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Pharmacokinetics of Coadministered Ritonavir-Boosted Elvitegravir Plus Maraviroc

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Introduction

- Elvitegravir (EVG; GS-9137) is an HIV integrase inhibitor being developed for the treatment of HIV-infected patients
- Ritonavir-boosted elvitegravir (EVG/r, 125/100 mg) displayed superior antiviral activity compared to PI/r in combination with an optimized background regimen containing NRTIs ± enfuvirtide[1]
- Maraviroc (MVC) is a CCR5 antagonist that displayed superior antiviral activity compared to placebo in combination with an optimized background regimen in treatment-experienced patients[2,3]

Background

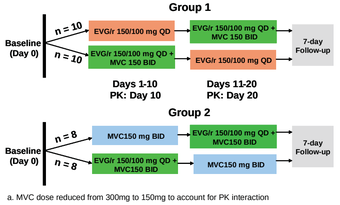
- EVG is metabolized by CYP3A4 and glucuronidation; coadministration of EVG with ritonavir results in a 20-fold increase in plasma EVG exposures
- MVC is a substrate of CYP3A and P-glycoprotein
- MVC dose reduction of 50% is recommended when given with CYP3A inhibitors, including most protease inhibitors
- Given their likelihood for coadministration and overlapping metabolic pathways, it is important to determine the potential for interaction between EVG/r and MVC

Objectives

- To evaluate the effect of co-administration of EVG/r and MVC on the pharmacokinetics of EVG and MVC
- To evaluate the short-term safety and tolerability of administration of EVG/r and MVC alone and in combination

Methods

Figure 1. Study Design[a]



a. MVC dose reduced from 300mg to 150mg to account for PK interaction

- EVG/r administered with an AM meal (~ 400kcal, 13 g fat), MVC administered 1 hr prior or 2 hr after an AM and PM meal
- Plasma PK sampling performed over 12 hours (MVC) or 24 hours (EVG, ritonavir (RTV)); EVG, MVC and RTV levels determined using validated LC/MS/MS assays on Day 10 and Day 20
- PK parameters (EVG, RTV: Group 1; MVC: Group 2) estimated using non compartmental methods and WinNonlin™ 5.2 (Pharsight Corp., CA, USA)
- Effect of EVG/r on MVC PK estimated. ANOVA and 90% confidence interval (co-administration: alone) lack of PK alteration bounds for geometric mean ratio as follows:
  - EVG – AUC_{tau}, C_{max}, and C_{tau}: 70% to 143%
  - RTV (exploratory) – AUC_{tau}, C_{max}: 70% to 143%

Results

Demographics

- 36 healthy subjects enrolled; 28 completed study
- 22 males, 14 females
- Mean age: 25 yrs (range: 18 – 44)
- Mean weight: 71 kg (range: 55 – 96)
- Ethnicity: 24 White, 10 Black, 2 Other

Safety

- No Grade 3/4 adverse events (AEs) or serious AEs
- 8 discontinuations
  - 4 withdrawn consent, 3 protocol violation, 1 for postural hypotension (EVG/r + MVC arm; an AE known to be associated with MVC)
- EVG/r and MVC administered alone and in combination generally well tolerated
  - Most frequent AE across treatment arms was headache

Table 1. Plasma Pharmacokinetic Parameters of EVG Following EVG/r Alone and EVG/r + MVC Dosing (N=17)

PK Parameters	EVG/r	EVG/r + MVC	GMR (%) (90%CI)
C_{max} (ng/ml)	1590 (39.3)	1580 (25.9)	101 (88.7, 115)
AUC_{tau} (ng·hr/ml)	19100 (34.8)	20300 (28.7)	107 (96.4, 118)
C_{tau} (ng/ml)	404 (51.6)	427 (36.9)	109 (94.7, 126)
$T_{1/2}$ (hr)*	11.4 (9.6, 12.5)	11.1 (9.5, 12.1)	NA
T_{max} (hr)*	4.5 (4.0, 5.0)	4.5 (4.0, 4.5)	NA

Data expressed as arithmetic mean (%CV) or *median (Q1,Q3)
GMR: Geometric Mean Ratio; CI: Confidence Interval; NA: Not applicable

Table 2. Plasma Pharmacokinetic Parameters of MVC Following MVC Alone and EVG/r + MVC Dosing (N=11)

