# DNL343 in Amyotrophic Lateral Sclerosis: Results from Regimen G in the Healey Platform Trial

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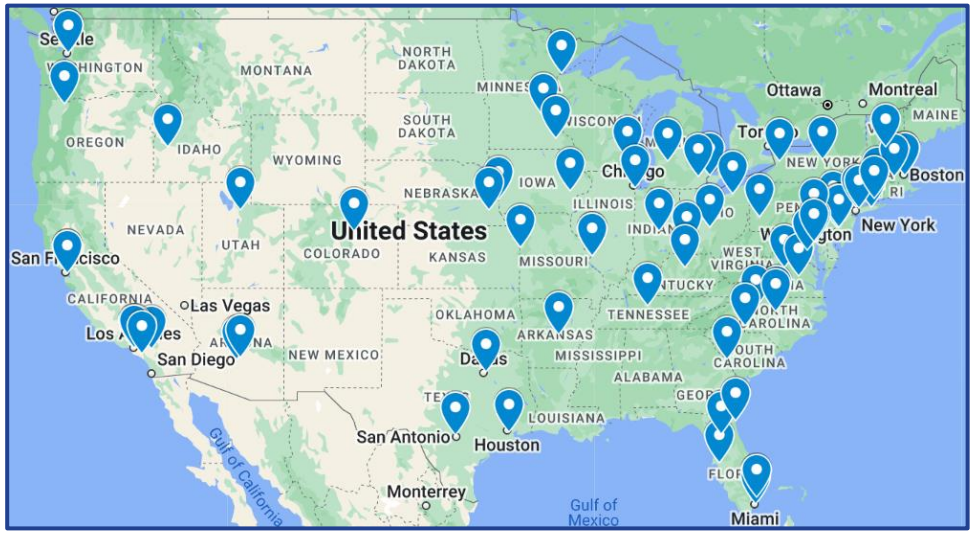
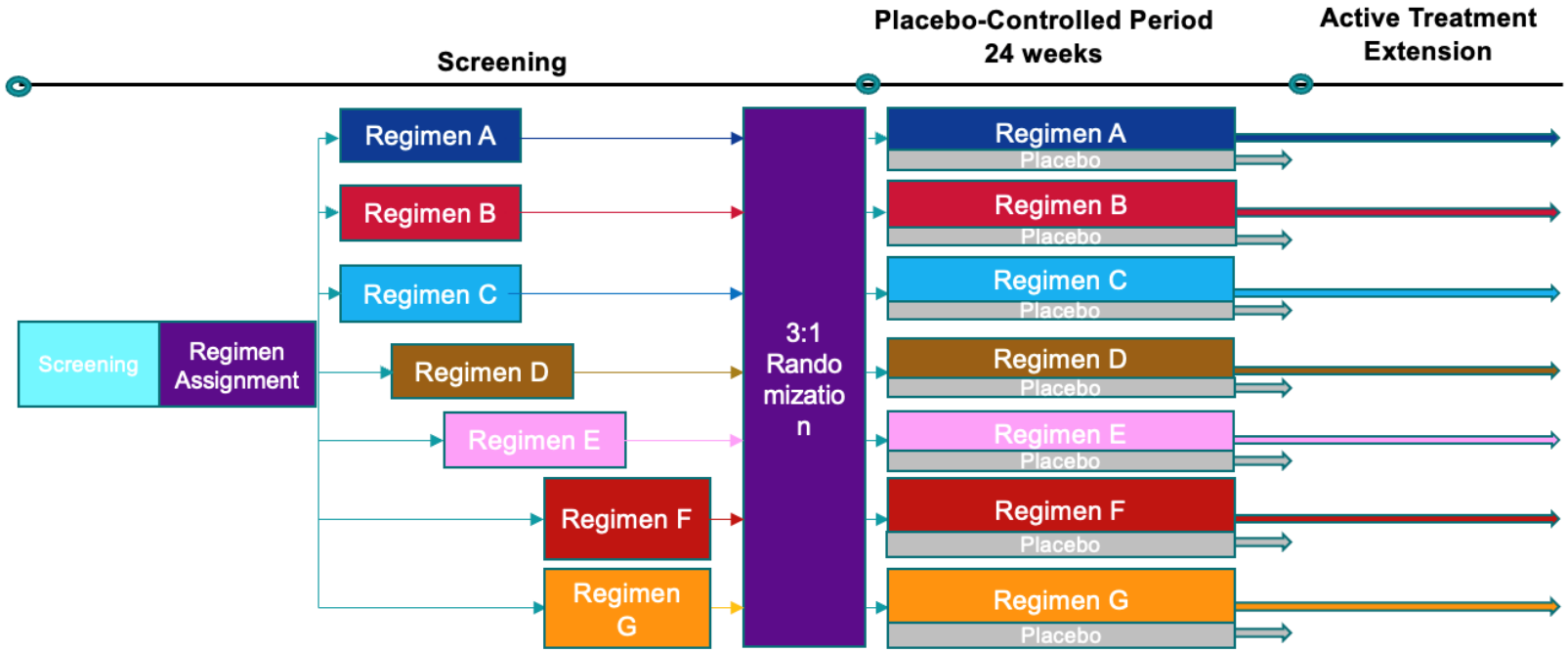
# The HEALEY ALS Platform Trial

- Perpetual, adaptive trial testing multiple drugs
- Enrolling at over 70 NEALS sites
- Shared infrastructure with improved efficiency by sharing of placebos
- Efficient startup and rapid enrollment
- Expert investigators, biostatisticians, and sites
- Each regimen designed to provide efficient go / no go decisions to inform the clinical development plan
- Each regimen includes active drug and matching placebo




