RepairPD

Evidence for Target Engagement and Brain Cellular Energy Metabolism Improvements in Parkinson's Disease: Results From The Phase 2 REPAIR-PD Clinical Trial With CNM-Au8

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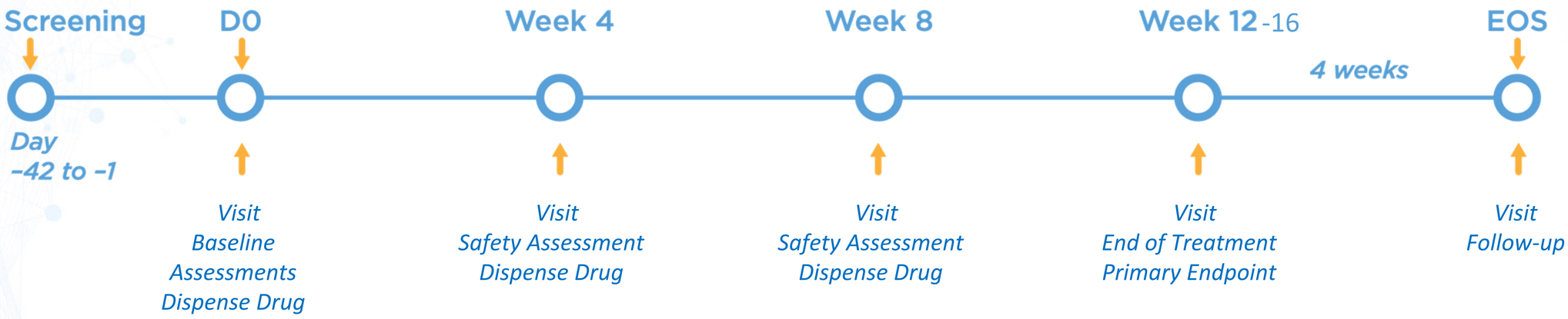
Phase 2

RepairPD

RepairMS

CNM-Au8 Effects on Brain Energetic Metabolites

A Phase 2, Open Label, Sequential Group, Investigator Blinded Study of Magnetic Resonance Spectroscopy (^{31}P-MRS) to Assess the Effects of CNM-Au8 for the Bioenergetic Improvement of Impaired Neuronal Redox State (REPAIR)



1°

Change in Brain Bioenergetic Potential
(NAD+/NADH)
vs. Baseline

N = Up to 15 per dosing cohort

(7.5, 15, 30, or 60 mg)

