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 22, 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

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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

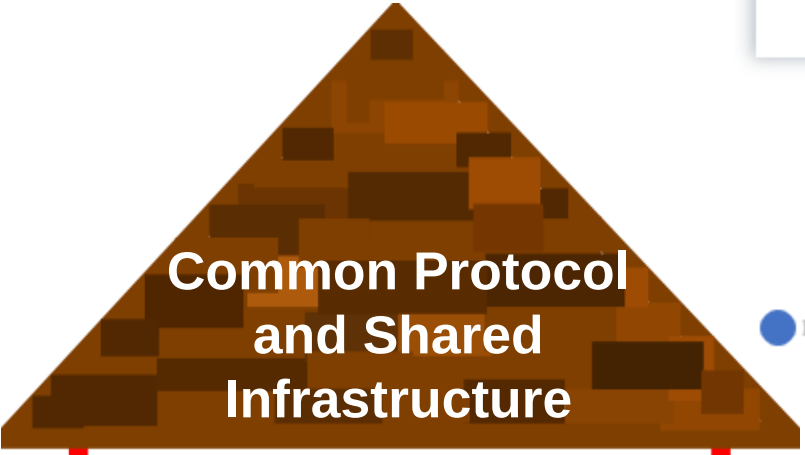
RUN2REVIVE MIND · BODY · POTENTIAL

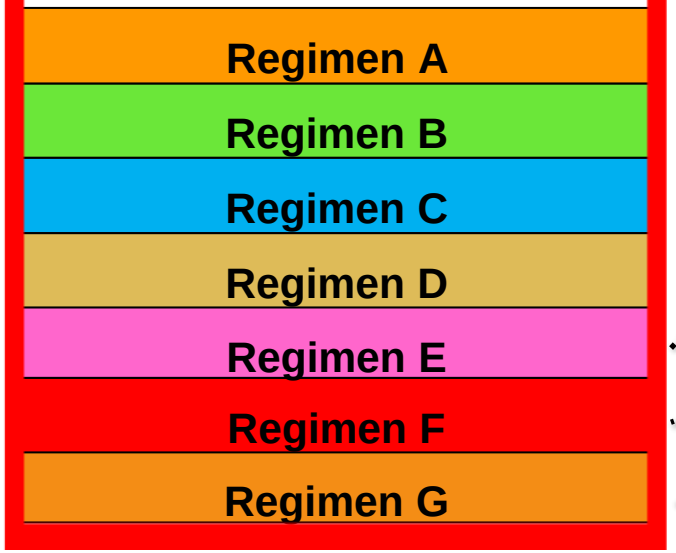
THE ARTHUR M. BLANK FAMILY FOUNDATION

BASEBALL WINTER MEETINGS SAN DIEGO 2019

AMG The AMG Foundation

HEALEY ALS Platform Trial:





SEELOS THERAPEUTICS | ENROLLMENT COMPLETE

Calico | ENROLLING

DENALI THERAPEUTICS | ENROLLING

Checking Site Status Online

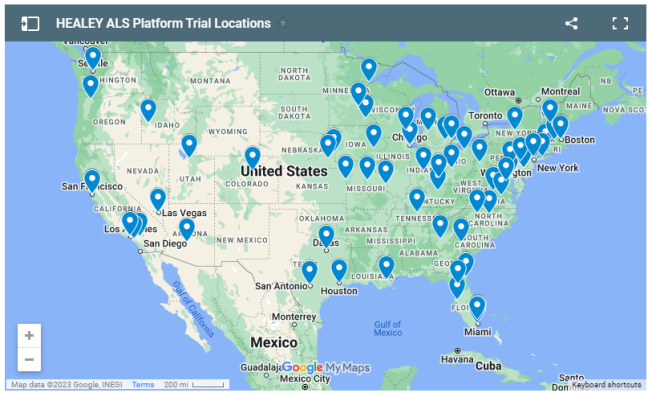
Contact a study team near you to discuss enrollment opportunities

List of Participating Sites

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.

