Clene Nanomedicine

is a late clinical-stage biopharmaceutical company focused on improving mitochondrial health and protecting neuronal function to treat neurodegenerative diseases, including ALS, Parkinson's disease and multiple sclerosis.

Benjamin Greenberg, MD, MHS, FAAN
Clene, Head of Medical

January 25, 2024

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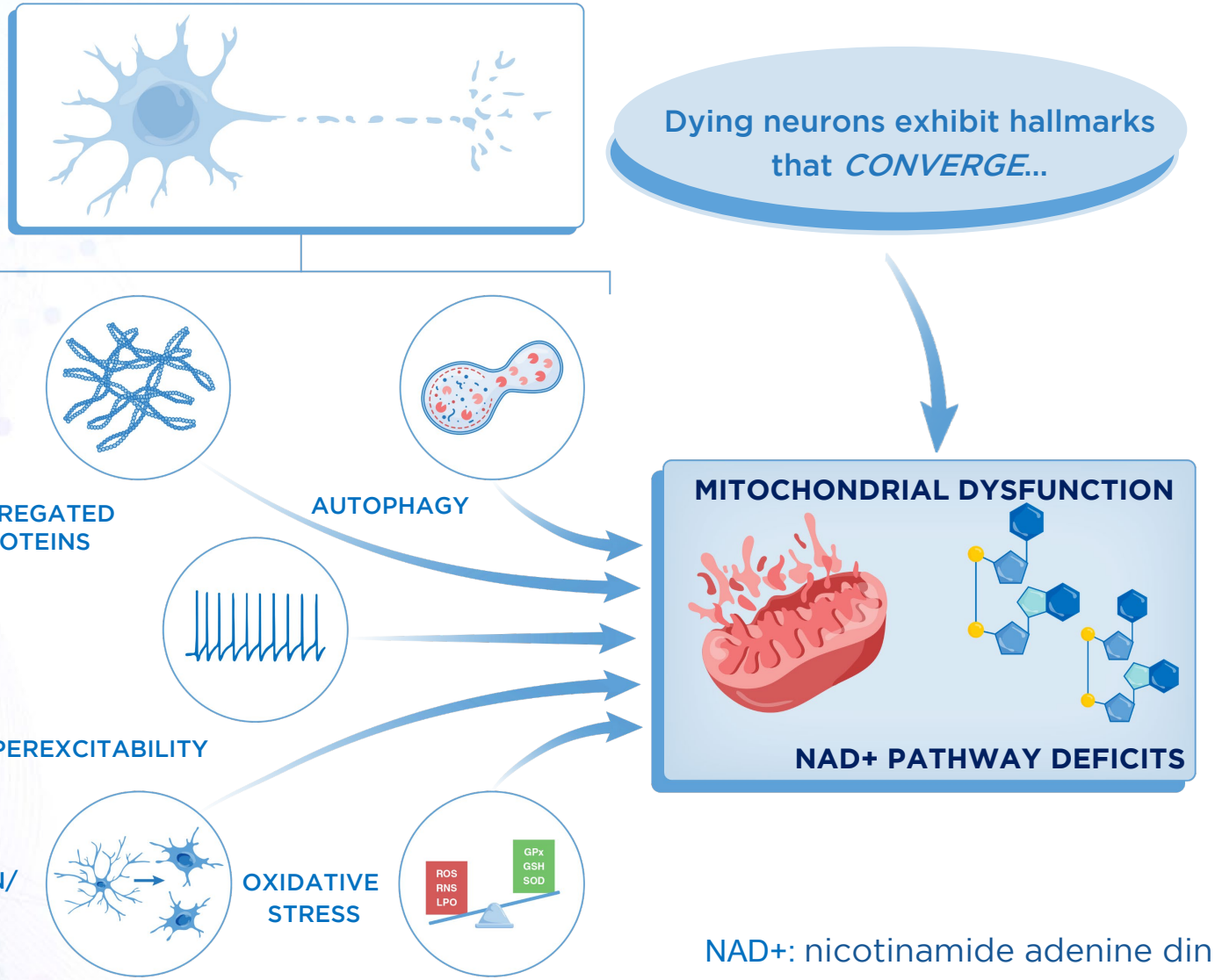
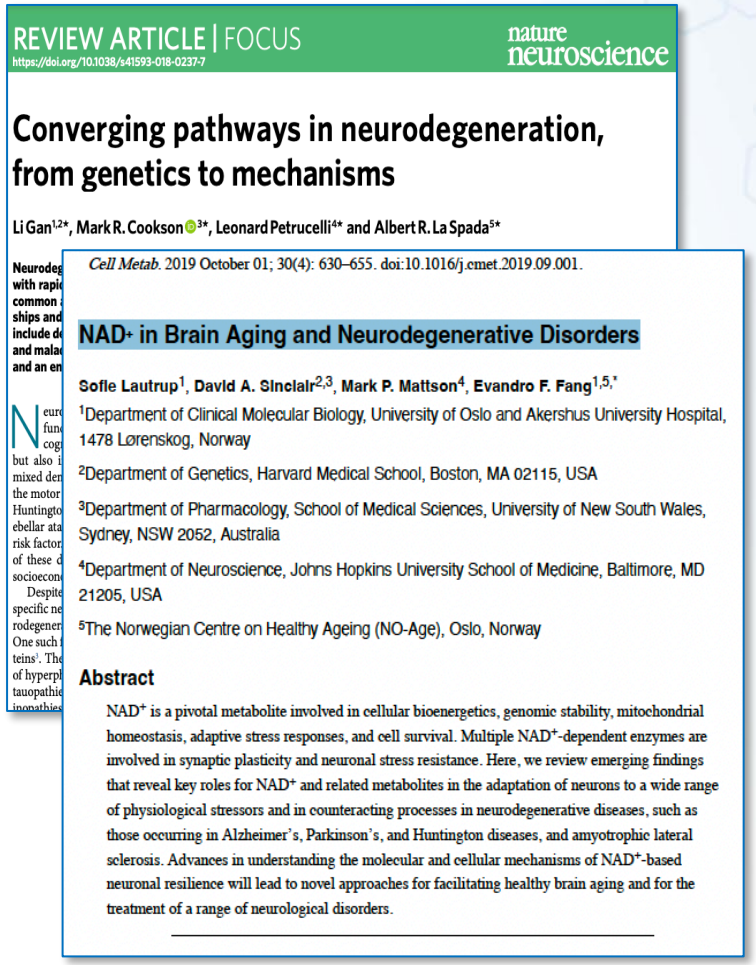
Hallmarks of Neuronal Death Converge on *Mitochondrial Dysfunction* and *NAD+ Pathway Deficits*





