Pharmacodynamic Target Evaluation of a Novel Oral Glucan Synthase Inhibitor, SCY-078 (MK-3118), Using an *In Vivo* Murine Invasive Candidiasis Model

Alexander J. Lepak, Karen Marchillo, David R. Andes

University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA

Echinocandins inhibit the synthesis of β -1,3-D-glucan in *Candida* and are the first-line therapy in numerous clinical settings. Their use is limited by poor oral bioavailability, and they are available only as intravenous therapies. Derivatives of enfumafungin are novel orally bioavailable glucan synthase inhibitors. We performed an *in vivo* pharmacodynamic (PD) evaluation with a novel enfumafungin derivative, SCY-078 (formerly MK-3118), in a well-established neutropenic murine model of invasive candidiasis against *C. albicans*, *C. glabrata*, and *C. parapsilosis*. The SCY-078 MICs varied 8-fold. Oral doses of 3.125 to 200 mg/kg SCY-078 salt in sterile water produced peak levels of 0.04 to 2.66 $\mu\text{g/ml}$, elimination half-lives of 5.8 to 8.5 h, areas under the concentration-time curve from 0 to 24 h ($\text{AUC}_{0-24\text{ h}}$) of 0.61 to 41.10 $\mu\text{g} \cdot \text{h/ml}$, and AUC from 0 to infinity ($\text{AUC}_{0-\infty}$) values of 0.68 to 40.31 $\mu\text{g} \cdot \text{h/ml}$. The pharmacokinetics (PK) were approximately linear over the dose range studied. Maximum response (E_{max}) and PK/PD target identification studies were performed with 4 *C. albicans*, 4 *C. glabrata*, and 3 *C. parapsilosis* isolates. The PD index AUC/MIC was explored by using total (tAUC) and free (fAUC) drug concentrations. The maximum responses were 4.0, 4.0, and 4.3 $\log_{10}$ CFU/kidney reductions for *C. albicans*, *C. glabrata*, and *C. parapsilosis*, respectively. The AUC/MIC was a robust predictor of efficacy (R^2 , 0.53 to 0.91). The 24-h PD targets were a static dose of 63.5 mg/kg, a tAUC/MIC of 500, and an fAUC/MIC of 1.0 for *C. albicans*; a static dose of 58.4 mg/kg, a tAUC/MIC of 315, and an fAUC/MIC of 0.63 for *C. glabrata*; and a static dose of 84.4 mg/kg, a tAUC/MIC of 198, and an fAUC/MIC of 0.40 for *C. parapsilosis*. The mean fAUC/MIC values associated with a 1-log kill endpoint against these species were 1.42, 1.26, and 0.91 for *C. albicans*, *C. glabrata*, and *C. parapsilosis*, respectively. The static and 1-log kill endpoints were measured relative to the burden at the start of therapy. The static and 1-log kill doses, as well as the total and free drug AUC/MIC PD targets, were not statistically different between species but were numerically lower than those observed for echinocandins. SCY-078 is a promising novel oral glucan synthase inhibitor against *Candida* species, and further investigation is warranted.

Candida species are the most commonly encountered fungal pathogens in the hospital setting, are the fourth most common cause of nosocomial bloodstream infection, and are associated with the highest mortality rates among infections caused by bloodstream isolates (1–3). In recent years, the etiological species has shifted in the United States and other parts of the world (3–5). Currently, non-*albicans* *Candida* species are implicated in >50% of cases of invasive candidiasis (IC) in the United States. This epidemiological shift has important treatment implications, as triazoles have limited effectiveness against some of these emerging non-*albicans* species, with resistance rates of up to 5% (6).

A major medical advance in fungal therapeutics was the development of the echinocandin drug class, which targets cell wall glucan synthesis, a major cell wall structural component in *Candida* species (7–10). The echinocandins provide coverage for a broad range of *Candida* species, including *C. glabrata*. Clinically, outcomes in patients treated with echinocandins against various forms of candidiasis, including IC, have demonstrated the equivalence or superiority of these compounds versus triazoles or amphotericin B (1, 11). Therefore, they have become the preferred therapeutic option in numerous clinical scenarios when *Candida* species are the infecting pathogen.

