PHOENIX

Results From the Global Phase 3 Trial 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
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Please Note

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

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

- PB&TURSO is an investigational drug in the European Union, UK, and Switzerland and not currently approved for use

Background: CENTAUR Study Design[1,2]

Screened
(N=177)

Key Eligibility Criteria

- Sporadic or familial ALS
- Clinically Definite ALS (3+ body regions)
- ≤18 mo from symptom onset
- SVC >60%
- Riluzole/IV edaravone use permitted

Randomized 2:1
(N=137)

- PB&TURSO (n=89)
- Placebo (n=48)

Entered OLE Phase
(N=90)

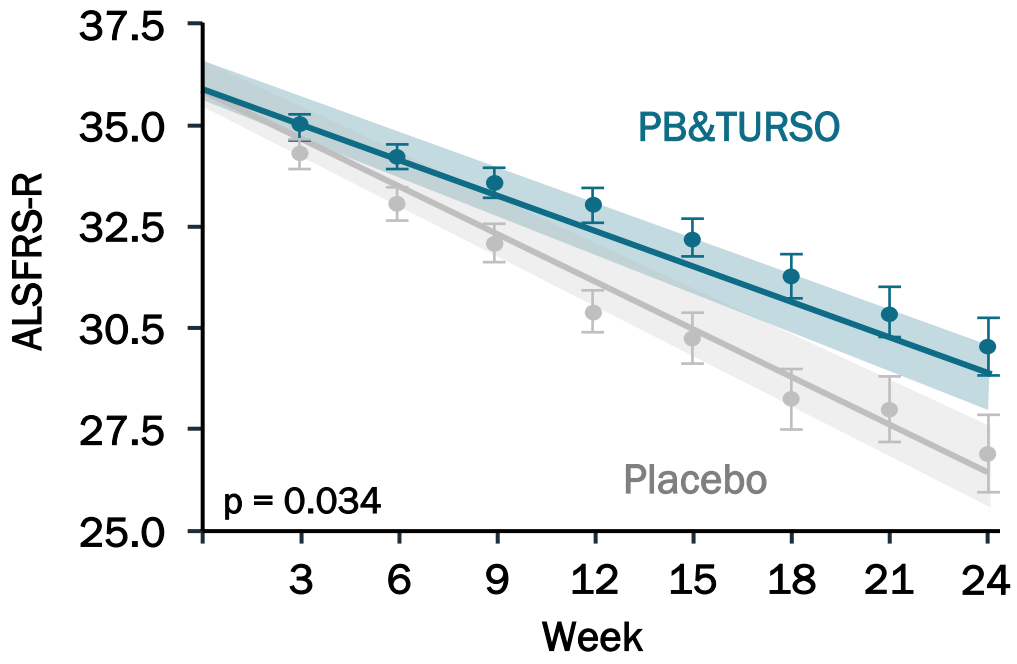
- PB&TURSO (n=56)
- PB&TURSO (n=34)

Screening	Randomized Phase	OLE Phase
≤6 wk	24 wk	Up to 152 wk (42 mo)

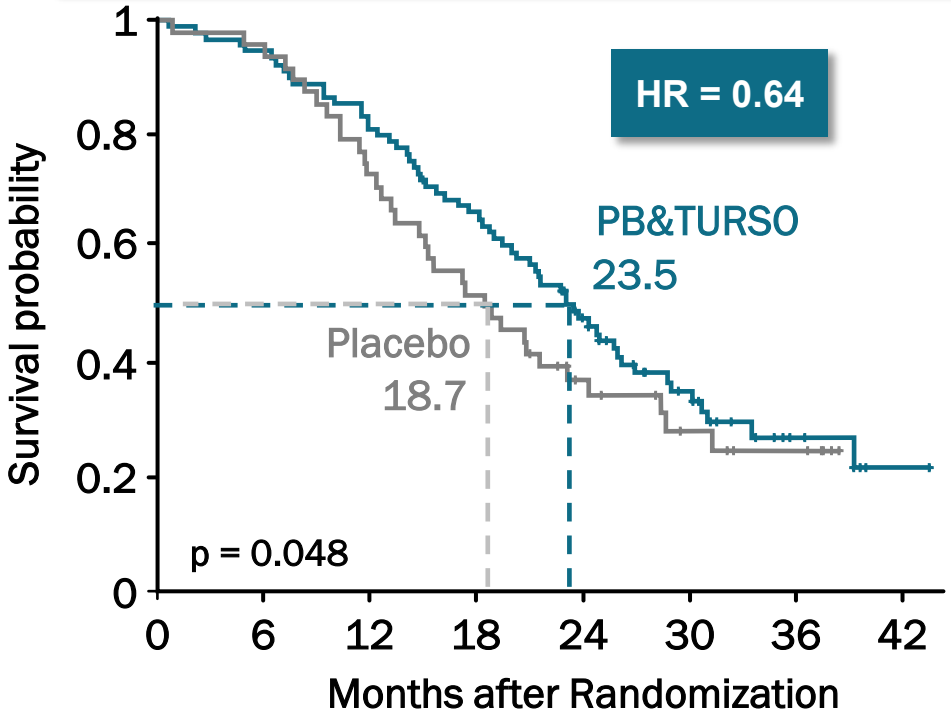
1. Paganoni S, et al. *N Engl J Med.* 2020;383:919-930. **2.** Paganoni S, et al. Muscle Nerve. 2022;66(2):136-141.

