Pharmacokinetics of the HIV integrase inhibitor S/GSK1349572 co-administered with acid-reducing agents and multivitamins in healthy volunteers


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Objectives: To evaluate the effect of pH-altering agents on S/GSK1349572 exposure in healthy subjects.

Methods: S/GSK1349572 is an unboosted, once-daily, next-generation HIV integrase inhibitor. In the first study, 16 subjects received four single-dose treatments: (i) S/GSK1349572 50 mg; (ii) S/GSK1349572 50 mg with a multivitamin (MVI; One A Day Maximum); (iii) S/GSK1349572 50 mg with a liquid antacid (Maalox Advanced Maximum Strength); and (iv) S/GSK1349572 50 mg 2 h before an antacid. In the second study, 12 subjects received a single dose of S/GSK1349572 alone and on day 5 of omeprazole.

Results: All treatments were well tolerated. MVI co-administration modestly decreased S/GSK1349572 AUC by 33%. Concurrent antacid co-administration reduced S/GSK1349572 AUC by 74% and staggered antacid dosing significantly diminished this interaction, with a reduction in S/GSK1349572 AUC of 26%. Omeprazole did not significantly affect S/GSK1349572 exposure.

Conclusions: S/GSK1349572 can be taken with proton pump inhibitors and MVIs without dose adjustment but should be administered 2 h before or 6 h after antacids.

Keywords: drug interaction, metal cations, antiretroviral therapy

Introduction

HIV integrase inhibitors (INIs), which target the viral integrase enzyme and block viral DNA strand transfer inside the host cell, are the newest class of potent antiretroviral agents. INIs currently approved or in late-stage development have demonstrated durable viral suppression and favourable safety and tolerability profiles.1,2 S/GSK1349572 is a next-generation INI, currently under development, that is administered once daily without the need for pharmacokinetic (PK) boosting. In a Phase IIb dose-ranging study in HIV-infected patients, ≥90% of patients at all three doses of 10, 25 and 50 mg once daily had undetectable HIV RNA at 16 weeks compared with 60% of those taking efavirenz.3 In vitro data indicate that S/GSK1349572 has limited cross-resistance to other INIs with the potential for a higher genetic barrier to resistance than first-generation INIs.4,5 S/GSK1349572 has also demonstrated a clear dose–response relationship with low intersubject PK variability without the need for PK boosting.6,7 S/GSK1349572 exhibited in vitro activity against most clinical isolates obtained from patients failing raltegravir-based therapy.2 As S/GSK1349572 progresses into Phase III trials, it is likely that it will be co-administered in patients receiving acid-reducing therapy, such as antacids and proton pump inhibitors (PPIs), and multivitamins (MVIs).

The activity of all investigational or approved INIs is dependent on binding to magnesium ions located at the catalytic site of the integrase enzyme to prevent viral DNA strand transfer into the host genome. Therefore, chelation with therapeutic products containing metal cations is possible. Previous studies with INIs raltegravir and elvitegravir have shown clinically significant effects of concomitant administration with antacids,8,9 which were significantly improved for elvitegravir when dosing was separated by 2 and 4 h.8 S/GSK1349572 is not an inducer or inhibitor of CYP isozymes and is primarily metabolized through glucuronidation via UGT1A1, and CYP3A4 to a minor extent.7 Therefore, the potential for a drug–drug interaction between S/GSK1349572 and antacids or MVIs is based primarily on the potential for chelation rather than through a metabolic or pH interaction. To maximize the potential for metal chelation, a non-prescription antacid and MVI with the highest metal-cation content were chosen for this study. In contrast, an interaction with a PPI is likely to occur either through a change...
in absorption-limiting solubility resulting from increasing pH or a metabolic interaction largely via CYP2C19, CYP3A or other CYP isozymes.\textsuperscript{10} Raltegravir plasma concentration increases with omeprazole co-administration in healthy subjects.\textsuperscript{11} It is unknown whether omeprazole is an inhibitor of glucuronidation. Therefore, two one-way interaction studies were performed to determine whether an antacid (simultaneous and staggered administration), MVI and omeprazole separately impact the PK of S/GSK1349572.

