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

DNL343 (Regimen G) Background Information

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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)

FOCUSED ON DEFEATING NEURODEGENERATION

Mission

To defeat neurodegenerative diseases through rigorous therapeutic discovery and development

Focus

LYSOSOMAL STORAGE DISORDERS

PARKINSON'S

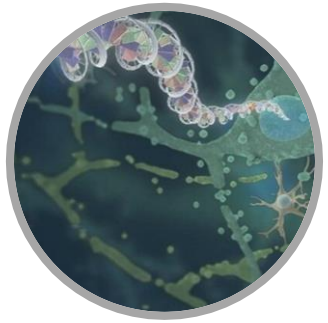
ALS/FTD

ALZHEIMER'S

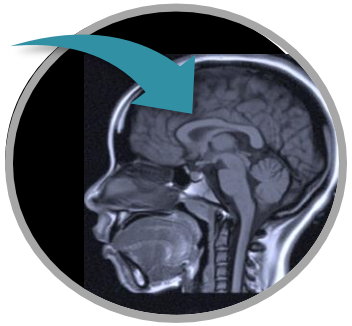
COMMITTED TO SCIENTIFIC PRINCIPLES AND THE ALS COMMUNITY

Scientific Principles

GENETIC PATHWAY POTENTIAL



ENGINEERING BRAIN DELIVERY



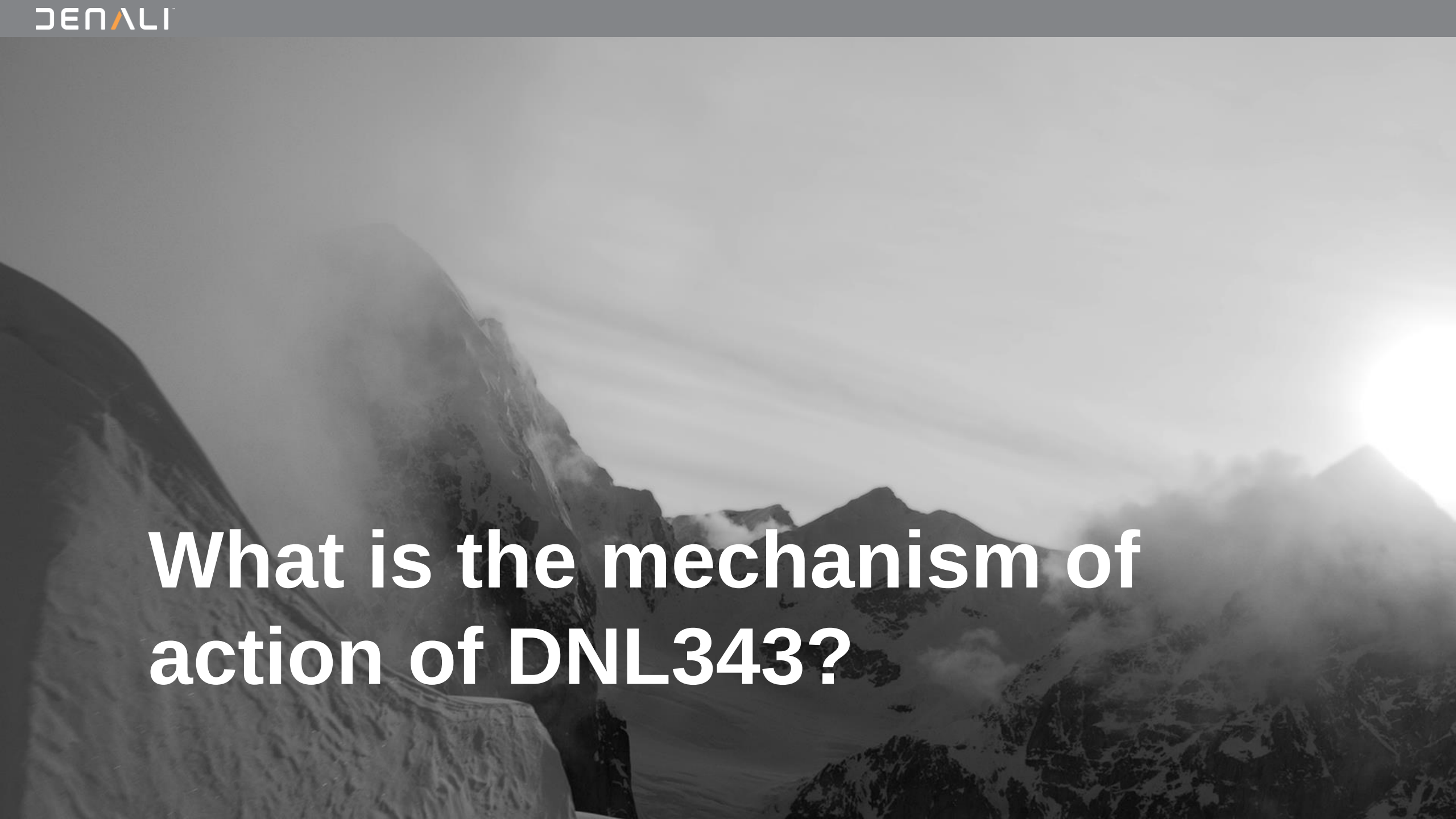
BIOMARKER-DRIVEN DEVELOPMENT

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.

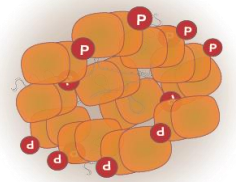
DENALI'S COMMITMENT TO ALS: TWO PROGRAMS IN CLINICAL DEVELOPMENT

	DNL343	SAR443820 (DNL788)
How it aims to work?	**eIF2B Activator**	**RIPK1 Inhibitor (partnered program with Sanofi)**
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?

