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

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CONCLUSIONS

- DAZALS did not achieve its primary endpoint of slowing functional decline as measured by the ALSFRS-R scale
- Secondary and exploratory endpoints showed improvement in overall survival for patients who received dazucorilant 300 mg, especially in the subgroup treated for >24 weeks
- Dazucorilant-treated patients discontinued at higher rates than patients in the placebo group due to suboptimal gastrointestinal tolerability that generally occurred in the first 3 weeks
- Dazucorilant-treated patients showed similar rates of serious and severe adverse events as the placebo group
- These findings merit further investigation of glucocorticoid receptor modulation in patients with ALS

BACKGROUND

Cortisol

- Dysregulation of cortisol signaling is common in people with ALS[1, 2]
- Cortisol is proinflammatory in parts of the CNS[3]
- GR modulation may benefit people with ALS by reducing the neurotoxic effects of excess cortisol activity[3]

Dazucorilant

- Dazucorilant is an oral, selective GR modulator that competes with cortisol and reversibly binds to the GR[4]

Wobbler Mice

- Dazucorilant improved motor performance and reduced forepaw atrophy in wobbler mice, a model of sporadic ALS[5]

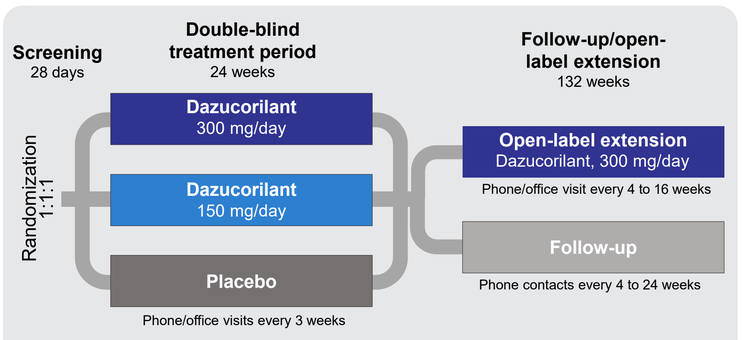
Phase 1 Studies

- Across multiple phase 1 studies, dazucorilant was generally well-tolerated and pharmacodynamically active[6]
- In a phase 1 study, distribution to the CSF was observed, confirming brain penetration[6]

METHODS

- The phase 2 DAZALS study had a 24-week randomized, placebo-controlled, double-blind period followed by a 132-week OLE (**Figure 1**)
- The study was conducted at 35 sites in 10 countries
- The data cutoff was November 25, 2024 for all analyses (including safety) except OS, which had a data cutoff of April 23, 2025
- P-values are log-rank test unless otherwise noted

Figure 1: DAZALS Study Design



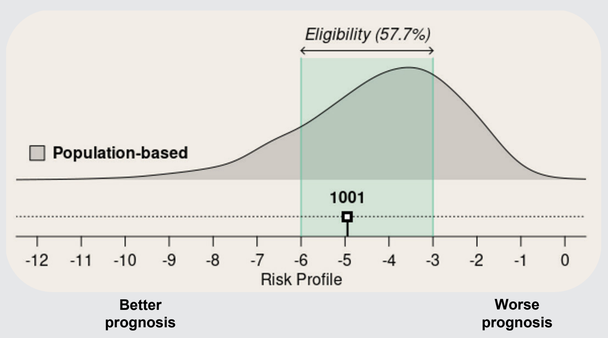
Stratified by prior ALS therapy and region of onset.
Study drug provided as 75-mg softgel capsules and administered once daily with food and water.

- Study registered as NCT05407324 and Eudra CT: 2021-005611-31

Population

- Adults ≥18 years of age with sporadic or familial ALS per Gold Coast criteria
- Prior stable dose of riluzole and/or edaravone allowed
- Able to swallow capsules
- Not currently using glucocorticoids or history of regular systemic glucocorticoid use
- ENCALS risk profile score −6 to −3 (**Figure 2**)

Figure 2. ENCALS Risk Profile Scoring



Endpoints

- The primary endpoints were change from baseline to week 24 in ALSFRS-R total score and safety
- Other key endpoints include:
  - Change in slow vital capacity, change in muscle strength with handheld dynamometry, time to death, biomarker analysis, and change in neurofilament light

