Expert Review of Cardiac Adverse Events and Electrocardiographic Abnormalities and Parameters in a Phase 2 Trial of Sodium Phenylbutyrate and Taurursodiol in Amyotrophic Lateral Sclerosis (CENTAUR)

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BACKGROUND

- In the multicenter CENTAUR study encompassing a 24-week randomized placebo-controlled phase (RCP; NCT03127514) and an open-label extension (OLE) long-term follow-up phase (NCT03488524), an oral, fixed-dose combination of sodium phenylbutyrate (PB) and taurursodiol (also known as ursodoxicoltaurine; TURSO) significantly slowed functional decline compared with placebo in the RCP in participants with amyotrophic lateral sclerosis[1,2]
  - A total of 137 participants were randomized in CENTAUR (PB and TURSO, n=89; placebo, n=48), with 90 enrolling in the OLE phase (56 originally randomized to PB and TURSO and 34 originally randomized to placebo)
- While the overall incidence of treatment-emergent adverse events (TEAEs) was similar between the PB and TURSO group and placebo group in the RCP and between those continuing versus switching to PB and TURSO in the OLE phase, treatment-emergent cardiac adverse events (TECAEs) and centrally read electrocardiogram (ECG) abnormalities were reported more frequently among those receiving PB and TURSO in both phases.[1-3] However, these results did not account for the 2:1 PB and TURSO–to-placebo randomization ratio, longer PB and TURSO exposure inclusive of the OLE phase, or potential pre-existence of or alternative causes such as use of concomitant medications for reported events

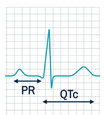
OBJECTIVE

- Describe the findings from expert reviews of (1) centrally recorded ECG parameters and (2) reported TECAEs and treatment-emergent ECG abnormalities in CENTAUR

METHODS

- The occurrence of TEAEs, including in the cardiac disorders system organ class, was assessed at each visit during both phases in addition to spontaneous reporting of events
- Standard 12-lead ECGs were performed at baseline in both phases and at a total of 2 visits (weeks 12 and 24) in the RCP and ≤10 visits over ≤152 weeks of therapy in the OLE phase. All ECGs were blinded and centrally and prospectively read (ERT, Inc.)
- ECG parameters and changes from baseline were summarized by visit and treatment group using descriptive statistics
- Unblinded expert reviews focusing on cardiac safety were performed after study completion as described in **Figure 1**

Figure 1. Expert Reviews Focused on Cardiac Safety in CENTAUR

Review Focus	Materials Reviewed	Reviewer Assessments
 ECG parameters and their changes from baseline	▪ Summary statistics for HR, PR, QRS, QTcB, QTcF, and changes from baseline for each parameter by visit and treatment group ▪ Data from categorical analyses of ECG parameters	▪ Comparability of summary ECG parameters and changes from baseline between the active and placebo groups ▪ Comparative incidence of ECG parameters (or changes in ECG parameters) above/below categorical thresholds[a] in the active and placebo groups
 TECAEs and treatment-emergent ECG abnormalities	▪ Full listing of TECAEs and treatment-emergent ECG abnormalities reported in CENTAUR ▪ Details regarding medical history, concomitant medications, investigational drug administration all the recorded ECGs for participants with reported TECAEs and treatment-emergent ECG abnormalities	▪ Diagnostic accuracy of reported TECAEs and treatment-emergent ECG abnormalities ▪ Confirmation of treatment emergence of reported events, based on absence at baseline or lack of an identifiable alternative cause

[a]ECG category parameters were HR <55 bpm, HR >100 bpm, PR interval >200 ms, QRS duration >120 ms, QTcB >480 ms, QTcB >500 ms, QTcB change from baseline >30 ms, QTcB change from baseline >60 ms, QTcF >480 ms, QTcF >500 ms, QTcF change from baseline >30 ms, and QTcF change from baseline >60 ms. ECG, electrocardiogram; HR, heart rate; PR, PR interval; QRS, QRS duration; QTcB, QT interval corrected for HR using Bazett formula; QTcF, QT interval corrected for HR using Fridericia formula; TECAE, treatment-emergent cardiac adverse event.

