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The Effect of Food and Formulation on the Pharmacokinetics, Safety, and Tolerability of GSK1322322 in Healthy Volunteers

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Abstract

GSK1322322 is the first in a new class of antibiotics that inhibit peptide deformylase, necessary for bacterial protein maturation. Previously, low absolute bioavailability was observed for the 1500-mg oral tablet formulation, resulting in a less than dose-proportional increase from the 1000-mg dose. Furthermore, high variability of pharmacokinetic (PK) parameters within cohorts was suggested to be associated with differences in body weight. This open-label, randomized, 4-period, crossover, single-dose phase I study in healthy individuals compared the PK, safety, and tolerability of free base oral tablets under fasted or fed conditions with intravenous and oral mesylate salt solution of GSK1322322 under fasted conditions. Absolute bioavailability of GSK1322322 1500-mg free base tablets under fasted conditions, fed conditions, and oral mesylate salt solution was 57%, 77%, and 92%, respectively. Moderate-fat/calorie food intake increased area under the concentration–time curve ($AUC_{0-\infty}$) by 36%, maintained maximum observed concentration (C_{max}), and delayed time to C_{max}. It appeared that $AUC_{0-\infty}$ decreased with body weight, whereas clearance increased. GSK1322322 administration resulted in only mild-to-moderate adverse events. These results support future clinical investigations of the free base oral tablet formulation of GSK1322322 1500 mg after intake of a moderate-fat/calorie meal, including further investigation of a potential weight-based dosage change.

Keywords

GSK1322322, peptide deformylase, free base, mesylate salt solution, pharmacokinetics

Bacterial resistance to antibiotics is increasing, creating a need for the development of novel antimicrobial agents that target essential bacterial processes.[1–3] Peptide deformylase (PDF), a metalloprotease that removes the N-formyl group present in all newly synthesized bacterial polypeptides, is required for proper protein maturation in prokaryotes but not mammalian cells.[4] However, PDF is an unexploited clinical target as a novel antimicrobial agent.[5] GSK1322322 is a potent inhibitor of PDF, discovered by a combination of structure-based drug design and iterative medicinal chemistry (Figure 1).[6]

Several phase I studies have investigated single- and repeat-dose administration of different formulations of oral and intravenous (IV) GSK1322322.[7–10] The tablet formulation of GSK1322322 at 1500 mg demonstrated lower absolute bioavailability (56%) and higher variability than expected from the pharmacokinetic (PK) profiles of the previously described single-dose powder-in-bottle formulation.[10] Also, preliminary population PK analysis based on four phase I studies suggests that the PK of GSK1322322 was affected by body weight as individuals with lower body weight had lower clearance and thus higher systemic exposure than those with higher body weight.[11] Therefore, optimization of exposure after administration of the oral tablet formulation of GSK1322322 and more robust data on PK versus body weight are important for suggesting potential dose modifications.

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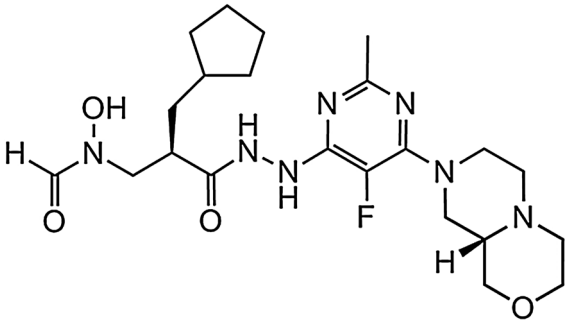

Figure 1. Chemical structure of GSK1322322.

In the present study, the PK, safety, and tolerability of a free base tablet, an oral mesylate salt solution, and an IV mesylate salt solution of GSK1322322 administered as a single 1500-mg (free base equivalent) dose were assessed in healthy volunteers. The relative bioavailabilities of the free base tablet in a fed or fasted state and the oral mesylate salt solution of GSK1322322 in a fasted state were compared. Pharmacokinetic parameters of IV GSK1322322 1500 mg were measured to calculate the absolute bioavailability of the oral formulations. Lastly, potential trends of the effects of body weight on clearance and other PK parameters for IV and oral formulations of GSK1322322 were investigated.

