Revolutionizing Treatment to Protect and Restore Neuronal Health for Those Living with Neurodegenerative Diseases

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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 regarding our or our management team’s expectations, hopes, beliefs, intentions or strategies regarding our future operations. 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. Forward-looking statements in this presentation may include, for example, statements about our drug candidate’s trial results and potential impact on disease states, and other factors detailed under “Risk Factors” in our most recent Annual Report on Form 10-K and any subsequent Quarterly Reports on Form 10-Q. 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 our substantial dependence on the successful commercialization of our drug candidates, if approved, in the future; our significant net losses and net operating cash outflows; our ability to demonstrate the efficacy and safety 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 ability to obtain and maintain protection of intellectual property for our technology and drug candidates; our reliance on third parties to conduct research, drug development, and other services; our limited operating history and our ability to obtain additional funding for operations and to complete the licensing or development and commercialization of our drug candidates; the impact of any future epidemics, pandemics, or conflicts; changes in applicable laws or regulations; the effects of inflation; the effects of staffing and materials shortages; the possibility that we may be adversely affected by other economic, business, and/or competitive factors; 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.

ALS is a Progressive, Fatal Disease with No Cure

ALS is a progressive and fatal neurodegenerative disease that destroys motor neurons that control movement, speech, swallowing, and breathing.

~35,000 people in the U.S are living with ALS.

Most people live only 3 – 5 years after diagnosis, and there is no cure today.

~100

Diagnosed Weekly

~100

Deaths Weekly

~35,000

People Living with ALS in the U.S.

CDC, “About Amyotrophic Lateral Sclerosis (ALS),” November 12, 2024; NINDS, “Amyotrophic Lateral Sclerosis (ALS),” March 13, 2026.

People Living with ALS Experience Substantial Burden

ALS patients often experience diagnostic delays, progressive loss of function, and increasing care needs throughout every stage of the disease journey.

ALS Patient Journey

1

Early Symptoms

Early weakness or speech changes

2

Diagnosis

*Diagnostic delays are often **10-16 months** from symptom onset*

3

Functional Decline

Loss of mobility, speech, swallowing, and function

4

Advanced Disease

Increasing dependence on caregivers

5

End Stage

Respiratory failure and premature mortality

Sethi et al., *Patient Prefer Adherence*. 2026;20:566747; Richards et al., *J Neurol Sci*. 2020;417:117054; Feldman et al., *Lancet*. 2022;400:1363–1380.

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Significant Unmet Need Remains Despite the Current Standard of Care

These suboptimal outcomes underscore the need for new approaches that meaningfully slow disease progression and improve long-term outcomes.

NO CURE

01

No cure currently exists for ALS.

TREATMENT GAP

02

FDA-approved therapies have advanced ALS care, but progress is needed to better preserve function and extend survival.

DISEASE PROGRESSION

03

Many people continue to experience loss of mobility, communication, swallowing, breathing function, and independence.

BURDEN PERSISTS

04

Ongoing disease progression contributes to substantial disability and shortened survival.

NINDS, “Amyotrophic Lateral Sclerosis”; FDA, “FDA Approves Oral Form for the Treatment of Adults With ALS”; Feldman et al., Lancet. 2022;400:1363–1380; Masrori and Van Damme, Eur J Neurol. 2020;27:1918–1929.

Our Mission: Extend Survival for People Living with ALS

Clene Nanomedicine is a clinical-stage biopharmaceutical company advancing CNM-Au8® for ALS.

CNM-Au8® is a proprietary gold nanocrystal therapeutic designed to improve neuronal energy metabolism and protect neuronal function

Enhance cellular energy production

Improves neuronal resilience

Protect neuronal function

Targets function and survival

Restore mitochondrial health

Supports cellular bioenergetics

Robinson et al. Sci Rep. 2020 Feb 11;10(1):1936. Wang et al 2023, Small. 2023 Sep 28:e2304082.

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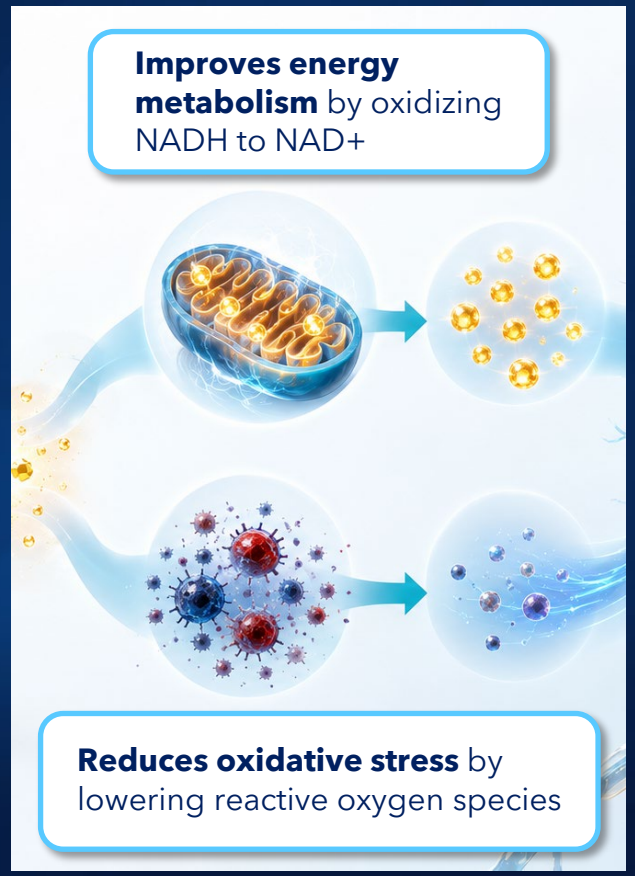
CNM-Au8 is Precisely Designed and Scientifically Shown to Support Mitochondrial Function and Enhance Neuronal Resilience

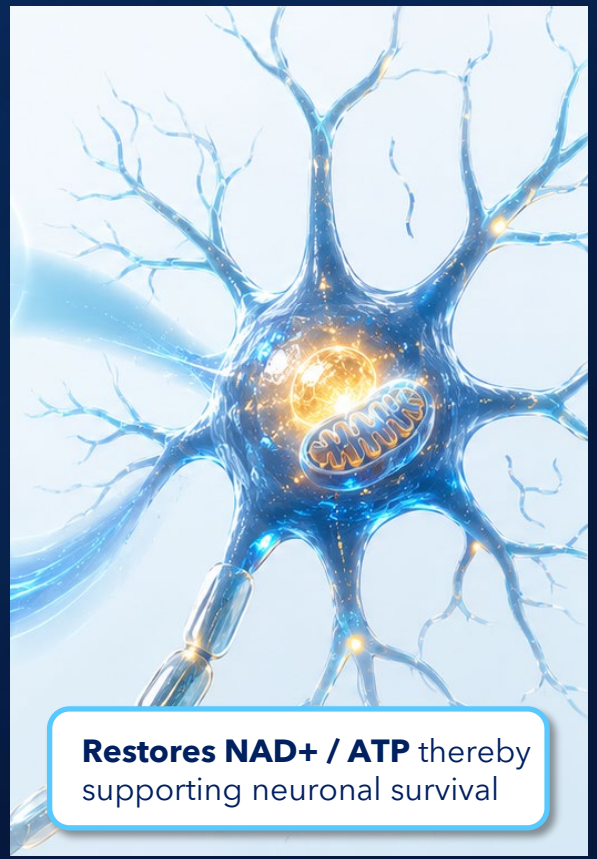
CNM-Au8 Clean-surfaced, catalytically active suspension

