Focused on developing treatments that make a meaningful difference for people and families living with ALS

DNL343 (Regimen G) Background Information

Danna Jennings, MD
Denali Therapeutics Inc.
Danna Jennings is an employee of Denali Therapeutics Inc.

DNL343 is an investigational drug and is not approved by any Health Authority, such as the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA)
FOCUSED ON DEFEATING NEURODEGENERATION

Mission

To defeat neurodegenerative diseases through rigorous therapeutic discovery and development

Focus

LYSOSOMAL STORAGE DISORDERS

PARKINSON’S

ALS/FTD

ALZHEIMER’S
COMMITTED TO SCIENTIFIC PRINCIPLES AND THE ALS COMMUNITY

Scientific Principles

GENETIC PATHWAY POTENTIAL

ENGINEERING BRAIN DELIVERY

BIOMARKER-DRIVEN DEVELOPMENT

Commitment

We listen to people and families living with ALS. We engage individuals, families, caregivers, and advocacy groups in our work as we strive to develop impactful solutions that address your needs.
## DENALI’S COMMITMENT TO ALS: TWO PROGRAMS IN CLINICAL DEVELOPMENT

<table>
<thead>
<tr>
<th>How it aims to work?</th>
<th>DNL343</th>
<th>SAR443820 (DNL788)</th>
</tr>
</thead>
<tbody>
<tr>
<td>eIF2B Activator</td>
<td></td>
<td>RIPK1 Inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(partnered program with Sanofi)</td>
</tr>
</tbody>
</table>

| What are we addressing? | TDP-43 pathology | Inflammatory pathway pathology and cell death |

| Clinical stage          | • Phase 1b is ongoing (ClinicalTrials.gov identifier: NCT0500635) |
|                        | • HEALEY ALS Platform Trial (Regimen G) **recruiting by invitation** (NCT05842941) |
|                        | • We will discuss DNL343 in detail today! |
|                        | • Now recruiting a Phase 2 Study **(HIMALAYA)** (NCT05237284) |
What is the mechanism of action of DNL343?
GENETIC PATHWAY POTENTIAL IN ALS

≥ 95% of individuals with ALS have harmful aggregates of a protein called TDP43 in their cells which accumulate during stress.

TDP43 can be found in structures called stress granules and many genes linked to ALS are a part of stress granule-related pathways.

In individuals with ALS, stress granule pathways may play an important role in driving the accumulation of harmful TDP43 and neuron death.

ALS-associated gene discovery over the past decade highlights the importance of stress granule biology and TDP43 in ALS.
**Therapeutic Hypothesis for DNL343 Impact on ALS**

**Cellular Stress and/or ALS Genetics**

- elf2B OFF
  - Integrated stress response (ISR) pathway active
  - Cells make fewer proteins

**Disease Biology**

- Stress Granules
- ISR biomarkers (e.g., ATF4 and CHAC1)
- Abnormal TDP43

**Nerve Cell Death**

- Harmful TDP43

---

**Cellular Stress and/or ALS Genetics + DNL343**

- elf2B ON
  - Integrated stress response (ISR) pathway inhibited
  - Cells make normal amounts of proteins

**Disease Biology + DNL343**

- Stress Granules Dissolve
- ISR biomarkers (e.g., ATF4 and CHAC1)
- Normal TDP43

**Healthy Nerve Cell**
What evidence do we have that DNL343 inhibits the stress response?
DNL343 DISSOLVES STRESS GRANULES AND TDP43 CLUSTERS IN CELLS

Stress

DNL343

20 min

90 min

Stress granules

Cytoplasmic TDP43

Overlap between stress granules and TDP43

H4 neuroglioma cells in culture

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Sun L, et al., AAN abstract P8.8.010, 2023
DNL343 PROTECTS CELL AGAINST DEGENERATION IN MOUSE MODEL

### Animal Model
- We first tested DNL343 in healthy wild-type mice with short term injury.
- When the optic nerve is pinched/crushed, cells in the retina activate the Integrated Stress Response which leads to cell death.

