VISIONARY-MS STUDY

Phase 2 Results

In Stable RRMS Participants with Chronic Optic Neuropathy

Michael Barnett, MBBS PhD FRACP FRCP

On behalf of the VISIONARY-MS Investigators

CLene NANOMEDICINE

Disclosures

- The University of Sydney received industry standard financial renumeration as a clinical trial site
- I am a consulting research director for Sydney Neuroimaging Analysis Centre (SNAC), which was contracted to analyse blinded MRI and VEP data
- I am a consulting physician to RxPx Cor
- I have received institutional support for research from Biogen, Merck, Novartis, Roche, BMS and Sanofi Genzyme
- I have received institutional support for speaking, participation in advisory boards or consulting from Biogen, Merck, Novartis, Roche, BMS, Sanofi Genzyme and Autobahn Therapeutics

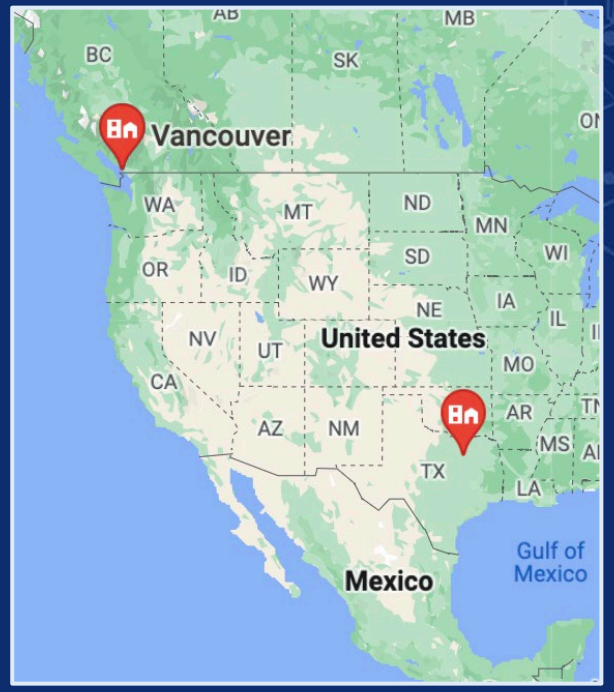
Acknowledgements

- We thank the study participants and their families for participating in clinical research
- We thank the site investigators for their research excellence and dedication to patients

Australia[1]

- U. Sydney, Brain Mind Centre
- U. Sydney, Westmead Hospital
- Austin Health, Melbourne
- The Alfred Hospital, Melbourne
- Princess Alexandra Hospital, Brisbane
- U. Tasmania, Menzies Institute, Hobart
- John Hunter Hospital, Newcastle
- Lyell McEwin Hospital, Adelaide

US & Canada[1]

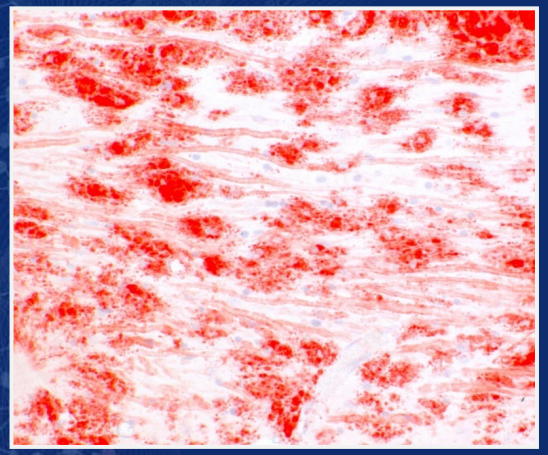


- U. British Columbia, Vancouver
- UT Southwestern, Dallas

[1] Clinical trial sites that enrolled participants

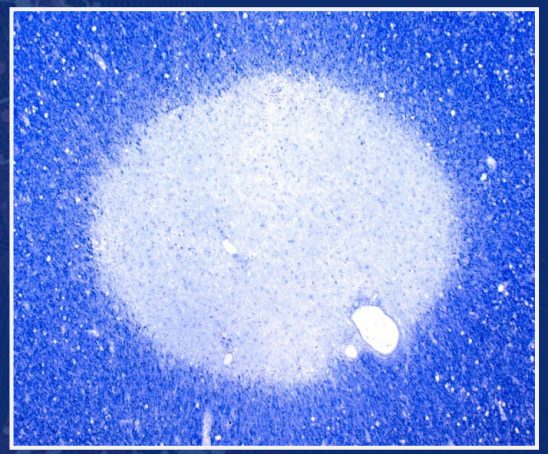
MS Unmet Need: Remyelination and Neuroprotection

