



Role of cortisol in ALS

Distortions in cortisol levels have been reported in people with ALS,¹ particularly in people with rapid progression²

Prolonged cortisol exposure in the CNS can:

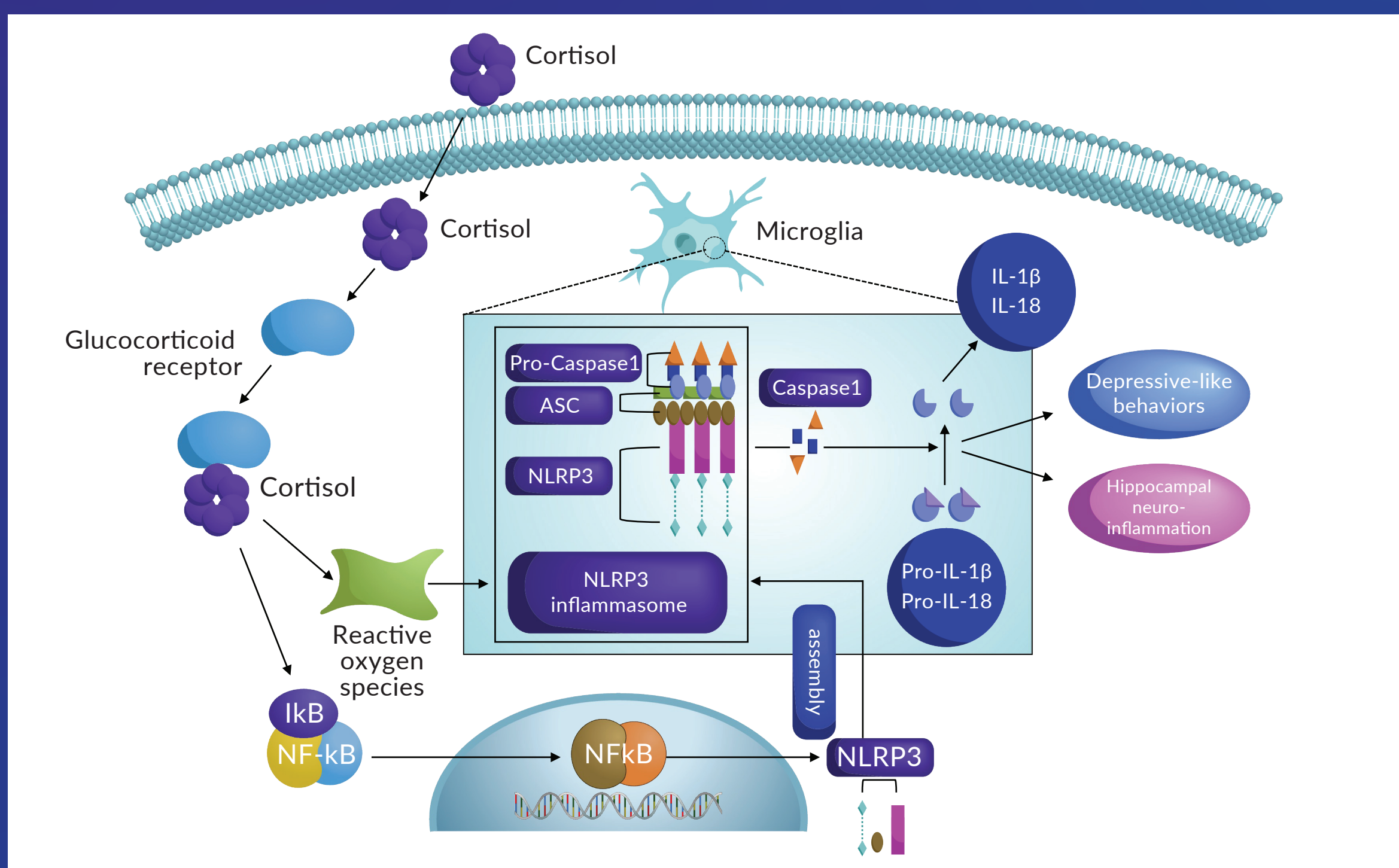
Increase myeloid activity and glial cell activation³

Promote proinflammatory effects in the CNS⁴

Promote excitotoxicity and glutamatergic toxicity⁵

Cortisol is proinflammatory in the brain and CNS

Cortisol promotes proinflammatory cytokine production (TNF α , IL-1 β) in the hippocampus and isolated microglial cells from rats⁶



By reducing the neurotoxic effects of excess cortisol activity, GR modulation may benefit patients with ALS

