Use of Expanded Non-Genetically Modified Natural Killer Cells (SNK01) with Enhanced Cytotoxicity in Patients with Alzheimer's Disease — Interim Report of a Phase I Trial

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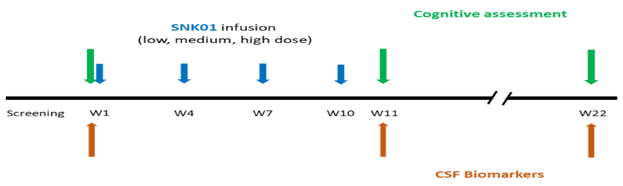
PURPOSE / OBJECTIVES

- The accumulation of misfolded proteins is known to elicit a cascade of neuroinflammation by CNS-resident or infiltrating immune cells, resulting in neuronal cell death in Alzheimer's disease (AD). It is now recognized that only clearing these proteins would not be the best treatment strategy for AD.
- Natural Killer (NK) cells are an essential part of the innate immune system that have been shown pre-clinically to slow progression of amyloid deposition as well as to decrease neuroinflammation by recognizing and eliminating autoreactive immune cells and damaged neurons.
- SNK01 is a first-in-kind, autologous non-genetically modified NK cell product with high cytotoxicity and over 90% activating receptor expression. It can be consistently produced from any patients for clinical use.
- We hypothesize that SNK01 can be safely infused to reduce neuroinflammation by crossing the blood brain barrier (BBB) in AD patients.

MATERIAL & METHODS

- In this Phase 1 dose escalation study (Study SNK01-MX04, NCT04678453), SNK01 was administered intravenously (IV) every three weeks for a total of 4 treatments using a 3+3 dose escalation design [low dose (1 x 10^9 cells), medium dose (2 x 10^9 cells), and high dose (4 x 10^9 cells)] in subjects with either mild, moderate or severe AD confirmed by MRI and PET scans. Assessment of baseline severity was based on the CDR-SB score.
- Cognitive assessments (CDR-SB, ADAS-Cog and MMSE) and CSF analyses (by electrochemiluminescent multiplexed immunoassays) were performed at baseline and at one week and 12 weeks after the final dose (Weeks 11 and 22, respectively) (See Study Design).
- Primary endpoint was safety and secondary endpoints included changes in cognitive assessments and CSF biomarker levels. Minimal Clinically Important Differences (MCID) in cognitive assessment scores were set at the level for mild AD and taken from Andrews et al 2019* (CDR-SB, 2; ADAS-Cog, 3; and MMSE, 2)

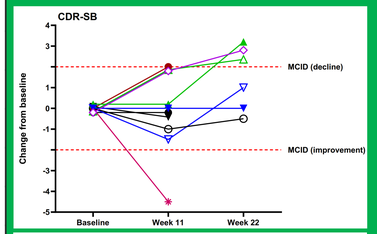
STUDY DESIGN

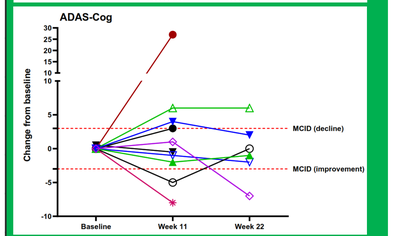


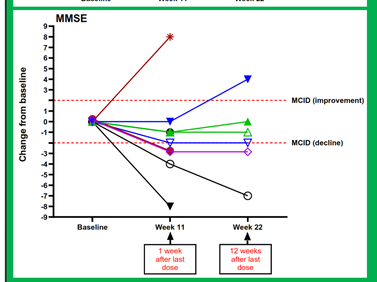
*Andrews JS, Desai U, Kirson NY, Zichlin ML, Ball DE, Matthews BR. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. *Alzheimers Dement (N Y)* 5: 354-363, 2019.

