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A Phase 1 Single Ascending Dose Study Evaluating the Safety, Tolerability, and Pharmacodynamic Effects of MDK-703, an IL-7 Mimetic With Extended Half-life

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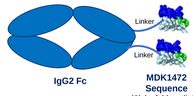
Introduction

IL-7 receptor (IL-7R) signaling is essential for the development and homeostasis of T-cell subpopulations and the maintenance of the T-cell receptor clonal repertoire. Emerging evidence indicates the potential clinical utility of IL-7R agonists for immunotherapy of lymphopenia, oncology, and other indications. However, IL-7-based proteins studied in humans show a propensity to induce anti-drug antibodies (ADAs), including those that neutralize natural IL-7(1). Previously, we reported the discovery of MDK-1472, a peptidyl agonist of IL-7R with MW <5 KD, which is structurally unrelated to IL-7 and therefore unlikely to generate IL-7 neutralizing antibodies. MDK-703, an Fc fusion of MDK-1472, activated IL-7R signaling, and expanded T cells, particularly stem-like memory T cells (Tscm) in vitro and in vivo mouse and NHP studies(2).

Here, we report interim data from the first 2 Cohorts of the Phase 1 clinical trial, NCT05366634, a randomized, single-blind, placebo-controlled, single ascending dose, single-site study, to determine the safety, tolerability, and PK/PD of MDK-703 in healthy adult subjects.

MDK1472 and MDK-703

MDK-703



Binding Affinity (by BLI)	K_D (nM)	
	hIL-7Rα	hγc
MDK1472	300	17
IL-7	2.3	ND

Potency (ex vivo hPBMCs)	pSTAT5 EC50 (pM)	
	CD8	CD4
MDK-703	780	1300
IL-7	4.4	4.3

MDK-1472 (IL-7 PEPTIKINE™)

- Synthetic peptide contains a peptide ligand to IL-7Rα connected to a peptide ligand for γc
- Sequence is unrelated to IL-7 or other human proteins

MDK-703 (Fc Fusion with C-terminal MDK-1472 Sequence)

- In NHP, MDK-703 intramuscular injection demonstrated high bioavailability, with an MDK-703 AUC similar to intravenous injection(2)
- Did not block the activity of IL-2, IL-4, IL-9, IL-15, or IL-21(3)
- In silico assessment of potential immunogenicity (EPIVAX) indicated a low probability of the presence of Class II (HLA-DR) restricted HLA ligands and putative T cell epitopes(4)

Phase 1 Clinical Trial Design

Objectives: Establish safety, tolerability, PK, and PD of MDK-703 and the absence of IL-7 neutralizing antibodies in healthy volunteers

Study Design

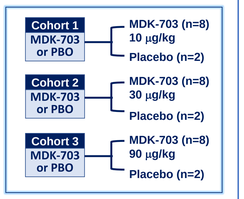
- Single IM dose
- Three sequential cohorts: N=10 per cohort

PD Biomarkers

- Absolute lymphocyte counts
- Immunophenotyping

ADAs/ Nabs

- MDK-703 and IL-7



Demographics

Demographics	Category	Placebo (N=4)	MDK-703 10 μg/kg (N=4)	MDK-703 30 μg/kg (N=8)
Median age (range)	-	31.3 (23-43)	36.8 (23-49)	27.5 (18-50)
Gender, n (%)	Male	2 (50)	3 (75)	6 (75)
	Female	2 (50)	1 (25)	2 (25)
Ethnicity, n (%)	Not Hispanic or Latino	2 (50)	1 (25)	6 (75)
	Hispanic or Latino	1 (25)	2 (50)	1 (12.5)
	Unknown	1 (25)	1 (25)	1 (12.5)

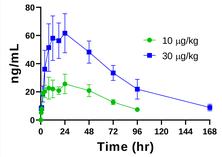
Fig 1. Phase 1 Clinical Design. The Phase 1 clinical trial is a randomized, placebo-controlled, single-blind, single ascending dose study to evaluate the safety, tolerability, PK, and PD of MDK-703 in healthy adult volunteers. The table above shows demographic information.

Safe and Well-Tolerated

TEAEs	Placebo N = 4 nS (%)	MDK-703 10 μg/kg (N = 4) nS (%)	MDK-703 30 μg/kg (N = 8) nS (%)
Abdominal pain	1 (25.0%)	0	0
Aphthous ulcer	0	1 (25.0%)	0
Nausea	1 (25.0%)	0	0
Catheter site injury	1 (25.0%)	0	0
Feeling of body temperature change	1 (25.0%)	0	0
Injection site pruritus	0	1 (25.0%)	0
Vessel puncture site bruise	0	0	1 (12.5%)
COVID-19	0	1 (25.0%)	0
Folliculitis	1 (25.0%)	0	0
Upper respiratory tract infection	1 (25.0%)	0	0
Fall	1 (25.0%)	0	0
Limb injury	1 (25.0%)	0	0
Headache	0	0	2 (25.0%)
Rhinorrhea	1 (25.0%)	0	0
Dermatitis contact	1 (25.0%)	0	0

Table 1. Adverse events of MDK-703 in healthy volunteers. All AEs were Grade 1 and 2. nS = number of subjects with an adverse event; N = number of subjects; % = percentage of subjects with an adverse event (nS/N×100).

