Paganoni Sabrina (Orcid ID: 0000-0003-0505-1168)
Goutman Stephen (Orcid ID: 0000-0001-8780-6637)

Long-Term Survival of Participants in the CENTAUR Trial of Sodium Phenylbutyrate-Taurursodiol in ALS

Authors: Sabrina Paganoni, MD, PhD[1,2]; Suzanne Hendrix, PhD[3]; Samuel P. Dickson, PhD[3]; Newman Knowlton, MS[3]; Eric A. Macklin, PhD[4]; James D. Berry, MD[1]; Michael A. Elliott, MD[5]; Samuel Maiser, MD[6]; Chafic Karam, MD[7]; James B. Caress, MD[8]; Margaret Ayo Owegi, DO[9]; Adam Quick, MD[10]; James Wymer, MD, PhD[11]; Stephen A. Goutman, MD[12]; Daragh Heitzman, MD[13]; Terry D. Heiman-Patterson, MD[14]; Carlayne E. Jackson, MD[15]; Colin Quinn, MD[16]; Jeffrey D. Rothstein, MD, PhD[17]; Edward J. Kasarskis, MD, PhD[18]; Jonathan Katz, MD[19]; Liberty Jenkins, MD[19]; Shafeeq Ladha, MD[20]; Timothy M. Miller, MD, PhD[21]; Stephen N. Scelsa, MD[22]; Tuan H. Vu, MD[23]; Christina N. Fournier, MD[24]; Jonathan D. Glass, MD[24]; Kristin M. Johnson, DO[25]; Andrea Swenson, MD[26]; Namita A. Goyal, MD[27]; Gary L. Pattee, MD[28]; Patricia L. Andres, MS, DPT[29]; Suma Babu, MBBS, MPH[1]; Marianne Chase, BA[1]; Derek Dagostino, BA[1]; Meghan Hall, MS[20]; Gale Kittle, RN, MPH[20]; Matthew Eydinov, MS[1]; Michelle McGovern, BS[1]; Joseph Ostrow, BS[1]; Lindsay Pothier, BA[1]; Rebecca Randall, MS, RD[20]; Jeremy M. Shefner, MD, PhD[20]; Alexander V. Sherman, MSc[1]; Maria E. St. Pierre, MA[1]; Eric Tustison, BA[1]; Prasha Vigneswaran, MS[1]; Jason Walker, BS[1]; Hong Yu, MS[1]; James Chan, MA[4]; Janet Wittes, PhD[30]; Zi-Fan Yu, ScD[30]; Joshua Cohen, BSE[31]; Justin Klee, ScB[31]; Kent Leslie, MS[31]; Rudolph E. Tanzi, PhD[1]; Walter Gilbert, PhD[32]; Patrick D. Yeramian, MD, MBA[31]; David Schoenfeld, PhD[4]; Merit E. Cudkowicz, MD[1]

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Author affiliations: [1]Sean M. Healey and AMG Center for ALS & the Neurological Clinical Research Institute, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; [2]Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, Massachusetts; [3]Pentara Corporation, Millcreek, Utah; [4]Biostatistics Center, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; [5]Swedish Neuroscience Institute, Seattle, Washington; [6]Hennepin Healthcare, Minneapolis, Minnesota; [7]Department of Neurology, Oregon Health & Science University, Portland, Oregon; [8]Department of Neurology, Wake Forest School of Medicine, Winston-Salem, North Carolina; [9]University of Massachusetts Memorial Medical Center, Worcester, Massachusetts; [10]Department of Neurology, The Ohio State University College of Medicine, Columbus, Ohio; [11]Department of Neurology, University of Florida College of Medicine, Gainesville, Florida; [12]Department of Neurology, University of Michigan, Ann Arbor, Michigan; [13]Texas Neurology, Dallas, Texas; [14]Department of Neurology, Lewis Katz School of Medicine, Temple University, Philadelphia, Pennsylvania; [15]The University of Texas Health Science Center at San Antonio, San Antonio, Texas; [16]Department of Neurology, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania; [17]Brain Science Institute and Department of Neurology, Johns Hopkins University, Baltimore, Maryland; [18]Department of Neurology, University of Kentucky College of Medicine, Lexington, Kentucky; [19]California Pacific Medical Center Research Institute and Forbes Norris MDA/ALS Research and Treatment Center, San Francisco, California; [20]Gregory

