DAZALS: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Dazucorilant in Patients with Amyotrophic Lateral Sclerosis

PRESENTER:
Grace Mann, PhD
Contact: gmann@corcept.com

Grace Mann[1], Ruben P. A. van Eijk[2,3], Dale Zhang[1], Hazel J. Hunt[1], Leonard H. van den Berg[2]

[1] Corcept Therapeutics, Menlo Park, CA, USA; [2] Department of Neurology, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht, The Netherlands; [3] Biostatistics & Research Support, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

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Background

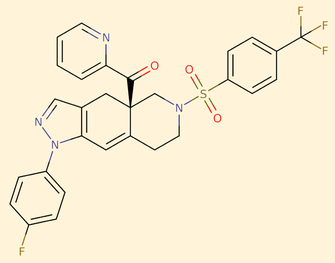
Role of Cortisol in Amyotrophic Lateral Sclerosis (ALS)

- ALS is a devastating disease with insufficient treatment options
- Distortions in cortisol levels have been reported in patients with ALS, including elevated cortisol levels[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 CNS[4], including proinflammatory cytokine production (TNFα, IL1ß) in the hippocampus[5] and isolated microglial cells[6] from rats
  - Promote excitotoxicity and glutamatergic toxicity[7,8,9,10]

Dazucorilant Modulates Cortisol Activity

- A small-molecule, selective glucocorticoid receptor modulator (SGRM) that competitively and reversibly binds to GR
- High affinity for the glucocorticoid receptor (GR) and no affinity for other hormone receptors
- Brain penetration observed in rats and distribution to the cerebrospinal fluid observed in humans

Dazucorilant (CORT113176)



Dazucorilant Reduces Neuronal Death in Wobbler Mice (a Model of Sporadic ALS)[11,12]

- Wobbler mice have adrenal hypertrophy and glucocorticoid elevation similar to patients with ALS
- Symptoms in Wobbler mice are similar to those in patients with ALS
- Dazucorilant (30 mg/kg/day dosed subcutaneously for 21 days) in the spinal cord
  - reduced vacuolated neurons, astro- and microgliosis, and neuroinflammation,
  - improved glutamate homeostasis, with increased glutamine synthase and glutamate transporter 1 expression, and
  - positively modulated a survival pathway in ventral horn homogenates and negatively modulated a death signal
- Dazucorilant also improved performance in the rotarod test and reduced forepaw atrophy[13]

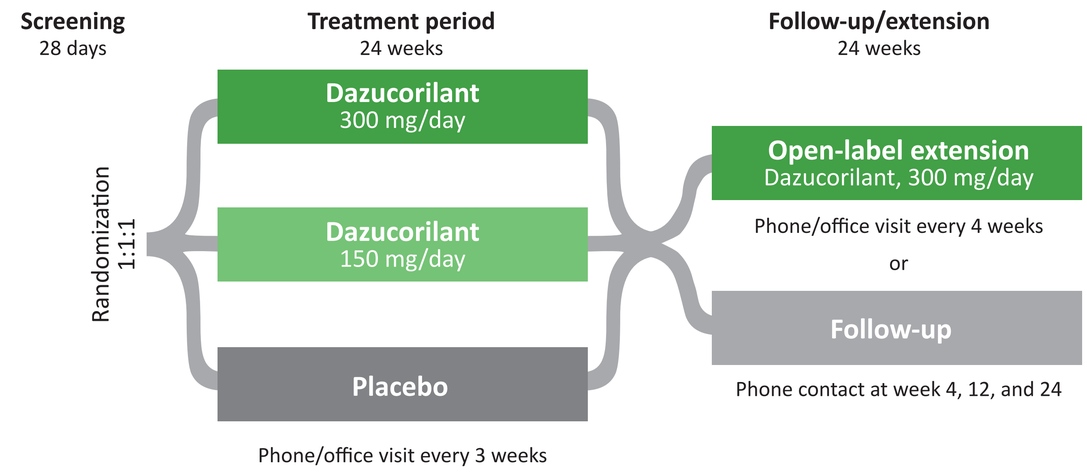
DAZALS: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating Safety and Efficacy of Dazucorilant in Patients with Amyotrophic Lateral Sclerosis

Study design

- To be conducted at sites in Europe and the United States (EudraCT 2021-005611-31)
- Target enrollment: 198 patients
- Stratification factors
  - Prior use of ALS medications riluzole and/or edaravone (yes/no)
  - Region of disease onset (bulbar/other)
- Plasma samples will be collected in ~20% of patients at week 3 for PK analysis
- Open-label extension (OLE)
  - Patients who complete the treatment period and meet OLE eligibility criteria may enroll and receive dazucorilant

Study Treatment and Administration

- Study drug (dazucorilant or placebo) provided as 75 mg softgel capsules
- Administered orally once daily with food and water, at approximately the same time each day