REVIEW ARTICLE | FOCUS

https://doi.org/10.1038/s41593-018-0237-7

nature neuroscience

Converging pathways in neurodegeneration, from genetics to mechanisms

Li Gan[1,2*], Mark R. Cookson[3*], Leonard Petrucelli[4*] and Albert R. La Spada[5*]

Cell Metab. 2019 October 01; 30(4): 630–655. doi:10.1016/j.cmet.2019.09.001.

NAD+ in Brain Aging and Neurodegenerative Disorders

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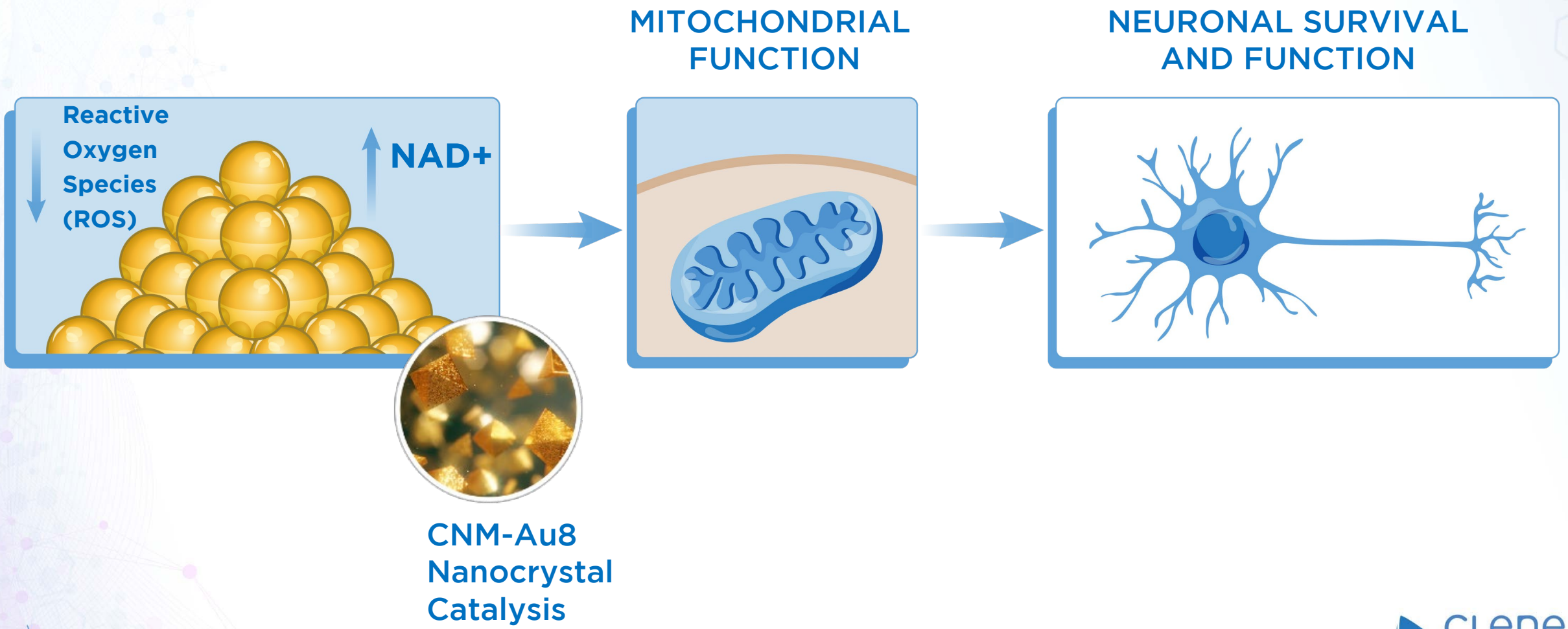
Abstract

NAD^+ is a pivotal metabolite involved in cellular bioenergetics, genomic stability, mitochondrial homeostasis, adaptive stress responses, and cell survival. Multiple NAD^+-dependent enzymes are involved in synaptic plasticity and neuronal stress resistance. Here, we review emerging findings that reveal key roles for NAD^+ and related metabolites in the adaptation of neurons to a wide range of physiological stressors and in counteracting processes in neurodegenerative diseases, such as those occurring in Alzheimer's, Parkinson's, and Huntington diseases, and amyotrophic lateral sclerosis. Advances in understanding the molecular and cellular mechanisms of NAD^+-based neuronal resilience will lead to novel approaches for facilitating healthy brain aging and for the treatment of a range of neurological disorders.

NAD+: nicotinamide adenine dinucleotide

Lautrup et al. Cell Metab. 2019 Oct 1;30(4):630-655. Gan et al. Nat Neurosci. 2018 Oct;21(10):1300-1309.

CNM-Au8® | Surface Catalysis Improves Mitochondrial Function



Robinson et al. Sci Rep. 2020 Feb 11;10(1):1936. Wang et al 2023, Small. 2023 Sep 28:e2304082.