W. Fulton ALS Center, Barrow Neurological Institute, Phoenix, Arizona; [21]Department of Neurology, Washington University School of Medicine in St. Louis, St. Louis, Missouri; [22]Department of Neurology, Mount Sinai Beth Israel, Icahn School of Medicine at Mount Sinai, New York, New York; [23]Department of Neurology, University of South Florida Morsani College of Medicine, Tampa, Florida; [24]Departments of Neurology and Pathology, Emory University School of Medicine, Atlanta, Georgia; [25]Department of Neurology, Ochsner Health System, New Orleans, Louisiana; [26]Department of Neurology, University of Iowa Carver College of Medicine, Iowa City, Iowa; [27]Department of Neurology, University of California, Irvine School of Medicine, Irvine, California; [28]Neurology Associates, Lincoln, Nebraska; [29]Independent consultant, Nobleboro, ME; [30]Statistics Collaborative, Inc., Washington, DC; [31]Amylyx Pharmaceuticals, Inc., Cambridge, Massachusetts; [32]Harvard University, Cambridge, Massachusetts

Correspondence to:

Sabrina Paganoni, MD, PhD

Sean M. Healey and AMG Center for ALS

Massachusetts General Hospital

165 Cambridge Street, Suite 600

Boston, MA 02114

Email: spaganoni@mgh.harvard.edu

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Long-Term Survival of Participants in the CENTAUR Trial of Sodium Phenylbutyrate-Taurursodiol in ALS

Abstract

Introduction: An orally administered, fixed-dose coformulation of sodium phenylbutyrate-taurursodiol (PB-TURSO) significantly slowed functional decline in a randomized, placebo-controlled, phase 2 trial in ALS (CENTAUR). Here, we report results of a long-term survival analysis of participants in CENTAUR.

Methods: In CENTAUR, adults with ALS were randomized 2:1 to PB-TURSO or placebo. Participants completing the 6-month (24-week) randomized phase were eligible to receive PB-TURSO in the open-label extension (OLE). An all-cause mortality analysis (35-month maximum follow-up post-randomization) incorporated all randomized participants. Participants and site investigators were blinded to treatment assignments through the duration of follow-up of this analysis.

Results: Vital status was obtained for 135 of 137 participants originally randomized in CENTAUR. Median overall survival was 25.0 months among participants originally randomized to PB-TURSO and 18.5 months among those originally randomized to placebo (hazard ratio, 0.56; 95% CI, 0.34–0.92; P=0.023).

Discussion: Initiation of PB-TURSO treatment at baseline resulted in a 6.5-month longer median survival as compared to placebo. Combined with results from CENTAUR, these results suggest that PB-TURSO has both functional and survival benefits in ALS.

Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder associated with motor neuron degeneration in the motor cortex and spinal cord leading to muscle weakness and atrophy.[1] Riluzole and edaravone are the only medications approved by the US Food and Drug Administration for disease-modifying treatment of ALS.[2] Riluzole has been shown to prolong survival in ALS.[3-5] The effect of edaravone on survival is unknown.[6,7]

An orally administered, fixed-dose coformulation of 2 compounds, sodium phenylbutyrate (PB) and taurursodiol (TURSO; also known as tauroursodeoxycholic acid), was designed to reduce neuronal death by mitigating both endoplasmic reticulum (ER) stress and mitochondrial dysfunction. Joint dysfunction of these 2 organelles within motor neurons has been recognized as a potential pathogenic factor in ALS, motivating development of this coformulation.[8-10] Preclinical data support a mitigating effect of PB and TURSO both alone[11-16] and in combination[17] on neuronal death and other disease-specific features in models of neurodegenerative diseases and mitochondrial dysfunction. In addition, pilot clinical studies confirmed the individual safety of both compounds in individuals with ALS.[18,19]

The recently completed randomized, double-blind, placebo-controlled CENTAUR trial evaluated efficacy and safety of sodium phenylbutyrate-taurursodiol (PB-TURSO) in individuals with ALS.[20] The trial met its primary efficacy end point—slowing of decline in Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R) total score in participants treated with