Merit Cudkowicz
**Platform Trial PI**

Suma Babu and Sabrina Paganoni
**Regimen G lead investigators**

**Regimen G and Regimen F shared placebo data**

# DNL343 Regimen G

# THERAPEUTIC HYPOTHESIS FOR DNL343 IN ALS

**Cellular Stress**
*and / or*
**ALS Genetics**

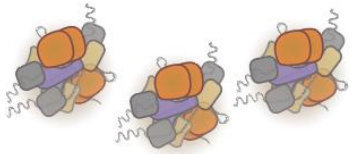
eIF2B OFF

**Integrated stress response (ISR) pathway active**

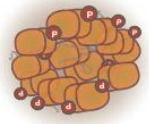
**Cells make fewer proteins**

## Disease Biology

**Stress Granules**

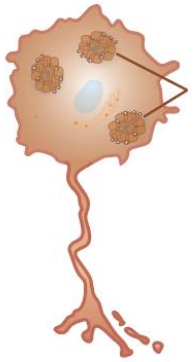


**Abnormal TDP43**



**ISR biomarkers (e.g., ATF4 and *CHAC1*)**

**Nerve Cell Death**



**Harmful TDP43**

**Cellular Stress**
*and / or*
**ALS Genetics**

**+ DNL343***

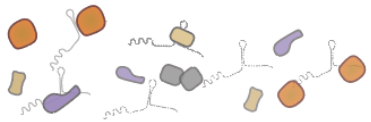
DNL343 eIF2B ON

**Integrated stress response (ISR) pathway inhibited**

**Cells make normal amounts of proteins**

## Disease Biology + DNL343

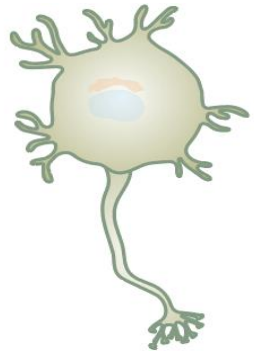
**Stress Granules Dissolve**



**Normal TDP43**

**ISR biomarkers (e.g., ATF4 and *CHAC1*)**

**Healthy Nerve Cell**

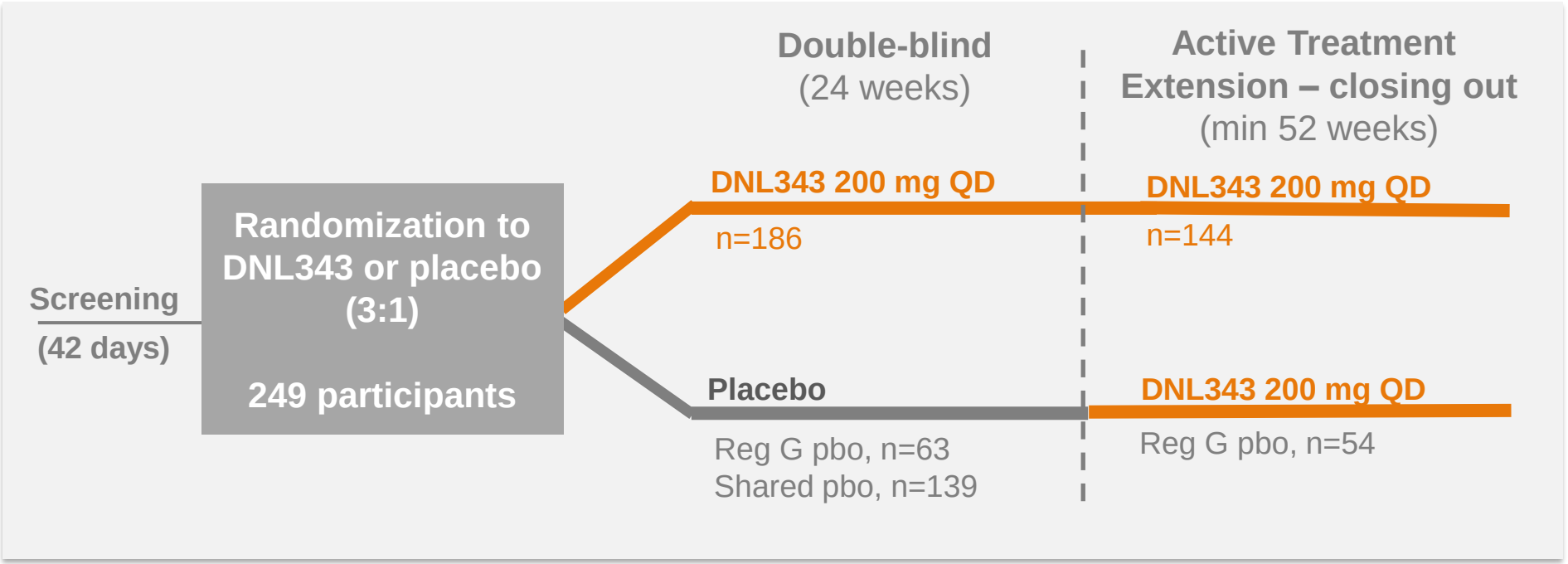


*DNL343 s an investigational drug and has not been approved by any Health Authority

