The Impact of Mucositis on Absorption and Systemic Drug Exposure of Isavuconazole

Running Title: Impact of Mucositis on Isavuconazole Exposure

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ABSTRACT

Isavuconazonium sulfate is the water-soluble prodrug of isavuconazole. Population analyses have demonstrated relatively predictable pharmacokinetic (PK) behavior in diverse patient populations. We evaluated the impact of mucositis on the oral isavuconazole exposure using population PK modeling.

METHODS: We evaluated patients treated in two phase 3 trials of isavuconazole, SECURE for treatment of invasive aspergillosis (IA) and other filamentous fungi and VITAL for patients with mucormycosis, invasive fungal disease (IFD) caused by other rare fungi, or IA and renal impairment. Mucositis was reported by site investigators and its impact on oral bioavailability was assessed. Use of the oral formulation was at the discretion of the investigator. Patients with plasma samples collected during the use of isavuconazonium sulfate were included in the construction of population PK model.

RESULTS: Of 250 patients included, 56 patients had mucositis at therapy onset or as an adverse event during oral isavuconazole therapy. Oral bioavailability was comparable of 98.3% and 99.8%, respectively. The average drug exposures (AUCave) calculated from either the mean or median parameter estimates were not different between patients with and without mucositis. Mortality and overall clinical response was similar between patients receiving oral therapy with and without mucositis.

CONCLUSION: Isavuconazole exposures and clinical outcomes in this subset of patients with mucositis who were able to take oral isavuconazonium sulfate were comparable to those without mucositis, despite the difference in oral bioavailability. Therefore, mucositis may not preclude use of the oral formulation of isavuconazonium sulfate.
INTRODUCTION

Invasive mould diseases (IMDs) are life-threatening conditions that require timely and intensive treatment. Patients with hematological disorders or who have undergone hematopoietic stem cell transplantation (HSCT) are a leading risk group for IMDs. Anti-neoplastic chemotherapy for acute myeloid leukemia (AML) or acute lymphocytic leukemia (ALL) and conditioning regimens for HSCT often cause mucosal disruption of the gastrointestinal (GI) tract (i.e. mucositis) that may compromise oral bioavailability (1). An evaluation of the impact of mucositis on the oral absorption of antifungal agents is required to ensure optimal antifungal therapy (2).

Isavuconazonium sulfate, the water-soluble prodrug of the triazole antifungal agent isavuconazole, is approved by the US FDA for the treatment of invasive aspergillosis (IA) and invasive mucormycosis (IM) and by the EMA for the treatment of IA, and for IM in patients for whom amphotericin B is inappropriate (3, 4). The clinical formulations include both intravenous and oral capsules. The pharmacokinetics have been well characterized from sub-studies embedded in clinical trials (5-8). The pivotal clinical trials included more than 400 patients with >60% with hematological malignancies or other conditions that required intensive chemotherapy and the potential for mucositis (9, 10).

Here, we examine the impact of mucositis on the bioavailability and drug exposure following the administration of oral isavuconazonium sulfate. We fitted a population pharmacokinetic model to the plasma concentrations from patients receiving oral isavuconazole in patients with and without mucositis and used this model to
bioavailability and the ultimate drug exposure. We consider the potential impact for dosing and therapeutic drug monitoring of isavuconazole in the setting of mucositis.
METHODS

Study design. Patients treated with isavuconazonium sulfate from two Phase 3 clinical trials, SECURE and VITAL, were eligible for inclusion if plasma concentrations were available. The SECURE trial (ClinicalTrials.gov identifier: NCT00412893) evaluated the efficacy and safety of isavuconazole compared with voriconazole for the primary treatment of invasive mould disease caused by Aspergillus spp. and other filamentous fungi (9). The VITAL trial (ClinicalTrials.gov identifier: NCT00634049) evaluated the efficacy and safety of isavuconazole for the treatment of IA in patients with renal impairment and in patients with IFD caused by Mucorales and other emerging moulds, yeasts, and dimorphic fungi (10). Eligibility criteria for both studies are detailed elsewhere (9, 10). Patients received a loading regimen of isavuconazonium sulfate at a dose of 372 mg (equivalent to isavuconazole 200 mg) every 8 h for the first 48 h. In the SECURE trial, the loading dose was required to be administered intravenously (i.v.), while in the VITAL trial treatment could commence using either the i.v. or oral formulation. The maintenance regimen for both studies was i.v. or oral isavuconazonium sulfate 372 mg once daily for up to 84 or 180 days, respectively. Patients received i.v. or oral drug at the discretion of site investigators.

