2-Year Overall Survival Results From DAZALS: A Phase 2, Randomized Controlled Trial of Dazucorilant, a Selective Glucocorticoid Receptor Modulator, in Amyotrophic Lateral Sclerosis

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Poster #199

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SUMMARY AND CONCLUSIONS

- Dazucorilant is an SGRM that antagonizes cortisol signaling
- SGRM treatment continued to reduce the risk of death in 2-year exploratory analyses
  - Dazucorilant 300 mg improved OS vs placebo-only, with an 87% reduction in the risk of death (HR: 0.13; 95% CI: 0.05–0.35)
  - Participants receiving dazucorilant 300 mg for >24 weeks had improved OS vs those receiving dazucorilant 150 mg or placebo without crossover to 300 mg (HR: 0.39; 95% CI: 0.17–0.92)
  - OS with dazucorilant 300 mg was similar regardless of baseline NfL levels or time since ALS symptom onset
- SGRM treatment reduced systemic levels of inflammatory biomarkers reported to be elevated in people with ALS
  - 24 weeks of treatment with dazucorilant 300 mg significantly reduced systemic MCP-1 and MIP-1β
- The safety of dazucorilant in the OLE was consistent with findings from the double-blind period
- These data support the potential of SGRMs to prolong survival in people with ALS

BACKGROUND AND OBJECTIVE

Neuroinflammation and Cortisol

- Neuroinflammation contributes to motor neuron death and impacts the rate of ALS disease progression[1]
- Cortisol, a glucocorticoid that activates the GR, is proinflammatory in the CNS[2–4]
  - Dysregulated cortisol signaling has been associated with ALS, and excessive GR activation can result in neuroinflammatory priming, oxidative stress, and downstream neurotoxic signaling[2–4]
- Serum levels of the neuroinflammatory chemokines MCP-1 and MIP-1β are elevated in ALS and may contribute to neuronal injury[5,6]

Dazucorilant

- Dazucorilant is an oral SGRM that competitively and reversibly binds the GR to antagonize cortisol signaling and is being investigated for the treatment of adults with ALS[7,8]
- In the phase 2 DAZALS study (NCT05407324), no significant difference in functional decline, as measured by the ALSFRS-R, was observed after 24 weeks between participants treated with dazucorilant 300 mg or 150 mg and those treated with placebo (primary endpoint)[8]
- However, exploratory analyses of OS after 1 year of follow-up showed that dazucorilant 300 mg was associated with improved OS vs placebo-only (HR: 0.16; *P*=0.0009), with a greater benefit being observed in participants who received dazucorilant for >24 weeks[8]

Objective

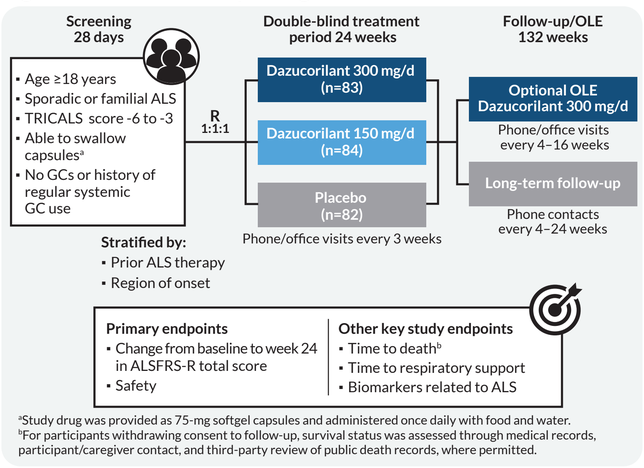
- Here, we present additional exploratory analyses from DAZALS, assessing OS at 2 years and changes in inflammatory biomarkers after 24 weeks

METHODS

Study Design

- DAZALS was a phase 2, randomized, placebo-controlled study in adults (≥18 years) with sporadic or familial ALS (**Figure 1**)

Figure 1. DAZALS Study Design



[a]Study drug was provided as 75-mg softgel capsules and administered once daily with food and water.
[b]For participants withdrawing consent to follow-up, survival status was assessed through medical records, participant/caregiver contact, and third-party review of public death records, where permitted.

