

# **Relative Bioavailability and Pharmacokinetics of Darunavir when boosted with the Pharmacoenhancer GS-9350 versus Ritonavir**

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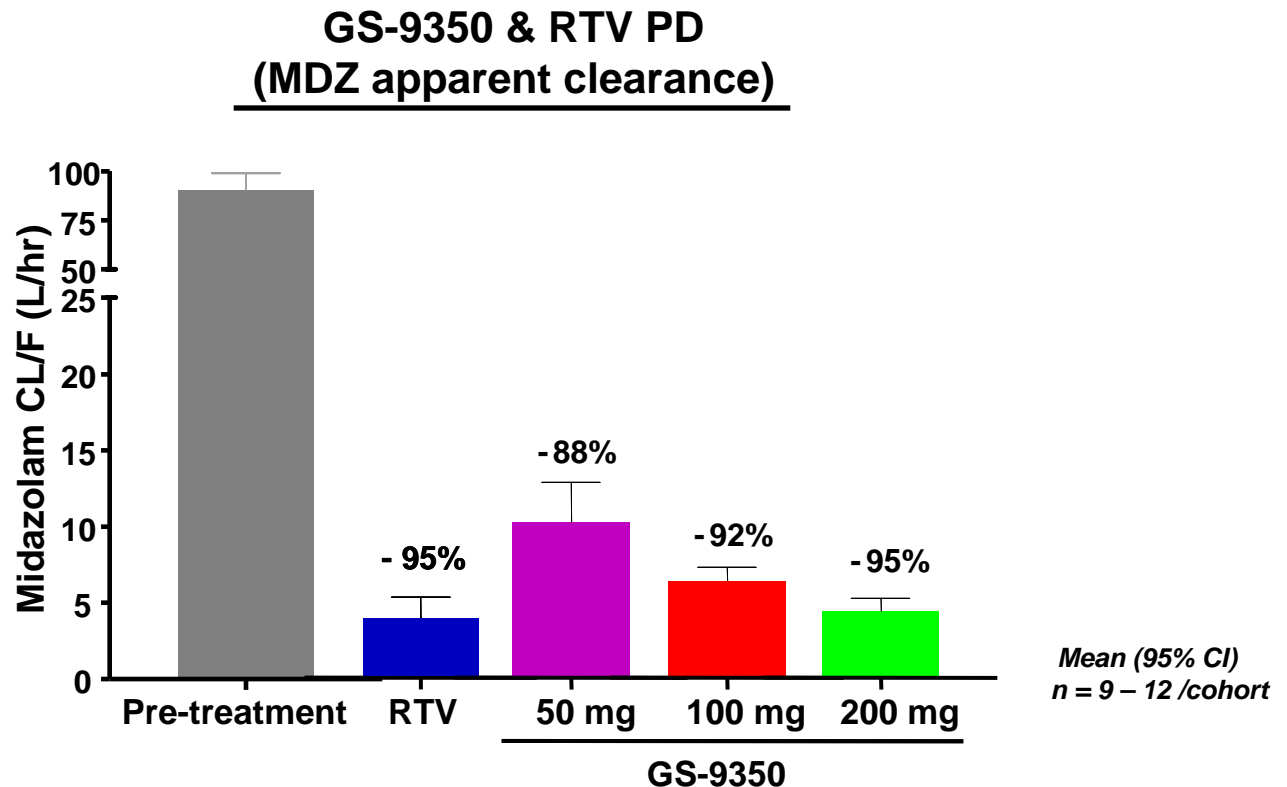
# Introduction

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- ◆ GS-9350 is a potent, mechanism-based inhibitor of human cytochrome P450 3A (CYP3A)
- ◆ *In vitro*
  - No antiviral activity up to 30  $\mu\text{M}$
  - Greater CYP450 enzyme inhibition specificity
  - Less induction liability
  - Reduced potential for lipid abnormalities
  - Improved physicochemical properties- amenable for co-formulation

