Long-Term CNM-Au8 Treatment Reduces Neurofilament Light Levels and Improves Survival: Results from the HEALEY ALS Platform Trial

HEALEY ALS Platform Trial

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CONCLUSIONS: Long-Term CNM-Au8 30mg Treatment Resulted in 1) Improved Survival vs. PRO-ACT Matched Controls, and 2) Decreased Plasma NfL Levels; NfL Decreases Were Greatest In Participants With Higher Baseline Levels (≥ Median)

NfL Analysis Methods

Plasma NfL was tested by the Quanterix Simoa Neurology 4-PLEX A assay. Change from baseline by treatment group was analyzed as the least-squares mean (LS mean) change of the natural logarithm (Ln) of the plasma NfL values (delta-Ln units).

Analyses by mixed model repeated measures (MMRM) with prespecified covariates including: (i) pre-treatment ALSFRS-R slope (delta-FS), (ii) months from symptom onset, (iii) use of riluzole, (iv) use of edaravone; (v) treatment by visit interaction. All visits graphed with n ≥ 10 participant data.

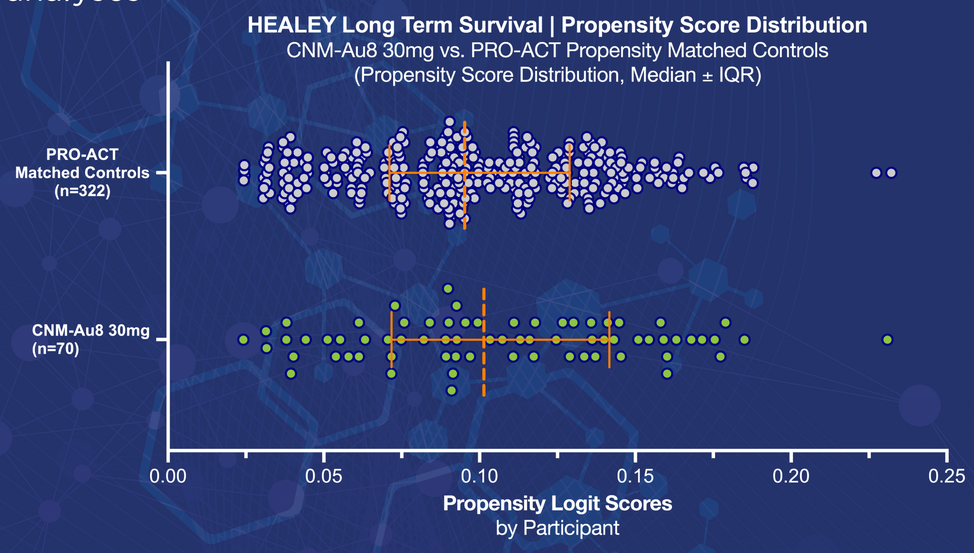
Survival Analysis Methods

Propensity score matching methods were prespecified and matching was conducted by an independent statistician blinded to survival outcomes. Nearest neighbor matching with a caliper of 0.2 was used based on the following pre-treatment (baseline) covariates: (i) age at onset, (ii) site of onset (bulbar or limb), (iii) TRICALS risk score, (iv) sex, (v) ALSFRS-R pre-treatment slope (delta-FS), (vi) body mass index (BMI), and (vii) diagnostic delay (in months). All participants exposed to CNM-Au8 30mg, including ex-placebo to OLE, with complete evaluable baseline covariates, were included (n=70).

