Pharmacokinetics of MK-8591, Dolutegravir and Tenofovir Disoproxil Fumarate Are Not Altered After Coadministration When Compared to Single Agent Administration

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BACKGROUND

- Globally, there are an estimated 36.7 million people living with HIV, with approximately 2.1 million new infections each year[1]
- HIV infection has become a chronic condition that can be controlled with combination antiretroviral treatment (cART), with approximately 17.0 million people on cART worldwide[2]
- cART involves the coadministration of multiple therapeutic agents to suppress HIV replication and generally consists of nucleotide reverse transcriptase inhibitors (NRTI) with a non-nucleotide reverse transcriptase inhibitor (NNRTI), integrase strand transfer inhibitor (InSTI), or protease inhibitor[2]
- Dolutegravir (DTG), an InSTI, and the NRTI tenofovir disoproxil fumarate (TDF), a prodrug of tenofovir (TFV), are commonly used together in cART and do not pharmacokinetically interact with one another[3]
- MK-8591 is a novel nucleoside reverse transcriptase translocation inhibitor (NRTTI), with potent antiviral activity against wild-type and drug-resistant HIV-1 variants, and is currently under development for treatment of HIV infection[4,5]
- MK-8591 did not have a clinically meaningful pharmacokinetic interaction with Doravirine (DOR), a recently FDA approved NNRTI, that is currently being investigated as a possible combination treatment with MK-8591 for HIV-1 infection
- In addition to a combination treatment with DOR, MK-8591 may potentially be co-administered with other antiretroviral drugs, such as DTG and/or TDF, so additional drug interactions must be assessed; this study was conducted to assess a two-way interaction between MK-8591 and the combination of DTG+TDF

METHODS

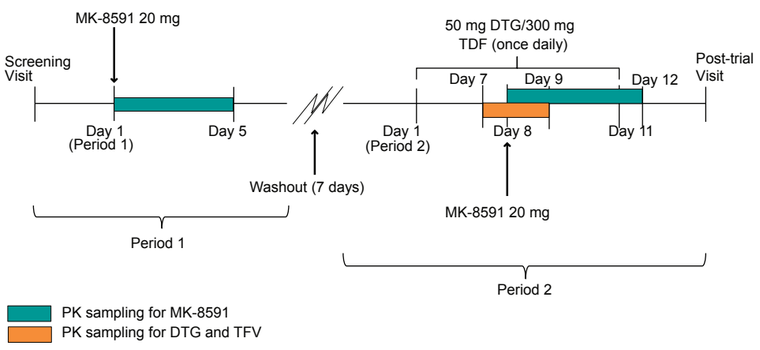
Study Design

- Open-label, fixed-sequence, 2-period study to assess the two-way interaction of MK-8591 and DTG+TDF in healthy participants
- Eligible participants:
  - Healthy male and female participants between the ages of 18 and 65 (inclusive)
  - Body mass index (BMI) of 19-32 kg/m²
- Key exclusion criteria:
  - Pre-existing health conditions determined by the investigator to be clinically significant
  - Infected with HIV, hepatitis B, or hepatitis C
  - Tested positive for nicotine, drugs, or alcohol
  - Creatinine clearance <80 mL/min
  - Unable to discontinue clinically relevant medications or supplements

Treatments

- Period 1: Single oral dose of 20 mg MK-8591, followed by a minimum 7-day washout interval
- Period 2: 50 mg DTG + 300 mg TDF once daily for 11 days, with 20 mg MK-8591 coadministered on Day 8

Figure 1. Study Design



Assessments

- Participants were screened for eligibility requirements within 28 days prior to dosing
- Plasma for MK-8591 analysis was collected predose and then at hours 0.125, 0.33, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, and 96 in Period 1 and Period 2; samples collected at hours 24, 48, and 72 during Period 2 were collected prior to the dosing of DTG + TDF
- Plasma for DTG and TFV analysis was collected predose and then at hours 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 24.5, 25, 26, 27, 28, 30, 32, 36, and 48 in Period 2
- Safety and tolerability were assessed throughout the study by repeated clinical evaluations, including standard laboratory tests, physical examination, electrocardiograms, vital sign assessments, and reporting of adverse events (AE)