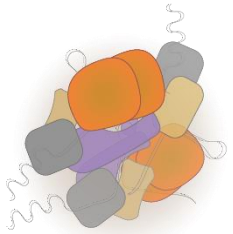
GENETIC PATHWAY POTENTIAL IN ALS

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



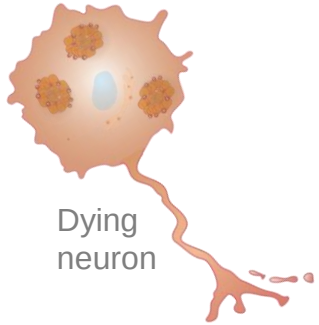
Harmful TDP43

TDP43 can be found in structures called **stress granules**[2] and many genes linked to ALS are a part of stress granule-related pathways[3]



Stress granule

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



Dying neuron

ALS-associated gene discovery over the past decade highlights the importance of stress granule biology and TDP43 in ALS

[1]Neumann et al. *Science* 2006
[2]Li et al. *J Cell Biol* 2013
[3]Fernandes et al. Adv Neurobiol 2018

THERAPEUTIC HYPOTHESIS FOR DNL343 IMPACT ON ALS

Cellular Stress
and / or
ALS Genetics

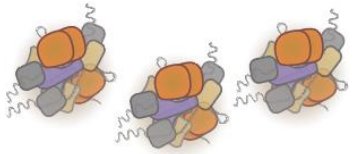
eIF2B OFF

Integrated stress response (ISR) pathway active

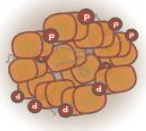
Cells make fewer proteins

Disease Biology

Stress Granules

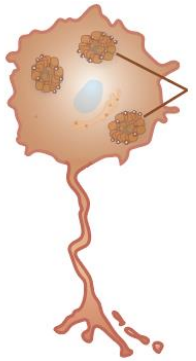


Abnormal TDP43



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

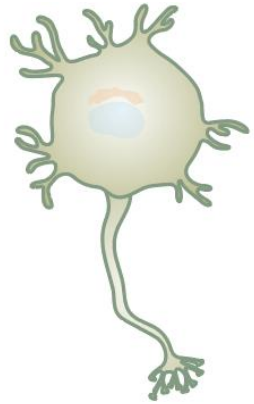
Disease Biology + DNL343

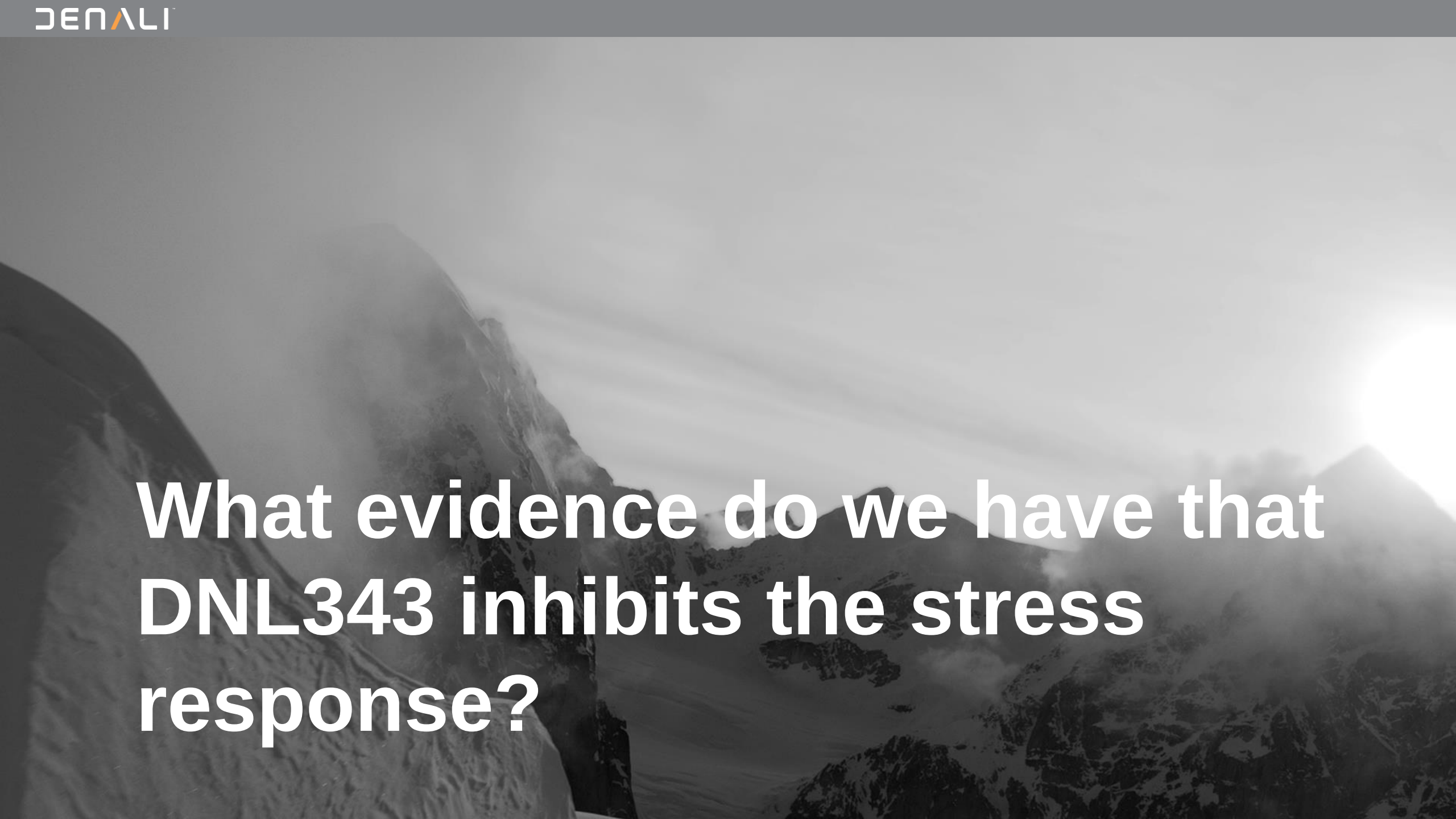
Stress Granules Dissolve

Normal TDP43

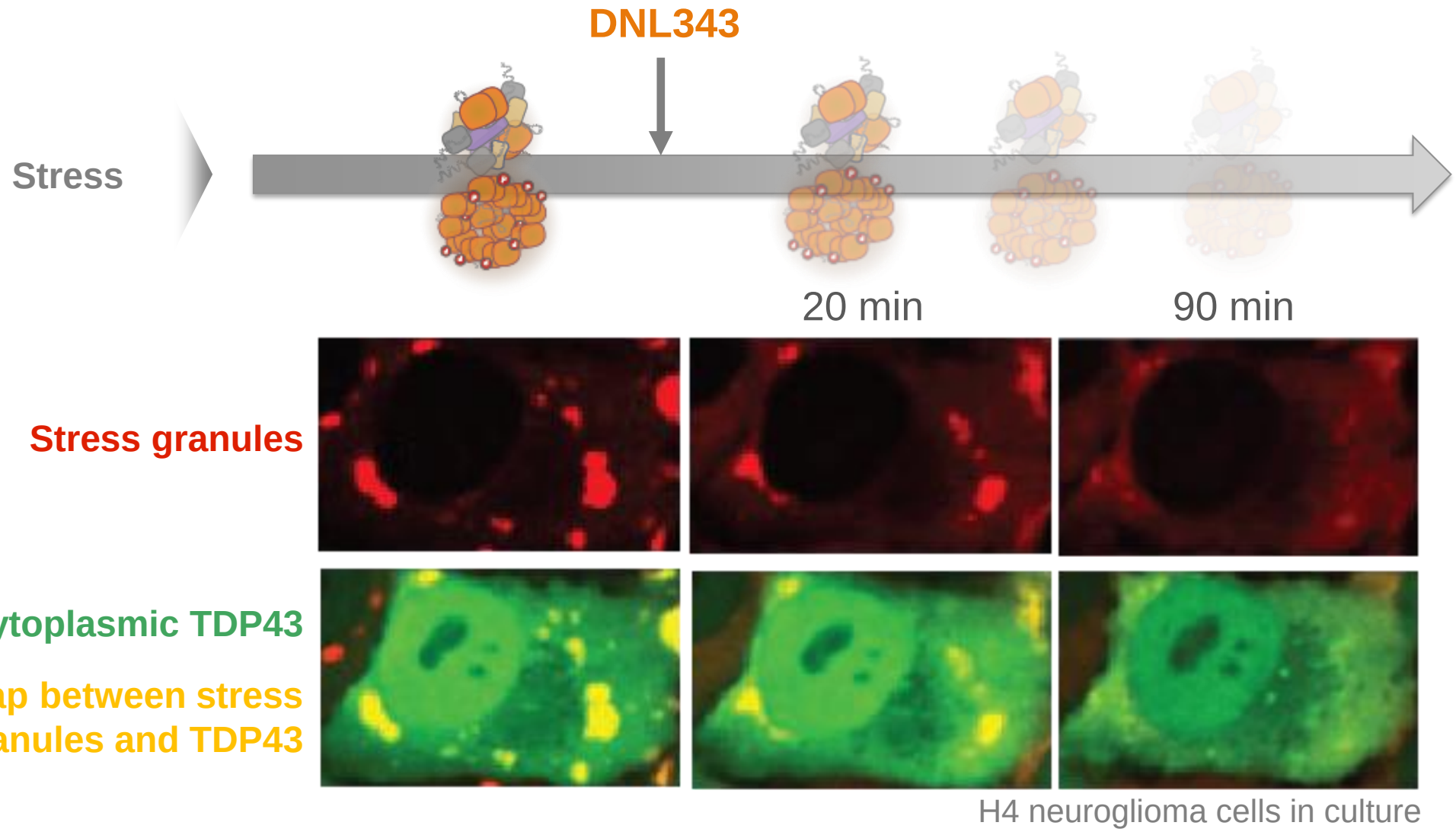
ISR biomarkers (e.g., ATF4 and *CHAC1*)

Healthy Nerve Cell




What evidence do we have that DNL343 inhibits the stress response?

