

Thank you for joining the weekly webinar!

We are admitting audience members from the waiting room.

Please allow a few moments for the webinar to begin.



HEALEY ALS Platform Trial

Weekly Q&A – June 15, 2023



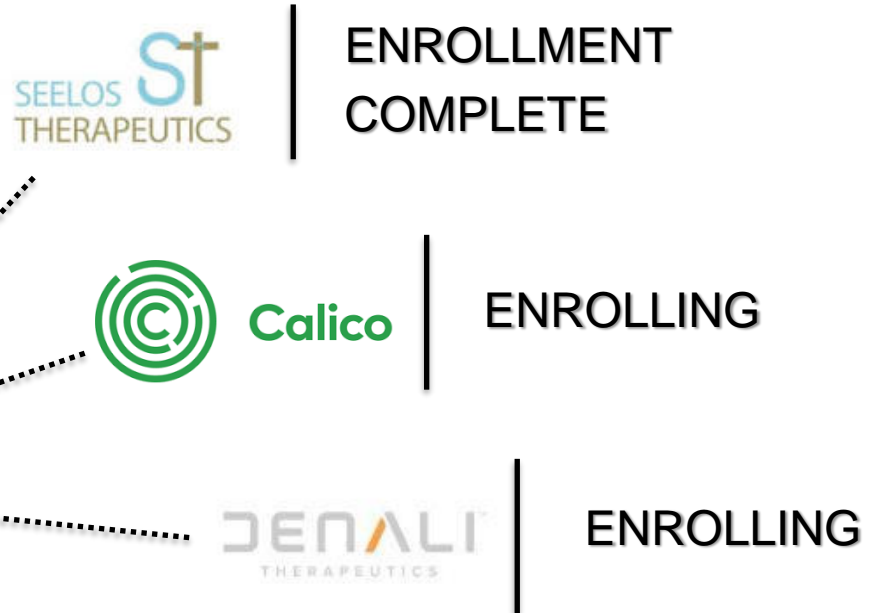
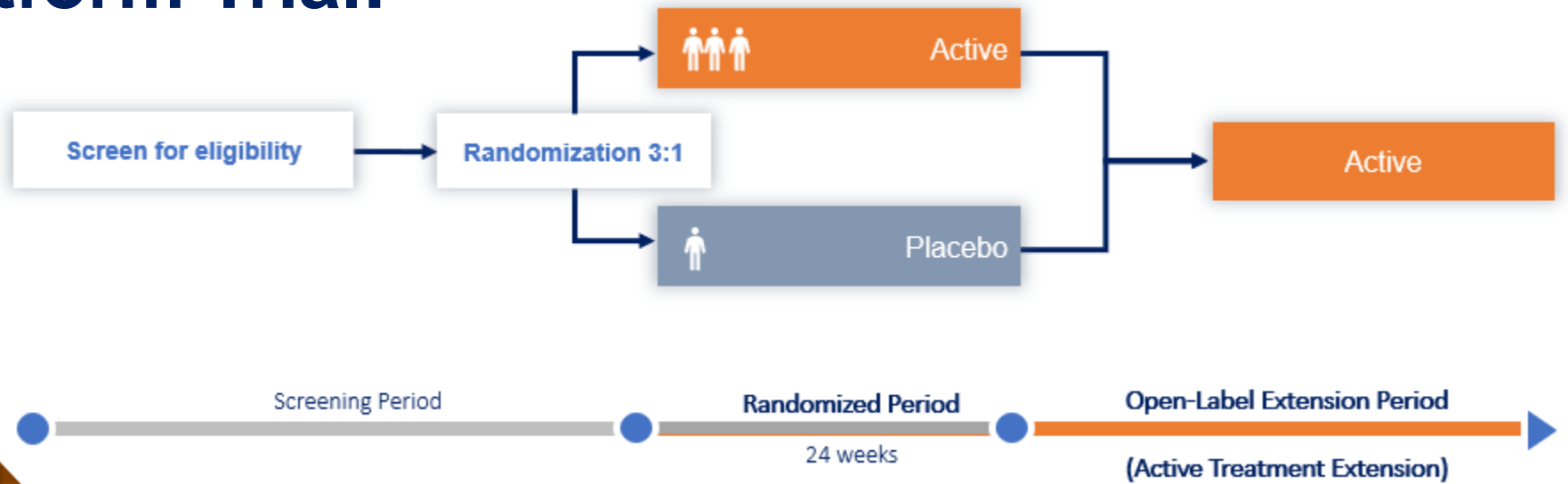
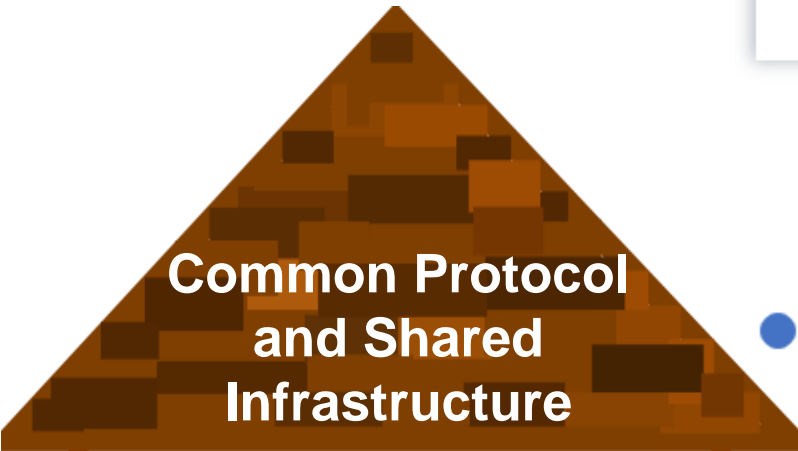
Healey & AMG Center