Subjects and Methods

Study Design and Population

This was an open-label, randomized, 4-period, balanced, crossover, single-dose study of the free base oral tablet and oral and IV mesylate salt solutions of GSK1322322 1500 mg to assess the PK, safety, and tolerability of different formulations in healthy volunteers under fasted or fed conditions (GlaxoSmithKline Clinical Study Register, study identifier: PDF116595). Treatments were randomized according to one of four dosing sequences. At the beginning of each period, volunteers received a 60-minute infusion of GSK1322322 1500 mg of IV mesylate salt solution, free base tablet under fasted conditions, free base tablet with a moderate-fat/calorie meal (490 calories composed of approximately 77 g of carbohydrates, 28 g of protein, and 13 g of fat), or oral mesylate salt solution under fasted conditions followed by a 3-day washout period (i.e., up to 72 hours between doses). A moderate-fat/calorie meal, which is considered a typical meal, was chosen on the basis of the modest effect a high-fat/calorie meal demonstrated in a previous phase I study.[8] Dose selection was based on the safety and PK results obtained in several phase I oral single- and repeat-dose studies with GSK1322322.[7–10]

Adults aged 18–65 years with a body weight $\geq$40 kg and in good general health with no clinically relevant abnormalities as determined by medical history, physical exam, laboratory tests, and cardiac monitoring were eligible for the trial. Female volunteers were eligible for enrollment if they were of non-childbearing potential and excluded if they were lactating or pregnant, as determined by positive human chorionic gonadotropin test at screening or before dosing. Volunteers were excluded from the study if they met any of the following conditions: regularly used alcohol and drugs of abuse; had hepatitis B, hepatitis C, or HIV infection; had used an investigational drug within 30 days, five half-lives, or twice the duration of the biological effect of the investigational drug (whichever was longer) before the day of dosing; or had been exposed to >4 new chemical entities within 12 months before the day of dosing. Concomitant prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug was a potential enzyme inducer) or five half-lives (whichever was longer) were prohibited before the first dose of study medication until completion of the follow-up visit. Use of antacids, vitamins, and iron supplements was strictly prohibited within 7 days before the first dose of study medication and for the duration of the trial, including follow-up. Volunteers were advised not to take any medications that were sensitive substrates for the CYP3A4/5 enzyme from 14 days before baseline visit to the last study assessment. Volunteers were recruited and stratified by body weight, ensuring that a sufficient number of them were enrolled in the low (<60 kg) and high (>80 kg) weight categories. Weight stratification was based on the modeling-based prediction with allometrically scaled body weight as a covariate on clearance up to a body weight of ~65 kg, whereas clearance in patients >80 kg seems unchanged relative to weight.[11] The study was conducted at a single study center (DaVita Clinical Research, Minneapolis, MN) and was approved by an institutional review board (Independent Investigational Review Board, Inc., Plantation, FL) in accordance with International Conference on Harmonization guidelines. All volunteers provided written informed consent.

Pharmacokinetic Assessments

Plasma PK samples were collected for each period at predose (within 15 minutes before dosing) and 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 36, 48, and 72 hours after oral dose/infusion start. In periods 1, 2, and 3, the 72-hour sample was the predose sample in periods 2, 3, and 4, respectively, while period 4 had a blood draw at 72 hours solely to complete its sampling schedule. Some predose samples had measurable concentrations due to incomplete washout; however, the majority of the measurable concentration values were <0.1% of the following C_{max} and hence were included in the non-compartmental PK analysis. Plasma and GSK1322322 concentrations were determined by Worldwide Bioanalysis (GlaxoSmithKline)