The large chemical structure (each ~1,200 kDa) likely reduces the oral bioavailability of the current echinocandins. Therefore, only intravenous formulations of each of the three approved echinocandins are available for clinical use. The development of glucan synthase inhibitors that can be administered orally would rep-

resent a major step forward by providing a simple therapy transition to the ambulatory setting. The goal of the current studies was to identify the pharmacodynamic (PD) target for a novel oral glucan synthase inhibitor, SCY-078 (formerly MK-3118), an enfumafungin derivative under clinical development, against the three most commonly encountered *Candida* species, *C. albicans*, *C. glabrata*, and *C. parapsilosis*, using an *in vivo* neutropenic murine model of disseminated candidiasis.

MATERIALS AND METHODS

Antifungal agent. The oral glucan synthase inhibitor SCY-078 was obtained from Merck as a preliminary salt in powder form, and drug formulations for administration were prepared in sterile distilled water. The formulations were typically suspensions, indicating that future formulation optimization may enhance exposure.

Received 30 September 2014 Returned for modification 29 November 2014
Accepted 7 December 2014

Accepted manuscript posted online 15 December 2014

Citation Lepak AJ, Marchillo K, Andes DR. 2015. Pharmacodynamic target evaluation of a novel oral glucan synthase inhibitor, SCY-078 (MK-3118), using an *in vivo* murine invasive candidiasis model. Antimicrob Agents Chemother 59:1265–1272. doi:10.1128/AAC.04445-14.

Address correspondence to David R. Andes, dra@medicine.wisc.edu.

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doi:10.1128/AAC.04445-14

TABLE 1 *In vitro* susceptibilities of select *Candida* isolates to SCY-078 and *in vivo* fitness in the neutropenic murine invasive candidiasis model

Organism	MIC (μg/ml)	<i>In vivo</i> growth in control animals over 24 h (log ₁₀ CFU/kidney)
<i>C. albicans</i> isolates		
98-17 ^a	0.03	2.75
98-210 ^a	0.03	2.05
580 ^a	0.03	2.92
K1	0.03	2.18
All isolates (mean ± SD)		2.47 ± 0.43
<i>C. glabrata</i> isolates		
5592	0.25	2.02
513	0.06	1.92
5376	0.03	2.01
33616	0.03	0.76
All isolates (mean ± SD)		1.68 ± 0.61
<i>C. parapsilosis</i> isolates		
20519.069	0.25	2.02
20477.048	0.125	2.55
20423.072	0.06	1.96
All isolates (mean ± SD)		2.18 ± 0.33
All organisms (mean ± SD)		2.10 ± 0.56

^a Fluconazole nonsusceptible.

Strains. Eleven clinical *Candida* isolates were used for the *in vivo* treatment studies, including four *C. albicans*, four *C. glabrata*, and three *C. parapsilosis* isolates (Table 1). The organisms were chosen based on similar fitness in the animal model as defined by the amount of growth in control animals over 24 h (Table 1). We also attempted to choose strains with various susceptibilities to the study drug. The strain set is susceptible to the echinocandins (12, 13). A subset of the collection is triazole resistant (14). The organisms were maintained, grown, and quantified on Sabouraud's dextrose agar (SDA) plates.

***In vitro* susceptibility testing.** All isolates were tested in accordance with the standards in CLSI document M27-A3 (15). The MICs were determined visually after 24 h of incubation as the lowest concentration of drug that causes a significant diminution (≥50%) of growth of control levels. MICs were determined on three separate occasions in duplicate. Results are expressed as the medians of these results.

Animals. Six-week-old ICR Swiss/CD1 specific-pathogen-free female mice (Harlan Sprague-Dawley, Indianapolis, IN) weighing 23 to 27 g were used for all the studies. The animals were maintained in accordance with American Association for Accreditation of Laboratory Care criteria (16). The animal studies were approved by the Animal Research Committee of the William S. Middleton Memorial Veterans Affairs Hospital and the University of Wisconsin.

Infection model. A neutropenic, murine, disseminated candidiasis model was used for the treatment studies (17–19). The mice were rendered neutropenic (polymorphonuclear cell count, <100/mm³) by injecting cyclophosphamide (Mead Johnson Pharmaceuticals, Evansville, IN) subcutaneously 4 days before infection (150 mg/kg of body weight), 1 day before infection (100 mg/kg), and 2 days after infection (100 mg/kg). Prior studies have demonstrated that this regimen produces neutropenia throughout the 96-h study period (20).

