

MCLENA-1: A Phase I-B Clinical Trial for the Assessment of Safety, Tolerability, and Efficacy of Lenalidomide in Patients with Mild Cognitive Impairment Due to Alzheimer’s Disease: Safety and Feasibility Demonstrated



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BACKGROUND

• Accumulating evidence indicates that inflammation mediated by tumor necrosis factor alpha (TNF alpha), interleukins (e.g. IL-1 beta, IL-2, and IL-6), and chemokines (e.g. IL-8), are elevated in Alzheimer’s disease (AD) patients, suggesting that systemic inflammation plays a crucial role in the cause and effects of AD neuropathology.

OBJECTIVES

To investigate immunomodulatory, anti-cancer agent **drug lenalidomide as possible treatment for AD.**

- **Primary Aim:** to assess the effect of 12 months of treatment with lenalidomide on cognition and imaging parameters.
- **Secondary Aim:** to assess the safety and tolerability of lenalidomide in aMCI patients.

METHODS

- **Design:** Phase I-B, proof-of mechanism, placebo-controlled clinical study on single and multiple domain amnesic mild cognitive impairment (aMCI) subjects.
 - **Treatment:** 10 mg/day of lenalidomide (n=3) or placebo (n=3) for 12 months on a 1:1 ratio followed by a 6 months washout period.
- Inclusion criteria:**
- Outpatients 50–89, community-dwelling.
 - Diagnosis of aMCI.
 - MMSE score 22–28 at screening.
 - Evidence of cerebral amyloid deposition on Florbetapir PET imaging
 - Stable dose of cholinesterase inhibitors for at least 3 months prior to enrollment.
- Exclusion criteria:**
- Significant neurological or psychiatric disorders within the past 3 years (e.g., Parkinson's disease, major depression, seizure disorders).
 - Living alone, pregnancy, MRI/PET ineligible, cardiac pacemaker/defibrillator, HIV+.
 - Active cancer, unstable cardiovascular disease, severe pulmonary disease, or organ failure.
 - Recent Interventions: Investigational drugs (<30 days) or devices (<2 weeks).

RESULTS

Table 1. Demographics

Demographics	Placebo (N=3)	Lenalidomide (N=3)
Age, Mean (SD)	74.3 (7.3)	70.3 (5.5)
Sex, F	1 (33%)	2 (66%)
Baseline MMSE, Mean (SD)	27.0 (1.0)	27.0 (1.0)

Table 2. Adverse events summary

System/ Organ System	Number of AEs
Hematological	34
Other	33
Gastrointestinal	27
Skin	18
Urinary/ Renal	15
Cardiovascular	10
Infections	9
Neurological	6
Injury	2
Respiratory	1

