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

BACKGROUND

- Globally, there are an estimated 33.7 million people living with HIV, with approximately 2.1 million new infections each year
- HIV infection has become a chronic condition that can be controlled with combination antiretroviral therapy (cART), with approximately 17.0 million people on cART worldwide
- cART involves the coadministration of multiple therapeutic agents to suppress HIV replication and generally consists of a nucleoside reverse transcriptase inhibitor (NRTI) with a non-nucleoside reverse transcriptase inhibitor (NNRTI), integrase strand transfer inhibitor (INSTI), and/or protease inhibitor
- Dolutegravir (DTG), an INSTI, and the NRTI tenofovir disoproxil fumarate (TDF), with potent antiretroviral activity against wild-type and drug-resistant HIV-1 variants, and is currently under development for treatment of HIV infection
- MK-8591 is a novel nucleoside reverse transcriptase translocation inhibitor (NRTTI), with potent antiretroviral activity against wild-type and drug-resistant HIV-1 variants, and is currently under development for treatment of HIV infection
- In addition to a combination treatment with DTG, 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 and TDF

METHODS

Study Design
- Open-label, fixed-sequence, 2-period study to assess the two-way interaction of MK-8591, DTG, and TFV
- Participants:
  - Healthy male and female participants between the ages of 18 and 65 (inclusive)
  - Body mass index (BMI) of 19-32 kg/m²
  - Caucasian ethnicity
  - None of the participants had a history of methadone or any other opioid dependency
  - None of the participants had prior exposure to MK-8591, DTG, or TDF
  - They were not taking any medication known to interact with MK-8591, DTG, TDF, or any other concomitant medication
  - They were not pregnant or breastfeeding
  - All 12 participants who received study therapy were included in the safety population

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, 0.25, 0.5, 1, 1.5, 2, 3, 4, 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 and TDF
- Plasma for DTG and TFV analysis was collected predose and then at hours 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 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, electrocardiogram, vital sign assessments, and reporting of adverse events (AEs)

Pharmacokinetic Analysis
- Plasma concentrations of MK-8591, DTG, and TFV were determined by inVentiv Health Clinical, Inc. (Queens, Canada), using a high-performance liquid chromatography (HPLC) method with a validated calibration range of 0.1 to 100.00 ng/mL for MK-8591, 10.00 to 100,000 ng/mL for DTG, and 0.1 to 500.00 ng/mL for TFV
- PK parameters were calculated using the software Phoenix WinNonlin® (Version 6.3)
- Cmax and Tmax values were obtained directly from the observed plasma concentration-time data
- AUC0-24 and Cmax were calculated using the linear trapezoidal method for obtaining concentrations and the log trapezoidal method for deriving pharmacokinetic parameters
- The apparent terminal t½ was derived 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 AUC0-24 and Cmax 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 unconditional convergence matrix was used for unequal treatment variances and to model the correlation between the treatment measurements within each participant
- Treatment and period effects were used to calculate the denominator degrees of freedom for the fixed effects
- Two-sided 90% confidence intervals (CI) were constructed for the differences in log back-transformed means on the log scale for AUC0-24 and Cmax
- Exponentializing the log scale, 90% CIs were provided for the AUC0-24 and Cmax geometric mean ratios (GMR) (MK-8591 + DTG + TDF/MK-8591 alone)

RESULTS

Table 1. Summary of Plasma Pharmacokinetics of MK-8591 Following Multiple Doses of DTG+TDF With and Without a Single Dose of MK-8591

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MK-8591 (n=12)</th>
<th>MK-8591 + DTG + TDF (n=12)</th>
<th>MK-8591 + DTG + TDF/MK-8591</th>
<th>GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-24 (ng·h/mL)</td>
<td>291.0 (197.3, 427.3)</td>
<td>291.0 (197.3, 427.3)</td>
<td>1.00 (0.88, 1.12)</td>
<td>1.00 (0.88, 1.12)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>339 (297, 387)</td>
<td>339 (297, 387)</td>
<td>0.98 (0.88, 1.10)</td>
<td>0.98 (0.88, 1.10)</td>
</tr>
<tr>
<td>Time (hr)</td>
<td>8.50</td>
<td>8.50</td>
<td>1.00 (0.88, 1.12)</td>
<td>1.00 (0.88, 1.12)</td>
</tr>
<tr>
<td>Apparent terminal t½ (hr)</td>
<td>13.70</td>
<td>12.20</td>
<td>1.07 (0.93, 1.22)</td>
<td>1.07 (0.93, 1.22)</td>
</tr>
</tbody>
</table>

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 and TDF
- One participant reported drug-related AEs after coadministration of MK-8591 and DTG and TDF
- Most common drug-related AE was headache, reported by 3 participants (25%)
- All other drug-related AEs (abdominal discomfort, constipation, nausea, chest discomfort, oral infection, back pain, dysgeusia, and anorexia) were reported by 1 participant each (8%)

CONCLUSIONS
- This study showed that coadministration of MK-8591 with DTG and 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 and TDF was generally well tolerated in healthy participants

Acknowledgments
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- Statistical analysis was provided by Mark Campbell, Ph.D., and external statistical support from Aronson, Moon, Bath & O’Connor, Inc., Kenilworth, N.J., USA

References

Figure 3. 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)

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)