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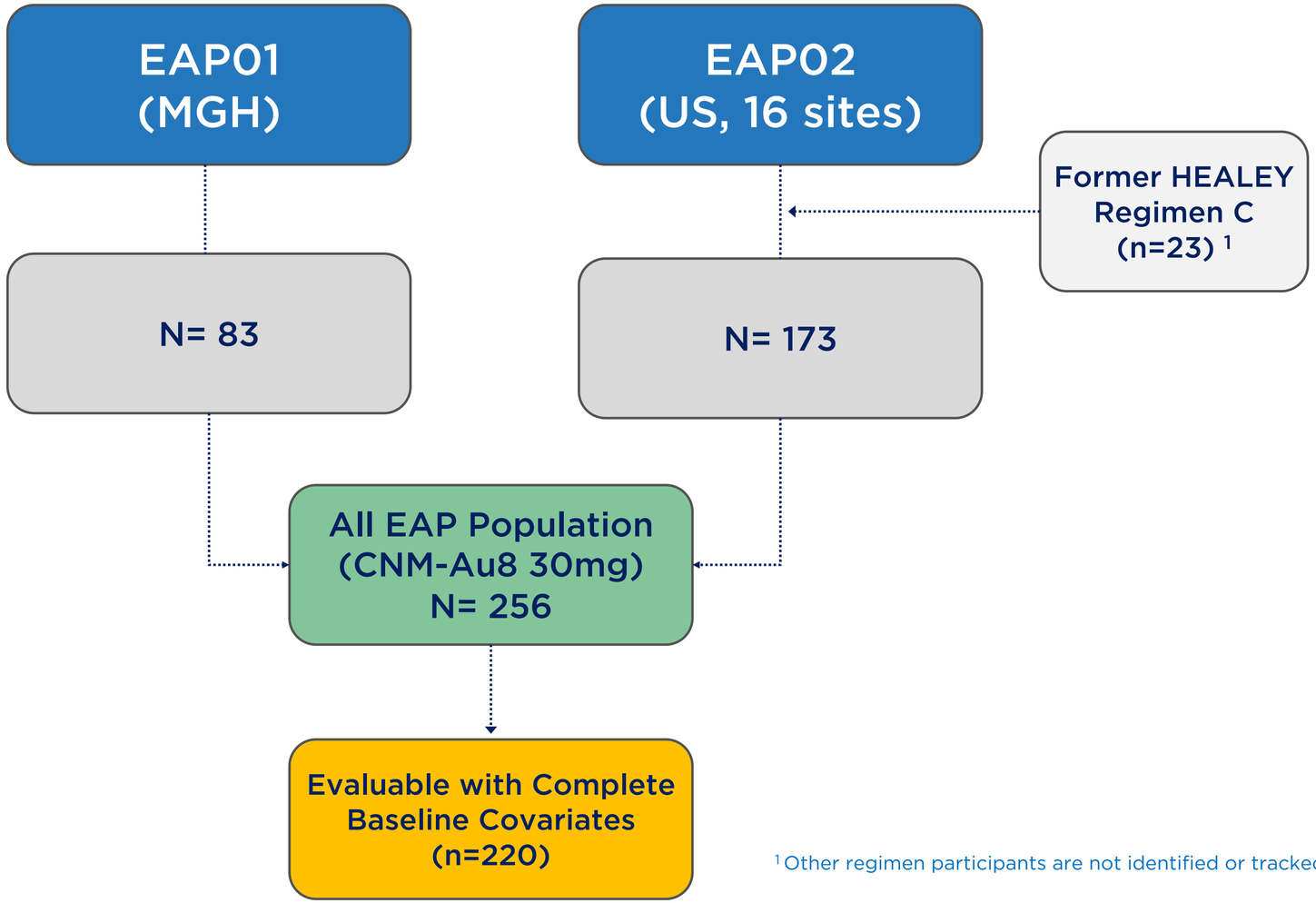
EAP Participant Enrollment

- All EAP participants (CNM-Au8 30mg) enrolled through 15-December-2023 with EDC data entry
- Survival updated through the 14-January-2024 data cut

EAP01 in collaboration with the:

Healey Center
Sean M. Healey & AMG Center for ALS at Mass General

The Healey center covered all site costs and EDC management through philanthropic donations; Clene provided CNM-Au8 and conducted analyses



[1] Other regimen participants are not identified or tracked separately.

Data on File, Clene Nanomedicine, Inc.

EAP Baseline Demographics | At Study Entry

ALS EXPANDED ACCESS PROTOCOLS (EAP)

Healey Center
Sean M. Healey & AMG Center for ALS at Mass General

Baseline Category Mean (SD) or n (%) Range [Min, Max]	EAP01 (n=83)	EAP02 (n=173)	All EAP (n=256)
Age at Baseline, (n= 256)	55.5 (12.2) [27, 78]	61.1 (10.9) [22, 84]	59.3 (11.6) [22, 84]
Months from Symptom Onset, (n= 256)	40.5 (39.4) [5.7, 244]	54.2 (32.1) [6.5, 234.4]	49.7 (35.2) [5.7, 244]
Diagnostic Delay (Months), (n= 256)	16.6 (24.8) [0, 203]	20.7 (23.2) [0.5, 192]	19.4 (23.7) [0, 203]
Vital Capacity (% predicted), (n= 225)	69.3 (25.4) [22, 118]	57.6 (24.9) [9, 146]	60.4 (25.4) [9, 146]
ALSFRS-R (Total), (n=256)	31.4 (10.7) [1, 48]	25.9 (9.8) [1, 47]	27.7 (10.4) [1, 48]
Delta-FS (Pre-treatment Slope), (n=256)	0.60 (0.48) [0, 2.56]	0.50 (3.9) [0, 2.24]	0.53 (0.42) [0, 2.56]
TRICALS Risk Score (6-factor), (n=225)	-5.1 (2.3) [-10.2, -1.5]	-4.8 (2.1) [-11.4, 2.03]	-4.86 (2.1) [-11.4, 2.03]
BMI (kg/m^2), (n= 228)	25.5 (5.2) [17.4, 51]	25.6 (5.3) [14, 46.2]	25.6 (5.2) [14, 51]
Sex, Male (%), (n= 256)	69%	61%	63%
Bulbar Onset (%), (n=256)	23%	25%	24%
El Escorial, Clinically Definite (%), (n= 256)	57%	58%	58%
Riluzole Background Treatment (%), (n= 254)	76%	70%	72%

