

Pharmacokinetics (PK) and Safety in Healthy Subjects of S/GSK1349572, a Next Generation, Once-Daily HIV Integrase Inhibitor (INI)

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Abstract

Background: S/GSK1349572 is an HIV integrase strand transfer inhibitor that demonstrates potent *in vitro* anti-HIV activity and a favorable preclinical profile.

Methods: Randomized, double-blind, placebo-controlled first in human single-dose (SD) and multiple-dose (MD), dose escalation studies were conducted. In the SD study, 2 cohorts of 10 subjects (8 active, 2 placebo) received suspension doses of 2, 5, 10, 25, 50 and 100 mg in an alternating panel design. In the MD study, 3 cohorts of 10-12 subjects (8 or 10 active, 2 placebo) received suspension doses of 10, 25 and 50mg once daily for 10 days, and a CYP3A substrate, midazolam, was given on Day -1 alone and on Day 10 with the 25 mg dose. An additional 12 subjects received 20mg suspension and two 10mg tablets with and without a 30% fat meal in a crossover design. Laboratory testing, vital signs, ECGs and PK sampling were performed at regular intervals.

Results: Most adverse events (AE) were mild; headache was the most common AE. No laboratory or ECG trends were noted. PK was dose proportional and time-invariant over the dosage range studied. Median elimination half-life was 15 hours. Steady state geometric mean (CV%) AUC(0-24) and C_{max} ranged from 16.7 (15) µg²h/mL and 1.5 (24) µg/mL at 10 mg once daily to 76.8 (19) µg²h/mL and 6.2 (15) µg/mL at 50mg once daily, respectively. The geometric mean steady-state C₂₄ at 50mg was 1.5 µg/mL, ~23-fold higher than the *in vitro* protein-adjusted IC₉₀. S/GSK1349572 had no impact on midazolam PK. The tablet demonstrated relative bioavailability of 70% compared to suspension. Food had no impact on tablet exposure.

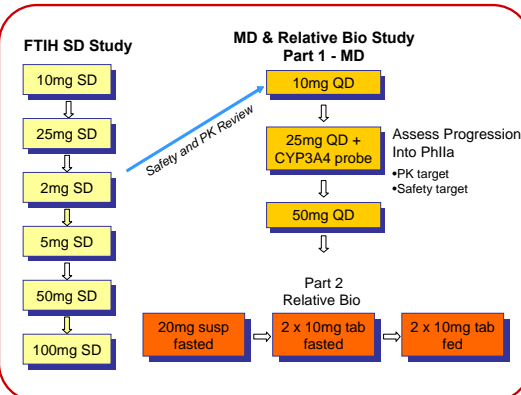
Conclusions: S/GSK1349572 was well tolerated in healthy subjects. The PK profile indicates once daily low doses of S/GSK1349572 will achieve target therapeutic concentrations. S/GSK1349572 does not affect CYP3A. S/GSK1349572 is being evaluated in HIV-infected patients.

Introduction

- Next generation integrase inhibitors should provide real advances for patients including:
 - A unique resistance profile allowing treatment of raltegravir and elvitegravir resistant virus
 - QD dosing without the need for concomitant pharmacokinetic boosters
- S/GSK1349572 was engineered to deliver these attributes