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

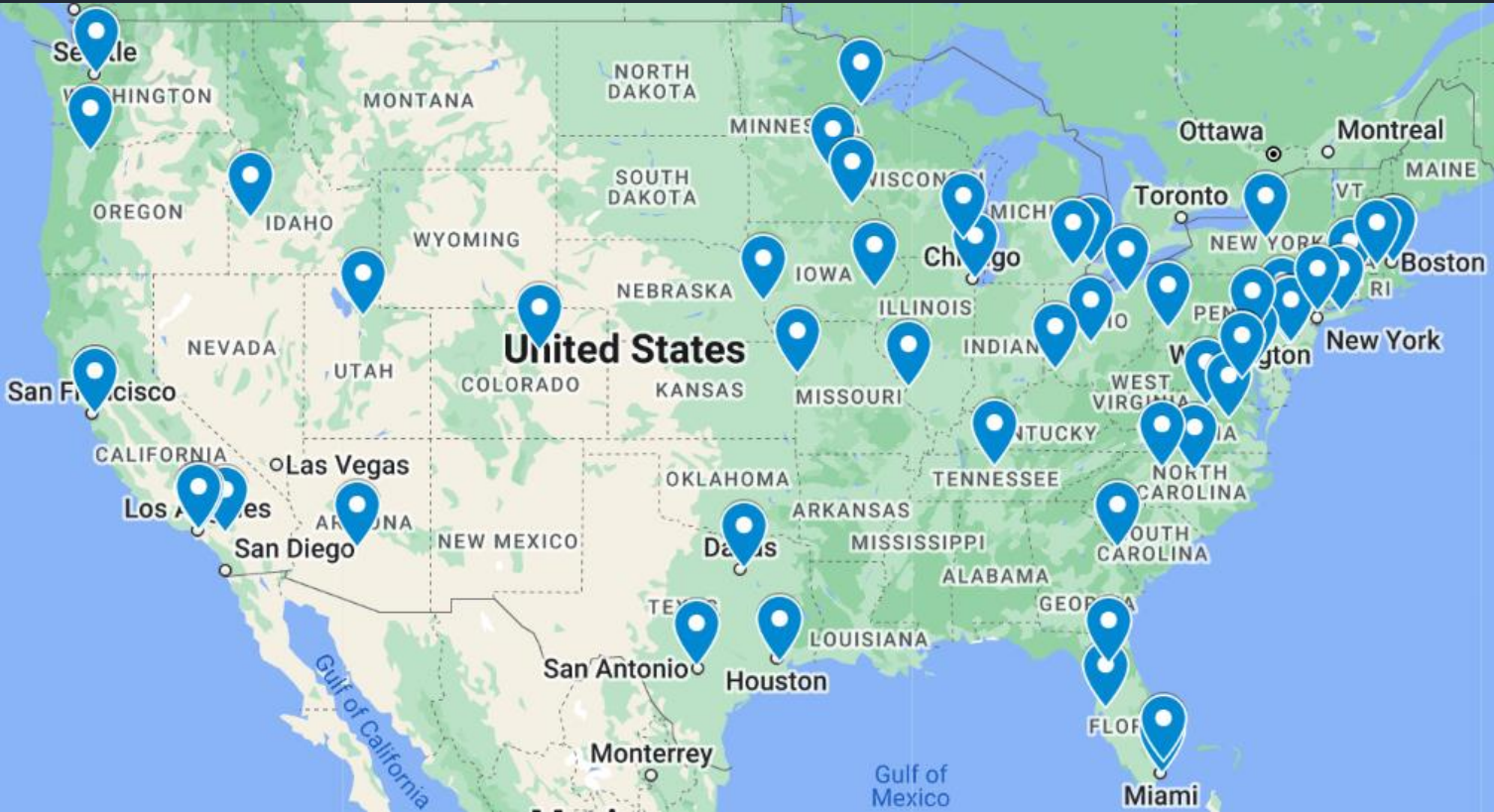


The AMG Foundation

HEALEY ALS Platform Trial:



56 Sites Currently Active for Regimen F



(as of 6/15/23)

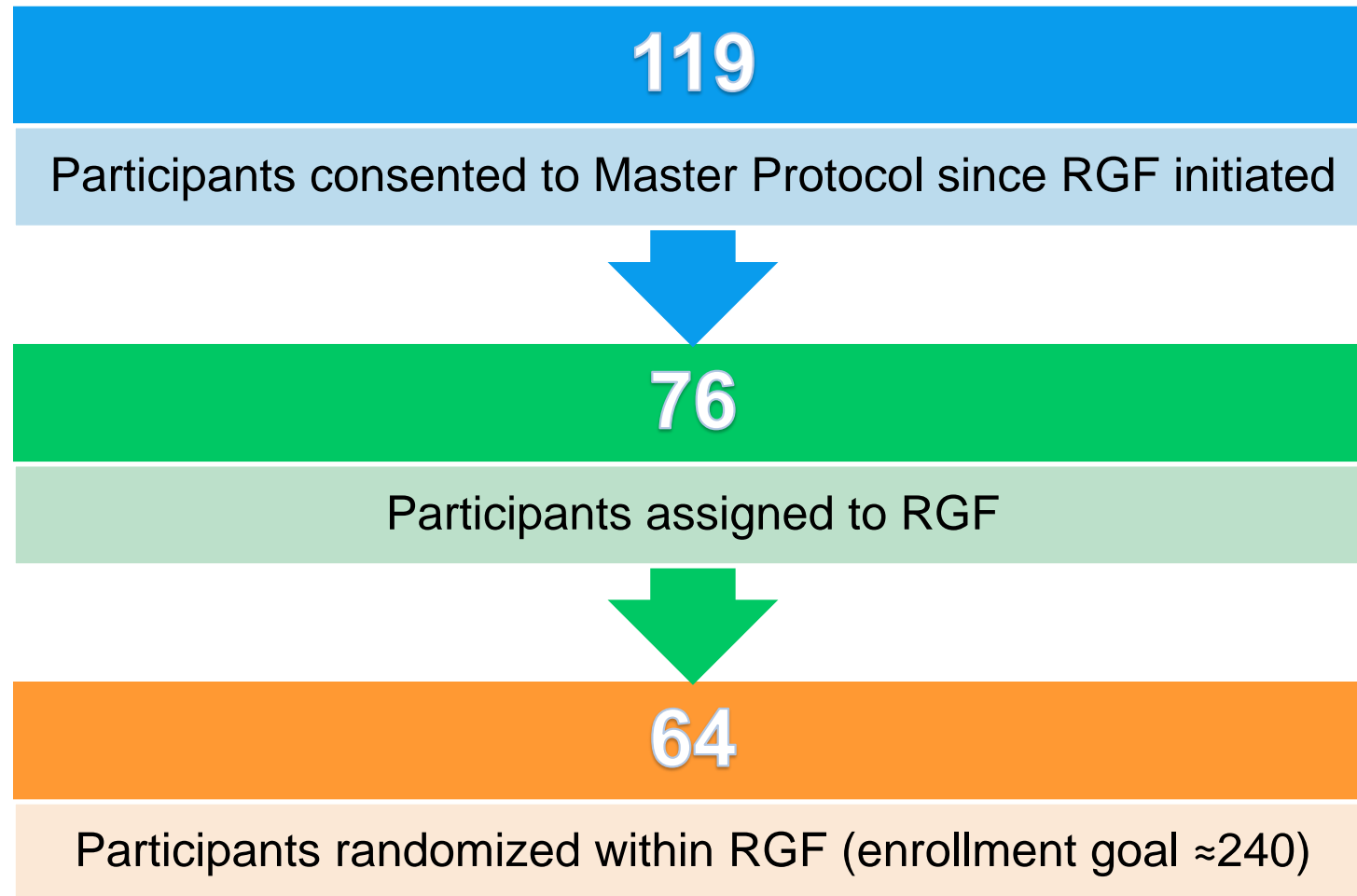
- ✓ Nova Southeastern University
- ✓ Essentia Health
- ✓ Texas Neurology
- ✓ Mass General Hospital
- ✓ University of Nebraska
- ✓ Hospital for Special Care
- ✓ Henry Ford Hospital
- ✓ Augusta University
- ✓ Beth Israel Deaconess
- ✓ University of Texas HSC
- ✓ University of Colorado
- ✓ Loma Linda University
- ✓ Ohio State University
- ✓ Cedars Sinai Medical Center
- ✓ Duke University
- ✓ Wake Forest University
- ✓ Saint Alphonsus
- ✓ UMass Worcester
- ✓ Lehigh Valley
- ✓ Thomas Jefferson
- ✓ University of South Florida
- ✓ University of Pennsylvania
- ✓ SUNY Upstate
- ✓ University of Iowa
- ✓ California Pacific Med Center
- ✓ Houston Methodist
- ✓ Vanderbilt University
- ✓ University of Minnesota
- ✓ Washington University
- ✓ Barrow Neurological Institute
- ✓ University of Miami
- ✓ Temple University
- ✓ University of Virginia
- ✓ Johns Hopkins University
- ✓ University of Southern CA
- ✓ Holy Cross Hospital
- ✓ University of Washington
- ✓ University of Utah
- ✓ Penn State Hershey
- ✓ University of Michigan
- ✓ University of Kansas
- ✓ Stony Brook University
- ✓ University of Cincinnati
- ✓ Mayo Clinic Rochester
- ✓ Northwestern University
- ✓ Georgetown University
- ✓ Kaiser, Los Angeles
- ✓ University of Pittsburgh
- ✓ Virginia Commonwealth
- ✓ Med College Wisconsin
- ✓ University of CA, San Fran
- ✓ University of Florida, Gainesville
- ✓ Providence Brain and Spine
- ✓ Cleveland Clinic
- ✓ George Washington University
- ✓ Hackensack University