# DNL343 STUDIES IN ALS PARTICIPANTS

| | Phase 1b Study<br>ALS Participants | Healey Platform Trial<br>Regimen G |
|---|---|---|
| *Population* | 29 Participants with ALS | 249 Participants with ALS |
| *Study Design* | Randomized (2:1, DNL343:placebo)<br>**28-day** double-blind treatment period<br>18-month OLE | Randomized (3:1, DNL343:placebo)<br>**24-week** double-blind treatment period<br>52-week active treatment extension |
| *Endpoints* | • Safety<br>• DNL343 levels (pharmacokinetics)<br>• Biomarkers of neurodegeneration (NfL)<br>• ISR pathway biomarkers (ATF-4, *Chac1*) | • Clinical efficacy<br>• Biomarkers of neurodegeneration (NfL)<br>• ISR pathway biomarker (GDF-15)<br>• Safety |
| | Clinicaltrials.gov: **NCT05006352** | Clinicaltrials.gov: **NCT05842941** |

# HEALEY REGIMEN G (DNL343) STUDY DESIGN




**Key Inclusion Criteria**

- ≤ 36 months from symptom onset
- SVC ≥50% predicted capacity
- If on SOC (Riluzole, Edaravone, Relyvrio) on stable dose

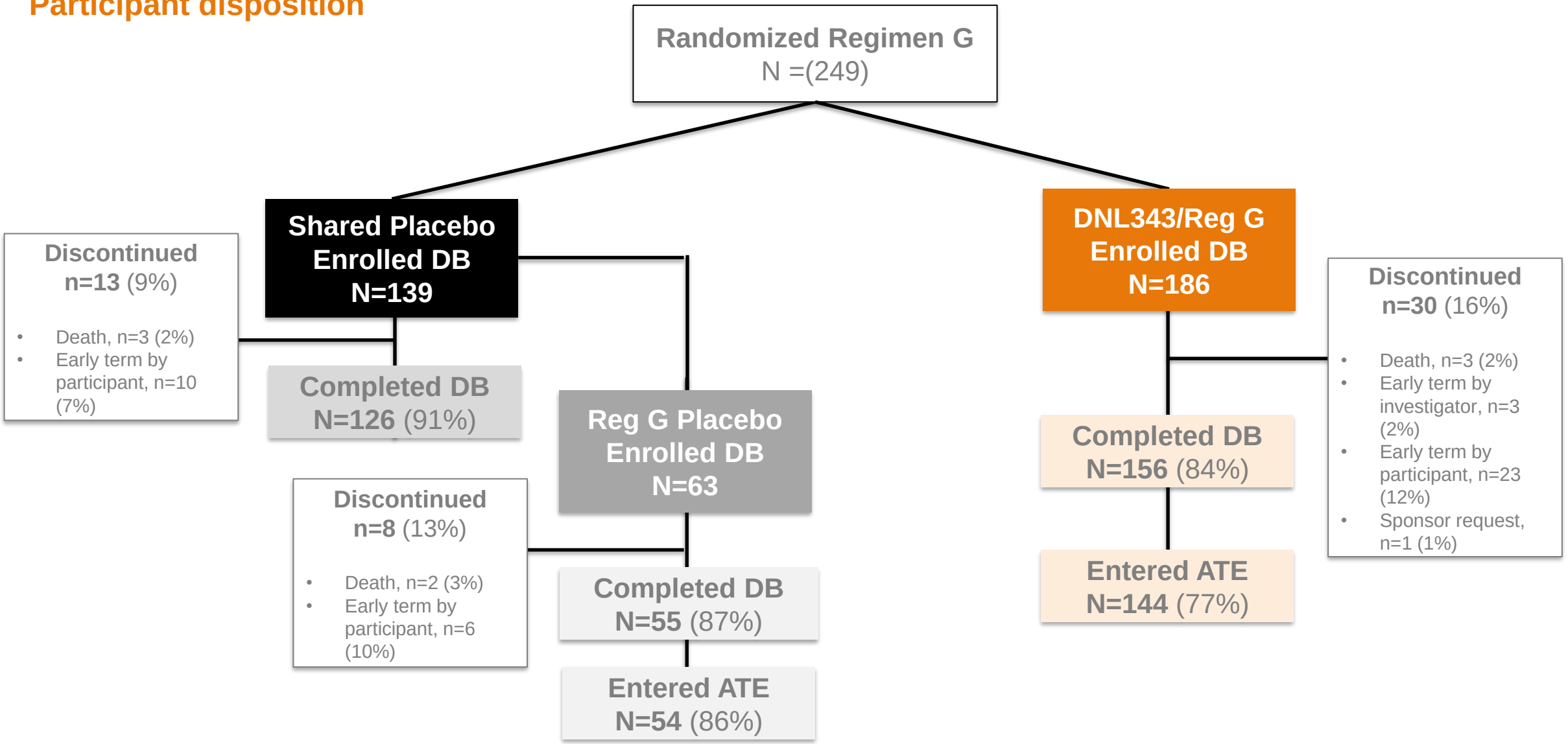
| Primary Endpoint | Secondary Endpoints (@24 weeks) | Exploratory Endpoints |
|---|---|---|
| Change from Baseline in disease severity measured by ALSFRS-R total score and survival (Bayesian approach) | Change from BL in:<br>▪ ALSFRS-R<br>▪ CAFS<br>▪ SVC % Predicted<br>▪ Serum NfL<br>▪ Muscle Strength (HHD)<br>▪ Survival (death/PAV) | Change from BL in:<br>• ISR pathway and disease biomarkers<br>• Plasma and optional CSF PK<br>• Patient-reported outcomes (ALSAQ-40, ROADS, PGI-C, PGI-S)<br>• CGI-C |