CLene NANOMEDICINE

Promising Evidence from Two Phase 2 Trials and Long-Term Data

CNM-Au8 Demonstrated Survival, Delayed Clinical Worsening, and Preserved Function

	RESCUE-ALS	RESCUE-OLE	HEALEY ALS Platform	HEALEY OLE	EAP
ALS Patient Demographics	Early-to-Mid-Stage (45)	Early-to-Mid-Stage	Mid-to-Late-Stage (161 Regimen C)	Mid-to-Late-Stage	Real-World Experience (256)
Duration	36-weeks	Up to 173 weeks	24-weeks	Up to 133 weeks	Over 4.0 years
Survival	--	✅	✅	✅ PRO-ACT	✅
Delayed Time to Clinical Worsening	✅	✅	✅	Pending data 1Q 2024	Not routinely collected
Preserved Function (ALSFRS-R)	--	✅	--		
Progression Biomarkers	p75 trend	↓ UCHL1 *	✅ NfL ↓	✅ NfL ↓	
Safety	>500 Years of Subject Exposure Without Identified Safety Signals Across ALS, MS, and PD				

Consistent Evidence for CNM-Au8 30mg Dose Across Broad ALS Patient Population

Data on File, Clene Nanomedicine, Inc. *Small sample available for analyses in RESCUE OLE

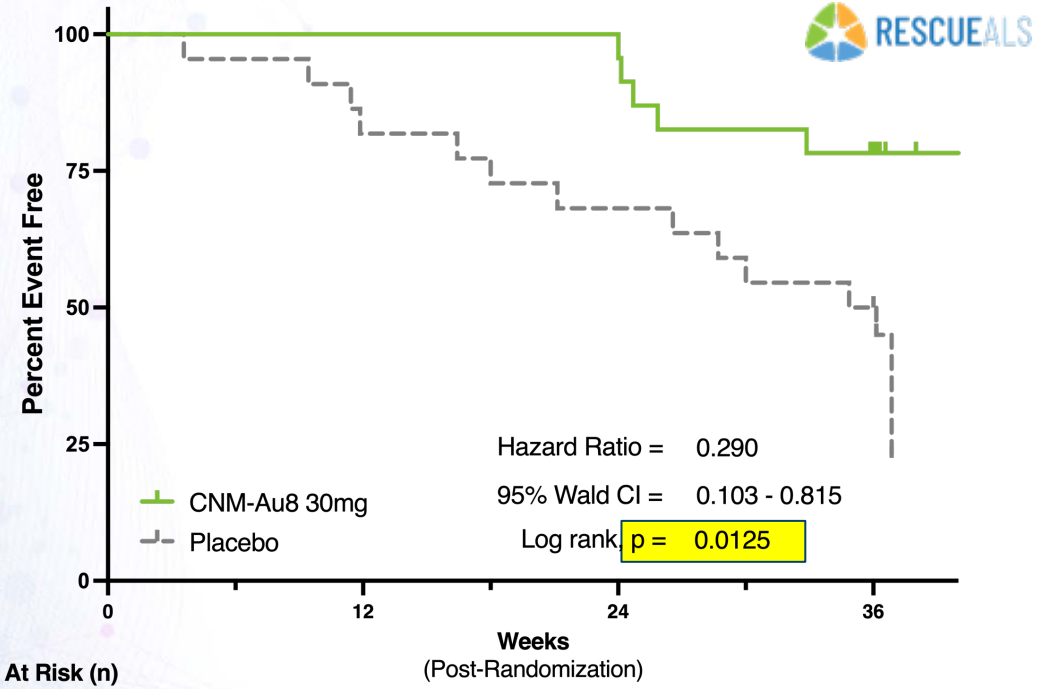
CNM-Au8 | Clinical Worsening Concordant in Two Phase 2 Trials

