RESTORE-ALS
Phase 3 Trial Design

RestoreALS

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Objective: to investigate the effects of CNM-Au8 on survival and delayed clinical worsening events in ALS

Participant criteria: ALS diagnosis per Gold Coast criteria; symptom onset within 36 months of the Screening visit; ≥ 60% predicted vital capacity; TRICALS Risk Score: -2.5 to -6.5

Investigational Product **CNM-Au8 30 mg** randomized 2:1 (or matched placebo)

Study Center(s): Expert ALS centers

- ❑ North America
- ❑ Europe
- ❑ Australia
- ❑ Asia/Pacific

CNM-Au8

Design Scheme

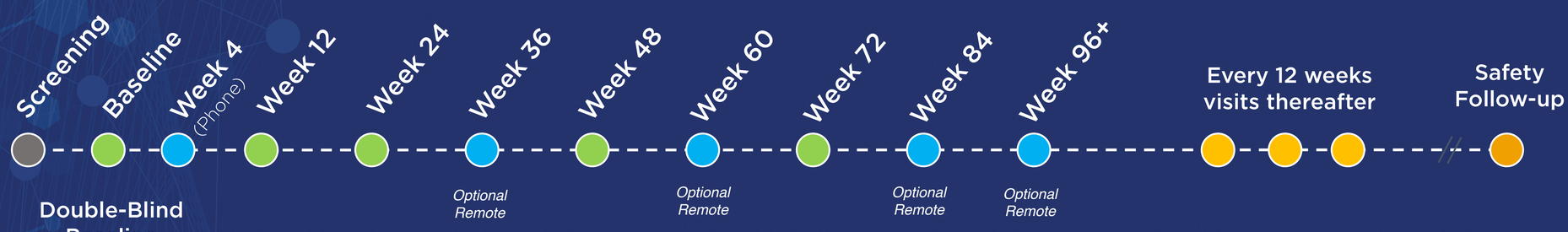
- Interim Futility analysis at 50% and 75% of events
- Interim efficacy at 75% of events

Screening (~6 weeks)

Event Driven Trial
Double-blind Treatment Period Until 190 Events Accrue
CNM-Au8 30mg or Placebo
(Planned: n=561; n=374 active, n=187 placebo)

Open Label Extension
Continued until study is terminated or study drug is approved

End of Study Safety Follow-up (4-weeks)



Enrollment Criteria

Key Inclusion Criteria:

1. Aged ≥ 18 years at the Screening
2. Confirmed diagnosis of ALS per Gold Coast criteria
3. Time since onset of ALS symptoms ≤ 36 months
4. Upright forced vital capacity (FVC) ≥ 60% of predicted
5. TRICALS risk score (6-factor model) range: -2.5 to -6.5
6. Screening biofluid (plasma) NfL ≥ 45 pg/mL
7. Stable background treatment (e.g., riluzole, edaravone, both)

Key Exclusion Criteria:

1. Presently use or at risk of needing: (i) Feeding tube, (ii) NIV, or (iii) Tracheostomy
2. Clinically significant findings on standard renal, hepatic, hematologic panels
3. Nonstable background treatment; treatment with antisense oligonucleotides
4. Allergy to gold