Methods

Figure 1. Study Design



Results

Figure 2. Single Dose Pharmacokinetics

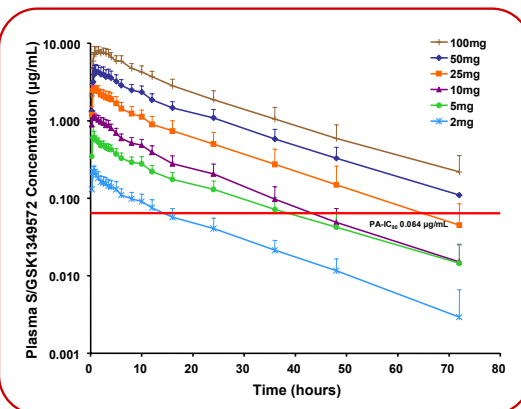


Table 1. Single Dose Pharmacokinetic Parameters

Treatment	N	C _{max} (µg/mL)	T _{max} ² (h)	AUC(0-t) (µg.h/mL)	AUC(0-∞) (µg.h/mL)	AUC(0-24) (µg.h/mL)	t _{1/2} (h)	C ₂₄ (µg/mL)
2mg	8	0.231 (20)	0.63 (0.25-1.00)	2.63 (28)	2.78 (26)	2.07 (21)	12.7 (20)	0.0382 (41)
5mg	7	0.661 (20)	0.50 (0.50-1.50)	8.54 (25)	8.87 (27)	6.23 (18)	14.3 (25)	0.126 (28)
10mg	8	1.23 (9)	0.63 (0.25-1.50)	14.3 (21)	14.6 (21)	11.2 (16)	12.7 (9)	0.196 (34)
25mg	8	2.76 (12)	0.75 (0.50-1.50)	34.3 (28)	35.1 (30)	26.2 (21)	12.7 (21)	0.469 (41)
50mg	6	4.56 (21)	1.25 (0.50-3.00)	70.8 (19)	73.2 (19)	51.4 (18)	14.2 (19)	1.06 (27)
100mg	5	8.14 (12)	1.00 (0.75-3.00)	131 (22)	136 (24)	97.4 (15)	14.7 (23)	1.80 (33)

1. geometric mean (CV%)
2. median (range)

- S/GSK1349572 demonstrates linear pharmacokinetics, a long half-life supporting once daily dosing and low inter-subject variability

Figure 3. Multiple Dose Pharmacokinetics

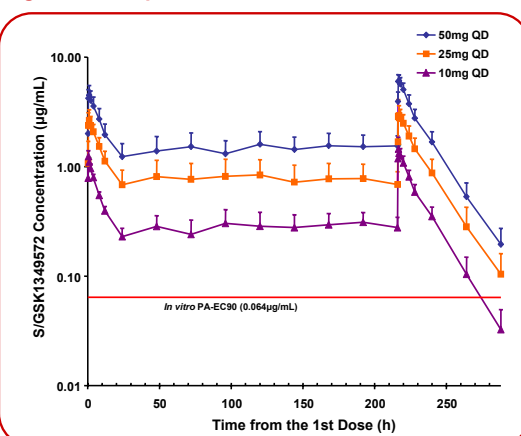
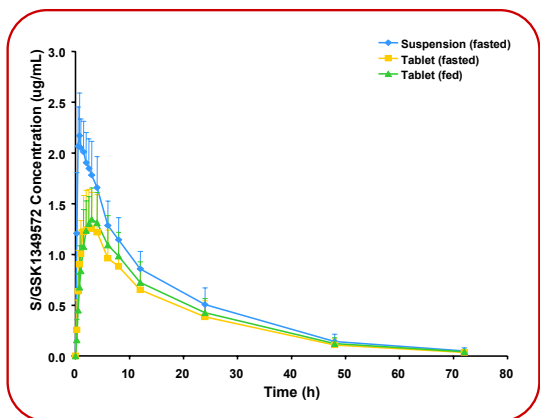


Table 2. Multiple Dose Pharmacokinetic Parameters (Day 10)

Treatment	N	C _{max} (µg/mL)	t _{max} ^b (h)	AUC(0-τ) (µg.h/mL)	t _{1/2} (h)	C _τ (µg/mL)
10mg	8	1.47 (24)	0.50 (0.25-2.00)	16.7 (15)	13.7 (15)	0.35 (20)
25mg + MDZ	10	3.09 (26)	1.00 (0.50-2.00)	38.4 (23)	15.0 (16)	0.84 (33)
50mg	8	6.16 (15)	1.00 (0.50-2.00)	76.8 (19)	15.3 (8)	1.64 (25)

