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S/GSK1349572: A Next Generation Integrase Inhibitor with Activity Against Integrase Inhibitor-Resistant Clinical Isolates from Patients Experiencing Virologic Failure while on Raltegravir Therapy

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Author Conclusions

S/GSK1349572 exhibited *in vitro* activity against most clinical isolates obtained from patients failing RAL-based therapy.

These data, combined with other *in vitro* virology data presented at this meeting, suggest a virologic resistance profile superior to RAL.

When combined with the unprecedented virologic responses observed during 10 day S/GSK1349572 monotherapy¹, these data suggest potential to treat patients with RAL

These observations need to be confirmed in clinical studies, and support further development of S/GSK1349572 for patients across the treatment spectrum.

ABSTRACT

Background: S/GSK1349572 is a next generation integrase inhibitor (INI) with low nM potency. Susceptibility to S/GSK1349572 and raltegravir (RAL) was determined for INI resistant clinical isolates from therapy experienced patients treated with RAL plus optimized background regimen.

Methods: Thirty-nine clinical isolate samples were examined; 30 had IN coding region mutations and 21 of those (21/30) were longitudinal samples from 9 patients. Mutations included: N155H; G140S,Q148H; G140S,Q148R; T97A,Y143R; T97A,Y143C; and more complex samples including: E92Q,N155N/H,G140G/S,Q148Q/R; and E138E/K,G140G/S,Q148Q/H,N155N/D. Susceptibility was evaluated using Monogram Biosciences Integrase PhenoSense assay.

Results: Representative mutant fold change (FC) in IC50 versus wild-type

| Genotype | S/GSK1349572 | | RAL | | N |
|-------------|--------------|-----------|-----------|-----------|---|
| | Median FC | Range FC | Median FC | Range FC | |
| N155H | 1.37 | 1.22–1.45 | 19.0 | 14.0–36.0 | 5 |
| G140S,Q148H | 3.75 | 2.05–15.0 | >87 | 58.0–>87 | 7 |
| G140S,Q148R | 13.3 | 7.57–19.0 | >87 | >87–>87 | 2 |
| T97A,Y143R | 1.05 | 1.04–1.06 | >81 | >81–>81 | 2 |

Median FC in IC50 against the 30 IN-mutant isolates was 1.52 (range 0.87-19.0) for S/GSK1349572, and >81 (range 3.74->87) for RAL. Although high level resistance to RAL was common, only 4 IN-mutant isolates had a S/GSK1349572 FC >5. No consistent correlation existed between FCs for S/GSK1349572 and RAL. All longitudinal virologic failure samples were more susceptible (and 19/21 were >5-fold more susceptible) to S/GSK1349572 than RAL.

These data in combination with robust virologic responses and inhibitory quotients observed during 10 day S/GSK1349572 monotherapy suggest potential to treat patients with RAL resistance.

Conclusions: S/GSK1349572 exhibited in vitro activity against clinical isolates obtained from patients failing raltegravir-based therapy. These data suggest a virologic profile distinct from RAL, and consistent with potential for S/GSK1349572 to treat patients with RAL resistance. These observations need to be confirmed in clinical studies, and support further development of S/GSK1349572.

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}

S/GSK1349572 has demonstrated a predictable, well-characterized exposure-response relationship and low PK variability.³

