

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

216660Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: September 29, 2022
Requesting Office or Division: Division of Neurology 1 (DN 1)
Application Type and Number: NDA 216660
Product Name and Strength: Relyvrio (sodium phenylbutyrate and taurursodiol)
for oral suspension, 3 grams/1 gram
Applicant/Sponsor Name: Amylyx Pharmaceuticals Inc. (Amylyx)
OSE RCM #: 2021-2157-2
DMEPA 2 Safety Evaluator: Beverly Weitzman, PharmD
DMEPA 2 Acting Team Leader: Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

Amylyx submitted revised carton labeling and container label received on September 27, 2022 and September 28, 2022 for Relyvrio. The Division of Neurology 1 (DN 1) requested that we review the revised container label and carton labeling for Relyvrio (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review memorandum.^a

2 ASSESSMENT AND CONCLUSION

Amylyx provided clarification on the container and carton labeling submitted on September 23, 2022, noting that (b) (4)
(b) (4)
(b) (4). Thus, Amylyx (b) (4)
(b) (4) and submitted revised carton labeling and container (packet) label for the to-be-marketed product only, which is the subject of this review. Amylyx implemented all of our recommendations and we have no additional recommendations at this time.

^a Weitzman, B. Label and Labeling Review for sodium phenylbutyrate and taurursodiol (NDA 216660). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 SEP 23. [DARRTS date 2022 SEP 25]. RCM No.: 2021-2157-1.

APPENDIX A. IMAGES OF LABEL AND LABELING

Container (Packet) Label

(b) (4)



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/s/

BEVERLY WEITZMAN
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STEPHANIE L DEGRAW
09/29/2022 11:05:05 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

*****Pre-decisional Agency Information*****

Memorandum

Date: September 27, 2022

To: Emily Freilich, Clinical Reviewer, M.D.
Division of Neurology Products I (DN1)

Michelle Mathers, Regulatory Project Manager, (DN1)

Tracy Peters, Associate Director for Labeling, (DN1)

From: Sapna Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for **RELYVRIO (sodium phenylbutyrate and taurursodiol), for oral suspension**

NDA: 216660

In response to DN1's consult request dated December 7, 2021, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for RELYVRIO (sodium phenylbutyrate and taurursodiol), for oral suspension (Relyvrio).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DN1 on September 20, 2022 and are provided below.

Patient Prescribing Information (PPI): A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI was sent under separate cover on September 27, 2022.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on September 23, 2022, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Sapna Shah, at (240) 402-6068.

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/s/

SAPNA SHAH
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: September 26, 2022

To: Michelle Mathers,
Regulatory Project Manager
Division of Neurology I (DN1)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Mary Carroll, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Sapna Shah, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): RELYVRIO (sodium phenylbutyrate and taurursodiol)

Dosage Form and Route: for oral suspension

Application Type/Number: NDA 216660

Applicant: Amylyx Pharmaceuticals Inc.

1 INTRODUCTION

On October 29, 2021, Amylyx Pharmaceuticals, Inc. submitted for the Agency's review an original New Drug Application (NDA) 216660 for RELYVRIO (sodium phenylbutyrate-taurusodiol), for oral suspension, a New Molecular Entity (NME). The proposed indication for RELYVRIO (sodium phenylbutyrate-taurusodiol) is for the treatment of amyotrophic lateral sclerosis (ALS).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology I (DN1) on December 7, 2021 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for RELYVRIO (sodium phenylbutyrate-taurusodiol), for oral suspension.

2 MATERIAL REVIEWED

- Draft RELYVRIO (sodium phenylbutyrate-taurusodiol) PPI, received on October 29, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 20, 2022.
- Draft RELYVRIO (sodium phenylbutyrate-taurusodiol) Prescribing Information (PI) received on October 29, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 20, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

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SAPNA SHAH
09/26/2022 08:47:19 PM

MARCIA B WILLIAMS
09/27/2022 06:39:00 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 23, 2022
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 216660
Product Name and Strength:	Relyvrio (sodium phenylbutyrate and taurursodiol) for oral suspension, 3 grams/1 gram
Applicant/Sponsor Name:	Amylyx Pharmaceuticals Inc. (Amylyx)
OSE RCM #:	2021-2157-1
DMEPA 2 Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

Amylyx submitted revised container label, (b) (4), and carton labeling received on September 23, 2022 for Relyvrio. The Division of Neurology 1 (DN 1) requested that we review the revised container label, (b) (4), and carton labeling for Relyvrio (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 ASSESSMENT AND CONCLUSION

Amylyx answered all previous questions and implemented most recommendations; however, in response to the Agency's recommendation to relocate the net quantity statement away from the strength to the bottom of the principal display panel (PDP), Amylyx removed the net quantity from the PDP and move it to (b) (4). The net quantity statement is critical information that should be included on the PDP. Additionally, we note the (b) (4) does not include a net quantity statement. As such, we provide recommendations for Amylyx in Section 3 below.

^a Weitzman, B. Label and Labeling Review for sodium phenylbutyrate and taurursodiol (NDA 216660). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 FEB 25. RCM No.: 2021-2157.

3 RECOMMENDATIONS FOR AMYLYX PHARMACEUTICALS INC.

1. Carton Labeling

We acknowledge the relocation of the net quantity statement to reduce the risk of numerical confusion with the strength. However, failure to include the net quantity statement on the principal display panel (PDP) may result in confusion regarding the contents of the various size cartons. As such, we recommend that you relocate the net quantity statements (i.e., “contains 7 single-dose packets” (b) (4) and “contains 56 single-dose packets, contained in 4 boxes of 14 single-dose packets”) to the bottom of the PDP for the 7-count, (b) (4) and 56-count carton labeling.

2. (b) (4)

As currently presented, the (b) (4) does not contain a net quantity statement. We recommend revising “single-dose packet” to read “Contains one single-dose packet”. We recommend using the word “one” to avoid numerical confusion with the strength statement.

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BEVERLY WEITZMAN
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STEPHANIE L DEGRAW
09/25/2022 04:23:38 PM



MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: May 31, 2022

To: Eric Bastings, MD, Director
Division of Neurology I

Through: Dominic Chiapperino, Ph.D., Director
Chad Reissig, Ph.D., Supervisory Pharmacologist
Controlled Substance Staff

From: Jovita Randall-Thompson, PhD, Pharmacologist
Controlled Substance Staff

Subject: **Drug:** AMX0035 or (b) (4) (sodium phenylbutyrate and ursodoxicoltaurine)
NDA Number: 216660
(IND 129563)
Indication: Treatment of amyotrophic lateral sclerosis (ALS) (as known as Lou Gehrig's disease)
Dosage: a single-use sachet containing 3 grams of sodium phenylbutyrate and 1 gram of ursodoxicoltaurine administered via feeding tube or mixed in water and ingested orally
Applicant: Amylyx Pharmaceuticals, Inc.
PDUFA Goal Date: June 29, 2022

Materials Reviewed:

- NDA 216660, submitted October 29, 2021 (Sequence#0001/Supporting Doc.# 1)

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I. EXECUTIVE SUMMARY

1. Background

This memorandum responds to a consult request by the Division of Neurology I (DN1) to evaluate a New Drug Application (NDA) for AMX0035, a sodium phenylbutyrate (PB) and ursodexicoltaurine (taurursodiol, TURSO) fixed-dosed combination product. DN1 requested the Controlled Substances Staff's comments and input regarding the submission and proposed labeling. The rationale for development is to make available an additional FDA-approved product to patients diagnosed with amyotrophic lateral sclerosis (ALS).

The Applicant filed AMX0035 as a 505(b)(1) NDA which cross referenced drug master file (DMF) (b) (4) for PB, and DMFs (b) (4) and (b) (4) for TURSO. Based on filing, the product is considered a new molecular entity (NME). However, sodium phenylbutyrate is approved in the United States (US) for treatment of urea cycle disorders (UCDs; Buphenyl, NDA 020572 and 020573), taurursodiol is approved in Italy for the treatment of cholesterol gallstones. Sodium phenylbutyrate is a pan-histone deacetylase (HDAC) inhibitor that decreases endoplasmic

reticulum (ER) stress through the upregulation of chaperone proteins. Ursodoxicoltaurine decreases mitochondrial stress by reducing mitochondrial permeability and increasing the apoptotic threshold of the cell. Together, it is hypothesized that the drugs can reduce neuronal death linked to ALS. The specific mechanism of AMX0035's therapeutic effects in ALS patients is unknown.

The Applicant (Amylyx Pharmaceuticals, Inc.) performed a phase 1 study in healthy volunteers and a phase 2 double-blind, placebo-controlled study with a follow-on open-label extension in ALS patients, as well as several nonclinical safety pharmacology, and toxicology studies.

Table 1: Tabular Listings of All Clinical Studies

Type of Study	Study Number	Location of Study Report in CTD	Study Objectives	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 1, Food Effect	A35-002	5.3.3.1	Determine the plasma levels and PK parameters of sodium phenylbutyrate, taurursodiol, and major metabolites following single oral dose administration of AMX0035; Evaluate the effect of a high-fat standardized breakfast on the extent and rate of absorption of sodium phenylbutyrate, taurursodiol and active metabolites	Open label, 2 sequence, 2-period, cross-over	AMX0035; 1 sachet (1 g taurursodiol and 3 g sodium phenylbutyrate); Oral	14	Healthy	Single dose	Completed; Final CSR
Phase 2, Efficacy	AMX3500	5.3.5.1	Confirm the safety and tolerability of a fixed-dose combination of phenylbutyrate and taurursodiol; Measure the impact of a fixed-dose combination of PB and taurursodiol using the slope of progression with the (ALSFRS-R)	Randomized, Placebo-controlled	AMX0035; 1 sachet BID (1 sachet = 1 g taurursodiol and 3 g sodium phenylbutyrate); Oral	137	ALS	24 weeks	Completed; Final CSR
Phase 2, Efficacy	AMX3500-OLE	5.3.5.2	Assess the long-term safety of AMX0035; Assess rate of progression on the ALSFRS-R scale; Determine the rate of key study events including tracheostomy, hospitalization, and death	Open-label extension	AMX0035; 1 sachet BID (1 sachet = 1 g taurursodiol and 3 g sodium phenylbutyrate); Oral	90	ALS	Up to 132 Weeks	Completed; Final CSR

Source: Section 5.2 Tabular Listing of All Clinical Studies

2. Conclusions

The active pharmaceutical ingredients (APIs) in AMX0035, PB and TURSO have several metabolites. Binding assays performed by the Applicant revealed that a metabolite of PB, phenylacetyl glutamine (PAGN), binds to N-methyl-D-aspartate (NMDA) and serotonin 2B (5-HT_{2B}) receptors and the gamma-aminobutyric acid (GABA) transporter, targets that are linked to abuse-related effects. However, AMX0035 did not alter centrally-mediated responses in the rat when a functional observational battery (FOB) was conducted by the Applicant. When administered to healthy subjects, no centrally-mediated adverse events (AEs) potentially related to abuse were reported. When AMX0035 was administered in ALS subjects, abuse related AEs were limited and included anxiety and euphoric mood, which were reported by less than 0.6 % of subjects or at a rate that did not differ between treatment and placebo. Based on these data, the administration of AMX0035 did not present a relevant signal of drug abuse potential.

3. Recommendations

Based on our findings as captured in the Conclusions section, we recommend the following:

1. AMX0035, does not appear to present a potential for abuse and does not warrant scheduling under the Controlled Substances Act (CSA).
2. AMX0035 does not have abuse potential and the labeling for drugs containing PB, Buphenyl (NDAs 020572 and 020573), does not include warnings, data, or language pertaining to drug abuse and dependence and withdrawal and there is no Section 9, Drug Abuse and Dependence. Therefore, Section 9 should not be included in the labeling for AMX0035. Other related listed PB products with no Section 9, include Ravicti (glycerol phenylbutyrate, NDA 203284) and Ammonul (PB and sodium benzoate, NDA 020645).

