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.

HEALEY ALS Platform Trial

Regimen G Science Q&A Webinar– November 16, 2023

Massachusetts General Hospital
Founding Member, Mass General Brigham

HARVARD MEDICAL SCHOOL

Healey & AMG Center

Sean M. Healey & AMG Center for ALS
at Massachusetts General Hospital

NEALS Northeast Amyotrophic Lateral Sclerosis Consortium

NCRI NEUROLOGICAL CLINICAL RESEARCH INSTITUTE

BARROW Neurological Institute

Berry Consultants
Statistical Innovation

1850 MELIORA

ucb

biohaven pharmaceuticals

CLene NANOMEDICINE

prilenia

SEELOS THERAPEUTICS

Calico

DENALI THERAPEUTICS

TACKLE ALS "DON'T BE SORRY LETS BEAT THIS"

ALS ASSOCIATION

MDA Muscular Dystrophy Association

SALSA For a Cure

alsFINDINGaCURE

IAM ALS

TAMBOURINE

ALS ONE

RUN2REVIVE MIND · BODY · POTENTIAL

THE ARTHUR M. BLANK FAMILY FOUNDATION

BASEBALL WINTER MEETINGS SAN DIEGO 2019

AMG The AMG Foundation

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

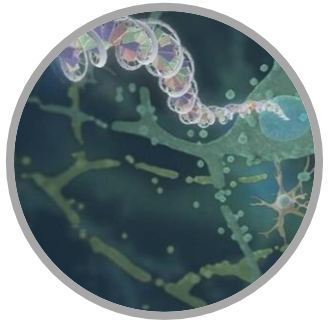
Danna Jennings is an employee of Denali Therapeutics Inc.

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)

DENALI IS COMMITTED TO SCIENTIFIC PRINCIPLES

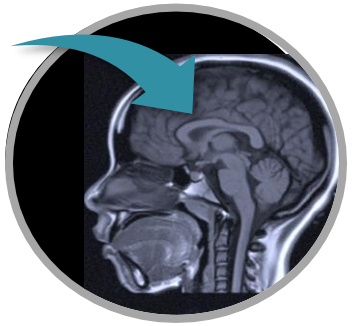
Scientific Principles

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

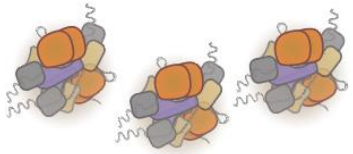
eIF2B OFF

Integrated stress response (ISR) pathway active

Cells make fewer proteins

Disease Biology

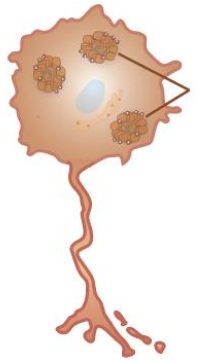
Stress Granules



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

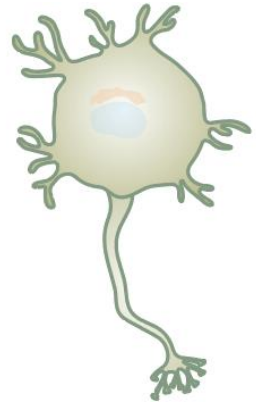
Disease Biology + DNL343

Stress Granules Dissolve

Normal TDP43

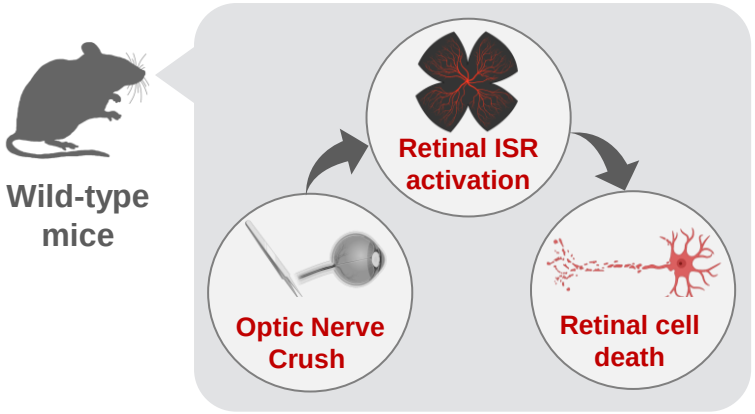
ISR biomarkers (e.g., ATF4 and *CHAC1*)

