number of patients with missing 24-week ALSFRS-R data. In the placebo group, 46/48 survived the double-blind phase and 8/46 (17.4%) had missing week 24 ALSFRS-R data. In the AMX0035 group, 84/89 survived the double-blind phase and 15/84 (17.9%) had missing week 24 ALSFRS-R data.

Dr. Massie also describes in detail a problem with implementation of randomization early in the trial, in which the first 17 patients were apparently assigned to drug and the next 9 were all assigned to placebo due to a reported drug production/shipping problem. The unblinded statistician on the DSMB detected the issue and worked with the drug distributor to correct the problem and restore the 2:1 allocation ratio. The implications of the randomization error are discussed in detail in the results section of Dr. Massie's review.

There were no baseline demographic differences between the AMX0035 and placebo arm populations. Although baseline disease characteristics were generally similar for participants assigned to AMX0035 and placebo, there were a few minor imbalances that could potentially influence study outcomes. ATLIS scores were better at baseline in the AMX0035 treatment arm compared to placebo and could have favored the treatment group. There were imbalances in baseline disease characteristics that could have favored placebo, including more patients with limb-onset ALS in the placebo arm, and more bulbar-onset ALS patients in the treatment arm. As patients with bulbar onset ALS tend to have faster rates of disease progression than limb-onset ALS patients, this could lead to the potential for faster disease progression in the treatment group. There were no noted clinically significant differences between treatment groups in baseline ALSFRS-R, SVC% predicted, or time since onset of diagnosis and symptoms. Without further information on the specific genetic mutations, the impact of baseline differences in family history are unclear.

There were small differences noted in the del-FS, or the pre-study slope of ALSFRS-R, which may have some prognostic implications for in-trial progression rate. The small difference noted in the baseline rate of decline (0.953 in the treatment arm vs. 0.926 in the placebo arm) is unlikely to be clinically meaningful. However, as with any small study, the minor imbalances noted above indicate the potential for more differences, both known and unknown, between the arms that may account for differences in prognosis between the treatment arms.

Finally, there was a higher baseline use of concomitant riluzole and/or edaravone in the placebo group (50% edaravone and 77.1% riluzole use in placebo arm vs. 25.3% edaravone and 67.8% riluzole use in treatment arm). There was a lack of stratification based on concomitant use of these FDA-approved medications. Given that riluzole doses were required to be stable for 30 days prior to study entry and there was no significant imbalance in the ALSFRS-R or rate of decline at baseline, it is unlikely that the noted imbalance in concomitant medication use at baseline would have an impact on disease progression throughout the study. However, edaravone was approved after the study was initiated, and patients were allowed to start edaravone during the study. An imbalance occurred in the number of patients in each arm initiating new treatment with edaravone during the study. There was a higher proportion of patients starting edaravone or riluzole post-baseline in the AMX0035 arm (14/89, 15.7%) compared to placebo arm (2/48, 4.2%). It is possible that baseline imbalances in background ALS therapy may have inadvertently led to a higher incidence of initiation of riluzole or edaravone post-baseline in the treatment arm. This post-baseline starting of ALS medications more in the drug arm is a potential confounder for the primary analysis, as ALSFRS-R assessments after starting concomitant ALS medications were not censored in the primary analysis.

Primary Endpoint

The Applicant met its prespecified primary endpoint, demonstrating a statistically significant ($p = 0.034$) slowing of disease progression as measured by the ALSFRS-R total score compared to placebo, at the end of the 24-week, randomized, controlled phase of the study. The estimated least squares (LS) mean ALSFRS-R total score was 2.32 points higher at Week 24 compared to placebo. The primary prespecified model was a shared baseline, linear, mixed effects model, as noted in Table 2.

Table 2 ALSFRS-R Total Score at Week 24 - mITT

	Estimate (SE)				
	AMX0035+SOC (N=87)	Placebo+SOC (N=48)	Estimated Difference (SE)	95% CI	p-value
ALSFRS-R Total Score					
Week 24	29.06 (0.781)	26.73 (0.975)	2.32 (1.094)	0.18, 4.47	0.0340

Abbreviations: ALSFRS-R = ALS Functional Rating Scale – Revised; CI = confidence interval; ITT = intention to treat; mITT = modified intent to treat; SE = standard error; SOC = standard of care.

Source: Table 14.2.1.3 Part 1 Main CSR

Although the analysis method was prespecified, there are questions about the statistical robustness of the results. The primary analysis result uses a slope analysis, which assumes linearity of ALSFRS-R over time. However, linearity over time is not established for the ALSFRS-R in patients with ALS and exploratory analyses raise questions about the validity of the linearity assumption. As noted above, if any quadratic terms for time were significant ($p < 0.10$), a quadratic model was to be used for the primary analysis instead of the linear model. Dr. Massie notes that there were no significant quadratic effects for time for the prespecified quadratic model ($p = 0.1016$), which supports use of the linear model, although it was very close to the significance cut-off value. Although reliance on the primary slope analysis was supported, the Applicant chose to conduct a back-up quadratic model analysis, which differed from the quadratic model specified in the event of non-linearity as described in Table 13 in Dr. Massie's review.

There are limitations to the primary analysis. This analysis was conducted in the mITT population, which excludes two deaths in patients who were randomized to drug but did not have any post-baseline ALSFRS-R measurements, which could lead to bias in the analysis. There was considerable missing data, as 17-18% of patients on drug were alive but had missing ALSFRS-R total score values at Week 24. The analysis relies on unverifiable missing data assumptions.

This model does not incorporate deaths in the primary analysis. Functional endpoints can be confounded by loss of data because of patient deaths, which is why the Division typically recommends an analysis method that combines survival and function in a single overall measure in ALS, such as the joint rank test. There were seven deaths in the study, which makes a joint rank analysis important, as the occurrence of death creates functional data that are missing not at random, or the anomalous result that death appears to be a better outcome than a lower ALSFRS-R score.

The Applicant also performed a change from baseline analysis in the mITT population, which resulted in a mean change from baseline least squares mean difference after 24 weeks was 2.92, $p = 0.01$. This analysis was not prespecified and still relies on a questionable linearity of

ALSFRS-R over time assumption because it prescribes a slope model for the functional form of the trend in ALSFRS-R changes over time. In a sensitivity analysis, Dr. Massie used a more common model frequently used in FDA review work, a Mean-By-Visit MMRM model of change from baseline which does not rely on a linearity assumption. This model also does not incorporate deaths in the analysis. This analysis did not show a nominally significant treatment difference in ALSFRS-R at Week 24 in the mITT population, with an estimated difference of 1.86 (SE 1.04), p = 0.0749.