Pharmacokinetic Analysis

- Plasma concentrations of MK-8591, DTG, and TFV were determined by inVentiv Health Clinique, Inc. (Québec, Canada), using a high-performance liquid chromatography system with tandem mass spectrometry with a validated calibration range of 0.1 to 100.00 ng/mL for MK-8591, 10.00 to 10,000.00 ng/mL for DTG, and 0.50 to 500.00 ng/mL for TFV
- PK parameters were calculated using the software Phoenix® WinNonlin® (Version 6.3)
- C_{max} and T_{max} values were obtained directly from the observed plasma concentration-time data. $AUC_{0-\infty}$ and AUC_{0-24} were calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations (linear-up/log-down)
- The apparent terminal $t_{½}$ was calculated as the quotient of the natural log(ln) of 2 and λz (ln[2]/λz), where λz was the apparent first-order terminal elimination rate constant calculated from the slope of the linear regression of the terminal log-linear portion of the plasma concentration-time profile

Statistical Analysis

MK-8591 Statistical Analysis

- Individual $AUC_{0-\infty}$ and C_{max} values for MK-8591 were natural log-transformed prior to analysis with a linear mixed-effects model with a fixed-effect term for treatment
- An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between the treatment measurements within each participant. Kenward and Roger's method was used to calculate the denominator degrees of freedom for the fixed effects. Two-sided 90% confidence intervals (CI) were constructed for the difference in least-squares means on the log scale for $AUC_{0-\infty}$ and C_{max}. Exponentiating the log scale, 90% CIs were provided for the $AUC_{0-\infty}$ and C_{max} geometric mean ratios (GMR) (MK-8591 + DTG + TDF/MK-8591 alone)

DTG/TFV Statistical Analysis

- Individual AUC_{0-24}, C_{24}, and C_{max} of DTG and TFV were natural log-transformed and analyzed using the same model described for MK-8591 analysis with the point estimates and the corresponding 90% CIs for GMRs provided

RESULTS

Participants

- A total of 12 participants were enrolled into the study; all participants completed both study periods. Baseline characteristics are summarized in **Table 1**
- All participants were included in both the PK and safety analyses

Table 1. Summary of Study Participant Demographics

Study Participants, N	12
Sex, n (%)	
Male	5 (41.7)
Female	7 (58.3)
Age (years)	
Mean (SD)	39.2 (8.1)
Median	39.0
Range	25-53
Weight (kg)	
Mean	71.7
Range	58-88
BMI (kg/m²)	
Mean	26.7
Range	21-31
Race, n (%)	
Black or African American, Asian	1 (8.3)
White	11 (91.7)
Ethnicity, n (%)	
Hispanic or Latino	11 (91.7)
Not Hispanic or Latino	1 (8.3)

Pharmacokinetic Analysis

Plasma PK Analysis for MK-8591

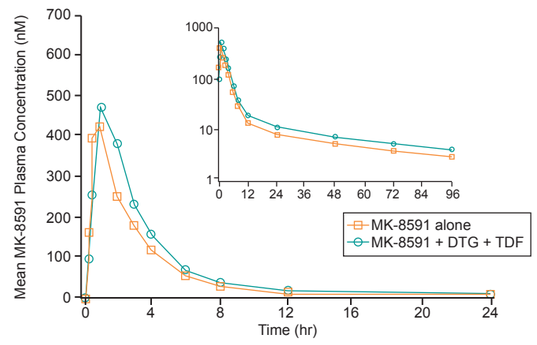
- Coadministration of MK-8591 with steady-state DTG and TDF increased MK-8591 $AUC_{0-\infty}$ by 28% (**Table 2** and **Figure 2**)
- The median T_{max} and geometric mean (GM) apparent terminal $t_{½}$ values of MK-8591 were comparable between both treatments (**Table 2**)

Table 2. Summary of Plasma Pharmacokinetics of MK-8591 After a Single Dose of MK-8591 With or Without Coadministration of Multiple Doses of DTG+TDF

Pharmacokinetic Parameter	MK-8591 Alone[a] N=12 GM	95% CI	MK-8591 + DTG + TDF[b] N=12 GM	95% CI	(MK-8591 + DTG + TDF)/(MK-8591 Alone) GMR	90% CI	Within-Participant CV (%)[d]
$AUC_{0-\infty}$ (μM·hr)[f]	1.97	(1.77, 2.9)	2.51	(2.31, 2.74)	1.28	(1.19, 1.37)	9.8%
C_{max} (μM)[f]	0.479	(0.403, 0.568)	0.510	(0.438, 0.593)	1.07	(0.93, 1.22)	18.6%
T_{max} (hr)[c]	0.75	(0.50, 3.01)	1.00	(0.50, 2.01)			
Apparent terminal $t_{1/2}$ (hr)[e]	56.59	15.1	55.89	10.1			

