

Corporate Presentation  
August 2022



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NASDAQ: CLNN

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# CLENE | Entering a Transformative Period



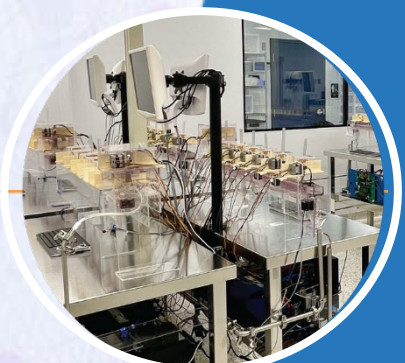
## Significant Opportunity

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



## CNM-Au8<sup>®</sup> 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

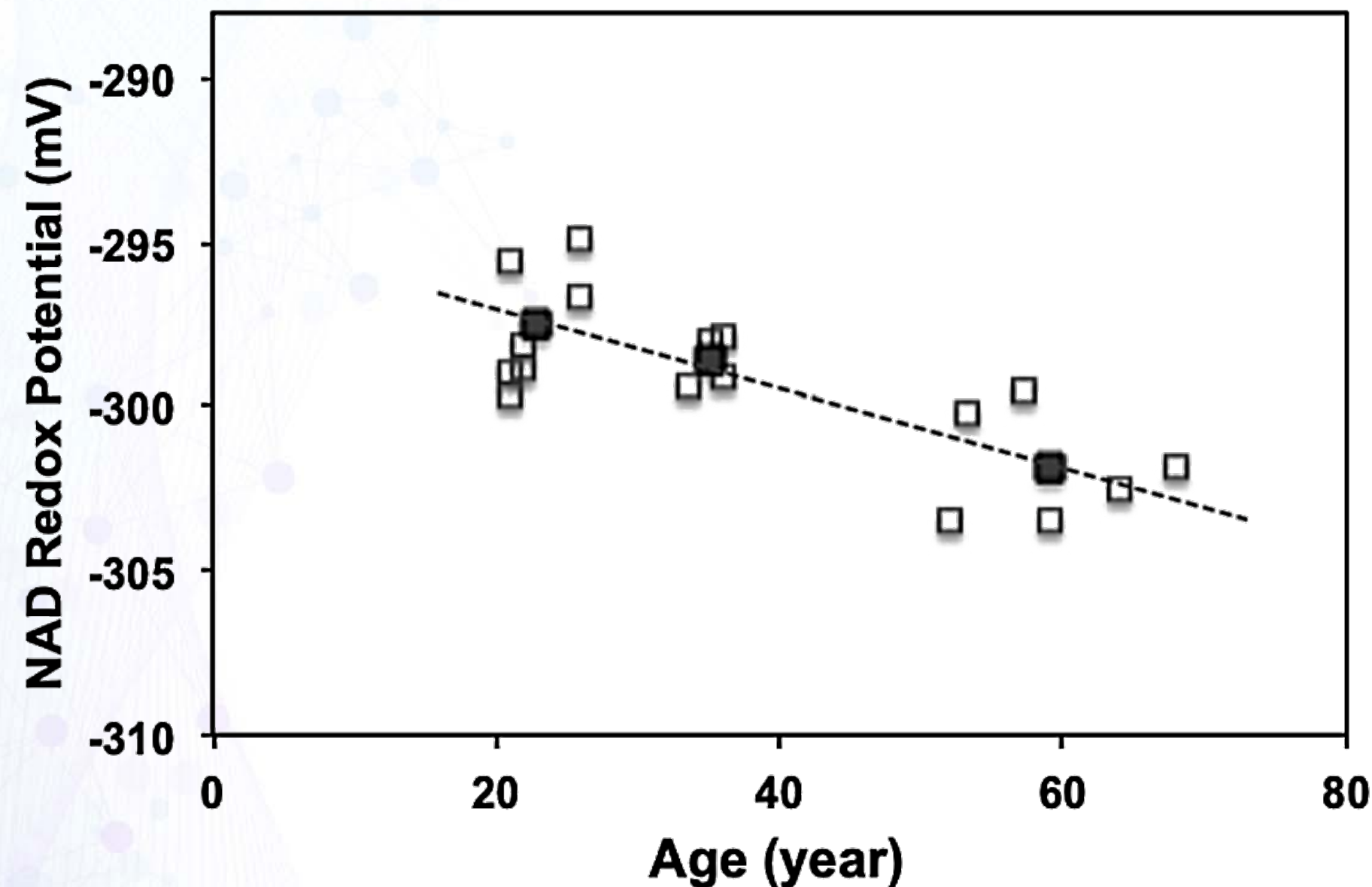


## Proprietary Platform Strong IP

- 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

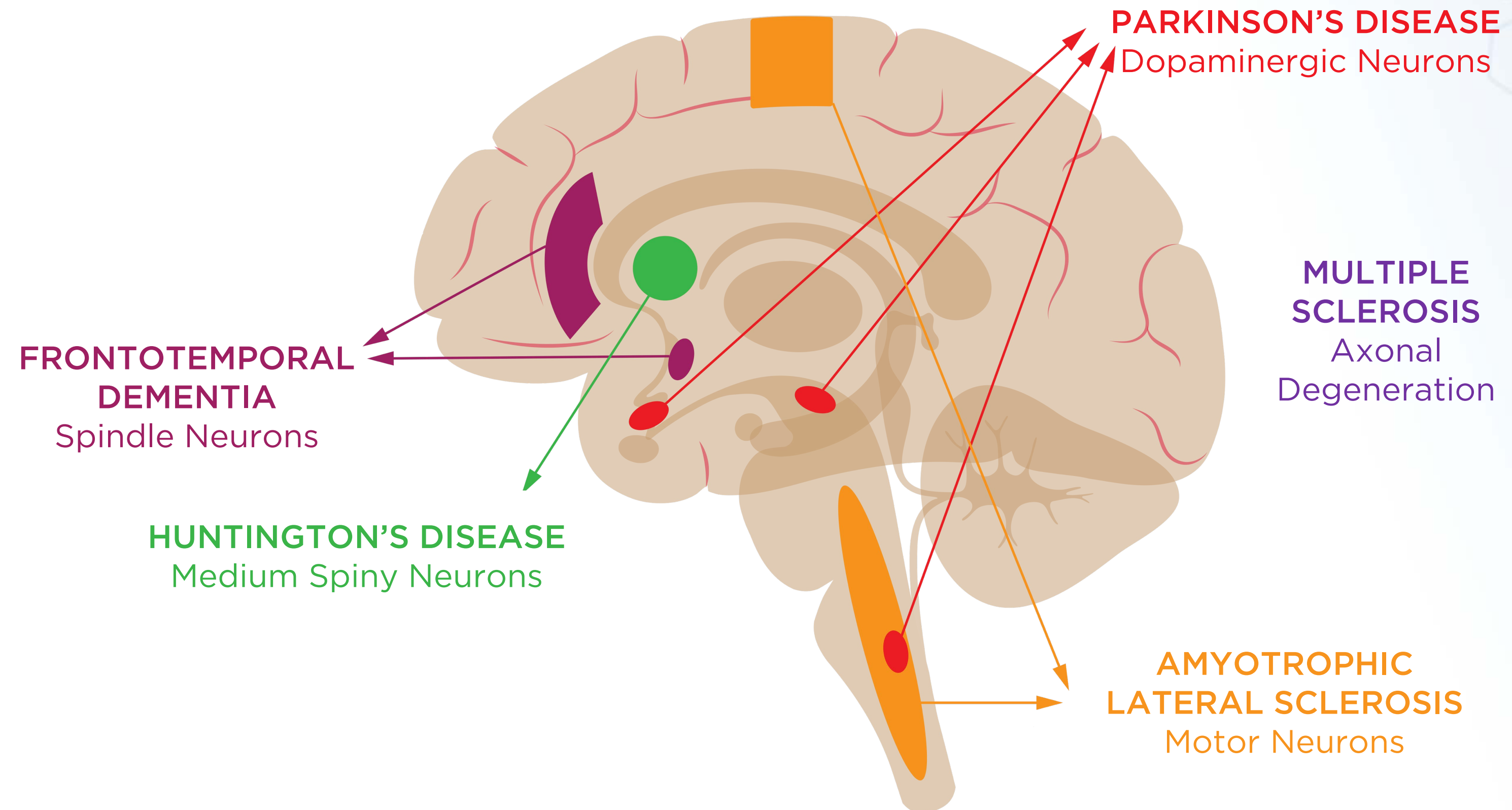
## Brain Energy Potential Declines With Normal Aging



**~0.5% NAD<sup>+</sup>/NADH unit decline per decade**  
(~0.13 mV units per year by <sup>31</sup>P-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

## Specific Neuronal Populations Are Vulnerable to Energetic Failure



**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

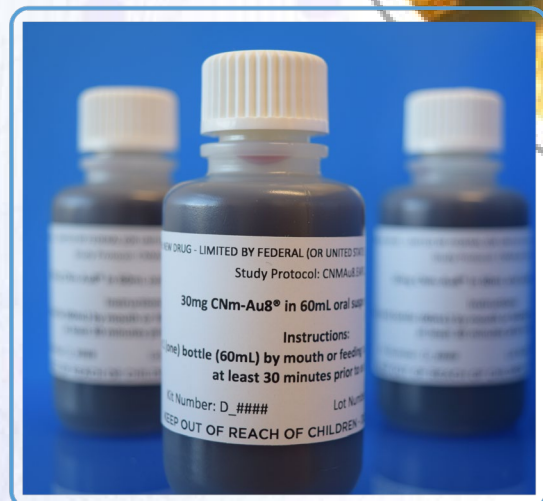
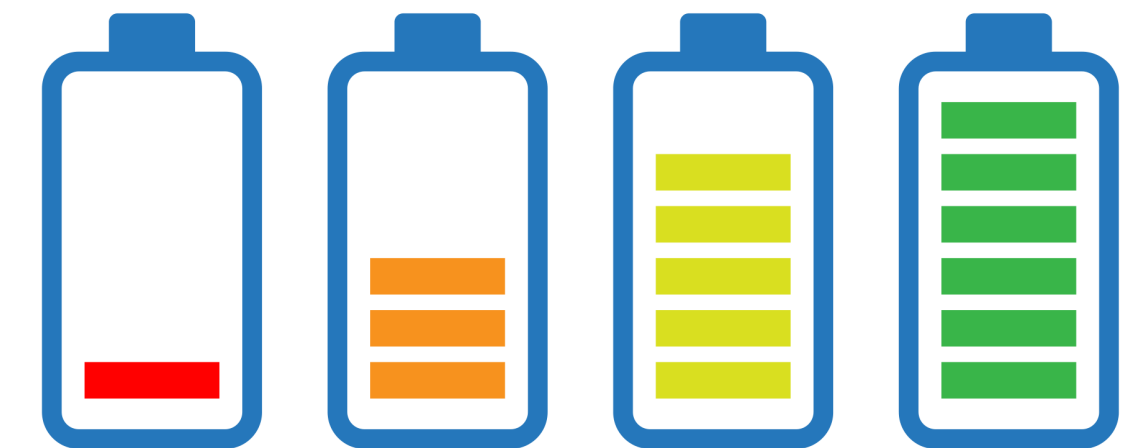
↑ Increased ATP

