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Lack of Impact by SCY-078, a First-in-Class Oral Fungicidal Glucan Synthase Inhibitor, on the Pharmacokinetics of Rosiglitazone, a Substrate for CYP450 2C8, Supports the Low Risk for Clinically Relevant Metabolic Drug-Drug Interactions

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Abstract

SCY-078, the first in a new class of β 1,3-glucan synthesis inhibitors, is being developed as an oral and intravenous antifungal treatment for *Candida* and *Aspergillus* species fungal infections. In vitro, studies indicated SCY-078 is an inhibitor of cytochrome P450 (CYP) 2C8 with markedly lower effect over other CYP isozymes. To examine clinically relevant effects of the potential interaction with SCY-078, this phase 1, open-label, 2-period crossover study evaluated the pharmacokinetic parameters of rosiglitazone, a sensitive substrate of CYP2C8 metabolism, in the absence and presence of SCY-078 dosed to therapeutically relevant SCY-078 concentration exposure after repeat dosing. Healthy adult subjects were randomized to 2 treatment sequences: a single oral 4-mg rosiglitazone dose alone on day 1 or a 1250-mg SCY-078 loading dose on day 1 followed by a once-daily 750-mg SCY-078 dose for an additional 7 days (reflecting the clinical regimen evaluated during phase 2 studies for infections by *Candida* species) and concurrent administration of a single oral 4-mg rosiglitazone dose on day 3, before alternating following a $\geq$10-day washout. The exposure to SCY-078 observed in this study was in line with the intended exposure for treatment of invasive fungal infections. The 90% confidence intervals for rosiglitazone exposure geometric mean ratios were within the prespecified no effect interval of 0.70-1.43. Additionally, maximum concentration values for rosiglitazone and its metabolite, N–desmethylrosiglitazone, were not significantly affected by co-administration with SCY-078. Overall, rosiglitazone exposure was not impacted to a clinically meaningful extent with co-administration of therapeutically relevant SCY-078 concentration exposure after repeat dosing. The results are indicative of low risk for interaction of SCY-078 with drugs metabolized via the CYP family of enzymes.

Keywords

antifungal agent, CYP drug interaction, enfumafungin derivative, glucan synthase inhibitor, SCY-078

Morbidity and mortality associated with invasive *Candida* and *Aspergillus* species fungal infections remains a cause for concern in the health-care environment; candidemia is reported to be the third or fourth most common cause of health-care–associated bloodstream infection in US hospitals.[1,2] Three main classes of antifungal agents are currently available for the treatment of these invasive infections: azoles, polyenes, and echinocandins.[3] However, the emergence of strains that are resistant to azoles and echinocandins indicates the need for new agents that retain activity against resistant strains.[4,5]

SCY-078, an enfumafungin derivative, represents the first compound of the triterpenoid class of β 1,3-glucan synthesis inhibitors in development for the treatment of fungal infections.[6] SCY-078 was documented to have potent in vitro activity against *Candida* and *Aspergillus* species clinical isolates, and retained activity against azole-resistant, most echinocandin-resistant, and multidrug-resistant strains of *Candida* species.[7–10] SCY-078 recently met primary end points in two phase 2 clinical studies in invasive candidiasis and vulvovaginal candidiasis,[11,12] which evaluated a 1250-mg loading dose on day 1 followed by once-daily doses of 750 mg. A loading dose strategy was employed to achieve a therapeutically relevant antifungal concentration in plasma on the first day of treatment, as early target attainment has been correlated with improved patient outcomes.[1]

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Thus, this novel antifungal agent represents a new class of non-azole, orally bioavailable treatment for *Candida* and *Aspergillus* species infections, having the potential to treat multidrug-resistant fungal isolates.[6]