using high-performance liquid chromatography with tandem mass spectrometry. Briefly, the analytical system consisted of an Acquity UPLC® system (Waters, Milford, MA), Acquity UPLC HSS T3 analytical column (1.8-μm particle size, 2.1 by 50 mm; Waters, Milford, MA; mobile phase was 0.1% formic acid in water and 90/10 acetonitrile/methanol), and a mass spectrometer (API 4000™/API 5500™; Applied Biosystems/MDS Sciex, Framingham, MA) with turbo ion spray, operated in positive mode. GSK1322322 was extracted from samples by protein precipitation with acetonitrile after the addition of an isotopically labeled internal standard ([$^{13}C_2$ $^{15}N_2$]-GSK1322322). Extracts were analyzed by UPLC–MS/MS using a TurboIonSpray® interface and multiple reaction monitoring. Mass-to-charge ratios of 480–267 were monitored for GSK1322322. Using a 25-μL aliquot, the lower limit of quantification for the plasma assay was 5.0 ng/mL, and the upper limit of quantification was 5000 ng/mL. The standard curve for GSK1322322 in plasma was linear ($r^2 \geq 0.999$) over the concentration range of 5–5000 ng/mL. The accuracy ranged from −4.0% to 9.5%. The within- and between-run precision values (percent coefficient of variation [% CV]) were ≤6.0% and ≤4.4%, respectively. Computer systems used to acquire and quantify data included Analyst software (version 5.1, Applied Biosystems/MDS Sciex) and Study Management System 2000 (version 2.3, GlaxoSmithKline). Pharmacokinetic analyses of plasma GSK1322322 concentration–time data were conducted using non-compartmental Model 200 (for extravascular administration) or Model 202 (for IV administration) of WinNonlin®, version 5.2 (Pharsight Corporation, St Louis, MO). The following plasma GSK1322322 PK assessments were calculated: AUC from time zero extrapolated to infinity ($AUC_{0-\infty}$), maximum observed plasma concentration (C_{max}), time of C_{max} (T_{max}), terminal phase half-life ($t_{1/2}$), systemic clearance (CL; IV formulation only), apparent clearance after oral dosing (CL/F; oral formulations only), volume of distribution by the area method (V_{area}; also called V_z; IV formulation only), and volume of distribution at steady state (V_{ss}; IV formulation only). Absolute bioavailability was determined by comparing oral $AUC_{0-\infty}$ with IV $AUC_{0-\infty}$.

Safety Assessments

Safety was assessed by observed AEs and changes over time in hematology, clinical chemistry, urinalysis, vital signs, and electrocardiograms.

Statistical Methods

Statistical analyses were performed using SAS® Version 9 (SAS Institute, Inc., Cary, NC). Baseline and demographic characteristics, safety data, and PK parameters were summarized using descriptive statistics. The PK parameters AUC and C_{max} and the factor dose were $\log_e$-transformed before the analyses. After log-transformation, $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} of GSK1322322 were separately analyzed using a mixed effects model as appropriate to the study design, fitting fixed effect terms for period and regimen and treating subject within sequence as a random effect. Point estimates and 90% confidence intervals (CIs) for the differences of PK parameters of treatments of interest (fasted-oral mesylate salt solution, fed-oral mesylate salt solution, fasted-IV, fed-IV, oral mesylate salt solution-IV, fed-fasted) were constructed using the residual variance. Point and interval estimates were then exponentially back-transformed to construct point and 90% CI estimates for the ratios of PK parameters of interest (fasted to oral mesylate salt solution, fed to oral mesylate salt solution, fasted to IV, fed to IV, oral mesylate salt solution to IV, fed to fasted). Estimates of within-subject variability for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} of GSK1322322 were provided, where CVw (%) = sqrt[exp (MSE) − 1] × 100 and MSE was the residual mean squared error from the model. CVw (%) represented a pooled measure of within-subject variability across regimens. Below limit of quantification values were entered as zero and included in the calculations of the means.

