CLENE ANNOUNCES STATISTICALLY SIGNIFICANT ALS BIOMARKER RESULTS SUPPORTING ACCELERATED APPROVAL PATHWAY FOR CNM-Au8®

NIH-Sponsored EAP and HEALEY ALS Platform Trial Data

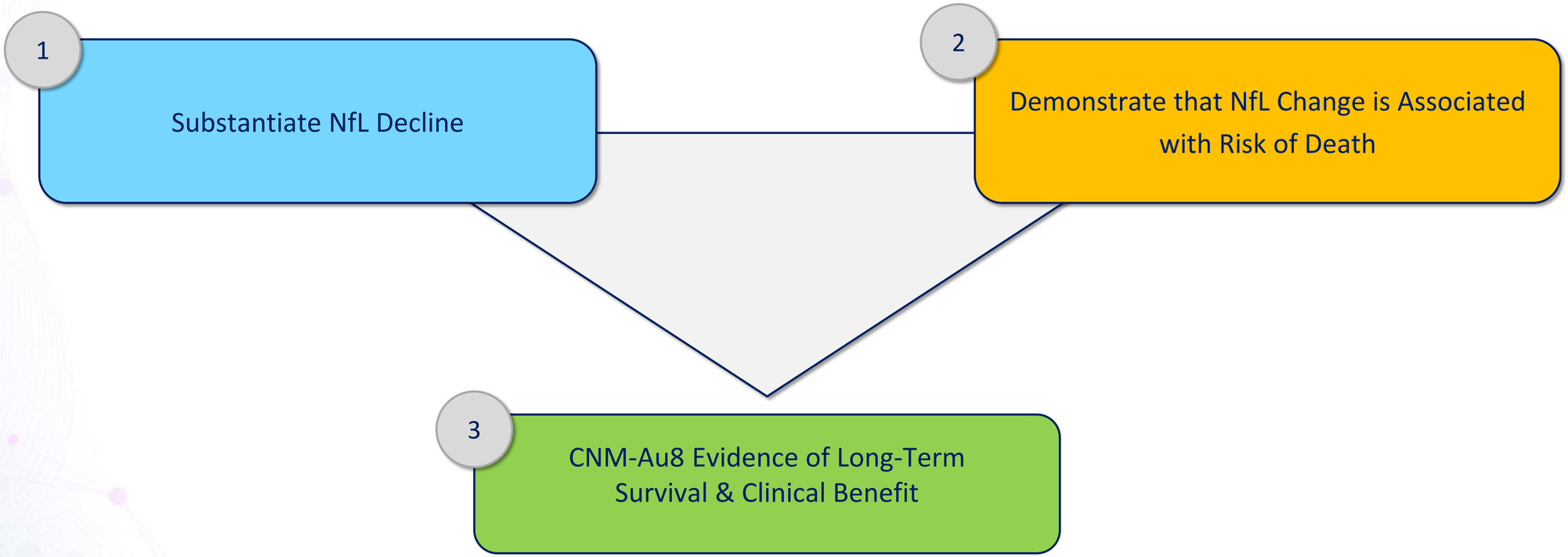
CLene NANOMEDICINE

Forward Looking Statements

This presentation contains “forward-looking statements” within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended, and Section 27A of the Securities Act of 1933, as amended, which are intended to be covered by the “safe harbor” provisions created by those laws. Clene’s forward-looking statements include, but are not limited to, statements that the substantiation of the NfL biomarker effect may support acceptance of survival analyses. In addition, any statements that refer to projections, forecasts or other characterizations of future events or circumstances, including any underlying assumptions, are forward-looking statements. The words “anticipate,” “believe,” “contemplate,” “continue,” “could,” “estimate,” “expect,” “intends,” “may,” “might,” “plan,” “possible,” “potential,” “predict,” “project,” “should,” “will,” “would,” and similar expressions may identify forward-looking statements, but the absence of these words does not mean that a statement is not forward-looking. These forward-looking statements represent our views as of the date of this presentation and involve a number of judgments, risks and uncertainties. We anticipate that subsequent events and developments will cause our views to change. We undertake no obligation to update forward-looking statements to reflect events or circumstances after the date they were made, whether as a result of new information, future events or otherwise, except as may be required under applicable securities laws. Accordingly, forward-looking statements should not be relied upon as representing our views as of any subsequent date. As a result of a number of known and unknown risks and uncertainties, our actual results or performance may be materially different from those expressed or implied by these forward-looking statements. Some factors that could cause actual results to differ include general market conditions, whether clinical trials demonstrate the efficacy and safety of our drug candidates to the satisfaction of regulatory authorities, or do not otherwise produce positive results which may cause us to incur additional costs or experience delays in completing, or ultimately be unable to complete the development and commercialization of our drug candidates; the clinical results for our drug candidates, which may not support further development or marketing approval; actions of regulatory agencies, which may affect the initiation, timing and progress of clinical trials and marketing approval; our ability to achieve commercial success for our drug candidates, if approved; our limited operating history and our ability to obtain additional funding for operations and to complete the development and commercialization of our drug candidates; and other risks and uncertainties set forth in “Risk Factors” in our most recent Annual Report on Form 10-K and any subsequent Quarterly Reports on Form 10-Q. In addition, statements that “we believe” and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based upon information available to us as of the date of this presentation, and while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information. These statements are inherently uncertain, and you are cautioned not to rely unduly upon these statements. All information in this presentation is as of the date of this presentation. The information contained in any website referenced herein is not, and shall not be deemed to be, part of or incorporated into this presentation.

FDA Guidance | Substantiation of NfL Biomarker Effect May Support Survival Analyses

"If you are able to provide substantiation of the effects on NfL, we would be willing to consider whether the 24-week data from the HEALEY Platform Trial and the post-hoc analyses on long-term survival are capable of providing evidence that the change in NfL is reasonably likely to predict clinical benefit or potentially serve as confirmatory evidence; however, that would ultimately require a review of the data."



Data on File, Clene Nanomedicine, Inc.

FDA Guidance | Regulatory Path for Accelerated Approval

Excerpted FDA Letters to Clene

NIH-Sponsored EAP NfL Change

*"…**analysis of** change from baseline for NfL at 24 weeks or longer from subjects in the ongoing expanded access protocols"*

NIH·EAP with CNM-Au8®

HEALEY Ex-Placebo to CNM-Au8 NfL Change

"…analysis of change from baseline for NfL in subjects in the OLE of HEALEY who were initially placebo and then received Au8 during OLE"

HEALEY ALS Platform Trial

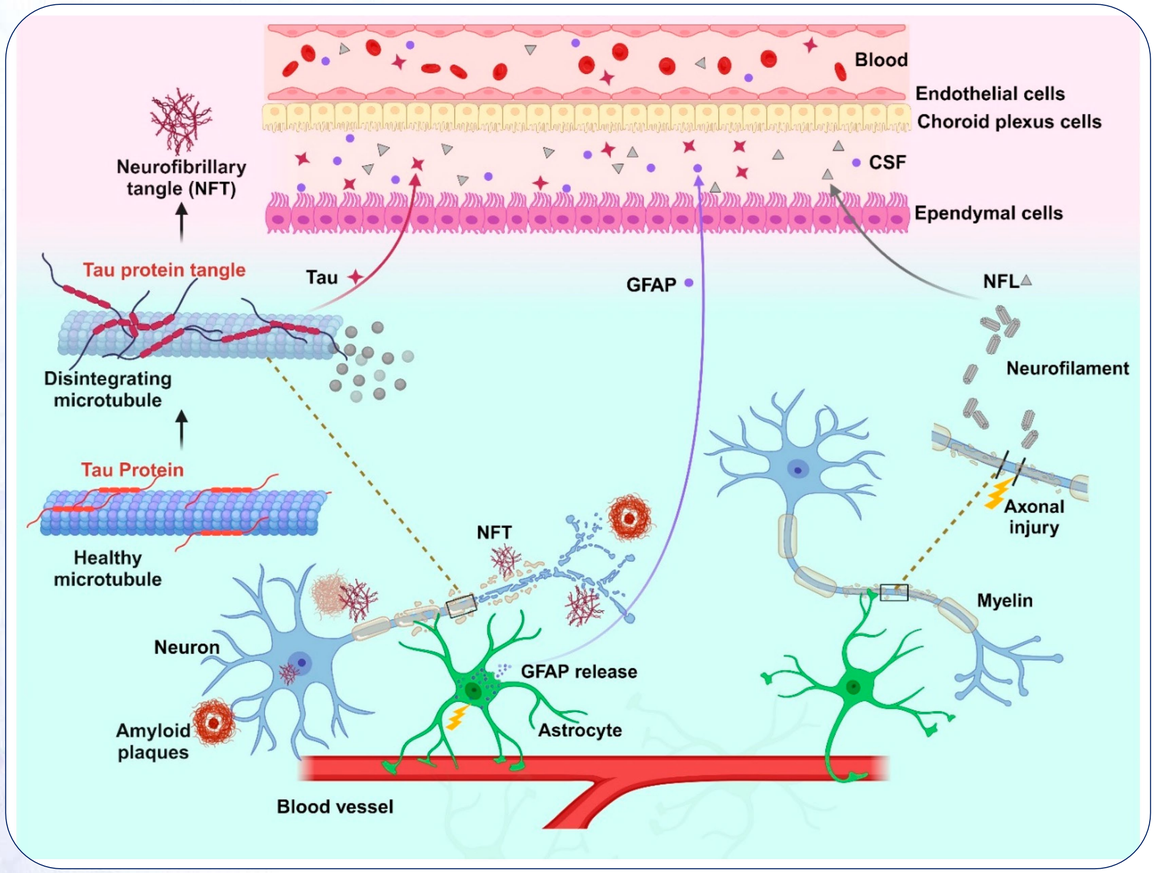
Other Supportive Biomarkers

"..the Division noted that a consistent effect of CNM-Au8 on additional appropriate disease-specific biomarkers could support a drug effect."

HEALEY ALS Platform Trial

Data on File, Clene Nanomedicine, Inc.

ALS Disease-Relevant Biomarkers | What are NfL & GFAP ?



Neurofilament Light Chain (NfL)

- ✓ Structural protein of neuronal axons
- ✓ NfL is released as a sensitive biomarker of neuroaxonal injury when axons are damaged or degenerate in ALS
- ✓ Elevated NfL levels strongly correlate with faster ALS progression rates and shorter survival

Glial Fibrillary Acidic Protein (GFAP)

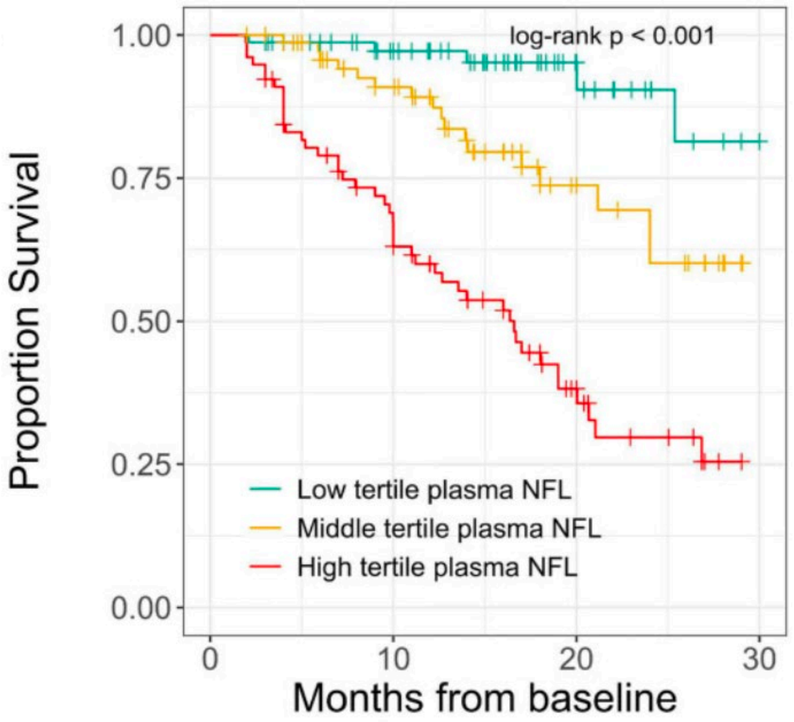
- ✓ A structural protein in astrocytes, which are crucial for supporting neurons
- ✓ GFAP increase reflects harmful inflammatory and degenerative processes contributing to motor neuron loss in ALS

Source(s): Park et al. Int. J. Mol. Sci. 2024, 25(12), 6295. Wagner et al. Neurology. 2025 Feb 26;104(6):e213400. Jung et al. Journal of Neurology (2025) 272:532.

High NfL and GFAP Levels Are Associated with Mortality Risk in ALS

High NfL Levels are Significantly Associated with ALS Mortality

Multivariate Cox HR (1 SD Rise in Log_{10} NfL): 2.99, 95% CI: 1.7–5.4, p=0.016

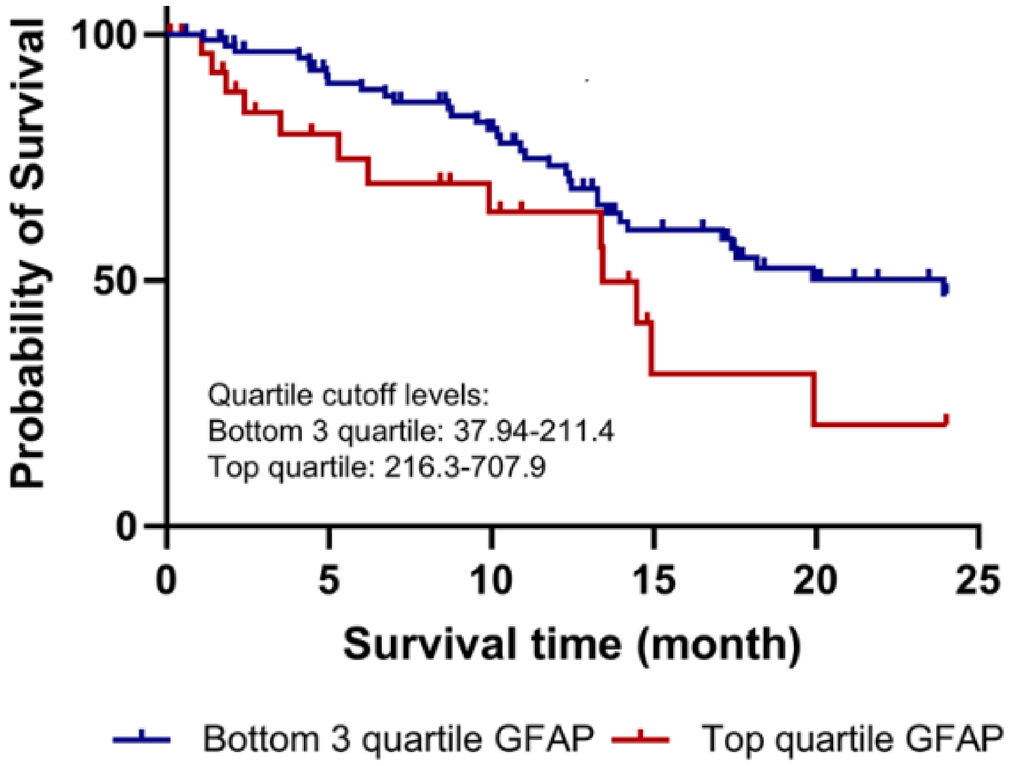


Plasma NfL (By Baseline Tertile, n=238)

High GFAP Levels are Significantly Associated with ALS Mortality

(Upper Quartile vs. Lower Quartiles)

Multivariate Cox HR = 2.65, 95% CI: 1.06 – 6.65, p= 0.038



Source(s): Thompson et al., 2022. Brain Communications, Volume 4, Issue 1, 2022. Jung et al. Journal of Neurology (2025) 272:532.

