Short report

Effect of sodium phenylbutyrate/taurursodiol on tracheostomy/ventilation-free survival and hospitalisation in amyotrophic lateral sclerosis: long-term results from the CENTAUR trial

Sabrina Paganoni,1,2 Suzanne Hendrix,3 Samuel P Dickson,3 Newman Knowlton,3 James D Berry,4 Michael A Elliott,5 Samuel Maiser,6 Chafic Karam,7 James B Caress,8 Margaret Ayo Owegi,9 Adam Quick,10 James Wymer,11 Stephen A Goutman,12 Daragh Heitzman,13 Terry D Heiman-Patterson,14 Carlyne Jackson,15 Colin Quinn,7 Jeffrey D Rothstein,16 Edward J Kasarskis,17 Jonathan Katz,18 Liberty Jenkins,18 Shafeeq S Ladha,19 Timothy M Miller,20 Stephen N Scelsa,21 Tuan H Vu,22 Christina Fournier,23 Kristin M Johnson,24 Andrea Swenson,25 Namita Goyal,26 Gary L Patte,27 Suma Babu,1 Marianne Chase,1 Derek Dagostino,1 Meghan Hall,19 Gale Kittle,21 Mathew Eydinov,1 Joseph Ostrow,1 Lindsay Pothier,1 Rebecca Randall,28,29 Jeremy M Shefner,19 Alexander V Sherman,1 Eric Tustison,1 Prasha Vigneswaran,1 Hong Yu,1 Joshua Cohen,30 Justin Klee,30 Rudolph Tanzi,31 Walter Gilbert,32 Patrick Yeramian,30 Merit Cudkowicz1

ABSTRACT

Background Coformulated sodium phenylbutyrate/taurursodiol (PB/TURSO) was shown to prolong survival and slow functional decline in amyotrophic lateral sclerosis (ALS).

Objective Determine whether PB/TURSO prolonged tracheostomy/ventilation-free survival and/or reduced first hospitalisation in participants with ALS in the CENTAUR trial.

Methods Adults with El Escorial Definite ALS ≤18 months from symptom onset were randomised to PB/TURSO or placebo for 6 months. Those completing randomised treatment could enrol in an open-label extension (OLE) phase and receive PB/TURSO for ≤30 months. Times to the following individual or combined key events were compared in the originally randomised treatment groups over a period spanning trial start to July 2020 (longest postrandomisation follow-up, 35 months): death, tracheostomy, permanent assisted ventilation (PAV) and first hospitalisation.

Results Risk of any key event was 47% lower in those originally randomised to PB/TURSO (n=87) versus placebo (n=48; 71% of whom received delayed-start PB/TURSO in the OLE phase) (HR=0.53; 95% CI 0.35 to 0.81; p=0.003). Risks of death or tracheostomy/PAV (HR=0.51; 95% CI 0.32 to 0.84; p=0.007) and first hospitalisation (HR=0.56; 95% CI 0.34 to 0.95; p=0.03) were also decreased in those originally randomised to PB/TURSO.

Conclusions Early PB/TURSO prolonged tracheostomy/PAV-free survival and delayed first hospitalisation in ALS.

Trial registration number NCT03127514; NCT03488524.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive motor neuron disorder typically culminating in death from respiratory failure.1 2 Non-invasive ventilation (NIV) or, when NIV is not possible, tracheostomy and invasive ventilation may prolong survival and maintain or improve quality of life in people with ALS.1 3 From a societal standpoint, interventions such as assisted ventilation and hospitalisation are significant drivers of aggregate costs attributable to ALS in the USA each year.4 5 By slowing disease progression, therapies have the potential to reduce the short-term clinical burden associated with ALS.6

A fixed-dose sodium phenylbutyrate/taurursodiol (PB/TURSO) coformulation was designed to reduce neuronal death by simultaneously mitigating endoplasmic reticulum and mitochondrial dysfunction. PB/TURSO safety and efficacy were evaluated in the CENTAUR trial consisting of a randomised, double-blind, placebo-controlled phase (NCT03127514) and open-label extension (OLE) phase (NCT03488524). PB/TURSO administration was associated with a significantly slower rate of decline in ALS Functional Rating Scale–Revised (ALSFRS-R) total score compared with placebo over the 6-month randomised phase (primary outcome).7 In an intent-to-treat (ITT) analysis encompassing all 137 randomised participants in CENTAUR followed for up to 3 years after randomisation, long-term survival duration was significantly increased among those originally randomised to PB/TURSO versus placebo.8 Here, we report the results of prespecified analyses...
evaluating the occurrence of key events in addition to death in CENTAUR, including tracheostomy, permanent assisted ventilation (PAV), and first hospitalisation.