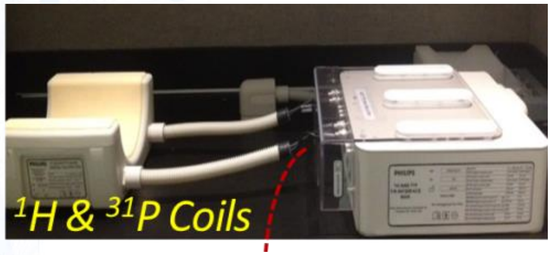
2°

Exploratory

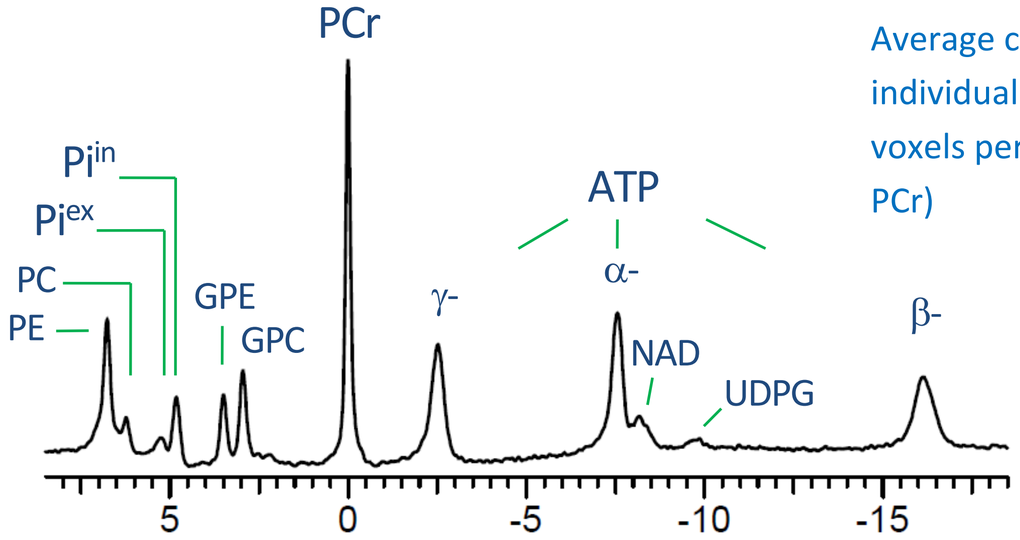
- Difference in brain NAD+ and NADH fraction at Week 12-16
- Difference in bioenergetic metabolites (e.g., ATP, PCr, NAD) concentration at Week 12 – 16
- Difference in brain membrane markers (PE, PC, etc.) at Week 12 – 16

REPAIR Program | ^{31}P MRS Imaging Modality at 7T

Partial Volume Coil



Full Volume Coil



Average change in Area Under Curve by individual 31P peak (per 2 cm^3 voxel, ~600 voxels per subject; all voxels normalized by PCr)

ATP-α, ATP-β, ATP-γ

NAD+/NADH (partial coil only)

NAD Pool (Full coil)

UDPG – uridine diphosphate glucose

PCr – phosphocreatine (normalization factor)

Pi^{in} - intracellular inorganic phosphate

Pi^{ex} - extracellular inorganic phosphate

PC - phosphocholine

PE - phosphoethanolamine

GPE - glycerophosphoethanolamine

GPC - glycerophosphocholine

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REPAIR-PD | Baseline Demographics

Baseline Values	**Subjects** n (%)	**Age** [yrs.] mean (SD)	**Time from Diagnosis to BL** [Months] mean (SD)	**MMSE** [Score] mean (SD)	**Hoehn & Yahr Stage** mean (SD)	**Background Dopaminergic Therapy** (%)
All	13 (100%)	65.9 (7.8)	17.2 (8.8)	28.8 (1.3)	2.0 (0.0)	100%
Female	6 (46%)	67.0 (7.8)	13.5 (9.3)	28.5 (1.0)	2.0 (0.0)	100%
Male	7 (54%)	65.0 (8.3)	20.4 (8.1)	29.1 (1.5)	2.0 (0.0)	100%

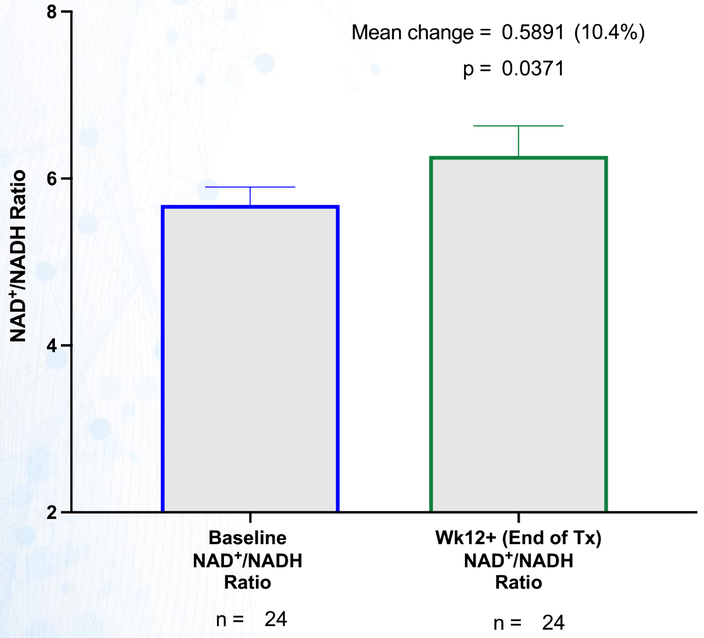
REPAIR Program Primary Endpoint
Pre-specified Integrated Analysis (MS & PD Cohorts)