Dr. Massie also used the primary analysis to check for the impact of individual sites, and found more influential sites, some of which affected the significance of the treatment difference. In other words, the removal of a single site from the study renders the primary analysis treatment effect no longer statistically significant [e.g., without site 701 (n = 13): slope difference = -0.079; SE=0.049; p=0.1027 with a corresponding Week 24 mean difference of 1.90]. This particular site had a within site estimated treatment difference more than twice as large as the overall estimate (5.75 vs 2.32). Dr. Massie also notes that this same site had a substantive quantitative difference for time to death in the OLE phase, with a within-site hazard ratio (0.23, drug over placebo) more than two times smaller than the overall hazard ratio (0.64).

The Applicant conducted a post hoc joint rank analysis, performed by ranking subjects first by time to death then by change from baseline in ALSFRS-R, as recommended on several occasions by our statistical team. The results of this analysis were statistically significant (Table 3) and were consistent with the results of the pre-specified primary efficacy analysis.

Table 3 Joint Rank Analysis ALSFRS-R Total Score and Death, mITT population (N = 135)

	AMX0035+SOC Rank Estimate	**Placebo+SOC Rank Estimate**	**Difference**	**p-value**
Joint Rank Analysis	72.93 (3.92)	59.07 (5.29)	13.85 (6.61)	0.0381

Source: AMX3500 CSR Table 11, 14.2.29.2

It is noted that the joint rank analysis performed above is in the mITT population. The joint rank analysis performed by the Applicant in the ITT population gives a p = 0.056.

According to Dr. Massie's review, the Applicant did not use an appropriate missing data handling method in the joint rank analysis. The Applicant used last observation carried forward (LOCF) which is not appropriate in a degenerative disease such as ALS because ALSFRS-R scores tend to worsen over time in ALS. LOCF imputes no change from the last observed time to the final time.

Dr. Massie performed a joint rank analysis with a preferred method of handling missing data of ALSFRS-R and death, using multiple imputation based on a missing-at-random assumption. This multiple imputation regression model included covariates of age and pre-randomization ALSFRS-R slope and each assessment prior to the missing ALSFRS-R assessment. This joint rank analysis method has a p= 0.063 for the mITT population. If the ITT population is used,

which would include the 2 deaths in the treatment arm who were dosed but had no post-baseline ALSFRS-R assessments, the joint rank analysis has a p = 0.079.

Secondary Endpoint

None of the secondary endpoints were statistically significant. The Total ATLIS, a previously described method of strength measurement, showed a non-significant difference of 2.8 percentage points (p = 0.1129). The Applicant did additional exploratory analyses of the individual components of the ATLIS, which showed a nominally significant treatment difference of 4.3 percentage points (p = 0.0420) in Upper ATLIS, and non-significant difference of 2.1 percentage points (p = 0.3424) in Lower ATLIS. These analyses used the same slope model as the primary analysis and includes similar concerns regarding the linearity assumption. There was more missing data at Week 24 for ATLIS than for ALSFRS-R. Deaths are similarly ignored in this analysis, which may also result in bias.

The Applicant also included a secondary endpoint analysis of the plasma biomarker, pNF-H. There were no significant differences between AMX0035 and placebo groups for rate of change from baseline in plasma levels of pNF-H (3.58 pg/nL per month for AMX0035 and -2.35 pg/mL per month for placebo, p = 0.2601). pNF-H is a marker of neuronal axonal injury and neurodegeneration. There was not a significant difference between the rate of change from baseline in plasma levels of pNF-H and appears to improve more in the placebo arm.

The final secondary endpoint was a measure of Slow Vital Capacity (SVC), a measure of breathing capacity. At Week 24, patients in the AMX0035 treatment arm were observed to have 66.2% of normal breathing capacity compared to those in the placebo arm who had a 61.1% of normal breathing capacity (percent predicted). This numerical result was not statistically significant, p = 0.076).

Composite Survival Analysis

The Applicant also conducted a composite survival endpoint as a prespecified secondary endpoint in the 24-week double-blind period. Single and combined survival analyses over the double-blind period were performed using the Cox proportional hazards model with covariates of del-FS and age at baseline for the outcomes of death, death equivalent, and hospitalization (death equivalent was defined as time to death, permanent assisted ventilation (PAV), or tracheostomy).

Note that time to PAV only and tracheostomy only were not analyzed as there was only one event of each in a singular placebo patient (both occurred in the same placebo subject). As shown in the Table below, while some of the analyses directionally favored AMX0035 and while the numbers of events (particularly deaths) were small, none of the analyses were statistically significant.

Table 4 Double-blind Phase Survival Analysis at 24 weeks

Categorical Outcome	Estimated Percentage of Event (SE)		Hazard Ratio: Active vs. Placebo (95% CI)	P-Value
	AMX0035	Placebo		
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

Source: Table 14 AMX3500 CSR

Open-Label Extension Study

After completion of the double-blind treatment period, patients were eligible to enroll in an open-label extension study (AMX3500OLE), in which all patients received active treatment for up to 132 weeks. The primary objective of the study was to assess the long-term safety of oral administration of AMX0035 twice daily. The OLE study also had a number of secondary objectives to measure efficacy at the end of 24 weeks in the OLE (48 weeks overall since randomization). In addition to the OLE (with analyses in the OLE limited to the patients that enrolled in the OLE), a vital status search was conducted to gather information on when a subject had died through a professional firm, Omnitrace. The vital status was conducted using cutoff dates of February 29, 2020, July 20, 2020, and March 1, 2021, to determine survival rates at each date.

Participating in the OLE study was not mandatory, and participation in the OLE may have been affected by outcomes in the double-blind phase of the study; therefore, these treatment groups may not be comparable in important demographics or disease characteristics. There were 97 patients who completed the AMX3500 double-blind main study on study medication that were eligible for enrollment into the OLE. Of these, a total of 90 patients enrolled in the OLE, 34 patients originally randomized to placebo and 56 who had been originally randomized to active drug. Only 2 patients reached the final 132- week visit of AMX3500OLE on treatment without death or discontinuation. The most common reasons for discontinuation were participant decision and death.

Of the 34 patients initially randomized to placebo who enrolled in the OLE, only 19 patients remained at 48 weeks. Of the 56 patients initially randomized to AMX0035 who enrolled in the OLE, 36 patients had week 48 data on the ALSFRS-R.