- ✓ Blood-brain-barrier penetrant
- ✓ Taken orally, by mouth or feeding tube
- ✓ 30 mg / 60 mL once daily

A Catalytic Dual Mechanism

Bioenergetic support + reduced oxidative stress





Robinson et al. Sci Rep. 2020 Feb 11;10(1):1936. Wang et al 2023, Small. 2023 Sep 28:e2304082.

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NfL Enables Assessment of Neuroaxonal Injury During CNM-Au8 Treatment

What is Neurofilament Light Chain (NfL)

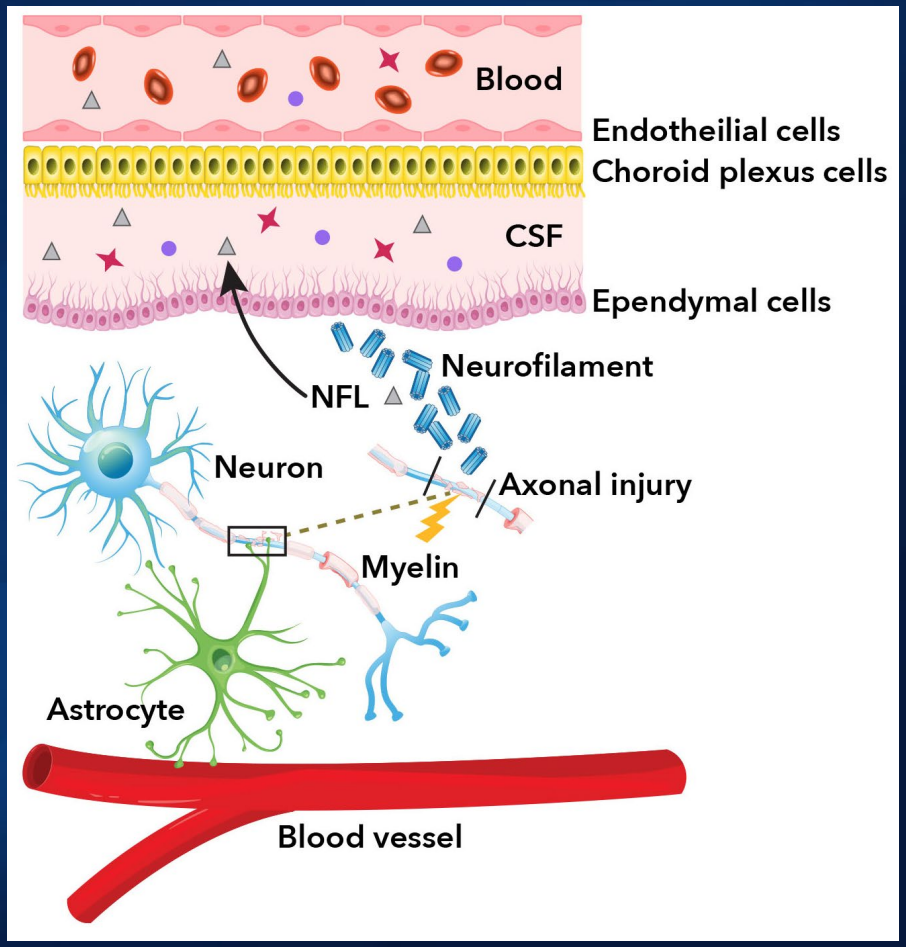
NfL is a structural protein abundant in axons. Neuronal axonal injury releases NfL into CSF and blood, enabling repeat measurement from plasma or serum.

Why NfL Matters in ALS

Higher NfL is associated with faster functional decline and shorter survival. Longitudinal reductions may provide an early pharmacodynamic signal of reduced neuronal injury. NfL was therefore evaluated as a downstream marker of neuroaxonal injury during CNM-Au8 treatment.

Regulatory Precedent

FDA accepted plasma NfL reduction as a surrogate endpoint reasonably likely to predict clinical benefit for tofersen in SOD1-ALS (accelerated approval, 2023). The determination was program-specific.



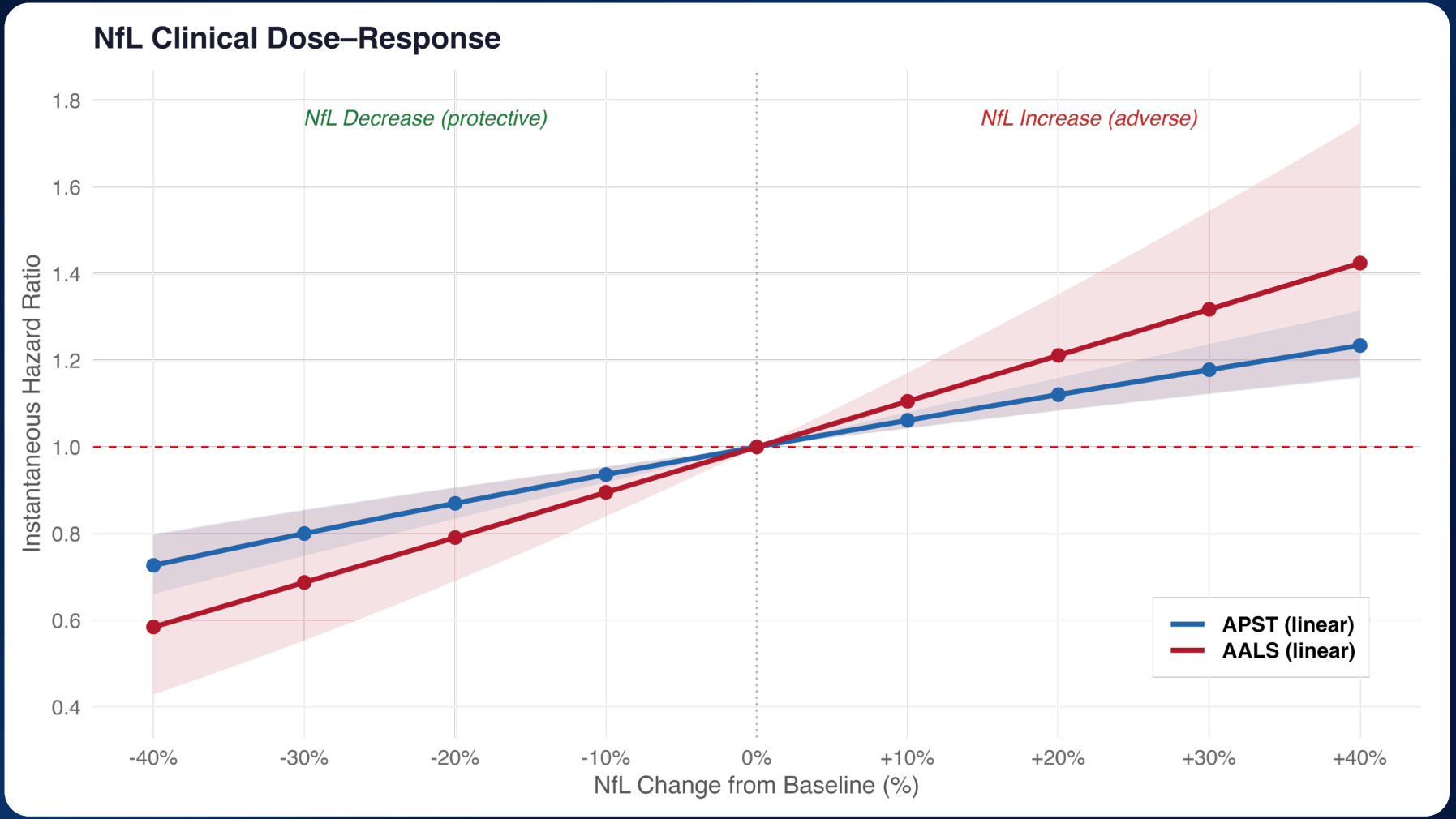
NfL is not ALS-specific, is not a stand-alone diagnostic, and is not universally accepted as a surrogate across ALS programs.