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 Results

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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

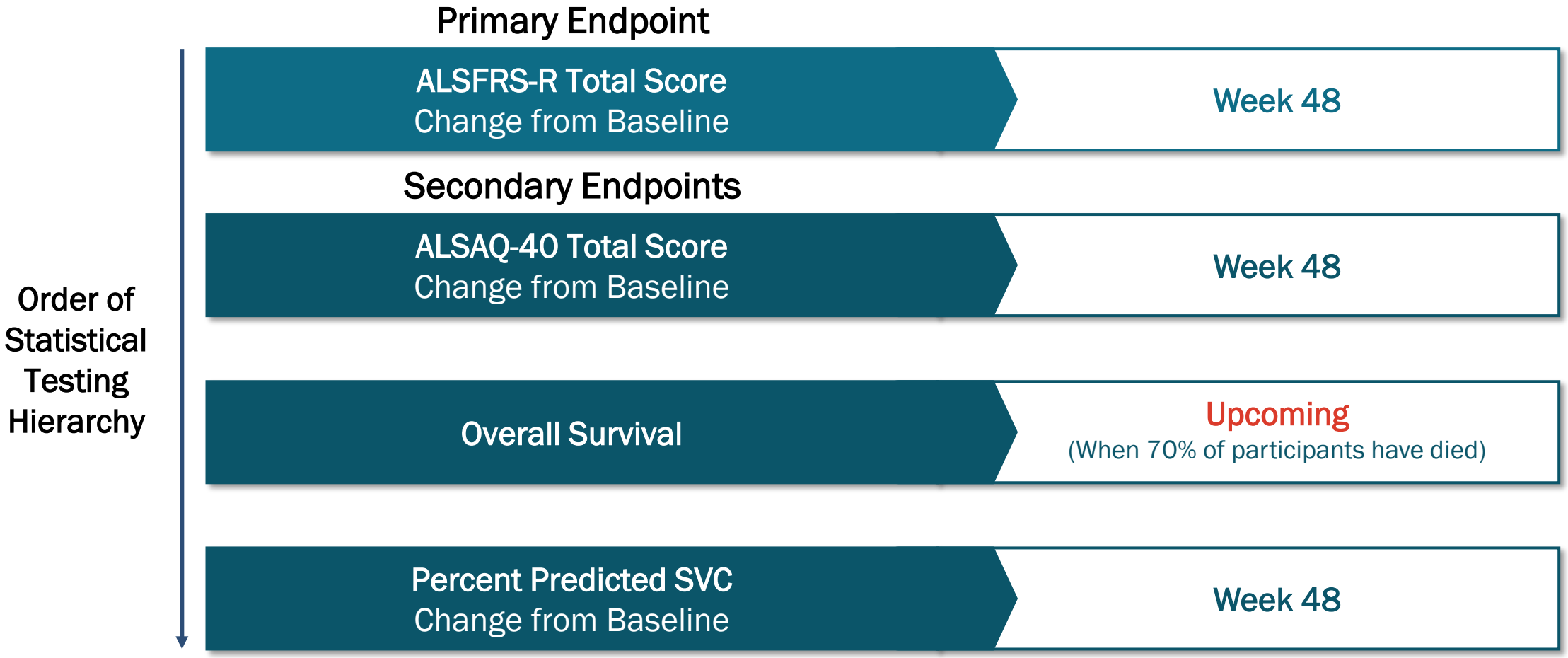
