Findings From a Pharmacokinetic and Pharmacodynamic Study of Sodium Phenylbutyrate and Taurursodiol in Participants With Amyotrophic Lateral Sclerosis

Poster M217

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BACKGROUND

- Sodium phenylbutyrate and taurursodiol (PB&TURSO) is an oral, fixed-dose combination of 3 g PB and 1 g TURSO[1,2]
  - PB&TURSO is approved for the treatment of amyotrophic lateral sclerosis (ALS) in adults in the United States and approved with conditions in Canada[1,3]
  - The approved PB&TURSO dosing is 1 sachet daily (QD) for the first 3 weeks, then 1 sachet twice daily (BID) thereafter[1]
  - The major metabolites of PB are phenylacetate (PAA) and phenylacetylglutamine (PAGN)[4] and those of TURSO are ursodeoxycholic acid (UDCA) and glycoursodeoxycholic acid (GUDCA)[5]

OBJECTIVE

- Determine pharmacokinetic (PK) parameters of PB, TURSO, and their major metabolites in participants with ALS after single and multiple oral administrations

METHODS

- This was a phase 2a, open-label, sequential period study of PB&TURSO PK in participants with ALS
  - All participants received PB&TURSO
  - Adult participants with sporadic ALS and either not taking or on a stable dose of riluzole or intravenous edaravone were considered eligible for this study
- The study comprised a screening period (≤42 days), Period 1 (14±4 days), and Period 2 (5-25 days)
  - Participants who met all eligibility criteria during the screening period were admitted to Period 1, in which vital signs, weight, and height were collected before administration of the first dose of PB&TURSO and subsequent collection of blood and urine PK samples
  - Participants received 1 dose of PB&TURSO daily throughout Period 1, with dosing escalation according to the label during Period 2
  - In the event of intolerable treatment-emergent adverse events (TEAEs), PB&TURSO dose was reduced; in response to serious AEs, the treatment was stopped
- Urine and blood samples were collected at Period 1 Day 1 (P1D1) after a single dose (treatment naïve), Period 2 Day 1 (P2D1) to evaluate steady state (SS) on QD dosing, and Period 2 Day 15 (P2D15) to evaluate SS on BID dosing

RESULTS

Participants

- Eleven out of 12 screened participants with ALS were enrolled and completed the study
- The mean (SD) age of participants was 61.2 (11.01) years; most were White (81.8%) and male (63.6%) (**Tables 1A & 1B**)

Table 1A. PARTICIPANT BASELINE CHARACTERISTICS

	Male	Female		
Sex, No. (%)	7 (63.6)	4 (36.4)		
	Hispanic	Not Hispanic		
Ethnicity, No. (%)	0 (0)	11 (100)		
	White	Black	Asian	Other
Race, No. (%)	9 (81.8)	1 (9.1)	1 (9.1)	0 (0)

Table 1B. PARTICIPANT BASELINE DEMOGRAPHICS

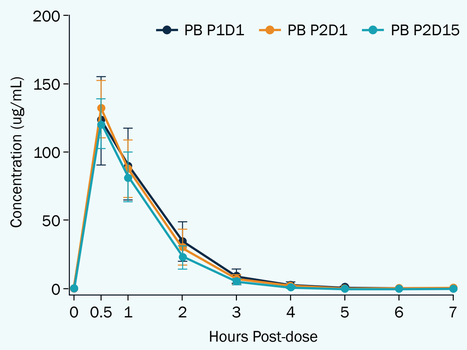
	Mean (SD)	Median	Min, Max
Age, y	61.2 (11.01)	62.0	38, 78
Height, cm	171 (8.1)	175	157, 183
Weight, kg	79.8 (16.5)	78.9	57.1, 113.4
BMI, kg/m^2	27.0 (4.1)	26.1	22.0, 36.9

BMI, body mass index.