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.

ALS NfL Trajectory Increase is Associated with Mortality Risk

NfL Trajectory

In observational datasets, increasing NfL levels are associated with a significantly increased risk of death, while decreasing NfL levels are protective



Data on File, Clene Nanomedicine, Inc.

Two Randomized Trials + an NIH-Sponsored EAP Strengthen Cross-Study Confirmation of CNM-Au8 NfL Findings

HEALEY ALS Platform Trial Design

NfL Biomarker Collection	3 Active:1 Placebo Randomization	N = 161
24-Week *Double-Blind*	Open Label Extension *up to 133 weeks*	

PRIMARY ENDPOINT
ALSFRS-R

SECONDARY / EXPLORATORY ENDPOINTS
NfL Biomarker, CAFS (Joint-Rank), SVC, Survival (Death + PAV), Clinical Worsening

Phase 2 · Multi-Center · Randomized · Double-Blind · Placebo Controlled

HEALEY ALS Platform Trial

RESCUE ALS Trial Design

NfL Biomarker Collection	1:1 Randomization	N = 45
36-Week *Double-Blind*	Open Label Extension *up to 133 weeks*	

PRIMARY ENDPOINT
MUNIX

SECONDARY / EXPLORATORY ENDPOINTS
NfL Biomarker, FVC, Clinical Worsening, Survival, ALSFRS-R

Phase 2 · Multi-Center · Randomized · Double-Blind · Placebo Controlled

RESCUEALS

NIH Expanded Access Program

NfL Biomarker Collection	All Active	N = 183
> 108 Weeks & Ongoing		

DATA COLLECTION & ANALYSIS
NfL Biomarker, Survival, FVC, ALSFRS-R, Changes in Clinical Care, Fatigue, Quality of Life

Multi-Center · Non-Randomized · Open-Label

ACT·EAP with CNM-Au8

HEALEY: JAMA, 2025; 333;(13):1138-1149; RESCUE: https://www.thelancet.com/action/showPdf?pii=S2589-5370%2823%2900213-4; NIH EAP: https://clinicaltrials.gov/study/NCT06408727.

NfL Reduction Connected to Survival in Phase 2

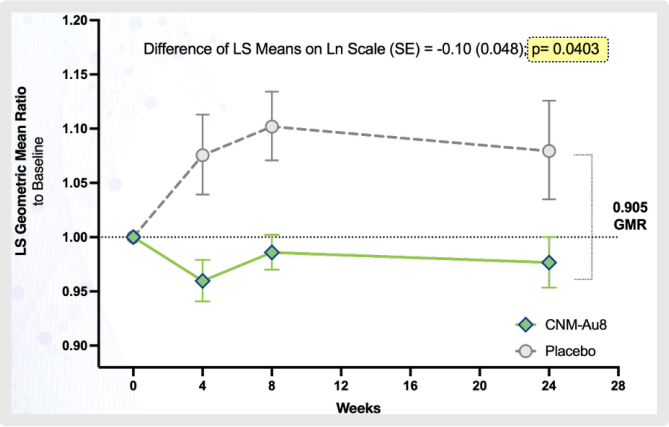
Missed ALSFRS-R endpoint during double-blind period; CNM-Au8 significantly reduced NfL and improved survival.

24-WEEK RANDOMIZED PERIOD

10%

Lower Plasma NfL vs placebo

HEALEY Regimen C full cohort (n=161)



Early NfL Reduction

Survival Signal

Improved survival
(double-blind period)

24-WEEK RANDOMIZED PERIOD

94%

Lower Adjusted Hazard of Death or PAV[1]*

CNM-Au8 30 mg (n=59) vs placebo full analysis set (n=162)

Data on File, Clene Nanomedicine, Inc. 1. Adj HR: 0.0560 (0.0018, 0.5603), p=0.0095; CI by Profile Likelihood (PL), p-value by Likelihood Ratio test (LR). *PAV = Permanently Assisted Ventilation: defined as continuous ventilatory support (>23 hr/day by tracheostomy or non-invasive ventilation for at least 7-days). Prespecified covariate adjusted hazard ratios.

~10% NfL Reduction Was Reproduced Across Two Independent ALS Populations

Confirmatory analyses conducted in response to FDA feedback.

RANDOMIZED, DOUBLE-BLIND CONTROLLED TRIAL

HEALEY ALS Platform Trial

~10% lower plasma NfL vs. placebo

24 Weeks

GMR 0.905; p=0.040

Reproducible NfL Reduction

CONCORDANT RESULTS

Magnitude Associated with Survival

REAL-WORLD EVIDENCE

NIH-SPONSORED EAP

ACT·EAP with CNM-Au8®

~10% lower plasma NfL vs. placebo

36 Weeks

AUC difference -0.90
p=0.037

Data on File, Clene Nanomedicine, Inc.; the NIH-EAP comparisons are externally / observationally controlled (not randomized); the AUC difference in the full analysis set was a prespecified supportive analysis (not the primary endpoint).