Data on File, Clene Nanomedicine, Inc.

CLene NANOMEDICINE

Propensity Matched ALS Controls | Sources

PRO-ACT

The PRO-ACT database

Design, initial analyses, and predictive features

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ABSTRACT

Objective: To pool data from completed amyotrophic lateral sclerosis (ALS) clinical trials and create an open-access resource that enables greater understanding of the phenotype and biology of ALS.

Methods: Clinical trials data were pooled from 16 completed phase II/III ALS clinical trials and one observational study. Over 8 million de-identified longitudinally collected data points from over 8,600 individuals with ALS were standardized across trials and merged to create the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database. This database includes demographics, family histories, and longitudinal clinical and laboratory data. Mixed effects models were used to describe the rate of disease progression measured by the Revised ALS Functional Rating Scale (ALSFRS-R) and vital capacity (VC). Cox regression models were used to describe survival data. Implementing Bonferroni correction, the critical p value for 15 different tests was $p = 0.003$.

Results: The ALSFRS-R rate of decline was 1.02 (±2.3) points per month and the VC rate of decline was 2.24% of predicted (±6.9) per month. Higher levels of uric acid at trial entry were predictive of a slower drop in ALSFRS-R ($p = 0.01$) and VC ($p < 0.0001$), and longer survival ($p = 0.02$). Higher levels of creatinine at baseline were predictive of a slower drop in ALSFRS-R ($p = 0.01$) and VC ($p < 0.0001$), and longer survival ($p = 0.01$). Finally, higher body mass index (BMI) at baseline was associated with longer survival ($p < 0.0001$).

Conclusion: The PRO-ACT database is the largest publicly available repository of merged ALS clinical trials data. We report that baseline levels of creatinine and uric acid, as well as baseline BMI, are strong predictors of disease progression and survival. *Neurology*® 2014;83:1719–1725

GLOSSARY

ALS = amyotrophic lateral sclerosis; **ALSFRS** = ALS Functional Rating Scale; **ALSFRS-R** = revised ALS Functional Rating Scale; **BMI** = body mass index; **CDS** = common data structure; **CI** = confidence interval; **HR** = hazard ratio; **PRO-ACT** = Pooled Resource Open-Access ALS Clinical Trials; **VC** = vital capacity.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder that affects motor neurons in the brain and spinal cord. People with ALS have progressive voluntary muscle weakness involving the arms, legs, speech, swallowing, and breathing.[1]

Because ALS is a rare disease with an annual incidence of 2/100,000,[2] clinical trials have typically been relatively small, with the largest studies including fewer than 1,000 participants.[3] Therefore, aggregation of studies is needed to allow enough statistical power to answer important questions about ALS natural history and clinical symptoms in order to overcome some of the barriers associated with drug development for orphan diseases.

The Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database was designed to provide just such an opportunity. This database represents the largest aggregation of ALS clinical trial data available. Sixteen phase II and III ALS trials and one large observational study, conducted over the past 2 decades, are currently included, and this number is expected to increase. The database has been made publicly available with the goal of facilitating research that might

Supplemental data at Neurology.org

*These authors contributed equally to this work.

From the Neurological Clinical Research Institute (NCRI), Department of Neurology (N.A., J.B., A. Sherman, E.S., J.W., I.K., M.C.), and the Biostatistics Center (A. Shui, D.S.), Massachusetts General Hospital, Boston; and Prize4Life (N.Z., M.L.), Cambridge, MA.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

ALS Natural History Study

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2023; 0: 1–9

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RESEARCH ARTICLE

The natural history of ALS: Baseline characteristics from a multicenter clinical cohort

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*Data used in the preparation of this article were obtained from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) Database. As such, the following organizations and individuals within the PRO-ACT Consortium contributed to the design and implementation of the PRO-ACT Database and/or provided data, but did not participate in the analysis of the data or the writing of this report:

- ALS Therapy Alliance
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- Prize4Life Israel
- Regeneron Pharmaceuticals, Inc.
- Sanofi
- Teva Pharmaceutical Industries, Ltd.
- The ALS Association

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Atassi et al. Neurology. 2014 Nov 4;83(19):1719-25. Berget et al. Amyotroph Lateral Scler Frontotemporal Degener. 2023 Jul 17:1-9.

Survival Analyses | Methodology

ALS EXPANDED ACCESS PROTOCOLS (EAP)

- Utilize longitudinal data from historical ALS controls:

PRO-ACT

ALS Natural History Study

- Propensity matching based on baseline covariates (nominal caliper: 0.4)

Age at Onset

Bulbar Onset

TRICALS Risk Score

Pre-Treatment ALSFSR-R Slope

Sex

BMI

Diagnostic Delay

Matching covariates

- Observation time as an additional matching covariate for sensitivity analyses

Data on File, Clene Nanomedicine, Inc.

