PHOENIX

Results From a Global Phase 3 Trial Evaluating an Oral, Fixed-Dose Combination of Sodium Phenylbutyrate and Taurursodiol in Amyotrophic Lateral Sclerosis

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Disclosures

- The institution of Dr. van den Berg has received compensation in the range of $500-$4,999 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

Please Note

- This presentation is intended to provide scientific information about sodium phenylbutyrate and taurursodiol (PB&TURSO)

- Some of the statements and content shared in this presentation have not been evaluated by any health authority

About PB&TURSO

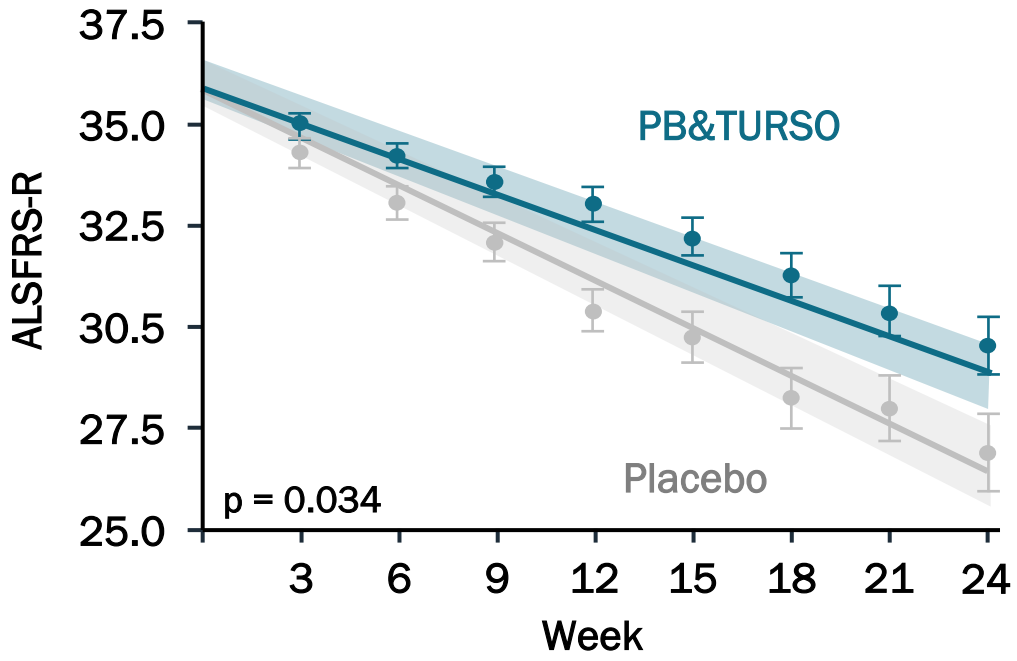
- Fixed-dose combination of 2 small molecules, sodium phenylbutyrate and taurursodiol (PB&TURSO)[1]

- Hypothesized to simultaneously mitigate endoplasmic reticulum stress and mitochondrial dysfunction, 2 pathways leading to neuronal degeneration and death in ALS and other neurodegenerative diseases[2-6]