Given the significant number of patients who did not enroll in the OLE and the many patients who dropped out during the OLE study, it is difficult to interpret any of the exploratory functional endpoints that were assessed at 48 weeks, including the analyses of rate of progression of ALSFRS-R, ATLIS, or SVC. The Applicant reports an extended slope treatment difference of 4.23 points in total ALSFRS-R at Week 48 between those patients

originally randomized to AMX0035 compared to those originally randomized to placebo. The extended slope analysis is uninterpretable given the significant patient discontinuations during the first 24 weeks of the OLE leading to missing data, the statistical concerns of the linearity assumption, and the ignoring of the 23 deaths that had occurred by this point in the study, contributing to additional bias. Similar analyses of ATLIS and SVC also have limited interpretability and even fewer subjects with available data on these endpoints at the Week 48 time point. There are also concerns regarding potential for functional unblinding in patients who had received placebo in the double-blind phase and then experienced the bitter taste and acute gastrointestinal symptoms when switching to active drug.

The Applicant conducted a composite analysis of overall survival at Week 48 and at Week 132. The initial planned analysis was a composite of time to death, death equivalent, hospitalization, or tracheostomy. This composite survival analysis is difficult to interpret given the large number of dropouts during the OLE study. There are additional limitations of using tracheostomy and hospitalizations as an efficacy outcome measure, as described above. The survival data were largely collected through vital status searches for death, including death records, obituaries, etc. Death equivalent data was not systematically collected in the OLE study; therefore, there is limited information regarding clinical care after discontinuation from the study, including information on tracheostomy, hospitalizations, and/or additional experimental treatments that could potentially affect survival. The protocol-specified composite survival endpoint is very difficult to reliably interpret.

The Applicant conducted a post hoc exploratory analysis of time to death alone at Week 132, as determined by vital status search data. Vital status was collected on 136 of the originally randomized 137 patients. The Applicant reports a nominally significant overall survival benefit (HR = 0.64) in the ITT population, with longer median overall survival (23.5 months) in patients initially randomized to AMX0035 than the median overall survival of patients initially randomized to placebo (18.7 months) for a difference of 4.8 months in survival between arms. The apparent survival benefit has a nominal p-value of 0.0475. Dr. Massie notes the supplementary SAP specified a likelihood ratio test for survival which gives a slightly larger p value = 0.0518, and points out that the focus on this endpoint, and the submission of a new supplementary OLE SAP for survival, occurred after preliminary survival analyses. Therefore, there are limitations to interpreting this exploratory endpoint, including that the original OLE protocol and SAP did not include an analysis on time to death alone. Some alternative analyses of time to death provide less convincing results.

Major Amendment Submission

The Applicant provided several additional analyses intended to serve as potential sources of confirmatory evidence to support the findings in Study AMX3500.

The first additional analysis was an individual responder analysis that uses participants as their own controls and compares the response rate in the AMX0035 group to the response rate in the placebo group. The Applicant proposed that this post hoc analysis provided confirmatory evidence of an individual effect of the treatment, less affected by potential baseline differences between the treatment arms. The Applicant defined response as patients whose actual rate of

change in the ALSFRS-R at Week 18 was greater than or equal to their own pre-baseline progression rate in ALSFRS-R (Del-FS). The Applicant reports that an individual response was observed in a greater proportion of patients receiving AMX0035 (41%) vs placebo (19%), odds ratio, 3.06, p = 0.0076 at Week 18 of the 24-week study. However, this post hoc analysis is highly correlated with the primary analysis, includes the same data as the primary analysis, and cannot be considered independent confirmatory evidence. It is also unclear why Week 18 was chosen for this analysis.

The Applicant also provided additional survival analyses of the data from Study AMX3500 and AMX3500OLE. The Applicant notes that because the majority of placebo patients crossed over and entered the OLE and received AMX0035, the ITT survival analysis reported above does not account for treatment crossover and may underestimate the survival benefit of the drug. The Applicant conducted additional post hoc sensitivity analyses to address this potential crossover effect.

The Applicant compared the median overall survival (mOS) in the ITT AMX0035 treatment arm (N = 89, mOS = 23.5 months) to the predicted natural history of patients with ALS from both the ENCALS survival predication model and the PRO-ACT database. The ENCALS survival prediction model published in 2018 was developed to predict survival of patients with ALS based on 16 different baseline characteristics. The model used over 15,000 patient records across the European Union to predict survival. The Applicant's analysis shows a prolongation of median overall survival compared to the ENCALS model-predicted median survival of 13.6 months, p < 0.0001, for a predicted 9.9-month treatment benefit for patients receiving AMX0035.

The second post hoc survival analysis, which was presented in the Applicant's briefing document for the September 7 Advisory Committee meeting, compared survival of the ITT AMX0035 treated patients to a subset of patients of the Pooled Resource Open-Access ALS Clinical Trial (PRO-ACT) database. PRO-ACT is a publicly available database of longitudinal ALS clinical trial data on over 11,000 patients from 23 completed ALS trials. The analysis demonstrated an 11-month median survival benefit for patients randomized to AMX0035 (mOS = 23.5 months) as compared to a propensity score-matched population in the PRO-ACT group (mOS = 12.5 months predicted), HR = 0.48, p = 0.00017.

Dr. Massie notes a number of limitations for these analyses because the use of external controls is subject to potential confounding due to differences in the AMX0035-treated patients and the external controls in unmeasured prognostic factors, prognostic factors not accurately measured or captured in the natural history model, and/or supportive care and interventions. Patients in the natural history database were not in a clinical trial, which could lead to differences in standard of care between the groups. Additionally, these post hoc analyses were not prespecified and there are multiplicity issues.

Additionally, the Applicant conducted a Rank Preserving Structural Failure Time Model (RPSFTM) to account for treatment crossover. This approach attempts to estimate the survival benefit in placebo patients, had crossover (treatment switching) not occurred. This approach estimates a median survival benefit for AMX0035 of 9.7 months. The estimated hazard ratio

was 0.42, compared to the original hazard ratio of 0.64. However, Dr. Massie notes that this post hoc analysis is based on strong, untestable assumptions. Because switching of placebo patients to AMX0035 in the OLE phase of the study was mandated by study design, it reduces the ability to answer the question of a possible survival benefit of the original AMX0035 arm to a hypothetical, unswitched placebo arm. Because most eligible placebo patients switched to AMX0035 by design, the ineligible placebo group that did not complete the double-blind period is not a random subset.

