Physiologic and Anatomical Evidence of Neuronal Repair and Remyelination from the Long-Term Open-Label Extension of the Phase 2 VISIONARY-MS Trial

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VISIONARY-MS STUDY

Long Term Open-Label Extension (LTE)

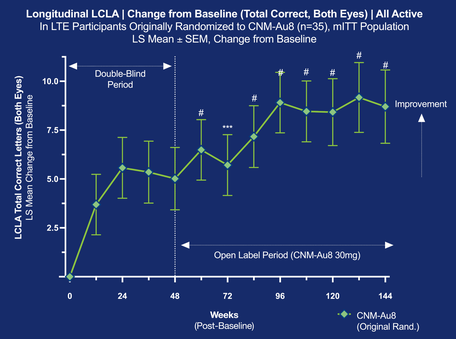
Long-Term CNM-Au8 30 mg Treatment Resulted in Functional, Structural, and Clinical Improvements In the Same Participants Evidencing Remyelination and Neuroreparative Activity

Phase 2 Study: 48-Week Double-Blind Placebo-Controlled Treatment Period With Up to 96-Week Long-Term Open Label Extension (LTE)

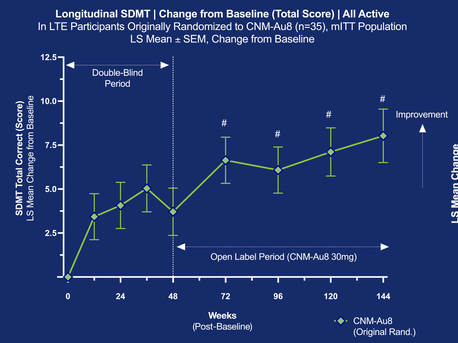
- Enrolled stable relapsing remitting MS participants with chronic optic neuropathy on background DMTs (53% monoclonal antibody infusion, 32% oral DMT; 92% total treated with DMT)
- n=73 of 150 planned – study ended prematurely due to COVID pandemic-related enrollment challenges; mITT population included all participants with valid clinical data
- LTE was offered to participants in Australia; n=55 were enrolled (n=46 within the mITT population) and continued treatment in the LTE through Week 144 (n=35 active; n=11 ex-placebo)

Clinical Outcomes | Improved LCLA and Symbol Digit Modalities Test (SDMT)

LCLA Change (CNM-Au8)



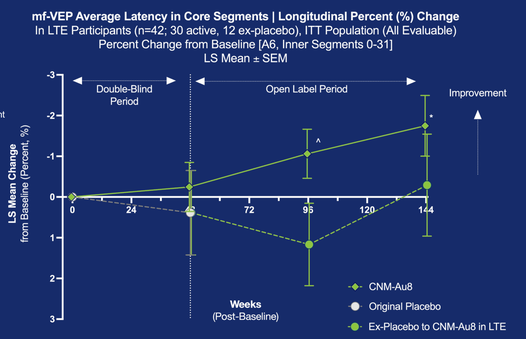
SDMT Change (CNM-Au8)



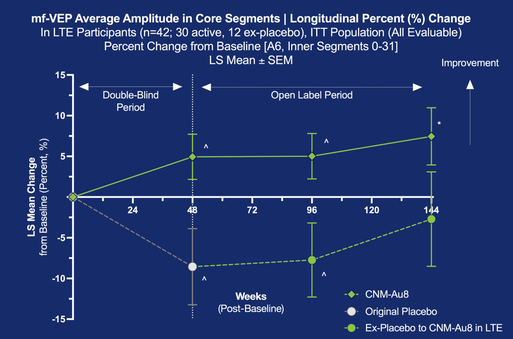
Improvement of Multi-Focal Visual Evoked Potential (mf-VEP) [Visual Pathway]

Core Inner Segments (n=32 of 56 segments)

