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Topline Results in HEALEY ALS Platform Trial with Denali Therapeutics eIF2B Agonist DNL343

- **Primary endpoint of overall function (ALSFRS-R) and survival, and key secondary endpoints of muscle strength and respiratory function, were not met at 24 weeks.**
- **Overall, DNL343 was found to be safe and well-tolerated.**
- **Additional analyses, including neurofilament light (NfL) and other fluid biomarkers, pre-specified sub-group analyses and analyses from the active treatment extension period are expected later in 2025.**

The Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital announced topline results from an analysis of Regimen G evaluating DNL343, an eIF2B agonist developed by Denali Therapeutics, in adults with amyotrophic lateral sclerosis (ALS).

For the primary analysis, a total of 186 participants who were randomized to receive DNL343 treatment were compared to 139 participants randomized to receive placebo in this Regimen (n=63) or shared from a concurrently enrolling regimen (n=76).

The primary endpoint of overall function as measured by the ALS functional rating scale-revised (ALSFRS-R) and survival from baseline through 24 weeks was not met. Key secondary endpoints, measuring muscle strength and respiratory function, were also not statistically different between the active and placebo groups at week 24. Overall, DNL343 was found to be safe and well-tolerated. Additional analyses, including pre-specified subgroup analyses, longer term clinical effects from the active treatment extension period data, target engagement, NfL and other disease biomarker data are expected later in 2025.

“Though the initial top-line clinical results of this trial were not what we hoped, the data collected is valuable in helping to understand the next stage of ALS research,” says Merit Cudkowicz, MD, MSc, principal investigator and sponsor of the HEALEY ALS Platform Trial, director of the Sean M. Healey & AMG Center for ALS, chief of the Department of Neurology at MGH, and the Julieanne Dorn Professor of Neurology at Harvard Medical School. “We have additional pre-specified subgroup analyses and biomarker work, including NfL, pending

from this regimen, as well as long term efficacy data from participants who continued in the active treatment extension period. We remain deeply committed to fully understanding the effects of DNL343 in ALS, and will further evaluate the data before determining next steps."

Regimen G is co-led by Suma Babu, MBBS, MPH, and Sabrina Paganoni, MD, PhD, physician investigators at the Healey & AMG Center for ALS at MGH.

"Every study contributes valuable insights that bring us one step closer to finding effective therapies for this challenging disease," said Drs. Babu and Paganoni. "We are grateful to the participants and their families for their dedication and support in this critical research."

About DNL343

DNL343 is a novel investigational ALS therapy that targets eIF2B, a central regulator of the integrated stress response (ISR). The ISR appears to be overactive in ALS, leading to the formation of stress granules containing TDP-431,2. Buildup of TDP-43 is harmful and leads to neuronal degeneration. In preclinical data, inhibition of the ISR by DNL343 dissolves TDP-43 containing stress granules and decreases ISR biomarkers. The safety, pharmacokinetics, and pharmacodynamics of DNL343 have been characterized in both healthy participants and people with ALS, in a Phase 1 (N=47) and a Phase 1b (N=29) study, respectively, with dosing for up to 28 days. Results from both studies demonstrated that once-daily oral dosing with DNL343 was generally well tolerated and exhibited extensive cerebrospinal fluid (CSF) penetration. In addition, robust inhibition of biomarkers associated with the ISR pathway was observed in blood samples from study participants. DNL343 is an investigational therapeutic and has not been approved by any regulatory authority for any commercial use.

Fang, MY et al. "Small-Molecule Modulation of TDP-43 Recruitment to Stress Granules Prevents Persistent TDP-43 Accumulation in ALS/FTD." *Neuron* 2019 Sep 4;103(5):802-819
Luan, W et al. "Early activation of cellular stress and death pathways caused by cytoplasmic TDP-43 in the rNLS8 mouse model of ALS and FTD." *Mol Psychiatry* 2023 Jun;28(6):2445-2461

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