TUPE020

Weekly oral prophylaxis with MK-8527 protects rhesus macaques from rectal challenge with simian-human immunodeficiency virus

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Background

- Human immunodeficiency virus (HIV) continues to be a major worldwide public health issue[1]
- Pre-exposure prophylaxis (PrEP) has proven to be effective in reducing the acquisition of HIV-1;[2] however, despite a 39% decline in new HIV infections since 2010, there were 1.3 million new cases in 2023[1]
- MK-8527 is a novel nucleoside reverse transcriptase translocation inhibitor (NRTTI) in clinical development for HIV PrEP[3]
- MK-8527 is phosphorylated intracellularly to its active MK-8527 triphosphate (MK-8527-TP) form, which is a potent inhibitor of HIV replication[3]
- MK-8527 has been evaluated in the clinic
  - Phase 1 studies in adults without HIV demonstrated that MK-8527 was generally well tolerated, with a pharmacokinetic (PK) profile that supports once-weekly (QW) oral and longer dosing[4]
  - In persons living with HIV-1 that were treatment naive, single doses of MK-8527 as low as 0.5 mg achieved ≥1.0 log_{10} copies/mL decreases in HIV-1 RNA at Day 7 after dose administration[5]
- Challenge studies using simian immunodeficiency virus (SIV) or simian-human immunodeficiency virus (SHIV) in rhesus macaques are well-established models for evaluating HIV-1 prevention strategies, including PrEP[6-8]