↓ Decreased reactive oxygen species

↑ Increased proteostasis

=

## Improved Energy Production and Utilization

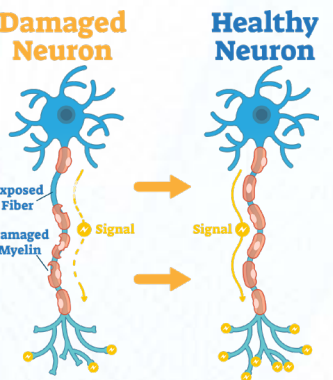


CNM-Au8 Nanocrystal Suspension

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

# Preclinical Evidence of Remyelination and Neuroprotection

## Remyelination



## CNM-Au8 Supports Remyelination

## Neuroprotection



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

www.nature.com/scientificreports

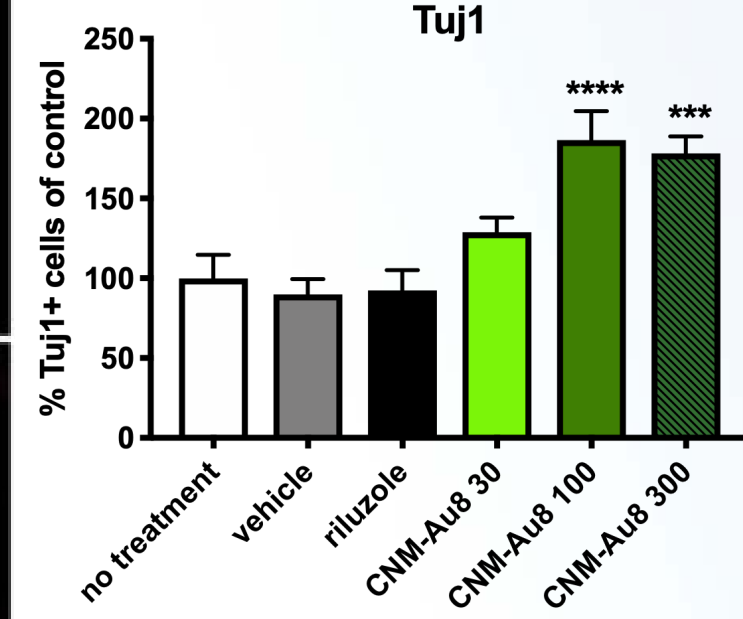
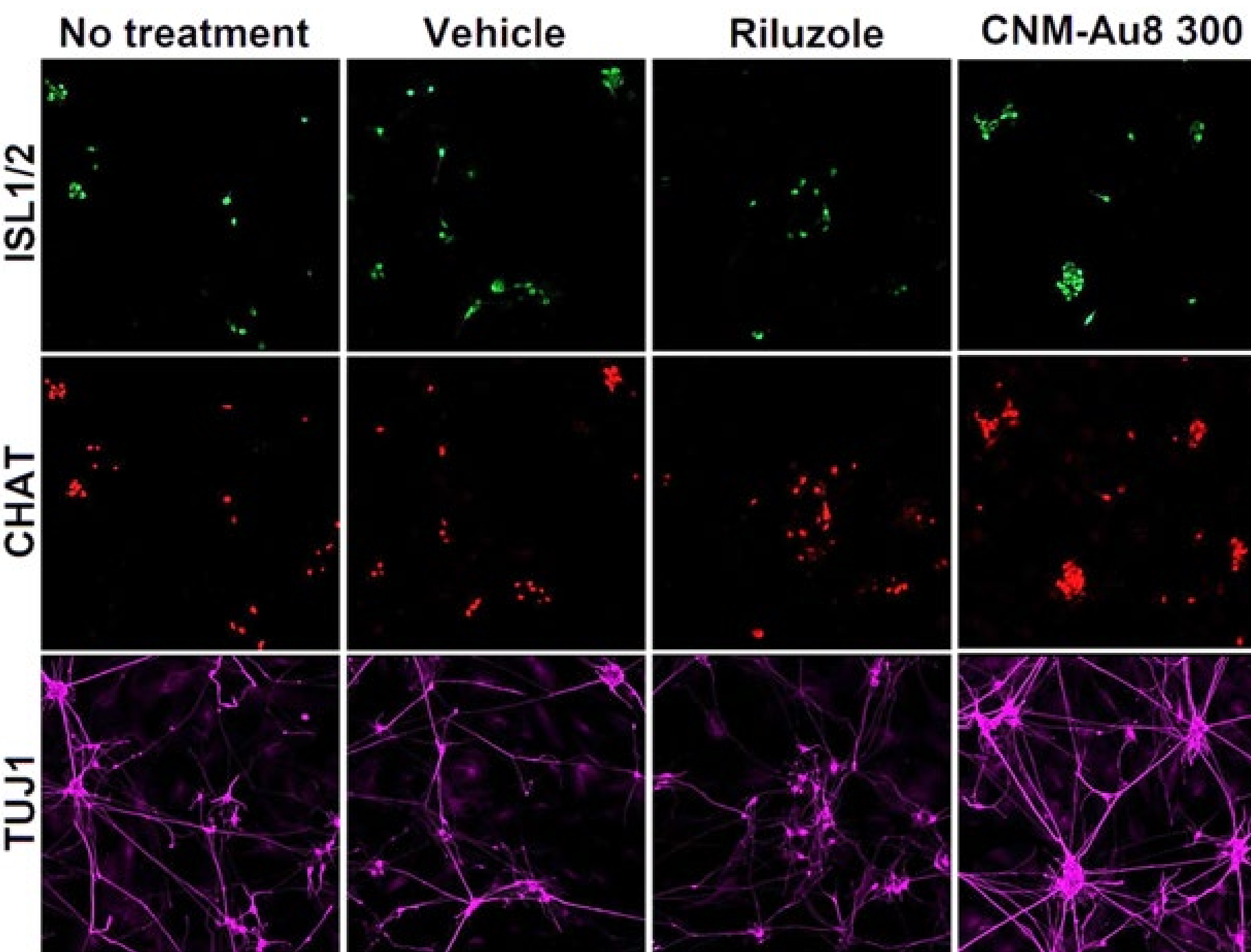
**SCIENTIFIC REPORTS**  
nature research

**OPEN** **Nanocatalytic activity of clean-surfaced, faceted nanocrystalline gold enhances remyelination in animal models of multiple sclerosis**

Andrew P. Robinson<sup>1,9</sup>, Joanne Zhongyan Zhang<sup>2,9</sup>, Haley E. Titus<sup>1</sup>, Molly Karl<sup>3</sup>, Mikhail Merzliakov<sup>2</sup>, Adam R. Dorfman<sup>2</sup>, Stephen Karlik<sup>4</sup>, Michael G. Stewart<sup>5</sup>, Richard K. Watt<sup>5</sup>, Benjin D. Facer<sup>6</sup>, Jon D. Facer<sup>5</sup>, Noah D. Christian<sup>7</sup>, Karen S. Ho<sup>2,8\*</sup>, Michael T. Hotchkin<sup>2,9</sup>, Mark G. Mortenson<sup>2,9</sup>, Robert H. Miller<sup>3,9</sup> & Stephen D. Miller<sup>1,9</sup>

Robinson et al. Sci Rep. 2020 Feb 11;10(1):1936.

## Induced Pluripotent Stem Cell *In Vitro* Results - Motor Neuron Markers



Karen S. Ho et al. "Redox-enhancing nanocatalysis improves motor neuron survival in vitro and SOD1 mouse motor function and survival in vivo." Presented at 30th International Symposium on ALS/MND 2019. December 4-6, 2019.

**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)

ALS PATIENTS IN US & EU **~40K**<sup>1</sup>  **\$1B** GLOBAL SALES BY 2029<sup>1</sup>



Current drugs are largely ineffective, mostly generic.

**2-5 YEARS**<sup>2</sup> LIFE EXPECTANCY  **100% FATAL**

## Multiple Sclerosis (MS)

MS PATIENTS GLOBALLY **2.2M**  **\$23B** MARKET<sup>3</sup>



Existing treatments only target immunomodulation

EMERGING EVIDENCE THAT EARLY MS IS NEURODEGENERATIVE



## Parkinsons Disease (PD)

**2ND** MOST COMMON DISORDER  **\$6B** PROJECTED BY 2026<sup>4</sup>



No disease-modifying treatments available, only symptom-targeted options

**30%** OF DOPAMINERGIC NEURONS ARE LOST AT DIAGNOSIS<sup>5</sup> 

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

# Building the Case for Neuroprotection & Remyelination

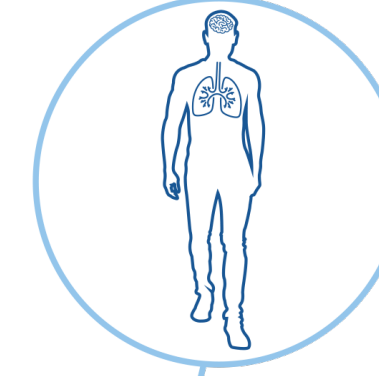
 RepairPD

 RepairMS



 RESCUEALS

 HEALEY ALS  
Platform Trial



 VISIONARY-MS  
STUDY



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

# Two REPAIR Trials Demonstrated Target Brain Engagement and Improved Energy Metabolism in Early Parkinson's and Stable Relapsing MS

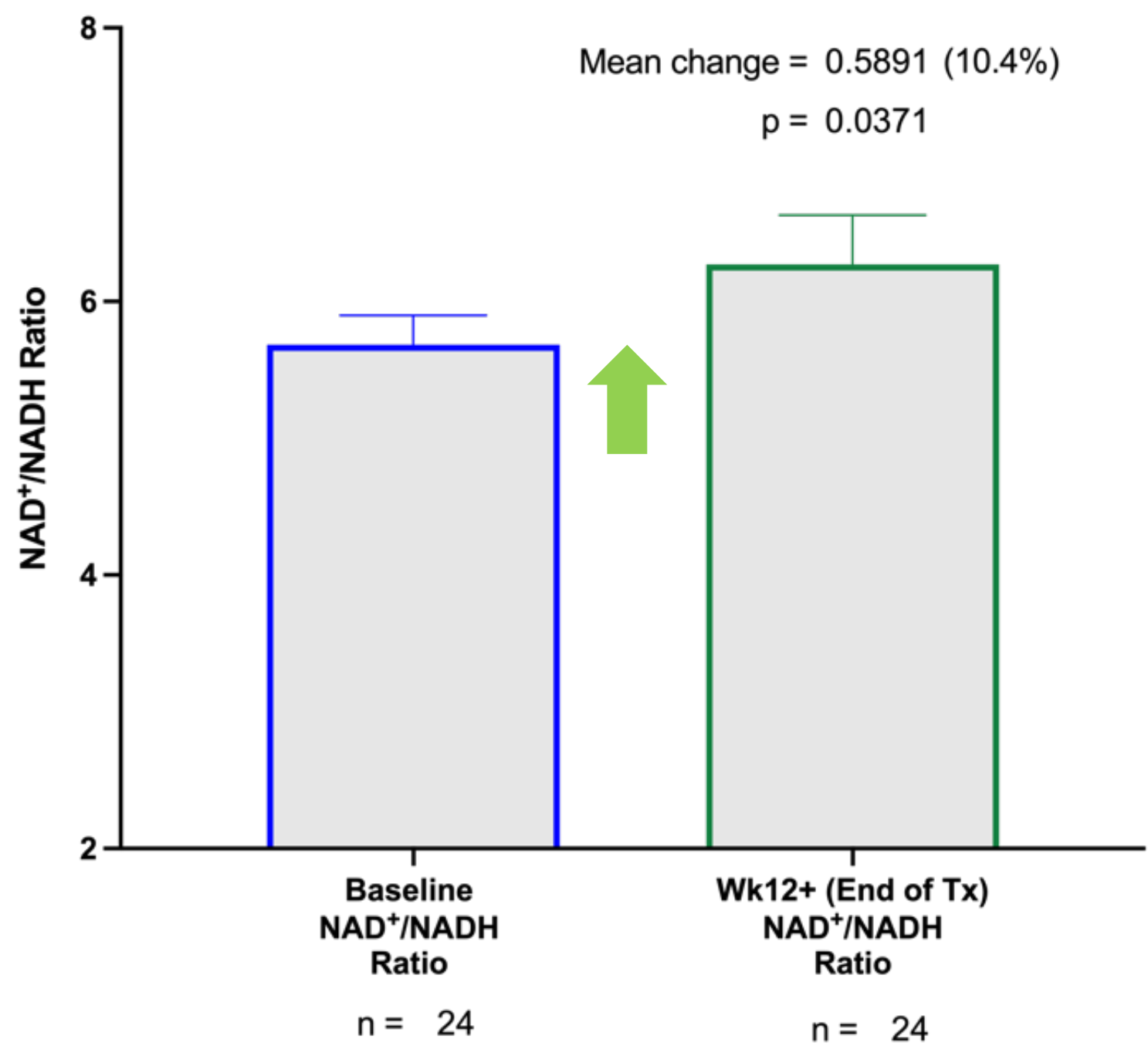
**Study Objective:** to demonstrate target engagement for CNM-Au8 on CNS biomarkers related to energetic effects in the brain using Magnetic Resonance Spectroscopy (<sup>31</sup>P-MRS)

Results demonstrated a potentially meaningful 10% improvement in NAD<sup>+</sup>/NADH ratio, an essential molecule for energy production<sup>1</sup>

