

MCLENA-1 - A Phase 1b Trial of Lenalidomide in Mild Cognitive Impairment: Preliminary Data on Plasma Inflammatory Markers



Boris Decourt, PhD¹, Jeffrey R. Wilson, PhD², Liliana Dumitrescu MSc³, Katia Azarfar, PhD¹, Ellie M. Reyna, BSc¹, Jessica M. Kennedy, BSc¹, and Marwan N. Sabbagh, MD⁴

¹ Texas Tech Health Sciences Center, Lubbock, TX, USA; ² Arizona State University, Tempe, AZ, USA; ³ Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas NV, USA; ⁴ Barrow Neurological Institute, Phoenix, AZ, USA



Abstract

Background: It is increasingly admitted that inflammation is pervasive to neurodegenerative disorders, including Alzheimer's disease (AD). Previous attempts to lower inflammation via targeted therapeutics (e.g., anti-TNF- α antibodies) and limited spectrum small molecules (e.g., NSAIDs and acetaminophen) have failed to demonstrate clinical efficacy in AD patients. To bypass the limitations of targeted therapies, in the past 15 years our team has brought to AD clinical trials very potent, pleiotropic, small molecule immunomodulatory drugs affecting both the innate and adaptive immune responses. We hypothesize that strong modulation of both systemic and central inflammation is a putative therapeutic intervention if administered at a proper time window during the course of the disease. In this brief report, we analyzed the effects of the anti-cancer, immunomodulatory, anti-TNF- α drug lenalidomide and placebo on 10 markers of inflammation in the plasma of early AD patients.

Method: This was a Phase 1b, proof-of-mechanism, placebo-controlled clinical trial on single and multiple domain amnesic mild cognitive impairment (aMCI) male and female subjects administered 10 mg/day lenalidomide for 12 months on a 1:1 ratio (planned: 15 placebo + 15 drug-treated subjects total) followed by a 6 months washout period. All enrolled subjects underwent frequent blood draws for both safety and research purposes. As an Exploratory Objective, we investigated the potential of blood inflammatory markers as surrogate markers of the therapeutic efficacy of the study drug. We used the Meso Scale Discovery (MSD) 10-plex assay (V-Plex: IFN- γ , IL-1 β , IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNF- α).

Results: The study did not meet its enrollment goals before the conclusion of the funding period, but a total of 6 participants (3 placebo + 3 drug-treated) have completed 12 months of treatment. No significant differences were noted between the two groups for all 10 markers, likely due to a lack of statistical power. Overall, placebo-treated subjects had higher baseline values. However, and importantly, subjects treated with lenalidomide did not experience any increase in the levels of inflammatory markers over the dosing period. A trend towards a stabilization of TNF- α after treatment stoppage was noted in drug-treated participants, while placebo treatment tended to go higher over time. Thus, non-significant trends favoring treatment over placebo were observed in this panel of plasma inflammatory outcome measures.

Conclusion: Our study demonstrates feasibility and safety in administering lenalidomide to MCI participants for at least 12 months continuously. A more advanced analysis using sensitive multiplex ELISA is in preparation to confirm these results and analyze additional markers. Because the null hypothesis was not met, this suggests that lenalidomide should be explored further for the treatment of early AD patients.

Objectives

To test the potential of the immunomodulatory, anti-cancer drug lenalidomide to treat AD when administered at early stages of the disease.