For the relative bioavailability assessment, T_{max} was analyzed non-parametrically using the Wilcoxon matched pairs method to compute the point estimate and 90% CI for the median difference for each comparison of interest listed above.

Sample size was based on preliminary estimates of the coefficient of variation of $AUC_{0-\infty}$ (17.16%) and C_{max} (36.34%) of a single 1500-mg GSK1322322 dose. Twenty-four subjects would provide a precision of 8.55% for $AUC_{0-\infty}$ and 18.5% for C_{max}, where precision represents the half-width of the 90% CI. On the basis of the upper bound of the 90% CI for the CV for $AUC_{0-\infty}$ and C_{max} of 33.5% and 75.9%, respectively, a sample size of 24 subjects provided a precision of 17% for $AUC_{0-\infty}$ and 38.4% for C_{max}, where precision represents the half-width of the 90% CI.

Results

A total of 24 healthy volunteers enrolled in the study and were randomized to receive four single doses of GSK1322322 with a washout period of 3 days between doses. Most volunteers were white (67%), not Hispanic or Latino (92%), and male (63%). The average age of volunteers was approximately 42 years. The average weight was 74.9 kg (range, 49.6–114.4 kg), but volunteers were recruited to ensure a bimodal distribution, with most of them being in the low (42%) or high (42%) weight category, defined as <60 and >80 kg, respectively.

Pharmacokinetics

Plasma PK parameters after single-dose administration of GSK1322322 1500 mg are shown in Table 1 and Figure 2.

Table 1. Mean (SD) Plasma Pharmacokinetic Parameters of Three GSK1322322 Formulations[a]

Parameter	IV (n = 24)[b]	Fasted (n = 24)	Fed (n = 24)	MS (n = 23)
$AUC_{0-\infty}$ (μg·h/mL)	75.4 (24.8)	46.1 (22.4)[b]	58.9 (21.5)	69.7 (23.1)
C_{max} (μg/mL)	28.6 (8.6)	17.1 (9.2)	15.5 (7.9)	25.8 (7.2)
CL/F (L/h)	NA	42.6 (26.6)	28.4 (9.0)	23.8 (7.3)
CL (L/h)	22.0 (7.1)	NA	NA	NA
V_{area} (L)	317.2 (131.5)	NA	NA	NA
V_{ss} (L)	69.2 (25.5)	NA	NA	NA
$t_{1/2}$ (h)	10.3 (3.4)	9.4 (3.8)[b]	8.7 (2.6)	9.6 (3.6)
T_{max} (h)[c]	1.0 (1.0–1.0)	0.5 (0.25–1.5)	1.5 (0.5–4.0)	0.5 (0.25–1.5)

$AUC_{0-\infty}$, area under the concentration–time curve from time zero extrapolated to infinity; CL, systemic clearance; CL/F, apparent clearance following oral dosing; C_{max}, maximum observed plasma concentration; IV, intravenous; MS, mesylate salt; SD, standard deviation; $t_{1/2}$, terminal elimination half-life; T_{max}, time to C_{max}; V_{area}, volume of distribution by the area method; V_{ss}, volume of distribution at steady state.
[a]IV, GSK1322322 1500-mg IV MS solution; fasted, GSK1322322 1500-mg free base tablet (fasted state); fed, GSK1322322 1500-mg free base tablet (fed state); MS, GSK1322322 1500-mg oral MS solution (fasted state).
[b]Blood samples were obtained from only 23 of 24 volunteers.
[c]Median (range).

After single-dose IV or oral administration, GSK1322322 was eliminated with a short $t_{1/2}$ (8.7–10.3 hours). The extent of exposure, represented by $AUC_{0-\infty}$, was greater after oral mesylate salt solution (69.7 μg h/mL) than after the free base tablet (58.9 μg h/mL after a meal, 46.1 μg h/mL in a fasted state). Food intake delayed T_{max} (1.5 and 0.5 hours for fed and fasted states, respectively) but did not change C_{max} after administration of the free base tablet.