Overall, there are limitations to these additional analyses of previously submitted Study AMX3500 and AMX3500OLE data, as noted above. Despite the limitations, the new analyses are generally consistent with the prior survival analysis that demonstrated a nominally significant benefit on survival.

Finally, the Applicant submitted mechanistic evidence for an impact on neurodegeneration and neuroinflammation in the CSF in another neurodegenerative disease population. A recent Phase 2 study in patients with clinical Alzheimer's disease or mild cognitive impairment (PEGASUS) enrolled 95 patients, randomized 1:1 to receive either AMX0035 or placebo twice daily for 24 weeks. The primary outcome was safety and tolerability, and the study did not demonstrate efficacy on the prespecified exploratory efficacy outcomes. The study also assessed a panel of 18 CSF biomarkers on an exploratory basis. Select CSF biomarkers showed a nominally significant improvement over placebo, including total tau, phosphorylated tau, neurogranin, YKL-40, and the $A\beta_{42}/A\beta_{40}$ ratio. Several other biomarkers showed no change compared to placebo. Neurofilament light chain (NfL), a frequently measured biomarker, did not show a nominally significant change during the 24-week study. There is no clear or consistent relationship between the biomarkers that had nominally significant findings and those that did not to suggest a treatment benefit on nervous system inflammation or neuronal degeneration. The underlying pathophysiology of AD and ALS are also different. It is unclear if these findings, even if demonstrated to potentially indicate benefit in AD, would be generalizable to patients with ALS. The 18 biomarkers were assessed as exploratory biomarkers and were not adjusted for multiplicity; the interpretation of the p-values is limited. The biomarker data are not clear evidence of a CNS effect or a potential for clinical benefit in patients with ALS.

Efficacy Conclusions

The Applicant has submitted data intended to support the approval of AMX0035 for the treatment of ALS based on a single adequate and well-controlled investigation and confirmatory evidence. The Applicant has conducted an adequate and well-controlled study (Study AMX3500) of AMX0035 in ALS that demonstrated a statistically significant benefit using a prespecified analysis on an acceptable functional efficacy endpoint of ALSFRS-R (2.32-point difference, $p = 0.034$). Although the secondary endpoints generally trended in a positive direction, no results reached statistical significance. No benefit in survival was observed at the end of this 24-week study.

There are statistical concerns regarding the analysis method that relies on an assumption of linearity of the ALSFRS-R and does not account for deaths during the study, which decrease

the overall persuasiveness of the study. There are differences of opinion between the Applicant and Dr. Massie regarding the most appropriate handling of missing data and the linearity assumptions; the results of various post hoc and sensitivity analyses performed by Applicant and Dr. Massie give p-values ranging from p = 0.03 to 0.07. Overall, there is a consistency across the sensitivity analyses, despite small differences in the p-values, to suggest a true treatment benefit in patients with ALS that results in a slower rate of reduction in the ALSFRS-R.

Additional concerns were identified regarding a randomization error that occurred early in the study, initiation of edaravone and riluzole in some patients during the study, and the potential for bias due to both identified and unknown imbalances in baseline disease characteristics. Although not clearly observed during the study, a potential source of bias from functional unblinding due to bitter taste of the drug or adverse events was identified during the review. Although these are potential sources of bias, it is unclear how or if these issues impacted clinical outcomes.

Given these limitations, Study AMX3500 is unable to serve as a single study capable of independently providing substantial evidence of effectiveness, without substantiation.

The Applicant also submitted analyses conducted in patients who continued in the open-label extension study, as well as a survival analysis based on the vital status of 136 of 137 who were initially enrolled in Study AMX3500, for consideration as confirmatory evidence. The Applicant reports a nominally significant overall survival benefit (HR = 0.64) in the ITT population, with longer median overall survival (23.5 months) in patients initially randomized to AMX0035 than the median overall survival of patients initially randomized to placebo (18.7 months) for a difference of 4.8 months in survival between arms. The apparent survival benefit has a nominal p-value of 0.0475. The analyses conducted on clinical outcome assessments are generally not interpretable due to the large number of dropouts in the OLE and the lack of a control. Similarly, these same limitations apply to the interpretation of the composite survival analyses which included hospitalizations and death equivalents (e.g., tracheostomy).

The Division considered the data from Study AMX3500 and the survival analysis to be promising but noted the limitations in the data. Therefore, the Peripheral and Central Nervous System Advisory Committee (PCNS) was convened on March 30, 2022, to advise the Agency on the adequacy of the data to establish a conclusion of effectiveness for AMX0035. The Committee voted 6-4 that the available data were not sufficient to establish a conclusion that AMX0035 is effective in the treatment of ALS.

Following the advisory committee meeting, the Applicant submitted several new analyses to the NDA that it felt were capable of potentially serving as confirmatory evidence. This included additional analyses of the survival data, as well as an individual responder analysis of the Study AMX3500 data, and biomarker findings from a recently completed study in Alzheimer’s disease. The submission constituted a major amendment to the application, which extended the review timeline by three months, to September 29, 2022, to allow for adequate consideration of the new information.

As part of that review, the PCNS Advisory Committee was reconvened on September 7, 2022, to discuss the additional evidence that was submitted by the Applicant to provide confirmatory evidence. The Division also provided additional context regarding the regulatory framework concerning the exercise of regulatory flexibility in applying the applicable statutory standards to the review of an application for a drug intended to treat a serious and life-threatening disease with significant unmet medical need. See Section 9 for additional details. The Committee voted 7-2 (one member absent) in favor of approval.

The Agency must now consider if the available data are adequate to provide substantial evidence of effectiveness. There are notable limitations to the interpretability of the data submitted by the Applicant. However, the regulations allow for FDA to exercise regulatory flexibility in applying the statutory standards for establishing the safety and effectiveness of new therapies intended to treat persons with life-threatening and severely debilitating illnesses, especially where no satisfactory alternative therapy exists. For example, FDA's regulation at 21 CFR 312.80 notes, "while the statutory standards of safety and effectiveness apply to all drugs, the many kinds of drugs that are subject to them, and the wide range of uses for those drugs, demand flexibility in applying the standards. 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." This approach is reiterated in FDA's guidance for industry, *ALS: Developing Drugs for Treatment* (September 2019), which states: "The statutory standards for effectiveness apply to drugs for ALS just as the standards apply for all other drugs. However, FDA has long stressed the appropriateness of exercising regulatory flexibility in applying the statutory standards to drugs for serious diseases with unmet medical needs, while preserving appropriate assurance of safety and effectiveness."

