A Single Monotherapy Dose of MK-8591, a Novel NRTI, Suppresses HIV for Ten Days

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Abstract

Background: MK-8591 is a nucleoside reverse transcriptase inhibitor (NRTI) in early clinical development. MK-8591-triphosphate (TP), the active phosphorylated anabolite of MK-8591, exhibited protracted intracellular persistence in human and monkey peripheral blood mononuclear cells (PMBCs) in vitro. In preclinical experiments, MK-8591 administered once-weekly in an SIV rhesus macaque model demonstrated potent antiviral efficacy. Clinically, MK-8591-TP exhibited a half-life of ~150-160 hrs in human PBMCs with C168hr exceeding projected efficacious concentrations at doses of >10 mg. A Phase 1b monotherapy proof-of-concept efficacy study is currently underway to assess the potential for once weekly oral dosing in the clinic. The antiviral potency, human pharmacokinetics (PK), and physical properties of MK-8591 have the potential to open new paradigms for extended duration HIV treatment and prophylaxis approaches.

Methods: In an open-label study in HIV-1–infected subjects naïve to antiretroviral treatment (ART), subjects are being administered a single dose of MK-8591 across a range of doses. Doses were chosen based on PK/PD simulations. Bloodsamples are being collected for viral load (VL), MK-8591 PK, and MK-8591-TP PK at prespecified time points up to 10 days postdose. Following completion of Day 10 procedures, subjects are being offered standard of care ART. Safety, PK, and VL data from the 10-mg dose (N=6) are available.

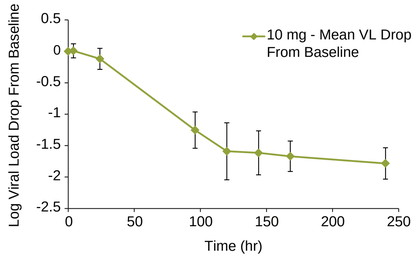
Results: A single 10-mg dose of MK-8591 was associated with a rapid and robust reduction in VL. At 168 hours postdose, a mean (95% CI) VL reduction of 1.67 $\log_{10}$ (1.47, 1.87) was observed. Mean VL continued to decline through Day 10 with a mean reduction of 1.78 $\log_{10}$ (1.59, -1.98) and no evidence of recrudescence. The 10-mg dose was generally well tolerated with a limited number of mild/moderate adverse experiences reported. MK-8591 plasma and MK-8591-TP PBMC PK were similar to previously reported data in healthy subjects.

Conclusions: MK-8591 suppressed HIV replication for at least ten days when administered as a single 10-mg dose. The low dose and potent antiviral effect of MK-8591 provide a platform for extended duration oral and parenteral formulations.

Patient Demographics

Subject Number	Gender	Age	Weight (kg)	Height (cm)	BM (kg/m^2)	Prestudy CD4 Count (cells/μL)	Prestudy Viral Load (copies/mL)
19	Male	49	71.8	177	22.9	535	21,100
20	Male	32	63.2	182	19.1	506	35,000
21	Male	24	65.2	180	20.1	646	10,200
22	Male	24	66.6	173	22.3	365	165,000
23	Male	24	59.8	183	17.9	915	470,000
24	Male	36	76.6	182	23.1	525	123,000

MK-8591: Time vs Log_{10} Viral Load Reduction (N=6)



- No NRTI related resistance mutations were identified predose or postdose in any patient

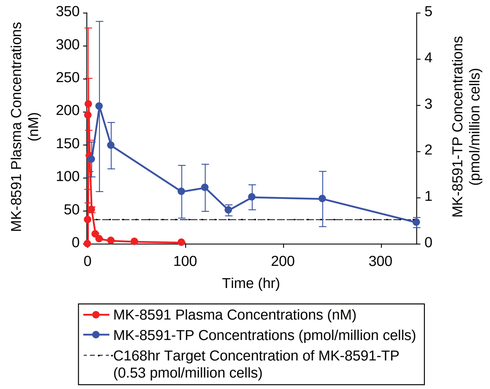
Viral Load Results Table

Treatment	N	Min	Median	Max	SD†	LS mean‡ (95% CI§)
Placebo	20	-0.52	-0.04	0.42	0.25	-0.03 (-0.13, 0.08)
10-mg MK-8591	6	-1.97	-1.63	-1.31	0.24	-1.67 (-1.88, -1.46)

Placebo adjusted data	Posterior mean#	PP‖
10-mg MK-8591	-1.64	>99.9%

†SD = standard deviation.
‡LS = least squares.
§CI = confidence interval.
#The placebo data were pooled from historical placebo data from 4 recent monotherapy studies in HIV-1 patients and fitted with a longitudinal data analysis (LDA) model containing fixed effects for study and time, and a random effect for subject. The MK data were fitted with an LDA model containing fixed effects for treatment, time and treatment by time interaction, and a random effect for subject.
‖PP = posterior probability of true mean difference in the plasma HIV-1 RNA reduction from baseline between MK-8591 and placebo at least 0.5 $\log_{10}$ copies/mL.

Plasma and PBMC PK Plots



MK-8591-TP PBMC Pharmacokinetics Table

Preliminary MK-8591-TP in PBMC pharmacokinetic parameter values following administration of one 10 mg oral dose of MK-8591 to HIV-1–infected patients

	C_{max} ({pmol/10^6cells})	T_{max} (hr)	$AUC_{0\text{-}168}$ (hr*{pmol/10^6cells})	$t_{1/2}$ (hr)	C168 (pmol/10^6cells)
N	6	6	6	4	6
Mean	3.11	52.0	237	108	1.01
SD	1.72	92.2	73.3	35.4	0.271
SE	0.702	37.7	29.9	17.7	0.110
Min	1.8	12	150	70	0.77
Median	2.4	12	240	110	0.92
Max	6.3	240	310	140	1.4
Geometric Mean	2.81	22.2	227	103	0.983
CV% Geometric Mean	49.9	179.2	33.3	35.4	26.0

MK-8591 Plasma Pharmacokinetics Table

	C_{max} (μM)	T_{max} (hr)	$t_{1/2}$ (hr)	$AUC_{0\text{-}inf}$ (hr*μM)	$AUC_{0\text{-}last}$ (hr*μM)
N	6	6	6	6	6
Mean	0.246	0.833	60.3	1.11	0.934
SD	0.0820	0.258	9.18	0.180	0.144
SE	0.0335	0.105	3.75	0.0735	0.0587
Min	0.16	0.50	48	0.84	0.73
Median	0.22	1.0	60	1.2	1.0
Max	0.39	1.0	73	1.3	1.0
Geometric Mean	0.235	0.794	59.7	1.10	0.924
CV% Geometric Mean	32.1	37.0	15.4	17.4	16.5
CI 95% Lower Mean	0.2	0.6	50.6	0.9	0.8
CI 95% Upper Mean	0.3	1.1	69.9	1.3	1.1

AE Summary

Adverse Experience†	Incidence
Acne	1
Abdominal pain	1
Anal warts	1
Apathy	1
Diarrhea	1
Dizziness	1
Headache	6
Joint pain	1
Nausea	1
Sore throat	1

†AE are represented as number of events, in some cases multiple events were reported by one subject.
Note: N = 6 subjects.

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