Placebo
N = 267

Placebo-Controlled Phase
48 weeks

PB&TURSO

The PHOENIX Open-Label Extension will close
1 October 2024

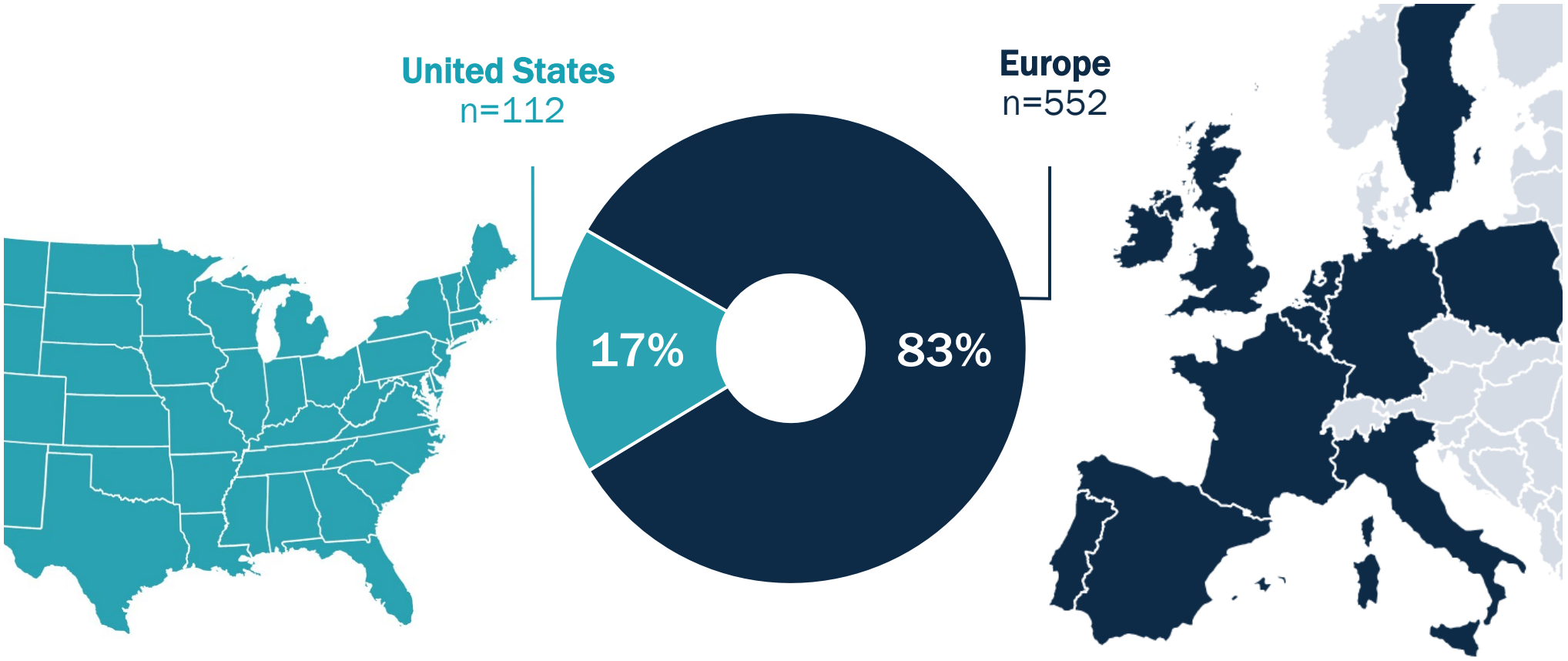
Pre-Specified Primary and Secondary Endpoints