Site Map & Contacts:



<https://bit.ly/3g2NZr5>

Enrollment Update: Regimen F (as of 6/15/23)



Thank You

for your partnership in ALS research

Regimen F Resources on MGH Website

Regimen F: ABBV-CLS-7262, by Calico and AbbVie- Now Recruiting

ABBV-CLS-7262 is an investigational drug developed by Calico Life Sciences LLC in collaboration with AbbVie Inc. ABBV-CLS-7262 aims to restore function in cells affected by ALS by normalizing protein synthesis and preventing further sequestration and aggregation of TDP-43, thereby protecting neurons, and possibly slowing ALS progression.

The integrated stress response (ISR) is a fundamental transient process that regulates cell function during various stressful conditions. Tissue studies suggest that the ISR is chronically induced in people with ALS. It is proposed that TDP-43 aggregates, a hallmark feature in the motor neurons of people with ALS, could be formed by a chronically induced ISR. ABBV-CLS-7262 activates the protein complex eIF2B, which is a key regulator of the ISR. Binding of ABBV-CLS-7262 desensitizes eIF2B to stress and decreases the ISR. Reduction of the ISR restores normal protein synthesis, reduces TDP-43 sequestration in stress granules, and may decrease TDP-43 aggregation.

A prior first-in-human study of ABBV-CLS-7262 showed that this drug was well-tolerated by participants, demonstrated target engagement by increasing eIF2B enzymatic activity, and suppressed the ISR in blood cells. ABBV-CLS-7262 crossed the blood brain barrier at concentrations predicted to be efficacious in ALS. ABBV-CLS-7262 is currently being investigated in a Phase 1b study in people with ALS (NCT04948645), and will be studied further as part of the HEALEY ALS Platform Trial.


[Watch a webinar about the science behind ABBV-CLS-7262](#)


[Watch this video](#) for more information on the mechanism of action behind ABBV-CLS-7262.

[Download Regimen F Brochure](#)

[Download Lumbar Puncture Brochure](#)



**Healey Center**
Sean M. Healey & AMG Center
for ALS at Mass General

**NEALS**
Northeast Amyotrophic
Lateral Sclerosis
Consortium

HEALEY ALS Platform Trial


Regimen F

ABBV-CLS-7262
Developed by Calico Life Sciences LLC
in collaboration with AbbVie Inc.

Investigational products included in the HEALEY ALS Platform Trial are selected by a team of experts after careful review of the study drug and the science supporting its treatment potential in Amyotrophic Lateral Sclerosis (ALS). Regimen F is testing an experimental medication called ABBV-CLS-7262, and the trial will involve in-person study visits every 4 to 8 weeks (about 6 visits total over the course of 24 weeks).

Please discuss the possible benefits and risks of this investigational product with your study team.

Visit our website to learn more about what to expect in the trial process:
<https://bit.ly/3ExPa1B>




About Regimen F:

Regimen F is a Phase 2/3 trial enrolling approximately 240 participants to evaluate the safety and efficacy of ABBV-CLS-7262 as a potential treatment for ALS. This regimen involves biomarker analysis and cerebrospinal fluid collection via lumbar punctures to assess the effects of ABBV-CLS-7262.

3:1 Active Drug to Placebo Ratio: Participants who enroll in this trial have a 3 in 4 (75%) chance of being assigned to active study drug and a 1 in 4 (25%) chance of being assigned to placebo during the initial 24-week randomized controlled trial (RCT) period.

Active Treatment Extension (ATE): Participants have the option to enroll in the ATE for ABBV-CLS-7262 upon completion of the 24-week RCT. During ATE, all participants will receive the active study drug.

To see if you may qualify, please review the list of eligibility criteria:
<https://bit.ly/3Qctvnm>



For general questions about the HEALEY ALS Platform Trial, Contact the Patient Navigator:
healeyalsplatform@mgh.harvard.edu
833-425-8257 (HALT ALS)



<https://bit.ly/3SIwH4X>

Printable Brochures!

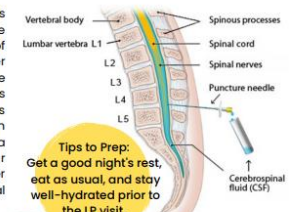


Regimen F Brochure
Lumbar Puncture Brochure
General Platform Trial Brochure

Understanding HEALEY ALS Platform Trial Study Procedures

LUMBAR PUNCTURE

A Lumbar Puncture (LP), or Spinal Tap, is a procedure to remove a small sample (10-15mL or ~1 tablespoon) of cerebrospinal fluid (CSF) from the lower spine. CSF is the fluid that surrounds the brain and spinal cord, and it contains proteins, cells, and other substances that may be important biomarkers in ALS research. During the procedure, a needle is inserted between two lumbar vertebrae (backbones) in the lower back and into the space in the spinal canal that contains CSF.



Tips to Prep:
Get a good night's rest, eat as usual, and stay well-hydrated prior to the LP visit.

Sometimes, people feel worried that a lumbar puncture could be risky or painful. In reality, this is a safe and common procedure to collect CSF!