In vitro, SCY-078 was shown to be a possible inhibitor of cytochrome P450 (CYP) 2C8 (CYP2C8; 50% inhibitory concentration [IC_{50}] ~0.3 μM) and a substrate for CYP3A4. The potential for SCY-078 to inhibit other CYP isoforms is weaker, as IC_{50} values were >5-fold higher (Wring SA, Park SM, unpublished data on file). Therefore, the purpose of this study was to examine the clinically relevant effects of any interaction of SCY-078 with drugs metabolized by CYP2C8, reflecting the highest potential for a CYP-mediated drug-drug interaction. Regulatory guidance published by the US Food and Drug Administration suggests that repaglinide may be employed as a sensitive substrate of CYP2C8 metabolism; however, it is also a substrate of the drug transporter organic anion transporting polypeptide 1B1 and is not, therefore, recommended for clinical drug-drug interaction studies if potential interactions between the coadministered drug and the transporter have not been fully elucidated.[13] As an alternative, rosiglitazone, a thiazolidinedione antidiabetic agent, is a sensitive substrate of CYP2C8 metabolism and is not impacted by drug transporter interactions.[14,15] As no clinical interaction studies have been performed between SCY-078 and organic anion transporting polypeptide 1B1substrates, rosiglitazone was selected as the prototypical substrate for the current study. Rosiglitazone is metabolized primarily by CYP2C8 via N-demethylation and *p*-hydroxylation and has been used as a prototypical substrate to assess potential drug-drug interactions with potential inhibitors of this CYP isoform.[15–17] These studies typically assess the impact of potential CYP2C8 inhibitors on the pharmacokinetics (PK) of rosiglitazone and on the formation of its metabolite, N-desmethylrosiglitazone. As SCY-078 is a potential inhibitor of CYP2C8 in vitro and peak plasma concentration of SCY-078 following administration of the proposed therapeutic dosing regimen is expected to be in the range of potentially inhibitory concentration,[11,12] the present study was performed to determine the potential of SCY-078 to decrease the metabolism of drugs that are primarily metabolized by CYP2C8 in vivo. SCY-078 is not metabolized by CYP2C8 and is not considered at risk of being a victim of drug-drug interactions on co-administration with CYP2C8 substrates or inhibitors. Therefore, the objective of this study was to compare the plasma PK parameters of rosiglitazone and its metabolite, N-desmethylrosiglitazone, when rosiglitazone was administered alone and when it was coadministered with SCY-078 dosed to therapeutically relevant SCY-078 concentration exposure after repeat dosing.

Methods

Study Design

The study protocol and other study documents, including written informed consent forms, received approval from the IntegReview Institutional Review Board (3815 S. Capital of Texas Highway, Suite 320, Austin, Texas 78704) before the study was initiated. All subjects provided written informed consent before participating in the study, which was obtained in adherence with Good Clinical Practice. The study was conducted in full compliance with the principles of the Declaration of Helsinki, International Conference on Harmonization guidelines, and all applicable US Code of Federal Regulations.

This was a phase 1, open-label, 2-period crossover study conducted in healthy adult male and female subjects. Subjects were randomly assigned to a treatment sequence (AB or BA), using a computer-generated randomization schedule, and were studied in 2 periods (period 1 and period 2) separated by a minimum washout of 10 days. After the washout period, subjects crossed over and received the alternate treatment (Figure 1).

Treatment A. Treatment A was a single oral 4-mg dose of rosiglitazone maleate (GlaxoSmithKline; 1 × 4-mg capsule) administered alone on day 1. Blood samples for PK analysis of rosiglitazone and its metabolite, N-desmethylrosiglitazone, were collected prior to dosing (time 0) and at 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, and 120 hours after dosing.

Treatment B. Treatment B was an oral 1250-mg loading dose of SCY-078 citrate (SCYNEXIS, Inc.; 5 × 250-mg tablets) on day 1, followed by a once-daily 750-mg dose of SCY-078 citrate (3 × 250-mg tablets) for an additional 7 days. On day 3 of treatment B, subjects also received concurrent administration of a single oral 4-mg dose of rosiglitazone. Blood samples for PK analysis of SCY-078 were collected prior to dosing (day 1, time 0) and at 0.5, 1, 2, 4, 6, 8, 12, 16, and 24 hours after dosing and prior to dosing (day 3) and at 0.5, 1, 2, 4, 6, 8, 12, and 16 hours after dosing. Blood samples for PK analysis of rosiglitazone and its metabolite, N-desmethylrosiglitazone, were collected prior to dosing (day 3, time 0) and at 0.5, 1, 2, 4, 6, 8, 12, 16, 24 (day 4), 36, 48 (day 5), 72 (day 6), 96 (day 7), and 120 (day 8) hours after dosing. Blood samples for determination of trough SCY-078 concentrations were collected prior to dosing (on days 4, 5, 6, 7, and 8).

Study Procedure. For both treatment A and B, subjects were admitted to the clinical site on the evening of day −1 of each period. Subjects were required to remain at the clinic for at least 72 hours after dosing or until discharged and were required to return

