# Safety, Tolerability and Pharmacokinetics Following Single- and Multiple-Dose Administration of the Novel NNRTI MK-8507 With a Midazolam Interaction Arm

Wendy Ankrom[1]; Andrea Schaeffer[1]; Deborah Panebianco[1]; Evan Friedman[1]; Charles Tomek[2]; S. Aubrey Stoch[1]; Marian Iwamoto[1]

[1]Merck & Co., Inc., Kenilworth, NJ, USA; [2]Celerion, Inc., Lincoln, NE, USA

## BACKGROUND

- New HIV antiretrovirals that are well tolerated, highly efficacious, with a high barrier to resistance, and offer extended dosing intervals are needed[1,2]
- Here, we report the first-in-human trials of single and multiple ascending doses of MK-8507, a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) with strong antiviral potency and *in vitro* activity against common NNRTI associated resistance mutations

## METHODS

- Single (**Table 1**) and multiple (**Table 2**) rising-dose clinical trials of MK-8507 in participants without HIV

**Table 1. Study 1: Single Rising-Dose Trial of MK-8507**

| Panel | N[a] | Period 1 | | Period 2 | | Period 3 | | Period 4 | Final safety evaluation[c] |
|---|---|---|---|---|---|---|---|---|---|
| A | 8 | 2 mg or placebo | | 30 mg or placebo | | 200 mg or placebo | | | |
| B | 8 | | 10 mg or placebo | | 100 mg or placebo[b] | | 400 mg or placebo | 100 mg or placebo[b] (with food) | |

[a]Randomized, double-blind, 3:1 active treatment:placebo. [b]Same participants received MK-8507 for crossover food effect assessment. [c]+21 days from last dose.

**Table 2. Study 2: Single and Multiple Once-Weekly Rising-Dose Trial of MK-8507 with Midazolam Interaction Arm**

| Panel | N[a] | Day -1 | Single Dose | Multiple Dose | | Final safety evaluation[b] |
|---|---|---|---|---|---|---|
| | | | Day 1 | Days 22 and 29 | Day 36 | |
| A | 8 | - | 400 mg or placebo | 100 mg or placebo | 100 mg or placebo | |
| B | 8 | - | 800 mg or placebo | 200 mg or placebo | 200 mg or placebo | |
| C | 8 | 2 mg midazolam | 1200 mg or placebo | 400 mg or placebo | 400 mg or placebo and 2 mg midazolam | |

[a]Randomized, double-blind, 3:1 active treatment:placebo. [b]+21 days from last dose.

- Eligible participants: Adults without HIV; in good health and not using prescription or non-prescription medication or herbal remedies

### Assessments

- Safety/tolerability (adverse events [AEs], vital signs, electrocardiograms [ECGs], and laboratory safety tests)
- Plasma pharmacokinetics (PK) of MK-8507

## RESULTS

**Table 3. Baseline Demographics**

| | Study 1 (N=16) | Study 2 (N=24) |
|---|---|---|
| **Sex, n (%)** | | |
| Male | 16 (100.0) | 21 (87.5) |
| Female | 0 (0.0) | 3 (12.5) |
| **Age** | | |
| 18 to 60 years, n (%) | 16 (100.0) | 24 (100.0) |
| Mean (range), years | 36 (24 to 53) | 34 (21 to 54) |
| **Race, n (%)** | | |
| White | 10 (62.5) | 22 (91.7) |
| Black or African American | 4 (25.0) | 0 (0.0) |
| Black or African American, White | 1 (6.3) | 0 (0.0) |
| Asian | 1 (6.3) | 2 (8.3) |
| **Ethnicity[a], n (%)** | | |
| Not Hispanic or Latino | 15 (93.8) | 24 (100.0) |
| Hispanic or Latino | 0 (0.0) | 0 (0.0) |

[a]The ethnicity of one participant in Study 1 was listed as 'Unknown'.

### Safety

- All single and multiple oral doses of MK-8507 were generally well tolerated
- All AEs were mild in intensity, non-serious, resolved by end of study, and no one discontinued due to an AE
- Most common AEs were headache, cough and rhinorrhea
  - One AE of decreased appetite was considered to be drug related in Study 2
- No trends with dose and no clinically meaningful changes were observed in clinical laboratory values, vital signs, or ECG safety parameter values following treatment with MK-8507

