



FDA Provides Roadmap for Accelerated Approval Pathway Through Submission of Additional CNM-Au8® Biomarker Data in ALS

December 10, 2024

- *FDA recommends that Clene leverage additional Neurofilament Light (NfL) data from its three Expanded Access Protocols (EAPs) and the HEALEY ALS Platform Trial to support earlier presented findings*
- *FDA recommends a follow-up meeting to discuss in more detail the analyses needed to support the accelerated approval pathway*
- *Additional NfL biomarker collection and analyses are underway and planned to be completed during the second quarter of 2025*
- *Clene is proceeding with its New Drug Application (NDA) for ALS with a planned submission in mid-2025 following incorporation of the EAP NfL biomarker analyses*
- *Clene plans to commence the confirmatory Phase 3 trial (RESTORE-ALS) evaluating the survival benefit of CNM-Au8 with initial participant enrollment prior to the NDA submission*

SALT LAKE CITY, Dec. 10, 2024 (GLOBE NEWSWIRE) -- Clene Inc. (Nasdaq: CLNN) (along with its subsidiaries, "Clene") and its wholly owned subsidiary Clene Nanomedicine Inc., a late clinical-stage biopharmaceutical company focused on revolutionizing the treatment of neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS), today announced that it recently received written guidance from the Division of Neurology 1 (DN1), of the U.S. Food and Drug Administration (FDA) regarding a potential accelerated approval pathway for CNM-Au8® in ALS.

As announced previously on September 16, 2024, Clene was initially advised that the data presented in its briefing package for CNM-Au8 was not adequate to support an NDA submission under the accelerated approval pathway. However, following Clene's November 1, 2024 meeting with DN1 and presentation of additional data and analyses, the FDA has provided guidance on a potential path to meet the regulatory standard for substantial evidence of effectiveness supporting accelerated approval. The FDA recommended that Clene investigate whether additional data from the ongoing compassionate use EAPs could be leveraged to substantiate the effect of CNM-Au8 on NfL decline.

Clene intends to follow the FDA's recommendation to provide data from the ongoing EAPs and believes that it can address the FDA's requests. This additional NfL biomarker collection and analyses to support NDA submission is planned to be completed during second quarter of 2025, as summarized below:

- **NfL Biomarker Analyses:** Provide supportive evidence of NfL declines in participants from the three ongoing FDA-authorized compassionate use EAPs. Clene will meet with the FDA in early 2025 to review and finalize its statistical analysis plan for the EAP NfL biomarker analyses.
- **Survival Pharmacometric Modeling:** Provide analyses of NfL and related disease-specific biomarkers linked to clinical survival benefit and clinical changes from the Phase 2 trial data.
- **Additional ALS-specific biomarkers:** Provide analyses of additional ALS-disease specific biomarkers to support the pharmacodynamic activity of CNM-Au8 for treatment of ALS.

The FDA noted that whether NfL can serve as a reasonably likely surrogate endpoint for the effects of CNM-Au8 in ALS and whether the magnitude of change observed on NfL in patients treated with CNM-Au8 is reasonably likely to predict clinical benefit for ALS would be a matter of review.

Clene plans to commence the confirmatory Phase 3 RESTORE-ALS trial with participant enrollment beginning prior to the submission of the NDA. The study is designed to investigate the effects of CNM-Au8 on improved survival (primary endpoint) and delayed time to ALS clinical worsening events (secondary efficacy endpoint).

"We are incredibly grateful for the FDA's willingness to consider how the available data from our expanded access programs may be able to support the existing clinical study data to allow for the review of an application for approval of CNM-Au8 for ALS via an accelerated regulatory pathway, and for the valuable feedback we have received to date," said Rob Etherington, President and CEO of Clene. "Together with the survival and supportive biomarker data generated thus far, the drug's benign safety profile, and the emerging EAP NfL data, we look forward to continued discussions with the Agency. Clene plans to include the additional data in an NDA submission under the accelerated approval pathway in mid-2025. We remain dedicated to the ALS community and honored to help critically ill patients and their families."

Jinsy A. Andrews, MD, MSc, FAAN, Associate Professor of Neurology and the Director of Neuromuscular Clinical Trials at Columbia University, and Primary Investigator of the CNM-Au8 Clene NIH EAP Compassionate Use Protocol, said, "Having seen first-hand the potential benefits of CNM-Au8 in both its clinical and compassionate use EAP programs, I am grateful that the FDA has recognized the power of real-world experience for a drug in ALS, and is willing to consider how EAP data can help ALS drugs advance on regulatory pathways."

