

Safety of a Fixed-Dose Coformulation of Sodium Phenylbutyrate and Taurursodiol in Amyotrophic Lateral Sclerosis and Alzheimer Disease: Summary of Clinical Trials Experience

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Disclosures

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Background

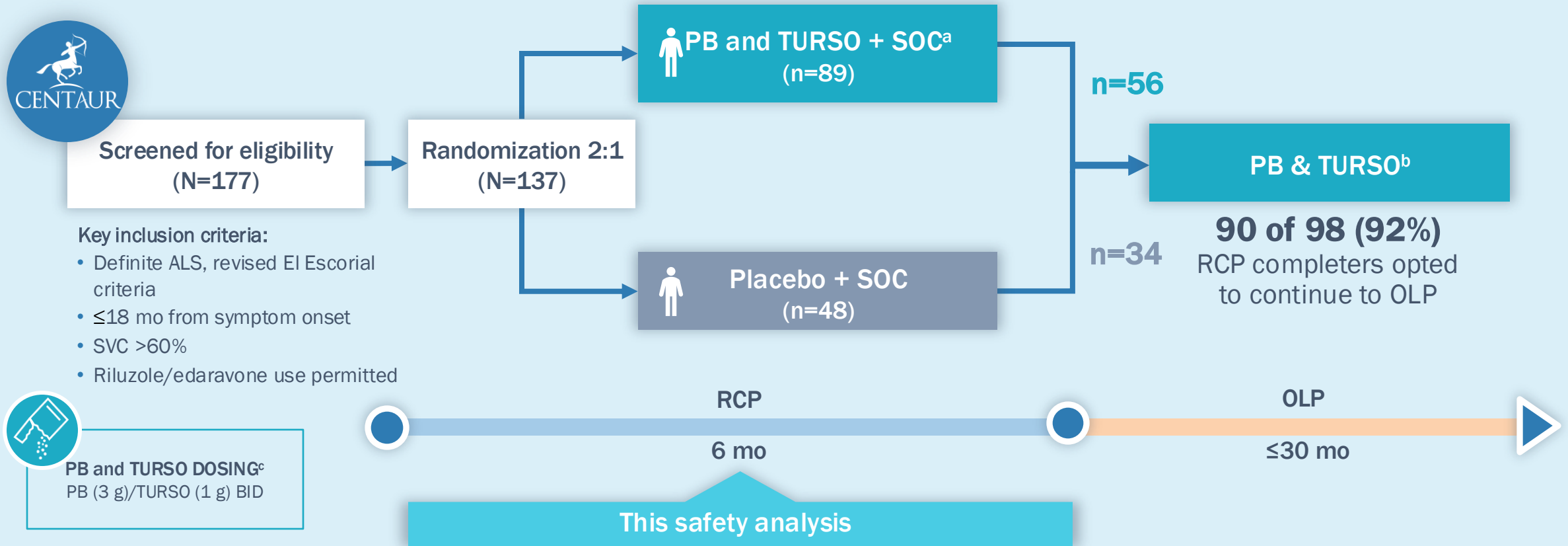
- A coformulation of sodium phenylbutyrate and taurursodiol (PB and TURSO) was designed to reduce neurodegeneration by targeting endoplasmic reticulum and mitochondrial stress, both of which are implicated in the pathophysiology of ALS and AD¹⁻³
- The safety of the individual components has been previously described
 - **PB** use in urea cycle disorders has been primarily associated with gastrointestinal AEs (eg, decreased appetite, vomiting, nausea, abdominal pain) and less frequently with rash and headache⁴⁻⁶
 - **TURSO** (also known as TUDCA) has been primarily associated with diarrhea or abnormal stools in clinical studies, with rare reports of calcification of gallstones and urticaria⁷

The safety and tolerability of PB and TURSO were assessed in phase 2 studies in both ALS (CENTAUR) and AD (PEGASUS)

AD, Alzheimer disease; AE, adverse event; ALS, amyotrophic lateral sclerosis; TUDCA, tauroursodeoxycholic acid.