The 2019 FDA draft guidance, *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* further states, "In all cases, FDA must reach the conclusion that there is substantial evidence of effectiveness to approve a drug; however, the degree of certainty supporting such a conclusion may differ, depending on clinical circumstances (e.g., severity and rarity of the disease and unmet medical need)." The guidance also outlines the general requirements for determination of substantial evidence of effectiveness, the situations in which a single adequate and well-controlled study could adequately support an effectiveness claim, and cites the ability of the Agency to consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence" to constitute substantial evidence of effectiveness.

ALS is clearly such a severely debilitating and life-threatening disease with substantial unmet need, and the exercise of regulatory flexibility in applying our statutory standards is appropriate.

In this situation, there is a single study that has won on the primary endpoint. Although it is a positive study reaching statistical significance on the prespecified primary endpoint, there are limitations that impact the robustness of conclusions from this study such that it does not provide a highly persuasive result. In such a situation, the single study can be supported by confirmatory evidence to reach a conclusion that there is substantial evidence of effectiveness.

There is an observed nominally significant longer median overall survival in the post hoc analysis based on 136 of 137 patients originally randomized in Study AMX3500, which was a comparison of vital status in the patients originally randomized to AMX0035 to those originally randomized to placebo. There are also limitations to the survival analysis that limit the persuasiveness of the findings; however, the observed survival benefit, in addition to the 24-week change on the ALSFRS-R, remains. Additional analyses of survival submitted in the major amendment, including a comparison of overall survival to natural history databases, consistently demonstrate an observed survival benefit over natural history and/or predicted survival, which taken together tend to strengthen the survival findings, recognizing the limitations of using external controls to draw robust conclusions.

The choice of outcome assessment (ALSFRS-R) used in the development program was appropriate and captures clinically meaningful aspects of function for patients living with ALS. It is expected with the progressive nature of ALS to see some correlation between outcome assessments. The ALSFRS-R and survival capture distinct concepts, and so the survival analysisis not simply a recapitulation of the results for the primary endpoint. Although the long-term survival benefit is observed in the same population that participated in the original placebo-controlled study, it is an important finding that supports the use of the observed survival benefit as confirmatory evidence.

Therefore, we conclude that the single, positive study, along with confirmatory evidence from the observed benefit on long-term survival, together demonstrate substantial evidence of effectiveness to support approval of AMX0035 for the treatment of ALS.

It also needs to be noted that AMX0035 is a fixed-combination drug product consisting of two drugs and is subject to the requirements under 21 CFR 300.50. This regulation states that two or more drugs may be combined when each component makes a contribution to the claimed effects of the product. The Applicant has submitted a conceptual basis for the combination of sodium phenylbutyrate and taurursodiol based on the role of phenylbutyrate as a pan-histone deacetylase (HDAC) inhibitor that ameliorates endoplasmic reticulum stress through upregulation of chaperone proteins, and the potential for taurursodiol to ameliorate mitochondrial stress by reducing mitochondrial permeability and increasing the apoptotic threshold of the cell. Although the Applicant has not performed additional clinical studies to assess these claims, applying an appropriately high degree of regulatory flexibility in the setting of the severity and unmet need in ALS, and given the functional benefits observed in the AMX3500 trial and the observed survival benefit in long-term follow-up, this mechanistic argument provides a rationale that is sufficient in this case to address considerations described in 21 CFR 300.50.

8. Safety

Dr. Veneeta Tandon performed the safety review for this submission.

Dr. Tandon's safety review is based on analysis of data from the controlled phase of study AMX3500 (CENTAUR) and the open-label extension study AMX3500OLE. The safety population consisted of all randomized patients who received at least 1 dose of AMX0035. The controlled data from Study AMX3500 was used for the calculation of the frequency of adverse events. All datasets were reviewed for adverse events, serious adverse events, deaths, and laboratory value assessments. Overall, the quality and format of the safety data was adequate for review.

Overall Exposures

The randomized, controlled phase of Study AMX3500 included 89 patients randomized to AMX0035 who were treated for a median of 23.9 weeks (mean 19.7, SD 7.89) and 48 patients randomized to placebo treated for a median 23.9 weeks (mean 21.5, SD 5.82). There were 90 patients total who entered the OLE, with median exposure of 33 weeks in the patients who were previously randomized to placebo (PA group) and median exposure of 44 weeks in patients previously randomized to AMX0035 (AA group). A total of 27 patients were treated for > 48 weeks in either treatment arm. The overall safety database was determined to be adequate given the prevalence and severity of ALS.

Deaths and Serious Adverse Events

There were similar numbers of deaths and serious adverse events (SAEs) in the treatment arm and placebo in the controlled phase of Study AMX3500, with a total of 5 (5.6%) reported deaths in the treatment arm and 2 (4.2%) deaths in the placebo arm. There were 11 SAEs reported in patients receiving AMX0035 (12.4%), with a slightly higher percentage of SAEs (16.7%) in the placebo arm. The majority of deaths appeared to be largely related to ALS progression and not secondary to treatment. A single patient died from diverticular perforation, which could not be ruled out as potentially related to use of the medication; however, that patient only received 5 doses of the drug, so it seemed less likely to be drug related.

The SAEs were also mainly attributed to ALS disease progression. The only SAEs occurring in more than 1 patient per arm included respiratory failure and pneumonia which are common causes of death in ALS. There were 2 SAEs of nephrolithiasis that occurred during the study in 1 patient on AMX0035 and 1 patient on placebo. The patient on treatment (Patient (b) (6)) developed bilateral kidney stones after treatment with AMX0035 for 1 week. This patient had a history of nephrolithiasis, and it was unclear if the stones could have developed in the one week since treatment initiation. However, Dr. Tandon did note that "crystal urine present" was also reported in 4 patients in the drug group only, which may be a drug-related adverse event (AE).

There were additional 15 deaths that were reported on treatment during the OLE study. The causes of death were respiratory failure (10 patients), disease progression (2 patients), and 1 patient each for pneumonia aspiration, amyotrophic lateral sclerosis, and cardiac arrest.