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Survival Analyses | All-Cause Mortality

ALS EXPANDED ACCESS PROTOCOLS (EAP)

- Log-rank (unadjusted) of all EAP (n=256) vs. propensity matched controls (n=220)
- Covariate adjusted hazard ratio (EAP treatment vs. controls)
  - EAP participants with baseline covariates (n=220) vs. propensity matched (n=220)
  - Baseline Covariates:
    - Onset Age
    - Sex
    - BMI
    - Delta-FS (ALSFRS-R Pretreatment Slope)
    - ALSFRS-R Total Score
    - Diagnostic Delay (Months)
    - Vital Capacity (% predicted)
    - TRICALS Risk Score

Data on File, Clene Nanomedicine, Inc.

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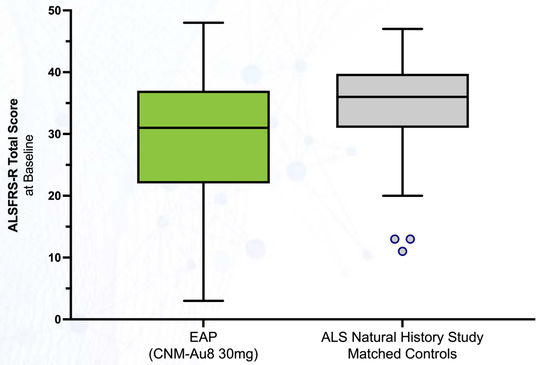
EAP Participants vs. Propensity Matched Controls

ALS Natural History Study

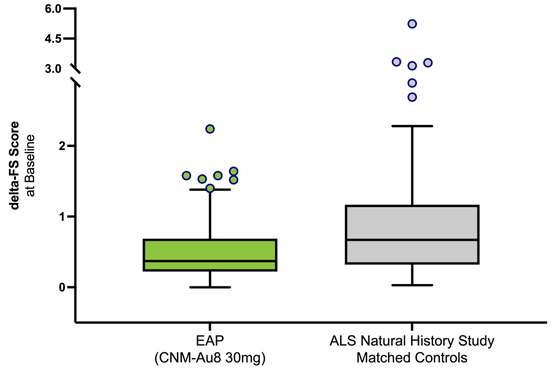
ALSFRS-R Score

EAP Long Term Survival | ALSFRS-R Total Scores
CNM-Au8 30mg vs. ALS Natural History Matched Controls
(Tukey Box Plot, n=220 per group)



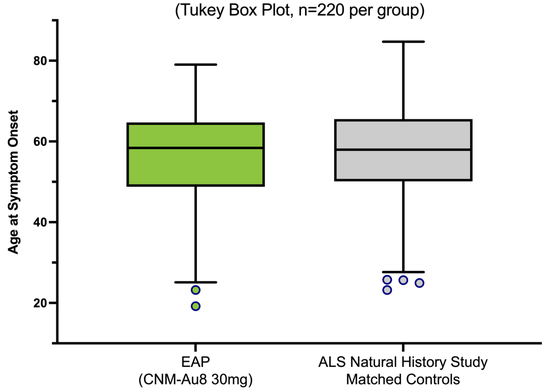
Delta-FS

EAP Long Term Survival | Pre-Treatment ALSFRS-R Slope
CNM-Au8 30mg vs. ALS Natural History Controls
(Tukey Box Plot, n=220 per group)



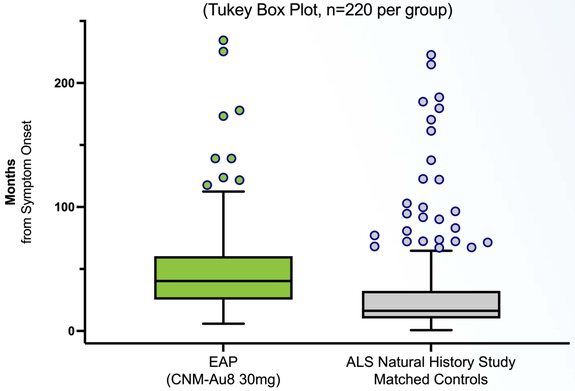
Onset Age

EAP Long Term Survival | Age at Onset
CNM-Au8 30mg vs. ALS Natural History Matched Controls
(Tukey Box Plot, n=220 per group)



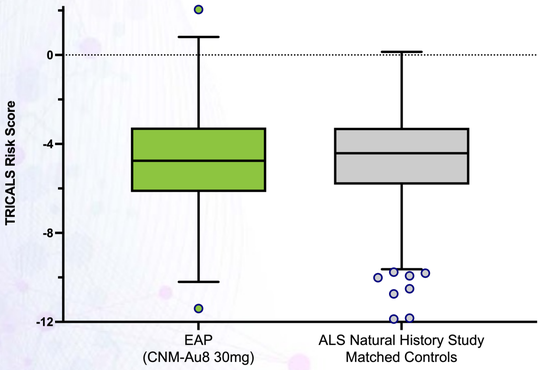
Months Post-Onset

EAP Long Term Survival | Months from Symptom Onset
CNM-Au8 30mg vs. ALS Natural History Matched Controls
(Tukey Box Plot, n=220 per group)



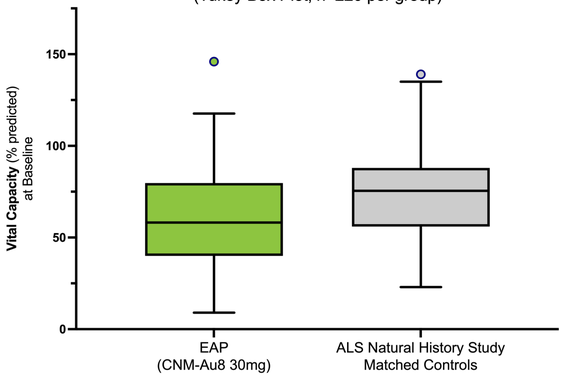
TRICALS Risk Score

EAP Long Term Survival | TRICALS Risk Score (6-factor)
CNM-Au8 30mg vs. ALS Natural History Matched Controls
(Tukey Box Plot, n=220 per group)