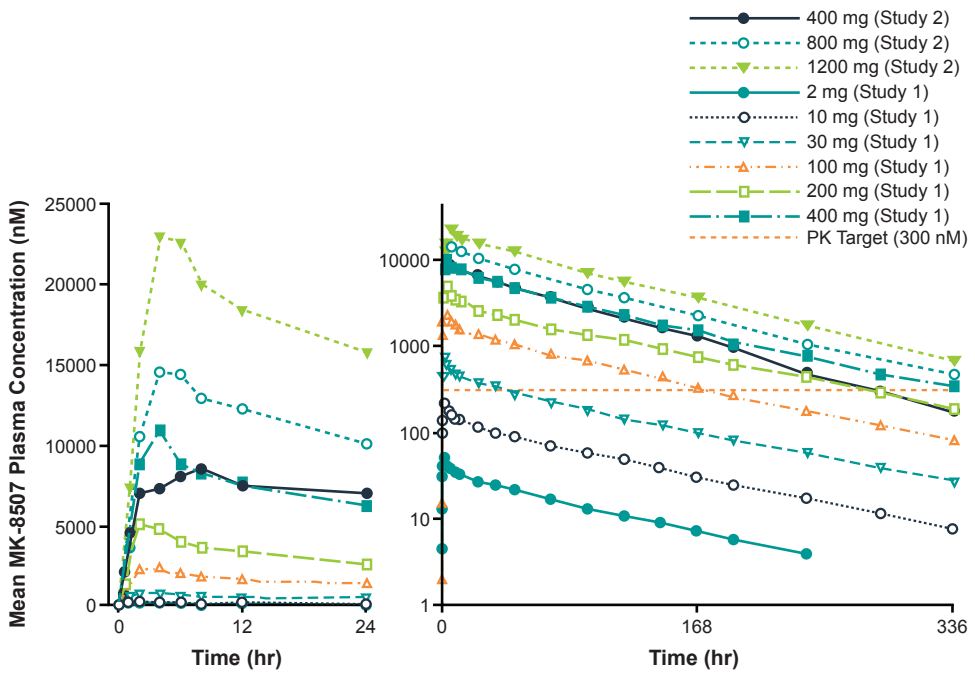
### Plasma PK

- PK of MK-8507 was dose proportional between 2 mg and 1200 mg (**Figure 1**)
- Mean apparent terminal half-life ($t_{1/2}$) was ~58–84 hours and median time to maximal concentration ($T_{max}$) was 2–7 hours (fasted)
- There was minimal accumulation with once-weekly dosing
- Doses ≥100 mg exceeded the PK target (300 nM) at 1 week
  - Defined as plasma concentration at 168 hours ($C_{168hr}$) >6 x *in vitro* half-maximal inhibitory concentration ($IC_{50}$) based on meta-analysis of minimum plasma concentration ($C_{min}$)/$IC_{50}$ of other NNRTIs[3]

## CONCLUSIONS

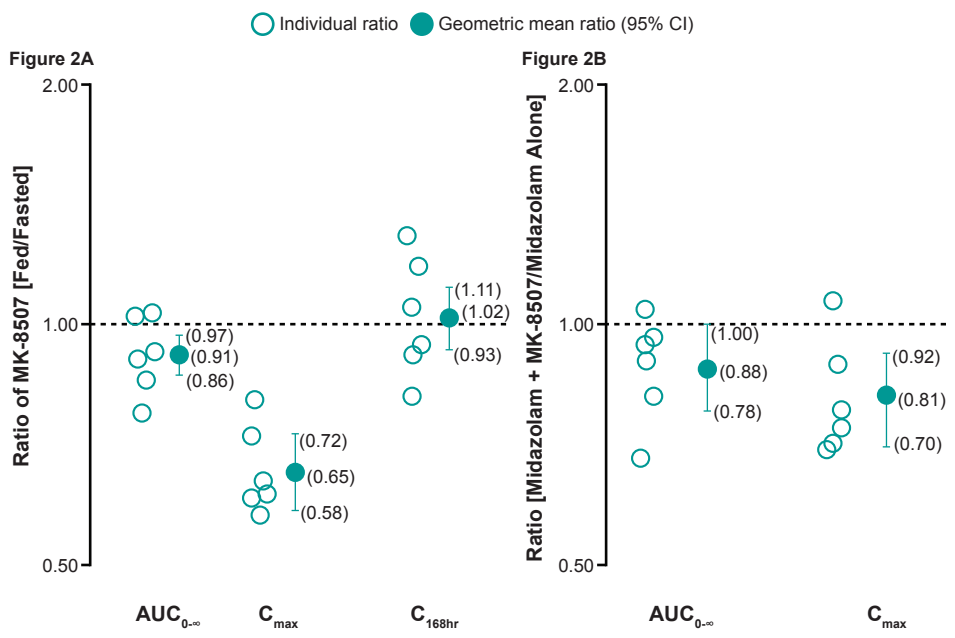
- MK-8507 is a novel NNRTI that was generally well tolerated in participants without HIV
- MK-8507 PK is supportive of once weekly oral administration
- MK-8507 doses ≥100 mg achieved the $C_{168hr}$ PK target (eg, trough plasma concentration [$C_{trough}$] at 1 week)

**Figure 1. Mean Plasma Concentration vs Time Profiles of Single Oral Doses of MK-8507 in the Fasted State (Study 1 and Study 2)**




The time point in Study 1 for the proceeding period was used in the preceding period, resulting in an additional time point of 480 hours. PK, pharmacokinetic.

**Figure 2. MK-8507 Plasma PK under Fed and Fasted Conditions (Study 1) (A), and Interactions with Midazolam (Study 2) (B)**




AUC0-∞, area under the concentration–time curve from 0 to infinity; $C_{168hr}$, plasma concentration at 168 hours; CI, confidence interval; $C_{max}$, maximum plasma concentration; PK, pharmacokinetics.

- High-fat meal had no clinically meaningful effect on MK-8507 PK (**Figure 2A**)
- MK-8507 400 mg once weekly had no clinically meaningful interaction with midazolam (**Figure 2B**)

### References

1. FDA. HIV-1 Infection: Developing Antiretroviral Drugs for Treatment Guidance for Industry. 2015.
2. Chesna LK, Fellner C. *Pharm Ther.* 2017;42:647–649.
3. Xu Y et al. *Clin Transl Sci.* 2016;9:192–200.

### Disclosures

- W Ankrom, A Schaeffer, D Panebianco, E Friedman, SA Stoch, and M Iwamoto are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD)
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