Use of Non- genetically Modified Natural Killer Cells (SNK01) With Enhanced Activity in Subjects with Active Alzheimer's Disease: Further Biomarker Analysis and Implications for Use in Prevention

#P105

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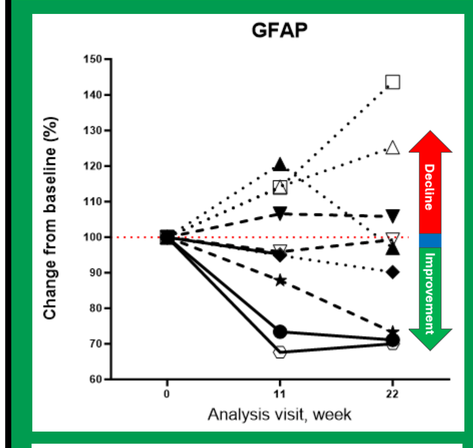
Purpose / Objectives

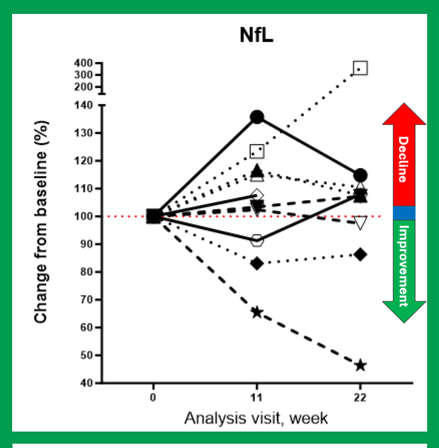
- Dementia remains an enormous global problem of which Alzheimer's disease (AD) is the leading cause. By 2030, the number of cases is expected to exceed 80 million.
- Due to the lack of disease modifying therapies, more emphasis is being placed on pre-emptive diagnosis and developing preventative therapies.
- A recent study by Guo* correlated elevated serum/plasma levels of GFAP, NF-L, GDF15 and LTBP2 with a 2.32 times greater risk of developing dementia in the U.K., while a study by Cai** found that Aβ42, p-tau181, and NF-L could be detected 8 years before clinical onset of AD in Chinese populations.
- SNK01 is an autologous non-genetically modified NK cell product with highly enhanced cytotoxicity and activating receptor expression which has been previously shown to cross the blood brain barrier to reduce neuroinflammation and improve protein levels in CSF and plasma.
- We reanalyzed our biobank to see if SNK01 had any effect on these additional implicated biomarkers associated with increased AD risk.

