

RESTORE-ALS Phase 3 Clinical 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; $\geq 60\%$ predicted vital capacity; TRICALS Risk Score: -2.5 to -6.5, screening plasma NfL ≥ 45 pg/mL

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

Study Center(s): Expert ALS centers

- North America
- Europe
- Australia
- Asia/Pacific

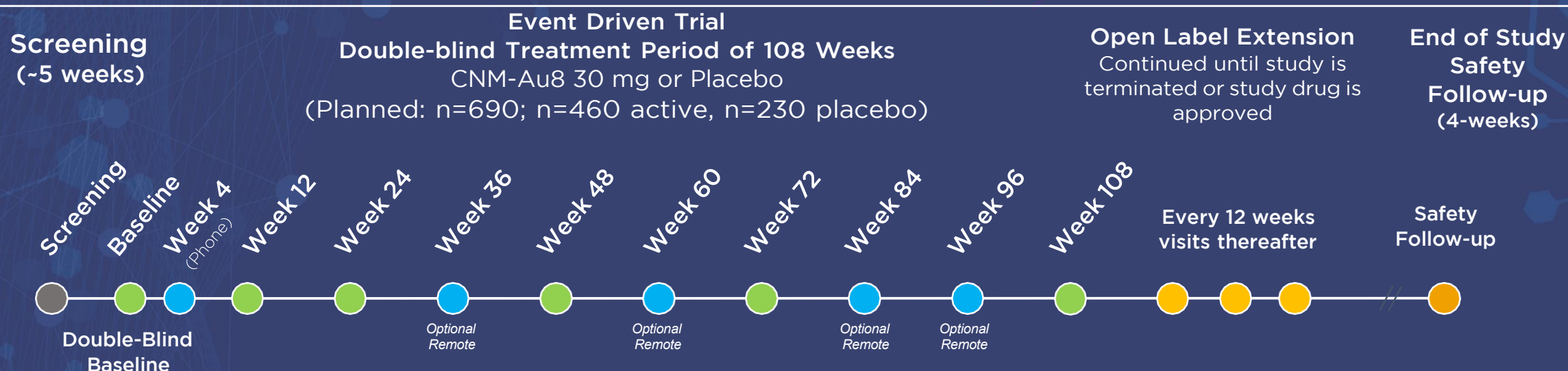


CNM-Au8



Design Scheme

Interim Futility analysis at 50% and 75% of death or PAV events (n=220)



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 slow vital capacity (SVC) $\geq 60\%$ 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:

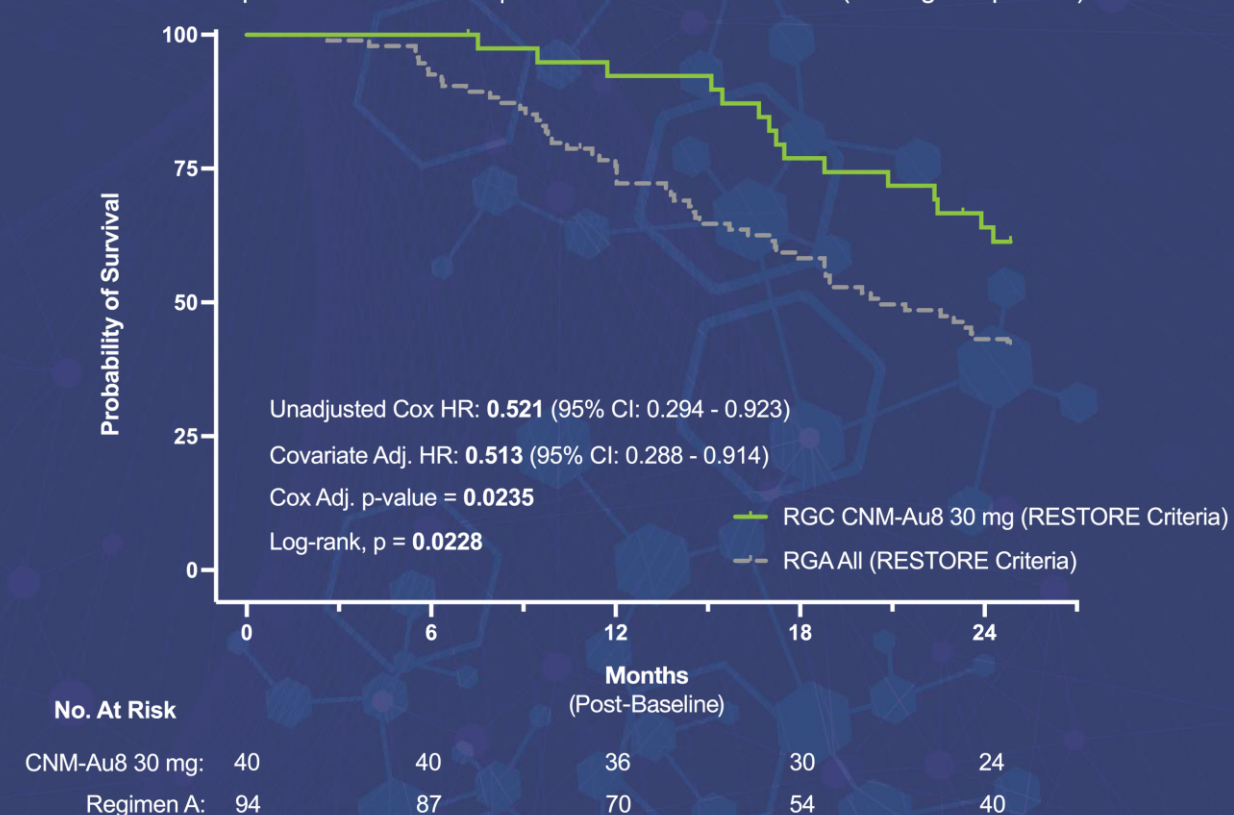
1. Presently use or at risk of needing: (i) Feeding tube, (ii) NIV, or (iii) Tracheostomy
2. Clinically significant findings on standard renal, hepatic, hematologic panels
3. Nonstable background treatment; treatment with antisense oligonucleotides
4. Allergy to gold