Site	State	Enrollment Status	Trial Contact Information
Barrow Neurological Institute	AZ	Recruiting	Whitney Dailey
Cedars-Sinai Medical Center	CA	Recruiting	Sophia Mostowy
Forbes Norris MDA/ALS Research Center, California Pacific Medical Center	CA	Recruiting	Teji Dulai
Kaiser Permanente, Los Angeles Medical Center	CA	Recruiting	Mary H. Berganza

Map of Participating Sites



https://bit.ly/3g2NZr5

Enrollment Update: Regimen F (as of 6/22/23)

132

Participants consented to Master Protocol since RGF initiated

89

Participants assigned to RGF

69

Participants randomized within RGF (enrollment goal ≈240)

Thank You

for your partnership in ALS research

Enrollment Update: Regimen G (as of 6/22/23)

84

Participants consented to Master Protocol since RGG initiated

17

Participants assigned to RGG

7

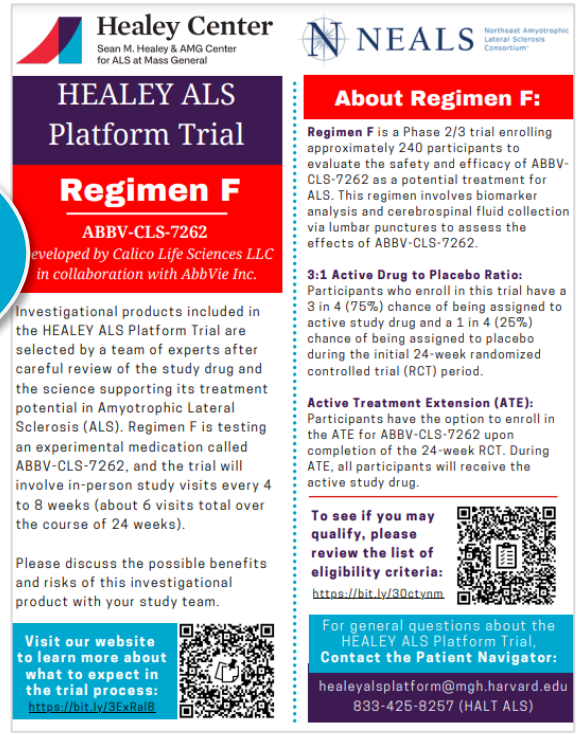
Participants randomized within RGG (enrollment goal ≈240)

Thank You

for your partnership in ALS research

Reg F and Reg G Resources on MGH Website

Visit Our Website



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/3ExRal8

About Regimen F:

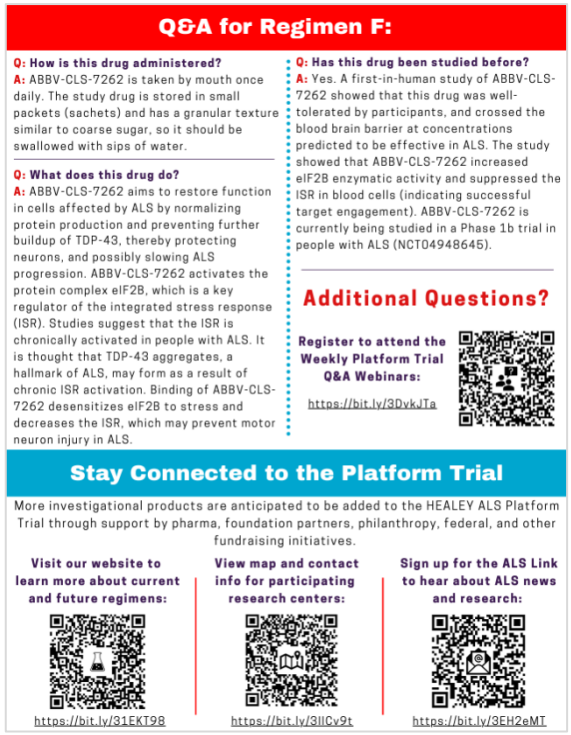
Regimen F is a Phase 2/3 trial enrolling approximately 240 participants to evaluate the safety and efficacy of ABBV-CLS-7262 as a potential treatment for ALS. This regimen involves biomarker analysis and cerebrospinal fluid collection via lumbar punctures to assess the effects of ABBV-CLS-7262.

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/30ctynm

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



Q&A for Regimen F:

Q: How is this drug administered?
A: ABBV-CLS-7262 is taken by mouth once daily. The study drug is stored in small packets (sachets) and has a granular texture similar to coarse sugar, so it should be swallowed with sips of water.