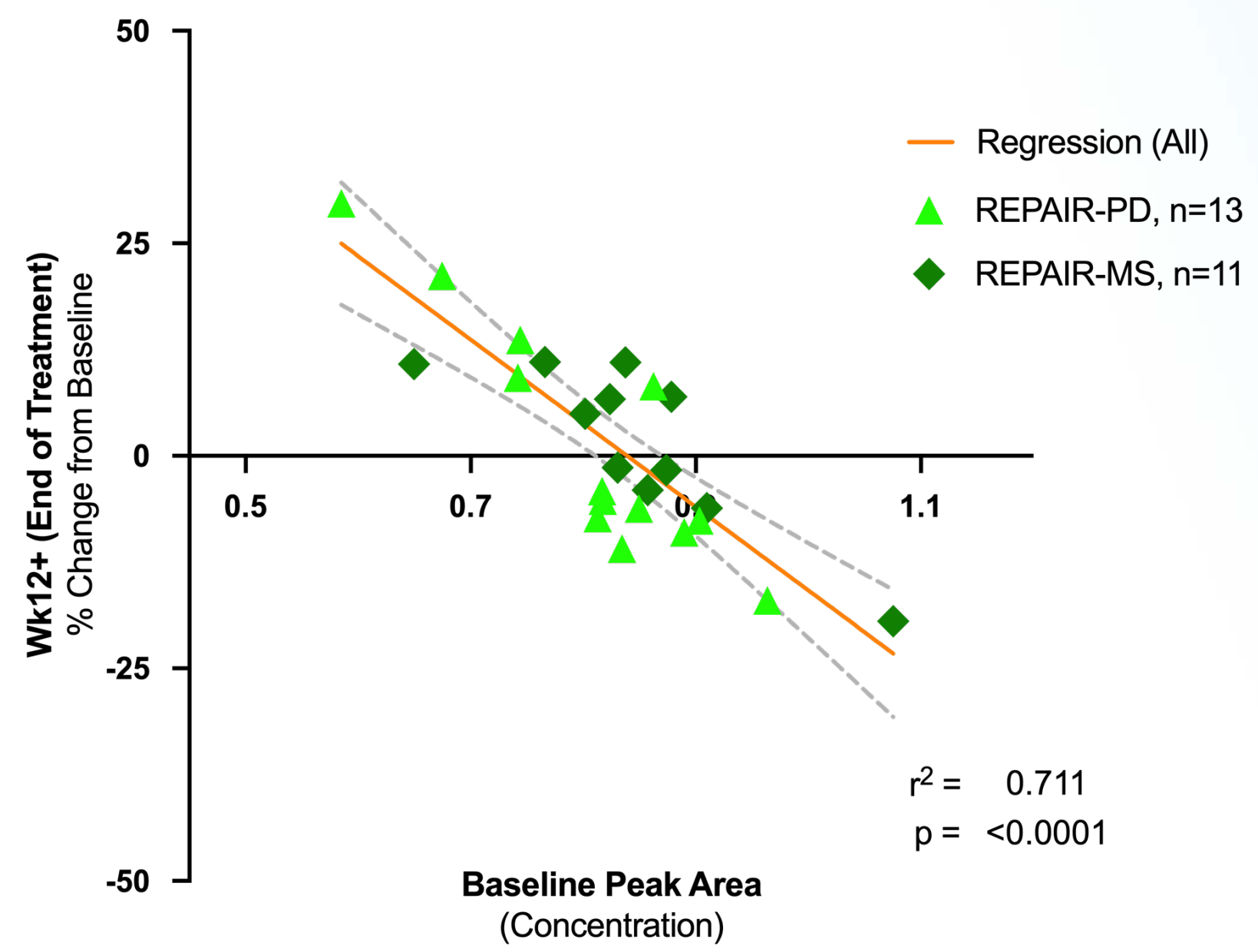
1° Endpoint (integrated PD & MS)<sup>2</sup>

Exploratory (ATP Normalization)

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



**REPAIR Integrated Analysis**  
<sup>31</sup>P-MRS Change in β-ATP at End of Treatment  
 Full Volume Coil <sup>31</sup>P Signal Area (Integral)  
 Exploratory Endpoint, Percent (%) Change vs. Baseline Value



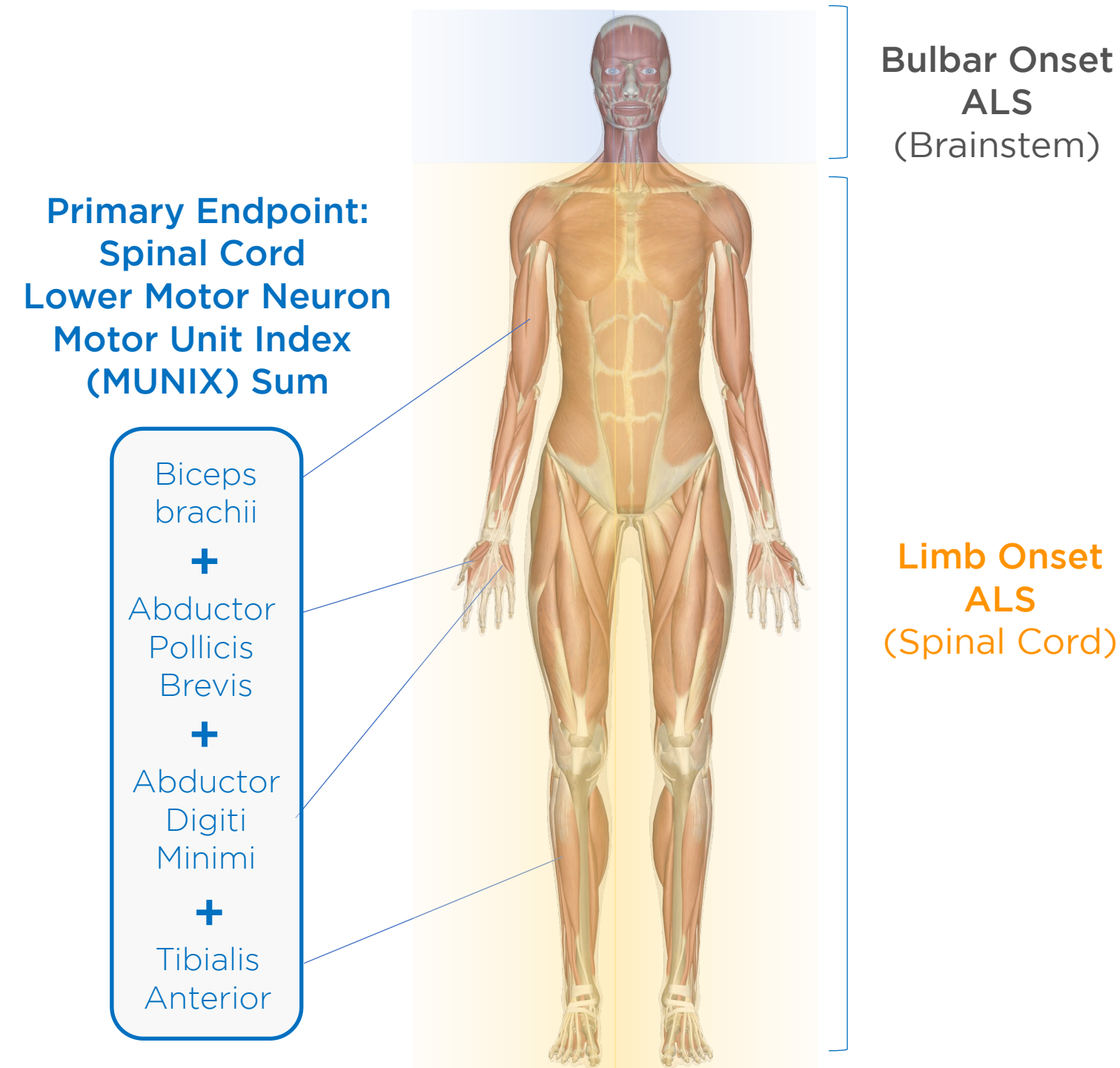
- RepairPD**  
Early Parkinson's Disease
- RepairMS**  
Stable Relapsing MS
- RepairMS**  
Non-Active Progressive MS (Ongoing)



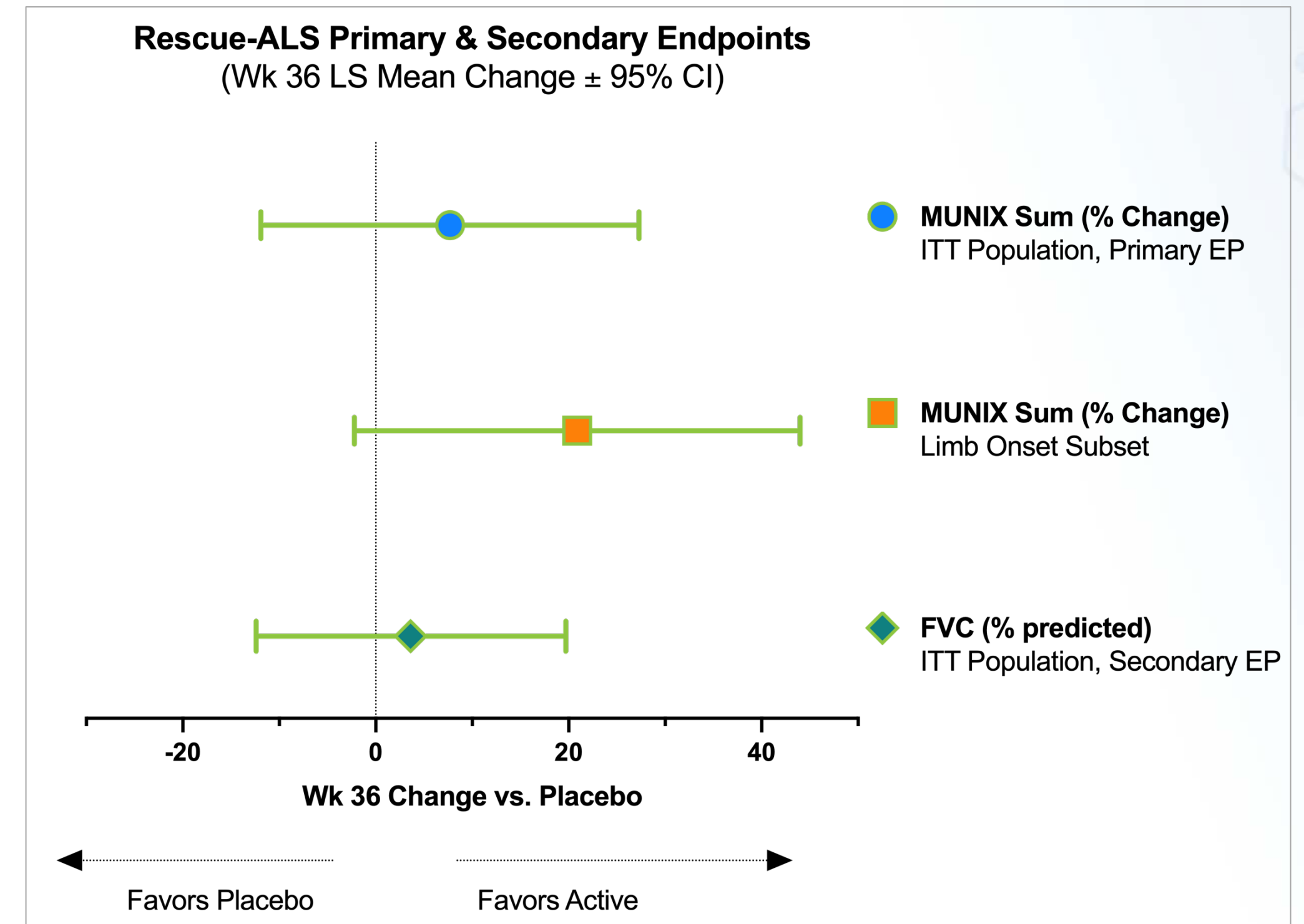
# RESCUEALS Encouraging Efficacy Signals in Phase 2 Trial

