Treatment of Alzheimer's Disease Subjects With Expanded Non-genetically Modified Natural Killer Cells (SNK01) With Enhanced Activity — Final Report of a Phase I Dose Escalation Study

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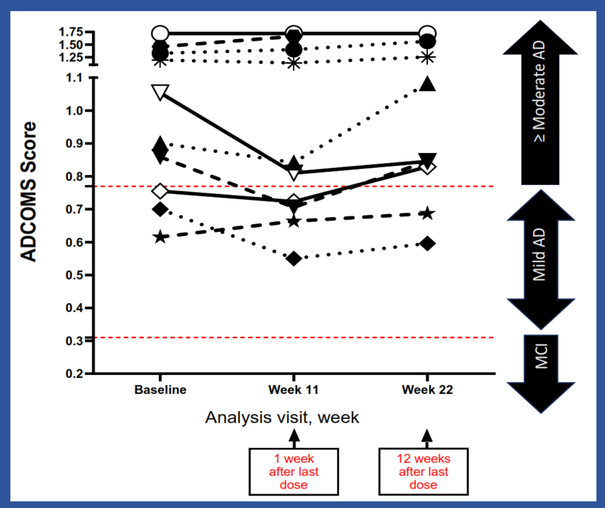
#LP129

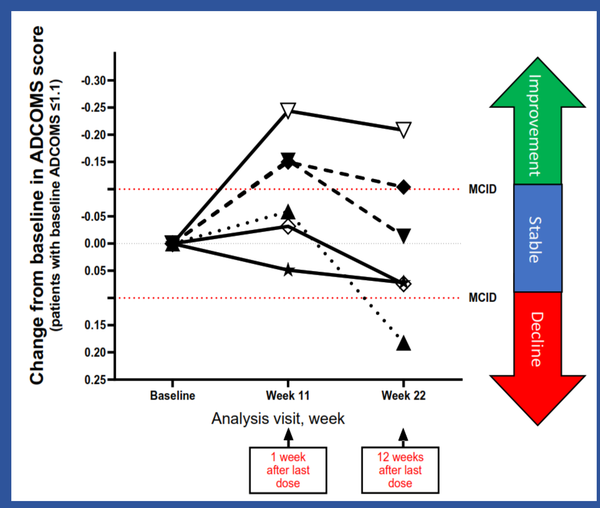
PURPOSE / OBJECTIVES

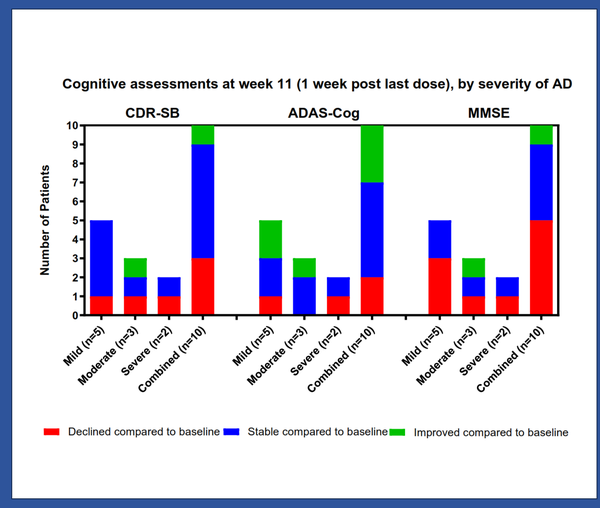
- Misfolded protein deposits are known to elicit a cascade of reactive neuroinflammation and damage in Alzheimer's disease (AD).
- Natural Killer (NK) cells are an essential part of the innate immune system. NK cells can shape the adaptive response by eliminating activated autologous CD4+ T cells (not resting cells). NK cells' effects may be related to their capability of balancing the ratio of protective microglia to proinflammatory microglia, the secretion of IL-10 leading to the inactivation of inflammatory cells, and their ability to degrade neurotoxic aggregates such as α-synuclein and amyloid-β.
- SNK01 is a first-in-kind, autologous non-genetically modified NK cell product with significantly increased activity and over 90% activating receptor expression that can be consistently produced from any donor.
- We hypothesized that SNK01 is safe, can cross the blood brain barrier (BBB) and can reduce inflammation in AD patients.