PHOENIX Methods

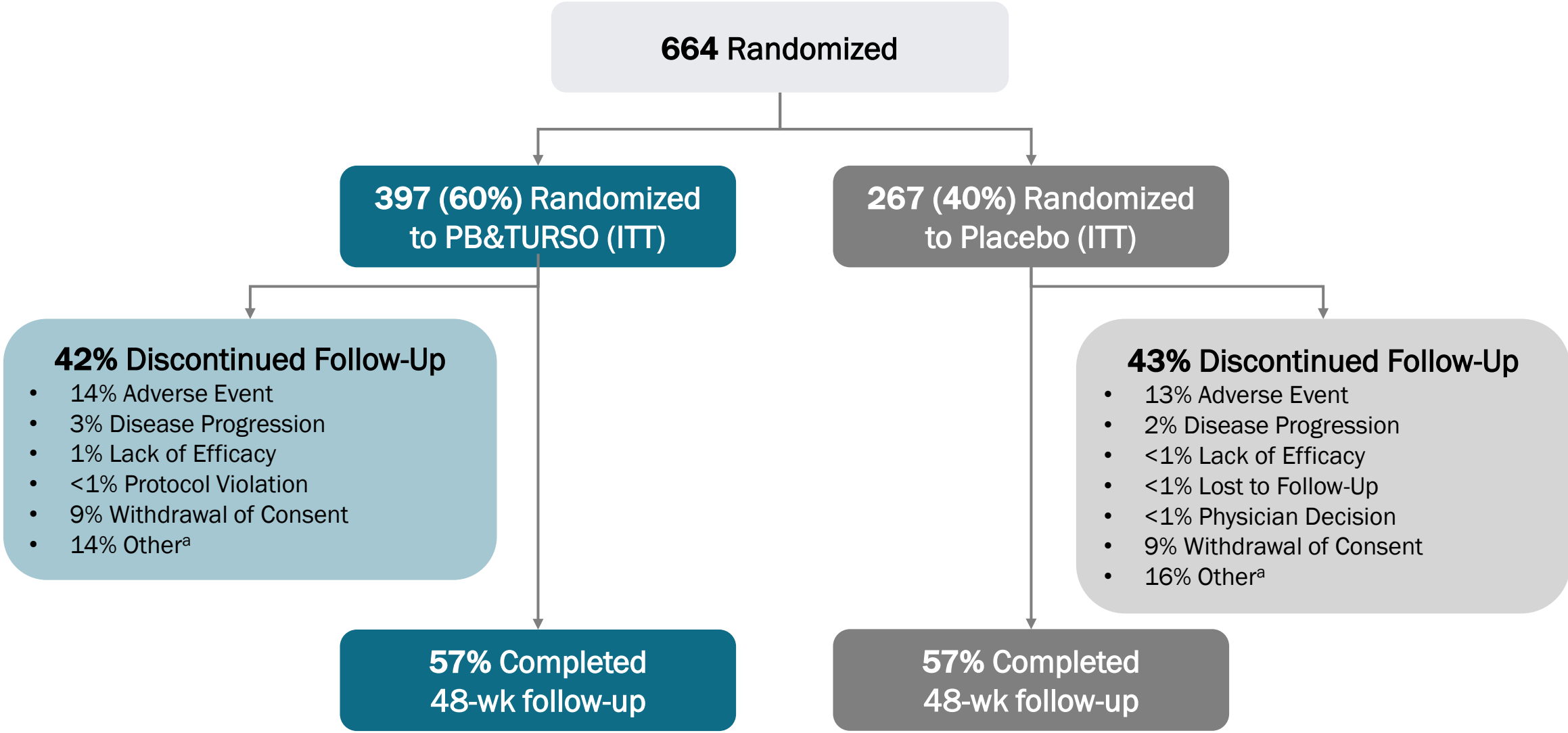
- Randomization in PHOENIX was balanced across 2 stratification factors
  - Met/did not meet **CENTAUR-Like** criteria
    - **CENTAUR-Like:** Clinically definite ALS (3+ body regions), SVC >60%, <18 mo from symptom onset
  - Taking/not taking **edaravone** at time of screening
- Efficacy analyses were performed in intent-to-treat (ITT) population
  - Pre-specified subgroups:
    - CENTAUR-Like Yes/No
    - Edaravone Use Yes/No
    - Europe only
- Primary analysis accounted for deaths using a joint model
  - ALSFRS-R: analyzed using mortality-adjusted mixed effects model (Mortality Adjusted Progression)
  - ALSAQ and SVC: analyzed using mixed model for repeated measures (MMRM)

Majority of Participants in PHOENIX Were Enrolled in Europe



U.S. Participants Discontinued and Transitioned to Commercial Drug in 2022 When FDA Approval Occurred