RESULTS

Disposition

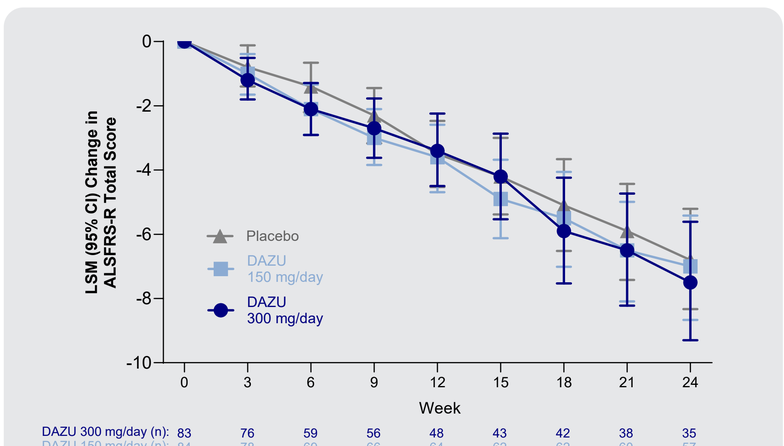
- 249 patients were randomized
  - 83 patients in the dazucorilant 300 mg arm; 68 (82%) discontinued treatment before 24 weeks and 13 (16%) enrolled in the OLE
  - 84 patients in the dazucorilant 150 mg arm; 41 (49%) discontinued treatment before 24 weeks and 40 (48%) enrolled in the OLE
  - 82 patients in the placebo arm; 17 (21%) discontinued treatment before 24 weeks and 64 (78%) enrolled in the OLE

Table 1. Baseline Characteristics at the Start of the Double-Blind Period

	Dazucorilant 300 mg N=83	Dazucorilant 150 mg N=84	Placebo N=82
Age, mean (SD), years	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)
ENCALS risk score, mean (SD)	-4.36 (0.95)	-4.42 (0.93)	-4.43 (0.77)
Time since ALS symptom onset, mean (SD), months	21 (12)	20 (9)	23 (13)
Time since ALS diagnosis, mean (SD), months	10 (11)	9 (8)	11 (13)
Baseline NfL, 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)
Concurrent ALS therapy, 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)
PB-TURSO	3 (3.6)	6 (7.1)	5 (6.1)

- The DAZALS study enrolled the intended patient population
- Patient characteristics were well-balanced across treatment arms (**Table 1**)

Figure 3. Primary Endpoint: ALSFRS-R Total Score During the Double-Blind Period



LSM (95% CI) are from Mixed Model for Repeated Measures.

- No significant changes in ALSFRS-R total score were observed between treatment arms during the double-blind period (**Figure 3**)

Table 2: Key Endpoints During the Double-Blind Period

	Dazucorilant 300 mg N=79	Dazucorilant 150 mg N=80	Placebo N=82
Change in muscle strength, LSM (95% CI)			
Left elbow flexion	-56.9 (-91.1, -22.7)	-44.8 (-74.1, -15.5)	-55.7 (-81.9, -29.6)
Right elbow flexion	-46.2 (-83.6, -8.8)	-39.3 (-69.9, -8.7)	-65.5 (-93.0, -38.0)
Left hip flexion	-62.9 (-103.4, -22.4)	-34.4 (-69.1, 0.3)	-55.4 (-87.7, -23.1)
Right hip flexion	-51.3 (-90.4, -12.2)	-28.6 (-62.9, 5.7)	-57.3 (-88.9, -25.7)
Change in slow vital capacity, liters, LSM (95% CI)	-0.71 (-0.97,-0.46)	-0.50 (-0.70, -0.30)	-0.49 (-0.67, -0.31)
Change in EQ-5D-5L score, LSM (95% CI)	-13.6 (-20.9, -6.4)	-11.9 (-17.9, -5.9)	-6.3 (-12.1, -0.6)
CAFS rank score, LSM (95% CI)	120.5 (95.8, 145.3)	116.5 (92.2, 140.8)	118.8 (94.0, 143.5)
Change in NfL, %, LSM GMR (95% CI)	20.0 (3.8, 38.6)	6.7 (-3.7, 18.2)	8.11 (-1.6, 18.7)

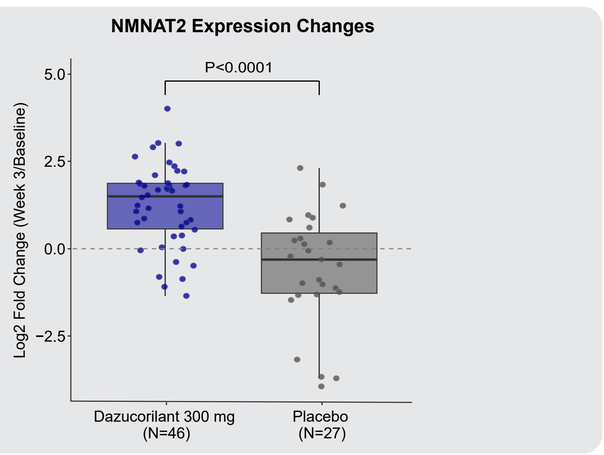
LSM (95% CI) for CAFS rank score are from analysis of covariance model. LSM (95% CI) for other endpoints are from Mixed Model for Repeated Measures. Change in NfL was anlayzed in the biomarker population (DAZU 300 mg, n=33; DAZU 150 mg, n=61; placebo, n=69).

