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 ALS Platform Trial:

Regimen A
Regimen B
Regimen C
Regimen D
Regimen E
Regimen F
Regimen G

Common Protocol and Shared Infrastructure

Screen for eligibility → Randomization 3:1 → Active
Placebo → Active

Screening Period → Randomized Period (24 weeks)
Open-Label Extension Period (Active Treatment Extension)

ENROLLMENT COMPLETE

ENROLLING

ENROLLING
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)

119
Participants consented to Master Protocol since RGF initiated

76
Participants assigned to RGF

64
Participants randomized within RGF (enrollment goal ≈240)

Thank You
for your partnership in ALS research
Regimen F: ABBV-CLS-7262, by Calico and AbbVie- Now Recruiting

Regimen F: 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 destabilizes 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 (NCT04948845), 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


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 puncture to assess the effects of ABBV-CLS-7262.

3:1 Active Drug to Placebo Ratio: Participants are enrolled in this trial with a 3:1 (75%) chance of being assigned to active study drug and a 1:1 (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 a 24-week extension study 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:

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

https://bit.ly/3g2NZr5
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 >50% 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, eIF2α 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 (NCT05063352) in people with ALS.

Download Regimen G Brochure

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

B) Active Drug to Placebo Ratio: Participants who enroll in this trial have a 50% chance of being assigned to placebo during the initial 24 month randomized controlled trial (RCT) period. Active Treatment Extension (ATE): Participants who continue onto 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 visit the site for eligibility criteria:
https://www.dnl343.com/app/

For general guidance on the HEALEY ALS Platform Trial
Contact the Patient Navigator:
healeyplatform@mgh.harvard.edu
800-420-8267 (toll-free ATLS)

Q&A for Regimen G:
Q. Who is this drug administered to?
A. DNL343 is only for people with ALS. The study drug is in the form of granules that are mixed in milk before oral administration. These granules can be mixed with water or taken with soft foods such as applesauce or soup.

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 granules are meant to be mixed in milk, administered in milk, and consumed in milk. The drug reduces eIF2α activity in cells, which leads to improved protein synthesis and restoration of stress granules containing TDP-43. TDP-43 containing stress granules are thought to lead to TDP-43 inclusions, a hallmark of ALS. The drug also helps to preserve normal neural function, and improve the experience of living with ALS.

Q. What happens if this drug doesn’t work?
A. If this drug isn’t effective, the participants will be reassigned to a new drug in one of the trials that are currently ongoing. If this drug isn’t effective, the participants will be reassigned to a new drug in one of the trials that are currently ongoing. If this drug isn’t effective, the participants will be reassigned to a new drug in one of the trials that are currently ongoing.

Q. Is this treatment being studied in any ongoing Phase 1 or 2 trials?
A. Yes, DNL343 is currently being studied in an ongoing Phase 1 trial (NCT05063352) 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
https://www.mgh.org/ALSerends

Stay Connected to the Platform Trial
Visit our website to learn more about current and future regimens:

Sign up for the ALSLink to hear about ALS news and research:
Regimen G Drug Science Q&A Webinar

Topic: DNL343 Drug Science and Mechanism of Action

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

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

<table>
<thead>
<tr>
<th>Site</th>
<th>State</th>
<th>Enrollment Status</th>
<th>Trial Contact Information</th>
</tr>
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<tbody>
<tr>
<td>Mayo Clinic Florida</td>
<td>FL</td>
<td>Active, Not recruiting</td>
<td>Jany Paulet</td>
</tr>
<tr>
<td>Nova Southeastern University</td>
<td>FL</td>
<td>Recruiting</td>
<td>Donovan Mott</td>
</tr>
</tbody>
</table>

Contact a study team near you to discuss enrollment opportunities

https://bit.ly/3g2NZr5
Register Here:

https://bit.ly/3oubqBo
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)

Patient Navigation
Central resource for people living with ALS

Phone: 833-425-8257 (HALT ALS)
E-mail: healeyalsplatform@mgh.harvard.edu

Weekly webinar registration: [QR Code]
ALS Link sign-up: [QR Code]

https://bit.ly/3o2Ds3m
https://bit.ly/3r6Nd2L