

1 **The Impact of Mucositis on Absorption and Systemic Drug Exposure of**

2 **Isavuconazole**

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4 Running Title: Impact of Mucositis on Isavuconazole Exposure

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24 **ABSTRACT**

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

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

36 **RESULTS:** Of 250 patients included, 56 patients had mucositis at therapy onset or as an
37 adverse event during oral isavuconazole therapy. Oral bioavailability was comparable of
38 98.3% and 99.8%, respectively. The average drug exposures (AUC_{ave}) calculated from
39 either the mean or median parameter estimates were not different between patients with
40 and without mucositis. Mortality and overall clinical response was similar between
41 patients receiving oral therapy with and without mucositis.

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

46

47 **INTRODUCTION**

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

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

65 Here, we examine the impact of mucositis on the bioavailability and drug
66 exposure following the administration of oral isavuconazonium sulfate. We fitted a
67 population pharmacokinetic model to the plasma concentrations from patients receiving
68 oral isavuconazole in patients with and without mucositis and used this model to

69 bioavailability and the ultimate drug exposure. We consider the potential impact for
70 dosing and therapeutic drug monitoring of isavuconazole in the setting of mucositis.
71

72 METHODS

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

89 *Identification of Patients with Mucositis.* The medical history (MH) and adverse
90 event (AE) records from the case report forms were reviewed for MedDRA preferred
91 terms suggestive of “mucositis” or “stomatitis” (e.g. mucosal inflammation, radiation
92 mucositis, stomatitis, gastrointestinal inflammation). From there, the patients were further
93 reviewed to determine the degree of likelihood that the MH and AE reported represented
94 significant disease, such as recent radiation therapy or intensive chemotherapy. Patients

95 with mucositis were only included if administration of the oral formulation occurred
96 during the episode of mucositis AND plasma PK concentrations coincided with the oral
97 administration and episode of mucositis. Patients without mucositis with plasma PK
98 measurements during oral administration were classified as non-mucositis patients.

99 *Plasma PK sampling.* Blood samples were collected on treatment days 7, 14, 42,
100 and end of therapy (EOT) in both trials. Collection was targeted for 24 hours after the
101 start of the infusion or the oral dose on the previous day (i.e., trough concentration). Full
102 24-hour profiles were obtained from a subset of 43 patients (including 6 patients with
103 mucositis). After collection, samples were processed immediately and stored at -80°C
104 until shipment to the central research laboratory. Isavuconazole concentrations were
105 measured at the completion of the study using a validated LC-MS/MS method as
106 previously described (5).

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

$$F = F1 \cdot (1 - MUC) + F12 \cdot MUC$$

115 where, F1 refers to the oral bioavailability in patients without mucositis (MUC=0) and
116 F12 refers to the oral bioavailability in patients with mucositis (MUC=1).

117 Data were weighted by the inverse of the estimated assay variance. The final
118 model was assessed by a visual inspection of the observed-versus-predicted concentration
119 values before and after the Bayesian step, the coefficient of determination (r^2) from the
120 linear regression of the observed-versus-predicted values, as well as estimates for bias
121 (mean weighted error) and precision (adjusted mean weighted squared error).

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

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

133

134 **RESULTS**

135 *Study Population.* A total of 250 patients were included in the analysis of which
136 56 had mucositis. **Figure 1** shows the flow of patient inclusion in the study. The majority
137 of the mucositis patients had a hematologic malignancy (89.3%) that was active at the
138 time of enrollment and were neutropenic at the start of antifungal treatment (78.2%)
139 (**Table 1**). Only 6 patients did not have a hematological malignancy [aplastic anemia
140 (n=3), uterine leiomyosarcoma (n=1), X-linked adrenomyeloneuropathy (n=1), squamous
141 cell carcinoma of the tongue (n=1)]. A quarter (26.8%) of the patients with mucositis had
142 received a HSCT. Sixteen percent of mucositis patients had baseline renal impairment
143 (eGFR-MDRD < 60 mL/min/1.73m²) compared with 27.6% of those without mucositis.
144 The majority of the overall population were males (62%), Caucasian (78.8%), and the
145 average age (\pm SD) and weight (\pm SD) were 50.3 \pm 16.1 years and 70.0 \pm 18.3 kg,
146 respectively.