Materials and methods

Two studies were conducted to evaluate the effect of an antacid, MVI and PPI on S/GSK1349572 exposure in healthy adult male and female subjects. Maalox\textsuperscript{\textregistered} Advanced Maximum Strength Liquid antacid (Novartis Consumer Health, Inc., Parsippany, NJ, USA) and One A Day\textsuperscript{\textregistered} Maximum MVI tablets (Bayer Corporation, Morristown, NV, USA) were selected because of their high metal divalent cation content, whereas omeprazole 40 mg (Prilosec\textsuperscript{\textregistered}; AstraZeneca, Wilmington, DE, USA) capsules were chosen as placebo.

One A Day Maximum contains 162 mg of elemental calcium and 100 mg of magnesium per tablet, in addition to iron, zinc and copper, while Maalox Advanced Maximum Strength contains 400 mg each of aluminum hydroxide and magnesium hydroxide per 5 mL with 40 mg of simethicone. The MVI/antacid study was an open-label, randomized, four-period, cross-over study conducted at a single inpatient centre. The PPI evaluation was an open-label, randomized, cross-over study conducted at a single inpatient centre in which S/GSK1349572 was administered with a PPI. In both studies, subjects were judged to be healthy on the basis of physical examination, medical history, 12-lead electrocardiogram (ECG) and laboratory testing. Excluded subjects were those with a pre-existing condition interfering with normal gastrointestinal anatomy or motility; hepatic dysfunction, renal dysfunction or both that could have interfered with the absorption, metabolism or excretion of the study drugs; or positive hepatitis B surface antigen, positive hepatitis C antibody or positive test for HIV antibody. Subjects were prohibited from ingesting any prescription or non-prescription drugs, including vitamins, herbal supplements and dietary supplements, within 7 days before the first dose of study medication.

In the MVI/antacid study, subjects were randomized to begin period 1 with one of four randomized treatment sequences (iii/ii/iii/iv, iii/ii/iv/iii, iii/iv/i/i, and iv/i/iii/ii). All treatments were given under fasted conditions, with S/GSK1349572 administered as a single 50 mg dose dispensed as five 10 mg tablets in each treatment period. Subjects received the following four treatments: (i) S/GSK1349572 alone; (ii) S/GSK1349572 concurrently with a single 20 mL dose of antacid; and (iii) S/GSK1349572 simultaneously with a single 20 mL dose of antacid; and (iv) S/GSK1349572 2 h before a single 20 mL dose of antacid. There was a 7 day washout period between treatments.

In the omeprazole study, subjects received a single 50 mg dose of S/GSK1349572 administered as two 25 mg tablets, under fasted conditions in treatment period 1. In treatment period 2, subjects received omeprazole 40 mg once daily for 5 days. On day 5, subjects also received a single 50 mg dose of S/GSK1349572 2 h after the omeprazole dose under fasted conditions. There was no washout between treatment periods.

For both studies, safety evaluations (clinical chemistry and haematology, urinalysis, vital signs and 12-lead ECG) were performed and serial PK samples for determination of plasma concentration of S/GSK1349572 were collected during each treatment period. In each period, subjects were asked daily, in an open-ended fashion, about adverse events (AEs) and their use of concomitant medications. Written informed consent was obtained from all subjects, and the protocols were approved by the institutional review boards of the two study sites.

Bioanalytical methods

After extraction from plasma by protein precipitation, S/GSK1349572 concentrations were determined by validated, HPLC tandem mass spectrometry methods [ Analyst\textsuperscript{\textregistered} Version 1.4.2 (AB SCIEX, Foster City, CA, USA) and Broersofters SIMS 2000 Version 2.1] using TurbolonSpray\textsuperscript{\textregistered} (AB SCIEX) and multiple reaction monitoring at GlaxoSmithKline. For analysis of S/GSK1349572, [2H\textsubscript{7},15N]S/GSK1349572 was used as an internal standard. The validated linear concentration range was 5–5000 ng/mL, and three concentrations of quality control samples were included in each run at 20, 400 and 4000 ng/mL. Based on the results of the analysis of these quality control samples, the bias ranged from −3.5% to 3.7%, and the within-run precision and the between-run precision were ≤0.9% and ≤1.6%, respectively.