1. Paganoni S, et al. *N Engl J Med*. 2020;383:919-930. 2. Paganoni S, et al. Supplementary appendix. *N Engl J Med*. 2020;383:919-930. 3. Amylyx Pharmaceuticals. Data on file. 4. Mokhtarani M, et al. *Mol Genet Metab*. 2013;110:446-453. 5. Shchelochkov OA, et al. *Mol Genet Metab Rep*. 2016;8:43-47. 6. Nagamani SC, et al. *Mol Genet Metab*. 2015;116(1-2):29-34. 7. TUDCABIL Summary of Product Characteristics. Bruschettini s.r.l.; 2006.

CENTAUR: Phase 2 Study in ALS Encompassing a Randomized, Controlled Phase (RCP) and an Open-Label Phase (OLP)¹⁻³



BID, twice daily; SOC, standard of care; SVC, slow vital capacity.

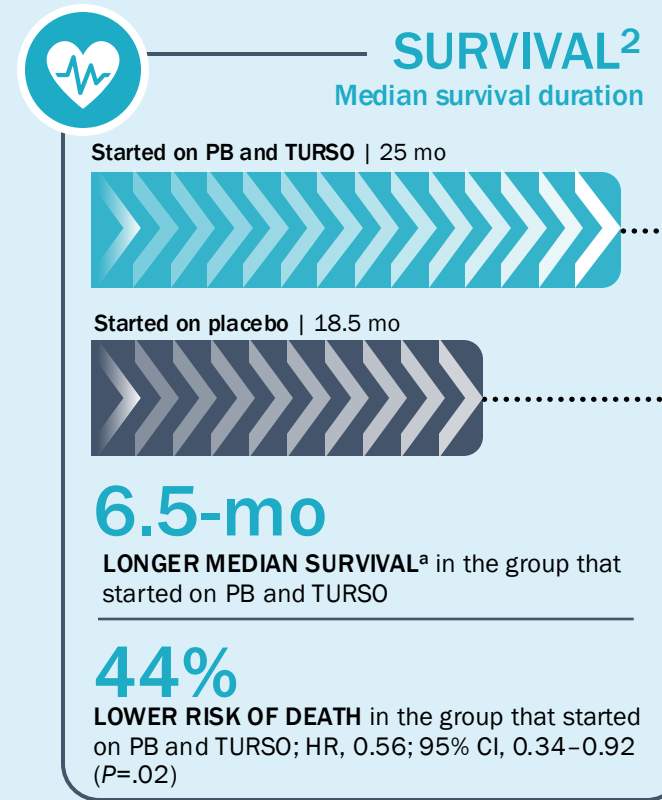
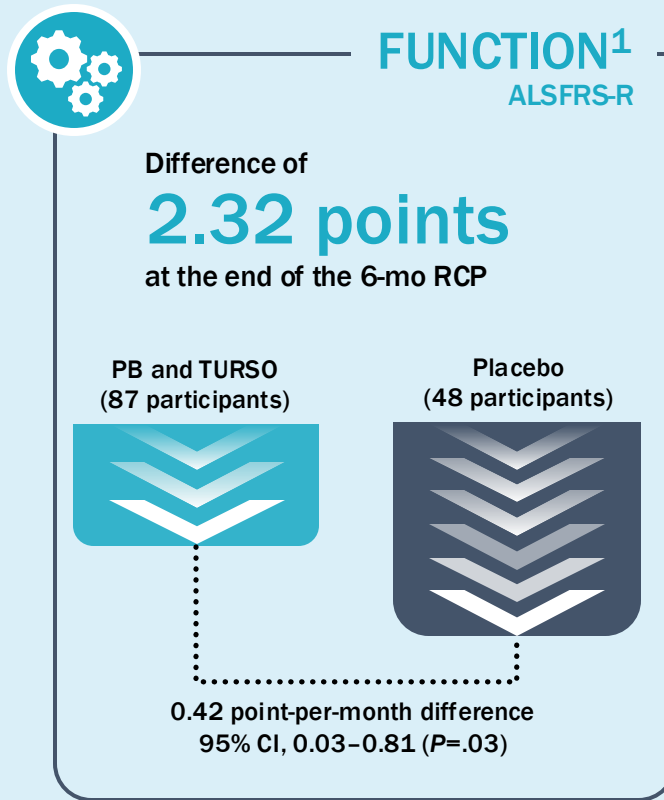
^a77% of participants were on riluzole or edaravone at or prior to study entry.