Discontinuations Balanced Between Groups



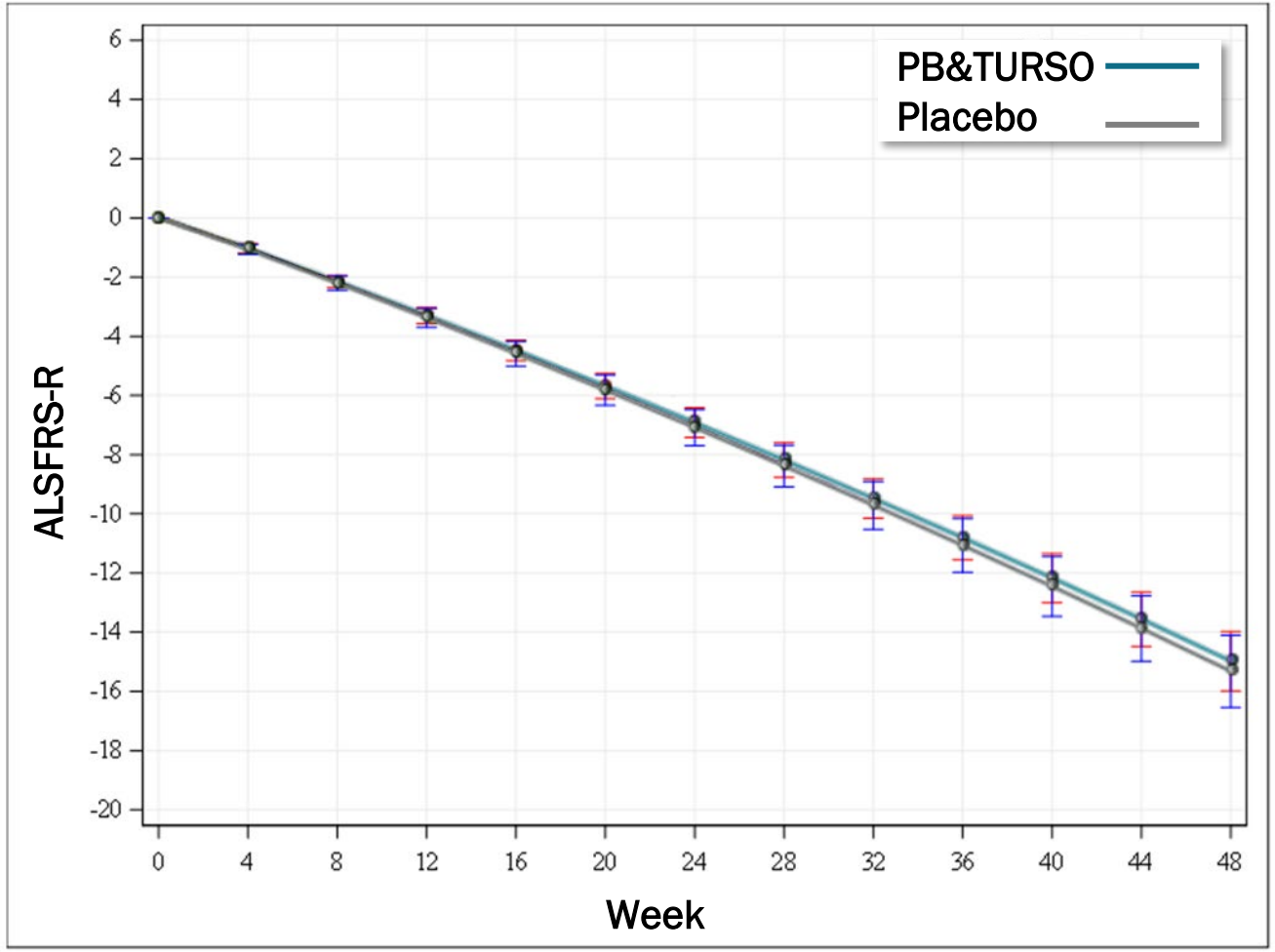
[a]Includes U.S. participants who discontinued the trial after PB&TURSO received U.S. FDA approval in September 2022.

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: No Difference Between Groups

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



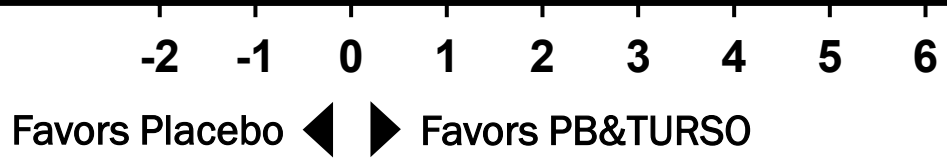
	PB&TURSO N = 397	Placebo N = 267
Mean Change from Baseline in ALSFRS-R Total Score (95% CI)	-14.98 (-15.98, -13.98)	-15.32 (-16.54, -14.11)
Difference (95% CI)	0.343 (-1.22, 1.91)	
p-value	0.667	

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 ALSAQ-40 and SVC: No Differences Between Groups

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 Generally Well-Tolerated in PHOENIX

Safety Results Concordant with CENTAUR Trial

Treatment Emergent 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%

Summary of PHOENIX Results

- Demographics and baseline disease characteristics were well-balanced
- No differences between groups for primary endpoint, ALSFRS-R, or secondary endpoints, ALSAQ-40 and SVC
  - **Overall survival secondary endpoint not yet mature, survival follow-up ongoing**
- PB&TURSO was generally well-tolerated

Note: Based on these results, 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

PHOENIX - Learnings on Trial Design

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Early Learnings from PHOENIX Can Help Inform Future Trial Design and Execution

- Entry criteria
- Trial duration and discontinuation rates
- Importance of evaluating novel biomarkers
- Survival analyses
- Defining “success”

PHOENIX CENTAUR-Like Subgroup Was Faster Progressing than Overall Population and Similar to CENTAUR at Baseline

CENTAUR-Like: Clinically definite ALS (3+ body regions), SVC >60%,<18 months from symptom onset