Current Analyses

- Exploratory OS analyses (Data cutoff: April 16, 2026)
  - OS analyses were performed approximately 2 years after the last participant was randomized
  - OS in participants treated with dazucorilant 300 mg was evaluated according to baseline NfL levels and time from ALS symptom onset to randomization
    - Elevated NfL levels have been associated with poorer survival and prognosis[9]
    - Time since ALS symptom onset has been identified as an important prognostic factor in historical ALS clinical trials[10–12]
- Exploratory biomarker analyses
  - Of 16 cytokines evaluated in serum, only MCP-1, MIP-1β, and IL-18 were detectable and included in analyses
- OLE safety (Data cutoff: July 9, 2026)
  - OLE safety analyses included all participants who entered the OLE and received ≥1 dose of dazucorilant 300 mg

RESULTS

Participants

- Baseline characteristics at the start of the double-blind period were balanced across treatment groups (**Table 1**)
- Of 249 randomized participants, 122 (49.0%) completed the 24-week double-blind treatment period and 117 (47.0%) entered the OLE

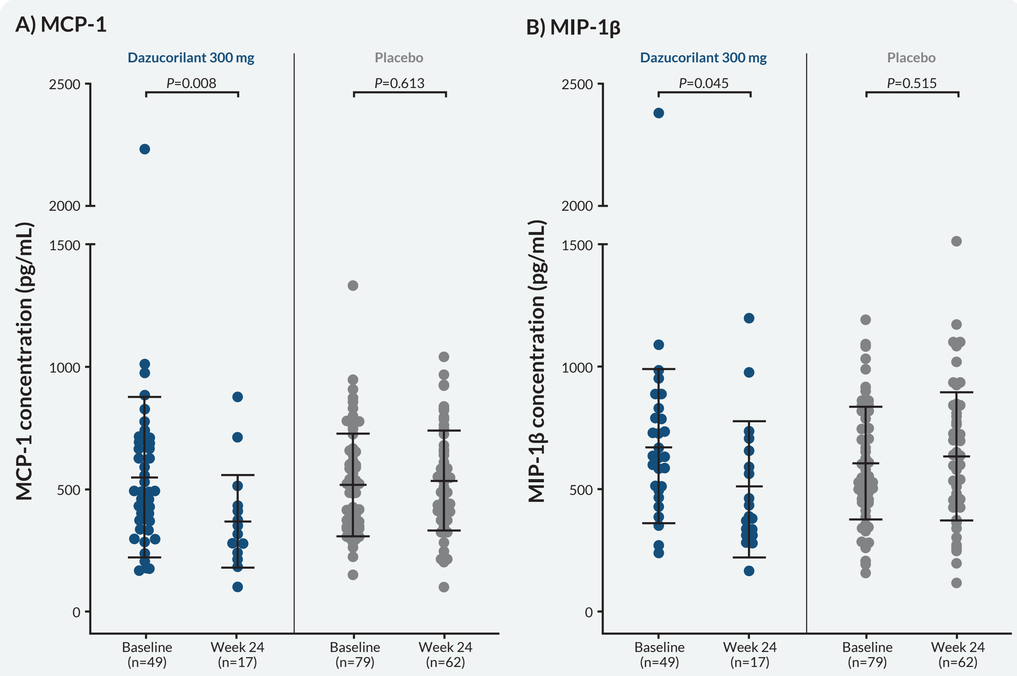
Table 1. Baseline Characteristics

	Dazucorilant 300 mg (n=83)	Dazucorilant 150 mg (n=84)	Placebo (n=82)
Age, y, mean (SD)	58 (10)	58 (11)	60 (9)
Male, n (%)	49 (59.0)	50 (59.5)	52 (63.4)
Region, n (%)			
North America	5 (6.0)	9 (10.7)	6 (7.3)
Europe	78 (94.0)	75 (89.3)	76 (92.7)
Bulbar site of onset, n (%)	14 (16.9)	12 (14.3)	12 (14.6)
