Thank you for joining the **Leap Day Special** 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 – February 29, 2024
The last leap day was February 29, 2020. As we reflect on progress over the last four years, we are immensely grateful to trial participants and everyone in the ALS community who has supported research in many different ways.

Progress in ALS research and advances in clinical care options would not be possible without your partnership.

Thank You
ALS Therapy Options Are Expanding

- Disease Modifying Medications - 4 approved drugs in the US
  - **Radicava** (edaravone; 2017-IV; May 2022-oral)
  - **Relyvrio** (PB and TURSO; September 2022)
  - **Tofersen, SOD1** (April 2023) - first ALS approval under the accelerated approval pathway

- Medications and supportive care to treat symptoms

*Early diagnosis and access to care are paramount*
Short-Term and Long-Term Goals:

• **Slow/Stop ALS**
  – Likely to require a cocktail of products
  – Targeted drugs, if applicable

• **Prevent ALS**
  – Gene carriers

• **Reverse ALS**

• > 250 companies in ALS space
• Active clinical trial networks
• Engaged patient population
• Engaged, collaborative foundations
Multiple mechanisms are implicated in ALS

- Astrocyte
  - Neuroinflammation
  - Glutamate excitotoxicity
  - Dysfunction of axonal transport systems
  - T-Reg
  - Monocyte/Macrophage
  - Schwann cell defects

- Microglia
  - Release of proinflammatory cytokines
  - Myeloperoxidase
  - Ca\(^{2+}\)-dependent enzymatic pathways
  - Integrated stress response (ISR)
  - Autophagy
  - C9orf72, TARDBP, FUS, and SOD1 mutations
  - TDP-43 aggregates

- Mitochondrial dysfunction
- Oxidative stress
- NAD+ catalysis and ATP production
- Sigma-1 receptor agonist
- ER stress
- RNA metabolism
- Nucleocytoplasmic trafficking

- Ion channel dysfunction
- Protein aggregates
- Complement
- Muscle
  - Neuromuscular junction defects
  - Muscle dysfunction
Common protocol and shared infrastructure allow for operational and scientific efficiencies.

Regimen: Active Study Drug + Matching Placebo

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

**Common Protocol**
- 1 Protocol (Phase 2/3)
- 1 single IRB
- Central Governance

- **7 Regimens**
- **70+ Enrolling Sites**
- **~1300 Participants**
Platform trials are 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 for upcoming regimens (new patient-reported outcomes; PBMCs for stem cell generation)
Enrollment Update: Regimen F and Regimen G

634
Participants consented to Master Protocol since RGF and RGG initiated

537
Participants assigned to RGF or RGG

469
Participants randomized within RGF or RGG

Thank You
for your partnership in ALS research

(as of 2/29/24)
Providing research access across a diverse network of 70+ NEALS sites

Contact a study team near you to discuss enrollment opportunities

https://bit.ly/3g2NZr5
Sharing our experience

Meetings with disease-specific networks both in the US and globally

Disease Areas
1. ALS
2. Alzheimer Disease
3. Duchenne Muscular Dystrophy
4. FSHD
5. Myotonic Dystrophy
6. Frontotemporal Dementia
7. Parkinson Disease
8. Progressive Supranuclear Palsy (PSP)
9. Traumatic Brain Injury
10. Spinal Cord Injury
11. Vanishing White Matter Disease
12. Depression
13. Neurofibromatosis (NF)
14. Scleroderma
15. Idiopathic Pulmonary Fibrosis
16. Fibrodysplasia Ossificans Progressiva (FOP)
17. Vascular Malformations

Master Protocol, Publications, and Other Documents Available at:
https://www.massgeneral.org/neurology/als/research/research-partners

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Sharing our experience

Research publications available via open access

Adaptive Platform Trials to Transform Amyotrophic Lateral Sclerosis Therapy Development
First published: 21 December 2021
Open Access

Design and Statistical Innovations in a Platform Trial for Amyotrophic Lateral Sclerosis
First published: 28 May 2023
Open Access
Upcoming Webinars:

- **March 7th**: Weekly Q&A
- **March 14th**: EAP Discussion with Dr. Jinsy Andrews (Columbia University)
- **March 21st**: Weekly Q&A

Patient Navigation
Central resource for people living with ALS

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Weekly webinar registration: [QR Code](https://bit.ly/3r6Nd2L)
ALS Link sign-up: [QR Code](https://bit.ly/3o2Ds3m)