II. DISCUSSION

1. Chemistry

1.1 Substance Information

Name: sodium phenylbutyrate and ursodoxicoltaurine (taurursodiol)

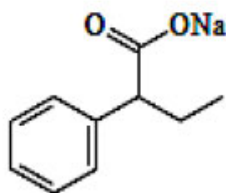
Chemical Properties

Chemical name: sodium 4-phenylbutanoate and

Chemical formula: C₁₀H₁₁NaO₂

Molecular weight: 186.2

Molecular Structure:



Name: ursodoxicolaurine (taurursodiol, TURSO)

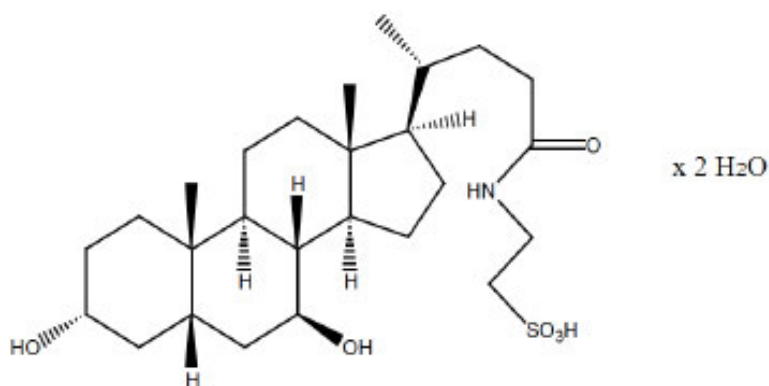
Chemical Properties

Chemical name: 2-[(3 α , 7 β -dihydroxy-24-oxo-5 β -cholan-24-yl) amino] ethane sulfonic acid, dihydrate N-3 α ,7 β -dihydroxy-24-oxo-5 β -cholan-24-yl taurine, dihydrate

Chemical formula: C₂₆H₄₅NO₆S.2H₂O

Molecular weight: 535.74

Molecular Structure:



2. Nonclinical Pharmacology

Pharmacokinetic effects (absorption, distribution, metabolism and excretion) of AMX0035 were evaluated in rats.

According to the Applicant, orally administered AMX0035 was well absorbed (NDA 216660, Pharmacokinetics Written Summary, page 7 to 8). Sodium phenylbutyrate was absorbed and reached peak plasma concentrations 1 to 2 hours after oral dosing. TURSO was absorbed at multiple peak concentrations (as demonstrated with enterohepatic recirculation of a biliary salt), at 2 and 12 hours after oral dosing.

After oral dosing in rodents, AMX0035-related material was widely distributed in plasma and to most tissues (NDA 216660, 2.4 Nonclinical Overview, pages 15 to 16). Brain levels (including brain tissues, spinal cord, and seminal vesicles) of AMX0035 were reported lower than in the blood (NDA 216660, 2.4 Nonclinical Overview, page 15). Rat PK findings are provided in the Applicant's table presented below (see Table 1).

Table 1: PK Parameters of PB and TURSO in Rat during 7-Day Study

	Day	Dose Level (mg/kg)	Sex	T _{1/2} (hr)	T _{max} (hr)	C _{max} (ng/mL)	AUC _{0-Tlast} (hr•ng/mL)	AUC _{INF} (hr•ng/mL)
PB	1	250	F	0.76	1.00	21487	40463	40507
			M	0.66	1.00	14510	54068	54095
		750	F	2.28	1.00	120033	288563	288740
			M	2.43	4.00	37000	281593	282091
		1000	F	2.84	1.00	101800	581683	583769
			M	1.52	1.00	56833	358542	358592
	7	250	F	1.17	1.00	23133	45902	45956
			M	3.86	1.00	21960	42026	42487
		750	F	5.28	2.00	30233	140157	141195
			M	3.27	1.00	26033	120029	121176
		1000	F	2.41	1.00	44467	218988	219509
			M	3.17	1.00	23633	156731	157633
TURSO	1	83.32	F	23.53	4.00	241.40	2475	4697
			M	15.98	2.00	58.67	763	1156
		250	F	NC	12.00	215.00	3573	NC
			M	NC	8.00	501.67	3821	NC
		333.28	F	NC	12.00	669.00	8004	NC
			M	NC	12.00	165.00	2773	NC
	7	83.32	F	40.87	2.00	120.70	1860	5389
			M	24.78	2.00	108.87	1074	1986
		250	F	NC	8.00	762.00	6691	NC
			M	55.16	4.00	204.00	3426	11458
		333.28	F	36.66	2.00	328.67	4929	15905
			M	16.04	4.00	457.00	4860	7755

Abbreviations: AUC_{0-Tlast} = area under the plasma drug concentration time curve up to the last quantifiable time-point; AUC_{INF} = area under the plasma drug concentration–time curve to infinite time; C_{max} = maximum plasma concentration; PB = phenylbutyrate; T_{1/2} = half-life; TURSO = tauroursodeoxycholic acid

Source: Amylyx Pharmaceuticals Inc., 8 October 2021, 2.6.4 Pharmacokinetics Written Summary, Table 4 PK Parameters of PB and TURSO in Rat during 7-Day Study, page 10

2.1 Receptor Binding and Functional Assays

The Applicant conducted a receptor screening of off-target receptors with AMX0035's APIs PB and TURSO, PB's primary metabolite phenyl acetate and secondary metabolite PAGN, and TURSO's metabolites ursodeoxycholic acid and glyoursodeoxycholic acid. As described previously, PAGN is formed from the conjugation of PB's primary metabolite phenyl acetate with glutamine via acetylation.

There was no significant binding by either of the APIs and the metabolites phenyl acetate, ursodeoxycholic acid, and glyoursodeoxycholic acid. However, the secondary metabolite PAGN was shown to bind ($\geq 50\%$ inhibition of binding) to the N-methyl-D-aspartate (NMDA) and serotonin 2B (5-HT_{2B}) receptors and the gamma-aminobutyric acid (GABA) transporter, see table below (Report 10058654). Functional assay testing with PAGN was not conducted. An assessment for abuse-related adverse events over all phases of development was conducted to further evaluate for any abuse signal.

Binding affinity of PAGN		
	rat cerebral cortex	human recombinant (CHO cells)
NMDA	68.4%	
5-HT _{2B}	—	66.4%
GABA transporter	98.6%	—
*Source Report 10058654		

2.2 Safety Pharmacology/Metabolites

Following the oral administration of AMX0035, PB (19.3% of total AUC0-8 h) was metabolized to several primary circulating components identified as phenyl acetate (15.6% of total AUC0-8 h), phenylacetyl glycine (45.5% of total AUC0-8 h), and phenyl crotonate (18.0% of total AUC0-8 h). Additionally, PAGN (percentages not provided) was formed when the primary metabolite phenyl acetate coagulated with glutamine. As for the second API, after oral administration of AMX0035, TURSO (9.21% of total AUC0-8h, rat plasma) was metabolized to its oxidation metabolite (oxidated TURSO), which was identified as a primary metabolite (90.8% of total AUC0-8 h) (NDA 216660, 2.6.4 Pharmacokinetic Written Summary, page 7, and 29 – 32; Study 3517N-2001).

2.3 Findings from Safety Pharmacology and Toxicology Studies

The following sections include a review of AMX0035 for inducing general behavioral effects and changes when the drug was tested in single and repeated-dose toxicology studies conducted in rats, which included:

- o One single-dose toxicology assessment, Study 73023, reports a no observable adverse effect level (NOAEL) to be 1000 mg/kg/day for PB and 333.28 mg/kg/day for TURSO.
- o Two repeat-dose toxicology assessments with recovery phases, Study 73024 reports a NOAEL to be 1000/333.28 mg/kg/day of PB/TURSO, and Study 01217005, reports a NOAEL to be 840 mg/kg/day of AMX0035 (male and female PB C_{max} values of 22,800 and 26,300 ng/ml and TURSO 244 and 2460 ng/mL, respectively).

Observations were gathered over multiple drug doses from 125 to 1500 mg/kg of PB, 41.66 to 500 mg of TURSO, and 250 to 840 mg/kg of AMX0035 given orally (PO, gavage).

A Functional Observational Battery (FOB) study was conducted (Study 73024). Rats orally (via gavage) administered 250/83.32 mg/kg/day, 750/250 mg/kg/day and 1000/333.28 mg/kg/day of PB/TURSO underwent behavioral, neurological and

autonomic testing and observations were conducted at pre-treatment, and 4 and 24 hours post-dose on Days 1 and 28 (Study 73024). The doses of AMX0035 produced drug exposure levels in rat that were comparable to human therapeutic exposure of the drug. No relevant behavioral changes were observed.

Signs of crusting, presence of lump, hair loss, fur stained, broken nail or claw, abnormal sound, lesions and discharge from the eye were noted (Study 73024). However, across all studies no relevant changes in behavior were observed. In addition, there were no changes observed during drug recovery periods, which evaluated the cessation of AMX0035 after repeated-dose exposures (Study 73024 and 01217005).

3. Clinical Pharmacology

3.1 Absorption, Distribution, Metabolism, Elimination (ADME)

The co-administration of PB and TURSO demonstrated protein binding in human plasma at 81.5 to 82.2%, and 98.5 to 98.6%, respectively (Study 19AMLXP3).

Sodium phenylbutyrate is a pro-drug that is rapidly metabolized to the primary metabolite PAA. Phenyl acetate is then metabolized in the liver and kidneys to the metabolite PAGN. As stated previously, PAA conjugates with glutamine. The metabolic activity occurs via the enzyme N-acyl coenzyme A-L-glutamine N-acyltransferase. PAGN is then excreted in urine. TURSO is transformed in the liver to ursodiol, and glyoursodeoxycholic acid, and is excreted mostly in feces. According to the Applicant, PB and TURSO do not overlap in cytochrome P450 interactions or excretion pathways and are not anticipated to exhibit a drug-drug interaction.

Following oral administration of a single dose of AMX0035 (3 g PB and 1 g TURSO) under fasting conditions, PB's mean C_{max} was 188 mcg/mL and T_{max} was 1 hour (Study A35002). While TURSO was slowly absorbed and reached a mean C_{max} of 0.871 mcg/mL with a T_{max} of 4.5 hours. Under Fed conditions, the TURSO plasma concentration profiles in many subjects demonstrated 2 to 3 peaks (Study A35002). A high-fat meal did not significantly affect the C_{max} for TURSO, but AUC was increased by 46%.