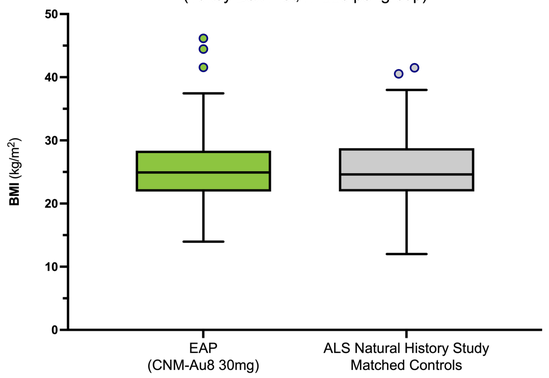
Vital Capacity (%)

EAP Long Term Survival | Vital Capacity (% predicted)
CNM-Au8 30mg vs. ALS Natural History Matched Controls
(Tukey Box Plot, n=220 per group)



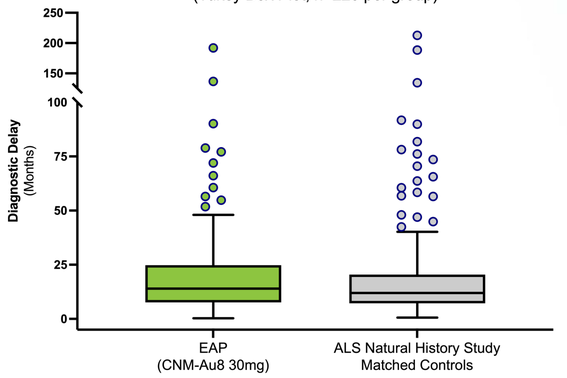
BMI

EAP Long Term Survival | BMI
CNM-Au8 30mg vs. ALS Natural History Matched Controls
(Tukey Box Plot, n=220 per group)



Diagnostic Delay

EAP Long Term Survival | Diagnostic Delay (Months)
CNM-Au8 30mg vs. ALS Natural History Matched Controls
(Tukey Box Plot, n=220 per group)



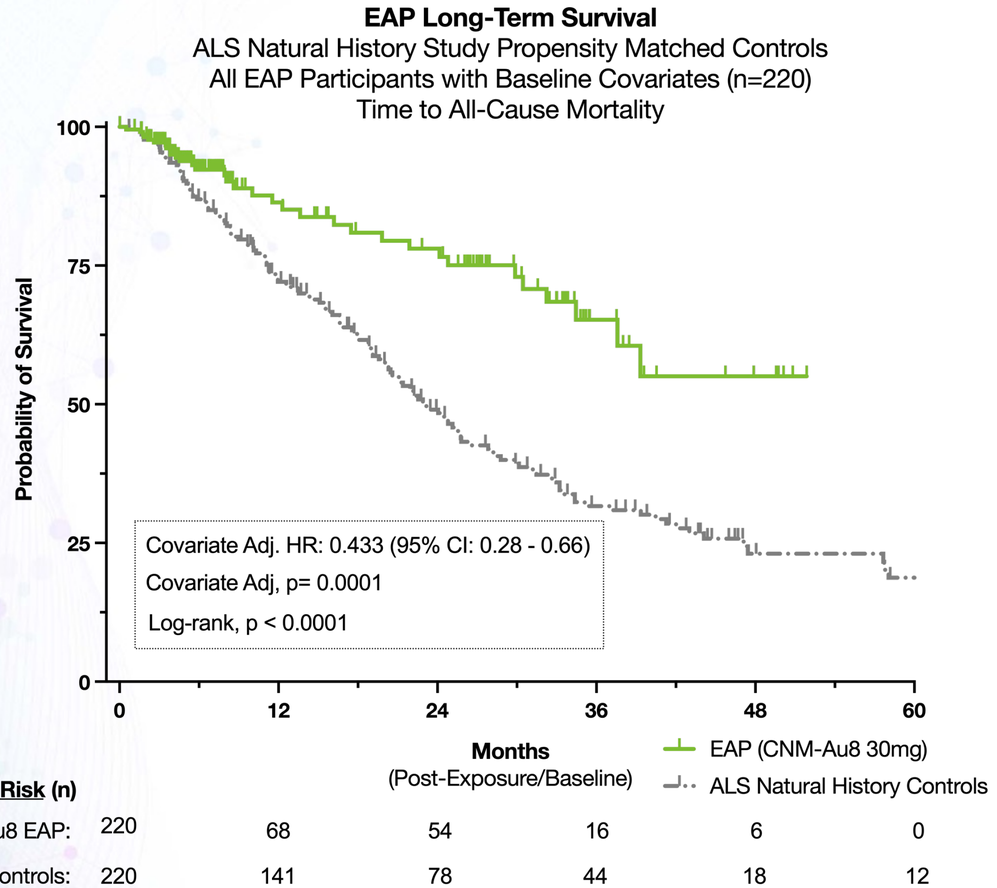
Matching covariates were balanced except for ALSFRS-R and vital capacity in favor of matched controls, while delta-FS favored EAP participants. Time from symptom onset was longer in EAP participants.

Data on File, Clene Nanomedicine, Inc.