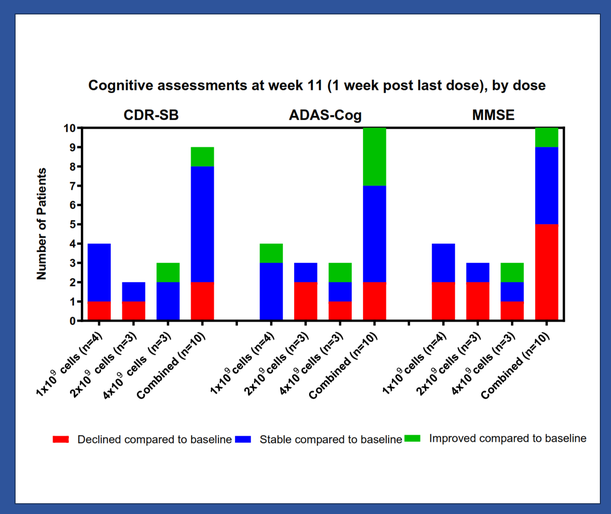
RESULTS

Cognitive Assessments

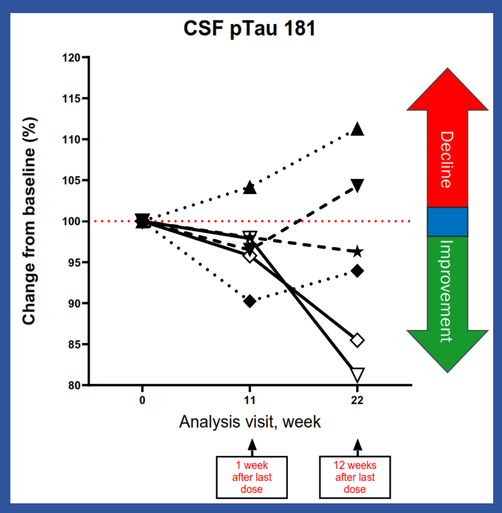


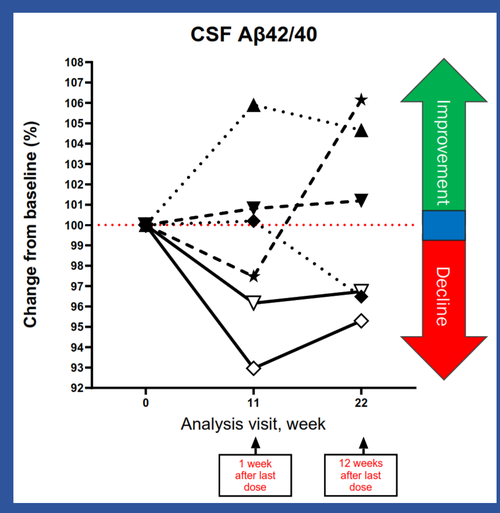


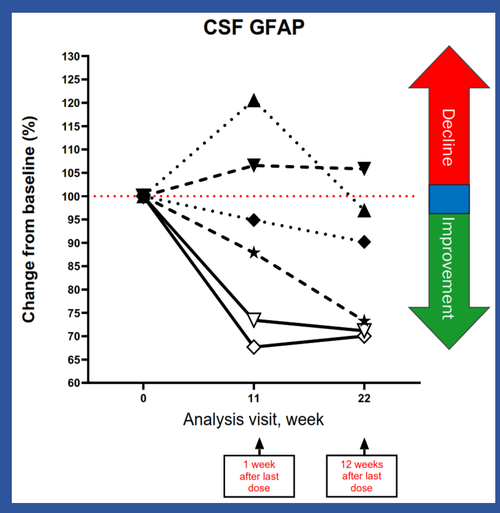


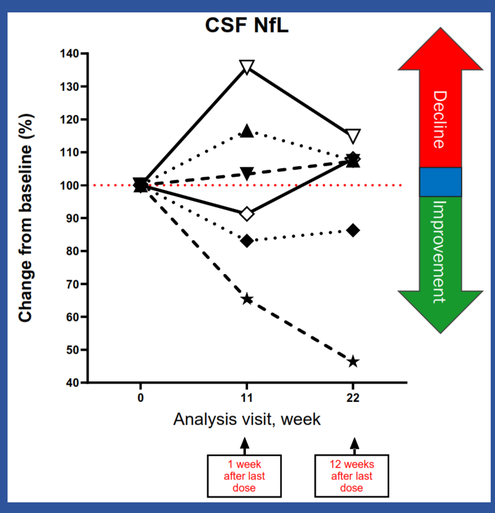


CSF Biomarkers









KEY

- MX04-201-002 (moderate AD, low dose)
- MX04-201-003 (moderate AD, low dose)
- MX04-201-004 (mild AD, low dose)
- MX04-201-005 (mild AD, low dose)
- MX04-201-006 (severe AD, mid dose)
- MX04-201-007 (mild AD, mid dose)
- MX04-201-011 (mild AD, mid dose)
- MX04-201-012 (severe AD, high dose)
- MX04-201-014 (moderate AD, high dose)
- MX04-201-015 (mild AD, high dose)