^bParticipants in the OLP continued receiving PB and TURSO at the same dose they had been receiving at the end of the RCP; participants who switched from placebo to PB and TURSO began dosing with PB and TURSO BID with no titration period.

^cParticipants received PB and TURSO once per day for the first 3 weeks and then escalated to PB and TURSO BID thereafter.

1. Paganoni S, et al. *N Engl J Med*. 2020;383:919-930. 2. Paganoni S, et al. *Muscle Nerve*. 2021;63:31-39. doi:10.1002/mus.27091. 3. Amylyx Pharmaceuticals. Data on file.

CENTAUR Efficacy Outcomes: Significant Slowing of ALS Progression and Longer Median Survival

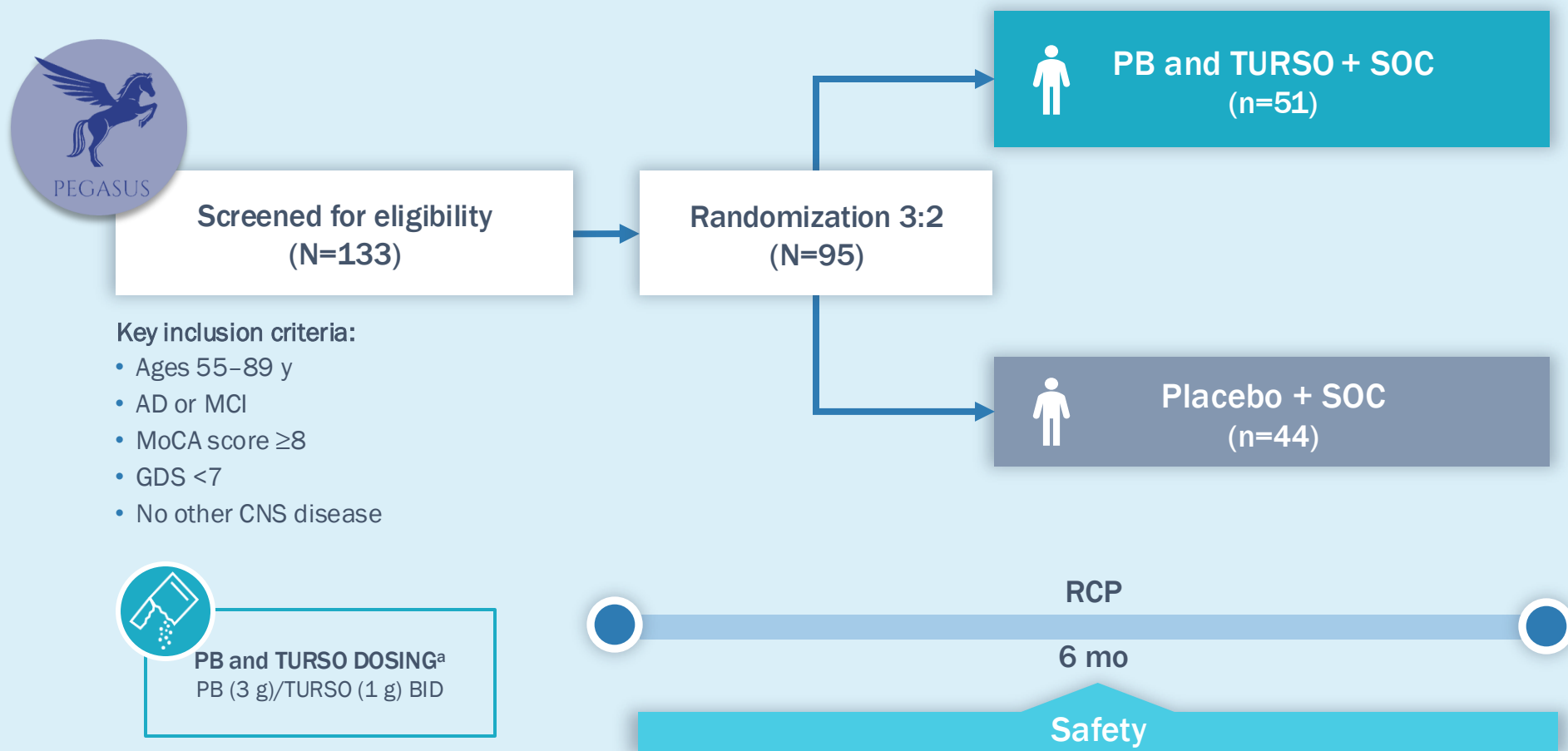


ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; HR, hazard ratio.

^aInterim analysis (cutoff date July 2020), with longest postrandomization follow-up time of 35 months.

1. Paganoni S, et al. *N Engl J Med*. 2020;383:919-930. 2. Paganoni S, et al. *Muscle Nerve*. 2021;63:31-39. doi:10.1002/mus.27091.

PEGASUS: Phase 2 Randomized, Placebo-Controlled Study in AD^{1,2}



CNS, central nervous system; GDS, Geriatric Depression Scale; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment.

^aParticipants received PB and TURSO once per day for the first week and then escalated to PB and TURSO BID thereafter.¹