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

154 *PPK Model.* Comparisons of the raw plasma concentrations for the patients with
155 mucositis and patients without mucositis during oral administration beyond Day 7
156 revealed a statistical difference between the 2 groups (**Fig. 2**), although the

157 concentrations largely overlapped. A 2-compartment model including an absorptive
158 compartment fit the data well. An illustration of the structural model is provided in **Fig. 3**
159 where the first compartment represents the gut (oral compartment) and the second
160 representing the central compartment. The fit of the model to the data was acceptable
161 based on visual inspection of the observed-versus-median predicted plots and the
162 coefficient of determination (r^2) of 0.813 after the Bayesian step (**Fig. 4**). The estimates
163 of bias and imprecision were also acceptable (0.11 and 0.938, respectively). The
164 observed-versus-mean predicted plots showed similar statistics with a coefficient of
165 determination (r^2) of 0.792 (slope = 0.976) after the Bayesian step. The median parameter
166 estimates are included in **Table 2**.

167 *Comparison of Oral Bioavailability.* The mean (range) oral bioavailability (F)
168 estimates for mucositis and non-mucositis patients were 86.0% (50.3-99.7%) and 97.4%
169 (70.2-99.9%), respectively. Comparison of the mean and median bioavailability estimates
170 for the two populations demonstrated a significant difference between the 2 groups ($p <$
171 0.001) (**Fig. 5**). However, this 11.4% difference in bioavailability did not have a
172 significant impact on the distribution of exposures (AUC_{ave}) between the two groups
173 ($p=0.706$) (**Fig. 6**).

174 *All-Cause Mortality through Day 42.* All-cause mortality through treatment day
175 42 for the patients with and without mucositis was 7.1% (4/56) and 14.4% (28/194),
176 respectively. The oral bioavailability and AUC_{ave} were 83.6% and 91.3 mg·h/L, 92.7%
177 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
178 patients with mucositis who died. The median bioavailability estimates for the non-

179 mucositis patients that died were all above 90% except for one patient with an estimate of
180 70.2%. The mean AUC_{ave} was 100.5 mg·h/L and ranged from 34.9-369.1 mg·h/L.

181 *Overall Response at the End of Therapy (EOT).* Overall Response at the EOT was
182 available for 232 mITT patients in the analysis. Fifty-eight percent [n=43; 95% CI 42.13,
183 72.99] and 42.9% [n=189, 95% CI 35.68, 50.42] of the patients with and without
184 mucositis had a successful response, respectively. In the mucositis patients who failed at
185 the EOT (n=25), the mean oral bioavailability was $84.9 \pm 17.9\%$, (range 50.4-99.7%;
186 median 90.3%) and the mean AUC_{ave} was 117.9 ± 69.4 mg·h/L, (range 45.9-315.5
187 mg·h/L; median 94.2 mg·h/L). Six of the patients (n=18; 33%) who failed at the EOT had
188 oral bioavailability estimates < 80% (range 50.4-69.5%) with AUC_{ave} values ranging
189 from 45.9-176.3 mg·h/L and 8 of the patients (n=25; 32%) with successful responses at
190 the end of therapy had bioavailability estimates of <80% (range 50.3-75.5%) with
191 AUC_{ave} ranging from 48.2-155.2 mg·h/L.

192

193 **DISCUSSION**

194 Biological factors that have an impact on drug absorption include the pH along
195 the GI tract, tissue perfusion, the presence of bile and mucus, the surface area per volume
196 of the lumen, and the epithelial integrity. Mucositis manifests as erythema, inflammation,
197 ulcerations, and hemorrhage of the mucosal surfaces of the GI tract and causes gastric
198 motility dysfunction. This mucosal disruption can significantly affect drug absorption
199 after the oral administration of medications. Using oral medications in the setting of
200 mucositis requires an understanding of the determinants of drug absorption.

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

216 such as mucositis differ markedly.