**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



Results in favor of CNM-Au8 treatment but study underpowered



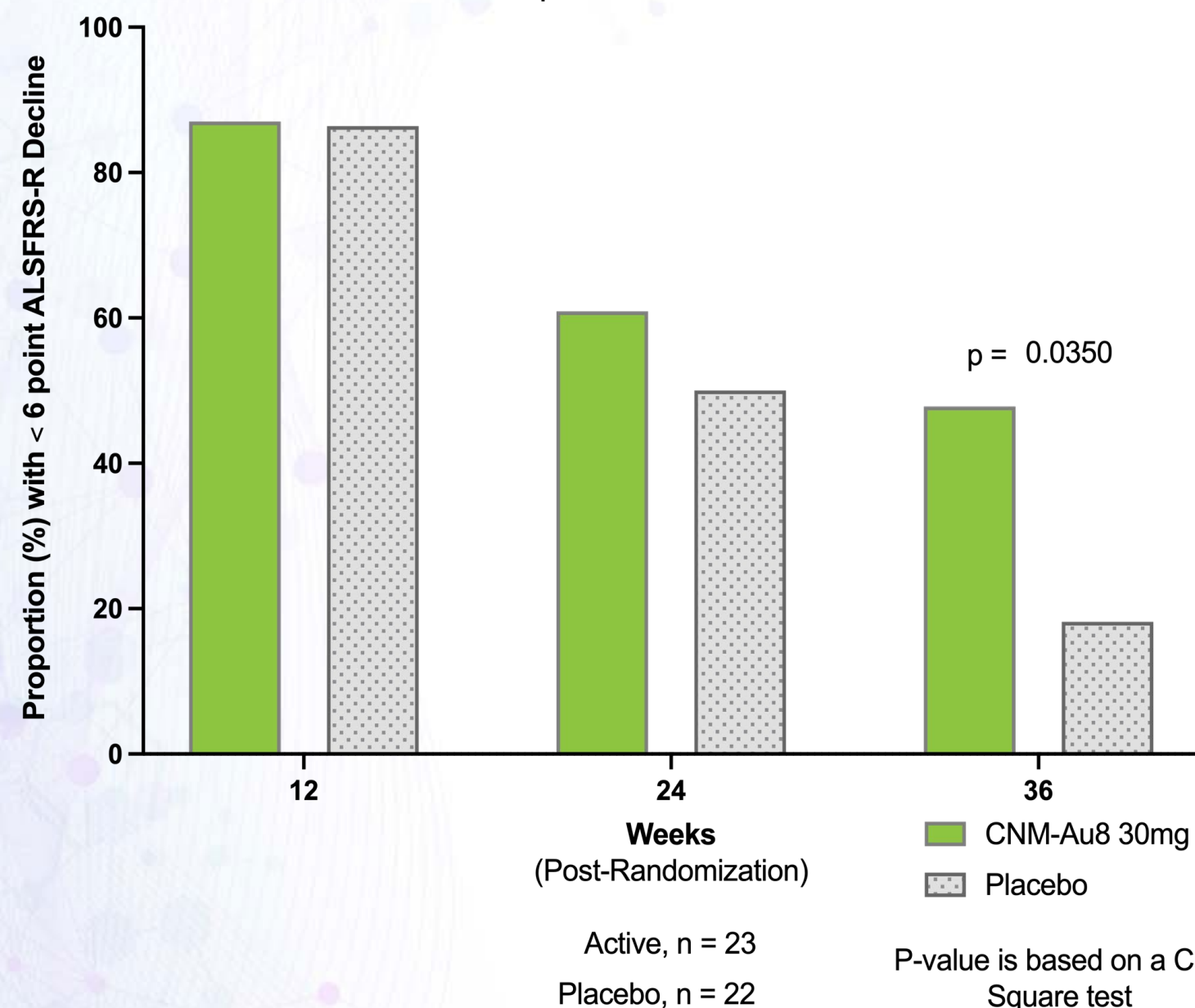
RESCUEALS

# CNM-Au8 Improved Patient Function and QOL, and Slowed ALS Disease Progression

## Across Multiple Pre-specified Exploratory Endpoints

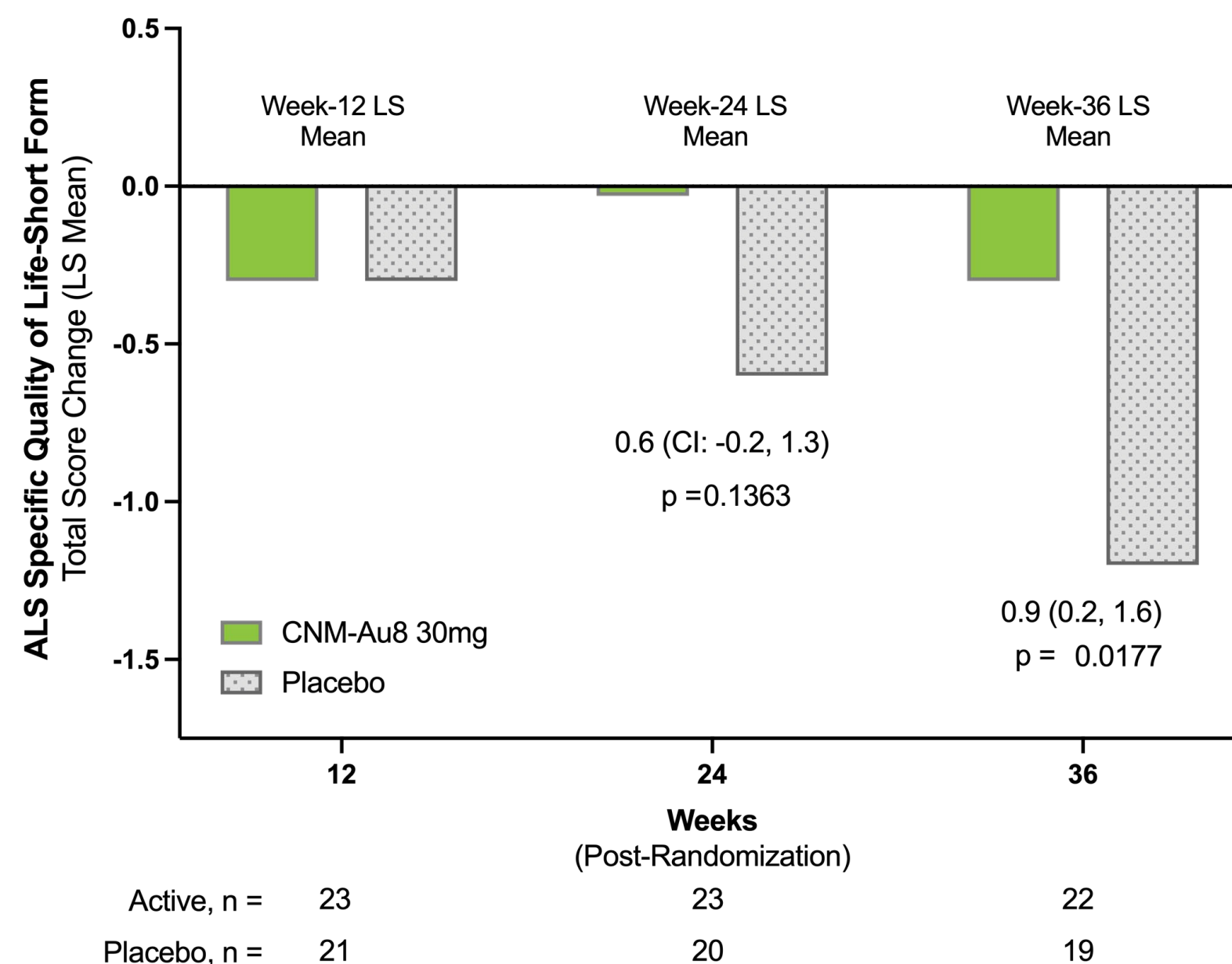
### Proportion with <6 point decline

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



### ALS Specific QOL

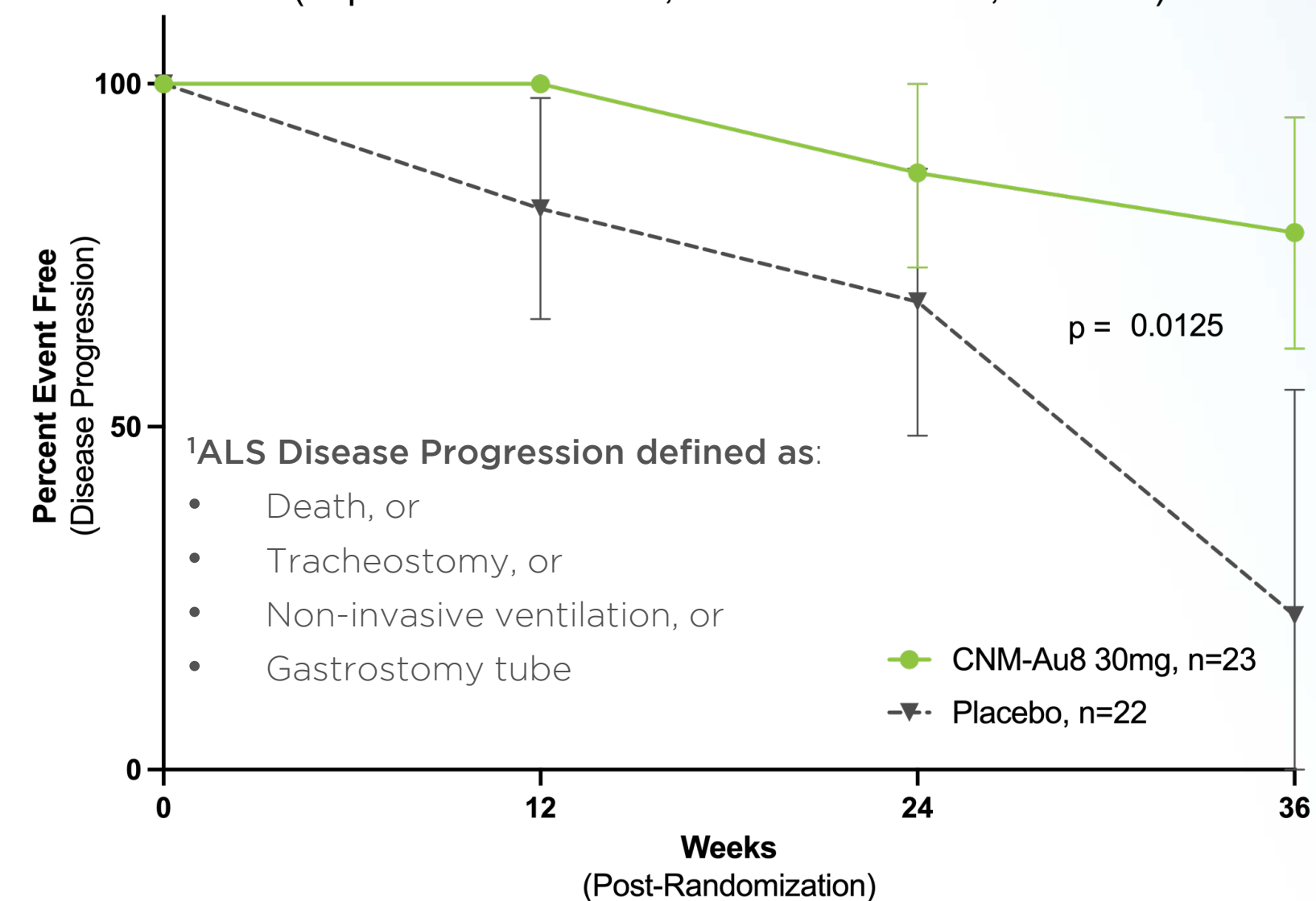
**ALS Specific Quality of Life-Short Form Total Score**  
RESCUE-ALS Exploratory Endpoint  
Mixed Model Repeat Measure (ITT Population, All Randomized)  
LS Mean Difference