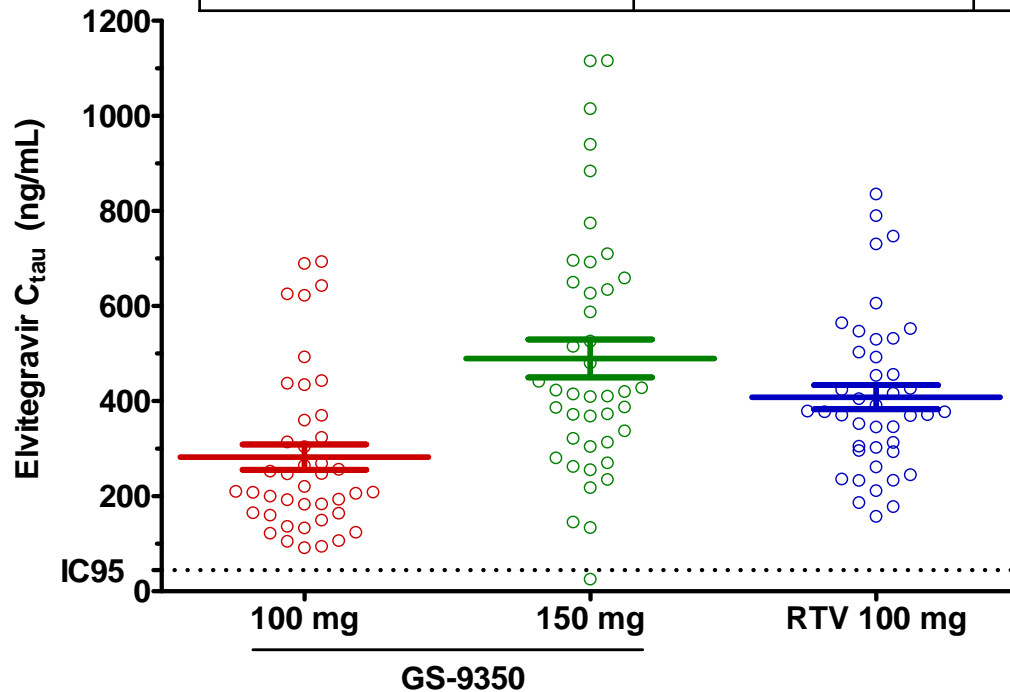
# Introduction

- ◆ GS-9350 exhibits non-linear increases in exposure with dose and time
  - Consistent with mechanism-based inhibition



# Introduction: Elvitegravir Pharmacokinetics

Mean (CV%) EVG PK (n = 42)	GS-9350 100 mg FDC	GS-9350 150 mg FDC	EVG + RTV 100 mg
AUC <sub>tau</sub> (ng.hr/mL)	21100 (25.4)	27000 (29.4)	22500 (23.4)
C <sub>max</sub> (ng/mL)	2250 (26.3)	2660 (27.6)	2500 (32.1)
C <sub>tau</sub> (ng/mL)	282 (60.4)	490 (52.9)	409 (40.5)

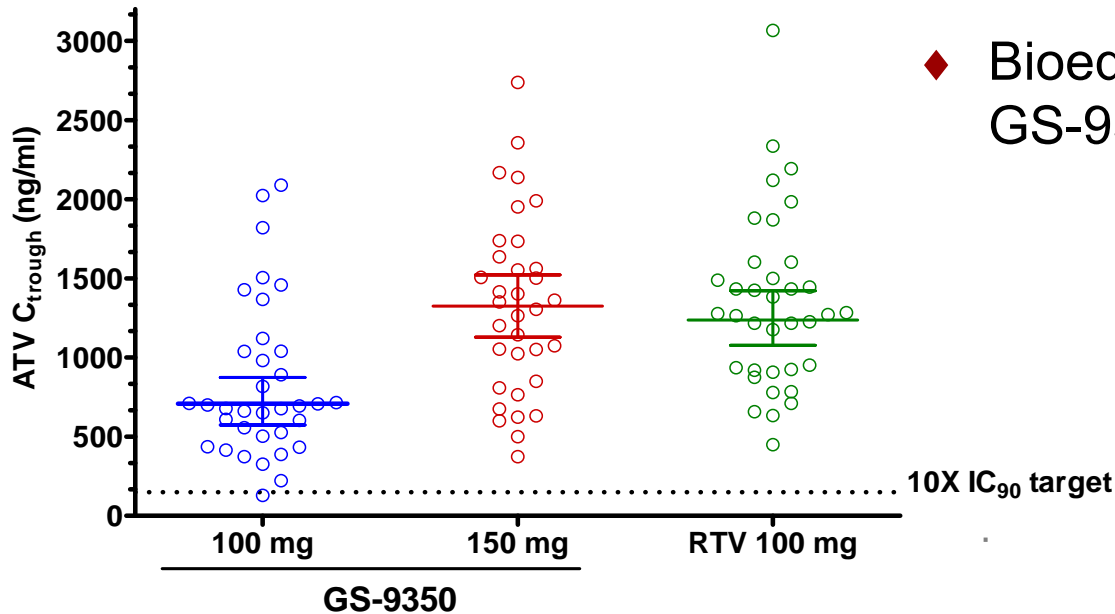


- ◆ GS-9350 effectively boosts EVG within fixed-dose combination (FDC) tablet
- ◆ GS-9350 150 mg maintains high EVG trough concentrations
  - 11-fold above the protein binding-adjusted IC<sub>95</sub> (44.5 ng/mL)
  - Low within-subject variability (15% CV)

