PHOENIX

Survival Results from the Global Phase 3 Trial (PHOENIX) Evaluating Sodium Phenylbutyrate and Ursodoxicoltaurine in ALS

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on behalf of the PHOENIX Writing Group

Disclosures

- The institution of Dr. van den Berg has received compensation for serving on a Scientific Advisory or Data Safety Monitoring board for:
  - Amylyx, Ferrer, Sanofi, Biogen, Takeda, Novartis, BMS, ArgenX, Projenx
- The institution of Dr. van den Berg has received research support from Netherlands ALS Foundation

PHOENIX Was 48 Weeks Long with an Open-Label Extension

Inclusion Criteria

- Clinically definite or clinically probable ALS (2+ body regions)
- <24 months from symptom onset
- Slow vital capacity ≥55%
- Stable riluzole/edaravone use permitted

Randomized
3:2
N = 664

PB&TURSO
N = 397

Placebo
N = 267

Placebo-Controlled Phase
48 weeks

PB&TURSO

The PHOENIX Open-Label Extension closed
October 2024

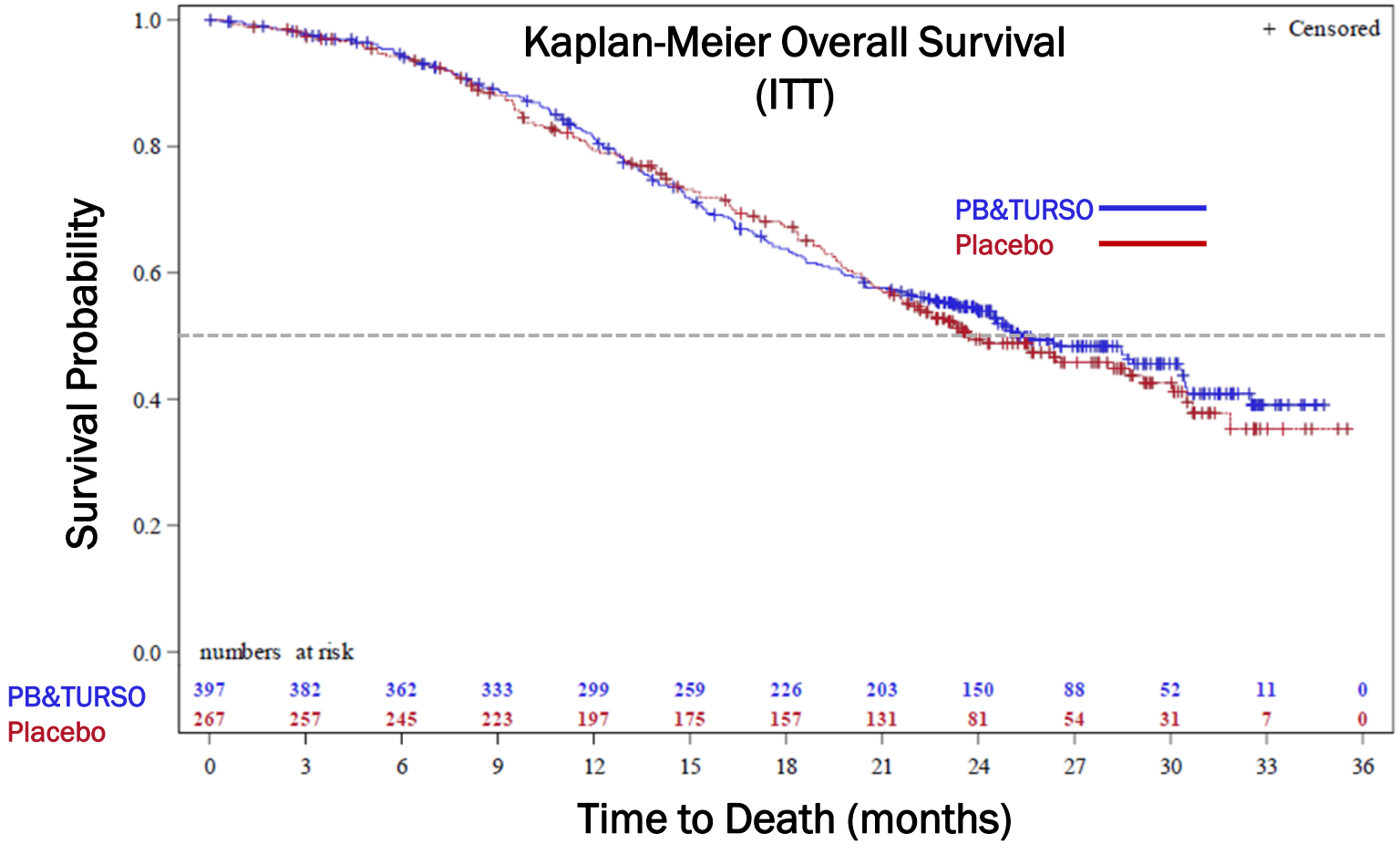
Survival status was collected beyond Week 48 until PHOENIX study closure