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

### ALS Disease Progression

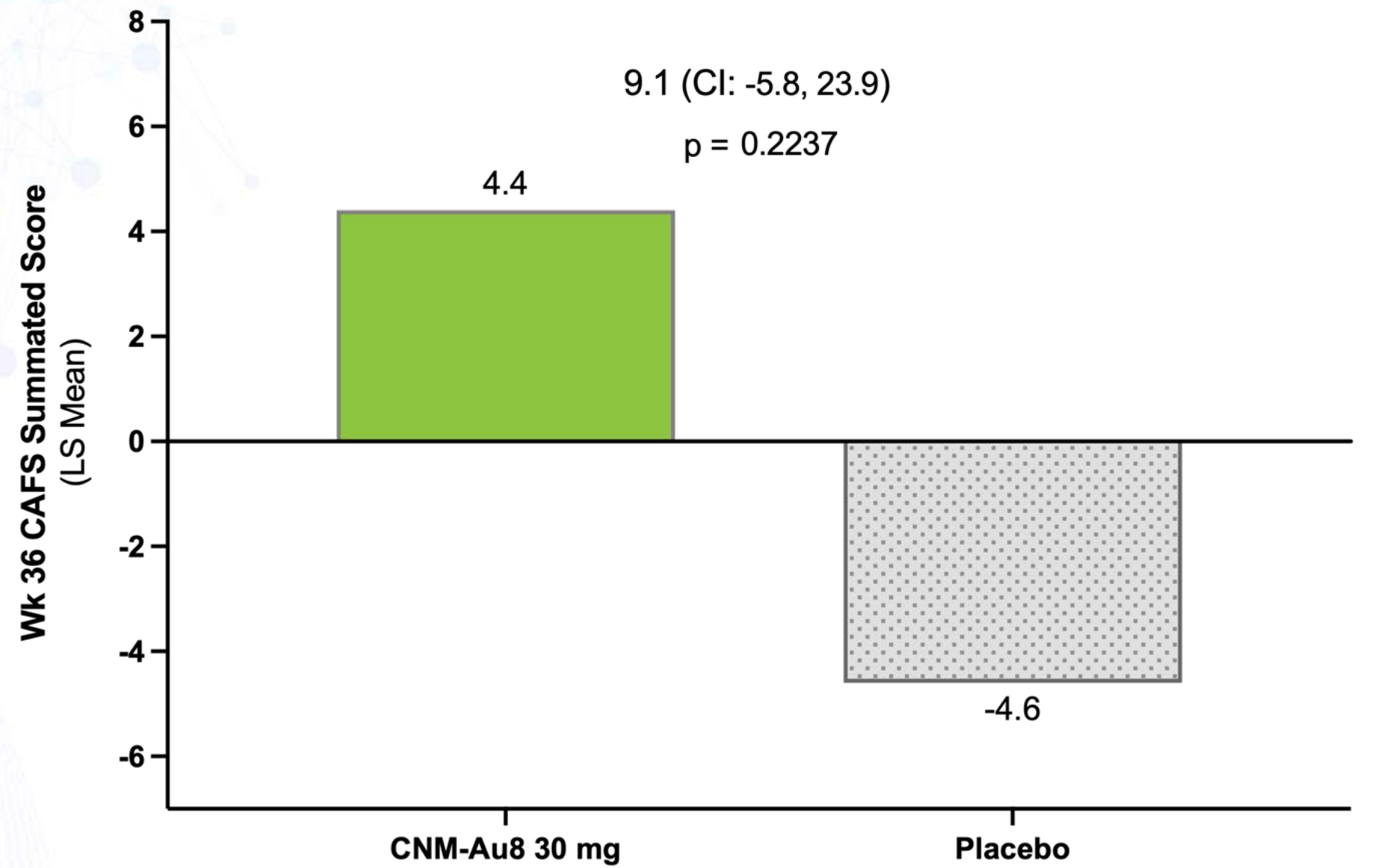
**ALS Disease Progression<sup>1</sup>**  
RESCUE-ALS Exploratory Endpoint  
ITT Population, All Randomized  
(Kaplan-Meier Estimate, Percent Event Free, ± 95% CI)



# RESCUEALS 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



Active, n = 23  
 Placebo, n = 22

■ CNM-Au8 30 mg  
 ▨ Placebo

P-value is based on ANCOVA model with baseline ENCALS score as a covariate. Change in ALSFRS-R total score and date of death were combined to determine the CAFS score.

### CAFS

Survival

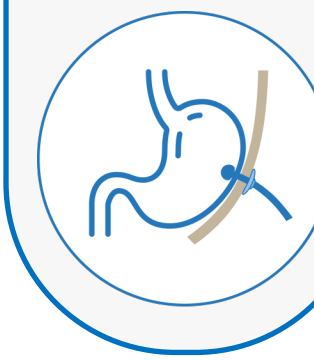


ALSFRS-R Decline



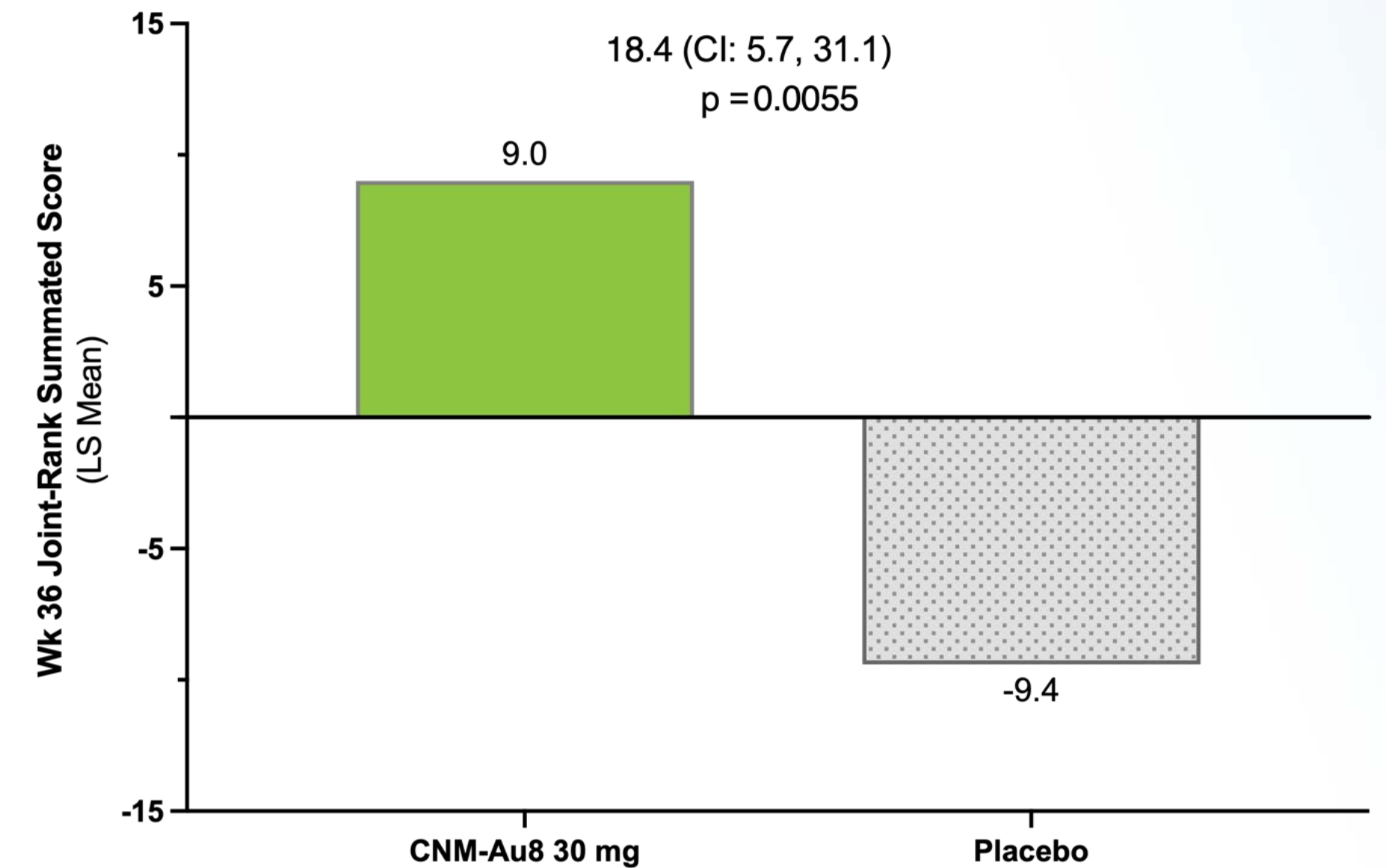
### Modified CAFS

King's Clinical Stage 4



## 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



Active, n = 23  
 Placebo, n = 22

■ CNM-Au8 30 mg  
 ▨ Placebo

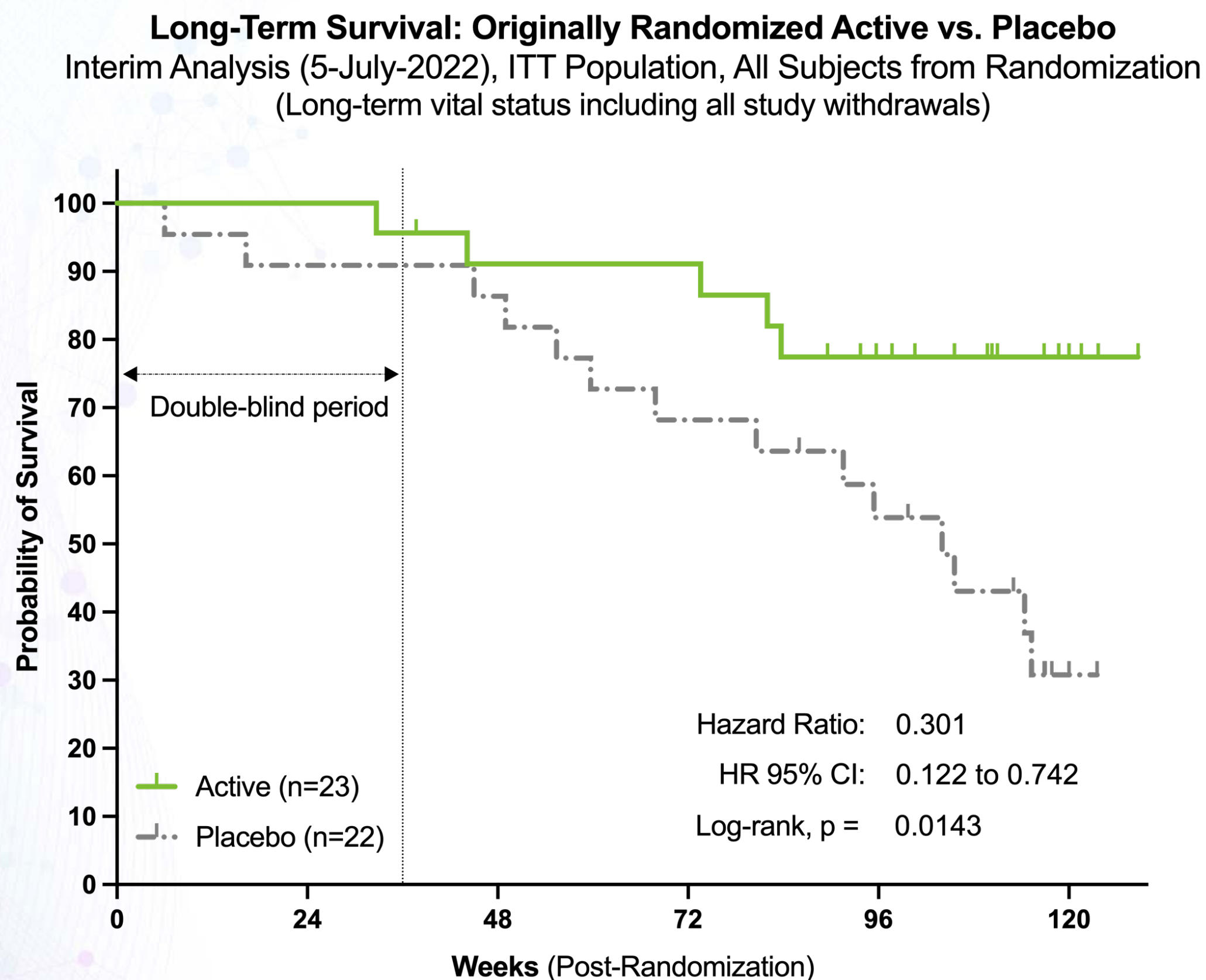
P-value is based on ANCOVA model with baseline ENCALS score as a covariate. Change in ALSFRS-R total score, date of non-invasive ventilation or gastrostomy, and date of death were combined to determine the joint-rank score.