Latency

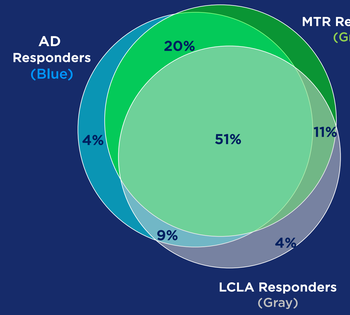


Amplitude



Extensive SDMT & LCLA Responder Overlap (96-98%) with MRI DTI AD and MTR Responders

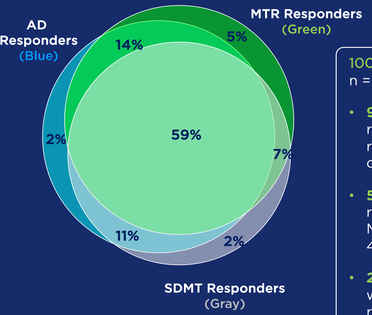
LCLA Responders (Venn Diagram)
with AD and/or MTR Improvement
In the Cerebrum or Optic Radiation *(Post Hoc)*



100% (all shaded regions; n = 45 of 45 evaluable)

- **96%** = those with LCLA response and MTR DTI response (AD, MTR; n = 43 of 45, all excluding gray)
- **51%** = those who responded to all three: AD, MTR, and LCLA (n = 22 of 45)
- **4%** = LCLA responders who are not MRI DTI responders (n = 2 of 45)

SDMT Responders (Venn Diagram)
with AD and/or MTR Improvement
In the Cerebrum or Optic Radiation *(Post Hoc)*

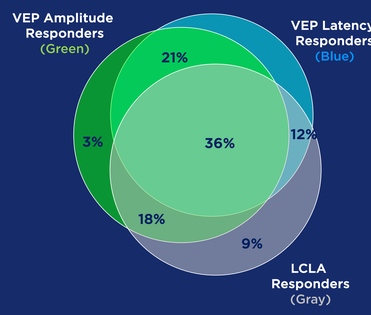


100% (all shaded regions; n = 44 of 45 evaluable)

- **98%** = those with SDMT response and MTR DTI response (AD, MTR; n = 43 of 44, all excluding gray)
- **59%** = those who responded to all three: AD, MTR, and SDMT (n = 26 of 44)
- **2%** = SDMT responders who are not MRI DTI responders (n = 1 of 44)

Extensive SDMT & LCLA Responder Overlap (91%) with mf-VEP Latency and Amplitude LTE Responders

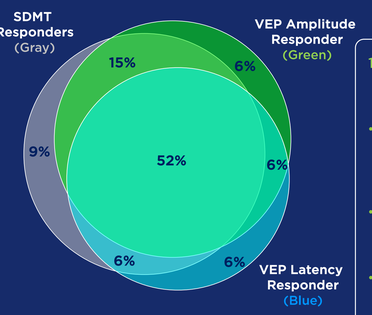
LCLA Responders (Venn Diagram)
with mf-VEP Latency and/or Amplitude
Improvement *(Post Hoc)*



100% (all shaded regions; n = 33 of 34 evaluable with mf-VEP LTE data)

- **91%** = those with LCLA response and VEP response (latency, amplitude); n = 30 of 33, all excluding gray)
- **36%** = those who responded to all three: latency, amplitude, and LCLA (n = 12 of 33)
- **9%** = LCLA responders who are not VEP responders (n = 3 of 33)

SDMT Responders (Venn Diagram)
with mf-VEP Latency and/or Amplitude
Improvement *(Post Hoc)*

