Regimen G is a Phase 2/3 trial enrolling approximately 240 participants to evaluate the safety and efficacy of DNL343 as a potential treatment for ALS. This regimen involves biomarker analysis and optional cerebrospinal fluid (CSF) collection to assess the effects of DNL343.

3:1 Active Drug to Placebo Ratio: Participants who enroll in this trial have a 3 in 4 (75%) chance of being assigned to active study drug and a 1 in 4 (25%) chance of being assigned to placebo during the initial 24-week randomized controlled trial (RCT) period.

Active Treatment Extension (ATE): Participants will continue into the ATE for DNL343 after completing the 24-week RCT. During ATE, all participants will receive the active study drug.

To see if you may qualify, please review the list of eligibility criteria: https://bit.ly/30ctynm

For general questions about the HEALEY ALS Platform Trial, contact the Patient Navigator: healeyalsplatform@mgh.harvard.edu 833-425-8257 (HALT ALS)
**Q:** How is this drug administered?
**A:** DNL343 is taken by mouth once daily. The study drug is in the form of granules that are stored in stick packs (foil packets). The granules can be mixed with water or taken with soft food such as applesauce or yogurt.

**Q:** What does this drug do?
**A:** DNL343 aims to slow ALS progression and improve survival of nerve cells by restoring normal protein production and decreasing potentially harmful buildup of TDP-43. The integrated stress response (ISR) appears to be overactive in ALS, and chronic activation can lead to cellular dysfunction. The ISR reduces eIF2B activity in cells, which leads to impaired protein synthesis and formation of stress granules containing TDP-43. TDP-43 containing stress granules are thought to lead to TDP-43 inclusions, a hallmark of ALS pathology. DNL343 is designed to inhibit the ISR, restore normal protein synthesis, and dissolve TDP-43 containing stress granules, which may have therapeutic effects in ALS.

**Q:** Has this drug been studied before?
**A:** Yes. Prior studies showed that DNL343 is generally well tolerated in individuals living with ALS and healthy participants. DNL343 administration led to a reduction in two ISR biomarkers in the blood, suggesting that DNL343 inhibits the ISR. Analysis of participants’ CSF (the fluid that surrounds nerve cells impacted by ALS) showed that DNL343 is well distributed in the spinal fluid. DNL343 is being studied in an ongoing Phase 1b trial (NCT05006352) in people with ALS. DNL343 is an investigational drug and has not been approved by any Health Authority.

**Additional Questions?**

Register to attend the Weekly Platform Trial Q&A Webinars:

https://bit.ly/3DvkJTa