

The Effect of Etravirine Alone and with Boosted Protease Inhibitors on the Pharmacokinetics of the Integrase Inhibitor, S/GSK1349572

I. Song, S. Min, J. Borland, Y. Lou, S. Chen, P. Patel,
T. Wajima, S. Piscitelli

GlaxoSmithKline, RTP, NC, USA and Shionogi & Co.,
Ltd., Osaka, Japan



S/GSK1349572

- **Next generation integrase inhibitor**
- **Unboosted, once daily dosing**
- **Potent antiviral activity in a 10 day monotherapy study**
- **In vitro resistance profile distinct from raltegravir and elvitegravir**
- **Predictable pharmacokinetics with well described PK/PD relationship**

Drug interaction profile

- **Primarily metabolized via UGT1A1 with minor CYP3A4 component**
- **Favorable drug interaction profile**
- **As perpetrator of DDIs:**
 - **No clinically significant effects on**
 - **Midazolam**
 - **Tenofovir**
 - **In vitro, no inhibitory effects on multiple CYPs or UGTs**

Min S, et al. IAS 2009, abstract WEPEA099.
Song, I et al, 49th ICAAC, 2009, abstracts 1303

Drug Interaction Profile

- **As a victim of DDIs, no clinically significant interactions with**
 - LPV/RTV
 - DRV/RTV
 - ATV
 - ATV/RTV
 - Tenofovir
 - Multivitamin
- **Administration with antacids requires separation**

Song, I et al. 17th CROI, 2010, abstract 616

Song, I et al, 49th ICAAC, 2009, abstracts 1303, 1304, 1305

Objectives

- **Two studies evaluated the effects of etravirine (ETV) alone (Study 1) and in combination with ritonavir (RTV)-boosted protease inhibitors (PIs) (Study 2) on S/GSK1349572 pharmacokinetics**

Study 1: 572 + ETV DDI study

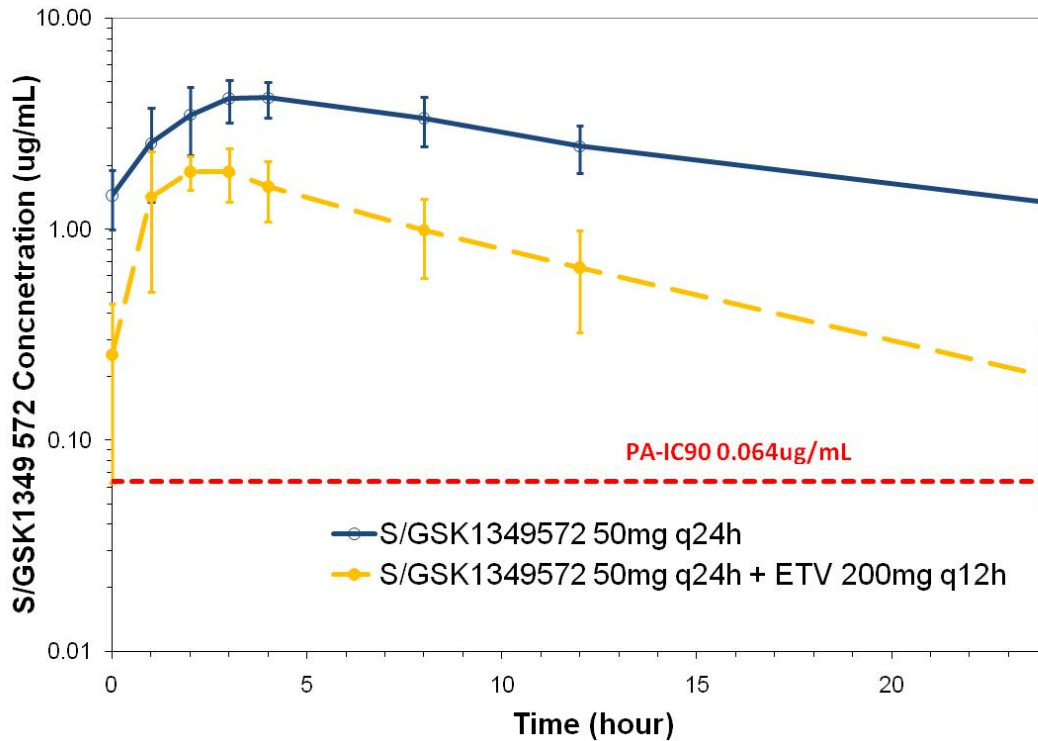
- **Open-label, two-period, crossover study in healthy adult subjects**

Cohort	Sample Size	Period 1; Days 1-5	Period 2; Days 1-14
1	16	572 50mg q24h with food	GSK1349572 50mg q24h + ETV 200mg BID with food

All doses were given with food.