Absolute and relative bioavailabilities of the oral formulations in fasted or fed states are listed in Table 2. In comparison with the mean $AUC_{0-\infty}$ of the IV formulation of GSK1322322 1500 mg, absolute bioavailability was greater after administration of the oral mesylate salt solution (92%) compared with the free base tablet (77% after a meal, 57% in a fasted state). Administration of the free base tablet resulted in 36% greater $AUC_{0-\infty}$ and similar C_{max} in a fed state compared with a fasted state. However, food intake resulted in a 0.88-hour delay in T_{max}. The relative bioavailability of the free base tablet under fasted and fed conditions compared with the oral mesylate salt solution under fasted conditions was 62% and 84%, respectively.

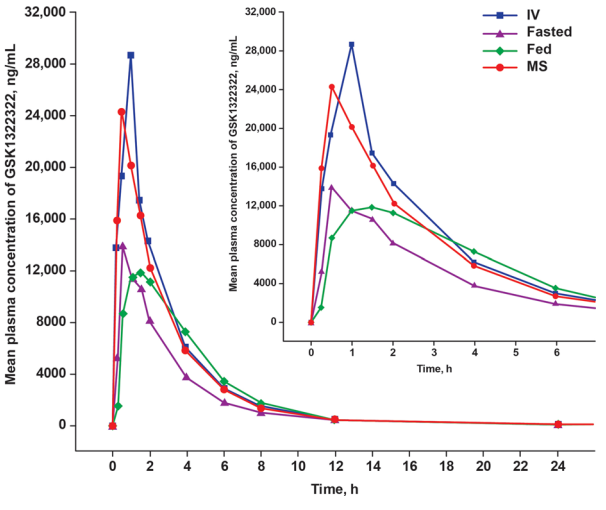

Figure 2. Mean plasma concentration of GSK1322322 at various times after GSK1322322 1500-mg IV formulation under fasted conditions (IV), free base tablet formulation under fasted or fed conditions, and oral MS solution under fasted conditions (MS). IV, intravenous; MS, mesylate salt.

Changes in PK values were associated with changes in body weight, as exemplified in Figure 3. Clearance increased with body weight, and this relationship can be described by the allometric scaling equation $CL = 21.5 \times (WT/70)^{0.75}$, based on population PK modeling of combined phase I data to date. This initial model may change during development. Accordingly, $AUC_{0-\infty}$ (data not shown) and C_{max} (Figure 3B) decreased with increase in body weight. There were no observed correlations between changes in body weight and either T_{max} or $t_{1/2}$ regardless of treatment regimen.

Safety and Tolerability

All adverse events (AEs) were mild to moderate in intensity in this study, and each treatment was associated with an AE in 42–65% of the volunteers. The most frequently reported AEs in all treatment groups were sensitivity of teeth (17% [oral mesylate salt solution] to 33% [fasted]) and headaches (17% [oral mesylate salt solution and fasted] to 29% [fed]). Throat irritation and nausea occurred in 52% and 26% of volunteers, respectively, only after treatment with the oral mesylate salt solution of GSK1322322 1500 mg. Other observed multiple AEs include dizziness (4% [IV and fed] to 13% [oral mesylate salt solution]), dry mouth (4% [oral mesylate salt solution and fed] to 13% [IV]), infusion site rash (13% [IV only]), and application site rash (8%

Table 2. Absolute Bioavailability, Relative Bioavailability, and Food Effect of GSK1322322 Plasma PK Parameters

	Ratio of geometric least square mean PK parameters (90% CI)		
Bioavailability by treatment[a]	$AUC_{0-\infty}$ (μg·h/mL)	C_{max} (μg/mL)	T_{max} (h)[b]
Absolute bioavailability[c]			
Fasted	0.57 (0.51, 0.63)	—	—
Fed	0.77 (0.69, 0.86)	—	—
MS	0.92 (0.82, 1.02)	—	—
Relative bioavailability			
Fasted to MS	0.62 (0.56, 0.69)	0.57 (0.48, 0.69)	0.13 (0.00, 0.37)[c]
Fed to MS	0.84 (0.76, 0.94)	0.57 (0.47, 0.68)	0.99 (0.63, 1.74)[d]
Food effect			
Fed to fasted	1.36 (1.22, 1.51)	0.99 (0.82, 1.18)	0.88 (0.50, 1.25)[e]
CVw (%)	22.0	38.7	NA

