Forward Looking Statements

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Entering a Transformative Period

Significant Opportunity

- Targeting neurodegenerative diseases such as ALS and Multiple Sclerosis
- >$1B commercial opportunity in each indication

CNM-Au8® Emerging Clinical Results

- Long-term follow-up of RESCUE-ALS Phase 2 participants demonstrated statistically significant survival benefit; 70% decreased risk of death in ALS
- Positive Topline Results from the Phase 2 VISIONARY-MS Trial; CNM-Au8 demonstrated neurological improvements in stable relapsing MS as adjunctive therapy to immunomodulatory DMTs
- HEALEY ALS Platform Trial Phase 2/3 topline results expected in 3Q 2022

Proprietary Platform Strong IP

- Proprietary nanotherapeutic manufacturing, scalable to commercialization
- Strong IP, including 150+ granted patents and manufacturing trade secrets
Neurodegenerative Diseases Share A Common Mechanism: A Decline In The Brain’s Ability To Produce Energy

Brain Energy Potential Declines With Normal Aging

特定的神经元群体对能量衰竭特别敏感

-0.5% NAD+/NADH unit decline per decade
(-0.13 mV units per year by 31P-MRS Imaging)

Closed squares = averaged data by age group: 21-26 yrs, 33-36 yrs, and 59-68 yrs old; Open squares = individual subject values

Energetic impairments in the CNS both pre-dispose and drive progression in neurodegenerative diseases

CNM-Au8® | Pioneering A New Drug Class To Improve Cellular Energy Production And Utilization

**CNM-Au8 Nanocrystals**
Clean Surfaced, Highly Faceted Shapes

**Mechanistic Effects**
- Increased NAD
- Increased ATP
- Decreased reactive oxygen species
- Increased proteostasis

**Improved Energy Production and Utilization**

By targeting energy metabolism, CNM-Au8 may protect and restore neuronal function.

Preclinical Evidence of Remyelination and Neuroprotection

**CNM-Au8 Supports Remyelination**

**CNM-Au8 Improves ALS Motor Neuron Function & Survival**

**Induced Pluripotent Stem Cell In Vitro Results – Motor Neuron Markers**


**CNM-Au8 novel MOA may be complementary to existing therapies to enable better disease control**
Significant Global Opportunity for Treatment in Combination with Standard of Care

Motor Neuron Disease (ALS, Other Orphan Disorders)

- Current drugs are largely ineffective, mostly generic.
- 2-5 years median life expectancy
- 100% fatal

Multiple Sclerosis (MS)

- Existing treatments only target immunomodulation
- Emerging evidence that early MS is neurodegenerative

Parkinson’s Disease (PD)

- No disease-modifying treatments available, only symptom-targeted options
- 30% of dopaminergic neurons are lost at diagnosis

Urgent unmet need to develop neuroprotective treatment to support cells’ energetic efficiency and resilience

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Building the Case for Neuroprotection & Remyelination

Established brain target engagement in early PD and stable relapsing MS patients

REPAIR-MS Phase 2 in non-active progressive MS underway

RESCUE-ALS trial supports CNM-Au8 slowed disease progression in ALS
Demonstrated statistically significant survival benefit; 70% decreased risk of death

HEALEY ALS Platform Trial topline results expected 3Q 2022

CNM-Au8 demonstrated neurological improvements in people with stable relapsing MS as adjunctive therapy to immunomodulatory DMTs

Results provide support to advance CNM-Au8 into Phase 3 clinical development

Growing Body of Evidence from Multiple Trials Supports CNM-Au8 Clinical Potential
Over 350 Years of Subject Exposure Without Identified Safety Signals Across ALS, MS & PD

**Clean Toxicology Findings**

All Animal Toxicology Studies Resulted in No-Adverse Effect Level (NOAEL) Findings

- Multiple species up to 9-months treatment
- Up to maximum feasible dosing without any toxicology findings related to CNM-Au8

**Well Tolerated Adverse Event (AE) Profile**

Assessed as Predominantly Mild-to-Moderate Severity and Transient

- No SAEs related to CNM-Au8 considered severe, life-threatening, or resulting in death
- AEs predominantly mild-to-moderate