Q: What does this drug do?
A: ABBV-CLS-7262 aims to restore function in cells affected by ALS by normalizing protein production and preventing further buildup of TDP-43, thereby protecting neurons, and possibly slowing ALS progression. ABBV-CLS-7262 activates the protein complex eIF2B, which is a key regulator of the integrated stress response (ISR). Studies suggest that the ISR is chronically activated in people with ALS. It is thought that TDP-43 aggregates, a hallmark of ALS, may form as a result of chronic ISR activation. Binding of ABBV-CLS-7262 desensitizes eIF2B to stress and decreases the ISR, which may prevent motor neuron injury in ALS.

Q: Has this drug been studied before?
A: Yes. A first-in-human study of ABBV-CLS-7262 showed that this drug was well-tolerated by participants, and crossed the blood brain barrier at concentrations predicted to be effective in ALS. The study showed that ABBV-CLS-7262 increased eIF2B enzymatic activity and suppressed the ISR in blood cells (indicating successful target engagement). ABBV-CLS-7262 is currently being studied in a Phase 1b trial in people with ALS (NCT04948645).

Additional Questions?

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

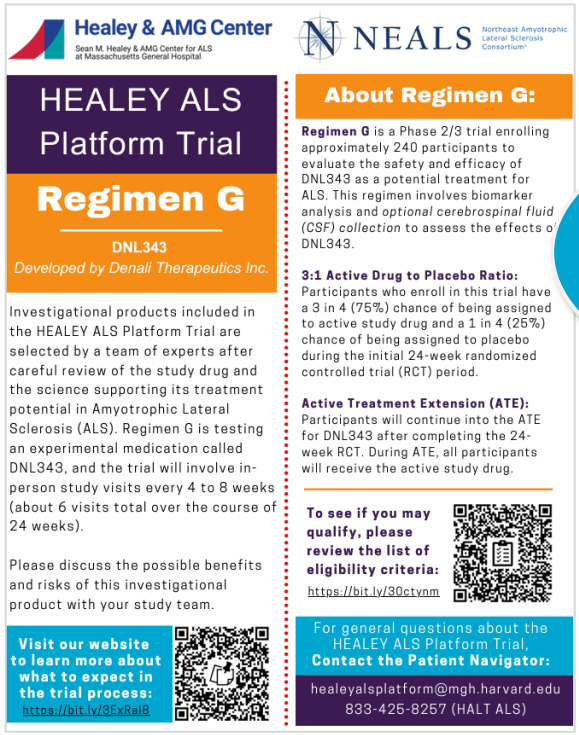
Stay Connected to the Platform Trial

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/31EKT98

View map and contact info for participating research centers: https://bit.ly/3IlCv9t

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



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

NEALS Northeast Amyotrophic Lateral Sclerosis Consortium

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/3ExRal8

About Regimen G:

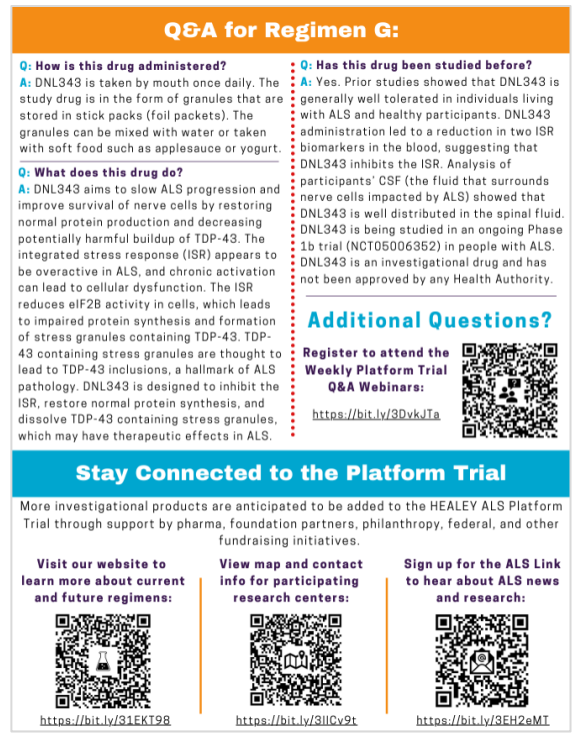
Regimen G is a Phase 2/3 trial enrolling approximately 240 participants to evaluate the safety and efficacy of DNL343 as a potential treatment for ALS. This regimen involves biomarker analysis and *optional cerebrospinal fluid (CSF) collection* to assess the effects o DNL343.