Recent Demyelination & Remyelination



Oil Red O - Lipid Stain

Chronic Demyelination

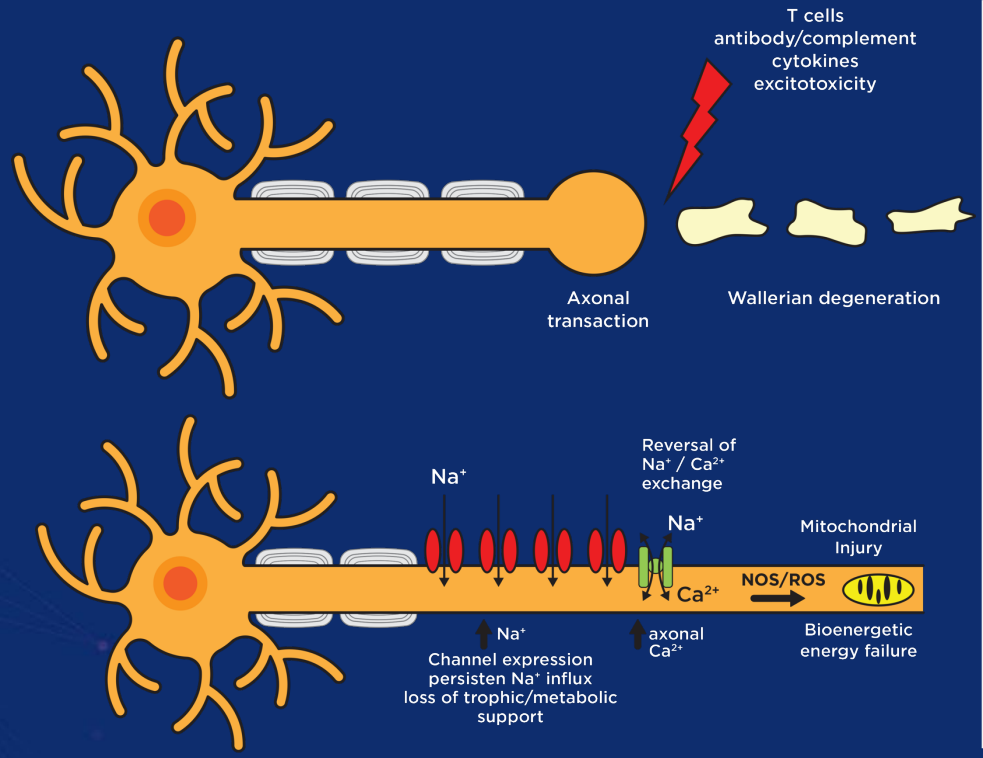


Luxol Fast Blue - Myelin Stain

Long-term Effect of Permanent Demyelination on Axonal Survival in Multiple Sclerosis

Alexandr Klistorner, PhD,* Samuel Klistorner, BSci,* Yuyi You, PhD, Stuart L. Graham, PhD, Con Yiannikas, PhD, John Parratt, PhD, and Michael Barnett, PhD

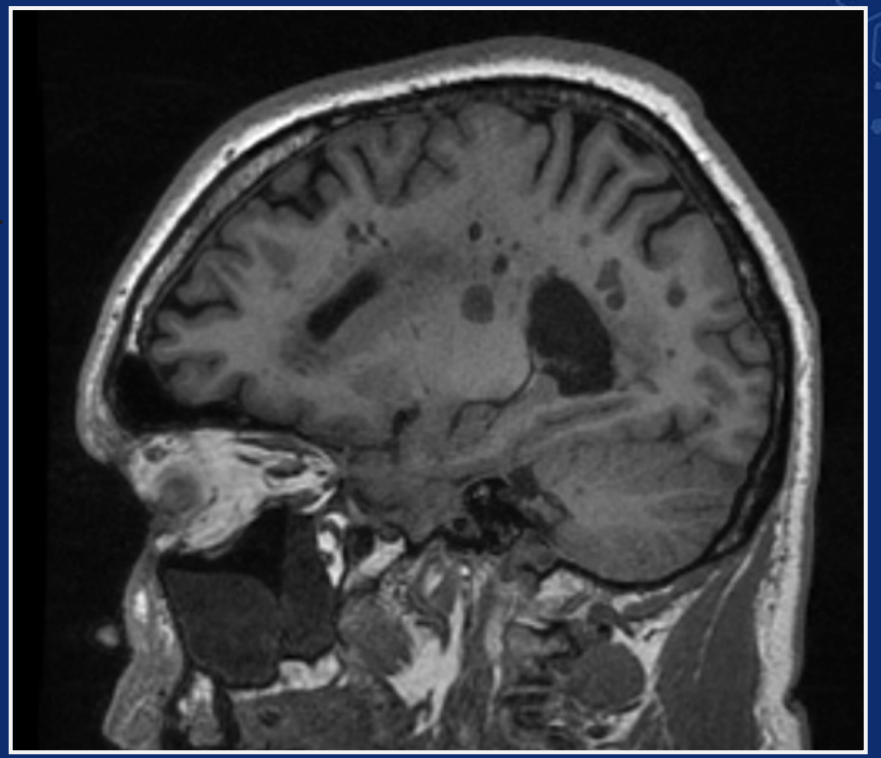
Mechanisms of Axonal Injury In Inflammatory Demyelinating Diseases