Healthy Nerve Cell



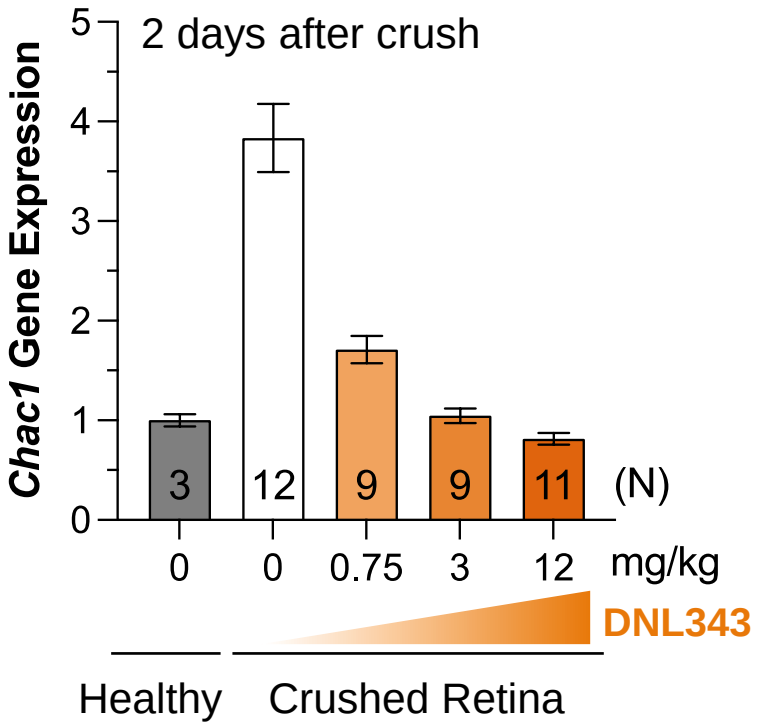
DNL343 PROTECTS CELL AGAINST DEGENERATION IN MOUSE MODEL

Animal Model

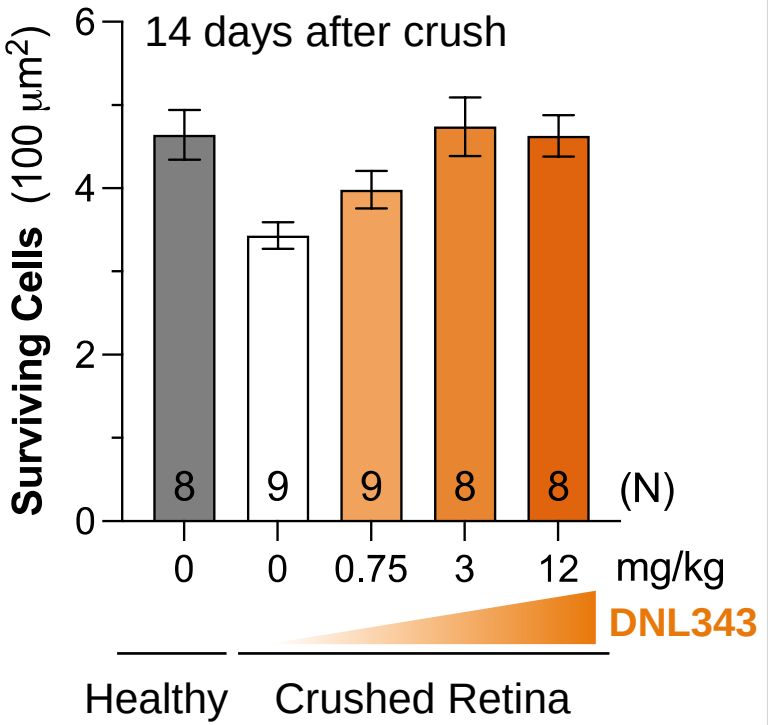


- We first tested DNL343 in healthy wild-type mice with short term injury
- When the optic nerve is pinched/ crushed, cells in the retina activate the **I**ntegrated **S**tress **R**esponse which leads to cell death[1]