Identification of Patients with Mucositis. The medical history (MH) and adverse event (AE) records from the case report forms were reviewed for MedDRA preferred terms suggestive of “mucositis” or “stomatitis” (e.g. mucosal inflammation, radiation mucositis, stomatitis, gastrointestinal inflammation). From there, the patients were further reviewed to determine the degree of likelihood that the MH and AE reported represented significant disease, such as recent radiation therapy or intensive chemotherapy. Patients...
with mucositis were only included if administration of the oral formulation occurred
during the episode of mucositis AND plasma PK concentrations coincided with the oral
administration and episode of mucositis. Patients without mucositis with plasma PK
measurements during oral administration were classified as non-mucositis patients.

**Plasma PK sampling.** Blood samples were collected on treatment days 7, 14, 42,
and end of therapy (EOT) in both trials. Collection was targeted for 24 hours after the
start of the infusion or the oral dose on the previous day (i.e., trough concentration). Full
24-hour profiles were obtained from a subset of 43 patients (including 6 patients with
mucositis). After collection, samples were processed immediately and stored at −80°C
until shipment to the central research laboratory. Isavuconazole concentrations were
measured at the completion of the study using a validated LC-MS/MS method as
previously described (5).

**Population Pharmacokinetic (PPK) Modeling.** Raw plasma concentration data
from the 2 groups during oral administration that was collected after Day 7 were
compared to determine if any trends in the data were observed. A PPK model was
developed using non-parametric estimation using Pmetrics (v1.4.1, University of
Southern California, Los Angeles, CA, USA) (11). The model-fitting process included
evaluation of both 2- and 3-compartment models including absorptive compartments and
a lag-time. The presence of mucositis (yes=1, no=0) was used as a covariate on oral
bioavailability (F) as a secondary equation, which took the following form:

\[ F = F_1 \cdot (1 - MUC) + F_{12} \cdot MUC \]

where, F1 refers to the oral bioavailability in patients without mucositis (MUC=0) and
F12 refers to the oral bioavailability in patients with mucositis (MUC=1).
Data were weighted by the inverse of the estimated assay variance. The final model was assessed by a visual inspection of the observed-versus-predicted concentration values before and after the Bayesian step, the coefficient of determination ($r^2$) from the linear regression of the observed-versus-predicted values, as well as estimates for bias (mean weighted error) and precision (adjusted mean weighted squared error).

The average AUC ($\text{AUC}_{\text{ave}}$) for each patient was calculated using the Bayesian posterior parameter estimates from the final model using the trapezoidal rule in Pmetrics. $\text{AUC}_{\text{ave}}$ was calculated by determining the total AUC over the entire dosing period and dividing by the number of days of therapy for each patient. Statistical comparisons were performed in MYSTAT 12 version 12.02 (https://systatsoftware.com) and GraphPad Prism version 6.0h (http://www.graphpad.com).

**Exposure-Response Analysis.** The $\text{AUC}_{\text{ave}}$ for patients with and without mucositis were compared by patient outcomes defined as All-Cause Mortality through Day 42 or Overall Response to explore if any impact on exposure was associated with differences in response. Statistical comparisons were performed in MYSTAT 12 (version 12.02, http://www.systat.com).
RESULTS

Study Population. A total of 250 patients were included in the analysis of which 56 had mucositis. Figure 1 shows the flow of patient inclusion in the study. The majority of the mucositis patients had a hematologic malignancy (89.3%) that was active at the time of enrollment and were neutropenic at the start of antifungal treatment (78.2%) (Table 1). Only 6 patients did not have a hematological malignancy [aplastic anemia (n=3), uterine leiomyosarcoma (n=1), X-linked adrenomyeloneuropathy (n=1), squamous cell carcinoma of the tongue (n=1)]. A quarter (26.8%) of the patients with mucositis had received a HSCT. Sixteen percent of mucositis patients had baseline renal impairment (eGFR-MDRD < 60 mL/min/1.73m²) compared with 27.6% of those without mucositis. The majority of the overall population were males (62%), Caucasian (78.8%), and the average age (± SD) and weight (± SD) were 50.3 ± 16.1 years and 70.0 ± 18.3 kg, respectively.

