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Preliminary Efficacy, Pharmacokinetics and Safety of Repeated Multiple Doses of MKC-442 in HIV-Infected Volunteers.

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Preliminary results of the efficacy, pharmacokinetics and safety of repeated multiple oral doses of MKC-442 are reported from an ongoing Phase IB double-blind, randomized, placebo-controlled study in HIV-1 infected, asymptomatic volunteers. Patients with $CD4^+$ counts of $\geq$ 100 cells/mL and HIV-1 RNA $\geq$ 10,000 copies/mL have been enrolled in one of six cohorts and given repeated oral doses of MKC-442 for up to 2 months. Changes in median $\log_{10}$ HIV-1 viral load from baseline during the first 4 weeks of monotherapy are:

Dose	Baseline	Week 1	Week 2	Week 3	Week 4
100 mg bid (n=5)	4.91	-0.83	-0.61	-0.36	0
250 mg qd (n=6)	4.08	-0.36	-0.20	-0.23	-0.15
250 mg bid (n=6)	4.72	-0.78	-0.70	-0.43	-0.34
350 mg bid (n=6)	4.71	-1.06	-0.91	-0.59	-0.41
500 mg qd (n=6)	ongoing	ongoing	ongoing	ongoing	ongoing
500 mg bid (n=6)	ongoing	ongoing	ongoing	ongoing	ongoing

Dose escalation is continuing to identify the dose having the greatest antiviral efficacy and best tolerance by patients. Preliminary pharmacokinetic analysis predicts a $t_{1/2}$ of ~6 hr consistent with results from single dose administration. Development of resistance to MKC-442 *in vivo* is being examined by genotyping the HIV-1 RT from all patients at monthly intervals as compared to baseline. MKC-442 has been well tolerated with headache (6/26) and loose stool (3/26) being the most frequent adverse events. Only one patient (100 mg bid) experienced rash and was the only patient to discontinue therapy. Elevations in liver transpeptidase levels (GGT) in 1/2 of the patients were considered inconsequential. No other patients have experienced any significant changes in other clinical safety parameters.