Abstract

Background: S/GSK1349572 is a novel HIV integrase strand transfer inhibitor (INIs) in development. The long-acting PK/PD relationship is critical for INIs to supporting once daily dosing and good tolerability in HIV-1 infected patients. While the PK-PD relationship of many INIs has been demonstrated, the PK-PD relationship of S/GSK1349572 has not been well characterized.

Methods: 20 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 to assess the exposure-activity relationship using the non-compartmental methods. Relationships between PK (AUC, Cmax, and Cmin) and 2 plasma measures were developed using linear regression analysis or non-linear Sigmoid Emax models. Model selection was based on Akaike Information Criteria value (AIC).

Results: S/GSK1349572 demonstrated linear variability and intra-subject variability, with antiviral S/GSK1349572 demonstrated low variability and time-invariant PK; steady state exposure-activity relationship, with antiviral activity. The relationship between Cmin and plasma HIV-1 RNA was linearly increase since baseline and presented log10 reduction in plasma HIV-1 RNA from baseline on Day 11 can be best described by a simple linear model with r2 = 0.668, p < 0.0001.

Conclusions: S/GSK1349572 demonstrated low variability and time-invariant PK; steady state exposure-activity relationship, with antiviral activity and a superior resistance profile.2,3

Keywords: S/GSK1349572; PK/PD relationship; integrase; monotherapy; once daily dosing; monotherapy; antiretroviral therapy; HIV-1.

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

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

Discussions

The relationship between S/GSK1349572 exposure and reduction in log10 HIV-1 RNA on Day 11 can be best described by an Emax model with PK measures on the original scale, Enza fixed to 2.4 µg/mL, and fixed to 1.

β (κ and σ) concentration of end of day (CeD) was the PK parameter that best predicted Day 11 plasma viral load reduction from baseline, or maximum reduction from baseline.

It should be noted that this study was not designed to differentiate these PK parameters 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)

Conclusion

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 in Cτ0, therefore achieving a high IQ will lead to successful clinical outcome.

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