**Patient Exposure Across ALS, MS & PD**

Over 350 Years of Subject Exposure Without Identified Safety Signals

- Long-term dosing experience up to 125 weeks

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Data on File, Clene Nanomedicine, Inc. | MS: Multiple Sclerosis, ALS: Amyotrophic lateral sclerosis, and PD: Parkinson’s Disease.
Two REPAIR Trials Demonstrated Target Brain Engagement and Improved Energy Metabolism in Early Parkinson’s and Stable Relapsing MS

Study Objective: to demonstrate target engagement for CNM-Au8 on CNS biomarkers related to energetic effects in the brain using Magnetic Resonance Spectroscopy ($^{31}$P-MRS)

Results demonstrated a potentially meaningful 10% improvement in NAD+/NADH ratio, an essential molecule for energy production

1° Endpoint (integrated PD & MS)

$^{31}$P-MRS Change in Brain NAD$^+$/NADH Ratio at End of Treatment
Partial Volume Coil; Ratio of NAD$^+$NADH (% Fraction of NAD$^+$ / % Fraction NADH)
Primary Endpoint, Mean ± SEM (Paired t-test)

Results demonstrated a potentially meaningful 10% improvement in NAD+/NADH ratio, an essential molecule for energy production

Exploratory (ATP Normalization)

REPAIR Integrated Analysis
$^{31}$P-MRS Change in $\gamma$-ATP at End of Treatment
Full Volume Coil $^{31}$P Signal Area (Integral)
Exploratory Endpoint, Percent (%) Change vs. Baseline Value

$^{31}$P-MRS Changes in Brain NAD$^+$/NADH Ratio: Baseline vs. End of Treatment

- Baseline NAD$^+$/NADH Ratio
  - n = 24

- Wk12+ (End of Tx) NAD$^+$/NADH Ratio
  - n = 24

Regression (All) and REPAIR Integrated Analysis

- Regression (All): r$^2$ = 0.711, p < 0.0001
- REPAIR-PD, n=13
- REPAIR-MS, n=11

### RepairPD
- Early Parkinson’s Disease

### RepairMS
- Stable Relapsing MS

### RepairMS
- Non-Active Progressive MS (Ongoing)
Encouraging Efficacy Signals in Phase 2 Trial

Study Objective:
Detect preservation of motor neuron function in people with early ALS as measured by MUNIX

Study Design:
36-week blinded treatment with ongoing long-term open-label follow-up

1° & 2° Endpoints

Rescue-ALS Primary & Secondary Endpoints (Wk 36 LS Mean Change ± 95% CI)

- MUNIX Sum (% Change)
  - ITT Population, Primary EP
- MUNIX Sum (% Change)
  - Limb Onset Subset
- FVC (% predicted)
  - ITT Population, Secondary EP

Results in favor of CNM-Au8 treatment but study underpowered

Vucic et al. RESCUE-ALS Trial Results: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of CNM-Au8 to Slow Disease Progression in Amyotrophic Lateral Sclerosis. Presented at International Symposium on ALS/MND; 7-10 December 2021.
CNM-Au8 Improved Patient Function and QOL, and Slowed ALS Disease Progression
Across Multiple Pre-specified Exploratory Endpoints

Proportion with <6 point decline

ALSFRS-R 6-point Decline Responder
(Proportion with < 6 point decline)
RESCUE-ALS Exploratory Endpoint
ITT Population, All Randomized

<table>
<thead>
<tr>
<th>Weeks (Post-Randomization)</th>
<th>Proportion (%) with &lt; 6 point ALSFRS-R Decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>80</td>
</tr>
<tr>
<td>24</td>
<td>70</td>
</tr>
<tr>
<td>36</td>
<td>60</td>
</tr>
</tbody>
</table>

p = 0.0350

P-value is based on a Chi-Square test

ALS Specific QOL

ALS Specific Quality of Life-Short Form Total Score
RESCUE-ALS Exploratory Endpoint
Mixed Model Repeat Measure (ITT Population, All Randomized)
LS Mean Difference