$AUC_{0-\infty}$, area under the concentration–time curve from time zero extrapolated to infinity; CI, confidence interval; C_{max}, maximum observed plasma concentration; CVw, within coefficient of variation; IV, intravenous; MS, mesylate salt; PK, pharmacokinetic; T_{max}, time to C_{max}.
[a]IV, GSK1322322 1500-mg IV MS solution; fasted, GSK1322322 1500-mg free base tablet (fasted state); fed, GSK1322322 1500-mg free base tablet (fed state); MS, GSK1322322 1500-mg oral MS solution (fasted state).
[b]Estimated difference from T_{max} of IV treatment.
[c]Estimated difference of fasted treatment from fed treatment.
[d]Estimated difference of fed treatment from MS treatment.
[e]Estimated difference of fed treatment from fasted treatment.

[fasted only]). No apparent trends or changes from baseline in vital signs, chemistry, or hematology data were observed.

One volunteer was withdrawn during the period with IV GSK1322322 1500 mg (period 3) because of a drug-related AE (bronchospasm). The volunteer, who had a history of exercise-induced asthma, experienced shortness of breath with accompanying cough 10 minutes after the infusion began. The infusion was discontinued 4 minutes after the AE, and the AE was resolved 3 minutes after the infusion was discontinued. During the AE, vital signs remained stable and per baseline measures. No medications were administered to treat the event.

Discussion

This study measured the absolute bioavailability (92%) of GSK1322322 as a solution (mesylate salt) to assess the extent of absorption of an oral formulation not requiring disintegration of particles and dissolution, and to compare it

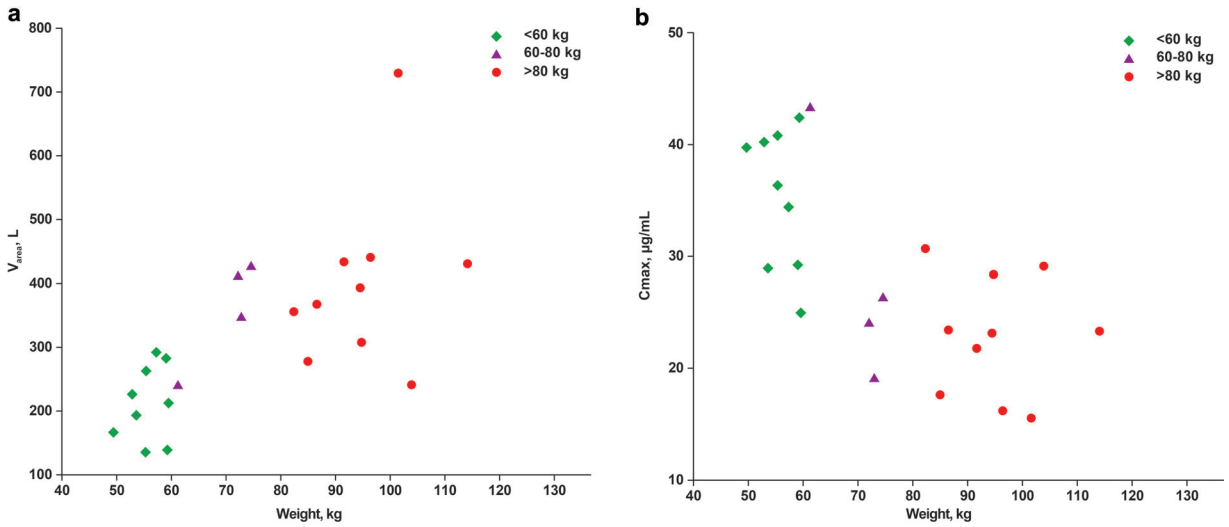

Figure 3. Individual plasma (a) V_{area} and (b) C_{max} versus weight after a single IV GSK1322322 1500-mg dose from this study with volunteers categorized by weight class (60–80, <60, and >80 kg). C_{max}, maximum observed plasma concentration; IV, intravenous; V_{area}, volume of distribution by the area method.