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

232 In this analysis, the presence of mucositis did not have a significant overall impact
233 on the clinical outcomes in the patients treated with isavuconazonium sulfate from the
234 SECURE and VITAL trials despite the statistical differences in oral bioavailability
235 between the groups with and without mucositis. In addition, the drug exposure between
236 the groups was not significantly different. The results held whether mean or median
237 parameter estimates were used for the comparisons.

238 The current study has several limitations. First, details on the presence or severity
239 of mucositis were not available for the majority of patients with the condition.
240 Quantification of severity may have allowed for a deeper understanding of the impact for
241 the degree of mucosal disruption and the impact on oral bioavailability. Second, patients
242 were allowed to switch back and forth from oral to intravenous medication during the
243 treatment period. However, only patients with mucositis coinciding with oral
244 administration were selected for analysis. Third, the administration of i.v. or oral
245 formulations was at the discretion of the site investigators making it difficult to assess the
246 impact of the severity of mucositis on oral bioavailability. Patients with more severe
247 grades of mucositis patients may have remained on i.v. therapy longer, while patients
248 with less severe mucositis may have been switched to oral therapy. In addition,
249 identification of mucositis patients for this study relied on the reporting of the events by
250 the treating investigator, which could be underrepresenting the incidence in the study. We
251 did not utilize a validated mucositis score or a biomarker, such as citrulline to capture
252 severity as has done in other studies (28). Finally, we assumed compliance was 100%,
253 which may be overly optimistic.

254 These analyses are important as many patients who will be treated with
255 isavuconazonium sulfate are at risk or could have mucositis at the onset of therapy caused
256 by the harsh treatments used to treat their underlying co-morbidities. Patients with
257 slightly lower bioavailability had outcomes similar to those with higher bioavailability.
258 Therefore, use of the oral formulation of isavuconazonium sulfate during episodes of
259 mucositis may be acceptable; however, treating physicians may consider extending
260 isavuconazole intravenous therapy during episodes of mucositis or monitoring levels to

261 ensure they are within the range reported from the clinical trial. However, additional
262 studies in this population may be warranted.

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396

397 **Figure Legends**

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422 **median parameter estimates after the Bayesian step).**
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424 **Table 1. Demographics, Background Disease and Duration of Therapy**

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

Oral formulation	58 (1-690)	79.8 (0.5-882)	73 (0.5-882)
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426 **Table 2. Median Parameter estimates from the PPK model**

	Mucositis				Non-Mucositis			
	Mean \pm SD	Median	Range	%CV	Mean \pm SD	Median	Range	%CV
Ka (h^{-1})	7.0 \pm 2.6	7.9	0.0-8.0	38%	6.5 \pm 3.0	7.9	0.0-8.0	46%
Cl/F (L/h)	2.2 \pm 1.0	1.9	0.5-4.1	44%	2.3 \pm 1.1	1.9	0.1-5.9	47%
V/F (L)	331.4 \pm 154.9	347.7	6.8-895.5	47%	354.1 \pm 182.5	349.8	5.8-895.5	52%
Lag time (h)	1.2 \pm 1.2	1.0	0.0-5.0	94%	1.3 \pm 1.3	1.0	0.0-5.0	103%
F (%)	86.0 \pm 18.5	98.3	50.3-99.7	21%	97.4 \pm 6.9	99.8	70.2-99.9	7%
AUC _{ave} (mg·h/L)	105.3 \pm 55.9	91.9	45.9-315.5	53%	114.1 \pm 141.2	100.2	30.8-1944.3	124%

427 Abbreviations: SD, standard deviation; Ka, first-order absorption rate constant; CL, clearance; F, bioavailability; V, volume in the central compartment, AUC_{ave}, average area-
 428 under-the concentration curve.