Plasma Pharmacokinetics of Sodium Phenylbutyrate and Metabolites

- **Sodium Phenylbutyrate (PB)**
  - After single administration (P1D1), 15 days of QD (P2D1), and 15 days of BID (P2D15), PB was rapidly absorbed with time to maximum concentration (t_{max}) occurring around 30 minutes after dose at each time point (**Figure 1**)
    - No differences were observed in peak concentration (C_{max}) or overall plasma exposure (AUC_{last}) after multiple QD or BID administration (**Table 2**)
  - PB C_{max} accumulation ratio was 0.92, indicating no PB accumulation at SS under QD or BID administration

Figure 1. MEAN PLASMA CONCENTRATION PROFILES OF SODIUM PHENYLBUTYRATE FOR EACH STUDY PERIOD



P1D1 = Period 1 Day 1; P2D1 = Period 2 Day 1; P2D15 = last day of Period 2 (Day 15); PB = sodium phenylbutyrate.

- **Phenylacetic Acid (PAA)**
  - After single administration (P1D1), 15 days of QD (P2D1), and 15 days of BID (P2D15), PAA was rapidly absorbed with t_{max} occurring around 2 hours after dose at each timepoint
  - No differences were observed in C_{max} or AUC_{last} after multiple QD or BID administration (**Table 2**)
- **Phenylacetyl-L-glutamine (PAGN)**
  - After single administration (P1D1), 15 days of QD (P2D1), and 15 days of BID (P2D15), PAGN was rapidly absorbed with t_{max} occurring around 2.5 hours after dose at each timepoint
  - No significant differences were observed in C_{max} and AUC_{last} after multiple QD or BID administration (**Table 2**)

Table 2. SODIUM PHENYLBUTYRATE AND METABOLITES (PAA AND PAGN) PLASMA PK PARAMETERS

PB	P1D1	P2D1	P2D15
C_{max}, µg/mL			
Geometric (G) mean (CV%)	111.64 (53)	127.60 (26)	117.59 (23)
95% CI	90.80-153.78	110.31-152.22	102.11-138.45
AUC_{last}, h*µg/mL			
G mean (CV%)	147.01 (56)	148.67 (42)	132.86 (34)
95% CI	113.64-215.14	118.46-220.76	109.52-169.18
PAA	**P1D1**	**P2D1**	**P2D15**
C_{max}, µg/mL			
G mean (CV%)	17.76 (33)	18.23 (22)	17.21 (22)
95% CI	14.90-22.19	16.07-21.13	15.12-20.03
AUC_{last}, h*µg/mL			
G mean (CV%)	51.45 (34)	53.02 (28)	49.82 (22)
95% CI	43.40-64.15	45.58-63.98	43.75-57.98
PAGN	**P1D1**	**P2D1**	**P2D15**
C_{max}, µg/mL			
G mean (CV%)	51.01 (23)	52.22 (24)	55.26 (27)
95% CI	44.21-60.19	45.20-61.94	47.36-66.55
AUC_{last}, h*µg/mL			
G mean (CV%)	201.24 (21)	201.45 (22)	211.44 (25)
95% CI	177.44-233.01	177.13-233.97	182.87-251.39

Effect of Age, Weight, and Sex on Plasma Sodium Phenylbutyrate PK Parameters

- Age and weight did not affect PB C_{max} or AUC_{last}
  - Following age and weight adjustment, PB C_{max} values were 111.6 µg/mL on P1D1, 127.6 µg/mL on P2D1, and 117.6 µg/mL on P2D15, consistent with the unadjusted values
  - Similarly, PB AUC_{last} values were 147.0 h*µg/mL on P1D1, 148.7 h*µg/mL on P2D1, and 132.9 h*µg/mL on P2D15 following age and weight adjustment, consistent with the unadjusted values
- Exposure to PB was slightly higher in females compared with males
  - Geometric C_{max} values for PB in males and females were 93.5 and 152.3 µg/mL on P1D1, 112.8 and 158.4 µg/mL on P2D1, and 108.6 and 135.2 µg/mL on P2D15, respectively
  - AUC_{last} values for PB in males and females were 116.0 and 222.4 h*µg/mL on P1D1, 121.4 and 211.9 h*µg/mL on P2D1, and 117.3 and 165.2 h*µg/mL on P2D15, respectively
  - However, after weight adjustment, no difference in C_{max} or AUC_{last} values were observed between sexes

Urine PK of PB and Metabolites

- The majority of the PB dose was excreted in urine as PAGN after single or multiple dose PB&TURSO administration (**Table 3**)
- Given the low renal clearance of PB and PAA, sex comparison was only performed for PAGN
  - PAGN renal clearance and total amount of the dose excreted in the urine were higher in male compared with female participants, consistent with the differences observed in the plasma exposure parameters