The Evidence Framework Supports NfL Response as a Surrogate Biomarker Reasonably Likely to Predict Clinical Benefit

EVIDENCE QUESTION	POPULATION COMPARISON
1 Treatment Effect Among CNM-Au8 treated participants, does NfL response correspond with clinical outcomes?	**HEALEY ALS Platform Trial** All CNM-Au8-treated participants → CNM-Au8 NfL responders VS CNM-Au8 NfL non-responders
2 NfL Response vs Randomized Control Do CNM-Au8 NfL responders demonstrate clinical benefit compared to randomized concurrent controls? **Concurrently Randomized Regimens:** ✓Same Trial Sites ✓Same Eligibility Criteria ✓Same Master Protocol ✓Same Follow-Up ✓Similar Inclusion/ Exclusion	**HEALEY ALS Platform Trial** CNM-Au8 NfL responders VS Randomized controls (n=329) *Enrolled concurrently*
3 Independent Replication Is the NfL–clinical benefit relationship consistent in an independent trial?	**RESCUE-ALS** CNM-Au8 NfL responders CNM-Au8 NfL non-responders VS Propensity-matched controls

Responder analyses are post hoc and exploratory; tertile stratification in HEALEY and median stratification in RESCUE.

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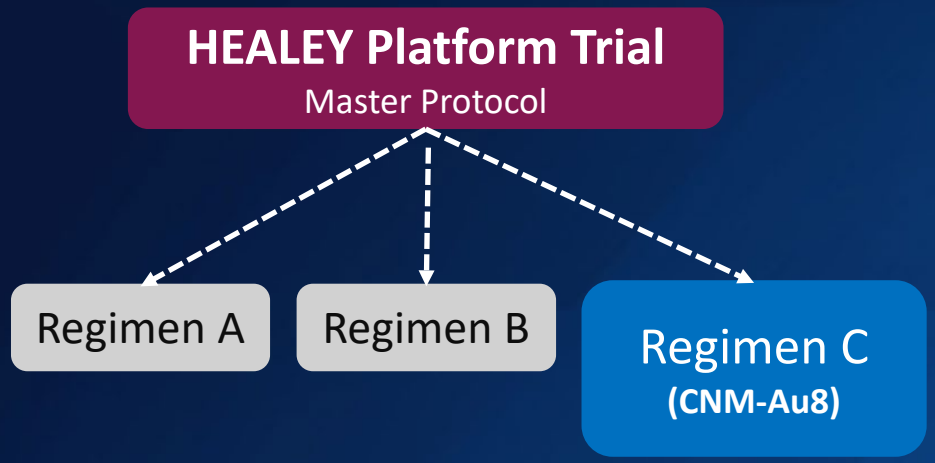
Concurrently Randomized Controls from HEALEY Enables Pooled Control Group for CNM-Au8 Survival Analyses

HEALEY ALS Platform Trial

1 RANDOMIZE WITHIN ONE MASTER PROTOCOL



Concurrently Randomized Regimens:

- ✓ Same Trial Sites
- ✓ Same Follow-Up
- ✓ Same Eligibility Criteria
- ✓ Similar Inclusion/Exclusion
- ✓ Same Master Protocol

2 ADJUST FOR PROGNOSTIC COVARIATES

Use prospectively captured covariates to align baseline prognosis.

Clinical Status

• SVC (%predicted) • ALSFRS-R • ΔFSR • BMI

Disease History

- Diagnostic delay
- Bulbar Onset
- Months from Onset
- Sex

+

Comparable Risk Set

Risk Markers

Modified TRICALS risk Score • Serum NfL

SVC = Sustained Vital Capacity; ΔFS = ALSFRS-R progression rate.

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CNM-Au8 30 mg Treatment NfL Response Improved Survival

NfL Response drives a survival benefit compared to non-NfL Responders | Within arm comparison.

HEALEY ALS Platform Trial

52%

Trend for lower adjusted mortality hazard

Adjusted Cox HR 0.48
(95% CI: 0.22–1.02)
p=0.056, n=57

NfL Decline/Stable Tertile vs. Increase

RESCUEALS

76%

Significantly lower adjusted mortality hazard

Adjusted Cox HR 0.24
(95% CI: 0.08–0.68)
p=0.008, n=22

NfL By Median Split

Data on File, Clene Nanomedicine, Inc. Post-hoc exploratory analyses; not adjusted for multiplicity. Cox covariates: HEALEY: age, symptom duration, delta-FS, riluzole, edaravone; RESCUE-ALS: Ln(baseline NfL).

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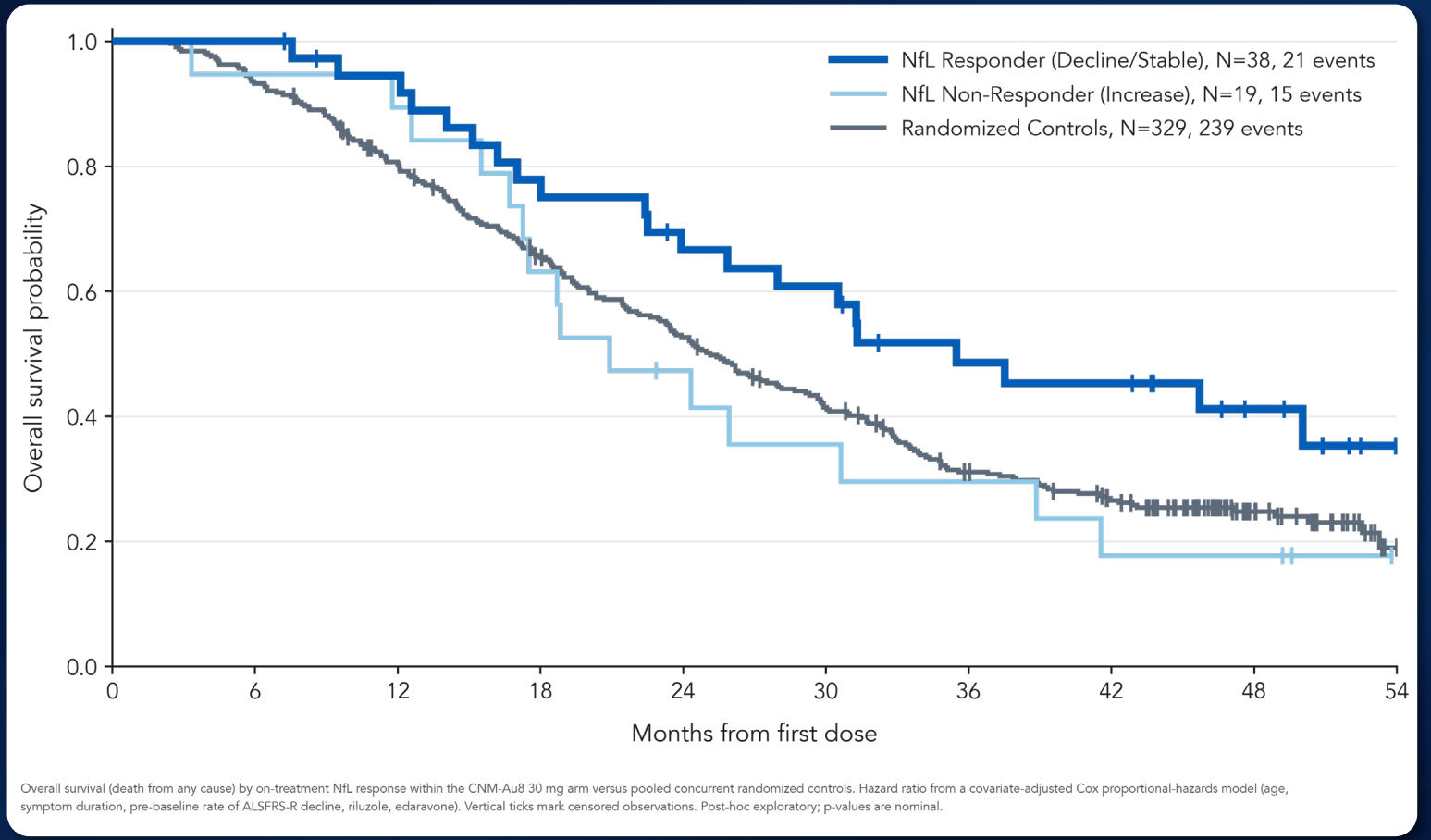
NfL Response Drives Survival Benefit, Consistent with a Biological Signal