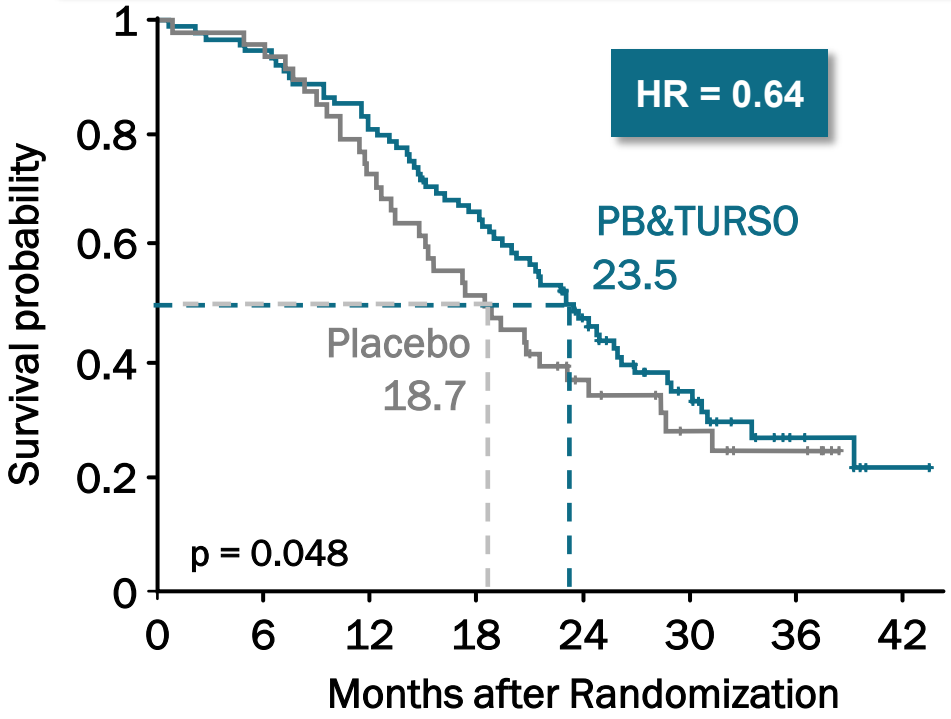
1 Paganoni S, et al. Supplementary appendix. *N Engl J Med.* 2020;383(10):919-930. Accessed August 16, 2023. https://www.nejm.org/doi/full/10.1056/nejmoa1916945. **2.** Paganoni S, et al. *N Engl J Med.* 2020;383(10):919-930. **3.** Zhou W. *J Biol Chem*. 2011;286(17):14941-14951. **4.** Wiley JC, et al. *PLOS One.* 2010; 5(2):e9135. **5.** Rodrigues CM, Steer CJ. *Expert Opin Investig Drugs*. 2001;10(7):1243-1253. **6.** Rodrigues CM, et al. *Biochemistry*. 2003;42(10):3070-3080.

Background: The CENTAUR Trial of PB&TURSO in ALS Met Primary Endpoint[1]

25% Slower Decline in Function (ALSFRS-R)[1]



4.8 Months Longer Median Survival[2]



Safety: Generally well-tolerated; GI adverse events generally mild or moderate[1]

- PB&TURSO was approved with conditions by Health Canada in June 2022 and granted a full approval by the U.S. Food and Drug Administration (FDA) in September 2022

1. Paganoni S, et al. *N Engl J Med.* 2020;383:919-930. **2.** Paganoni S, et al. Muscle Nerve. 2022;66(2):136-141.

PHOENIX Was a Global Collaboration

Steering Committee Co-Chairs

Leonard van den Berg, MD, PhD | Sabrina Paganoni, MD, PhD

PHOENIX Was 48 Weeks Long with an Ongoing 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

