DAZALS: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial of Dazucorilant, a Selective Glucocorticoid Receptor Modulator, in Amyotrophic Lateral Sclerosis

Leonard H. van den Berg,[1] Jakub Antczak,[2] Javier Mascias,[3] Mariusz Grudniak,[4] Pawel Lisewski,[5] Philip Van Damme,[6] Susanne Petri,[7] Annekathrin Rödiger,[8] Juan Francisco Vázquez Costa,[9] Orla Hardiman,[10] Jinsy Andrews,[11] Ruben P.A. van Eijk,[12] Amanda Kesner-Hays,[13] Iulia Cristina Tudor,[13] Grace Mann,[13] Magdalena Kuzma-Kozakiewicz,[14] on behalf of the DAZALS investigators

[1]Department of Neurology, UMC Utrecht Brain Centre, Utrecht, The Netherlands; [2]Department of Neurology, Jagiellonian University Medical College, Krakow, Poland; [3]ALS Unit, Neurology Department, Hospital La Paz Institute for Health Research, Madrid, Spain; [4]Centrum Medczne NeuroProtect, Warsaw, Poland; [5]Medical Center "Neuromed", Bydgoszcz, Poland; [6]Neurology Department, University Hospitals Leuven and Neuroscience Department, KU Leuven, Leuven, Belgium; [7]Department of Neurology, Hannover Medical School, Hannover, Germany; [8]Department of Neurology, University Hospital Jena, Jena, Germany; [9]ALS Unit, Hospital La Fe, IIS La Fe, CIBERER, University of Valencia, Valencia, Spain; [10]Academic Unit of Neurology, Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin, Ireland; [11]The Neurological Institute, Columbia University, New York, NY, USA; [12]Department of Neurology, UMCU Brain Center, University Medical Center Utrecht, Utrecht, The Netherlands; [13]Corcept Therapeutics Incorporated, Redwood City, CA, USA; [14]Department of Neurology, Medical University of Warsaw, Warsaw, Poland

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Disclosures

- Leonard H. van den Berg discloses consultancy for Novartis, Sanofi, Takeda, Calico, Denali, Amylyx, Ferrer, VectorY, and Corcept.

DAZALS | Key Takeaways

Glucocorticoid receptor modulation may benefit people with ALS by reducing the neurotoxic effects of excess cortisol activity[1-3]

Dazucorilant (DAZU) is an oral, selective glucocorticoid receptor modulator that competes with cortisol and reversibly binds to the glucocorticoid receptor[4]

While DAZALS did not meet its primary objective of slowing functional decline on the ALSFRS-R scale, improvements in overall survival in patients who received DAZU 300 mg were observed in secondary and exploratory analyses

[1]Patacchioli FR, et al. J Endocrinol Invest. 2003;26:RC23; [2]Spataro R, et al. J Neurol Sci. 2015;358:282; [3]Feng X et al. Front Molecul, Neurosci. 2019;12:210; [4]Beaudry JL, et al. PLoS one. 2014;9:e91248.
Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale-Revised; CNS, central nervous system; DAZU, dazucorilant.