Type of Fungal Infection in Patients with Mucositis. Thirty-two patients had proven or probable IA and 7 patients had possible IA (with appropriate host factors, clinical features but no mycological evidence of disease). Eight patients had proven or probable infection caused by various mould and rare yeasts including Mucorales (n=1), Fusarium spp. (n=3), Culvularia lunata (n=1), Alternaria spp. (n=1), Acremonium spp. (n=1), and Trichosporon spp. (n=1). Five patients did not have enough evidence for probable or proven IFD after review of the Data Review Committees.

PPK Model. Comparisons of the raw plasma concentrations for the patients with mucositis and patients without mucositis during oral administration beyond Day 7 revealed a statistical difference between the 2 groups (Fig. 2), although the
concentrations largely overlapped. A 2-compartment model including an absorptive compartment fit the data well. An illustration of the structural model is provided in Fig. 3 where the first compartment represents the gut (oral compartment) and the second representing the central compartment. The fit of the model to the data was acceptable based on visual inspection of the observed-versus-median predicted plots and the coefficient of determination ($r^2$) of 0.813 after the Bayesian step (Fig. 4). The estimates of bias and imprecision were also acceptable (0.11 and 0.938, respectively). The observed-versus-mean predicted plots showed similar statistics with a coefficient of determination ($r^2$) of 0.792 (slope = 0.976) after the Bayesian step. The median parameter estimates are included in Table 2.

Comparison of Oral Bioavailability. The mean (range) oral bioavailability (F) estimates for mucositis and non-mucositis patients were 86.0% (50.3-99.7%) and 97.4% (70.2-99.9%), respectively. Comparison of the mean and median bioavailability estimates for the two populations demonstrated a significant difference between the 2 groups ($p < 0.001$) (Fig. 5). However, this 11.4% difference in bioavailability did not have a significant impact on the distribution of exposures ($AUC_{ave}$) between the two groups ($p=0.706$) (Fig. 6).

All-Cause Mortality through Day 42. All-cause mortality through treatment day 42 for the patients with and without mucositis was 7.1% (4/56) and 14.4% (28/194), respectively. The oral bioavailability and $AUC_{ave}$ were 83.6% and 91.3 mg-h/L, 92.7% and 164.9 mg-h/L, 99.7% and 56.5 mg-h/L, and 99.7% and 216.9 mg-h/L for the four patients with mucositis who died. The median bioavailability estimates for the non-
mucositis patients that died were all above 90% except for one patient with an estimate of 70.2%. The mean $\text{AUC}_{\text{ave}}$ was 100.5 mg·h/L and ranged from 34.9-369.1 mg·h/L.

**Overall Response at the End of Therapy (EOT).** Overall Response at the EOT was available for 232 mITT patients in the analysis. Fifty-eight percent [n=43; 95% CI 42.13, 72.99] and 42.9% [n=189, 95% CI 35.68, 50.42] of the patients with and without mucositis had a successful response, respectively. In the mucositis patients who failed at the EOT (n=25), the mean oral bioavailability was 84.9 ± 17.9%, (range 50.4-99.7%; median 90.3%) and the mean $\text{AUC}_{\text{ave}}$ was 117.9 ± 69.4 mg·h/L, (range 45.9-315.5 mg·h/L; median 94.2 mg·h/L). Six of the patients (n=18; 33%) who failed at the EOT had oral bioavailability estimates < 80% (range 50.4-69.5%) with $\text{AUC}_{\text{ave}}$ values ranging from 45.9-176.3 mg·h/L and 8 of the patients (n=25; 32%) with successful responses at the end of therapy had bioavailability estimates of <80% (range 50.3-75.5%) with $\text{AUC}_{\text{ave}}$ ranging from 48.2-155.2 mg·h/L.
Biological factors that have an impact on drug absorption include the pH along the GI tract, tissue perfusion, the presence of bile and mucus, the surface area per volume of the lumen, and the epithelial integrity. Mucositis manifests as erythema, inflammation, ulcerations, and hemorrhage of the mucosal surfaces of the GI tract and causes gastric motility dysfunction. This mucosal disruption can significantly affect drug absorption after the oral administration of medications. Using oral medications in the setting of mucositis requires an understanding of the determinants of drug absorption.