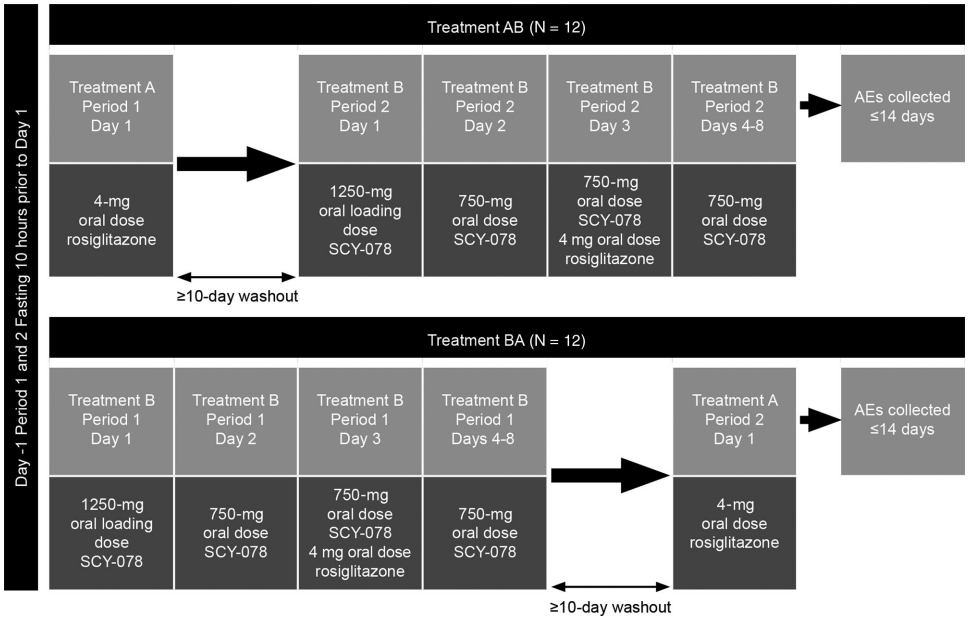

Figure 1. Treatment sequence flow diagram. AE, adverse event.

to the clinic for subsequent doses and blood sample collections. On dosing days, study medications were administered to subjects in a fasted state. Subjects were required to fast (except for water) for 10 hours prior to dosing with rosiglitazone and SCY-078. Water was restricted for 1 hour before until 1 hour after drug administration.

While in the research facility, meals were provided at 4 and 10 hours after dosing and a snack was offered at 7 and 13 hours after dosing. For each treatment period, the timing, composition, and calorie content of meals were equivalent. After the 24-hour postdose procedures were complete, the timing, consumption, and calorie content of meals were unrestricted.

Approximately 2 weeks prior to administration of the initial dose of the study drug, throughout the study, and until the post-study visit, subjects were required to refrain from consumption of grapefruit juice, grapefruits, grapefruit products, star fruit, blood oranges, apple juice and mulberry juice, vegetables from the mustard green family, and charbroiled meats. Subjects were also required to refrain from alcohol within 1 week prior to the administration of the initial dose of the study drug, throughout the study, and until the final study visit day; refrain from consumption of caffeinated beverages for 48 hours prior to clinical admission and throughout the study; refrain from consumption of all juices 24 hours prior to and 24 hours after administration of study drug on PK sampling days; refrain from smoking throughout the study and post-study evaluation; and avoid all unusual or strenuous activity from the screening visit, throughout the study, and until the post-study visit.

Study Population

Inclusion Criteria. The study population consisted of healthy (based on medical history, physical examination, vital sign measurements, laboratory safety tests, and 12-lead electrocardiograms at screening and/or prior to administration of the initial dose of the study drug), male and female volunteers aged 18-50 years (inclusive), with a body mass index of ≤ 32 kg/m^2, at screening. Subjects were nonsmokers who had not used nicotine or nicotine-containing products for at least 6 months. Female subjects were not to be pregnant and highly unlikely to become pregnant; male subjects must have been unlikely to impregnate a partner. All subjects were willing to comply with the study restrictions and participate for the full length of the study.

Exclusion Criteria. Subjects with an estimated creatinine clearance ≤ 80 mL/min, a history of macular edema or heart failure, or who were at risk of QT prolongation or torsade de pointes, were excluded from the study. Additionally, subjects with a history of stroke, chronic seizures, major neurological disorders, or clinically significant endocrine, gastrointestinal, cardiovascular, hematologic, immunologic, renal, respiratory, metabolic, dermatologic, or genitourinary abnormalities or diseases, or neoplastic disease, were excluded from the study, as were subjects with a history of liver disease or clinically significant elevated liver enzymes. Also excluded were subjects who had major surgery or lost 1 unit of blood within 4 weeks prior to screening or who have multiple allergies or allergies to rosiglitazone or its inactive ingredients.

Prior to the initial administration of the study drug and throughout the study until the post-study visit, subjects refrained from the use of any medication (including prescription and nonprescription drugs or herbal remedies). All medications taken within 28 days prior to randomization and until 14 days after the last dose of study medication were recorded.

Pharmacokinetic Sample Analysis

Blood samples collected after 24 hours after dosing could have been taken up to ±15 minutes from the scheduled time points. All samples were collected in tubes containing dipotassium ethylenediaminetetraacetic acid to ensure stability of SCY-078 in human plasma. Samples were centrifuged at 2000 g within 2 hours of collection, frozen within 1 hour of centrifugation, and stored at approximately −70°C before analysis. SCY-078, rosiglitazone, and N-desmethylrosiglitazone concentrations in the plasma samples were determined by Agilux Laboratories (Worcester, Massachusetts) using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods.