Mathias et al., 16<sup>th</sup> CROI 2009, Oral Abstract #40. Bars represent geometric mean (± 95% CI)

# Introduction: Atazanavir Pharmacokinetics

Mean (CV%) ATV PK (n = 34 - 36)	+ GS-9350 100 mg	+ GS-9350 150 mg	+ RTV 100 mg
AUC <sub>tau</sub> (ng.hr/mL)	45100 (31)	55900 (28)	55200 (28)
C <sub>max</sub> (ng/mL)	4420 (21)	4880 (25)	5270 (24)
C <sub>tau</sub> (ng/mL)	837 (59)	1330 (43)	1340 (41)



◆ Bioequivalent ATV PK achieved GS-9350 150 mg vs. RTV 100 mg

**GMR (90%CI) vs. RTV 100 mg**

AUC <sub>tau</sub> (ng.hr/ml)	C <sub>max</sub> (ng/mL)	C <sub>tau</sub> (ng/ml)
101 (94.5, 108)	92.3 (85.1, 100)	97.6 (88.1, 108)

Bars represent geometric mean (± 95% CI)

# Darunavir Pharmacokinetics

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## Primary Objective

- ◆ To evaluate the relative bioavailability and pharmacokinetics of darunavir when coadministered with GS-9350 versus ritonavir

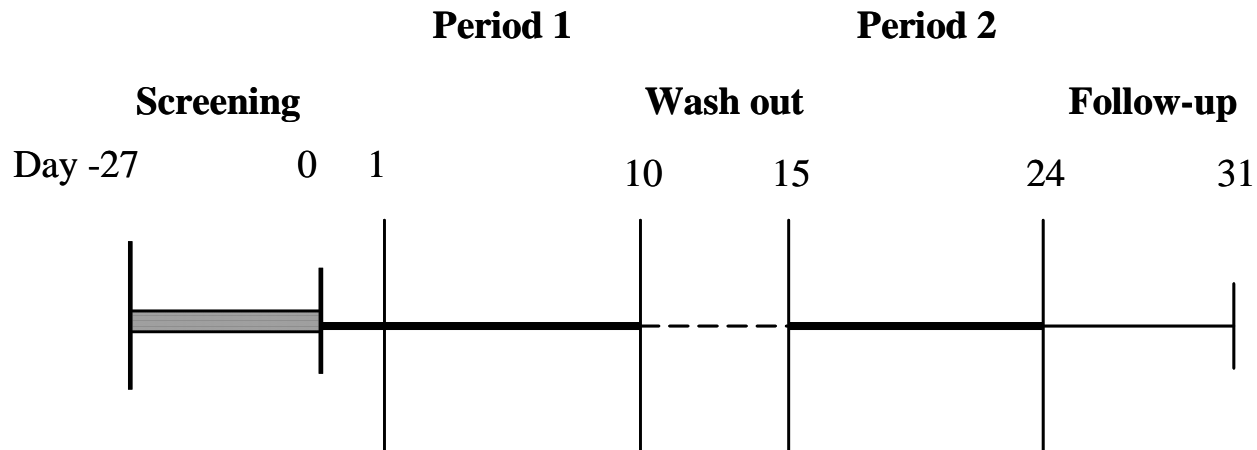
## Secondary Objective

- ◆ To evaluate the safety of administration of darunavir in combination with GS-9350 or ritonavir

# Methods

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- ◆ Open-label, multiple-dose, two-period cross-over study
  - **Treatment A:** Darunavir (800 mg) plus GS-9350 (150 mg) once-daily, in the AM
  - **Treatment B:** Darunavir (800 mg) plus Ritonavir (100 mg capsule) once-daily, in the AM



# Methods

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- ◆ All treatments administered with a standard meal (~ 400 kcal, 13 g fat)
- ◆ Plasma PK sampling performed over 24 hours; DRV, GS-9350, and RTV levels determined using validated LC/MS/MS assays
- ◆ PK parameters estimated via non-compartmental methods using WinNonlin™ 5.2 (Pharsight Corporation, USA)
- ◆ ANOVA and 90% confidence interval bounds for equivalence about the geometric mean ratio (Test:Reference) were 80% to 125% for DRV  $C_{0hr}$  (predose),  $C_{max}$ ,  $AUC_{tau}$  and  $C_{tau}$
- ◆ Descriptive PK for GS-9350 and RTV
- ◆ Adverse event (AE) monitoring, clinical laboratory, physical examination and ECG evaluations performed throughout study