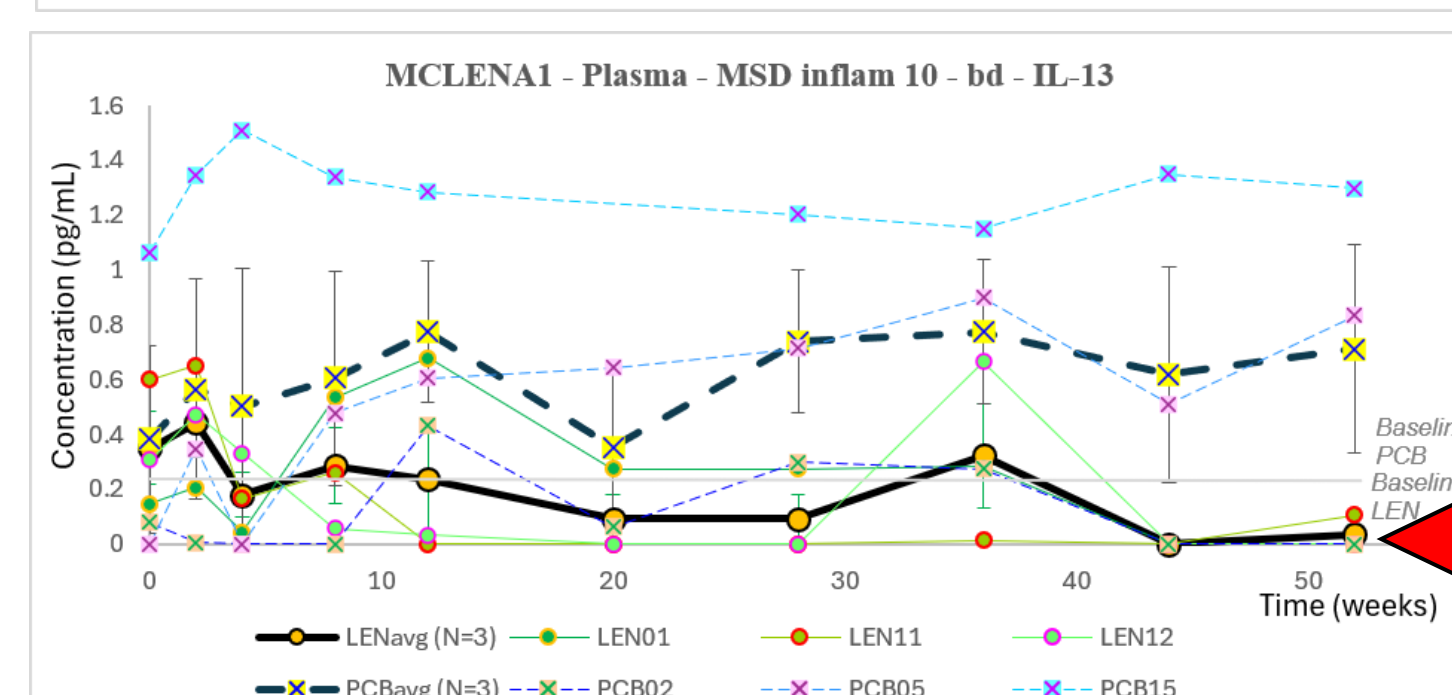
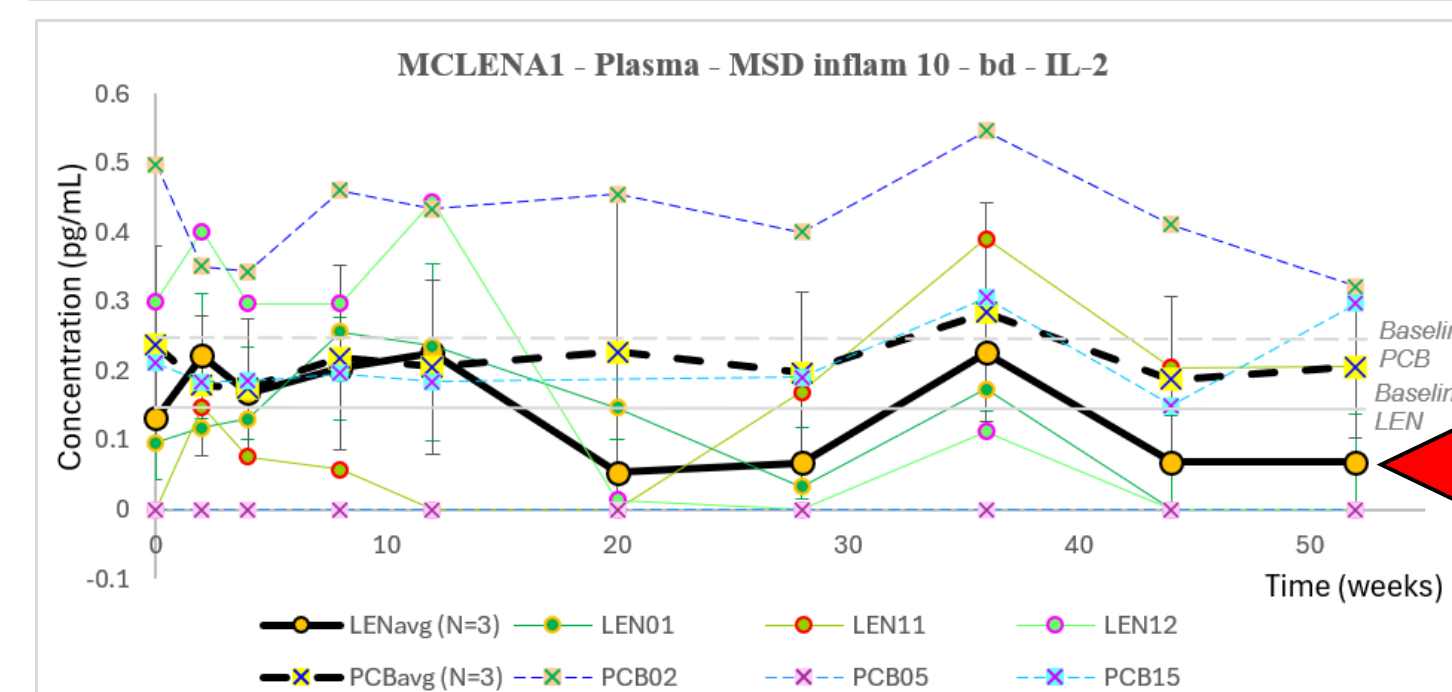
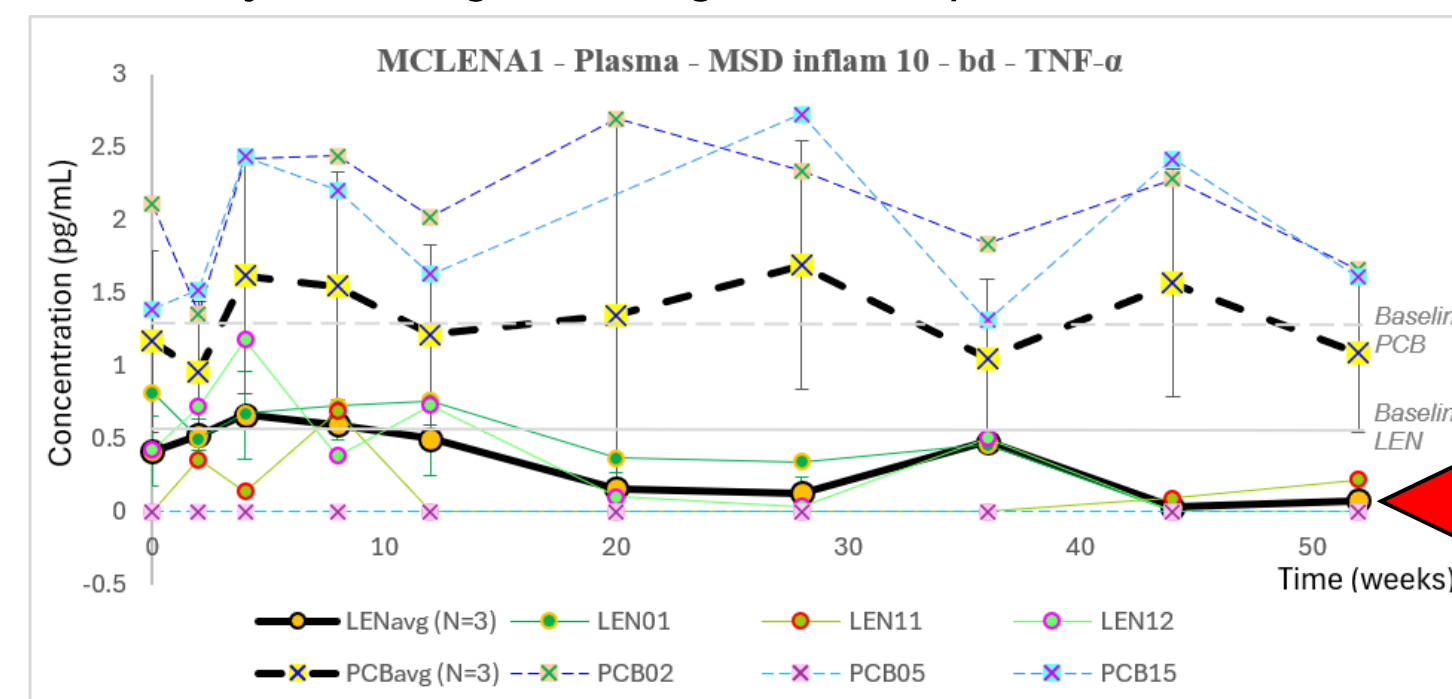
In this sub-study, which was an exploratory Aim in the overall Phase 1b trial (FDA Investigational New Drug Application (IND) #142121), we investigated whether 10 plasma inflammatory markers were affected by the drug throughout the dosing period. The main marker of interest was TNF- α , which is a key molecular target of lenalidomide.