PB-TURSO versus placebo over 6 months (24 weeks). Few participants died during the 6-month duration of CENTAUR; a joint rank analysis of function and survival confirmed an effect of PB-TURSO in slowing ALSFRS-R progression when accounting for potentially informative loss to follow-up from mortality. Participants who completed CENTAUR were eligible for enrollment in an open-label extension (OLE) aimed at assessing long-term safety and efficacy of PB-TURSO in ALS. This manuscript reports the results of a nearly 3-year survival analysis incorporating all participants who enrolled in CENTAUR, whether or not they continued long-term treatment with PB-TURSO in the OLE.

Methods

Trial Design and Oversight

Both the randomized controlled trial and the OLE were conducted in accordance with Good Clinical Practice guidelines of the International Conference on Harmonization and ethical principles of the Declaration of Helsinki. Protocol approval was obtained for all trial sites by a central Institutional Review Board, the Partners Human Research Committee.[21] Participants provided written informed consent prior to entering each phase of the study.

Randomized Controlled Trial

Detailed methods of the randomized study have been published.[20] In brief, CENTAUR (NCT03127514) was a randomized, double-blind, placebo-controlled trial conducted at 25

Northeast ALS Consortium (NEALS) centers in the United States between June 2017 and September 2019. The trial enrolled participants who were aged 18 to 80 years with a diagnosis of definite ALS by revised El Escorial criteria (ie, clinical evidence of both upper and lower motor neuron signs in ≥3 body regions[22]) and had symptom onset within the prior 18 months. Additional inclusion criteria included slow vital capacity >60% of predicted value for sex, height, and age[23] and either no use of riluzole at study entry or a stable dosage of riluzole for at least 30 days prior to screening. The study protocol was amended after edaravone became available in August 2017 to allow for unrestricted use of edaravone.

In the randomized trial, participants were randomized 2:1 to PB-TURSO (3 g PB and 1 g TURSO per sachet) or matching placebo administered twice a day by mouth or feeding tube for a planned duration of 6 months (24 weeks).

Open-Label Extension

Eligible participants in CENTAUR were given the option to enroll in an OLE (NCT03488524) and receive active drug for up to 30 months (132 weeks). Enrollment in the OLE occurred from March 2018 through September 2019. Participants who completed all visits in the randomized trial were eligible for OLE enrollment provided they enrolled within 28 days of their last visit in the randomized phase and did not prematurely discontinue study drug for reasons other than tracheostomy or initiation of permanent assisted ventilation (PAV). Four participants received a

protocol waiver and enrolled in the OLE more than 28 days after completion of CENTAUR, as the PB-TURSO drug supply for the OLE did not become available until approximately 2 months after the first participants had completed CENTAUR. Participants who received riluzole or edaravone during the randomized trial were permitted to continue these medications, and, as in the randomized phase, edaravone could be initiated during the OLE.

In the OLE, participants originally assigned to PB-TURSO or placebo were administered PB-TURSO by mouth or feeding tube, continuing the same dose of study drug they had been receiving at the end of the randomized phase of the trial (either 2 sachets daily [1 sachet dissolved in water, both in the morning and evening] or 1 sachet daily for 1 participant who had previously reduced dosage because of intermittent constipation). This regimen was implemented so that participants and investigators would remain blinded to original treatment assignment in the randomized phase during the OLE study.

Statistical Analysis

The prespecified survival analysis compared time to death (all-cause mortality) between participants originally randomized to active treatment and those originally randomized to placebo. A cutoff date of July 20, 2020 (longest follow-up, 35 months after randomization) was used to incorporate the most mature data to date for the purposes of providing the most complete analysis. The vital status and date of death for all participants randomized into the CENTAUR

trial (intent-to-treat population) were investigated by OmniTrace (a firm specializing in locating participants and ascertaining vital status via search of public records, obituary databases, property records, and social media). This vital status search was approved by the Partners Human Research Committee, which served as the central Investigational Review Board. The censoring date was designated as 30 days prior to the date the survival check was performed for each participant, allowing for the maximum time it may have taken for public record of death to be updated. Participants for whom vital status could not be obtained were censored at the date of their last follow-up.