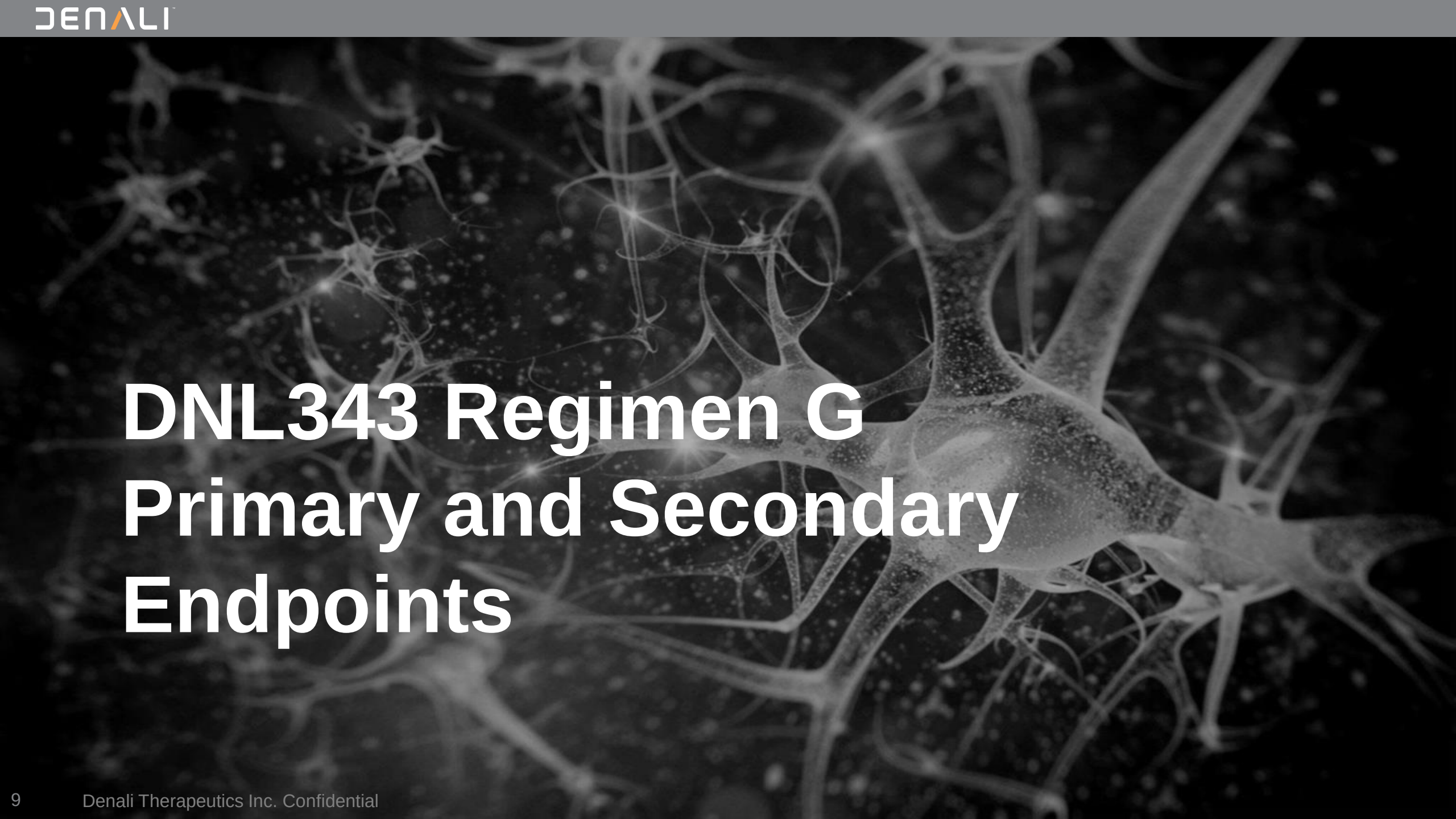
# DNL343/ REGIMEN G DEMOGRAPHICS AND BL CHARACTERISTICS

| Baseline Characteristics | | DNL343 200 mg QD (n=186) | Shared (Reg F+G) Placebo (n=139) | Regimen G Placebo (n=63) |
|---|---|---|---|---|
| **Age,** mean (SD) | | 59.5 ( 11.6) | 57.7 (11.5) | 57.3 ( 11.9) |
| **Sex**, n (%) | Male/Female | 104 (55.9%) **/ 82 ( 44.1%)** | 92 (66.2%) / 47 ( 33.8%) | 45 ( 71.4%) / 13 ( 20.6%) |
| **Race**<br>n (%) | Asian<br>Black<br>White | 5 ( 2.7%)<br>3 ( 1.6%)<br>175 ( 94.1%) | 6 ( 4.3%)<br>4 ( 2.9%)<br>126 (90.6%) | 1 ( 1.6%)<br>1 ( 1.6%)<br>61 ( 96.8%) |
| **Duration from onset (months)** mean (SD) | | 19.7 (8.1) | 20.3 (7.6) | 21.0 (7.9) |
| **Site of ALS Onset,** n (%) | Bulbar | **29 ( 15.6%)** | 17 (12.2%) | 6 ( 9.5%) |
| **ALSFRS-R score,** mean (SD) | | 36 (6.3) | 36.4 (6.3) | 36 (5.9) |
| **SVC % predicted,** mean (SD) | | 85.0 (18.9) | 84.4 (16.1) | 83.6 (15.1) |
| **Serum NfL: log-transformed,** mean (SD)<br>**pg/mL,** median (IQR) | | **4.08 (0.64)**<br>**62.5 (42.9, 90.1)** | 3.97 (0.65)<br>54.1 (35.5, 88.1) | 3.91 (0.62)<br>49 (33.4, 75.5) |
| **CSF NfL: log-transformed, n,** mean (SD)<br>**pg/mL,** median (IQR) | | 62, 8.5 (0.70)<br>5090 (3300, 6900) | 75, 8.4 (0.95)<br>5220 (3160, 8550) | 20, 8.6 (0.51)<br>5570 (4370, 7480) |
| **ALS medications**<br>n (%) | riluzole only<br>edaravone only<br>relyvrio only<br>All three medications | 161 (86.6)<br>115 (61.8)<br>102 (54.8)<br>74 ( 39.8%) | 119 (85.6)<br>86 (61.9)<br>81 (58.3)<br>58 ( 41.7%) | 54 (85.7)<br>40 (63.5)<br>35 (55.6)<br>25 ( 39.7%) |