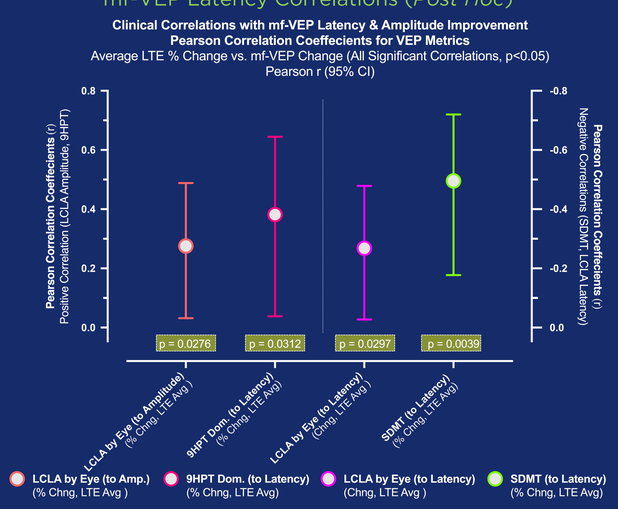


100% (all shaded regions; n= 33 of 34 evaluable with mf-VEP LTE data)

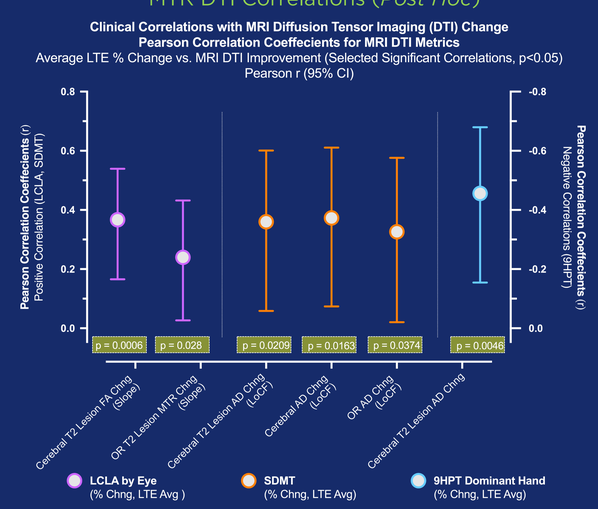
- **91%** = those with SDMT response and VEP response (latency, amplitude); n = 30 of 33, all excluding gray)
- **52%** = those who responded to all three: latency, amplitude, and SDMT (n = 17 of 33)
- **9%** = SDMT responders who are not VEP responders (n = 3 of 33)

Clinical LTE Changes Correlated with mf-VEP & MRI DTI Improvement

mf-VEP Latency Correlations (*Post Hoc*)



MTR DTI Correlations (*Post Hoc*)



Conclusions

Findings from the VISIONARY-MS trial long-term extension confirm that CNM-Au8 significantly enhanced cognition (working memory) and low-contrast vision, supported by MRI DTI and mf-VEP improvements:

- **96%** of vision-improved participants showed MRI DTI evidence of neuronal repair and remyelination
- **98%** of cognition-improved participants showed MRI DTI evidence of neuronal repair and remyelination
- **91%** of vision-improved participants had faster (latency) and stronger (amplitude) brain signal responses, evidence of neuronal repair and remyelination
- Clinical improvements of LCLA, SDMT, and 9HPT were correlated with VEP and MRI DTI change

Notes: LTE: MMRM analyses with age, gender, and baseline value as fixed covariates. LS mean difference vs. placebo or vs. randomization baseline (by graph): # p<0.0001, *** p<0.001, ** p<0.01, *p<0.05, ^ p<0.10. Pre-specified study alpha was set at 0.10. mITT population included all valid clinical data excluding one participant with an episode of acute optic neuritis (n=45). Responders (post hoc) include the top three quartiles for change from baseline. Abbreviations: AD = axial diffusivity; MTR = magnetization transfer (MTR); FA = fractional anisotropy; LCLA = low contrast letter acuity; SDMT = symbol digit modalities test; OR = optic radiation; LoCF = last observation carried forward; VEP = visual evoked potentials; 9HPT = 9-hole peg test. Disclosures: Dr. Greenberg has received consulting fees and holds equity in Clene. Acknowledgements: We thank the study participants and their families for their support and willingness to engage in clinical research. We thank the site investigators for their research excellence and dedication to patients.

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