Methods

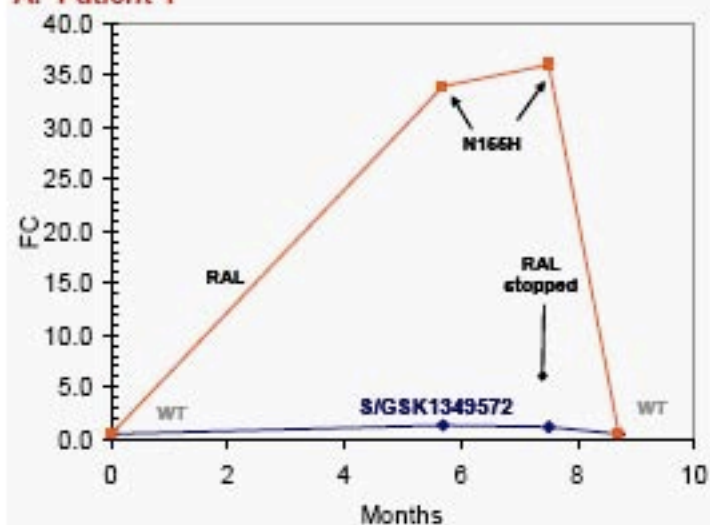
Integrase resistant HIV-1 sample phenotypes were evaluated at Monogram Biosciences using the Integrase PhenoSense assay. The compounds S/GSK1349572 and RAL were tested side by side and IC₅₀ and fold-change in IC₅₀ vs. wild-type (FC-IC₅₀) were generated. The samples included 11 site directed mutant (SDM) control HIV-1 IN sequences based on NL43 and eight clinical isolates containing IN resistance mutations from Monogram Biosciences library set. In addition, 31 clinical isolate samples were evaluated from subjects experiencing virologic failure on therapy which included RAL in the UCSF SCOPES Cohort.⁴ Altogether, 39 clinical isolate samples were examined; 30 had IN coding region mutations and 21 of those were longitudinal samples from 9 patients.

Results

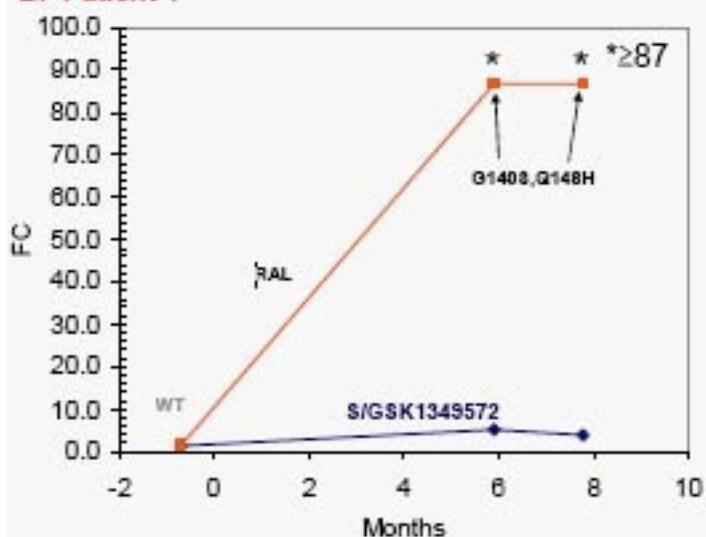
Figure 1. Longitudinal comparison of representative isolate sample fold-changes for S/GSK1349572 and RAL during months post-initiation of RAL therapy (plus OBR).

All longitudinal virologic failure samples with IN mutations were more susceptible (and 19/21 were >5-fold more susceptible) to S/GSK1349572 than RAL