**RESCUEALS**

# 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

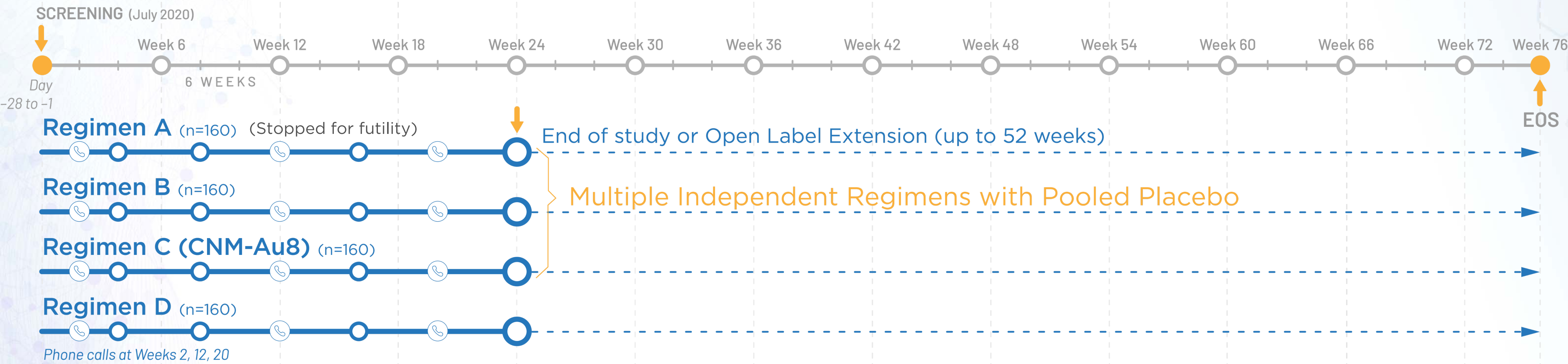
\*9-month delayed treatment start or no treatment

At Risk (n)

CMM-Au8:	23	23	20	20	14	6
Placebo:	22	20	19	15	11	2

**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**

**Registration Study: 24-Week Treatment Period** (3:1 randomization, 120 active [30mg, 60mg]: 40 placebo)



End of study or Open Label Extension (up to 52 weeks)

Multiple Independent Regimens with Pooled Placebo

1°

**Change in ALSFRS-R slope + survival**

Weighted Average of Slope Change & Hazard Ratio

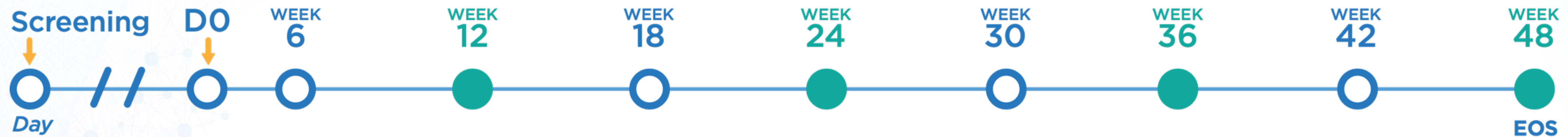
Weighting based on # of Mortality Events

2°

- CAFS (Joint-Rank) Survival & ALSFRS-R
- Slow Vital Capacity
- Survival

**Anticipated topline data:**  
 3Q 2022

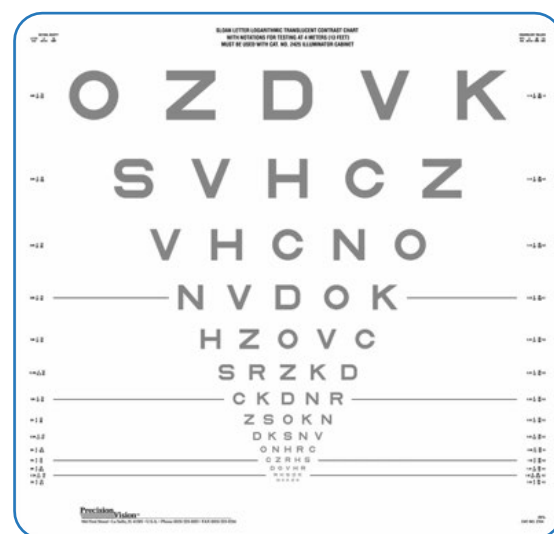
Phase 2 Study: 48-Week Placebo-Control Treatment Period 2:1 Randomization (Active [15mg, 30 mg]: Placebo)



- 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

1°

Change in Low Contrast Letter Acuity (LCLA)

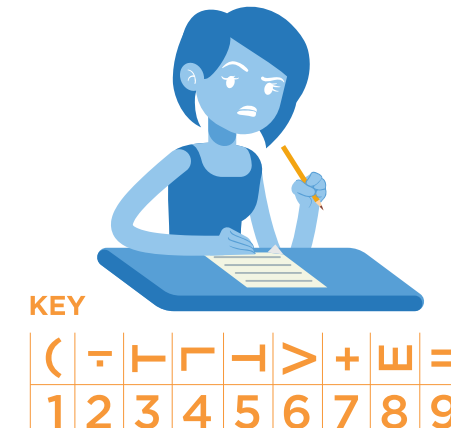


2°

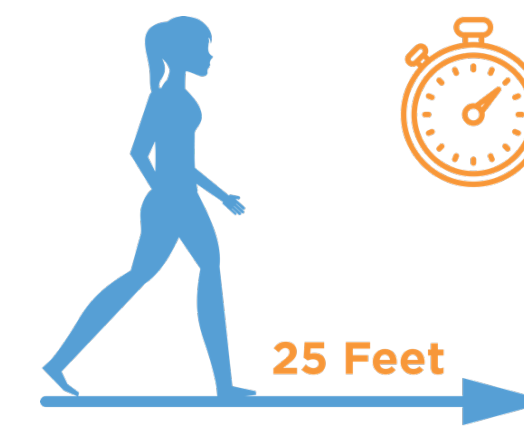
Change in modified MS Functional Composite (mMSFC)



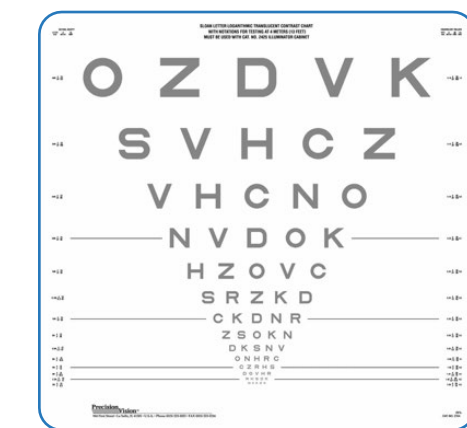
9HPT



SDMT



T25FWT



LCLA



# 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)

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

# 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**

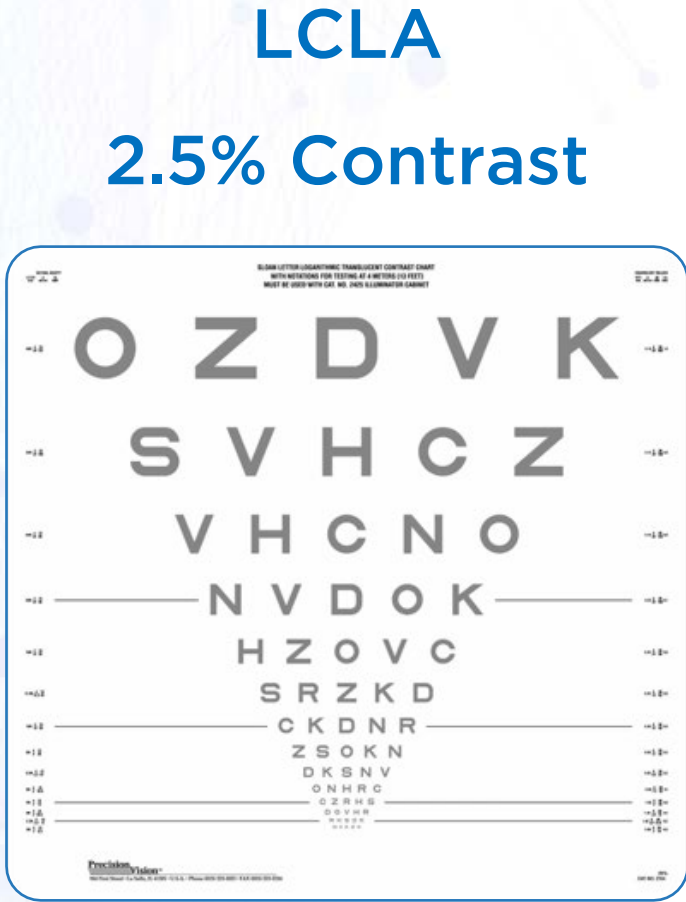
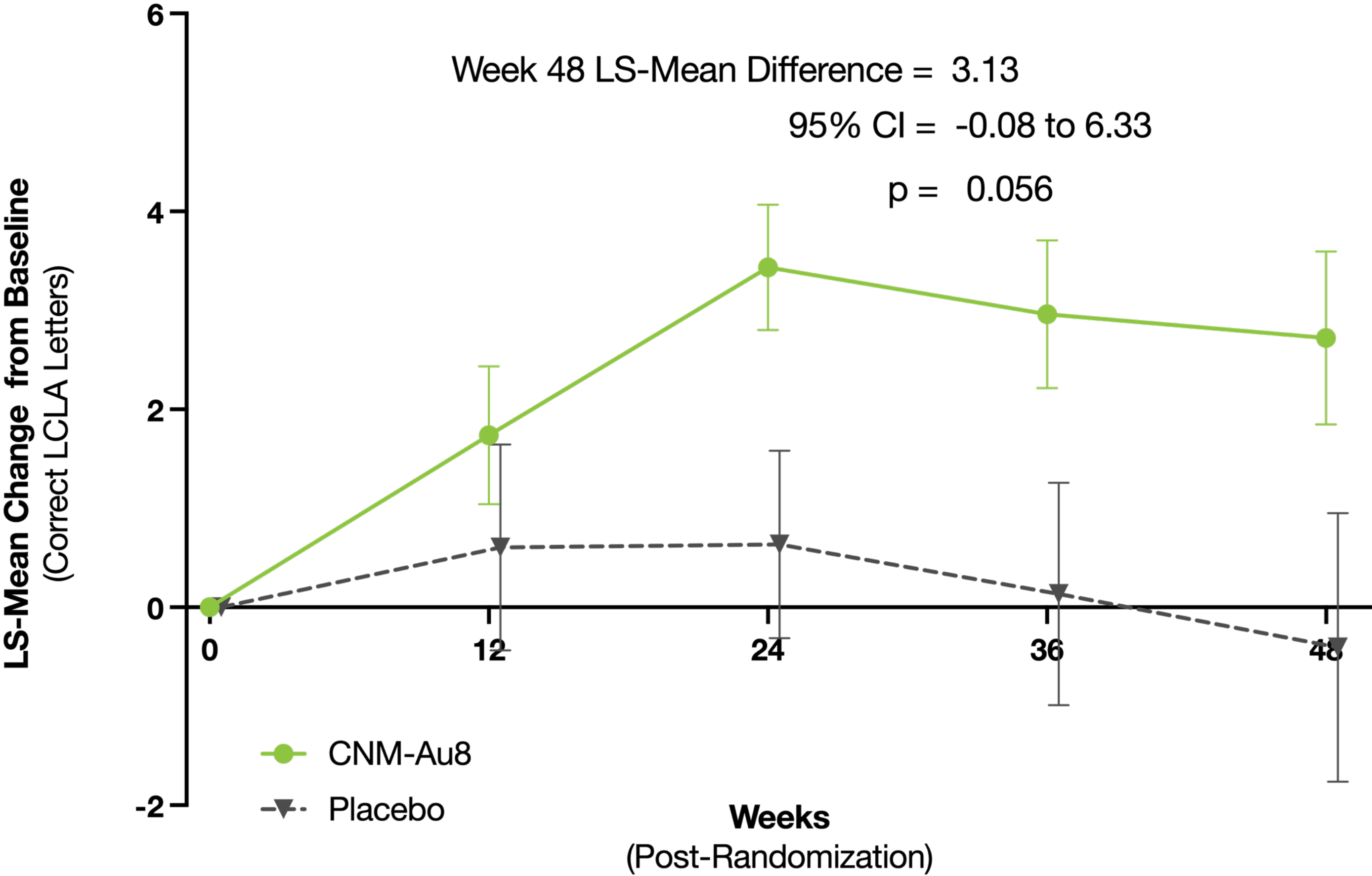
- Change in mobility assist device (cane to walker) for T25FW (n=1)
- Invalid data from 1 of 11 sites (n=9) with LCLA testing execution errors
  - Multiple testing locations with different light boxes and varying ambient lighting conditions
  - In consultation with study Principal Investigator and external 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