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/30ctynm

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



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/31EKT98

View map and contact info for participating research centers: https://bit.ly/3IlCv9t

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

Printable Brochures Available!

https://bit.ly/3SIwH4X

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

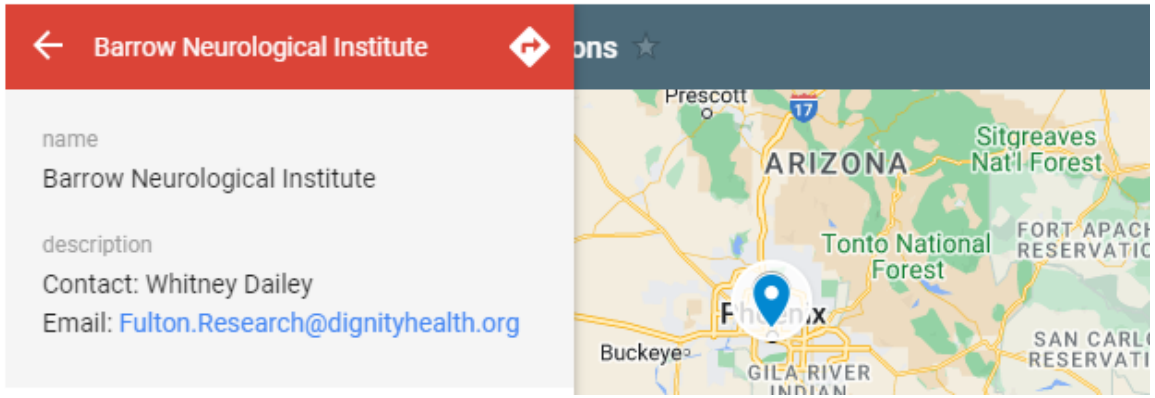
DENALI

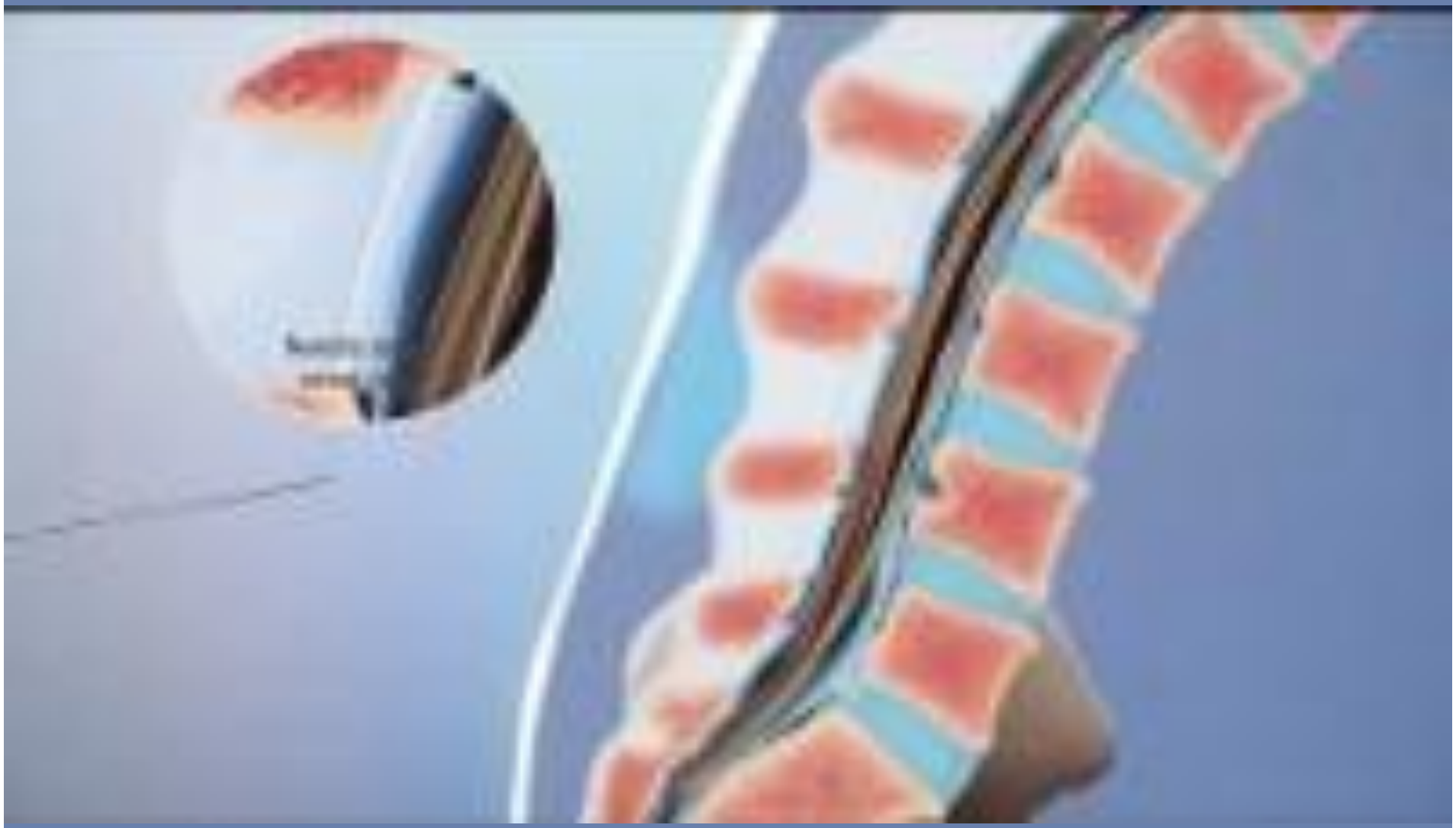
Guest Speaker

Shafeeq Ladha, MD

Platform Trial Site Investigator

Barrow Neurological Institute (Phoenix, AZ)





