Pharmacokinetic (PK) and Pharmacodynamic (PD) Relationship of S/GSK1349572, a Next Generation Integrase Inhibitor (INI), in HIV-1 Infected Patients

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Abstract

Background: S/GSK1349572 is a novel HIV integrase strand transfer inhibitor that demonstrated PK supporting once daily dosing and good tolerability in healthy subjects. A dose ranging, placebo-controlled 10-day monotherapy study showed unprecedented antiviral activity of S/GSK1349572 in HIV-1 infected subjects.

Methods: 35 subjects were randomized to doses of 2mg, 10mg, 50mg, or placebo once daily for 10 days. Serial HIV-1 RNA and PK samples were collected during the study. S/GSK1349572 concentrations were analyzed using a validated LC/MS/MS assay. PK parameters were calculated by non-compartmental methods. Relationship between PK (AUC_τ, Cmax, and C_τ) and PD measures (changes in HIV-1 RNA) was assessed using various Emax and linear models. Model selection was based on Akaike Information Criteria value and F-test.

Results: Day10 PK parameters, geometric mean (CV%), and mean change of HIV-1 RNA from baseline to Day 11 are presented.

	AUC_τ µg*h/mL	Cmax µg/mL	C_τ µg/mL	IQ	ΔLog_{10} HIV-1 RNA
2mg QD (n=9)	2.56 (29%)	0.22 (25%)	0.04 (50%)	0.6	-1.51
10mg QD (n=7)	10.1 (20%)	0.80 (23%)	0.19 (25%)	3	-2.03*
50mg QD (n=10)	43.4 (20%)	3.34 (16%)	0.83 (26%)	13	-2.46

IQ= C_τ / protein-adjusted IC_{90} [0.064 µg/mL]; *n=9.

S/GSK1349572 demonstrated low variability and time-invariant PK; steady state was achieved by 7 days of dosing, consistent with the known half-life (~14hours). Greater antiviral activity was associated with higher S/GSK1349572 plasma exposure. C_τ was the PK parameter that best predicted antiviral activity. The relationship between C_τ and reduction in log_{10} plasma HIV-1 RNA from baseline to Day 11 was best described by a simple Emax model with Emax = -2.6log_{10} and EC50 = 0.036 µg/mL (p<0.0001).

Conclusions: S/GSK1349572 demonstrated low PK variability and a clear, predictable, and well characterized exposure-activity relationship, with antiviral efficacy primarily driven by C_τ. These attributes distinguish S/GSK1349572 from raltegravir.

Introduction

- The long-standing Shionogi-GSK Joint Venture has made considerable progress in developing next-generation integrase inhibitors.
- S/GSK1349572 is the only once-daily, unboosted integrase inhibitor currently in development with unprecedented antiviral activity and a superior resistance profile.[1,2,3]
- To date, the PK-PD relationship for INI has not been well characterized. There has been a lack of PK-PD relationship demonstrated for raltegravir (RAL); this can largely be attributed to high RAL PK variability.[4,5] Elvitegravir (ELV), another INI currently in Phase III clinical development has demonstrated exposure-dependent antiviral activity.[6]
- S/GSK1349572 demonstrated low PK variability which provides a good foundation for understanding the PK-PD relationship of this drug, and can also be applied to better understanding the class.[7]
- A dose ranging, placebo-controlled 10-day monotherapy study of S/GSK1349572 in HIV-1 infected subjects showed a mean 2.5 log decrease from baseline in plasma HIV RNA with the 50mg dose, and a clear dose-response relationship.[1]
- The design and dose selection of this study provided data to better understand the PK-PD relationship of this compound and provide inference across all INIs.

Methods

- 35 subjects were randomized to doses of 2mg, 10mg, 50mg, or placebo once daily (QD) for 10 days.
- Serial HIV-1 RNA and PK samples were collected during the study. S/GSK1349572 concentrations were analyzed using a validated LC/MS/MS assay.
- S/GSK1349572 PK parameters were calculated by non-compartmental methods. Relationship between PK and PD measures (changes in HIV-1 RNA) was assessed using various Emax and linear models. Model selection was based on Akaike Information Criteria value and F-test.
- PK measures: AUC_τ, Cmax, and C_τ on Day 10
  - PD measures: reduction in log_{10} plasma HIV-1 RNA on Day 11 from baseline (pre-dose on Day1), reduction in log_{10} plasma HIV-1 RNA from baseline to the on treatment nadir.
  - Log-linear models: PD = a + b*log_{10}(PK)
  - Sigmoid Emax models: $$PD = \frac{E\max * PK^{\gamma}}{EPK50^{\gamma} + PK^{\gamma}}$$

  where PK measure is either original or log-transformed; Emax was either estimated or fixed to 2.6, 2.7, or 2.8 to help model converge. γ was either estimated or fixed to 1.

Results

Figure 1. Mean (±SD) S/GSK1349572 Concentration-time Profiles by Dose

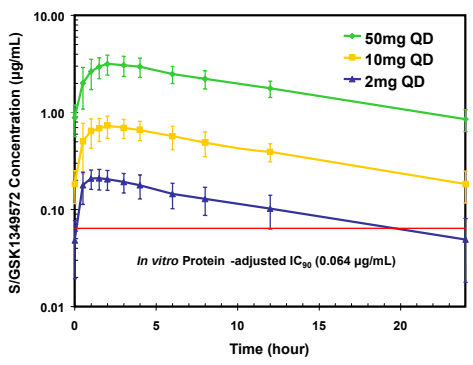


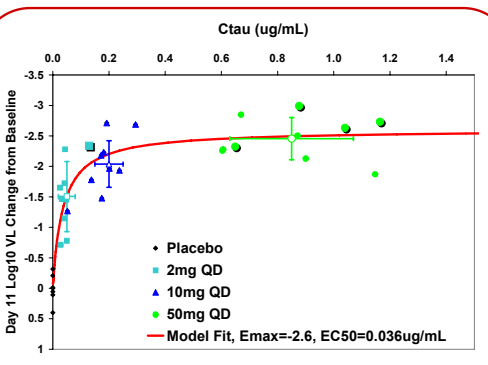
Table 1. Summary of S/GSK1349572 PK Parameters and Mean HIV-1 RNA Reduction from Baseline by Dose

