Clene Announces Biomarker Analyses To Be Included in NDA Submission Supporting ALS Accelerated Approval

August 10, 2026

- ***Survival benefit is concentrated in participants with NfL biomarker response:*** *CNM-Au8®-treated patients whose NfL declined or stabilized lived significantly longer than concurrently randomized controls*
- ***Functional benefit concentrated in participants with NfL biomarker response:*** *CNM-Au8-treated patients whose NfL declined or stabilized had significantly better outcomes on combined measures of survival and function, including daily function (ALSFRS-R) and breathing capacity (Slow Vital Capacity), than concurrently randomized controls*

SALT LAKE CITY, Aug. 10, 2026 (GLOBE NEWSWIRE) -- Clene Inc. (Nasdaq: CLNN) today announced results from new analyses examining clinical outcomes among CNM-Au8®-treated patients whose neurofilament light chain (NfL) biomarker levels declined or stabilized. These findings will be included in Clene's planned New Drug Application (NDA) seeking accelerated approval and are intended to address the questions raised by the U.S. Food and Drug Administration (FDA) during a March 2026 Type C meeting. At that meeting, the FDA acknowledged that NfL, a recognized blood marker of nerve-cell injury, has established prognostic value in amyotrophic lateral sclerosis (ALS) and could potentially serve as a reasonably likely surrogate endpoint to support accelerated approval.

New biomarker analyses of Clene's two completed Phase 2 ALS trials revealed additional evidence that CNM-Au8-treated patients whose NfL declined or stabilized lived significantly longer than concurrently randomized controls and performed significantly better on combined measures of survival and function, including ALS Functional Rating Scale-Revised (ALSFRS-R) and breathing capacity (Slow Vital Capacity; SVC).

These findings were derived from multiple lines of analysis: clinical benefit versus concurrently randomized controls; the relationship between the size of the NfL reduction and clinical outcome; a causal analysis that identified likely NfL responders from pre-treatment characteristics alone, preserving the randomized comparison; and replication of the association between NfL change and survival across independent datasets.

Among patients treated with CNM-Au8:

- Participants randomized to **CNM-Au8 30 mg had a 74% lower risk of death after 12 months of follow-up than concurrently randomized controls from another regimen in the HEALEY ALS Platform Trial (HEALEY) (p = 0.0124)**
- Analyses in more than 2,000 ALS patients who never received CNM-Au8 showed that a 10% NfL decline was associated with a 6% to 10% lower risk of death (APST, p < 0.0001; ANSWER ALS, p = 0.001)
- **Survival improved in participants whose NfL declined or stabilized, a 38% lower risk of death than concurrently randomized controls over the full follow-up period** (HR 0.621, 95% CI 0.397–0.972; p = 0.037) in HEALEY; the average survival gain reached nearly six months at four years of follow-up (p = 0.012)
- **Participants whose NfL declined or stabilized scored significantly better on the Combined Assessment of Function and Survival (CAFS),** whether measured by daily function (ALSFRS-R, p = 0.032) or breathing capacity (SVC, p = 0.003), compared with concurrently randomized controls from HEALEY
- An FDA-requested **causal analysis identifying likely NfL responders from pre-treatment characteristics alone found a 41% lower risk of death on CNM-Au8 30 mg versus controls in the predicted NfL responder group (HR 0.593; p = 0.026),** with no significant difference among those predicted not to respond

These biomarker analyses are *post hoc* and exploratory. We believe the totality of this evidence addresses the accelerated approval standard, which the FDA will evaluate during its review of the NDA.

Clinical Benefit Tracked NfL Response Across Phase 2 Trials

In HEALEY, the CNM-Au8 30 mg group was compared with concurrently randomized controls — participants originally randomized into concurrent regimens over the same period, under the same master protocol and the same core eligibility criteria. These controls comprise both placebo recipients and recipients of other investigational agents studied in those regimens, none of which met its primary endpoint, and none received CNM-Au8.

Survival improved in CNM-Au8-treated participants whose NfL declined or stabilized in HEALEY. Participants whose NfL declined or stabilized lived significantly longer than concurrently randomized controls at every measured timepoint, showing an expanding survival benefit that reached nearly six months (177 days) at four years of follow-up (Day 1,463; p = 0.012). By comparison, participants whose NfL increased did not demonstrate a statistically significant difference in survival benefit at any timepoint.

Relationship between longer survival and NfL decline or stabilization also observed in RESCUE-ALS. RESCUE-ALS, a smaller, nine-month placebo-controlled trial, was evaluated to test whether the NfL-to-outcome relationship observed in HEALEY was also present in a separate CNM-Au8 30 mg population; the comparisons below are within the treated group or against propensity-matched real-world ALS controls. Among the 22

CNM-Au8-treated participants whose NfL response could be classified, the 11 participants whose NfL declined or stabilized had a 76% lower adjusted risk of death than the 11 whose NfL increased (HR 0.24; p = 0.008), with median survival of 43.5 months versus 19.9 months (log-rank p = 0.040). In RESCUE-ALS, participants whose NfL declined or stabilized had a 69% lower risk of death than propensity-matched real-world ALS controls (MiNDAUS; HR 0.31; 95% CI 0.13–0.76; p = 0.011); those whose NfL rose did not differ significantly from the matched controls. Within the treated arm, NfL responders also scored significantly better on CAFS (rank difference +7.7, 95% CI 3.1–12.3; p = 0.002) compared to NfL non-responders.