### ISR in the Retina

<table>
<thead>
<tr>
<th>Chac1 Gene Expression</th>
<th>mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>Crushed Retina</td>
</tr>
<tr>
<td>0</td>
<td>0.75</td>
</tr>
</tbody>
</table>

| 3 | 12 | 9 | 9 | 11 |

2 days after crush

### Cell Survival

<table>
<thead>
<tr>
<th>Surviving Cells (100 μm²)</th>
<th>mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>Crushed Retina</td>
</tr>
<tr>
<td>0</td>
<td>0.75</td>
</tr>
</tbody>
</table>

| 8 | 9 | 9 | 8 | 8 |

14 days after crush

DNL343 decreases integrated stress response in retina and reduces cell death in mice.

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1Larhammar et al. eLife 2017
DNL343 PROTECTS MOTOR FUNCTION IN MOUSE MODEL

- To test DNL343 in the context of chronic disease, we used mice that have low eIF2B function (eIF2B mutant).
- These mice have hyperactive Integrated Stress Response in the brain that causes neuron death & impaired motor function.

**DNL343 decreases integrated stress response in the brain and protects motor function in mice**

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Sun L, et al., AAN abstract P8.8.010, 2023
What is the experience with DNL343 in the clinic?
# DNL343 STUDIES IN HEALTHY AND ALS PARTICIPANTS

<table>
<thead>
<tr>
<th>Who Participated?</th>
<th>Phase 1 Healthy Participant Study</th>
<th>Phase 1b Study in ALS Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>95 Healthy Volunteers</td>
<td>Phase 1b healthy volunteer study: NCT04268784</td>
<td>27 Participants Living with ALS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What was Tested?</th>
<th>Phase 1 Healthy Participant Study</th>
<th>Phase 1b Study in ALS Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single and multiple oral daily dosing over 14-day treatment period</td>
<td>Oral daily dosing over a 28-day treatment period</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What was Measured?</th>
<th>Phase 1 Healthy Participant Study</th>
<th>Phase 1b Study in ALS Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td>Safety</td>
<td>Safety</td>
</tr>
<tr>
<td>DNL343 levels (pharmacokinetics)</td>
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</tr>
<tr>
<td>Biomarkers of ISR pathway</td>
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</tr>
</tbody>
</table>

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WHO PARTICIPATED IN OUR PHASE 1B TRIAL IN PARTICIPANTS WITH ALS?

**Participant Demographics**

- **Sex Distribution**
  - 83% male
  - 17% female

- **Age Distribution**
  - Min Age: 36 years
  - Median Age: 57 years
  - Max Age: 76 years

**Age, sex, and race comparable across all dosing groups**

**Baseline Disease State**

- **El Escorial Diagnostic Criteria**
  - Definite: 24%
  - Probable: 59%
  - Probable LS: 17%

- **Duration from Symptom Onset**
  - Minimum: 4 months
  - Median Duration: 22 months
  - Maximum: 41 months

**Higher percentage of Definite ALS in low dose DNL343 group**

**Shorter duration from onset in DNL343 low dose group**

Sun L, et al., AAN abstract P8.8.010, 2023
DNL343 CONCENTRATIONS IN PLASMA AND CEREBROSPINAL FLUID (CSF)

- DNL343 concentration increased in a dose-dependent manner
- Long half-life supports oral once daily dosing
- Extensive distribution in the CSF in both healthy and ALS participants as demonstrated by CSF to unbound plasma ratio ~1

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Sun L, et al., AAN abstract P8.8.010, 2023
DNL343 inhibited ISR pathway activation in human blood cells

- DNL343 showed robust inhibition (>60%) of two ISR pathway biomarkers (ATF4 protein and CHAC1 mRNA) in blood cells from Ph1 and Ph1b trial participants.

- Similar level of inhibition observed in healthy and ALS participants.

