

# Evaluation of Ritonavir-boosted Elvitegravir PK upon Co-administration with a Second Potent CYP3A inhibitor, Ketoconazole

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# Background

- Elvitegravir (EVG) is an HIV-1 integrase inhibitor
  - Metabolized by CYP3A (M1/GS-9202), UGT1A1/3 (M4/GS-9200)
  - CYP3A inhibition (“boosting”) with ritonavir (RTV; /r) or GS-9350 (cobicistat) increases EVG exposures (20-fold)
  - Boosted EVG results in high  $C_{\text{trough}}$  values (~10-fold  $IC_{95}$ ) thus supporting once-daily (QD) dosing

## RTV Dose Ranging Experiment

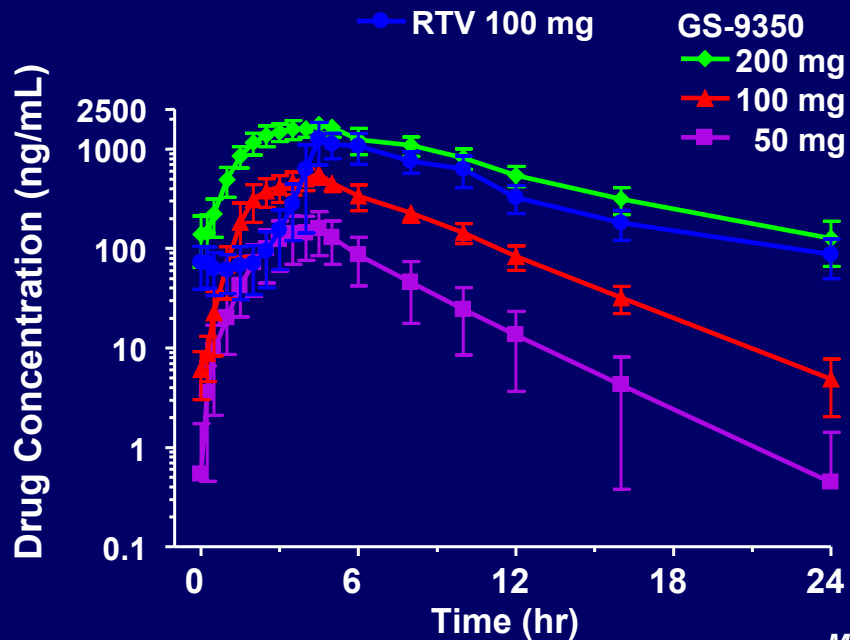
PK Parameter	20 mg RTV	50 mg RTV	100 mg RTV	200 mg RTV
$AUC_{\text{tau}}$ (ng.hr/ml)	134 (54.9)	1120 (61.3)	6530 (27.0)	16000 (43.8)
$C_{\text{tau}}$ (ng/ml)	0.718 (98.8)	11.3 (74.4)	53.8 (41.6)	78.5 (36.7)
$C_{\text{max}}$ (ng/ml)	19.5 (56.7)	130 (61.3)	807 (29.5)	2460 (50.5)
$T_{1/2}$ (hr)*	4.86 (3.02, 5.55)	6.49 (4.88, 7.70)	6.17 (5.34, 7.33)	5.79 (4.78, 6.67)

mean (%CV) or \*median (Q1,Q3)

Mathias AA, et al. *Clin Pharmacol Ther.* 2008;85(1):64-70.