Table 3 summarizes the determinants of oral bioavailability for triazole antifungal agents. Isavuconazole and fluconazole have similar characteristics that include the absence of clinically relevant effect on absorption from food, changes in pH, or increases in GI motility (3, 12, 13). Posaconazole and itraconazole oral solutions should be administered with high-fat meals, carbonated soda, or nutritional supplements (2, 14-19). Plasma concentrations are decreased when gastric acidity is reduced (2, 14-19). Absorption of posaconazole oral solution may be improved when daily doses are fractionated compared with less frequent dosing (20). The newer posaconazole tablets are not affected by changes in gastric pH and absorption is not improved by the consumption of high-fat meals (17, 21). Voriconazole plasma concentrations are reduced when taken with food; however, absorption is not clinically significantly affected by changes in pH or by drugs such as omeprazole (22). H2-blockers were not found to cause clinically significant changes in voriconazole absorption kinetics (23). Voriconazole exhibits decreased oral bioavailability in patients with cystic fibrosis (CF) compared to patients without CF after lung transplant (24). Thus, factors that affect the absorption of triazoles...
such as mucositis differ markedly.

Drugs that require food to increase bioavailability or experience decreased bioavailability with increased gastric emptying (increased gastric motility) suggest that passive diffusion is slow and likely occurs primarily from the stomach. In these circumstances, absorption is improved by longer transit times in the stomach and upper small intestine. Aside from the prodrug formulation of isavuconazole, the other azoles are limited by the insufficient dissolution in stomach prior to delivery in the duodenum, where absorption is maximal. A meal that is high in fat increases luminal volume and bile and pancreatic secretions, and delays gastric emptying. The absorption for drugs such as posaconazole may be optimized by the use a more fractionated regimen (14, 25, 26). However, studies have suggested that this may be due to the high-fat meal increasing the solubility versus delayed gastric emptying (14). Another study failed to associate factors such as P-glycoprotein on the absorption of posaconazole (27). In contrast, the absorption for isavuconazole and fluconazole (and to a lesser extent voriconazole) is not significantly influenced by these factors, suggesting passive diffusion occurs more quickly and the majority of the absorption occurs in the upper small intestine.

In this analysis, the presence of mucositis did not have a significant overall impact on the clinical outcomes in the patients treated with isavuconazonium sulfate from the SECURE and VITAL trials despite the statistical differences in oral bioavailability between the groups with and without mucositis. In addition, the drug exposure between the groups was not significantly different. The results held whether mean or median parameter estimates were used for the comparisons.
The current study has several limitations. First, details on the presence or severity of mucositis were not available for the majority of patients with the condition. Quantification of severity may have allowed for a deeper understanding of the impact for the degree of mucosal disruption and the impact on oral bioavailability. Second, patients were allowed to switch back and forth from oral to intravenous medication during the treatment period. However, only patients with mucositis coinciding with oral administration were selected for analysis. Third, the administration of i.v. or oral formulations was at the discretion of the site investigators making it difficult to assess the impact of the severity of mucositis on oral bioavailability. Patients with more severe grades of mucositis patients may have remained on i.v. therapy longer, while patients with less severe mucositis may have been switched to oral therapy. In addition, identification of mucositis patients for this study relied on the reporting of the events by the treating investigator, which could be underrepresenting the incidence in the study. We did not utilize a validated mucositis score or a biomarker, such as citrulline to capture severity as has done in other studies (28). Finally, we assumed compliance was 100%, which may be overly optimistic.

These analyses are important as many patients who will be treated with isavuconazonium sulfate are at risk or could have mucositis at the onset of therapy caused by the harsh treatments used to treat their underlying co-morbidities. Patients with slightly lower bioavailability had outcomes similar to those with higher bioavailability. Therefore, use of the oral formulation of isavuconazonium sulfate during episodes of mucositis may be acceptable; however, treating physicians may consider extending isavuconazole intravenous therapy during episodes of mucositis or monitoring levels to
ensure they are within the range reported from the clinical trial. However, additional studies in this population may be warranted.
ACKNOWLEDGMENTS

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References


Figure Legends

FIG 1. Flowchart illustrating flow of isavuconazole-treated patients into the mucositis and non-mucositis populations.