The organisms were subcultured on SDA plates 24 h prior to infection. The inoculum was prepared by placing 3 to 5 colonies into 5 ml of sterile pyrogen-free 0.15 M NaCl warmed to 35°C. The final inoculum was adjusted to a 0.6 transmittance at 530 nm. The fungal count of the inoculum determined by viable counts on SDA was 6.22 ± 0.4 log₁₀ CFU/ml.

Disseminated infection with the *Candida* organisms was achieved by injection of 0.1 ml of the inoculum via the lateral tail vein 2 h prior to the start of antifungal therapy. At the end of the study period, the animals were sacrificed by CO₂ asphyxiation. Then, the kidneys of each mouse were immediately removed and placed in 0.15 M NaCl at 4°C. The kidneys were homogenized and serially diluted 1:10, and the aliquots were plated onto SDA for viable fungal colony counts after incubation for 24 h at 35°C. The lower limit of detection was 100 CFU/ml. The results are expressed as the mean CFU/kidney for three mice.

Pharmacokinetics. The single-dose pharmacokinetics (PK) evaluation of SCY-078 was undertaken following oral doses of 3.125, 12.5, 50, and 200 mg/kg of SCY-078 salt. Plasma from the groups of three mice per time point was collected. The plasma drug concentrations were determined by liquid chromatography-tandem mass spectrometry. A non-compartmental model was used in the pharmacokinetic analysis. Elimination half-lives were calculated by nonlinear least-squares techniques. The areas under the concentration-time curve (AUC) were calculated by the trapezoidal rule. For treatment doses in which no kinetics were determined, the pharmacokinetic indexes were estimated by linear extrapolation for higher and lower dose levels and by interpolation for dose levels within the dose range studied. Protein binding (99.8%) was based on a report of binding in mice from the sponsor.

FIG 1 Plasma concentrations of SCY-078 after oral administration of single doses of 3.125, 12.5, 50, and 200 mg/kg in infected neutropenic mice. The PK parameters, including half-lives (T_{1/2}), maximum plasma concentrations (C_{max}), and areas under the concentration-time curve from 0 to infinity (AUC), are indicated. Each symbol represents the geometric mean ± standard deviation of the results determined for three mice.

FIG 2 *In vivo* dose-response curves for SCY-078 against *C. albicans* (A; 4 isolates), *C. glabrata* (B; 4 isolates), and *C. parapsilosis* (C; 3 isolates). Mice received one of a series of five 4-fold increasing doses of SCY-078 every 12 h over a 96-h treatment period. Each symbol represents the mean organism burden in the kidneys of three mice. The error bars represent the standard deviations.

Treatment efficacy and pharmacodynamic target determination.

Neutropenic mice were infected with 11 *Candida* strains as described above. The dosing regimens were chosen to vary the magnitude of the 24-h AUC/MIC index and to attempt to produce treatment effects that ranged from no effect to a maximal effect. Five dose levels that varied from 0.78 to 200 mg/kg were administered every 12 h in a 0.2-ml volume by the oral route for the 96-h study period. Groups of three mice were used for each dosing regimen. At the end of the treatment period, the mice were euthanized, and their kidneys were immediately processed for CFU determination as described above.

Data analysis. A sigmoid dose-effect (Hill) model was used to measure the *in vivo* potency of SCY-078. The efficacy endpoints included the dose level required to produce a 24-h net static effect (no change in organism burden compared to that at the start of therapy) and the dose required to achieve a 1- $\log_{10}$ reduction in colony counts (relative to the burden at the start of therapy). The maximum response ($E_{\max}$) was measured as the difference in the number of CFU/kidney relative to that of the untreated control animals. The PK/PD target associated with these endpoints was calculated from the equation $\log_{10} D = \{\log_{10} [E/(E_{\max} - E)]/N\} + \log_{10} ED_{50}$, where D is the drug dose, E is the control growth in untreated animals, $E_{\max}$ is the maximal effect, N is the slope of the dose-response relationship, and ED_{50} is the dose needed to achieve 50% of the maximal effect. We used the PK/PD index AUC/MIC for calculating targets, as this has been shown to be associated with treatment efficacy in previous *in vivo* studies with the echinocandins (12, 17, 21–27). The calculations were performed using both total and free drug concentrations. The coefficient of determination (R^2) was used to estimate the variance that might be due to regression with the PK/PD index. Kruskal-Wallis one-way analysis of variance (ANOVA) was used to determine if the differences in PK/PD targets were significant between the species.