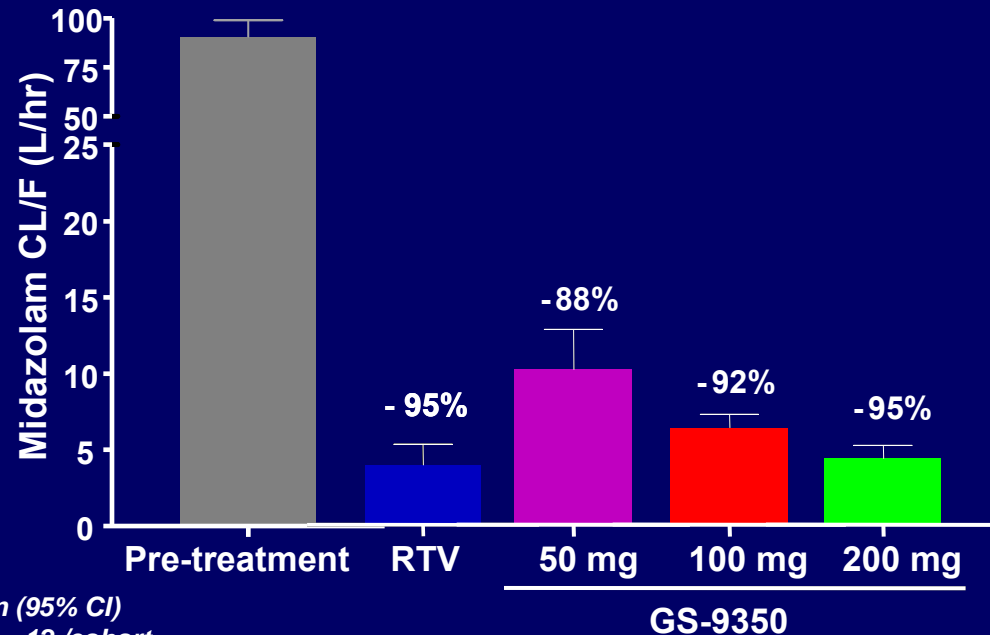
# Pharmacokinetics / Pharmacodynamics

## Steady-state GS-9350 & RTV PK



Mean (95% CI)  
n = 9 - 12 / cohort

## GS-9350 & RTV PD (MDZ apparent clearance)



- **GS-9350 exhibited non-linear increases in exposure with dose and time**
  - Time- and dose-dependent PK consistent with mechanism-based inhibition
- **GS-9350 achieved potent inhibition of CYP3A activity**
  - Near-maximal inhibition achieved at  $\geq 100$ mg

# Background / Objective / Issue

- FDA Request: “Study the effect of additional CYP3A inhibition on boosted-EVG with a second strong inhibitor like ketoconazole (KTZ)”

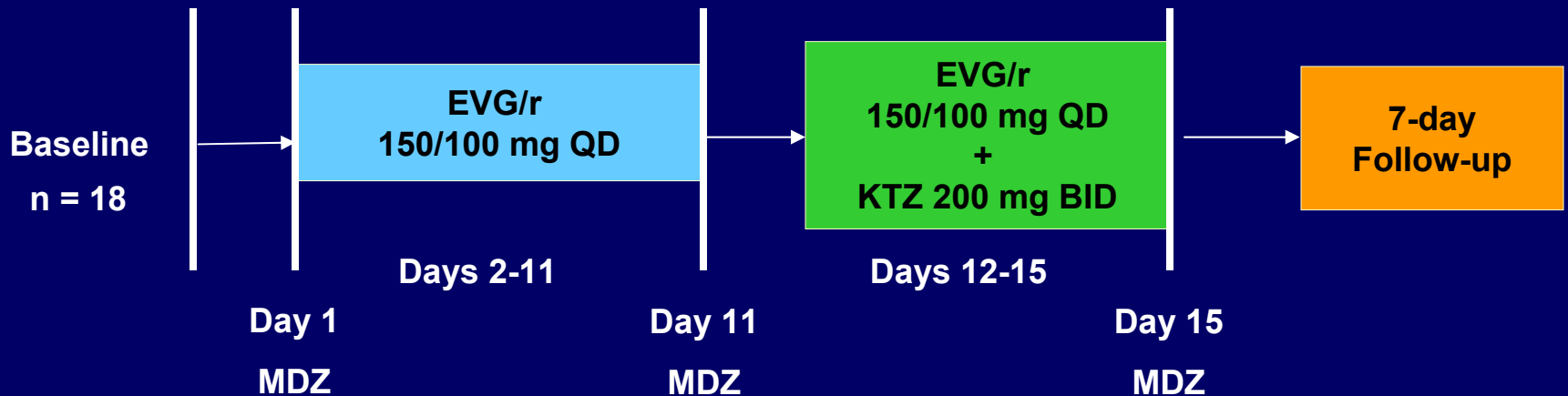
Inhibition from BL	Fold-increase from BL in substrate exposure	Potential fold-change with additional inhibition
90%	10	-
95%	20	2
99%	100	5

- KTZ is a broad-spectrum antifungal agent
  - Prototypical (competitive) CYP3A inhibitor before RTV
    - Therapeutic dose 200 – 400 mg QD
    - A dose of 200 mg BID dose can be used to experimentally study CYP3A inhibition <sup>1</sup>
  - **KTZ is also a UGT1A1 and UGT2B7 inhibitor** <sup>2</sup>