A Quick PHOENIX Recap from ENCALS 2024

- Demographics and baseline disease characteristics were well-balanced
- PB&TURSO was generally well-tolerated
- No differences between groups for primary endpoint, ALSFRS-R, or secondary endpoints, ALSAQ-40 and SVC at Week 48
  - Overall survival secondary endpoint was not presented in 2024 as follow-up was ongoing

Today's Presentation:
Overall Survival and Ventilation-Free Survival Results From PHOENIX

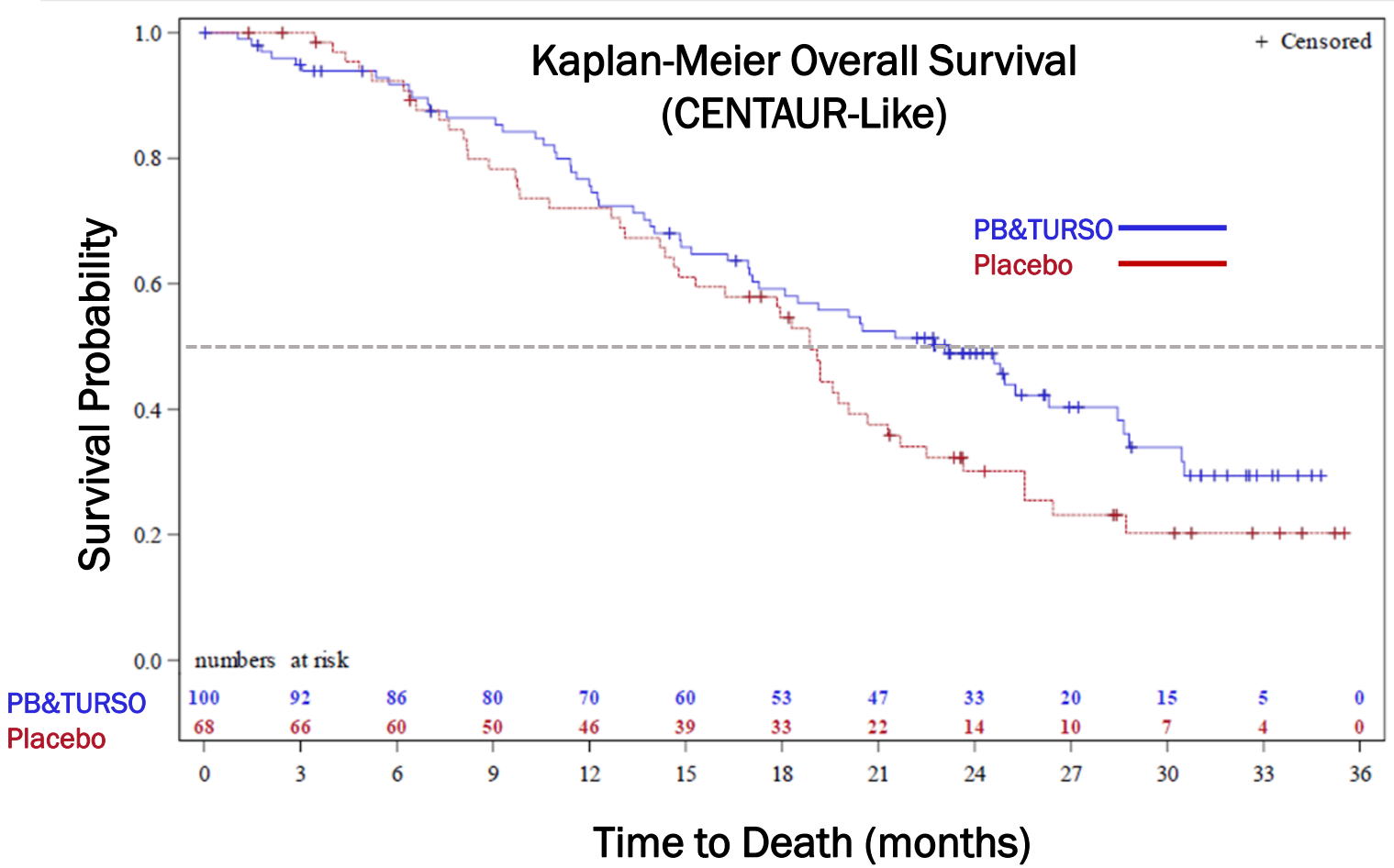
Overall Survival (ITT)