ISR in the Retina



Cell Survival

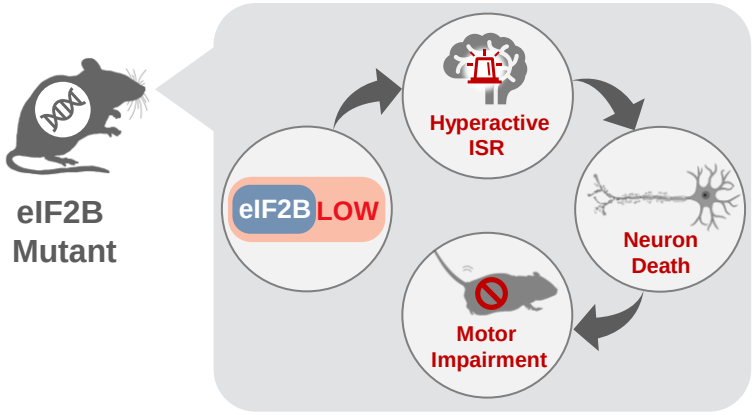


DNL343 decreases integrated stress response in retina and reduces cell death in mice

[1]Larhammar et al. *eLife* 2017

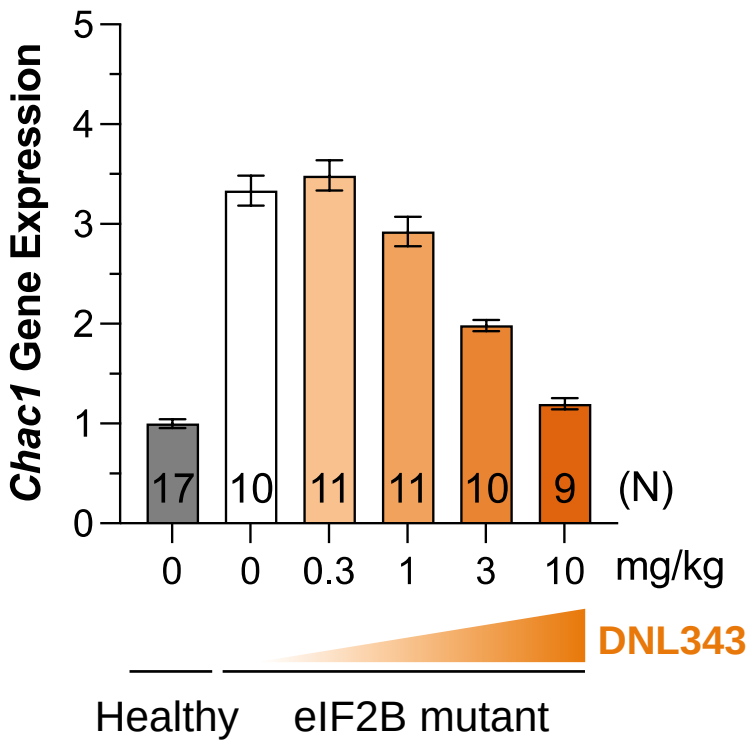
DNL343 PROTECTS MOTOR FUNCTION IN MOUSE MODEL

Animal Model

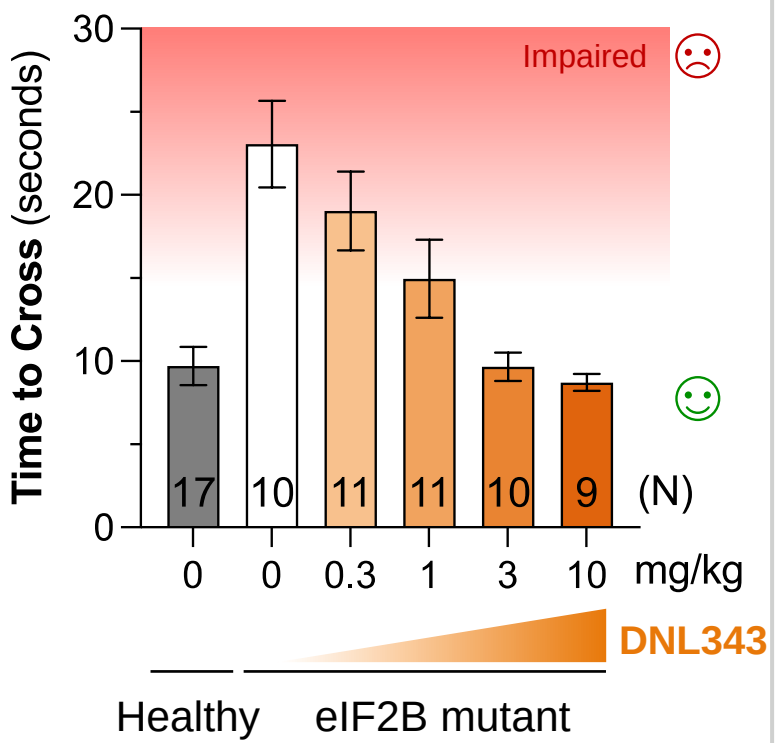


- To test DNL343 in the context of chronic disease, we used mice that have low eIF2B function (eIF2B mutant)
- These mice have hyperactive Integrated Stress Response in the brain that causes neuron death & impaired motor function