Characteristic		PHOENIX Total N = 664	PHOENIX CENTAUR-Like N = 168	CENTAUR N = 137
Age (years), mean (SD)		59.5 (10.8)	58.4 (12.1)	57.7 (9.6)
Sex	Male	62%	55%	68%
	Female	38%	45%	32%
Region	Europe	83%	80%	0
	U.S.	17%	20%	100%
Time Since Symptom Onset (months), mean (SD)		14.4 (5.3)	12.4 (3.6)	13.5 (3.8)
Bulbar Onset		22%	28%	26%
ALS Meds	Riluzole	92%	92%	72%
	Edaravone	3%	4%	34%
Met CENTAUR-Like Criteria		25%	100%	100%
ALSFRS-R Total Score, mean (SD)		36.7 (6.1)	36.3 (6.1)	36.0 (5.5)
Pre-baseline ALSFRS-R slope (del-FS), mean (SD)		0.86 (0.6)	0.98 (0.6)	0.94 (0.5)
SVC (% predicted normal), mean (SD)		83% (17)	83% (16)	83% (18)

Placebo ALSFRS-R and SVC Progression to Week 24 PHOENIX CENTAUR-Like vs. CENTAUR

Mean Change from Baseline at Week 24	PHOENIX		CENTAUR
	ITT Placebo N = 267	CENTAUR-Like Placebo N = 68	CENTAUR Placebo N = 48
ALSFRS-R Total Score	-7.30	-8.44	-9.18
SVC	-11.3% n = 180	-12.1% n = 39	-15.5% n=34

PHOENIX Treatment Discontinuation Rate 35% When Accounting for Discontinuations Due to U.S. FDA Approval

42% Discontinued Follow-Up

- 14% Adverse Event
- 3% Disease Progression
- 1% Lack of Efficacy
- <1% Protocol Violation
- 9% Withdrawal of Consent
- 14% Other

43% Discontinued Follow-Up

- 13% Adverse Event
- 2% Disease Progression
- <1% Lack of Efficacy
- <1% Lost to Follow-Up
- <1% Physician Decision
- 9% Withdrawal of Consent
- 16% Other

- **50** U.S. participants discontinued and transitioned to commercial drug in 2022 when FDA approval occurred – captured under "other"
- Excluding these, discontinuation rate is 35%

How does this compare to other trials?

- 24-week CENTAUR trial: **23%**[1]
- 48-week oral edaravone open-label safety and tolerability study: **25%**[2]
- 52-week dexpramipexole phase 3 trial: **30%**[3]
- 76-week arimoclomol phase 3 trial: **23%**[4]
- 78-week TUDCA-ALS trial: **~50%**[5]

1. Paganoni S, et al. N Engl J Med. 2020;383:919-930. **2.** Genge A, et al. Muscle Nerve. 2023;67(2):124-129. **3.** Cudkowicz M, et al. Lancet Neurol. 2013;12(11):1059-1067. **4.** ClinicalTrials.gov identifier: NCT03491462. Updated August 8, 2023. Accessed June 14, 2024. https://clinicaltrials.gov/study/NCT03491462?tab=results. **5.** News release. The TUDCA-ALS consortium; March 27, 2024. Accessed June 14, 2024. https://www.tudca.eu/top-line-results-announcement/.

Plasma Biomarkers: Difference Between Groups in YKL-40

Plasma Biomarkers Change from Baseline at Week 48 (log-transformed MMRM)

Biomarker	Geometric Mean Ratio to Baseline (95% CI)		Geometric Mean Ratio (95% CI)	p-value
	PB&TURSO N = 397	Placebo N = 267		
NfL (pg/mL)	**0.986** (0.951, 1.02) n = 217	**0.997** (0.954, 1.04) n = 143	**0.989** (0.934, 1.05)	0.691
YKL-40* (ng/mL)	**1.05** (0.997, 1.11) n = 214	**1.19** (1.11, 1.27) n = 142	**0.884** (0.815, 0.959)	0.003
CRP (ng/mL)	**1.13** (0.973, 1.31) n = 211	**1.21** (1.01, 1.45) n = 141	**0.934** (0.738, 1.18)	0.570
Total tau (fg/mL)	**0.933** (0.885, 0.984) n = 216	**0.922** (0.863, 0.985) n = 142	**1.01** (0.930, 1.10)	0.781
p-tau 181 (fg/mL)	**1.28** (1.19, 1.39) n = 132	**1.26** (1.14, 1.38) n = 90	**1.02** (0.900, 1.15)	0.762

See poster CL-65 for additional biomarker analyses

*Also known as chitinase-3-like protein 1 (CHI3L1)