ITT	PB&TURSO (N=397)	Placebo (N=267)
Median Survival Time, mo (95%CI)	25.3 (23.2, 30.4)	23.8 (21.6, 29.1)
HR[a] (95% CI)	0.95 (0.76, 1.19)	
p-value[b]	0.520	

[a]HR obtained from Cox proportional hazards model - covariates: del-FS, CENTAUR-like, baseline ALSFRS-R, age
[b]Stratified log-rank test

Overall Survival (CENTAUR-Like)

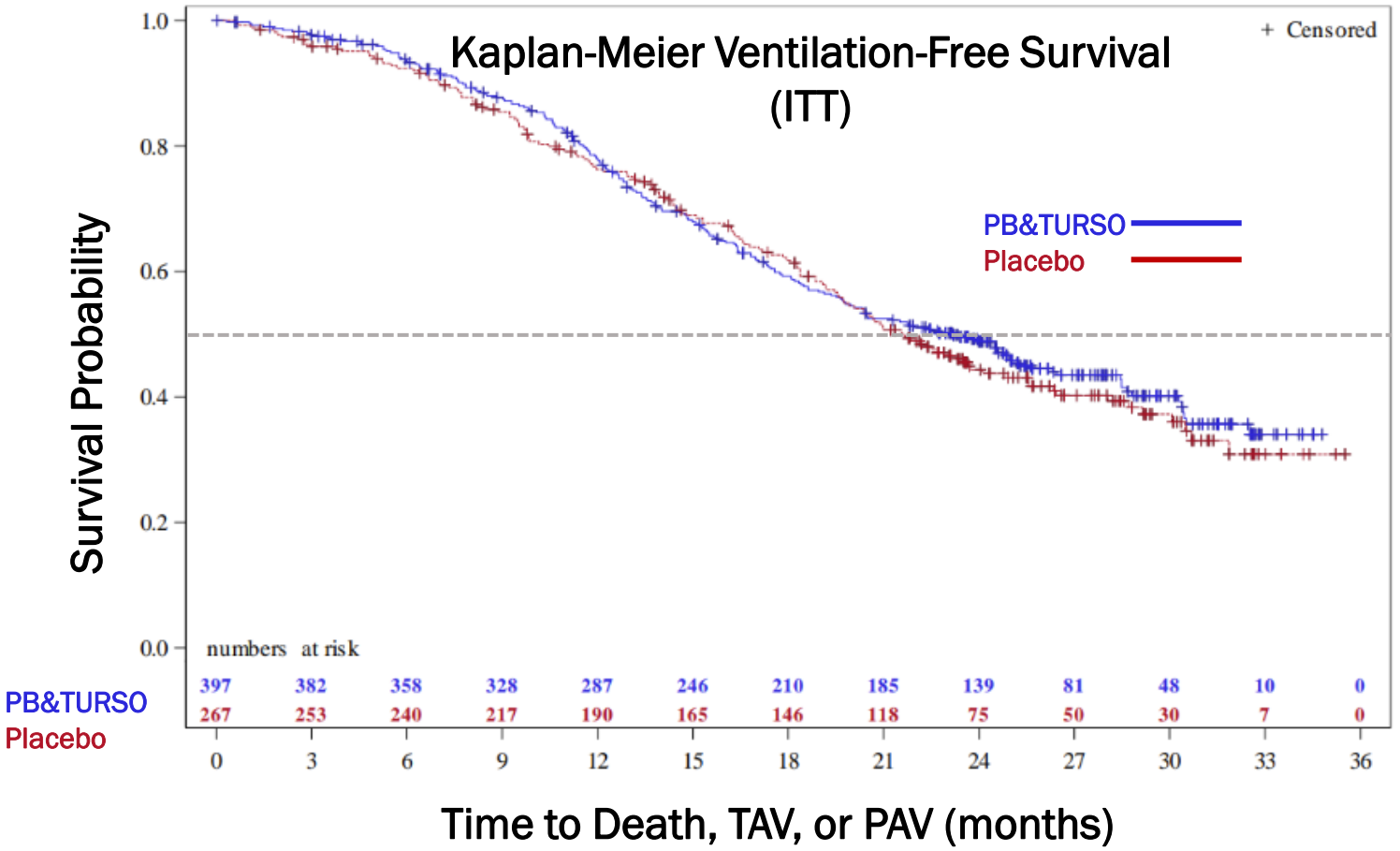


CENTAUR-Like	PB&TURSO (N=100)	Placebo (N=68)
Median Survival Time, mo (95%CI)	**23.2** (17.3, 28.5)	**18.9** (14.8, 20.7)
HR[a] (95% CI)	**0.82** (0.55, 1.23)	
p-value[b]	0.099	

Adjusted for baseline NfL
- HR[a] (95%CI): **0.74** (0.49, 1.12)

CENTAUR-like definition: <18 months from symptom onset, slow vital capacity (SVC)>60%, and clinically definite ALS diagnosis
[a]**HR obtained from Cox proportional hazards model:** covariates: del-FS, baseline ALSFRS-R, age (adjusted for baseline NfL also includes baseline NfL as covariate)
[b]**Log-rank test**

Ventilation-Free Survival (ITT) [includes OLE events]