Evidence for Decreased Clinical Worsening Events Across Two Phase 2 Studies

Phase 2 RESCUE-ALS CNM-Au8 30mg
Decreased Time to Clinical Worsening

Time to ALS Clinical Worsening

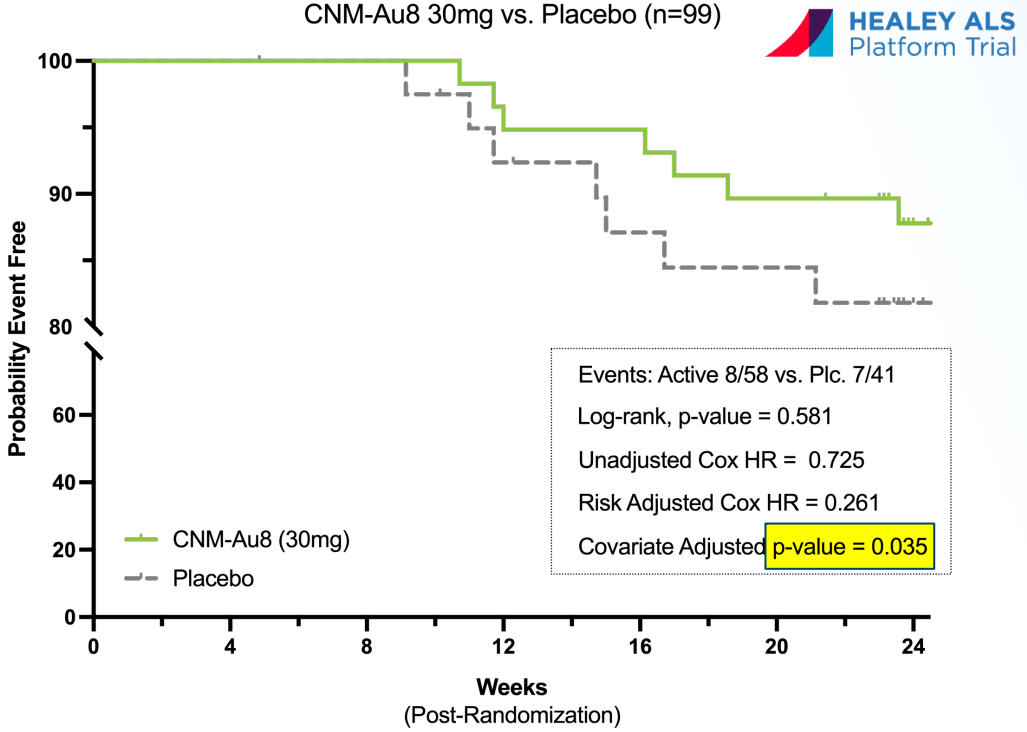
First Occurence of Death, Tracheostomy, Assisted Ventilation, or Feeding Tube
ITT Population (All Randomized), Kaplan-Meier Estimate



No. At Risk (n)				
CNM-Au8:	23	23	23	18
Placebo:	22	19	16	12

Phase 2 HEALEY ALS Platform CNM-Au8 30mg
Decreased Time to Clinical Worsening

Time to Clinical Worsening | CNM-Au8 30mg
First Occurence of Death, PAV, Tracheostomy or Feeding Tube
HEALEY ALS Platform Trial | Kaplan-Meier Estimate
Regimen C Population, Efficacy Regimen Only
CNM-Au8 30mg vs. Placebo (n=99)



Vucic et al. EClinicalMedicine. 2023 Jun 8;60:102036. Data on File, Clene Nanomedicine, Inc.