ALSFRS-R and SVC function and survival improved together among participants who had NfL decline or stabilization in HEALEY. On CAFS, NfL responders scored significantly better than concurrently randomized controls on both function and breathing: a least-squares mean difference of 62.6 (95% CI 5.3–119.9; p = 0.032) combining ALSFRS-R with survival, and 86.3 (95% CI 30.3–142.2; p = 0.003) combining SVC (% predicted) with survival. On death-imputed analyses, which score participants zero after death and therefore capture survival and function jointly, the advantage reached 7.0 points on the ALSFRS-R (p < 0.0001) and 15.6 points on SVC (% predicted; p = 0.004) at Week 52. Participants whose NfL increased showed no statistically significant difference on any of these measures.

Evidence Connecting the Magnitude of NfL Reduction to Clinical Benefit

- **CNM-Au8 reduced NfL during the randomized, double-blind period.** As previously reported, plasma NfL declined in CNM-Au8-treated participants and increased in placebo recipients over the 24-week double-blind period of HEALEY, a least-squares mean difference of −0.100 on the natural log scale (SE 0.048; p = 0.040), with larger differences in faster progressors (−0.144; p = 0.014) and in participants with above-median baseline NfL (−0.150; p = 0.031) (Berry et al., JAMA 2025).
- **A decline of ~10% was associated with a measurable survival difference.** In prespecified analyses of the ALS observational cohorts, German/Austrian APST (1,671 evaluable) and U.S. ANSWER ALS (380 evaluable), none of whose participants received CNM-Au8, a 10% decline in NfL was associated with a 6% to 10% reduction in the hazard of death (p < 0.0001 and p = 0.001, respectively), independent of baseline NfL level.
- **Dramatic biomarker reductions were not required with CNM-Au8.** Modeling the relationships observed in HEALEY, a 5% to 10% reduction in NfL corresponded to 1.4 to 2.9 additional points on the ALSFRS-R at Week 64 and a 7.8% to 15.3% reduction in the modeled hazard of death. These are model-derived projections rather than observed treatment effects. Holding NfL steady, or achieving even a modest decline, was associated with better outcomes.

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

Because participants were grouped by how their NfL responded after treatment began, the comparisons reported above are observational. A principal stratum analysis was performed to address this, classifying every participant, treated and control, by pre-treatment characteristics alone and thereby preserving the randomized comparison in HEALEY. The survival benefit of CNM-Au8 30 mg was concentrated in the predicted NfL-responder stratum: a 41% reduction in the hazard of death (HR 0.593, 95% CI 0.374–0.940; p = 0.026) and approximately 3.4 months of survival gain at Day 878, the end of the open-label extension (p = 0.004), with no statistically significant difference in the predicted NfL increase stratum (HR 1.199, 95% CI 0.643–2.239; p=0.568). The same pattern was observed across the functional endpoints tested. This is the strongest causal evidence in the planned NDA package that the CNM-Au8 30 mg treatment benefit operates through a mechanism related to NfL response.

CNM-Au8 30 mg Treatment Benefit Operates through a Mechanism Specific to NfL Response

The benefit was specific to NfL, not an artifact of the analytic method. Four negative controls (sex, body mass index change, glial fibrillary acidic protein change and Tau change) were each substituted for NfL and run through the identical analysis in the HEALEY dataset. All four analyses were null for both composite functional benefit and survival, whereas the NfL analysis was positive on both. RESCUE-ALS also reproduced the same null result for the negative controls, BMI and sex.

Safety and Tolerability Profile

CNM-Au8 has demonstrated a consistent safety and tolerability profile across its clinical trial and expanded access programs, now totaling more than 1,280 collective participant-years of treatment as of July 31, 2026, including more than 1,100 participant-years in ALS, with the longest continuous treatment duration for ALS exceeding 6.8 years. As of August 10, 2026, no serious adverse events have been assessed as related to CNM-Au8, and no safety signals have been associated with long-term use. The safety-tolerability profile of CNM-Au8 is directly relevant to the benefit-risk assessment the FDA will conduct in reviewing the NDA.

Phase 3 Confirmatory Trial Will Evaluate the NfL Relationship Prospectively

Clene's planned Phase 3 confirmatory trial, RESTORE-ALS, is designed to evaluate the NfL biomarker relationship prospectively. The trial will use a patient's baseline NfL level as a prospective enrollment stratification factor and will include prespecified, NfL-stratified analyses, building on the concordance evidence described here.