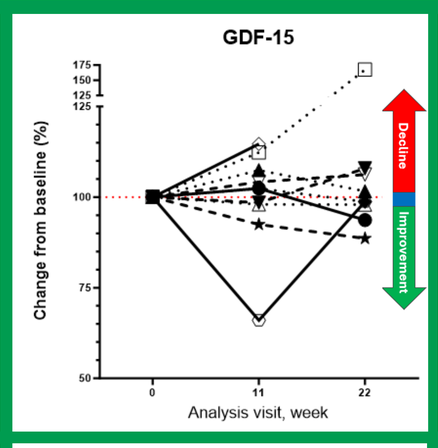
Material & Methods

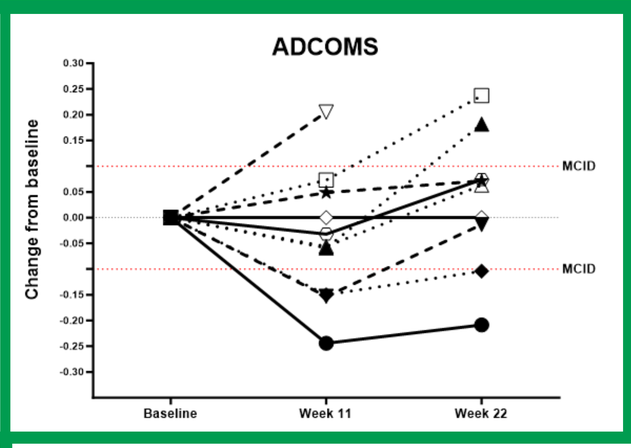
- In this Phase 1 study, SNK01 was administered IV every three weeks for a total of 4 treatments using a 3+3 dose escalation design (1, 2 and 4 x 109 cells) in subjects with either mild, moderate, or severe AD (Median MMSE of 14).
- Cognitive assessments and CSF and plasma biomarker analyses were performed at baseline and at 1 and 12 weeks after the final dose.
- The ADCOMS is a composite measure that incorporates clinically sensitive items from the ADAS-Cog, MMSE, and CDR-SB scales. A change of 0.1 in the ADCOMS score is considered clinically meaningful, representing the Minimal Clinically Important Difference (MCID)*** .
- The primary endpoint was safety and secondary endpoints included changes in cognitive assessments and biomarker levels. Samples were re-analyzed for GDF-15 and LTBP2

Results







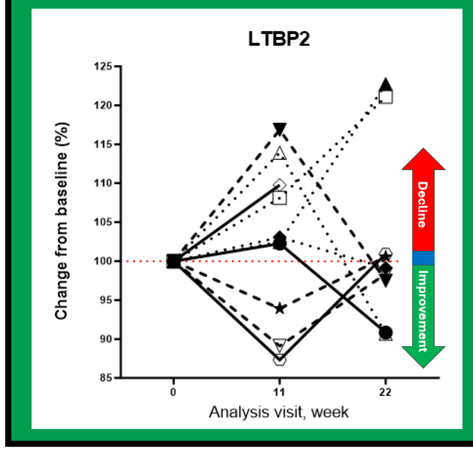


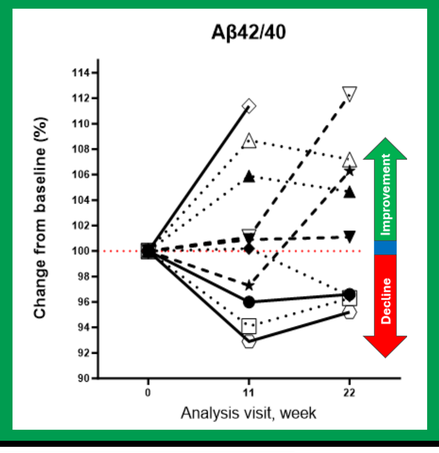
CSF and cognitive evaluation at one-week (Week 11) and 12-weeks (Week 22) after the final dose

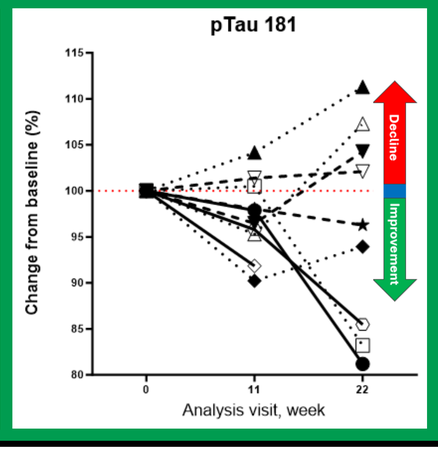
002 (moderate)
003 (moderate)
004 (mild)
005 (mild)
006 (severe)
007 (mild)
011 (mild)
012 (severe)
014 (moderate)
015 (mild)

Subject 006 – Did not complete W22 cognitive assessments
Subject 012 – Did not complete W22 biomarker assessments

