Accelerating innovation for a cure

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Traditional Clinical Trial

vs.

HEALEY ALS Platform Trial

Cuts time in 1/2
Cuts costs by 1/3
Reduces placebo

1/3
Shared Infrastructure and Master Protocol Allow for Operational and Scientific Efficiencies

Enroll in HEALEY ALS Platform Trial

Shared infrastructure and common protocol allow sharing of placebo data

Participant Flow

Randomization

Active

Placebo

Active

Placebo

Active

Placebo

Shared Placebo

Regimen A

Regimen B

Regimen C

Regimen D

Cuts time in 1/2

Cuts costs by 1/3

Reduces placebo

1/3
Assessing emerging biomarkers/outcome measures

- **DNA** – genetic analysis for all regimens
- **Neurofilaments** – NfL analysis for all regimens
- **Biomarkers** (Blood, Urine, CSF) – several drug-specific biomarkers in each regimen
- **Speech Analysis** – data collected for regimens A-D
- **Home Spirometry** – critical during the pandemic for regimens A-D

Additional biomarkers/outcome measures being considered for upcoming regimens (PBMCs, ROADS)
Schema for Each Regimen

- Screen for eligibility
- Randomization 3:1
  - Active
  - Placebo
- Open-Label Extension Period (Active Treatment Extension)
  - 24 weeks

Screening Period
Randomized Period
The HEALEY ALS Platform Trial is a Perpetual Adaptive Trial

- **Regimen A** (n=160 for each regimen):
  - CNM-Au8
  - Placebo

- **Regimen B**:
  - 3:1 Randomization within each Regimen
  - Zilucoplan
    - Placebo
  - Verdiperstat
    - Placebo
  - CNM-Au8
    - Placebo

- **Regimen C** (n=120 for active drug, n=40 for placebo):
  - Open Label Extension
  - Placebo

- **Screening**
  - Regimen Assignment
  - (n=160 for each regimen)
The HEALEY ALS Platform Trial is a Perpetual Adaptive Trial

Regimen A
Regimen B
Regimen C
Regimen D

3:1 Randomization within each Regimen

(n=160 for each regimen)

(n=120 for active drug; n=40 for placebo)

Screening
Regimen Assignment

Regimen A
Regimen B
Regimen C
Regimen D

Zilucoplan
Verdiperstat
CNM-Au8
Pridopidine

Placebo
Placebo
Placebo
Placebo

Open Label Extension
Open Label Extension
Open Label Extension
Open Label Extension
The goal of the HEALEY ALS Platform Trial is to screen drugs rapidly and efficiently, get solid answers, and determine next steps.

**Screening**

- Regimen A: (n=160 for each regimen)
  - CNM-Au8 Placebo
  - Verdiperstat Placebo
  - Zilucoplan Placebo
  - Pridopidine Placebo
  - Trehalose Placebo
  - Shared Placebo

- Regimen B: 3:1 Randomization within each Regimen
  - (n=120 for active drug; n=40 for placebo)

- Regimen C
- Regimen D
- Regimen E

**24 weeks on study drug (active:placebo = 3:1)**

**Open Label Extension**
**Initial Regimen Updates – trial gave clear answers and direction, efficient execution (time, resources, less placebo)**

- **February 2022:** Regimen A stopped early for futility

- **September 2022:** Regimen B top line results announced
  * Did not meet the prespecified primary endpoint and there were no statistically significant benefits on key secondary measures; full study results, including data on biomarkers and exploratory measures, are expected in the coming months

- **October 2022:** Regimen C top line results announced
  * While the primary endpoint was not met, a secondary endpoint analysis of survival demonstrated a significant reduction in risk of death or permanently assisted ventilation when adjusting for baseline risk imbalances in the CNM-Au8 regimen for the 30 mg dose; full study results, including data on biomarkers and exploratory measures, are expected in the coming months
Regimen G
Regimen C
Regimen D
Regimen E
Regimen F
Regimen G

MASTER PROTOCOL

2023

ENROLLING

IN START-UP
Informational Webinars about Regimen E

Trehalose/SLS-005 Drug Science and Mechanism of Action Q&A Webinar
Hosted by Seelos Therapeutics on 10 March 2022

Recording Available!