# WELL-CONDUCTED STUDY WITH HIGH RATE OF RETENTION

## Participant disposition

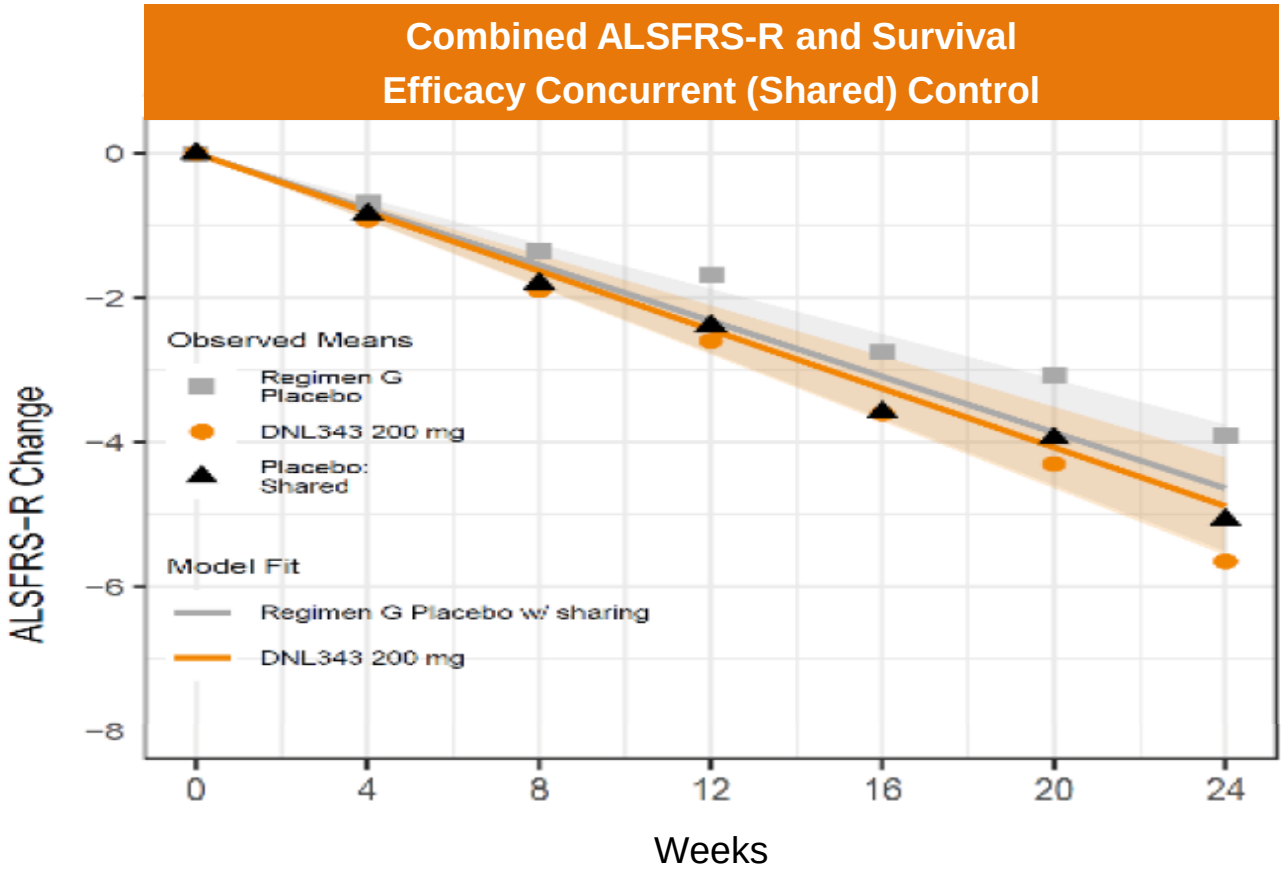




# DNL343 Regimen G Primary and Secondary Endpoints

# DNL343/REGIMEN G PRIMARY ENDPOINT:

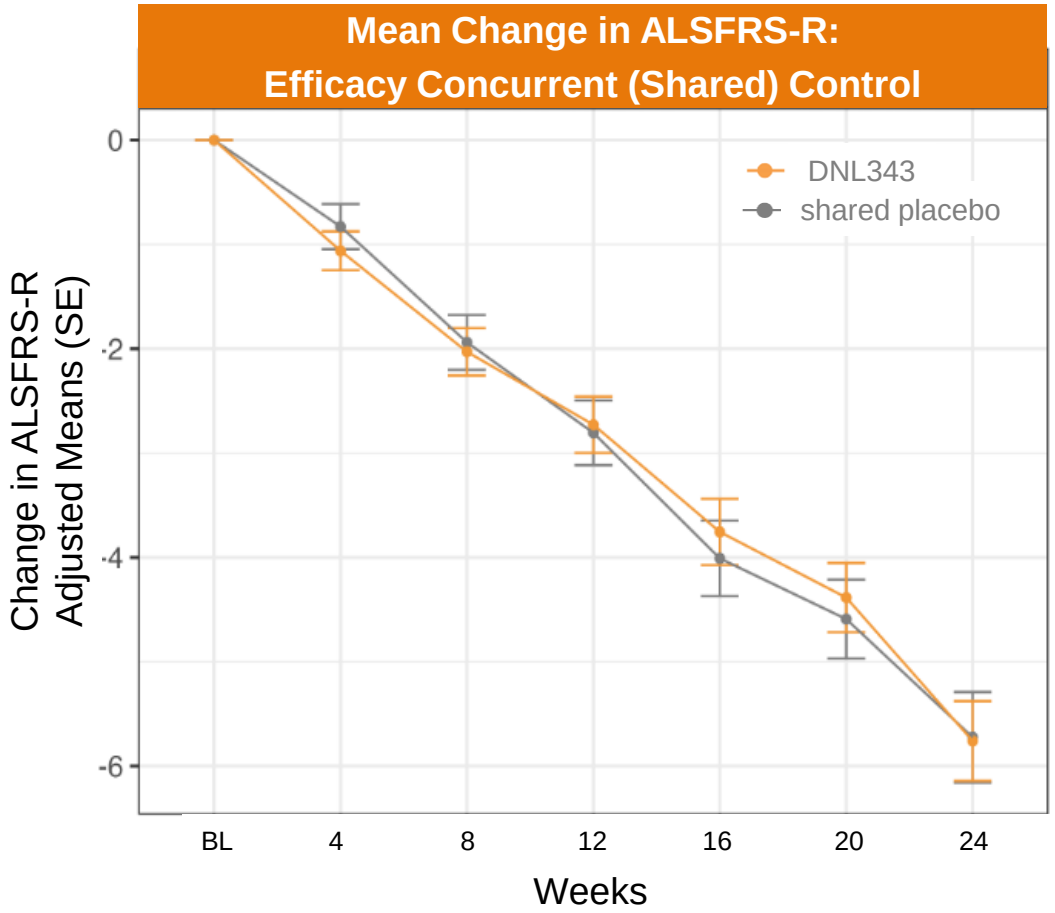