with that of the more stable free base solid formulations (tablets) developed for future clinical studies. Compared with the absolute bioavailability of the mesylate salt solution, the free base tablet showed a lower absolute bioavailability under fasted conditions (57%), consistent with 56% absolute bioavailability observed with the 1500-mg dose from a tablet formulation in a previous phase I study.[10] Furthermore, absolute bioavailability of the free base tablet increased with food intake (77% vs. 57% in fed and fasted states, respectively). The relative bioavailability of the free base tablet after a meal was 136% compared with a fasted state, an increase similar to the previously published corresponding values for the free base tablet of GSK1322322 1000 mg (119%).[8] The within coefficient of variation of AUC and C_{max} were 22% and 39%, respectively, suggesting that GSK1322322 has moderate variability. These combined results indicate that a moderate-fat/calorie meal increased the extent of absorption of the free base tablet, suggesting that the increased bioavailability of a 1500-mg free base tablet administered with food may be important when considering future GSK1322322 regimens.

Although there has been no official regulatory decision yet, GSK1322322 has the characteristics of a Biopharmaceutics Classification System Class 2 compound indicating high permeability and poor solubility. High permeability of GSK1322322 is exemplified by the 92% absolute bioavailability of the mesylate salt oral solution. However, the solubility drops from 40 mg/mL at pH 3.5 to approximately 0.5 mg/mL at pH 6.5 in fasted state-simulated intestinal fluid. Therefore, the enhanced absorption associated with concomitant food intake observed in this study may result from increased GSK1322322 solubility in the lower pH, higher fluid volume environment, and longer gastric residence time of the fed stomach. Glucuronidation appears to be a major metabolic pathway but is unstable in the gastrointestinal tract, possibly because of low solubility at higher pH in the intestines.[12]

Previous studies had shown within-cohort variability of AUC and CL that could potentially be explained by differences in body weight.[10] In the current study, the cohorts were stratified by weight with most volunteers weighing <60 or >80 kg, the body weight groups that were less represented in previous studies. In general, CL (data not shown) and V_{area} (Figure 3A) increased, and correspondingly, $AUC_{0-\infty}$ and C_{max} decreased, with increase in body weight. However, this study is limited by the small population size, and further analysis, especially PK modeling based solely on data from IV administration, would be important to assess the need for a weight-based change in dosing scheme.

The present study was designed on the basis of PK data from previous phase I studies. To determine absolute bioavailabilities of oral GSK1322322 formulations in this study, PK parameters after 60-minute IV infusion of GSK1322322 1500 mg were assessed. This regimen resulted in linear PK at single-dose increases between 500 and 3000 mg. The $AUC_{0-\infty}$ (75.4 μg h/mL) and C_{max} (28.6 μg/mL) in this study (Table 1) were similar to the corresponding values of single 1500-mg doses reported in the first-time-in-human IV study (61.0 μg h/mL and 25.5 μg/mL, respectively).[10]

All AEs reported during the study were mild to moderate in intensity. One volunteer was withdrawn because of an AE (bronchospasm) during the IV administration period, which was drug related, resolved 3 minutes after the infusion was terminated, and required no medical treatment. Follow-up interviews with the individual revealed that the AE could have been associated with anxiety in receiving IV study medication. The quick resolution of the bronchospasm argues against a possible allergic reaction to the drug. Sensitivity of teeth was commonly reported across all treatments in this study. Sensitivity of teeth has been previously reported after administration of a single 3000-mg dose of GSK1322322, repeat dosing at 500 and 1000 mg (in an elderly cohort), and after 1500-mg IV administration (data on file).[10] The symptoms were mostly mild and resolved spontaneously. High rates of throat irritation and nausea were reported only after administration of the oral mesylate salt solution (52% and 26%, respectively), likely due to the apparent bad taste of the solution. Throat irritation and nausea were not observed with other formulations in this study and were not commonly reported in previous studies.[7–10]