Evidence of progressive tissue loss in the core of chronic MS lesions: A longitudinal DTI study☆

Alexander Klistorner[a,b,c,*], Chenyu Wang[c,d], Con Yiannikas[e], John Parratt[e], Michael Dwyer[f], Joshua Barton[d], Stuart L. Graham[b], Yuyi You[a,b], Sidong Liu[a,c,d], Michael H. Barnett[c,d]

"Black Holes" Reflecting Severe Axonal Loss in MS Lesions



[1] Barnett et al. Curr Opin Neurol. 2016 Jun;29(3):213-21. [2] Klistorner et al. Neuroimage Clin 2017;Dec 8;17:1028-1035. [3] Klistorner et a. Neurol Neuroimmunol Neuroinflamm. 2022 Mar 3;9(3):e1155.

CNM-Au8 | Cellular Energetic Nanocatalyst

VISIONARY-MS STUDY

CNM-Au8 Oral Suspension

Clean Surfaced, Highly Faceted Nanocrystals

Mechanistic Effects
In Neurons and Glia[1]

- ↑ Increased NAD
- ↑ Increased ATP
- ↓ Decreased reactive oxygen species
- ↑ Increased proteostasis

Improved Energy Production and Utilization

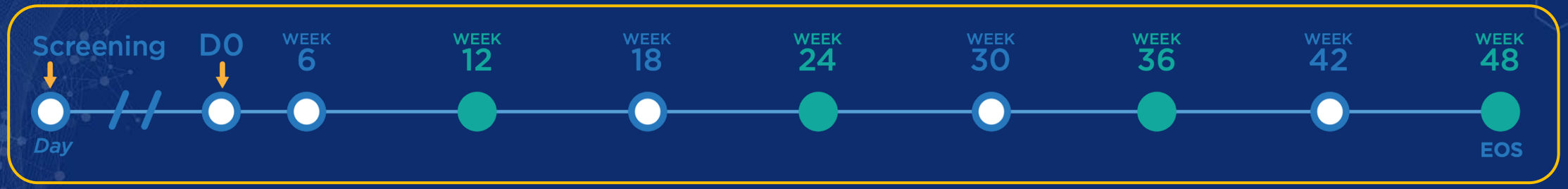
[1] Robinson et al. Sci Rep. 2020 Feb 11;10(1):1936

CLene NANOMEDICINE

Phase 2 Trial Design – Change to Week 48

VISIONARY-MS STUDY

- Randomised Double-Blind, 48-week, 2:1 Randomization (Active [15mg, 30 mg]: Placebo)
- n=73 of 150 planned; Study Ended Prematurely Due to Pandemic-related Enrollment Challenges



1° EP

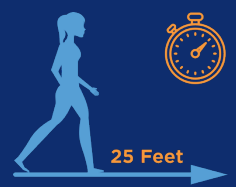
Change in Low Contrast Letter Acuity (LCLA)

2° EP

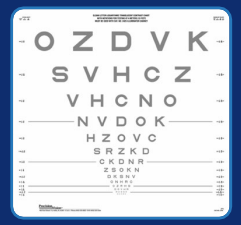
Change in modified MS Functional Composite (mMSFC)
6-domain Z-Score

9HPT
(Dominant / Non-Dominant)

SDMT



T25FWT



LCLA
(Affected / Fellow)

CLene NANOMEDICINE

Analyses

- Modified Intent to Treat (mITT) population excluded data from:
  - ✓ One participant from with change in mobility device (cane to walker)
  - ✓ One site (n=9) with LCLA testing execution errors
- Change to Week 48 was calculated with a mixed model for repeat measures (MMRM) with covariates including baseline value, age, sex, and visit
- CNM-Au8 doses (15mg and 30mg) were combined for these analyses
- Statistical threshold prespecified at p=0.10 [1]

[1] Fox et al. N Engl J Med 2018; 379:846-855. Phase 2 Trial of Ibudilast in Progressive Multiple Sclerosis.