Discontinuations due to Adverse Events

There was a significantly higher percentage of patients who discontinued treatment due to an AE in the AMX0035 group (20.2%) compared to the placebo group (10.4%). The most

common AEs leading to discontinuation were abdominal pain, diarrhea, and nausea. It is also noted that in the OLE, 44% of the patients transitioning from placebo to treatment (PA) discontinued due to AEs, compared to only 19.6% who continued on treatment (AA group). The AEs that led to discontinuation in the OLE that occurred in ≥ 2 patients were respiratory failure, nausea, vomiting, and diarrhea.

Common Treatment Emergent Adverse Events (TEAEs)

The most common treatment emergent adverse events (TEAEs) that occurred in ≥ 5% of AMX0035-treated patients and greater than placebo are shown below in Table 5. This table was adapted from Dr. Tandon's common TEAE review showing all TEAEs in ≥ 2% of patients treated with AMX0035.

Table 5 TEAEs in ≥5% of Study AMX3500 Treated Subjects and >1% Difference Compared to Placebo in Controlled Phase (Safety Population)

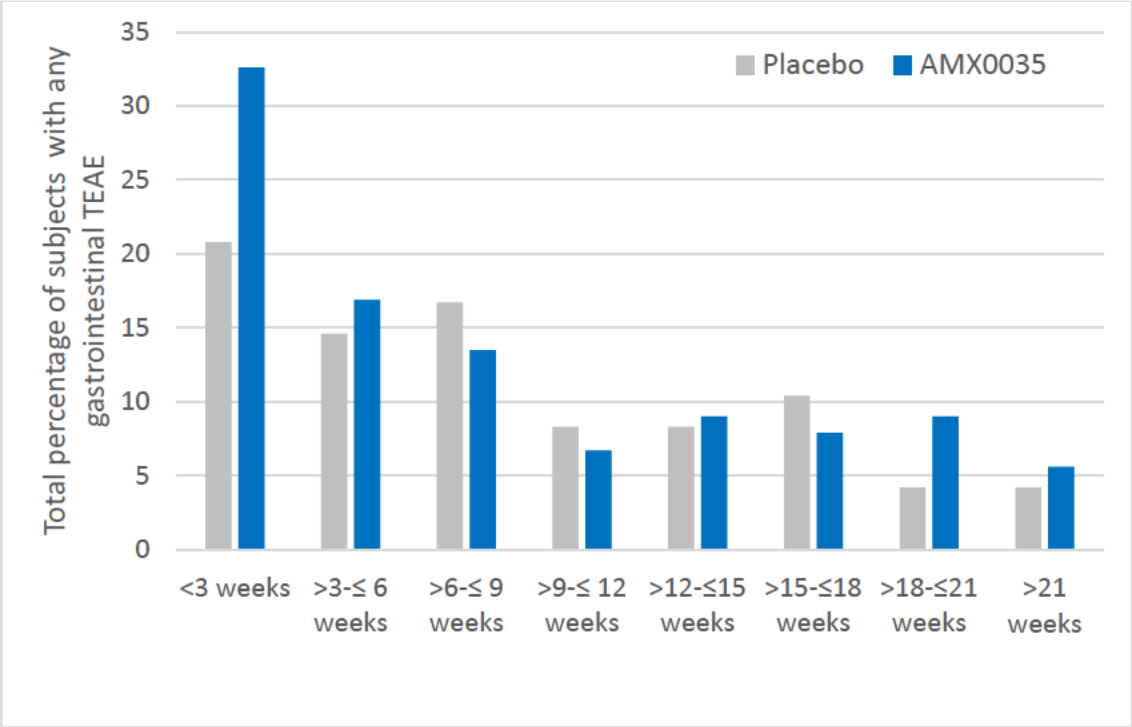
Preferred Terms	Placebo (N = 48)	AMX0035 (N = 89)
Total Subjects with any Adverse Events	46 (95.8%)	86 (96.6%)
Diarrhea	9 (18.8%)	22 (24.7%)
Abdominal pain	6 (12.5%)	19 (21.3%)
Nausea	6 (12.5%)	16 (18.0%)
Respiratory tract infection	5 (10.4%)	16 (18.0%)
Fatigue	3 (6.3%)	11 (12.4%)
Dyspnea	4 (8.3%)	10 (11.2%)
Salivary hypersecretion	1 (2.1%)	10 (11.2%)
Dizziness	2 (4.2%)	9 (10.1%)
Decreased appetite	2 (4.2%)	7 (7.9%)
Dysarthria	2 (4.2%)	7 (7.9%)
Proteinuria	2 (4.2%)	6 (6.7%)
Arthralgia	2 (4.2%)	5 (5.6%)
Weight decreased	1 (2. 1%)	5 (5.6%)

Adapted from Dr. Tandon's Clinical Review

Dr. Tandon notes that the table differs from the table proposed by the Applicant for labeling because the Applicant proposed just to include drug-related TEAEs in the proposed label and excluded TEAEs that were felt to be related to (b) (4). The TEAEs that occurred in greater than 10% of patients in the AMX0035 arm and greater than 1% more than placebo were diarrhea, muscular weakness, nausea, viral respiratory tract infection, salivary hypersecretion, dyspnea, dizziness, abdominal pain, and fatigue. Many of the additional common TEAEs reported above are symptoms consistent with ALS progression. The higher percentage of patients with bulbar-onset ALS in the AMX0035 group (30%) compared to placebo (21%) may be related to the increased incidence of salivary hypersecretion noted in the AMX0035-treated patients.

Dr. Tandon also noted that gastrointestinal TEAEs were significantly more common in patients receiving AMX0035 than in patients receiving placebo. This is a known side effect of TUDCA. All gastrointestinal TEAEs occurred in greater than 5% of patients throughout the study; however, gastrointestinal TEAS were most notable in the first three weeks of treatment as shown in Figure 2 below. The most common gastrointestinal TEAEs were diarrhea, abdominal pain, and nausea. The acute onset and transient nature of the GI symptoms raise concern for the potential for functional unblinding of patients during the study, as well as upon transition to the open-label phase of the study. GI adverse events were listed in the informed consent form, which may have alerted patients to the treatment they were receiving. In the first three weeks of the double-blind study, 32.6% of patients in the AMX0035 arm, and 20% of patients in the placebo arm reported GI adverse events.

Figure 2 Total percentage of patients with any gastrointestinal TEAE by study duration



Source: Dr. Tandon's Clinical Review

Laboratory Findings and Vital Signs

There were no clinically significant differences between the treatment arms in laboratory findings or vital signs.

