



Clene Announces New CNM-Au8® Biomarker and Clinical Efficacy Data Submitted to FDA In Support of Treatment For ALS

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- CNM-Au8 treated participants in the HEALEY ALS Platform Trial with substantial neurofilament light (NfL) declines (CNM-Au8 NfL Responders) demonstrated significant clinical improvements in survival, functional status (slowed ALSFRS-R decline), and combined function and survival (CAFS scores) compared to NfL non-responders
- Independent of NfL responder status, significant survival benefits in CNM-Au8 30mg treated participants were observed in the long-term extension compared to matched natural history controls
- Nicotinamide adenine dinucleotide (NAD) and glutathione improvements were consistent and sustained with CNM-Au8 treatment, supporting a dual mechanism of action and indicating target engagement in ALS patients
- CNM-Au8 treated participants who demonstrated NAD/glutathione improvements demonstrated concordance in the same participants who were CNM-Au8 NfL Responders

SALT LAKE CITY, Aug. 06, 2024 (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 neurological diseases, including amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS), today announced new CNM-Au8 biomarker and clinical efficacy data submitted to the FDA, including *post hoc* analyses from two independently conducted Phase 2 clinical trials of CNM-Au8 for the treatment of ALS. This new information supplements the original data previously discussed with FDA in late 2023 and is intended to guide the planned FDA Type C interaction expected to occur in the third quarter of 2024 to discuss an accelerated approval regulatory pathway.

The level of neurofilament light (NfL) in plasma is considered an important biomarker of ALS disease progression and mortality risk.

CNM-Au8 NfL Responders, defined as those who had consistent and sustained NfL reductions, comprising nearly half of all CNM-Au8 treated patients, demonstrated a 28% mean reduction in NfL levels compared to baseline, while NfL levels continued to increase in CNM-Au8 NfL non-responders (all doses; geometric mean ratio (GMR) difference at week 76 post-baseline: 0.57, 95% CI: 0.50 – 0.64, $p < 0.00001$).

New analyses of the CNM-Au8 NfL Responders demonstrated efficacy in all-cause mortality, functional, and combined assessment of function and survival (CAFS):

- **All-cause mortality (survival):**
 - **Improved survival of CNM-Au8 NfL Responders compared to propensity matched controls** from the PRO-ACT database: HR: 0.504, 95% Wald CI: 0.28 – 0.904, covariate adjusted $p = 0.022$
 - **Improved survival of CNM-Au8 NfL Responders compared to CNM-Au8 NfL non-responders:** hazard ratio (HR): 0.350, 95% CI: 0.188 – 0.649; covariate adjusted, $p = 0.0009$
- **ALS Functional Improvement:** the ALS Functional Rating Scale (ALSFRS-R) is an instrument for evaluating the functional status of patients with ALS and is used to monitor functional change in a patient over time. CNM-Au8 NfL Responders demonstrated:
 - **Significantly less decline in ALSFRS-R total score compared to CNM-Au8 NfL non-responders:** $p < 0.01$ at the Week 64, 76, 88, and 100 visits post-randomization (Mixed model repeated measures (MMRM) was used to compare least squares mean change from baseline).
 - **Significantly less decline in the respiratory subdomain score of the ALSFRS-R compared to CNM-Au8 NfL non-responders:** $p < 0.01$ at the Week 64, 76, 88, and 100 visits post-randomization (MMRM was used to compare least squares mean change from baseline).
- **Improvements in the Combined Assessment of Function and Survival:** CAFS ranks clinical outcomes based on survival time and change in the ALSFRS-R:
 - CNM-Au8 NfL Responder demonstrated improvements compared to CNM-Au8 NfL non-responders starting at Week 48 ($p < 0.10$) and all later timepoints with significance reached at Weeks 88 and later ($p < 0.05$).