LUMBAR PUNCTURE STEP BY STEP

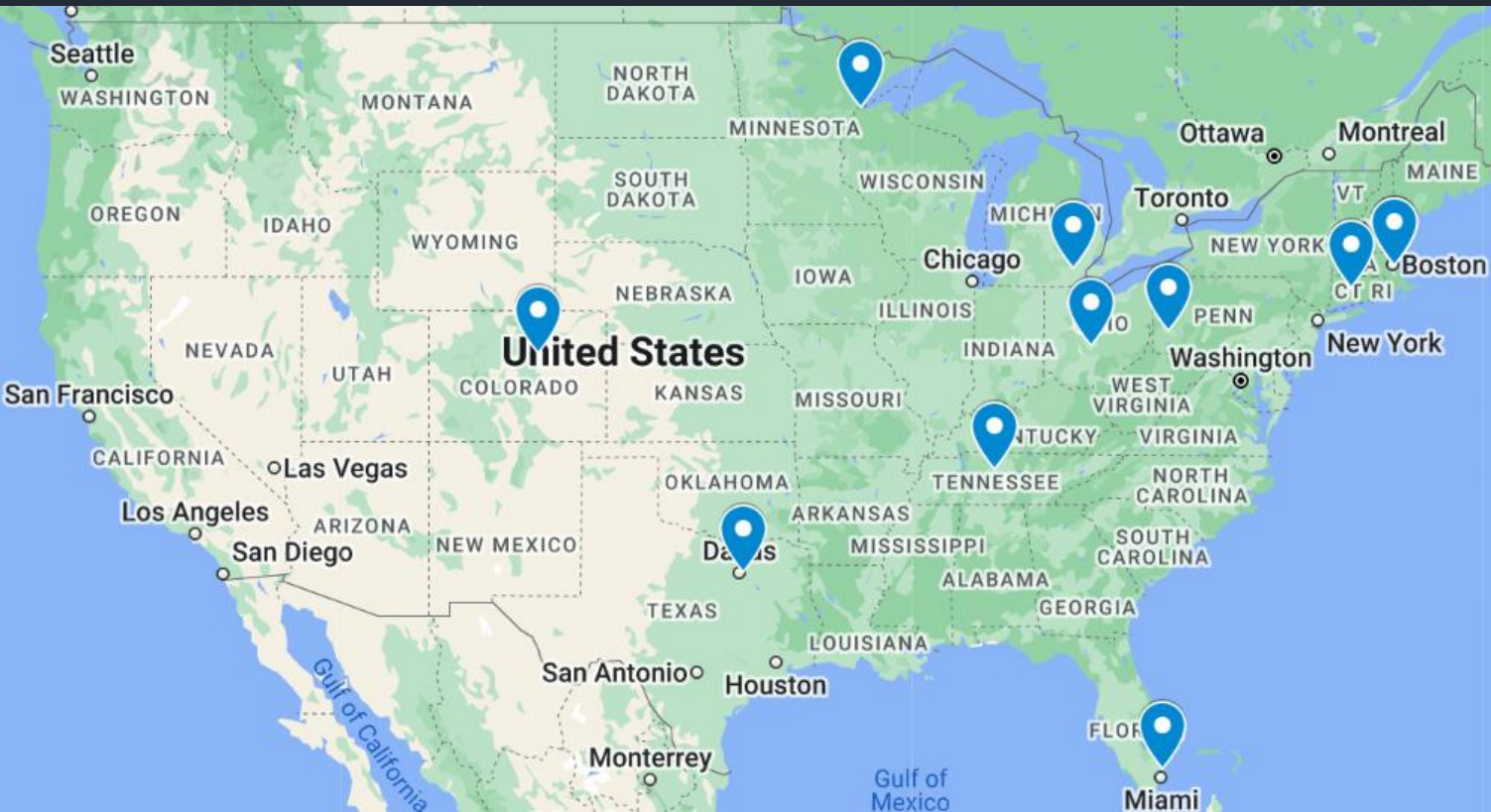
- 1) You will be asked to sit or lie down in a position that helps widen the spaces between the bones of the lower spine.
- 2) The doctor will cleanse the skin on your lower back to reduce risk of infection, then use a small needle to inject a local anesthetic (such as lidocaine) to numb the site.
- 3) The LP needle is inserted into the space containing CSF. A special atraumatic spinal needle (Sprotte) is typically used to reduce the chance of a post-puncture headache. The doctor may need to readjust the needle if CSF cannot be drawn with the first insertion.
- 4) Spinal fluid is collected into specimen tubes for lab testing. The LP needle is removed, your back is cleaned, and a band-aid is placed over the LP site.
- 5) For your comfort and safety, it is recommended that someone drive you to and from the LP study visit.



QUESTIONS?

Prior to enrolling in a clinical trial, your study team will discuss the LP procedure with you. Please ask your study team for clarification if you have any questions while reviewing the informed consent form.