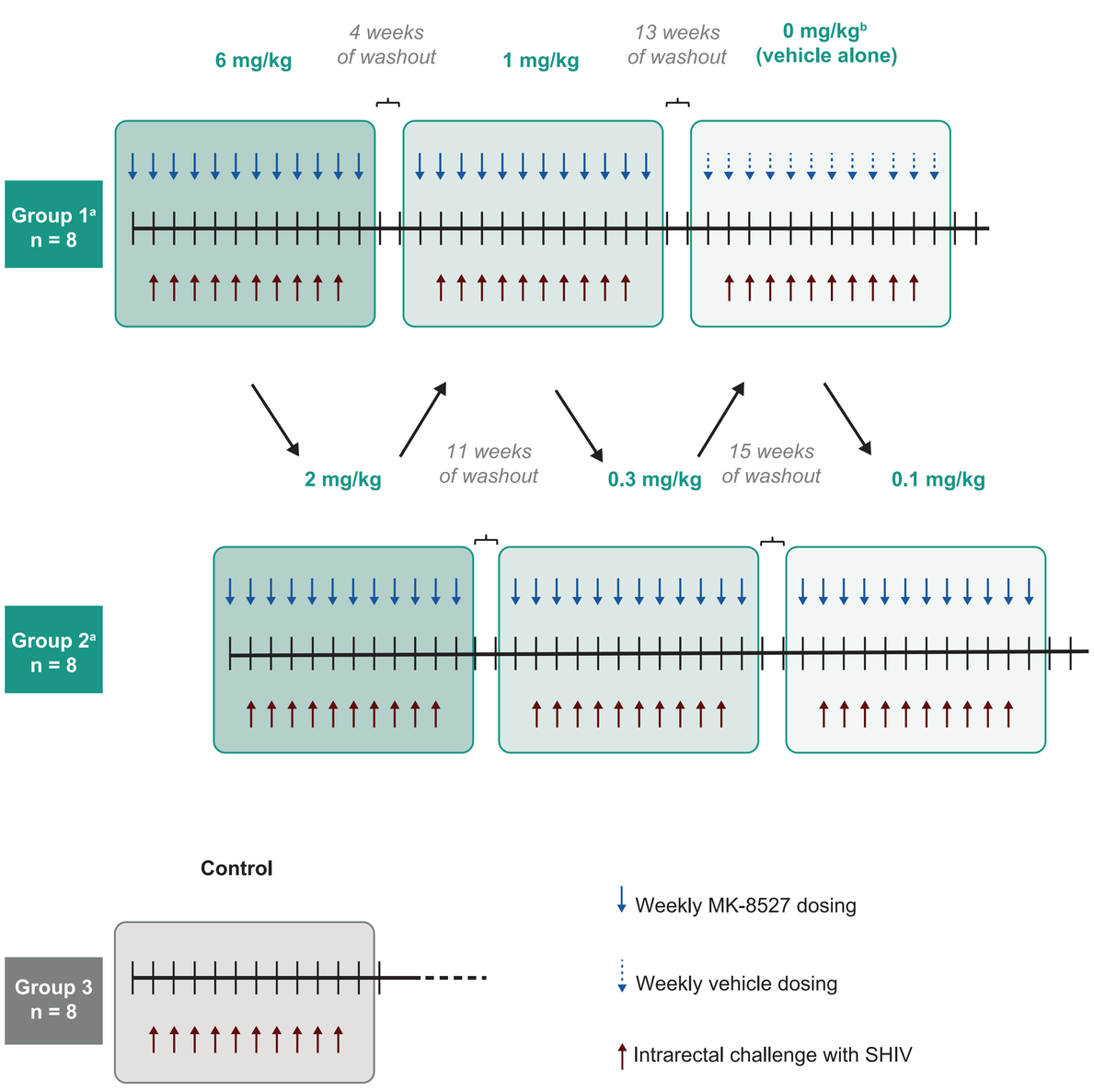
Objective

- To evaluate the effectiveness of QW MK-8527 dosed orally in a rhesus macaque PrEP model with SHIV intrarectal challenge

Methods

- 24 male rhesus macaques, naive to SHIV infection were assigned to 1 of 3 groups (8 per group)
- Groups 1 and 2 were administered oral MK-8527 QW for 12 consecutive weeks. The animals were challenged intrarectally with SHIV (SHIV162p3 variant) QW, starting 1 week after initiation of MK-8527, for a total of 10 challenges. Group 3 (control group) was challenged intrarectally with SHIV QW in the absence of MK-8527 prophylaxis (**Figure 1**)
- There were 3 dose panels for Groups 1 and 2 (Group 1: 6 mg/kg, 1 mg/kg, and 0 mg/kg [vehicle alone]; Group 2: 2 mg/kg, 0.3 mg/kg, and 0.1 mg/kg). Groups 1 and 2 were staggered temporally, with dosing proceeding from the highest to the lowest dose, alternating between groups
  - There was a washout period at the end of each dose panel of 4 to 15 weeks due to time to evaluate PK and viral load data from the previous dose level
  - Uninfected animals were dosed and rechallenged in a subsequent dose panel
- Plasma viral load was monitored weekly for at least 4 weeks after each dose panel was completed. Animals were considered to be infected with SHIV when 2 consecutive plasma viral load measurements were >100 copies/mL
- To confirm that no infections occurred below the limit of quantification of the viral load assay, cell-associated viral DNA from peripheral blood mononuclear cells (PBMCs) obtained at the end of each dose panel was quantified by real-time polymerase chain reaction

Figure 1. Schematic of intrarectal challenge model in male rhesus macaques



SHIV, simian-human immunodeficiency virus.
[a]Uninfected animals were rechallenged at a lower dose after ≥4 weeks of drug washout.
[b]0-mg/kg (vehicle alone) dosing was included for Group 1 to verify that animals maintained susceptibility to SHIV infection after 20 challenges.