Substantiation of NfL Biomarker Effect May Support Acceptance of Survival Analyses (NIH-EAP)

NIH·EAP
with CNM-Au8®

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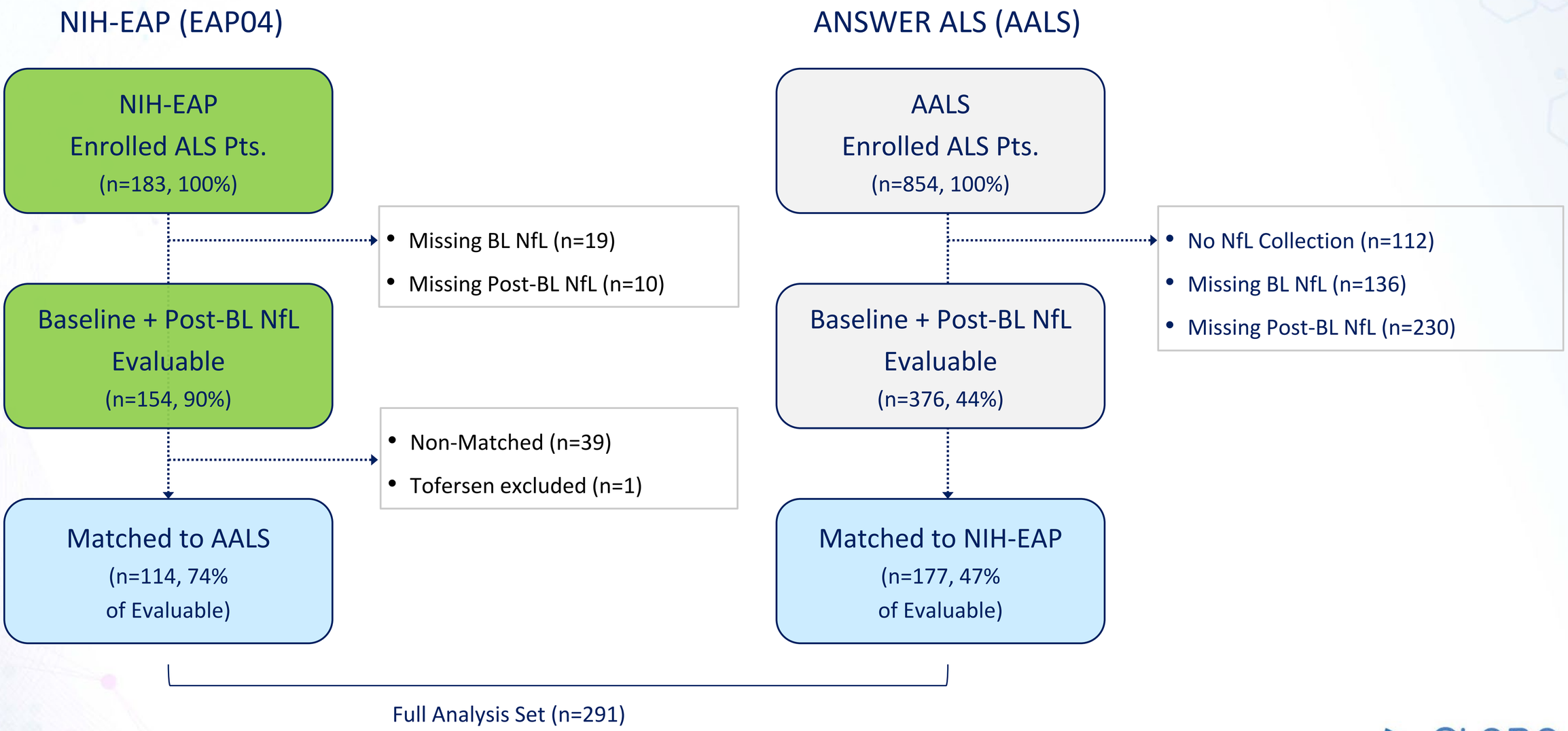
NIH-EAP Interim NfL Analyses | Full Analysis Set

ANSWER ALS Matched Controls | Participant Flow

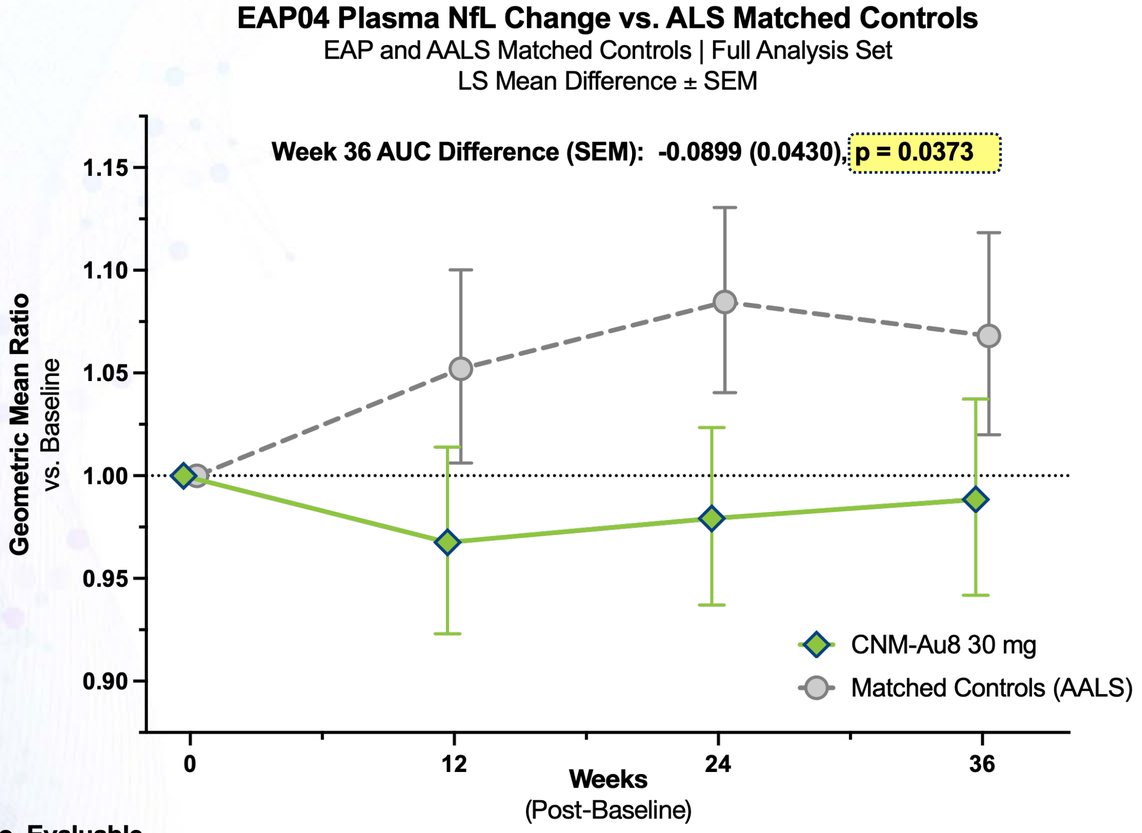


Data on File, Clene Nanomedicine, Inc.

Significant NfL AUC Difference Across All Matched Participants

Full Analysis Set | Comparison to AALS Matched Controls at W36

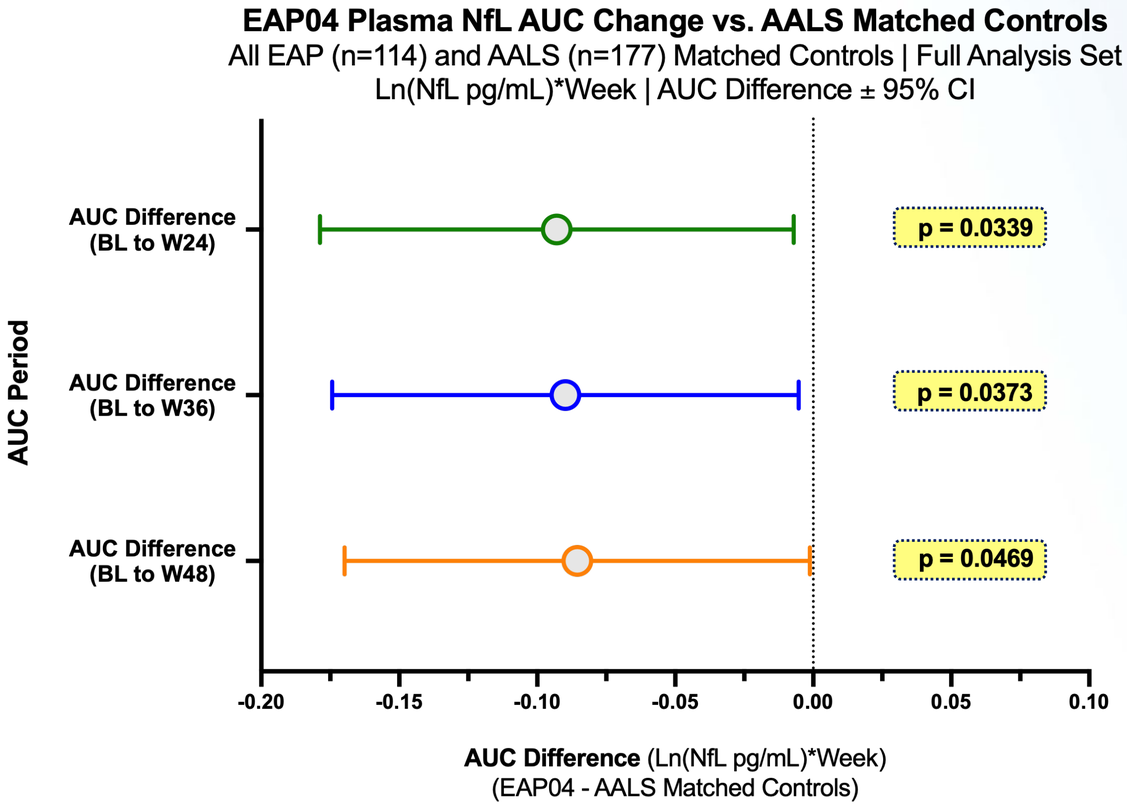
Full Analysis Set | All Matched Participants



No. Evaluable				
EAP04 CNM-Au8 30 mg:	114	108	106	76
AALS Matched Controls:	177	105	99	68

NfL Change vs. AALS Matched Controls

AUC Difference | Ln(NfL pg/mL)*Week



Model covariates are the same as those used for propensity matching: (i) Baseline Ln(NfL), (ii) Sex, (iii) Riluzole, (iv) delta-FS, (v) Bulbar Onset, (vi) Age, and (vii) Onset Months and (viii) ALSFRS-R

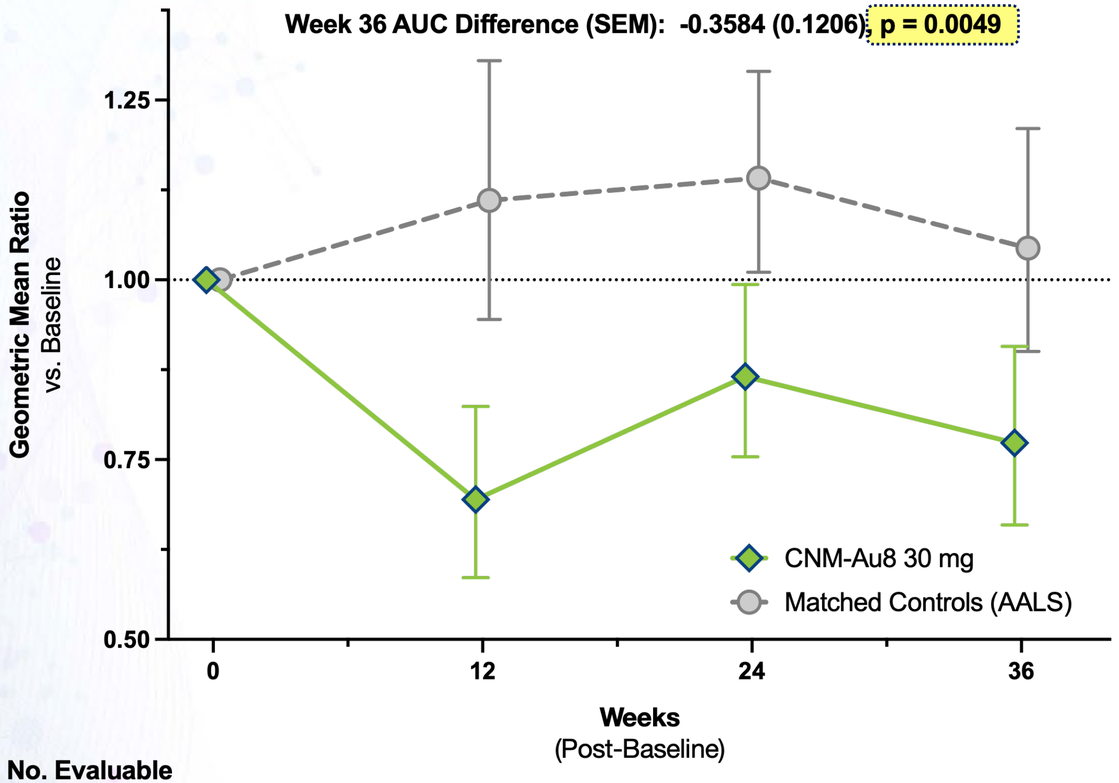
Data on File, Clene Nanomedicine, Inc.