RESULTS

ECGs Were Generally Normal, and Parameters Were Comparable Between Treatment Groups

- ECGs were interpreted as normal in the majority of participants overall
  - No statistically significant differences between treatment groups with respect to ECGs interpreted as abnormal over the course of the RCP
- Changes from baseline and threshold-based categorical analyses in all ECG parameters were comparable between the PB and TURSO group and placebo group
  - No participants with treatment-emergent QT interval corrected for HR using Fridericia formula (QTcF) values exceeding 480 ms or change from baseline in QTcF exceeding 60 ms in either treatment group

Cardiac Adverse Events and ECG Abnormalities Were Similar Between Treatments After Expert Validation and Normalization

- A total of 418 ECGs from 121 participants (98 who received PB and TURSO during either or both phases and 44 who received placebo in the RCP) were reviewed
- Of 11 initially reported TECAEs in 10 participants receiving PB and TURSO in either phase, 8 TECAEs in 8 participants were assessed as valid TECAEs by the expert reviewer (**Table 1**). The 3 remaining events were either present at baseline (n=1) or had other identifiable causes (n=2)
  - There were no reported TECAEs among participants receiving placebo
- Of 22 ECG abnormalities initially reported in 17 participants receiving PB and TURSO in either phase, 10 abnormalities in 9 participants were validated as treatment-emergent findings on expert review (**Table 2**)
- Of 6 ECG abnormalities initially reported in 4 participants receiving placebo, 1 abnormality in 1 participant was validated (**Table 2**)
- After normalizing for treatment duration, number of ECGs, and number of participants receiving each treatment, the number of participants who experienced valid cardiac events (ie, TECAEs and/or ECG abnormalities) while on PB and TURSO was found to be comparable to the number who experienced cardiac events on placebo (**Figure 2**)

Table 1. Assessment of Diagnostic Accuracy and Treatment Emergence of Reported TECAEs in CENTAUR[a]

Participant[b]	Reported TECAE	Clinical Observations	Disposition
Participant 1	▪ Cardiac arrest	▪ Arrest due to respiratory failure 9 days after PB and TURSO was discontinued	TECAE excluded (identifiable alternative cause)
Participant 2	▪ Left anterior hemiblock	▪ Left anterior hemiblock also reported as a treatment-emergent ECG abnormality	TECAE confirmed
Participant 3	▪ First-degree AV block	▪ First-degree AV block also reported as a treatment-emergent ECG abnormality ▪ Abnormality present on baseline ECG	TECAE excluded (present at baseline)
Participant 4	▪ Tachycardia	▪ Died of respiratory failure 17 days after discontinuing treatment in the OLE phase (considered unrelated to treatment by investigator)	TECAE confirmed
Participant 5	▪ Tachycardia	▪ Sinus tachycardia also reported as a treatment-emergent ECG abnormality ▪ HR increase of 11 bpm	TECAE confirmed
Participant 6	▪ Cardiac arrest (PEA) ▪ Rapid AF	▪ Cardiac arrest was clearly attributable to aspiration pneumonia ▪ Rapid AF event was not well documented (timing with regard to AF unknown)	TECAE cardiac arrest excluded (identifiable alternative cause); TECAE rapid AF confirmed
Participant 7	▪ Palpitations	▪ Past medical history of hypertension and valvular disease; all study ECGs normal	TECAE confirmed
Participant 8	▪ Rapid AF	▪ AF self-limited	TECAE confirmed
Participant 9	▪ Tachycardia	▪ No clear predisposing factors; all study ECGs normal	TECAE confirmed
Participant 10	▪ Palpitations	▪ No clear predisposing factors; prior ECG normal	TECAE confirmed