Sun L, et al., AAN abstract P8.8.010, 2023
DNL343 TOLERABILITY IN HEALTHY PARTICIPANTS*

<table>
<thead>
<tr>
<th>Condition</th>
<th>DNL343</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>56%</td>
<td>54%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>Dizziness postural</td>
<td>18%</td>
<td>15%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3%</td>
<td>15%</td>
</tr>
<tr>
<td>Blood CPK increased</td>
<td>3%</td>
<td>15%</td>
</tr>
</tbody>
</table>

- Generally well tolerated
- No serious adverse events
- Majority of adverse events were mild
- Two discontinuations:
  - Personal circumstances (PBO)
  - Anxiety (on DNL343, not related to study drug)

* Includes all non-procedure related AEs; in ≥2 participants

Phase 1b healthy volunteer study: NCT04268784
DNL343 TOLERABILITY IN PARTICIPANTS WITH ALS (DOUBLE-BLIND)*

- Generally well tolerated
- No serious adverse events
- All treatment-emergent AEs were Grade 1 or 2
- One discontinuation due to rash

* Includes all non-procedure related AEs; in ≥2 participants

Phase 1b ALS diagnosis study: NCT05006352
DNL343 KEY TAKEAWAYS FROM HEALTHY AND ALS PARTICIPANT STUDIES

- **Once daily oral dosing** is supported by pharmacokinetic profile

- Extensive distribution to the Cerebrospinal Fluid (CSF)

- Inhibition of the integrated stress response demonstrated by biomarker data

- **Generally well tolerated** and no clinically meaningful trends in safety labs, electrocardiogram (ECGs), or vital signs during double-blind period

- Data from early phase studies support further development of DNL343
- DNL343 is Regimen G in the HEALEY Platform Phase 2/3 Study
- Enrollment in Regimen G is ongoing
REGIMEN G SPECIFIC STUDY SCHEMATIC

Randomization to DNL343 or placebo (3:1)
240 participants

Double-blind (24 weeks)

DNL343

Active Treatment Extension (52 – 78 weeks)

Denali is committed to a 52-week minimum Active Treatment Extension (ATE)

Screening (42 days)

In clinic visits
5 visits

Remote visits
3 visits

6 to 9 visits

Every 13 weeks until 102 weeks

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HEALEY REGIMEN G STUDY GOALS

**Efficacy**
To evaluate the effect of DNL343 as compared to placebo on ALS progression

**Safety**
To evaluate the safety of DNL343 in participants with ALS

**Biomarker Changes**
To evaluate the effect of DNL343 on select biomarkers
## CSF COLLECTION AND BIOMARKERS FOR REGIMEN G

### What is CSF?

- A clear, colorless, watery fluid that flows in and around the brain and spinal cord
- In adults, the CSF volume is ~120 mL
- The normal rate of CSF production is approximately 20 mL per hour

### Volume and timepoints

- **Timepoints for CSF collection:**
  - Baseline
  - Week 24 (double blind)
- **Volume:** 20mL
- **CSF is an important biofluid**
  - Most closely associated with the nervous system as the best surrogate accessible in clinical setting
- **Biomarker changes in CSF would most closely reflect the changes in brain and spinal cord**

### What biomarkers will we measure?

- **Biomarkers to assess impact on the ISR pathway**
  - Levels measured at Baseline and following DNL343 treatment to determine how DNL343 modulates the stress response
- **Biomarkers to assess impact on neurodegeneration, including:**
  - NfL (neuronal injury and degeneration biomarker),
  - GFAP (astrogliosis biomarker),
  - UCHL1 (neuron injury biomarkers)
THANK YOU

The individuals and families participating in our current and future clinical studies

Investigators and study teams collaborating on the DNL343 clinical studies

Center for Human Drug Research, Leiden, NL
  Geert Jan Groeneveld, MD
  Maurits Vissers, PharmD
  Jules A.A.C. Heuberger, PhD

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  Tommy Bunte, PA
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  Steve Hopkins, CRM

Hospital for Special Care, New Britain, CT
  Kevin Felice, MD
  Honora Dalamagas
  Zanib Iqbal

Honor Health, Scottsdale, AZ
  Todd Levine, MD, PhD

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<table>
<thead>
<tr>
<th><strong>Established Team</strong></th>
<th><strong>Science-Focused</strong></th>
<th><strong>Growing Presence</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Now &gt;450 strong</td>
<td>• 2/3 of our team works in R&amp;D</td>
<td>• California based with a global presence</td>
</tr>
<tr>
<td>• Continually growing</td>
<td></td>
<td>• 7 programs in clinical trials</td>
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</tbody>
</table>
THANK YOU