Significant NfL AUC Difference Across All Matched Participants

Bulbar Onset | Comparison to AALS Matched Controls at W36

Bulbar Onset | All Matched Participants

EAP04 Plasma NfL Change vs. ALS Matched Controls
All EAP and AALS Matched Participants | Bulbar Onset Only
LS Mean Difference ± SEM

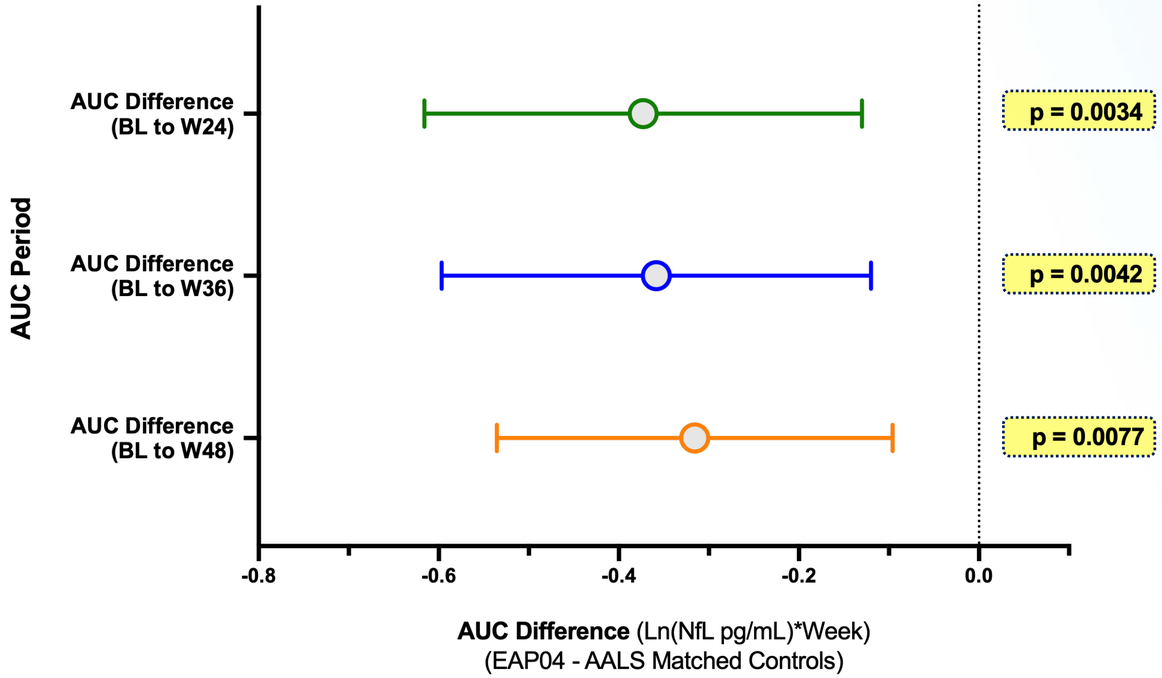


No. Evaluable				
EAP04 CNM-Au8 30 mg:	19	18	19	13
AALS Matched Controls:	35	20	17	12

NfL Change vs. AALS Matched Controls

AUC Difference | Ln(NfL pg/mL)*Week

EAP04 Plasma NfL AUC Change vs. AALS Matched Controls
All EAP (n=19) and AALS (n=35) Matched Controls | Bulbar Onset
Ln(NfL pg/mL)*Week | AUC Difference ± 95% CI



Model covariates are the same as those used for propensity matching: (i) Baseline Ln(NfL), (ii) Sex, (iii) Riluzole, (iv) delta-FS, (v) Bulbar Onset, (vi) Age, and (vii) Onset Months and (viii) ALSFRS-R

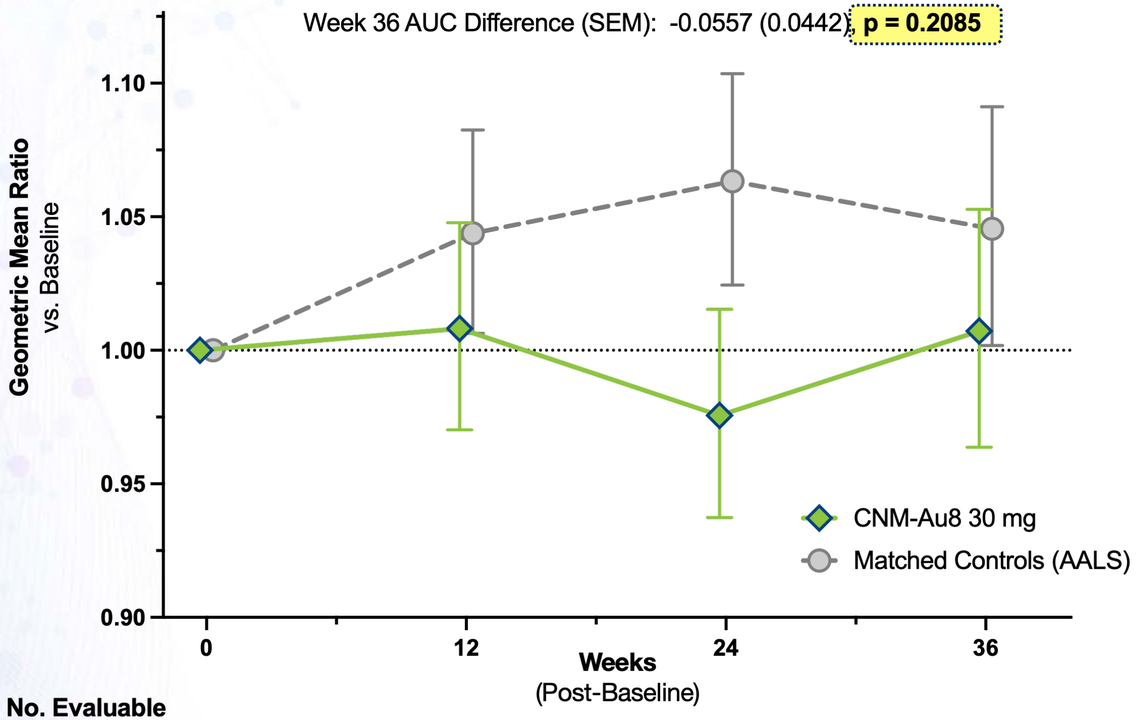
Data on File, Clene Nanomedicine, Inc.

Primary Efficacy for NfL Analysis | Non-Bulbar Population

NfL Reduction Non-Significant in Non-Bulbar AALS Matched Participants

Non-Bulbar Onset (Limb, Thoracic) | All Matched Participants

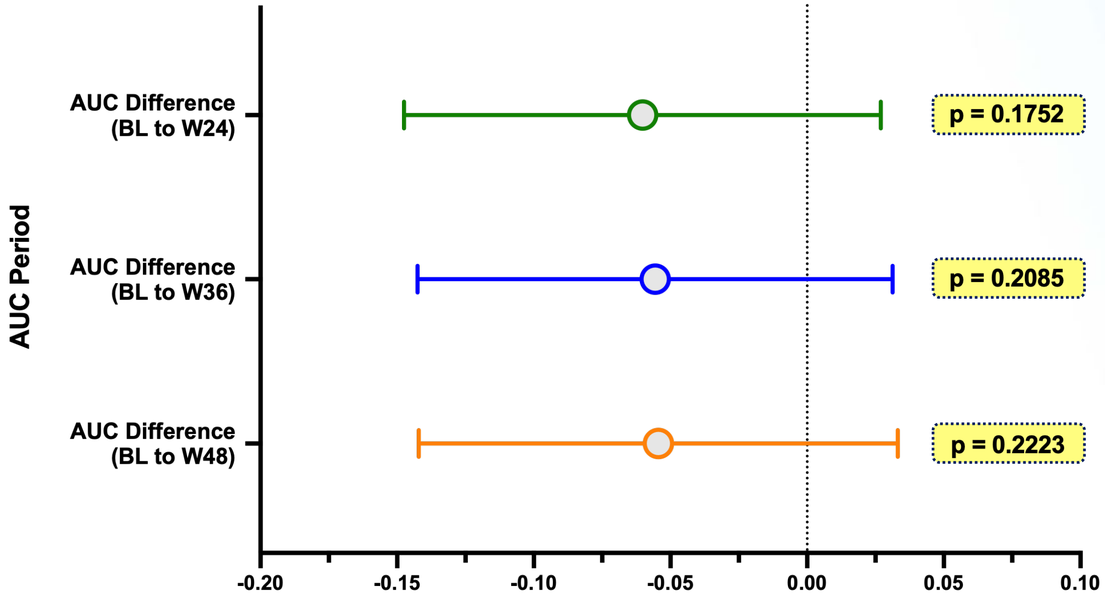
EAP04 Plasma NfL Change vs. ALS Matched Controls
Primary Interim NfL Efficacy
All EAP and AALS Matched Participants | Non-Bulbar Onset Only
LS Mean Difference ± SEM



No. Evaluable				
EAP04 CNM-Au8 30 mg:	95	90	87	63
AALS Matched Controls:	142	85	82	56

NfL Change vs. AALS Matched Controls
AUC Difference | Ln(NfL pg/mL)*Week

EAP04 Plasma NfL AUC Change vs. ALS Matched Controls
All EAP (n=95) and AALS (n=142) Matched Controls | Non-Bulbar Onset
AUC Difference ± 95% CI



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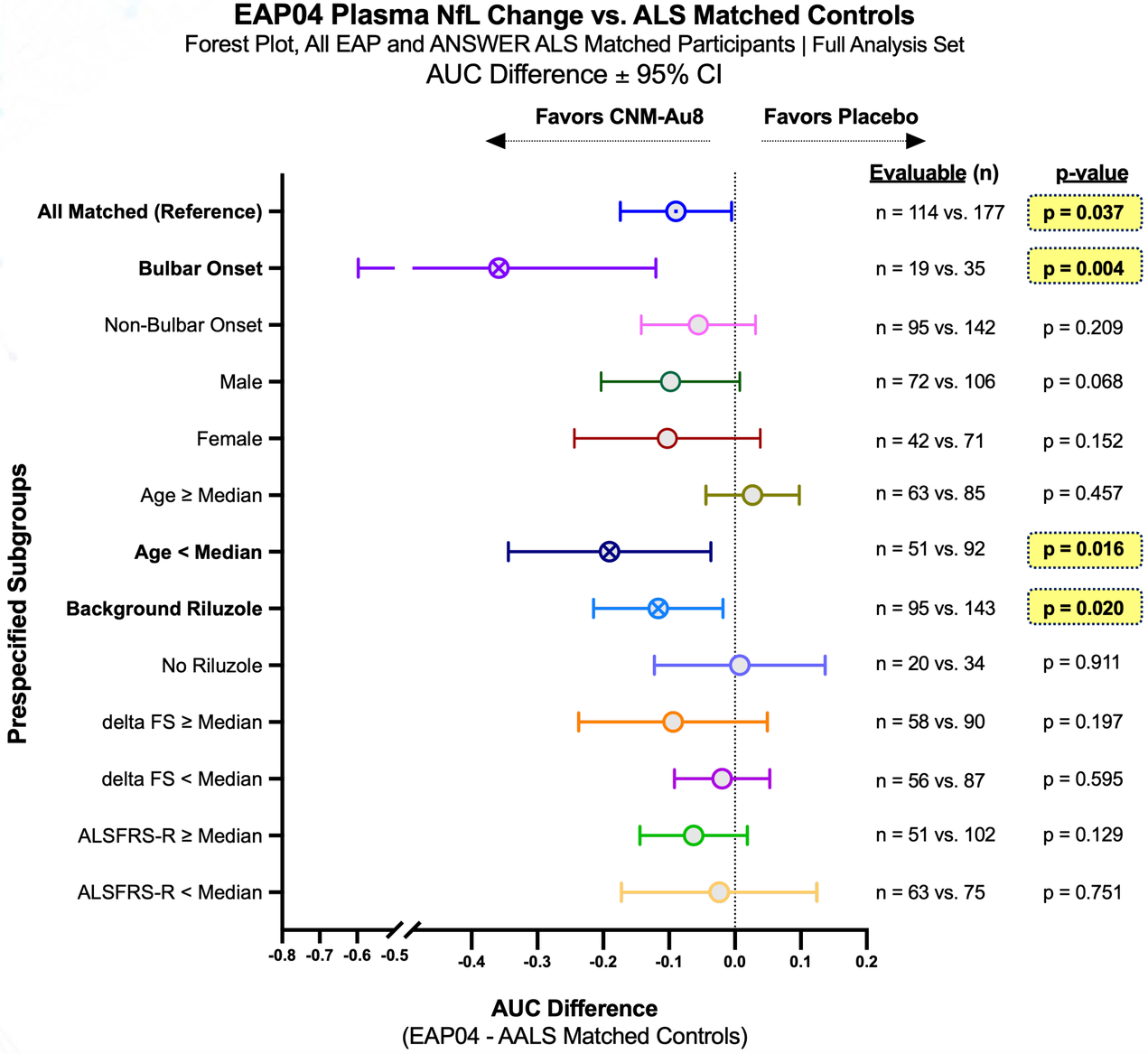
Data on File, Clene Nanomedicine, Inc.

Significant NfL Decline | All, Bulbar, Younger, Riluzole-Treated

Comparison to AALS Matched Controls | Prespecified Subgroups

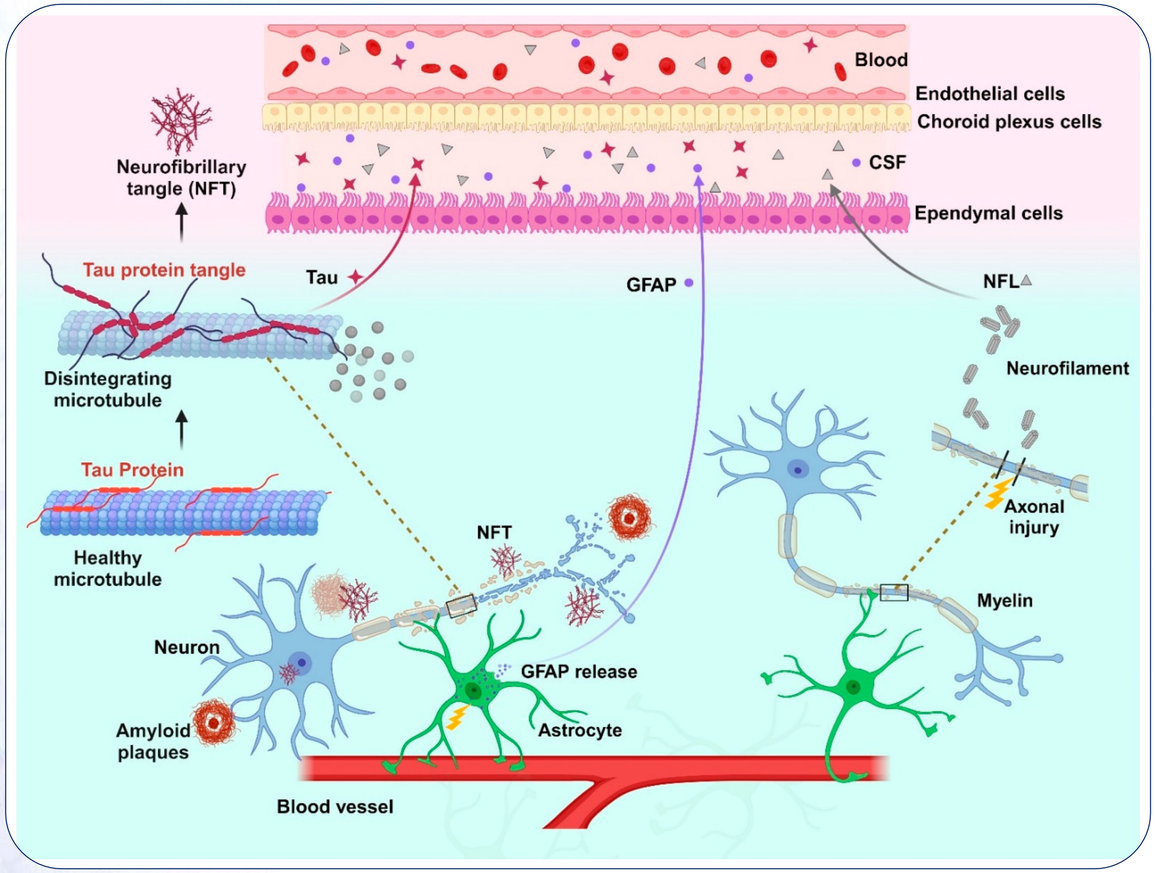


Model covariates are the same as those used for propensity matching: (i) Baseline Ln(sNfL), (ii) Sex, (iii) Riluzole Treatment, (iv) delta-FS, (v) Bulbar Onset, (vi) Age, and (vii) Months from Symptom Onset

Data on File, Clene Nanomedicine, Inc.