Study Endpoints

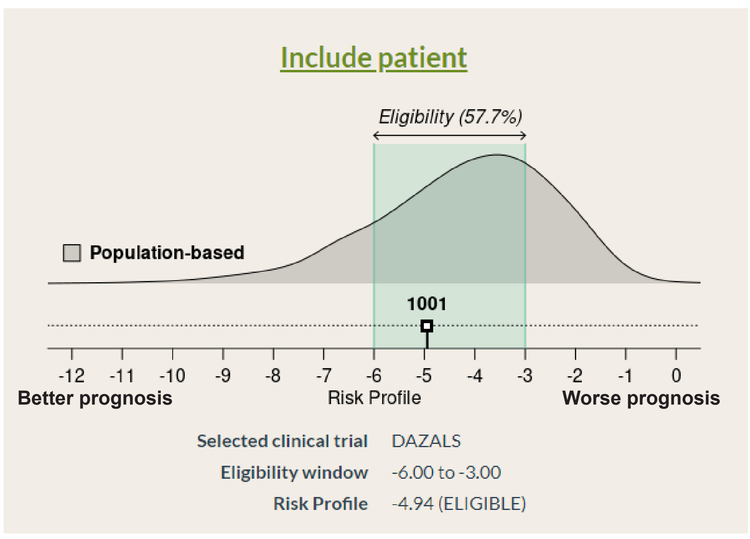
- Primary endpoints
  - ALS Functional Rating Scale-Revised (ALSFRS-R) total score (change from baseline to week 24)
  - Safety
- Key secondary endpoints
  - Changes in % slow vital capacity, muscle strength (using hand-held dynamometer), quality of life
  - Time to event:
    - Death of any cause
    - Hospitalization due to ALS-related event
    - Tracheostomy (for respiratory failure, saliva management, or both)
    - Respiratory support >22 h per day for 7 days
- Key additional endpoints
  - Pharmacokinetics
  - Biomarkers related to ALS (serum neurofilament, IL-18 and/or IL-18 binding protein)
  - Patient-reported outcomes

ENCALS Risk Profile Score & DAZALS Patient Population

- The key objective of eligibility criteria is to exclude patients in advanced disease stages or those that are progressing slowly
  - But: Progression rates in ALS are determined by the sum of multiple interdependent patient characteristics
- The ENCALS Risk Profile[14,15,16] sums the prognostic effects of 7 patient characteristics into a single score to better estimate the patient's overall prognosis when determining study eligibility
- Required patient information
  1. Study ID
  2. Study subject ID
  3. Date of screening
  4. Date of birth
  5. Date of diagnosis
  6. Date of symptom onset
  7. El Escorial Definite classification
  8. Site of symptom onset
  9. Presence of fronto-temporal dementia
  10. ALSFRS-R total score at screening
  11. Vital capacity at screening

DAZALS eligibility: ENCALS score ≥-6 and ≤-3

- Excludes patients with a very slow progression (long survival) and patients with a very fast progression (very short survival)



DAZALS: Key inclusion criteria
Patients ≥18 years of age with ALS (sporadic or familial)
Prior riluzole and/or edaravone allowed but not required. If ongoing, patient must be on a stable dose.
ENCALS risk profile score ≥-6 and ≤-3
DAZALS: Key exclusion criteria
History of clinically significant non-ALS neurologic disorder
Inability to swallow capsules
Renal or hepatic impairment or low platelet count
At screening, any use of non-invasive ventilation (eg, CPAP) for any portion of the day, mechanical ventilation via tracheostomy, or on any form of oxygen supplementation
Currently using glucocorticoids or requirement for regular systemic glucocorticoid use
History of any clinically significant disorder or unstable medical condition other than ALS

Conclusions

- Distortion 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
- DAZALS will be the first study assessing whether GR modulation with dazucorilant can reduce the neurotoxic effects of cortisol activity and benefit patients with ALS by slowing functional loss
- The ENCALS risk profile score will be used to assess eligibility. This method is expected to enroll a homogeneous patient population with a similar predicted prognosis
- Enrollment is planned to begin mid-2022

References

1. Patacchioli et al., *J Endocrinol Invest* (2003).
2. Spataro et al., *J Neurol Sci* (2015).
3. Frank et al., *BB&I* (2012).
4. Duque et al., *Front Endocrinol* (2016).
5. Munhoz et al., *J Neurosci* (2010).
6. Feng et al., *Front Mol Neurosc* (2019).
7. Stein-Behrens et al., *J Neurochem* (1992).
8. Elliott & Sapolsky, *Brain Res* (1993).
9. McIntosh et al., *Exp Neurol* (1996).
10. Behl et al., *Eur J Neurosci* (1997).
11. Moser et al., *Mol. Genet. Genomics* (2013).
12. Meyer et al., *Neuroscience* (2018).
13. Meyer et al., *Brain Res* (2020).
14. Westeneng et al., *Lancet Neurol* (2018).
15. van Eijk et al., *Neurology* (2019).
16. van Eijk et al., *Neurology* (2021).

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Disclosures

RPAvE: none.

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