1. Amylyx Pharmaceuticals. Data on file. **2.** ClinicalTrials.gov. Study to assess the safety and biological activity of AMX0035 for the treatment of Alzheimer's disease (PEGASUS). Updated November 11, 2021. Accessed March 31, 2022. <https://www.clinicaltrials.gov/ct2/show/NCT03533257?term=amx0035&draw=2&rank=7>.

PEGASUS Efficacy Outcomes: Significant Changes in Exploratory Biomarkers of AD Pathology



Clinical

Study was not powered to see differences on **primary** and **secondary** clinical efficacy outcomes

No differences were seen



Biomarker



PB and TURSO significantly decreased CSF **p-tau 181** and **t-tau**

Change [95% CI] in mean from baseline at month 6 (active vs placebo)

p-tau 181	-10.47 [-16.42, -4.51]	P=.0008
t-tau	-51.37 [-79.37, -23.37]	P=.0005



PB and TURSO significantly increased CSF **A β 42/A β 40 ratio** and CSF **8-OHdG**

Change [95% CI] in mean from baseline at month 6 (active vs placebo)

A β 42/A β 40 ratio	6.58 [1.24, 11.93]	P=.0166
8-OHdG	0.37 [0.11, 0.62]	P=.0055

Baseline Characteristics^a

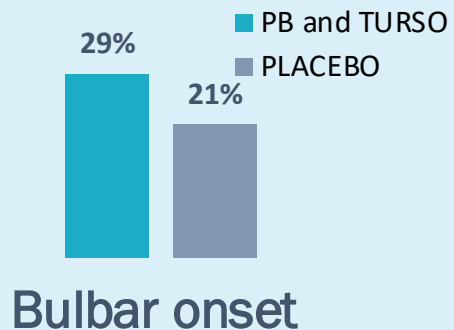


137 participants with ALS enrolled

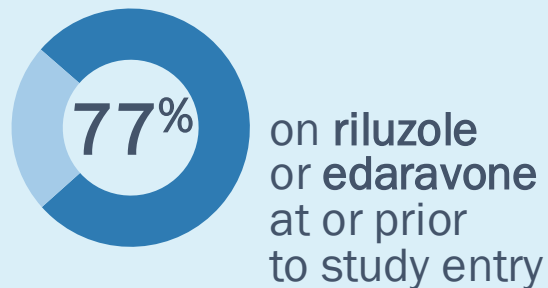
Average age:



Male: 68%
Female: 32%



13.5 mo since symptom onset and 6.1 mo since diagnosis

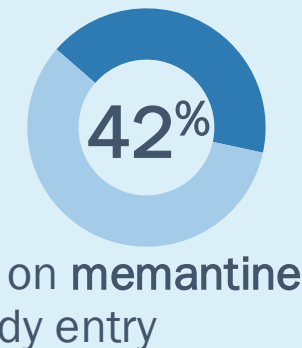
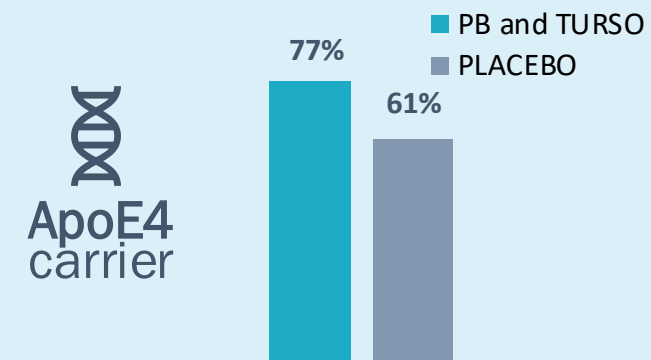


95 participants with AD/MCI enrolled

Average age:



Male: 55%
Female: 45%



^aSafety population.
Amylyx Pharmaceuticals. Data on file.

Trial Drug Exposure and Compliance^a

Most participants received treatment for the majority of the trial and were compliant with treatment in both trials



Summary of Trial Drug Exposure (ALS)

Trial Drug Exposure Duration, wk	PB and TURSO (n=89)	Placebo (n=48)
Mean (SD)	19.7 (7.89)	21.5 (5.82)
Median	23.9	23.9

- Proportion in PB and TURSO group who received treatment for ≥ 21 weeks: **68.4%**
- Compliance with trial medication administration was **>90%** in both treatment groups



Summary of Trial Drug Exposure (AD)

Trial Drug Exposure Duration, wk	PB and TURSO (n=51)	Placebo (n=44)
Mean (SD)	21.0 (6.93)	23.0 (4.27)
Median	24.1	24.0

- Proportion in PB and TURSO group who received treatment for ≥ 21 weeks: **78.5%**
- Compliance with trial medication administration was **>85%** in both treatment groups

^aSafety population.
Amylyx Pharmaceuticals. Data on file.

Overall Safety Summary

	CENTAUR (ALS)		PEGASUS (AD)	
	PB and TURSO (n=89)	Placebo (n=48)	PB and TURSO (n=51)	Placebo (n=44)
TEAEs, no. (%)	86 (97)	46 (96)	34 (67)	26 (59)
SAEs, no. (%)	11 (12)	8 (17)	3 (6)	1 (2)
TEAE leading to death, no. (%)	5 (6) ^a	2 (4) ^a	0	0
TEAEs leading to treatment withdrawal, no. (%)	18 (20)	5 (10)	4 (8)	1 (2)
TEAEs leading to treatment interruption, no. (%)	12 (14)	5 (10)	5 (10)	2 (5)

Overall TEAE incidence in CENTAUR is likely complicated by the rapid progression of ALS and symptoms of the disease

^aMajority of TEAEs that led to death were consistent with ALS manifestations or complications (PB and TURSO: respiratory failure/arrest [n=3], subdural hematoma [n=1], and diverticular perforation [n=1]; placebo: respiratory failure/arrest [n=2]. No deaths were related to study medication.

SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Amylyx Pharmaceuticals. Data on file.