Geometric mean (geometric coefficient of variation [CV%]) plasma PK parameters for PB and primary metabolite phenyl acetate (PAA, ≥10% of total drug-related exposure) following single oral doses of AMX0035 to healthy male and female subjects in the fed and fasted states are presented below:

Treatment Status Analyte No. of Subjects Parameter	AMX0035 Fasted PB N=13	AMX0035 Fed PB N=14	AMX0035 Fasted PAA N=13	AMX0035 Fed PAA N=14
Tmax ^a (h)	0.500 (0.25-0.50)	1.000 (0.25-1.50)	2.500 (1.50-3.50)	2.500 (2.00-4.50)
Cmax (µg/mL)	188 (39.0)	46.8 (45.4)	26.4 (30.7)	15.9 (39.1)
AUC(0-last) (µg.h/mL)	236 (45.2)	109 (45.4)	81.8 (38.0)	56.7 (43.0)
AUC(0-inf) (µg.h/mL)	237 (44.9)	122 (28.6) [n=13]	83.4 (37.4)	58.3 (42.1)
AUCextrap (%)	0.628 (51.0)	2.231 (70.7) [n=13]	1.779 (36.1)	2.485 (42.8)
T1/2 (h)	0.461 (15.1)	0.599 (41.4) [n=13]	0.813 (11.5)	0.780 (16.3)
Lambda-z (1/h)	1.5051 (15.1)	1.1579 (41.4) [n=13]	0.8527 (11.5)	0.8886 (16.3)
CL/F (mL/min)	211 (44.9)	410 (28.6) [n=13]	NA	NA
Vz/F (L)	8.4 (45.8)	21.3 (67.0) [n=13]	NA	NA
Frel Cmax (%)	NC	24.259 (18.1) [n=13]	NC	60.480 (20.6) [n=13]
Frel AUC(0-last) (%)	NC	45.124 (19.9) [n=13]	NC	70.024 (15.4) [n=13]
Frel AUC(0-inf) (%)	NC	45.982 (19.3) [n=12]	NC	70.606 (15.0) [n=13]
MR Cmax	NA	NA	0.168 (40.3)	0.407 (45.6)
MR AUC(0-last)	NA	NA	0.416 (38.9)	0.626 (49.2)
MR AUC(0-inf)	NA	NA	0.421 (38.5)	0.598 (46.8) [n=13]

^a Median (range), NA not applicable, NC not calculated
Source: Study A35-002, page 4

In addition, the geometric mean (geometric coefficient of variation [CV%]) plasma PK parameters for TURSO and metabolites ursodeoxycholic acid (UDCA, ≤10% of total drug-related exposure) and glyoursodeoxycholic acid (GUDCA, ≤10% of total drug-related exposure) following single oral doses of AMX0035 to healthy male and female subjects in the fed and fasted states are presented below:

Treatment Status Analyte No. of Subjects Parameter	AMX0035 Fasted TURSO N=13	AMX0035 Fed TURSO N=14	AMX0035 Fasted UDCA N=13	AMX0035 Fed UDCA N=14	AMX0035 Fasted GUDCA N=13	AMX0035 Fed GUDCA N=14
Tmax ^a (h)	4.500 (1.50-10.00)	5.000 (4.50-10.00)	6.000 (0.25-20.00)	16.000 (6.00-24.00)	16.000 (6.00-20.00)	16.000 (0.50-24.00)
Cmax (mass unit/mL) ^b	0.741 (71.6)	0.762 (44.0)	639 (73.0)	654 (135.2)	381 (76.6)	463 (91.2)
AUC(0-last) (mass unit.h/mL) ^b	4.36 (79.4)	6.13 (62.7)	5540 (72.5)	6770 (108.3)	4140 (70.4)	5060 (88.2)
AUC(0-inf) (mass unit.h/mL) ^b	3.91 (58.9) [n=5]	4.84 (24.1) [n=6]	11300 (NC) [n=1]	8580 (NC) [n=1]	NC	NC
AUCextrap (%)	8.242 (53.9) [n=5]	3.149 (44.2) [n=6]	2.835 (NC) [n=1]	17.944 (NC) [n=1]	NC	NC
T1/2 (h)	4.337 (49.7) [n=5]	3.359 (45.1) [n=6]	4.773 (73.0) [n=2]	5.312 (NC) [n=1]	12.744 (NC) [n=1]	16.513 (62.0) [n=2]
Lambda-z (1/h)	0.1598 (49.7) [n=5]	0.2063 (45.1) [n=6]	0.1452 (73.0) [n=2]	0.1304 (NC) [n=1]	0.0543 (NC) [n=1]	0.0419 (62.0) [n=2]
CL/F (mL/min)	4260 (58.9) [n=5]	3440 (24.1) [n=6]	NA	NA	NA	NA
Vz/F (L)	1600 (22.1) [n=5]	1000 (41.2) [n=6]	NA	NA	NA	NA
Frel Cmax (%)	NC	102.06 (53.0) [n=13]	NC	111.43 (136.6) [n=13]	NC	135.16 (72.6) [n=13]
Frel AUC(0-last) (%)	NC	139.26 (56.9) [n=13]	NC	136.58 (99.2) [n=13]	NC	139.72 (60.0) [n=13]
Frel AUC(0-inf) (%)	NC	146.82 (22.9) [n=3]	NC	75.818 (NC) [n=1]	NC	NC
MR Cmax	NA	NA	1.099 (119.9)	1.093 (169.5)	0.571 (107.4)	0.675 (92.9)
MR AUC(0-last)	NA	NA	1.620 (149.3)	1.406 (148.8)	1.056 (114.8)	0.918 (103.4)
MR AUC(0-inf)	NA	NA	NC	NC	NC	NC

a Median (range), NC not calculated, NA not applicable

b Note: mass units for parent (TURSO) are µg, mass units for metabolites (UDCA and GUDCA) are ng

Source: Study A35-002, page 5

4. Clinical Studies

The Applicant conducted two main clinical studies, phase 1 Study A35-002 and phase 2 Study AMX3500, and an extended use assessment, AMX3500 OLE, added to the end of the phase 2 study.

Study A35-002 evaluated AMX0035 in healthy volunteers to examine the pharmacokinetic (PK) and pharmacodynamics (PD) of PB, and TURSO, and major metabolites following single oral dose administration with and without food.

Study AMX3500 (also known as CENTAUR) was a placebo-controlled assessment followed by the non-placebo extension (OLE) in ALS patients that examined the safety, tolerability, efficacy, PK, and biological activity of AMX0035. The first 24 weeks included a randomized and double-blind design which evaluated the effects of AMX0035 on independent functioning as measured by the ALS Functional Rating Scale (ALSFRS-R) and the Accurate Test of Limb Isometric Strength (ATLIS). AMX0035 (1 sachet OD for 3 weeks and BID thereafter) administration was followed by a meal or snack (not mandatory) intended to improve tolerability. Patients who completed treatment in the AMX3500 trial were offered to participate in the open-label extension (and not included in this review an extended use protocol (A35-003)).

A dose of 3 grams of PB and 1 gram of TURSO twice a day (6 grams per day for PB and 2 grams per day for TURSO) was formulated as a powder for oral suspension and supplied as sachets each containing 3 g sodium PB and 1 g TURSO. AMX0035 was administered as an oral (or via feeding tube) product in all clinical studies. The commercial formulation is similar to the clinical trial sachet formulation used in the phase 2 study (AMX3500). The open-label extension (OLE) study used the commercial formulation, (b) (4).

Table 1: List of Studies Included in this Review

Study ID (Period)	Phase	Design	Subjects	Drug dose range	Population	Single or multiple dose	Age/Sex
A35002 (8/13/19 – 9/4/19)	1	Open label, 2 sequence, 2-period, cross-over trial	14	Placebo or 1 g TURSO and 3 g PB oral, Fasted/Fed	Healthy	Single	40 to 65/ male and female
AMX3500 (6/22/17 – 9/25/19)	2	Multicenter, randomized, placebo- controlled, double- blind, parallel group, 24-week study	137	Placebo, or 1 g TURSO and 3 g PB oral, once a day for 3 weeks, BID for remaining 24-week period	ALS	Multiple	18 to 80/ male and female

AMX3500- OLE (3/29/18 – 3/1/21)	Multicenter, 90 open-label extension study; treatment given up to 132 weeks	1 g TURSO and 3 g PB oral (or feeding tube), BID	ALS	Single	18 to 80/ male and female
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4.2 Adverse Event Profile Through all Phases of Development

There were no abuse-related AEs reported in the phase 1 Study A35002. For phase 2, abuse-related AEs were reported. The AEs were shown to occur at levels below 1% of trial population or levels did not differ from placebo. Therefore, the abuse-related AEs reported in phase 2 do not support that AMX0035 has abuse potential.

Phase 2*			
Adverse Event PT	PBO (N=82) n (%) [#]	AMX0035 (1 g TURSO and 3 g PB) (N=145) n (%) [#]	Drug Overall (N=145) n (%) [#]
Euphoria			
Euphoric mood	0	1 (0.6%) [1]	1 (0.6%) [1]
Elevated mood			
Mood alteration			
Feeling drunk			
Feeling abnormal			
Mood elevation			
Sedation			
Psychotomimetic events			
Hallucination			
Aberrant behavior (suicidal/homicidal ideation, aggression, disruptive disorders, symptoms of stress, anxiety, etc.)	8 (9.7%) [10]	14 (9.6%) [16]	14 (9.6%) [16]
Other major CNS Abuse related events			
Abuse			
Misuse			
Overdose			
Other (e.g.; lost to follow up; lost study drug; study drug theft; lack of efficacy; positive urine screens;			

noncompliance; drug diversion)			
*source: Study AMX3500, Listing 16.2.7.1 All Adverse Events by Center and Subject and Listing 16.2.1 Discontinued Subjects by Center; and AMX3500 OLE, Listing 16.2.7.1 All Adverse Events by Center and Subject and Listing 16.2.1 Discontinued Subjects by Center			

*n = number of patients who reported an AE for a particular category; # is the number of individual reports.

4.4 Evidence of Abuse, Misuse and Diversion in Clinical Trials

There were no reports of drug accountability issues, or nonmedical use/diversion.

4.5 Tolerance and Physical Dependence Studies in Humans

The effects of withdrawal and rebound after discontinuation of AMX0035 was not evaluated.

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/s/

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Clinical Inspection Summary

Date	05/19/2022
From	Cara Alfaro, Pharm.D., Clinical Analyst Phillip Kronstein, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Division Director/(Acting) Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Michelle Mathers, Regulatory Project Manager Veneeta Tandon, Ph.D., Clinical Reviewer Emily Freilich, M.D., Team Leader Division of Neurology 1 Office of Neuroscience
NDA #	216660
Applicant	Amylyx Pharmaceuticals
Drug	Sodium phenylbutyrate/Ursodolicolaurine acid (AMX0035)
NME	Yes
Proposed Indication	Treatment of amyotrophic lateral sclerosis (ALS)
Consultation Request Date	1/5/2022
Summary Goal Date	4/29/2022, extended to 5/20/2022
Priority/Standard Review	Priority
Action Goal Date	6/29/2022
PDUFA Date	6/29/2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Berry, Maiser, and Rothstein were inspected as well as the Neurological Clinical Research Institute (NCRI) and Barrow Neurological Institute (BNI) in support of this NDA and covering Protocol AMX3500. In the NDA submission, the sponsor described an incident that impacted the randomization schedule. The inspection of NCRI verified that, due to a reported shortage of placebo, the randomization schedule was not followed and the first 16 kits shipped to clinical sites contained active drug (AMX0035). Of the 15 subjects receiving AMX0035 (one subject was not randomized), four should have received placebo according to the original randomization schedule. There was no evidence that the site or subjects were unblinded due to this error. The sponsor performed a sensitivity analysis excluding the initial block of subjects who deviated from the original randomization schedule. We recommend that the review division confirm this sensitivity analysis. Otherwise, the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

II. BACKGROUND

AMX0035 (sodium phenylbutyrate/ursodexicoltaurine) powder for oral suspension is being developed under NDA 216660 (IND 129563) for the treatment of amyotrophic lateral sclerosis (ALS). Sodium phenylbutyrate (Buphenyl®), one of the components in this combination product, is approved for the treatment of urea cycle disorders.

The sponsor has submitted the results of one Phase 2 study, Protocol AMX3500 (CENTAUR), to support the efficacy and safety of AMX0035 in the treatment of ALS. A Phase 3 study is currently ongoing.

Different nomenclature is used for one of the two components in AMX0035. Ursodexicoltaurine is also known as taurursoldiol (established name) and tauroursodeoxycholic acid. These names are used interchangeably in proposed labeling, protocols, and elsewhere.

Protocol AMX3500 (CENTAUR)

Title: "Evaluation of the safety, tolerability, efficacy and activity of AMX0035, a fixed combination of phenylbutyrate (PB) and tauroursodeoxycholic acid (TUDCA), for treatment of amyotrophic lateral sclerosis (ALS)"

Subjects: 137

Sites: 25 Northeast ALS Consortium (NEALS) sites in the United States

Study Initiation and Completion Dates: 6/22/2017 – 9/25/2019

This was a Phase 2, randomized, double-blind, placebo-controlled, study in subjects with amyotrophic lateral sclerosis (ALS). Subjects were screened from approximately 25 Northeast ALS Consortium (NEALS) centers in the U.S. Included were males or females; 18 to 80 years of age; sporadic or familial ALS; ≤ 18 months since ALS symptom onset; Slow Vital Capacity (SVC) $>60\%$ of predicted value for gender, height, and age at screening visit; if taking riluzole, must be on stable dose for at least 30 days prior to screening visit; and adequate birth control/contraception during and for 3 months after the last dose of investigational product (IP). Subjects were allowed to take concomitant edaravone at the time of screening or if started while enrolled in the study.

