MOZART THERAPEUTICS

Orchestrating The Immune System

Phase 1a Study Evaluating the Safety, Pharmacokinetics, and Pharmacodynamics of MTX-101 in Healthy Adults

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BACKGROUND

Regulatory CD8 T cells (CD8 Treg) selectively kill pathogenic T cells which can attack host tissues. In autoimmune disease, CD8 Treg are dysfunctional and fail to control the expansion of pathogenic T cells. This dysfunction is related to the expression of inhibitory killer immunoglobulin-like receptors (KIR; KIR2DL isoforms 1–3) on CD8 Treg. MTX-101 is a bispecific antibody that targets inhibitory KIR and CD8 to restore CD8 Tregs ability to kill pathogenic T cells. We conducted a Phase 1a study to evaluate the safety, pharmacokinetics, and pharmacodynamics of MTX-101 in healthy adults.

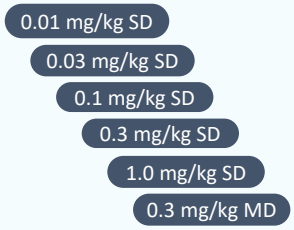
METHODS AND RESULTS

Healthy adults (N=36) were randomized to receive MTX-101 or Placebo (2:1) in 5 single-dose (SD) escalating dose cohorts (0.01mg/kg to 1mg/kg) and one multiple-dose (MD) cohort (2 doses at 0.3mg/kg administered 3 weeks apart). No serious adverse events occurred. Nearly all treatment-emergent adverse events were mild or moderate (grades 1 and 2) in severity and transient. All participants who received MTX-101, regardless of dose, experienced a transient (24–48h) dose-independent decrease in lymphocyte count (2 were grade 3), consistent with target engagement. Pharmacokinetic parameters were dose-proportional, predictable, and weight-independent. 100% KIR receptor occupancy was achieved at the lowest dose (0.01mg/kg). Dose-proportional extension of the duration at ≥75% KIR receptor occupancy was observed with higher doses, the longest of which was 42 days at 1.0mg/kg. All participants who received MTX-101 experienced transient dose-independent increases in serum cytokines, along with selective CD8 Treg activation and proliferation.

These findings indicate that among healthy adults, MTX-101 was safe and well-tolerated, has a PK and RO profile that will likely support flat dosing at a minimum frequency of every four weeks, and has pharmacodynamic properties that indicate highly selective engagement and activation of CD8 Treg. MTX-101 continues to be developed as a promising novel targeted approach to restoring immune homeostasis.

Phase 1a: Healthy Adults (N=36)

- Six participants per cohort
- Randomized 2:1, MTX101:Placebo



MD: 2 doses, 3 weeks apart

MTX-101 is Well-Tolerated in Healthy Adults

Treatment-Emergent Adverse Events n (%)	Placebo (n=12)	MTX-101 All (n=24)	MTX-101 SAD (n=20)	MTX-101 MD (n=4)
Any TEAE	5 (41.7)	22 (91.7)[1]	18 (90.0)	4 (100)
Grade 1	3 (25)	18 (75)[2]	15 (75.0)	3 (75.0)
Grade 2	2 (16.7)	11 (45.8)[3]	8 (40.0)	3 (75.0)
Grade 3	0 (0)	2 (8.3)[4]	2 (10.0)	0 (0)

Note: each participant is counted once per AE grade

[1] TEAE occurring in >1 participant receiving MTX-101: headache (n=8), lymphocyte count decreased (n=8), myalgia (n=5), chills (n=3), URTI (n=3), vascular access site bruising (n=2), back pain (n=2), dermatitis contact (n=2), dizziness (n=2)

[2] Includes one Grade 1 CRS (0.03 mg/kg dose); managed with 1000mg paracetamol, resolved within 4hr. Premedication with paracetamol and cetirizine instituted for all subsequent dose cohorts

[3] Includes lymphocyte count decreased (n=6)

[4] lymphocyte count decreased (n=2); neutrophil count decreased (n=1)

Table 1: Treatment-Emergent Adverse Events in MTX-101 Phase 1A Study.
Five single-dose and one multi-dose cohorts were evaluated. No serious or grade ≥4 events were observed, and no evidence of immunosuppression. No significant laboratory-related events were seen other than transient (~24hr) lymphocyte and neutrophil changes. Each participant was counted once per AE grade.