Clene NANOMEDICINE

CNM-Au8 | ALS Survival at 30mg Concordant in Two Phase 2 Trials

RESCUEALS

Up to 75% decreased risk of death through 168 weeks

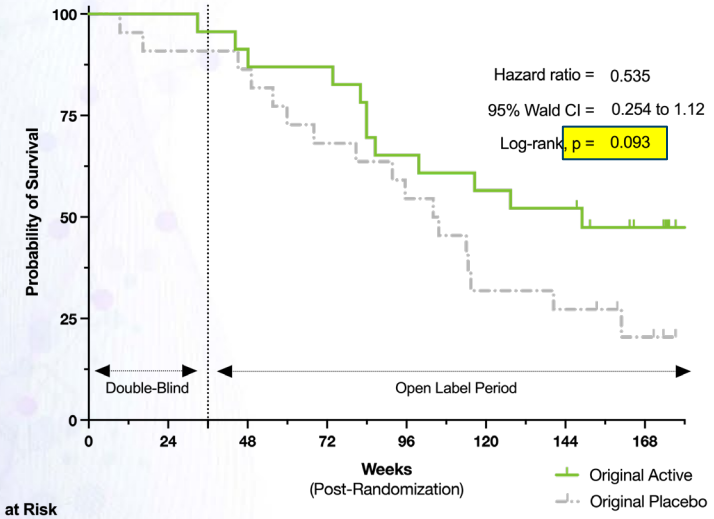
HEALEY ALS Platform Trial

>90% risk reduction of death at 30mg at 24 weeks

Unadjusted Survival

10.1 Months Survival Difference

Overall Survival (All-Cause Mortality)
RESCUE-ALS (24-month LPLV data cut), ITT Population (n=45)
Proportion Event Free, Kaplan-Meier Analyses

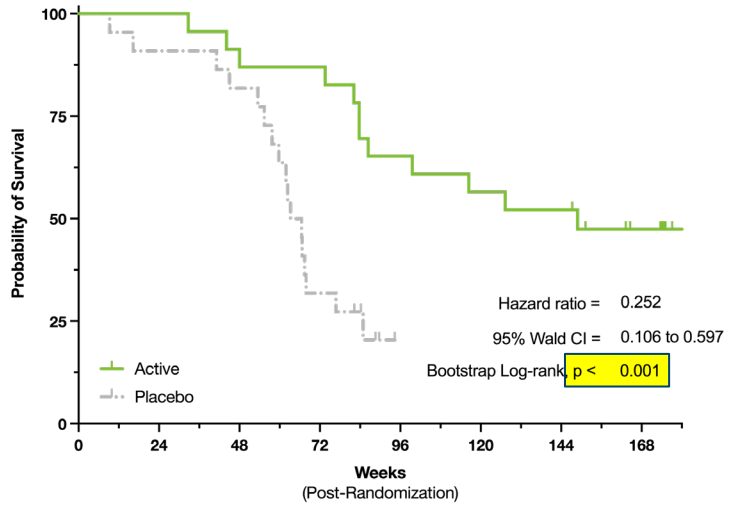


No. at Risk								
Original CNM-Au8:	23	23	21	21	16	14	13	8
Original Placebo:	22	21	20	16	13	8	7	7

Cross-Over Adjusted Survival

Up to 19.3 Month Survival Benefit vs. Original Pbo

Cross-Over Adjusted Analysis of Survival
RESCUE-ALS (24-month LPLV data cut), ITT Population (n=45)
RPSTFM, Proportion Event Free, Kaplan-Meier Analyses