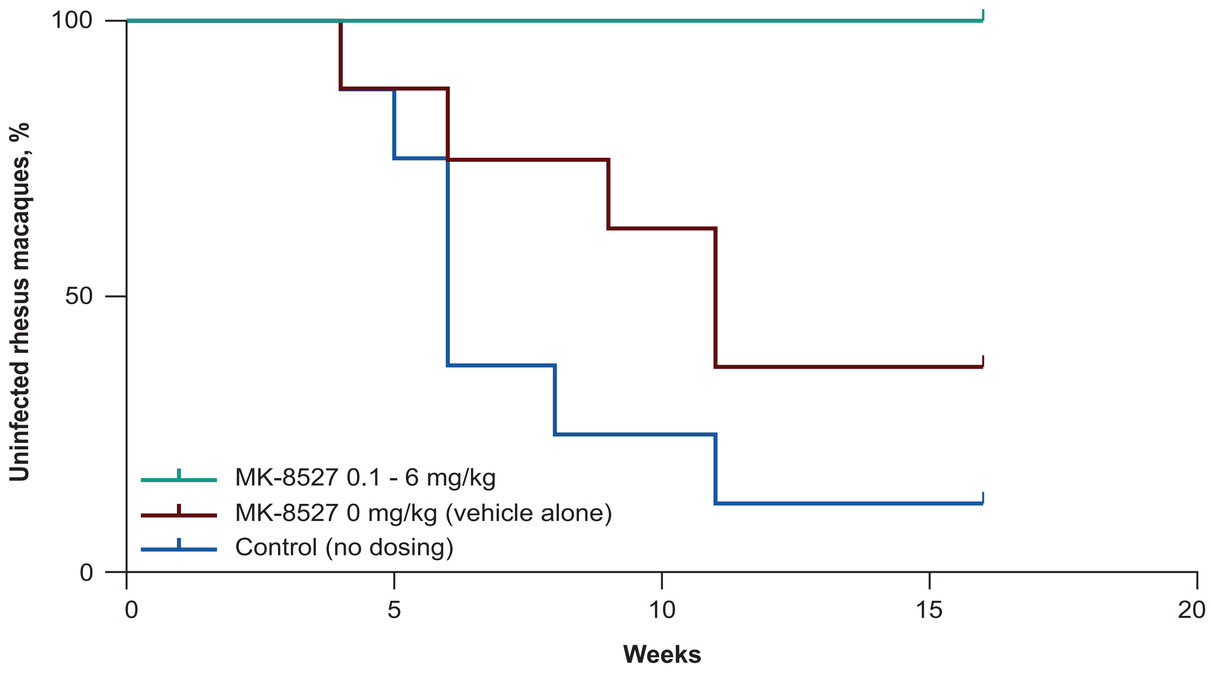
- Blood samples were collected for measuring plasma viral load, MK-8527 concentrations in plasma, MK-8527-TP concentrations in PBMCs, and cell-associated viral DNAin PBMCs
  - Rectal biopsy specimens were collected to measure MK-8527-TP concentrations after each dose panel
  - Concentrations of MK-8527 and MK-8527-TP were determined using liquid chromatography with tandem mass spectrometry
- MK-8527-TP C_{trough} levels were measured at t = 168 hours after dosing (observed) or extrapolated from the measured MK-8527-TP concentration at 24 hours after dosing using the experimentally determined half-life
- The mean inhibitory quotient (IQ; trough concentration [C_{trough}]/in vitro half-maximal inhibitory concentration [IC_{50}]) was calculated for each C_{trough} value, using the in vitro IC_{50} for MK-8527-TP in rhesus PBMCs (0.0063 pmol/10^6 cells; ~0.0315 µM) against SHIV

Results

Evaluation of the state of infection of rhesus macaques challenged with SHIV that received MK-8527 as prophylaxis

- There were no confirmed infections in any rhesus macaques challenged with SHIV that received MK-8527 (0.1-6 mg/kg) (**Figure 2**)
- 7 of 8 macaques (87.5%) in the control group and 5 of 8 macaques (62.5%) in the 0-mg/kg (vehicle alone) group became infected after 3 to 10 intrarectal challenges with SHIV (**Figure 2**).
- Infection status was confirmed in all animals by the presence or absence of cell-associated viral DNA in PBMCs