Change in ALSFRS-R and survival in 24-week double-blind period




**DNL343 showed no effect on progression measured by the ALSFRS-R Scale**

# DNL343/REGIMEN G SECONDARY ENDPOINTS:

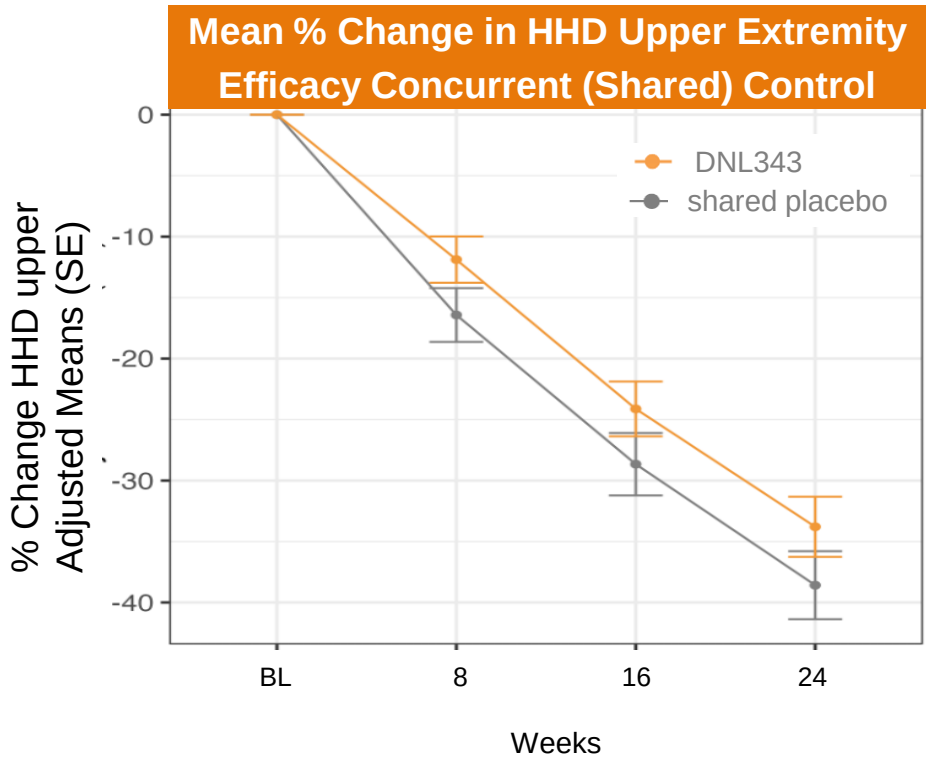
## Change in ALSFRS-R in 24-week double-blind period