430 **Table 3. Comparison of factors impacting oral absorption of triazole antifungal drugs**

	Isavuconazonium sulfate	Voriconazole	Posaconazole (15)		Itraconazole (16)		Fluconazole (13)
Formulation	capsule	tablets	solution	tablets	solution	capsule	tablet
Water Solubility	Y (prodrug)	N	N		N		Y
Bioavailability (%)							
Healthy Subjects	98 (12)	96 (29)	8-48 (fasted)	54 (fasted)	55		90
Patients	97 (5)	64 (30)					
GI motility agents	none	No data found	Decreases	none	No data found		No data found
pH Effect	none	none	Decreases in reduced acidity	none	Decreased in reduced acidity		none
Food Effect	none	Decreases	Increases	Cmax and	Increases		none

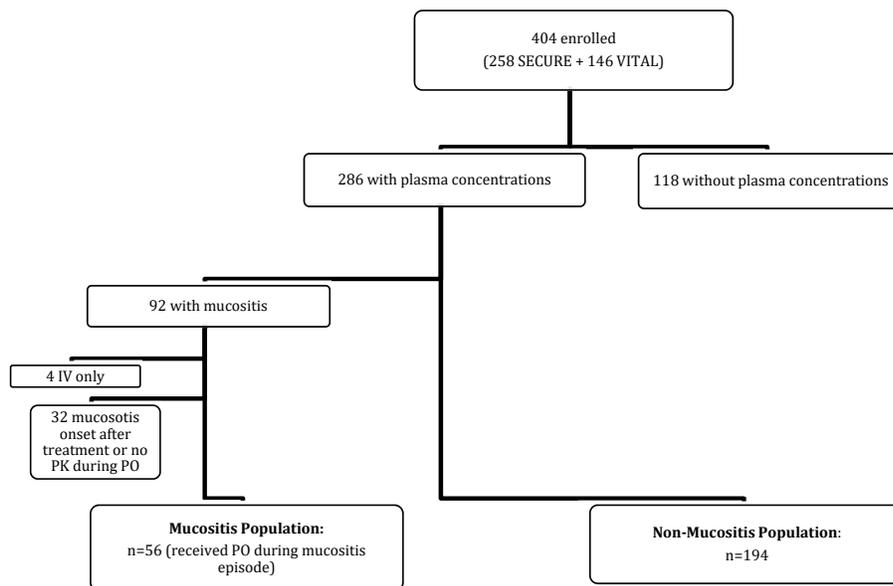
		concentrations	concentrations (especially high fat, nutritional supplement or acidic carbonated beverage)	AUC increases 16% and 51% with high fat foods	concentrations	
Other		F significantly lower in CF lung tx (23%) pts versus non-CF lung tx (63%) (24); 2 factors significant association with F in lung tx pts: CF, post- operative time (increased with increasing time) (24)	Divided doses increases absorption			

Substrate of Pgp	no	no	yes	yes	yes	yes	no
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431 Abbreviations: Y: yes; N: no; GI: gastrointestinal; F: bioavailability; CF: cystic fibrosis; Pgp: P-glycoprotein

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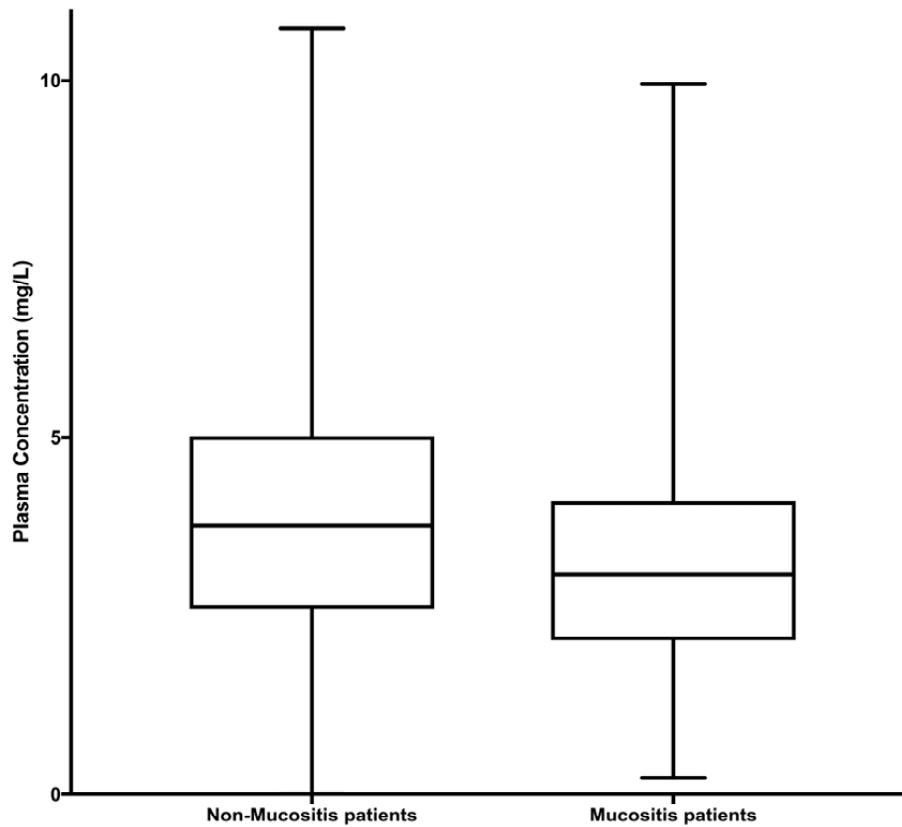


