Perpetual Adaptive Trial
Shared Placebo; Randomization Ratio 3:1
Open Label Extension (OLE) offered

Regimen A
(n=160 for each regimen)

Regimen B

Regimen C

Regimen D
(n=120 for active; n=40 for placebo)

3:1 Randomization within each Regimen

Zilucoplan
Placebo

Verdiperstat
Placebo

CNM-Au8
Placebo

Pridopidine
Placebo

Shared Placebo

Screening

Regimen Assignment

Informed Consent

Assign to Regimen

Randomize within Regimen (active/placebo)

Up to 6 weeks

24 weeks (about 6 months)

Open Label Extension
• 851 individuals with ALS signed informed consent
• 675 individuals were assigned to a regimen
• 605 individuals were randomized within a regimen (active or placebo)
• 263 have entered the Open Label Extension (OLE)
• 160 individuals were randomized within Regimen A
• 167 individuals were randomized within Regimen B
• 161 individuals were randomized within Regimen C
• 117 individuals were randomized within Regimen D
Guest Speakers

Robert Glanzman, MD, FAAN
Chief Medical Officer
Clene Nanomedicine, Inc.

Michael Hotchkin
Chief Development Officer
Clene Nanomedicine, Inc.

Lori Chibnik, PhD, MPH
Assistant Professor & Biostatistician
Harvard TH Chan School of Public Health & MGH
Guest Speakers

James Berry, MD, MPH
Regimen C, Co-Lead Investigator
Massachusetts General Hospital

Nicholas Maragakis, MD
Regimen C, Co-Lead Investigator
Johns Hopkins University
Trial Statisticians

**MGH Biostatistics**

Eric Macklin, PhD; Lori B. Chibnik, PhD, MPH; Douglas Hayden, PhD; Marie-Abele Bind, PhD; James Chan, MA; PoYing Lai, MS

**Berry Consultants**

Michelle Detry, PhD; Melanie Quintana, PhD; Ben Saville, PhD; Matteo Vestrucci, PhD
INTRODUCTION TO BIOSTATISTICS
WEBINAR SERIES
Impetus

- Curated questions from
  - Past webinars
  - Facebook sessions and AMA
  - Emailed questions

What determined n=160 as the magic number for each regimen?

- How does the platform randomization work given that there are 3 drugs that have over 200 patients enrolled, the placebo, and now Pridopidine is new with just 1 patient?

For the next round, will the current placebo data be combined with that to be acquired in the next round?

- One of the slides mentioned a non-statistically significant difference. Can you explain that please, since you were so positive on the positive results.

How are deaths included in the statistical analysis of adverse consequences if the death is from ALS and not trial complications?

- How come trials are set up in a way to “prove statistical significance”, but even when they are deemed “positive”, they are not “significant” ENOUGH for the FDA?

- Can you explain to people how the FDA's statistical penalty works for manufacturers who decide to do an interim analysis and how you or a manufacturer decides if they will be doing those in the Healey trials?
TO THINK LIKE A BIOSTATISTICIAN
ALS PLATFORM TRIAL THROUGH THE EYES OF A STATISTICIAN
Generic Clinical Trial

Consent to Study

Active Drug (n=120)

Placebo (n=120)

Analysis

OLE Active

unblinded  blinded  unblinded
Generic Clinical Trials

Consent to Study

- Active Drug (n=120)
- Placebo (n=120)

Analysis

- OLE Active

Consent to Study

- Active Drug (n=120)
- Placebo (n=120)

Analysis

- OLE Active

Consent to Study

- Active Drug (n=120)
- Placebo (n=120)

Analysis

- OLE Active

Consent to Study

- Active Drug (n=120)
- Placebo (n=120)

Analysis

- OLE Active
Healey ALS Platform trial

Consent to Platform

Regimen A
Drug A (n=120)
Placebo A (n=40)
Drug B (n=120)
Placebo B (n=40)
Drug C1 (n=60)
Placebo C (n=40)
Drug C2 (n=60)