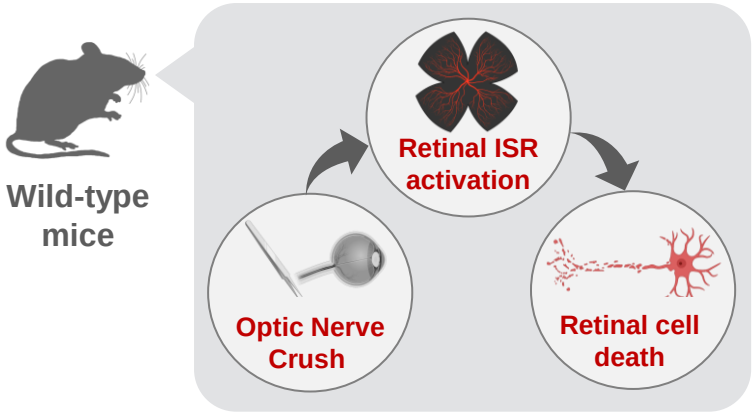
DNL343 DISSOLVES STRESS GRANULES AND TDP43 CLUSTERS IN CELLS



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

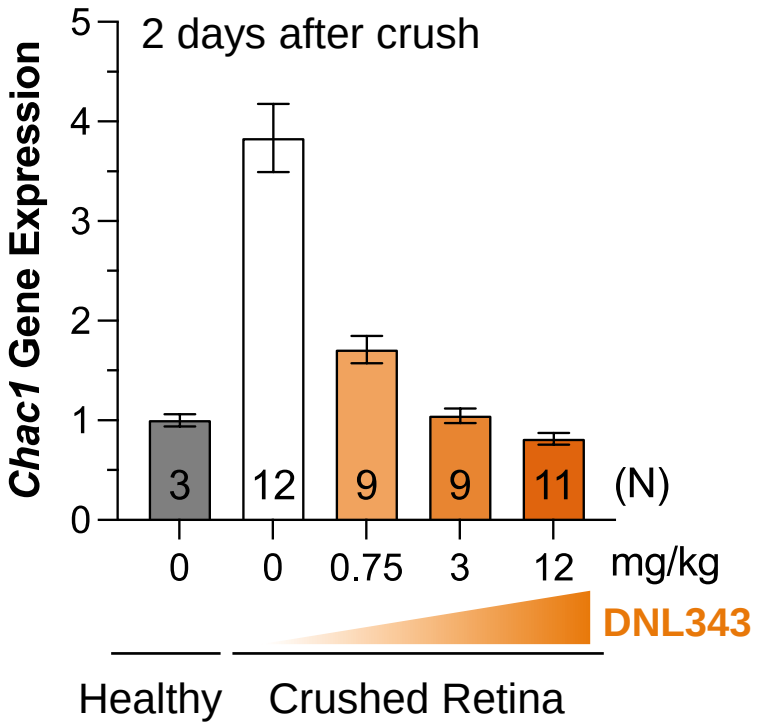
DNL343 PROTECTS CELL AGAINST DEGENERATION IN MOUSE MODEL

Animal Model

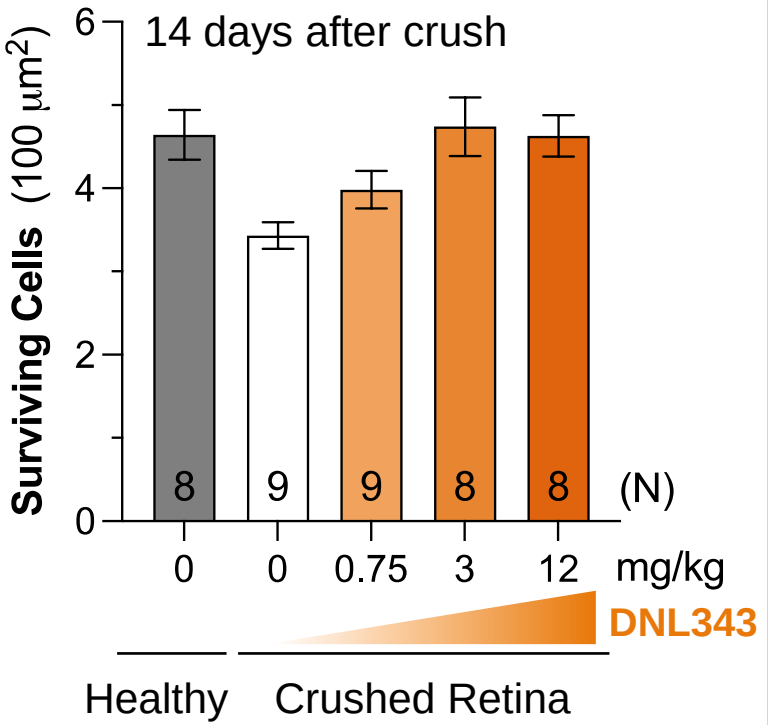


- We first tested DNL343 in healthy wild-type mice with short term injury
- When the optic nerve is pinched/ crushed, cells in the retina activate the **I**ntegrated **S**tress **R**esponse which leads to cell death[1]

ISR in the Retina



Cell Survival

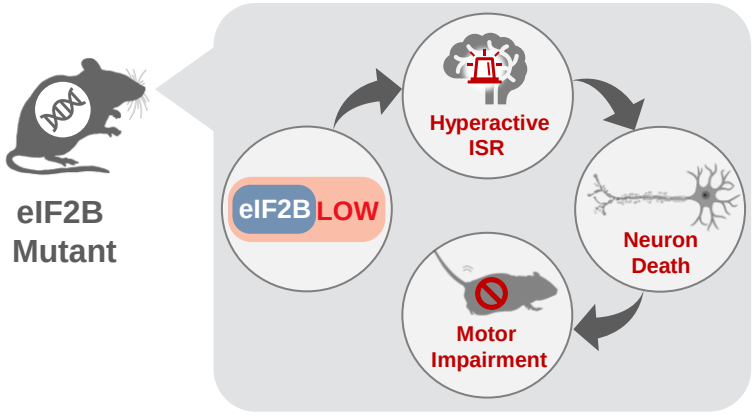


DNL343 decreases integrated stress response in retina and reduces cell death in mice

[1]Larhammar et al. *eLife* 2017

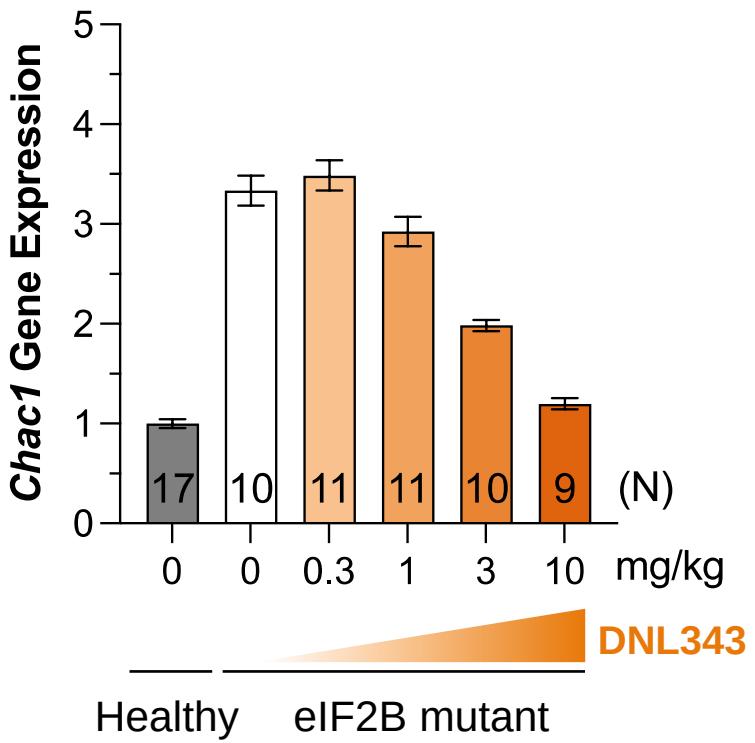
DNL343 PROTECTS MOTOR FUNCTION IN MOUSE MODEL