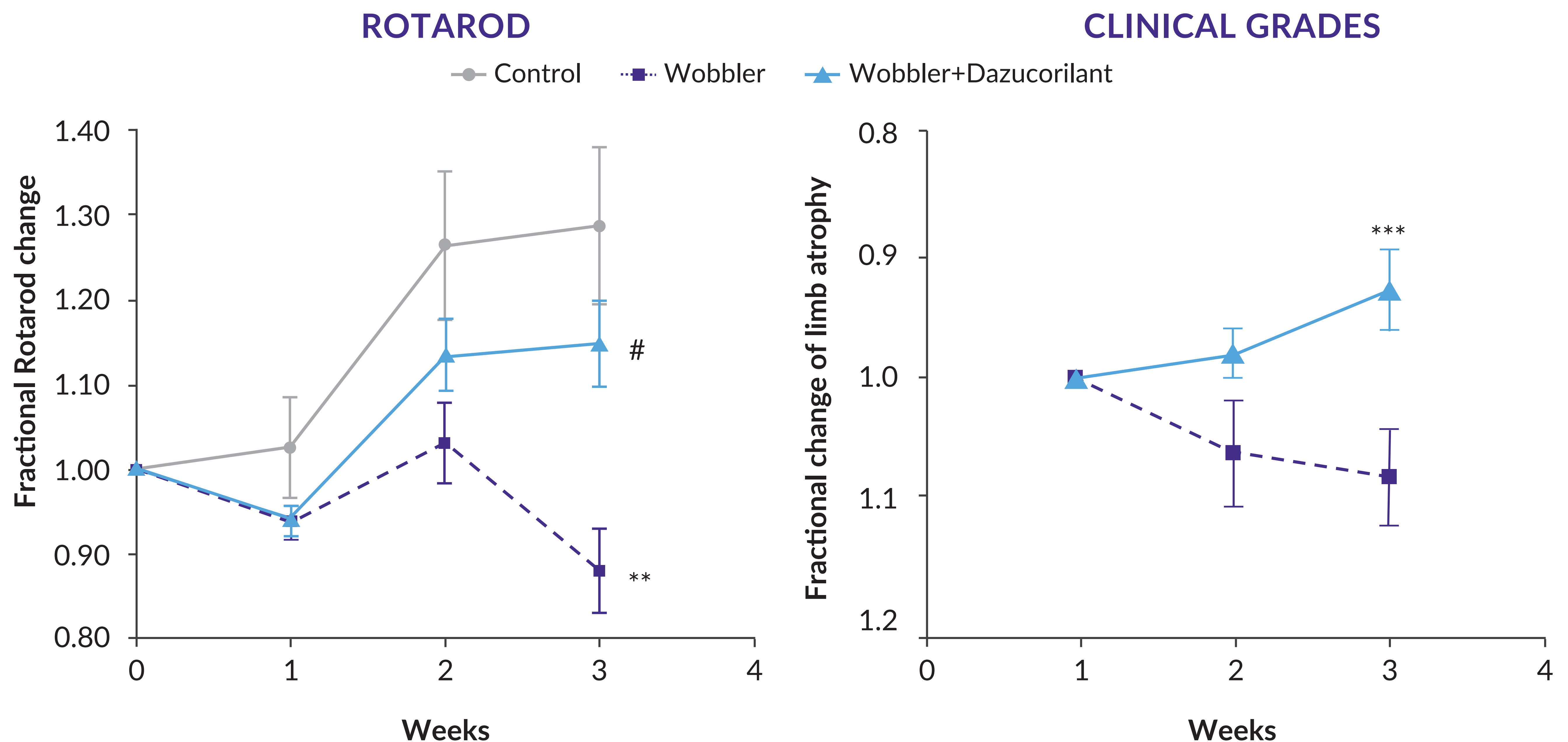
Dazucorilant modulates cortisol activity

Dazucorilant is a small-molecule, selective GR modulator

- Competitively and reversibly binds to the GR
- High affinity for the GR and no affinity for other hormone receptors⁷
- Distribution to the cerebrospinal fluid observed in humans⁸

Dazucorilant improved motor performance and reduced forepaw atrophy in wobbler mice

- Wobbler mice have adrenal hypertrophy and glucocorticoid elevation similar to patients with ALS⁹
- Dazucorilant (30 mg/kg daily s.c. for 3 weeks) in the spinal cord
 - Reduced vacuolated neurons, astro- and microgliosis, and neuroinflammation⁹
 - Improved glutamate homeostasis, with increased glutamine synthase and glutamate transporter 1 expression⁹
 - Positively modulated a survival pathway in ventral horn homogenates and negatively modulated a death signal⁹



#Wobbler+Dazucorilant vs Wobbler, $p < 0.01$.
 **Wobbler vs control mice, $p < 0.01$.

***Wobbler+Dazucorilant vs Wobbler, $p < 0.001$.

Definition of clinical scores

- | | |
|--------------------------|-----------------------------|
| 0: Normal | 3: Curled wrist |
| 1: Atrophy of paw finger | 4: Forelimb flexed to chest |
| 2: Curled fingers | |