Baseline Demographics

VISIONARY-MS STUDY

- **Stable RRMS participants** with chronic optic neuropathy
- Background DMTs: **92% treated with DMT** (53% monoclonal antibodies, 32% oral)

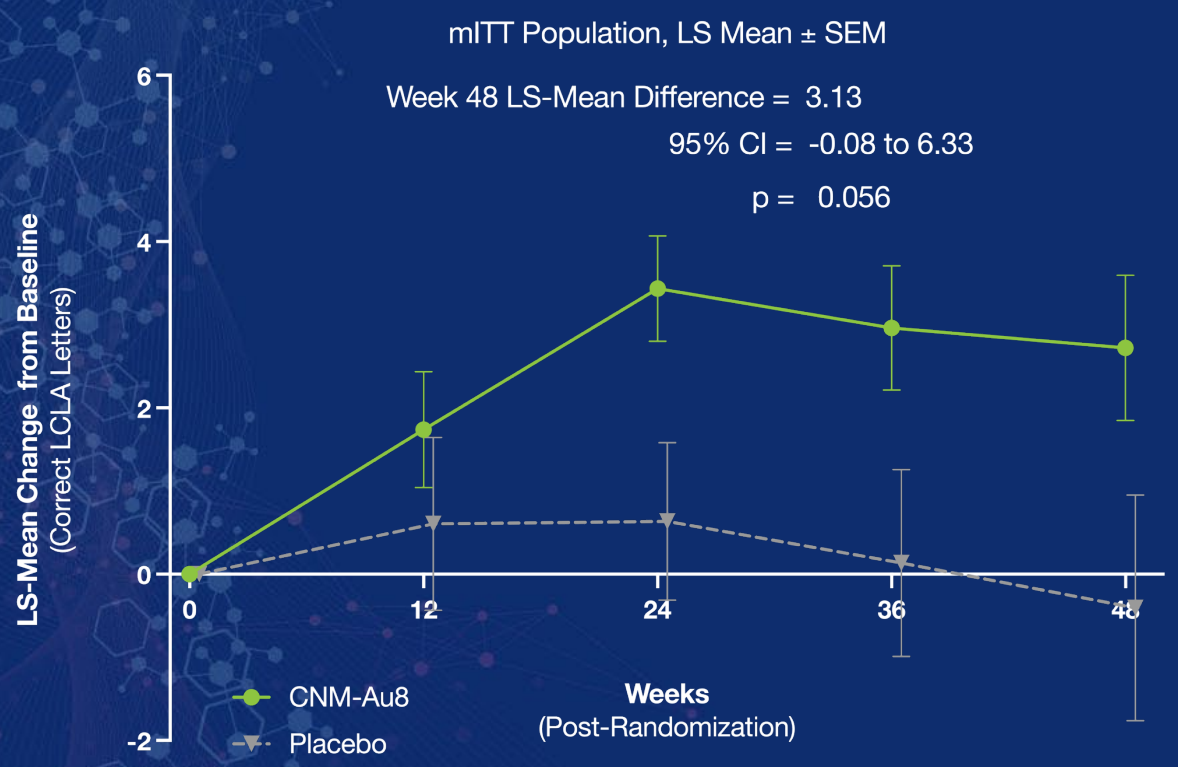
Baseline Value mean (sd), n (%)	**Age** (yrs)	**Female Sex** n, (%)	**Race** n, (%) White	**Weight** (kg)	**EDSS Score**	**Years from Dx**	**Months Since Relapse**
CNM-Au8 15 mg (n=24)	38.4 (10.2)	15 (63%)	23 (96%)	78.0 (17.1)	1.83 (1.3)	6.5 (5.0)	53 (57)
CNM-Au8 30 mg (n=25)	39.6 (7.6)	16 (64%)	24 (96%)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