DAZALS
STUDY OF DAZUCORILANT FOR ALS

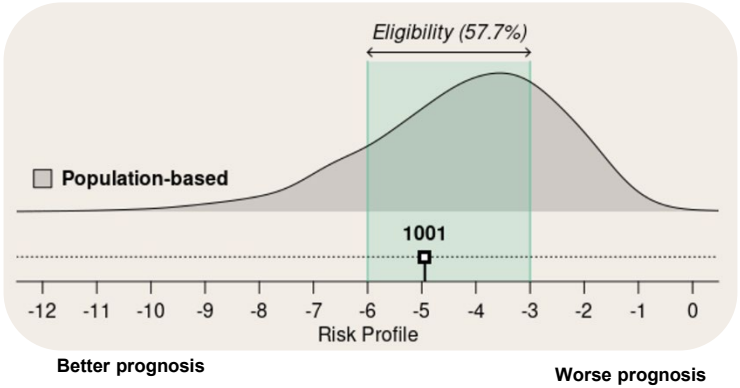
A Phase 2 Study of Dazucorilant in ALS

NCT05407324; EudraCT: 2021-005611-31

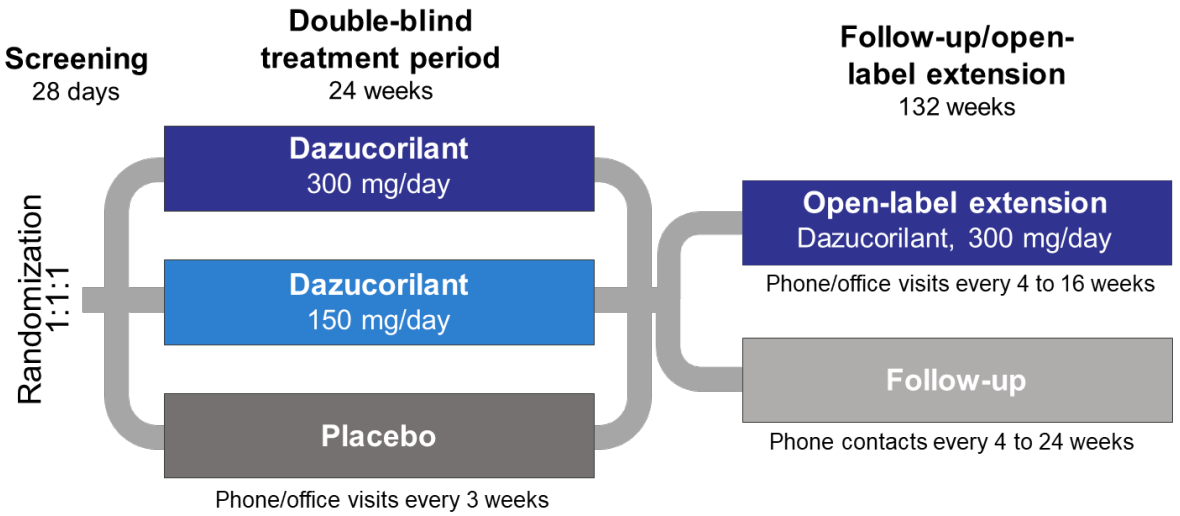
Population

- Adults ≥18 years of age with sporadic or familial ALS per Gold Coast criteria
- Stable doses of approved therapies were allowed
- Able to swallow capsules
- Not currently using glucocorticoids and no history of regular systemic glucocorticoid use
- TRICALS risk profile score −6 to −3

TRICALS Risk Profile Scoring



Stratified by prior ALS therapy and region of onset
Study drug provided as 75-mg capsules and administered QD with food and water