RESULTS

Cognitive Assessments

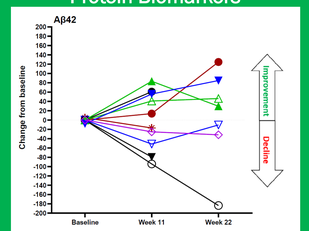


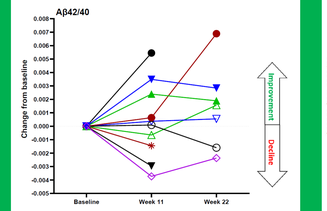


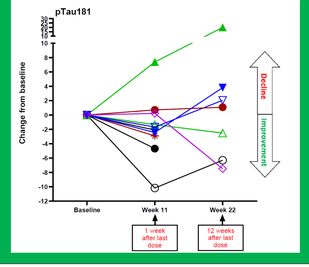


CSF Biomarkers

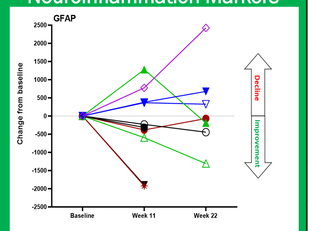
Protein Biomarkers

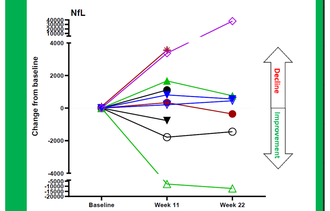


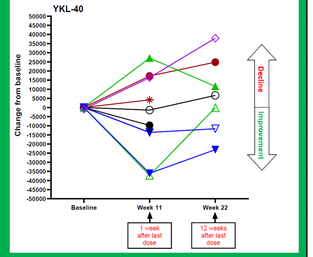




Neuroinflammation Markers







- Ten subjects with mild (n=5) and moderate to severe AD subjects (n=5) were enrolled in the three dose-escalation cohorts. Median age was 79 (56-85). Baseline median scores for CDR-SB, ADAS-Cog, and MMSE were 9 (4-18), 27.5 (18-65), and 14 (2-23), respectively.
- SNK01 was successfully activated/expanded from all enrolled subjects' peripheral blood and then administered.
- No treatment related adverse events have been observed to date.
- Treatment with SNK01 showed a tendency to stabilize or improve cognition by cognitive assessments with changes in some CSF biomarker levels when tested 1 week after the last dose. Some subjects maintained this treatment effect and biomarker levels when tested at 12 weeks after the last dose. Especially, subject 014 treated with high dose showed a marked improvement of cognition by cognitive assessments as well as favorable changes in GFAP and pTau181 levels.

Subject ID (dose level, AD severity)

- MX04-201-002 (low, mod)
- MX04-201-003 (low, mod)
- MX04-201-004 (low, mild)
- MX04-201-005 (low, mild)
- MX04-201-006 (mid, sev)
- MX04-201-007 (mid, mild)
- MX04-201-011 (mid, mild)
- MX04-201-012 (high, sev)
- MX04-201-014 (high, mod)
- MX04-201-015 (high, mild)

SUMMARY

	Week 11 (1 week post last dose)		Week 22 (12 weeks post last dose)
Cognitive Assessments	**Stable or Improved**		**Stable or Improved compared to Week 11 using MCID**
CDR-SB	7/10 (70%)		4/6¨ (67%)
ADAS-Cog	6/10 (60%)		5/6¨ (83%)
MMSE	5/10 (50%)		5/6¨ (83%)
Protein Biomarkers	**Stable or Improved**	**Improved**	**Rebound from Stable or Improved**
Aβ42	5/10 (50%)	5/10 (50%)	1/4 (25%)†
Aβ42/40	6/10 (60%)	3/10 (30%)	3/5 (60%)†
pTau181	9/10 (90%)	7/10 (70%)	3/6 (50%)† and **
Neuroinflammation Markers	**Stable or Improved**	**Improved**	**Rebound from Stable or Improved**
GFAP	6/10 (60%)	6/10 (60%)	1/3 (33%)† and **
NfL	5/10 (50%)	3/10 (30%)	1/4 (25%)§
YKL-40	6/10 (60%)	5/10 (50%)	4/4 (100%)† and §

¨ 2 subjects early terminated before reaching Week 22, 2 subjects are pending Week 22 visits
** 2 subjects are pending Week 22 visits
† 1 subject early terminated from the study
§ 1 subject is pending Week 22 visit

Effect of SNK01 Dose: Dose responses were seen for the following outcome measures (data not shown)

● CDR-SB ● MMSE ● pTAU181 ● GFAP ● YKL-40

CONCLUSIONS

- SNK01 was safe and well tolerated.
- SNK01 appears to have substantial clinical activity in AD.
- Based on the CSF biomarker data, SNK01 given via peripheral IV seems to reduce pTau181 and neuroinflammation in a dose-dependent manner by crossing the blood brain barrier. There appears to be a rebound effect when SNK01 treatment is discontinued.
- This result warrants a further investigation in a larger Phase II trial with a higher dose and longer treatment duration.

CONTACT

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