CLene NANOMEDICINE

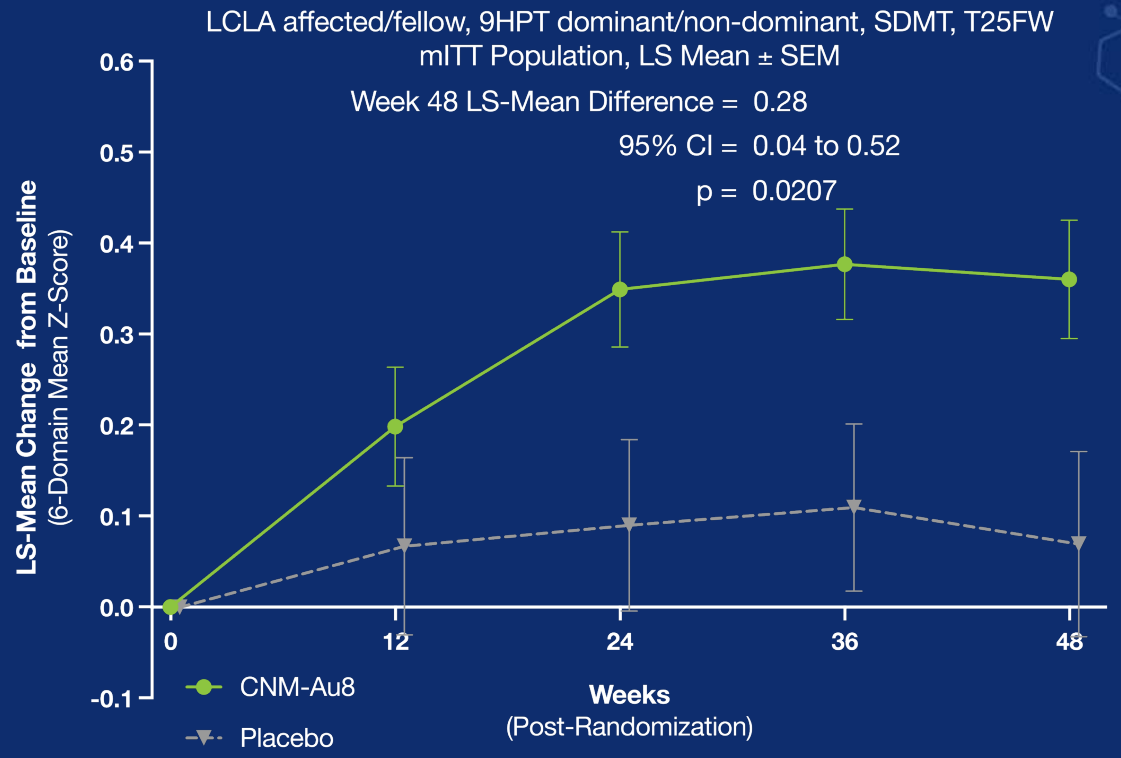
Primary and Secondary Clinical Outcomes Significantly Improved

VISIONARY-MS STUDY

1° | LCLA Change in the Affected Eye



2° | Global Neurological Improvement
(mMFSC Mean Standardized Change)