1. Zhao, P. et. al. *J. Clin. Pharmacol.* 2009;49:351-359.

2. Yong WP, et al. *Clin Cancer Res.* Sep 15 2005;11(18):6699-6704.

# Methods



1. Utilize KTZ CYP3A inhibition
  2. Address KTZ UGT inhibition
    - Utilize midazolam (oral) as probe to directly measure CYP3A change
- Steady-state PK assessments for EVG, GS-9202, GS-9200, RTV and KTZ
  - Single-dose MDZ PK assessments
  - Sample analyses using validated LC/MS/MS assays; PK calculated via noncompartmental analysis
  - Lack of PK interaction boundaries of 70-143% for EVG

# Results

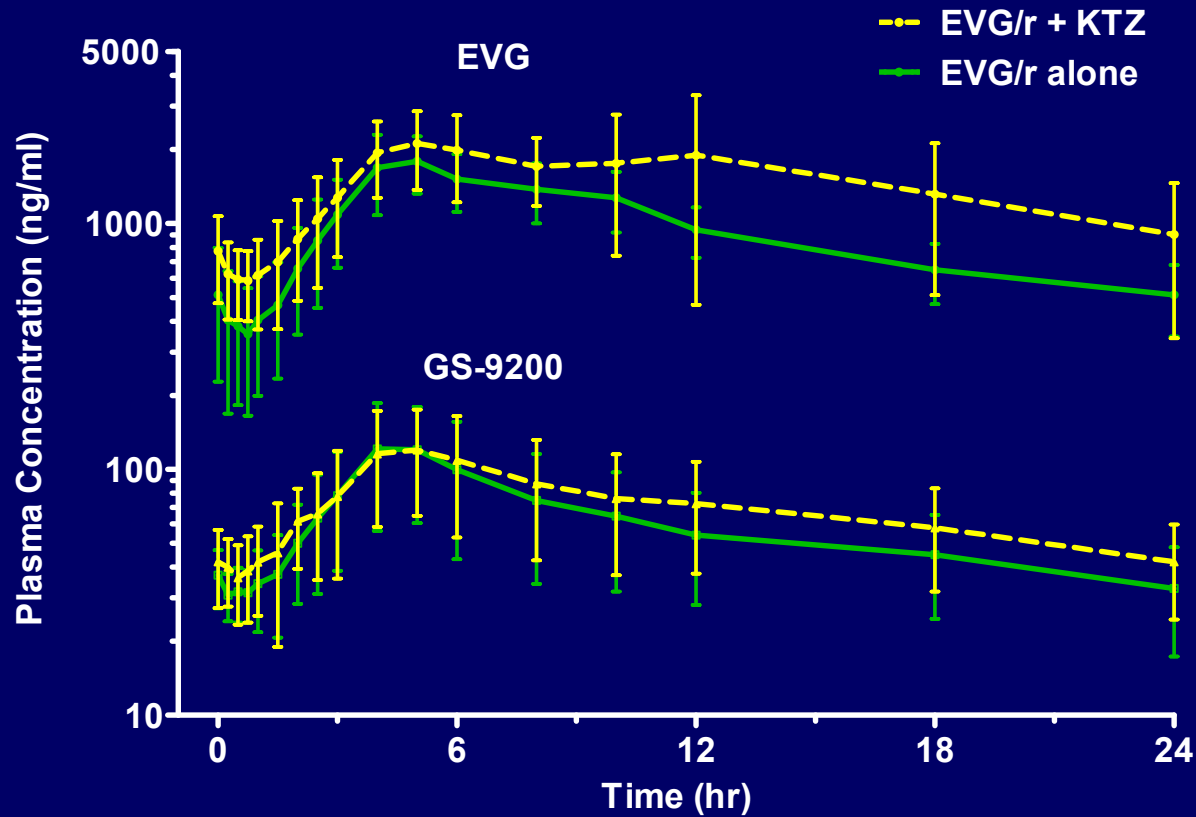
## Demographics

- 18 subjects enrolled and completed the study
  - 6 females, 12 males
  - Mean age: 27 years (range: 19 to 44)
  - Mean weight: 77 kg (range: 57 to 97 kg)

## Safety

- No Grade 3/4 adverse events (AE) or serious adverse events
- Single treatment-related Grade 2 AE: somnolence w/ EVG/r + MDZ
- Most common treatment-related AEs:
  - Headache: 1 subject (MDZ), 1 subject (EVG/r), 3 subjects (EVG/r + KTZ)
  - Nausea: 2 subjects (EVG/r), 3 subjects (EVG/r + KTZ)