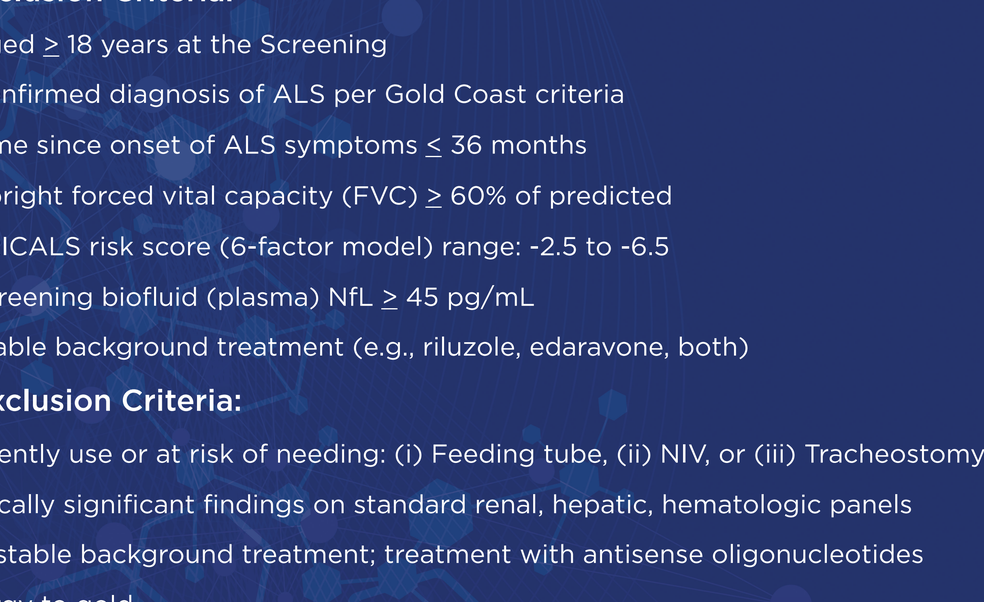
Methods, Statistics, and Powering

- **Enrollment plan:** approximately 561 randomized participants
  - 2:1 treatment allocation (CNM-Au8 30 mg: Placebo)
- **Primary endpoint: delayed time to death (all-cause mortality)**
  - Assumed hazard ratio (HR) of 0.625
  - One-sided alpha < 0.025; Power = 87% with 190 events
- **Statistical model: Covariate adjusted cox proportional hazard**
- **Randomization Stratification factors:**
  - Screening biofluid (plasma) NfL level: < 110 pg/mL versus ≥ 110 pg/mL
  - Symptom onset age: < 50 years versus ≥ 50 years
  - BMI < 25 kg/m² versus ≥ 25 kg/m²
- **Secondary endpoints:**

  (i) Time to death or death equivalent (PAV), (ii) Composite ALS clinical worsening hierarchy, (iii) joint-rank of time to death or PAV and ALSSQOL-SF change to Week 72, (iv) joint-rank of time to death or PAV and ALSFRS-R change to Week 72, (v) joint-rank of time to death or PAV and ROADs change to Week 72, (vi) joint-rank of time to death or PAV and SVC% change to Week 72

Survival Effect Planning Considerations

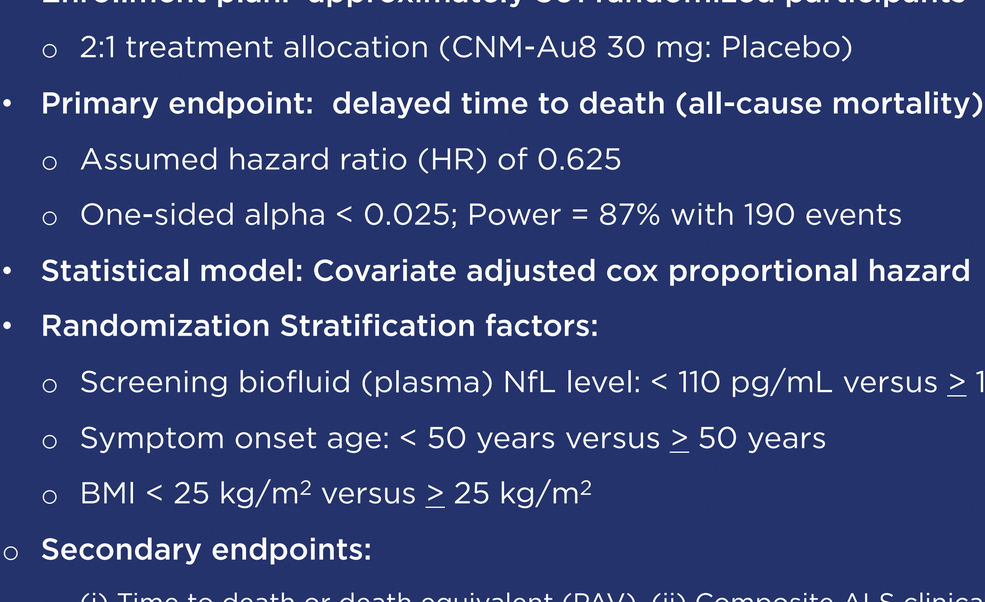
RESTORE-ALS Treatment Effect Scenario (Clinical)
Pooled CNM-Au8 30 mg (RESCUE-ALS & HEALEY ALS Platform Trial)
All CNM-Au8 30 mg Exposed and Meeting Key* RESTORE Inclusion Criteria vs.
Propensity Matched Controls (Pooled PRO-ACT, ALS NHC, ANSWER-ALS)



At Risk						
CNM-Au8:	70	70	64	56	45	34
Matched Controls:	194	166	128	68	40	24

*Key Inclusion Criteria: VC% prediced > 60%, TRICALS: -2.5 to -6.5, Onset ≤ 36 months; 1:3 Match

RESTORE-ALS Treatment Effect Scenario (Expanded Access Programs)
Pooled EAP01 and EAP02 That Met Key* RESTORE Inclusion Criteria vs.
Propensity Matched Controls (Pooled PRO-ACT, ALS NHC, ANSWER-ALS)



At Risk						
CNM-Au8:	47	37	27	20	19	18
Matched Controls:	117	102	79	39	24	19

*Key Inclusion Criteria: VC% prediced > 60%, TRICALS: -2.5 to -6.5, Onset ≤ 36 months; 1:3 Match

Acknowledgements: We thank the RESTORE-ALS Steering Committee and key ALS advisors who have contributed to the planning and design of the RESTORE-ALS trial. We are indebted to the participants and investigators of the HEALEY ALS Platform Trial and the RESCUE-ALS trial whose contributions have led to the design of the RESTORE-ALS trial.

CLene NANOMEDICINE