ISR in the Brain



Motor Function



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

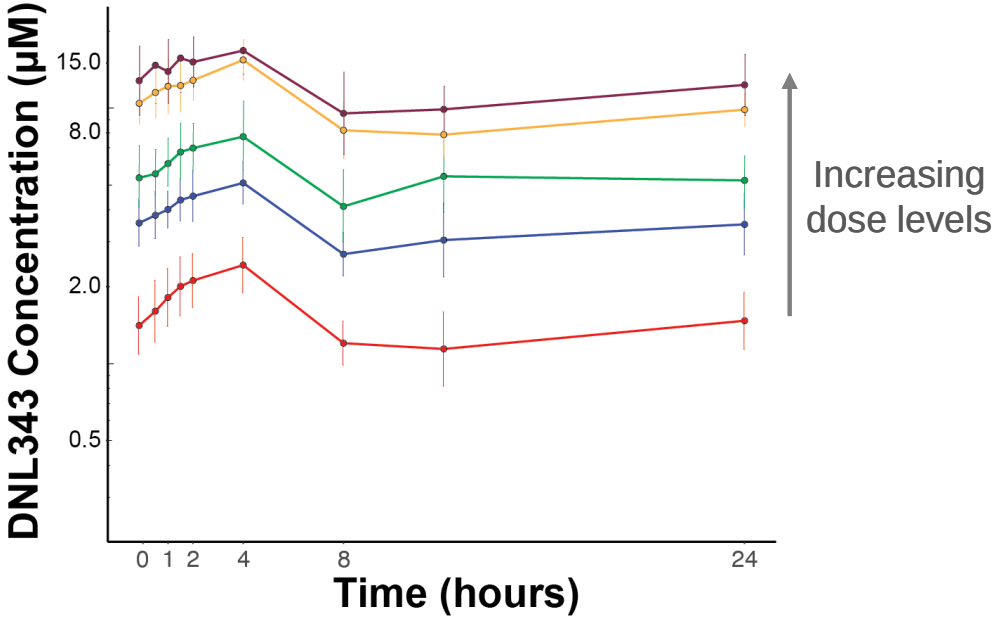
Sun L, et al., AAN abstract P8.8.010, 2023

DNL343 STUDIES IN HEALTHY AND ALS PARTICIPANTS

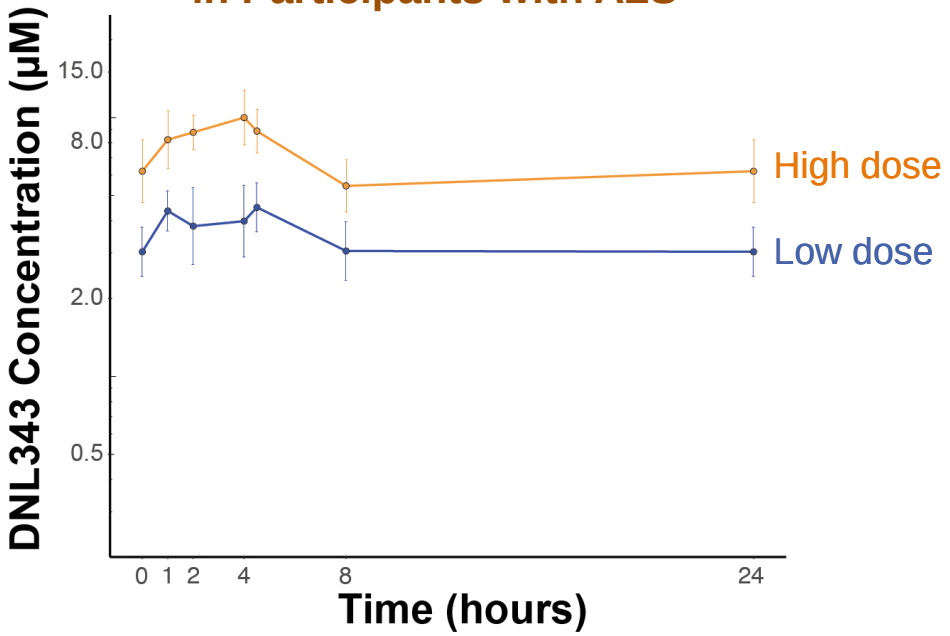
	Phase 1 Healthy Participant Study	Phase 1b Study in ALS Participants
	Phase 1b healthy volunteer study: NCT04268784	Phase 1b ALS diagnosis study: NCT05006352
Who Participated?	95 Healthy Volunteers	27 Participants Living with ALS
What was Tested?	Single and multiple oral daily dosing over 14-day treatment period	Oral daily dosing over a 28-day treatment period
What was Measured?	• Safety • DNL343 levels (pharmacokinetics) • Biomarkers of ISR pathway	• Safety • DNL343 levels (pharmacokinetics) • Biomarkers of ISR pathway