Methods

- Study Design: Phase 1b, proof-of mechanism, placebo-controlled clinical study on single and multiple domain amnesic mild cognitive impairment (aMCI) subjects. Primary goal: safety.
- Treatment: lenalidomide 10 mg/day (n=3) or placebo (n=3) for 12 months on a 1:1 ratio followed by a 6-month washout period
- Main inclusion criteria:
 - Outpatients age 50–89 years old, community-dwelling
 - Diagnosis of aMCI - MMSE score 22–28 at screening
 - Positivity on Florbetapir PET imaging
- Main exclusion criteria:
 - Significant neurological or psychiatric disorders within the past 3 years (e.g., Parkinson's, major depression, seizures)
 - 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).
- Biomarkers measurement: blood sampling at weeks 0, 2, 4, 8, 12, 20, 28, 36, 44, 52. After all samples were collected, plasma samples were subjected to MSD 10-plex assay (see abstract).

Results

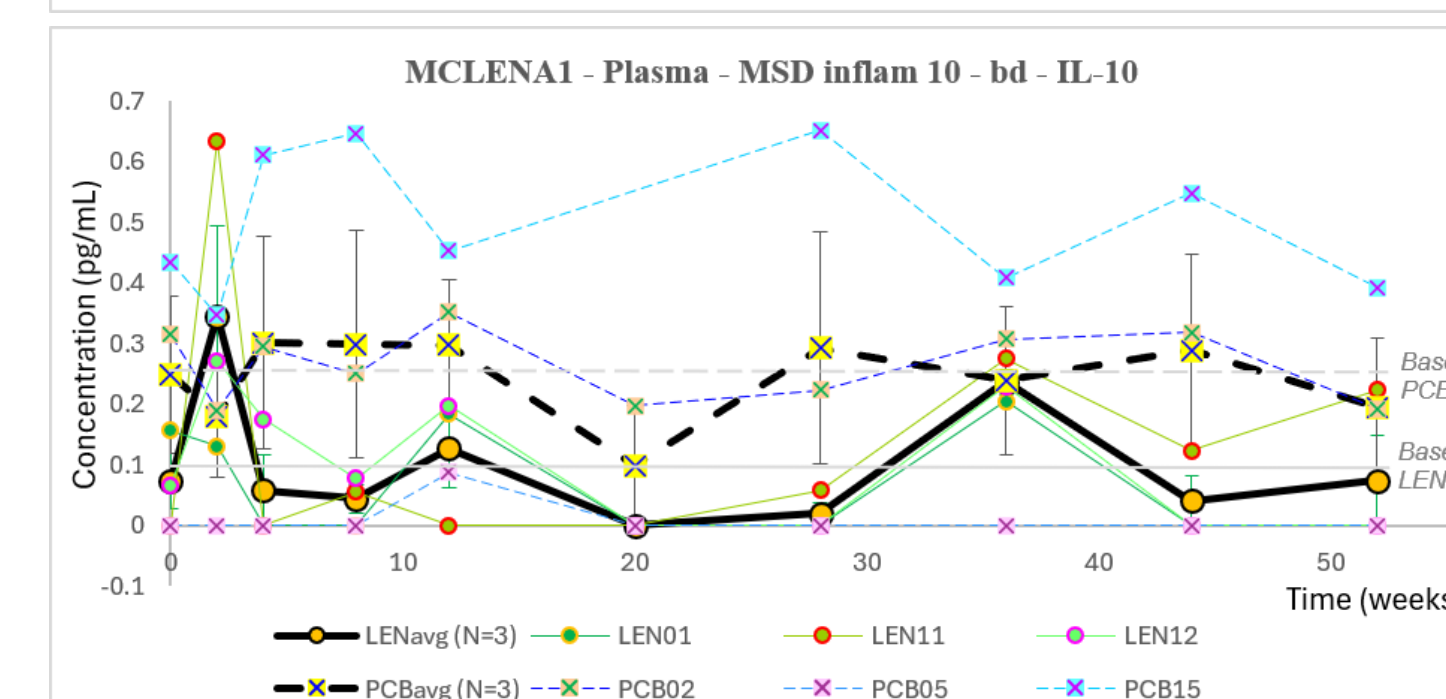
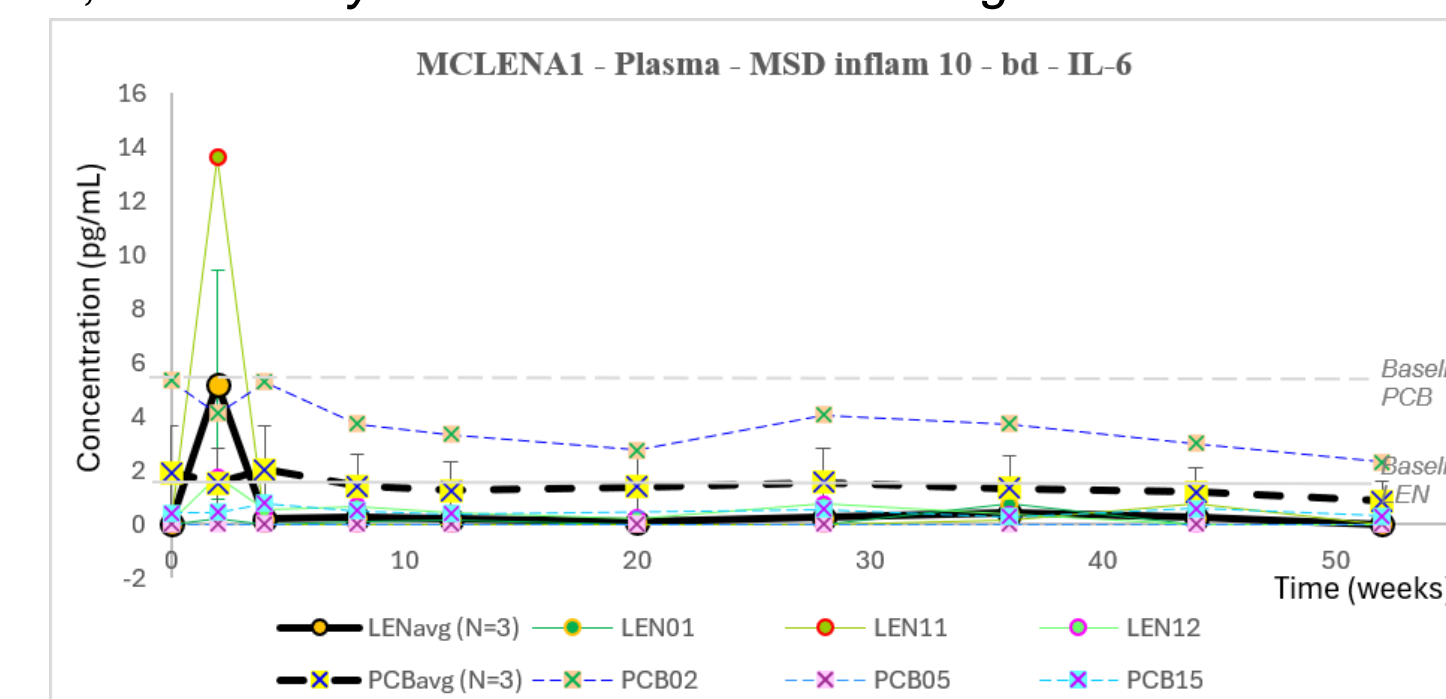
Figure 1: Plasma levels of TNF- α , IL-2, and IL-13 were lower at week 52 (red arrows) compared to baseline in lenalidomide (LEN)-treated subjects. "avg": average, "PCB": placebo.