# Results

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## Demographics

- ◆ Thirty-three subjects enrolled; 31 completed the study
  - 31 Male and 2 Female
  - Mean age: 27 yrs (range: 20 - 45)
  - Mean weight: 74.9 kg (range: 52.2- 90.7)
  - Race
    - White: 54.5%
    - Black/African heritage: 33.3%
    - Asian/Others: 12.1%
  - Ethnicity
    - Non-Hispanic: 97%
    - Hispanic: 3%

# Results

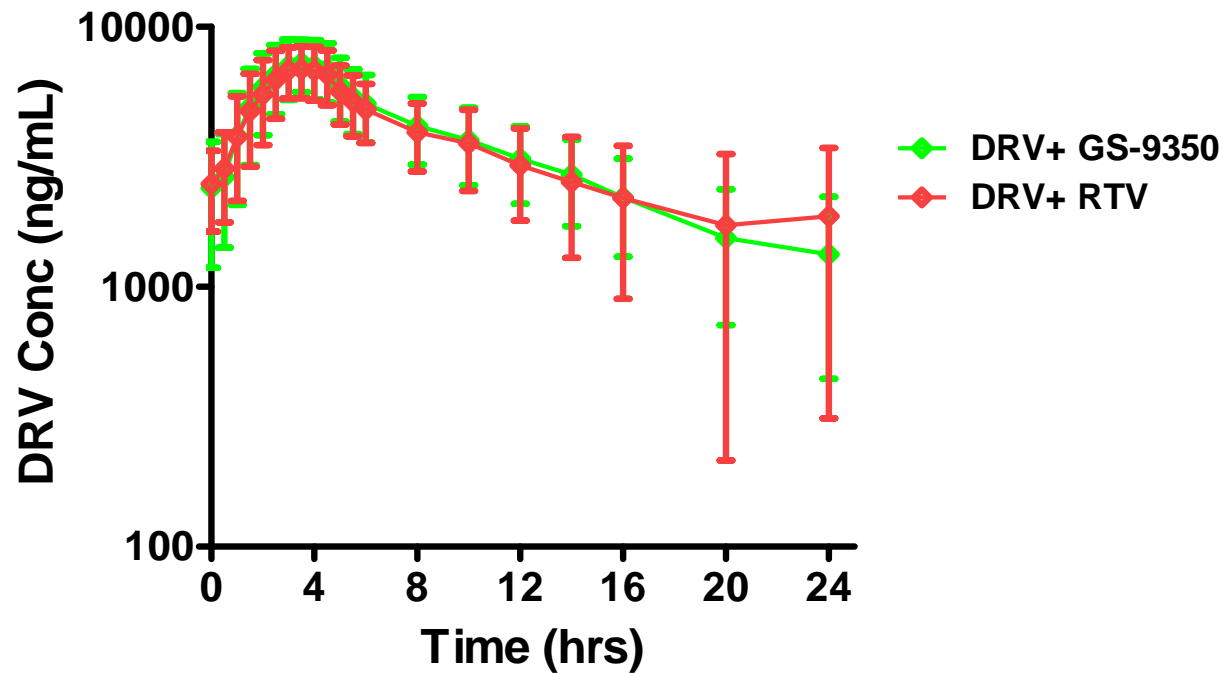
## Safety

- ◆ Treatments were generally well tolerated in this study
- ◆ No Grade 3 or 4 AE or treatment-emergent laboratory abnormalities reported in this study
- ◆ Two subjects prematurely discontinued study drug
  - One subject discontinued due to investigator discretion after completing Treatment A
  - One subject discontinued study drug of Treatment A due to an AE (Grade 2 maculopapular rash)

Number (%) of Subjects Experiencing AE by System Organ Class and Preferred Term	DRV	
	GS-9350 (N=33)	RTV (N=31)
Any Treatment-Emergent AE	11 ( 33.3%)	13 ( 41.9%)
<b>Nervous System Disorders</b>		
Headache	2 ( 6.1%)	4 ( 12.9%)
<b>Skin and Subcutaneous Tissue Disorders</b>		
Rash Maculo-Papular	2 ( 6.1%)	2 ( 6.5%)