DNL343 CONCENTRATIONS IN PLASMA AND CEREBROSPINAL FLUID (CSF)

DNL343 Plasma Concentration in Healthy Participants



DNL343 Plasma Concentration in Participants with ALS



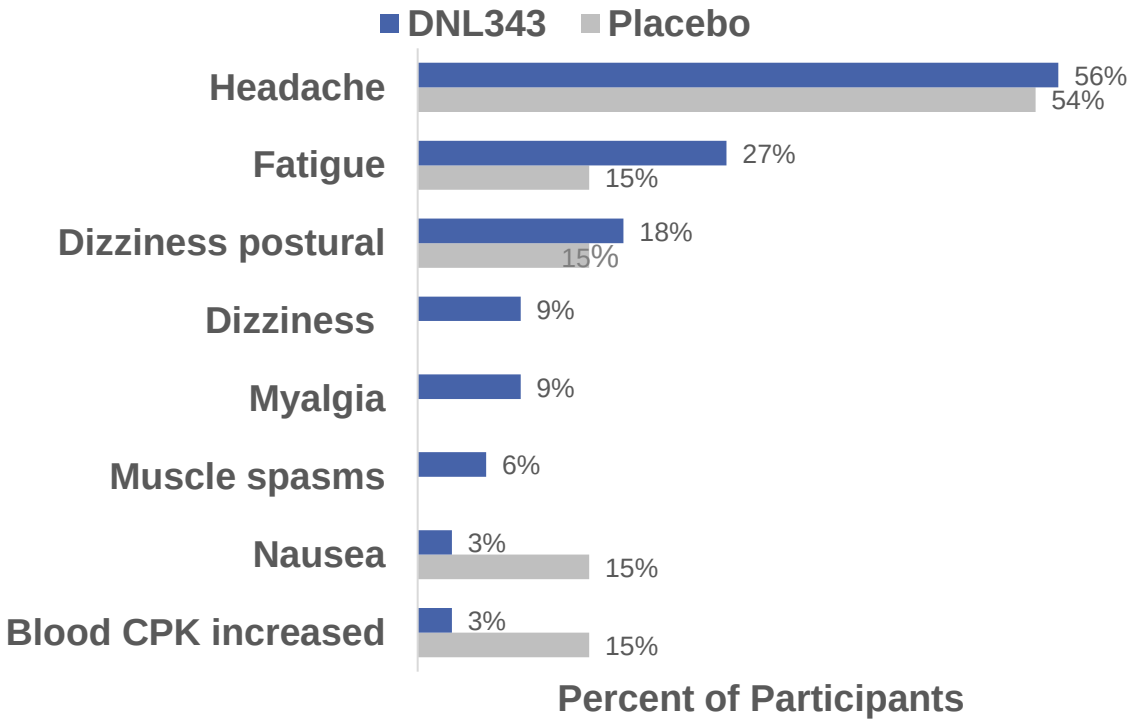
- DNL343 concentration increased in a dose-dependent manner
- Long half-life supports oral once daily dosing
- Extensive distribution in the CSF in both healthy and ALS participants as demonstrated by CSF to unbound plasma ratio ~1