[a]Single dose of 20 mg of MK-8591
[b]Multiple oral QD doses of 50 mg DTG and 300 mg TDF on Days 1 to 11 coadministered with a single oral dose of 20 mg MK-8591 on Day 8
[c]Median (Min, Max) reported for T_{max}
[d]Within-Participant CV (%) estimated based on the elements of the variance-covariance matrix: CV (%) $=100*\sqrt{[(s^2_A + s^2_B - 2*s_{AB})/2]}$
[e]Geometric CV (%) is reported for $t_{1/2}$
[f]Back-transformed least-squares means and confidence intervals from linear mixed-effects model performed on natural log-transformed values

Figure 2. Arithmetic Mean Plasma Concentration-Time Profiles of MK-8591 Following a Single Dose of MK-8591 With and Without Coadministration of Multiple Doses of DTG+TDF (N=12)



Plasma PK Analysis for DTG

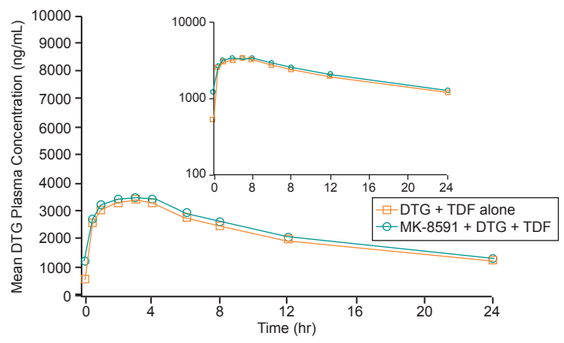
- Coadministration of multiple QD oral doses of DTG and TDF with a single oral dose of MK-8591 resulted in comparable steady-state DTG AUC_{0-24} and C_{24} (**Table 3** and **Figure 3**)
- The steady-state C_{max} was nearly identical between the 2 treatments
- The median T_{max} and GM apparent terminal $t_{½}$ values of DTG were comparable between both treatments

Table 3. Summary of Plasma Pharmacokinetics of DTG Following the Administration of Multiple Doses of DTG+TDF With and Without a Single Dose of MK-8591

Pharmacokinetic Parameter	DTG + TDF Alone[a] N=12 GM	95% CI	MK-8591 + DTG + TDF[b] N=12 GM	95% CI	(MK-8591 + DTG + TDF)/(DTG + TDF Alone) GMR	90% CI	Within-Participant CV (%)[d]
AUC_{0-24} (ng·hr/mL)[f]	48000	(37900, 60900)	52000	(42700, 63200)	1.08	(1.02, 1.14)	7.5%
C_{max} (ng/mL)[f]	3500	(2770, 4430)	3570	(2950, 4330)	1.02	(0.94, 1.11)	11.5%
C_{24} (ng/mL)[f]	1120	(861, 1470)	1240	(990, 1550)	1.10	(1.03, 1.17)	8.6%
T_{max} (hr)[c]	2.50	(0.50, 4.13)	3.00	(1.00, 6.03)			
Apparent terminal $t_{1/2}$ (hr)[e]	15.19	14.0	15.48	16.2			

[a]Multiple oral QD doses of 50 mg DTG and 300 mg TDF on Days 1 to 7
[b]Multiple oral QD doses of 50 mg DTG and 300 mg TDF on Days 1 to 11 coadministered with a single oral dose of 20 mg MK-8591 on Day 8
[c]Median (Min, Max) reported for T_{max}
[d]Within-Participant CV (%) estimated based on the elements of the variance-covariance matrix: CV (%) $=100*\sqrt{[(s^2_A + s^2_B - 2*s_{AB})/2]}$
[e]Geometric CV (%) is reported for $t_{1/2}$
[f]Back-transformed least-squares means and confidence intervals from linear mixed-effects model performed on natural log-transformed values

Figure 3. Arithmetic Mean Plasma Concentration-Time Profiles of DTG Following Multiple Doses of DTG+TDF With and Without a Single Dose of MK-8591 (N=12)