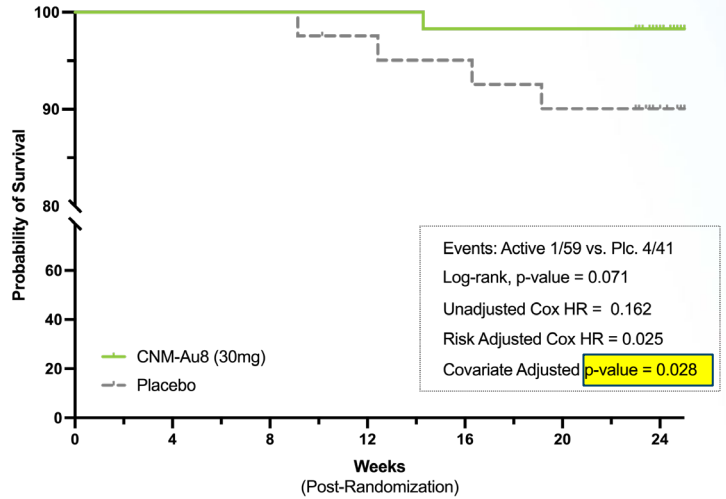


No. at Risk								
Original CNM-Au8:	23	23	21	21	16	14	13	8
Original Placebo:	22	21	19	8	1	0	0	0

RPSFTM (Rank Preserving Structural Failure Time Model) removes estimated benefit from cross-over to active treatment in ex-placebo participants

Survival During Blinded Period

Time to Death or Death Equivalent (PAV) | CNM-Au8 30mg
HEALEY ALS Platform Trial | Kaplan-Meier Estimate
Regimen C Population, Efficacy Regimen Only
CMM-Au8 30mg vs. Placebo (n=100)



Data on File, Clene Nanomedicine, Inc.

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Global Phase 3 RESTORE-ALS

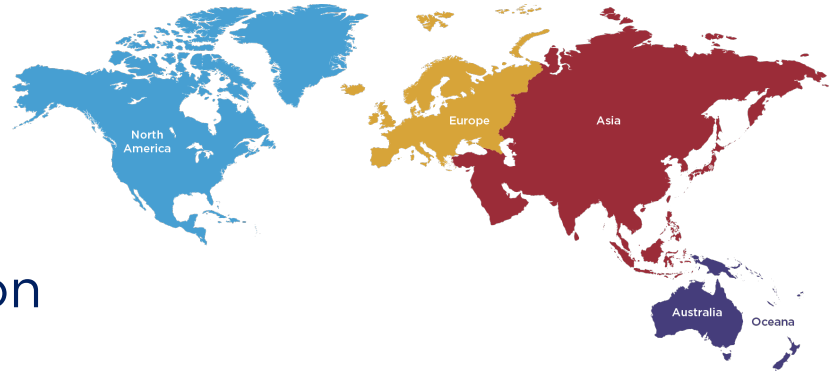
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial in Early Symptomatic Participants on Stable Background Therapy to Reduce Mortality and Clinical Worsening Events in Amyotrophic Lateral Sclerosis (RESTORE-ALS)

Investigational Product | Randomized 2:1

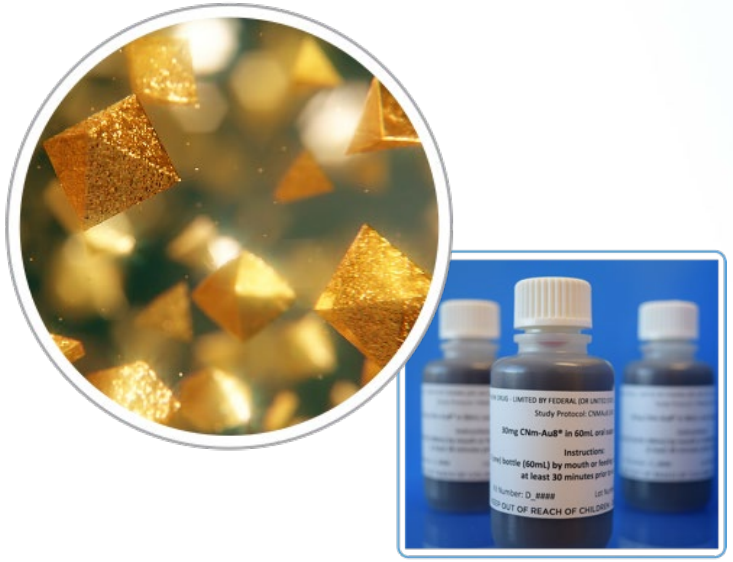
- ❑ CNM-Au8 30 mg (or matched placebo)

Study Center(s): Expert ALS clinical care centers across

- ❑ North America
- ❑ Europe
- ❑ Asia/Pacific region



CNM-Au8



RESTORE-ALS design is in the planning phase and not yet final.