PK Parameters	MVC	EVG/r + MVC	GMR (%) (90%CI)
C_{max} (ng/ml)	465 (46.8)	1010 (48.8)	215 (171, 269)
AUC_{tau} (ng·hr/ml)	999 (37.2)	2850 (39.4)	286 (233,351)
C_{tau} (ng/ml)	19.4 (37.8)	78.7 (26.3)	NA

Data expressed as arithmetic mean (%CV); GMR: Geometric Mean Ratio; CI: Confidence Interval; NA: Not Applicable

Table 3. Plasma Pharmacokinetic Parameters of RTV Following EVG/r Alone and EVG/r + MVC Dosing (N=17)

PK Parameters	EVG/r	EVG/r + MVC	GMR (%) (90%CI)
C_{max} (ng/ml)	1000 (46.1)	874 (30.6)	91.8 (78.4, 107)
AUC_{tau} (ng·hr/ml)	7370 (35.7)	7170 (31.9)	98.2 (91.0, 106)
C_{tau} (ng/ml)	80.6 (45.6)	88.6 (60.1)	103 (88.7, 120)
$T_{1/2}$ (hr)*	5.6 (5.0, 6.3)	5.8 (5.3, 6.2)	NA
T_{max} (hr)*	4.6 (4.5, 5)	4.6 (4.5, 6.0)	NA

Data expressed as arithmetic mean (%CV) or *median (Q1,Q3)
GMR: Geometric Mean Ratio; CI: Confidence Interval; NA: Not applicable

Pharmacokinetics

- EVG and RTV: %GMR (90% CI) for AUC_{tau}, C_{max}, and C_{tau} within predefined lack of PK alteration bounds
- MVC exposures were increased with EVG/r:
  AUC_{0-12} = 186% higher, C_{max} = 115% higher
- MVC exposures with EVG/r were in the range of observed increases when dosed with CYP3A inhibitors

Figure 1. EVG Plasma Concentration-Time Profile (n=17; mean ± SD)

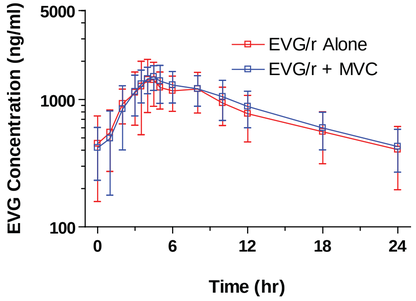


Figure 2. MVC Plasma Concentration-Time Profile (n=11; mean ± SD)

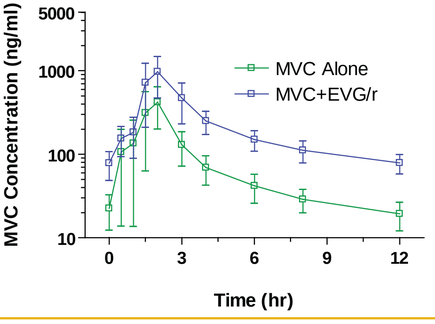
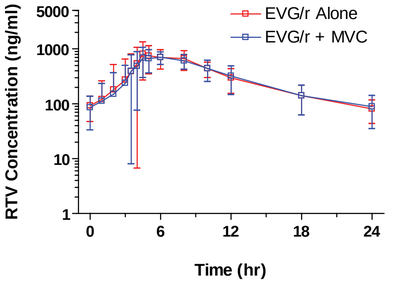


Figure 3. RTV Plasma Concentration-Time Profile (n=17; mean ± SD)



Conclusions

- **Co-administration of EVG/r and MVC was well tolerated**
- **EVG pharmacokinetics was unaltered upon EVG/r plus MVC coadministration**
- **As recommended with CYP3A inhibitors (including RTV-boosted protease inhibitors (except tipranavir/r), a reduced 150 mg dose of MVC should be used with EVG/r**

References

1. Zolopa A, Mullen M, Berger D, et al. The HIV integrase inhibitor GS-9137 demonstrates potent antiretroviral activity in treatment-experienced patients. 14th Conference on Retrovirus and Opportunistic Infections; Los Angeles, USA; 2007 [Abstract 143LB].
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3. Nelson M, Fätkenheuer G, Konourina I, et al. Efficacy and safety of maraviroc plus optimized background therapy in viremic, ART-experienced patients infected with CCR5-tropic HIV-1 in Europe, Australia, and North America: 24-Week Results. 14th Conference on Retroviruses and Opportunistic Infections; Los Angeles, USA; 2007 [Abstract 104aLB].