Primary Endpoints

- Change from baseline to week 24 in the ALSFRS-R total score
- Safety

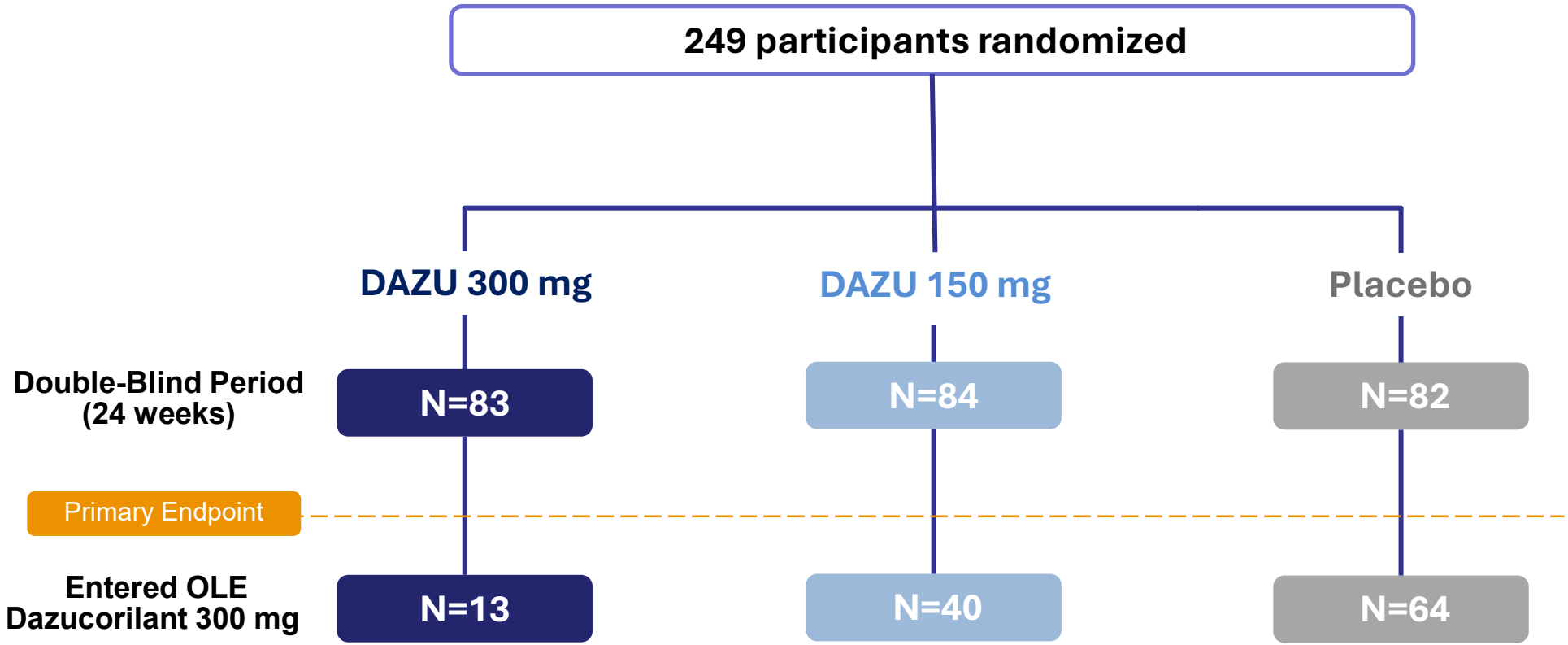
Other Key Endpoints

- Mortality
- Change in slow vital capacity
- Change in muscle strength with handheld dynamometry
- CAFS
- Change in neurofilament light

First patient randomized: 09Dec2022
Last patient randomized: 29Mar2024
Conducted at 35 sites in 10 countries

Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale-Revised; CAFS, Combined Assessment of Function and Survival; ENCALS, European Network to Cure ALS; QD, every day.

DAZALS | Patient Disposition



Data cutoff: 25Nov2024

Abbreviations: DAZU, dazucorilant; OLE, open label extension.

DAZALS | Baseline Characteristics Were Well Balanced

		DAZU 300 mg N=83	DAZU 150 mg N=84	Placebo N=82
Age, mean		58 years	58 years	60 years
Gender	Male	59.0%	59.5%	63.4%
Region	Europe	94.0%	89.3%	92.7%
	North America	6.0%	10.7%	7.3%
Site of onset	Bulbar	16.9%	14.3%	14.6%
ENCALS risk score, mean		-4.36	-4.42	-4.43
Time since ALS symptom onset, mean		21 months	20 months	23 months
Time since ALS diagnosis, mean		10 months	9 months	11 months
Baseline NfL (ng/L), mean		75.2	93.9	87.6
ALSFRS-R total score, mean		37	37	37
Concurrent riluzole		95.2%	91.7%	95.1%