The study was comprised of four phases:

Screening – up to 42 days

During the screening visit, subjects underwent study procedures to confirm study eligibility. Study procedures included, but were not limited to, confirmation of ALS diagnosis/history, neurological/physical examination, safety labs, and ALSFRS-R.

Double-Blind Treatment - 24 weeks

Subjects were randomized (2:1) to one of the following arms:

- AMX0035 (Phenylbutyrate [3 grams] and tauroursodeoxycholic acid [1 gram]):
1 sachet once daily for 3 weeks then 1 sachet twice daily thereafter
- Placebo: 1 sachet once daily for 3 weeks then 1 sachet twice daily thereafter

Investigational product (IP) was provided as a powder in an aluminum foil-lined sachet. Per protocol, subjects were to open the sachet containing IP powder, pour the powder into a cup, add approximately 8 ounces of room temperature water, and stir vigorously. The IP mixture was to be consumed completely within one hour of combining the contents of the sachet with water. For subjects with a gastrostomy or nasogastric tube, IP may be dissolved in water and administered via the feeding tube.

Follow-up

A follow-up telephone call was conducted 4 weeks after the last dose of IP.

Open Label Phase – 132 weeks

Protocol Amendment 3 (10/20/2017) added a 52-week open-label phase. Protocol Amendment 6 (1/11/2019) increased the open-label phase to 132 weeks. Subjects who completed the double-blind phase were eligible for this open-label phase and received AMX0035, one sachet twice daily.

The primary efficacy endpoint for the double-blind treatment phase was the rate of decline (slope of decline) in the total ALS Functional Rating Scale-Revised (ALSFRS-R) score.

The primary objective of the open-label phase was to determine the long-term safety of AMX0035. Efficacy endpoints were secondary and included rate of decline (slope of decline) in the ALSFRS-R score and overall survival. The survival endpoint (death or death equivalent) was defined as death, tracheostomy, or permanent assisted ventilation (PAV) meaning >22 hours daily of non-invasive mechanical ventilation for more than 7 days.

Rationale for Site Selection

The clinical sites were chosen primarily based impact on efficacy analyses, enrollment, and inspection history.

III. RESULTS

1. James Berry, M.D.

Site #701

Neurological Clinical Research Institute
Massachusetts General Hospital
165 Cambridge St., Suite 600
Boston, MA 02114

Inspection Dates: 1/20/2022 – 1/26/2022

Dr. Berry is a clinical investigator and a co-director of the Neurological Clinical Research Institute (NCRI). NCRI was also inspected for this application.

At this site for Protocol AMX3500, 20 subjects were screened, 13 subjects were randomized, 9 subjects completed the double-blind phase of the study and continued into the open-label phase. Four subjects discontinued the study during the double-blind phase due to:

- Withdrawal by subject (Subject # (b) (6), AMX0035). This subject discontinued the study due to entering hospice. This subject died approximately one week later.
- Discontinuation due to AE, respiratory failure/death (Subject # (b) (6), Placebo)
- Met criteria for death equivalent, permanent assisted ventilation (PAV) (Subject # (b) (6), Placebo)
- Discontinuation due to AE, subdural hematoma/death (Subject # (b) (6), AMX0035)

Narratives for these discontinuations were included in the NDA submission. Three subjects who entered the open-label phase discontinued the study and died after study discontinuation. The clinical investigator had entered the date of death in the eCRF, and these dates were verified during the inspection.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all enrolled subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, survival data (dates of death), and primary efficacy data (Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised [ALSFRS-R]).

All ALSFRS-R raters were Northeast Amyotrophic Lateral Sclerosis Consortium (NEALS) certified, as required by protocol. ALSFRS-R ratings were recorded on paper source and transcribed into the eCRF. ALSFRS-R component and total scores on paper source were verified against sponsor data listings for all randomized subjects; no discrepancies were identified. Source records for dates of subject deaths were verified against sponsor data

listings; no discrepancies were identified. There was no evidence of underreporting of adverse events.

2. Samuel Maiser, M.D.

Site #745

Hennepin Healthcare

701 Park Ave

Suite PPC4.440

Minneapolis, MN 55415

Inspection Dates: 2/7/2022 – 2/11/2022

At this site for Protocol AMX3500, 11 subjects were screened, 10 subjects were randomized, 9 subjects completed the double-blind phase of the study, and 8 subjects continued into the open-label phase. Subject # (b) (6), randomized to placebo, discontinued the study during the double-blind phase due to “withdrawal by subject”. However, the reported term included discontinuation due to an AE (fall) and SAE (pelvic fracture), for which investigational product was withdrawn. The narrative for this SAE was included in the NDA submission.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all enrolled subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, survival data (dates of death), and primary efficacy data (ALSFRS-R).

All ALSFRS-R raters were NEALS certified, as required by protocol. ALSFRS-R ratings were recorded on paper source and transcribed into the eCRF. ALSFRS-R component and total scores on paper source were verified against sponsor data listings for all randomized subjects; no discrepancies were identified. None of the subjects at this site died while participating in this protocol, and this was verified against the data line listings.

There was no evidence of under-reporting of adverse events. There was one instance of late reporting of an SAE. During the open-label phase of the study, Subject # (b) (6) experienced the SAE “shortness of breath” from (b) (6) resulting in hospitalization. The site became aware of the event on (b) (6) but did not report the SAE within 24 hours of awareness, a reporting requirement of the protocol. The site entered the SAE into the electronic data capture (EDC) system on (b) (6). (b) (4)

The narrative for this SAE is included in the NDA submission.

Reviewer’s comment: The late reporting of this SAE, which is also a typical symptom of ALS, was an isolated event.

3. Jeffrey Rothstein, M.D., Ph.D.**Site #713**

Johns Hopkins Hospital
601 North Caroline Street
Suite 5070A
Baltimore, MD 21287

Inspection Dates: 1/31/2022 – 2/3/2022

At this site for Protocol AMX3500, 5 subjects were screened, all of whom were randomized and completed the double-blind phase of the study. Four subjects continued into the open-label phase.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all enrolled subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, survival data (dates of death), and primary efficacy data (ALSFRS-R).

All ALSFRS-R raters were NEALS certified, as required by protocol. ALSFRS-R ratings were recorded on paper source and transcribed into the eCRF. ALSFRS-R component and total scores on paper source were verified against sponsor data listings for all randomized subjects; no discrepancies were identified. Source records for dates of subject deaths were verified against sponsor data listings; no discrepancies were identified. There was no evidence of underreporting of adverse events.

4. Neurological Clinical Research Institute

Massachusetts General Hospital
165 Cambridge Street, 6th Floor
Boston, MA 02114

Inspection Dates: 2/9/2022 – 2/16/2022

This inspection covered the Neurological Clinical Research Institute's (NCRI) transferred responsibilities pertaining to Protocol AMX3500. NCRI is part of the Massachusetts General Hospital Neurology Department. NCRI also has a Clinical Research Center to conduct studies (see Site #701 above). The inspection focused primarily, but not exclusively, on the three clinical investigator sites that had been selected for inspection (Site #s 701, 713, 745).

Study records reviewed included, but were not limited to, transfer of regulatory obligations (TORO), correspondence with the sponsor and Barrow Neurological Institute (BNI; see below); SOPs, organization and personnel; electronic data capture systems; safety reporting

processes; protocol deviation processes; investigational product management; randomization documents, and (b) (4).

According to the TORO, NCRI responsibilities included, but were not limited to, (b) (4)

(b) (4)

(b) (4)

Not Following Randomization Schedule When Shipping IP

In the Randomization-Scheme-Codes document included in Appendix 16.1.7, the sponsor described an incident that impacted the randomization schedule during the conduct of the study. Included in this document was a report entitled "AMX0035 Centaur Study: (b) (4) Pick List Investigation". This report, which was finalized on 1/26/2020 and signed by the (b) (4) unblinded statistician, (b) (4) blinded statistician, (b) (4) personnel, and sponsor personnel on 2/1/2020; described the root-cause of the error and corrective actions taken. This report also stated that, as part of the investigation, email correspondence to and from (b) (4), the unblinding quality consultant, (b) (4), the (b) (4) unblinded statistician, and (b) (4), the project manager at (b) (4), pertaining to this randomization issue were reviewed.

According to the sponsor, the error was identified in 11/2017 by the unblinded statistician, (b) (4), and addressed at that time. In a meeting on January 17, 2020, (b) (4) informed the sponsor that a shipping correction had occurred early in the conduct of Protocol AMX3500.

The inspection was able to verify the following:

- (b) (4) was the unblinded statistician for Protocol AMX3500. He was responsible for generating the randomization schedule. As a voting member of the DSBM, he was

- In preparation for the 11/7/2017 DSMB meeting, (b) (4) noticed that the first 16 subjects enrolled in the study had all received AMX0035.
- (b) (4) contacted (b) (4), the vendor responsible for packaging and distributing investigational product and managing the randomization scheme.
- The root-cause of the error appears to have been an error by (b) (4) in not following the randomization schedule. (b) (4) created the randomization schedule and sent it to (b) (4).

According to (b) (4), (b) (4) stated that there was a shortage in the number of placebo kits available from the manufacturer. Due to this deficiency, (b) (4) shipments of investigational product (IP) deviated from the original pick list. Since the pick list was blinded, (b) (4) did not detect the issue. (b) (4), who was unblinded, identified the issue while preparing for the DSMB meeting.

Email correspondence relating to this randomization issue was reviewed. Correspondence was primarily between (b) (4) and (b) (4) personnel. There was no evidence of unblinding in these correspondences. The investigative report, as referenced above, also listed a blinded (b) (4) statistician involved with Protocol AMX3500. The blinded statistician was not included on any of the email correspondences discussing this randomization issue.

(b) (4) stated that they no longer use the randomization process that was used in this study.

Reviewer comments: The sponsor performed a sensitivity analysis excluding the initial block of subjects who deviated from the original randomization schedule. We recommend that the review division confirm this sensitivity analysis.

5. Barrow Neurological Institute

St. Joseph's Hospital and Medical Center
350 West Thomas Road
Phoenix, AZ 85013

Inspection Dates: 3/14/2022 – 3/16/2022

This inspection covered Barrow Neurological Institute's (BNI) (b) (4) in Protocol AMX3500. The inspection focused primarily, but not exclusively, on the three clinical investigator sites that had been selected for inspection (Site #s 701, 713, 745).

Study records reviewed included, but were not limited to, (b) (4), transfer of regulatory obligations (TORO), communications with the sponsor and data management CRO (b) (4); SOPs; organization and personnel; clinical investigator and site qualification; (b) (4); training and certification (ALSFRS-R); investigator agreements; financial disclosure; electronic data capture systems; safety reporting process; protocol deviation process; and investigational product management.

BNI performed only (b) (4)

The inspection reviewed the timeliness of reporting SAEs (b) (4)

(b) (4) there were 6 sites (#'s 701, 704, 764, 769, 781, 842) with "trending issues" regarding compliance; only Site #701 was chosen for inspection for this application. During the inspection, compliance issues for Sites #701 and #842 were reviewed. Some issues noted were lack of source documentation for IP administration (data entered directly into EDC), laboratory reports lacking CI review and signature, nurse practitioner consenting subjects rather than CI/Sub-I, and late data entry. There was documentation that root cause analyses

and corrective and preventive actions (CAPAs) were completed for these sites. (b) (4)

. No sites were terminated for noncompliance.