# EVG and GS-9200 Concentration-Time Profiles



mean  $\pm$  SD, n = 18

- GS-9202 concentrations below quantifiable limits in both treatments

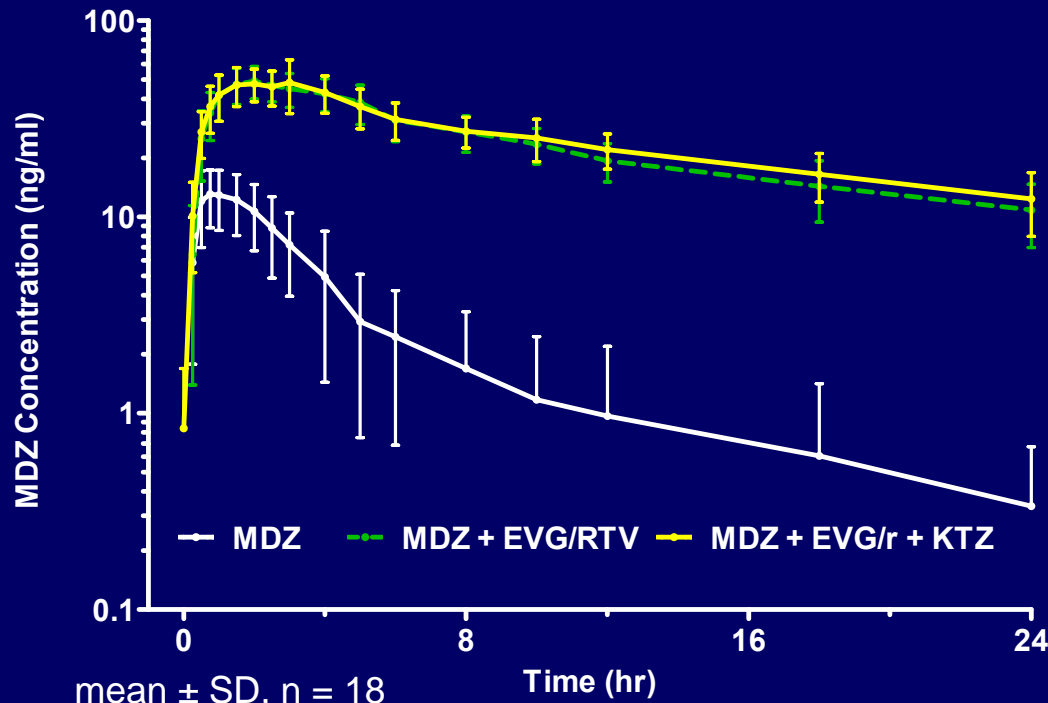
# EVG Plasma PK Parameters

Parameter	EVG/r	EVG/r + KTZ	%GMR (90%CI)
$C_{max}$ (ng/ml)	1990 (24.6)	2450 (52.8)	117 (104, 133)
$AUC_{tau}$ (ng·hr/ml)	22400 (23.9)	34800 (50.0)	148 (136, 162)
$C_{tau}$ (ng/ml)	511 (32.3)	900 (62.1)	167 (148, 188)
$T_{1/2}$ (hr)*	11.8 (10.2, 13.9)	12.6 (9.39, 16.6)	NA

n = 18, mean (%CV) or \*median (Q1,Q3)

- Modest increase in EVG exposures with addition of KTZ BID to EVG/r
- Further inhibition of CYP3A or UGT1A1 pathway (UGT1A1) affected?

# MDZ Pharmacokinetics



Additional CYP3A inhibition  
1.0 to 1.5%

Parameter	MDZ + EVG/r	MDZ + EVG/r +KTZ	%GMR (90%CI)
$C_{max}$ (ng/ml)	51.9 (16.6)	52.7 (26.2)	100 (90.3, 111)
$AUC_{inf}$ (ng·hr/ml)	774 (29.7)	912 (29.4)	117 (104, 132)
$AUC_{last}$ (ng·hr/ml)	556 (19.2)	594 (18.3)	107 (93.5, 122)

n = 18, mean (%CV)

# GS-9200 Plasma PK Parameters

Parameter	EVG/r	EVG/r + KTZ	%GMR (90%CI)
C <sub>max</sub> (ng/ml)	139 (42.2)	138 (44.1)	97.9 (93.2, 103)
AUC <sub>tau</sub> (ng-hr/ml)	1340 (48.2)	1620 (46.3)	121 (111, 131)
T <sub>1/2</sub> (hr)*	11.2 (8.56, 12.1)	13.1 (11.5, 14.1)	NA
GS-9200 : EVG (%) AUC <sub>tau</sub>	6.1	5.0	81.4 (p < 0.05)

n = 18, mean (%CV) or \*median (Q1,Q3)