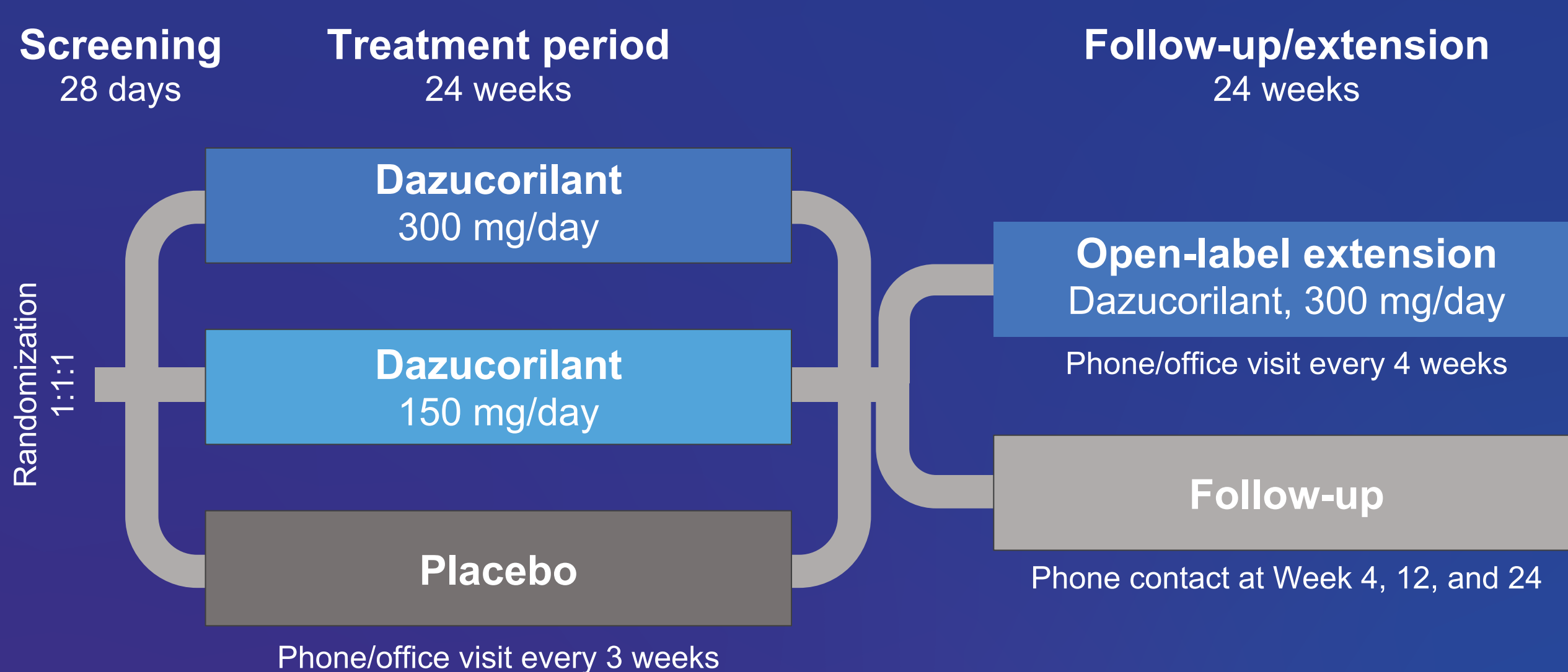
References

¹Patacchioli FR, et al. *J Endocrinol Invest*. 2003;26:RC23. ²Spataro R, et al. *J Neurol Sci*. 2015;358:282. ³Frank MG, et al. *Brain Behav Immun*. 2012;26:337. ⁴Duque E, Munhoz CD. *Front Endocrinol*. 2016;7:78. ⁵Sorrells SF, et al. *Neuroendocrinology*. 2014;100:129. ⁶Feng X, et al. *Front Mol Sci*. 2019;12:210. ⁷Beaudry JL, et al. *PLoS one*. 2014;9:e91248. ⁸Donaldson K, et al. Safety, Pharmacokinetics, and Pharmacodynamics of the Selective Glucocorticoid Receptor Modulator Dazucorilant in Healthy Volunteers. Poster presentation at Northeast Amyotrophic Lateral Sclerosis Consortium (NEALS); October 4-6, 2023; Clearwater, Florida. ⁹Meyer M, et al. *Brain Research*. 2020;1727:146551.



Dazucorilant in patients with ALS

NCT05407324; EudraCT: 2021-005611-31; EU CTR: 2204-514082-19-00



Study drug provided as four 75-mg softgel capsules and administered once daily with food and water.

Key Inclusion Criteria

- Patients ≥ 18 years of age with sporadic or familial ALS
- Prior stable dose of riluzole and/or edaravone allowed but not required
- ENCALS risk profile score ≥ -6 and ≤ -3

Key Exclusion Criteria

- Inability to swallow capsules
- Currently using glucocorticoids or history of regular systemic glucocorticoid use

Primary Endpoints

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

Other Endpoints

- Combined Assessment of Function and Survival (CAFS)
- Slow vital capacity
- Muscle strength with handheld dynamometry
- Change in neurofilament light

DAZALS enrollment is complete, with 249 participants enrolled across 35 sites in 10 countries in Europe and North America

Abbreviations

ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale-Revised; CNS, central nervous system; ENCALS, European Network for the Cure of ALS; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; GR, glucocorticoid receptor; IL-1 β , Interleukin-1 beta; s.c., subcutaneous; TNF α , tumor necrosis factor alpha.