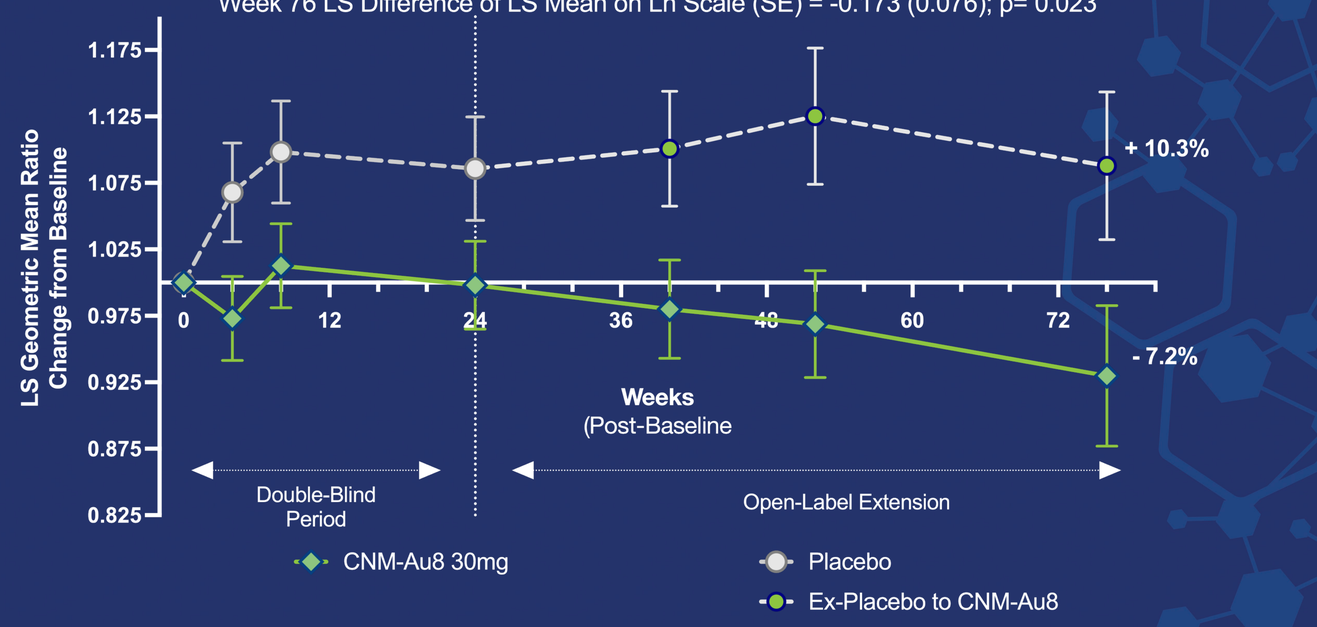
Pre-specified covariates associated with survival risk were included in the cox model: (i) age at disease onset, (ii) sex, (iii) BMI, (iv) delta-FS, (v) ALSFRS-R Total Score, (vi) diagnostic delay (in months), (v) vital capacity (% predicted), (vi) vital capacity slope, and (vii) TRICALS risk score. Participants were right censored at last observed value (PRO-ACT) or through March/April 2024 (HEALEY).

Propensity Match Logit Scores Were Balanced

Supporting the validity of the matched set for survival analyses

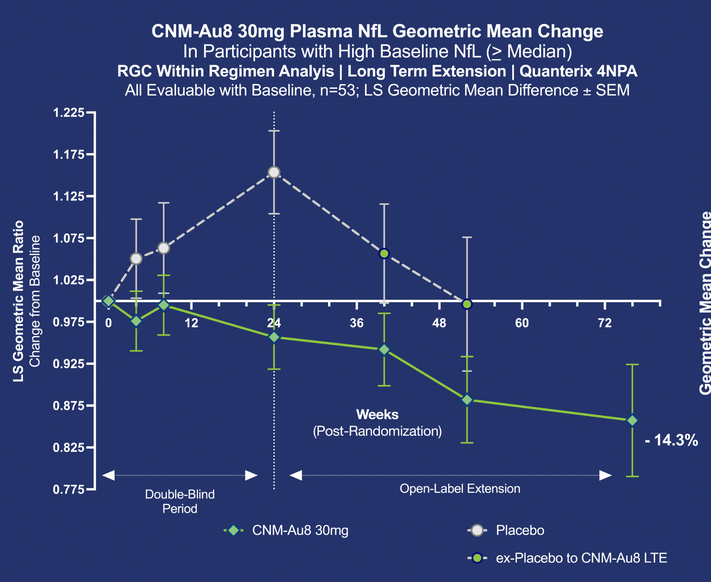


Long-Term NfL Decline (All Evaluable)