Animal Model

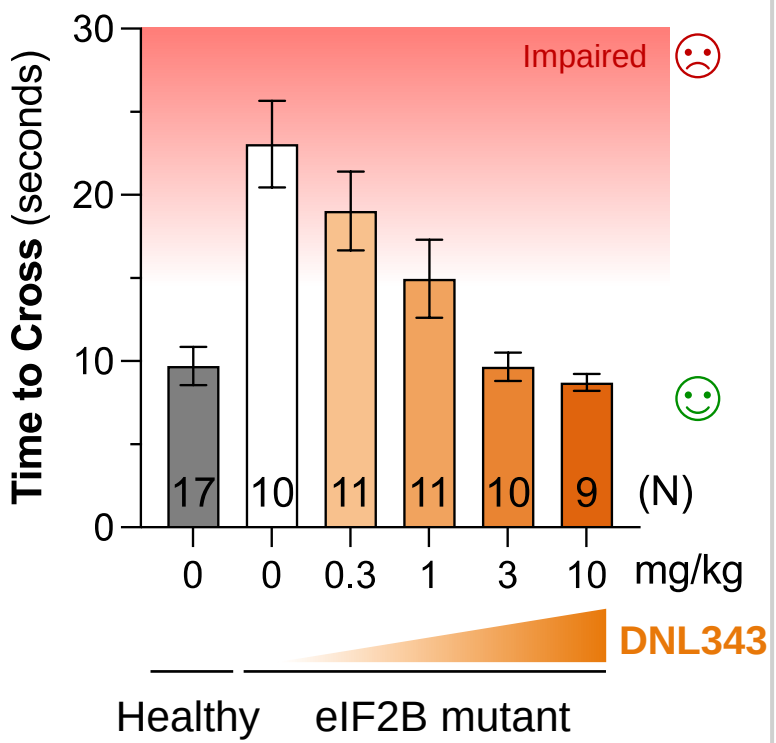


- To test DNL343 in the context of chronic disease, we used mice that have low eIF2B function (eIF2B mutant)
- These mice have hyperactive Integrated Stress Response in the brain that causes neuron death & impaired motor function

ISR in the Brain

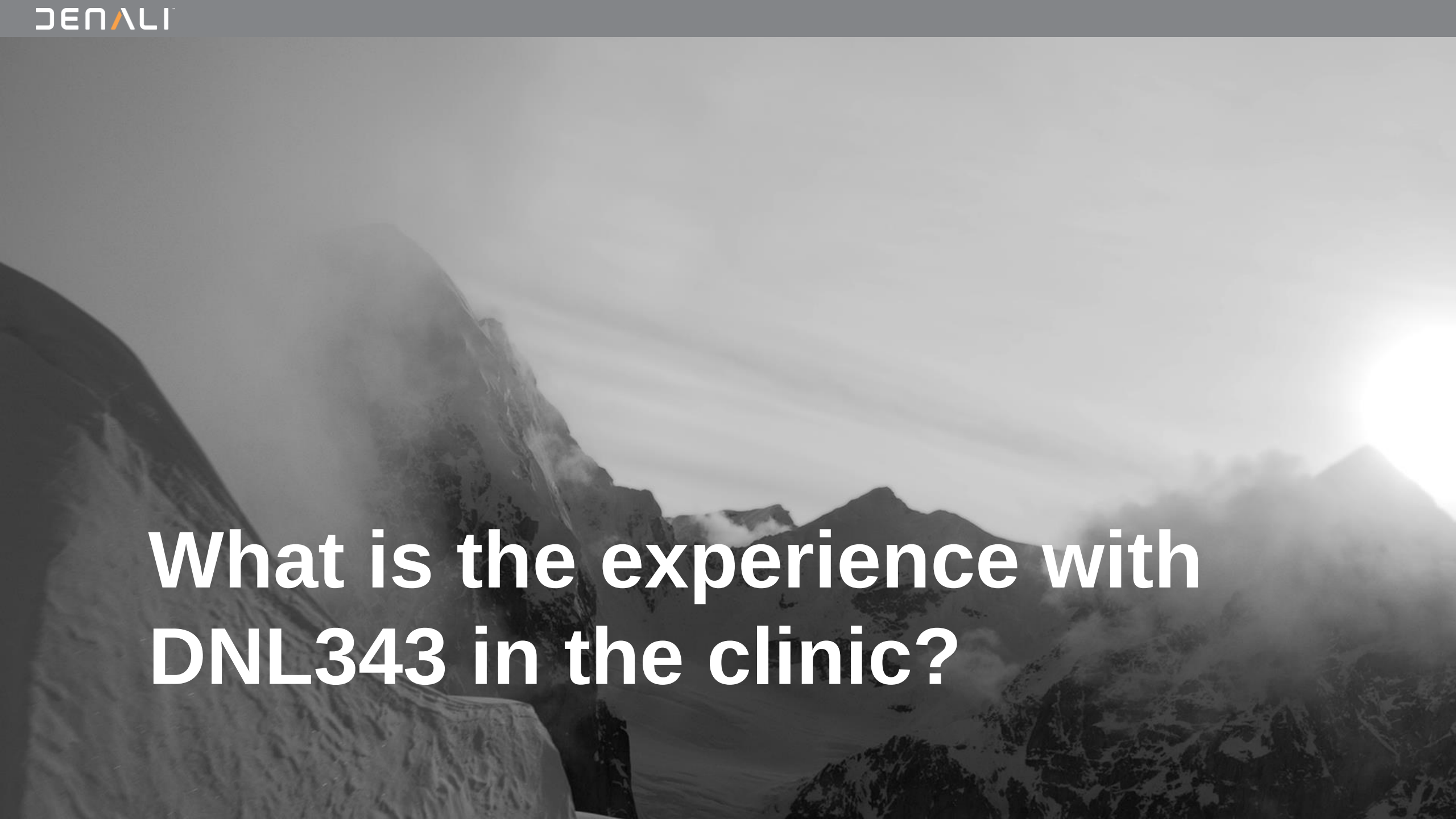


Motor Function



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

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


What is the experience with DNL343 in the clinic?

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

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

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

Duration from Symptom Onset

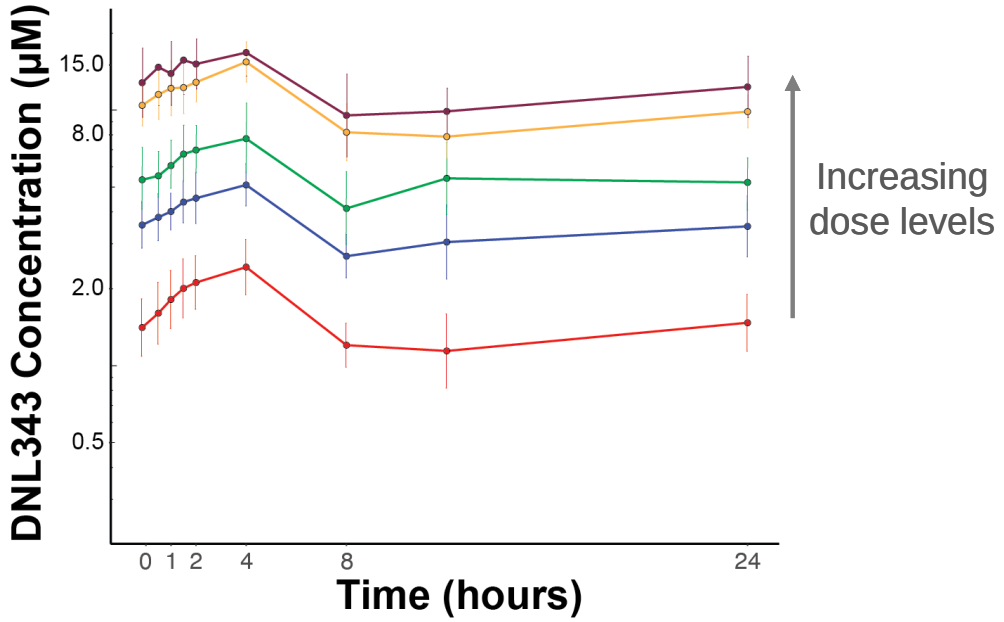
Minimum: 4 months | **Median Duration: 22 months** | Maximum: 41 months