<table>
<thead>
<tr>
<th>Weeks (Post-Randomization)</th>
<th>ALS Specific Quality of Life-Short Form Total Score Change, LS Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week-12 LS Mean</td>
<td>0.6 (CI: -0.2, 1.3) p = 0.1363</td>
</tr>
<tr>
<td>Week-24 LS Mean</td>
<td></td>
</tr>
<tr>
<td>Week-36 LS Mean</td>
<td>0.9 (0.2, 1.6) p = 0.0177</td>
</tr>
</tbody>
</table>

P-value is based on MMRM model with treatment, visit, treatment by visit interaction as fixed effects, and baseline value, and ENCSALS score as covariates. An unstructured covariance model was used.

ALS Disease Progression

ALS Disease Progression defined as:
• Death, or
• Tracheostomy, or
• Non-invasive ventilation, or
• Gastrostomy tube

p = 0.0125

P-value is based on Kaplan-Meier Estimate, Percent Event Free, ± 95% CI
CAFS Results: Slowed Disease Progression

**Exploratory Endpoint Pre-specified**

CAFS Joint Rank: (i) Survival and (ii) ALSFRS-R Change

RESCUE-ALS Exploratory Endpoint

ANCOVA Model (ITT Population, All Randomized)

Week 36 LS Mean Difference

CAFS Survival

ALSFRS-R Decline

**Exploratory Endpoint Post Hoc**

Joint-Rank of (i) Survival, (ii) King’s Clinical Stage 4, and (iii) ALSFRS-R Change

RESCUE-ALS Post Hoc Endpoint

ANCOVA Model (ITT Population, All Randomized)

Week 36 LS Mean Difference

CAFS

Modified CAFS

Total 100%
Demonstrated Significant Impact on Long-Term Survival with 70% Decreased Risk of Death

RESCUE-ALS Active vs. Placebo Randomization
Long-Term Observed Survival (Interim Analysis)

Early CNM-Au8 treatment demonstrated a significant survival benefit:

- Long-term follow-up compared to initial placebo randomization*
- 70% decreased risk of death

*9-month delayed treatment start or no treatment
Registration Study: 24-Week Treatment Period (3:1 randomization, 120 active [30mg, 60mg]: 40 placebo)

- Change in ALSFRS-R slope + survival
- Weighted Average of Slope Change & Hazard Ratio
  - Weighting based on # of Mortality Events

- Multiple Independent Regimens with Pooled Placebo

A Multi-center, Randomized Double-Blind, Placebo-Controlled Clinical Trial Assessing the Efficacy, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of CNM-Au8 in Participants with Amyotrophic Lateral Sclerosis
### Core Design Elements

**Phase 2 Study: 48-Week Placebo-Control Treatment Period** 2:1 Randomization (Active [15mg, 30 mg]: Placebo)

- Enrolled stable relapsing remitting MS participants with chronic optic neuropathy on background DMTs
- n=73 of 150 planned – study ended prematurely due to pandemic-related enrollment challenges

<table>
<thead>
<tr>
<th>Screening</th>
<th>DO</th>
<th>WEEK 6</th>
<th>WEEK 12</th>
<th>WEEK 18</th>
<th>WEEK 24</th>
<th>WEEK 30</th>
<th>WEEK 36</th>
<th>WEEK 42</th>
<th>WEEK 48</th>
<th>EOS</th>
</tr>
</thead>
</table>

1° Change in Low Contrast Letter Acuity (LCLA)

2° Change in modified MS Functional Composite (mMSFC)

Baseline Demographics Showed Balanced Randomization and Clinical Profile

- All participants were diagnosed with stable relapsing remitting MS with chronic optic neuropathy
- 92% treated with background DMTs (53% monoclonal antibodies, 32% oral)