Substantiation of Additional Biomarker Effects to Support Survival Analyses

ALS Disease-Relevant Biomarkers | What are NfL & GFAP ?



Neurofilament Light Chain (NfL)

- ✓ Structural protein of neuronal axons
- ✓ NfL is released as a sensitive biomarker of neuroaxonal injury when axons are damaged or degenerate in ALS
- ✓ Elevated NfL levels strongly correlate with faster ALS progression rates and shorter survival

Glial Fibrillary Acidic Protein (GFAP)

- ✓ A structural protein in astrocytes, which are crucial for supporting neurons
- ✓ GFAP increase reflects harmful inflammatory and degenerative processes contributing to motor neuron loss in ALS

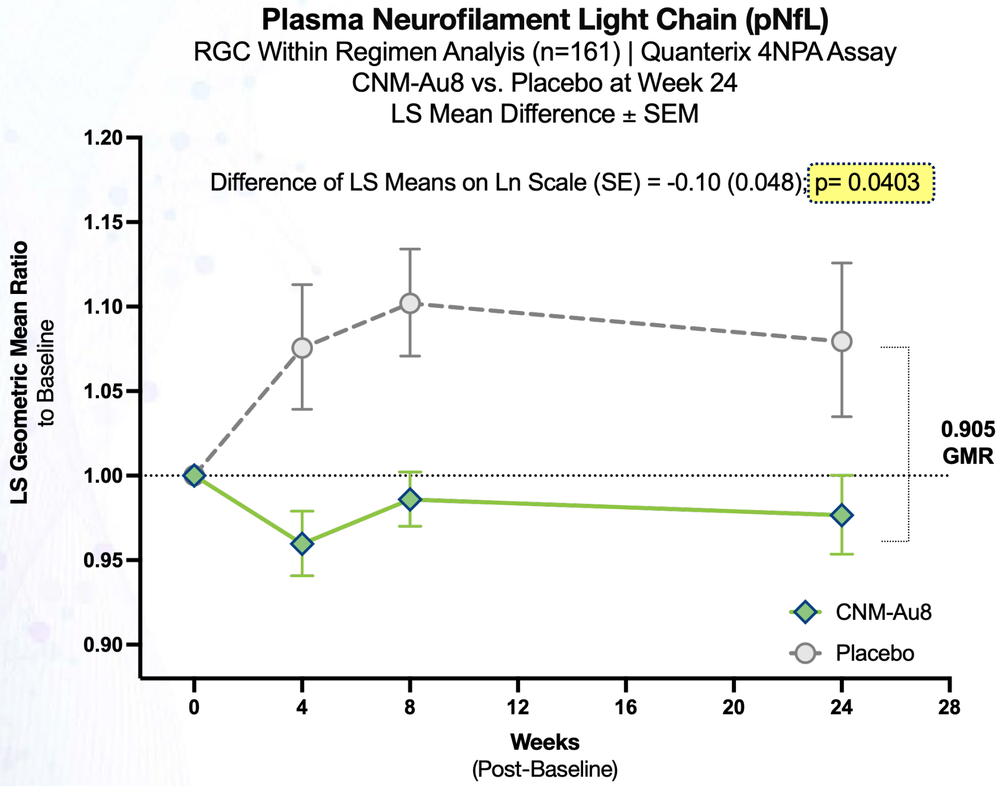
Source(s): Park et al. Int. J. Mol. Sci. 2024, 25(12), 6295. Wagner et al. Neurology. 2025 Feb 26;104(6):e213400. Jung et al. Journal of Neurology (2025) 272:532.

HEALEY NfL and GFAP Biomarker Effects Are Consistent

Biomarker Changes from Baseline to End of the Double-Blind Period (W24)

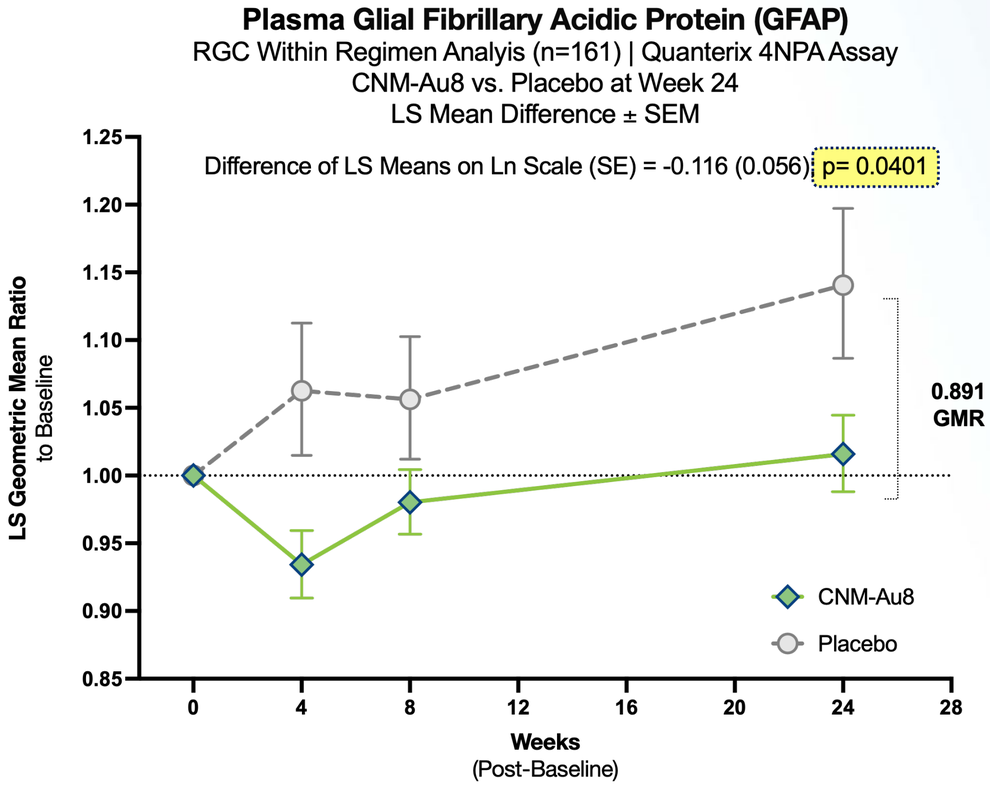
HEALEY ALS Platform Trial

Neurofilament Change



Plasma NfL	GMR	95% CI	p-value
W24 LS Mean	0.905	0.822 – 0.996	p = 0.0403
W24 AUC	0.901	0.845 – 0.959	p = 0.0013

Glial Fibrillary Acidic Protein (GFAP) Change



Plasma GFAP	GMR	95% CI	p-value
W24 LS Mean	0.891	0.798 – 0.995	p = 0.0401
W24 AUC	0.913	0.841 – 0.990	p = 0.0278

Data on File, Clene Nanomedicine, Inc. Prespecified covariates included: months from symptom onset, pre-treatment ALSFRS-R slope (delta-FRS), riluzole treatment, and edaravone treatment.

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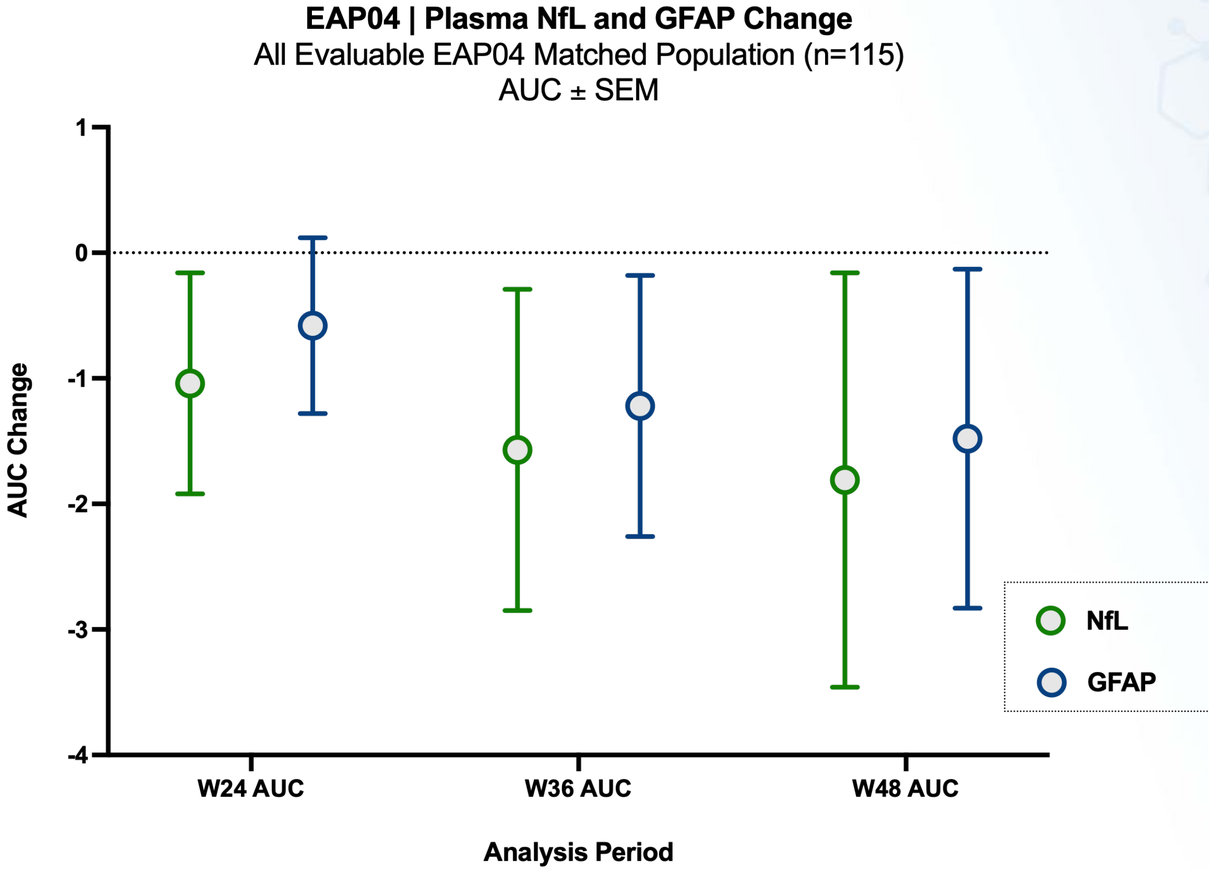
NIH-EAP NfL and GFAP AUC Decline is Also Consistent

Concordant Effect on NfL and GFAP AUC Change

AUC Period	N	Pearson r	p-value	Concordance
Week 0 – 24 AUC	115	0.911	p < 0.001	80.9%
Week 0 – 36 AUC	115	0.919	p < 0.001	78.3%
Week 0 – 48 AUC	115	0.941	p < 0.001	78.3%



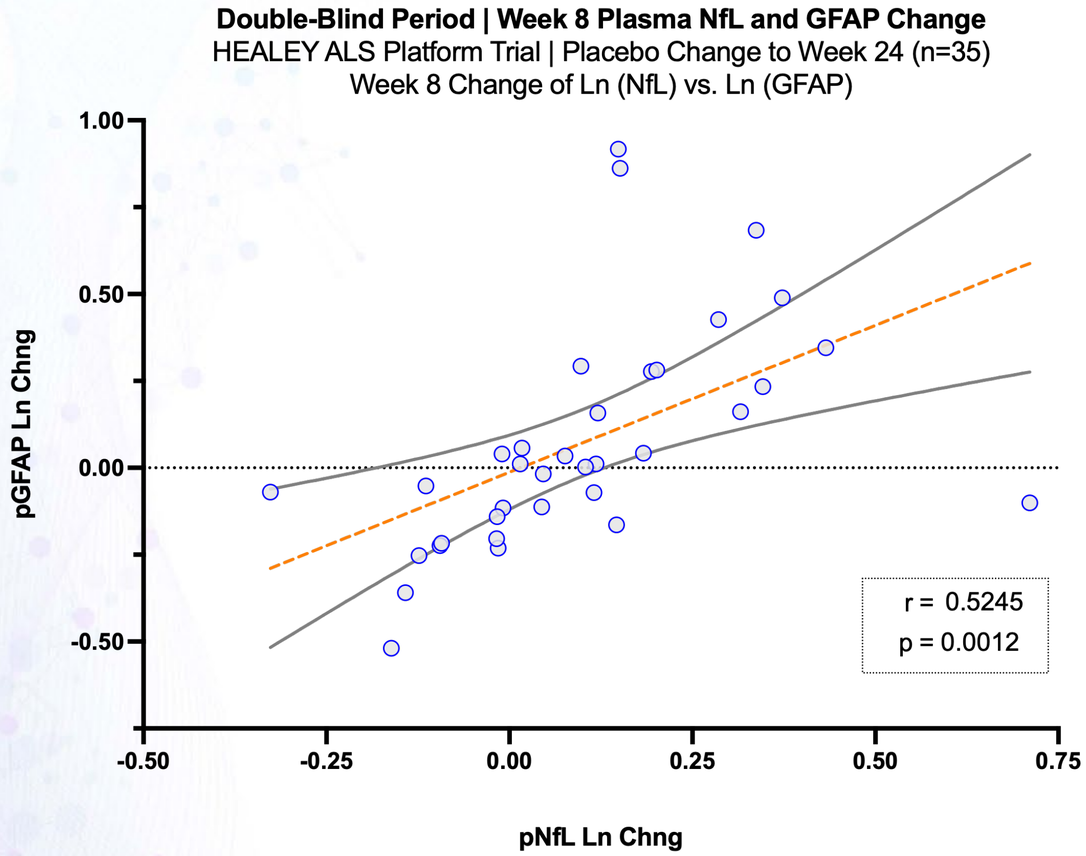
NfL and GFAP AUC Change
Ln(NfL pg/mL)*Week

Data on File, Clene Nanomedicine, Inc.