PB&TURSO Has Lowered YKL-40 Compared to Placebo in 3 Trials

Same dose used in all trials

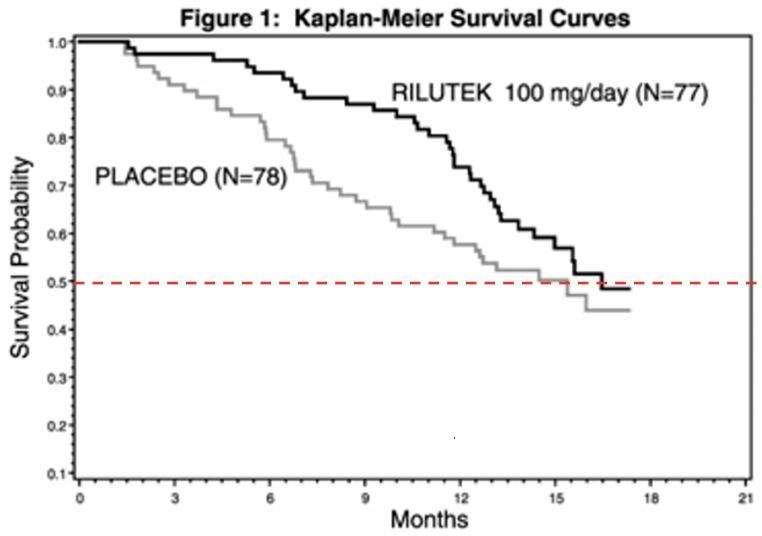
Trial	Fluid	Reduction with PB&TURSO vs. Placebo	No Difference Between Groups
PHOENIX ALS Trial N=664	Plasma	• YKL-40	• NfL • CRP • Total tau • p-tau 181 • SPP1
CENTAUR ALS Trial N=137	Plasma	• YKL-40 • CRP	• NfH • NfL
PEGASUS Alzheimer's Trial N=95	CSF	• YKL-40 • Total tau • p-tau 181	• NfL • GFAP

YKL-40

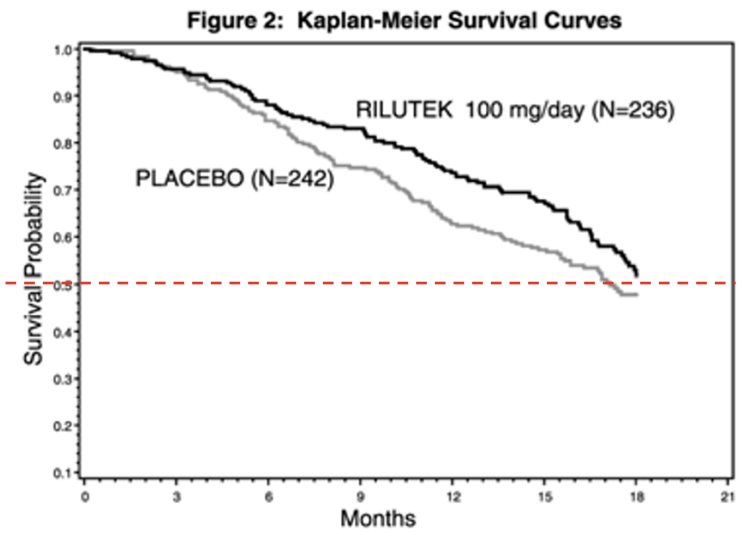
- **CENTAUR:** 20% lower at Week 24 in AMX0035 group compared to placebo
- **PHOENIX:** 12% lower at Week 48 in AMX0035 group compared to placebo in overall population (not seen in CENTAUR-like)

The Evolution of Survival Analysis in ALS Trials

Riluzole Study 1
(13 to 18-month duration)



Riluzole Study 2
(12 to 18-month duration)



Both studies included participants with either familial or sporadic ALS, disease duration of less than **5 years**, and a baseline forced vital capacity (FVC) ≥ 60% of normal

Rilutek. Prescribing information. Covis Pharma; 2020.

Flexible and Comprehensive Follow-Up Important to Capture Long-Term Maturity of Overall Survival Data

CENTAUR		Week 24	
Treatment Arm (ITT)	Total	N of Deaths	% Deaths
PB&TURSO	89	5	6%
Placebo	48	2	4%

PHOENIX		Week 48	
Treatment Arm (ITT)	Total	N of Deaths	% Deaths
PB&TURSO	397	70	18%
Placebo	267	50	19%