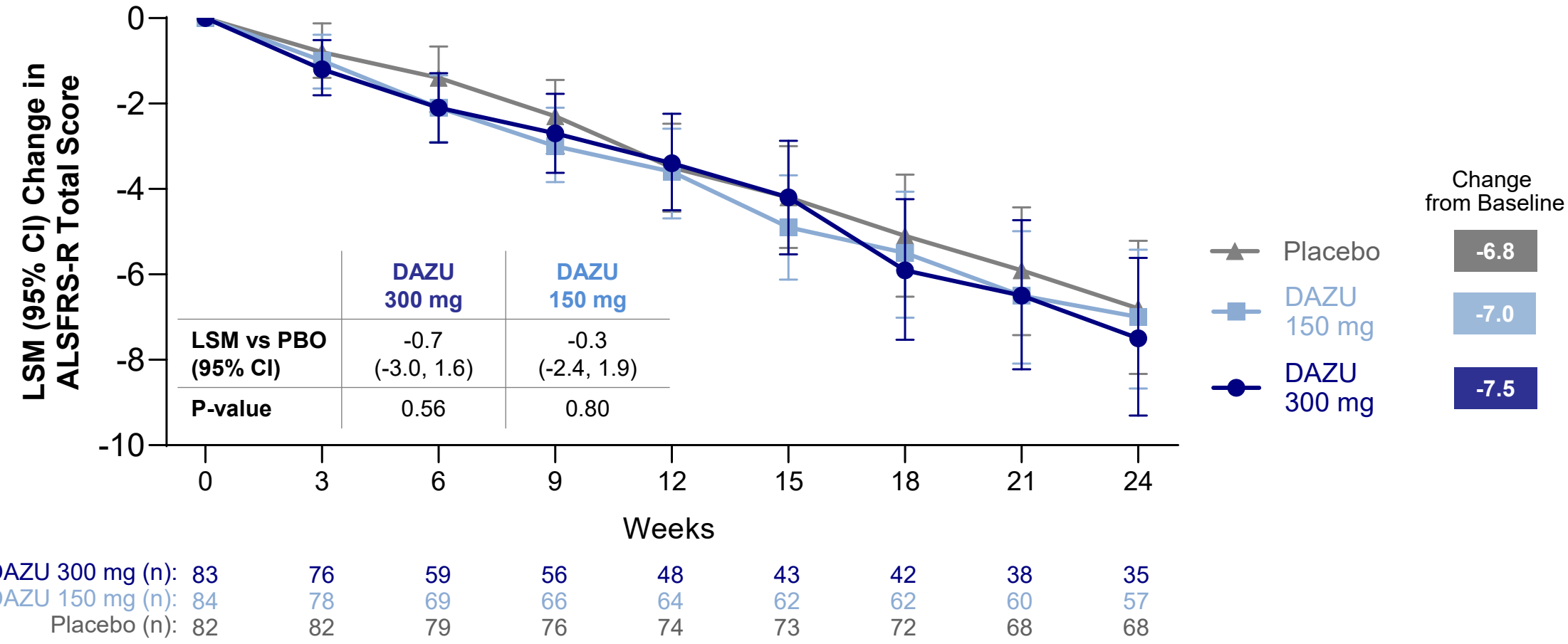
Data cutoff: 25Nov2024

DAZALS STUDY OF DAZUCORILANT FOR ALS

Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale-Revise; DAZU; dazucorilant; ENCALS, European Network to Cure ALS; NfL, neurofilament light chain.

DAZALS | ALSFRS-R and Survival (Double-Blind Period)

The primary objective of slowing functional decline on the ALSFRS-R scale was not met



Secondary Endpoint: there were no deaths in the DAZU 300 mg arm, 2 deaths in the DAZU 150 mg arm, and 5 deaths in the placebo arm (P=0.02, log-rank test comparing DAZU 300 mg to placebo)

The Kenward-Roger approximation was used to model denominator degrees of freedom and an unstructured covariance structure was used to model within-patient error. Estimates are from Mixed Model for Repeated Measures model with treatment, visit, and treatment-by-visit interaction as fixed effects, baseline ALSFRS-R and stratification factors from IRT as covariates, and patients within treatment groups as random effects.

Abbreviations: ALSFRS-R, ALS Functional Rating Scale-Revised; CI, confidence interval; DAZU, dazucorilant; IRT, interactive response technology; LSM, least squares mean; PBO, placebo.