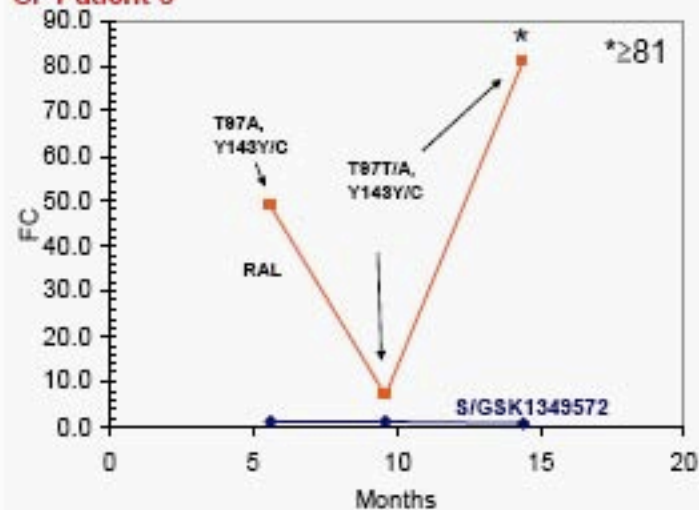
A. Patient 4



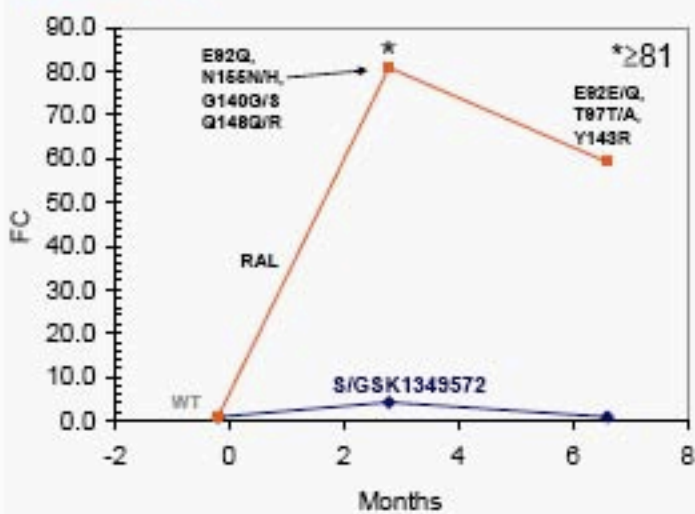
B. Patient 1



C. Patient 6



D. Patient 10



E. Patient 9

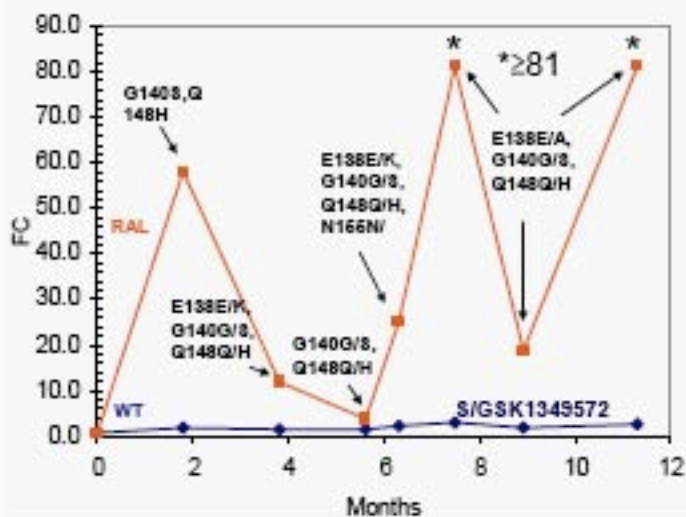
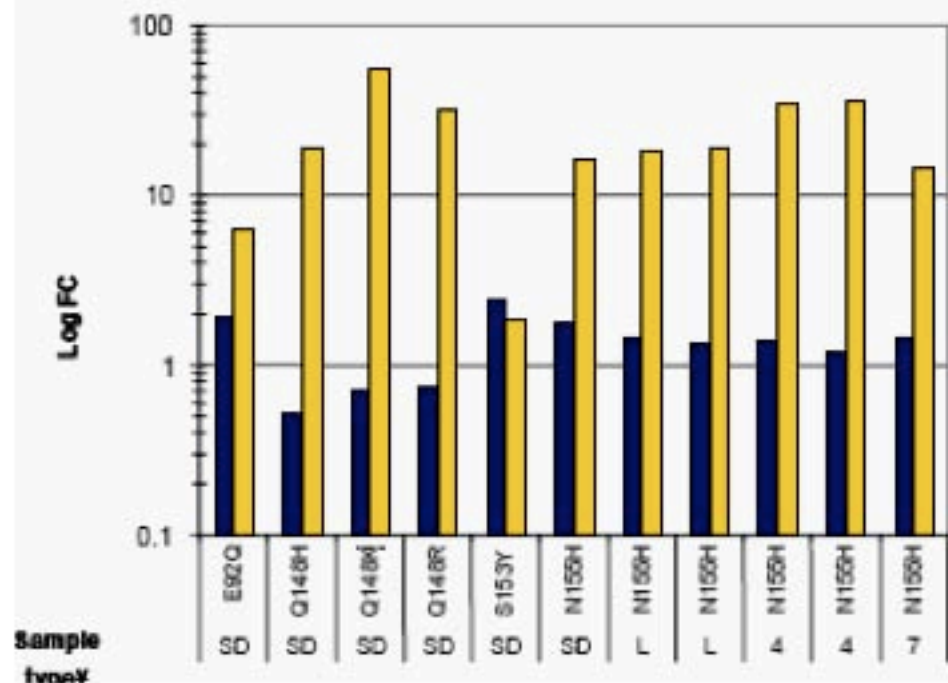


