HEALEY ALS Platform Trial

Investigational Products Tested in the Trial

CNM-Au8
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# Accelerating ALS Therapy Development

## Traditional

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Disease</th>
<th>Treatment A</th>
</tr>
</thead>
</table>

## Platform

<table>
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<tr>
<th>Intervention</th>
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<th>Treatment B</th>
<th>Treatment C</th>
<th>Treatment D</th>
</tr>
</thead>
</table>
Perpetual Adaptive Trial
Randomization Ratio 3:1; Shared Placebo
Open Label Extension offered

Screening  
Regimen Assignment
(n=160 for each regimen)

Regimen A
Regimen B
Regimen C
Regimen D

3:1 Randomization within each Regimen

Zilucoplan
Placebo

Verdiperstat
Placebo

CNM-Au8
Placebo

Pridopidine
Placebo

Shared Placebo

Open Label Extension

Screening

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

James Berry, MD, MPH
MGH, Boston, MA
Regimen co-Lead

Nicholas Maragakis, MD
Johns Hopkins, Baltimore, MD
Regimen co-Lead
Overview | CNM-Au8 (Regimen C)

1. What It Is

2. How It Works

3. Evidence Supporting Treatment of ALS
In bulk form, gold is inert and unreactive. It resists corrosion and doesn’t rust.

When gold is made into tiny nanocrystals, gold becomes highly active as a Nanocatalyst.
What is a Nanocatalyst?

In a biological or chemical reaction, Reactant A and Reactant B combine to make a totally new Product C.

A **nanocatalyst** is a very, very small catalyst that makes specific biological reactions go faster, so that more of Product C is produced rapidly.
ALS | Restoring Neuronal Energetic Loss Is Essential

**ALS Neuronal Metabolic Failure**

- Atrophied Muscle
- Impaired Neuromuscular Junction
- Activated Astrocyte
- Compromised Axon
- Dendritic Retraction

**CNM-Au8 catalysis supports cellular energy in neurons ...**

![Diagram showing metabolic pathways]

- ATP
- NADH
- NAD+
- Glycolysis & TCA Cycle
- Mitochondrial ETC Complex

... providing the brain, spinal cord, and motor neurons with more access to key energy metabolites, improving motor neuron health and survival

**ALS Neuronal Metabolic Support**

- Dendritic Network
- Supportive Astrocyte
- Healthy Myelinated Axon
- Healthy Muscle


Data on File, Clene Nanomedicine.
CNM-Au8 | ALS Neuroprotection in Human Neurons

Induced Pluripotent Stem Cell *In Vitro* Results – Motor Neuron Markers

CNM–Au8 | Treatment Results in ALS Neuroprotection

In Vivo SOD1 Congenic Mouse

CNM-Au8 Improves Healthspan

Neurological Score
(TDI Rodent Scale)
(Mean ± SEM)

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(TDI Rodent Scale)
(Mean ± SEM)

Kaplan-Meier Survival Curve
SOD1G93A Mice

Vehicle

CNM-Au8

p = 0.0074,
two-way ANOVA

1. Median Survival
   23 days
2. Wilcoxon test
   p=0.03
3. Hazard Ratio
   0.3730
4. 95% CI of Ratio
   0.1300 to 1.070

CNM-Au8 | Clean Animal Toxicology Findings
All Studies Resulted in No Adverse Effect Level (NOAEL)\textsuperscript{a}

Standard ICH M3(R2) Toxicology Program

- **Genotoxicity**
  - In Vitro & In Vivo (Rodent)

- **Single Dose Toxicokinetics**
  - Canine

- **Max Feasible Toxicokinetics**
  - Rodent (1-Wk, SQ)

- **Chronic Toxicity**
  - Rodent (6-Month)

- **Safety Pharmacology**
  - CNS, CV, Renal

- **Multi-Dose Toxicokinetics**
  - Canine (7-Day)

- **Max Feasible Toxicokinetics**
  - Canine (3-Wk)

- **Chronic Toxicity**
  - Canine (9-Month)

- **Dose Range Finding**
  - Rodent, Minipig

- **MTD Toxicokinetics**
  - Canine (4-Wk)

- **High Dose Toxicokinetics**
  - Rodent (3-Wk)

\textsuperscript{a} NOAEL = No Dose Limiting Toxicities Observed

Data on File, Clene Nanomedicine.
CNM-Au8 | Well Tolerated Safety Profile

No Related SAEs or Related Study Discontinuations Across >75 Yrs. Cumulative Exposure

Phase 1 First In Human Study

- Most frequent Adverse Events by System Organ Class: Nervous/GI – Nearly all were Grade 1 severity (mild)
- No serious TEAEs, TEAEs leading to discontinuation of treatment, or TEAEs considered severe, life-threatening, or resulting in death
- No dose responsive TEAEs observed in SAD or MAD

Phase 2 MS & Parkinson’s

- VISIONARY-MS STUDY
  - Up to 48-weeks exposure

- RepairPD
  - Up to 21-weeks exposure

- RepairMS
  - Up to 18-weeks exposure

Phase 2 & 3 ALS

- HEALEY ALS Platform Trial
  - Up to 16-weeks exposure

- RESCUE ALS
  - Up to 36-weeks exposure

- MGH ALS Expanded Access Protocol
  - Up to 50-weeks exposure

Data on File, Clene Nanomedicine.
THANK YOU | From All of Us at Clene

Your trial participation means the world to us ...

... together we will discover treatments for neurodegenerative diseases that help people with ALS, and empower them to **thrive**
For More Updates

• **Weekly webinars**
  The idea of came from our Patient Advisory Committee: we are excited to be talking with you on a weekly basis and take any questions you might have

• **Find the schedule and registration links on our website**

  https://www.massgeneral.org/neurology/als/research/platform-trial-news/