11 Sites Currently Active for Regimen G



(as of 6/15/23)

- ✓ Nova Southeastern University
- ✓ Texas Neurology
- ✓ University of Colorado
- ✓ Essentia Health
- ✓ University of Pittsburgh
- ✓ Beth Israel Deaconess
- ✓ Mass General Hospital
- ✓ Ohio State University
- ✓ University of Michigan
- ✓ Hospital for Special Care
- ✓ Vanderbilt University

Site Map & Contacts:



<https://bit.ly/3g2NZr5>

Regimen G Resources on MGH Website

Regimen G: DNL343, by Denali Therapeutics



DNL343 is an investigational drug developed by Denali Therapeutics Inc. DNL343 aims to improve survival of nerve cells and slow ALS progression by restoring normal protein production and decreasing potentially harmful buildup of TDP-43 in cells affected by ALS. Abnormal TDP-43 buildup in nerve cells is found in >95% of individuals living with ALS.

The integrated stress response (ISR) appears to be overactive in ALS, and chronic activation of the ISR can lead to cellular dysfunction. In stressed cells, eIF2B activity is suppressed by the ISR, which leads to impaired protein synthesis and the formation of stress granules containing TDP-43. TDP-43 containing stress granules are thought to lead to TDP-43 inclusions, a hallmark of ALS pathology. DNL343 is a drug that is designed to inhibit the ISR, restore normal protein synthesis, and prevent the formation of TDP-43 containing stress granules as well as dissolve existing ones; the effects of which may be beneficial in the treatment of ALS.

Prior studies of DNL343 showed that this drug is generally well tolerated in healthy participants and individuals living with ALS. Experimental treatment with DNL343 showed a reduction in ISR biomarkers measured in the blood, suggesting that DNL343 inhibits the ISR. Analysis of cerebrospinal fluid (the fluid that surrounds the brain, spinal cord, and nerve cells impacted by ALS) obtained from participants in these studies showed that DNL343 is well distributed in the spinal fluid. Results from previous studies support continued evaluation of DNL343 as a potential treatment for ALS in the HEALEY ALS Platform Trial. DNL343 is also being studied in an ongoing Phase 1b trial (NCT05006352) in people with ALS.

[Download Regimen G Brochure](#)





HEALEY ALS Platform Trial


Regimen G

DNL343
Developed by Denali Therapeutics Inc.

Investigational products included in the HEALEY ALS Platform Trial are selected by a team of experts after careful review of the study drug and the science supporting its treatment potential in Amyotrophic Lateral Sclerosis (ALS). Regimen G is testing an experimental medication called DNL343, and the trial will involve in-person study visits every 4 to 8 weeks (about 6 visits total over the course of 24 weeks).

Please discuss the possible benefits and risks of this investigational product with your study team.

Visit our website to learn more about what to expect in the trial process:
<https://bit.ly/3ExRe18>




About Regimen G:

Regimen G is a Phase 2/3 trial enrolling approximately 240 participants to evaluate the safety and efficacy of DNL343 as a potential treatment for ALS. This regimen involves biomarker analysis and *optional cerebrospinal fluid (CSF) collection* to assess the effects of DNL343.

3:1 Active Drug to Placebo Ratio: Participants who enroll in this trial have a 3 in 4 (75%) chance of being assigned to active study drug and a 1 in 4 (25%) chance of being assigned to placebo during the initial 24-week randomized controlled trial (RCT) period.

Active Treatment Extension (ATE): Participants will continue into the ATE for DNL343 after completing the 24-week RCT. During ATE, all participants will receive the active study drug.

To see if you may qualify, please review the list of eligibility criteria:
<https://bit.ly/30ctvnm>



For general questions about the HEALEY ALS Platform Trial, Contact the Patient Navigator:
healeyalsplatform@mg.harvard.edu
833-425-8257 (HALT ALS)



<https://bit.ly/3SIwH4X>



Q&A for Regimen G:

Q: How is this drug administered?
A: DNL343 is taken by mouth once daily. The study drug is in the form of granules that are stored in stick packs (foil packets). The granules can be mixed with water or taken with soft food such as applesauce or yogurt.