REPAIR Integrated Analysis

^{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)

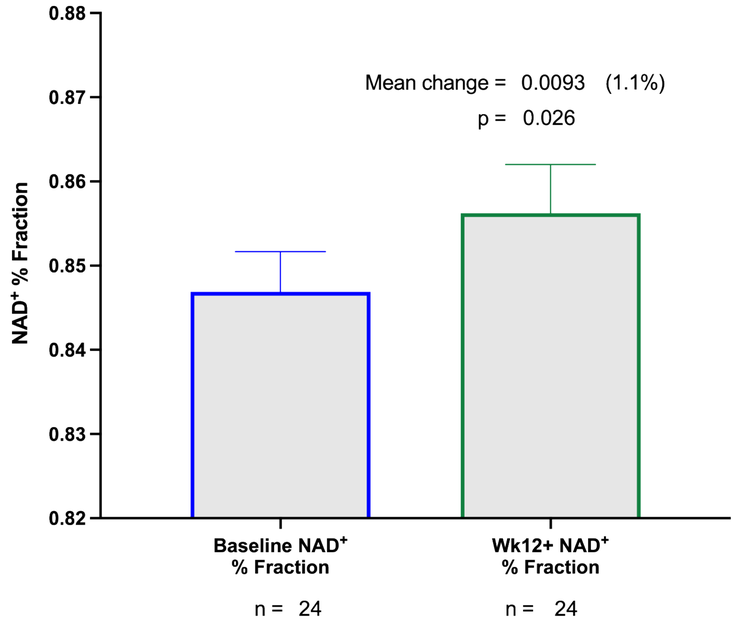


REPAIR Integrated Analysis

^{31}P-MRS Change in Brain NAD$^+$ % Fraction at End of Treatment

Partial Volume Coil; % Fraction of NAD$^+$, (NAD$^+$, NADH Couple)

Secondary Endpoint, Mean ± SEM (Paired t-test)

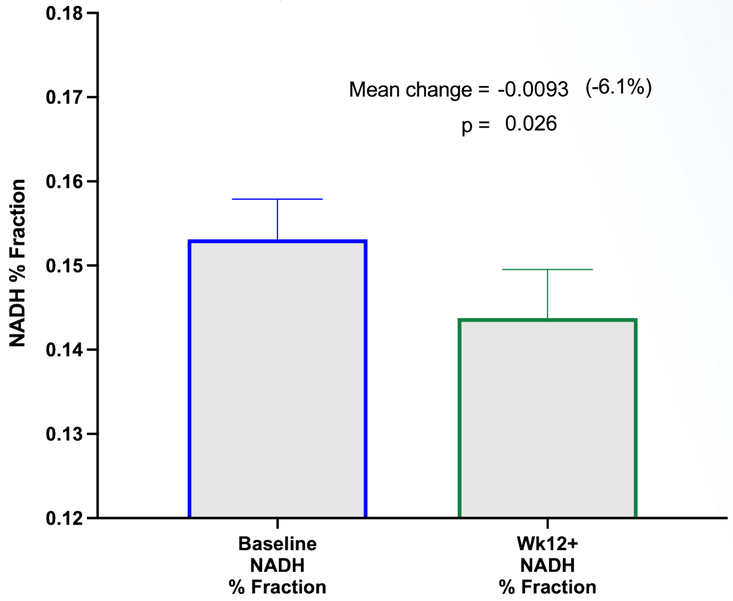


REPAIR Integrated Analysis

^{31}P-MRS Change in Brain NADH % Fraction at End of Treatment

Partial Volume Coil; % Fraction of NADH, (NAD$^+$, NADH Couple)

Secondary Endpoint, Mean ± SEM (Paired t-test)