572 PK samples collected on Day 5 in P1 and Day 14 in P2, Ctrough collected on Days 8, 11, 13, and 14 in P2

Study 1: Results



ETV reduced 572 exposure (\downarrow 88% C_{τ} ; \downarrow 70% AUC; \downarrow 52% C_{max});

PK parameter	GMR [90%CI]
AUC(0- τ)	0.294 [0.257, 0.337]
C_{max}	0.484 [0.433, 0.542]
C_{τ}	0.121 [0.093, 0.157]
$t_{1/2}$	0.518 [0.474, 0.566]

Study 2: 572 + ETV + LPV/RTV or DRV/RTV

- Open label, 2 cohort, single sequence crossover in healthy adults subjects

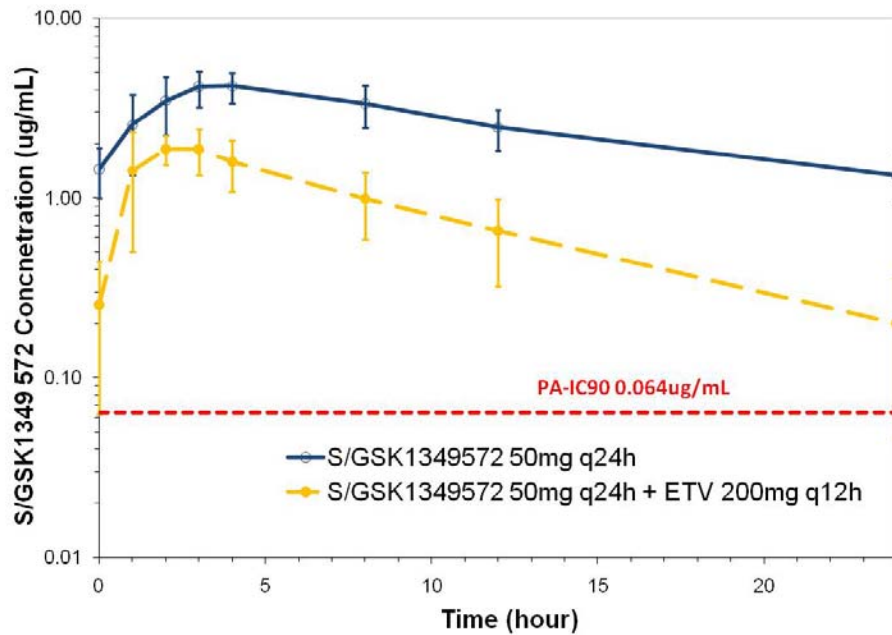
Cohort	Sample Size	Period 1; Days 1-5	Period 2; Days 1-14
1:/LPV/RTV	9	572 50mg q24h	572 50mg q24h + ETV 200 BID + LPV/RTV 400/100 BID
2:/DRV/RTV	9	572 50mg q24h	572 50mg q24h + ETV 200 BID + DRV/RTV 600/100 BID

All doses were given with food.

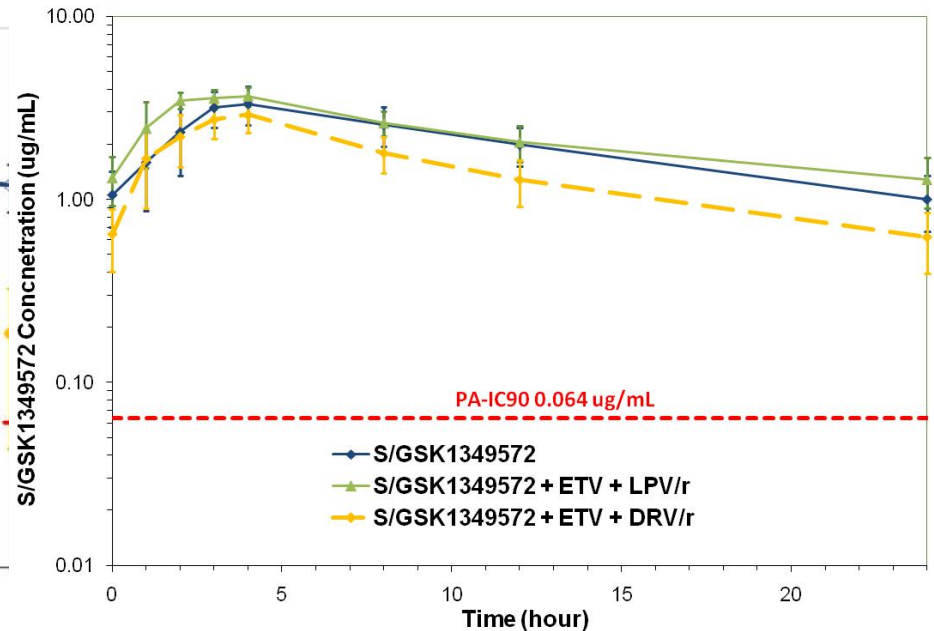
572 PK samples collected on Day 5 in P1 and Day 14 in P2, Ctrough collected on Days 8, 11, 13, and 14 in P2