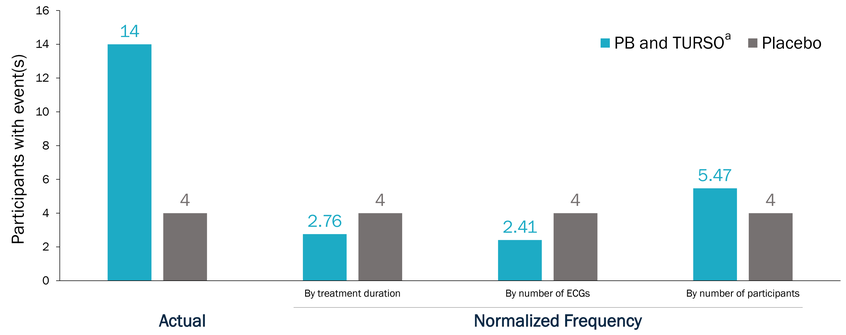
[a]All reported TECAEs occurred in participants who received PB and TURSO in the RCP or OLE phase. [b]The participant numbers used in the table are arbitrary and do not relate in any way to order of enrollment, randomization procedures, or assigned participant identification numbers. AF, atrial fibrillation; AV, atrioventricular; ECG, electrocardiogram; HR, heart rate; OLE, open-label extension phase; PB and TURSO, sodium phenylbutyrate and taurursodiol; PEA, pulseless electrical activity; RCP, randomized placebo-controlled phase; TECAE, treatment-emergent cardiac adverse event.

Table 2. Assessment of Diagnostic Accuracy and Treatment Emergence of Reported ECG Abnormalities in CENTAUR

Study Treatment	Reported		Validated on Expert Review		Reasons for Exclusion of Events
	No. Participants	No. Events	No. Participants	No. Events	
PB and TURSO[a]	17	22	9	10	▪ Present at baseline (n=3) ▪ Not present per expert review (n=3) ▪ Present on prior ECGs (n=3) ▪ Artifact (n=3)
Placebo	4	6	1	1	▪ Prior or normal finding (n=4) ▪ Alternative identifiable cause (n=1)

[a]Inclusive of both randomized and OLE phases. ECG, electrocardiogram; OLE, open-label extension; PB and TURSO, sodium phenylbutyrate and taurursodiol.

Figure 2. Number of Participants With Validated TECAEs and ECG Abnormalities in CENTAUR: Actual and Normalized Frequencies



[a]Inclusive of participants who received PB and TURSO in the RCP and OLE phases.
ECG, electrocardiogram; OLE, open-label extension; PB and TURSO, sodium phenylbutyrate and taurursodiol; RCP, randomized placebo controlled; TECAE, treatment-emergent cardiac adverse event.

CONCLUSIONS

- Based on findings from posttrial expert reviews of data from CENTAUR, we conclude that the incidence of cardiac adverse events and ECG changes or abnormalities was low with PB and TURSO and similar to placebo when normalized to treatment duration
- PB and TURSO was not responsible for any serious events of cardiac origin and was also unlikely the cause of any of the reported minor cardiac adverse events in CENTAUR

PB and TURSO is an investigational drug in EMA and not approved for use.

Acknowledgements

Expert reviews were provided by Martin Bedigian, MD, and Jay Mason, MD, under consultancy with Amylyx Pharmaceuticals, Inc. The authors would like to thank the CENTAUR trial participants and their families and caregivers and the Northeast Amyotrophic Lateral Sclerosis Consortium (NEALS). Funding support for CENTAUR was provided by The ALS Association, the ALS Finding a Cure Foundation, and Amylyx Pharmaceuticals.

References

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3. Data on file. Amylyx Pharmaceuticals, Inc.

Disclosures

SB is a full-time employee of Amylyx Pharmaceuticals; JWM reports consulting fees from Amylyx for one of the expert reviews reported herein; SP reports research grants from Amylyx, Revalesio Corporation, Ra Pharma, Biohaven, Clene, Prilenia, The ALS Association, the American Academy of Neurology, ALS Finding a Cure, the Salah Foundation, the Spastic Paraplegia Foundation, and the Muscular Dystrophy Association, and consulting fees from Orion and Amylyx; JT and PY are full-time employees of and have stock option ownership in Amylyx Pharmaceuticals, Inc.; and MC reports grants from Massachusetts General Hospital during the conduct of the study; grants from Clene Nanomedicine, Ra Pharma, Biohaven, and Prilenia; and consulting fees from Amylyx, Takeda, Biogen, Wave Life Sciences, QurAlis, Avexis, Disarm, ALSpharma, Helixmith, Orion, Transposon, Cytokinetics, and Immunity Pharma.

Presented at the 33rd International Symposium on ALS/MND; December 6–9, 2022