Ongoing and Planned Studies to Further Elucidate the Efficacy, Safety, and Pharmacokinetics of Sodium Phenylbutyrate and Taurursodiol in Amyotrophic Lateral Sclerosis

Poster #125

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BACKGROUND

- AMX0035, an oral, fixed-dose combination of sodium phenylbutyrate and taurursodiol (PB&TURSO), significantly slowed functional decline and prolonged survival in participants with amyotrophic lateral sclerosis (ALS) in the CENTAUR trial, encompassing a 24-week, randomized, placebo-controlled phase and an open-label extension phase[1-3]
- In CENTAUR, PB&TURSO was generally well-tolerated with an acceptable safety profile; gastrointestinal events occurred with greater frequency in the PB&TURSO group[1,4]

OBJECTIVES

- To describe the design and status of clinical studies aimed at:
  - Further assessing PB&TURSO efficacy and safety in people living with ALS (PLWALS), including in real-world settings
  - Fulfilling post-marketing requirements by:
    - Examining the potential for drug–drug interactions
    - Evaluating PB&TURSO pharmacokinetics (PK) in specific populations

CONCLUSION

Ongoing and planned studies will further elucidate the efficacy and safety profile of PB&TURSO in ALS

ONGOING AND PLANNED STUDIES

	Studies Further Assessing PB&TURSO Efficacy and Safety in PLWALS		
	PHOENIX[a]	Single-Center Experience	Collaborative Real-World Studies: Payer Database Observational Study
Key inclusion criteria	▪ Clinically definite or clinically probable ALS (revised El Escorial criteria[5]) ▪ <24 months from symptom onset ▪ SVC ≥55%[b]	▪ All PLWALS who received PB&TURSO at a large center affiliated with a US academic institution over timeframe of study ▪ Synthetic or propensity score–matched cohort from center that did not receive PB&TURSO	▪ All PLWALS who received PB&TURSO within a large nationally representative US claims/electronic health record (EHR) database ▪ Propensity score–matched cohort from database that did not receive PB&TURSO
Study design	▪ Phase 3, global trial with 48-week double-blind treatment ▪ Participants completing the double-blind treatment are eligible to enroll in the open-label extension	▪ Retrospective chart review study	▪ Observational study of a large national US payer database comprising claims and/or EHR information
Objective	▪ To assess PB&TURSO efficacy and safety in a larger population and for a longer duration than in CENTAUR	▪ To obtain early insights into real-world use and outcomes associated with PB&TURSO vs propensity score–matched PB&TURSO-naïve cohort	▪ To obtain early insights into real-world use and outcomes associated with PB&TURSO vs propensity score–matched PB&TURSO-naïve cohort
Status	▪ Enrollment complete (N=664) ▪ Topline results anticipated in mid-2024	▪ Ongoing	▪ Ongoing

[a]Clinicaltrials.gov identifier NCT05021536. [b]Of predicted normal value. SVC, slow vital capacity; US, United States.

	Studies Fulfilling Post-Marketing Requirements				
	Studies Examining Potential for Drug-Drug Interactions			Studies Evaluating PB&TURSO Pharmacokinetics in Specific Populations	
	CYP450 Enzyme Substrates	Transporter Protein Substrates	OATP Inhibitors	Hepatic Impairment	Renal Impairment
Key inclusion criteria	▪ Healthy adults aged 18-55 years ▪ Excluded if poor metabolizer[b] of CYP2C8 or CYP2C19 or do not express the CYP2B6 functional protein as determined by genotypic testing	▪ Healthy male aged 18-55 years ▪ Carriers of *OATP1B1 (521CC)* or *BCRP (421AA)* transporter allele with reduced functional activity excluded	▪ Healthy adult aged 18-55 years	▪ Group 1: Normal hepatic function ▪ Group 2: Mild hepatic impairment (Child-Pugh class A [score of 5-6 points])[e] ▪ Group 3: Moderate hepatic impairment (Child-Pugh class B [score of 7-9 points])[e] ▪ Group 4: Severe hepatic impairment (Child-Pugh class C [score of 10-15 points])[e]	▪ Group 1: Normal renal function (eGFR ≥90 mL/min/1.73 m^2) ▪ Group 2: Nondialyzed, mild GFR decrease (eGFR=60-89 mL/min/1.73 m^2) ▪ Group 3: Nondialyzed, moderate GFR decrease (eGFR=30-59 mL/min/1.73 m^2) ▪ Group 4: Nondialyzed, severe GFR decrease (eGFR=15-29 mL/min/1.73 m^2)
Study design	▪ Phase 1, multiple-dose, single-center open-label study	▪ Phase 1, multiple-dose, single-center, open-label study	▪ Phase 1, multiple-dose, single-center, open-label study	▪ Phase 1, multiple-dose, single-center, parallel-group, open-label study	▪ Phase 1, multiple-dose, single-center, parallel-group, open-label study
Objective[a]	▪ To evaluate the effect of multiple doses of PB&TURSO on the PK of a cocktail of selective CYP450 enzyme substrates (caffeine [CYP1A2], omeprazole [CYP2C19], bupropion [CYP2B6], and midazolam [CYP3A]) and a substrate of CYP2C8 (pioglitazone) when PB&TURSO is administered concurrently with drug cocktail[c]/pioglitazone[d]	▪ To evaluate the effect of multiple doses of PB&TURSO on the PK of a cocktail of transporter protein substrates (digoxin, rosuvastatin, and tenofovir)	▪ To evaluate the effects of multiple doses of coadministered OATP1B3 and OATP1B1 inhibitors (atazanavir and ritonavir) on PB&TURSO PK	▪ To evaluate PK characteristics of PB, TURSO, and their major metabolites after single and multiple PB&TURSO doses in participants with hepatic function impairment vs healthy participants	▪ To evaluate PK characteristics of PB, TURSO, and their major metabolites after single and multiple PB&TURSO doses in participants with renal function impairment vs healthy participants
Status	Pending completion				

[a]As a secondary objective, all studies will evaluate safety and tolerability of PB&TURSO in the respective study settings and populations. [b]Poor metabolizers are defined as carriers of CYP2C19*2/*2, CYP2C19*2/*3, or CYP2C19*3/*3 alleles of CYP2C19; CYP2B6*6/*6 or CYP2B6*6/*9 alleles of CYP2B6; or CYP2C8*8 or CYP2C8*3 alleles of CYP2C8 isozymes. [c]Drug cocktail consists of the selective substrates of CYP1A2 (caffeine), CYP2C19 (omeprazole), CYP2B6 (bupropion), and CYP3A (midazolam). Pioglitazone is administered individually. [d]Compared with administration of the drug cocktail/pioglitazone alone. [e]In addition to meeting Child-Pugh criteria, have [1] chronic liver disease and/or cirrhosis documented by ≥1 of the following: (a) liver biopsy results with histological findings consistent with cirrhosis; (b) computerized tomographic or ultrasonographic evidence of hepatic fibrosis, with or without portal hypertension; (c) physical examination evidence of chronic liver disease; and/or (d) colloid shift on a liver-spleen scan; and [2] history of stable cirrhosis based on clinical and/or laboratory evidence.

BCRP, breast cancer resistance protein; CYP450, cytochrome P450; eGFR, estimated glomerular filtration rate; OATP, organic anion-transporting polypeptide.

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Disclosures

JT, MG, RM, JK, and HP are full-time employees of and may have stock option ownership in Amylyx Pharmaceuticals, Inc.

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