Merit Cudkowicz, MD, Chair, Neurology Department, Massachusetts General Hospital, Director, Sean M Healey & AMG Center for ALS, and the Principal Investigator of the HEALEY ALS Platform Trial, said, "It was my pleasure to assist Clene in these varied supportive analyses, including NfL biomarker data from participants in our trials. Given the limited therapeutic options for ALS and a high sense of urgency, I am grateful to participate in

considering multiple paths forward in ALS.”

Presentation at the November 1, 2024 FDA In-person Meeting: As previous noted, at the FDA in-person meeting on November 1, 2024, Clene and recognized ALS experts presented new supportive prespecified and *post hoc* analyses of its Phase 2 data, which included:

- **78% Risk Reduction in Time to Death (Improved Survival) during the Open Label Extension** to Month 12 from the HEALEY ALS Platform Trial (CNM-Au8 30 mg vs. original placebo randomization; covariate adjusted Cox Hazard Ratio (HR) = 0.224, 95% CI: 0.053 – 0.949, p-value = 0.042)
- **Evidence Linking Baseline NfL Burden with a CNM-Au8 Survival Benefit** (*post hoc*) included:
 - **83% Risk Reduction of Time to Death or PAV** (Permanently Assisted Ventilation) observed in CNM-Au8 participants with the highest baseline Upper NfL Tertile from the HEALEY ALS Platform Trial through Month 12 (CNM-Au8 30 mg vs. original placebo randomization; covariate adjusted Cox HR = 0.174, 95% CI: 0.036 – 0.830, p-value = 0.0283)
 - **84% Risk Reduction of Time to Death or PAV** seen in CNM-Au8 Participants with baseline NfL \geq Median from the HEALEY ALS Platform Trial through Month 12 (CNM-Au8 30 mg vs. original placebo randomization; covariate adjusted Cox HR = 0.155, 95% CI: 0.035 – 0.693, p-value = 0.0147)
- **Evidence Linking NfL Decline with a CNM-Au8 Survival Benefit** (*post hoc*) included:
 - **57% of CNM-Au8 30 mg treated participants demonstrated NfL decline at week 24** (the end of the HEALEY-ALS Platform double-blind trial)
 - **91% Risk Reduction in Time to Death or PAV** observed in participants with any level of NfL decline (or missing NfL data) at week 24 in the HEALEY ALS Platform Trial with follow-up through Month 12; (CNM-Au8 30 mg vs. original placebo randomization; covariate adjusted Cox HR = 0.0925, 95% CI: 0.22 – 0.382, p-value = 0.001)
- **Long-Term Survival from Real-World Expanded Access Compassionate-use Protocols** showing a 31% risk reduction in CNM-Au8 participants who were unable to enter other ALS clinical trials due to advanced disease severity, when compared to propensity matched controls pooled from three different natural history and clinical trial datasets (covariate adjusted Cox HR = 0.689, 95% CI: 0.529 – 0.898, p-value = 0.0059)

In over 700 patient years of use of CNM-Au8, no significant safety concerns or safety trends have been identified. No serious adverse events (SAEs) have been identified as related to CNM-Au8 treatment by any investigator to date.

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.

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 Clene’s expectations regarding the availability of an accelerated approval regulatory pathway, the timing of clinical trials and the submission of an NDA, Clene’s intention to follow the FDA’s recommendation to provide data from the ongoing EAPs and address the FDA’s requests, and that Clene can provide the additional evidence to meet the FDA’s data requests. In addition, any statements that refer to 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, Clene’s expectations regarding the availability of an accelerated approval regulatory pathway, the timing of clinical trials and the submission of an NDA, Clene’s intention to follow the FDA’s recommendation to provide data from the ongoing EAPs and address the FDA’s requests, and that Clene can provide the additional evidence to meet the FDA’s data requests 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 of our drug candidates fail to demonstrate safety and efficacy 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; Clene's ability to demonstrate the efficacy and safety of its drug candidates; the clinical results for its 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; Clene's ability to achieve commercial success for its drug candidates, if approved; Clene's limited operating history and its ability to obtain additional funding for operations and to complete the development and commercialization of its 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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