"ALS is a heterogeneous disease, and it matters that a biomarker signal, NfL decline or stabilization, marks the patients in whom CNM-Au8 appears to be providing the greatest benefit," said Ben Greenberg, Head of Medical at Clene. "In the HEALEY analyses, we were able to go a step further: using pre-treatment characteristics alone, we could identify the patients likely to show NfL response, and the treatment benefit was concentrated in exactly that group. The FDA's accelerated approval of another drug for SOD1-ALS established that a reduction in NfL can be reasonably likely to predict clinical benefit in a defined ALS population."

"Observing the NfL biomarker-to-clinical-benefit relationship replicated in two independent trials, and NfL's prognostic value confirmed in more than 2,000 patients who never received CNM-Au8, is exactly the kind of evidence that gives us confidence in what we're submitting to the FDA," said Rob Etherington, President and Chief Executive Officer of Clene. "HEALEY and RESCUE-ALS were designed differently and enrolled under different

criteria, and in both, the patients whose NfL responded to CNM-Au8 lived substantially longer, strengthening our New Drug Application planned for filing early Q4."

About Clene

Clene Inc. (Nasdaq: CLNN), along with its subsidiaries, "Clene" and its wholly owned subsidiary Clene Nanomedicine, Inc., is a late clinical-stage biopharmaceutical company focused on improving mitochondrial health and protecting neuronal function to treat neurodegenerative diseases, including amyotrophic lateral sclerosis, Parkinson's disease, and multiple sclerosis. CNM-Au8 ® is an investigational first-in-class therapy that improves central nervous system cells' survival and function via a mechanism that targets mitochondrial function and the NAD pathway while reducing oxidative stress. CNM-Au8® is a federally registered trademark of Clene Nanomedicine, Inc. The company is based in Salt Lake City, Utah, with R&D and manufacturing operations in Maryland. For more information, please visit www.clene.com or follow us on X (formerly Twitter) and LinkedIn.

About CNM-Au8®

CNM-Au8 is an oral suspension of gold nanocrystals developed to restore neuronal health and function by increasing energy production and utilization. The catalytically active nanocrystals of CNM-Au8 drive critical cellular energy producing reactions that enable neuroprotection and remyelination by increasing neuronal and glial resilience to disease-relevant stressors. CNM-Au8® is a federally registered trademark of Clene Nanomedicine, Inc.

About These Analyses

The HEALEY and RESCUE-ALS biomarker analyses described in this release are *post hoc* and exploratory; neither trial met its prespecified primary efficacy endpoint, no adjustment was made for multiple comparisons, and reported p-values are nominal. The HEALEY analyses are based on 57 CNM-Au8 30 mg treated participants with an evaluable NfL trajectory (38 NfL Decline/Stable, 19 NfL Increase); the RESCUE-ALS analyses on 22 participants (11 per group). Each NfL stratum was compared with concurrently randomized controls rather than with the other stratum; with 38 and 19 participants respectively, these analyses were not powered for a direct statistical comparison between the two strata. The principal stratum analysis provides the randomization-preserving assessment of whether treatment benefit depends on NfL response. Because patients were classified by NfL response after treatment began, responder-versus-control comparisons are observational; the principal stratum analysis, which classifies patients on pre-treatment characteristics only, was included to provide a randomization-anchored estimate, and is itself *post hoc*. The HEALEY comparator comprised all 329 participants randomized to concurrent regimens, approximately three-quarters of whom received another investigational agent and one-quarter placebo; survival did not differ between active and placebo recipients within either control regimen at the timepoints assessed. By contrast, the supporting observational-cohort analyses in the APST (1,671 evaluable of 2,059 enrolled) and ANSWER ALS (380 evaluable of 742 enrolled) cohorts were prespecified, and their primary and secondary analyses each rejected the null hypothesis in both cohorts. No participant in either cohort received CNM-Au8; approximately 55% and 69% respectively were receiving riluzole. These cohorts establish that NfL trajectory is prognostic at the individual level; whether a treatment's effect on NfL predicts its effect on survival is addressed by the trial analyses described above. FDA accepted NfL reduction as reasonably likely to predict clinical benefit in SOD1-ALS in the context of the tofersen accelerated approval; the acceptability of a surrogate endpoint is determined program by program, and FDA has made no such determination for CNM-Au8.

Forward-Looking Statements

This press release 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 the timing of the Company's NDA submission, that the biomarker findings support an NDA submission, and the timing of the initiation of the Phase 3 trial. Clene's forward-looking statements also include, but are not limited to, statements regarding whether the FDA will agree that a change in NfL is reasonably likely to predict clinical benefit in ALS, whether the FDA will accept the NDA for filing or grant accelerated approval, and whether the results of *post hoc*, exploratory analyses will be confirmed in the planned Phase 3 confirmatory trial. 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," "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 press release 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; the *post hoc* and exploratory nature of the biomarker analyses described in this press release, which were not prespecified, were not adjusted for multiplicity, and are based on small patient numbers, and which may not be predictive of results in future trials; 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 press release, 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 press release is as of the date of this press release. The information contained in any website referenced herein is not, and shall not be deemed to be, part of or incorporated into this press release.

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