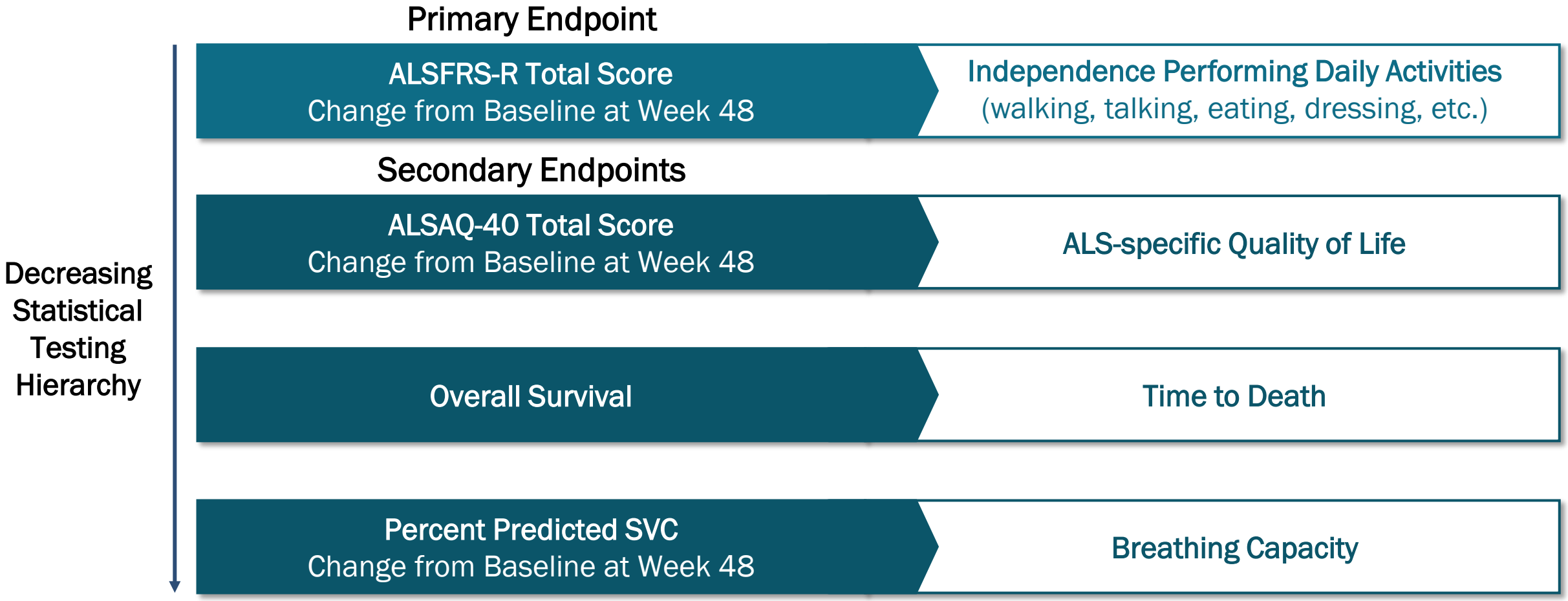
Open-Label Extension Phase
108 weeks

PHOENIX Methods

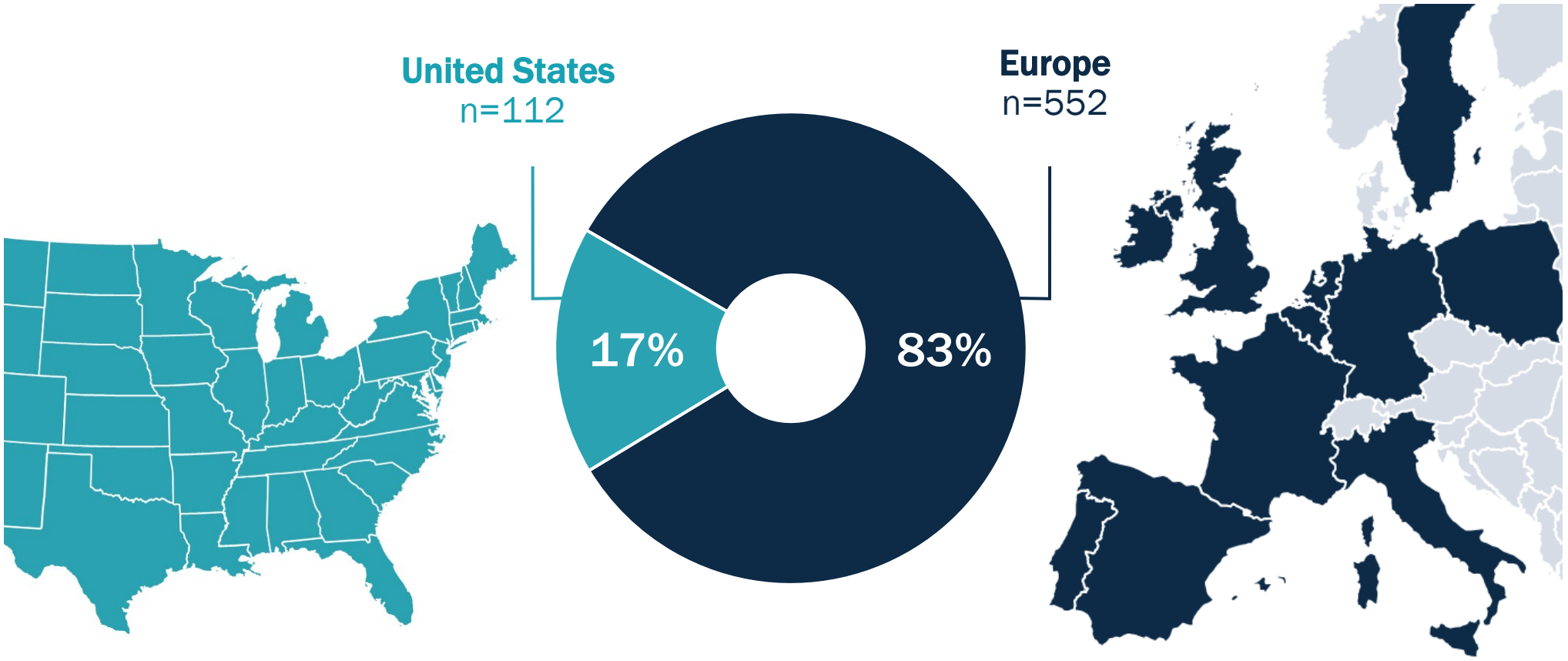
Stratification Factors

- **CENTAUR-Like Population:**
  - Clinically Definite ALS (3+ body regions), SVC >60%, <18 mo from symptom onset
- **Edaravone use** (at time of screening)