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

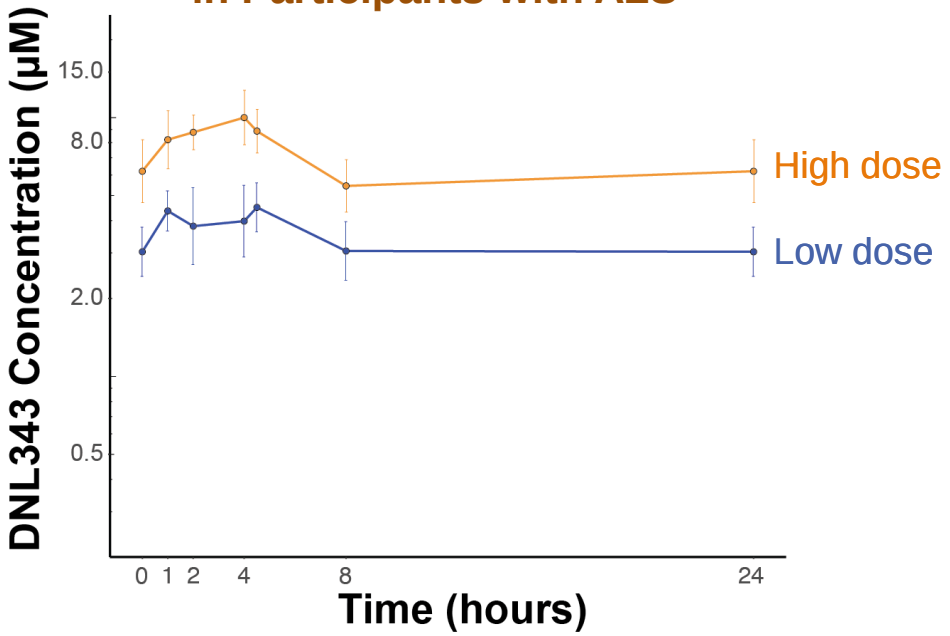
Sun L, et al., AAN abstract P8.8.010, 2023

DNL343 CONCENTRATIONS IN PLASMA AND CEREBROSPINAL FLUID (CSF)

DNL343 Plasma Concentration in Healthy Participants



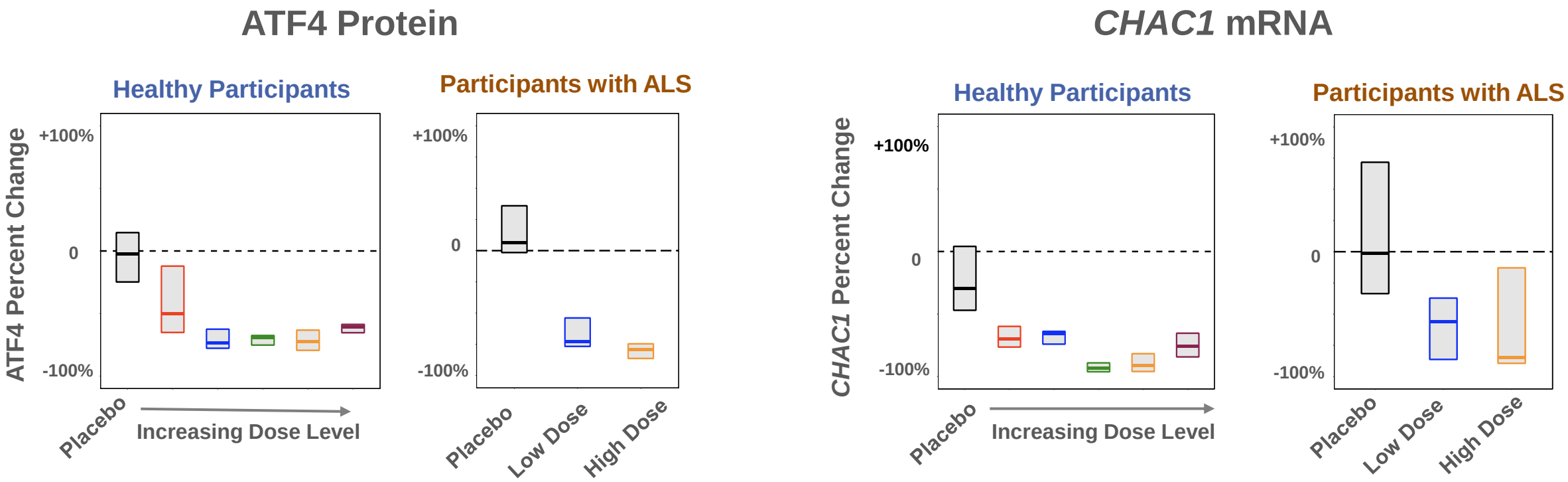
DNL343 Plasma Concentration in Participants with ALS