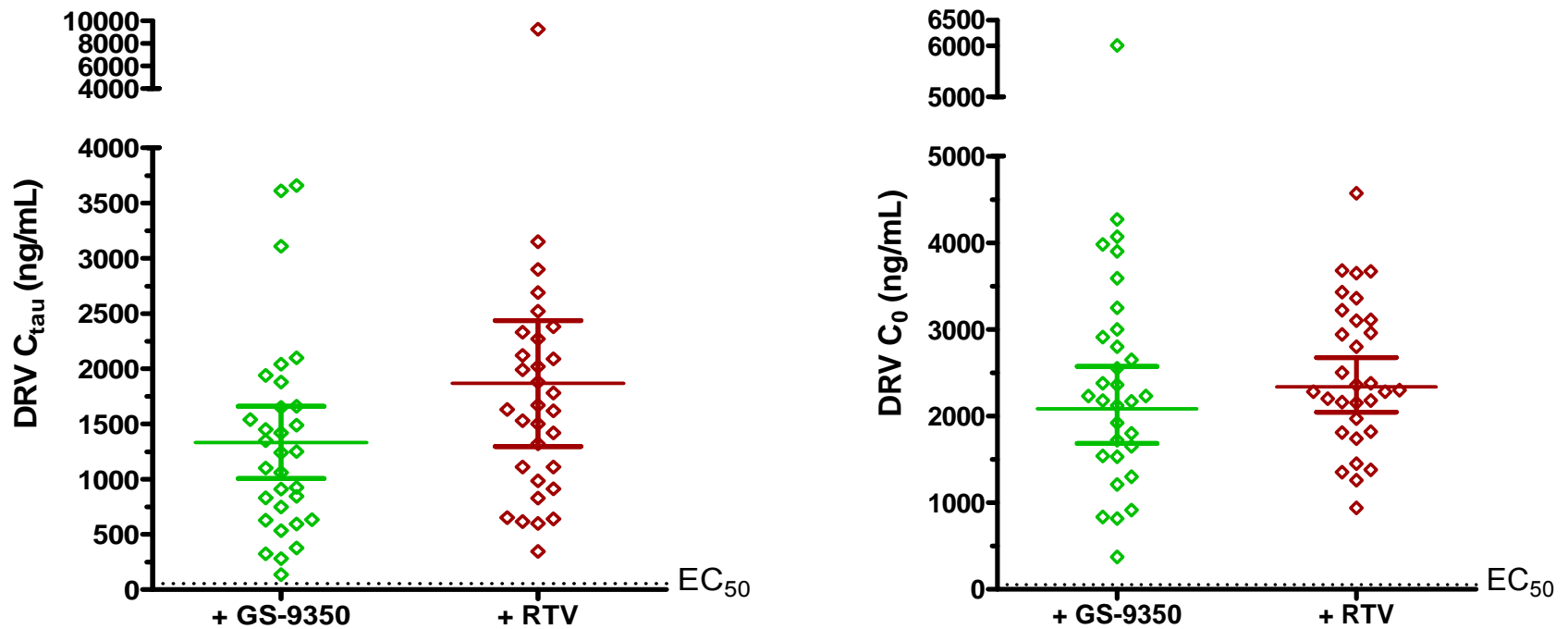
# Results

## Mean (SD) Plasma Concentration-Time Profile of DRV



# Results: DRV Pharmacokinetics

Mean (CV%) DRV PK (n = 31)	+ 150 mg GS-9350	+ 100 mg RTV	GMR (90% CI)
AUC <sub>tau</sub> (ng.hr/mL)	81100 (31.0)	80000 (34.0)	102 (97.4, 106)
C <sub>max</sub> (ng/mL)	7740 (21.8)	7460 (20.3)	103 (100, 106)
C <sub>tau</sub> (ng/mL)	1330 (66.8)	1870 (83.3)	69.4 (59.0, 81.7)
C <sub>0</sub> (ng/mL)	2400 (50.7)	2480 (34.3)	89.4 (80.4, 99.4)



Bars represent geometric mean ( $\pm$  95%CI)

# Results

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- ◆ GS-9350 effectively boosts DRV
- ◆  $C_{\text{tau}}$  maintained above (geometric mean > 18-fold) the protein-adjusted  $EC_{50}$  for wild-type virus (55 ng/mL)
- ◆  $C_0$  > 37-fold above the protein-adjusted  $EC_{50}$  for wild-type virus
- ◆ The pharmacokinetic parameters of GS-9350 (150 mg once daily) and RTV (100 mg once daily) were similar to those reported in previous studies

# Conclusion

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- ◆ GS-9350 adequately boosts DRV
- ◆ GS-9350 provided bioequivalent exposures ( $C_{\max}$  and  $AUC_{\tau}$ ) to RTV
- ◆ Trough concentrations comparable to those established to have effective and durable antiviral response in treatment-naïve patients
- ◆ Safety results indicated that DRV 800 mg, dosed once daily for 10 days, was well tolerated when coadministered with GS-9350 or RTV