Thank you for joining the webinar!
We are admitting audience members from the waiting room.
Please allow a few moments for the webinar to begin.
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.
DISCLOSURES

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).
### Scientific Principles

**GENETIC PATHWAY POTENTIAL**

Our programs are aimed at addressing genetically-defined pathways.

**ENGINEERING BRAIN DELIVERY**

Denali utilizes technologies to designed to facilitate our drugs effectively passing through the blood brain barrier.

**BIOMARKER-DRIVEN DEVELOPMENT**

Biomarkers are employed to monitor drug effects and inform dose and participant selection.
THERAPEUTIC HYPOTHESIS FOR DNL343 IMPACT ON ALS

Cellular Stress and/or ALS Genetics

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

Stress Granules
ISR biomarkers (e.g., ATF4 and CHAC1)
Abnormal TDP43
Nerve Cell Death
Harmful TDP43

Disease Biology

DNL343

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

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

Disease Biology + DNL343
**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>2 days after crush</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/kg</td>
<td>Healthy</td>
</tr>
<tr>
<td></td>
<td>Crushed Retina</td>
</tr>
<tr>
<td>0</td>
<td>3, 12, 9, 9, 11</td>
</tr>
<tr>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

**Cell Survival**

<table>
<thead>
<tr>
<th>Surviving Cells (100 μm²)</th>
<th>14 days after crush</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/kg</td>
<td>Healthy</td>
</tr>
<tr>
<td></td>
<td>Crushed Retina</td>
</tr>
<tr>
<td>0</td>
<td>8, 9, 9, 8, 8</td>
</tr>
<tr>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

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

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¹Larhammar et al. *eLife* 2017
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.
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></td>
<td>95 Healthy Volunteers</td>
<td>27 Participants Living with ALS</td>
</tr>
</tbody>
</table>

| What was Tested? | Single and multiple oral daily dosing over 14-day treatment period | Oral daily dosing over a 28-day treatment period |

<table>
<thead>
<tr>
<th>What was Measured?</th>
<th>安全性</th>
<th>DNL343 levels (pharmacokinetics)</th>
<th>Biomarkers of ISR pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Safety</td>
<td>DNL343 levels (pharmacokinetics)</td>
<td>Biomarkers of ISR pathway</td>
</tr>
</tbody>
</table>

Phase 1b healthy volunteer study: NCT04268784
Phase 1b ALS diagnosis study: NCT05006352
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
DNL343 SAFETY AND TOLERABILITY*

Healthy Participants

- Generally well tolerated
- No serious adverse events
- Majority of adverse events were mild
- 2 discontinuations (personal circumstance, anxiety considered not r/t study drug)

<table>
<thead>
<tr>
<th></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>27%</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>6%</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>6%</td>
<td>3%</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>

Percent of Participants

Participants with ALS (DB period)

- Generally well tolerated
- No serious adverse events
- Majority of adverse events were mild
- One discontinuation due to rash

<table>
<thead>
<tr>
<th></th>
<th>DNL343</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>37%</td>
<td>22%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32%</td>
<td>22%</td>
</tr>
<tr>
<td>Hypogeusia</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>Presyncope</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>Nausea</td>
<td>11%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Percent of Participants

* Includes all non-procedure related AEs; in ≥2 participants
DNL343 INHIBITED ISR PATHWAY ACTIVATION IN HUMAN BLOOD CELLS

- DNL343 showed robust inhibition including >60% reduction of ATF4 protein and CHAC1 mRNA in blood cells from Ph1 and Ph1b trial participants.

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

\[\text{ATF4 Protein} \quad \text{CHAC1 mRNA}\]

\[\begin{array}{c|c|c}
\text{Placebo} & \text{Low Dose} & \text{High Dose} \\
\hline
\text{Healthy Participants} & & \\
\text{Participants with ALS} & & \\
\end{array}\]

\[\begin{array}{c|c|c}
\text{Placebo} & \text{Low Dose} & \text{High Dose} \\
\hline
\text{Healthy Participants} & & \\
\text{Participants with ALS} & & \\
\end{array}\]

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Sun L, et al., AAN abstract P8.8.010, 2023
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
Randomization to DNL343 or placebo (3:1)
240 participants

Double-blind (24 weeks)
DNL343
Placebo

Active Treatment Extension (52 – 78 weeks)
Denali is committed to a 52-week minimum Active Treatment Extension (ATE)

In clinic visits
5 visits
6 to 9 visits
Every 13 weeks until 102 weeks

Remote visits
3 visits
4 visits
DNL343 (REGIMEN G) BIOMARKER STRATEGY

Pathway Engagement:
Does DNL343 inhibit ISR

- Measure ISR biomarkers in CSF

Disease Biomarkers:
Does inhibiting the ISR alter ALS biomarkers?

- NfL and other disease markers, in plasma and CSF
- TDP-43 pathology biomarkers (assays being developed across the research community)

Patient Selection Biomarkers:
Can we identify subsets of participants that respond DNL343?

- ISR pathway biomarkers
- Disease biomarkers
What is CSF?
• Evaluating biomarkers in the cerebrospinal fluid (CSF) is important for verifying that DNL343 is truly impacting the ALS disease mechanism in the central nervous system

• We will be collecting a small amount of CSF (~20 mL) at the baseline and 24-week visits and people make this amount of CSF in about an hour

Why collect CSF for Regimen G?
• To determine how DNL343 impacts the stress response in the central nervous system using ISR pathway biomarkers
• To evaluate the effect of DNL343 on Disease biomarkers (e.g., NfL, GFAP, and TDP-43)
• To Identify subsets of patients that may respond to DNL343 using ISR and disease biomarkers
THANK YOU FROM THE DENALI THERAPEUTICS TEAM

Established Team
- Now >450 strong
- Continually growing

Science-Focused
- 2/3 of our team works in R&D

Growing Presence
- California based with a global presence
- Multiple programs in clinical trials
THANK YOU