In conclusion, this study demonstrated favorable PK and safety profiles for the free base tablet formulation of GSK1322322 1500 mg after intake of a moderate-fat/calorie meal, suggesting that GSK1322322 has the potential to become the first-in-class PDF inhibitor for clinical use as an oral tablet. Further interrogation of weight differences on PK parameters will be evaluated in future clinical programs.

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Disclosures

All authors are employees of GlaxoSmithKline and own GlaxoSmithKline stock. The authors have no additional financial disclosures.

References

1. Schmieder R, Edwards R. Insights into antibiotic resistance through metagenomic approaches. *Future Microbiol.* 2012; 7:73–89.
2. Davies J, Davies D. Origins and evolution of antibiotic resistance. *Microbiol Mol Biol Rev.* 2010;74:417–433.
3. Coates ARM, Halls G, Hu Y. Novel classes of antibiotics or more of the same? *Br J Pharmacol.* 2011;163:184–194.
4. Takeda M, Webster RE. Protein chain initiation and deformylation in *B. subtilis* homogenates. *Proc Natl Acad Sci USA.* 1968;60:1487–1494.
5. Sutcliffe JA. Antibiotics in development targeting protein synthesis. *Ann N Y Acad Sci.* 2011;1241:122–152.
6. Lewandowski T, Peters T, Simon N, Kulkarni S. Potent activity of GSK1322322 a novel peptide deformylase inhibitor in a *Haemophilus influenzae* and *Streptococcus pneumoniae* respiratory tract infection model. Poster presented at: 50th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; September 12–15, 2010; Boston, MA Poster F1-2115.
7. Naderer OJ, Dumont E, Zhu J, Kurtinecz M, Jones LS. Single-dose safety, tolerability, and pharmacokinetics of the antibiotic GSK1322322, a novel peptide deformylase inhibitor. *Antimicrob Agents Chemother.* 2013;57:2005–2009.
8. Naderer OJ, Dumont E, Zhu J, Kurtinecz M, Jones LS. Effect of H2 blockade and food on single-dose pharmacokinetics of GSK1322322, a peptide deformylase inhibitor antibacterial. *Antimicrob Agents Chemother.* 2013;57: 2556–2561.
9. Naderer OJ, Dumont E, Zhu J, Kurtinecz M, Jones LS. Safety, tolerability and pharmacokinetics of repeat dosing of the antibiotic GSK1322322, a peptide deformylase inhibitor: a randomized placebo-controlled study. *J Antimicrob Chemother.* 2013;68:1901–1909.
10. Naderer OJ, Jones LS, Zhu J, Kurtinecz M, Dumont E. Safety, tolerability, and pharmacokinetics of oral and intravenous administration of GSK1322322, a peptide deformylase inhibitor. *J Clin Pharmacol.* 2013;53: 1168–1176.
11. Zhu J, Naderer OJ, Dumont E, Tenero D. Pharmacokinetic–pharmacodynamic (PK–PD) and Monte Carlo simulation (MCS) analyses of GSK1322322 to evaluate the need for weight-based dosing and support dose selection for a phase IIb lung infection study. Poster presented at: 42nd Annual Meeting of the American College of Clinical Pharmacology; September 22–24, 2013; Bethesda, MD.
12. Mamaril-Fishman D, Zhu J, Lin M, et al. Investigation of metabolism and disposition of GSK1322322, a peptide deformylase inhibitor, in healthy humans using the entero-test for biliary sampling. *Drug Metab Dispos.* 2014;42: 1314–1325.