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Safety, Pharmacokinetics, and Pharmacodynamics of the Selective Glucocorticoid Receptor Modulator Dazucorilant in Healthy Volunteers

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Summary & Conclusions

- Dysregulation of cortisol levels in patients with ALS, along with cortisol's proinflammatory effects in the CNS, provide a strong rationale for the role of SGRMs, like dazucorilant, in the treatment of ALS.
- The presented studies established the PK, safety, tolerability, and pharmacological effect of dazucorilant in healthy volunteers.
- Across the presented studies, 111 healthy volunteers received dazucorilant. AEs were mild to moderate; no significant safety concerns were identified.
- A phase 2 study (DAZALS, NCT05407324, EudraCT 2021-005611-31) is ongoing to assess whether dazucorilant can benefit patients with ALS by slowing functional loss.

AEs, adverse events; ALS, amyotrophic lateral sclerosis; CNS, central nervous system; PK, pharmacokinetics; SGRM, selective glucocorticoid receptor modulator.

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The authors thank the study participants and their families as well as the clinical sites.

Disclosures

GM, HJH, and JMC are employees of Corcept Therapeutics, Inc. KD is an employee and director of Jade Consultants, which received consulting fees from Corcept Therapeutics, Inc.

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Background

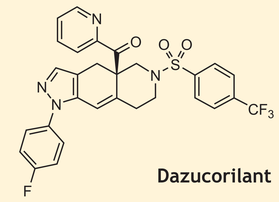
Role of cortisol in amyotrophic lateral sclerosis (ALS)

- ALS is a devastating disease with insufficient treatment options.
- Dysregulation of cortisol levels has been reported in patients with ALS, including elevated levels of cortisol[1], particularly in patients with rapid progression[2].
- Despite the known immunosuppressive effects of glucocorticoids, prolonged cortisol exposure can:
  - Increase myeloid activity and glial cell activation[3],
  - Promote proinflammatory effects in the brain and central nervous system (CNS)[4], including proinflammatory cytokine production (TNFα, IL1B) in the hippocampus[5] and isolated microglial cells[6] from rats, and
  - Promote excitotoxicity and glutamatergic toxicity[7–10].
- *NR3C1*, the gene coding for the glucocorticoid receptor (GR), has been proposed as a potential therapeutic target for the treatment of ALS.[11]

Dazucorilant modulates cortisol activity

- Dazucorilant (CORT113176, Corcept Therapeutics) is a small-molecule, selective GR modulator (SGRM) in development for the treatment of ALS.
  - It competitively and reversibly binds to the GR with high affinity and has no affinity for other hormone receptors.
  - Brain penetration has been observed in rats.
- In Wobbler mice, a model of sporadic ALS, dazucorilant reduced forepaw atrophy, improved performance in the rotarod test, and inhibited neurodegeneration and neuroinflammation.[12-14]

► Here, we describe the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of orally administered dazucorilant capsules in healthy volunteers.



Dazucorilant

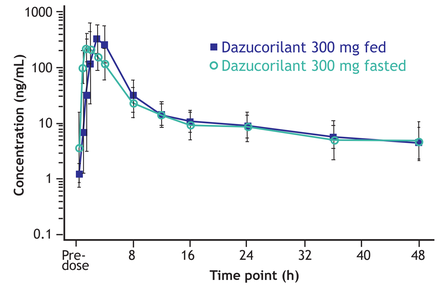
Results: Pharmacokinetics & Pharmacodynamics

Greater than dose-proportional increase in exposures and positive food effect observed

- In the FIH study, a greater than dose-proportional increase in dazucorilant exposures ($AUC_{0\text{-}inf}$, C_{max}) was observed following single ascending dose escalation from 150 mg to 450 mg fasted.
- Further 2-fold dose escalation (450 mg to 900 mg fed, single dose) increased exposures by 2.2- and 2.8-fold (C_{max} and $AUC_{0\text{-}inf}$, respectively).
- The PK study demonstrated a modest but statistically significant positive food effect (1.3- to 1.7-fold increased exposure with food; **Figure 1**).

AUC, area under the curve; C_{max}, maximum concentration.

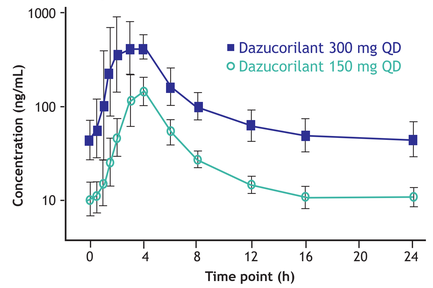
Figure 1. Plasma concentrations of dazucorilant 300 mg with and without food in the PK study.



Steady state exposures achieved after ~7 days with ~2-fold accumulation in plasma

- In the brain penetration study, dazucorilant exposures increased 1.7- to 1.9-fold from days 1 to 7 and 1.6- to 2.0-fold from days 1 to 14 (based on accumulation ratios of $AUC_{0\text{-}24}$ and C_{max}).
- No significant change in accumulation was observed in the second week of dosing, indicating that steady-state exposure had been reached within 1 week of dosing.
- The accumulation pattern was similar at both doses (150 and 300 mg QD fed).
- Steady state exposures (C_{max}, $AUC_{0\text{-}24}$) were approximately 4-fold higher with 300 vs. 150 mg dazucorilant.