Sun L, et al., AAN abstract P8.8.010, 2023

DNL343 SAFETY AND TOLERABILITY*

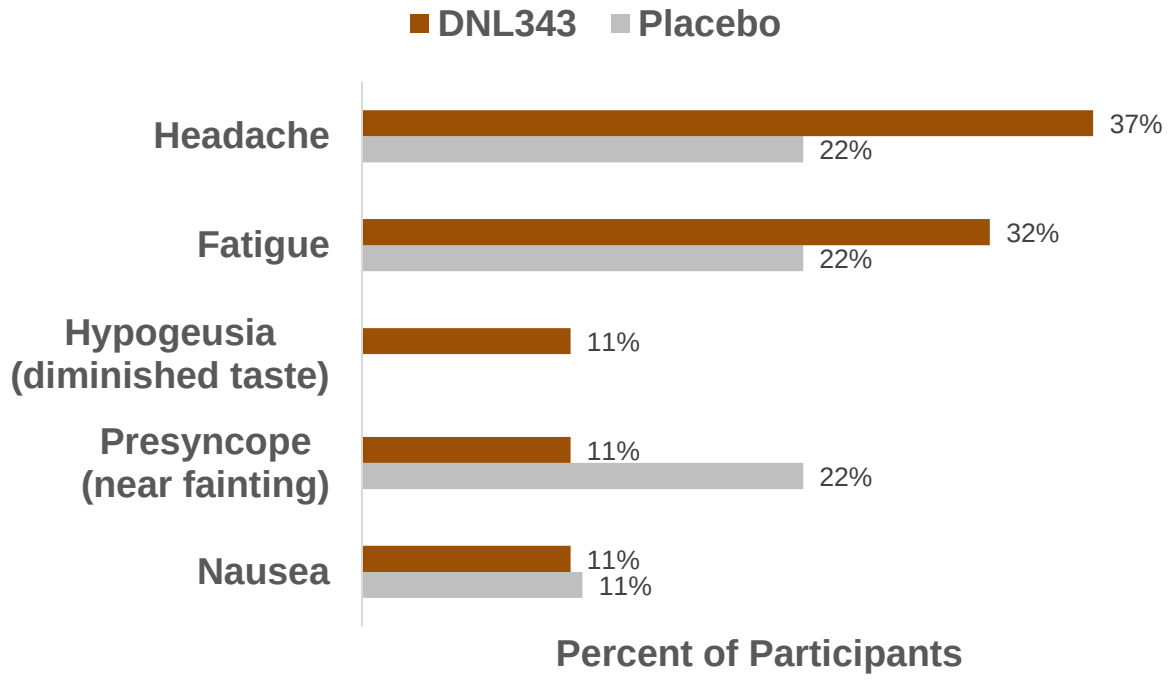
Healthy Participants

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



Participants with ALS (DB period)