Three subjects were discontinued from the study due to “termination of participation by site investigator”. (b) (4). Subject # (b) (6), randomized to AMX0035, could not take the medication consistently due to the taste. Subject # (b) (6), randomized to placebo, and Subject # (b) (6), randomized to AMX0035, were noncompliant with the medication (reason not provided).

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Division of Neurology 1/Clinical Reviewer/Veneeta Tandon
Division of Neurology 1/Project Manager/Michelle Mathers
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OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Clinical Analyst/Cara Alfaro
OSI/GCPAB Program Analyst/Yolanda Patague

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	February 25, 2022
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 216660
Product Name and Strength:	sodium phenylbutyrate and taurursodiol ^a for oral suspension, 3 grams/1 gram
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Amylyx Pharmaceuticals, Inc
FDA Received Date:	October 29, 2021 and November 10, 2021
OSE RCM #:	2021-2157
DMEPA 2 Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA 2 Team Leader (Acting):	Stephanie DeGraw, PharmD

^a A proprietary name has not yet been determined for this application.

1 REASON FOR REVIEW

As part of the approval process for sodium phenylbutyrate and taurursodiol for oral suspension, the Division of Neurology 1 (DN 1) requested that we review the proposed sodium phenylbutyrate and taurursodiol prescribing information (PI), patient information (PPI), container label and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), patient information (PPI), container label, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 (Table 2) for the Division and in Section 5 (Table 3) for Amylyx Pharmaceuticals, Inc.

4 RECOMMENDATIONS FOR DIVISION OF NEUROLOGY 1 (DN 1)

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information (PI) and Patient Information (PPI) – General Issues			

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The proprietary name, (b) (4), is used throughout the PI and PPI labeling.	The proposed proprietary name, (b) (4), was found unacceptable by DMEPA on January 18, 2022 ^b due to potential confusion with a currently marketed product.	Remove the proposed proprietary name “(b) (4)” throughout the PI and PPI. Until a new proprietary name is found to be conditionally acceptable, the placeholder “Tradename” may be used.
2.	The prescribing information (PI) and Patient Information (PPI) refers to the primary container closure system for the powder as a “sachet” which is inconsistent with the container label and carton labeling which refers to the primary container closure system as a “packet.” Furthermore, the term “sachet” is not defined by the CDER Data Standards Manual.	The terminology used in the PI and PPI (i.e., sachet) should be consistent with the terminology used in the container and carton labeling (i.e., packet) for the drug product in order to minimize the potential for confusion. Furthermore, CDER Data Standards Manual defines a packet as an envelope into which only one dose of a drug product, usually in the form of granules or powder, has been directly placed. Thus, the term ‘sachet’ is not defined by the CDER Data Standards Manual.	We recommend replacing the term “sachet” with “packet” throughout the PI and PPI labeling to be consistent with the container label and carton labeling, and to be in alignment with CDER Data standards.
3.	The presentation of the finished dosage form (i.e., powder for oral suspension) is not in alignment with USP requirements [General chapter <1121> nomenclature].	The dosage form is designated as “powder for oral suspension” is inconsistent with USP requirements for this type of pharmaceutical dosage form which is “for oral suspension.”	We recommend revising the dosage form “powder for oral suspension” to read “for oral suspension” throughout the labels and labeling.

^b Weitzman, B. Proprietary Name Review for (b) (4) (NDA 216660). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 JAN 18. Panorama No. 2021-1044724277.

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
4.	We note that the non-proprietary name “sodium phenylbutyrate/ ursodoxicoltaurine” is not the accepted official USAN name. We also note the slash “/” used between the two ingredients.	The accepted official USAN name for this product is “sodium phenylbutyrate and taurursodiol.” Additionally, the slash mark “/” in “sodium phenylbutyrate/ taurursodiol” could be misinterpreted to mean “sodium phenylbutyrate <u>or</u> taurursodiol” instead of “sodium phenylbutyrate <u>and</u> taurursodiol.”	We recommend revising the non-proprietary name to be consistent with the official USAN name as well as replacing the slash symbol between the two ingredients with the word “and” across all labels and labeling as follows: “sodium phenylbutyrate and taurursodiol”.
Highlights of Prescribing Information			
1.	The presentation of the <u>product title</u> “(b) (4)” (sodium phenylbutyrate/ ursodoxicoltaurine), for oral (b) (4) is not in compliance with the FDA guidance for Industry “Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products” and is inconsistent with the official USAN name.	As presented, the product title does not comply with the FDA industry guidance “Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Product” and is not in alignment with the official USAN name “taurursodiol.”	We recommend revising the product title “(b) (4)” (sodium phenylbutyrate/ ursodoxicoltaurine), for oral (b) (4) to read “TRADENAME (sodium phenylbutyrate and taurursodiol) for oral suspension” to be in alignment with recommendations number one, three and four under the heading “PI and PPI – General Issues” above.
2.	The presentation of the Dosage Forms and Strengths statement can be improved for accuracy (specifically, the USAN name, dosage form and the terminology used to describe the primary container closure system (i.e., sachet)).	This statement does not align with our recommendations as stated above under the <i>heading PI and PPI – General issues</i> , numbers one through three regarding USAN name, dosage form and container terminology (i.e., sachet).	We recommend revising the Dosage Forms and Strengths statement (b) (4) to read: “For oral suspension: 3 g sodium phenylbutyrate and 1 g taurursodiol in single-dose packets.”

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			We defer to OPQ to determine the appropriate format.
3.	In the highlights of the PI (Dosage and Administration), we note the statement (b) (4) " does not clearly define a frequency of administration (i.e., (b) (4)). We also note that the proposed recommended dosage statement in the HL is inconsistent with the dosage statement in the Dosage and Administration of the Full PI (Section 2) and the Patient package information (PPI).	Lack of consistency and clarity may lead to confusion and dosing errors.	We defer to clinical team to determine the appropriate dosage statement for this product. We do, however, recommend including the strength "3 g/1 g" in addition to "1 packet" in the recommended dosage statement. Ensure the dosage statement information is clearly defined and consistent throughout the labeling. Also, refer to recommendation number two under the heading "<i>PI and PPI – General Issues</i>" above for discussion of the container terminology and recommendation number one under the heading "<i>FPI Section 2 Dosage and Administration and PPI</i>" below for discussion of dosage and administration information in the full PI.
Full Prescribing Information (PI)- Section 2 Dosage and Administration and Patient Information (PPI)			
1.	We note that the proposed recommended dosage statement is not consistent throughout the PI and PPI labeling as noted below: Full PI: (b) (4)	Lack of consistency may lead to confusion and dosing errors.	We defer to clinical team to determine the appropriate dosage statement for this product. We do, however, recommend including the strength "3 g/1 g" in addition to "1 packet" in the recommended dosage statement.

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4) HL: (b) (4) PPI: (b) (4)		Ensure the dosage statement is consistent across all labeling. Also, refer to recommendation number two under the heading “<i>PI and PPI – General Issues</i>” for discussion of the container terminology and number three under the heading “<i>Highlights of prescribing Information</i>” above for discussion of dosage and administration information in HL.
2.	The preparation and administration instructions (section 2.2) are not clearly written and contain an undefined abbreviation “oz”. Additionally, we note the instructions do not include separate instructions for administration via feeding tube. Furthermore, we note inconsistencies in terminology to describe how to stir the suspension and expression of “unit of time.” For example, the PI and PPI states “(b) (4) ...”	Lack of clarity and consistency may lead to confusion and dosing errors.	To improve for clarity, and to be in alignment with the container label and carton labeling, we recommend the following: Revise the instructions “(b) (4)” to read: “Empty contents of one packet in a cup containing 8 ounces of room temperature water and stir (b) (4). Take orally or administer via feeding tube within 60 minutes of

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	within 1 hour...” whereas the container label and carton labeling states “Sir well...within 60 minutes.”		preparation” or something similar. We defer to OPQ and Clinical for final determination for appropriate instructions, language, and terminology (i.e., (b) (4) and 60 minutes vs 1 hour). Also, refer to recommendation number two under the heading “<i>PI and PPI – General Issues</i>” above for discussion of the container terminology. • Include specific and separate instructions for feeding tube administration. We also defer to OPQ and Clinical for final determination on appropriate instructions (i.e., language) for feeding tube administration. Ensure, the administration and preparation instructions and whichever terms are used in the PI and PPI are consistent across all labels and labeling.
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	The Dosage Forms and Strengths includes (b) (4). Additionally, we note that the package type “single-	(b) (4) could lead to misinterpretation of the strength resulting in potential dosing errors.	We recommend revising the Dosage Form and Strength statements “Powder for oral suspension” and “(b) (4) containing 3 g sodium

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	dose” and the description of the powder is not included.	Lack of identifying characteristics may prevent users from easily identifying the product (e.g., white to yellow powder) and is not presented in accordance with 21 CFR 201.57(c)(4)(ii).	phenylbutyrate and 1 g taurursodiol” to read: “For oral suspension: white to yellow powder packaged in single-dose packets. Each packet contains 3 g sodium phenylbutyrate and 1 g taurursodiol.” Also, refer to recommendations number two and three under the heading “<i>PI and PPI- General Issues</i>” above for discussion of the container terminology and the dosage form statement. We defer to OPQ for the appropriateness of including (b) (4) and the appropriate format.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The storage statement does not include the Fahrenheit temperature range.	All of the temperature ranges for which the product can be stored should be clearly displayed to prevent the risk of administration of deteriorated drug product.	Revise the storage statement to read “Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.”
2.	The “How Supplied” section can be improved.	The readability of the How Supplied/Storage and Handling information in Section 16 of the PI can be improved to increase the prominence of critical information.	We recommend adding the following sub-headings to improve readability: 16.1 How Supplied 16.2 Storage
3.	The packaging configuration/units in	To improve readability and remove unnecessary	Revise Section 16 to include the associated NDC number.

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	which the dosage form is ordinarily available for prescribing by practitioners as presented in Section 16 in not clear and is confusing. Also, we note the National Drug Code (NDC) for each sellable package configuration is not included in Section 16.	packaging information (i.e., (b) (4) . Additionally, to be in accordance with 21 CFR 201.57 (c)(17)(iii), the NDC number should be listed for each of the package configurations in the “How Supplied” section.	Additionally, we recommend revising the statements “ (b) (4) to read as follows or something similar: “ TRADENAME for oral suspension is supplied as single-dose packets containing white to yellow powder. Each packet contains 3 g sodium phenylbutyrate and 1 g taurursodiol. Carton of 7 single-dose packets (NDC #: 73063-035-04) Carton of 4 boxes. Each box contains 14 single-dose packets for a total of 56 single-dose packets (NDC #: 73063-035-03).”
Full Prescribing Information – Section 17 Patient Counseling			
1.	This section does not include instructions to inform/advise patients regarding proper preparation and administration of TRADENAME.	Lack of counseling instructions directed to the patients for preparation and administration of TRADENAME both orally and through a feeding tube may	We recommend including counseling instructions directed to the patient specifying how to prepare/administer TRADENAME. For example, “Advise patients to take TRADENAME before a snack or

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		result in preparation and administration errors.	meal. (b) (4) Direct patients to empty the entire contents of the TRADENAME packet into a cup containing 8 ounce of room temperature water. Patients should be told to stir the mixture well and drink it within 60 minutes [see Dosage and Administration (2)].” We defer to OPQ and Clinical for the appropriate terminology (i.e., (b) (4)) and (i.e., 60 minutes or 1 hour). We also defer to OPQ and Clinical for the final determination on the appropriate instructions (i.e., language) for oral use as well as providing instructions for feeding tube administration. Ensure, the instructions and whichever terms are used in the PI and PPI are consistent across all labels and labeling.
Patient Information (PPI)			
1.	The preparation and administration instructions are not clearly written and contain an undefined abbreviation. Additionally, we note the instructions do not include separate	Lack of clarity and consistency may lead to confusion and dosing errors.	We defer to the patient labeling team for appropriate instructions for oral administration as well as through a feeding tube. Also, refer to recommendation number two under the heading “Full PI - Section 2 Dosage and Administration and Patient