PK analysis

A non-compartmental PK analysis of the concentration–time data was performed with WinNonlin\textsuperscript{\textregistered} (Version 5.2; Pharsight Corporation, Mountain View, CA, USA). Plasma PK parameters for S/GSK1349572 were calculated using actual recorded times for each treatment. Parameters that were determined included the AUC from time zero extrapolated to infinity (AUC\textsubscript{0–∞}), the AUC from time zero to the time of last quantifiable concentration (AUC\textsubscript{0–t}), the maximum observed plasma concentration (C\textsubscript{max}) and the plasma concentration at 24 h post-dose (C\textsubscript{24h}).

Statistical analysis

For S/GSK1349572, the statistical analysis was performed on the log-transformed PK parameters, AUC\textsubscript{0–t}, AUC\textsubscript{0–∞}, C\textsubscript{max} and C\textsubscript{24h}. Analysis of variance was performed using an SAS Mixed Linear Models procedure (SAS Institute, Inc., Cary, NC, USA) to assess the effect of the antacid, MVI and PPI. Subject data were fitted as random effects, and treatment was fitted as a fixed effect in the model. The ratios of geometric least squares (GLS) means and associated 90% confidence intervals (CIs) were estimated for the PK parameters of interest. S/GSK1349572 given alone was considered to be the reference treatment, and the test treatments were S/GSK1349572 co-administered with the antacid, MVI or PPI.

Results

A total of 30 subjects were enrolled, and 28 subjects completed the studies (16 in the MVI/antacid study and 12 in the PPI evaluation). In the MVI/antacid study, all subjects were male, the mean age was 30.8 years, 31% were African American and the mean weight was 79.6 kg. In the PPI evaluation, 86% were male, the mean age was 40.6 years, 50% were African American and the mean weight was 84.7 kg.

Single doses of S/GSK1349572, MVI and antacid and repeat doses of PPI (with and without S/GSK1349572) were well tolerated during the studies. No deaths were reported in either study; however, two withdrawals were reported in the PPI study, including one non-drug-related serious AE. One healthy subject, who did not initially disclose an extensive psychiatric history and cocaine use, was randomized to treatment ii in period 1; this subject experienced a non-drug-related serious manic episode on day 5 of period 1 and was withdrawn from the study before the start of the PPI evaluation. One other subject failed to report for the second dosing period and was withdrawn. A total of 10 of

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Effect of pH on S/GSK1349572

Table 1. Summary of most commonly reported drug-related AEs in the MVI/antacid study

<table>
<thead>
<tr>
<th></th>
<th>S/GSK1349572 (N=16)</th>
<th>S/GSK1349572 + MVI (N=16)</th>
<th>S/GSK1349572 + antacid to antacid (N=16)</th>
<th>Overall (N=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with any AE, n (%)</td>
<td>0</td>
<td>3 (19)</td>
<td>1 (6)</td>
<td>5 (31)</td>
</tr>
<tr>
<td>nausea</td>
<td>0</td>
<td>3 (19)</td>
<td>1 (6)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>diarrhoea</td>
<td>0</td>
<td>0</td>
<td>1 (6)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>chills</td>
<td>0</td>
<td>0</td>
<td>1 (6)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>anorexia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (6)</td>
</tr>
<tr>
<td>headache</td>
<td>0</td>
<td>0</td>
<td>1 (6)</td>
<td>1 (6)</td>
</tr>
</tbody>
</table>

28 subjects (36%) reported at least one AE during both studies. The most frequently reported AEs were nausea and headache (Tables 1 and 2). Abdominal pain and dyspepsia were reported by one subject each (17%) during S/GSK1349572 + PPI administration. All AEs were mild (grade 1) in intensity. Nausea was the most commonly reported drug-related AE (Table 1). All other drug-related AEs were reported by only one subject each. No clinically significant trends in laboratory values, vital signs or ECGs were observed in either study.