Most Common TEAEs ($\geq 10\%$)^a by System Organ Class

MedDRA System Organ Class Summary Category, no. (%)	CENTAUR (ALS)		MedDRA System Organ Class Summary Category, no. (%)	PEGASUS (AD)	
	PB and TURSO (n=89)	Placebo (n=48)		PB and TURSO (n=51)	Placebo (n=44)
Gastrointestinal disorders	59 (66)	30 (62)	Gastrointestinal disorders	20 (39)	6 (14)
Musculoskeletal and connective tissue disorders	37 (42)	19 (40)	Nervous system disorders	13 (26)	11 (25)
Injury, poisoning, and procedural complications	31 (35)	22 (46)	Injury, poisoning, and procedural complications	5 (10)	9 (21)
Nervous system disorders	35 (39)	20 (42)	General disorders and administration site conditions	5 (10)	3 (7)
Infections and infestations	28 (32)	19 (40)	Infections and infestations	5 (10)	4 (9)
Respiratory, thoracic and mediastinal disorders	27 (30)	12 (25)	Investigations	5 (10)	2 (4)
Investigations	23 (26)	10 (21)	Metabolism and nutrition disorders	5 (10)	4 (9)
General disorders and administration site conditions	20 (22)	13 (27)			
Skin and subcutaneous tissue disorders	17 (19)	7 (15)			
Psychiatric disorders	14 (16)	10 (21)			
Renal and urinary disorders	11 (12)	8 (17)			
Metabolism and nutrition disorders	10 (11)	4 (8)			
Vascular disorders	9 (10)	3 (6)			

- The majority of TEAEs were gastrointestinal in both CENTAUR and PEGASUS
- TEAEs consistent with symptoms of natural ALS progression, namely muscular weakness (20%) and falls (31%), were also among the most common TEAEs in CENTAUR

MedDRA, Medical Dictionary for Regulatory Activities.

^aIn either treatment group.

Amylyx Pharmaceuticals. Data on file.

Profile of Gastrointestinal TEAEs Differed Between Treatments

MedDRA System Organ Class Preferred Term, no. (%)	CENTAUR (ALS)	
	PB and TURSO (n=89)	Placebo (n=48)
Diarrhea	19 (21)	8 (17)
Nausea	16 (18)	6 (12)
Salivary hypersecretion	10 (11)	1 (2)
Abdominal discomfort	5 (6)	0
Vomiting	4 (4)	1 (2)
Abdominal distension	4 (4)	1 (2)
Abdominal pain upper	4 (4)	1 (2)
Dyspepsia	3 (3)	0
Gastrointestinal hypermotility	2 (2)	0
Retching	2 (2)	0
Constipation	12 (14)	12 (25)
Dry mouth	3 (3)	4 (8)
Dysphagia	3 (3)	4 (8)
Anal incontinence	0	1 (2)
Eructation	0	1 (2)
Frequent bowel movements	0	1 (2)
Stomatitis	0	1 (2)

Greater in
PB and
TURSO
(≥2%)

Greater
in
Placebo
(≥2%)

MedDRA System Organ Class Preferred Term, no. (%)	PEGASUS (AD)	
	PB and TURSO (n=89)	Placebo (n=48)
Diarrhea	8 (16)	3 (7)
Dyspepsia	2 (4)	0
Constipation	2 (4)	0
Eructation	2 (4)	0
Abdominal distension	1 (2)	0
Abdominal pain	1 (2)	0
Abdominal pain upper	1 (2)	0
Gastrointestinal hypermotility	1 (2)	0
Gastrointestinal sounds abnormal	1 (2)	0
Change of bowel habit	1 (2)	0
Defecation urgency	1 (2)	0
Hematochezia	1 (2)	0

Diarrhea and, to a lesser extent, abdominal discomfort/pain, abdominal distension, and dyspepsia were more frequent with PB and TURSO vs placebo in both trials

No Other Safety Concerns Were Identified

- No emerging safety concerns were noted in either trial, including no new laboratory abnormalities
- Although the majority of participants in the phase 2 studies experienced TEAEs, they were largely nonserious, mild or moderate in intensity, and assessed as unrelated to treatment with study medication

Conclusions

- PB and TURSO was safe and well tolerated in clinical trials in ALS and AD
- No emerging safety concerns or signals were identified
- The majority of TEAEs associated with PB and TURSO were gastrointestinal, consistent with the known individual safety profiles for PB and TURSO
 - Diarrhea and, to a lesser extent, abdominal discomfort or pain, abdominal distension, and dyspepsia were more frequent with PB and TURSO vs placebo in both trials
- Findings in AD further elucidated the safety profile of PB and TURSO, as TEAEs in CENTAUR appear to have been largely disease driven

Acknowledgments

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