<table>
<thead>
<tr>
<th>Baseline Value</th>
<th>Age (yrs)</th>
<th>Sex n, (%)</th>
<th>Race n, (%)</th>
<th>Weight (kg)</th>
<th>EDSS Score</th>
<th>Years from Dx</th>
<th>Months Since Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNM-Au8 15 mg (n=24)</td>
<td>38.4 (10.2)</td>
<td>15 (63%)</td>
<td>23 (96%)</td>
<td>78.0 (17.1)</td>
<td>1.83 (1.3)</td>
<td>6.5 (5.0)</td>
<td>53 (57)</td>
</tr>
<tr>
<td>CNM-Au8 30 mg (n=25)</td>
<td>39.6 (7.6)</td>
<td>16 (64%)</td>
<td>24 (96%)</td>
<td>78.6 (17.3)</td>
<td>1.50 (1.1)</td>
<td>3.4 (3.3)</td>
<td>37 (35)</td>
</tr>
<tr>
<td>Placebo (n=24)</td>
<td>38.1 (8.3)</td>
<td>20 (83%)</td>
<td>22 (92%)</td>
<td>83.0 (23.3)</td>
<td>1.85 (1.4)</td>
<td>6.6 (3.7)</td>
<td>57 (38)</td>
</tr>
<tr>
<td>All Participants (n=73)</td>
<td>38.7 (8.6)</td>
<td>51 (70%)</td>
<td>69 (95%)</td>
<td>79.9 (19.3)</td>
<td>1.75 (1.5)</td>
<td>5.5 (4.3)</td>
<td>49 (45)</td>
</tr>
</tbody>
</table>

Data on File, Clene Nanomedicine, Inc.
Pandemic Significantly Impacted Study Conduct

• Study was ended prematurely due to COVID enrollment challenges (as announced February 2022)
  - Enrolled 73 of 150 planned
  - Underpowered due to limited enrollment
  - Pre-specified statistical threshold set at $p=0.10$
  - COVID restrictions precluded direct Sponsor monitoring

• Objectives
  - Learn from results
  - Evaluate strength of evidence for further MS development
modified ITT (mITT) Analysis Population

• Censored observations included

- Change in mobility assist device (cane to walker) for T25FW (n=1)
- Invalid data from 1 of 11 sites (n=9) with LCLA testing execution errors
  - Multiple testing locations with different light boxes and varying ambient lighting conditions
  - In consultation with study Principal Investigator and external experts, all clinical data from the site were excluded
CNM-Au8 treatment significantly improved vision
Primary outcome - low contrast letter acuity (LCLA)

LCLA in the Affected Eye

mITT Population, LS Mean ± SEM

Week 48 LS-Mean Difference = 3.13
95% CI = -0.08 to 6.33
p = 0.056

Data on File, Clene Nanomedicine, Inc. mITT excludes one site where data inconsistencies were observed in both active and placebo participants
CNM-Au8 demonstrated global neurological improvement by the modified MS functional composite.

Lead 2nd EP | (m)MFSC Composite Mean Standardized Change (6-domain)

LCLA affected/fellow, 9HPT dominant/non-dominant, SDMT, T25FWT
(mITT Population, LS Mean ± SEM)

Week 48 LS-Mean Difference = 0.28
95% CI = 0.04 to 0.52
p = 0.0207

Data on File, Clene Nanomedicine, Inc. mITT excludes one site where data inconsistencies were observed in both active and placebo participants.
CNM-Au8 neurological improvement was driven by cognition, manual dexterity, and low contrast vision.

Modified MS Functional Composite | Domain Improvements
LCLA affected/fellow, 9HPT dominant/non-dominant, SDMT, T25FWT
(mITT Population, LS Mean Difference ± SEM)
CNM-Au8 Less Placebo

Data on File, Clene Nanomedicine, Inc. mITT excludes one site where data inconsistencies were observed in both active and placebo participants.
CNM-Au8 treatment improved functional outcomes
Improvement relative to placebo decline

Score all subjects versus all other subjects by each mMSFC domain

<table>
<thead>
<tr>
<th>If...</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better function than comparison</td>
<td>+1</td>
</tr>
<tr>
<td>Same function as comparison</td>
<td>0</td>
</tr>
<tr>
<td>Worse function than comparison</td>
<td>-1</td>
</tr>
</tbody>
</table>

2nd EP | mMFSC Averaged Rank Sum Score

mMSFC Average Rank Sum Score (6-domain)
LCLA (affected/fellow), 9HPT (dominant/non-dominant), SDMT, T25FW
(mITT Population, LS Mean ± SEM)