- 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

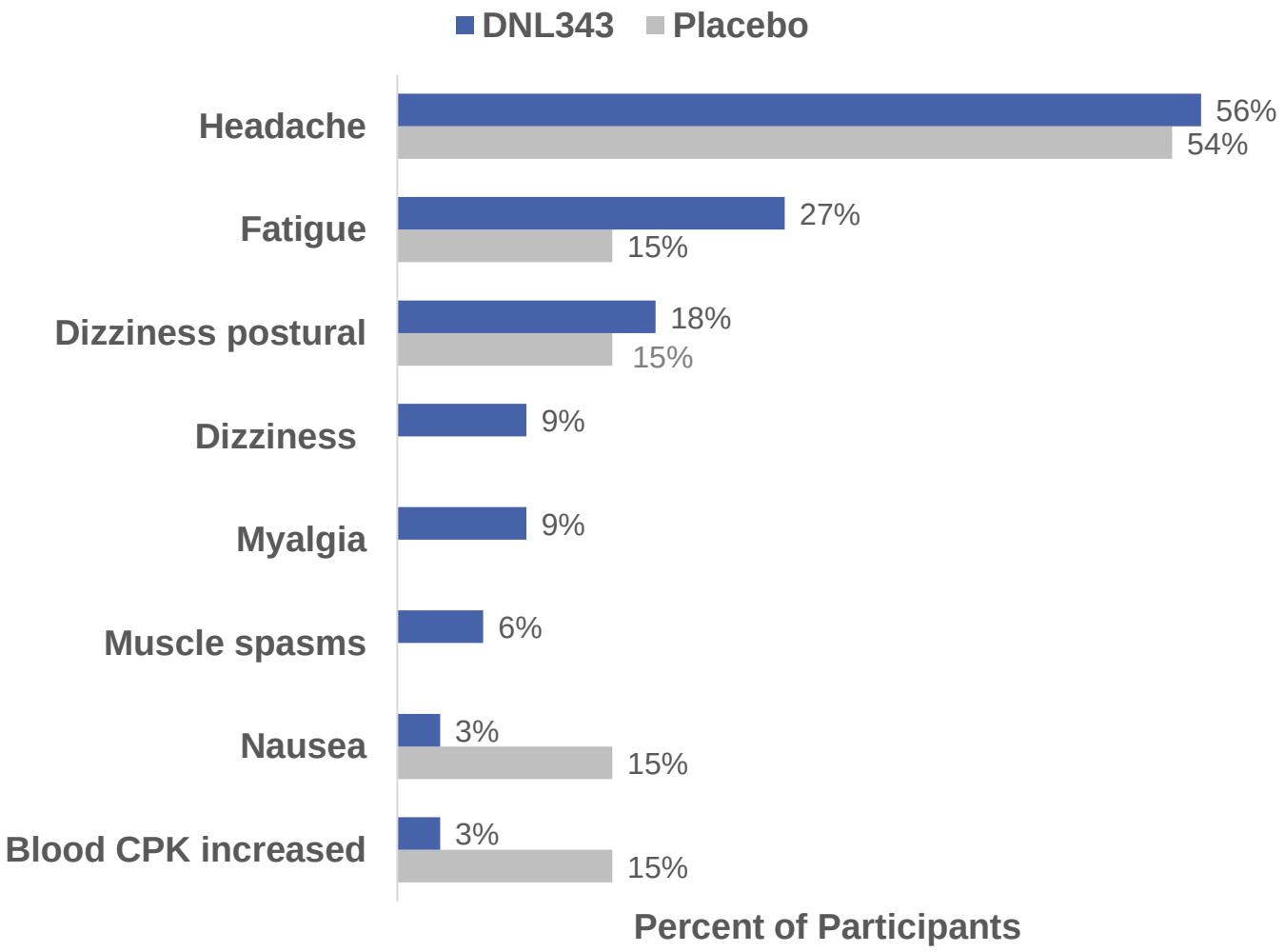
DNL343 INHIBITED ISR PATHWAY ACTIVATION IN HUMAN BLOOD CELLS



- 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*

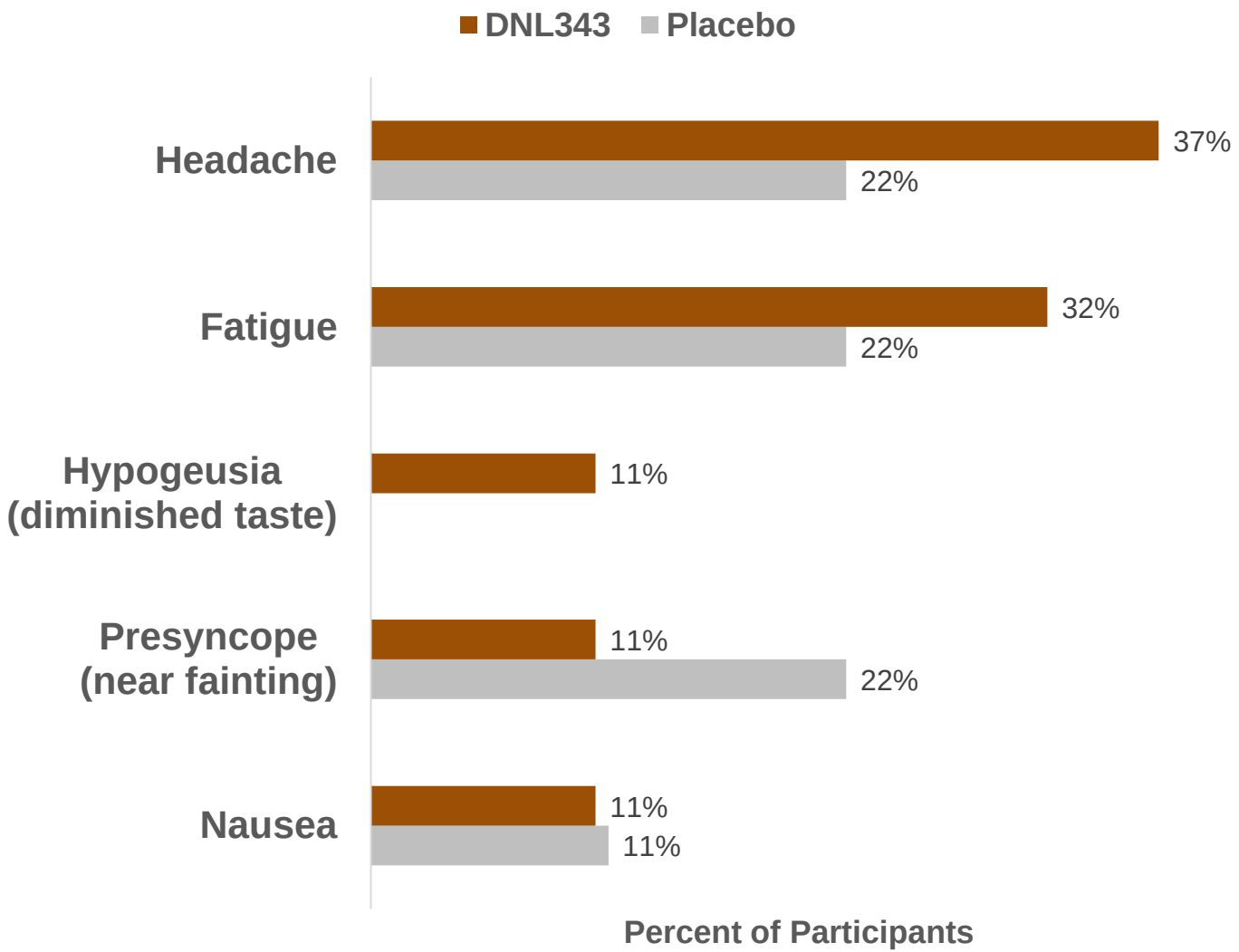


- Generally well tolerated
- No serious adverse events
- Majority of adverse events were mild
- Two discontinuations:
- Personal circumstances (PBO)
    - Anxiety (on DNL343, not related to study drug)

Phase 1b healthy volunteer study: NCT04268784

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

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

Phase 1b ALS diagnosis study: NCT05006352

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

DNL343 KEY TAKEAWAYS FROM HEALTHY AND ALS PARTICIPANT STUDIES

Once daily oral dosing is supported by pharmacokinetic profile

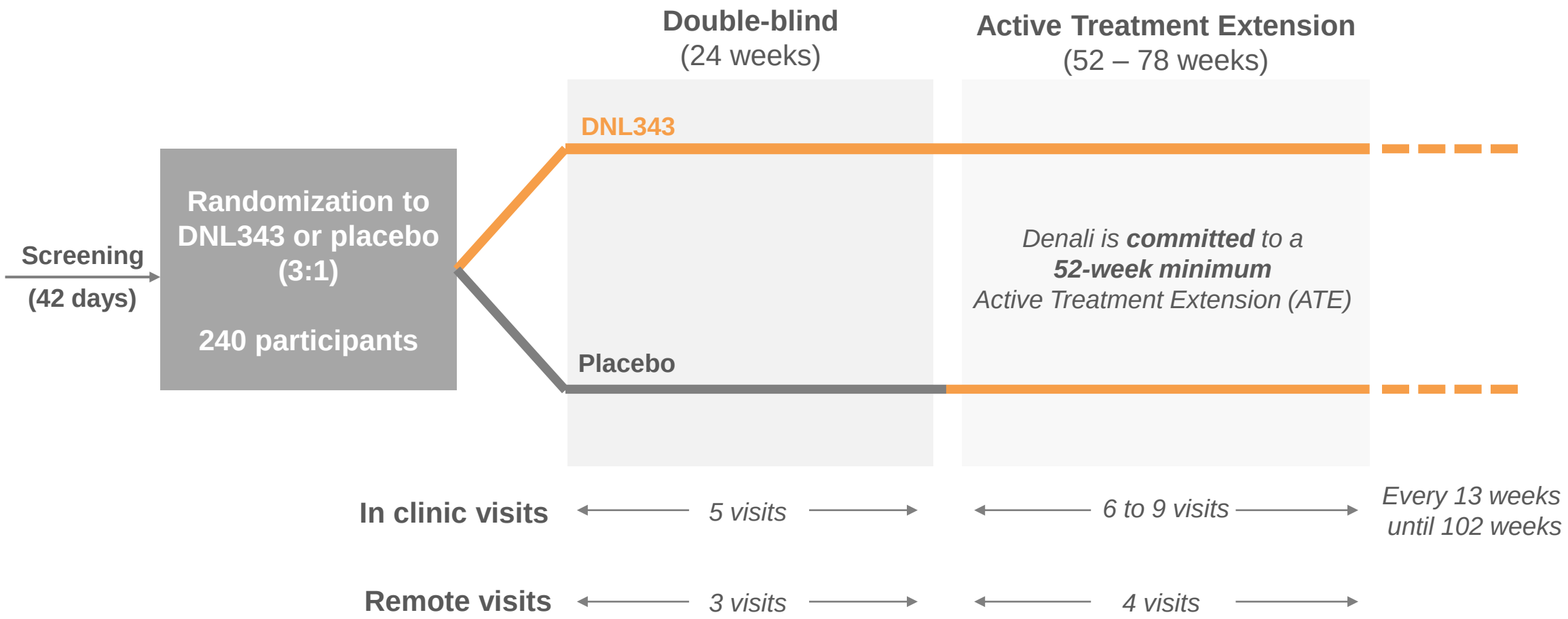
Extensive distribution to the Cerebrospinal Fluid (CSF)