RESULTS

***In vitro* susceptibility testing and *in vivo* organism fitness.** The MICs of SCY-078 against the study organisms are listed in Table 1. The MICs did not vary for *C. albicans*; all strains tested had the same MIC (0.03 $\mu\text{g/ml}$). The MIC range varied 8-fold for *C. glabrata* (range, 0.03 to 0.25 $\mu\text{g/ml}$) and 4-fold for *C. parapsilosis* (range, 0.06 to 0.25 $\mu\text{g/ml}$). All *C. albicans* and *C. parapsilosis* strains exhibited similar fitness levels with, on average, more than 2- $\log_{10}$ growth over a 24-h period (Table 1). Similar results were noted for three of the four *C. glabrata* isolates; however, one *C. glabrata* isolate (33616) exhibited a slightly decreased growth phenotype in untreated animals.

Pharmacokinetics. The time-course plasma levels of SCY-078 in infected neutropenic mice after oral doses of 3.125, 12.5, 50, and 200 mg/kg SCY-078 salt are shown in Fig. 1. The pharmacokinetics of the drug were relatively linear over the dose range. The elimination half-life ranged from 5.9 h to 8.5 h in plasma. The maximum concentration of drug in serum ($C_{\max}$) increased from 0.04 mg/liter to 2.66 mg/liter over the dose range. The AUC from 0 to 24 h ($AUC_{0-24\text{ h}}$) ranged from 0.61 $\mu\text{g} \cdot \text{h/ml}$ to 41.10 $\mu\text{g} \cdot \text{h/ml}$, and the AUC from 0 to infinity ($AUC_{0-\infty}$) ranged from 0.68 $\mu\text{g} \cdot \text{h/ml}$ to 40.31 $\mu\text{g} \cdot \text{h/ml}$. Protein binding (99.8%) was based on previous studies in mice by the sponsor.

Pharmacodynamic target. At the start of therapy, the mice had $4.20 \pm 0.38 \log_{10}$ CFU/kidney. The organisms grew $2.10 \pm 0.56 \log_{10}$ CFU/kidney in the untreated control mice over 24 h follow-

The dashed horizontal lines at 0 on the y axis represent the organism burden at the start of therapy. Symbols above the line represent net growth, whereas symbols below the line represent organism reduction, or killing, over the treatment period.

FIG 3 Relationship between SCY-078 AUC and AUC/MIC index using total drug concentrations (tAUC) and *in vivo* efficacy against four *C. albicans* (A), four *C. glabrata* (B), and three *C. parapsilosis* (C) isolates. The panels on the left show outcome relative to 24-h AUC drug concentrations alone, and those on the right include an assessment of the AUC/MIC. Mice received one of a series of five 4-fold increasing doses of SCY-078 every 12 h over a 96-h treatment period. Each symbol represents the mean organism burden in the kidneys of three mice. The dashed horizontal lines at 0 on the y axis represent organism burden at the start of therapy. Symbols above the line represent net growth, whereas symbols below the line represent organism reduction, or killing, over the treatment period. The best-fit line for the Hill equation and the coefficient of determination (R^2) are shown for each group.

FIG 4 Relationship between SCY-078 AUC/MIC index using total ($tAUC$) and free (non-protein-bound, $fAUC$) drug concentrations and *in vivo* efficacy against *C. albicans* (4 isolates), *C. glabrata* (4 isolates), and *C. parapsilosis* (3 isolates). The panel on the left represents total drug concentrations, and the one on the right, free drug concentrations. Mice received one of a series of five 4-fold increasing doses of SCY-078 every 12 h over a 96-h treatment period. Each symbol represents the mean organism burden in the kidneys from three mice. The dashed horizontal lines at 0 on the y axis represent the organism burden at the start of therapy. Symbols above the line represent net growth, whereas symbols below the line represent organism reduction, or killing, over the treatment period. Also shown are the best-fit curves based on the Hill equation and the E_{max} , ED_{50} , slope (N), and coefficient of determination (R^2).