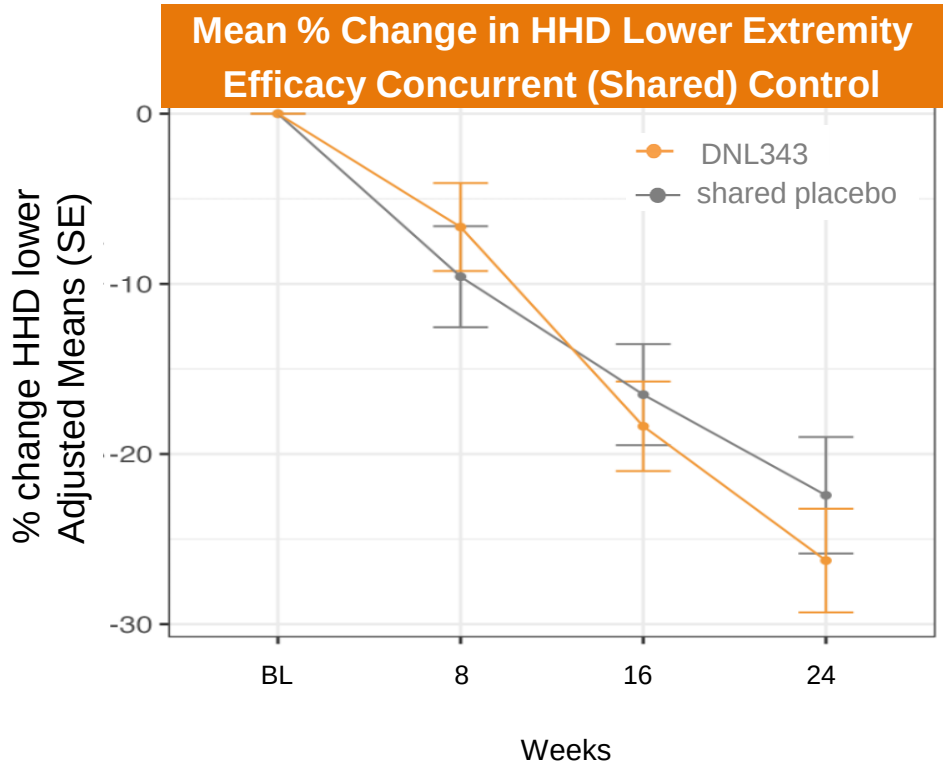



**Similar rate of progression on ALSFRS-R in DNL343 treated and shared placebos (~1 pt/month)**

# DNL343/REGIMEN G SECONDARY ENDPOINTS:

Mean % change in hand-held dynamometry (upper and lower) in 24-week double-blind period

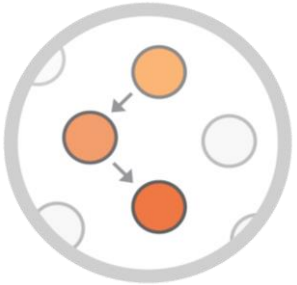



**Small percent greater worsening in shared placebo in upper HHD outcome compared to DNL343; not replicated for the lower extremity HHD composite outcome**

# Biomarkers

# DNL343 (REGIMEN G) BIOMARKER STRATEGY



**Pathway Engagement:**
Does DNL343 inhibit ISR?

- ISR biomarkers measured in CSF

**Disease Biomarkers:**
Does inhibiting the ISR alter ALS biomarkers?

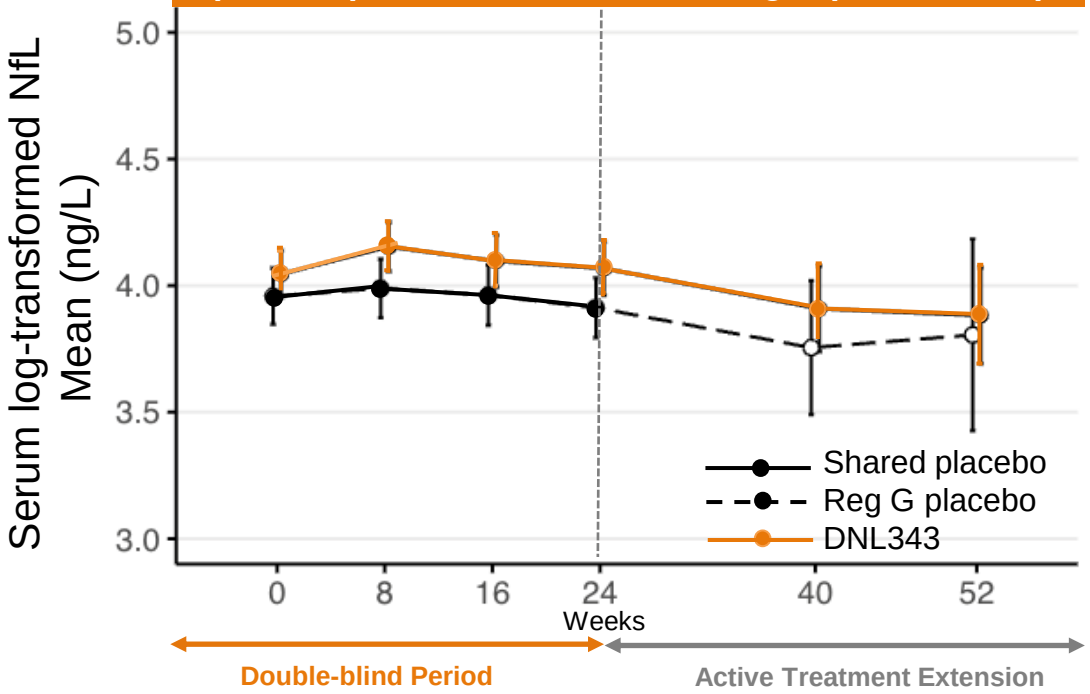
- NfL and other disease markers measured, in plasma and CSF
- Cryptic exon biomarkers of TDP-43 pathology (developed at DNLI)

**Biomarker strategy focused on NfL with other exploratory disease biomarkers included to understand correlation with clinical endpoints**