	AUC_τ µg*h/mL	Cmax µg/mL	C_τ µg/mL	IQ	ΔLog_{10} HIV-1 RNA
2mg QD (n=9)	2.56 (29%)	0.22 (25%)	0.04 (50%)	0.6	-1.51
10mg QD (n=7)	10.1 (20%)	0.80 (23%)	0.19 (25%)	3	-2.03*
50mg QD (n=10)	43.4 (20%)	3.34 (16%)	0.83 (26%)	13	-2.46

Geometric mean (CV%); IQ=C_τ/PA-IC_{90}, PA-IC_{90}=0.064 µg/mL; *n=9

- Time-invariate PK and steady state is achieved by 7 days of dosing
- PK supports once daily dosing without boosting
- Robust antiviral responses achieved with low mg doses
- Very low inter- and intra-subject variability provides foundation for understanding PK/PD relationship and is key in defining therapeutic target

Figure 2. Exposure-Response Relationship of S/GSK1349572



Subjects with VL <50 cp/mL in highlighted square or circles; Open symbols with lines are mean (+/SD)

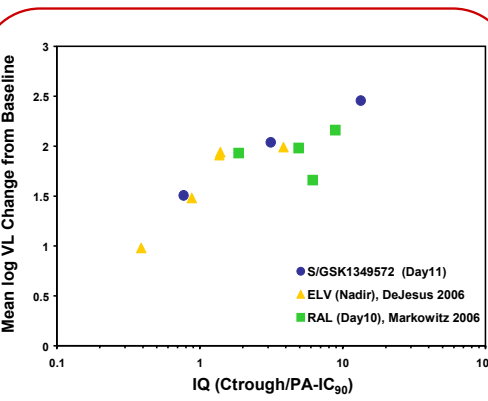
Table 2. AIC Values of Selected Models of Relationship between S/GSK1349572 PK Parameters and Day 11 HIV-1 RNA Reduction from Baseline

Model	AUC_τ	Cmax	C_τ
$PD = \frac{E\max * PK}{EPK50 + PK}$	34.6	37.3	32.0
$PD = \frac{E\max * PK^{\gamma}}{EPK50^{\gamma} + PK^{\gamma}}$	36.3	39.0	33.0
$PD = \frac{E\max * \log_{10}(PK)}{EPK50 + \log_{10}(PK)}$	50.4	49.4	45.9
$PD = \frac{E\max * (\log_{10}(PK))^{\gamma}}{EPK50^{\gamma} + (\log_{10}(PK))^{\gamma}}$	36.6	39.2	33.7
PD = a + b*log10(PK)	39.7	42.1	37.5

Emax is fixed to 2.6.

- The relationship between S/GSK1349572 exposure and reduction in log_{10} HIV-1 RNA on Day 11 can be best described by an Emax model with PK measures on the original scale, Emax fixed to 2.6 log_{10}, and γ fixed to 1.
- C_τ (concentration at end of dosing interval) was the PK parameter that best predicted Day 11 plasma viral load reduction from baseline or maximum plasma viral load reduction from baseline.
- It should be noted that this study was not designed to differentiate these PK predictors as all doses were given QD and all PK parameters are correlated.

Figure 3. PK-PD Relationship of S/GSK1349572, RAL, and ELV in 10-day Monotherapy (Pooled Data)



IQ is calculated based on mean C_τ divided by Protein-adjusted IC_{90} (PA-IC_{90}). Mean C_τ values for RAL and ELV are from published data. PA-IC_{90} were determined based on vitro data using the same assay and viral strand for S/GSK1349572 (152nM), RAL(23nM), and ELV (78nM). RAL: 100, 200, 400, and 600mg BID; plasma HIV RNA LLQ of 400c/mL, BQL treated as 200c/mL. ELV: 800mg QD, 200, 400, 800mg BID, 50mg/r QD.

Discussions

- The pooled data from S/GSK1349572 and ELV in 10-day monotherapy shows a PK-PD relationship for the integrase inhibitors as a group, in that higher exposure drives higher antiviral activity.
- IQ (calculated by C_τ/PA-IC_{90}) is a good predictor of antiviral activity (in short-term monotherapy) for S/GSK1349572.
- S/GSK1349572 50mg QD demonstrated unprecedented antiviral activity, attributable to superior IQ achieved.
- RAL failed to show PK-PD relationship in 10-day monotherapy due to the narrow dose range studied and unpredictable PK.
- In contrast, the Phase 2a study of S/GSK1349572 studied a wide dose range, allowing in-depth understanding of the PK-PD relationship.
- The clear PK-PD relationship observed for S/GSK1349572 empowers integrated drug-disease modeling and dose selection in currently on-going Phase 2B clinical trials across different patient populations and the confidence in chronic dosing of S/GSK1349572 in HIV-infected patients.

Conclusions

- S/GSK1349572 demonstrated low PK variability and a clear, predictable, and well characterized exposure-response relationship.
- Antiviral activity for INIs is exposure driven.
- S/GSK1349572 achieved greater antiviral activity than RAL and ELV after 10-day monotherapy.
- The PK parameter that best predicts S/GSK1349572 efficacy is C_τ; therefore achieving a high IQ will lead to successful clinical outcomes.

Acknowledgements

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