- S/GSK1349572 achieves steady-state after 5 days of dosing, has time invariant PK, and demonstrates low interpatient variability

Figure 4. Tablet Bioavailability and Food Effect



- S/GSK1349572 can be given with or without food

Table 3. MDZ Probe Results

PK parameter	MDZ alone GLSmean	MDZ+572 GLSmean	Ratio (+572/alone)	90% CI
AUC(0-t) (µg ² h/ml)	16.3	15.4	0.946	[0.815,1.10]
AUC(0-inf) (µg ² h/ml)	18.4	17.5	0.953	[0.789,1.15]

- 90% CI of treatment ratio fell in the BE window of [0.8, 1.25] for AUC(0-t). GSK1349572 has no impact (inhibition or induction) on CYP3A enzyme activity.

Table 4. Safety Data in Single Dose Summary of all AEs Occurring in 2 or More Subjects

Preferred Term	2mg N=8 n (%)	5mg N=7 n (%)	10mg N=8 n (%)	25mg N=8 n (%)	50mg N=6 n (%)	100mg N=5 n (%)	Placebo N=5 n (%)
Subjects with Any AE	2 (25)	1 (14)	2 (25)	3 (38)	3 (50)	2 (40)	3 (60)
Headache	1 (13)	0	1 (13)	0	0	0	2 (40)
Somnolence	0	0	0	0	2 (33)	0	0

- No SAEs or severe AEs.
- 2 subjects were withdrawn due to AEs (3-beat NSVT, URI)
- 1 subject receiving 2mg (previously received 25mg) had asymptomatic G3 lipase which resolved in 4 days off drug
- No clinically significant trends in post-dose laboratory abnormalities were evident.
- No clinically significant trends in vital sign or ECG (telemetry or 12-lead ECG) abnormalities were observed. No ΔQTc ≥ 60msec or QTc ≥ 450msec was reported.

Table 5. Safety Data in Multiple Dose Summary of all AEs Occurring in 2 or More Subjects

Preferred Term	10mg N=8 n (%)	25mg N=10 n (%)	50mg N=9 n (%)	MDZ N=12 n (%)	MDZ + 25mg N=10 n (%)	Placebo N=5 n (%)
Subjects with Any AE	4 (50)	1 (10)	7 (78)	1 (8)	1 (10)	1 (20)
Headache	1 (13)	0	2 (22)	0	0	0
Pharyngolaryngeal pain	1 (13)	0	1 (11)	0	0	1 (20)
Application site pruritis	0	0	1 (11)	0	1 (10)	0
Pruritis	0	0	2 (22)	0	0	0

Treatment: 10mg = 10mg S/GSK1349572 suspension once daily x 10 days, 25mg = 25mg S/GSK1349572 suspension once daily x 9 days, 50mg = 50mg S/GSK1349572 suspension once daily x 10 days, MDZ = 3mg MDZ single dose, 25mg + MDZ = 25mg S/GSK1349572 suspension + 3mg MDZ once daily x 1 day

- Part 2 (food effect study): Headache was most common AE (2 subjects overall). 1 subject with severe unrelated AE.
- No SAEs or severe AEs in MD. No withdrawals due to AEs.
- 1 subject receiving 50mg MD with asymptomatic G3 TG & G2 ALT increases, resolved off drug.
- No clinically significant trends in post-dose laboratory abnormalities were evident.
- No clinically significant vital sign or ECG trends were evident. No ΔQTc ≥ 60msec or QTc ≥ 450msec was reported.

Conclusions

- S/GSK1349572 was generally well tolerated in healthy subjects
- S/GSK1349572 can be given with or without food
- S/GSK1349572 does not affect CYP3A
- S/GSK1349572 demonstrates predictable and consistent pharmacokinetics with low PK variability
- The PK profile supports low dose, once daily dosing and will achieve target therapeutic concentrations without the need for a PK booster