METHODS
Detailed methodology for the trial is reported elsewhere,7 8 (see online supplemental file 2 for the full trial protocol and amendments). Briefly, adults with Definite ALS (revised El Escorial criteria)9 who were ≤18 months from symptom onset with a slow vital capacity >60% of predicted value were randomised 2:1 to receive PB/TURSO (3 g PB/1 g TURSO) or placebo by mouth or feeding tube for 6 months.7 Those completing randomised treatment were eligible to enrol in an OLE phase and receive PB/TURSO for up to 30 months. Continuation of a stable dose of riluzole and/or edaravone was permitted throughout the trial. Investigators, evaluators and participants were blinded to originally randomised treatment assignments.

Rates of the following key events were evaluated as a secondary efficacy outcome in CENTAUR: death (all-cause), tracheostomy (either for respiratory distress or airway clearance), PAV and first hospitalisation. Of 177 screened individuals, 137 were randomised in the ose and PAV phases (PB/TURSO, n=89; placebo, n=48); of 98 participants eligible for OLE phase enrolment, 90 (92%) elected to enrol (56 and 34 originally randomised to PB/TURSO and placebo, respectively). Two participants in the PB/TURSO group who died shortly after randomisation did not undergo a post-baseline ALSFRS-R assessment and were excluded from the prespecified mITT population. Detailed baseline characteristics of the mITT population are published elsewhere. Average participant age was 58 years, with mean durations of 13.5 and 6.0 months since ALS symptom onset and diagnosis, respectively. The majority (77%) of participants, including 71% originally randomised to PB/TURSO and 88% originally randomised to placebo, were receiving riluzole and/or edaravone at or prior to trial entry; among participants originally randomised to PB/TURSO and placebo, 68% and 77%, respectively, were receiving riluzole and 25% and 50%, respectively, were receiving edaravone. PB/TURSO exposure data for the originally randomised groups are summarised in online supplemental table 1.

RESULTS
Of 177 screened individuals, 137 were randomised in the double-blind phase (PB/TURSO, n=89; placebo, n=48); of 98 participants eligible for OLE phase enrolment, 90 (92%) elected to enrol (56 and 34 originally randomised to PB/TURSO and placebo, respectively). Two participants in the PB/TURSO group who died shortly after randomisation did not undergo a post-baseline ALSFRS-R assessment and were excluded from the prespecified mITT population. Detailed baseline characteristics of the mITT population are published elsewhere. Average participant age was 58 years, with mean durations of 13.5 and 6.0 months since ALS symptom onset and diagnosis, respectively. The majority (77%) of participants, including 71% originally randomised to PB/TURSO and 88% originally randomised to placebo, were receiving riluzole and/or edaravone at or prior to trial entry; among participants originally randomised to PB/TURSO and placebo, 68% and 77%, respectively, were receiving riluzole and 25% and 50%, respectively, were receiving edaravone. PB/TURSO exposure data for the originally randomised groups are summarised in online supplemental table 1.

Over the period spanning randomisation to the analysis cut-off date (longest postrandomisation follow-up, 35 months), the risk of any key event was 47% lower in those originally randomised to PB/TURSO versus placebo (HR=0.53; 95% CI 0.35 to 0.81; p=0.003); median (IQR) event-free durations were 14.8 (6.5–29.1) and 10.0 (4.0–15.0) months, respectively (figure 1A). Risk of death or tracheostomy/PAV was 49% lower among those originally randomised to PB/TURSO versus placebo (HR=0.51; 95% CI 0.32 to 0.84; p=0.007), with median (IQR) tracheostomy/PAV-free survival durations of 25.8 (14.8–33.6) months and 18.5 months (11.7 months–not reached (NR)), respectively (figure 1B). Risk of first hospitalisation was 44% lower in the group originally randomised to PB/TURSO (HR=0.56; 95% CI 0.34 to 0.95; p=0.03); median (IQR) hospitalisation-free duration was NR (6.9 months–NR) in those originally randomised to PB/TURSO versus 14.1 months (4.2 months–NR) in those originally randomised to placebo (figure 1C). Similar to the previously published ITT survival analysis, which included the two participants excluded from the mITT population who died shortly after randomisation,8 results of the death-only analysis in the prespecified mITT population showed a significantly lower risk of death with early-start PB/TURSO (online supplemental figure 2). Results for the remaining key event analyses were likewise similar between the mITT and ITT populations (online supplemental table 2).

DISCUSSION
In this long-term analysis of CENTAUR, the risk of key events including death, tracheostomy, PAV and first hospitalisation was significantly lower in those originally randomised to PB/TURSO compared with those originally randomised to placebo, most of whom went on to receive 6-month delayed-start PB/TURSO in the OLE phase. Median key event-free survival duration was 4.8 months longer in participants originally randomised to PB/TURSO versus placebo, and median tracheostomy/PAV-free survival duration was 7.3 months longer. As of the analysis cut-off, median time to first hospitalisation was not yet reached in the group originally randomised to PB/TURSO, compared with 14.1 months in the group originally randomised to placebo.

