The Integrated Stress Response is modulated by eIF2B agonist DNL343: Results from Preclinical, Phase 1 Healthy Participant, and Phase 1b ALS Patient Studies


BACKGROUND

In ALS, TDP-43 pathology is linked to cellular stressology resulting from chronic activation of the Integrated Stress Response (ISR) via modulation of the eukaryotic initiation factor 2B (eIF2B). eIF2B activation has potential to slow neurodegeneration in ALS.

PHASE 1 STUDY DESIGN

- Study Overview
  - Study Objective: To evaluate the safety, tolerability, and pharmacokinetics of DNL343 in healthy participants
  - Study Design: Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) studies
  - Study Population: 95 healthy participants
  - Treatment: DNL343 administered orally or via gastrostomy tube once daily

PHASE 1 STUDY HEALTHY PARTICIPANTS

- Pharmacokinetics
  - DNL343 is administered orally or via gastrostomy tube once daily.
  - Geometric Mean (95% CI) DNL343 Plasma Conc. (µM)
    - DNL343 Treatment
      - DNL343 plasma concentration increased in a dose-dependent manner
      - Linear, and peak plasma levels of DNL343 steady state were observed.

DNL343 is a novel therapeutic designed to inhibit the ISR and restore cells to a healthy state.

DNL343 suppresses increased stress granules in neurons derived from patients with ALS.

PHASE 1b STUDY ALS PARTICIPANTS

- Pharmacokinetics
  - DNL343 PK demonstrates extensive CSF distribution and supports once-daily oral administration.

CONCLUSION

- Preclinical Experimental Models
  - DNL343 suppresses increased stress granules in t-/g-/p- treated CHAC1 patient-derived neurons.
  - DNL343 was BBB penetrant, achieved CNS pathway modulation and preserved motor function in an eIF2B mutant mouse model

Phase 1 and Phase 1b (DDR) PK demonstrated lower variability, predictable dose-related increases in exposure, and a half-life supporting once-daily dosing.

- Clinical and non-clinical PD data demonstrate extensive CNS distribution of DNL36.

- DNL343 reduces inflammatory cytokines and decreases autophagy in cell and whole animal models.

In conclusion, DNL343 was generally safe and well-tolerated in healthy participants and patients supporting continued study of DNL343 as a potential investigational drug. An OLE for Phase 1 participants is ongoing, with median CLE exposure duration of 4 months and maximum duration of 12 months as of Dec-2022.