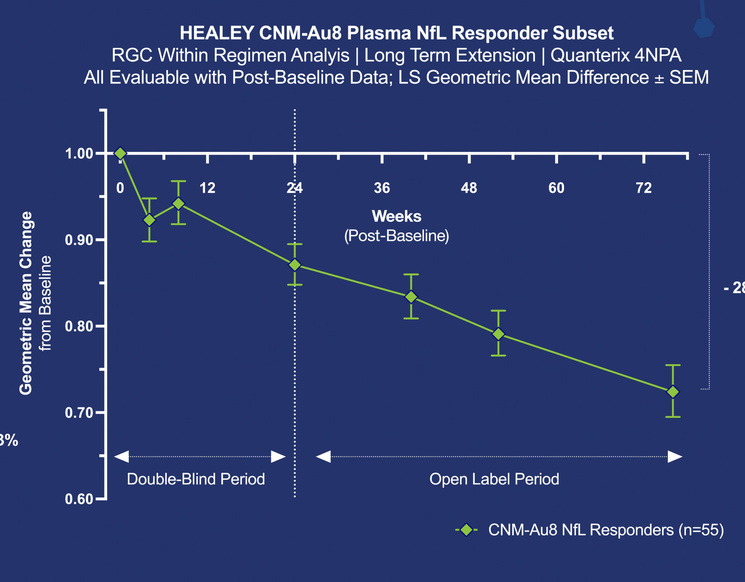


Long-Term NfL Decline by Subset

Baseline NfL ≥ Median

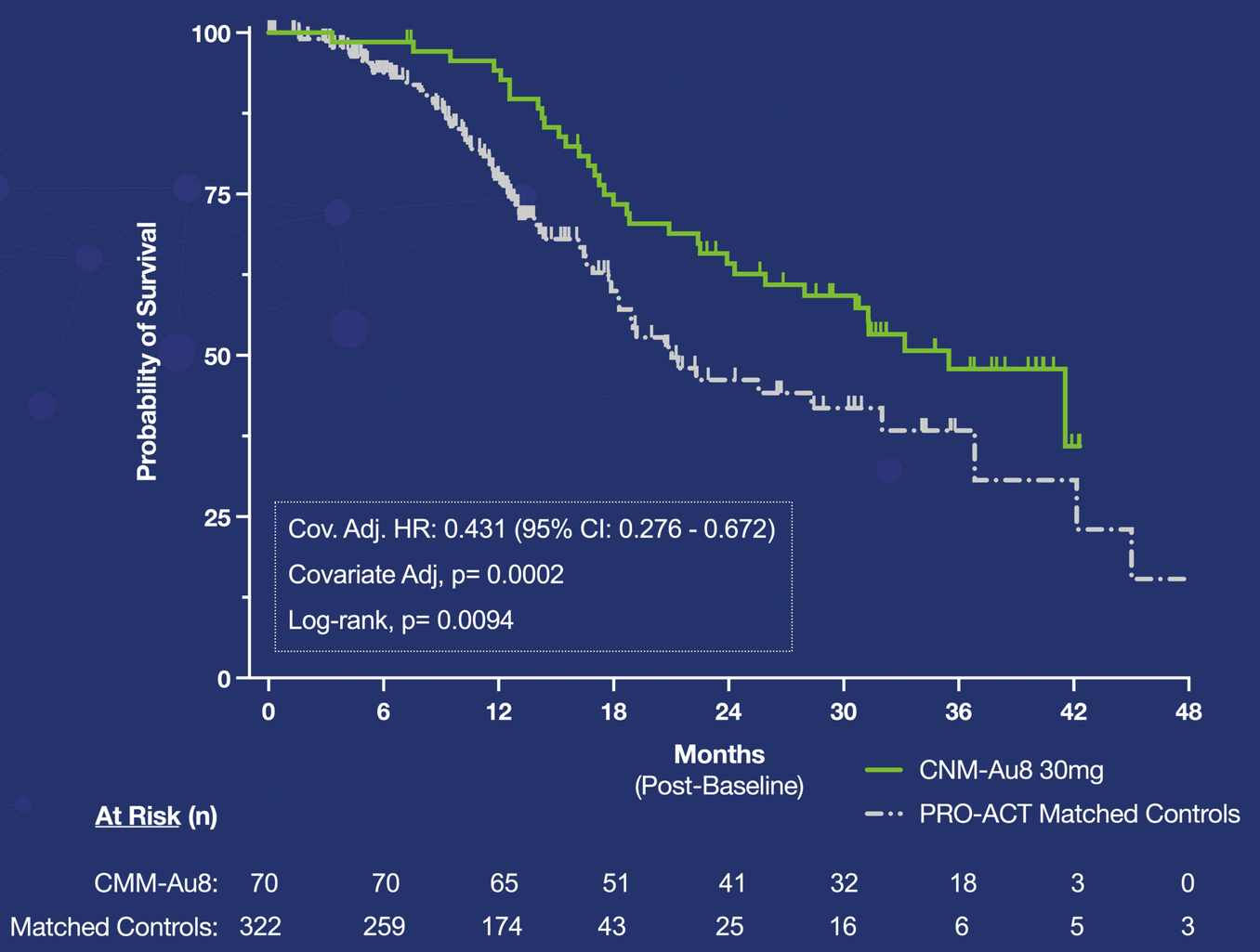


CNM-Au8 NfL Responder Subset[2]



2. NfL responders were defined all participants with consistent repeated post-baseline declines of at least 10 pg/mL, or with all post-baseline values declined

CNM-Au8 30 mg Treatment vs. PRO-ACT Matched Controls



Sensitivity Analyses Demonstrated Consistent Evidence Supporting a Survival Benefit

Sensitivity Analyses: With Additional Matching Covariates	Primary Covariate Model [1]	Added Matching Covariate: Time from Symptom Onset	Added Matching Covariates: Both Time from Symptom Onset and Observation Time
Covariate Adjusted HR (95% Wald CI)	0.431 (0.276 -0.672)	0.399 (0.252 -0.631)	0.551 (0.359 – 0847)
Covariate-adjusted p-value	p= 0.0002	p <0.0001	p= 0.007
Unadjusted Cox HR (95% Wald CI)	0.574 (0.376 - 0.876)	0.542 (0.352 -0.833)	0.692 (0.461 – 1.039)
Log-rank, p-value	p = 0.0094	p = 0.0048	p = 0.074

1. Primary covariate model: (i) age at disease onset (p<0.0001), (ii) sex (p=0.276), (iii) BMI (p=0.01), (iv) delta-FS (p=0.185), (v) ALSFRS-R Total Score (p=0.344), (vi) diagnostic delay (p=0.698), (v) vital capacity (% predicted) (p=0.005), (vi) vital capacity slope (p=0.808), and (vii) TRICALS risk score (p=0.778)

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