Plasma PK Analysis for TFV

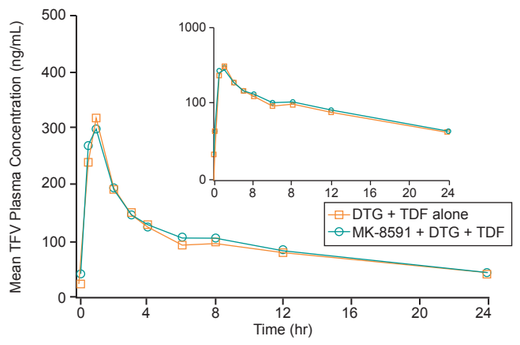
- Coadministration of multiple QD oral doses of DTG and TDF with a single oral dose of MK-8591 resulted in comparable steady-state TFV AUC_{0-24} and C_{max} (**Table 4** and **Figure 4**)
- The steady-state C_{24} GMR (90% CI) was also very similar between the 2 treatments
- The median T_{max} and GM apparent terminal $t_{½}$ values of TFV were comparable between both treatments

Table 4. Summary of Plasma Pharmacokinetics of TFV Following the Administration of Multiple Doses of DTG+TDF With and Without a Single Dose of MK-8591

Pharmacokinetic Parameter	DTG + TDF Alone[a] N=12 GM	95% CI	MK-8591 + DTG + TDF[b] N=12 GM	95% CI	(MK-8591 + DTG + TDF)/(DTG + TDF Alone) GMR	90% CI	Within-Participant CV (%)[d]
AUC_{0-24} (ng·hr/mL)[f]	2220	(1990, 2480)	2330	(2110, 2570)	1.05	(0.96, 1.14)	11.4%
C_{max} (ng/mL)[f]	339	(297, 387)	333	(282, 393)	0.98	(0.88, 1.10)	15.5%
C_{24} (ng/mL)[f]	42.6	(37.3, 48.8)	48.8	(40.3, 49.7)	1.05	(0.97, 1.14)	10.9%
T_{max} (hr)[c]	1.00	(0.50, 1.01)	1.01	(0.51, 2.01)			
Apparent terminal $t_{1/2}$ (hr)[e]	13.70	12.2	13.20	11.0			

[a]Multiple oral QD doses of 50 mg DTG and 300 mg TDF on Days 1 to 7
[b]Multiple oral QD doses of 50 mg DTG and 300 mg TDF on Days 1 to 11 coadministered with a single oral dose of 20 mg MK-8591 on Day 8
[c]Median (Min, Max) reported for T_{max}
[d]Within-Participant CV (%) estimated based on the elements of the variance-covariance matrix: CV (%) $=100*\sqrt{[(s^2_A + s^2_B - 2*s_{AB})/2]}$
[e]Geometric CV (%) is reported for $t_{1/2}$
[f]Back-transformed least-squares means and confidence intervals from linear mixed-effects model performed on natural log-transformed values

Figure 4. Arithmetic Mean Plasma Concentration-Time Profiles of TFV Following Multiple Doses of DTG+TDF With and Without a Single Dose of MK-8591 (N=12)



Safety

- All 12 participants who received study therapy were included in the safety population
- There were no deaths or serious AEs
- Six participants (50.0%) in the study reported AEs
- Five participants (42%) reported AEs considered to be drug-related
  - Three participants reported drug-related AEs after administration of MK-8591 alone
  - Three participants reported drug-related AEs after administration of DTG+TDF alone
  - One participant reported drug-related AEs after coadministration of MK-8591 and DTG+TDF
  - Most common drug-related AE was headache, reported by 3 participants (25%)
  - All other drug-related AEs (abdominal discomfort, constipation, nausea, chest discomfort, viral infection, back pain, dysgeusia, and alopecia) were reported by 1 participant each (8%)

CONCLUSIONS

- This study showed that coadministration of MK-8591 with DTG+TDF did not have a clinically meaningful effect on the PK of DTG or TDF (measured as TFV)
- These results suggest that MK-8591 would be acceptable for coadministration with DTG and TDF
- Coadministration of MK-8591 with DTG+TDF was generally well tolerated in healthy participants

Acknowledgments

- We thank the participants, investigators, and trial site personnel for their contributions to the study
- Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA provided financial support for the study. Medical writing assistance was provided by Dean Campbell, PhD, and editorial assistance by Carol Zecca, BS, both of Merck & Co., Inc., Kenilworth, NJ, USA

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Presented at HIV Glasgow; Glasgow, UK; 28-31 October 2018.