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	instructions for feeding tube administration.		<i>Information (PPI)</i> ” above for discussion of dosage and administration information in the full PI.
2.	We note inconsistencies in terminology for describing how to stir the suspension and expression of “unit of time.” For example, the PI and PPI states “(b) (4) ... within 1 hour...” whereas the container labels and carton labeling states “Sir well...within 60 minutes.”	Lack of clarity and consistency may lead to confusion and dosing errors.	We defer to the Patient labeling team for appropriate terminology (i.e., (b) (4)) and (i.e., 60 minutes or 1 hour). Ensure whichever terms are used in the PPI are consistent across all labels and labeling. Also, refer to recommendation number two under the heading “<i>Full PI - Section 2 Dosage and Administration and Patient Information (PPI)</i>” above for discussion of dosage and administration information in the full PI.
3.	Product Title: The presentation of the dosage form (i.e., powder for oral suspension) is not consistent with USP requirements. Additionally, the non-proprietary name “sodium phenylbutyrate/ ursodoxicoltaurine” is not the accepted official USAN name. We also note the slash “/” used between the two ingredients.	To be consistent with the USP requirements and the official USAN name. Additionally, the slash mark “/” in “sodium phenylbutyrate/ taurursodiol” could be misinterpreted to mean “sodium phenylbutyrate or taurursodiol” instead of “sodium phenylbutyrate and taurursodiol.”	Revise title to read “ TRADENAME (pronunciation) (sodium phenylbutyrate and taurursodiol) for oral suspension.” Also, refer to recommendation number one under the heading “<i>PI and PPI-General Issues</i>” for discussion of proposed proprietary name, (b) (4), which has been found unacceptable.
4.	The patient/caregiver is not told how to store the	The absence of storage instructions for the	We recommend including a section titled “How should I

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	product in the patient information labeling.	patient/caregiver may contribute to deteriorated drug medication errors.	store (b) (4) ?” as well as instructions to “Store TRADENAME for oral suspension at room temperature between 68°F to 77°F (20°C to 25°C). Protect from moisture.” We defer to the patient labeling team for the appropriate storage statement format.

5 RECOMMENDATIONS FOR AMYLYX PHARMACEUTICALS, INC

Table 3. Identified Issues and Recommendations for Amylyx Pharmaceuticals, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	The proprietary name, (b) (4), is used on the container label and carton labeling.	We reference our January 25, 2022 Proprietary Name Request Denial Letter informing you that the proposed proprietary name, (b) (4), was found to be unacceptable.	Remove the proposed proprietary name, (b) (4), from all labels and labeling. You may replace it with a “TRADENAME” placeholder until a new name is found to be conditionally acceptable.
2.	As, currently presented, the color used for the proprietary name can be improved for ease of readability.	The chosen color for the proprietary name could pose issues with readability considering the low color contrast between the (b) (4) green font and the white background. Inability to read this important information may lead to product selection medication errors.	If you plan to use the same or similar font color for your new (proposed) proprietary name, then we recommend you ensure there is adequate color contrast to support ease of readability. Also refer to comment number one directly above.

Table 3. Identified Issues and Recommendations for Amylyx Pharmaceuticals, Inc (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	We note inconsistencies between the placement of your bar codes on your container label and carton labeling. We also note the presence of 2 QR barcodes on the container label (front and back) and the 7-count carton labeling. Furthermore, we note that the QR barcode is located near the linear barcode on the principal display label of the container label (back panel).	It is unclear what is being presented in your product identifier on your container label and carton labeling and which of the barcodes are intended for product identification or are for internal use. In addition, it is unclear why there are two QR bar codes on your container label and 7-count carton labeling. Since the drug barcode is often used as an additional verification before drug administration in the inpatient setting, the presence of multiple barcodes may be confusing to healthcare providers and may lead to scanning errors. ^c	Identify what information is contained in each of the bar codes on your container label and all carton labeling. Also clarify why 2 QR barcodes appear on the container label and 7-count carton labeling. Additionally, ensure there is sufficient white space between the linear barcode and QR barcode to prevent confusion between the two bar codes. For further guidance we recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf
4.	The format for the expiration date is not defined.	Lack of a clearly defined expiration date may cause confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only

^c Institute for Safe Medication Practices. Safety briefs: More barcodes than needed. ISMP Med Saf Alert Acute Care. 2014;19(2):1-3.

Table 3. Identified Issues and Recommendations for Amylyx Pharmaceuticals, Inc (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
5.	The presentation of the finished dosage form (i.e., powder for oral suspension) is not in alignment with USP requirements [General chapter <1121>) nomenclature].	The dosage form is designated as “powder for oral suspension” is inconsistent with the USP requirements for this type of pharmaceutical dosage form which is “for oral suspension.”	We recommend revising the dosage form “powder for oral suspension” to read “for oral suspension” on all panels of the container label and carton labeling.
6.	It is not immediately clear that the product strength (i.e., 3 g/1 g) is the amount per single unit (one packet).	Failure to express the designated strength as the amount per single unit (i.e., 3 g/1 g per packet) may lead to wrong dose medication errors. ^d	We recommend revising the strength statement “3 g/1 g” on the container label and all carton labeling to read “3 g/1 g per packet” so there is no confusion as to how many packets are needed for one dose or how much product is

^d Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

Table 3. Identified Issues and Recommendations for Amylyx Pharmaceuticals, Inc (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			contained in a single unit as compared to the total contents of the entire carton. Also refer to recommendation number six directly below.
7.	The statement of strength and dosage form lacks sufficient prominence and is difficult to read. Additionally, we note that the location of the strength and dosage form is not consistent across the container label and carton labeling (i.e., either appearing below the established name or to the far-right of the established name). Furthermore, we note that the statement of strength appears before the dosage form.	We are concern that users may have difficulty reading the statement of strength and dosage form due to lack of prominence and varying locations, specifically where the strength and dosage form appears to the far right of the established name. Additionally, displaying the strength statement before the dosage form is not the customary order for this information which may hinder a provider's ability to quickly and easily identify this information on the label.	To increase readability, we recommend increasing the prominence/size of the expression of strength "3 g/1 g per packet" and dosage form "for oral suspension." If more space is needed for this critical information, consider (b) (4) Additionally, we recommend that the strength and dosage form be presented in a consistent location throughout the label and labeling. Specifically, we recommend the dosage form appear after or below the established name followed by the strength statement. For example, Tradename (sodium phenylbutyrate and taurursodiol) for oral suspension 3 g/1 g per packet Also refer to recommendation number five directly above.
8.	We note a slash "/" is used between the two active ingredients. This format is not in alignment with the FDA guidance for Industry	The slash mark "/" in "sodium phenylbutyrate and taurursodiol" could be misinterpreted to mean "sodium phenylbutyrate or taurursodiol" instead of	We recommend replacing the slash symbol between the two ingredients with the word "and" throughout the labels and labeling as follows:

Table 3. Identified Issues and Recommendations for Amylyx Pharmaceuticals, Inc (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	Product Title guidance (lines 223 through 229) ^e and USP nomenclature guidelines. ^f	“sodium phenylbutyrate and taurursodiol.”	“sodium phenylbutyrate and taurursodiol”.
9.	We note the undefined abbreviation “oz” in the preparation instructions.	Misinterpretation and confusion over abbreviations may lead to prescribing or administration errors.	To provide clarity and minimize the potential for misinterpretation, we recommend replacing the abbreviation “oz” with its intended meaning “ounce” across all labels and labeling.
10.	The preparation instructions can be improved for clarity. We also note there are two potential routes of administration, oral and feeding tube, but as currently presented, the preparation instructions states (b) (4) ”	Unclear instructions may result in preparation and administration errors. Additionally, the instruction (b) (4) does not describe administration via all intended routes of administration (i.e., oral or via feeding tube).	We recommend revising the preparation instruction as follows: “Empty contents of one packet in a cup containing 8 ounces of water. Stir well and take (or administer) within 60 minutes of preparation.”
11.	The recommended dosage statement can be improved.	To ensure consistency with the prescribing information and across the container label and carton labeling.	<u>Carton</u> : Revise the statement, “(b) (4)” to read “Recommended Dosage: See prescribing information.” <u>Container</u> : Revise the statement, “(b) (4)” to read “Recommended Dosage: See prescribing information.”
Container Label			

^e Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-title-and-initial-us-approval-highlights-prescribing-information-human-prescription-drug-and>

^f Available from: <https://www.usp.org/sites/default/files/usp/document/usp-nomenclature-guidelines.pdf>

Table 3. Identified Issues and Recommendations for Amylyx Pharmaceuticals, Inc (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The storage statement does not contain the unit of measure and temperature scale designation (i.e., °C and °F) after each numerical value.	Misinterpretation of the storage statement may pose a risk of drug degradation.	We recommend including the degree symbol and, if space allows, the temperature scale after each numeric value denoting temperature ranges. For example, revise “68 to 77°F” to read “68°F to 77°F” or “68° to 77°F” to increase clarity.
Carton Labeling			
1.	We note that the package term “single-dose” is missing.	To be consistent with your PI labeling include the package term “single-dose” in the net quantity statement.	Revise the net quantity statement “Contains X or XX packets” to read “Contains X or XX single-dose packets.”
2.	The storage statement does not contain the unit of measure and temperature scale designation (i.e., °C and °F) after each numerical value.	Misinterpretation of the storage statement may pose a risk of drug degradation.	We recommend including the degree symbol and temperature scale after each numeric value denoting temperature ranges. For example, revise “68 to 77°F” to read “68°F to 77°F” to increase clarity.
3.			
4.			
4.	We note duplicate statements appear on the principal display panel (PDP) and on the back or side panels of all carton labeling (e.g.,	Clutter on the PDP, including duplicative statements, may reduce readability.	To ensure important information is the most prominent on the carton labeling, and to increase the white space for ease of

(b) (4)

Table 3. Identified Issues and Recommendations for Amylyx Pharmaceuticals, Inc (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	preparation statement, storage statement, total packet contents statement, dosage statement).		readability consider the following: <u>7-count Carton:</u> We recommend deleting from the PDP the duplicate (b) (4) (b) (4) . You may also consider enlarging the preparation statement on the PDP (b) (4) (b) (4) <u>56-count Cartons:</u> We recommend deleting from the PDP the (b) (4) (b) (4) . You may also consider enlarging the preparation statement on the PDP and (b) (4) (b) (4)
Packaging			
1.	We note that you intend to package 4 boxes (smaller cartons) each containing 14 single-dose packets into one larger (outer) carton for a total of 56 packets; however, it is unclear if you intend		(b) (4)

Table 3. Identified Issues and Recommendations for Amylyx Pharmaceuticals, Inc (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4)		

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for sodium phenylbutyrate and taurursodiol that Amylyx Pharmaceuticals, Inc submitted on October 29, 2021.

Table 4. Relevant Product Information for sodium phenylbutyrate and taurursodiol	
Initial Approval Date	N/A
Active Ingredient	sodium phenylbutyrate and taurursodiol
Indication	Treatment of Amyotrophic Lateral Sclerosis (ALS)
Route of Administration	Oral and via feeding tube
Dosage Form	for oral suspension (Single dose packets of powder)
Strength	3 grams/1 gram
Dose and Frequency	For the first 3 weeks of treatment, take 1 sachet daily. After 3 weeks, dosing should be increased to 1 sachet twice a day.
How Supplied	The primary packaging of the drug product is a laminate-pouch sachet. The secondary packaging configurations are: • Seven individual sachets filled into a carton (7 sachets total) • 14 individual sachets filled in a small carton; 4 small cartons are packed into a larger carton (56 packets total).
Storage	Store at controlled room temperature 20°C to 25°C; excursions permitted to 15°C to 30°C. Protect from moisture.
Container Closure	Laminate Pouch (b) (4) (b) (4)

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁹ along with postmarket medication error data, we reviewed the following sodium phenylbutyrate and taurursodiol labels and labeling submitted by Amylyx Pharmaceuticals, Inc.

