MK-8527 PK/PD Threshold and Phase 2 Dose Selection for Monthly Oral HIV-1 Preexposure Prophylaxis

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Background

- HIV continues to be a major worldwide public health issue; however, despite a 39% decrease in new HIV infections between 2010 and 2023, there were 1.3 million new cases in 2023[1]
- Preexposure prophylaxis (PrEP) reduces the chances of acquiring HIV-1[2]
- MK-8527 is a nucleoside reverse transcriptase translocation inhibitor (NRTTI) that is phosphorylated intracellularly to the pharmacologically active triphosphate (TP) form, MK-8527-TP[3]
- Preclinical assessment in nonhuman primates (NHPs) showed that oral MK-8527 administered once weekly (QW) at doses ≥0.1 mg/kg as PrEP provided protection against intrarectal acquisition of simian-human immunodeficiency virus (SHIV) in rhesus macaques[4]
- MK-8527 is in clinical development as a monthly oral antiretroviral agent for the prevention of HIV-1
- In two Phase 1 studies, single doses (0.5-200 mg) and multiple doses (5-40 mg QW for 3 weeks) of MK-8527 administered to adults without HIV were generally well tolerated, and the safety and pharmacokinetic (PK) profiles of MK-8527 support QW and longer dosing intervals[5]
- In people living with HIV-1 who had not previously taken any antiretroviral agents, single doses (0.25-10 mg) of MK-8527 were generally well tolerated, and the safety and antiviral activity of MK-8527 support continued clinical investigation[6]

Objective

- To develop a pharmacokinetic/pharmacodynamic (PK/PD) model for MK-8527-TP using NHP and clinical data to inform Phase 2 dose selection for MK-8527 as HIV-1 PrEP

Methods

- The MK-8527-TP PK threshold for protection against HIV-1 was determined using preclinical and clinical data[4,6]
- Male rhesus macaques were administered oral MK-8527 (ranging from 0.1 to 6.0 mg/kg) QW for 12 consecutive weeks as PrEP in animals intrarectally challenged weekly with SHIV.[4] MK-8527-TP trough concentrations (C_{trough}) were measured or extrapolated using the experimentally determined half-life
- In two Phase 1 studies, single doses of MK-8527 were evaluated to determine antiretroviral activity in people living with HIV-1[6]
  - Adults who had not previously taken any antiretroviral agents were included in these 2 open-label, multi-panel studies (P002: NCT03615183; P004: NCT05494736); each participant received a single oral dose of MK-8527 (0.25, 0.5, 1.0, 3.0, or 10.0 mg)[5]
  - The mean change in HIV-1 RNA from baseline was measured for 10 days after a single dose of MK-8527[5]
  - Reduction in viral load (VL; measured as log_{10} plasma HIV-1 RNA copies/mL) on Day 7 (168 hours) and the PK of MK-8527-TP in peripheral blood mononuclear cells (PBMCs) after 1 week (C_{trough} or concentration at 168 hours [C_{168}]) were used to establish the PK/PD relationship utilizing the observed clinical MK-8527-TP C_{168} and a model-based analysis. A simple maximum response (E_{max}) model was used to evaluate the PK/PD relationship (EC_{50}, half-maximal effective concentration)