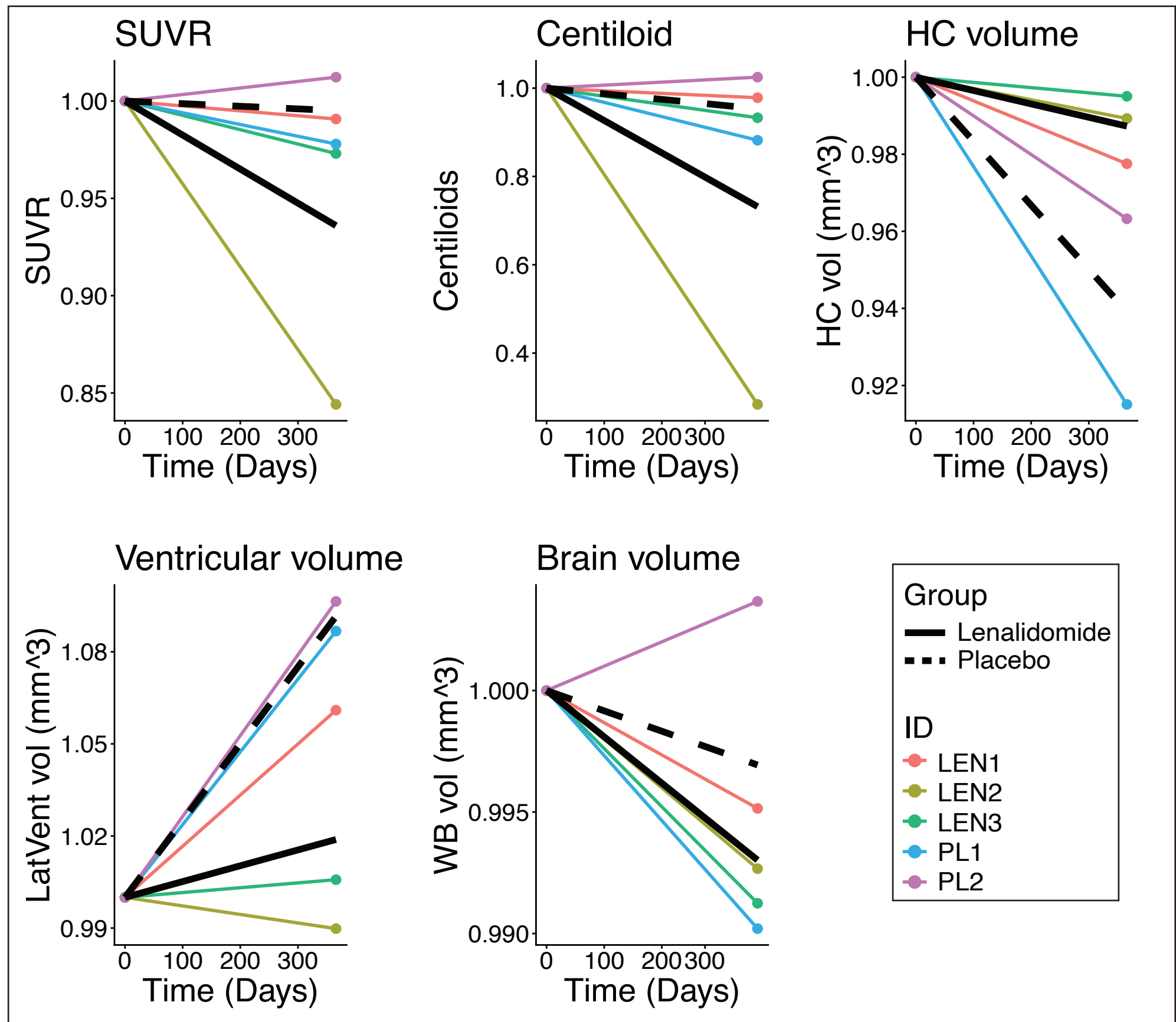


Figure 1. Changes in neuroimaging outcomes over time. Colored lines represent change for each subject and the black lines represent mean change per group. Participants underwent MRI and florbetapir PET imaging at baseline and follow-up approximately 1 year later (mean interval = 384 ± 12 days). MRI was acquired at 3T (Siemens Skyra) following ADNI protocols. Cortical amyloid burden was quantified using SUVR (cortical gray matter/cerebellum) and Centiloid values derived from the Florbetapir static images. Abbreviations: Standardized Uptake Value Ratio, SUVR; Hippocampal Volume HC vol; Lateral Ventricular Volume, LatVent vol; Whole Brain Volume WB vol.

