HEALEY ALS Platform Trial

Weekly Q&A – March 16, 2023

Healey Center
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Guest Speaker

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The HEALEY ALS Platform Trial is a unique opportunity to advance science

- DNA – whole genome sequencing
- Neurofilaments – for all regimens
- Biomarkers (Blood, Urine, CSF) – several drug-specific biomarkers
- Speech Analysis – emerging digital biomarker
- Home Spirometry – critical during the pandemic

Additional biomarkers/outcome measures are being considered for upcoming regimens (e.g., new patient-reported outcomes; PBMCs for stem cell generation)
TDP-43 nuclear clearing is a pathological hallmark of most sALS: Loss of TDP-43 nuclear function leads to mis-regulation of hundreds of RNA species.
TDP-43 loss of function generated cryptic peptide detected in sALS and C9 ALS CSF

Irwin et al, BioRxiv, 2023
Identification of multiple TDP-43 dependent cryptic peptides in ALS CSF

Detection of cryptic peptides RNA in ALS patients

(Seddighi et al, BioRxiv, 2023)
Functional Biomarkers for sALS: TDP-43

• Multiple TDP-43 readouts coming:
  • cryptic peptides (e.g. ELISA), RNA analytics

• Needed studies
  • The first two identified- more are likely to come
  • Need data on reliability, reproducibility, sensitivity
    • Banked CSF may be used
  • Correlation with disease parameters
    • rate of progression, clinical subtypes, age, sex, etc
  • Response to drugs ??
  • Correlation with existing biomarkers: NFL?, inflammation, etc
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

ENROLLMENT COMPLETE

SEELOS THERAPEUTICS

IN START-UP

Calico

IN START-UP

DENAAL THERAPEUTICS
11 Sites Currently Active for Regimen F

- 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

(as of 3/16/23)

https://bit.ly/3g2NZr5
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 (NCT04949645), and will be studied further as part of the HEALEY ALS Platform Trial.

Watch this video for more information on the mechanism of action behind ABBV-CLS-7262.

Regimen F: 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 on subjects who were exposed to the effects of ABBV-CLS-7262.

3. Place Drug to Plasma: Participants who are in this trial will 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 12-week randomized controlled trial (RCT) period.

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 on subjects who were exposed to the effects of ABBV-CLS-7262.

3. Active Drug to Plasma: Participants who are in this trial will 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 12-week randomized controlled trial (RCT) period.

Active Treatment Extension (ATE): Participants have the option to stay in the study for up to 12 additional weeks after the completion of the 24-week RCT. During this time, participants will receive the active study drug.

Is your eligibility status ready? To see if you may qualify, please review the list of eligibility criteria: bit.ly/RegimenF-Eligibility

For more information, visit the HEALEY ALS Platform Trial website or call the Patient Navigator: 888-425-9757 (H&L ALTS)

Visit our website to learn more about what to expect in the trial process.

Download brochure

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]

Upcoming (Spring!) Webinars:

March 23- Biomarker Discussion with Jeffrey Rothstein, MD PhD (Johns Hopkins)
March 27- Regimen F Drug Science Q&A with Calico
March 30- Weekly Q&A