Figure 2. Dazucorilant steady-state PK profile after 14 days of QD dosing in the brain penetration study.



Dazucorilant distribution to the CSF observed, confirming brain penetration

- In the brain penetration study, dazucorilant was detectable in the CSF in all study participants after 1 week of QD dosing (150 and 300 mg fed).

Proof of pharmacological effect established

- In part 3 of the FIH study, a single dose of prednisone decreased eosinophils, lymphocytes, and osteocalcin, and increased neutrophils, as expected.
- Dazucorilant ameliorated the effect of prednisone on most of these parameters (**Table 1**).
- Similar to other SGRMs[15], no notable effects of dazucorilant on morning or evening cortisol or ACTH levels were observed in part 2 of the FIH study.

Table 1. Effect of dazucorilant (450 mg fed, single dose) after prednisone 25 mg challenge in part 3 of the FIH study.

$AUEC_{0\text{-}24}$ change from baseline	Prednisone	Prednisone + dazucorilant	*P*-value
Eosinophils, 10^9*h/L	-2.80	-1.86	0.019
Lymphocytes, 10^9*h/L	-2.47	0.134	0.019
Neutrophils, 10^9*h/L	74.7	82.4	ns
Osteocalcin, µg*h/L	-151	-123	0.032

Showing adjusted arithmetic mean from a linear mixed model of PD parameter estimates. n=9 except for osteocalcin, where n=8. AUEC, area under the effect curve; ns, not significant.

Results: Safety and Tolerability

- Single doses of dazucorilant up to 1000 mg fasted and 900 mg fed were considered safe and well tolerated.
- Multiple doses up to 300 mg QD were considered safe; multiple doses up to 200 mg QD were generally well tolerated.
  - In the FIH study, 3 participants discontinued the 300 mg QD dose at the investigator's discretion due to adverse events (AEs; upper abdominal pain, abdominal pain and dyspepsia, and musculoskeletal chest pain).
  - In the brain penetration study, 3 AEs (constipation, thrombocytopenia, SARS-CoV-2 infection [unrelated]) led to withdrawal of study drug.
  - In the participant with thrombocytopenia, platelet count recovered substantially 7–14 days after withdrawal of dazucorilant, indicating that platelets were not being destroyed. Transient reduction in platelet count has also been observed with other SGRMs.
- No serious or severe treatment-emergent AEs were reported.
- The most common AEs were gastrointestinal (GI), nervous system, musculoskeletal and connective tissue disorders.
  - In a majority of participants, GI and musculoskeletal and connective tissue treatment-emergent AEs were manageable with analgesics, laxatives, or antacids and resolved quickly after drug was discontinued.

Table 2. Most frequent treatment-emergent AEs during 14 days of dazucorilant dosing in healthy volunteers.

Number of participants reporting each treatment-emergent AE (%)	FIH Study, Part 2[1] (n=27)	Brain Penetration Study[2] (n=12)	Total (n=39)
Gastrointestinal disorders			
Abdominal pain[3]	11 (41)	6 (50)	17 (44)
Abdominal distention	4 (15)	4 (33)	8 (21)
Constipation	5 (19)	2 (17)	7 (18)
Diarrhoea	4 (15)	0	4 (10)
Dyspepsia	4 (15)	0	4 (10)
Nervous system disorders			
Headache	12 (44)	4 (33)	16 (41)
Musculoskeletal and connective tissue disorders			
Back pain	8 (30)	0	8 (21)

[1]Dosing: 100 mg QD (fed), 200 mg QD (fasted), 300 mg QD (fasted). [2]Dosing: 150 mg QD (fed), 300 mg QD (fed). [3]Includes abdominal discomfort, abdominal pain, and abdominal pain lower.

Methods

First-in-human (FIH) study

- An adaptive dose, double-blind, placebo-controlled study in 110 healthy volunteers (18–60 years; BMI 18–30 kg/m²; weight ≤102 kg; NCT04249323, EudraCT 2019-004258-27)
- Tested single ascending doses (50–1000 mg) +/- food (part 1, n=63); multiple doses (100–300 mg QD for 14 days; part 2, n=36); and aimed to demonstrate pharmacological effect (part 3, n=11)
- **Primary objective:** To assess dazucorilant safety and tolerability; PK and PD assessments were secondary objectives

Brain penetration study

- A phase 1, randomized, partially double-blind, placebo-controlled study in 16 healthy male volunteers (18–65 years; BMI 18–30 kg/m²; weight ≤100 kg; NCT04994743, EudraCT 2021-002456-36)
- **Primary objective:** To evaluate the PK of multiple oral dazucorilant doses (150 or 300 mg QD fed for 14 days) in plasma and cerebrospinal fluid (CSF)

PK study

- A phase 1, randomized, open-label, 2-cohort, 2-period crossover study in 16 healthy volunteers (18–60 years old; BMI 18–30 kg/m²; weight ≤102 kg; EudraCT 2022-000181-18)
- **Primary objective:** To evaluate the PK of dazucorilant softgel capsules (150 or 300 mg single dose) administered +/- food

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