PK parameters of S/GSK1349572 are shown in Table 3. Mean concentration–time curves of S/GSK1349572 with and without MVI or antacid are shown in Figure 1. Simultaneous co-administration of an MVI with high divalent cation content had a modest effect on the single-dose PK of S/GSK1349572, with GLS mean ratios for PK parameters ranging from 0.92 to 1.00 and 90% CIs within the bounds 0.75–1.25 (Table 4).

Table 2. Summary of most commonly reported drug-related AEs in the PPI study

<table>
<thead>
<tr>
<th></th>
<th>S/GSK1349572 (N=14)</th>
<th>S/GSK1349572 + omeprazole (N=12)</th>
<th>Overall (N=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with any AE, n (%)</td>
<td>1 (7)</td>
<td>2 (17)</td>
<td>3 (21)</td>
</tr>
<tr>
<td>headache</td>
<td>1 (7)</td>
<td>0</td>
<td>1 (7)</td>
</tr>
<tr>
<td>abdominal pain</td>
<td>0</td>
<td>1 (8)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>dyspepsia</td>
<td>0</td>
<td>1 (8)</td>
<td>1 (7)</td>
</tr>
</tbody>
</table>

PK parameters of S/GSK1349572 with and without omeprazole are shown in Table 3. Mean concentration–time curves of S/GSK1349572 with and without omeprazole are shown in Figure 2. Co-administration of omeprazole had no effect on the single-dose PK of S/GSK1349572, with GLS mean ratios for PK parameters ranging from 0.92 to 1.00 and 90% CIs within the bounds 0.75–1.25 (Table 4).

Discussion

Significant drug interactions between acid-suppressing agents and antiretroviral therapy have been previously described. In addition, the divalent metal binding effect of INIs lends itself to interactions with metal cation-containing medications. Thus, a study to evaluate the effect of acid-reducing agents and an MVI on S/GSK1349572 exposure was warranted. Products with the greatest potential for interaction because of high cation content or acid-suppression activity were selected for these studies to assess the worst case scenario in clinical use.

Maelox Advanced Maximum Strength Liquid antacid co-administration reduced single-dose plasma S/GSK1349572 PK when given simultaneously. Administration of an antacid 2 h after S/GSK1349572 administration attenuated the impact of the interaction as S/GSK1349572 AUC, Cmax and C24 were reduced by 26%, 18% and 30% on average, respectively. This observation is consistent with the hypothesis that reduced oral absorption of S/GSK1349572 results from chelation with metal cations contained in the antacid product. The mean C24 of 0.36 μg/mL, observed with a 2 h separation of S/GSK1349572 and an antacid, is 6-fold greater than the wild-type HIV in vitro protein-adjusted 90% inhibitory concentration (PA-IC90) of 0.064 μg/mL. In addition, this C24 value would be expected to achieve a >2 log decrease in HIV RNA based on a PK/pharmacodynamic model for S/GSK1349572 in HIV-infected subjects. Therefore, the trough concentrations attained with S/GSK1349572 2 h before antacid administration would be expected to show potent, long-term antiviral activity, even with the minor reduction in exposure. Similar interactions have been observed with quinolone antibiotics, which are also divalent metal binders with similar guidance for dose separation; thus S/GSK1349572 should be administered 2 h before or 6 h after antacids.

Concurrent administration of the MVI decreased S/GSK1349572 exposure to a similar extent to staggered antacid administration. Therefore, the effect of an MVI is unlikely to be clinically relevant because the mean C24 of S/GSK1349572 50 mg once daily as a single dose when co-administered with an MVI is still 5.3-fold greater than the in vitro PA-IC90. In addition, the MVI product used in this study probably represents the maximal effect of metal chelation among most MVI products because of its high metal cation content; therefore, S/GSK1349572 can be co-administered with an MVI without dose adjustment.