Safety Analysis

Safety and tolerability were monitored by clinical assessment of adverse experiences and by clinical and laboratory measurements, including vital signs (heart rate, blood pressure, respiratory rate and temperature), physical examinations, 12-lead electrocardiograms, and standard laboratory safety tests (hematology, coagulation, chemistry, and urinalysis). Adverse events (AEs) were collected from the time of informed consent until 14 days after the last dose of study medication.

Statistical Analyses

Statistical analysis was performed with SAS Version 9.3 (SAS Institute, Cary, North Carolina). Primary and secondary PK end points in this study included AUC and maximum observed plasma concentration (C_{max}) values for rosiglitazone. Overall, drug exposure (ie, AUC) was considered to be the most relevant PK parameter for this study.

It is considered that AUC and C_{max} parameters for SCY-078, rosiglitazone, and N-desmethylrosiglitazone are likely to be log-normally distributed; therefore, these variables were log transformed before analysis.[18] Confidence intervals (CIs) constructed for PK parameters were based on a linear mixed effects model containing a fixed effect for treatment and a random effect for subject.

A 90%CI was generated from the above linear mixed effect model for the AUC geometric mean ratio (GMR; test [rosiglitazone coadministered with SCY-078]/reference [rosiglitazone alone]) and compared with the prespecified interval (0.70-1.43). The hypothesis that the co-administration of the therapeutic dose regimen of SCY-078 does not alter the single-dose of rosiglitazone 4 mg in a clinically meaningful manner would be supported if the 90%CI for the rosiglitazone AUC GMR (test/reference) was contained within the interval (0.70-1.43).[16] Similar analysis was applied to C_{max}, with a point estimate and 90%CI provided for the C_{max} GMR (test/reference).

Determination of Population Size. Assuming an expected mean exposure ratio of 1.20 for test/reference and an intrasubject coefficient of variation percentage (CV%) of 24%, a sample size of 24 subjects was considered sufficient to achieve the 90%CIs within the interval of 0.70-1.43 on the GMRs for plasma rosiglitazone AUC.[15] Discontinued subjects were not replaced in this study, as a sample size of 17 subjects was anticipated to be adequate to address the primary study objective and achieve the expected GMR and 90%CIs. Based on the observed GMRs and variability in the 17 subjects included in the PK analyses, the beta value was >0.90 for 0.70-1.43 boundaries, as well as for 0.80-1.25 boundaries for the AUC of rosiglitazone and N-desmethylrosiglitazone and for C_{max} of N-desmethylrosiglitazone. The C_{max} for rosiglitazone was more variable than for the N-desmethyl metabolite and the beta value for rosiglitazone C_{max} based on 17 subjects was 0.65.

Safety Analyses. All AEs were tabulated for each SCY-078 dose at the relevant time points. AEs were coded using the most recent version of the Medical Dictionary for Regulatory Activities.

Bioanalysis of Plasma Samples. Samples were provided to Agilux Laboratories, Inc. (Worchester, Massachusetts) for bioanalysis. All samples were assayed using Good Laboratory Practices-validated reversed-phase LC-MS/MS methods and utilized calibration standards, quality controls, study samples. Incurred sample re-analyses met acceptance criteria. SCY-078 plasma samples were analyzed for the presence of SCY-078 according to Agilux Laboratories' Method BAC-SI-L001 "Analysis of SCY-078 in K2EDTA Human Plasma by LC-MS/MS." Additional plasma samples were analyzed for the presence of rosiglitazone and N-desmethylrosiglitazone according to Agilux Laboratories Method BAC-AG-L011, "Analysis of Rosiglitazone and its Metabolite N-Desmethyl Rosiglitazone in Human K2EDTA Plasma by LC-MS/MS." The lower limit of quantitation (LLOQ) for the LC-MS/MS method for rosiglitazone and N-desmethylrosiglitazone in human plasma was 0.500 ng/mL and for SCY-078 in human plasma

Table 1. Baseline Demographics of Study Subjects

Characteristic	Total (n = 24)
Age, years, mean (SD)	34.2 (8.5)
Sex, n (%)	
Male	17 (70.8)
Female	7 (29.2)
Race, n (%)	
American Indian or Alaska Native	1 (4.2)
White	16 (66.7)
Black or African American	7 (29.2)
Ethnicity, n (%)	
Hispanic or Latino	13 (54.2)
Not Hispanic or Latino	11 (45.8)
Body mass index, kg/m^2, mean (SD)	26.1 (3.74)

SD, standard deviation.