- Secondary endpoints were also not statistically different between arms (**Table 2**)
- Overall treatment effect was consistent across subgroups, including baseline ALSFRS-R total score, ENCALS risk score, and King's Stage

Pharmacokinetics and Pharmacodynamics

- Clinically relevant steady state plasma exposures of dazucorilant were observed in patients with ALS
- Pharmacological activity was demonstrated by modulation of a known GR-regulated gene, CDKN1C[7]

Figure 4. Pharmacodynamic Changes in Whole Blood mRNA



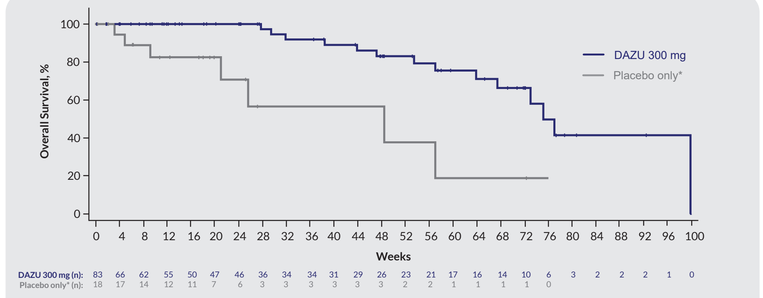
P−value was calculated using limma differential expression analysis, with Benjamini−Hochberg adjustment for multiple testing.

- Dazucorilant had a clinical pharmacodynamic effect on a marker of neuronal health in ALS, as shown by induction of NMNAT2 expression (**Figure 4**)

Overall Survival During the Double-Blind and Open-Label Extension Periods

- During the 24-week double-blind treatment period, no deaths were observed in the dazucorilant 300 mg arm (P=0.0221 vs placebo), 2 deaths were observed in the dazucorilant 150 mg arm (P=0.2052 vs placebo), and 5 deaths were observed in the placebo arm (data cutoff of November 25, 2024)
- At the data cutoff of April 23, 2025, approximately 1 year after the last patient was randomized, a total of 58 deaths were reported in the double-blind plus open-label extension periods
  - 14 deaths in the dazucorilant 300 mg arm (P=0.8515 vs placebo), 23 deaths in the dazucorilant 150 mg arm (P=0.7687 vs placebo), and 21 deaths in the placebo arm
- Further exploratory OS analyses are shown below

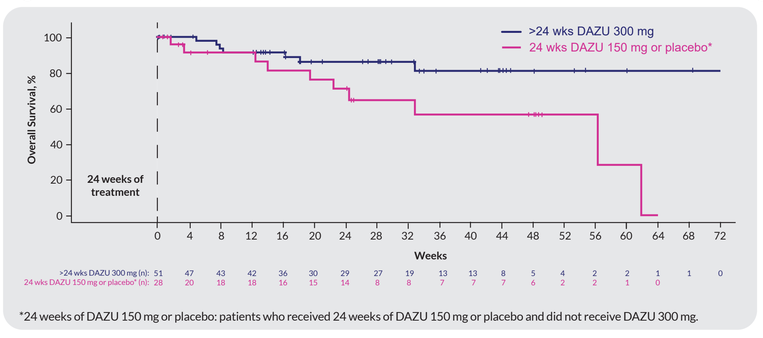
Figure 5. Exploratory OS Analysis: Exposure to Dazucorilant 300 mg



*Placebo-only: patients randomized to placebo that did not enter OLE (did not receive 300 mg DAZU).

- Patients who received dazucorilant 300 mg showed improved OS compared to patients who received placebo and did not receive dazucorilant in the OLE (HR, 0.16 [95% CI: 0.06, 0.41); P=0.0009) (**Figure 5**)

Figure 6. Exploratory OS Analysis: >24 Weeks Exposure to Dazucorilant 300 mg



*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.

