



# Treatment by Posaconazole Tablets, Compared to Posaconazole Suspension, Does Not Reduce Variability of Posaconazole Trough Concentrations

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**ABSTRACT** The delayed-release tablet formulation of posaconazole (POS-tab) results in higher plasma POS trough concentrations ( $C_{\min}$ ) than the oral suspension (POS-susp), which raises the question of the utility of therapeutic drug monitoring (TDM). We aimed to compare the variability of the POS  $C_{\min}$  for the two formulations and identify determinants of the POS-tab  $C_{\min}$  and its variability. Demographic, biological, and clinical data from 77 allogeneic hematopoietic stem cell transplant patients (874  $C_{\min}$ ) treated with POS-tab ( $n = 41$ ), POS-susp ( $n = 29$ ), or both ( $n = 7$ ) from January 2015 to December 2016 were collected retrospectively. Interpatient and within-subject coefficients of variation (CVs) of the  $C_{\min}$  adjusted to dose (D) were calculated for each formulation. Between-group comparisons were performed using a linear mixed effects model. The POS  $C_{\min}$  was higher for the tablet than for the suspension (median [25th–75th percentile]: 1.8 [1.2–2.4] mg/liter versus 1.2 [0.7–1.6] mg/liter,  $P < 0.0001$ ). Interpatient CVs for the tablet and suspension were 60.8 versus 63.5% ( $P = 0.7$ ), whereas within-subject CVs were 39.7 and 44.9%, respectively ( $P = 0.3$ ). Univariate analysis showed that age and treatment by POS-tab were significantly and positively associated with the POS  $C_{\min}$ , whereas diarrhea was associated with a diminished POS  $C_{\min}$ . Multivariate analysis identified treatment with POS-tab and diarrhea as independent factors of the POS  $C_{\min}$ , with a trend toward a lower impact of diarrhea during treatment with POS-tab ( $P = 0.07$ ). Despite increased POS exposure with the tablet formulation, the variability of the POS  $C_{\min}$  was not significantly lower than that of the suspension. This suggests that TDM may still be useful to optimize tablet POS therapy.

**KEYWORDS** hematopoietic stem cell transplantation, posaconazole, therapeutic drug monitoring, trough concentration, variability

Posaconazole (POS) is an antifungal agent widely used for prophylaxis of invasive fungal infections in patients with hematological malignancies at high risk, especially allogeneic hematopoietic stem-cell transplant (AHSCT) patients with graft-versus-host disease. Since 2015, POS has been commercially available in Europe as a new formulation, i.e., delayed-release tablets (POS-tab), allowing a single 300-mg dose per day (1). This new formulation improves POS bioavailability relative to the former oral suspension formulation (POS-susp) (2–4). Hence, the proportion of patients achieving the recommended target goal of  $>0.7$  mg/liter (5) while taking the tablet has increased over that of patients taking the oral suspension formulation (3, 6), which raises the question of the utility of POS therapeutic drug monitoring (TDM).

