Single Doses of MK-8507, a Novel HIV-1 NNRTI, Reduced HIV Viral Load for at Least a Week

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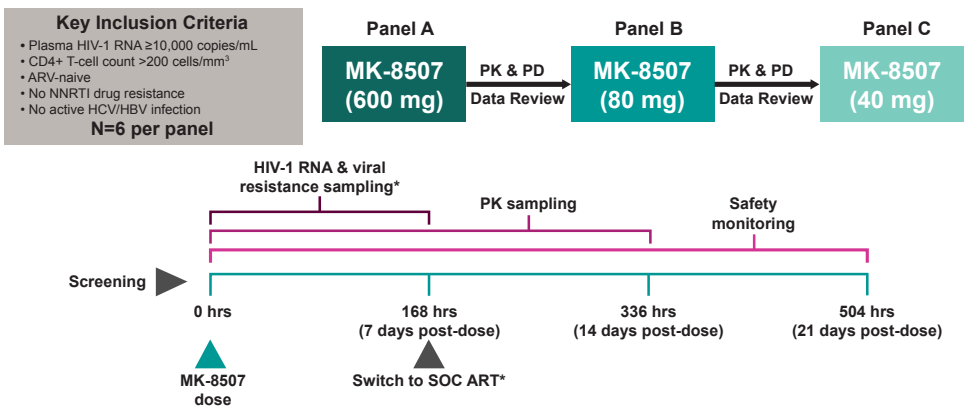
BACKGROUND

- MK-8507 is a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) in clinical development for HIV-1 treatment
- MK-8507 preclinical data indicate:
  - Favorable safety profile in the anticipated clinical dose range
  - High antiviral potency (half-maximal inhibitory concentration [IC_{50}] = ~50 nM)
  - Activity against common NNRTI resistance-associated mutations
- MK-8507 single and multiple ascending dose clinical trials show:
  - MK-8507 is generally well tolerated up to 1200 mg (single dose) and up to 400 mg (3 x once weekly)
  - Pharmacokinetics (PK) support once-weekly oral administration
- This trial evaluated the antiviral efficacy, PK, and safety of single oral doses of 40, 80, and 600 mg MK-8507 in treatment-naive people living with HIV (PLWH)

METHODS

- Single oral dose proof-of-concept single-center trial in treatment-naive PLWH (NCT02174159; **Figure 1**)

Figure 1. Study Design



*3 participants in Panel A were assessed for PK and HIV-1 RNA through 336 hr (14 days post-dose), initiating SOC ART immediately thereafter. 1 participant in Panel C declined SOC ART; PK and HIV-1 RNA samples were therefore analyzed through 336 hr.

ART, antiretroviral therapy; ARV, antiretroviral; HBV, hepatitis B virus; HCV, hepatitis C virus; NNRTI, non-nucleoside reverse transcriptase inhibitor; PD, pharmacodynamic; PK, pharmacokinetic; SOC, standard of care.

- **HIV-1 RNA reduction target:** Change from baseline ≥1 log_{10} copies/mL relative to historical placebo data[1]
- **PK target:** Plasma concentrations at 168 hrs (C_{168hr}) ≥6 x IC_{50}[1]
  - Levels expected to provide robust long-term efficacy in combination therapy
- Adverse events (AEs), vital signs, physical examinations, electrocardiograms (ECGs), and laboratory tests were monitored

RESULTS

Table 1. Baseline Demographics and Disease Characteristics

	MK-8507 (600 mg)	MK-8507 (80 mg)	MK-8507 (40 mg)	Overall
	n=6	n=6	n=6	N=18
Sex				
Male, n (%)	6 (100.0)	6 (100.0)	6 (100.0)	18 (100.0)
Age (years)				
Median (min, max)	36.0 (22, 46)	36.0 (31, 45)	31.0 (29, 56)	34.5 (22, 56)
Race/Ethnicity				
White, n (%)	6 (100.0)	6 (100.0)	6 (100.0)	18 (100.0)
Hispanic or Latino, n (%)	0 (0.0)	0 (0.0)	1 (16.7)	1 (5.6)
Baseline Plasma HIV-1 RNA (log_{10} copies/mL)				
Median (min, max)	4.7 (4.0, 4.9)	4.9 (4.1, 5.1)	4.4 (4.1, 5.0)	4.6 (4.0, 5.1)

Safety

- All doses of MK-8507 were generally well tolerated
- No clinically meaningful trends in vital signs, ECGs, or laboratory tests were detected
- Most common AEs: nasopharyngitis (n=3) and headache (n=3)
  - Headache (n=3) was the only AE considered to be study drug related
- 1 serious AE of diffuse large B-cell lymphoma, not considered to be related to study drug