- A subset analysis showed prolonged survival in patients who were treated with dazucorilant 300 mg for >24 weeks compared to patients who received dazucorilant 150 mg or placebo and were followed for 24 weeks but never received dazucorilant at 300 mg (HR, 0.36 [95% CI: 0.14, 0.97]; P=0.0239) (**Figure 6**)

Safety

Table 3. Safety Summary for the Double-Blind Period

	Dazucorilant 300 mg N=83	Dazucorilant 150 mg N=83	Placebo N=82
Patients with at least one TEAE, n (%)	82 (98.8)	80 (96.4)	62 (75.6)
TEAE leading to dose interruption	34 (41.0)	30 (36.1)	8 (9.8)
TEAE leading to treatment discontinuation	48 (57.8)	25 (30.1)	7 (8.5)
TEAE related to study drug	77 (92.8)	59 (71.1)	24 (29.3)
TEAE leading to death	0	2 (2.4)	4 (4.9)
Patients with at least one severe TEAE, n (%)	17 (20.5)	14 (16.9)	11 (13.4)
Patients with at least one serious TEAE, n (%)	16 (19.3)	14 (16.9)	14 (17.1)

During the double-blind period, treatment-emergent adverse events were defined as those that occurred between the first dose of study drug through 28 days after the last dose of study drug administered in double-blind treatment period but prior to the date of the first dose of study drug in OLE.

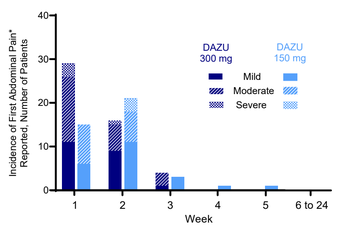
- Patients who received dazucorilant experienced more TEAEs, resulting in more treatment interruptions and discontinuations (**Table 3**)
- The 150 mg dose of dazucorilant was better tolerated than the 300 mg dose, based on fewer treatment discontinuations due to TEAEs
- The frequency of severe and serious TEAEs reported in the dazucorilant arms was similar to the placebo arm

Table 4. TEAEs Occurring in >15% of Patients in the Double-Blind Period

	Dazucorilant 300 mg N=83	Dazucorilant 150 mg N=83	Placebo N=82
Abdominal pain upper	29 (34.9)	14 (16.9)	1 (1.2)
Abdominal pain	24 (28.9)	28 (33.7)	2 (2.4)
Headache	18 (21.7)	8 (9.6)	6 (7.3)
Diarrhea	17 (20.5)	7 (8.4)	6 (7.3)
Decreased appetite	14 (16.9)	11 (13.3)	0
Back pain	13 (15.7)	16 (19.3)	1(1.2)
Constipation	8 (9.6)	14 (16.9)	4 (4.9)
Fall	5 (6.0)	9 (10.8)	14 (17.1)

- Patients who received dazucorilant experienced more gastrointestinal and musculoskeletal disorders than those on placebo (**Table 4**)
- Overall, TEAEs were mild to moderate in severity and typically resolved following interruption or discontinuation of study treatment
- Abdominal pain was the most frequent TEAE resulting in discontinuation of study treatment
- In general, abdominal pain onset occurred during the first 3 weeks and resolved following interruption or discontinuation (**Figure 7**)
- Serious TEAEs reported in more than 1 patient in the dazucorilant-treated arms included respiratory failure, dysphagia, hypoventilation, deep vein thrombosis, pericarditis, and abdominal pain
- Statistically significant reductions in weight from baseline were observed at week 24 in the dazucorilant 300 mg (P<0.0001) and 150 mg (P<0.01) arms
- TEAEs with fatal outcomes during the double-blind period (n=6) were all reported as not related to study treatment

Figure 7. Abdominal Pain in the Double-Blind Period



*Includes preferred terms of abdominal pain and abdominal pain upper

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Disclosures

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Abbreviations

AE, adverse events; ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale-Revise; CAFS, Combined Assessments for Function and Survival; CI, confidence interval; CDKN1C, cyclin-dependent kinase inhibitor 1C; CNS, central nervous system; CSF, cerebrospinal fluid; DAZU, dazucorilant; EQ-5D-5L; EuroQol 5-Dimension 5-Level; ENCALS, European Network to Cure ALS; GMR, geometric mean ratio; GR, glucocorticoid receptor; HR, hazard ration; LSM, least square means; mo, month; NfL, neurofilament light chain; NMNAT2, nicotinamide mononucleotide adenylyltransferase 2; OLE, open-label extension; OS, overall survival; PBO, placebo; PB-TURSO, sodium phenylbutyrate and taurursodiol; SD, standard deviation; TEAE, treatment-emergent adverse events.

European Network to Cure ALS Annual Conference; June 3-6, 2025; Turin, Italy