FIG 2. Comparison of plasma concentrations drawn during oral administration after day 7 of therapy between the mucositis and non-mucositis patients. (Mann-Whitney U Test p-value = 0.0011).

FIG 3. Illustration of the Structural Model: Compartment 1 represents the gut for oral administration; Compartment 2 represents the central compartment; CL, clearance; F, bioavailability; Ka, first-order absorption rate constant; Tlag, lag-time; V, volume in the central compartment; RATEIV(1) specifies infusions going directly into the central compartment.

FIG 4. Observed versus median posterior predicted concentrations (mg/L) from the final model after the Bayesian step ($r^2 = 0.813$, slope $= 0.98$ [95%CI 0.956 to 1], intercept $=-0.0181$ [95%CI $-0.115$ to $0.0792$]). Dotted line is line of unity where observed concentrations equal predicted concentrations.

FIG 5. There is a significant difference in the median estimates for bioavailability between the 2 groups. (Mann-Whitney U Test p-value $< 0.0001$).
FIG 6. No significant difference in average AUCs between Mucositis and Non-Mucositis Patients (p=0.706; Mann Whitney U test) (AUCs calculated from the median parameter estimates after the Bayesian step).
Table 1. Demographics, Background Disease and Duration of Therapy

<table>
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<tr>
<th></th>
<th>Mucositis N=56</th>
<th>Non-Mucositis N=194</th>
<th>Total N=250</th>
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<tbody>
<tr>
<td>Age (years)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Median (min-max)</td>
<td>50 (18-79)</td>
<td>52 (19-92)</td>
<td>52 (18-92)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>32 (57%)</td>
<td>123 (63%)</td>
<td>155 (62%)</td>
</tr>
<tr>
<td>Race</td>
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<tr>
<td>White</td>
<td>48 (86%)</td>
<td>149 (77%)</td>
<td>197 (79%)</td>
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<tr>
<td>Asian</td>
<td>7 (13%)</td>
<td>31 (16%)</td>
<td>38 (15%)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (2%)</td>
<td>9 (5%)</td>
<td>10 (4%)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>5 (3%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>71.7 ± 18.1</td>
<td>69.5 ± 18.4</td>
<td>70.0 ± 18.3</td>
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<tr>
<td>Underlying Disease</td>
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<td></td>
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<tr>
<td>Hematological Malignancy</td>
<td>50 (89.3%)</td>
<td>101 (52.1%)</td>
<td>151 (60.4%)</td>
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<tr>
<td>Active Malignancy</td>
<td>40 (71.4%)</td>
<td>76 (39.2%)</td>
<td>116 (46.4%)</td>
</tr>
<tr>
<td>Allogeneic HSCT</td>
<td>15 (26.8%)</td>
<td>33 (17.0%)</td>
<td>48 (19.2%)</td>
</tr>
<tr>
<td>Baseline Neutropenia</td>
<td>43 (78.2%)</td>
<td>64 (41.8%)</td>
<td>107 (51.4%)</td>
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<tr>
<td>T-cell Immunosuppressants</td>
<td>23 (41.8%)</td>
<td>82 (51.9%)</td>
<td>105 (49.3%)</td>
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<tr>
<td>Use of Corticosteroids</td>
<td>8 (14.3%)</td>
<td>47 (24.2%)</td>
<td>55 (22.0%)</td>
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<td>Duration of Therapy (days)</td>
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<td></td>
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</tr>
<tr>
<td>Median (range)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Total duration</td>
<td>75.5 (8-735)</td>
<td>83 (1-882)</td>
<td>82 (1-882)</td>
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<tr>
<td>IV formulation</td>
<td>9 (2-45)</td>
<td>7 (0.5-77)</td>
<td>7.5 (0.5-77)</td>
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Table 2. Median Parameter estimates from the PPK model