HEALEY ALS Platform Trial

NfL Responders lived significantly longer vs *concurrently randomized controls.*



Overall survival (death from any cause) by on-treatment NfL response within the CNM-Au8 30 mg arm versus pooled concurrent randomized controls. Hazard ratio from a covariate-adjusted Cox proportional-hazards model (age, symptom duration, pre-baseline rate of ALSFRS-R decline, riluzole, edaravone). Vertical ticks mark censored observations. Post-hoc exploratory; p-values are nominal.

38%

Significantly lower adjusted mortality hazard

NfL-Stratified Responders vs Concurrently Randomized Controls

HR 0.621
95% CI: 0.397–0.972
p=0.037

Data on File, Clene Nanomedicine, Inc. Post-hoc exploratory analyses; not adjusted for multiplicity. NfL responder = NfL levels declined or remained stable; NfL non-responder = NfL levels increased.

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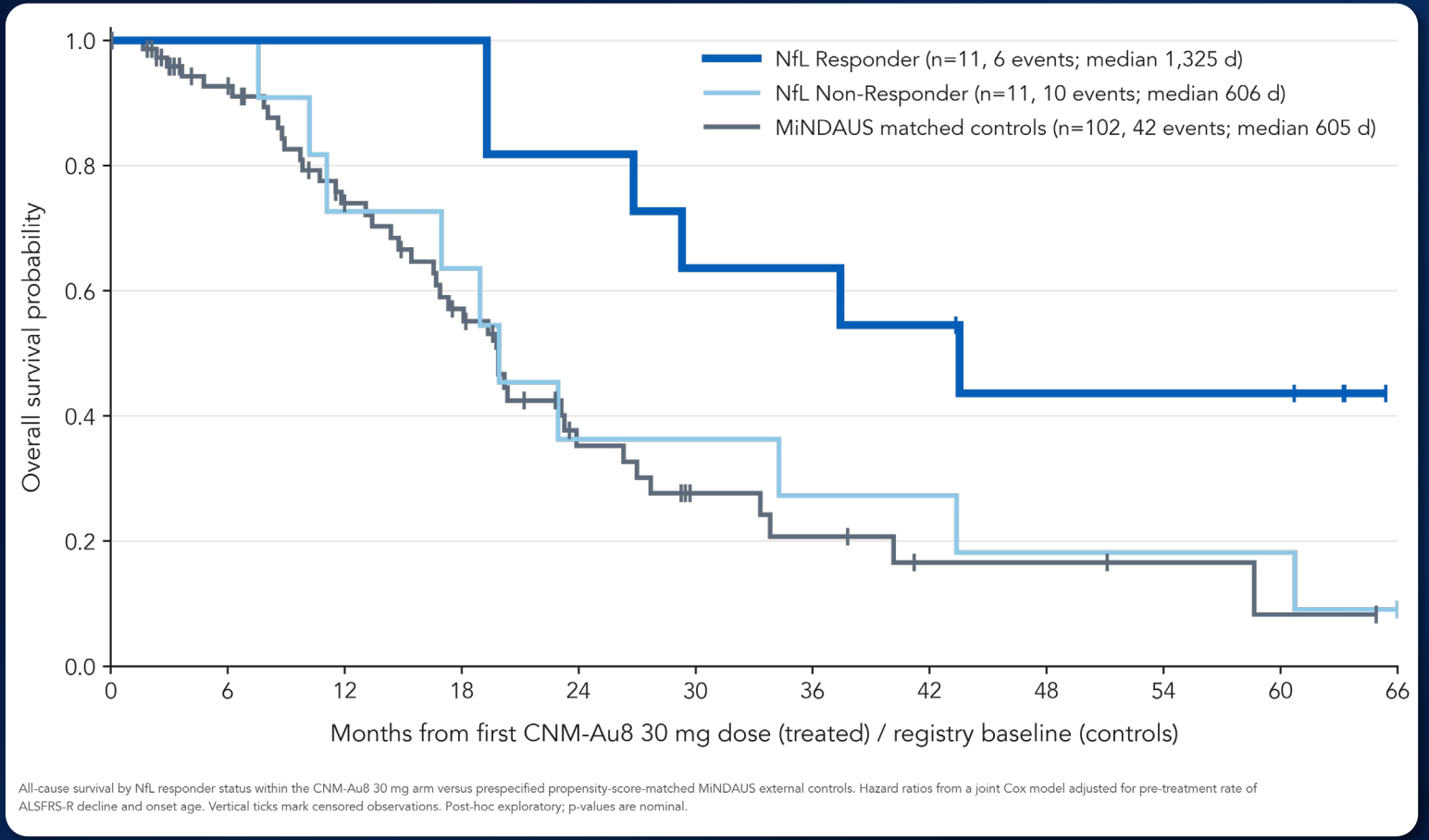
RESCUE-ALS Provides Supportive Evidence, Linking NfL Response to Long-Term Survival Benefit

NfL responders demonstrated a survival benefit vs *propensity-matched controls.*



All-cause survival by NfL responder status within the CNM-Au8 30 mg arm versus prespecified propensity-score-matched MiNDAUS external controls. Hazard ratios from a joint Cox model adjusted for pre-treatment rate of ALSFRS-R decline and onset age. Vertical ticks mark censored observations. Post-hoc exploratory; p-values are nominal.