- 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

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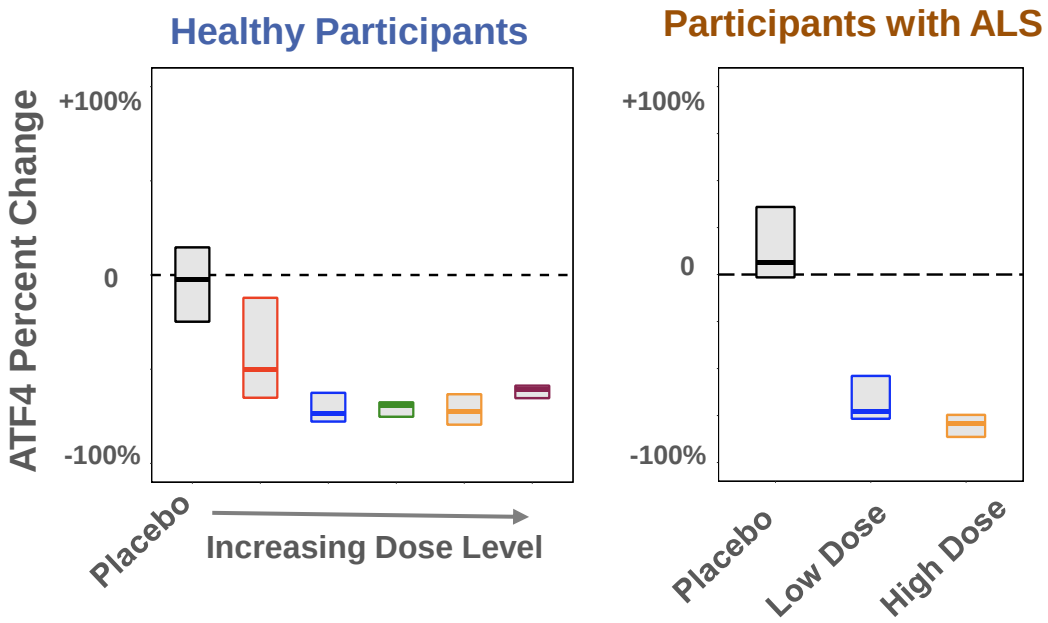
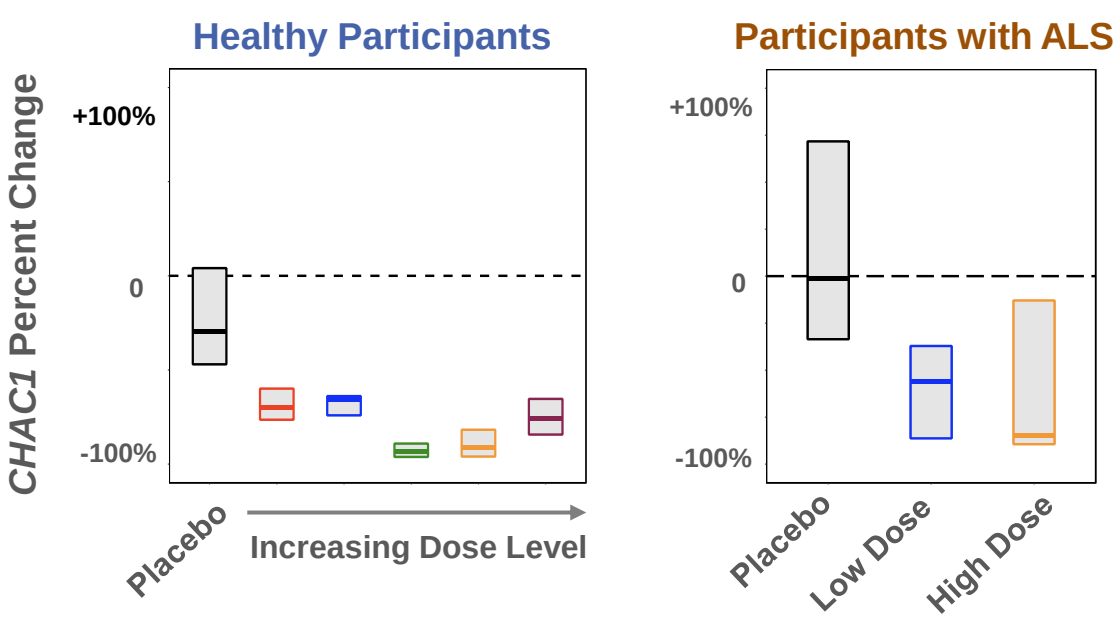
DNL343 INHIBITED ISR PATHWAY ACTIVATION IN HUMAN BLOOD CELLS