Pre-Specified Primary and Secondary Endpoints

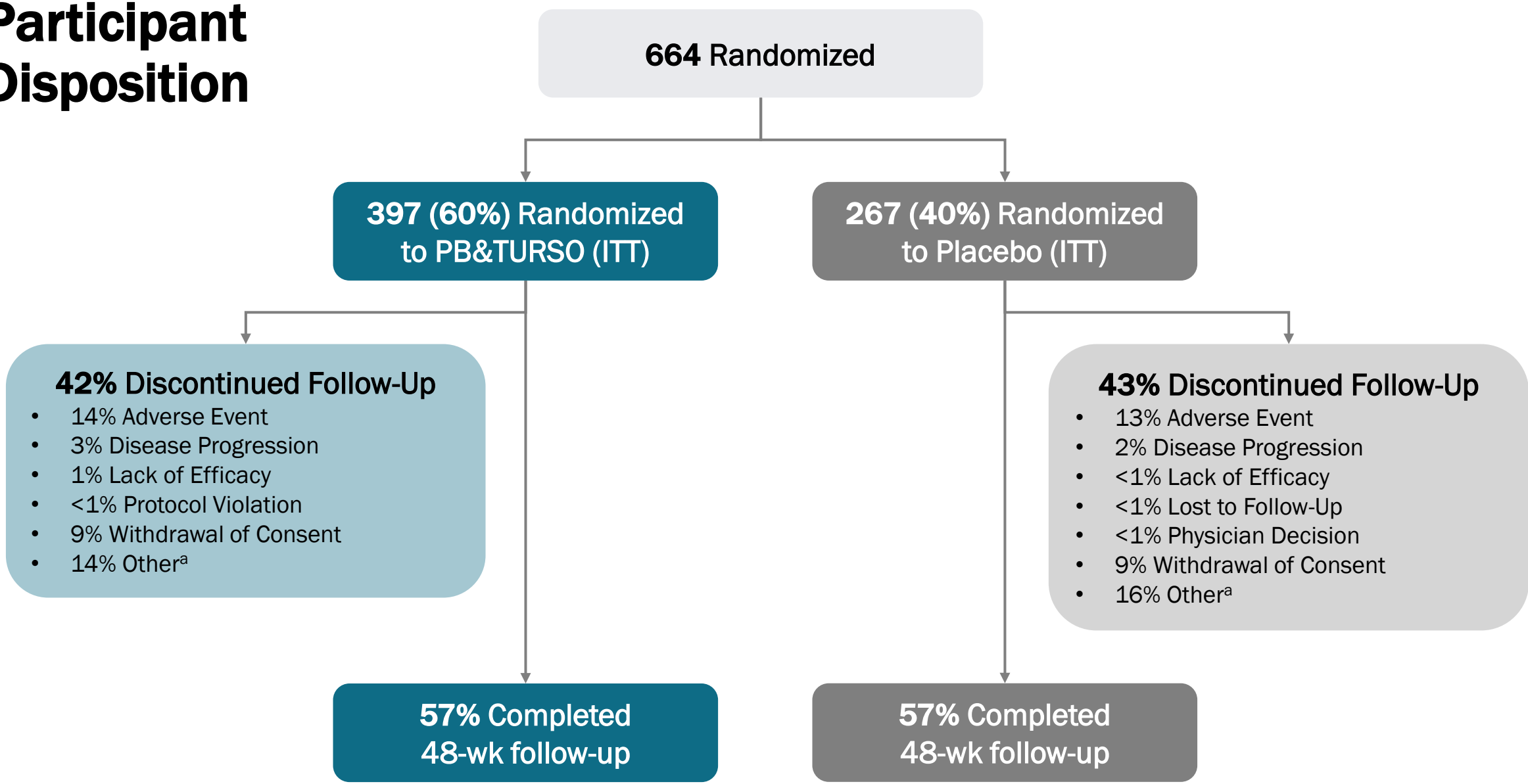


Majority of Participants in PHOENIX Were Enrolled in Europe



U.S. Participants Rolled Off PHOENIX in 2022 When FDA Approval Occurred

Participant Disposition



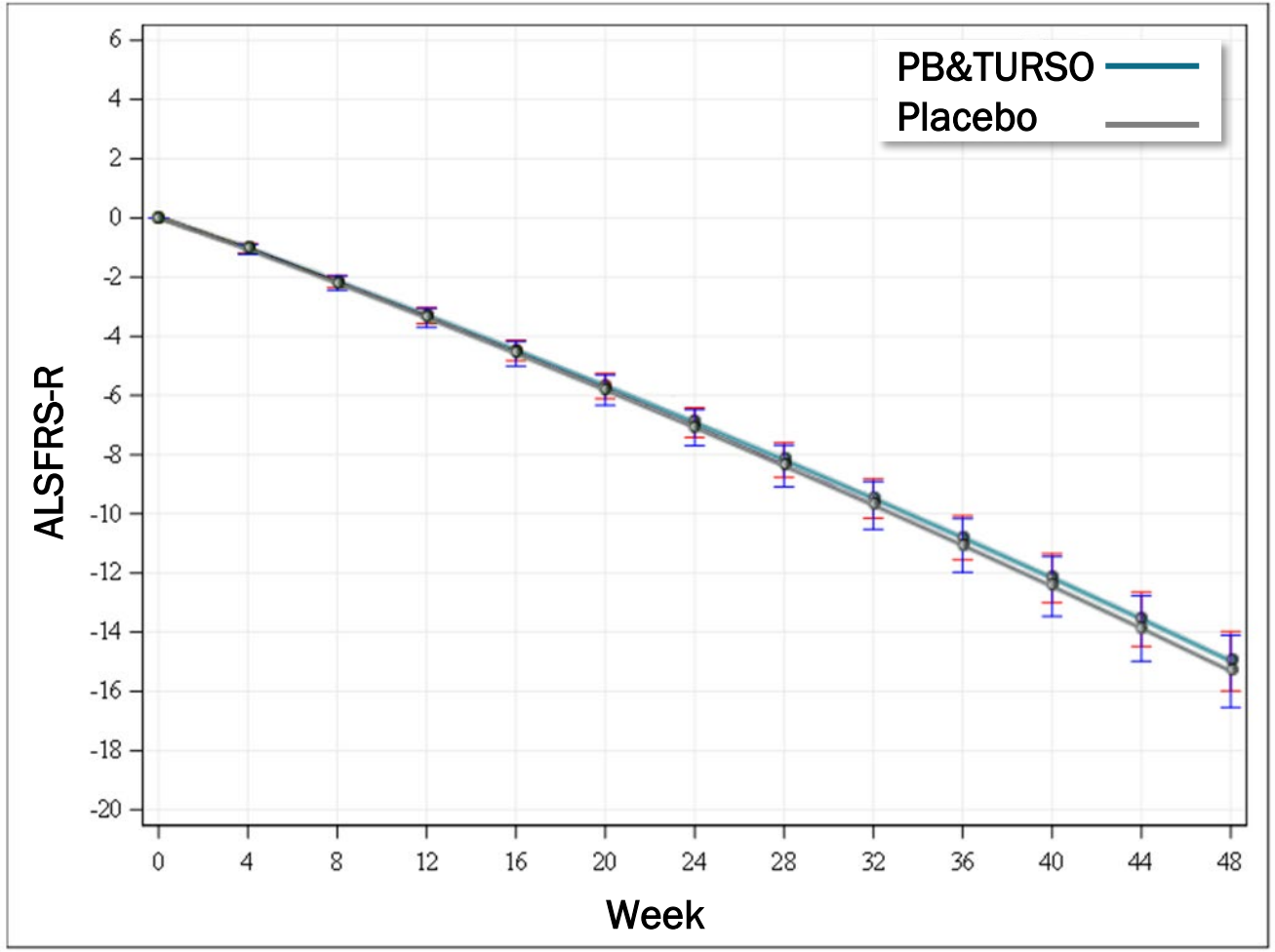
[a]Includes U.S. participants who discontinued the trial when PB&TURSO received U.S. FDA approval in September 2022.

Demographics and Baseline Characteristics Were Well Balanced

Characteristic		PB&TURSO N = 397	Placebo N = 267
Age (years), mean (SD)		60.0 (11.0)	58.8 (10.5)
Sex	Male	63%	60%
	Female	37%	40%
Region	Europe	83%	83%
	U.S.	17%	17%
Time Since Symptom Onset (months), mean (SD)		14.8 (5.3)	13.8 (5.2)