$$VL\ Decline = \frac{E_{max} \times C_{168}}{EC_{50} + C_{168}}$$

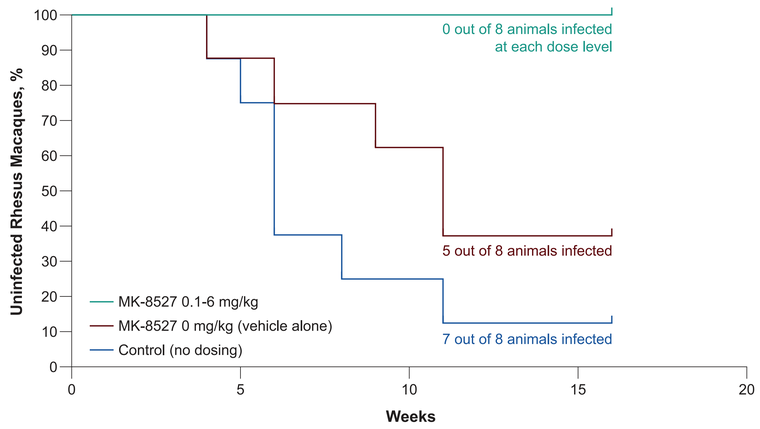
- The PK efficacy threshold was compared with clinical and preclinical data for approved oral PrEP agents
- A fit-for-purpose population PK model was developed to relate MK-8527 dose to intracellular MK-8527-TP concentrations in PBMCs. The model included PBMC MK-8527-TP concentration data from the two Phase 1 studies, and the model was used for simulations to support the Phase 2 dose selection

Results

PK/PD assessment

- There were no confirmed infections in any rhesus macaques that received weekly oral MK-8527 (0.1-6 mg/kg) before SHIV challenge (**Figure 1**)
- The mean inhibitory quotient (IQ; [C_{trough}]/ [IC_{50}] in vitro half-maximal inhibitory concentration) 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) against SHIV.[4] MK-8527-TP C_{trough} values with the 0.1-mg/kg dose corresponded to a mean IQ of 2.2 (range, 0.5-5.8)[4]
- The lowest estimated MK-8527-TP C_{168} at 0.1 mg/kg/week was 0.003 pmol/10^6 cells

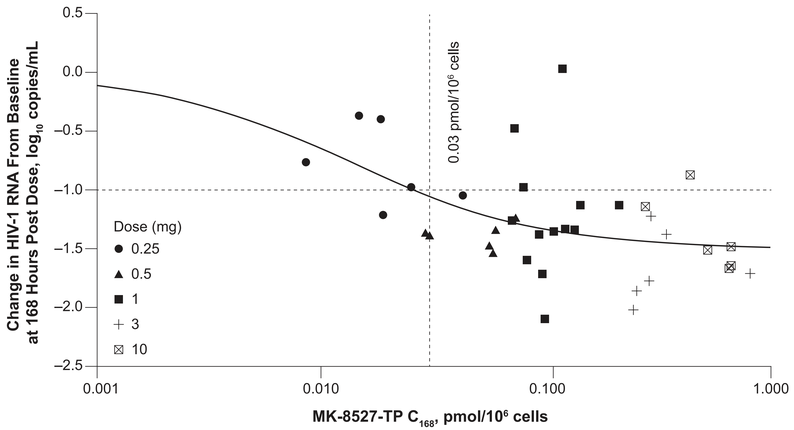
Figure 1. Infection status of rhesus macaques challenged with SHIV



SHIV, simian-human immunodeficiency virus.

- Reduction in viral load on Day 7 (168 hours) and the C_{168} of MK-8527-TP in PBMCs from the Phase 1 studies are presented in **Figure 2**. Of note, 2 of the 6 participants receiving a single dose of MK-8527 0.5 mg and who had an ~1.4 log_{10} decrease in VL, had MK-8527-TP C_{168} of ~0.03 pmol/10^6 PBMCs
- A PK efficacy threshold for MK-8527-TP was set at 0.03 pmol/10^6 PBMCs (0.15 µM), which is expected to provide >1 log_{10} decrease in VL in people living with HIV-1 who had not previously taken any antiretroviral agents.
- Using the in vitro IC_{50} for MK-8527-TP against HIV-1 in human PBMCs (0.0092 pmol/10^6 PBMCs)[7] the IQ at the 0.03 pmol/10^6 PBMCs PK efficacy target is ~3. The PK efficacy threshold is 10-fold higher than the lowest estimated protective MK-8527-TP concentration (0.003 pmol/10^6 PBMCs) in preclinical rhesus macaque study[4]