ATF4 Protein



CHAC1 mRNA



- 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

Sun L, et al., AAN abstract P8.8.010, 2023

DNL343 KEY TAKEAWAYS FROM HEALTHY AND ALS PARTICIPANT STUDIES

Once daily oral dosing is supported by pharmacokinetic profile

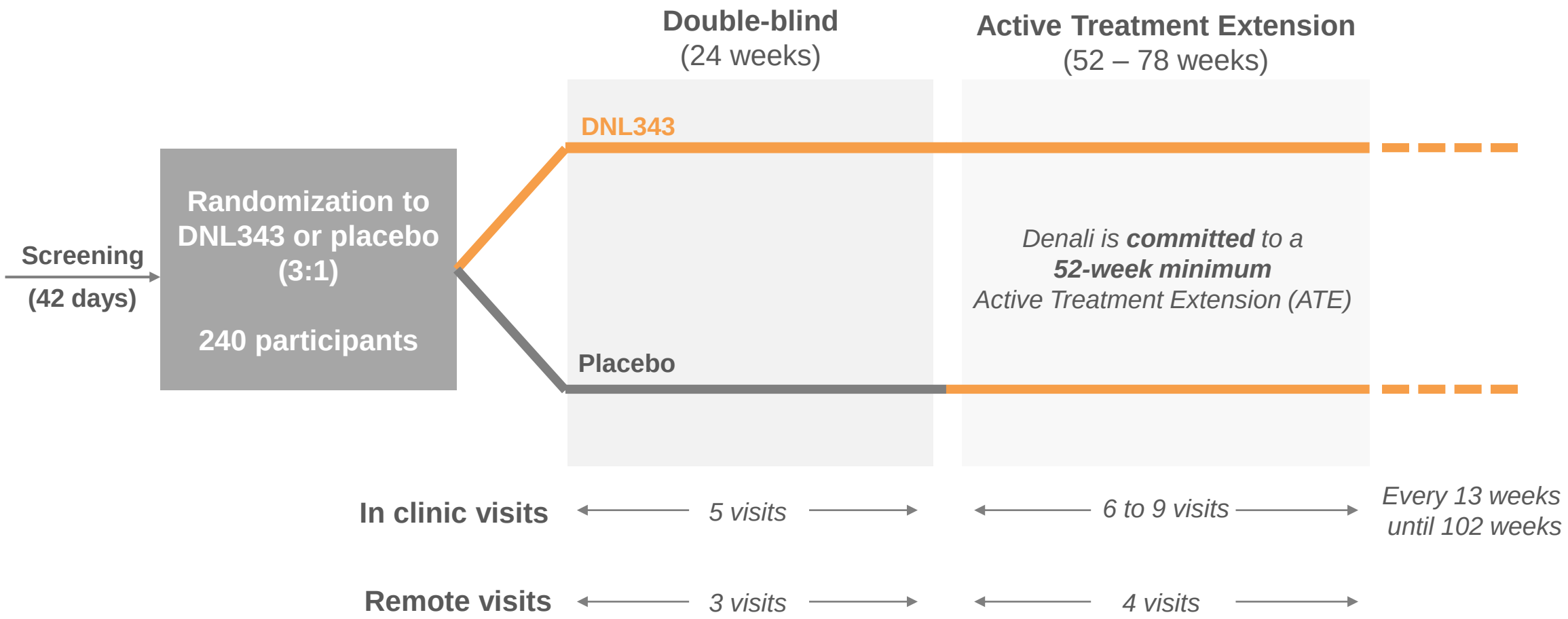
Extensive distribution to the Cerebrospinal Fluid (CSF)

Inhibition of the integrated stress response demonstrated by biomarker data

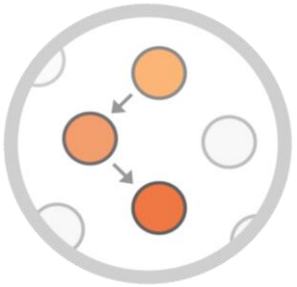
Generally well tolerated and no clinically meaningful trends in safety labs, electrocardiogram (ECGs), or vital signs during double-blind period

- **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



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**

CSF BIOMARKERS FOR DNL343 (REGIMEN G)

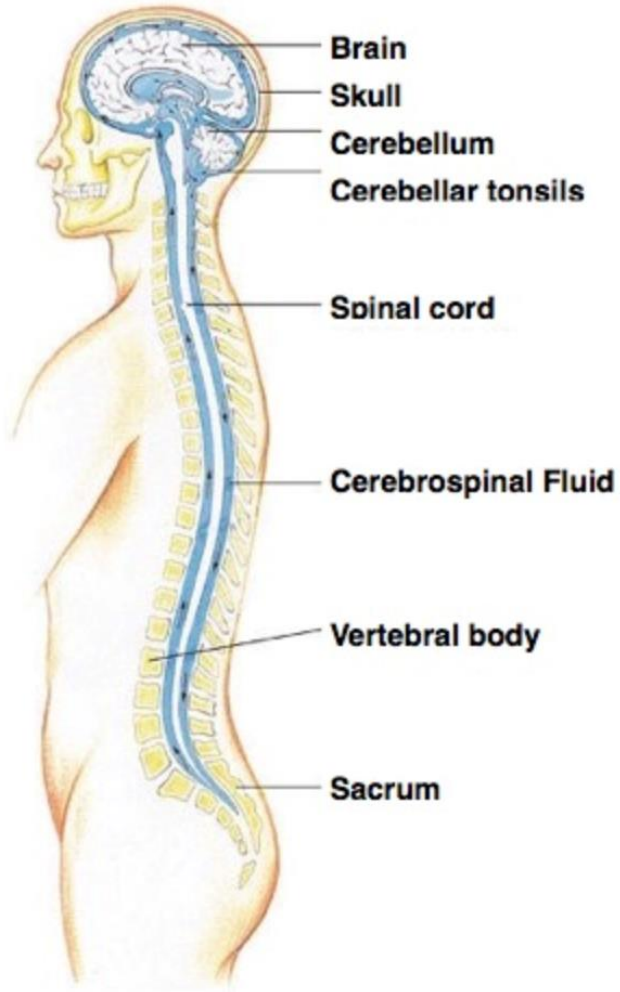
What is CSF?

- 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