Effect of Food on Pharmacokinetics of Elvitegravir, Emtricitabine, Tenofovir DF and the Pharmacoenhancer GS-9350 as a Fixed-Dose Combination Tablet

P German,1 D Warren,2 L Wei,1 L Zhong,1 J Hui,1 and BP Kearney1

1Gilead Sciences, Inc., Foster City, CA, USA; 2Gilead Sciences, Inc., Durham, NC, USA

Introduction

• Gilead’s investigational HIV-1 integrase inhibitor, elvitegravir (EVG), is primarily metabolized by CYP3A enzymes.
• GS-9350 lacks antiretroviral activity and is in development as a pharmacoenhancer (booster) to increase the systemic levels of coadministered CYP3A substrates (e.g., EVG and HIV protease inhibitors (PIs)).
• GS-9350 may be an alternative to ritonavir (RTV) as the pharmacoenhancer of EVG.
• Administration of a single unboosted 400 mg EVG dose results in Cmax,ss increases of 3.3-fold and 2.7-fold, respectively in the fed (575 kcal, 33% fat) versus fasted state.
• The current dosing recommendation for RTV-boosted EVG is administration of a meal to improve pharmacokinetics (PK) and tolerability and due to its concurrent administration with RTV-boosted PIs.

Background

• The fixed-dose combination of emtricitabine (FTC)/tenofovir DF (TDF), is a preferred agent for the treatment of antiretroviral-naïve HIV patients.1
• FTC pharmacokinetics is unaffected by food.2
• Tenofovir (TFV) exposure (AUC0–inf) is modestly increased (~40%) with high fat meal.3
• No Grade 3/4 adverse events or serious adverse events (AEs)4
• No discontinuations due to adverse events.
• Treatment emergent drug-related adverse events: 1 subject: nausea (light meal); 1 subject: headache, dizziness (high calorie/high fat meal).

Objectives

Primary:
• To evaluate the pharmacokinetics of EVG, FTC, TFV and GS-9305, administered as a fixed-dose combination tablet (EVG/FTC/TDF/GS-9350) under fasted and fed (light and high calorie/high fat) conditions.

Secondary:
• To evaluate the safety and tolerability of administration of the EVG/FTC/TDF/GS-9350 fixed-dose combination tablet under fed and fasted conditions.

Methods

• HIV-1 uninfected healthy subjects (N=24) were randomized to receive single doses of FDC fasted, with a light meal (373 kcal, 20% fat), and with a high fat meal (800 kcal, 50% fat).
• Blood was collected over 48 hours post-dosing for the evaluation of AUClast.
• Plasma concentrations were measured by validated LC/MS/MS using WinNonlin™ 5.2 (Pharsight Corporation, Mountain View, CA, USA).
• Geometric least-squares means ratios and 90% CIs for AUC0–inf increases of 3.3-fold and 2.7-fold, respectively in the fed (575 kcal, 33% fat) versus fasted state.
• The current dosing recommendation for RTV-boosted EVG is 326 (33.4) 2240 (24.4) 2580 (24.2).

Results

Demographics:
• 24 subjects enrolled and completed the study.
• Age: Mean 35 years (range: 21 to 45 years).
• Weight: Mean 73 kg (range: 61 to 91 kg).

Safety:
• No Grade 3/4 adverse events or serious adverse events (AEs).
• No discontinuations due to adverse events.

Table 1. EVG Plasma Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cmax (ng·ml⁻¹)</th>
<th>AUCinf (ng·hr·ml⁻¹)</th>
<th>AUClast (ng·hr·ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasted</td>
<td>1190 (34.5)</td>
<td>8050 (69.0)</td>
<td>8370 (49.7)</td>
</tr>
<tr>
<td>Light Meal</td>
<td>1240 (38.5)</td>
<td>10700 (84.7)</td>
<td>11000 (51.0)</td>
</tr>
<tr>
<td>HC/HF Meal</td>
<td>944 (43.9)</td>
<td>6570 (61.7)</td>
<td>6680 (49.3)</td>
</tr>
</tbody>
</table>

Figure 1. EVG Plasma Concentration-Time Profiles

Figure 2. GS-9350 Plasma Concentration-Time Profiles

Figure 3. TFV Plasma Concentration-Time Profiles

Figure 4. FTC Plasma Concentration-Time Profiles

Conclusions

• EVG exposures were increased with food vs. fasted state.
• GS-9350 exposures were lower with high calorie/high fat meal relative to light meal or fasted administration.
• Lower GS-9350 exposures with high calorie/high fat meal did not adversely affect EVG exposures.
• TFV and FTC PK were consistent with their established profiles.
• FTC exposures were bioequivalent.
• TFV exposures were slightly higher with food vs. fasted state.

References

1. Internal Gilead Data on file.