Independent of NfL responder status, **long-term treatment with CNM-Au8 30 mg was associated with improved survival in participants from the RESCUE-ALS and HEALEY ALS Platform Trials using updated long-term follow-up of survival status** compared to propensity matched controls from the clinical trial data registry PRO-ACT, the ALS/MND Natural History Consortium (NHC), and the Australian MiNDAUS registry. Matching methods and covariates were prespecified and conducted by an independent statistician.

- Long-term treatment with CNM-Au8 30mg in the HEALEY ALS Platform Trial demonstrated a **57% decreased risk of all-cause mortality vs. PRO-ACT propensity matched controls:** (HR: 0.431, 95% CI: 0.276 to 0.672; covariate adjusted,

p = 0.0002)

- Long-term treatment with CNM-Au8 30 mg in the HEALEY ALS Platform Trial demonstrated a **48% decreased risk of all-cause mortality vs. ALS NHC propensity matched controls** (HR: 0.519, 95% CI: 0.347 to 0.776; covariate adjusted, p = 0.0014).
- Long-term treatment with CNM-Au8 30 mg in the RESCUE-ALS Phase 2 Trial demonstrated a **70% decreased risk of all-cause mortality vs. PRO-ACT propensity matched controls**: (HR: 0.311, 95% CI: 0.142 to 0.682; covariate adjusted, p = 0.0035)
- Long-term treatment with CNM-Au8 30 mg in the RESCUE-ALS Phase 2 Trial demonstrated a **51% decreased risk of all-cause mortality vs. MiNDAUS propensity matched control**: (HR: 0.487, 95% CI: 0.287 to 0.824; covariate adjusted, p = 0.0074).

CNM-Au8 mechanism of action responders demonstrated concordance with CNM-Au8 NfL Responders. Data provided to the FDA also included an association of responses between CNM-Au8 mechanism responders (defined as those who had consistent and sustained NAD+ and GSH/GSSG glutathione improvements) and CNM-Au8 NfL Responders. The connection between CNM-Au8 mechanism responders and CNM-Au8 NfL Responders links the mechanism of action to NfL declines. Biomarkers of oxidative stress, including the GSH/GSSG ratio, demonstrated consistent improvement following CNM-Au8 treatment with increased activity associated with the duration of treatment. These data support a dual mechanism of action of neuronal metabolic support and decreased oxidative stress. Clene further provided mechanistic evidence from preclinical models that established improved neuronal integrity and survival, where CNM-Au8 simultaneously decreased the release of NfL from damaged motor neurons axons.

Merit Cudkowicz, M.D., 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, "The strong safety profile of CNM-Au8, with its NfL biomarker response now linked to survival evidence, and new information on mechanisms of action support proceeding to a confirmatory Phase 3 clinical trial and regulatory discussions on approval pathways."

Over 650 patient years of safety data continue to show that CNM-Au8 demonstrates a safety profile with no significant safety concerns or safety trends identified. No serious adverse events (SAEs) have been identified as related to CNM-Au8 treatment by any investigators to date.

"The risk-benefit assessment evidence of CNM-Au8 is strong. Our next step is discussing this new CNM-Au8 biomarker and efficacy data with the FDA, with the hope that ALS patients will benefit from this drug, sooner rather than later," said CEO and President of Clene, Rob Etherington.

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.

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 Company's expectations, hopes, beliefs, intentions or strategies, including expectations regarding interactions with the FDA and the next steps regarding the Company's efforts to seek an accelerated approval pathway from the FDA. 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, the Company's expectations, hopes, beliefs, intentions or strategies, including expectations regarding the timing of the Type C meeting, may be materially different from those expressed or implied by these forward-looking statements. Some factors that could cause actual results to differ include the Company'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; the Company's ability to achieve commercial success for its drug candidates, if approved; the Company'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.

Media Contact

Ignacio Guerrero-Ros, Ph.D., or
David Schull

Russo Partners, LLC
Ignacio.guerrero-ros@russopartnersllc.com
David.schull@russopartnersllc.com
(858) 717-2310

Investor Contact

Kevin Gardner
LifeSci Advisors
kgardner@lifesciadvisors.com
(617) 283-2856