MTX-101 Induces Transient Changes in Lymphocyte and Neutrophil Populations

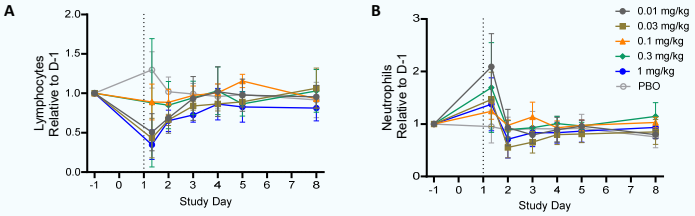


Figure 1: Transient Changes in Lymphocyte and Neutrophil Counts after MTX-101 Dosing
Absolute numbers of **(A)** Lymphocytes and **(B)** Neutrophils were taken from complete blood counts. Differences relative to Study Day -1 were then calculated.

MTX-101 Induces Increase in Serum Cytokines and Selective Activation of CD8 Treg

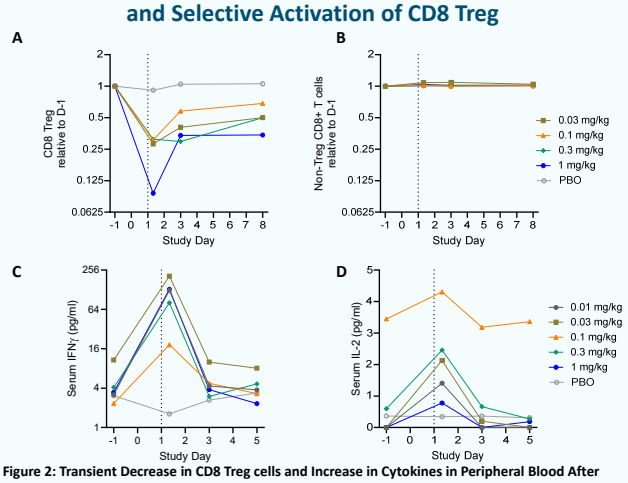


Figure 2: Transient Decrease in CD8 Treg cells and Increase in Cytokines in Peripheral Blood After Dosing with MTX-101
Changes in CD8 Treg (A) and conventional non-Treg CD8 T cells (B) were assessed by flow cytometry. (C, D) Mean levels of cytokines IFNγ and IL-2 were assessed in serum derived from peripheral blood by MSD V-Plex assay. Changes were transient, modest and consistent with other antibody therapies (e.g., teplizumab, nivolumab).

Pharmacokinetics and Receptor Occupancy in Healthy Adults Enables Convenient and Competitive Dosing Regimen

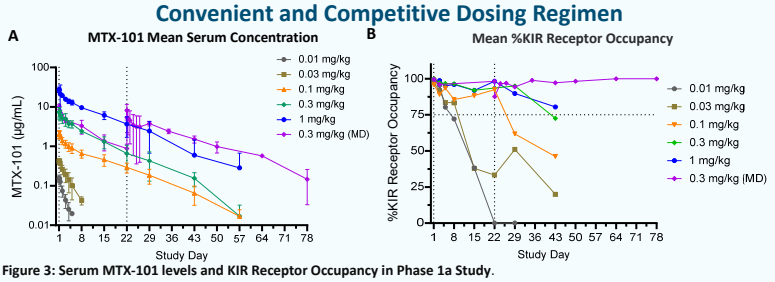


Figure 3: Serum MTX-101 levels and KIR Receptor Occupancy in Phase 1a Study.
(A) Mean MTX-101 serum concentration (µg/mL) by Cohort. Single-dose participants dosed on Day 1 only, with sample collection through Day 57. Multidose (MD) participants dosed on Day 1 and Day 22, with sample collection through Day 78. Results less than the assay Lower Limit of Quantification (LLOQ) of 0.005 µg/mL not shown. **(B)** Mean % KIR receptor occupancy (RO) by cohort. KIR receptor occupancy was measured using flow cytometry and calculated as the degree of MTX-101 blocking of anti-KIR antibody, relative to anti-KIR antibody binding at saturating levels in the absence of drug. Single-dose subject samples collected through Day 57 with timepoints after day 43 excluded due to incongruous results. Multidose (MD) subject samples collected through Day 78.

CONCLUSIONS

- MTX-101 is well-tolerated in healthy adults without serious adverse events
- Pharmacokinetic profile of MTX-101 enables convenient dosing regimen
- Pharmacodynamic data demonstrates selective activation and target engagement by MTX-101
- MTX-101 is a novel and promising therapeutic approach for the treatment of autoimmune disease

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