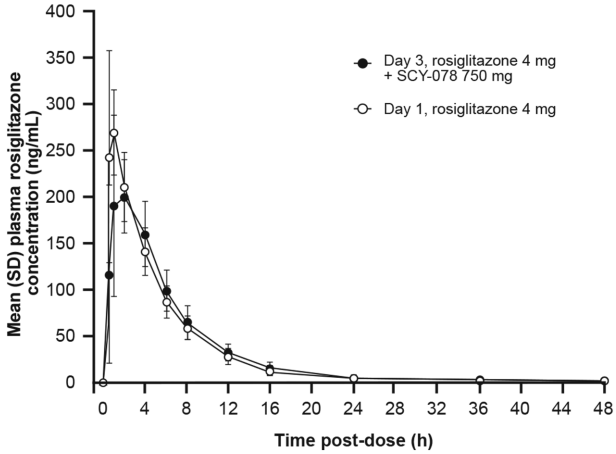

Figure 2. Mean (SD) plasma rosiglitazone concentration-time profile following a single dose of rosiglitazone 4 mg (administered alone on day 1) or when a single dose of rosiglitazone 4 mg was co-dosed on day 3 with a SCY-078 dose regimen of 1250 mg on day 1 followed by 750 mg daily (ie, steady-state SCY-078 exposure) (linear plot, 0-48 hours x-axis), rosiglitazone PK population (n = 17). PK, pharmacokinetic; SD, standard deviation.

was 5.00 ng/mL. All samples were collected, stored, and assayed under conditions demonstrated to provide analyte stability during validation studies. All performance characteristics were within acceptable limits.

Results

Study Population

A total of 24 subjects were enrolled in the study and randomized to treatment; 21 subjects received all planned treatment doses; 20 subjects completed all study procedures. One subject received all treatment but did not return for the post-study visit and was considered lost to follow-up, two subjects withdrew from the study after receiving the loading dose of 1250 mg SCY-078, and one subject was discontinued due to a positive cotinine test prior to period 2, having received 1 dose of 4-mg rosiglitazone. The baseline demographic characteristics of study subjects are shown in Table 1.

Pharmacokinetics of Rosiglitazone Following a Single Dose Administered Alone and When Coadministered With Repeat Doses of SCY-078

Plasma concentration-time profiles for rosiglitazone following a single 4-mg dose of rosiglitazone (day 1) and when coadministered with SCY-078 dosed to therapeutically relevant SCY-078 concentration exposure after repeat dosing (day 3) are shown in Figure 2. Rosiglitazone PK parameters and results of statistical analyses of rosiglitazone PK parameters following administration alone and when coadministered with SCY-078 are shown in Table 2.

Administration of rosiglitazone alone resulted in a geometric mean AUC of 1464 μg·hr/mL, C_{max} of 295.1 ng/mL, area under the plasma concentration-time curve from 0 to 24 hours after dose administration ($AUC_{0\text{-}24h}$) of 1445 μg·hr/mL, and a median time point where C_{max} is observed (T_{max}) of 0.5 hours. Rosiglitazone co-administrated with SCY-078 resulted in a geometric mean AUC of 1454 μg·hr/mL, C_{max} of 234.6 ng/mL, $AUC_{0\text{-}24h}$ of 1420 μg·hr/mL, and a median T_{max} of 1.0 hours (Table 2).

Least squares mean values based on test/reference GMR (90%CI) results of AUC, C_{max}, and $AUC_{0\text{-}24h}$ were 0.99 (0.90-1.10), 0.80 (0.70-0.90), and 0.98 (0.89-1.08), respectively (Table 2). These GMRs and upper 90%CI values were within the prespecified interval of 0.70-1.43, indicating that these rosiglitazone parameters were not significantly affected by co-administration with SCY-078. The median T_{max} when rosiglitazone was coadministered with SCY-078 was 1 hour compared with 0.5 hours when rosiglitazone was administered alone. This difference was statistically significant ($P < .001$) but not considered clinically meaningful (Table 2).

Pharmacokinetics of N-Desmethylrosiglitazone Following a Single Dose of Rosiglitazone Administered Alone and When Coadministered With Repeat Doses of SCY-078

Plasma concentration-time profiles for N-desmethylrosiglitazone following a single 4-mg dose of rosiglitazone (day 1) and when coadministered with SCY-078 dosed to therapeutically relevant SCY-078 concentration exposure after repeat dosing (day 3) are shown in Figure 3. N-desmethylrosiglitazone PK parameters and results of statistical analyses of N-desmethylrosiglitazone PK parameters following administration alone and when coadministered with SCY-078 are shown in Table 3.