The hazard ratio (HR) of death comparing the group originally randomized to active treatment versus the group originally randomized to placebo was estimated using a Cox proportional hazards model with covariates of age at randomization, pre-baseline ALSFRS-R slope, and baseline ALSFRS-R total score, variables shown to be predictors of disease progression in historical data.[24-26] Pre-baseline ALSFRS-R slope, defined as the rate of decline in ALSFRS-R total score between symptom onset and study baseline, was calculated during the baseline visit using the formula [(48 – baseline ALSFRS-R) / (number of months between symptom onset and study baseline)].[24] All covariates were prespecified prior to completing the vital status check. Median duration of survival and the associated 95% CI were estimated from Kaplan-Meier curves, and tests were declared significant if the 2-tailed *P* value was ≤0.05. The duration of exposure to PB-TURSO in each group was summarized using descriptive statistics.

Number and time to death-equivalent events (defined as tracheostomy or PAV >22 hours daily for >7 days, with date of PAV onset being the first of the 7 days) were summarized for the 2 groups as potential confounders of survival outcomes; unlike the occurrence of death, which could be ascertained for all randomized participants, occurrence of death-equivalent events was determined prospectively in the course of participant monitoring as part of the double-blind period and the OLE, but could not be ascertained for those who discontinued from study or were lost to follow-up. Sensitivity analyses were performed to assess the potential impact of use of concomitant medications at baseline on the overall survival analysis. Three sensitivity models were tested: adding baseline use of riluzole, edaravone, or both as covariates, with baseline ALSFRS-R; age at randomization; and pre-baseline ALSFRS-R slope as additional covariates.

Results

Participants

The disposition of participants in CENTAUR and the subsequent OLE is shown in Figure 1. A total of 137 participants were randomized in CENTAUR, of whom 89 were randomized to PB-TURSO and 48 were randomized to placebo. Vital status was obtainable for all but 2 of the participants randomized in CENTAUR; per the statistical analysis plan, these participants were censored at the date of last contact with the clinical site. Ninety-eight participants who completed CENTAUR were eligible for the OLE; 97 participants completed the study on drug, and 1

participant had a brief (~1-week) drug disruption at the very end of the study and was permitted to enter the OLE. Of these, 90 (92%) continued into the OLE, 34 of whom had been originally randomized to placebo and 56 to active drug. The longest follow-up was 35 months after randomization in CENTAUR, with 18 participants originally randomized to active treatment and 9 participants originally randomized to placebo remaining in follow-up.

Baseline demographic and disease characteristics for participants at the start of the randomized phase were generally similar for the 2 treatment groups (Table S1 online). Most (77%) participants were receiving riluzole or edaravone at or before study entry. Higher proportions of participants originally randomized to placebo were receiving edaravone and both edaravone and riluzole at or before study entry compared with the group originally randomized to PB-TURSO.

Survival Analysis

In the overall survival analysis encompassing all participants randomized in CENTAUR, the risk of death was 44% lower among those originally randomized to active treatment compared with those originally randomized to placebo (HR, 0.56; 95% CI, 0.34–0.92; *P*=0.023) (Figure 2). Median survival duration was 25.0 months (95% CI, 19.0–33.6 months) in the group originally randomized to active treatment and 18.5 months (95% CI, 13.5–23.2 months) in the group originally randomized to placebo, a 6.5-month difference. The estimated probability of survival at 12 months among participants originally randomized to PB-TURSO and placebo was 80.9%

(95% CI, 71.1–87.7%) and 72.9% (95% CI, 58.0–83.3%), respectively. At 24 months, the estimates were 51.6% (95% CI, 38.9–62.9%) and 33.9% (95% CI, 19.4–49.1%), respectively. The median time to censoring was 21.3 months. The duration of PB-TURSO exposure is summarized for each randomized participant by originally randomized groups in Figure S1 online. Inclusive of all randomized participants, including those who did not enroll in the OLE, those originally randomized to active treatment had a median (range; first and third quartiles) PB-TURSO exposure duration of 8.8 (0.1–33.0; 3.7–15.8) months, and those originally randomized to placebo had a median PB-TURSO exposure of 1.9 (0–22.5; 0–9.1) months (all in the OLE). Mean PB-TURSO exposure duration was 10.6 months in the group originally randomized to PB-TURSO and 4.7 months in the group originally randomized to placebo.