TRICALS risk score, mean (SD)	-4.4 (1.0)	-4.4 (0.9)	-4.4 (0.8)
Time since ALS symptom onset, mo, mean (SD)	21 (12)	20 (9)	23 (13)
Time since ALS diagnosis, mo, mean (SD)	10 (11)	9 (8)	11 (13)
Baseline NfL, ng/L, mean (SD)	75.2 (50.3)	93.9 (54.5)	87.6 (48.4)
ALSFRS-R total score, mean (SD)	37.2 (4.6)	36.8 (5.2)	36.7 (5.1)
Prior approved ALS medication, n (%)	79 (95.2)	77 (91.7)	79 (96.3)
Riluzole	79 (95.2)	77 (91.7)	78 (95.1)
Edaravone	6 (7.2)	5 (6.0)	4 (4.9)
Sodium phenylbutyrate/ taurursodiol	3 (3.6)	6 (7.1)	5 (6.1)

Inflammatory Biomarkers

- In participants who received dazucorilant 300 mg, the mean MCP-1 concentration decreased significantly from 552.3 pg/mL at baseline to 371.6 pg/mL at week 24; no significant change was observed in participants who received placebo (**Figure 2A**)
- MIP-1β concentrations decreased significantly from 662.2 pg/mL at baseline to 492.9 pg/mL at week 24 with dazucorilant 300 mg, but no significant change from baseline to week 24 was observed with placebo (**Figure 2B**)
- IL-18 concentrations did not change significantly from baseline to week 24 in either treatment group (data not shown)

Figure 2. Change From Baseline to Week 24 for A) MCP-1 and B) MIP-1β

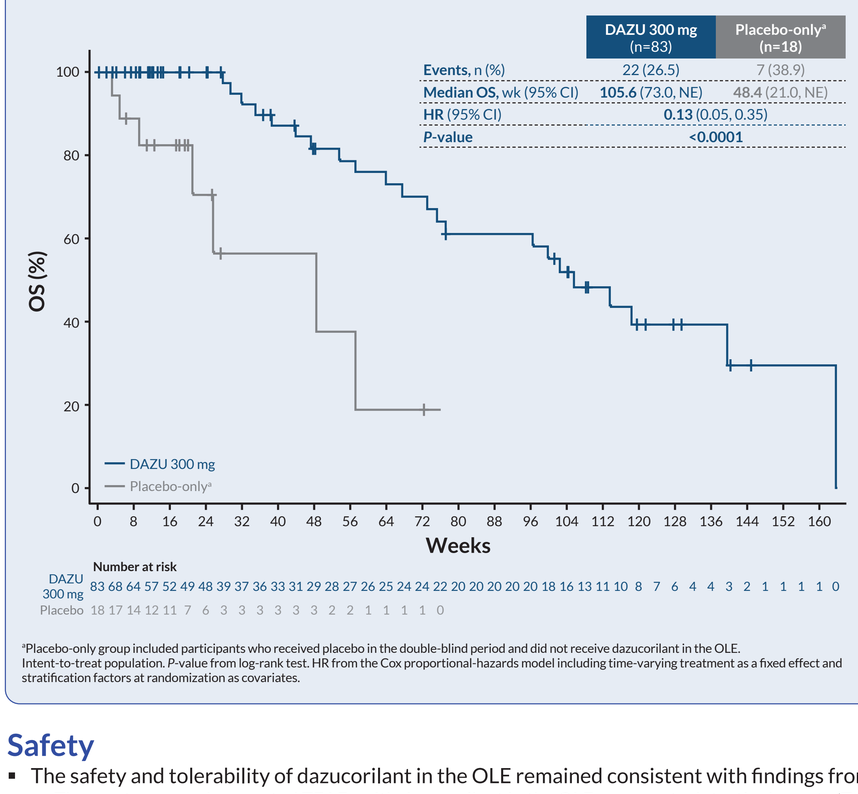


Intent-to-treat population. Bars represent mean ± SD. Two-sample *P*-values based on Welch's t-test, which does not assume equal variances. Samples were collected at baseline, week 3, and week 24, but only baseline and week 24 data are shown.