<table>
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<tr>
<th></th>
<th>Mucositis</th>
<th>Non-Mucositis</th>
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<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Median</td>
</tr>
<tr>
<td>Ka (h⁻¹)</td>
<td>7.0 ± 2.6</td>
<td>7.9</td>
</tr>
<tr>
<td>Cl/F (L/h)</td>
<td>2.2 ± 1.0</td>
<td>1.9</td>
</tr>
<tr>
<td>V/F (L)</td>
<td>331.4 ± 154.9</td>
<td>347.7</td>
</tr>
<tr>
<td>Lag time (h)</td>
<td>1.2 ± 1.2</td>
<td>1.0</td>
</tr>
<tr>
<td>F (%)</td>
<td>86.0 ± 18.5</td>
<td>98.3</td>
</tr>
<tr>
<td>AUCAVE (mg·h/L)</td>
<td>105.3 ± 55.9</td>
<td>91.9</td>
</tr>
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</table>

Abbreviations: SD, standard deviation; Ka, first-order absorption rate constant; Cl, clearance; F, bioavailability; V, volume in the central compartment, AUCAVE, average area-under-the concentration curve.
<table>
<thead>
<tr>
<th>Isavuconazonium sulfate</th>
<th>Voriconazole</th>
<th>Posaconazole (15)</th>
<th>Itraconazole (16)</th>
<th>Fluconazole (13)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formulation</strong></td>
<td>capsule</td>
<td>tablets</td>
<td>solution</td>
<td>solution</td>
</tr>
<tr>
<td><strong>Water Solubility</strong></td>
<td>Y (prodrug)</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td><strong>Bioavailability (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Healthy Subjects</strong></td>
<td>98 (12)</td>
<td>96 (29)</td>
<td>8-48 (fasted)</td>
<td>54 (fasted)</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>97 (5)</td>
<td>64 (30)</td>
<td></td>
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<tr>
<td><strong>GI motility agents</strong></td>
<td>none</td>
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<td>Decreases</td>
<td>none</td>
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<td><strong>pH Effect</strong></td>
<td>none</td>
<td>none</td>
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<tr>
<td><strong>Food Effect</strong></td>
<td>none</td>
<td>Decreases</td>
<td>Increases</td>
<td>Cmax and</td>
</tr>
<tr>
<td>Other</td>
<td>concentrations (especially high fat, nutritional supplement or acidic carbonated beverage)</td>
<td>AUC increases 16% and 51% with high fat foods</td>
<td>concentrations</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>----------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F significantly lower in CF lung tx (23%) pts versus non-CF lung tx (63%) (24); 2 factors significant association with F in lung tx pts. CF, post-operative time (increased with increasing time) (24)</td>
<td>Divided doses increases absorption</td>
<td></td>
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<tr>
<td>Substrate of Pgp</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
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</tbody>
</table>

Abbreviations: Y: yes; N: no; GI: gastrointestinal; F: bioavailability; CF: cystic fibrosis; Pgp: P-glycoprotein
FIG 1. Flowchart illustrating flow of isavuconazole-treated patients into the mucositis and non-mucositis populations

404 enrolled
(258 SECURE + 146 VITAL)

286 with plasma concentrations
118 without plasma concentrations

92 with mucositis

4 IV only

32 mucositis onset after treatment or no PK during PO

Mucositis Population:
\textbf{n=56} (received PO during mucositis episode)

Non-Mucositis Population:
\textbf{n=194}

118 without plasma concentrations

FIG 1. Flowchart illustrating flow of isavuconazole-treated patients into the mucositis and non-mucositis populations
FIG 2. Comparison of plasma concentrations drawn during oral administration after day 7 of therapy between the mucositis and non-mucositis patients. (Mann-Whitney U Test p-value = 0.0011).
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FIG 4. Observed versus median posterior predicted concentrations (mg/L) from the final model after the Bayesian step ($r^2 = 0.813$, slope = 0.98 [95%CI 0.956 to 1], intercept = -0.0181 [95%CI -0.115 to 0.0792]). Dotted line is line of unity where observed concentrations equal predicted concentrations.
FIG 5. There is a significant difference in the median estimates for bioavailability between the 2 groups. (Mann-Whitney U Test p-value < 0.0001).
FIG 6. No significant difference in average AUCs between Mucositis and Non-Mucositis Patients (p=0.706; Mann Whitney U test) (AUCs calculated from the median parameter estimates after the Bayesian step).