Regimen B
Drug A (n=120)
Placebo A (n=40)
Drug B (n=120)
Placebo B (n=40)

Regimen C
Drug C1 (n=60)
Placebo C (n=40)
Drug C2 (n=60)

Regimen D

Analysis

Drug A (n ≤ 160)
Drug B (n ≤ 160)
Drug C1 (n ≤ 80)
Drug C2 (n ≤ 80)
Placebo ABCD (n~120)

unblinded
unblinded
blind
unblinded
Healey ALS Platform trial

Study design
‘clinically meaningful’ results
Sample Size
Randomization

Consent to Platform

Regimen A
Drug A (n=120)
Placebo A (n=40)

Regimen B
Drug B (n=120)
Placebo B (n=40)

Regimen C
Drug C1 (n=60)
Drug C2 (n=60)
Placebo C (n=40)

Regimen D
Drug D (n=120)
Placebo D (n=40)

Regimen X

Analysis
Drug A (n ≤ 160)
Drug B (n ≤ 160)
Drug C1 (n ≤ 80)
Drug C2 (n ≤ 80)
Drug D (n=120)
Placebo ABCD (n~120)

Sample Size
Randomization

Study design
‘clinically meaningful’ results

Analysis

Drug A (n=120)
Placebo A (n=40)

Drug B (n=120)
Placebo B (n=40)

Drug C1 (n=60)
Drug C2 (n=60)
Placebo C (n=40)

Drug D (n=120)
Placebo D (n=40)

Placebo ABCD (n~120)

Healey ALS Platform trial

Study design
‘clinically meaningful’ results
Sample Size
Randomization

Consent to Platform

Regimen A
Drug A (n=120)
Placebo A (n=40)

Regimen B
Drug B (n=120)
Placebo B (n=40)

Regimen C
Drug C1 (n=60)
Drug C2 (n=60)
Placebo C (n=40)

Regimen D
Drug D (n=120)
Placebo D (n=40)

Regimen X

Analysis
Drug A (n ≤ 160)
Drug B (n ≤ 160)
Drug C1 (n ≤ 80)
Drug C2 (n ≤ 80)
Drug D (n=120)
Placebo ABCD (n~120)

Sample Size
Randomization

Study design
‘clinically meaningful’ results

Consent to Platform

Regimen A
Drug A (n=120)
Placebo A (n=40)

Regimen B
Drug B (n=120)
Placebo B (n=40)

Regimen C
Drug C1 (n=60)
Drug C2 (n=60)
Placebo C (n=40)

Regimen D
Drug D (n=120)
Placebo D (n=40)

Regimen X

Analysis
Drug A (n ≤ 160)
Drug B (n ≤ 160)
Drug C1 (n ≤ 80)
Drug C2 (n ≤ 80)
Drug D (n=120)
Placebo ABCD (n~120)

Sample Size
Randomization

Study design
‘clinically meaningful’ results

Consent to Platform

Regimen A
Drug A (n=120)
Placebo A (n=40)

Regimen B
Drug B (n=120)
Placebo B (n=40)

Regimen C
Drug C1 (n=60)
Drug C2 (n=60)
Placebo C (n=40)

Regimen D
Drug D (n=120)
Placebo D (n=40)

Regimen X

Analysis
Drug A (n ≤ 160)
Drug B (n ≤ 160)
Drug C1 (n ≤ 80)
Drug C2 (n ≤ 80)
Drug D (n=120)
Placebo ABCD (n~120)

Sample Size
Randomization

Study design
‘clinically meaningful’ results
Questions?

Be rational

Get real.
Planned topics

- Why and when Placebos are important
- Statistical Significance
- Randomization
- Determining optimal sample sizes
- Statistical tests used in ALS clinical trials and how they are modified for a platform design
- The statistics behind biomarkers discovery and use