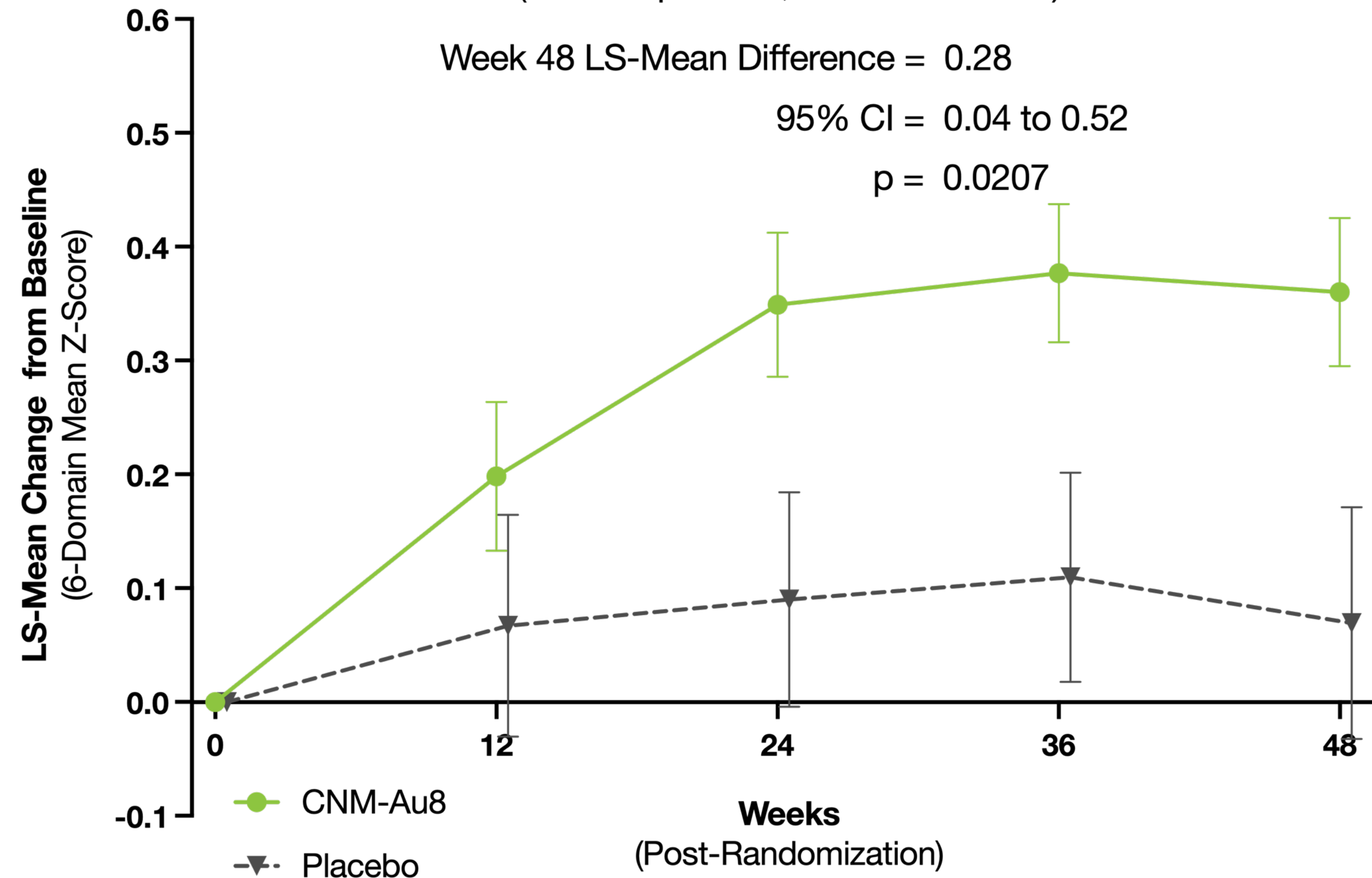
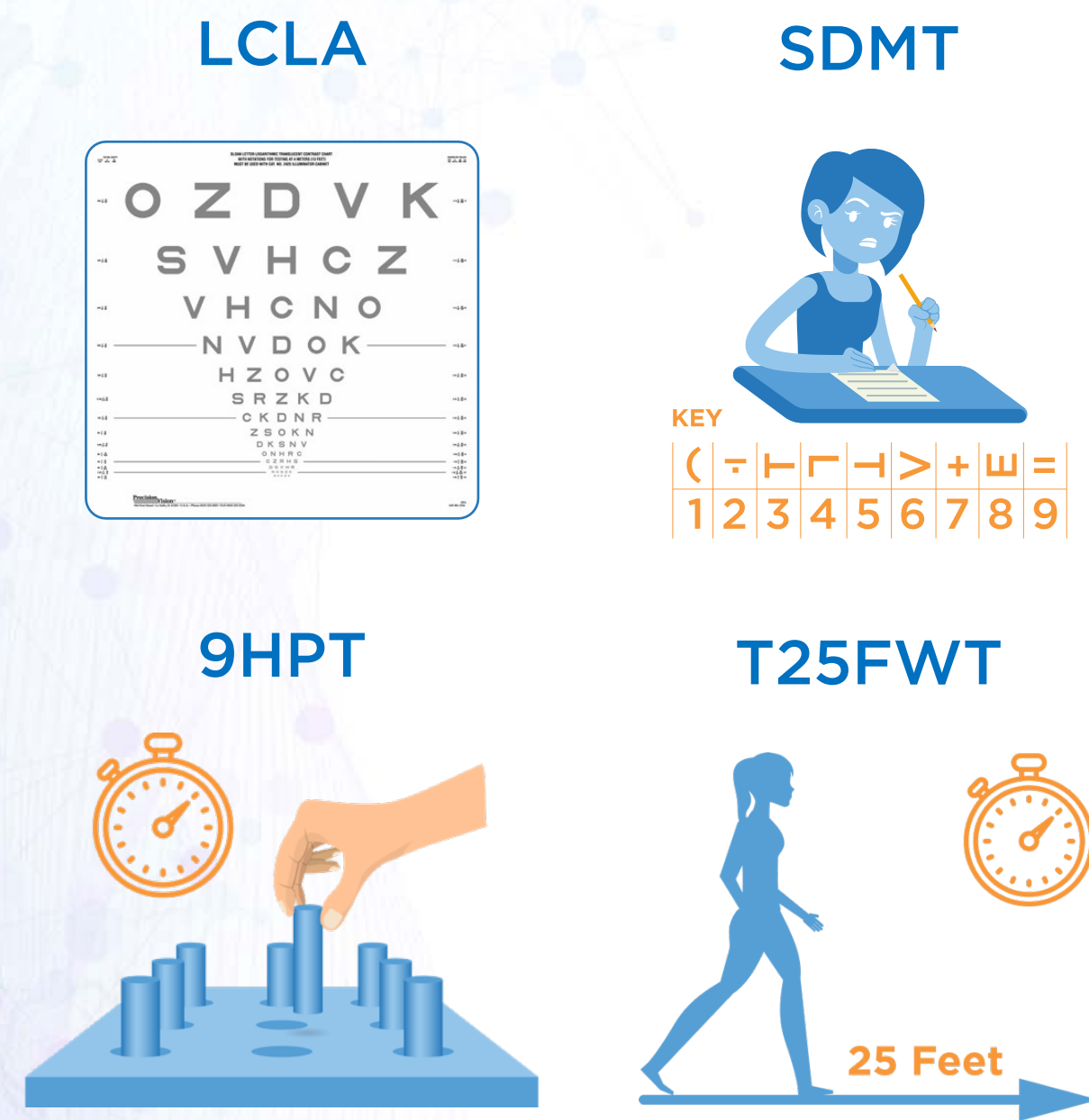
mITT Population, LS Mean ± SEM



# CNM-Au8 demonstrated global neurological improvement by the modified MS functional composite

## Lead 2<sup>nd</sup> EP | (m)MFSC Composite Mean Standardized Change (6-domain)

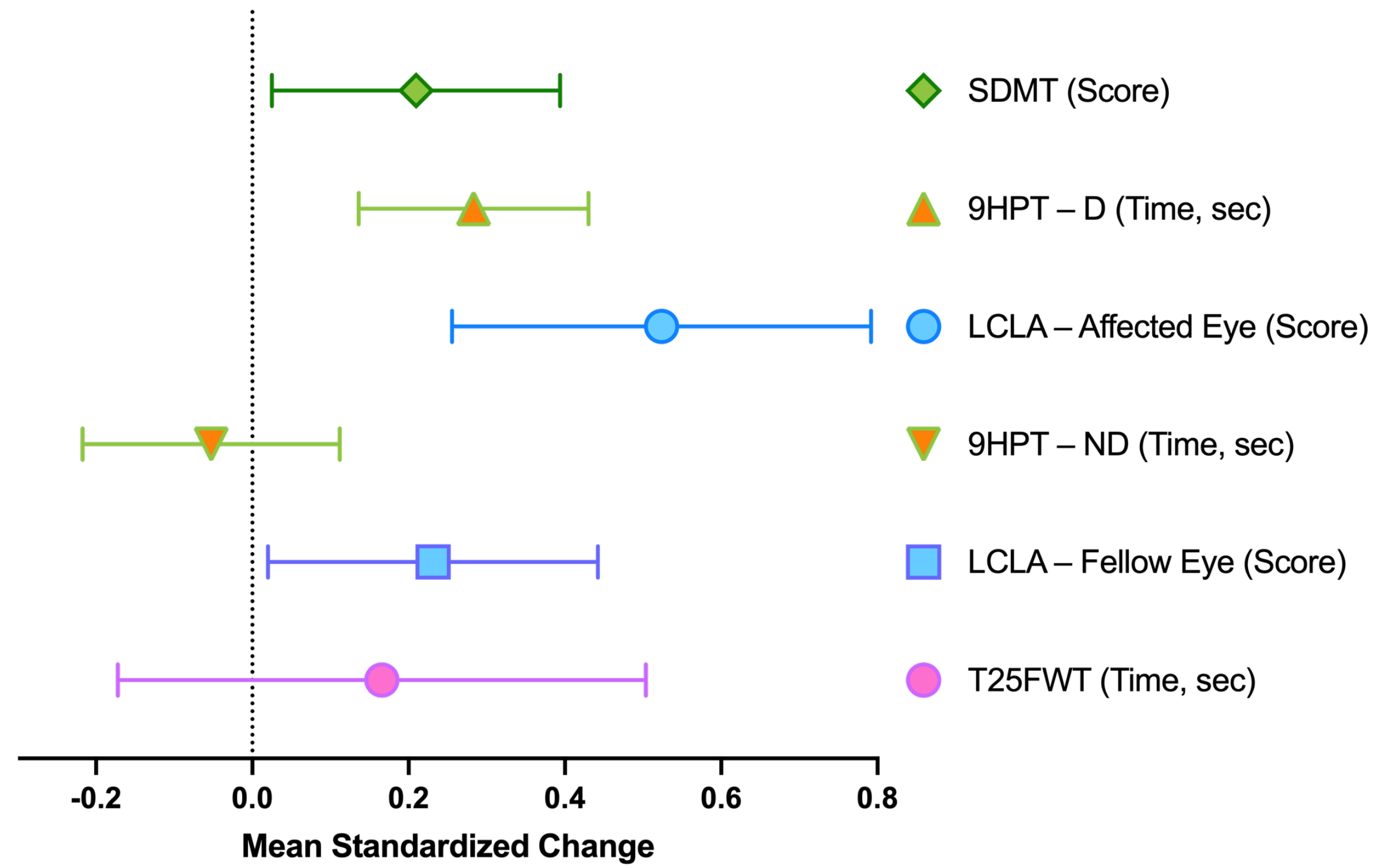
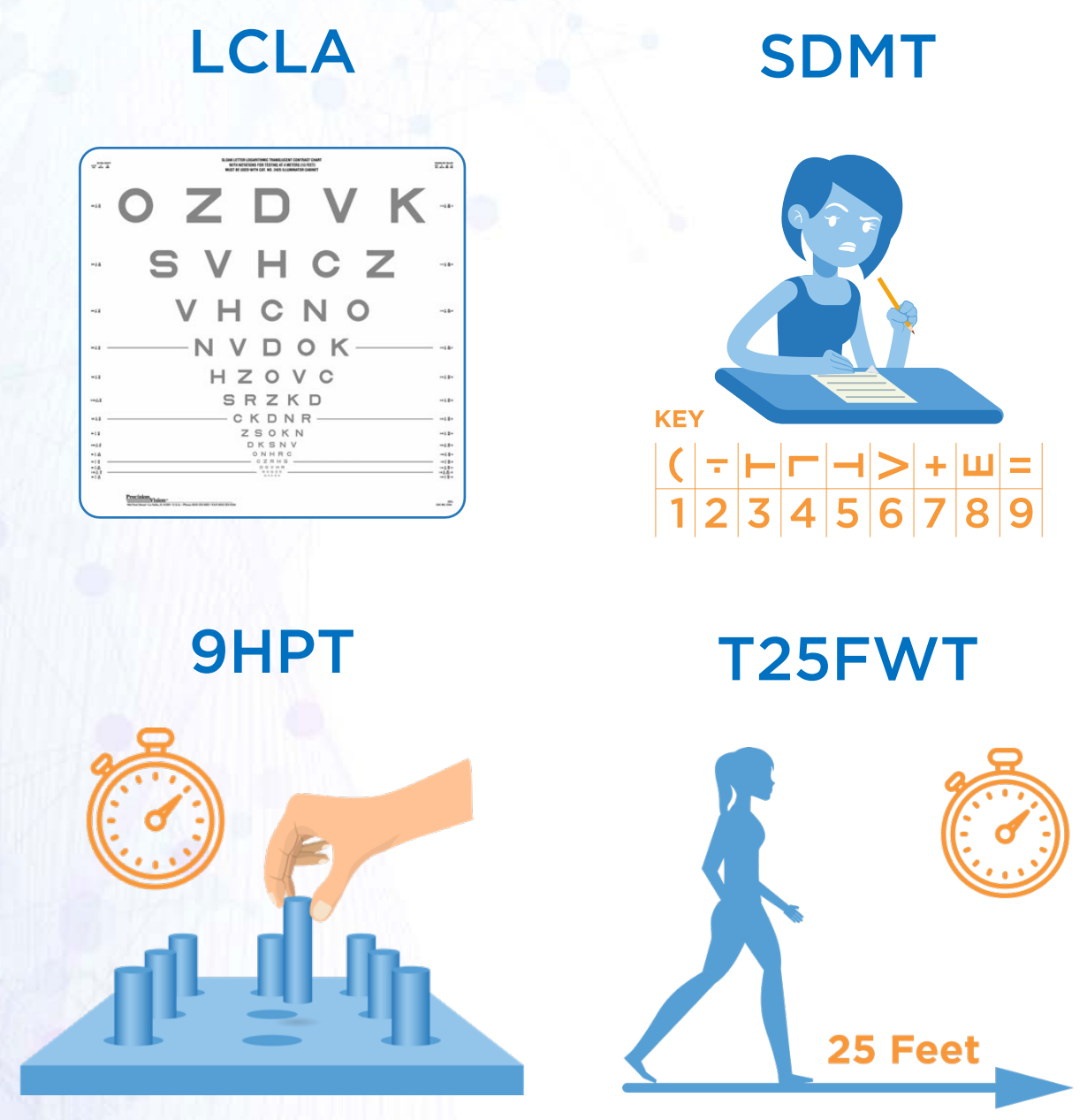
LCLA affected/fellow, 9HPT dominant/non-dominant, SDMT, T25FW (mITT Population, LS Mean ± SEM)