Figure 2. S/GSK1349572 and RAL fold-change IC50s against integrase site directed mutants and clinical isolates from patients with virologic failure on RAL



For Sample type, SD indicates site direct mutant, L indicates Monogram library isolate, single digit indicates SCOPES isolate

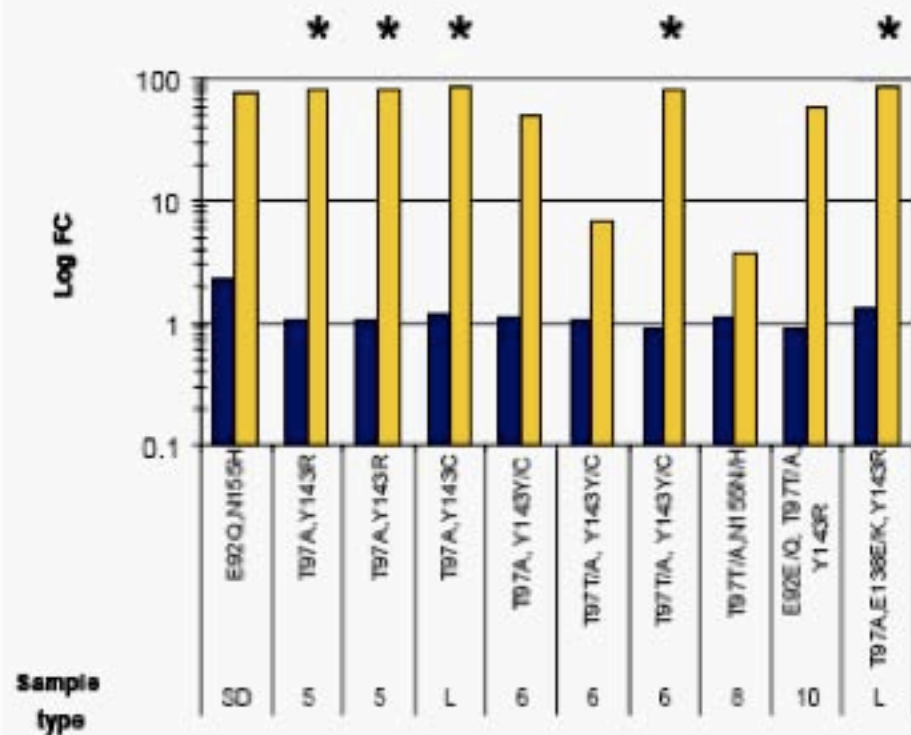
A. Single mutation



S/GSK1349572 had greater activity (range 0.51-2.45) for all single mutants examined than RAL (range 1.81-36) except S153Y. All except S153Y had FC < 2 versus S/GSK1349572; indeed, single Q148 mutations appeared to have increased susceptibility to S/GSK1349572.