Cardiac Events/QT

Refer to the Interdisciplinary Review Team for Cardiac Studies (IRT) for further discussion of cardiac safety. None of the patients in the study experienced QTcF > 450 msec with or without change from baseline > 60 msec, and none of the patients experienced a change in QTcF > 60 msec in any of the treatment groups. There were no large mean increases in the QTcF interval detected in the QT assessment at the therapeutic dose. However, as noted in the

IRT review, the team was unable to draw a conclusion of lack of an effect in the absence of a positive control, large exposure margin, or integrated nonclinical safety assessment. Therefore, Study AMX3500 was only acceptable to exclude a large mean increase in QTc interval (> 20 msec).

There was a numerically higher number of cardiac events in the AMX0035 group (7) compared to placebo (0). The difference was not felt to be clinically significant. There were 2 events of atrial fibrillation, 2 events of palpitations, 1 event of atrioventricular block, 1 event of left bundle branch block, and 1 event of tachycardia reported. Of the 2 events of atrial fibrillation, one occurred in the setting of respiratory arrest and cardiac resuscitation, and the other occurred in an elderly patient with other risk factors for atrial fibrillation. None of the cardiac events noted were felt to be of clinical importance or related to the study drug.

Adverse Events of Special Interest

Depression and suicidality were reviewed by Dr. Tandon as an adverse event of special interest (AESI). Depression was similar between treatment arms with 2 patients in the AMX0035 arm (2.2%) and one patient in the placebo arm (2.1%) reporting a TEAE of depression during the controlled phase of the study. There were high baseline number of patients reporting suicidal ideation in both treatment groups (16.9% in AMX0035 arm and 10.4% in the placebo arm). The percent of patients reporting suicidal ideation did not increase with treatment. There was no active suicidal ideation throughout the study. The data did not suggest that AMX0035 contributed to worsening of depression or suicidality.

The Applicant proposes to include [redacted (b) (4)]" in the "Warnings and Precautions" section of the prescribing information consistent with the approved sodium phenylbutyrate product, BUPHENYL. AMX0035 contains [redacted (b) (4)] mg of sodium. The Applicant proposes caution in use in patients with congestive heart failure, severe renal insufficiency, or other conditions associated with sodium retention with edema. Dr. Tandon analyzed the safety data for occurrence of edema or related preferred terms. The PT "peripheral edema" occurred in 3 patients on placebo (6.3%) and 5 patients on AMX0035 (5.6%), indicated no increased incidence of edema during the controlled study. However, it does appear that it could remain a concern in patients with underlying conditions that are associated with sodium retention. It is reasonable to include the proposed warning in labeling.

The Applicant also proposes to include "Enterohepatic circulation, pancreatic and intestinal disorders" in "Warnings and Precautions", recommending caution in use in patients with enterohepatic circulation disorders (e.g., frequent biliary colic, biliary infection), severe pancreatic disorders or intestinal disease which may alter the concentration of bile acids and affect taurursodiol levels. Pancreatic insufficiency or intestinal malabsorption may also reduce phenylbutyrate absorption. A similar warning is included in the RAVICTI label for an approved glycerol phenylbutyrate product, and appears acceptable to include. The risk appears to be potential worsening of diarrhea when administering bile acid to a patient who already has a disrupted enterohepatic circulation, and potential for decreased absorption of both taurursodiol and phenylbutyrate with certain underlying conditions, which may contribute to reduced efficacy of the drug. The precaution will be updated to advise caution and consultation with a specialist as needed.

The final AE of special interest was neurotoxicity, as Dr. Tandon indicates that published studies demonstrate high doses of sodium phenylbutyrate (> 400 mg/kg) or its major metabolite, phenylacetic acid (PAA), have been associated with CNS effects such as memory loss, sedation, and confusion when administered intravenously to cancer patients. Oral administration of sodium phenylbutyrate was also associated with fatigue, slurred speech, decreased concentration and confusion at doses of 9 to 45 g/kg/day. In healthy subjects administered glycerol phenylbutyrate (RAVICTI), doses of 13.2 g/day and 19.8 g/day demonstrated a dose-dependent increase in non-serious CNS adverse events. All of the doses mentioned above are higher than the amount in AMX0035 (3 g/sachet, up to 6 g/day). Dr. Tandon reviewed the Nervous System SOC for comparisons of TEAEs between treatment arms. The TEAEs that occurred more commonly in the AMX0035 group included dizziness, somnolence, and migraine. The other TEAEs that were more common in the AMX0035 group compared to placebo may be ALS-related, and it is unclear if the treatment caused worsening of any of these symptoms. Females had a higher incidence of dizziness than males, and Dr. Tandon notes they have higher concentrations of PAA, but the small numbers make it difficult to reach any firm conclusions.

Pregnancy
No pregnancies occurred during the study. A review of the literature suggests that pregnancies are rare in ALS, with just a few case reports over several decades. Current therapies are not changing the course of the disease. Therefore, although AMX0035 may be prescribed in women of childbearing potential, a pregnancy study will not be a post-marketing requirement.

Subgroup Analyses
There were no age-related differences in TEAEs identified (≤ 59 years of age or > 59 years of age). There were slightly higher incidences of dizziness, dysarthria, abdominal pain, nausea, and vomiting in females more than males. However, the small sample size makes it challenging to draw any conclusions about differences in the incidence of TEAEs in any of the demographic subgroups.

Safety Conclusions
Overall, AMX0035 appears generally well tolerated and safe. There were no major differences in fatal or serious adverse events between AMX0035 and placebo. Most of the adverse events were secondary to complications or manifestations of the underlying ALS. The common TEAEs belonged to the gastrointestinal SOC (including diarrhea, abdominal pain, nausea, and salivary hypersecretion). Other common TEAEs included dizziness, respiratory tract infection, fatigue, and dyspnea. The number of patients that discontinued treatment due to TEAEs were higher in the AMX0035 treatment group (20.2%) compared to the placebo group (10.2%) in the controlled phase of the study. These differences were largely due to higher incidences of diarrhea, abdominal pain, nausea, and dysgeusia in the AMX0035 arm.

9. Advisory Committee Meeting

This NDA was discussed at an Advisory Committee meeting of the PCNS Committee on March 30, 2022.