Overall Survival After ~2 Years

- Through April 16, 2026, a total of 81 deaths were reported in participants who had received ≥1 dose of study treatment: 22/83 (26.5%), 27/83 (32.5%), and 32/82 (39.0%) participants randomized to dazucorilant 300 mg, dazucorilant 150 mg, and placebo, respectively
- Participants who received dazucorilant 300 mg had prolonged OS compared with participants who received placebo and did not cross over to dazucorilant in the OLE (**Figure 3**)

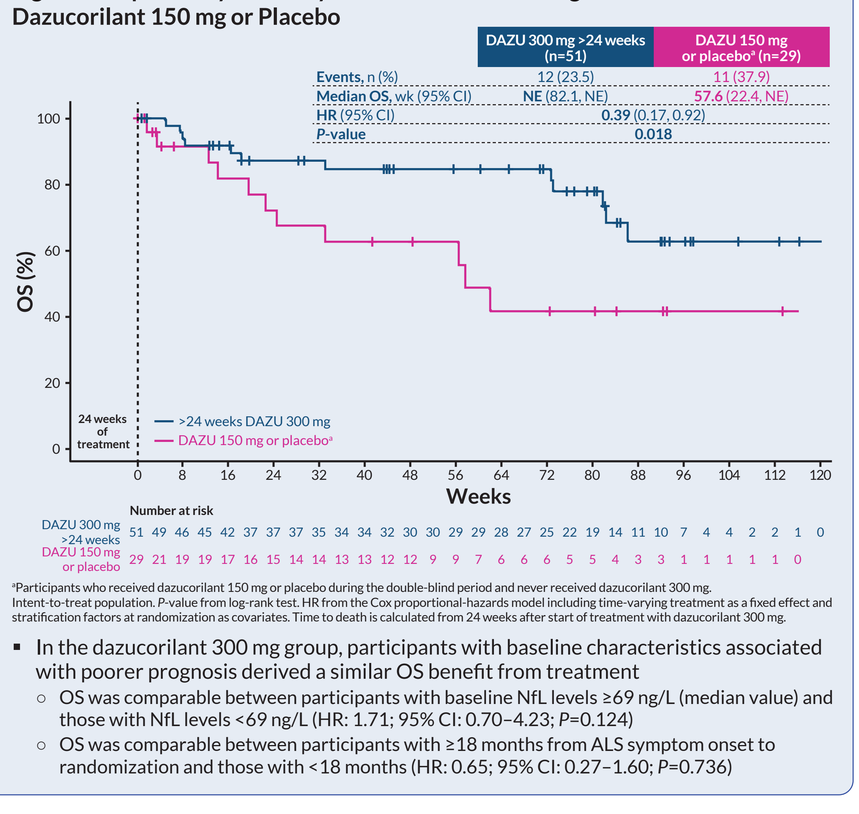
Figure 3. Exploratory OS Analysis: Dazucorilant 300 mg vs Placebo-Only



[a]Placebo-only group included participants who received placebo in the double-blind period and did not receive dazucorilant in the OLE.
Intent-to-treat population. *P*-value from log-rank test. HR from the Cox proportional-hazards model including time-varying treatment as a fixed effect and stratification factors at randomization as covariates.

- OS was also longer in the subset of participants who received dazucorilant 300 mg for >24 weeks compared with participants who received dazucorilant 150 mg or placebo-only (**Figure 4**)

Figure 4. Exploratory OS Analysis: Dazucorilant 300 mg for >24 Weeks vs Dazucorilant 150 mg or Placebo



[a]Participants who received dazucorilant 150 mg or placebo during the double-blind period and never received dazucorilant 300 mg.
Intent-to-treat population. *P*-value from log-rank test. HR from the Cox proportional-hazards model including time-varying treatment as a fixed effect and stratification factors at randomization as covariates. Time to death is calculated from 24 weeks after start of treatment with dazucorilant 300 mg.