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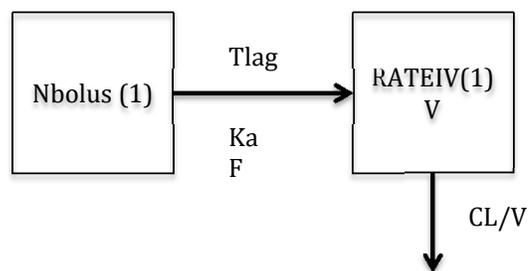
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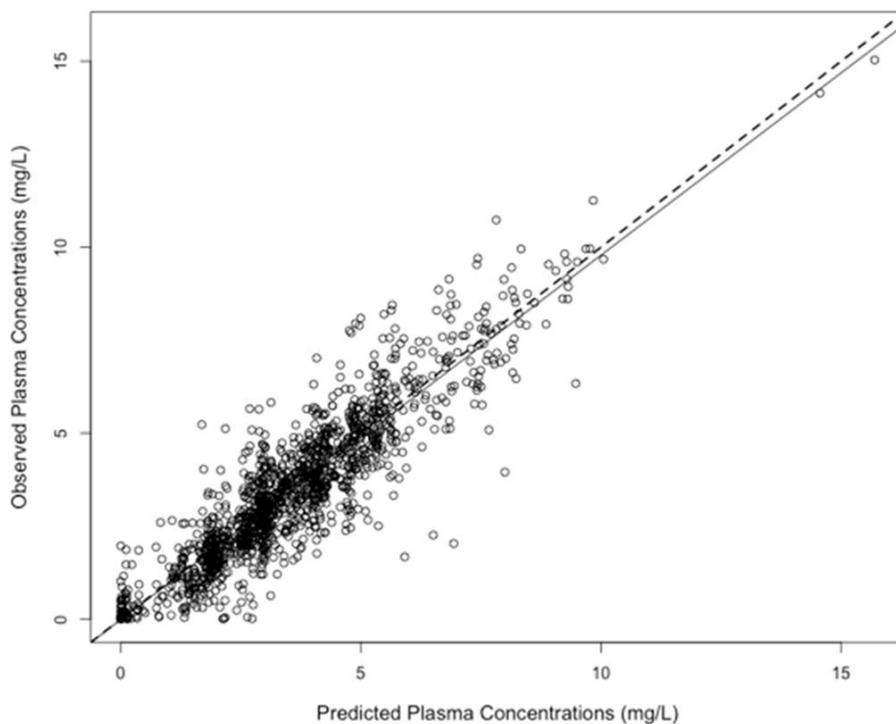