Key Clinical Endpoints

1° Endpoint: Improved Survival

Time to Death or Permanent Assisted Ventilation (PAV)

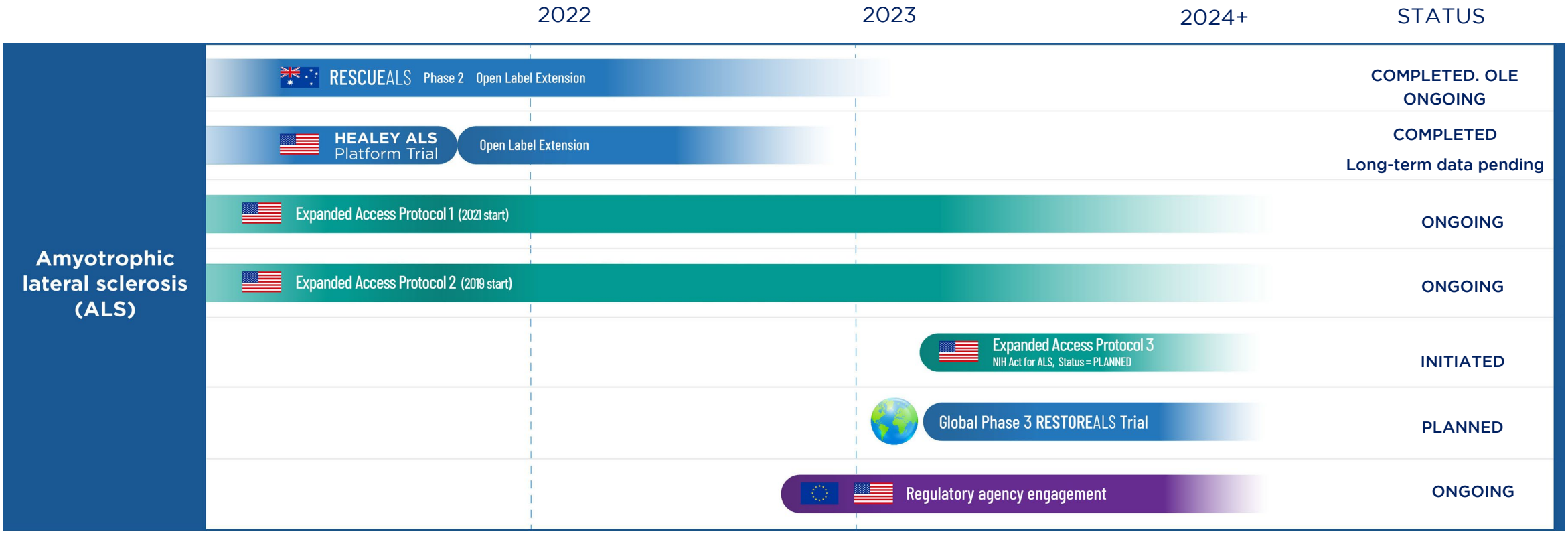
Lead 2° EP | Delayed Time to ALS Clinical Worsening Events

Composite Analysis of ALS Clinical Worsening Events:

- Survival
- Permanent Assisted Ventilation
- Need for Tracheostomy
- Need for Feeding Tube Initiation
- Need for Assisted Ventilation

RESTORE-ALS design is in the planning phase and not yet final.

CNM-Au8 | Timeline and Path Forward for ALS



2024 Priorities: Initiate Global Phase 3 Trial and Advance Regulatory Agency Engagement

Contact Us

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