69%

Significantly lower adjusted mortality hazard

NfL Responder vs Propensity-Matched MiNDAUS controls

HR 0.311
95% CI: 0.13–0.76
p=0.011

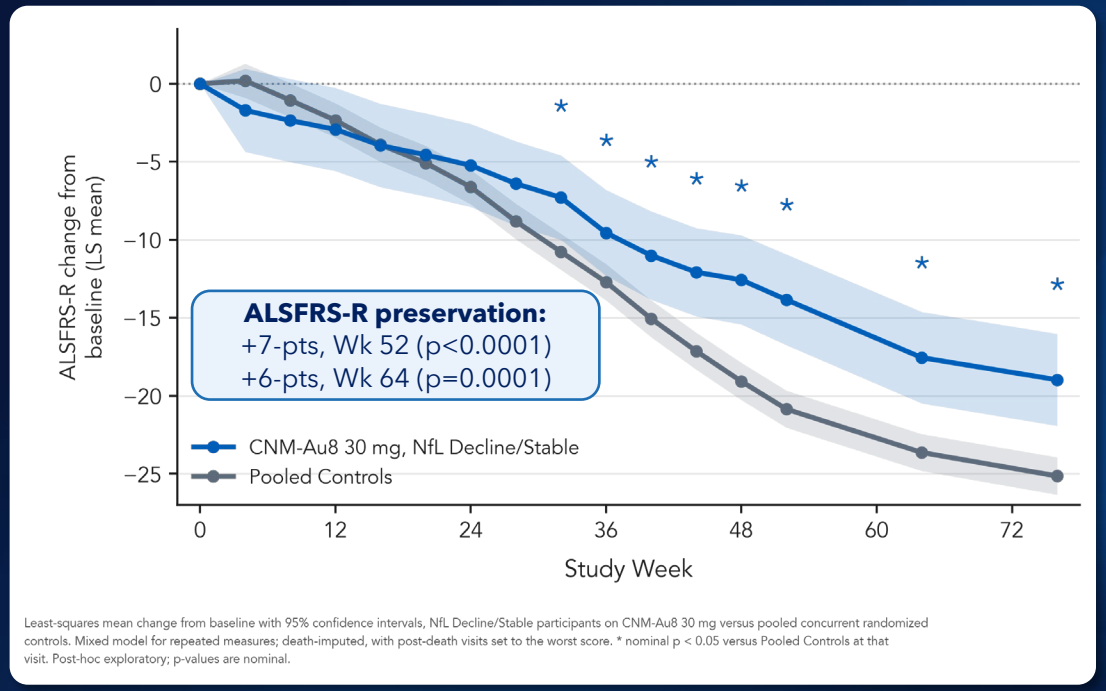
Data on File, Clene Nanomedicine, Inc. Post-hoc exploratory analyses; not adjusted for multiplicity. NfL responder = NfL levels declined or remained stable; NfL non-responder = NfL levels increased.

Significant Preservation of ALSFRS-R and SVC in NfL Responders

HEALEY ALS Platform Trial

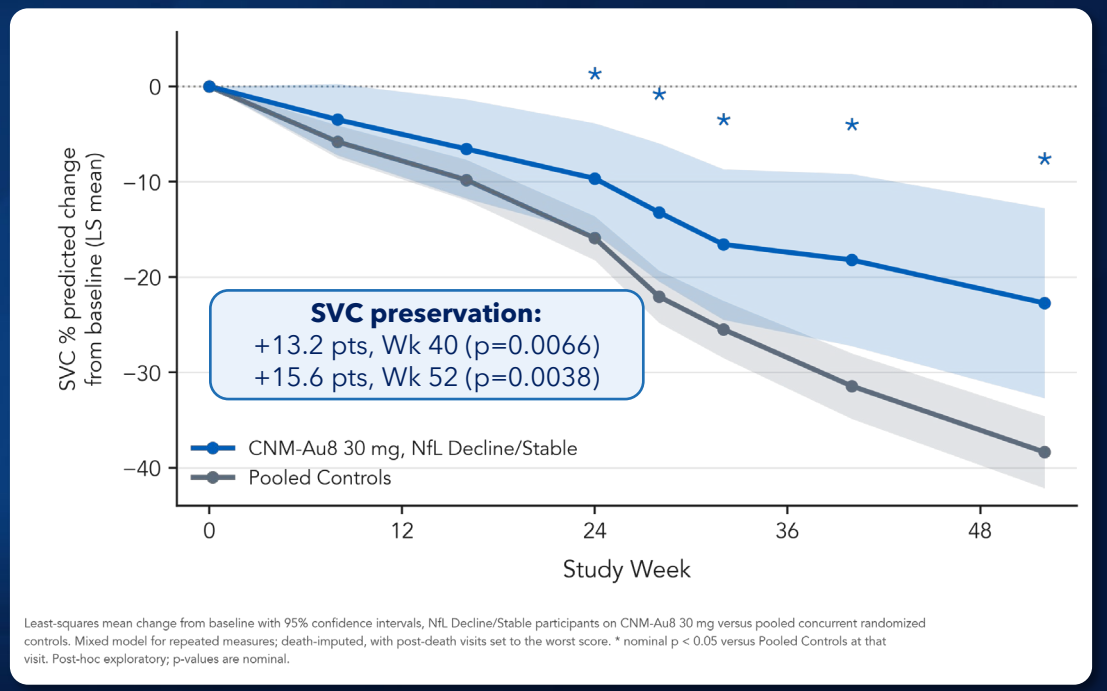
Among CNM-Au8-treated participants, NfL stabilization or decline was associated with clinical benefit versus randomized concurrent control, supporting NfL response as a clinically relevant biomarker.

Clinical Change in ALSFRS-R (Total Score)



Least-squares mean change from baseline with 95% confidence intervals, NfL Decline/Stable participants on CNM-Au8 30 mg versus pooled concurrent randomized controls. Mixed model for repeated measures; death-imputed, with post-death visits set to the worst score. * nominal p < 0.05 versus Pooled Controls at that visit. Post-hoc exploratory; p-values are nominal.

Clinical Change in SVC (% Predicted)



Least-squares mean change from baseline with 95% confidence intervals, NfL Decline/Stable participants on CNM-Au8 30 mg versus pooled concurrent randomized controls. Mixed model for repeated measures; death-imputed, with post-death visits set to the worst score. * nominal p < 0.05 versus Pooled Controls at that visit. Post-hoc exploratory; p-values are nominal.

Data on File, Clene Nanomedicine, Inc. Post-hoc exploratory analyses; not adjusted for multiplicity. Death-imputed functional change, linear mixed-effects contrasting NfL Decline/Stable participants against control at each scheduled visit.

