RESTORE-ALS
Phase 3 Trial Design

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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
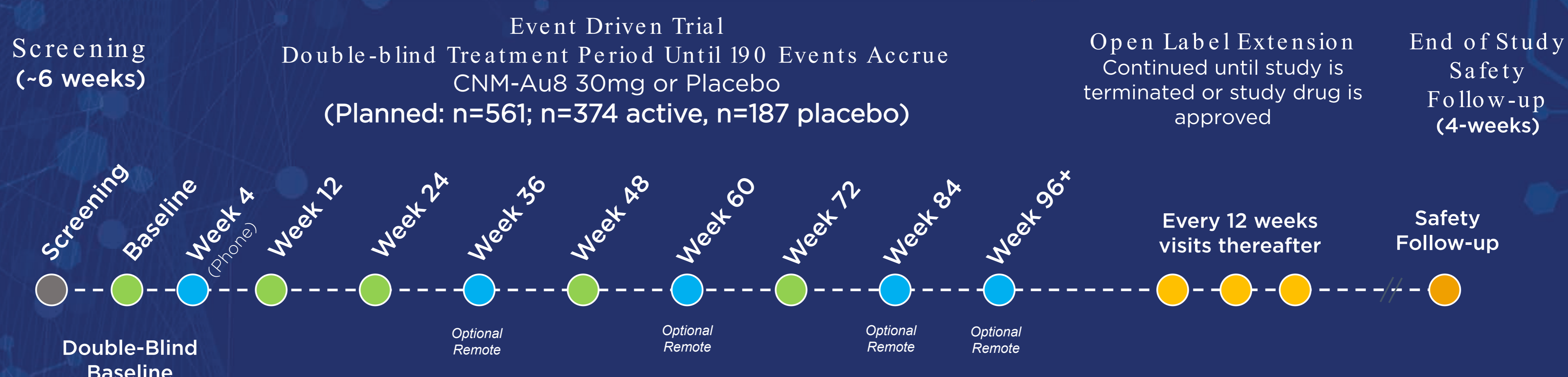- ☐ Europe
- ☐ Australia
- ☐ Asia/Pacific

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)

Screening · Baseline · Week 4 (Phone) · Week 12 · Week 24 · Week 36 · Week 48 · Week 60 · Week 72 · Week 84 · Week 96+ · Every 12 weeks visits thereafter · Safety Follow-up

Double-Blind Baseline

Optional Remote (Week 36, Week 60, Week 84, Week 96+)

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 ASO
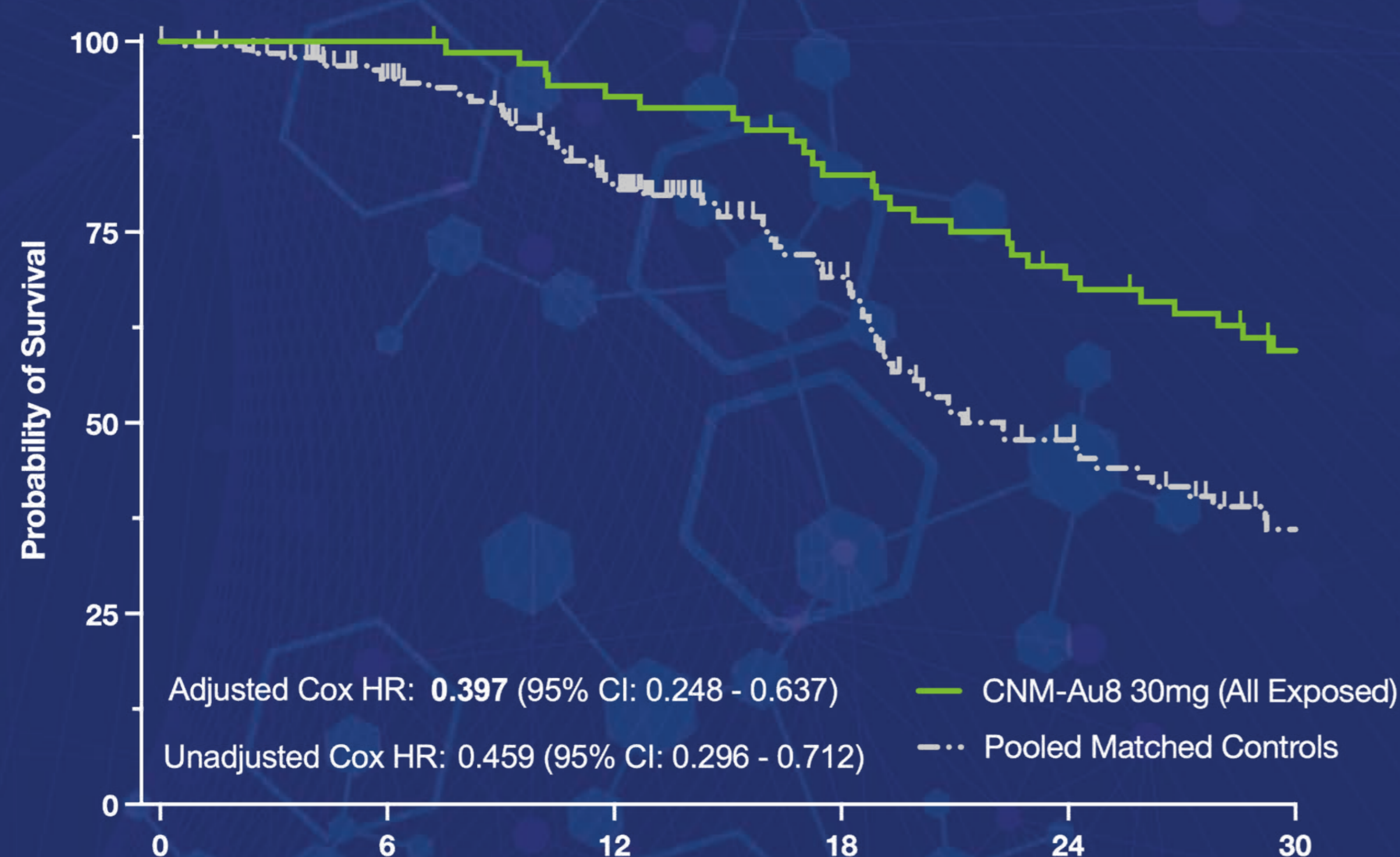4. Allergy to gold