Figure 2. Infection status of rhesus macaques challenged with SHIV



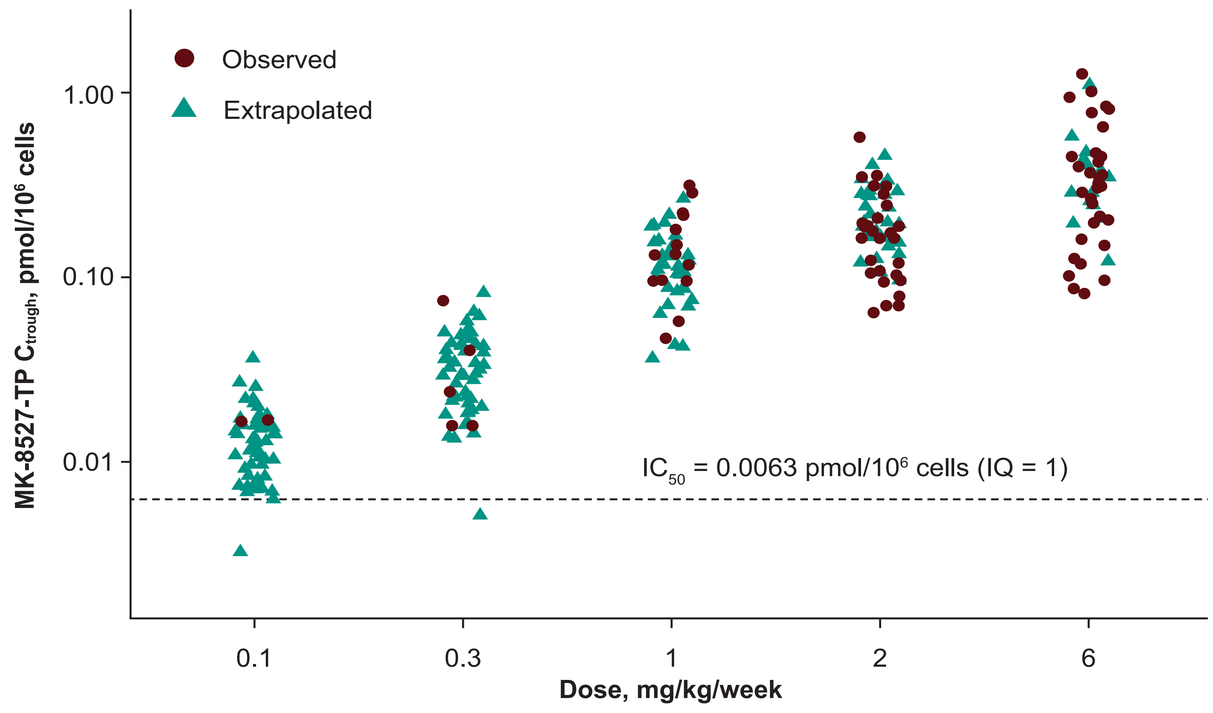
SHIV, simian-human immunodeficiency virus.

- Groups that received MK-8527 doses of ≥0.1 mg/kg had an 18-fold (95% CI, 3.6-90.2) lower risk of infection than the control group (P = 0.0004) and an 11.1-fold (95% CI, 1.8-67.7) lower risk of infection than those that received 0.0 mg/kg (vehicle alone; P = 0.009)

Study PK assessment

- The observed and extrapolated MK-8527-TP C_{trough} concentrations in PBMCs fell within the same ranges (**Figure 3**), providing confidence to the derived concentrations at the lowest dose (MK-8527 0.1 mg/kg), whereby most of the samples collected at 168 hours were below the limit of quantification (**not shown**)

Figure 3. MK-8527-TP C_{trough} levels in PBMCs



C_{trough}, trough concentration; IC_{50}, half-maximal inhibitory concentration; IQ, inhibitory quotient (C_{trough}/IC_{50}); MK-8527-TP, MK-8527 triphosphate; QW, once weekly.

- MK-8527-TP trough concentrations with the 0.1-mg/kg QW dose corresponded to a mean IQ of 2.2 (range, 0.5-5.8) (**Table 1**)

Table 1. Mean IQ determined for each weekly dose of MK-8527

MK-8527 mg/kg	Mean IQ ± SD	IQ Range
6	62.7 ± 44.2 (n = 48)	13.0-201.2
2	33.2 ± 16.1 (n = 60)	10.3-91.2
1	20.9 ± 10.1 (n = 47)	5.8-50.3
0.3	5.3 ± 2.6 (n = 53)	0.8-13.1
0.1	2.2 ± 1.0 (n = 50)	0.5-5.8

C_{trough}, trough concentration; IC_{50}, half-maximal inhibitory concentration; IQ, inhibitory quotient (C_{trough}/IC_{50}); n, number of IQ data points; SD, standard deviation.

- The measured mean concentrations of MK-8527-TP in rectal tissue for the 6-, 2-, and 1-mg/kg QW doses were 0.0505, 0.0171, and 0.0096 µM, respectively
- The concentration of MK-8527-TP in rectal tissue was below the limit of quantification (0.004 µM) for the 0.3-mg/kg QW dose and was not measured for the 0.1-mg/kg QW dose
- All animals at the 1-mg/kg QW dose had trough rectal MK-8527-TP concentrations below the in vitro IC_{50} (0.0315 µM) indicating an IQ of <1 in the rectal tissue for doses ≤1 mg/kg QW

Conclusions

- Doses of MK-8527 ≥0.1 mg/kg weekly provided protection against intrarectal acquisition of SHIV in rhesus macaques
- Results of this study support the clinical development of MK-8527 for the prevention of HIV-1 acquisition

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