Dose-Dependent, Extended Blood Concentrations



Treatment	Parameter	Units	Mean ± SD
10 μg/kg	T_{max}	hr	24 ± 17
	C_{max}	ng/mL	27.7 ± 5.4 (440 pM)
	AUC_{inf}	hr*ng/mL	2040 ± 278
	$t_{1/2}$	hr	31.5 ± 5.6
30 μg/kg	T_{max}	hr	15.7 ± 6.4
	C_{max}	ng/mL	63.1 ± 13.4 (990 pM)
	AUC_{inf}	hr*ng/mL	5390 ± 724
	$t_{1/2}$	hr	39.4 ± 16.1

Fig 2. The concentration of MDK-703 in plasma samples was determined at the indicated time points by a sandwich MCD-ESL immunoassay with an anti-MDK1472 antibody. PK parameters were determined using Phoenix WinNonlin v8.3 (Certara, Princeton, NJ).

Sustained Elevation of Blood Lymphocytes

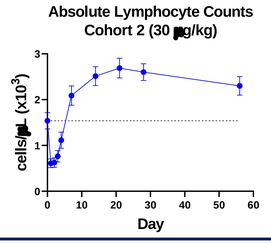


Fig 3. Blood samples were serially collected at the indicated times, and complete blood cell counts were determined. Absolute lymphocyte cell counts per μL of blood samples are shown as mean ± SEM. The dotted line indicates the baseline value.

Sustained Elevation of Blood CD8 and CD4 T Cells

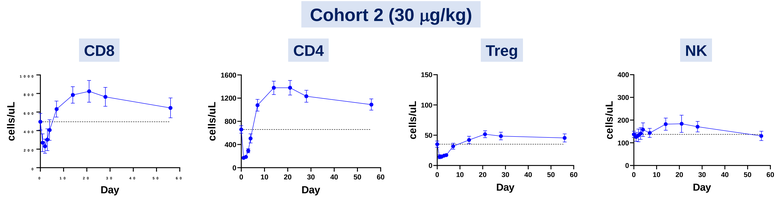


Fig 4. Blood samples were collected serially at the indicated times and analyzed by flow cytometry. The dotted lines indicate baseline values. Data are mean ± SEM.

Sustained Elevation of Blood Memory T Cells

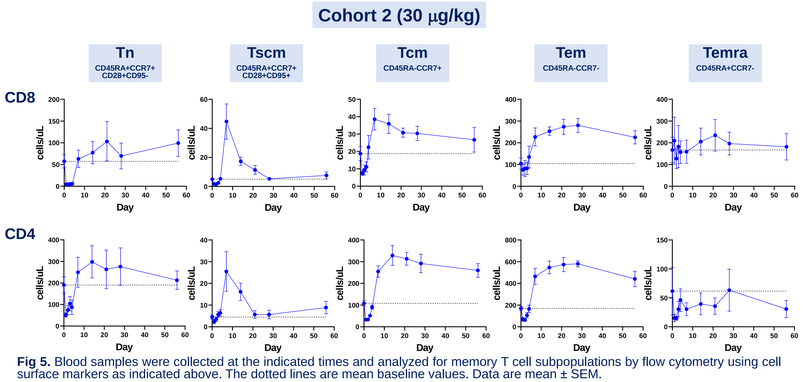


Fig 5. Blood samples were collected at the indicated times and analyzed for memory T cell subpopulations by flow cytometry using cell surface markers as indicated above. The dotted lines are mean baseline values. Data are mean ± SEM.

Summary & Conclusion

- At doses of 10 and 30 μg/kg, MDK-703 was safe and well-tolerated in healthy adults.
- MDK-703 blood levels were consistent with high bioavailability with a half-life of >30 hours.
- Compared to baseline, 30 μg/kg of MDK-703 produced sustained elevations of blood ALC, CD8, and CD4 T cells but no minimal increases in Tregs and NK cells.
- In addition, 30 μg/kg of MDK-703 produced sustained elevations of blood CD8 and CD4 central memory (Tcm) and effector memory (Tem) cells. Increased blood CD8 and CD4 stem-like memory T cells (Tscm) peaked at week 1. It is known that Tscm and Tcm populations exist primarily in lymphoid tissue(5) and that blood levels may not directly correlate with levels in lymphoid tissue.
- Further analysis of PD effects and the presence of ADAs, as well as completion of Cohort 3 (90 μg/kg) is ongoing (NCT05366634).

1) Clin Transl Sci (2020) 13, 1161–1169
2) AACR; Cancer Research (2022) 82_supplement. Abstract 2066
3) SITC-2020-SITC2020.0567
4) Human Vaccines & Immunotherapeutics (2015) 11, 2312-2321
5) Nat Rev Immunol. (2014) 14, 24–35