ing infection (Table 1). There was no significant difference in the burden at the start of therapy or growth in the untreated control animals among the three *Candida* species (Table 1). The dose-response curves for SCY-078 against *C. albicans*, *C. glabrata*, and *C. parapsilosis* are shown in Fig. 2. Escalating doses of each compound resulted in concentration-dependent killing of all three *Candida* species. We did not observe a paradoxical effect over the dose range with the organisms utilized in this study. In general, the shapes of the exposure-response curves were similar for all strains. The location of the exposure-response curve was, in most cases, related to the MIC for the organism. The relationship between efficacy and 24-h AUC drug exposures and the PD index 24-h AUC/MIC is shown in Fig. 3 for each species. In Fig. 4, the integration of the PD index total AUC/MIC ($tAUC/MIC$) and free drug AUC/MIC ($fAUC/MIC$) and outcome is presented for each isolate. The PK/PD relationships for each of the organism groups were strong, as reflected in the relatively high R^2 values (range, 0.53 to 0.91). This relationship was similarly strong when the data for the three species were considered together ($R^2 = 0.66$; Fig. 4).

SCY-078 achieved the stasis endpoint against all 11 isolates. The 1-log kill endpoint was observed for 9 of 11 strains. Both endpoints were measured relative to the burden before the start of treatment. The mean E_{max} values were 4.0, 4.0, and 4.3 $\log_{10}$ CFU/kidney reductions over the experiment's duration (96 h) for *C. albicans*, *C. glabrata*, and *C. parapsilosis*, respectively (Table 2). The AUC/MIC (both total and free drug) values associated with the stasis and 1-log kill endpoints are also shown in Table 2. The mean total and free drug AUC/MIC values associated with a stasis endpoint were, respectively, 500.3 and 1.00 for *C. albicans*, 314.8 and 0.63 for *C. glabrata*, and 197.5 and 0.40 for *C. parapsilosis*. The total and free drug AUC/MIC values associated with a 1-log kill endpoint were, respectively, 711.1 and 1.42 for *C. albicans*, 631.1 and 1.26 for *C. glabrata*, and 455 and 0.91 for *C. parapsilosis*. While the free drug targets were slightly higher for the net stasis and 1-log kill values for *C. albicans*, these differences were not statistically significant by one-way ANOVA ($P = 0.35$ for stasis and $P = 0.76$ for 1-log kill).

DISCUSSION

The synthesis of glucans in *Candida* has proven to be an effective drug target through the successful development of the echinocandin antifungal class. In a decade since their clinical introduction, echinocandins have become first-line therapy against *Candida* isolates in many clinical scenarios due to their broad activity against the commonly encountered *Candida* species, high potency, and low toxicity (1). As a group, though, they are available only as intravenous formulations. They are very large lipopeptides ($\sim 1,200$ kDa) and therefore have inherently very low oral bioavailability. The prevalence of *Candida* infections and the effectiveness of the echinocandin class make an oral glucan synthase inhibitor an attractive option. This class may assume the previous role of oral fluconazole for step-down therapy prior to the emergence of triazole-resistant infections.

Pharmacodynamic evaluation of echinocandins has been determined in a number of *in vivo* studies against *Candida* species (17, 21, 22, 24, 28, 29). Optimal therapeutic efficacy in studies of echinocandins was noted when the C_{max}/MIC was 1 to 10 and the AUC/MIC was 10 to 20 when free drug concentrations were considered. In the current study, we noted similar relationships for a novel oral glucan synthase inhibitor, SCY-078. The AUC/MIC was a robust predictor of therapeutic efficacy in the murine neutropenic model of IC, with an R^2 ranging from 0.53 to 0.91. The PD targets were numerically lower than those observed with the intravenous echinocandin formulations; a static dose free drug AUC/MIC target ranged from 0.40 to 1.00 (mean for all 11 organisms, 0.70). We also noted in the current study the lack of significant differences in species-specific PD targets which have been demonstrated with the echinocandins (12). Consistent with previous echinocandin results, a trend toward lower targets was observed for *C. glabrata* and *C. parapsilosis* in comparison to *C. albicans*. It is possible that small but potentially significant differences in PD targets do exist and were not demonstrated in the current study due to the limited number of isolates utilized.