Plasma NfL & GFAP *Change* are Closely Correlated in Placebo Participants in the HEALEY ALS Platform Trial

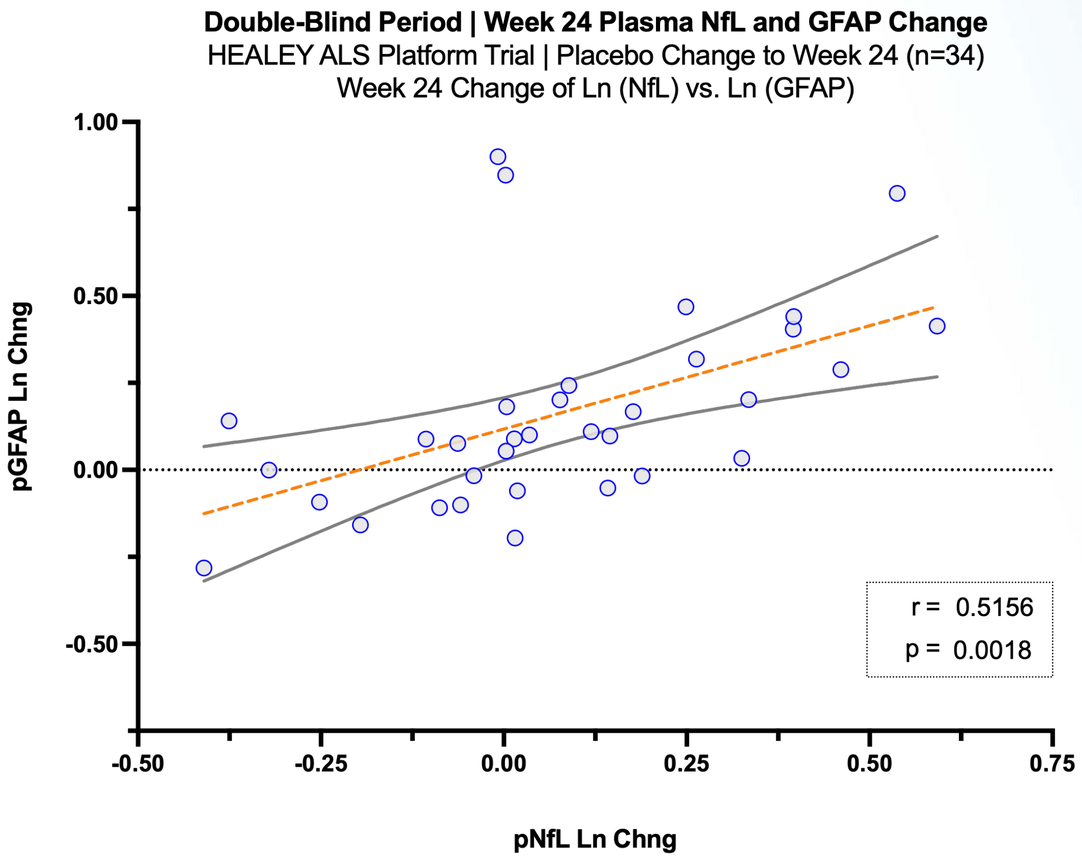
HEALEY ALS Platform Trial

CNM-Au8 Placebo | Week 8



Pearson R	95% CI	p-value
r = 0.525	0.232 to 0.730	p = 0.0012

CNM-Au8 Placebo | Week 24



Pearson R	95% CI	p-value
r = 0.516	0.215 to 0.727	p = 0.0018

Data on File, Clene Nanomedicine, Inc.

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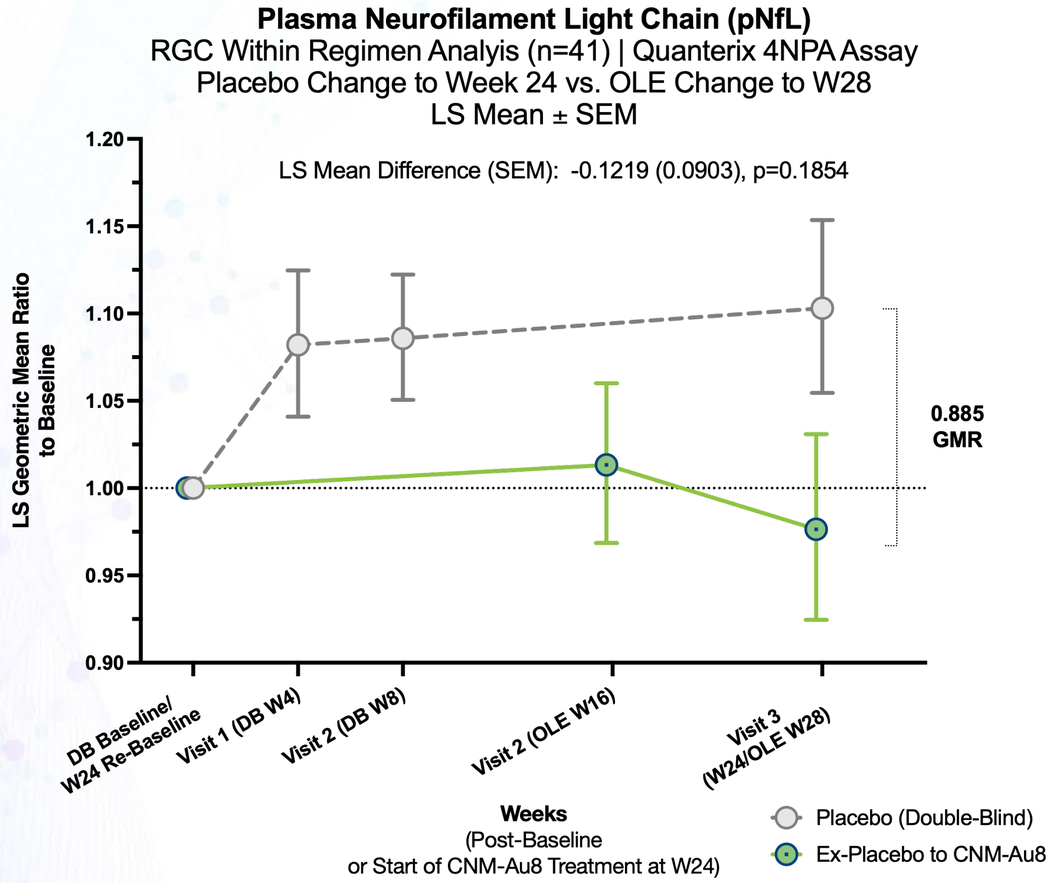
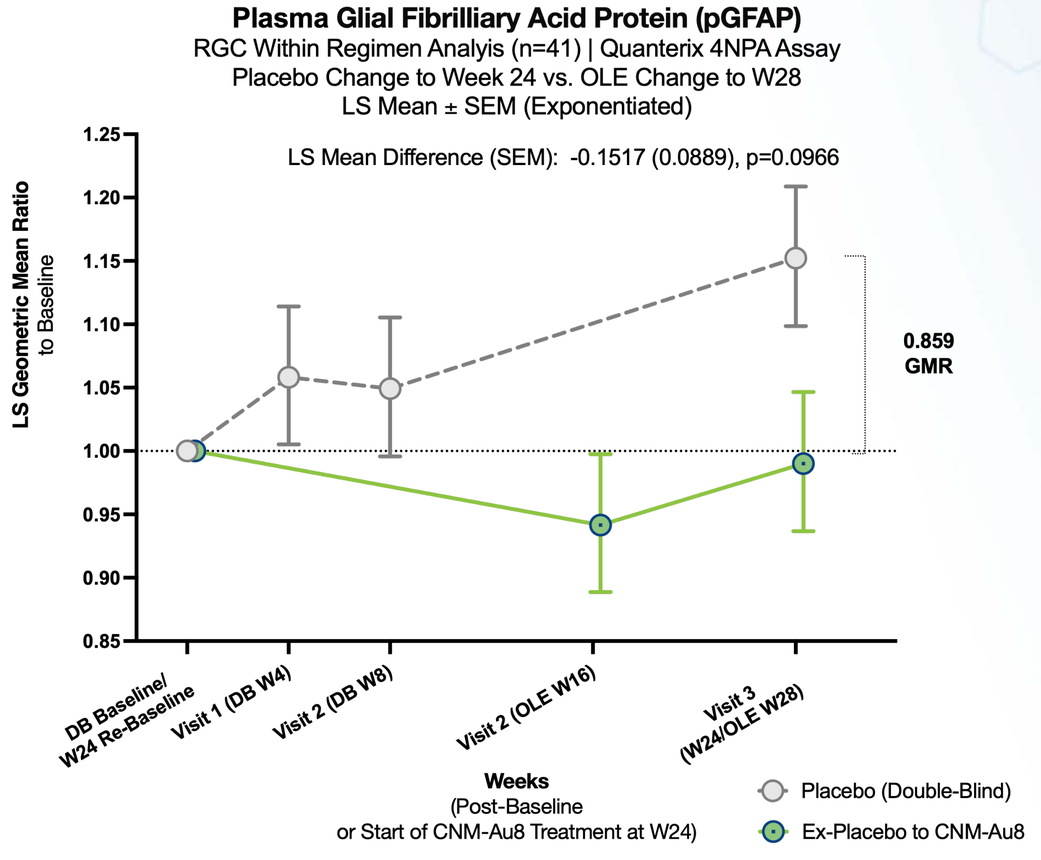
Similar NfL and GFAP Reduction in Ex-Placebo to CNM-Au8 Population

Only 31 Participants (Underpowered but with Comparable Treatment Difference)

HEALEY ALS Platform Trial





pNfL	GMR	95% CI	p-value
OLE W28 Difference	**0.885**	**0.737 – 1.063**	**p = 0.1854**

pGFAP	GMR	95% CI	p-value
OLE W28 Difference	**0.859**	**0.717 – 1.029**	**p = 0.0966**

Prespecified covariates included: months from symptom onset, pre-treatment ALSFRS-R slope (delta-FRS), riluzole treatment, and edaravone treatment.

Data on File, Clene Nanomedicine, Inc.

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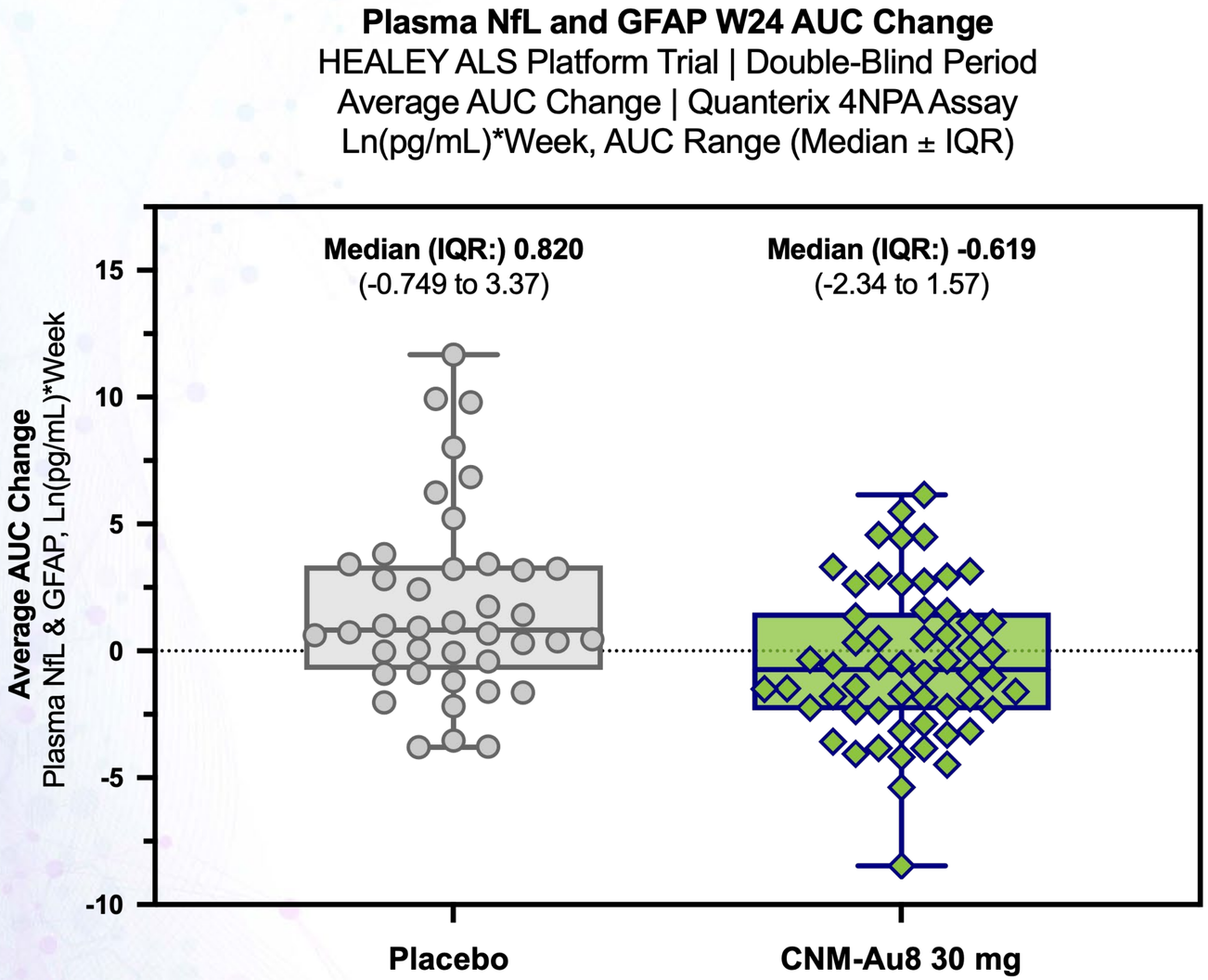
NfL & GFAP AUC Decline | Thresholds for Survival Analyses