Link to Lumbar Puncture Short Video:
https://www.youtube.com/watch?v=3omIOEnll8o

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.

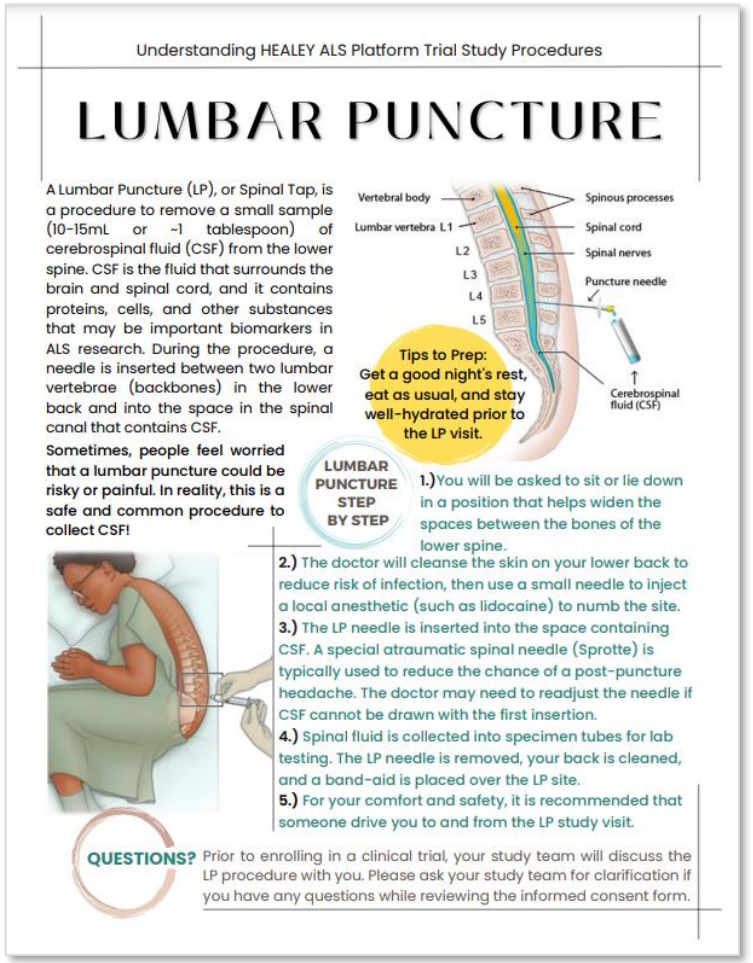
A prior first-in-human study of ABBV-CLS-7262 showed that this drug was well-tolerated by participants, demonstrated target engagement by increasing eIF2B enzymatic activity, and suppressed the ISR in blood cells. ABBV-CLS-7262 crossed the blood brain barrier at concentrations predicted to be efficacious 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



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.