S/GSK1349572 (50mg) PK Profiles

Effect of ETV on 572 PK



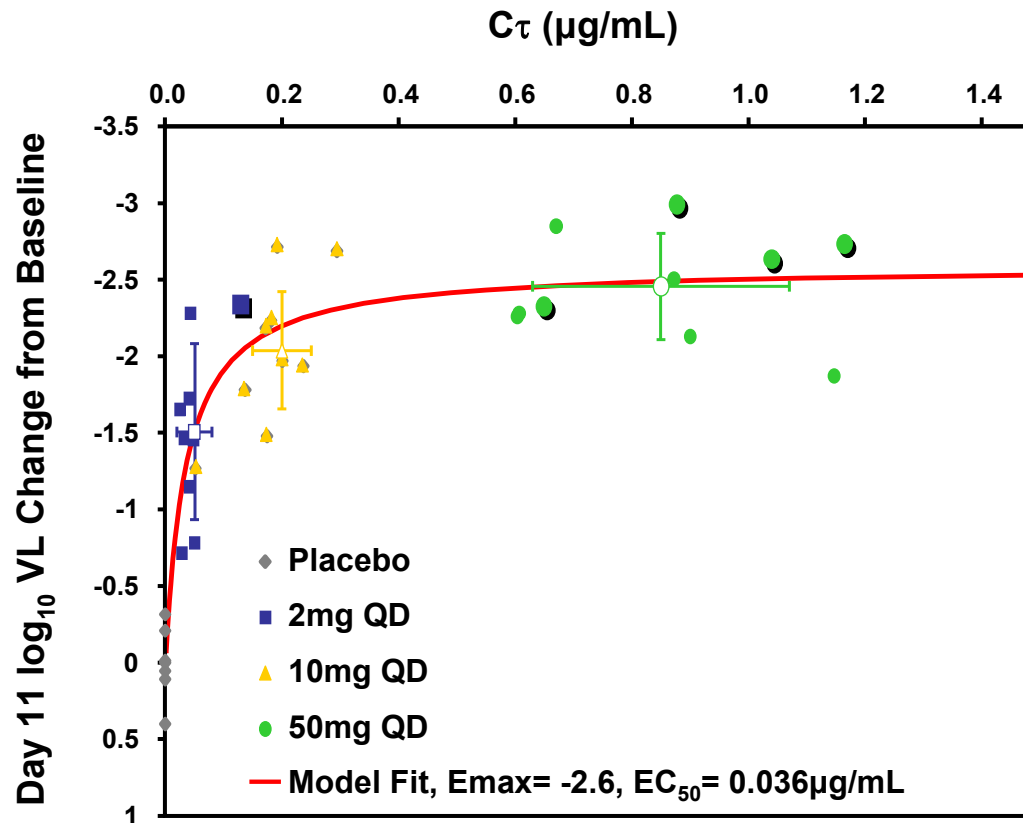
Effect of ETV+PI/r on 572 PK



S/GSK1349572 Results with ETV + LPV/RTV or DRV/RTV

Concomitant drug	N	572 dose	GM Ratio ((90% CI) 572 + drug / 572			Comment
			C24	AUC	Cmax	
ETV 200mg BID	16	50mg QD	0.12 (0.09-0.16)	0.29 (0.26-0.34)	0.48 (0.43-0.54)	Avoid concomitant use
ETV 200mg BID + LPV/r 400/100	8	50mg QD	1.28 (1.13-1.45)	1.11 (1.02-1.20)	1.07 (1.02-1.13)	Can use ETV if combined with LPV/r
ETV 200mg BID + DRV/r 400/100	9	50mg QD	0.63 (0.52-0.76)	0.75 (0.69-0.81)	0.88 (0.78-1.00)	Can use ETV if combined with DRV/r

PK/PD Relationship for S/GSK1349572



Modest decrease in C_{τ} with ETV+DRV/RTV would not lead to reduction in antiviral activity

Song I, et al. IAS 2009, Cape Town, abstract WEPEB250.

Safety

- The combination of GSK1349572 with ETV alone and with LPV/RTV or DRV/RTV was generally well-tolerated in healthy adult subjects
- No deaths, serious adverse events (SAE), severe AEs, or withdrawals due to adverse events were reported
- Study 1 (572+ETV)
 - Overall, 6 subjects reported at least one AE
 - All AEs were mild (Grade 1) in intensity
 - The most commonly reported drug-related AE was headache (4 subjects); abdominal pain, reported in 1 subject, was the only other AE considered to be drug-related
- Study 2 (572+ETV+ LPV/RTV or DRV/RTV)
 - The most frequently reported AEs were constipation (2 subjects) and headache (2 subjects). All other AEs were reported by only one subject each. Similar numbers of AEs were reported in each treatment group. All AEs were mild (Grade 1) in intensity.

Potential Mechanisms

- **Induction of UGT1A1 by ETV**
- **Induction of minor CYP3A4 pathway led to significant effect**
- **Boosted PI inhibits CYP3A4 component so pathway is minimized**

Conclusions

- **Co-administration of S/GSK1349572 with etravirine alone and with LPV/RTV and DRV/RTV was generally well tolerated**
- **The combination of etravirine with S/GSK1349572 resulted in a significant decrease in S/GSK1349572 exposure**
- **When ETV and S/GSK1349572 were administered with LPV/RTV or DRV/RTV, the magnitude of the interaction was markedly decreased**
- **S/GSK1349572 may be co-administered with ETV if LPV/RTV or DRV/RTV are also administered**