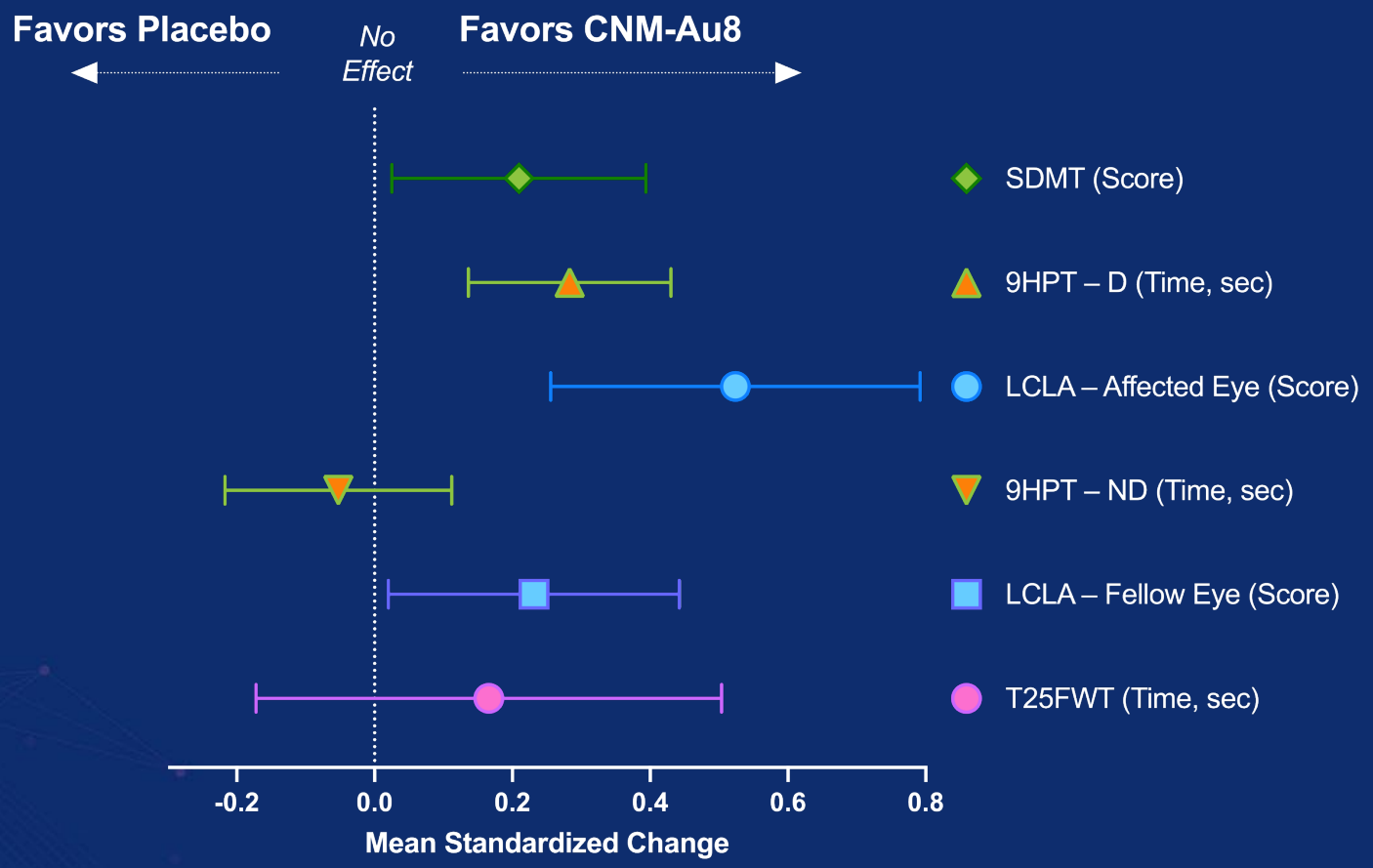
CLene NANOMEDICINE

Improvement Demonstrated Across Neuroaxis

VISIONARY-MS STUDY

mMSFC Individual Domain Changes

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



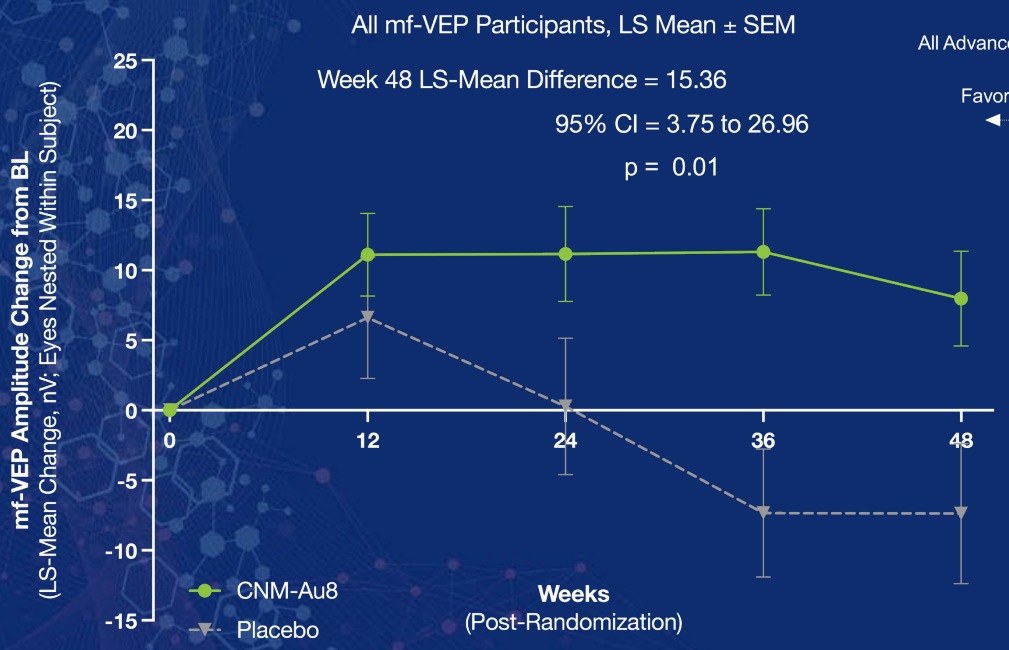
Week 48
Mixed Model Repeat Measures

CLene NANOMEDICINE