Among riluzole and edaravone, the two US Food and Drug Administration-approved therapies for ALS, only riluzole has shown a survival benefit in randomised clinical trials.10 11 However, the impact of riluzole on function in ALS is currently unclear.11 PB/TURSO has shown a dual benefit on survival9 and function10 in ALS. The findings of prolonged tracheostomy/PAV-free survival and reduced hospitalisation incidence in the analyses described
neuronal support potential added benefits of PB/TURSO on reducing health burden in ALS.

Limitations
Because most participants who were originally randomised to placebo continued into the OLE phase and thus crossed over to PB/TURSO, the observed effect of early PB/TURSO may have been somewhat diluted in these analyses. In addition, while the use of a participant-locating firm allowed for definitive determination of vital status for all randomised participants but one, ascertainment of other key events was limited to the on-trial period, as these events are not captured in public records. As such, some postdropout tracheotomy, PAV, or hospitalisation events may not have been recorded in the subset of participants who discontinued from the trial, were lost to follow-up, or did not enrol in the OLE despite eligibility.

CONCLUSIONS
Early administration of PB/TURSO in the phase 2 CENTAUR trial prolonged tracheostomy/PAV-free survival and reduced hospitalisation risk in ALS, thereby potentially reducing drivers of individual health burden. Adding to the previously reported overall survival and functional benefits attributable to PB/TURSO, these findings support a modifying effect of PB/TURSO on disease progression in ALS. The phase 3 PHOENIX trial (NCT05021536), which began enrolment in late 2021, will further evaluate PB/TURSO safety and efficacy outcomes, including the incidence of the key events analysed in CENTAUR, over 48 weeks in a more heterogeneous, international population of individuals with ALS.

Author affiliations
1Harvard Medical School, Sean M. Healey and AMG Center for ALS & the Neurological Clinical Research Institute, Massachusetts General Hospital, Boston, Massachusetts, USA
2Department of PM & R, Spaulding Rehabilitation Hospital, Charlestown, Massachusetts, USA
3Pentara Corporation, Millcreek, Utah, USA
4Neurological Clinical Research Institute, Massachusetts General Hospital, Boston, Massachusetts, USA
5Swedish Neuroscience Institute, Seattle, Washington, USA
6Department of Neurology, Hennepin Healthcare, Minneapolis, Minnesota, USA

Figure 1  Kaplan-Meier analyses of time to key events. Time to (A) any key event (ie, death, tracheostomy, PAV or first hospitalisation), (B) death or tracheostomy/PAV and (C) first hospitalisation and corresponding median event-free duration estimates are shown for each originally randomised group in the modified intent-to-treat population (ie, all randomised participants who received at least one dose of originally assigned trial drug and had at least one postbaseline Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised assessment; N=135). HRs and p values were estimated using a Cox proportional hazards model. The numbers at risk exclude participants who experienced the analysed event(s) or were censored before that time point. OLE, open-label extension; PAV, permanent assisted ventilation (defined as non-invasive ventilation >22 hours/day for >7 days); PB/TURSO, sodium phenylbutyrate/taurursodiol.
Acknowledgements
The authors would like to thank the people living with ALS who participated in the CENTAUR trial, as well as their families and caregivers; without them, this trial would not have been possible. We also thank the CENTAUR coordination centre and trial site staff. Lara Primak, MD, and Theresa Leichner, PhD, of PRECISIONscientia provided medical writing assistance with the development and revision of the manuscript under the direction of the authors, with financial support from Amylyx Pharmaceuticals, Inc. and in compliance with international Good Publication Practice guidelines.

Contributors
SP, SH, SPD, NK, JC, JK, PDT, and MEC contributed to conceptualisation and design of the trial and drafting of the manuscript, had full access to all trial data, and take responsibility for the integrity of the data and the accuracy of the data analysis. SH, SPD, and NK performed all statistical analyses. JC and JK obtained funding for the trial. All authors contributed to acquisition of data and critically reviewed interim and final versions of the manuscript.

Funding
The CENTAUR trial was funded by Amylyx Pharmaceuticals, Inc., ALS Finding a Cure®, and The ALS Association. The trial sponsor, Amylyx Pharmaceuticals, Inc. collaborated with the Northeast ALS Consortium network (www.neals.org) in the design and execution of the trial. Amylyx provided active drug and, during the randomised trial phase, placebo; participated in data analysis and manuscript development; and provided funding for writing support in the development of the manuscript. All other funders had no role in any aspect of the trial or manuscript development.