Q: What does this drug do?
A: DNL343 aims to slow ALS progression and improve survival of nerve cells by restoring normal protein production and decreasing potentially harmful buildup of TDP-43. The integrated stress response (ISR) appears to be overactive in ALS, and chronic activation can lead to cellular dysfunction. The ISR reduces eIF2B activity in cells, which leads to impaired protein synthesis and formation of stress granules containing TDP-43. TDP-43 containing stress granules are thought to lead to TDP-43 inclusions, a hallmark of ALS pathology. DNL343 is designed to inhibit the ISR, restore normal protein synthesis, and dissolve TDP-43 containing stress granules, which may have therapeutic effects in ALS.

Q: Has this drug been studied before?
A: Yes. Prior studies showed that DNL343 is generally well tolerated in individuals living with ALS and healthy participants. DNL343 administration led to a reduction in two ISR biomarkers in the blood, suggesting that DNL343 inhibits the ISR. Analysis of participants' CSF (the fluid that surrounds nerve cells impacted by ALS) showed that DNL343 is well distributed in the spinal fluid. DNL343 is being studied in an ongoing Phase 1b trial (NCT05006352) in people with ALS. DNL343 is an investigational drug and has not been approved by any Health Authority.

Additional Questions?

Register to attend the Weekly Platform Trial Q&A Webinars:
<https://bit.ly/3DvkJta>



Stay Connected to the Platform Trial

More investigational products are anticipated to be added to the HEALEY ALS Platform Trial through support by pharma, foundation partners, philanthropy, federal, and other fundraising initiatives.

Visit our website to learn more about current and future regimens:
<https://bit.ly/31EK198>



View map and contact info for participating research centers:
<https://bit.ly/31lCv9t>



Sign up for the ALS Link to hear about ALS news and research:
<https://bit.ly/3EH2eMT>



Regimen G Drug Science Q&A Webinar



Open to everyone!
Thursday, July 20th
5:00-6:00pm Eastern

Topic: DNL343 Drug Science and Mechanism of Action

Link to Register: <https://bit.ly/3NqJU1j>

DEALI

Checking Site Status Online

List of Participating Sites

Many sites are expected to start enrolling for Regimen F soon. Sites marked "Recruiting" are currently enrolling participants.

Sites marked "Active, Not recruiting" are active in the Platform Trial (for example, they are following participants in ongoing regimens that have already completed enrollment) but are not enrolling new participants at this time.

Contact a study team near you to discuss enrollment opportunities

Site	State	Enrollment Status	Trial Contact Information
Mayo Clinic Florida	FL	Active, Not recruiting	Jany Paulett
Nova Southeastern University	FL	Recruiting	Donovan Mott



<https://bit.ly/3g2NZr5>



THE ALS ASSOCIATION/NORTHEAST ALS CONSORTIUM

Educational Webinar

UNDERSTANDING STATISTICAL AND CLINICAL SIGNIFICANCE

SPEAKERS



JINSY ANDREWS, MD, MSC
COLUMBIA UNIVERSITY



CHRISTINA FOURNIER, MD, MSC
EMORY UNIVERSITY



ERIC MACKLIN, PhD
HARVARD MEDICAL
SCHOOL

~~THURSDAY | 15 JUNE
4:00 - 5:00 PM ET~~

What do researchers and scientists mean when they describe a study as “statistically significant?” How do people with ALS and clinicians understand whether or not a treatment option is “clinically significant?” This webinar and panel discussion will provide a framework for understanding the results of ALS clinical trials, using several recent studies as examples.

Rescheduled!
WED, JUN 21
1:00-2:00pm ET

Register Here:



<https://bit.ly/3oubqBo>

Patient Navigation

Central resource for people living with ALS



Catherine Small

Phone: 833-425-8257 (HALT ALS)

E-mail: healeyalsplatform@mgh.harvard.edu

Weekly webinar
registration:



<https://bit.ly/3r6Nd2L>

ALS Link sign-up:



<https://bit.ly/3o2Ds3m>

Upcoming Webinars:

June 22nd- Weekly Q&A and Lumbar Puncture Discussion with Shafeeq Ladha, MD

June 29th- Weekly Q&A with Hilda Gutierrez from Beth Israel Deaconess (Boston)

July 6th- Weekly Q&A with Bill Cho MD, PhD from Calico Life Sciences (Regimen F)



Allison Bulat