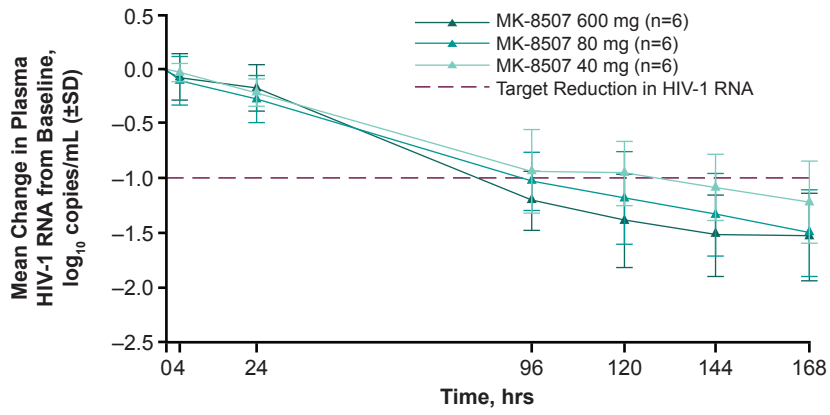
Table 2. Change in Plasma HIV-1 RNA from Baseline at 7 Days Post-Dose

	Historical Placebo	MK-8507 (600 mg)	MK-8507 (80 mg)	MK-8507 (40 mg)
	n=20	n=6	n=6	n=6
LS Mean, log_{10} copies/mL (95% CI)	–0.03 (–0.13, 0.08)	–1.53 (–1.84, –1.23)	–1.50 (–1.80, –1.19)	–1.22 (–1.52, –0.91)
Posterior Mean Adjusted by Placebo, log_{10} copies/mL	N/A	–1.56	–1.53	–1.24

Placebo data pooled from similar studies.

CI, confidence interval; LS, least squares; N/A, not applicable.

Figure 2. Mean Change in Plasma HIV-1 RNA Over 7 Days



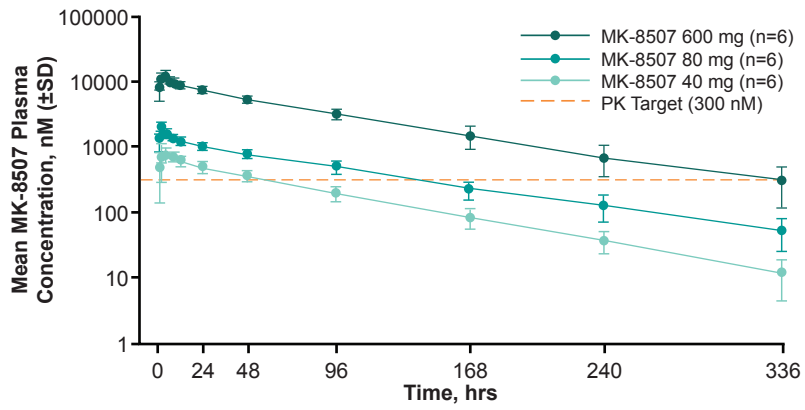
SD, standard deviation.

- Single oral doses of MK-8507 as low as 40 mg achieved the 7-day HIV-1 RNA reduction target with >99% posterior probability (**Table 2; Figure 2**)

Viral Resistance Analysis

- 0 of 14 participants initiating standard of care (SOC) antiretroviral therapy (ART) at 7 days post-dose exhibited viral rebound
- 1 of 4 participants initiating SOC ART after 14 days post-dose exhibited viral rebound
  - The reverse transcriptase resistance mutation F227C was first detected using Sanger sequencing 10 days post-dose (MK-8507 600 mg) in the participant exhibiting viral rebound
- F227C is an uncommon resistance mutation that is susceptible to other classes of antiretrovirals[2], the emergence of this mutant after 10 days of monotherapy is not considered to be clinically relevant in the context of combination ART administered weekly
- No other NNRTI resistance was detected
- Sanger sequencing was run at screening and on the last viral sample in participants with sufficient virus for amplification

Figure 3. MK-8507 Plasma Concentration Over Time



Plasma concentrations of MK-8507 had a lower limit of quantitation of 2.03 nM.

PK, pharmacokinetic; SD, standard deviation.

- MK-8507 PK supports once-weekly dosing (**Figure 3**)
  - Doses of MK-8507 >80 mg meet the PK target
- PK was approximately dose proportional and consistent with that in participants without HIV
- Mean apparent terminal half-life ($t_{1/2}$) was ~56–69 hrs

CONCLUSIONS

- MK-8507 reduced HIV-1 RNA levels in treatment-naive PLWH for up to 7 days following single oral doses as low as 40 mg
- MK-8507 was generally well tolerated at all doses evaluated
- The antiviral potency and PK profile of MK-8507 are supportive of once-weekly oral administration as part of combination ART
- Emergence of F227C in 1 participant after 10 days of monotherapy is not considered to be clinically significant in the context of combination ART administered weekly

References

1. Xu Y, et al. *Clin Transl Sci*. 2016;9:192–200.
2. Stanford University. HIV drug resistance database. Essential Data on NNRTI DRMs. 2016. Available at: https://hivdb.stanford.edu/pages/POC_NNRTIDRMs_Summary.html. Accessed September 2020.

Disclosures

- W Ankrom, D Jackson Rudd, A Schaeffer, I De Lepeleire, EJ Friedman, M Robberechts, S Zhang, SA Stoch, and M Iwamoto are/were employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD).
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