Methods, Statistics, and Powering

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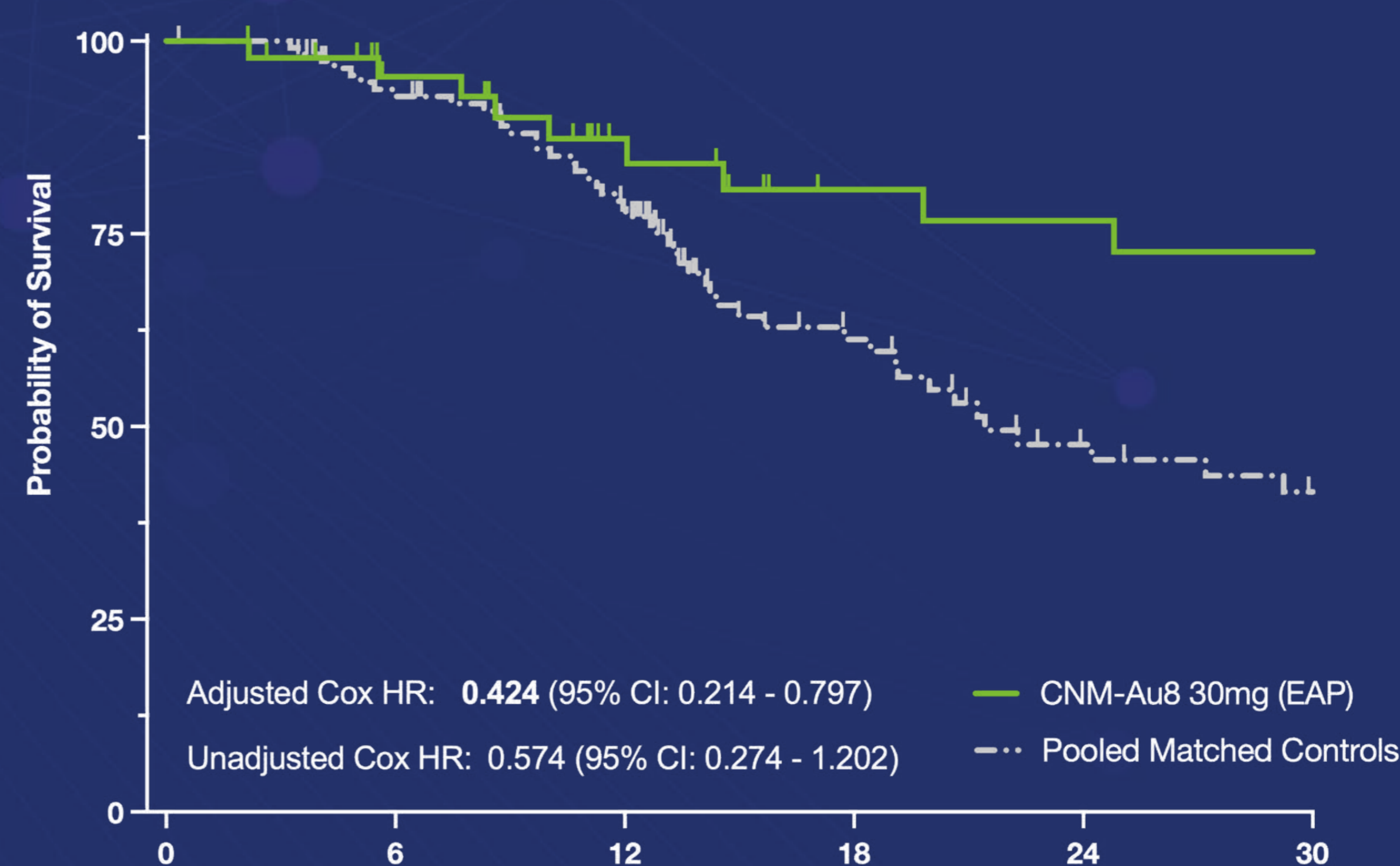Propensity Matched Controls (Pooled PRO-ACT, ALS NHC, ANSWER-ALS)

Adjusted Cox HR: **0.397** (95% CI: 0.248 - 0.637)
Unadjusted Cox HR: 0.459 (95% CI: 0.296 - 0.712)
— CNM-Au8 30mg (All Exposed)
-·- Pooled Matched Controls

At Risk						
	0	6	12	18	24	30
CNM-Au8:	70	70	64	56	45	34
Matched Controls:	194	166	128	68	40	24

Months (Post-Baseline)

*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)

Adjusted Cox HR: **0.424** (95% CI: 0.214 - 0.797)
Unadjusted Cox HR: 0.574 (95% CI: 0.274 - 1.202)
— CNM-Au8 30mg (EAP)
-·- Pooled Matched Controls

At Risk						
	0	6	12	18	24	30
CNM-Au8:	47	37	27	20	19	18
Matched Controls:	117	102	79	39	24	19

Months (Post-Baseline)

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

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