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

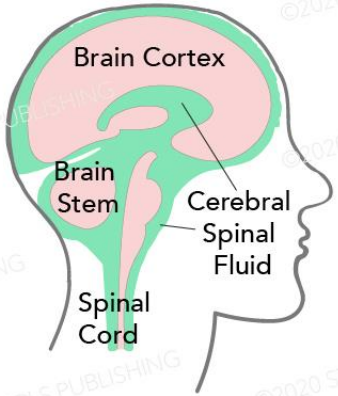


HEALEY REGIMEN G STUDY GOALS

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

University Medical Center, Utrecht, NL
- Leonard van den Berg, MD
- Tommy Bunte, PA
- Karen Vlaardingerbroek, RN

California Pacific M.C., San Francisco, CA
- Jonathan Katz, MD
- Henry Chen

University of California, San Diego, CA
- John Ravits, MD
- Rosemarie Previte, CRM

Emory University, Atlanta, GA
- Christina Fournier, MD
- Anna Partlow, RN, MSN

University of Rochester, NY
- Peter Creigh, MD
- Janet Sowden

PPD Orlando, Orlando, FL
- Dale Taylor, MD
- Ira Goodman, MD

Atrium Health, Charlotte, NC
- Leo McCluskey, MD
- Cynthia Lary, BSMT, RN

UT Southwestern, Dallas, TX
- Jeffrey Elliott, MD
- 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

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
- 7 programs in clinical trials


THANK YOU