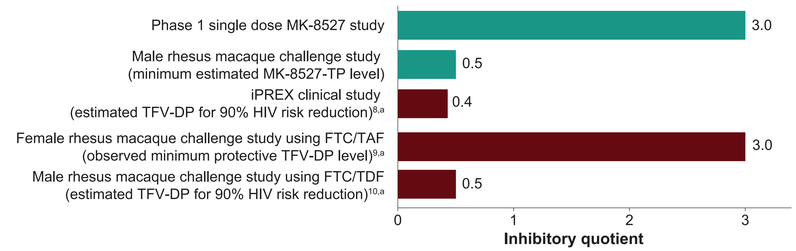
Figure 2. A threshold of 0.03 pmol/10^6 PBMCs (representing an IQ[a] ~3) would provide >1 log_{10} decrease in VL in adults living with HIV-1 who had not previously taken any antiretroviral agents



C_{168}, concentration at 168 hours; C_{trough}, trough concentration; IC_{50}, half-maximal inhibitory concentration; IQ, inhibitory quotient; PBMCs, peripheral blood mononuclear cells; PK, pharmacokinetics; VL, viral load.
[a]IQ is defined as the ratio of C_{trough} and in vitro potency (IC_{50}).
For 1 participant in the 1-mg panel, the PK sample at 168 hours was not analyzed due to bioanalytical limitations, and the C_{168} was estimated based on the 144- and 192-hour samples using linear interpolation. For 1 participant in the 0.25-mg panel, the C_{168} was below the limit of quantification. The concentration was estimated as half the lower limit of quantification (LLOQ/2).

- IQ data for MK-8527 and approved oral PrEP agents are presented in **Figure 3**. The comparative data suggests that achieving an IQ of 3 for MK-8527-TP would be effective for HIV-1 prevention

Figure 3. IQ comparison for MK-8527 and other oral PrEP therapies



DP, diphosphate; FTC, emtricitabine; IC_{50}, half-maximal inhibitory concentration; TAF, tenofovir alafenamide; TFV, tenofovir.
[a]IC_{50} for TFV-DP = 0.0415 pmol/10^6 PBMCs.

- The combined data from the rhesus macaque challenge study, two Phase 1 studies, and comparison to other oral PrEP agents suggest that the efficacy for HIV-1 prevention is predicted to be achieved with an approximate IQ ranging from 1 to 3

Phase 2 study dose selection

- MK-8527-TP PK was adequately described by a 2-compartment model. No covariates were included in the model. No differences were observed in PK between participants without HIV and those living with HIV
- Based on the PK/PD threshold for MK-8527-TP of 0.03 pmol/10^6 PBMCs and the population PK model, it is expected that a once-monthly (QM) oral dose of MK-8527 ≥6 mg will maintain MK-8527-TP levels above the PK/PD threshold in >90% of the population for a month (**Table 1**)

Table 1. Doses ≥6 mg QM are predicted to achieve efficacy thresholds for >90% of population at steady state

MK-8527 QM dose, mg	Percent of population achieving the PK/PD threshold at steady state,[a] %
3	67
6	91
12	99

PD, pharmacodynamics; PK, pharmacokinetics; QM, once monthly.
[a]Based on dosing every 31 days.

- Three oral dose levels of MK-8527 (3, 6, and 12 mg administered QM) were selected for evaluation in a Phase 2 study enrolling participants at low chance of HIV exposure (NCT06045507). The 3-mg dose, despite not being projected to be effective as PrEP, was selected to characterize PK and to further evaluate any PK/PD relationships

Conclusions

- Based on the rhesus macaque challenge study, Phase 1 clinical data, and comparison to other oral PrEP agents, the PK efficacy threshold of MK-8527-TP was set at 0.03 pmol/10^6 PBMCs for HIV-1 prevention
- Doses of MK-8527 (3, 6, and 12 mg administered QM) were selected to be studied in Phase 2 for safety and tolerability in people living without HIV and who had a low likelihood of HIV exposure

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