Competing interests
SP reports grant support from Amylyx during the conduct of the study; grant support from Reavelex, Biohaven, UCB, Clene, Priletina, and Seelos outside the submitted work; and personal fees from Biogen, Clene Nanomedicine, MTPA, MT Pharma Holdings of America, Sawai Pharmaceutical Co, Ltd, and Janssen outside the submitted work. MEC reports payment and personal fees from Amylyx for advisory board and speakers bureau participation outside the submitted work. CK reports consulting fees from Alnylam, Takeda, CSL Behring, Genentech, Silicone, and Sanofi; honoraria from Amylyx; and advisory board participation fees from Amylyx outside the submitted work. HG reports consulting fees from Alnylam, Takeda, CSL Behring, Genentech, Silicone, and Sanofi; honoraria from Amylyx; and advisory board participation fees from Amylyx outside the submitted work. ORP, outside the submitted work. JBC reports grants from AZ Therapies Inc, MTB Pharmaceuticals, and CytoDynamics outside the submitted work. JDR reports grants from the National Institute of Environmental Health Sciences and The ALS Association. THV reports consulting fees from Biogen and ITF Pharma outside the submitted work; lecture fees from Illinois State Neurological Society Lecture and Spectrum Health outside the submitted work; and personal fees for Data Safety Monitoring Board (DSMB) participation from Vertex. JK obtained funding for the trial. All authors contributed to acquisition of data and critically reviewed interim and final versions of the manuscript.

Competing interests
SP reports grant support from Amylyx during the conduct of the study; grant support from Reavelex, Biohaven, UCB, Clene, Priletina, and Seelos outside the submitted work; and personal fees from Biogen, Clene Nanomedicine, MTPA, MT Pharma Holdings of America, Sawai Pharmaceutical Co, Ltd, and Janssen outside the submitted work. MEC reports payment and personal fees from Amylyx for advisory board and speakers bureau participation outside the submitted work. CK reports consulting fees from Alnylam, Takeda, CSL Behring, Genentech, Silicone, and Sanofi; honoraria from Amylyx; and advisory board participation fees from Amylyx outside the submitted work. HG reports consulting fees from Alnylam, Takeda, CSL Behring, Genentech, Silicone, and Sanofi; honoraria from Amylyx; and advisory board participation fees from Amylyx outside the submitted work. ORP, outside the submitted work. JBC reports grants from AZ Therapies Inc, MTB Pharmaceuticals, and CytoDynamics outside the submitted work. JDR reports grants from the National Institute of Environmental Health Sciences and The ALS Association. THV reports consulting fees from Biogen and ITF Pharma outside the submitted work; lecture fees from Illinois State Neurological Society Lecture and Spectrum Health outside the submitted work; and personal fees for Data Safety Monitoring Board (DSMB) participation from Vertex. JK obtained funding for the trial. All authors contributed to acquisition of data and critically reviewed interim and final versions of the manuscript.
Therapeutics), Cytokinetics Incorporated, MTPA, Alexion, Medicinova, Ionis, Alector, and Orphazyme; royalties from UpToDate; consulting fees from Amylyx, Apic Biosciences, Neurosense, Cytokinetics, Denali, GSK, MTPA, Orphazyme, Pinteon, RRD, Swarbio, Helixsmith, Novartis, Sanofi, and EMD Serono; and honoraria from Amylyx (symposium) and Oakstone (online presentation); all outside the submitted work. JC and JK are co-CEOs of and own stock in Amylyx, the trial sponsor; and report grant support from ALS Finding a Cure and The ALS Association during the conduct of the study. RET is Founding Chair of Amylyx’s Scientific Advisory Board and holds equity in Amylyx. Dr Gilbert reports stock ownership in Amylyx. PDY reports full-time employment and stock option ownership with Amylyx outside the submitted work. MEC reports consulting fees from Faze, Regeneron, AB Sciences, AveXis, Orion, Lilly, Biohaven, Mt Pharma, Revalasio, Alexleox, Cytokinetics, Disarm, ALS Pharma, Immunity Pharma, Wave, Sunovian, Pontifex, Denali, Transposen, Quralis, Helixsmith, and RRD and is a board member for Praxis, all outside the submitted work.

Patient consent for publication Not applicable.

Ethics approval This study involved human participants and was approved by Partners Human Research Committee (central IRB; no reference number or ID is associated). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Deidentified participant data will be made available upon reasonable request. Requests for data sharing can be sent to info@amylyx.com.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any errors and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Sabrina Paganoni http://orcid.org/0000-0003-0505-1168
Stephen A Goutman http://orcid.org/0000-0001-8780-6637

REFERENCES