N-desmethylrosiglitazone PK parameters following administration of rosiglitazone alone were a geometric mean AUC of 2188 μg·hr/mL, C_{max} of 72.8 ng/mL,

Table 2. Rosiglitazone PK Parameters and Statistical Analyses of Single-Dose Rosiglitazone Administered Alone on Day 1 and When Single-Dose Rosiglitazone Was Coadministered on Day 3 With SCY-078 Dose Regimen of 1250 mg on Day 1 Followed by 750 mg Daily (ie, Steady-State SCY-078 Exposure)

Parameter	Rosiglitazone 4 mg, Day 1 (n = 17)	Rosiglitazone 4 mg + SCY-078 750 mg, Day 3 (n = 17)	GMR[a] Rosiglitazone + SCY-078 vs Rosiglitazone Alone	*P* Value[b]
AUC, μg·hr/mL[c]	1464 (16.3)	1454 (18.0)	0.99 (0.90-1.10)	
$AUC_{0\text{-}24h}$, μg·hr/mL[c]	1445 (16.0)	1420 (17.3)	0.98 (0.89-1.08)	
$AUC_{0\text{-}last}$, μg·hr/mL[c]	1454 (16.3)	1442 (18.3)	0.99 (0.90-1.10)	
AUC_%Extrap_obs, %[c]	0.58 (74.3)	0.71 (62.2)		
C_{max}, ng/mL[c]	295.1 (18.5)	234.6 (23.3)	0.80 (0.70-0.90)	
$t_{½}$, h[d]	3.7 (0.5)	4.6 (1.2)		
T_{max}, h[e]	0.5 (0.5, 1.0)	1.0 (0.5, 4.0)		.0005

AUC, area under the plasma concentration-time curve from 0 to infinity; $AUC_{0\text{-}24h}$, area under the plasma concentration-time curve from 0 to 24 hours after dose administration; $AUC_{0\text{-}last}$, area under the plasma concentration-time curve from 0 to last quantifiable concentration; AUC_%Extrap_obs, area under the plasma concentration-time curve extrapolated from time *t* to infinity as a percentage of total AUC; CI, confidence interval; C_{last}, last quantifiable plasma concentration; C_{max}, maximum observed plasma concentration; CV%, coefficient of variation percentage; GMR, geometric mean ratio; PK, pharmacokinetic; SD, standard deviation; $t_{1/2}$, terminal elimination half-life; T_{last}, time to C_{last}; T_{max}, time point where C_{max} was observed.

[a]Geometric mean ratio (90%CI).

[b]*P* value calculated by Wilcoxon signed-rank test.

[c]Geometric mean (CV%) unless otherwise stated.

[d]Mean (SD).

[e]Median (minimum, maximum).

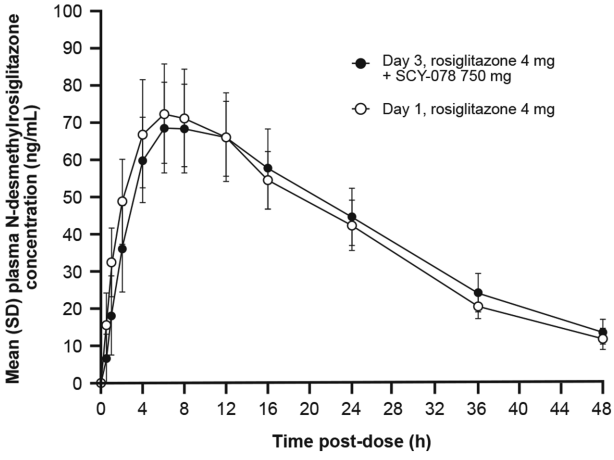

Figure 3. Mean (SD) plasma N-desmethylrosiglitazone concentration-time profile following a single dose of rosiglitazone 4 mg (administered alone on day 1) or when a single dose of rosiglitazone 4 mg was co-dosed on day 3 with a SCY-078 dose regimen of 1250 mg on day 1 followed by 750 mg daily (ie, steady-state SCY-078 exposure) (linear plot, 0-48 hours x-axis), rosiglitazone PK population (n = 17). PK, pharmacokinetic; SD, standard deviation.

$AUC_{0\text{-}24h}$ of 1342 μg·hr/mL, and a median T_{max} of 6.0 hours. Rosiglitazone co-administrated with SCY-078 resulted in an N-desmethylrosiglitazone geometric mean AUC of 2260 μg·hr/mL, C_{max} of 70.4 ng/mL, $AUC_{0\text{-}24h}$ of 1306 μg·hr/mL, and a median T_{max} of 8.0 hours (Table 3).

Least squares mean values based on test/reference GMR (90%CI) results of AUC, C_{max}, and $AUC_{0\text{-}24h}$ were 1.03 (0.95-1.12), 0.97 (0.88-1.07), and 0.97 (0.89-1.06), respectively (Table 3). These GMRs and upper 90%CI values were within the prespecified interval of 0.70-1.43, indicating that these N-desmethylrosiglitazone parameters were not significantly affected when rosiglitazone was coadministered with SCY-078. Median T_{max} for N-desmethylrosiglitazone was slightly delayed when rosiglitazone was coadministered with SCY-078 compared with that of rosiglitazone administration alone, although this was not considered clinically meaningful (Table 3).