Simultaneous administration of omeprazole minimally decreased S/GSK1349572 exposure. This result is consistent

Table 3. PK parameters of S/GSK1349572

<table>
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<td>diarrhoea</td>
<td>0</td>
<td>0</td>
<td>1 (6)</td>
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<td>chills</td>
<td>0</td>
<td>0</td>
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<tr>
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<td>0</td>
<td>1 (6)</td>
</tr>
<tr>
<td>headache</td>
<td>0</td>
<td>0</td>
<td>1 (6)</td>
</tr>
</tbody>
</table>

PK parameters of S/GSK1349572 with and without omeprazole are shown in Table 3. Mean concentration–time curves of S/GSK1349572 with and without omeprazole are shown in Figure 2. Co-administration of omeprazole had no effect on the single-dose PK of S/GSK1349572, with GLS mean ratios for PK parameters ranging from 0.92 to 1.00 and 90% CIs within the bounds 0.75–1.25 (Table 4).
with in vitro data demonstrating that the solubility of S/GSK1349572 does not change over the physiological pH range and its metabolism does not appear to be affected by interactions with CYP2C19. In addition, the PPI product and dose used in this study exhibit duration and extent of acid suppression that are comparatively long compared with other PPIs and greater than those observed with H2-receptor antagonists.\textsuperscript{16}

Because co-administration of omeprazole had a minimal effect on plasma S/GSK1349572 exposure and showed good tolerability, S/GSK1349572 can be co-administered with PPIs and H2-receptor antagonists without dose adjustment.

Limited data exist regarding the drug interaction potential of acid-reducing agents and the INIs raltegravir and elvitegravir.\textsuperscript{8,9,11,17} Raltegravir has pH-dependent solubility, is

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**Table 3. Summary of plasma S/GSK1349572 PK parameters**

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>N</th>
<th>$C_{\text{max}}$ (µg/mL)</th>
<th>$C_{24}$ (µg/mL)</th>
<th>AUC$_{0-1}$ (µg.h/mL)</th>
<th>AUC$_{0-\infty}$ (µg.h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S/GSK1349572$^a$</td>
<td>16</td>
<td>2.03 (25)</td>
<td>0.51 (38)</td>
<td>34.6 (31)</td>
<td>35.6 (33)</td>
</tr>
<tr>
<td>S/GSK1349572 + MVI$^b$</td>
<td>16</td>
<td>1.31 (25)</td>
<td>0.34 (33)</td>
<td>23.0 (29)</td>
<td>23.7 (30)</td>
</tr>
<tr>
<td>S/GSK1349572 + antacid$^c$</td>
<td>16</td>
<td>0.56 (29)</td>
<td>0.13 (41)</td>
<td>9.11 (36)</td>
<td>9.40 (36)</td>
</tr>
<tr>
<td>S/GSK1349572 2 h before antacid$^d$</td>
<td>16</td>
<td>1.67 (51)</td>
<td>0.36 (42)</td>
<td>25.7 (44)</td>
<td>26.3 (45)</td>
</tr>
<tr>
<td>S/GSK1349572 fasted$^e$</td>
<td>12</td>
<td>1.84 (44)</td>
<td>0.56 (63)</td>
<td>31.0 (53)</td>
<td>34.7 (57)</td>
</tr>
<tr>
<td>S/GSK1349572 fasted + omeprazole$^f$</td>
<td>12</td>
<td>1.69 (19)</td>
<td>0.53 (27)</td>
<td>30.0 (22)</td>
<td>34.8 (26)</td>
</tr>
</tbody>
</table>

CV, coefficient of variation.

$^a$S/GSK1349572 50 mg×1 dose.

$^b$S/GSK1349572 50 mg×1 dose + MVI×1 dose.

$^c$S/GSK1349572 50 mg×1 dose + 20 mL of antacid×1 dose.

$^d$S/GSK1349572 50 mg×1 dose 2 h before 20 mL of antacid×1 dose.