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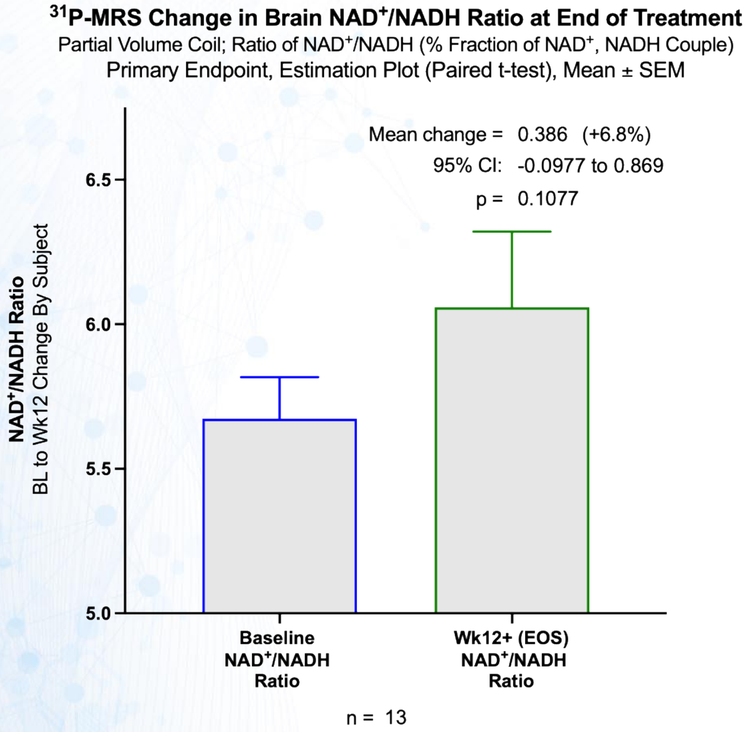
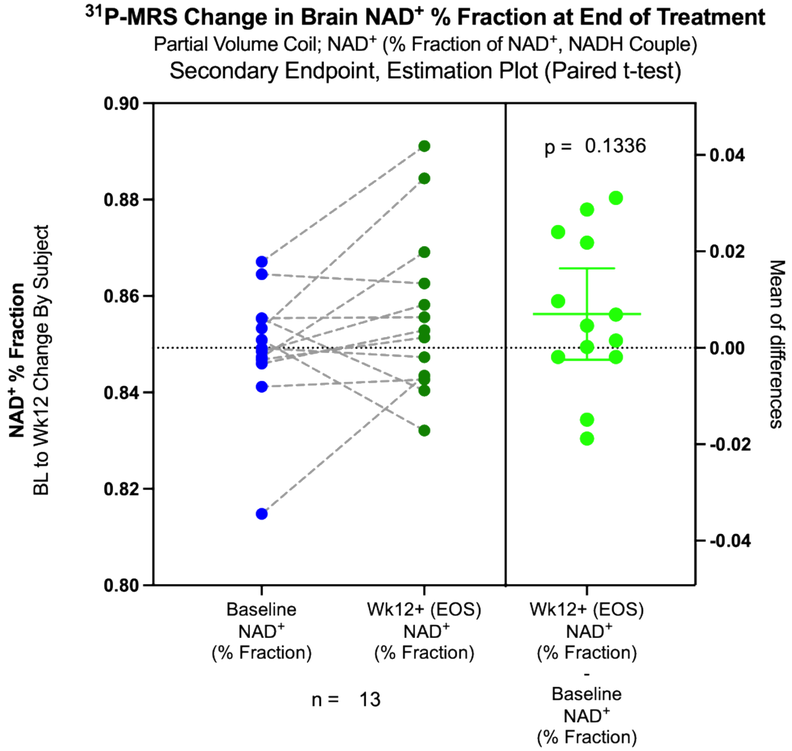
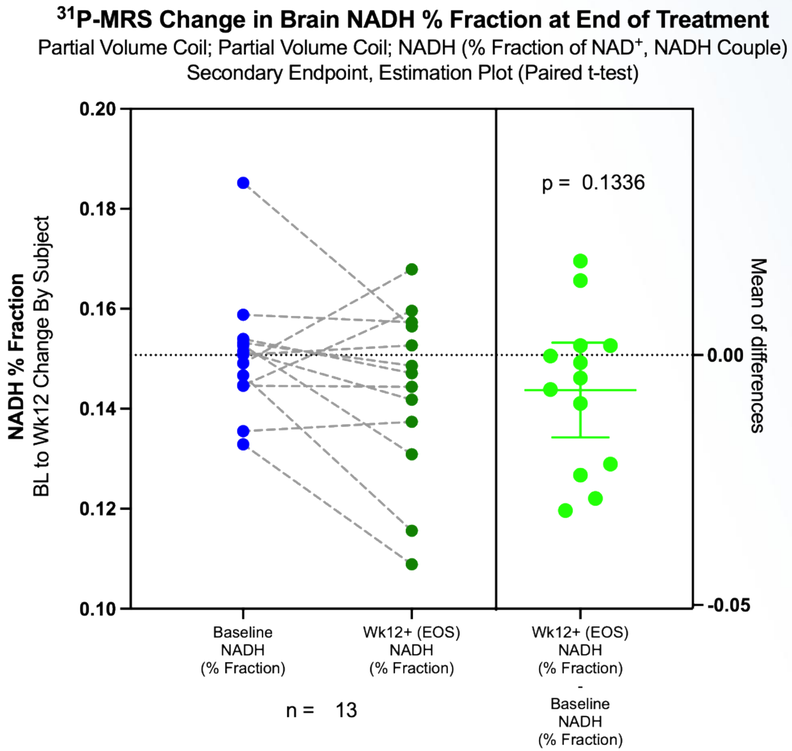
REPAIR-PD | NAD+/NADH Ratio and % Fractions