EAP Survival vs. ALS Natural History Matched Controls

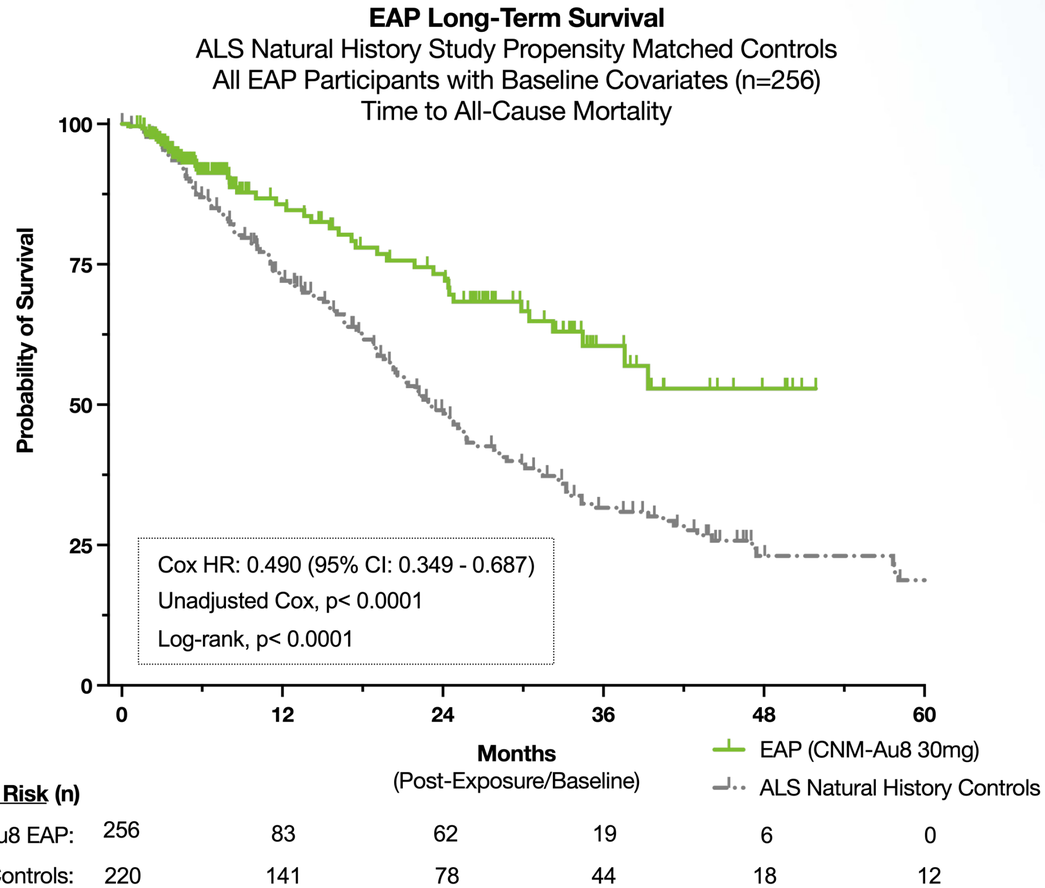
Control-Matched EAP and All EAP

ALS Natural History Study | EAP Matched (n=220)



At Risk (n)						
CMM-Au8 EAP:	220	68	54	16	6	0
Controls:	220	141	78	44	18	12

ALS Natural History Study | All EAP (n=256)



At Risk (n)						
CMM-Au8 EAP:	256	83	62	19	6	0
Controls:	220	141	78	44	18	12

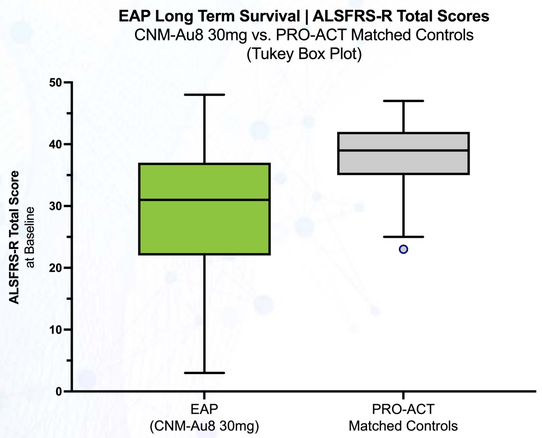
Baseline covariates include: (i) onset age, (ii) sex, (iii) BMI, (iv) pre-treatment ALSFRS-R slope, (v) ALSFRs-R, (vi) vital capacity (% predicted), (vii) vital capacity pre-treatment slope, and (viii) TRICALS risk score. Propensity matching caliper minimized at 0.41. All EAP participants alive are right censored as of the January 18, 2024 data cut.

Data on File, Clene Nanomedicine, Inc.

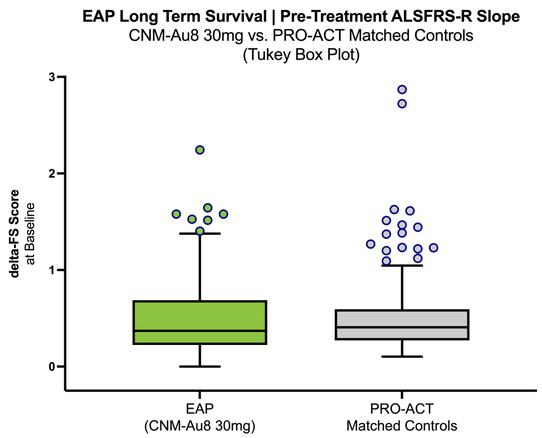
EAP Participants vs. Propensity Matched Controls