Pharmacokinetics of SCY-078 Following a Single 1250-mg Loading Dose of SCY-078 (Day 1) and Following Further Daily 750-mg Doses of SCY-078 (Days 2 and 3)

Administration of a 1250-mg loading dose of SCY-078 (day 1) resulted in a geometric mean (CV%) $AUC_{0\text{-}24h}$ of 11.64 (38.8) μg·hr/mL, consistent with the target antifungal exposure evaluated in phase 2 studies and the efficacy target was based on in vivo murine models for invasive fungal infections with *Candida* species is 11.2 $\mu g \cdot h^2$/mL.[6] Values for C_{max} of 0.783 (36.2) μg/mL, plasma concentration at 24 hours post-dose (C_{24h}) of 0.294 (49.7) μg/mL, and median T_{max} of 6.0 hours. A loading dose strategy was employed for consistency with phase 2 studies designed to achieve a therapeutically relevant antifungal concentration in plasma on the first day of treatment.

Two additional daily doses of 750-mg SCY-078 (days 2 and 3) resulted in a geometric mean (CV%) $AUC_{0\text{-}24h}$ of 14.82 (42.9) μg·hr/mL, C_{max} of 0.934 (43.3) μg/mL, C_{24h} of 0.385 (44.3) μg/mL, and median

Table 3. N-Desmethylrosiglitazone PK Parameters and Statistical Analyses Following Single-Dose Rosiglitazone Administered Alone on Day 1 and When Single-Dose Rosiglitazone Was Coadministered on Day 3 With a SCY-078 Dose Regimen of 1250 mg on Day 1 Followed by 750 mg Daily (ie, Steady-State SCY-078 Exposure)

Parameter	Rosiglitazone 4 mg, Day 1 (n = 17)	Rosiglitazone 4 mg + SCY-078 750 mg, Day 3 (n = 17)	GMR[a] Rosiglitazone + SCY-078 vs Rosiglitazone Alone	*P* Value[b]
AUC, μg·hr/mL[c]	2188 (12.2)	2260 (15.5)	1.03 (0.95-1.12)	
$AUC_{0\text{-}24h}$, μg·hr/mL[c]	1342 (14.5)	1306 (14.8)	0.97 (0.89-1.06)	
$AUC_{0\text{-}last}$, μg·hr/mL[c]	2166 (12.3)	2238 (15.7)	1.03 (0.95-1.12)	
AUC_%Extrap_obs, %[c]	0.91 (52.4)	0.90 (45.6)		
C_{max}, ng/mL[c]	72.8 (17.6)	70.4 (16.4)	0.97 (0.88-1.07)	
$t_{½}$, h[d]	14.5 (2.4)	15.2 (2.3)		
T_{max}, h[e]	6.0 (4.0, 12.0)	8.0 (6.0, 16.0)		.1440

AUC, area under the plasma concentration-time curve from 0 to infinity; $AUC_{0\text{-}24h}$, area under the plasma concentration-time curve from 0 to 24 hours after dose administration; $AUC_{0\text{-}last}$, area under the plasma concentration-time curve from 0 to last quantifiable concentration; AUC_%Extrap_obs, area under the plasma concentration-time curve extrapolated from time *t* to infinity as a percentage of total AUC; CI, confidence interval; C_{last}, last quantifiable plasma concentration; C_{max}, maximum observed plasma concentration; CV%, coefficient of variation percentage; GMR, geometric mean ratio; PK, pharmacokinetic; SD, standard deviation; $t_{1/2}$, terminal elimination half-life; T_{last}, time to C_{last}; T_{max}, time point where C_{max} was observed.

[a]Geometric mean ratio (90%CI).

[b]*P* value calculated by Wilcoxon signed-rank test.

[c]Geometric mean (CV%) unless otherwise stated.

[d]Mean (SD).

[e]Median (minimum, maximum).

T_{max} of 6.0 hours. Average trough levels of approximately 0.418-0.533 μg/mL were achieved on days 4-8.

Safety and Tolerability

Overall, rosiglitazone in the presence and absence of repeat doses of SCY-078 was generally well tolerated. The most common treatment-emergent AEs were diarrhea (14 subjects, 58.3%), abdominal pain (10 subjects, 41.7%), nausea (10 subjects, 41.7%), vomiting (6 subjects, 25%), headache (4 subjects, 16.7%), dizziness (2 subjects, 8.3%), somnolence (2 subjects, 8.3%), menstruation irregularity (3 subjects, 12.5%), and contact dermatitis (2 subjects, 8.3%). All treatment-emergent AEs were mild or moderate in intensity; there were no serious AEs reported during the study and no deaths. The majority of gastrointestinal AEs were self-limiting and associated with the loading dose of SCY-078.