Data cutoff: 25Nov2024

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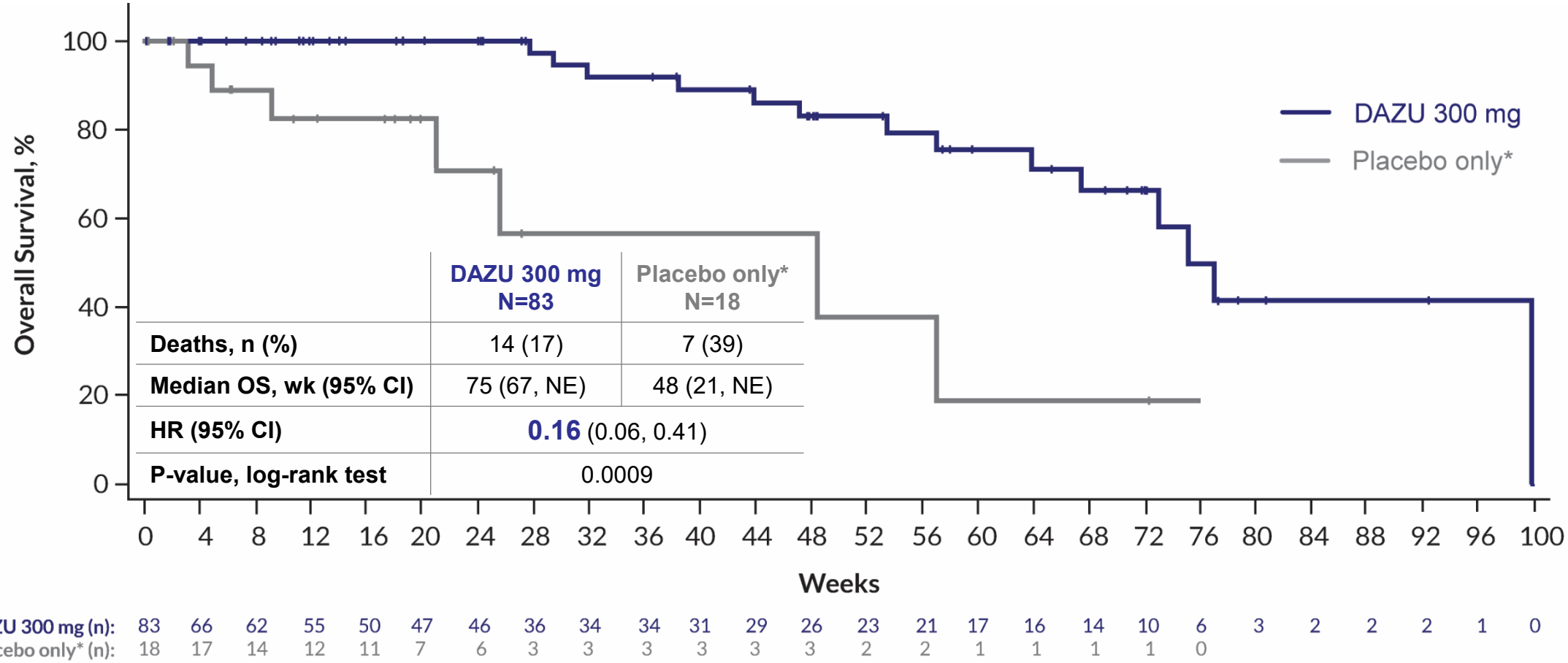
DAZALS | Exploratory Overall Survival Analysis

Comparing patients who received DAZU 300 mg only vs Placebo only*



	DAZU 300 mg N=83	Placebo only* N=18
Deaths, n (%)	14 (17)	7 (39)
Median OS, wk (95% CI)	75 (67, NE)	48 (21, NE)
HR (95% CI)	**0.16** (0.06, 0.41)	
P-value, log-rank test	0.0009	