- Container labeling received October 29, 2021
- Carton labeling received on October 29, 2021
- Patient Information received on November 2021, available from <\\CDSESUB1\evsprod\nda216660\0001\m1\us\patient-information.pdf>
- Prescribing Information (Image not shown) received on October 29, available from <\\CDSESUB1\evsprod\nda216660\0001\m1\us\draft-labeling-text.pdf>

F.2 Label and Labeling Images

Container label



3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

⁹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

BEVERLY WEITZMAN
02/25/2022 10:57:05 AM

STEPHANIE L DEGRAW
02/25/2022 11:09:58 AM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA-216660
Submission Number	001 (New NDA)
Submission Date	10/29/2021
Date Consult Received	11/9/2021
Drug Name	Phenylbutyrate and Taurursodiol
Indication	Amyotrophic Lateral Sclerosis
Therapeutic Dose	Initial treatment of 1 sachet daily (as once daily) for (b) (4) 21 days followed by 2 sachets daily (as 1 sachet twice daily).
Clinical Division	DN1
Protocol Review	This QT assessment plan was not submitted for review and concurrence.

Note: Any text in the review with a light background should be considered to be copied from the sponsor's document.

This review responds to your consult dated 11/9/2021 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Sponsor's clinical study protocol # A35-002 (SN0001; [link](#));
- Sponsor's statistical analysis plan # A35-002 (SN0001; [link](#));
- Sponsor's cardiac safety report # A35-002 (SN0004; [link](#));
- Sponsor's clinical study report # A35-002 (SN0001; [link](#));
- Sponsor's proposed product label (SN0001; [link](#)); and
- Highlights of clinical pharmacology and cardiac safety (SN0004; [link](#)).

1 SUMMARY

No large mean increases (i.e., >20 msec) in the QTcF interval was detected in this QT assessment of AMX-3500 (phenylbutyrate and taurursodiol combination) at the therapeutic dose. We are reluctant to draw conclusions of lack of an effect in an absence of a positive control or large exposure margin, or an integrated nonclinical safety assessment conduct according to best practices (ICH S7b Q&A 1.1 and 1.2).

The effect of AMX-3500 was evaluated in Study # A35-002. This was an open-label, single dose, cross-over study evaluating effect of food on the pharmacokinetics of phenylbutyrate and taurursodiol in healthy subjects. The highest dose evaluated was single dose of AMX-3500 (a combination of 3 g phenylbutyrate and 1g taurursodiol) at the proposed therapeutic dose level. The high clinical exposure scenario was not identified as the Applicant did not perform clinical pharmacology studies characterizing potential increases in exposure of parent drugs and metabolites due to drug interaction or organ impairment.

Data were analyzed using by-time analysis as the primary analysis, which did not suggest that phenylbutyrate and taurursodiol combination is associated with large mean increases in the QTcF interval (refer to Section 4.3) – see Table 1: Point Estimates and the 90% CIs (FDA Analysis) for overall results.

Table 1: Point Estimates and the 90% CIs (FDA Analysis)

ECG Parameter	Treatment	Time (h)	Δ QTcF (msec)	90% CI (msec)
QTc	AMX-3500, Single Dose	5.0	-3.0	(-7.0 to 8.0)
QTc	AMX-3500, Single Dose, Fed	7.0	1.5	(-7.0 to 8.0)

For further details of the FDA analysis, please see Section 4.

Findings of this analysis are further supported by the available categorical analysis (Section 4.4).

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

For characterization of QT effects of AMX-3500, the sponsor measured ECGs in 2 clinical studies (Study # A35-002 & CENTAUR). This assessment plan was not submitted to the IRT previously for agreement. Neither study is adequate as a substitution for a thorough QT study as per ICH E14 Q&A (R3) 5.1. Study # A35-002 was acceptable to exclude large mean increases (>20 msec) in the QTc interval at the therapeutic dose level (ICH E14 Q&A (R3) 6.1). Because the high clinical exposure scenario has not been identified, potential effects of parent drugs and metabolites on QTc at higher exposure are unknown.

We defer to the Division whether exclusion of large QT effects (i.e., >20 msec) is acceptable for the proposed indication. If not, we recommend that the sponsor conducts a TQT study, and the protocol should be submitted for our review.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN001 ([link](#)) from the CSS-IRT. Our changes are highlighted ([addition](#), ~~deletion~~). Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

(b) (4)

We propose to use labeling language for this product consistent with the “Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format” guidance.

3 SPONSOR’S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Amylyx Pharmaceuticals, Inc., is developing a combination of phenylbutyrate and taurursodiol ((b) (4)) for the treatment of amyotrophic lateral sclerosis. Phenylbutyrate (PB, sodium salt; MW: 186.2 Da) is a pan-histone deacetylase (HDAC) inhibitor which is believed to reduce endoplasmic reticulum stress through upregulation of chaperone proteins. Taurursodiol (taurine conjugate of ursodiol, TURSO, tauroursdeoxycholic acid, TUDCA; MW: 535.7 Da, dihydrate) is an ambiphilic (endogenous) bile acid which is expected to ameliorate mitochondrial stress by reducing mitochondrial permeability and increasing the apoptotic threshold of the cell. The sponsor expects synergistic activity in reducing neuronal death with the combination of sodium phenylbutyrate and taurursodiol offering simultaneous reduction of endoplasmic reticulum stress and mitochondrial stress. Phenylbutyrate is approved in the US for urea cycle disorders (NDA-020572, NDA-020573, and NDA-203284). Taurursodiol is approved ex-US for the treatment of biliary disorders.

The product is formulated as powder for suspension (fine to large granules in 10 g sachet; to be vigorously stirred with a cup of water) containing 3 g sodium phenylbutyrate and 1 g taurursodiol for oral administration (each sachet contains ~((b) (4)) mg of sodium). The proposed therapeutic dose includes initial treatment of 1 sachet daily (as once daily, under fed conditions) for ((b) (4)) 21 days followed by 2 sachets daily (as twice daily, under fed conditions). The peak concentrations of ~188 µg/mL (Tmax: ~0.5 h; half-life: ~0.46 h) for phenylbutyrate and ~0.741 µg/mL (Tmax: ~4.5 h; half-life: ~4.3 h) for taurursodiol were observed following single dose (Study # A35-002, under fasting conditions). The sponsor expects minimal accumulation for phenylbutyrate and taurursodiol (cross-study comparison) at steady state with the proposed maximum therapeutic dose.

No human mass balance study was conducted by the sponsor. The sponsor states that phenylbutyrate is extensively metabolized to phenylacetate (PAA: Cmax: ~26 µg/mL; Tmax: ~2.5 h; half-life: ~0.8 h) which is conjugated with glutamine via acetylation forming phenylacetylglutamine. Similarly, taurursodiol is reported to be deconjugated in the intestinal tract and liver forming ursodiol (UDCA, endogenous bile acid; Cmax: ~639 ng/mL; Tmax: ~6 h; half-life: ~4.77 h) which is conjugated with glycine to form glycine-ursodiol (GUDCA, endogenous bile acid; Cmax: ~381 ng/mL; Tmax: ~16 h; half-life: ~12 h) or taurine back to taurursodiol. Sponsor claims that both phenylbutyrate and taurursodiol are not significantly metabolized by the CYP450 enzymes and highlights that it has a low drug interaction potential as a victim drug. Thus, no formal clinical drug interaction studies have been conducted by the sponsor. The sponsor further highlights that the pharmacokinetics of phenylbutyrate and taurursodiol and their metabolites are not expected to be altered significantly in subjects with mild renal impairment and it was not studied in

subjects with moderate and severe renal impairment as well as end-stage renal disease. Similarly, the effect of hepatic impairment on the pharmacokinetics of phenylbutyrate and taurursodiol has not been studied.

For characterization of QT effects of AMX-3500 (a combination of 3 g phenylbutyrate and 1g taurursodiol), the sponsor measured ECGs in 2 clinical studies (Study # A35-002 & CENTAUR). This assessment plan was not submitted to the IRT previously.

Study # A35-002 was an open-label, single dose, 2 sequence, 2-period, cross-over study evaluating effect of food on the pharmacokinetics of phenylbutyrate and taurursodiol in healthy subjects (n=14). Subjects received a single dose of AMX0035 on 2 occasions (under fasting conditions or under fed conditions with a high-fat standardized meal). PK and ECGs (digital, triplicate) were acquired at pre-dose and at 1, 2, 3, 4, 5, 6, 7, 12 and 24 hours on Days -1 and 1. The exposure-response analysis was performed using a combined safety-PK analysis set. Data were analyzed using exposure-response analysis.

CENTAUR was a randomized, double-blind, placebo-controlled, parallel-group, study evaluating the safety, tolerability, efficacy, pharmacokinetics, and pharmacodynamics (biological activity) of AMX-3500 (as 1 sachet once daily for the first 3 weeks followed by 1 sachet twice daily; 24 weeks double-blind treatment period) in adult patients with sporadic or familial ALS. Subjects were randomized in a 2:1 ratio to receive either AMX0035 or matching placebo and visits were scheduled at screening, baseline (Day 1, initiation of study medication administration), and Weeks 3, 6, 12, 18, and 24. ECGs were collected at screening, at weeks 12 and 24 (or ET).

Since both studies were not adequate for substitution of a thorough QT study as per ICH E14 Q&A (R3) 5.1, Study # A35-002 was evaluated for exclusion of large mean increases (>20 msec) in the QTc interval (ICH E14 Q&A (R3) 6.1) at therapeutic doses.

3.1.2 Nonclinical Safety Pharmacology Assessments

Refer to the sponsor's highlights of clinical pharmacology and clinical safety.

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

In the sponsor's by-time analysis, AMX0035 excluded 20 msec threshold at the (therapeutic) dose level for $\Delta QTcF$. Sponsor provided descriptive statistics for all intervals.

Reviewer's comment: FDA reviewer provided non-parametric descriptive statistics for all intervals. Results are similar. Please see Section 4.3 for additional details.

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., >500 msec or >60 msec over baseline).

Reviewer's comment: FDA reviewer's analysis also shows no outliers for QTcF and Δ QTcF. FDA reviewer could not locate categorical analysis for other intervals in sponsor's report. FDA reviewer performed categorical analysis for all other intervals (HR, PR and QRS). One subject experienced HR greater than 100 beats/min in one treatment arm. Please see Section 4.4 for additional details.

3.2.3 Exposure-Response Analysis

The sponsor performed PK/PD analysis to explore the relationship between concentration of components of AMX0035 (PB and its metabolite PAA as well as TURSO and its metabolites UDCA and GUDCA) and Δ QTcF (change from baseline in QTcF) using a linear mixed-effects approach on all subjects in the analysis data set for cardiac assessment (Study # A35-002).

The model predicted Δ QTcF (upper confidence interval) values of -4.24 (0.56) msec at the mean peak concentrations of PB following single oral dose of AMX0035 (geomean C_{max} ~183.17 µg/mL). Similarly, the model predicted Δ QTcF (upper confidence interval) values of -5.14 (-2.75) msec at the mean peak concentrations of PAA (geomean C_{max} ~14.87 µg/mL). For TURSO, the model predicted Δ QTcF (upper confidence interval) values of -0.67 (1.60) msec at the mean peak concentrations of TURSO (geomean C_{max} ~0.61 µg/mL). The results of the sponsor's analysis suggest no large mean increased in QT interval at the proposed therapeutic dose under fed or fasting conditions.