PRO-ACT

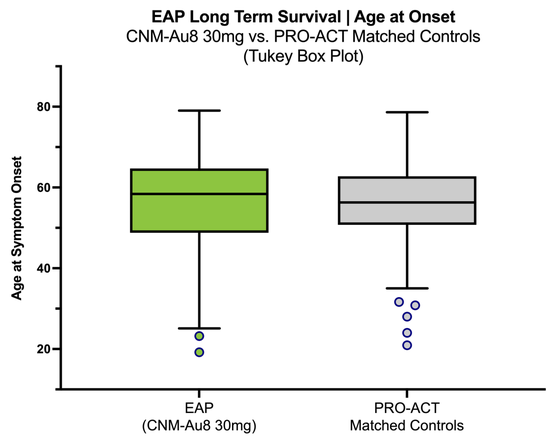
ALSFRS-R Score



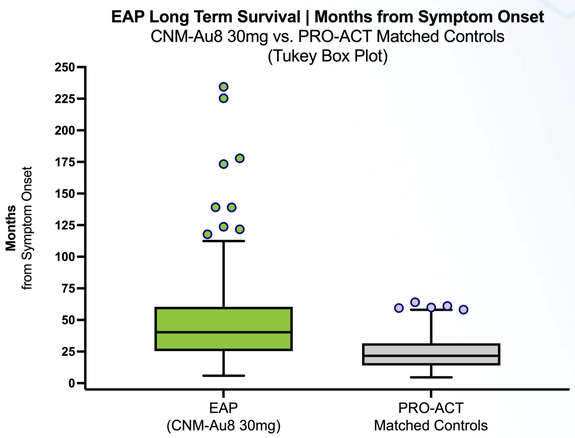
Delta-FS



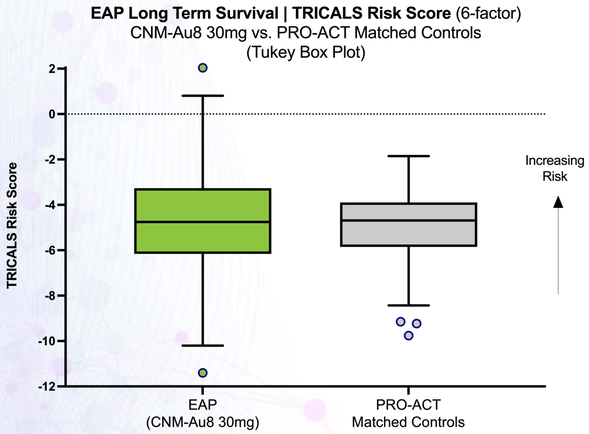
Onset Age



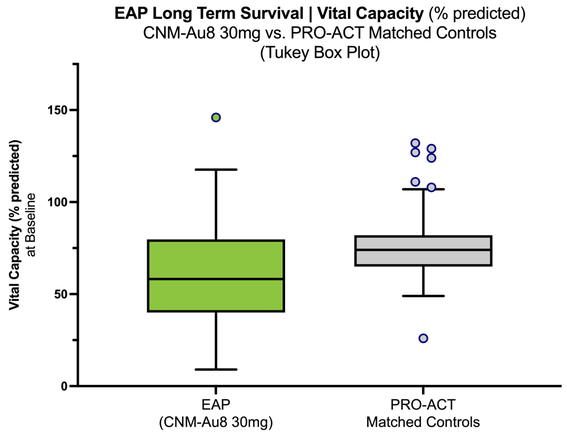
Months Post-Onset



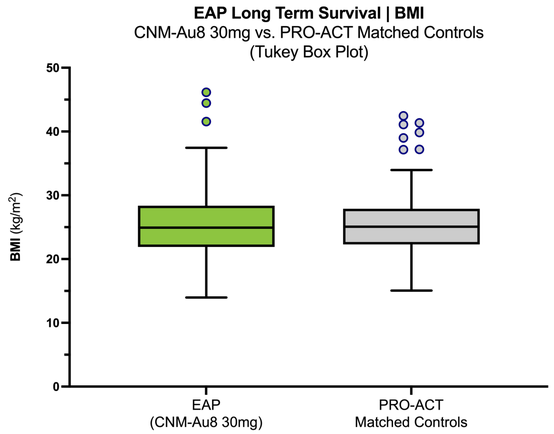
TRICALS Risk Score



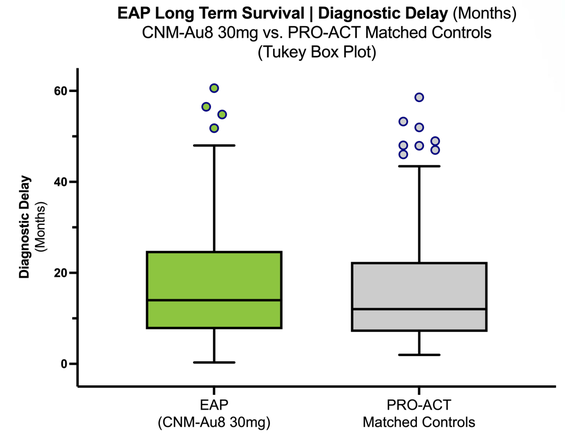
Vital Capacity (%)