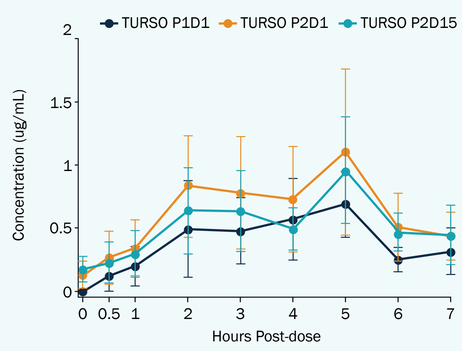
Table 3. PB AND METABOLITES (PAA AND PAGN) URINE PK PARAMETERS

PB	P1D1	P2D1	P2D15
Renal clearance (µg/(h*µg/mL))			
Mean (SD)	13.44 (7.76)	16.44 (7.72)	20.16 (20.52)
Min, max	3.5, 28.8	7.0, 34.2	0.2, 64.4
PAA	**P1D1**	**P2D1**	**P2D15**
Renal clearance (µg/(h*µg/mL))			
Mean (SD)	16.12 (8.94)	15.12 (7.94)	18.16 (18.59)
Min, max	7.9, 31.3	8.3, 29.6	3.4, 62.8
PAGN	**P1D1**	**P2D1**	**P2D15**
Renal clearance (µg/(h*µg/mL))			
Mean (SD)	13743.10 (4827.87)	13860.15 (5810.39)	13181.42 (6602.98)
Min, max	6160.10, 22782.70	7364.60, 24382.40	5773.7, 28740.10

Plasma PK of TURSO and Metabolites

- **TURSO**
  - After single administration (P1D1), 15 days of QD (P2D1), and 15 days of BID (P2D15), TURSO was moderately rapidly absorbed with t_{max} values occurring around 3.5 hours after dose on P1D1 and 4.3 hours on P2D1 and P2D15 (**Figure 2**)
    - No differences were observed in C_{max} or AUC_{last} after multiple QD or BID administration (**Table 4**)
  - TURSO C_{max} accumulation ratio was 0.98, indicating no TURSO accumulation at SS under QD or BID administration

Figure 2. MEAN PLASMA CONCENTRATION PROFILES OF TAURURSODIOL FOR EACH STUDY PERIOD



P1D1 = Period 1 Day 1; P2D1 = Period 2 Day 1; P2D15 = last day of Period 2 (Day 15); TURSO = taurursodiol.

- **UDCA**
  - After single administration (P1D1), 15 days of QD (P2D1), and 15 days of BID (P2D15), UDCA was measurable with t_{max} occurring around 4.2 hours after dose on P1D1, 5.3 hours after dose on P2D1, and 5 hours after dose on P2D15
  - No differences were observed in C_{max} or AUC_{last} after multiple QD or BID administration (**Table 4**)
- **GUDCA**
  - After single administration (P1D1), 15 days of QD (P2D1), and 15 days of BID (P2D15), GUDCA was measurable with t_{max} occurring around 4.8 hours after dose on P1D1 and 4.6 hours after dose on P2D1 and P2D15
  - No differences were observed in C_{max} or AUC_{last} after multiple QD or BID administration (**Table 4**)

Table 4. TURSO AND METABOLITES (UDCA AND GUDCA) PLASMA PK PARAMETERS

TURSO	P1D1	P2D1	P2D15
C_{max}, µg/mL			
G mean (CV%)	0.765 (77)	0.942 (100)	0.923 (71)
95% CI	0.548-1.29	0.608-1.93	0.670-1.51
AUC_{last}, h*µg/mL			
G mean (CV%)	2.41 (63)	3.57 (83)	3.27 (60)
95% CI	1.63-4.01	2.41-6.55	2.33-5.17
UDCA	**P1D1**	**P2D1**	**P2D15**
C_{max}, µg/mL			
G mean (CV%)	0.363 (200)	1.17 (131)	1.40 (81)
95% CI	0.0357-1.49	0.000-4.91	0.900-2.63
AUC_{last}, h*µg/mL			
G mean (CV%)	1.24 (231)	4.50 (140)	5.91 (84)
95% CI	0.278-5.09	0.00-17.4	3.89-11.1
GUDCA	**P1D1**	**P2D1**	**P2D15**
C_{max}, µg/mL			
G mean (CV%)	0.219 (131)	1.98 (61)	1.54 (54)
95% CI	0.0268-0.718	1.22-3.46	1.09-2.38
AUC_{last}, h*µg/mL			
G mean (CV%)	0.790 (109)	8.47 (60)	7.31 (56)
95% CI	0.366-1.93	5.63-14.1	5.22-11.4

