

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_{inf}) 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

Results (cont'd)

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

Figure 1. EVG Plasma Concentration-Time Profiles

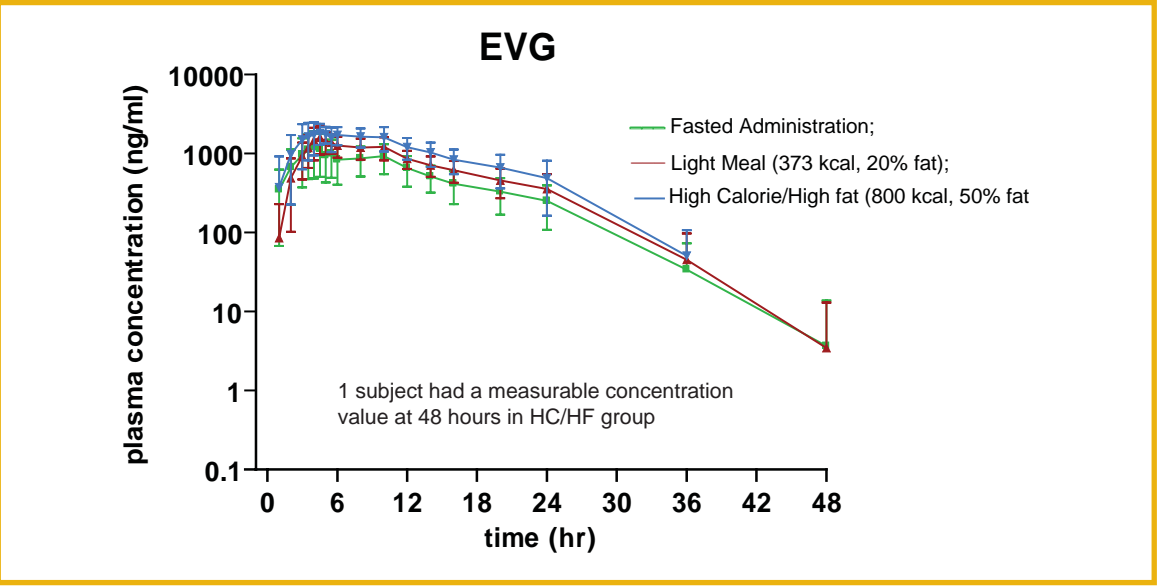


Figure 2. GS-9350 Plasma Concentration-Time Profiles

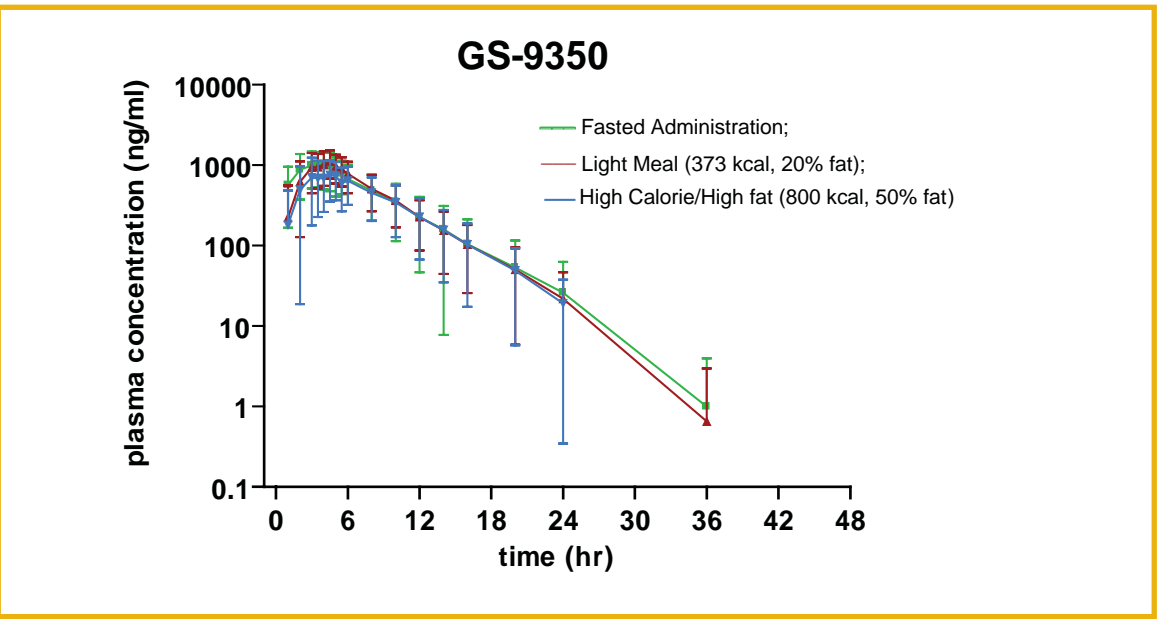


Figure 3. TFV Plasma Concentration-Time Profiles

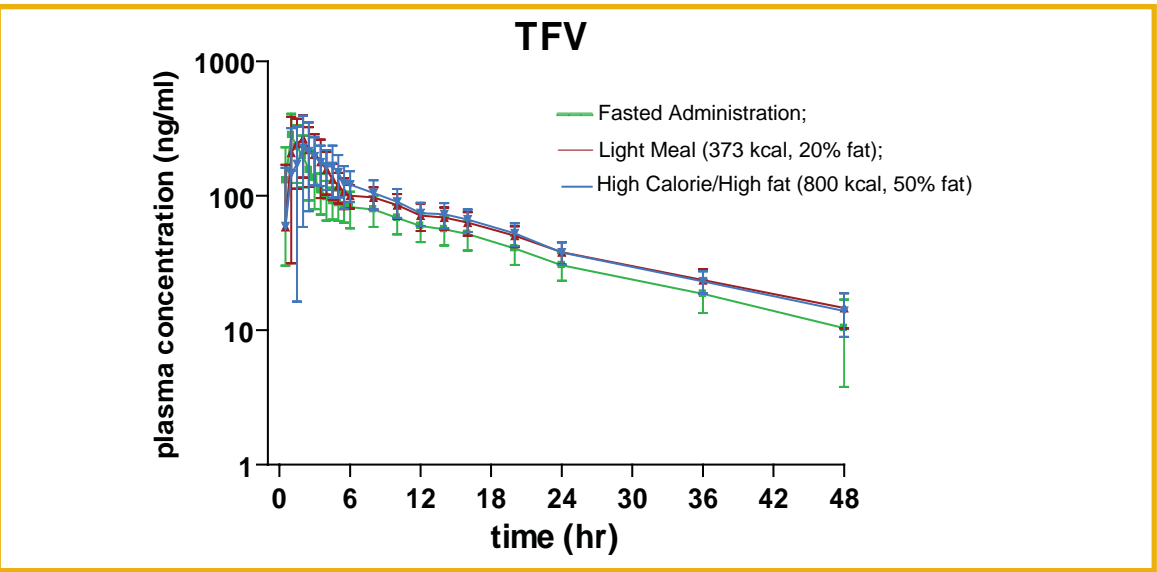