Week 48 LS-Mean Difference = 13.38
95% CI = 2.83 to 23.94
p = 0.0138

Week 48 Average Rank Score (ANCOVA)

Data on File, Clene Nanomedicine, Inc. mITT excludes one site where data inconsistencies were observed in both active and placebo participants
Safety Summary

- **CNM-Au8 treatment was safe and well-tolerated**
  - Treatment emergent adverse events (TEAEs) were predominantly mild-to-moderate and transient
  - No dose limiting adverse events; no related serious adverse events

<table>
<thead>
<tr>
<th>Treatment Emergent Adverse Events (TEAEs)</th>
<th>CNM-Au8 15 mg number (%)</th>
<th>CNM-Au8 30 mg number (%)</th>
<th>Placebo number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with any TEAE</td>
<td>21 (88%)</td>
<td>25 (100%)</td>
<td>22 (92%)</td>
</tr>
<tr>
<td>Subjects with SAE</td>
<td>1 (4%)</td>
<td>2 (8%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Subjects with Related TEAEs</td>
<td>2 (8%)</td>
<td>5 (20%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Subjects Discontinued due to TEAE</td>
<td>--</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

**Placebo** SAEs: (1) Lentigo maligna melanoma, (2) pregnancy; CNM-Au8 15mg SAEs: (1) Pneumonia, bacteremia (staph aureus), endocarditis; CNM-Au8 30mg SAEs: (1) Ketamine infusion for pain and paracetamol overdose; (2) deep vein thrombosis (6-months post-discontinuation)
CNM-Au8 Efficacy Summary

Clinical and functional improvements

- LCLA vision improvement
- mMFSC global neurological improvement

Independent quantitative biomarkers of myelin and axonal integrity

- VEP amplitude & latency improvements
- Structural MRI improvements
- Preservation of retinal structure

First therapy to demonstrate global neurological improvement in MS patients on top of background DMT standard of care
**Strong IP & Manufacturing Capability**

Extensive Patent Portfolio With Protection Through 2035\(^a\) & Proprietary Trade Secrets; Plus 7-year Orphan Drug Designation, and Scalable to Commercialization

### Global Patent Status\(^b\)

- **Issued & Allowed Patents**: 150+
- **Pending Applications**: ~20
- **Total Patents/Applications**: >170

### Patent Description

- **Process And Method/Device**
  - (Clean Surface; Gold CSN)
- **State of Matter**
  - (CNM-Au8)
- **Method of Use**
  - (Prevent Demyelination & MoA)
- **Method of Use**
  - (Bi-Metallic Au/Pt; Antimicrobial)

### Trade Secrets

- **Plasma Conditioning**
- **Electrode Design & Cycling**
- **Trough Flow, Temp, Pressure**
- **Concentration & Filtration**

### In-House ISO8 Clean Room Clinical Production in Maryland

\(^a\) With Patent Restoration Term (assuming 5-year extension). \(^b\) As of 31-December-2021.
Anticipated Timeline & Upcoming Milestones

2021

Amyotrophic Lateral Sclerosis (ALS)

HEALEY ALS Platform Trial Phase 2/3

Parkinsons Disease (PD)

RESCUEPD Phase 2

Multiple Sclerosis (MS)

VISIONARY-MS Study Phase 2

RepairMS Non-active, Progressive

Anti-Viral Anti-Microbial

ZnAgSTUDY BRAZIL

2022

1H

2H

DATA

2023

1H

2H

DATA

NDA SUBMISSION

2024

1H

2H

June 30, 2022

Cash and investments on hand (unaudited): $26.3M

Sufficient Cash to Hit Key Milestones in 2022
CNM-Au8®
a gold nanocrystal suspension, in development as the first cellular energetic catalyst to remyelinate & protect neurological function

ALS Registration Trial
Topline data in 3Q 2022²

>350 patient years of CNM-Au8 clinical exposure

Manufacturing expansion in progress, preparing for possible commercialization in 2023

Strong IP: 150+ patents on Clean-Surface-Nanocrystal technology (CSN®) platform

June 30, 2022 Cash and investments on hand (unaudited): $26.3M