B. ≥ 2 mutations without 148H/K/R

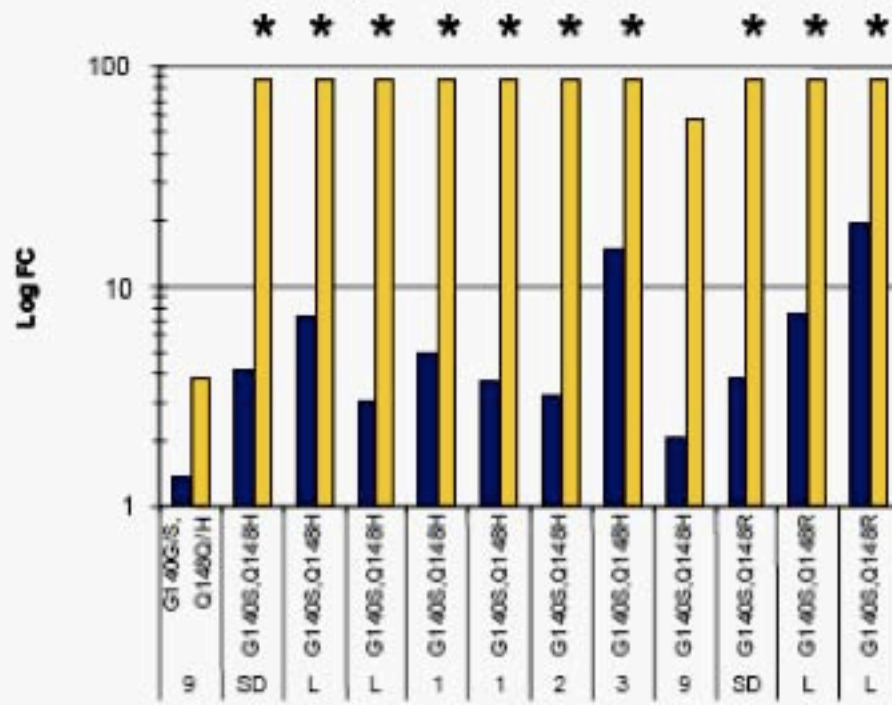
* >81



S/GSK1349572 had near wild type activity against SDMs and clinical isolates examined with ≥ 2 mutations and without 148H/K/R (range 0.87-2.25) while RAL had FC>5 (range 3.74>81) for all but one (T97T/A,N155N/H with FC=3.74) of this set of mutants.

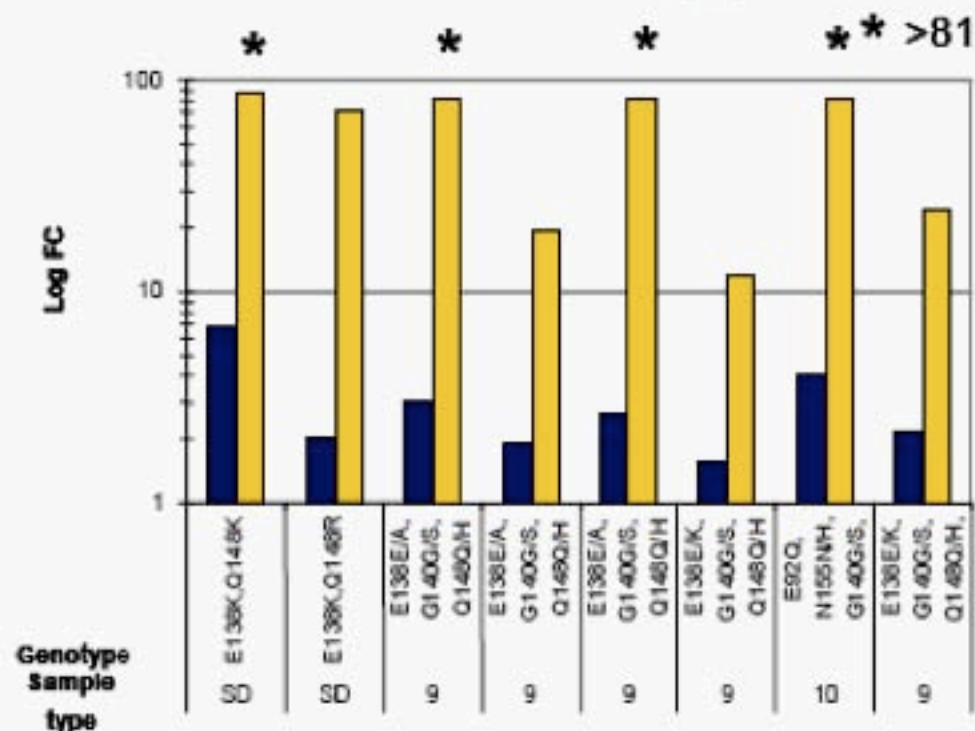
C. 2 mutations with 140S,148H/R

* >87



S/GSK1349572 had greater activity across all SDMs and clinical isolates examined with 140S,148H/R (range 1.38-19.0) than did RAL (range 3.74- >87). For RAL, all FCs except mixed isolate G140G/S, Q148Q/H were >50.

D. 2 mutations with 138K,148K/R or ≥ 3 mut



S/GSK1349572 had greater activity across all SDMs and clinical isolates examined with this grouping of 138K,148K/R or with ≥ 3 mut (range 1.58-6.9) than did RAL (range 12- >81).

References

1. Lalezari J. et al. IAS 2009, Cape Town, Oral #TUAB105.
2. Sato A. et al. IAS 2009, Cape Town, Poster #WEPEA097.
3. Song I, et al. IAS 2009, Cape Town, Poster #WEPEB250.
4. Hatano H. et al. June 10-14, 2008. Sitges, Spain.