

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

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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, such as 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 C_{max} and AUC_{inf} increases of 3.3-fold and 2.7-fold, respectively in the fed (575 kcal, 33% fat) versus fasted state¹

The current dosing recommendation for RTV-boosted EVG is administration with 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 patients²
- FTC pharmacokinetics is unaffected by food³
- Tenofovir (TFV) exposure (AUC_{0-24}) is modestly increased (~ 40%) with a high fat meal⁴

Objectives

Primary:

- To evaluate the pharmacokinetics of EVG, FTC, TFV and GS-9350, administered as a fixed-dose combination tablet (EVG/FTC/TDF/ GS-9350 [FDC]) 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)
- Each treatment was followed by a 1-week washout
- Blood was collected over 48 hours post-dosing for the evaluation of EVG, FTC, TFV, and GS-9350 PK
- Plasma concentrations were measured by validated LC/MS/MS
- PK parameters were estimated via non-compartmental analysis using WinNonlin™ 5.2 (Pharsight Corporation, Mountain View, CA, USA)
- Geometric least-squares means ratios and 90% CIs for AUC_{inf} , AUC_{last} and C_{max} were estimated using ANOVA with PK equivalence boundaries of 80-125%

Results

Demographics

- 24 subjects enrolled and completed the study
 - 12 females, 12 males
 - Mean age: 35 years (range: 21 to 45 years)
 - Mean weight: 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
- Treatment emergent drug-related adverse events:
 - 1 subject: nausea (light meal)
 - 1 subject: headache, dizziness (high calorie/high fat meal)

Table 1. EVG Plasma Pharmacokinetic Parameters

N=24	C_{max} (ng/ml)	AUC_{last} (ng·hr/ml)	AUC_{inf} (ng·hr/ml)
Fasted	1490 (40.3)	15600 (40.2)	16400 (38.6)
Light Meal	1760 (31.5)	20400 (28.0)	21100 (27.5)
HC/HF Meal	2230 (27.1)	28000 (22.6)	28800 (21.6)
GMR (90% CI) %			
Light Meal vs. Fasted	122 (108, 138)	136 (121, 154)	134 (119, 151)
HC/HF Meal vs. Fasted	156 (138, 176)	191 (170, 216)	187 (166, 210)
HC/HF Meal vs. Light Meal	128 (114, 145)	140 (124, 158)	139 (123, 157)

Data presented as arithmetic mean (%CV); GMR: Geometric Least-Squares Means Ratio; CI: Confidence Interval; HC/HF- high calorie/high fat

Table 2. GS-9350 Plasma Pharmacokinetic Parameters

N=24	C_{max} (ng/ml)	AUC_{last} (ng·hr/ml)	AUC_{inf} (ng·hr/ml)
Fasted	1190 (34.5)	8290 (49.5)	8370 (49.7)
Light Meal	1240 (35.5)	8010 (44.4)	8090 (44.5)
HC/HF Meal	944 (43.9)	6570 (49.1)	6680 (49.5)
GMR (90% CI) %			
Light Meal vs. Fasted	104 (93.6, 114)	103 (89.6, 118)	103 (89.9, 117)
HC/HF Meal vs. Fasted	75.7 (68.4, 83.6)	82.4 (71.9, 94.4)	82.9 (72.5, 94.7)
HC/HF Meal vs. Light Meal	73.1 (66.1, 80.8)	80.2 (70.0, 91.9)	80.7 (70.6, 92.2)

Data presented as arithmetic mean (%CV); GMR: Geometric Least-Squares Means Ratio; CI: Confidence Interval; HC/HF- high calorie/high fat

Table 3. TFV Plasma Pharmacokinetic Parameters

N=24	C_{max} (ng/ml)	AUC_{last} (ng·hr/ml)	AUC_{inf} (ng·hr/ml)
Fasted	326 (33.4)	2240 (24.4)	2580 (24.2)
Light Meal	386 (29.2)	2770 (17.1)	3140 (17.2)
HC/HF Meal	356 (45.7)	2780 (19.7)	3140 (18.9)
GMR (90% CI) %			
Light Meal vs. Fasted	120 (104, 139)	125 (119, 131)	124 (118, 130)
HC/HF Meal vs. Fasted	103 (89.4, 120)	125 (119, 131)	123 (117, 129)
HC/HF Meal vs. Light Meal	86.1 (74.5, 99.7)	99.9 (95.2, 105)	99.7 (94.8, 105)

Data presented as arithmetic mean (%CV); GMR: Geometric Least-Squares Means Ratio; CI: Confidence Interval; HC/HF- high calorie/high fat

Table 4. FTC Plasma Pharmacokinetic Parameters

N=24	C_{max} (ng/ml)	AUC_{last} (ng·hr/ml)	AUC_{inf} (ng·hr/ml)
Fasted	1910 (29.1)	11000 (21.8)	11300 (21.0)
Light Meal	1810 (28.8)	10300 (19.6)	10700 (18.6)
HC/HF Meal	1820 (26.5)	10400 (19.1)	10800 (18.8)
GMR (90% CI) %			
Light Meal vs. Fasted	95.4 (86.5, 105)	94.3 (90.3, 98.6)	95.3 (91.2, 99.6)
HC/HF Meal vs. Fasted	96.2 (87.2, 106)	95.6 (91.5, 99.9)	95.7 (91.6, 100)
HC/HF Meal vs. Light Meal	101 (91.4, 111)	101 (97.0, 106)	100 (96.1, 105)

Data presented as arithmetic mean (%CV); GMR: Geometric Least-Squares Means Ratio; CI: Confidence Interval; HC/HF- high calorie/high fat