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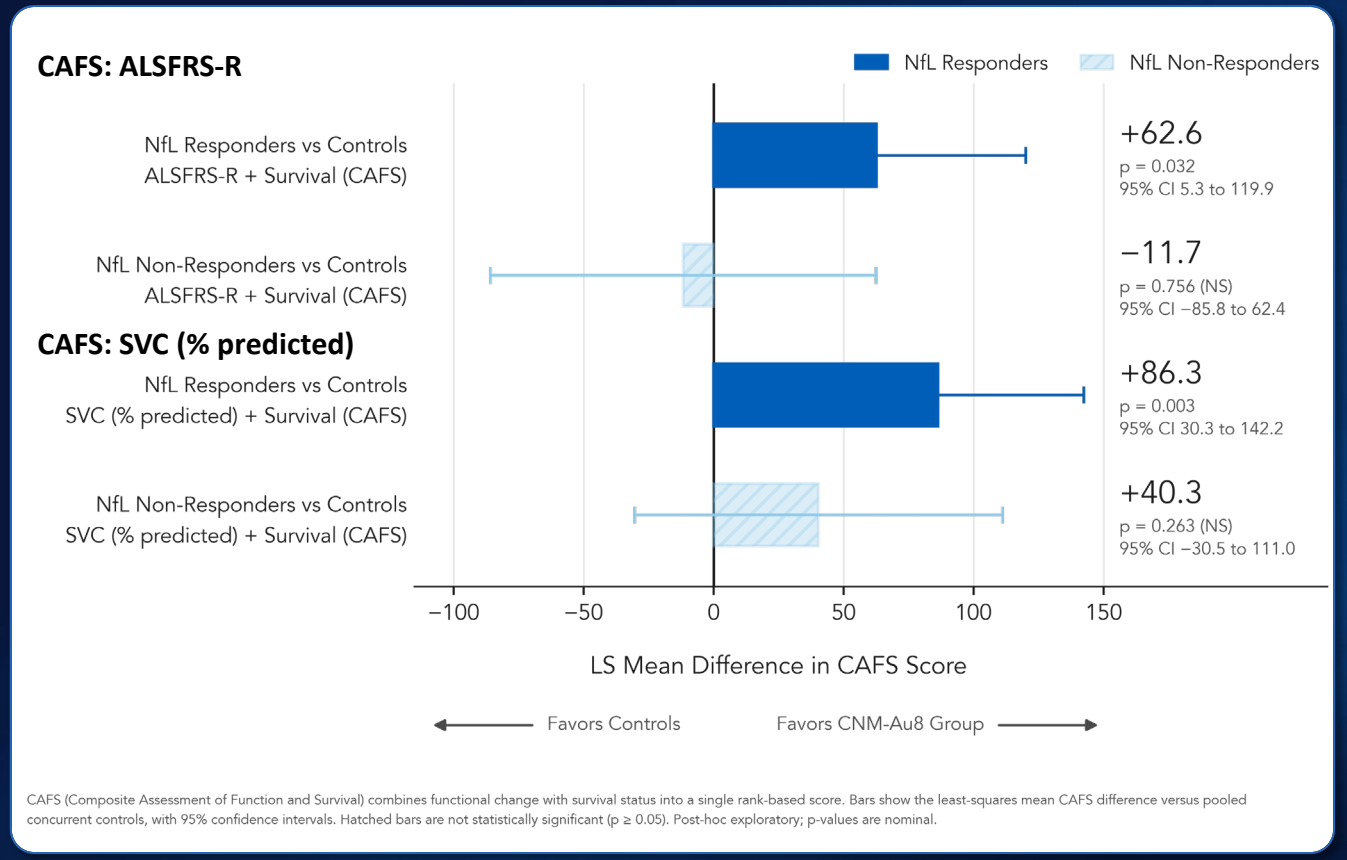
Composite Assessment of Function and Survival (CAFS) Outcomes Concentrated in NfL Responders

HEALEY ALS Platform Trial

Combined survival and functional benefits are greatest in NfL responders vs concurrently randomized controls.



CAFS (Composite Assessment of Function and Survival) combines functional change with survival status into a single rank-based score. Bars show the least-squares mean CAFS difference versus pooled concurrent controls, with 95% confidence intervals. Hatched bars are not statistically significant ($p \geq 0.05$). Post-hoc exploratory; p-values are nominal.

CAFS prioritizes survival outcomes before ranking functional decline

CAFS combines ALSFRS-R (daily function) or SVC (breathing capacity) change with survival status into one score

FDA strongly favors CAFS because it aligns with ALS development guidance

Every participant counts toward the score, including those who don't survive – balancing the short-term sensitivity of functional decline with survival data

Data on File, Clene Nanomedicine, Inc. Post-hoc exploratory analyses; not adjusted for multiplicity.

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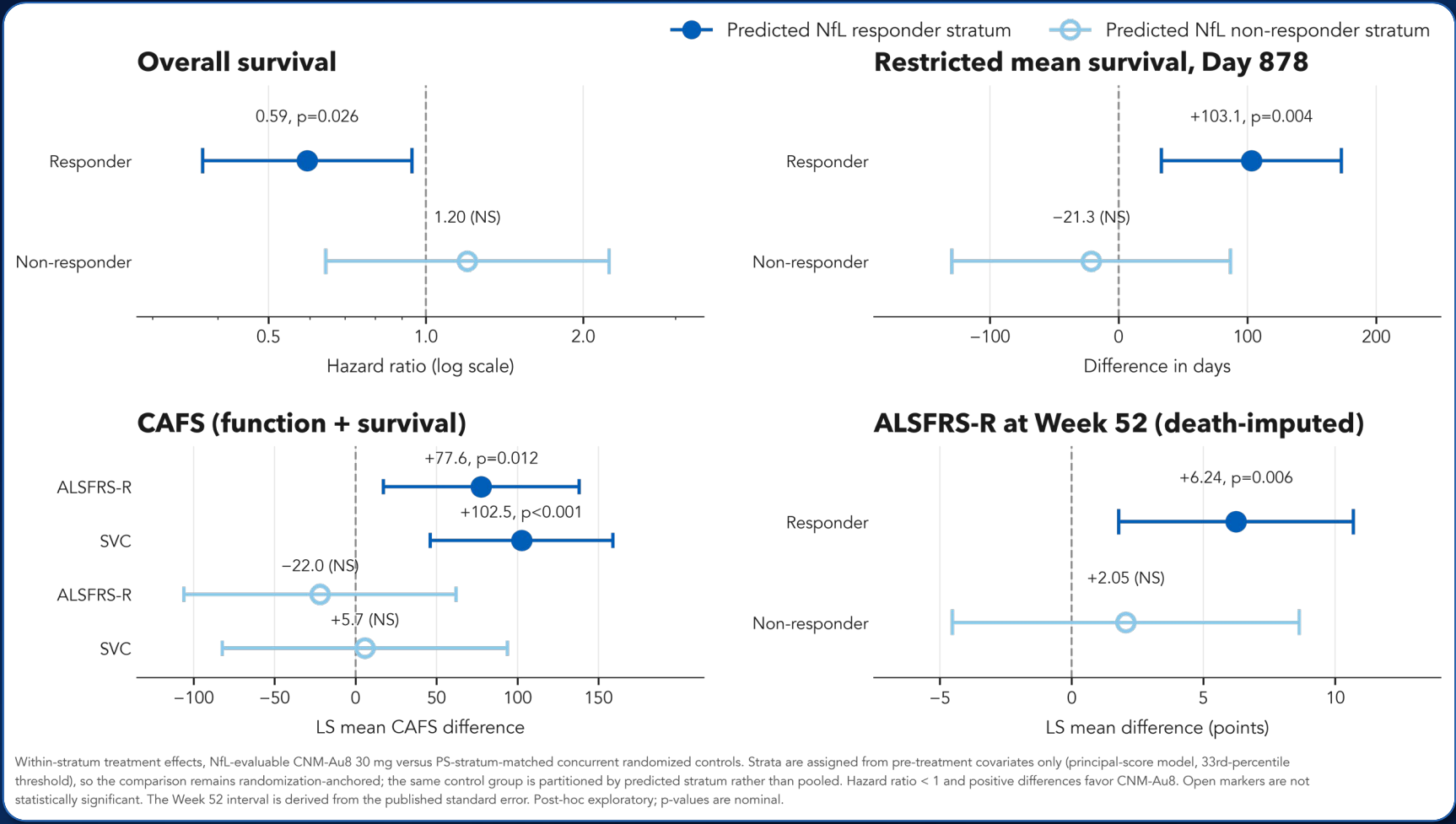
Clinical Benefit Concentrated in Predicted NfL Responders (Evidenced by Randomization-based Causal Analysis)