Change from Baseline During the 24-Week Double-Blind Period



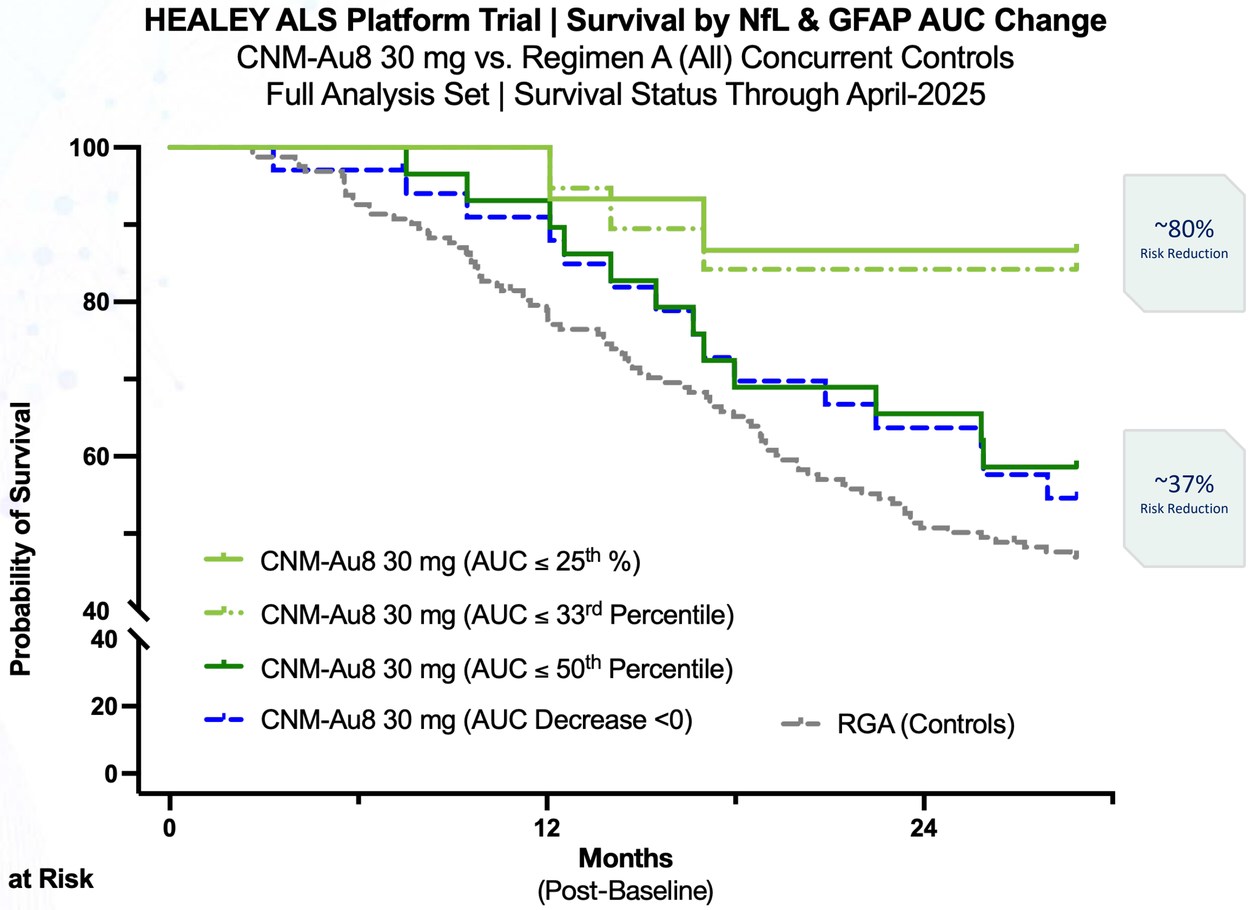
CNM-Au8 30 mg AUC Change Thresholds
(Nested Groups)

1. Any AUC Decline (n=34, 60%)
2. AUC Decline ≤ Median (n=29, 50%)
3. AUC Decline ≤ 33rd Percentile (n=19, 33%)
4. AUC Decline ≤ 25th Percentile (n=15, 26%)

Data on File, Clene Nanomedicine, Inc. Visualization excludes one outlier for graphing convenience.

NfL & GFAP AUC Decline Associated with Improved Survival

AUC Decline through the 24-Week Double-Blind Period (*Post Hoc*)



No. at Risk						
CNM-Au8 30 mg (AUC Δ ≤ 25th):	15	15	15	13	13	13
CNM-Au8 30 mg (AUC Δ ≤ 33rd):	19	19	19	16	16	16
CNM-Au8 30 mg (AUC Δ ≤ Median):	29	29	27	20	19	17
CNM-Au8 30 mg (AUC Δ < 0):	34	33	30	23	21	18
RGA Controls:	162	150	127	104	81	74

Cox Hazard Ratio Model

Full Analysis Set vs. RGA Controls to End of OLE

AUC Change Threshold	Cox HR (95% CI)	p-value
AUC Decline ≤ 25th Percentile	0.191 (0.047 – 0.782)	p=0.0210
AUC Decline ≤ 33rd Percentile	0.233 (0.073 – 0.739)	p=0.0130
AUC Decline ≤ Median	0.625 (0.339 – 1.154)	p=0.1330
Any AUC Decline (<0)	0.637 (0.366 – 1.110)	p=0.1115

AUC Change as Ln(pg/mL)*Week

Prespecified covariates included: months from symptom onset, pre-treatment ALSFRS-R slope (delta-FS), riluzole treatment, and edaravone treatment.

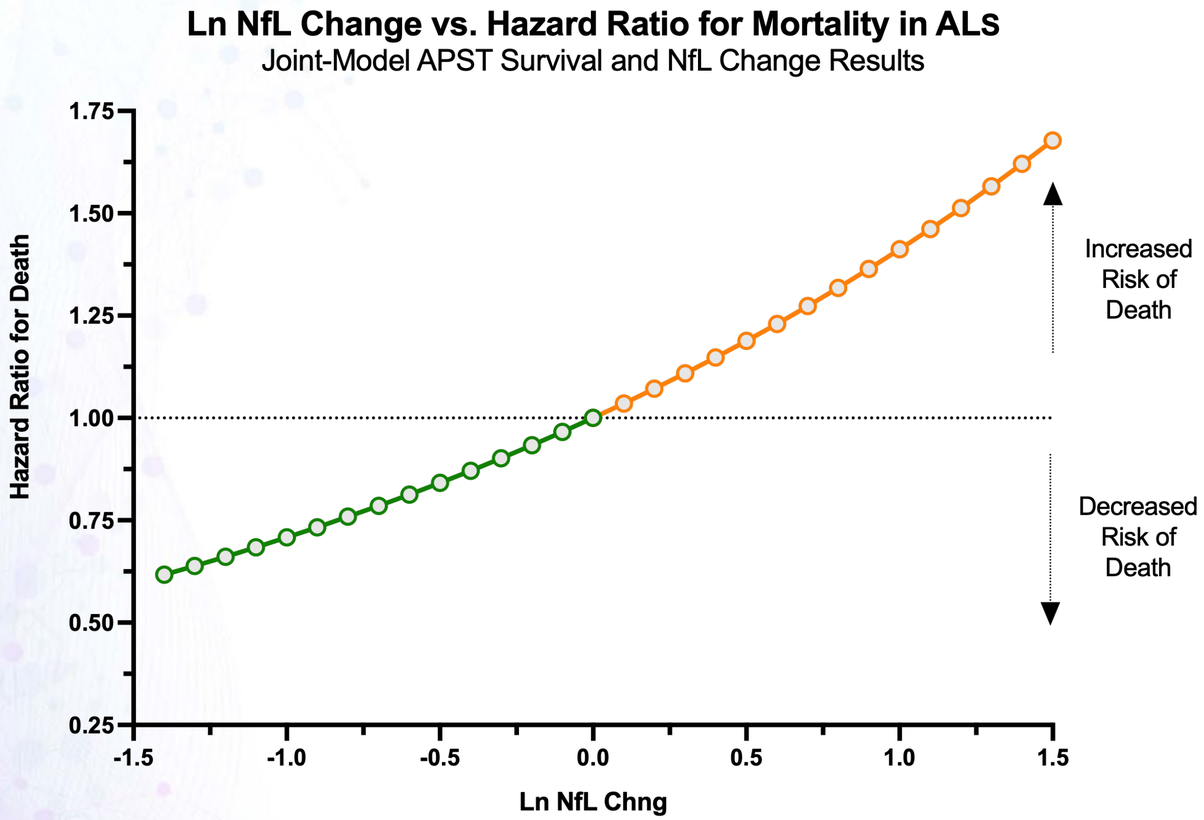
Data on File, Clene Nanomedicine, Inc.

Increased NfL is Associated with the Risk of Death in ALS

NfL *Change* Significantly Impacts ALS Survival

Joint-Model of NfL Change and Survival | APST Dataset

Association of NfL Change and Mortality Risk



Joint-Model
Hazard Ratio
Exp (0.339) = 1.40

ALS Longitudinal NfL & Mortality Dataset	Association Factor (SE)	Hazard Ratio (95% CI)	p-value
APST (n=1072)	**0.339 (0.036)**	**1.40 (1.31 – 1.51)**	**p < 0.0001**

- For each 1-unit increase in Ln(NfL), the hazard for death increases by 40%

Data on File, Clene Nanomedicine, Inc.

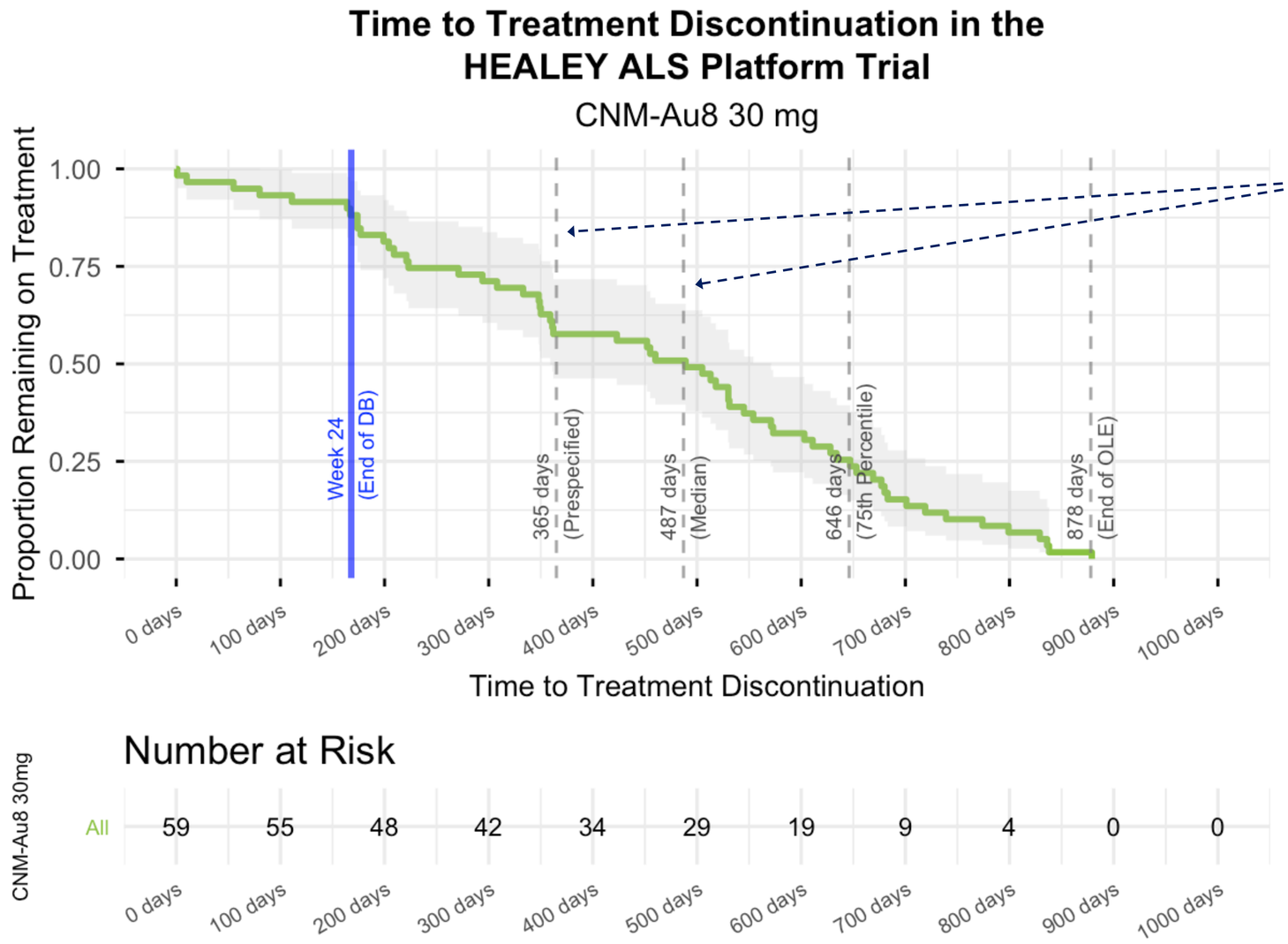
Long-Term Survival Evidence from the HEALEY ALS Platform Trial

Original CNM-Au8 30 mg vs.
Concurrently Randomized Controls
(Regimen A)

Original Placebo to CNM-Au8 vs.
Concurrently Randomized Controls
(Regimen A)

Survival Analysis Periods | CNM-Au8 30 mg

Analysis Anchored by Time to Treatment Discontinuation | Median = Month 16



Analysis Intervals

- Month 12
  - Prespecified Timepoint in RGC HEALEY OLE SAP
- Median Discontinuation Time
  - 50% Discontinuation at Month 16

Data on File, Clene Nanomedicine, Inc.

CNM-Au8 30 mg Survival vs. RGA Controls | Analysis Populations

HEALEY ALS Platform Trial

Full Analysis Set (FAS)

All Randomized Participants

Comparable Risk Set (CRS)

Filters At-Risk for Comparable Baseline Disease Severity

- Ln(NfL) ≥ 3.5
- TRICALS Risk Score (-2.5 to -6.5)

Population	CNM-Au8 30 mg	Regimen A
FAS	**n = 59 (100%)**	**n = 162 (100%)**
CRS	**n = 51 (86%)**	**n = 120 (74%)**

Data on File, Clene Nanomedicine, Inc.