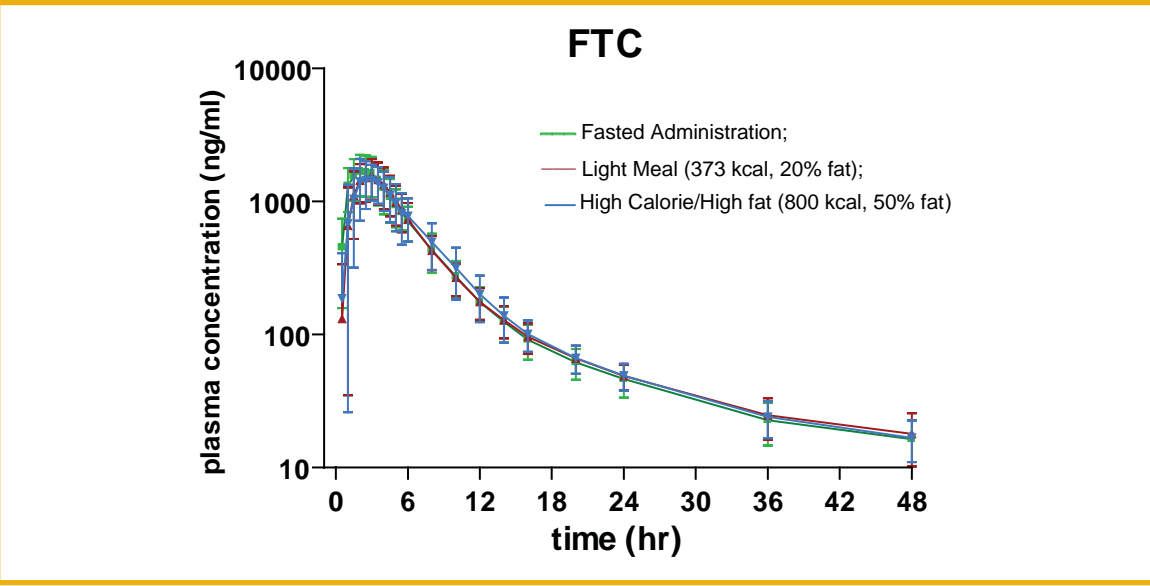


Figure 4. FTC Plasma Concentration-Time Profiles



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
- EVG/FTC/TDF/GS-9350 FDC should be administered with food to provide desired EVG exposures

References

- Internal Gilead Data on file.
- Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. January 29, 2008 .
- Truvada US Prescribing Information. May 2005.
- Viread US Prescribing Information. October 2003.