Methods, Statistics, and Powering

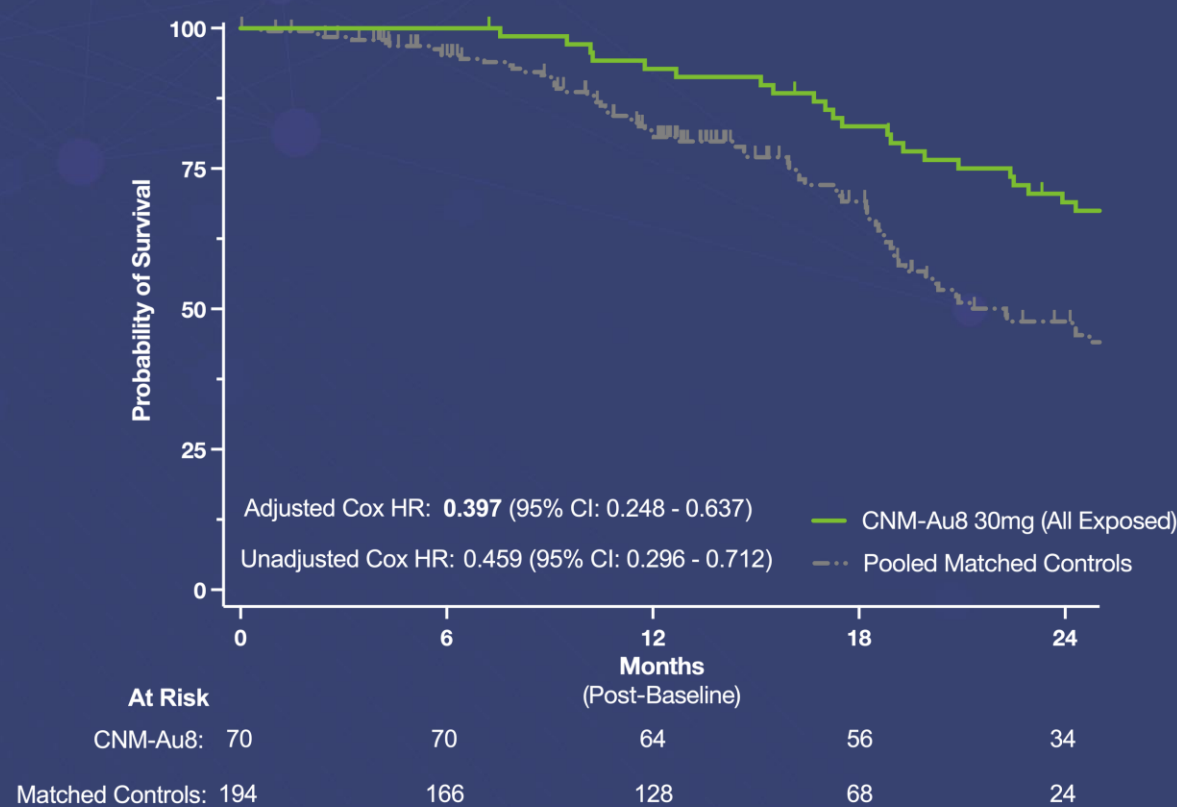
- **Enrollment plan:** approximately 690 randomized participants
 - 2:1 treatment allocation (CNM-Au8 30 mg: Placebo)
- **Primary endpoint:** delayed time to death or death equivalent (PAV)
 - Assumed hazard ratio (HR) of 0.625
 - One-sided alpha < 0.025 ; Power = 92.5% with 220 events
- **Statistical model:** Covariate adjusted cox proportional hazard
- **Randomization Stratification factors:**
 - Screening biofluid plasma NfL level: < 95 pg/mL versus ≥ 95 pg/mL
 - Modified 6-factor TRICALS risk score: < 4.1 versus ≥ 4.1
 - Use of background ALS treatment (e.g., riluzole, edaravone) vs. none
- **Secondary endpoints:**
 - (i) Combined Assessment of function & survival (CAFS), (ii) Composite ALS clinical worsening hierarchy, (iii) joint-rank of time to death or PAV and ALSFRS-R change to Week 108, (iv) joint-rank of time to death or PAV and ALSSQOL-SF change to Week 108, (v) joint-rank of time to death or PAV and SVC% change to Week 72

Survival Effect Planning Considerations

RESTORE-ALS Treatment Effect Considerations
HEALEY ALS Platform Trial | Long Term Survival
Filtered by RESTORE-ALS Core Inclusion Criteria
CNM-Au8 30 mg (Original Randomization) vs. Regimen A (All)
Kaplan-Meier Estimator | OmniTrace Survival Status (Through Sep-2024)



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



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

Core RESTORE-ALS Inclusion Criteria include: (i) Onset ≤ 36 months, (ii) SVC% ≥ 60 , (iii) TRICALS(6): -6.5 to -2.5, and (iv) baseline Ln sNFL ≥ 3.5 .

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