- In the dazucorilant 300 mg group, participants with baseline characteristics associated with poorer prognosis derived a similar OS benefit from treatment
  - OS was comparable between participants with baseline NfL levels ≥69 ng/L (median value) and those with NfL levels <69 ng/L (HR: 1.71; 95% CI: 0.70–4.23; *P*=0.124)
  - OS was comparable between participants with ≥18 months from ALS symptom onset to randomization and those with <18 months (HR: 0.65; 95% CI: 0.27–1.60; *P*=0.736)

Safety

- The safety and tolerability of dazucorilant in the OLE remained consistent with findings from the double-blind period (**Table 2**)
  - The most commonly reported TEAEs with dazucorilant in the OLE were gastrointestinal events (**Table 3**)
  - Most TEAEs in the OLE were mild to moderate in severity
  - In the OLE, 4 participants (3.4%) experienced ALT or AST ≥3× ULN; all were transient and resolved, with 1 leading to treatment discontinuation
- The tolerability of dazucorilant is being further evaluated in a separate cohort in the DAZALS study

Table 2. Summary of TEAEs During the OLE

Category, n (%)	Dazucorilant 300 mg (n=117)
Participants with ≥1 TEAE	109 (93.2)
TEAE related to study drug	80 (68.4)
TEAE leading to treatment discontinuation	64 (54.7)
TEAE leading to dose reduction	11 (9.4)
TEAE leading to dose interruption	40 (34.2)
Participants with ≥1 severe TEAE	42 (35.9)
Participants with ≥1 serious TEAE[a]	40 (34.2)
Serious TEAE related to study drug	9 (7.7)
Participants with TEAE leading to death[b]	16 (13.7)

The OLE treatment-emergent period extended from the first OLE dose through 28 days after the last OLE dose. [a]The most common serious TEAEs (>5% of participants) were pneumonia (6.8%) and respiratory failure (5.1%), both of which are recognized complications of ALS progression.[13] [b]TEAEs leading to death included respiratory failure (6 participants), cardiac arrest (2), pneumonia (2), ALS (1), choking (1), COVID-19 (1), pericardial effusion (1), pulmonary embolism (1), and respiratory tract infection (1).

Table 3. TEAEs Occurring in >10% of Participants During the OLE

Preferred term, n (%)	Dazucorilant 300 mg (n=117)
Decreased appetite	21 (17.9)
Abdominal pain upper	20 (17.1)
Abdominal pain	19 (16.2)
Nausea	17 (14.5)
Constipation	15 (12.8)
Headache	14 (12.0)
Fall	13 (11.1)

Participants were counted once within each preferred term. Adverse events coded using MedDRA v27.0.

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Presenter Disclosure

Shafeeq Ladha reports: Consultant for Annexon Biosciences, Biogen, Dyne Therapeutics, Genentech, and Sanofi.

Abbreviations

ALS, amyotrophic lateral sclerosis; **ALSFRS-R**, Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **CI**, confidence interval; **CNS**, central nervous system; **d**, day; **DAZALS**, Dazucorilant in Amyotrophic Lateral Sclerosis; **DAZU**, dazucorilant; **GC**, glucocorticoid; **GR**, glucocorticoid receptor; **HR**, hazard ratio; **IL-18**, interleukin 18; **MCP-1**, monocyte chemoattractant protein-1; **MedDRA**, Medical Dictionary for Regulatory Activities; **MIP-1β**, macrophage inflammatory protein-1 beta; **mo**, month; **NE**, not evaluable; **NfL**, neurofilament light chain; **OLE**, open-label extension; **OS**, overall survival; **R**, randomized; **SD**, standard deviation; **SGRM**, selective glucocorticoid receptor modulator; **TEAE**, treatment-emergent adverse event; **TRICALS**, Treatment Research Initiative to Cure ALS; **ULN**, upper limit of normal; **wk**, week; **y**, year.

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