Recording available under “science and mechanism of action series”

The ALS Association/Northeast ALS Consortium Educational Webinar

Update on Healey ALS Platform Trial Regimen E: Trehalose for ALS

Recording Available!

UPDATE ON REGIMEN E
TREHALOSE FOR ALS

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SEAN M. HEALEY & AME CENTER FOR ALS AT MGH

Shafeeq Ladha, MD
BARRON NEUROLOGICAL INSTITUTE

TUESDAY 4 OCTOBER 3 PM EDT

https://bit.ly/3X2u004
Recording available under “educational webinars” on neals.org
60 Sites Currently Activated for Regimen E

(as of 1/5/23)

Sites in blue participated in previous regimens. Sites in green (underlined to the side) are new additions to the Platform Trial!

Lehigh Valley Health Network
Mass General Hospital
University of Kansas
University of Maryland
California Pacific Medical Center
Northwestern University
Virginia Commonwealth University
University of Nebraska
Washington University
Wake Forest University
Hospital for Special Care
Saint Alphonsus Regional
University of Massachusetts
Duke University
Barrow Neurological Institute
Georgetown University
Texas Neurology
Beth Israel Deaconess Medical Center
SUNY Upstate
Spectrum Health
Henry Ford Hospital
Essentia Health
University of Southern California
University of South Florida
University of Colorado
Providence Brain and Spine
University of Minnesota
Loma Linda University
University of Iowa
Swedish Medical Center
Ohio State University
University of Cincinnati
Thomas Jefferson University
UC San Francisco
Mayo Rochester
University of Washington
Vanderbilt University
UPMC
Indiana University
Augusta University
University of Utah
Holy Cross Hospital
Penn State Hershey
University of CA, Irvine
Cedars Sinai Medical Center
University of Pennsylvania
Nova Southeastern University
Johns Hopkins University
Columbia University
Stony Brook University
Kaiser, Los Angeles
Cleveland Clinic
Medical College of Wisconsin
University of Michigan
Las Vegas Clinic
George Washington University
Mayo Clinic Florida
University of Kentucky
Houston Methodist
Hackensack University

https://bit.ly/3g2NZr5
Regimen E Updates (as of Jan 5, 2023)

- 193 participants consented to Master Protocol since RGE initiated
- 147 participants assigned to RGE
- 138 participants randomized within RGE

85.60% enrollment

137 out of 160 participants randomized within RGE.
Intermediate Size EAP - Trehalose

- In start up now
- Expected to enroll first participants in Q1 2023
- 25 sites
- 70 participants
- NIH-funded (PIs: Babu, Berry, Paganoni)
- Happening in parallel to Regimen E of the HEALEY ALS Platform Trial

Outcomes:
- Long-term safety in a broad population
- Biological impact (as measured by neurofilament light levels)
- Clinical efficacy signal (as compared to natural history cohorts)

Regimen F

Investigational drug ABBV-CLS-7262 initiates design phase for entry into the HEALEY ALS Platform Trial

- **ABBV-CLS-7262 is being developed by AbbVie Inc and Calico Life Sciences**

- It targets eIF2B, a key regulator of the integrated stress response (ISR). In neurons exposed to cellular stressors, inhibition of the ISR by ABBV-CLS-7262 restores protein synthesis and dissolves pre-formed TDP-43 containing stress granules. This effect of ABBV-CLS-7262 is of clinical interest because TDP-43 containing stress granules are thought to lead to TDP-43 inclusions, a hallmark of ALS pathology.
Regimen G

• DNL343 is being developed by Denali Therapeutics.
• It targets eIF2B, a key regulator of the integrated stress response, to restore protein synthesis and dissolve pre-formed TDP-43 containing stress granules which are thought to lead to TDP-43 inclusions, a hallmark of ALS pathology.

“By adding one more drug to the platform, we continue to push research forward in hopes of soon finding many more effective treatments for ALS.”

Merit Cudkowicz, MD, MSc
Director, Sean M. Healey & AMG Center for ALS, Massachusetts General Hospital

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]

Upcoming Webinars:
January 12 - Weekly Q&A
January 19 - Weekly Q&A
January 26 - Weekly Q&A

ALS Link sign-up: [QR Code]

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