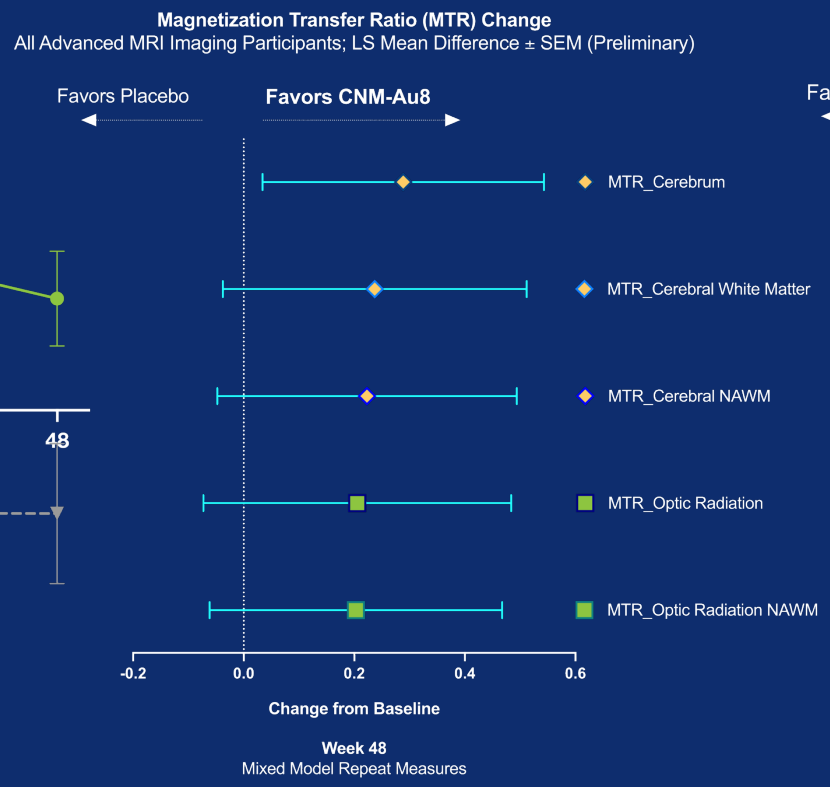
Paraclinical Biomarker Evidence for Improved Axonal & Myelin Integrity (Multi-focal VEP, MTR, and DTI)

VISIONARY-MS STUDY

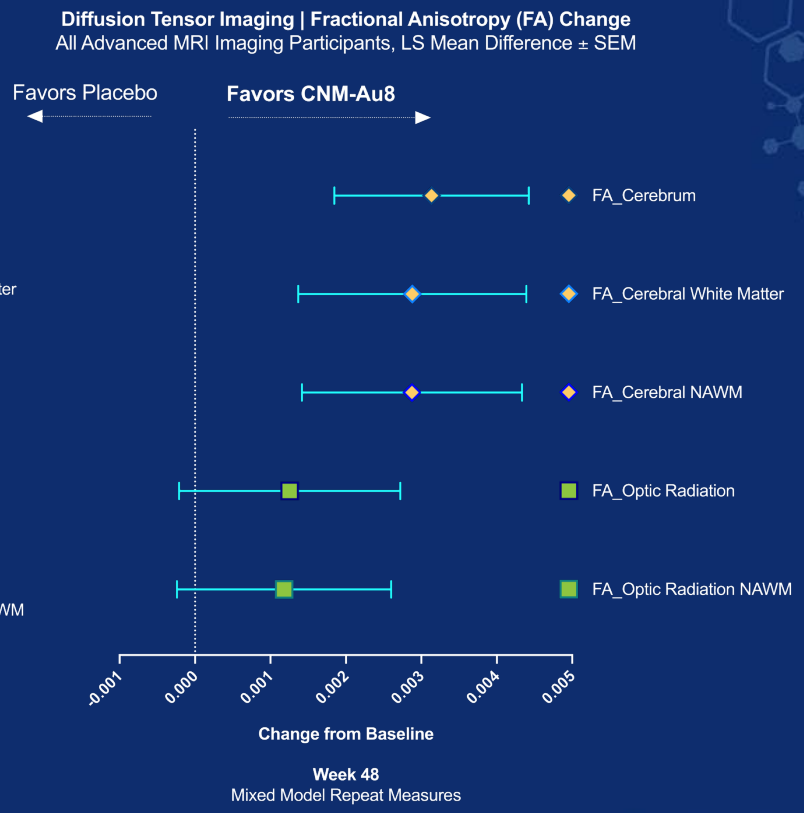
mf-VEP Amplitude
Week 48 Change[1]



MTR (Myelin Integrity)
Week 48 Change[1]



Fractional Anisotropy
(Axonal Integrity) Wk48 Change[1]