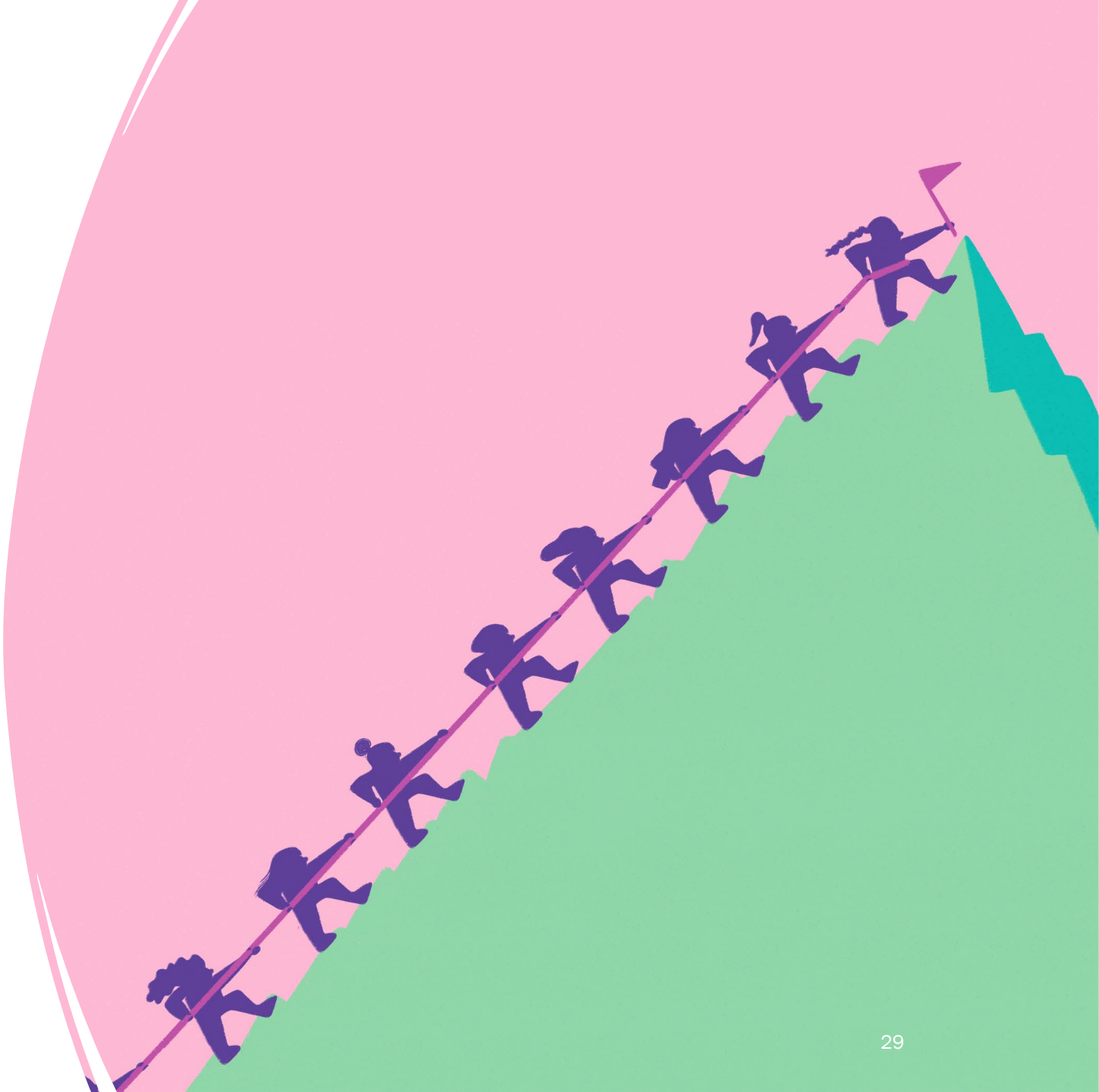
- Assessing long-term survival requires longer duration of follow-up than typical ALS trial duration of 24 or 48 weeks
  - Overall survival is event-driven; must wait for enough events to occur to perform analysis
- PHOENIX **pre-specified** that survival would be followed-up over longer timeframe, while still allowing participants to continue to OLE after Week 48
  - A critical part of this design is that survival status would be captured for **all participants** where applicable and possible, regardless of whether they discontinued treatment and assessments

Learnings from PHOENIX on Trial Design

- “CENTAUR-like” criteria reproduced a very similar population at baseline in PHOENIX compared to the CENTAUR trial. This is a fast-progressing population
- There is a trade off between selecting for faster progressing population and discontinuations, especially in longer trials
- Important to continue to evaluate novel biomarkers
- The PHOENIX approach for evaluating survival is novel for ALS trials and we hope to learn from these results to refine approach for future trials
  - **This is why we continue to follow survival in PHOENIX and ask all investigators to capture survival data on as many of your participants as possible**

No “Failed” Trials

- Sharing new design and analysis approaches (survival, subgroups)
- Learning about new biomarkers and endpoints
- Increasing our likelihood of future successes
  - Wealth of rigorously captured data and samples can be added to repositories to aid in future trial design and disease understanding
- Working and growing together as a global ALS community



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

- 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