Previous SCY-078 *in vitro* potency studies have demonstrated potency against the most common *Candida* spp., includ-

TABLE 2 *In vivo* activities of SCY-078 against *C. albicans*, *C. glabrata*, and *C. parapsilosis* in a neutropenic murine invasive candidiasis model

Isolate	Activity measures ^a						
	$E_{\max}$ (log ₁₀ CFU/kidney)	24-h single dose (mg/kg)	24-h single dose <i>t</i> AUC/MIC	24-h single dose <i>f</i> AUC/MIC	24-h 1-log kill dose (mg/kg)	24-h 1-log kill dose <i>t</i> AUC/MIC	24-h 1-log kill dose <i>f</i> AUC/MIC
<i>C. albicans</i>							
Isolate							
K1	3.5	69.3	547.1	1.09	146.5	1078.9	2.16
98-17	4.3	50.6	395.7	0.79	81.9	648.1	1.30
98-210	3.5	95.3	756.3	1.51			
580	4.8	38.9	302.1	0.60	51.9	406.3	0.81
Overall							
Mean	4.0	63.5	500.3	1.00	93.4	711.1	1.42
Median	3.9	59.9	471.4	0.94	81.9	648.1	1.30
SD	0.6	24.6	198.3	0.40	48.3	340.7	0.68
<i>C. glabrata</i>							
Isolate							
5592	4.7	55.3	54.2	0.11	130.4	122.6	0.25
513	4.3	45.3	176.8	0.35	138.7	515.7	1.03
5376	5.2	109.7	853.6	1.71	175.2	1254.8	2.51
33616	1.8	23.1	174.6	0.35			
Overall							
Mean	4.0	58.4	314.8	0.63	148.1	631.1	1.26
Median	4.5	50.3	175.7	0.35	138.7	515.7	1.03
SD	1.5	36.8	363.7	0.73	23.8	574.9	1.15
<i>C. parapsilosis</i>							
Isolate							
20519.069	4.3	48.7	47.5	0.10	116.2	111.7	0.22
20477.048	4.7	127.4	240.5	0.48	354.1	587.5	1.18
20423.072	4.0	77.0	304.6	0.61	187.7	665.7	1.33
Overall							
Mean	4.3	84.4	197.5	0.40	219.3	455.0	0.91
Median	4.3	77.0	240.5	0.48	187.7	587.5	1.18
SD	0.4	39.9	133.8	0.27	122.1	299.9	0.60
All species							
Mean	4.1	67.3	350.3	0.70	153.6	599.0	1.20
Median	4.3	55.3	302.1	0.60	138.7	587.5	1.18
SD	0.9	32.1	267.5	0.54	86.3	383.4	0.77

^a *t*AUC/MIC, total drug AUC/MIC; *f*AUC/MIC, free drug (non-protein bound) AUC/MIC.

ing *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei* (30, 31). The MIC₉₀s in these studies ranged from 0.5 to 2 mg/liter. An interesting finding in the study by Pfaller et al., given that the enfumafungin derivatives inhibit glucan synthesis similarly to the echinocandin class, is the retained potency that SCY-078 demonstrates for isolates with *FKS1* hot spot mutations that confer echinocandin resistance (30). Thus, oral glucan synthase inhibitors may provide more than just the convenient benefit of oral administration and may also be an additional therapeutic agent for azole and/or echinocandin drug-resistant *Candida* infections. This is particularly relevant given the emergence of echinocandin resistance and echinocandin/azole coresistance in *C. glabrata* (32–34).

The ability of preclinical PD studies to predict the efficacy of antimicrobial agents in patients is critical for translating these results to the clinical realm. The relationship between preclinical and clinical efficacy was recently examined for the echinocandin micafungin (35). Using data from two large randomized studies, a free drug AUC/MIC (*f*AUC/MIC) of >7.5 was

significantly associated with clinical success compared to an *f*AUC/MIC of <7.5 against all *Candida* species. When examined by species, *C. parapsilosis* had a significantly lower PD target in this clinical data set, with an *f*AUC/MIC of 0.7. These clinical PD targets were similar to those identified in the echinocandin animal model studies (12, 17, 21, 24) and are congruent with the targets identified in this study of a novel oral glucan synthase inhibitor. Whether these targets are achievable in humans is dependent on human PK studies and MIC distribution. The analysis of human PK data, MIC distribution, and protein binding data would also allow for the determination of preliminary susceptibility breakpoints based upon these preclinical data. Accordingly, the current *in vivo* studies demonstrate that SCY-078 stands as a promising oral option for *Candida* infections, including invasive candidiasis.

ACKNOWLEDGMENT

These studies were funded by a research grant from Merck.

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