Bulbar Onset		22%	22%
Stable Use of ALS Meds	Riluzole	93%	91%
	Edaravone	3%	3%
Met CENTAUR-Like Criteria		25%	26%
ALSFRS-R Total Score, mean (SD)		36.6 (5.9)	36.9 (6.3)
Pre-baseline ALSFRS-R slope (del-FS), mean (SD)		0.836 (0.546)	0.892 (0.663)
SVC (% predicted normal), mean (SD)		82% (17)	84% (18)

Primary Endpoint

Change from Baseline in ALSFRS-R Total Score at Week 48 (ITT; mortality adjusted progression model)



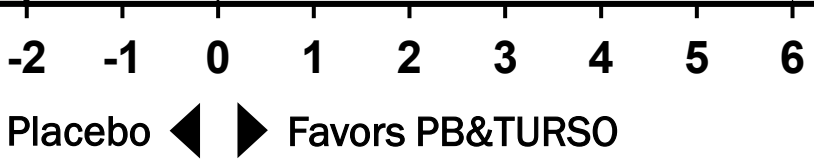
	PB&TURSO N = 397	Placebo N = 267
Mean Change from Baseline in ALSFRS-R Total Score (95% CI)	-14.98 (-15.98, -13.98)	-15.32 (-16.54, -14.11)
Difference (95% CI)	0.343 (-1.22, 1.91)	
p-value	0.667	