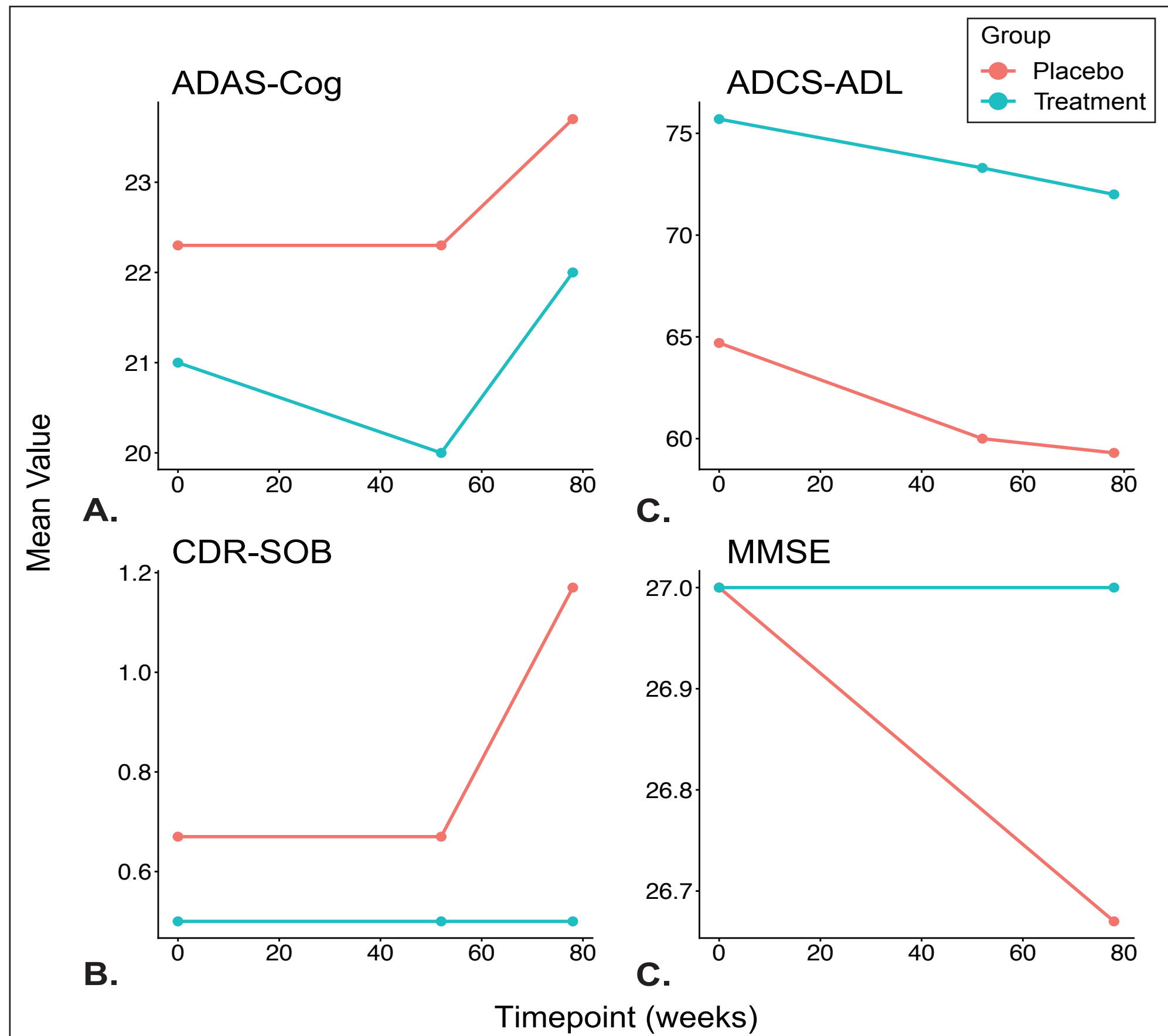


Figure 2. Changes in cognitive outcomes over time. Abbreviations: Alzheimer’s Disease Assessment Scale – Cognitive Scale; ADAS–Cog; Clinical Dementia Rating – Sum of Boxes, CDR–SOB; Alzheimer’s Disease Cooperative Study – Activities of Daily Living, ADCS–ADL; Mini Mental State Examination, MMSE

RESULTS (continued)

- The study did not meet its enrollment goals before the conclusion of the funding period.
- 15 participants signed consent, 7 screen failed, 2 withdrew consent and 6 completed treatment after 12 months.
- Adverse events were consistent with the label for lenalidomide. No SAEs occurred during the study.
- Importantly, assuming a 1:1 randomization in the blinded phase, participants have received lenalidomide continuously for 12 months.
- Compared to the placebo group, the treatment group exhibited a slower decline in hippocampal volume, slower increase in ventricular volume and faster decline in whole brain volume.
- Overall, improved outcomes across cognitive, global, and imaging domains were observed in the treatment group, although these differences did not reach statistical significance.

CONCLUSION

- The null hypothesis was not demonstrated. Our study demonstrates feasibility and safety in administering lenalidomide to MCI participants for at least 12 months continuously.
- The TEAEs were expected and safety and tolerability were manageable.

Limitations & future directions

- The sample size is too small to determine a robust efficacy signal but could be sufficient to inform a phase II or III design.
- A second study, termed MCLENA 2, has started with a focus on biomarker (CSF and plasma) endpoints following treatment for 6 months.

Acknowledgements

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