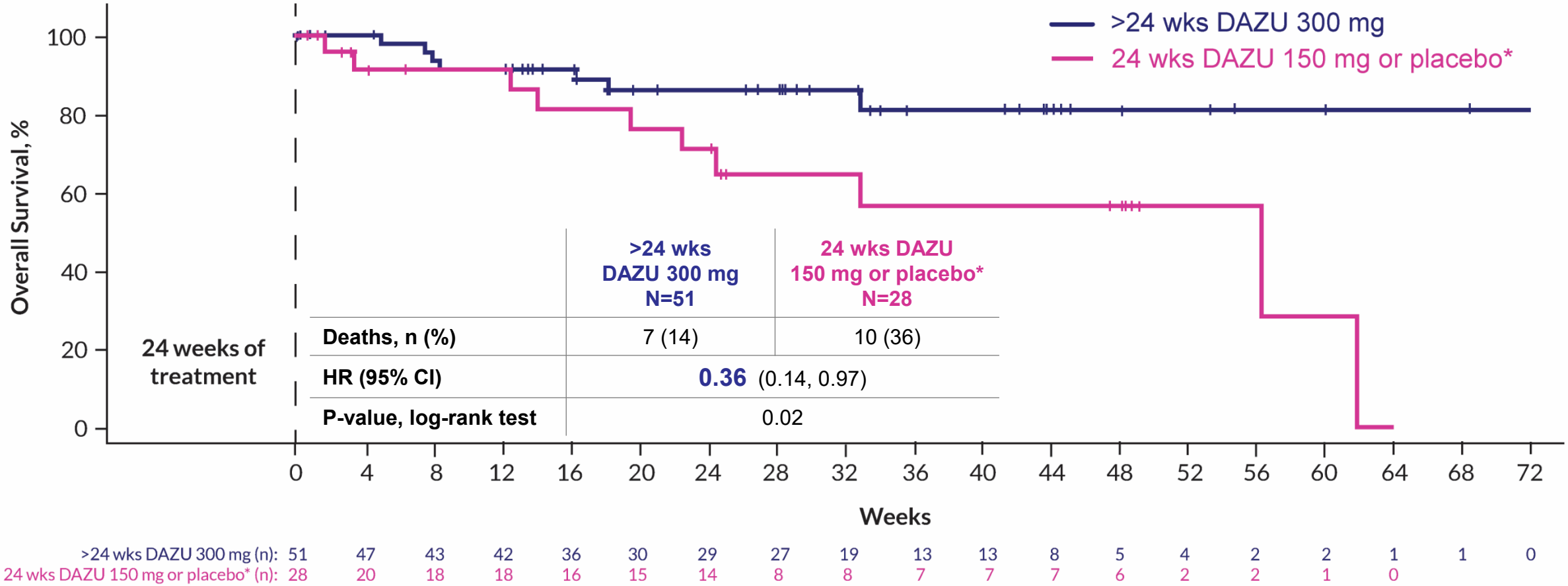
Patients who received DAZU 300 mg had improved overall survival (HR 0.16, P=0.0009) compared to patients who received placebo only

Data cutoff: 23Apr2025

*Placebo-only: patients randomized to placebo that did not enter OLE (did not receive 300 mg DAZU).
Abbreviations: CI, confidence interval; DAZU, dazucorilant; HR, hazard ratio; OLE, open-label extension; NE, not evaluable; wk, week.

DAZALS | Exploratory Overall Survival Analysis

Prolonged treatment with DAZU 300 mg was associated with longer survival*



Patients who were treated with DAZU 300 mg for >24 weeks had prolonged overall survival (HR 0.36, P=0.02)

Data cutoff: 23Apr2025

*24 weeks of DAZU 150 mg or Placebo: patients who received 24 weeks of DAZU 150 mg or placebo and did not receive DAZU 300 mg.
Abbreviations: CI, confidence interval; DAZU, dazucorilant; HR, hazard ratio; mo, month; NE, not evaluable; OLE, open-label extension; wk, week.

DAZALS | Safety Summary for the Double-Blind Period

	DAZU 300 mg N=83	DAZU 150 mg N=83	Placebo N=82
Patients with at least one TEAE	98.8%	96.4%	75.6%
TEAE leading to dose interruption	41.0%	36.1%	9.8%
TEAE leading to treatment discontinuation	57.8%	30.1%	8.5%
Patients with at least one severe TEAE	20.5%	16.9%	13.4%
Patients with at least one serious TEAE	19.3%	16.9%	17.1%

DAZU-treated patients experienced more gastrointestinal adverse events, resulting in more discontinuations

The frequency of severe and serious adverse events in the DAZU arms was similar to the placebo arm

There were no safety concerns – adverse events were mild to moderate and reflected tolerability

During the double-blind period, the treatment-emergent period is defined as the period from the date and time of the first dose of study drug through 28 days after the last dose of study drug in double-blind treatment period but prior to the date of the first dose of study drug in open-label extension period.
Abbreviations: TEAE, treatment-emergent adverse event.