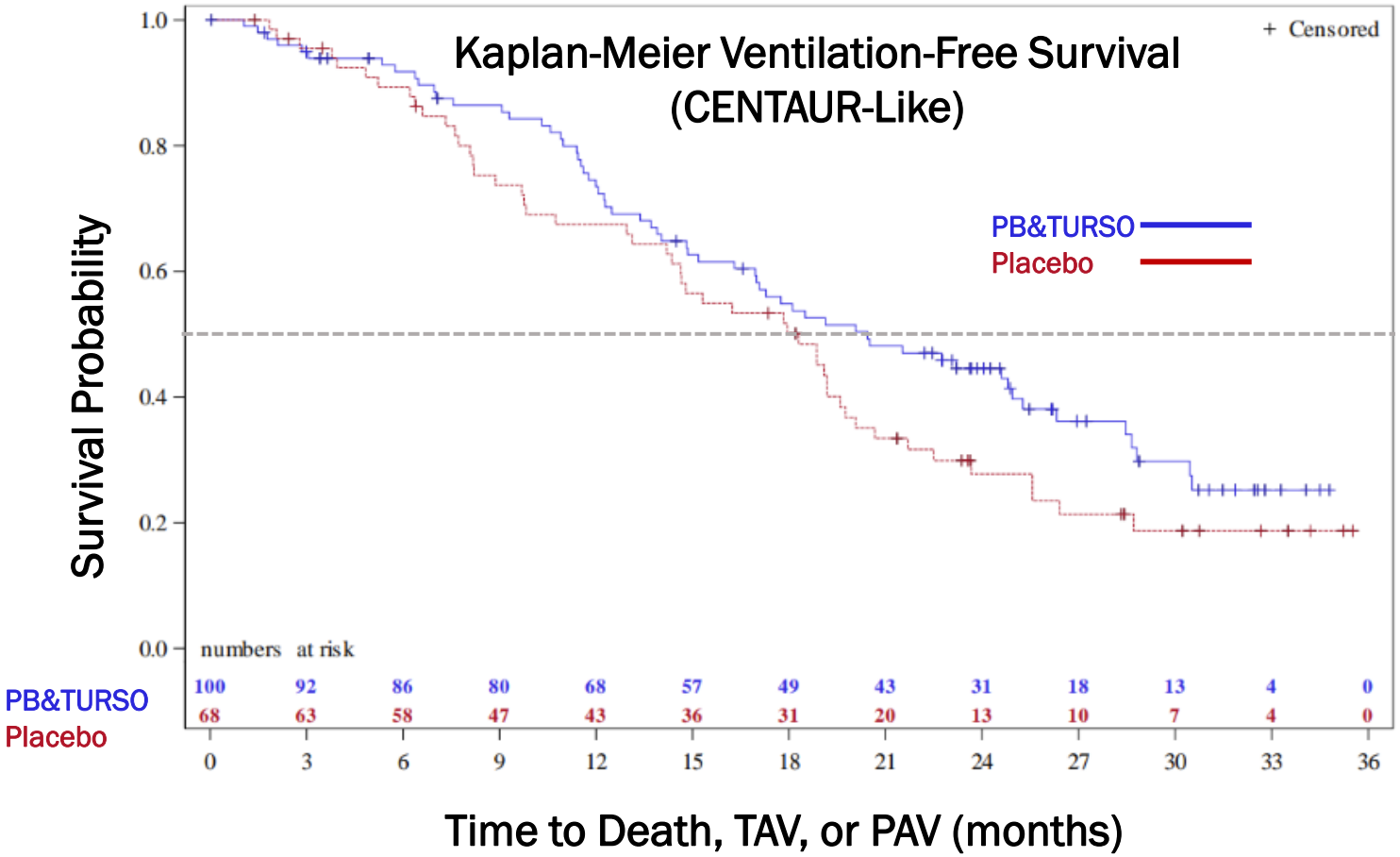
ITT	PB&TURSO (N=397)	Placebo (N=267)
Median Survival Time, mo (95%CI)	23.2 (19.7, 25.7)	21.6 (19.6, 24.9)
p-value[a]	0.485	

Definition: time to earliest date of tracheostomy for respiratory distress (TAV), permanent non-invasive ventilation (PAV), or the date of death due to any cause. TAV and PAV events were collected during OLE, but not following completion or after drop out.

[a]Stratified log-rank test

HR analysis not performed for this endpoint.

Ventilation-Free Survival (CENTAUR-Like) [includes OLE events]



CENTAUR-Like	PB&TURSO (N=100)	Placebo (N=68)
Median Survival Time, mo (95%CI)	20.4 (17.0, 25.3)	18.3 (14.4, 19.7)
HR[a] (95% CI)	0.87 (0.59, 1.28)	
p-value[b]	0.122	

Adjusted for baseline NfL
- HR[a] (95%CI): **0.80** (0.54, 1.19)

Definition: time to earliest date of tracheostomy for respiratory distress, permanent non-invasive ventilation (PAV), or the date of death due to any cause. TAV and PAV events were collected during OLE, but not following completion or after drop out.