HEALEY ALS Platform Trial

Survival and functional benefit is concentrated in participants whose baseline profile predicts NfL response.



Within-stratum treatment effects, NfL-evaluable CNM-Au8 30 mg versus PS-stratum-matched concurrent randomized controls. Strata are assigned from pre-treatment covariates only (principal-score model, 33rd-percentile threshold), so the comparison remains randomization-anchored; the same control group is partitioned by predicted stratum rather than pooled. Hazard ratio < 1 and positive differences favor CNM-Au8. Open markers are not statistically significant. The Week 52 interval is derived from the published standard error. Post-hoc exploratory; p-values are nominal.

Data on File, Clene Nanomedicine, Inc. Post-hoc exploratory analyses; not adjusted for multiplicity.

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Favorable Safety Profile with Long-Term Exposure

- **Over 1250 years of patient exposure**
- **CNM-Au8** continuous daily long-term **treatment duration over 6.8 years**
- **Nearly 900 patients treated** in clinical and EAP programs
- **No CNM-Au8®-related serious adverse events** reported across clinical and expanded access programs
- **Treatment-emergent adverse events** were predominantly **mild-to-moderate and transient**
- **Adverse-event incidence did not increase** with longer treatment exposure
- Oral nanocrystal suspension **administered by mouth or feeding tube**

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FDA Guidance Frames NfL as a Potential Surrogate Endpoint for Accelerated Approval

✓ Q1 2026 – Type C Meeting

The Agency requested that the Company provide additional information in its NDA, including to support a connection between the reported magnitude of reduction in NfL and clinical benefit

"NfL could potentially serve as a reasonably likely surrogate endpoint to support (an) accelerated approval."

-FDA Comment from Type C Meeting

Accelerated Approval Pathway Requirements

Serious Disease & Unmet Need

The indication must address a serious condition where current therapies are inadequate.

Surrogate Endpoint

A biomarker reasonably likely to predict clinical benefit may substitute for direct clinical endpoints.

Phase 3 Confirmatory Study

A post-approval trial must verify and describe the anticipated clinical benefit.

Important: Accelerated approval is not assured. Any NDA remains subject to FDA filing acceptance and review; continued approval would require verification of clinical benefit.

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Evidence Package Supports Planned NDA Submission and RESTORE-ALS Phase 3 Confirmatory Trial

Concordant biomarker and survival findings from HEALEY, RESCUE-ALS, and the NIH-EAP inform the planned accelerated approval submission and RESTORE-ALS Phase 3 confirmatory trial.

Integrated Evidence Package

RESCUEALS

HEALEY ALS Platform Trial

ALS EXPANDED ACCESS PROTOCOLS (EAP)

Concordant survival, clinical and biomarker findings across controlled and observational evidence

Submit Early Q4 2026

Planned NDA Submission

Subpart H accelerated approval pathway; NfL as a potential surrogate endpoint, subject to FDA review

Initiate Q2 2027

RESTORE-ALS Phase 3 Trial

Global, randomized, double-blind, placebo-controlled study designed to verify clinical benefit

RESTORE-ALS Phase 3 Trial Snapshot

Study Overview

- 108-week duration
- 2:1 randomization active to placebo
- N = 690
- Global

Inclusion

- Modified TRICALS risk score
- Baseline NfL stratification (Ln[NfL])≥ 3.5

Primary Endpoint

- Improved overall survival (delayed time to death or PAV)

Secondary & Exploratory Endpoints

- Delayed time to ALS clinical worsening
- SVC
- ALSFRS-R
- Quality of Life measures

PAV = Permanently Assisted Ventilation: defined as continuous ventilatory support (>23 hr/day by tracheostomy or non-invasive ventilation for at least 7-days); SVC = Sustained Vital Capacity.

Evidence Supports Pipeline in a Product Therapeutic Potential to Treat Neurodegeneration

CNM-Au8®

a gold nanocrystal suspension, in development as the first cellular energetic catalyst to remyelinate[1] & protect neurological function

HEALEY ALS Platform Trial

RESCUEALS

CNM-Au8 treated patients whose NfL declined or stabilized lived significantly longer than patients whose NfL increased

VISIONARY-MS STUDY

Demonstrated global neurological improvement in MS patients on adjunctive DMT standard of care

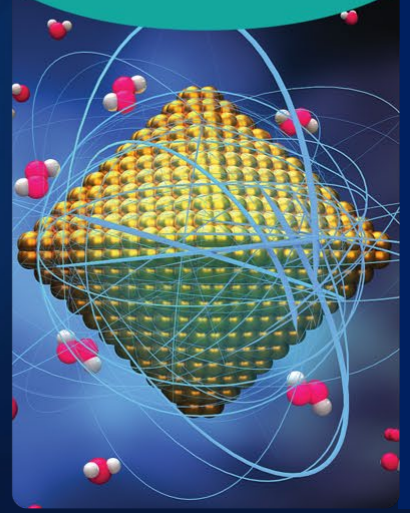
>1,200

participant years of CNM-Au8 clinical exposure

Strong IP:

150+

patents on nanotherapeutic platform, plus trade secret protection



Cash and equivalents on hand:

$13.7M*

Sufficient cash and equivalents to last until mid-first quarter 2027

*Includes 6/30/2026 cash and equivalents balance of $9.7M (unaudited) and $4.0M of gross proceeds from a registered direct offering subsequent to 6/30/2026.

Data on File, Clene Nanomedicine, Inc. 1. Robinson et al. Sci Rep. 2020 Feb 11;10(1):1936.2https://clinicaltrials.gov/ct2/show/NCT04414345.

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Clene Inc.
HQ & Clinical Development
6550 South Millrock Drive, Suite G50
Salt Lake City, UT 84121

R&D and Manufacturing
500 Principio Parkway, Suite 400
North East, MD 21901

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