Data cutoff: 25Nov2024

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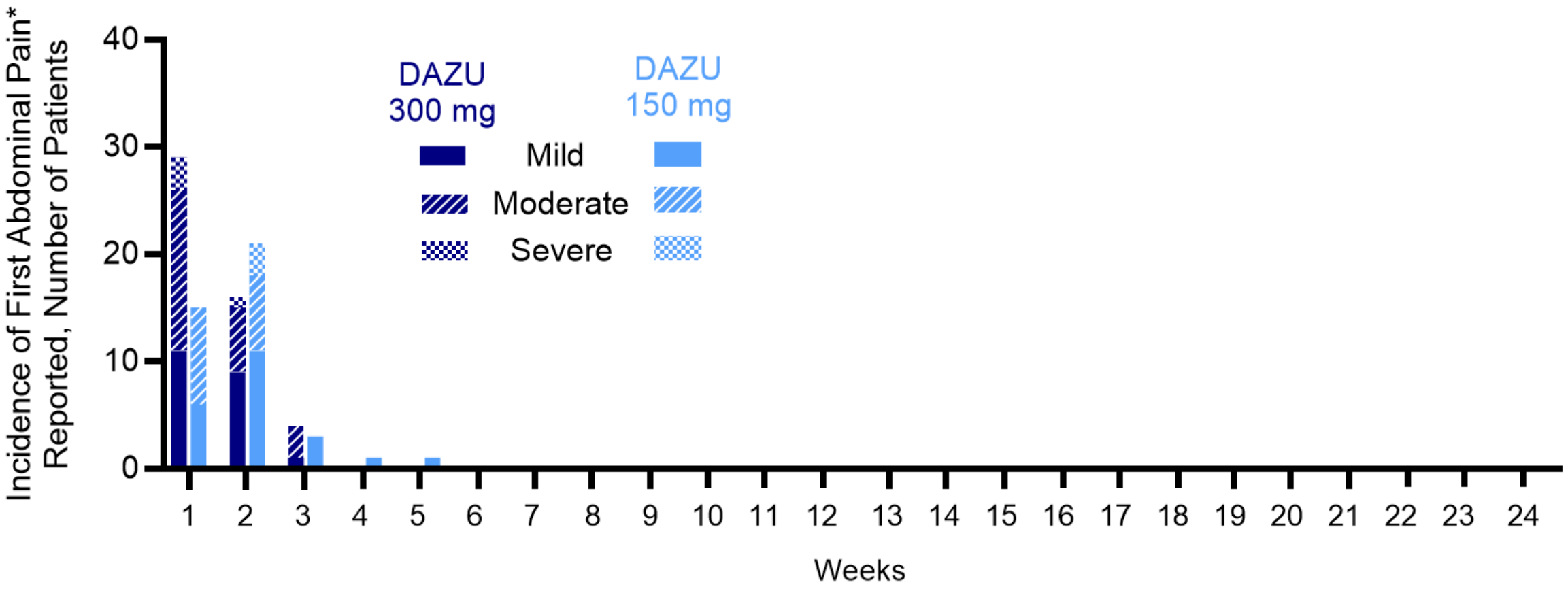
DAZALS | Abdominal Pain in the Double-Blind Period



Tolerability | Abdominal pain was the most frequently reported adverse event
Onset occurred during the first 3–5 weeks and resolved following interruption or discontinuation
Patients who continued DAZU after reporting abdominal pain had resolution with time

Data cutoff: 25Nov2024

*Abdominal pain includes preferred terms of abdominal pain and abdominal pain upper.
Abbreviations: AE, adverse event; DAZU, dazucorilant.