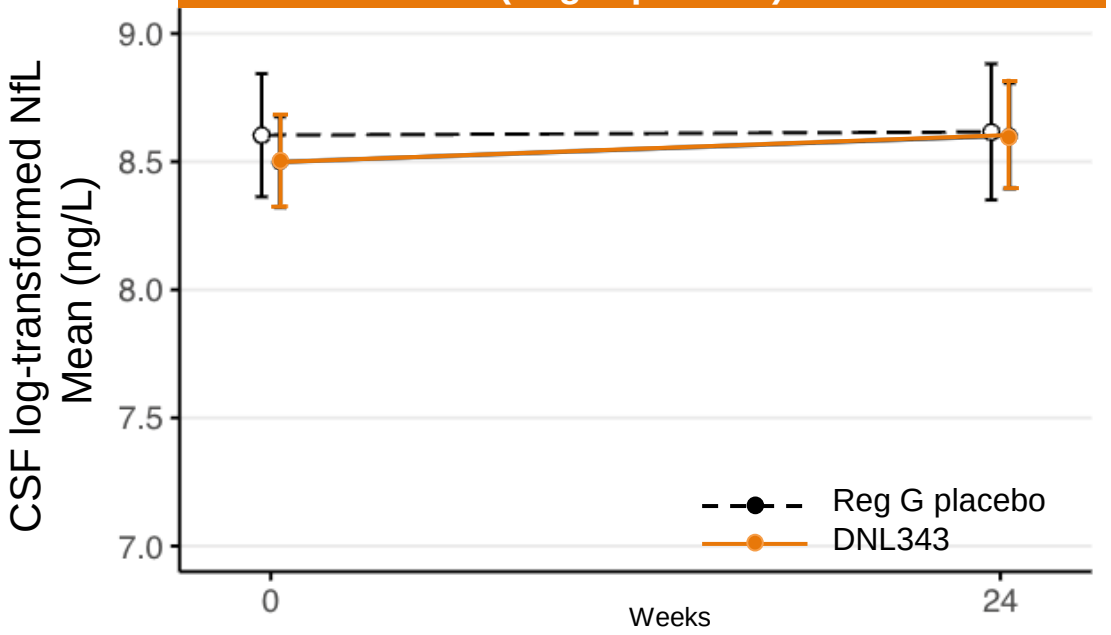
# DNL343/REGIMEN G SECONDARY ENDPOINTS:

- Serum Log-transformed NfL in 24-week double-blind period and ATE up to 52 weeks
- CSF Log-transformed NfL in up to 24 weeks

**Mean Log-transformed NfL (Serum)**
**(Shared placebo double-blind, Reg G placebo ATE)**




**Mean Log-transformed NfL (CSF)**
**(Reg G placebo)**




- **No reduction in serum or CSF NfL with DN343 treatment;**
- **~5% difference in serum log-transformed NfL at 24 weeks and ≤5% at 52 weeks**

Serum log-transformed NfL in the ERO population means, adjusted by baseline value in a repeated measures Model.

# DNL343/REGIMEN G SAFETY ENDPOINTS:

## Overview of safety and tolerability in 24-week double-blind period

| | DNL343 200 mg (N=186) | Shared Placebo (N=139) | Reg G Placebo (N=63) |
|---|---|---|---|
| Any TEAE | **173 (93%)** | 122 (88%) | 52 (83%) |
| Any Severe TEAE | 29 (16%) | 21 (15%) | 11 (18%) |
| Any Serious TEAE | 27 (15%) | 16 (12%) | 10 (16%) |
| Treatment-related Serious TEAE | **3 (1.6%)** | 0 | 0 |
| Any Fatal TEAE | 3 (1.6%) | 3 (2.2%) | 2 (3.2%) |
| Any TEAE Leading to Study Drug | | | |
| Withdrawal | **18 (10%)** | 8 (5.8%) | 5 (7.9%) |
| Interruption | **27 (15%)** | 16 (12%) | 8 (13%) |
| Reduction | **5 (2.7%)** | 1 (0.7%) | 1 (1.6%) |

Note: treatment-emergence was defined as occurring prior to or within 30 days of last treatment

- SAEs reported in 27 (15%) DNL343 treated participants
  - 3 SAEs related to DNL343 (Transaminase increase, ECG ST segment abnormal, Drug eruption), all non-fatal
- Most common TEAEs (>10% of participants) in RCT and more common in DNL343 treated vs PBO included:
  - Fall
    - DNL343 73 (39.2%), PBO 44 (31.7%)
  - Fatigue
    - DNL343 41 (22.0%), PBO 17 (12.2%)
  - Urinary tract infection
    - DNL343 20 (10.8%), PBO 4 (2.9%)
  - Increased transaminase level*
    - DNL343 19 (10.2%), PBO 2 (3.2%)
    - One withdrawal and 6 with dose interruptions, 4 successfully rechallenged

*includes multiple terms: Hypertransaminemia, Transaminitis, ALT increased, AST increased, Transaminase increased, Liver function test increased

# SUMMARY OF THE HEALEY PLATFORM REGIMEN G (DNL343)

- Primary and secondary endpoints of Regimen G were not met.
- The Healey Platform Trial for Regimen G was a well-conducted trial that provided decisional data.
- Given the lack of treatment effects observed, further investigations of DNL343 in ALS are not warranted.
- Data from DNL343/Regimen G will continue to be evaluated to better inform future trials in ALS.

# ACKNOWLEDGMENTS

**Thank you to all study participants and their families, investigators and site staff, and the Healey leadership for their generous contributions to the DNL343 clinical development program!**