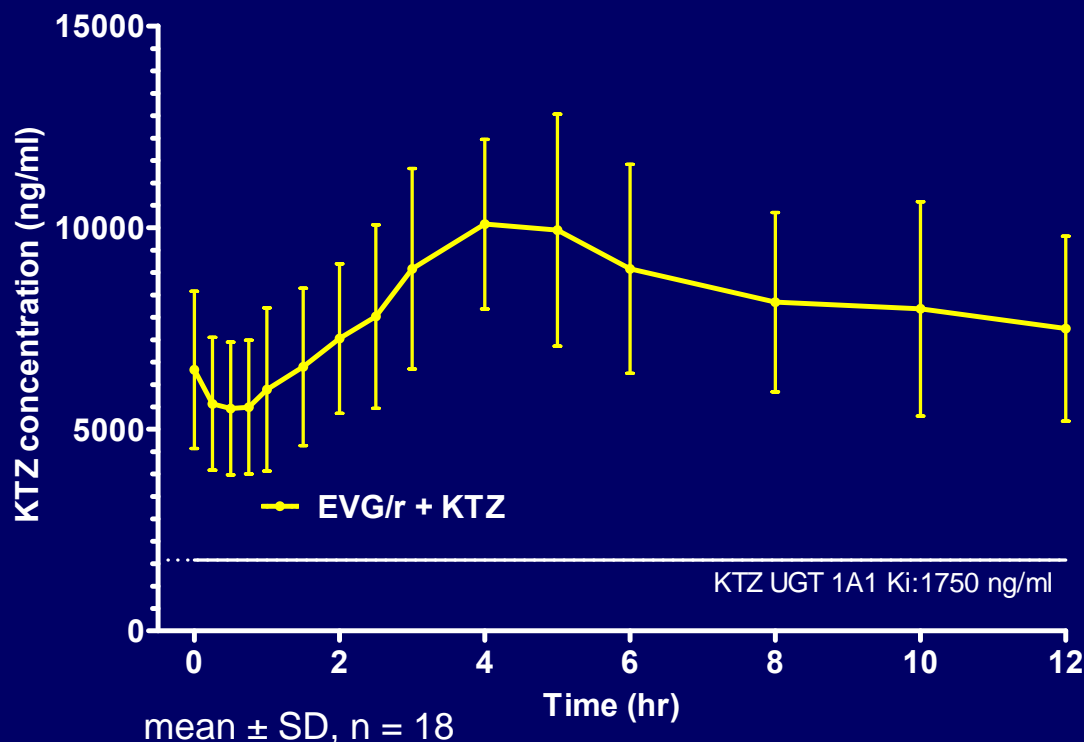
1. Increase in GS-9200 exposure in-line with CYP3A effect

-but-

2. Reduction in GS-9200 : EVG ratio indicates reduction in UGT1A1-mediated EVG clearance

- KTZ shown to inhibit of human UGT-mediated EVG turnover *in vitro*

# KTZ Pharmacokinetics



Parameter	KTZ
$C_{max}$ (ng/ml)	10700 (24.4)
$AUC_{tau}$ (ng·hr/ml)	97900 (25.5)
$C_{tau}$ (ng/ml)	7490 (30.6)

n = 18, mean (%CV)

- KTZ exposures higher with EVG/r, consistent with historical data with PI/r<sup>1-3</sup>

1. Sekar VJ, et al. *Br J Clin Pharmacol*. Aug 2008;66(2):215-221.

2. NORVIR® and KALETRA® US Prescribing Information. 3. Wire MB, et al. *Antimicrob Agents Chemother*. Aug 2007;51(8):2982-2984.

# Conclusions

- Co-administration of a potent CYP3A and UGT1A1 inhibitor modestly increases boosted-EVG exposure (~50%)
  - Minimal additional CYP3A inhibition (1.0 to 1.5%)
  - Inhibition of UGT1A1-mediated route of EVG metabolism
- RTV boosts KTZ exposures
- Study treatments generally well tolerated
  
- Clinical recommendations
  - Boosted-EVG dose reduction is not warranted based on safety profile to date
  - Clinically significant interactions via CYP3A or UGT interactions are not anticipated with boosted-EVG
  - A maximum recommended daily dose of KTZ is 200 mg with boosted-EVG