# 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, T25FW  
 (mITT Population, LS Mean Difference ± SEM)  
 CNM-Au8 Less Placebo

Favors Placebo ← No Effect → Favors CNM-Au8 →



Week 48  
 Mixed Model Repeat Measures

# CNM-Au8 treatment improved functional outcomes

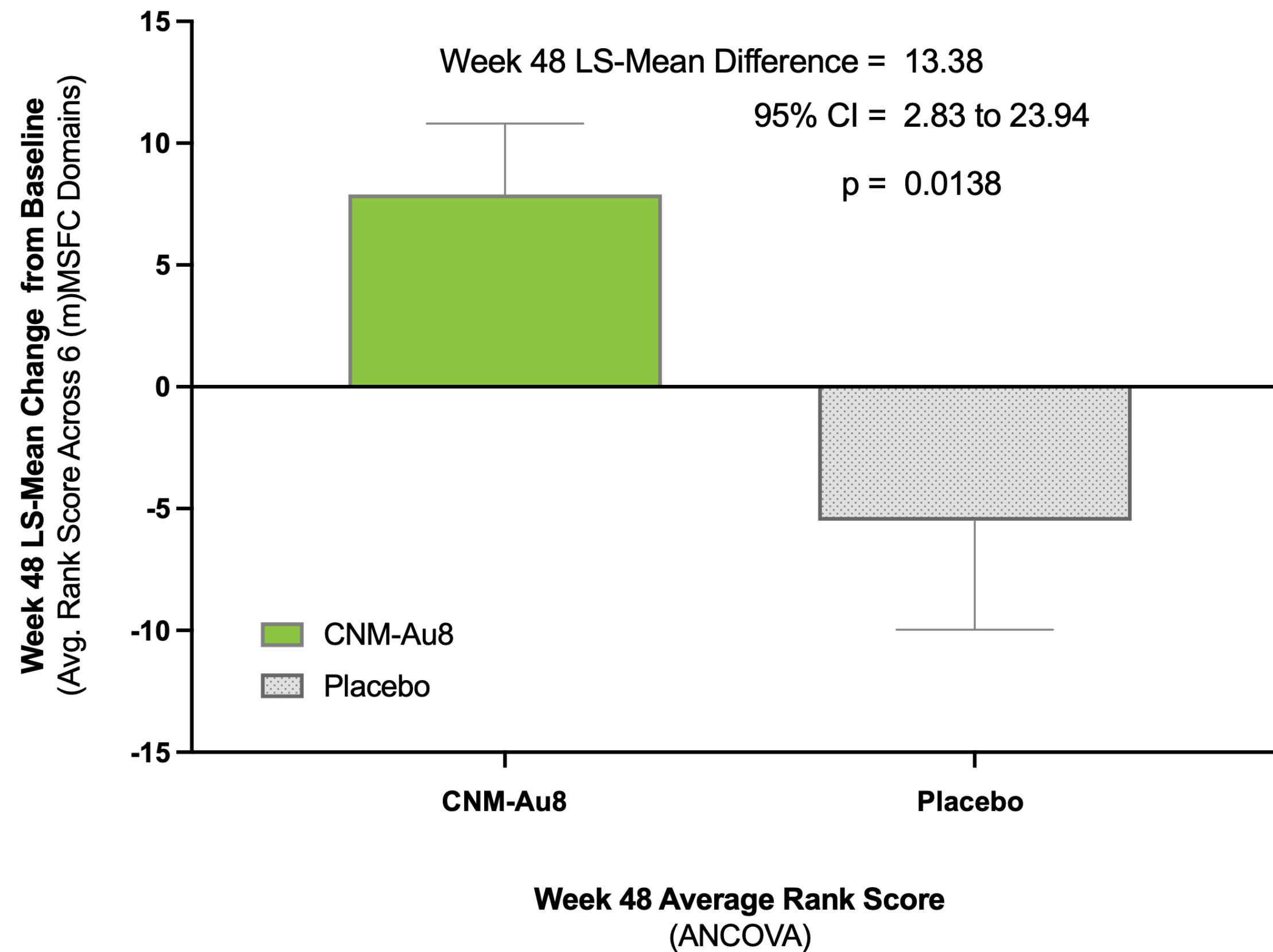
## Improvement relative to placebo decline

Score all subjects versus all other subjects by each mMSFC domain

If...	Score
Better function than comparison	+1
Same function as comparison	0
Worse function than comparison	-1

### 2<sup>nd</sup> 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)



# 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

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

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

First therapy to demonstrate global neurological improvement in MS patients on top of background DMT standard of care

## Independent quantitative biomarkers of myelin and axonal integrity

VEP amplitude & latency improvements

Structural MRI improvements

Preservation of retinal structure

# Strong IP & Manufacturing Capability

Extensive Patent Portfolio With Protection Through 2035<sup>a</sup> & Proprietary Trade Secrets; Plus 7-year Orphan Drug Designation, and Scalable to Commercialization

## Global Patent Status <sup>b</sup>

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

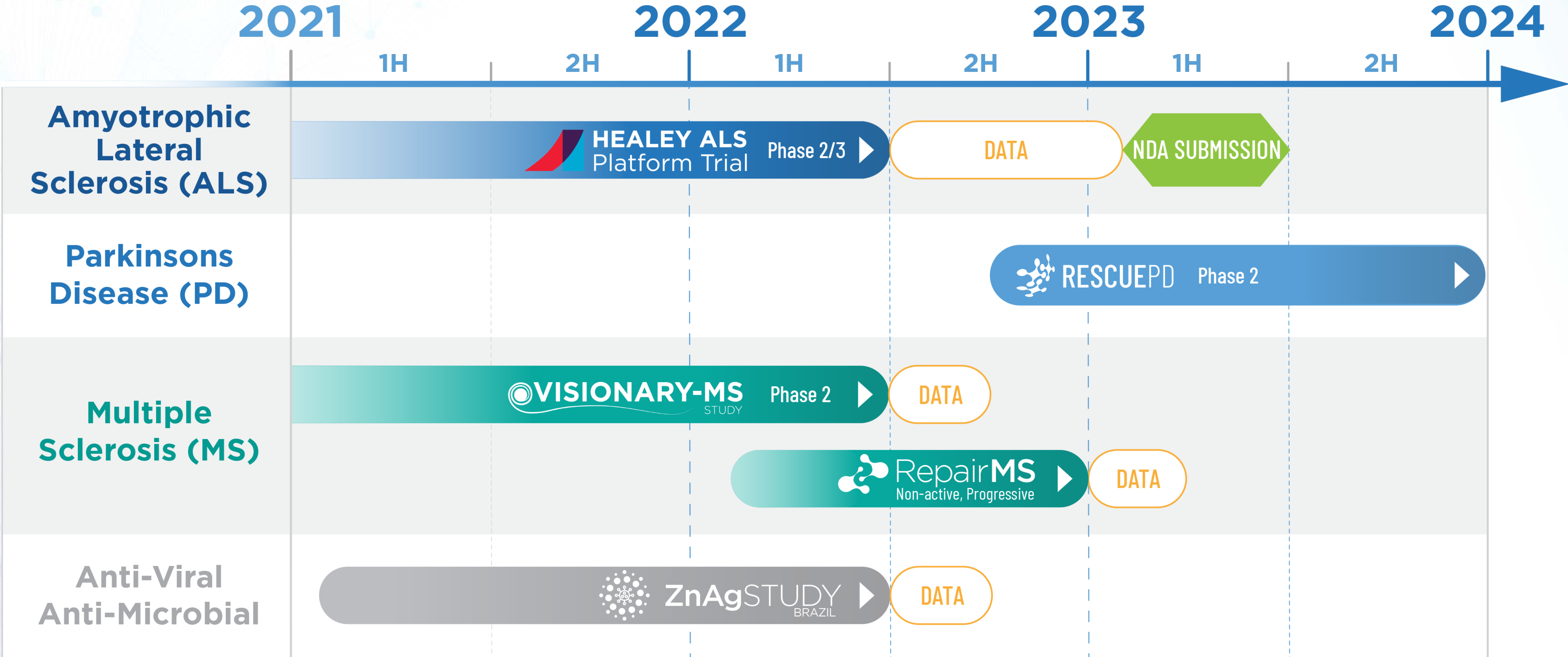
Trough Flow, Temp, Pressure

Concentration & Filtration

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



# Anticipated Timeline & Upcoming Milestones




Sufficient Cash to Hit Key Milestones in 2022

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

# CLENE | Growing Phase 2 Evidence Supports CNM-Au8 Commercial Potential


CNM-Au8<sup>®</sup>  
a gold nanocrystal  
suspension, in  
development as the  
first cellular  
energetic catalyst  
to remyelinate<sup>1</sup> &  
protect neurological  
function



ALS  
Registration  
Trial

Topline data in  
3Q 2022<sup>2</sup>

>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<sup>®</sup>)  
platform



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



**CLene**  
NANOMEDICINE

**Clene Inc.**

**HQ & Clinical Development**

6550 South Millrock Drive, Suite G50  
Salt Lake City, UT 84121

**R&D and Manufacturing**

500 Principio Parkway, Suite 400  
North East, MD 21901

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