BMI



Diagnostic Delay



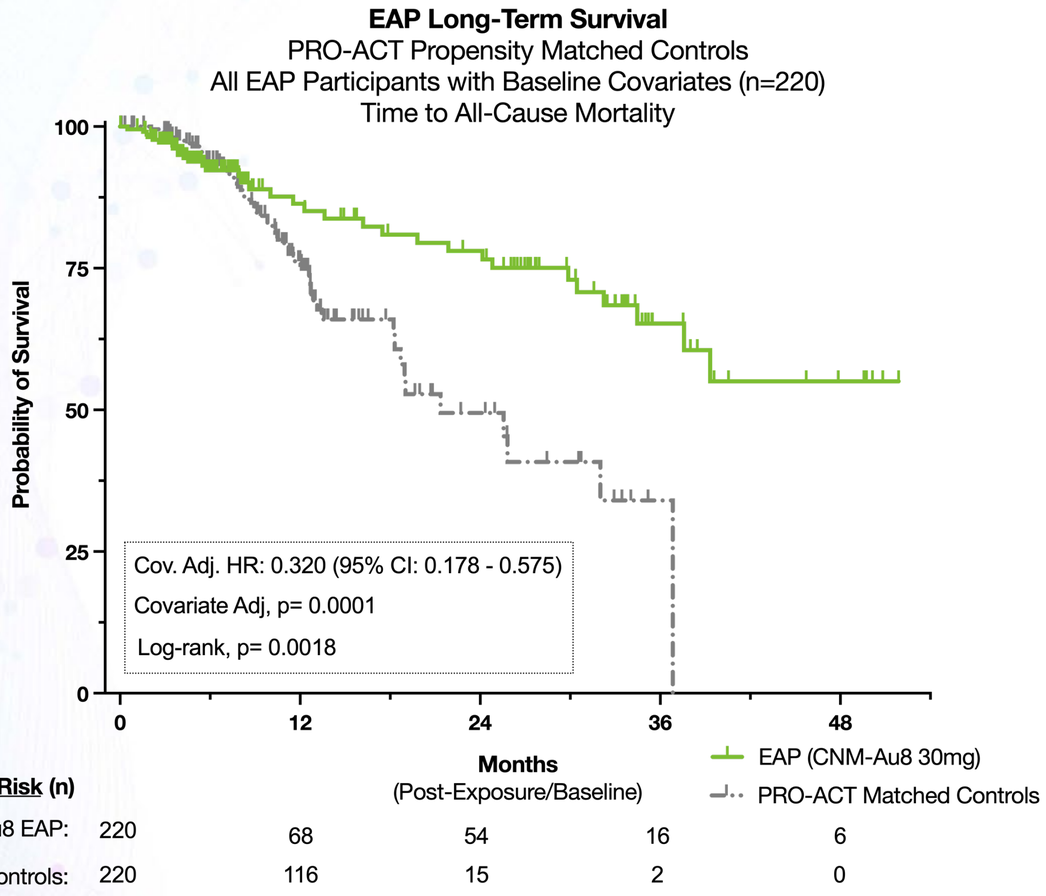
Matching covariates were balanced except for ALSFRS-R and vital capacity, which favored matched controls). Months post-symptom onset was longer in EAP participants.

Data on File, Clene Nanomedicine, Inc.

EAP Survival vs. PRO-ACT Matched Controls

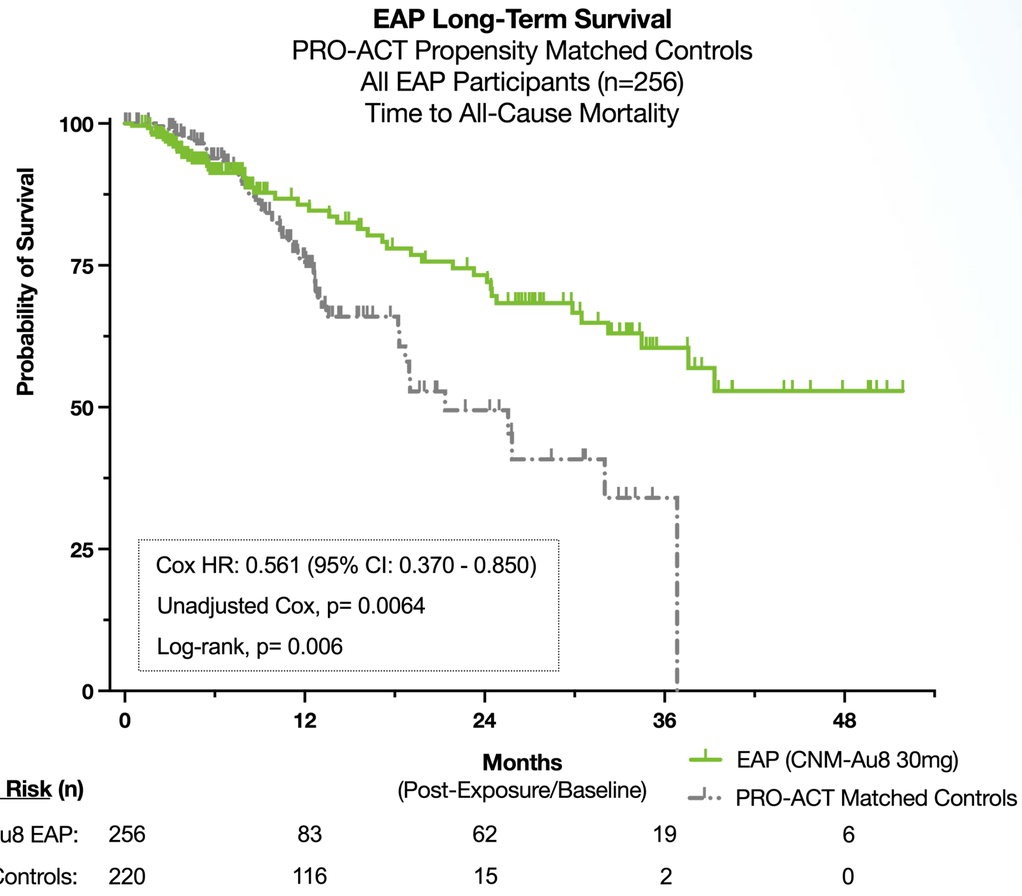
Control-Matched EAP and All EAP

PRO-ACT | EAP Matched (n=220)



At Risk (n)					
CMM-Au8 EAP:	220	68	54	16	6
Controls:	220	116	15	2	0

PRO-ACT | All EAP (n=256)



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Baseline covariates include: (i) onset age, (ii) sex, (iii) BMI, (iv) pre-treatment ALSFRS-R slope, (v) ALSFRs-R, (vi) vital capacity (% predicted), (vii) vital capacity pre-treatment slope, and (viii) TRICALS risk score. Propensity matching caliper minimized at 0.43. All EAP participants alive are right censored as of the January 18, 2024 data cut.