1x10^9 cells
2x10^9 cells
4x10^9 cells



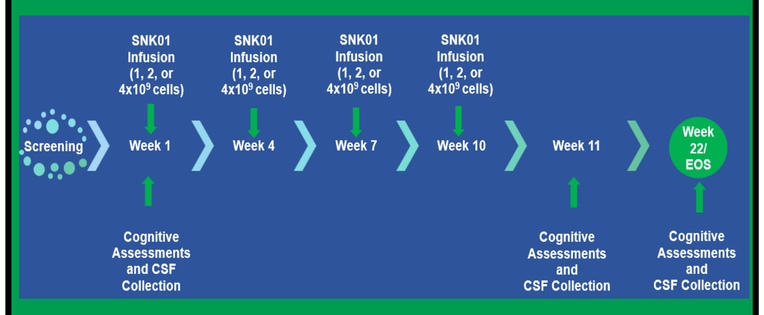




CSF Analysis		GFAP - cfb		NFL - cfb		GDF-15- cfb		LTBP2 - cfb		Aβ-42/40 - cfb		p-Tau 181- cfb	
Subject	AD Stage	Week 11	Week 22	Week 11	Week 22	Week 11	Week 22	Week 11	Week 22	Week 11	Week 22	Week 11	Week 22
MX04-201-002	Moderate	↑	↑	↑	↑	↑	↑	↑	↑	↓	↓	↑	↓
MX04-201-003	Moderate	↑	↑	↑	↑	↓	↓	↑	↓	↑	↑	↓	↑
MX04-201-004	Mild	↑	↓	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
MX04-201-005	Mild	↓	↓	↓	↓	↑	↓	↑	↓	↑	↓	↓	↓
MX04-201-006	Severe	↓	↓	↑	↓	↑	↑	↓	↓	↑	↑	↑	↑
MX04-201-007	Mild	↑	↑	↑	↑	↓	↑	↑	↓	↑	↑	↓	↑
MX04-201-011	Mild	↓	↓	↓	↓	↓	↓	↓	↑	↓	↑	↓	↓
MX04-201-012	Severe	↓		↑		↑		↑		↑		↓	
MX04-201-014	Moderate	↓	↓	↑	↑	↑	↓	↑	↓	↓	↓	↓	↓
MX04-201-015	Mild	↓	↓	↓	↑	↓	↓	↓	↑	↓	↓	↓	↓

cfb=change from baseline — Improved — Declined

Study Design



- Eleven subjects (5 males and 6 females) were enrolled, of which 10 were evaluable.
- The median age of the participants was 79 years (56 to 85 years).

Summary

- Eleven subjects (5 males and 6 females) were enrolled and 10 were evaluable. Median age was 79 years (56 to 85 years).
- No treatment related adverse events were observed.
- Despite 70% of subjects being treated at relatively low doses of SNK01, 90% of all evaluable subjects had either stable or improved (±0.1) composite ADCOMS scores at week 11 (one-week after the final dose).
- Additionally, one-week post-final dose, improvement in CSF biomarkers were observed in 70% p-Tau181, 60% AB42/40 ratio, 60% GFAP, 40% GDF-15, 30% LTBP2, and 30% NF-L.

Conclusions

- SNK01 was very safe
- Despite suboptimal dosing for 2/3 of subjects, SNK was able to positively affect biomarkers that are associated with increased AD development.
- Result may suggest SNK01 could potentially be a safe preventative intervention for high-risk individuals.
- Further study in markers related to predicting risk of AD and Dementia would be beneficial to support the investigation.

*Guo, Yu et al. "Plasma proteomic profiles predict future dementia in healthy adults." Nature aging vol. 4,2 (2024): 247-260. doi:10.1038/s43587-023-00565-0
**Cai, Huimin et al. "Plasma biomarkers predict Alzheimer's disease before clinical onset in Chinese cohorts." Nature communications vol. 14,1 6747. 24 Oct. 2023, doi:10.1038/s41467-023-42596-6
***Tahami Monfared, Amir Abbas et al. "Staging Disease Severity Using the Alzheimer's Disease Composite Score (ADCOMS): A Retrospective Data Analysis." Neurology and therapy vol. 11,1 (2022): 413-34. doi:10.1007/s40120-022-00326-y

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