Discussion

Emerging strains of invasive fungi *Candida* and *Aspergillus* species that are resistant to one or both of the main classes of antifungal agents, azoles and echinocandins, signify the need for new agents for the treatment of these life-threatening infections.[4,5] An enfumafungin derivative being developed for the treatment of fungal infections, SCY-078, retains activity against azole-resistant and most echinocandin-resistant strains in vitro and, as such, could represent an important alternative for the treatment of *Candida* and *Aspergillus* species infections.[7–9]

SCY-078 is an in vitro inhibitor of CYP2C8 (IC_{50} for inhibition of CYP2C8-mediated N-desethylamodiaquine activity ~0.3 μM) and a substrate for CYP3A4; in vitro CYP450 interaction data indicated a low risk of interaction with other CYP isoforms (Wring SA, Park SH, unpublished data on file). The maximum concentration of SCY-078 in plasma on day 3 for the once-daily oral dose regimen (after a loading oral dose of 1250 mg on day 1 and further repeat daily oral doses of 750-mg SCY-078 on days 2 and 3 to subjects who fasted overnight) in the current study was ~0.93 μg/mL (1.28 μM). This value exceeds the in vitro IC_{50} by approximately 4-fold, although the corresponding unbound concentration in plasma (based on 99.7% binding to plasma proteins) is markedly lower, at ~3% of the IC_{50}.[6] Thus, although in vitro data indicated that interaction with CYP2C8 substrates is possible based on total levels, they were considered unlikely based on unbound drug levels. To examine the clinically relevant effects of the potential interaction of SCY-078 with drugs metabolized via CYP2C8, the objective of this phase 1 study was to compare the PK parameters of rosiglitazone, a sensitive substrate of CYP2C8 metabolism, in the presence and absence of therapeutically relevant SCY-078 concentration exposure after repeat dosing in healthy subjects.

The primary objective of the study was to compare the plasma AUC of rosiglitazone after a single oral rosiglitazone dose and when coadministered with repeat doses of SCY-078. The results of this study show that co-administration of rosiglitazone with therapeutically relevant SCY-078 concentration exposure after

repeat dosing had no effect on rosiglitazone exposure compared with administration of rosiglitazone alone. In addition, maximum concentration values for rosiglitazone and its metabolite, N-desmethylrosiglitazone, were similar with co-administration of repeat dose SCY-078. Although there was a slight delay in rosiglitazone and N-desmethylrosiglitazone T_{max} with co-administration of repeat dose SCY-078, this appeared clinically insignificant. SCY-078 was well absorbed following the loading dose and repeated daily doses and rosiglitazone, in the presence and absence of repeat dose SCY-078, was generally well tolerated. A loading dose strategy was employed for consistency with phase 2 studies designed to achieve a therapeutically relevant antifungal concentration in plasma on the first day of treatment. Two additional daily doses of 750-mg SCY-078 (days 2 and 3) resulted in somewhat higher geometric mean (CV%) $AUC_{0\text{-}24h}$ of 14.82 (42.9) μg·hr/mL and C_{max} of 0.934 (43.3) μg/mL values. This does not negatively influence the primary result of this study, that therapeutically relevant exposures after repeat doses of SCY-078 do not inhibit rosiglitazone, a substrate drug cleared by CYP2C8 metabolism.

In vitro CYP450 interaction data indicated a 5- to 16-fold lower risk of interaction of SCY-078 with other CYP isoforms (Wring SA, Park SM, unpublished data on file). Indeed, no clinically relevant interaction was observed in a recent phase 1 drug-drug interaction study between SCY-078 and the CYP3A and P-glycoprotein substrate tacrolimus.[19] The absence of interaction with rosiglitazone, a sensitive probe of CYP2C8, along with the in vitro data demonstrating lower risk for interaction with other CYP isoforms and the results from the recent tacrolimus interaction study[19] indicate a low risk of clinically meaningful interaction when SCY-078 is coadministered at therapeutically relevant repeat dose exposures with drugs metabolized via the CYP450 pathway. This is particularly relevant considering that the only oral antifungal agents currently available for the treatment of invasive fungal infections, azoles, are known inhibitors of the CYP450 metabolic pathway, complicating the management of patients with these severe infections, who are often receiving multiple drugs.

Conclusions

Overall, the results from this study demonstrated that rosiglitazone, a sensitive CYP2C8 substrate, and N-desmethylrosiglitazone plasma PKs were not affected to a clinically meaningful extent in the presence of therapeutically relevant SCY-078 concentration exposure after repeat dosing of SCY-078. As SCY-078 elicits markedly weaker inhibitory potential of other CYP enzymes, the current study suggests a low risk for interaction with drugs metabolized via the CYP family of enzymes.

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Disclosures

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