Reviewer's comment: Study # A35-002 was not adequate for substitution of a thorough QT study as per ICH E14 Q&A (R3) 5.1, as it was neither a TQT study nor did it include - the PK and ECG data at a sufficiently high multiples of the clinically relevant exposure (e.g., twice the supratherapeutic exposures) such that a separate positive control would not be necessary (see ICH E14 Section 2.2.2). The reviewer did not conduct concentration-QTc analysis as there was no adequate data to select appropriate exposure metrics in presence of multiple drug-related moieties. Moreover, the expected high clinical exposure scenario is unknown for these moieties. As a conservative measure, the reviewer recommends reporting study finding based on central tendency analysis to exclude large mean increases (i.e., >20 msec) in the QTc interval (ICH E14 Q&A (R3) 6.1).

3.2.4 Cardiac Safety Analysis

Only one treatment emergent adverse event (TEAE) was reported in study A35-002. One subject after administration of AMX0035 under fed condition experienced musculoskeletal pain that led to withdrawal of the study drug.

In study AMX3500, the safety population included 89 subjects exposed to AMX0035 and 48 subjects exposed to placebo. Over the course of the 24-week, double-blind study, 5 subjects (6%) in the AMX0035 group and 2 subjects (4%) in the placebo group died. The majority of the deaths were caused by respiratory failure/arrest (5 out of 7), 3 following AMX0035 and 2 following placebo. Other causes of death were subdural hematoma and diverticular perforation. All deaths were unlikely related or not related to the study drug.

Similar number of subjects experienced any TEAE following AMX0035 (96.6%) and placebo (95.8%). More subjects had study medication withdrawn due to a TEAE following AMX0035 (20.2%) than placebo (10.4%). TEAEs leading to discontinuation of study medication occurred in more than 1 subject were diarrhea (5 subjects), respiratory failure (3 subjects), abdominal pain upper (2 subjects), dysgeusia (2 subjects), and nausea (2 subjects).

There was an imbalance in cardiac AEs. All 8 treatment emergent cardiac AEs (TECAEs) occurred in 7 subjects were from the AMX0035 treatment group (5.1%), including cardiac arrest (SAE, fatal, 1 subject), atrial fibrillation (2 subjects), palpitation (2 subjects), tachycardia (1 subject), first degree AV block (1 subject), and left bundle branch block (1 subject). Three cardiac events were assessed as possibly related to AMX0035 (first degree AV block, bundle branch block left, and one atrial fibrillation).

- A 74-year-old patient had a cardiac arrest at home 19 days after starting treatment. She died 3 days later in the hospital. The patient was found to have aspiration pneumonia that led to the pulseless electrical activity (PEA). There were no known cardiac risk factors except for hypertension. The patient also developed paroxysmal AF while in the study, though its precise timing with regards to the cardiac arrest is not known. The PI considered the cardiac arrest unlikely related to AMX0035 and the AF possibly related.

Two subjects in placebo group (4.2%) and 8 subjects in the treatment group (9.0%) had treatment emergent ECG abnormalities (TEEA). The most common ones were flat T-waves (4 subjects), sinus tachycardia (3 subjects), left anterior hemiblock (3 subjects), and inverted T-wave (2 subjects).

All TECAEs and TEEAs were reviewed by expert cardiologist (b) (4). The report ([link](#)) concluded that the incidence of cardiac events in this double-blind study in 137 ALS subjects was low and that incidence of ECG abnormalities was similar between the groups.

During the randomized controlled period and open label extension (OLE) period of AMX3500, there was 1 case of electrocardiogram QT prolonged, 5 cases of syncope (5 subjects), 1 case of seizure, and 1 case of cardiac arrest. There were no cases of ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation or Torsades de Pointes. One seizure suffered by a 57-year-old female occurred during the respiratory failure was due in part to ALS progression and in part to pneumonia and it was considered not related to the study drug.

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., significant ventricular arrhythmias) occurred in this study. The one seizure and one cardiac arrest were considered unlikely related to the study drug.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| <10 beats/min) were observed (Section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Paper ECGs were submitted. Automatic measurements were used in analysis. Overall, ECG acquisition and interpretation in this study appear acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG. The statistical reviewer evaluated the ΔQTcF effect using descriptive (nonparametric) statistics.

4.3.1 QTc

Figure 1 displays the time profile of ΔQTcF for different treatment groups. The maximum ΔQTcF values by treatment are shown in Table 2.

Figure 1: Median and 90% CI of ΔQTcF Time-course (unadjusted CIs).

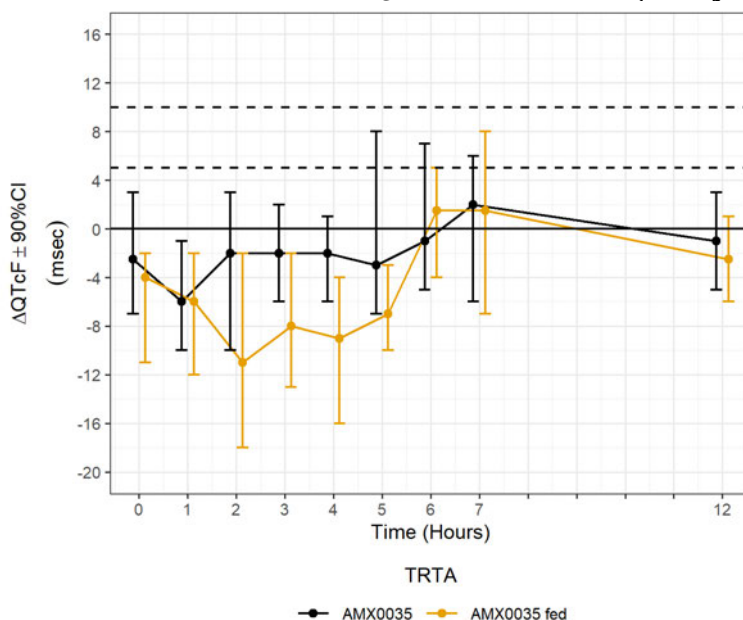


Table 2: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔQTcF

Actual Treatment	N	Time (Hours)	ΔQTcF (msec)	90.0% CI (msec)
AMX0035	13	5.0	-3.0	(-7.0 to 8.0)
AMX0035 fed	14	7.0	1.5	(-7.0 to 8.0)

4.3.1.1 Assay Sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔHR for different treatment groups. The maximum ΔHR values by treatment are shown in Table 3.

Figure 2: Median and 90% CI of ΔHR Time-course

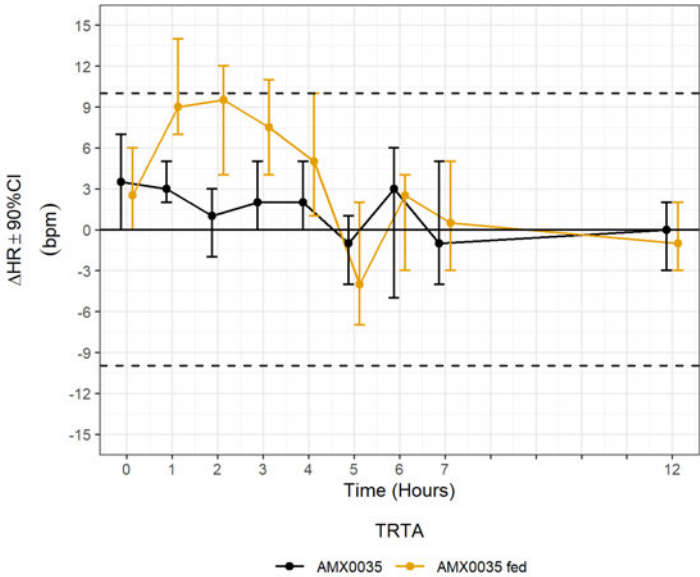


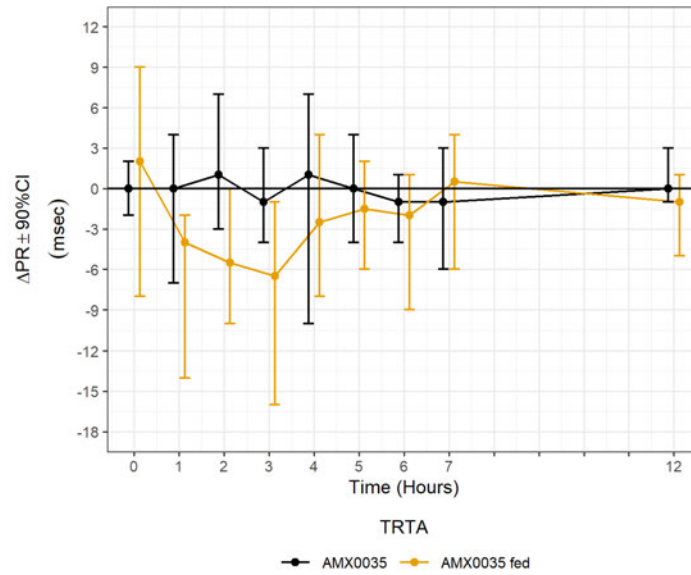
Table 3: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔHR

Actual Treatment	N	Time (Hours)	ΔHR (bpm)	90.0% CI (bpm)
AMX0035	14	0.0	3.5	(0.0 to 7.0)
AMX0035 fed	14	1.0	9.0	(7.0 to 14.0)

4.3.3 PR

Figure 3 displays the time profile of ΔPR for different treatment groups.

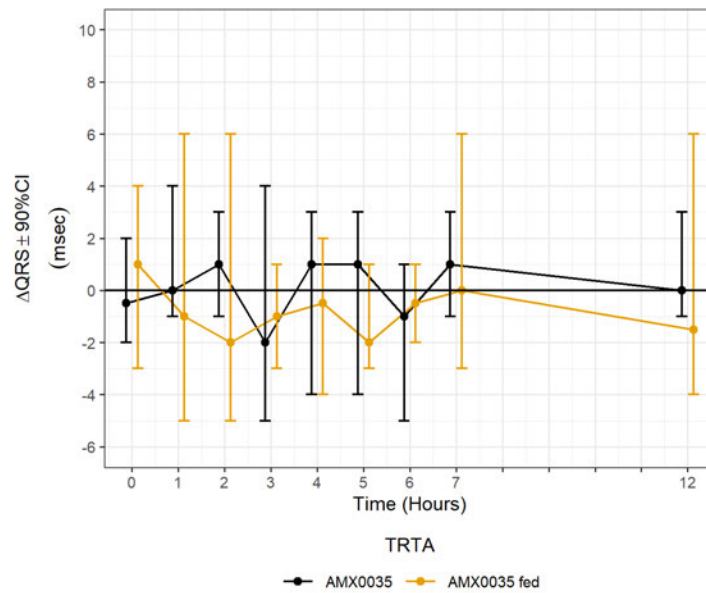
Figure 3: Median and 90% CI of Δ PR Time-course



4.3.4 QRS

Figure 4 displays the time profile of Δ QRS for different treatment groups.

Figure 4: Median and 90% CI of Δ QRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

None of the subjects experienced QTcF >450 msec with or without a change from baseline >60 msec and none of the subjects experienced Δ QTcF >60 msec in any of the treatment groups.

4.4.2 HR

Table 4 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). One subject in AMX0035 fed group experienced HR greater than 100 beats/min.

Table 4: Categorical Analysis for HR (maximum)

Actual Treatment	Total (N)		Value ≤100 bpm		Value >100 bpm	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
AMX0035	14	118	14 (100.0%)	118 (100.0%)	0 (0%)	0 (0%)
AMX0035 fed	14	126	13 (92.9%)	124 (98.4%)	1 (7.1%)	2 (1.6%)

4.4.3 PR

None of the subjects experienced PR >220 msec with and without 25% increase over baseline in any of the treatment groups.

4.4.4 QRS

None of the subjects experienced QRS >120 msec with and without 25% increase over baseline in any of the treatment groups.

4.5 EXPOSURE-RESPONSE ANALYSIS

The primary analysis was conducted using by-time analysis (Section 4.3) and exposure-response analysis was not conducted by the FDA reviewers.

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/s/

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