[a]**HR obtained from Cox proportional hazards model:** covariates: del-FS, baseline ALSFRS-R, age (adjusted for baseline NfL also includes baseline NfL as covariate)

[b]**Log-rank test**

Overall Survival Participant Disposition: Learnings

ITT	PB&TURSO (N=397)	Placebo (N=267)
Death	48%	50%
Censored	52%	50%
Lost to Follow-Up	1.5%	1.5%
Withdrawal of Consent	10%	15%
Study Termination	40%	34%

CENTAUR-Like	PB&TURSO (N=100)	Placebo (N=68)
Death	57%	69%
Censored	43%	31%
Lost to Follow-Up	1%	0
Withdrawal of Consent	9%	13%
Study Termination	33%	18%

Importance of avoiding loss to follow-up and withdrawal of consent for survival status collection whenever possible

We Extend our Sincere Gratitude to the PHOENIX Participants, Investigators, and Sites

TRICALS
The highway towards a cure

NEALS Northeast Amyotrophic Lateral Sclerosis Consortium

Belgium

- University Hospitals Leuven

France

- CHRU de Lille – Hôpital Roger Salengro
- CHU de Limoges – Hôpital Dupuytren
- CHU de Montpellier – Gui de Chauliac
- CHU de Nice
- Hôpital Pitié-Salpêtrière
- Hopital Gabriel Montpied Service de Neurologie
- Hôpital de La Timone
- Hospices Civils de Lyon Hôpital Neurologique Pierre Wertheimer Cellule Mutualisée de Recherche Clinique (CMRC)
- CHU de Tours

Germany

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- Hannover Medical School
- Universitätsklinikum Jena
- Universitätsmedizin Mannheim
- Uniklinikum Dresden
- Universitätsklinikum Ulm
- Universitätsmedizin Rostock

Ireland

- Trinity College Dublin/Beaumont Hospital

Italy

- Azienda Ospedaliero – Universitaria Di Modena
- Centro Clinico NEMO
- Università degli Studi della Campania "Luigi Vanvitelli"
- University of Bari Aldo Moro at Pia Fondazione "Card. G. Panico"
- IRCCS Istituto Italiano Auxologico
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- University Medical Center Utrecht

Poland

- Centrum Medyczne Linden
- City Clinic Warsaw

Portugal

- Centro Hospitalar Universitário Lisboa-Norte

Spain

- Biodonostia Health Research Institute; Hospital Universitario Donostia
- Hospital del Mar
- Hospital Universitario San Rafael
- Hospital Universitari de Bellvitge-IDIBELL
- Hospital Universitario y Politécnico La Fe

Sweden

- Karolinska Institutet
- Umeå University Hospital

United Kingdom

- King's College Hospital
- Salford Royal Hospital
- Royal Hallamshire Hospital
- UCL Queen Square Institute of Neurology
- University Hospitals Plymouth NHS Trust

United States

- Barrow Neurological Institute
- California Pacific Medical Center Research Institute
- University of California Irvine Medical Center
- University of Southern California
- University of Colorado Neurosciences Center - Anschutz
- University of Florida Fixel Institute for Neurological Diseases
- University of South Florida

United States (cont'd)

- Augusta University Neuroscience Center
- Emory Clinic
- Northwestern University
- Johns Hopkins University School of Medicine Outpatient Center
- Sean M. Healey and AMG Center for ALS Research at Massachusetts General Hospital
- University of Massachusetts Memorial Medical Center
- Hennepin Healthcare Research Institute
- Washington University School of Medicine
- Somnos Clinical Research
- Rutgers University
- Columbia University Medical Center
- University of North Carolina at Chapel Hill
- Wake Forest University Baptist Health
- The Ohio State University
- Temple University Hospital
- Penn Medicine
- National Neuromuscular Research Institute
- Texas Neurology
- VCU Neurology
- Swedish Medical Center
- University of Washington