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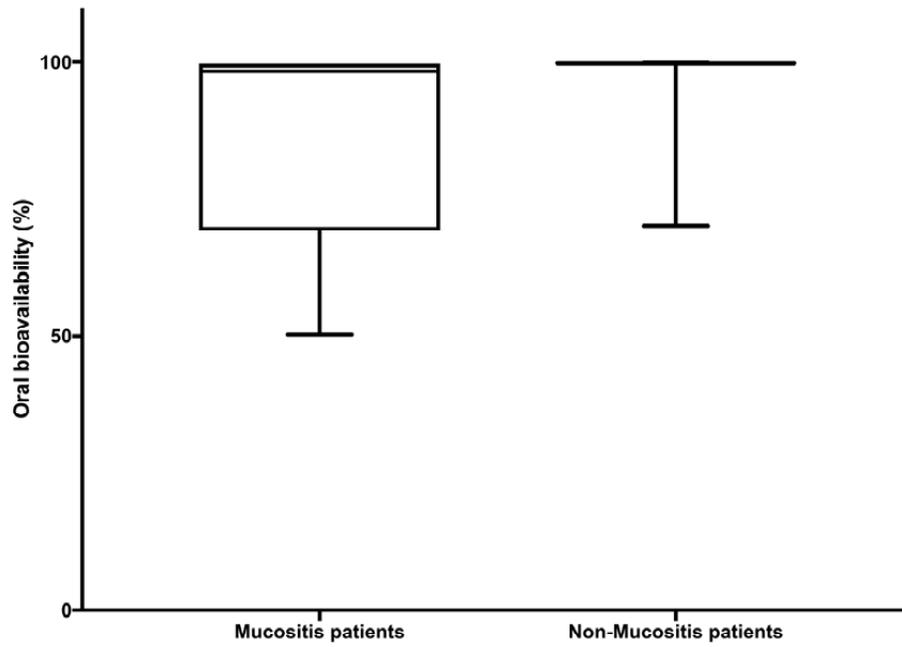
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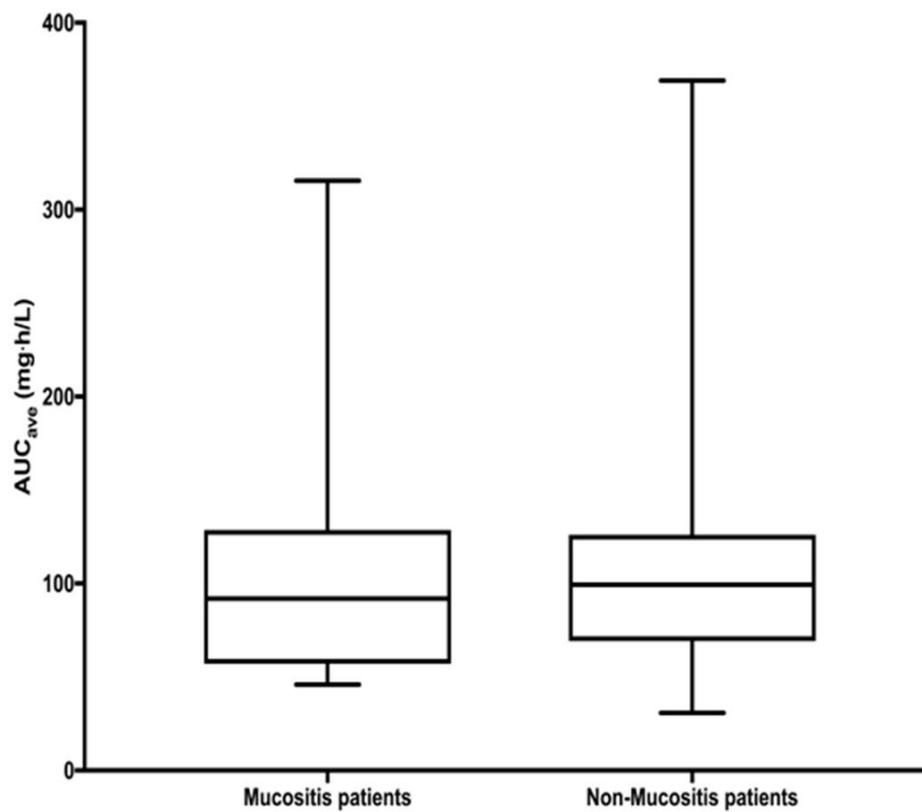
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