Clene Reports Reduction in Biomarker Plasma Neurofilament Light (NfL) Levels and Improved Survival With CNM-Au8® Treatment From HEALEY ALS Platform Trial Long-Term Open Label Extension

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- *CNM-Au8 30mg treatment demonstrated significantly reduced plasma neurofilament light chain (NfL) levels at 76 weeks relative to placebo (18 months from randomization, p=0.023)*
- *60% decreased risk of long-term all-cause mortality (>18 months, p=0.0167) in participants originally randomized to CNM-Au8 30mg compared to those originally randomized to placebo using the rank-preserving structural failure time model (RPSFTM)*
- *CNM-Au8 30mg had greater overall treatment effect in delaying the time to morbidity events in the highest risk participants based on baseline NfL levels*
- *NfL biomarker and survival data from the long-term open label extension reinforces evidence of a treatment effect consistent with time to event results observed in the original double-blind Phase 2 period*

SALT LAKE CITY, Dec. 21, 2023 (GLOBE NEWSWIRE) -- Clene Inc. (Nasdaq: CLNN) (along with its subsidiaries, “Clene”) and its wholly owned subsidiary Clene Nanomedicine Inc., a clinical-stage biopharmaceutical company focused on improving mitochondrial health and protecting neuronal function to treat neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS), today reported new data from the 12-month long-term open label extension (OLE) of the CNM-Au8® treatment arm in the HEALEY ALS Platform Trial.

Long-Term Plasma NfL Biomarker Findings from Regimen C (CNM-Au8) in the HEALEY ALS Platform Trial Open Label Extension (OLE)

Plasma neurofilament light chain (NfL), a blood-based biomarker associated with neurodegeneration, declined by 16% (95% CI: 2% to 28%) from baseline to 76 weeks of treatment in the HEALEY ALS Platform Trial Open Label Extension (OLE) in participants randomized to CNM-Au8 30 mg relative to participants initially randomized to placebo (p=0.023). CNM-Au8 was associated with a 10% relative reduction in plasma NfL over the 24-week double-blind treatment period of the HEALEY ALS Platform Trial (p=0.040). This effect on NfL appears durable over the long-term follow-up period.

NfL, a key biomarker of neurodegeneration, is released from neurons following axonal injury, especially in people living with ALS, where higher levels of NfL have been found to predict more rapid decline in clinical function and increased mortality risk. Biomarkers such as NfL that are considered reasonably likely to serve as surrogates of effects on clinical endpoints have recently been used to support an FDA approval of a drug for the treatment of ALS.

The *post hoc* NfL results are based on analyses of plasma NfL collected from participants in the HEALEY OLE who were treated with CNM-Au8 for up to 76 weeks compared to participants treated with placebo for 24 weeks prior to crossing over to active treatment.

CNM-Au8 30mg treatment reduced plasma NfL levels compared to baseline: Mixed Model with Repeat Measures (MMRM), Least Squared Means on a Natural Log (Ln) Scale for the 76-week change from baseline of plasma NfL: CNM-Au8 = -0.075 (SE: 0.053); placebo = +0.098 (SE: 0.056); CNM-Au8 30mg vs. original placebo difference of LS Means on a Ln Scale = -0.173 (SE: 0.076), p=0.023. Combined analyses of both CNM-Au8 doses (30mg and 60mg) also demonstrated nominally significant reductions in plasma NfL, CNM-Au8 vs. placebo difference of LS Means on a Ln Scale = -0.144 (SE: 0.066), p=0.029.

Participants were treated with CNM-Au8 in the OLE for as long as 2.6 years from original randomization, providing long-term data on treatment effects in people living with ALS.

James D. Berry MD, Associate Professor of Neurology, Chief of the Motor Neuron Disorder Division and Director of the Neurological Clinical Research Institute at Massachusetts General Hospital commented, “As consensus is building that neurofilament is an important biomarker reasonably likely to predict clinical benefit, it is important to see NfL continue to decrease during long-term follow-up, and correlate with time to event clinical outcomes in the Clene regimen of the double-blind and OLE portions of the HEALEY ALS Platform Trial.”