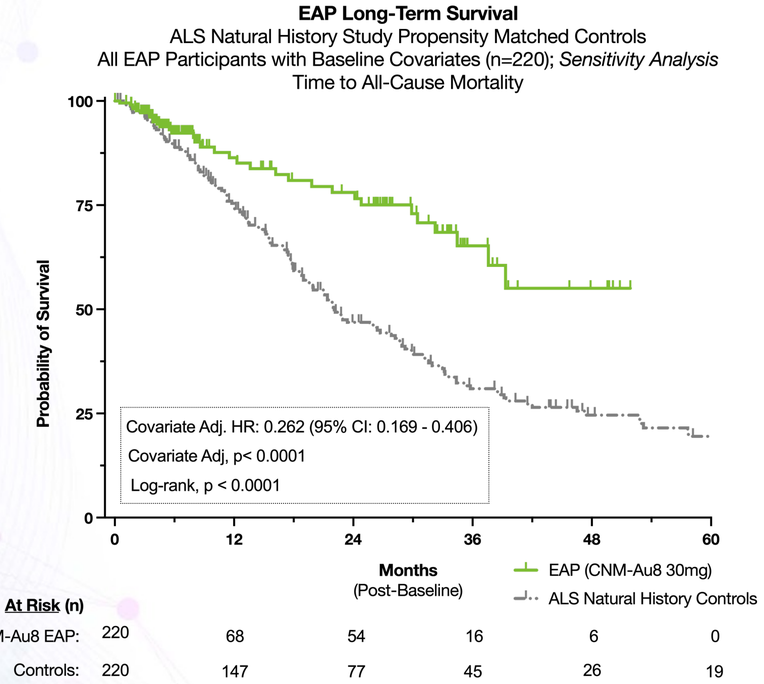
Data on File, Clene Nanomedicine, Inc.

Survival | Sensitivity Analyses

Including Observation Time as an Additional Covariate for Propensity Score Matching

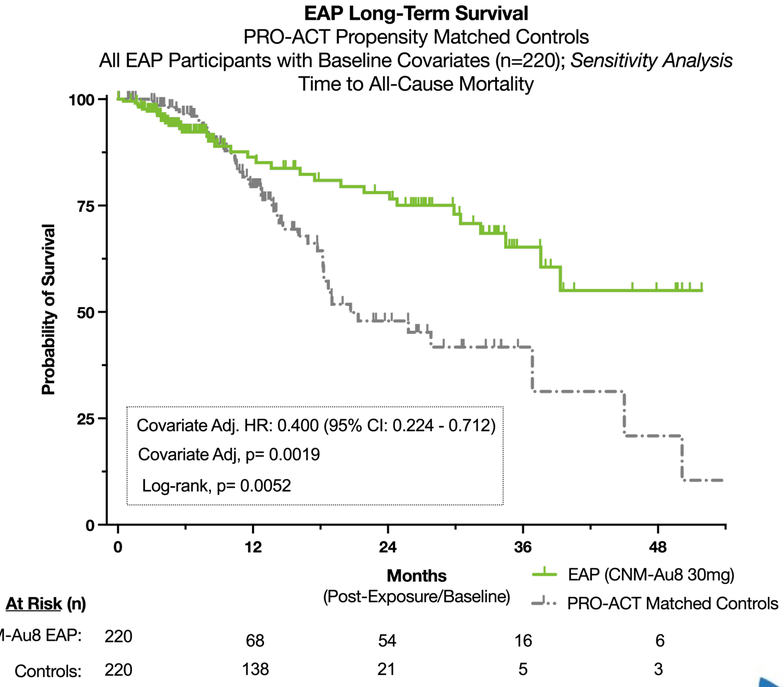
ALS Natural History Study | EAP Matched

ALS Nat. Hist. Scenario	Hazard Ratio	95% CI	p-value
Primary covariate model	0.433	0.282 – 0.663	p= 0.0001
+ Observation time for propensity matching	0.262	0.169 – 0.406	p< 0.0001



PRO-ACT | EAP Matched

PRO-ACT Scenario	Hazard Ratio	95% CI	p-value
Primary covariate model	0.320	0.178 – 0.575	p= 0.0001
+ Observation time for propensity matching	0.400	0.224 – 0.712	p= 0.0019



Data on File, Clene Nanomedicine, Inc.

Conclusions

- Clene's Expanded Access programs represent the longest continuous intermediate sized compassionate use program in ALS with over 256 participants treated
    - CNM-Au8 EAP longitudinal treatment duration exceeds 4 years of daily therapy
- A significant survival benefit was observed from long-term CNM-Au8 treatment in people living with later-stage ALS compared to two independently collected control groups
- Open-label long-term data from EAPs can provide evidence of efficacy and safety in broader ALS populations than traditionally enrolled in clinical studies
- Limitations: these are uncontrolled data (i.e., studies without randomization) that may not appropriately account for unknown covariates influencing ALS disease progression (e.g., standard of care may be different between EAP sites and those not participating in EAPs)

Data on File, Clene Nanomedicine, Inc.

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