[1] Exploratory Endpoints

CLene NANOMEDICINE

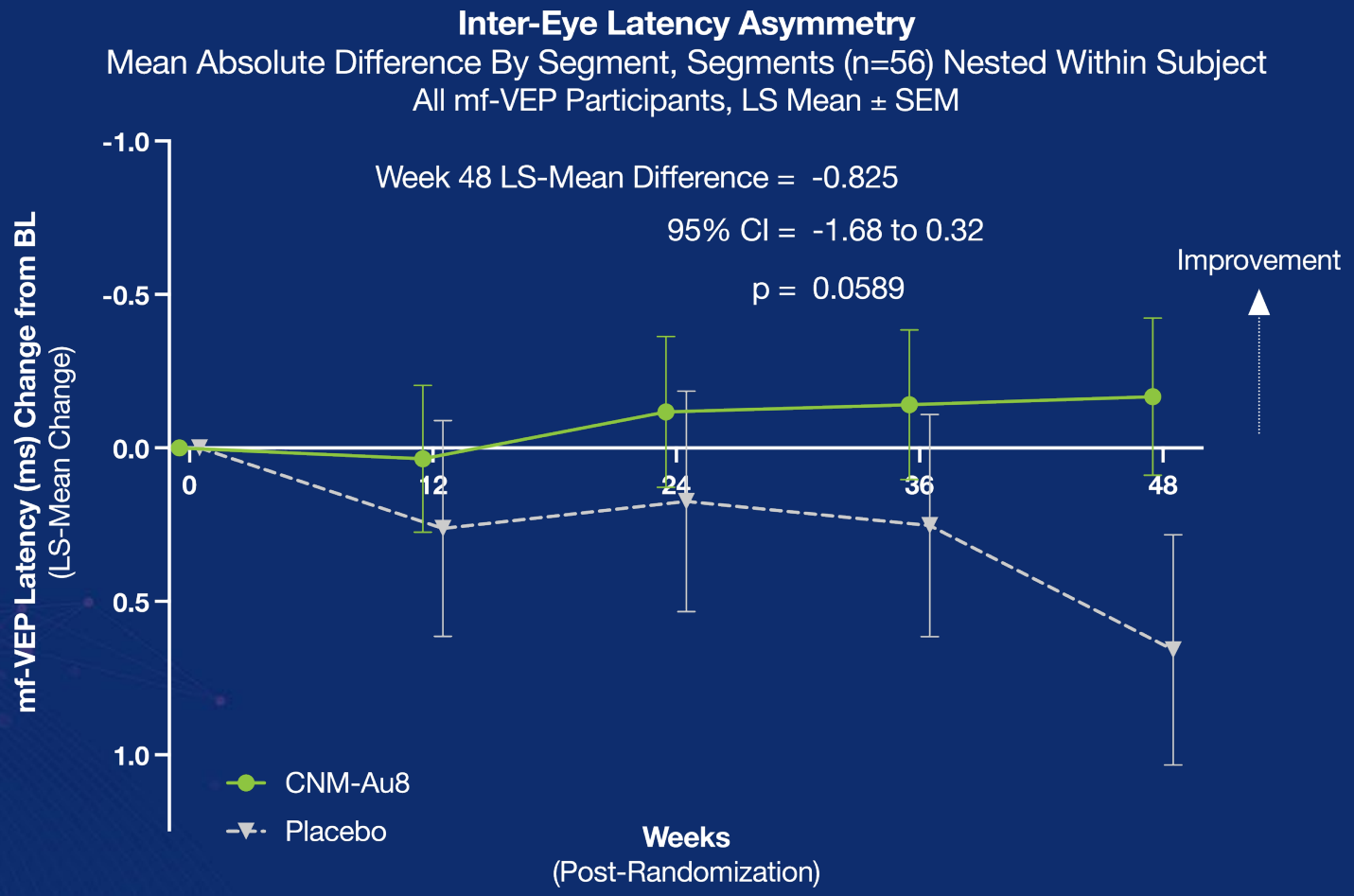
CNM-Au8 Improved Myelin Integrity

multi-focal VEP latency – marker of remyelination

VISIONARY-MS STUDY

Increased Conduction Velocity (Signal Speed)

Supports Remyelination or Enhanced Functional Myelin Integrity



CLene NANOMEDICINE

CNM-Au8 Was Safe & Well-Tolerated

VISIONARY-MS STUDY

- Treatment emergent adverse events (TEAEs) were transient and predominantly mild-to-moderate severity
- No dose limiting adverse events; no related serious adverse events (SAEs)

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).

No Related TEAEs listings were observed in more than one participant per group.

CLene NANOMEDICINE

Conclusions

VISIONARY-MS STUDY

1. Clinical Functional Improvements

- LCLA Vision Improvement
- Global Neuraxis Improvement (mMSFC)

2. Independent Quantitative Biomarkers of Myelin and Axonal Integrity

- mf-VEP Amplitude Improvement
- MTR & DTI Improvement

3. Safe & Well-Tolerated

CNM-Au8 Demonstrated Global Neurological Improvement in MS Patients Adjunctive to DMTs

CLene NANOMEDICINE

VISIONARY-MS STUDY

Phase 2 Results

In Stable RRMS Participants with Chronic Optic Neuropathy

CLene NANOMEDICINE