Results (continued)

Treatment of MCI patients with lenalidomide 10mg/day for 52 consecutive weeks was safe overall. The drug induced a small decrease in plasma levels of TNF- α , IL-2, and IL-13 at the end of dosing (Fig. 1). Two cytokines with opposite effects were transiently increased at week 2 in one lenalidomide-treated subject (Fig. 2). The other 5 markers of inflammation had dynamic changes throughout the trial, but no change at the end of dosing (Fig.3).

Figure 2: Plasma levels of IL-6 and IL-10 were transiently increased at week 2 in one LENA subject. Note that this subject, #11, had history of infections before dosing onset.



Conclusion

Lenalidomide appears to have engaged its targets because we observed the following changes in plasma biomarkers:

- a decrease in lenalidomide's main molecular target TNF- α after 52 weeks;
- a small alteration in IL-13 levels, which is one of the cytokines involved in chronic inflammatory conditions;
- a reduction in IL-2, which is one cytokine involved in T cells stimulation, including the proliferation of Tregs.

These Phase 1b results suggests that the null hypothesis is not met, which warrants further testing in a larger cohort.

Limitations and Future Directions

- Additional analyses using the NULISA platform are next.
- The sample size of this Phase 1b is too small to reach signal significance. However, the data support further development.
- A second study, termed MCLENA 2, has started with a focus on biomarker (CSF and plasma) endpoints over 6 months of lenalidomide exposure at 10 mg/day.

Acknowledgements

This project was funded by National Institute on Aging (NIA) grant #R01AG059008. Additional funding includes NIA #R01AG073212 and ADDF #GC-2013717. The funders had no role in study design, data collection and analysis, or preparation of the poster.

Results (continued)

Figure 3: Plasma levels of IL-1 β , IL-4, IL-8, IL-12p70, and IFN- γ had dynamic variations during drug exposure, but ended at the same as level as baseline at week 52.