The 2 groups had similar rates of death-equivalent events. Six (6.7%) participants originally randomized to PB-TURSO and 4 (8.3%) participants originally randomized to placebo experienced death-equivalent events.

Results of the 3 sensitivity analyses accounting for use of concomitant riluzole, edaravone, or both at baseline retained the statistically significant benefit of PB-TURSO over placebo (Table 1), consistent with the survival analysis. These results suggest that the benefit of PB-TURSO was independent of baseline concomitant medication use.

Discussion

In this analysis of survival encompassing all participants randomized in CENTAUR, the group originally randomized to PB-TURSO had a median overall survival that was 6.5 months longer than the group originally randomized to placebo. Median PB-TURSO exposure duration differed by approximately 7 months between the groups. Notably, most of the participants originally randomized to placebo received some exposure to PB-TURSO in the OLE, possibly diluting the survival benefit attributable to PB-TURSO in this analysis; however, it is not known whether those who were originally randomized to placebo but later received PB-TURSO in the OLE derived any survival benefit, as the OLE had no concurrent placebo control group.

Initiation of PB-TURSO at baseline was associated with longer survival, a finding that suggests a neuroprotective effect of PB-TURSO in ALS. The concept of neuroprotection involves early therapeutic intervention after an acute injury or in chronic neurodegenerative conditions with the aim of averting irreversible neuronal death or degeneration. Neuroprotection may be achieved by interrupting either upstream disease-specific processes that lead to neurodegeneration or downstream processes that secondarily promote neuronal death.[27] The coformulated compounds in PB-TURSO have shown mitigating effects on ER stress (PB)[28,29] and mitochondrial dysfunction (TURSO),[30] both mechanisms thought to underlie neurodegeneration in ALS.[10]

Our analysis was limited by a relatively small sample size but was strengthened by inclusion of the entire randomized sample from CENTAUR and assessment of vital status up to 35 months after randomization. Confirmation of vital status was facilitated by the use of a participant locating service, a novel approach that differentiated our survival analysis from those in other ALS studies. Data on vital status that are incomplete because of discontinuation or loss to follow-up may bias the results of survival analyses.[31,32] Participant tracing has been used in clinical trials to improve the accuracy of results by tracking long-term outcomes for as many trial participants as possible.[33-35] This method may be particularly useful in trials with large drop-out rates, such as those in ALS,[36] by accounting for potentially differing outcomes between participants who drop out and those who continue on study. Our confirmation of vital status for all but 2 randomized participants, regardless of duration of follow-up, provided the basis for statistically robust and comprehensive overall survival analyses.

In ALS, decisions to implement life-sustaining measures such as tracheostomy and PAV may be affected by patient choice and local practices; they have the potential to confound survival analyses and are thus considered to be death-equivalent events.[37] In this study, identification of all death-equivalent events may not have occurred, as these events were provided by the study sites and are not consistently searchable in public databases or records. Nevertheless, the low rates and similar proportions of participants affected by such events in both groups suggest survival was not likely to have been confounded by tracheostomy or initiation of PAV in either

group. Results of sensitivity analyses suggested that the PB-TURSO treatment effect was independent of baseline use of riluzole, edaravone, or both together.

Despite currently available therapies, ALS remains rapidly debilitating and fatal. PB-TURSO has previously demonstrated functional benefit in a randomized controlled trial.[20] The results presented here demonstrate a long-term survival benefit from early initiation of PB-TURSO treatment in participants with ALS, adding to the previously reported functional benefit.

Abbreviations

ALS, amyotrophic lateral sclerosis; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Scale–Revised; ER, endoplasmic reticulum; HR, hazard ratio; ITT, intent-to-treat; NEALS, Northeast ALS Consortium; OLE, open-label extension; PAV, permanent assisted ventilation; PB, sodium phenylbutyrate; PB-TURSO, sodium phenylbutyrate-taurursodiol; SVC, slow vital capacity; TURSO, taurursodiol.