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!

Vertebral body
Lumbar vertebra L1
L2
L3
L4
L5
Spinous processes
Spinal cord
Spinal nerves
Puncture needle
Cerebrospinal fluid (CSF)

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

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.

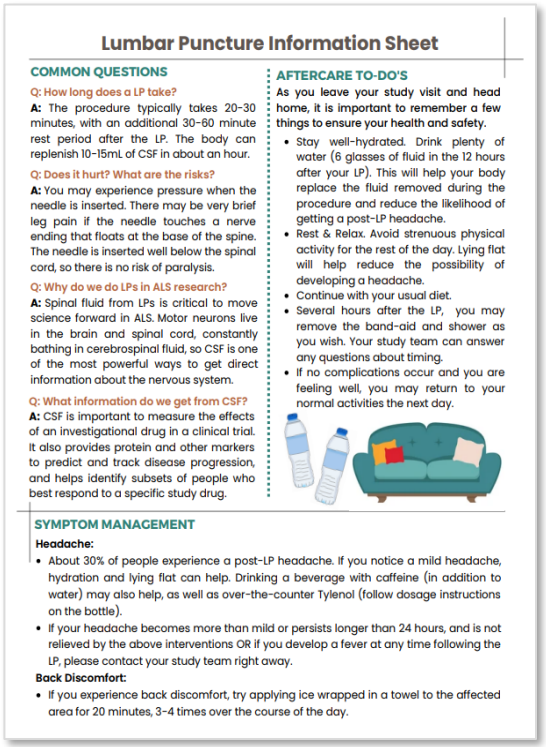
3.) The LP needle is inserted into the space containing CSF. A special atraumatic spinal needle (Sprotte) is typically used to reduce the chance of a post-puncture headache. The doctor may need to readjust the needle if CSF cannot be drawn with the first insertion.

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.

Printable Lumbar Puncture Info Sheet!



Lumbar Puncture Information Sheet

COMMON QUESTIONS

Q: How long does a LP take?
A: The procedure typically takes 20-30 minutes, with an additional 30-60 minute rest period after the LP. The body can replenish 10-15mL of CSF in about an hour.

Q: Does it hurt? What are the risks?
A: You may experience pressure when the needle is inserted. There may be very brief leg pain if the needle touches a nerve ending that floats at the base of the spine. The needle is inserted well below the spinal cord, so there is no risk of paralysis.

Q: Why do we do LPs in ALS research?
A: Spinal fluid from LPs is critical to move science forward in ALS. Motor neurons live in the brain and spinal cord, constantly bathing in cerebrospinal fluid, so CSF is one of the most powerful ways to get direct information about the nervous system.

Q: What information do we get from CSF?
A: CSF is important to measure the effects of an investigational drug in a clinical trial. It also provides protein and other markers to predict and track disease progression, and helps identify subsets of people who best respond to a specific study drug.

AFTERCARE TO-DO'S

As you leave your study visit and head home, it is important to remember a few things to ensure your health and safety.

- Stay well-hydrated. Drink plenty of water (6 glasses of fluid in the 12 hours after your LP). This will help your body replace the fluid removed during the procedure and reduce the likelihood of getting a post-LP headache.
- Rest & Relax. Avoid strenuous physical activity for the rest of the day. Lying flat will help reduce the possibility of developing a headache.
- Continue with your usual diet.
- Several hours after the LP, you may remove the band-aid and shower as you wish. Your study team can answer any questions about timing.
- If no complications occur and you are feeling well, you may return to your normal activities the next day.

SYMPTOM MANAGEMENT

Headache:

- About 30% of people experience a post-LP headache. If you notice a mild headache, hydration and lying flat can help. Drinking a beverage with caffeine (in addition to water) may also help, as well as over-the-counter Tylenol (follow dosage instructions on the bottle).
- If your headache becomes more than mild or persists longer than 24 hours, and is not relieved by the above interventions OR if you develop a fever at any time following the LP, please contact your study team right away.

Back Discomfort:

- If you experience back discomfort, try applying ice wrapped in a towel to the affected area for 20 minutes, 3-4 times over the course of the day.

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