The question to the committee was:

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 amyotrophic lateral sclerosis (ALS)?

a. 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

The Committee vote: NO: 6 YES: 4 Abstain: 0

All members who voted expressed similar sentiments that the decision was difficult. Those who voted "Yes" admitted that it was a difficult decision and could have decided either way. Amongst the 4 members that voted "yes", one was a consumer representative who wanted the consumers' voice to be heard and another was the patient representative who believed that the Agency should exercise regulatory flexibility given the lack of material harm with AMX0035, but looked forward to additional stronger data from the ongoing study. One member who voted yes thought that to "establish a conclusion" on effectiveness (as stated in the voting question) was not quite the same bar as meeting substantial evidence of effectiveness. This member agreed with the Applicant's statistical analyses using a shared baseline linear random effects model and though there were not many deaths in the study to require additional analyses.

Those who voted "No" concluded that the data from Study AMX3500 did not meet the statutory and regulatory threshold for substantial evidence and persuasiveness. Some key considerations on voting "No" included: lack of persuasive evidence required for approval based on a single study based on concerns on trial conduct, sample size, treatment of missing data, and modest effect on primary endpoint with no support on secondary endpoints. There were concerns on the exploratory nature of the open-label study to provide support as confirmatory evidence with serious limitations such as high rate of non-participation and dropouts, treatment of tracheostomy or hospitalization as death equivalents as composite endpoint, post hoc analyses of death alone and overall interpretability of the results. All those who voted "No" acknowledged that the ongoing larger Phase 3 trial (Study A35-004) would resolve the uncertainties on effectiveness of AMX0035.

Following submission by the sponsor of additional information intended to establish the effectiveness of AMX0035, the PCNS Committee was reconvened on September 7, 2022.

At that meeting the following questions were discussed and voted on:

1. **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.

2. **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.

The Committee Vote: YES: 7 NO: 2 Abstain: 0
We note that there was one less voting member at the September 7, 2022, meeting, as the consumer representative was unable to participate.

The Committee members expressed a range of viewpoints when discussing the strength of the currently available data (including the new information submitted and the information presented at the March 30, 2022, PCNS meeting) regarding the effectiveness of sodium phenylbutyrate/taurursodiol (AMX0035). Some members were in agreement that the overall evidence presented from both meetings was mild to moderately persuasive of the effectiveness of AMX0035, noting that while the data presented has its limitations and challenges, the endpoints trend in the same direction and may support the finding of prolonged survival with the product. Other members expressed being reassured by the absence of a safety signal, suggesting that AMX0035 is not likely to harm patients even if the Phase 3 trial (Study A35-004) fails to demonstrate a benefit.

Several members were in agreement that the biomarker analysis did not add much to support evidence of effectiveness, with members pointing to shortcomings such as measurements being taken from one time point, and the unclear relevance of biomarker data derived from patients with Alzheimer's Disease to ALS. The committee members were divided when discussing the strength of the new sensitivity analyses using external natural history data presented by the Applicant. Some members were less compelled, pointing to the analyses being conducted post hoc, and questioning the source and population base used. Other members noted the analyses were supportive of a real-world difference in patients treated with AMX0035 and the observed survival benefit seemed to make sense but acknowledged the limitations.

During the Committee's discussions, several members recognized the unmet medical need for treatment options for a rare and life-threatening condition such as ALS, with one member pointing to the importance of listening to the patient community and highlighting FDA's ability to exercise regulatory flexibility in this context.

10. Pediatrics

AMX0035 for the treatment of ALS was granted orphan drug designation on July 27, 2017, and is exempt from PREA requirements.

11. Other Relevant Regulatory Issues

- Dr. Tandon concludes that the Applicant has adequately disclosed financial interests/arrangements with clinical investigators.

- The Office of Scientific Investigations (OSI) conducted investigations at 3 clinical sites, as well as the Neurological Clinical Research Institute (NCRI) and Barrow Neurological Institute (BNI) in support of this NDA. See the primary OSI review by Cara Alfaro, Pharm.D. The data generated by the sites appear acceptable in support of the respective indication. The inspection of NCRI verified the randomization implementation error that resulted in the first 16 kits shipped to clinical sites containing active drug. There was no evidence that the site or subjects were unblinded due to this error.

12. Labeling

Labeling negotiations with the Applicant have been completed and the Applicant has accepted all recommended changes. Please refer to the final negotiated product labeling.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)
The Division of Risk Management (DRISK) reviewer for this application is Dr. Donella Fitzgerald. Dr. Fitzgerald concludes that a risk evaluation and mitigation strategy (REMS) is not necessary for AMX0035**.**

Postmarketing Requirements (PMRs) and Commitments (PMCs)
The following PMRs will be imposed:

Clinical Pharmacology
PMR 1:
Conduct an in vivo pharmacokinetic drug interaction study to evaluate the effect of Relyvrio on inhibiting and/or inducing CYP2C8, CYP1A2, CYP2B6, and CYP3A4 enzymes using an appropriate probe substrate for each enzyme. We recommend you evaluate these drug interactions as a single cocktail Drug Drug Interaction (DDI) study. Please refer to the Guidance for Industry Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions (https://www.fda.gov/media/134581/download).

PMR 2:
Conduct an in vivo drug interaction study to evaluate the effect of OATP1B3 transporter inhibitor on pharmacokinetics of Relyvrio. Please refer to the Guidance for Industry Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions (https://www.fda.gov/media/134581/download).

PMR 3:
Conduct an in vivo pharmacokinetic drug interaction study to evaluate the effect of Relyvrio as an inhibitor of OAT1, BCRP, and P-gP. We recommend you consider evaluating these drug interactions as a single cocktail DDI study with an appropriate probe substrate of each transporter. Please refer to the Guidance for Industry Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions (https://www.fda.gov/media/134581/download).

PMR 4:
Conduct a clinical trial to evaluate the effect of hepatic impairment on the exposure of sodium phenylbutyrate and taurursodiol after oral administration of Relyvrio (sodium phenylbutyrate and taurursodiol) relative to that in subjects with normal hepatic function. Please refer to the Guidance for Industry Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInform at ion/Guidances/ucm072123.pdf).

PMR 5:
Conduct a clinical trial to evaluate the effect of renal impairment on the exposure of sodium phenylbutyrate and taurursodiol after oral administration of Relyvrio (sodium phenylbutyrate and taurursodiol) relative to that in subjects with normal renal function. Please refer to the Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf).

Nonclinical
PMR 6:
A carcinogenicity study of sodium phenylbutyrate and taurursodiol in mouse.

PMR 7:
A carcinogenicity study of sodium phenylbutyrate and taurursodiol in rat.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EMILY R FREILICH
09/30/2022 11:31:07 AM

TERESA J BURACCHIO
09/30/2022 11:33:14 AM

WILLIAM H Dunn
09/30/2022 01:11:47 PM