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Figure Legends

Figure 1. Participant disposition: randomized controlled trial and open-label extension (through July 2020). Percentages may not add up precisely due to rounding. *As of July 2020; vital status for participants who discontinued from study was ascertained by OmniTrace as previously noted. PB-TURSO, sodium phenylbutyrate-taurursodiol

Figure 2. Overall survival in the entire randomized population. Starting at the conclusion of the randomized phase at month 6 (24 weeks), eligible participants could enroll in the open-label extension (OLE). Of 98 eligible participants, 90 (92%) continued into the OLE, 34 of whom were originally randomized to placebo and 56 to active drug. The survival analysis encompassed all participants randomized at time 0, including those who did not enter the OLE, discontinued from study, or were lost to follow-up. The hazard ratio for death in the group originally randomized to active treatment was 0.56 (P=0.023 vs group originally randomized to placebo). PB-TURSO, sodium phenylbutyrate-taurursodiol

Table 1. Comparative results of sensitivity analyses accounting for baseline concomitant medication use

Model*	Hazard Ratio	95% CI	*P* Value†
Primary	0.56	0.34–0.92	0.023
Riluzole use at baseline	0.54	0.33–0.89	0.018
Edaravone use at baseline	0.53	0.32–0.90	0.019
Riluzole and edaravone use at baseline	0.53	0.32–0.88	0.016

Abbreviations: ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; PB-TURSO, sodium phenylbutyrate-taurursodiol.
*Cox proportional hazards models, including baseline ALSFRS-R, age at randomization, and pre-baseline ALSFRS-R slope in addition to treatment (PB-TURSO) and concomitant medication use at baseline.
†*P* values are from the likelihood ratio test.

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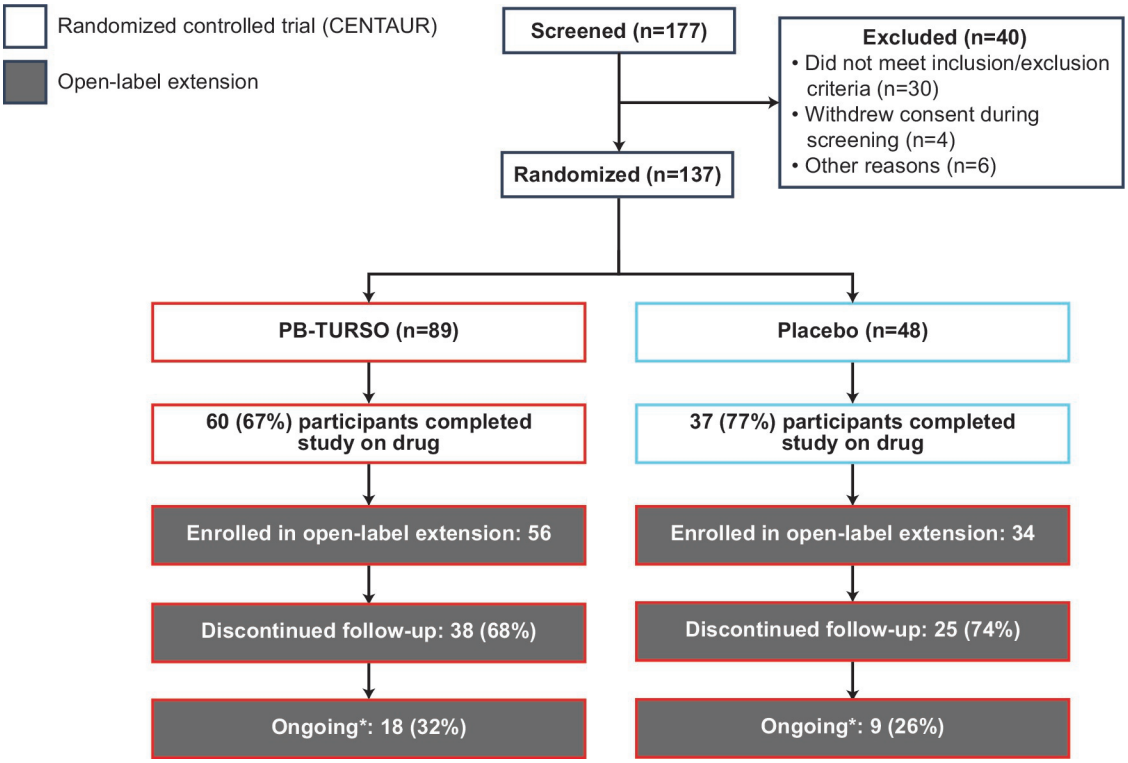