1x10⁹ cells
2x10⁹ cells
4x10⁹ cells

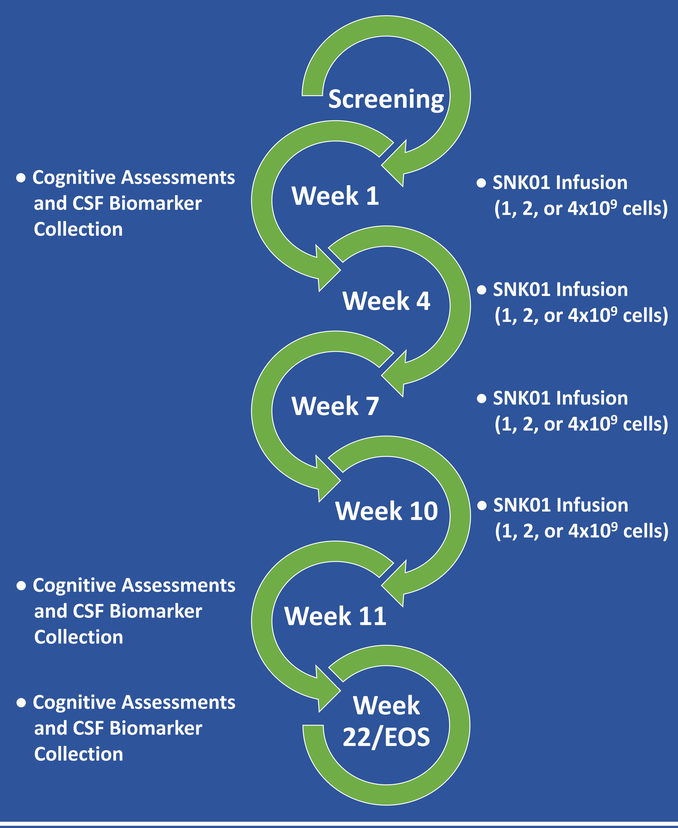
Subject 006 – Did not complete W22 cognitive assessments

Biomarkers shown for patients 004, 005, 007, 011, 014 & 015

MATERIALS & METHODS

- In this Phase 1 dose escalation study (Study SNK01-MX04: Single Center, Open-Label, Phase 1 Study to Evaluate the Safety, Tolerability and Exploratory Efficacy of SNK01 in Subjects with Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD); NCT04678453), SNK01 was administered intravenously (IV) every three weeks for a total of 4 treatments using a 3+3 dose escalation design (1, 2 & 4x10^9 cells) in patients with either mild, moderate or advanced disease confirmed by MRI and PET scans. Assessment of severity of AD was based on the baseline CDR-SB score. Participants were on standard of care for AD.
- Cognitive assessments (CDR-SB, ADAS-Cog and MMSE) and CSF biomarker analyses were performed at baseline and at one week and 12 weeks after the final dose (Weeks 11 and 22 respectively).
- MCIDs used to determine stable or improved status: CDR-SB +2 (mild, moderate and severe); ADAS-Cog +3 (mild) or +4 (moderate and severe); MMSE -2 (mild) or -3 (moderate and severe); ADCOMS -0.1*
- Primary endpoint was safety and secondary endpoints included changes in cognitive assessments and biomarker levels.

STUDY DESIGN



RESULTS

- 10 AD patients from the first three cohorts in the dose escalation were analyzed. Five patients had mild AD, three patients had moderate AD and two patients had severe AD.
- Median age was 79 (56—85). Median baseline scores for CDR-SB was 9 (4-18), for ADAS-Cog was 27.5 (18-65) and for MMSE was 14 (2-23).
- NK cells were successfully activated and expanded from every patient.
- No treatment-related adverse events have been observed to date.
- When tested 1 week after the last dose (week 11),
  - 30% of patients showed clinically important improvement on the composite ADCOMS score compared to baseline
  - 60% of patients showed a stable ADCOMS score compared to baseline
  - 50-70% of participants were stable or improved on the CDR-SB, ADAS-Cog and/or MMSE scores
  - One patient's score showed a switch from a moderate classification on the ADCOMS to a mild classification.
- When tested at 12 weeks after the last dose (week 22),
  - 44-89% of patients remained stable or improved in all cognitive scores compared to week 11
  - 50% of patients' ADCOMS scores remained stable compared to week 11.
- Based on the CSF biomarker data, SNK01 given via peripheral IV appears to cross the blood-brain barrier to reduce CSF pTau181 levels and GFAP (marker of neuroinflammation); this effect appears to be persistent at week 22.

CONCLUSIONS

- SNK01 was very safe and well tolerated.
- Results suggest that SNK01 may have significant clinical activity in AD.
- This data warrants further investigation in a larger Phase II trial with higher doses and a longer treatment duration, as no dose limiting toxicities were observed.

*Tahami Monfared AA, Houghton K, Zhang Q, Mauskopf J, for the Alzheimer's Disease Neuroimaging Initiative. Staging Disease Severity Using the Alzheimer's Disease Composite Score (ADCOMS): A Retrospective Data Analysis. Neurol Ther. 2022 Mar;11(1):413–34.

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