Effect of Age, Weight, and Sex on Plasma TURSO PK Parameters

- Age and weight did not affect TURSO or metabolites C_{max} or AUC_{last}
  - Following age and weight adjustment, C_{max} values for TURSO were 0.765 µg/mL on P1D1, 0.942 µg/mL on P2D1, and 0.923 µg/mL on P2D15, consistent with the unadjusted values
  - Similarly, AUC_{last} values for TURSO were 2.41 h*µg/mL on P1D1, 3.57 h*µg/mL on P2D1, and 3.27 h*µg/mL on P2D15 following age and weight adjustment, consistent with the unadjusted values
- Exposure to TURSO was slightly higher in females compared with males
  - Geometric C_{max} values for TURSO in males and females were 0.730 and 0.830 µg/mL on P1D1, 0.785 and 1.29 µg/mL on P2D1, and 0.920 and 0.930 µg/mL on P2D15, respectively
  - AUC_{last} values for TURSO in males and females were 2.24 and 2.72 h* µg/mL on P1D1, 2.72 and 5.74 h*µg/mL on P2D1, and 3.06 and 3.67 h*µg/mL on P2D15, respectively
  - However, after weight adjustment, no difference in C_{max} or AUC_{last} were observed between sexes

Safety and Tolerability

- AEs were coded using Medical Dictionary for Regulatory Activities 24.1 coding dictionary
- AEs were monitored from the time the participant signed the informed consent form until 30 days after the last dose of the study drug
- Ten (90.9%) participants reported at least 1 TEAE (**Table 5**)
  - No participants reported serious AEs or severe AEs
  - No AEs lead to death or participant discontinuation
  - Six (54.5%) participants experienced AEs considered to be related to the study drug

Table 5. TEAEs OCCURRING IN ≥5% OF PARTICIPANTS[a]

	No. (%)		No. (%)
Participants with ≥1 TEAE	10 (90.9)	**Infections and infestations**	2 (18.2)
Reported TEAEs	16	Gastroenteritis	1 (9.1)
Gastrointestinal disorders	5 (45.5)	Nasopharyngitis	1 (9.1)
Diarrhea	4 (36.4)	**Respiratory, thoracic, and mediastinal disorders**	2 (18.2)
Constipation	1 (9.1)	Cough	1 (9.1)
Nervous system disorders	4 (36.4)	Wheezing	1 (9.1)
Dizziness	2 (18.2)	**Injury, poisoning, and procedural complications**	1 (9.1)
Headache	1 (9.1)	Fall	1 (9.1)
Syncope	1 (9.1)		

[a]Participants were only counted once per AE. Participants may have had events in >1 system organ class.

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Disclosures

MG, MSP, AK are full-time employees of and may have stock ownership in Amylyx Pharmaceuticals, Inc. **AY** is a consultant for Amylyx Pharmaceuticals, Inc. **JW, WM, JS** participated in research funded by Amylyx Pharmaceuticals, Inc. **JFW** has been a consultant to Amylyx Pharmaceuticals, Inc.

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CONCLUSIONS

- No differences were observed in C_{max} or AUC_{last} of PB, TURSO, or their metabolites after multiple QD or BID dosing
- Age, weight, and sex (after weight adjustment) did not impact PB, TURSO, or their metabolites' plasma PK
- Consistent with the known safety profile of PB&TURSO, the most common related AEs were diarrhea and dizziness
  - No new safety signals were identified during this study

AMX0035 is an investigational drug in Asia Pacific, Latin America, the European Union, United Kingdom, and Switzerland and is currently not approved for use in those regions/countries.

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