Primary Endpoint Data from Parkinson's Disease Cohort







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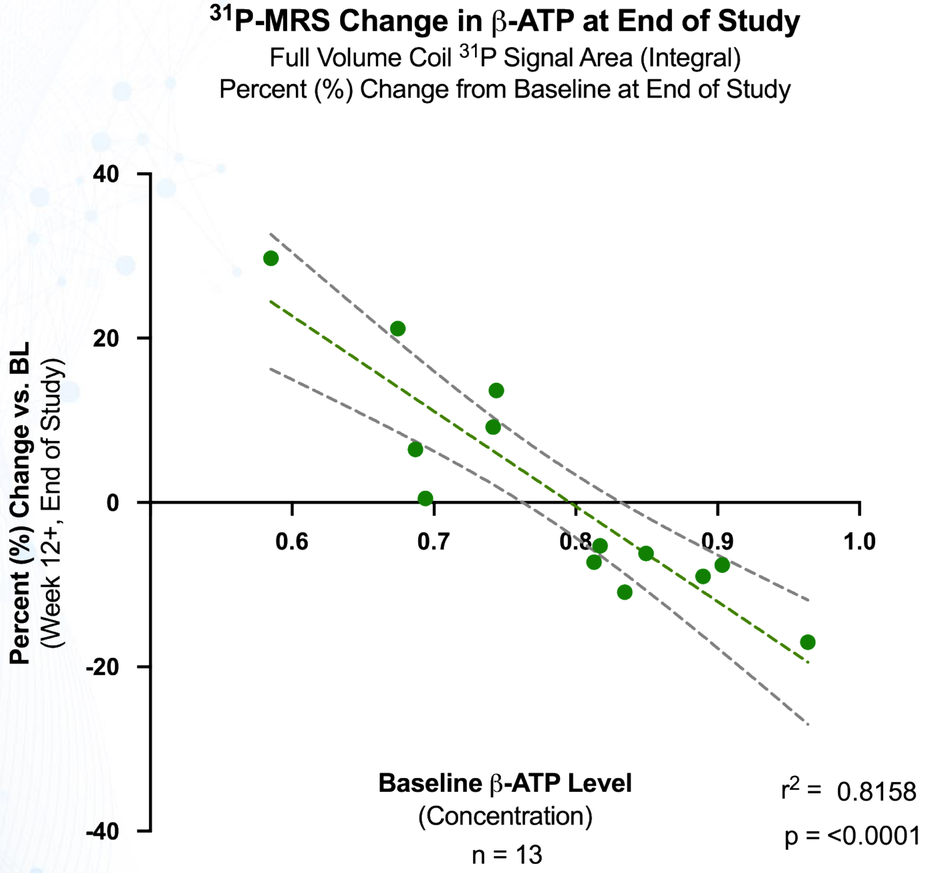
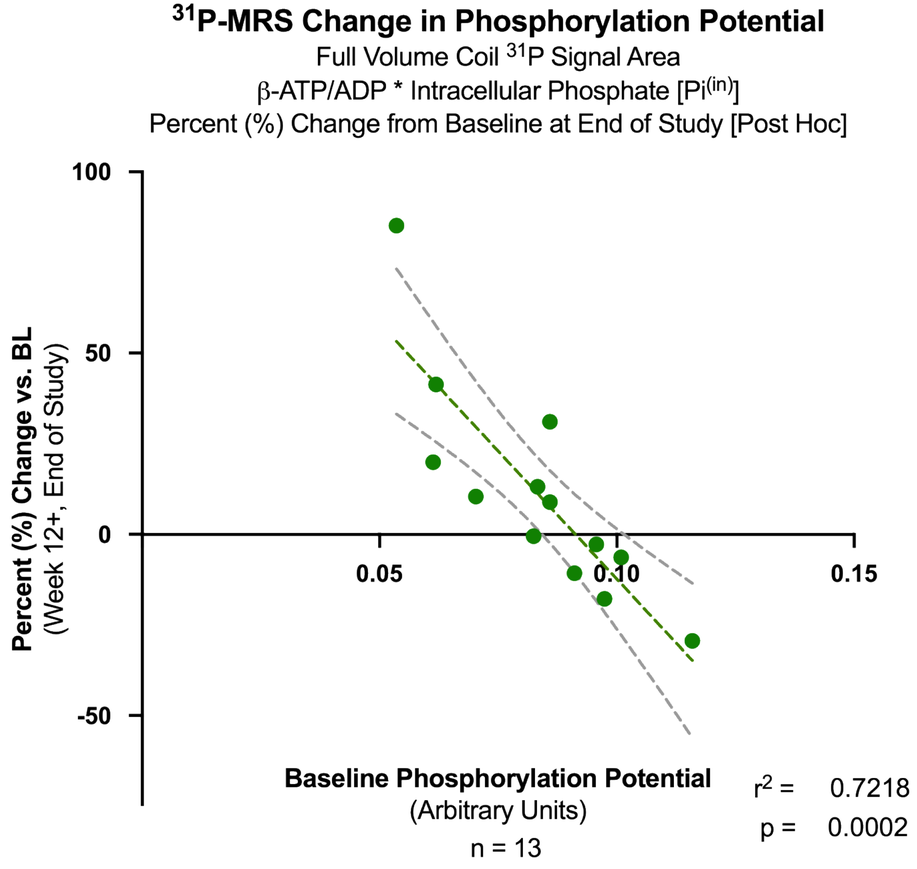
REPAIR-PD | β-ATP & Phosphorylation Potential Normalization by Wk12 (% Change vs. BL)





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REPAIR-PD | Safety Summary

- Treatment-emergent AEs were mild & transient
- No serious adverse events
- No subjects with clinically significant laboratory abnormalities
- No significant change (i.e., worsening) of UPDRS

REPAIR-PD | Results & Conclusions

- Statistically significant increase in NAD/NADH ratio based on integrated analyses of PD & MS cohorts
- PD population trend in NAD+/NADH ratio improvement driven by both increased NAD^+ and decreased NADH
- Homeostatic effects on brain energetic metabolites including β-ATP and phosphorylation potential
- Demonstration of CNS target engagement with CNM-Au8