

## **Safety and pharmacokinetics of MK-8527 oral once-monthly: a phase 2 study in adults at low risk of HIV-1 exposure**

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**Background:** Long-acting options for HIV-1 pre-exposure prophylaxis (PrEP) are needed. MK-8527 is a novel, oral, nucleoside reverse transcriptase translocation inhibitor (NRTTI) with pharmacokinetic properties supporting once monthly (QM) dosing. We studied the safety and pharmacokinetics of MK-8527 oral QM in adults at low risk of HIV-1 exposure.

**Methods:** In this double-blind, multicenter study (NCT06045507), adults 18–65 years of age were randomized 2:2:2:1 to receive MK-8527 (3, 6, or 12 mg) or placebo QM for 6 months. Adverse events and laboratory tests were monitored through 8 weeks after the last dose. MK-8527 in plasma was measured for all participants. MK-8527-triphosphate (TP), the active form, in peripheral blood mononuclear cells (PBMCs) was measured in a subset of participants. Pharmacokinetic exposures for MK-8527 and MK-8527-TP were based on non-compartmental analysis of the sparse data collected in the study.

**Results:** 350 participants were enrolled (58.3% female; median age 28 years; 51.4% White, 41.4% Black/African American, 2.3% Asian) and received at least one dose of study intervention; 328 (93.7%) received all six doses. The incidence of adverse events was similar for MK-8527 and placebo (Table 1). No clinically meaningful changes were seen in laboratory tests, including total lymphocyte and CD4 T-cell counts (Table1). Pharmacokinetic parameters for MK-8527 and MK-8527-TP were dose proportional (Table 2).

**Conclusions:** MK-8527 was well tolerated with a similar safety profile to placebo in adults at low risk of HIV-1 exposure. The pharmacokinetics of MK-8527 and MK-8527-TP support the continued development of MK-8527 oral QM for PrEP.

**Table 1. Summary of Safety through Follow-Up Week 8**

N (%) of participants with:	MK-8527 3 mg (N=101)	MK-8527 6 mg (N=101)	MK-8527 12 mg (N=99)	Placebo (N=49)
Any adverse event (AE)	62 (61.4)	69 (68.3)	66 (66.7)	31 (63.3)
Drug-related (DR) AE	15 (14.9)	16 (15.8)	20 (20.2)	9 (18.4)
Toxicity grade 3-4 AE	5 (5.0)	2 (2.0)	4 (4.0)	4 (8.2)
DR toxicity grade 3-4 AE	1 (1.0)	0 (0.0)	1 (1.0)	1 (2.0)
Serious AE	2 (2.0)	0 (0.0)	1 (1.0)	1 (2.0)
DR serious AE	1 (1.0)	0 (0.0)	0 (0.0)	1 (2.0)
Discontinued due to AE*	0 (0.0)	2 (2.0)	1 (1.0)	2 (4.1)
Discontinued due to DRAE	0 (0.0)	1 (1.0)	1 (1.0)	0 (0.0)
Mean % change (95% CI) in:	N=91	N=92	N=93	N=46
Total lymphocyte count	5.6 (0.9, 10.4)	0.8 (-3.7, 5.3)	3.7 (-0.9, 8.2)	-3.1 (-8.6, 2.4)
CD4 T-cell count	4.8 (-0.1, 9.7)	4.4 (-0.7, 9.5)	4.6 (-0.4, 9.6)	-0.2 (-6.1, 5.8)

\* AE's causing discontinuation of MK-8527: migraine (n=1) and decreased lymphocyte/CD4 T-cell count (n=1) in 6 mg group; hypoaesthesia (n=1) in 12 mg group.

**Table 2: Summary of Pharmacokinetic Parameters for MK-8527 in Plasma and MK-8527-TP in PBMCs Following Administration of Multiple Oral Doses of MK-8527**

Analyte	Dose	N	AUC <sub>0-last</sub> (h* $\mu$ mol/L) GM (%GCV)	C <sub>max</sub> ( $\mu$ mol/L) GM (%GCV)	T <sub>max</sub> (hr) Median (Range)
MK-8527	3 mg	78	0.129 (81.5)	0.0320 (67.5)	0.55 (0.25 - 4.28)
	6 mg	92	0.404 (37.3)	0.0538 (73.5)	0.56 (0.25 - 4.38)
	12 mg	95	0.836 (55.0)	0.108 (72.5)	0.57 (0.27 - 4.12)
Analyte	Dose	N	AUC <sub>0-last</sub> (h*pmol/10 <sup>6</sup> cells), GM (%GCV)	C <sub>max</sub> (pmol/10 <sup>6</sup> cells), GM (%GCV)	T <sub>max</sub> (hr) Median (Range)
MK-8527-TP	3 mg	20	20.7 (255.5)	0.325 (78.7)	23.44 (3.53 - 27.45)
	6 mg	23	128 (178.6)	0.782 (72.2)	23.55 (3.67 - 47.07)
	12 mg	19	287 (55.9)	1.23 (63.9)	23.10 (3.63 - 26.15)

AUC, area under the concentration time curve; C<sub>max</sub>, maximum concentration; GCV, geometric coefficient of variation; GM, geometric mean; T<sub>max</sub>, time to maximum concentration.