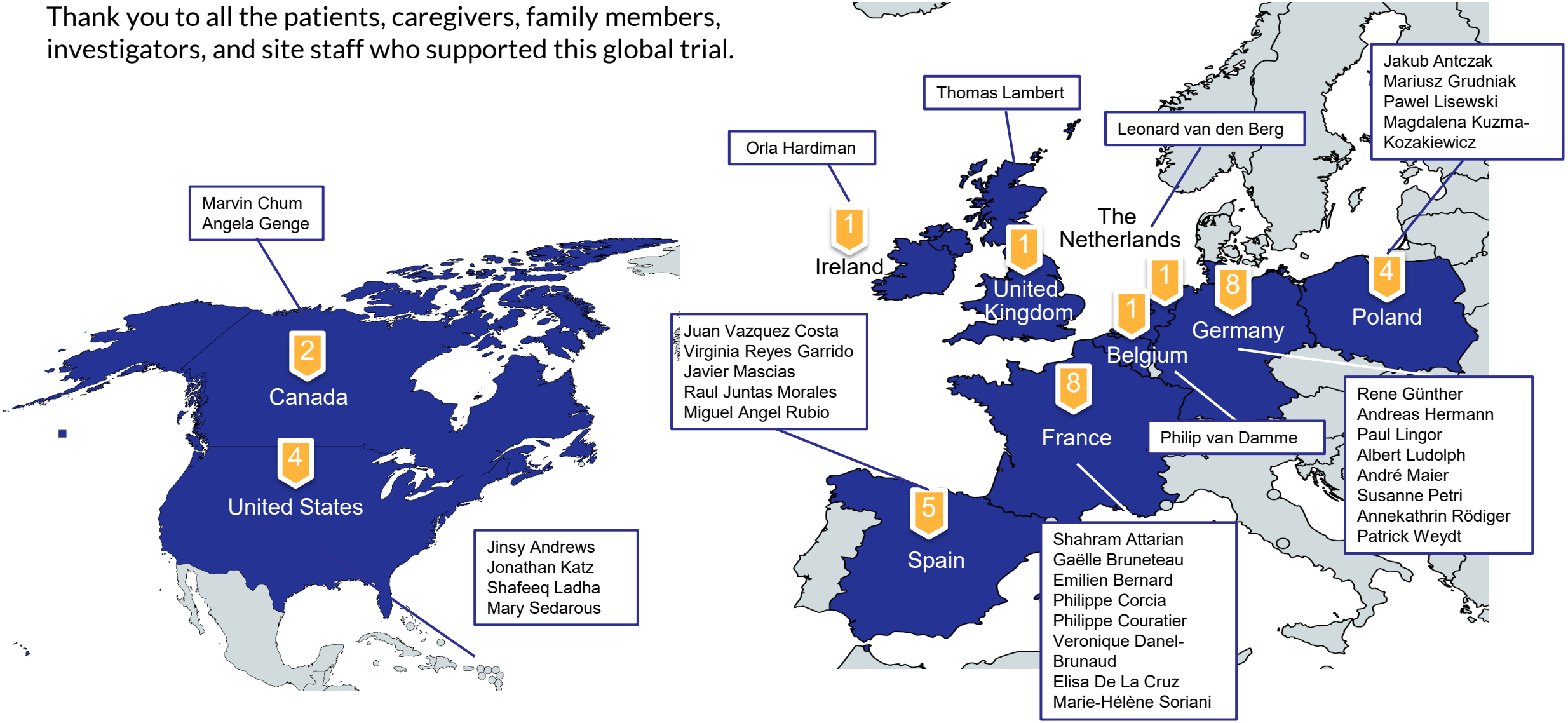
DAZALS | Conclusions

1 No Impact to ALSFRS-R	DAZALS did not achieve its primary endpoint of slowing functional decline as measured by the ALSFRS-R scale
2 Survival Improved by DAZU 300 mg	Secondary and exploratory endpoints showed improvement in overall survival for patients who received DAZU 300 mg, including those treated for >24 weeks
3 Tolerability	DAZU-treated patients discontinued at higher rates than placebo-treated patients due to abdominal pain, which occurred in the first 3–5 weeks. Abdominal pain resolved following treatment interruption and with time in patients who continued treatment
4 No Additional Serious or Severe AEs	DAZU-treated patients showed similar rates of serious and severe adverse events compared to placebo-treated patients

Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale-Revise.

DAZALS | Acknowledgements

Thank you to all the patients, caregivers, family members, investigators, and site staff who supported this global trial.



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