Long-Term Survival Improvement from Regimen C (CNM-Au8) in the HEALEY ALS Platform Trial Open Label Extension (OLE)

Long-term survival analyses included the prespecified rank-preserving structural failure time model (RPSFTM) to account for the effects of CNM-Au8 in participants randomized to placebo who crossed-over to treatment with CNM-Au8. Under an assumption of a constant common treatment effect from CNM-Au8, treatment with CNM-Au8 demonstrated a 60% decreased risk of long-term all-cause mortality in participants originally randomized to treatment with CNM-Au8 compared to those originally randomized to placebo, after adjusting for the estimated benefit received after switching to CNM-Au8 (Cox HR= 0.40, 95% CI: 0.19 to 0.85; p-value= 0.017).

The RPSFTM analysis estimates the survival gained by receiving active treatment using the data from all study participants and then subtracting the estimated benefit from ex-placebo participants switched to CNM-Au8 during the OLE to provide a comparison of CNM-Au8 versus placebo across the

entire study period.

Merit Cudkowicz, M.D., Chair Neurology Department, Director, Sean M Healey & AMG Center for ALS at Mass General Hospital, Julianne Dorn Professor of Neurology Harvard Medical School, and the Principal Investigator of the HEALEY ALS Platform Trial, said, “These long-term results provide additional promising evidence that CNM-Au8 may offer more time to people living with ALS. The survival analyses using RPSFTM is a well-recognized method that has been used to estimate cross-over effects in another recent ALS trial, as well as oncology and other rare diseases. Additional analyses of the open label data are underway.”

Post-hoc Analysis Validates Association of NfL levels with Clinical Morbidity Outcomes and the Effects of CNM-Au8 in High Risk ALS Patients

To investigate the role of NfL in the incidence of ALS clinical worsening events, the pooled population of the HEALEY ALS Platform and the RESCUE-ALS trial were stratified by baseline plasma NfL levels by quartile (<51 pg/mL, 51 – 76 pg/mL, >76 – 114 pg/mL, and >114 pg/mL). The average number of ALS clinical worsening events including death, tracheostomy, feeding tube placement, and initiation of assisted ventilation were calculated for each treatment group (CNM-Au8 30 mg vs. placebo) during the double-blind periods. Results of these analyses suggested a beneficial effects of CNM-Au8 in delaying occurrence of clinical worsening events in the highest risk NfL quartiles.

In participants with the highest baseline plasma NfL levels (≥ median), the apparent benefit of CNM-Au8 30 mg was enhanced (Cox HR: 0.25, 95% CI: 0.11 to 0.61; p-value= 0.003). In the same post hoc analyses, nominally significant reduced rates of time to death or permanently assisted ventilation (PAV), and all-cause mortality, were also observed.

Benjamin Greenberg, M.D., Head of Medical at Clene, said, “The clinical correlation seen with plasma neurofilament change, as well as long-term survival using RPSFTM, provides further independent evidence to strongly support CNM-Au8 as a potential treatment for ALS. The concordance of these long-term biomarker and survival results with previously reported clinical outcomes from two Phase 2 ALS trials is encouraging. Additional biomarker and clinical data from the HEALEY ALS Platform Trial open-label extension periods have been collected and are undergoing analysis for expected results to be reported in the first quarter of 2024.”

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 Healey ALS Platform Trial
The HEALEY ALS Platform Trial is a perpetual multi-center, randomized, double-blind, placebo-controlled Phase 2 program designed to evaluate the efficacy and safety of multiple investigational products in people living with ALS. This landmark platform trial tests multiple treatments utilizing a shared placebo group. 161 participants were randomized to 30 mg CNM-Au8, 60 mg CNM-Au8, or placebo as adjunct to standard of care for a 24-week treatment period. Active drug was offered to all participants who were eligible and elected to continue into the Open Label Extension (OLE). The primary outcome of the trial was the change in disease severity over time as measured by ALSFRS-R through 24 weeks accounting for mortality (analyzed using a Bayesian shared parameter model). Prespecified secondary efficacy endpoints included the Combined Assessment of Function and Survival joint rank test (CAFS), change in respiratory function as measured by slow vital capacity (SVC), and overall survival. For more information, please see ClinicalTrials.gov Identifier: NCT04297683.

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 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,” “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 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 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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