$^e$S/GSK1349572 50 mg (fasted)×1 dose.

$^f$Omeprazole 40 mg once daily×5 days (fasted) + S/GSK1349572 50 mg×1 dose (2 h after omeprazole on day 5 only).

**Table 4. Treatment comparisons for S/GSK1349572**

<table>
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<tbody>
<tr>
<td>AUC$_{0-\infty}$</td>
<td>0.667 (0.552, 0.805)</td>
<td>0.264 (0.219, 0.319)</td>
<td>0.740 (0.613, 0.893)</td>
<td>1.00 (0.808, 1.25)</td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>0.646 (0.540, 0.774)</td>
<td>0.276 (0.231, 0.331)</td>
<td>0.821 (0.686, 0.984)</td>
<td>0.915 (0.754, 1.11)</td>
</tr>
<tr>
<td>$C_{24}$</td>
<td>0.679 (0.560, 0.824)</td>
<td>0.256 (0.211, 0.311)</td>
<td>0.703 (0.579, 0.853)</td>
<td>0.954 (0.752, 1.21)</td>
</tr>
</tbody>
</table>

**Figure 1.** Mean concentration–time profiles of S/GSK1349572 administered with or without MVI or antacid.

**Table 4.** Treatment comparisons for S/GSK1349572

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1570
metabolized by UGT1A1 and has been studied with an antacid and omeprazole; no data on its interaction with staggered antacid administration or MVIs are currently available. Simultaneous administration of a magnesium- and aluminum-containing antacid resulted in an earlier time to maximum plasma concentration (T\text{max}) for raltegravir, presumably due to enhanced absorption with a higher gastric pH and a 67% lower C\text{12} without a corresponding change in AUC or C\text{max} compared with when raltegravir was given alone.\textsuperscript{9} The authors suggest that antacids may both increase raltegravir absorption and bind to raltegravir. In contrast, the mechanism of antacid interaction with S/GSK1349572 is consistent with metal binding only, as dose separation substantially ameliorated this effect. Raltegravir AUC and C\text{max} increased 3- to 4-fold and C\text{12} by 1.5-fold in the presence of omeprazole in healthy adult subjects, probably as a result of increased solubility with higher gastric pH.\textsuperscript{11} However, the authors state that a dose adjustment is unnecessary and that the increased raltegravir exposure is not clinically relevant. Omeprazole did not impact the PK of S/GSK1349572, demonstrating pH-independent absorption. Elvitegravir requires a PK enhancer to enable once-daily dosing and is primarily metabolized by CYP3A and glucuronidation (UGT1A1 and UGT1A3). Drug interactions between elvitegravir and antacids and omeprazole have been studied. Elvitegravir PK were unchanged when elvitegravir was administered with omeprazole; however, in the presence of an antacid, elvitegravir AUC, C\text{max} and C\text{min} were reduced by 55%, 53% and 59%, respectively, indicating that separation by at least 2 h is required.\textsuperscript{8} The impact on raltegravir absorption and exposure following dose separation with an antacid is unknown and requires further investigation. Moreover, interactions between acid-reducing agents and INIs should be investigated in HIV-infected patients as PK changes may differ, as demonstrated by a smaller impact of famotidine and omeprazole on the PK of raltegravir in patients.\textsuperscript{17}

S/GSK1349572 was well tolerated by subjects in all treatment groups in the two studies. All AEs were mild, and few drug-related AEs were reported for S/GSK1349572 with or without co-administered medications, which is consistent with other clinical trials of S/GSK1349572.\textsuperscript{3-5} Phase IIb clinical trials are ongoing to assess the long-term tolerability and safety profile of S/GSK1349572. This study demonstrates that S/GSK1349572 was well tolerated when given with an antacid, MVI or omeprazole in healthy adult subjects. S/GSK1349572 can be co-administered with MVIs, PPIs and histamine H\textsubscript{2}-receptor antagonists without dose adjustment. Additionally, S/GSK1349572 can be co-administered 2 h before or 6 h after an antacid without dose adjustment.

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