Covariates: baseline ALSFRS-R score, age, CENTAUR-like, delFS*time

Pre-Specified ALSFRS-R Subgroup Analyses

Change from Baseline in ALSFRS-R Total Score at Week 48 (ITT; mortality adjusted progression model)

Subgroup	PB&TURSO N	Placebo N	Difference in Mean Change from Baseline (95% CI)
Primary Endpoint (ITT Population)	397	267	0.343 (-1.22, 1.91)
CENTAUR-Like YES	100	68	2.01 (-1.31, 5.33)
CENTAUR-Like NO	297	199	-0.101 (-1.87, 1.67)
Europe Only	331	221	0.463 (-1.30, 2.22)
No Edaravone	385	259	0.431 (-1.16, 2.02)



Subgroup analyses not performed for Yes Edaravone use due to small sample size and not performed for U.S. participants at Week 48 given U.S. discontinuations due to PB&TURSO FDA approval.

Secondary Endpoints

Change from Baseline in ALSAQ-40 and SVC at Week 48 (ITT; Mixed Model Repeated Measures)

Week 48	PB&TURSO N = 397	Placebo N = 267	Difference in Mean Change from Baseline (95% CI)
Mean Change from Baseline in ALSAQ-40 (95% CI)	39.8 (36.9, 42.8)	38.4 (34.8, 42.1)	1.41 (-3.3, 6.2)
Mean Change from Baseline in SVC (95% CI)	-21.0 (-23.2, -18.7)	-23.0 (-25.8, -20.2)	2.02 (-1.5, 5.6)

Longer Follow-Up Past Week 48 Needed for Overall Survival Analysis to Reach Maturity

Endpoint

ALSFRS-R Total Score
Change from Baseline at Week 48

ALSAQ-40 Total Score
Change from Baseline at Week 48

Overall Survival

Percent Predicted SVC
Change from Baseline to Week 48

Overall Survival Maturity Definition:
Minimum of 70% of the participants have died or 3 years have passed since the last participant was randomized into the study (which would be Feb 2026), whichever comes first

PHOENIX will continue to collect survival data

PB&TURSO Was Generally Well-Tolerated in PHOENIX

Safety Results Concordant with CENTAUR Trial

Adverse Event	PB&TURSO N = 396	Placebo N = 267
Any	89%	88%
Drug-Related	53%	28%
Serious	26%	28%
Fatal	10%	15%
Treatment Emergent Adverse Events ≥10% In Either Treatment Arm		
Any TEAE (≥10%)	64%	55%
Fall	27%	27%
Diarrhea	31%	10%
Constipation	15%	12%
COVID-19	14%	11%
Respiratory failure	8%	11%

Current Status of PB&TURSO in ALS

- Amylyx has announced that it has started a process with the FDA and Health Canada to voluntarily discontinue the marketing authorizations for PB&TURSO
- This will remove the product from the market in the U.S. and Canada based on topline results from the Phase 3 PHOENIX trial
- PB&TURSO is no longer available for new patients
- Patients on therapy as of April 4 in the U.S. and Canada who, in consultation with their physician, wish to stay on treatment can be transitioned to a free drug program

Summary and Next Steps for PHOENIX

- Demographics and baseline disease characteristics were well-balanced
- No differences between groups for primary endpoint, ALSFRS-R, or secondary endpoints, ALSAQ-40 and SVC
  - Complete secondary endpoint survival data will not be available until 2025/2026
- PB&TURSO was generally well-tolerated

Next Steps: Continue to learn from PHOENIX to inform future ALS trials

- Biomarker analyses underway
- Subgroup analyses further evaluating CENTAUR-like population vs CENTAUR
- Continue to collect survival data

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

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

- Charité - Universitätsmedizin Berlin
- 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
- University of Padua – Azienda Ospedaliera di Padov
- A.O.U. CITTA della SALUTE e della SCIENZA di Torino

The Netherlands

- 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