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Improved Long-Term Survival vs. Regimen A Controls at 1-Year

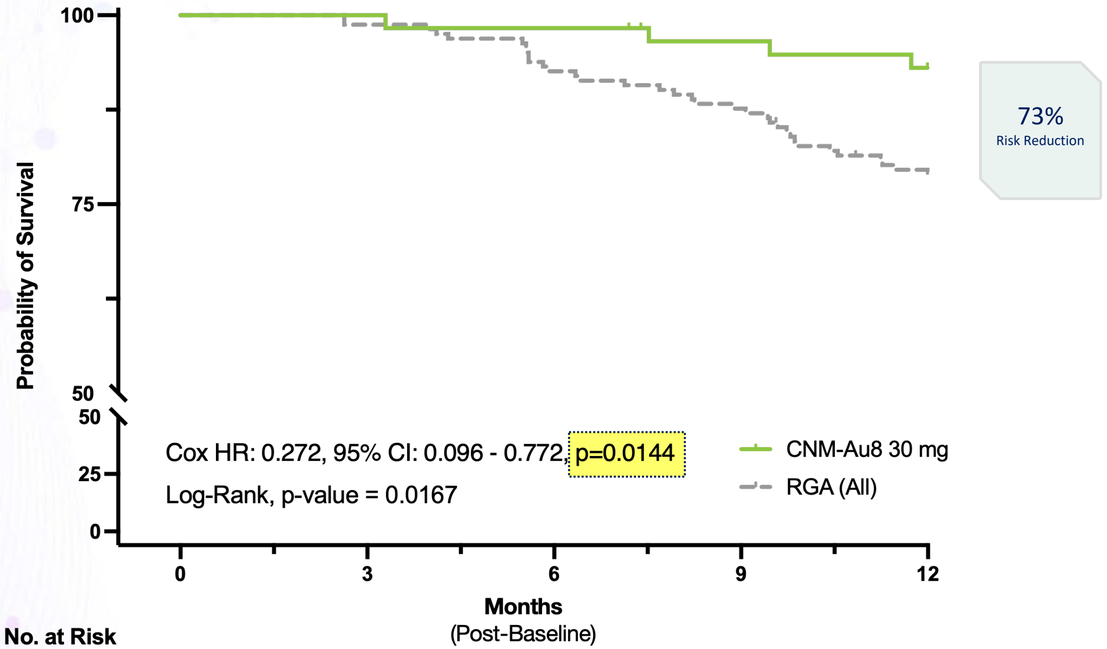
Significant Survival Difference at Month 12

HEALEY ALS Platform Trial

Full Analysis Set

Month 12 | Prespecified OLE Timepoint

HEALEY ALS Platform Trial | Survival Through Day 365
HEALEY OLE RGC SAP Prespecified Analysis Timepoint
CNM-Au8 30 mg vs. Regimen A (All) Concurrent Controls
Full Analysis Set | Kaplan-Meier Estimator
Survival Status Through April-2025

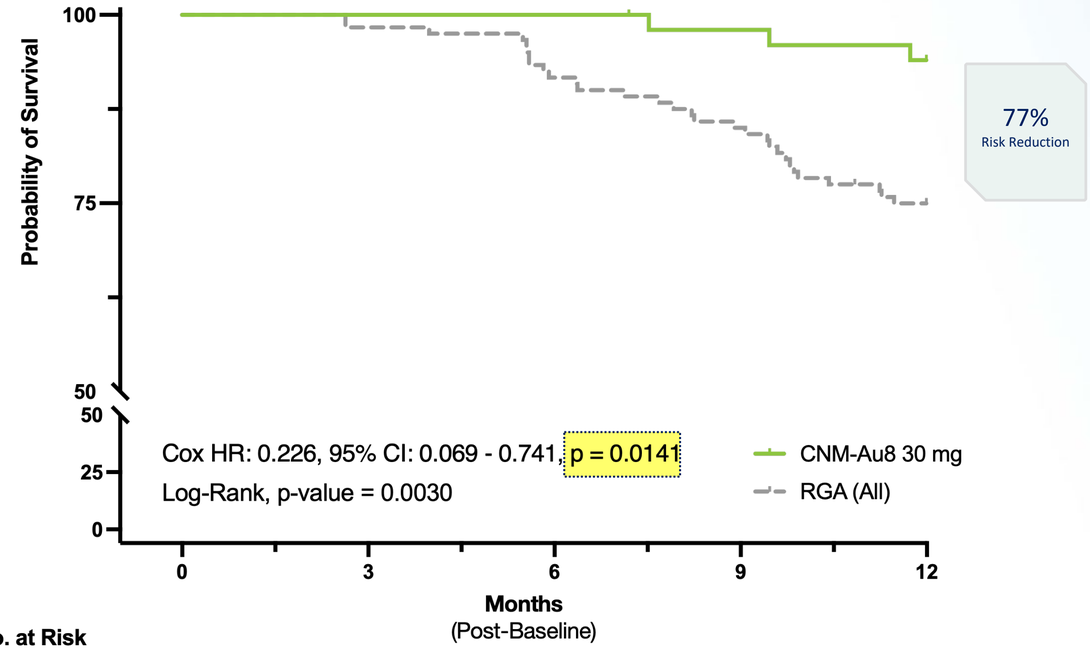


No. at Risk					
CNM-Au8 30 mg:	59	59	58	55	53
RGA Controls:	162	160	150	142	126

Comparable Risk Set

Month 12 | Prespecified OLE Timepoint

HEALEY ALS Platform Trial | Survival Through Day 365
(HEALEY OLE RGC SAP Prespecified Analysis Timepoint)
CNM-Au8 30 mg vs. Regimen A (All) Concurrent Controls
Comparable Risk Set | Kaplan-Meier Estimator
Survival Status Through April-2025



No. at Risk					
CNM-Au8 30 mg:	51	51	51	49	47
RGA Controls:	120	118	110	102	88

Prespecified HEALEY survival covariates included: age, months from symptom onset, pre-treatment ALSFRS-R slope (delta-FRS), riluzole treatment, edaravone treatment.

Data on File, Clene Nanomedicine, Inc.

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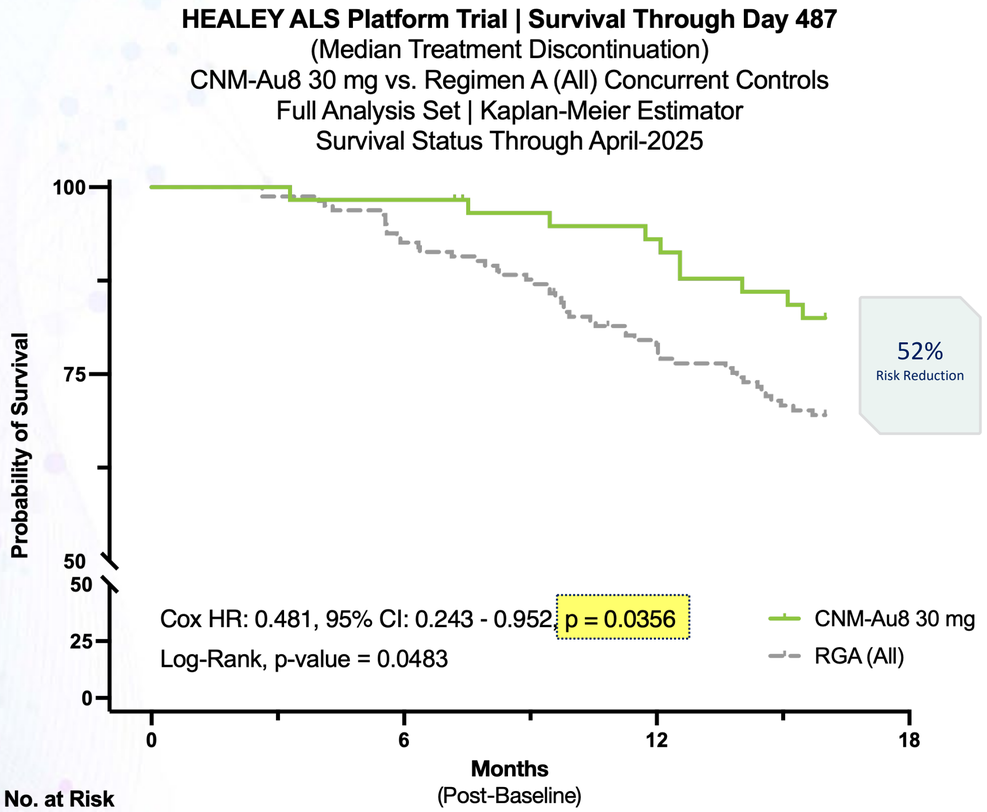
Results | Improved Long-Term Survival vs. Regimen A

CNM-Au8 30 mg vs. Regimen A Concurrent Controls (*Post Hoc*) | Month 16

Full Analysis Set

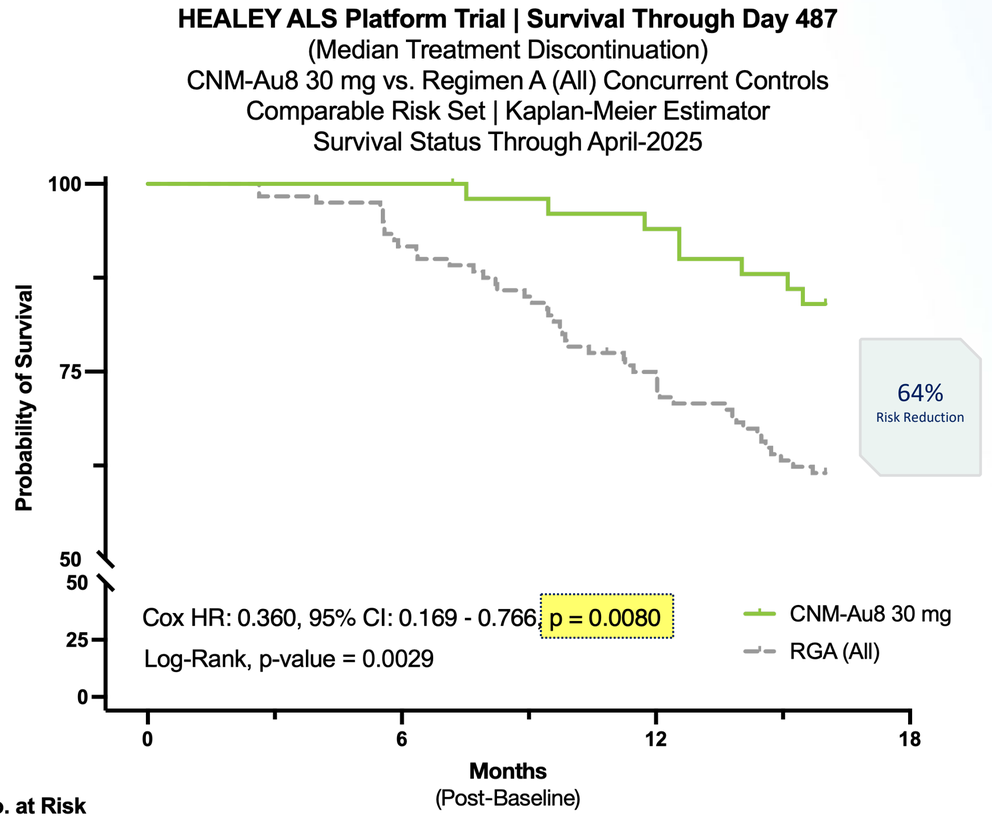
Month 16 | Median Treatment Discontinuation



No. at Risk				
CNM-Au8 30 mg:	59	58	53	40
RGA Controls:	162	150	126	104

Comparable Risk Set

Month 16 | Median Treatment Discontinuation



No. at Risk				
CNM-Au8 30 mg:	51	51	47	37
RGA Controls:	120	110	88	67

Prespecified HEALEY survival covariates included: age, months from symptom onset, pre-treatment ALSFRS-R slope (delta-FRS), riluzole treatment, edaravone treatment.

Data on File, Clene Nanomedicine, Inc.

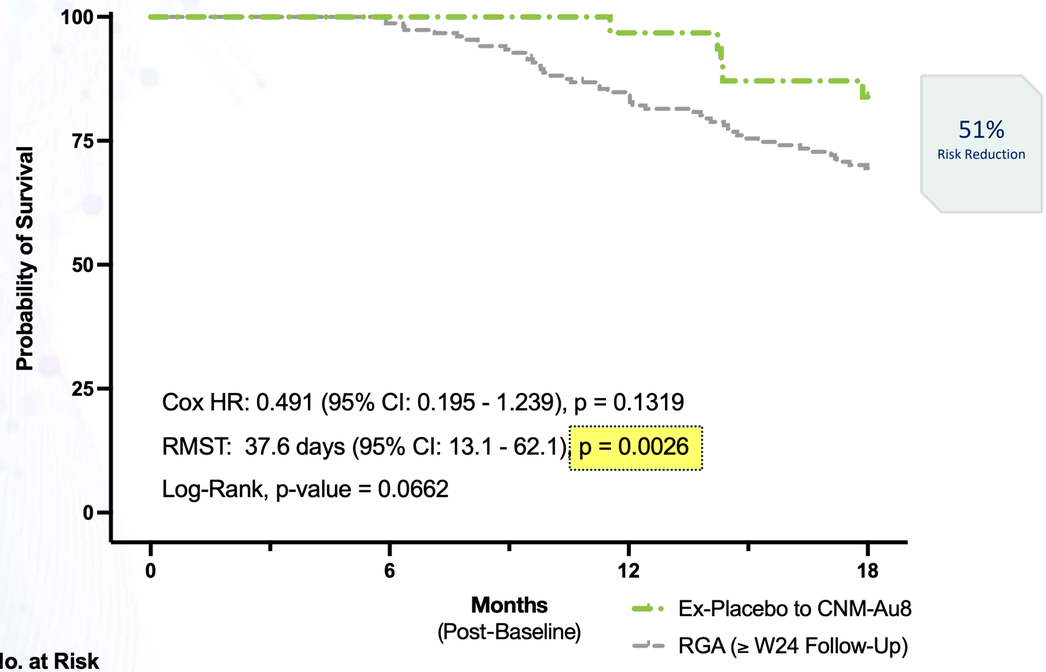
Improved Long-Term Survival in Ex-Placebo to CNM-Au8

Significant RMST Benefit vs. Regimen A at 12-Months Post Treatment Initiation & Beyond

HEALEY ALS Platform Trial

Ex-Placebo to Active Treatment
12-Months | Post-CNM-Au8 Treatment Initiation

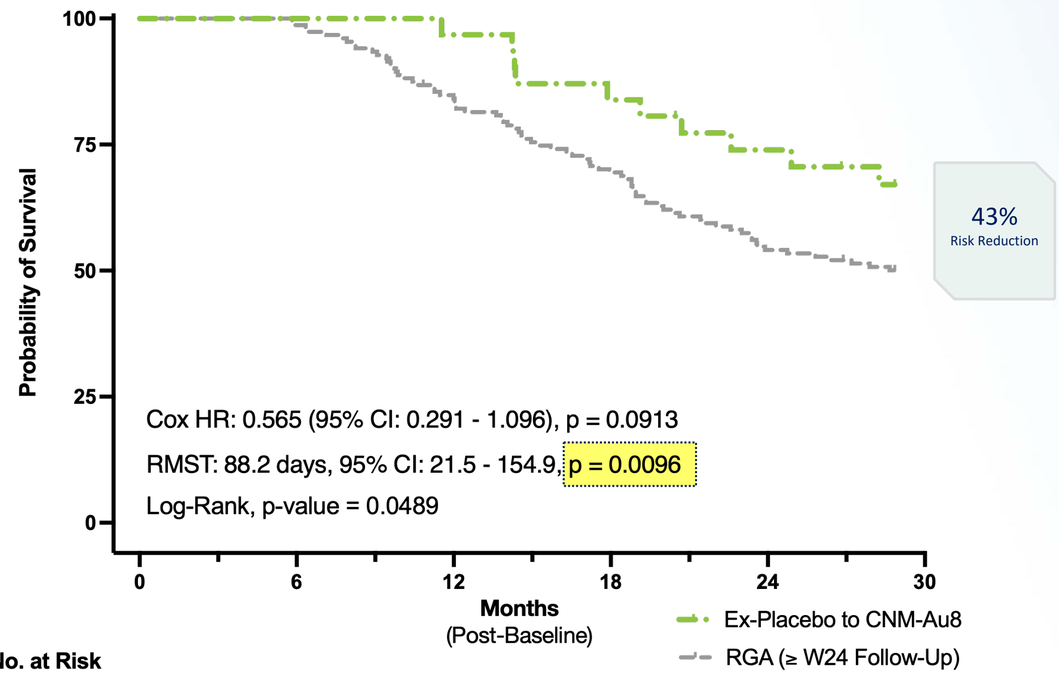
HEALEY ALS Platform Trial | Survival Through Month 12 Post-CNM-Au8 Exposure
Ex-Placebo to CNM-Au8 vs. Regimen A (All) Concurrent Controls
RGA with Follow-Up ≥ 168 Days | Kaplan-Meier Estimator to Day 548
Survival Status Through April-2025



No. at Risk				
Placebo to CNM-Au8:	31	31	30	26
RGA Controls:	156	150	126	104

Ex-Placebo to Active Treatment
To End of the Open Label Extension

HEALEY ALS Platform Trial | Survival Through End of the OLE
Ex-Placebo to CNM-Au8 vs. Regimen A (All) Concurrent Controls
RGA with Follow-Up ≥ 168 Days | Kaplan-Meier Estimator to Day 878
Survival Status Through April-2025



No. at Risk						
Ex-Placebo to CNM-Au8:	31	31	30	26	22	22
RGA Controls:	156	150	126	104	81	68

Prespecified HEALEY survival covariates included: age, months from symptom onset, pre-treatment ALSFRS-R slope (delta-FRS), riluzole treatment, edaravone treatment. RGA only includes participants who survived to Week 24 (Day 168) to ensure comparability of the ex-placebo participants who survived to the start of the OLE.