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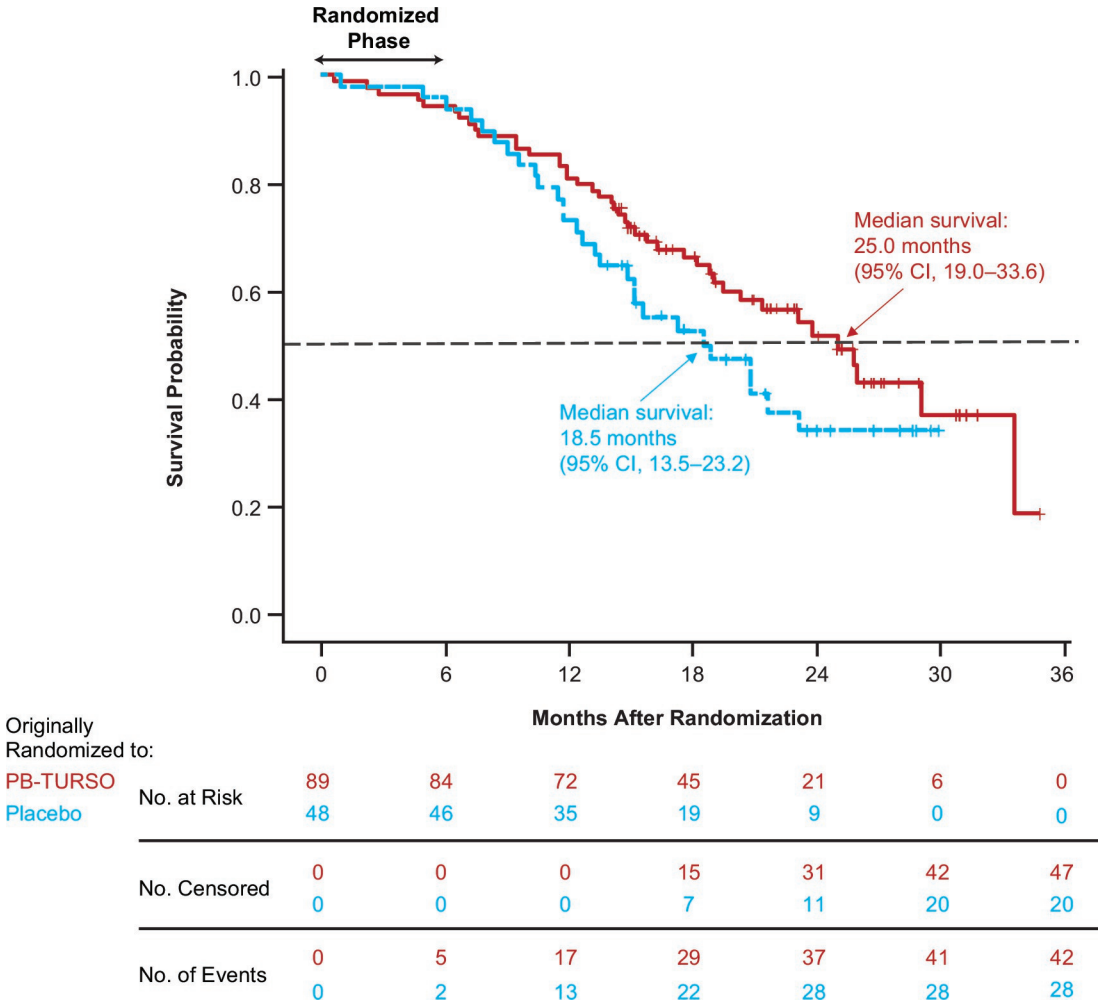

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