Data on File, Clene Nanomedicine, Inc.

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FDA Guidance for Accelerated Approval

To be accepted as a surrogate for accelerated approval,

the biomarker must have:

1. Treatment of serious condition; address unmet medical need
2. Meaningful benefit over available therapy on surrogate endpoint (e.g., a biomarker like NfL or GFAP) reasonably likely to predict clinical benefit
3. Requirement of post-approval confirmatory trial

Next STEPS

Type C Meeting Request Submitted

Meeting to Consider Biomarker & Overall Survival Evidence

Meeting Anticipated during 1st Quarter 2026

Currently Readying NDA for Submission

CLENE ANNOUNCES STATISTICALLY SIGNIFICANT ALS BIOMARKER RESULTS SUPPORTING ACCELERATED APPROVAL PATHWAY FOR CNM-Au8®

NIH-Sponsored EAP and HEALEY ALS Platform Trial Data

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Appendix

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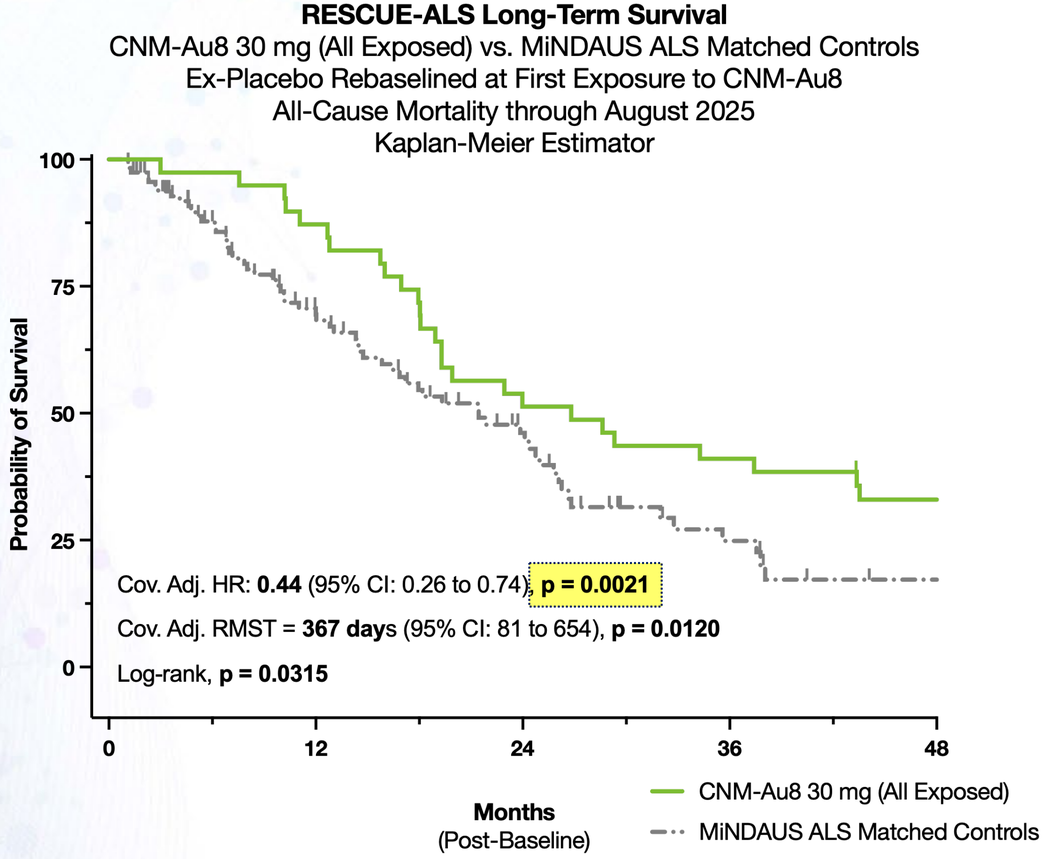
Beyond HEALEY | RESCUE-ALS Improved Long-Term Survival

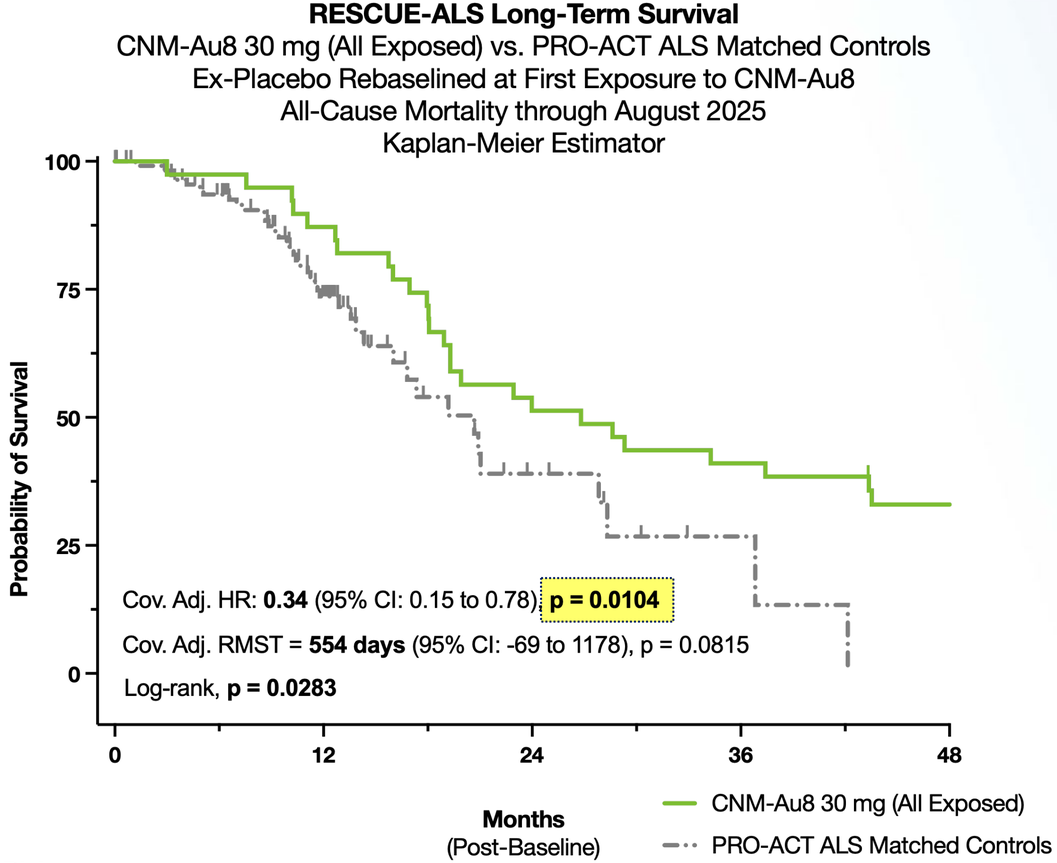
ALS Propensity Matched Controls from Australian MiNDAUS and PRO-ACT

CNM-Au8 30 mg vs. ALS MiNDAUS



No. At Risk					
CNM-Au8:	39	34	20	16	12
Placebo:	117	59	29	11	4

CNM-Au8 30 mg vs. ALS PRO-ACT



No. At Risk					
CNM-Au8:	39	34	20	16	12
Placebo:	117	61	8	2	0

Model covariates included variables associated with mortality risk: (i) sex, (ii) site of symptom onset (bulbar vs. non-bulbar), (iii) ALSFRS-R score, (iv) delta FS,(v) onset age, (vi) months since symptoms, (vii) VC% predicted, (viii) VC Slope, (iv) Diagnosis Delay, (x) TRICALS risk score

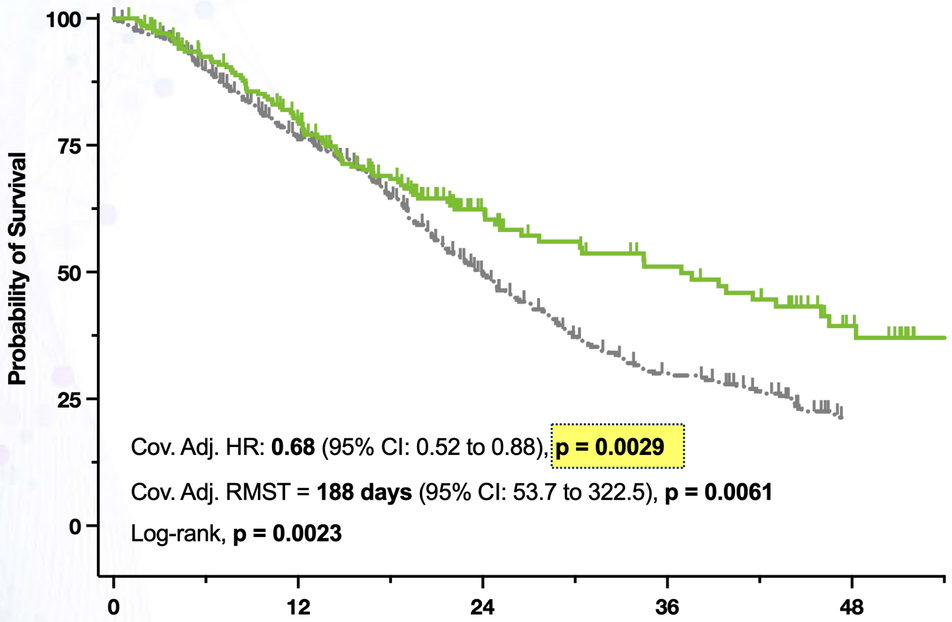
Data on File, Clene Nanomedicine, Inc.

Beyond HEALEY | EAP01-02 Improved Long-Term Survival

ALS Propensity Matched Controls

CNM-Au8 30 mg vs. ALS Natural History Consortium

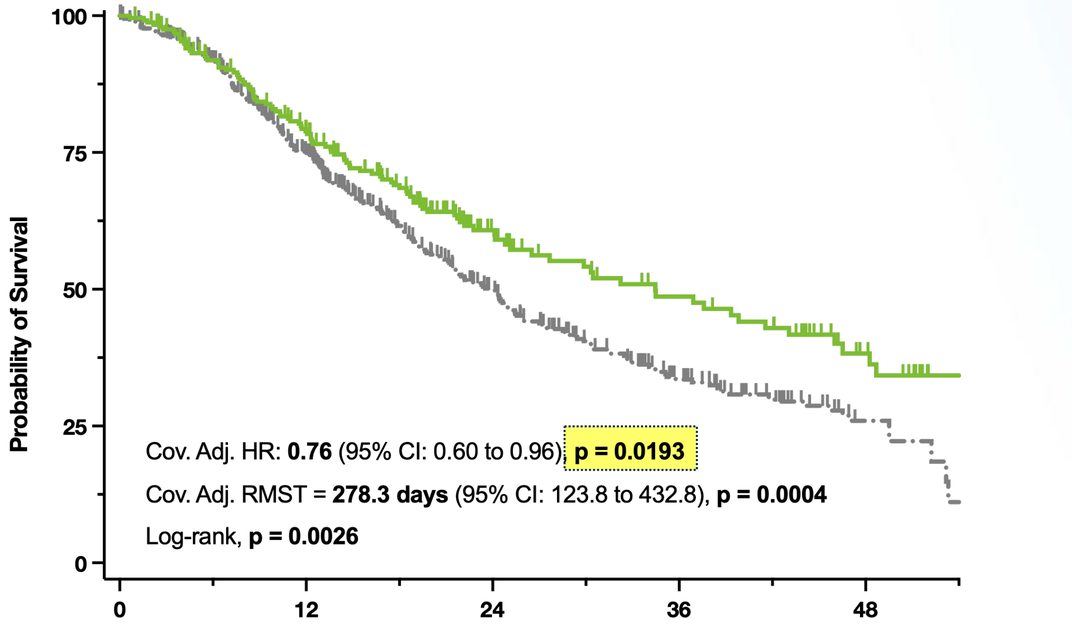
CNM-Au8 EAP Long-Term Survival | Primary Analysis
CNM-Au8 30 mg vs. ALS Natural History Consortium Matched Controls
Nearest Neighbor (Greedy) Propensity Matching
Studies EAP01-02 All Evaluable with Matches (1:2 Target)
All-Cause Mortality through August 2025 | Kaplan-Meier Estimator



No. At Risk					
CNM-Au8:	206	147	63	40	18
Matched Controls:	385	261	137	72	0

CNM-Au8 30 mg vs. All Available ALS Match Sets Combined

CNM-Au8 EAP Long-Term Survival | Primary Analysis
CNM-Au8 30 mg vs. ALS Matched Controls
Nearest Neighbor (Greedy) Propensity Matching (ALS NCH, PRO-ACT, AALS)
Studies EAP01-02 All Evaluable with Matches (1:2 Target)
All-Cause Mortality through August 2025 | Kaplan-Meier Estimator



No. At Risk					
CNM-Au8:	242	170	70	43	20
Matched Controls:	568	351	153	70	7

Model covariates included variables associated with mortality risk: (i) sex, (ii) site of symptom onset (bulbar vs. non-bulbar), (iii) ALSFRS-R score, (iv) delta FS,(v) onset age, (vi) months since symptoms, (vii) VC% predicted, (viii) VC Slope, (iv) Diagnosis Delay, (x) TRICALS risk score

Data on File, Clene Nanomedicine, Inc.