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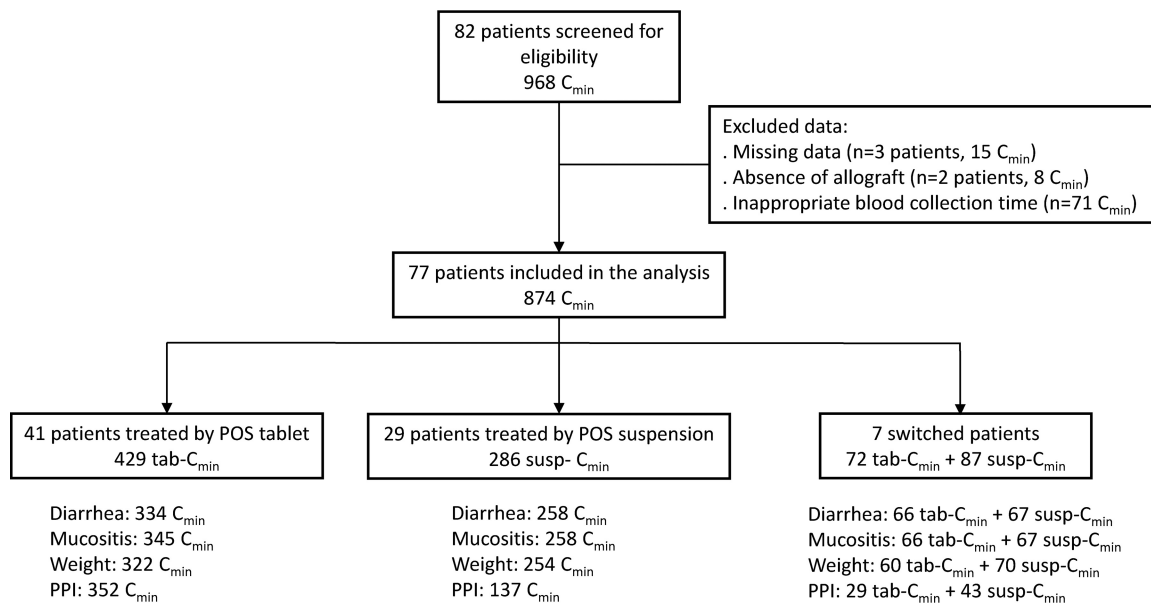
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**FIG 1** Flow chart. For each group of patients (tablet, suspension, and switched patients), the number of posaconazole trough concentrations (POS  $C_{min}$ ) for which potential factors that influence the POS  $C_{min}$  were known are specified at the bottom.

Increased POS exposure of patients using the tablet formulation over that of patients using the oral suspension is now well established (2–4). However, although the variability of the POS-susp trough concentrations ( $C_{min}$ ) is known to be significant, with interindividual and within-subject coefficients of variation (CV) as high as 64% and 49%, respectively (7), little is known about the variability of the POS-tab  $C_{min}$ . A recent crossover study showed lower within-subject CV for the POS-tab  $C_{min}$  in lung-transplant patients treated with POS-susp and then with POS-tab (8). However, the number of patients was quite low ( $n = 24$ ), and interindividual CVs were not studied. Moreover, determinants involved in such variability are yet to be clarified. Indeed, the impact of diarrhea (7), mucositis, and proton pump inhibitors (PPIs) on the POS  $C_{min}$  has been well described for POS-susp (9). However, the influence of these factors on the POS  $C_{min}$  during POS-tab therapy is not clear, as recent results are conflicting (3, 4, 10–14). For example, several studies reported a significant impact of diarrhea on the POS-tab  $C_{min}$  (11, 12), whereas others did not (4, 13–15).

The primary aim of this study was to compare the POS  $C_{min}$ , as well as its intra- and interindividual variability between the two galenic formulations (tablet versus suspension) in AHST patients. We further aimed to identify factors that influence the POS  $C_{min}$  and its variability.

## RESULTS

**Baseline characteristics of patients.** A total of 874 POS  $C_{min}$ , determined in 79 patients, were included in this study; 41 patients received POS-tab only, 31 received POS-susp only, and 7 switched from the suspension to the tablet formulation (see Fig. 1). The baseline characteristics of patients are shown in Table 1.

**Posaconazole trough concentrations and their determinants.** POS  $C_{min}$  were significantly higher during treatment with POS-tab than with POS-susp (Table 2; Fig. S1 in the supplemental material), resulting in a higher proportion of therapeutic POS  $C_{min}$  with POS-tab without reducing numbers of POS dose adjustment (Table 2). The results of univariate and multivariate analyses performed for all 874 POS- $C_{min}$  are shown in Table 3. Treatment with POS-tab was associated with a higher POS  $C_{min}$ , whereas the presence of diarrhea was significantly associated with a lower POS  $C_{min}$  (Table 3). Age was positively associated with the POS  $C_{min}$  in the univariate analysis, but did not reach statistical significance in the multivariate analysis. Conversely, mucositis, cotreatment

**TABLE 1** Baseline characteristics of patients<sup>a</sup>

Characteristic	All patients (n = 77)
<b>Demographics</b>	
Age (yrs)	53.0 (22.0–64.7)
Male (%)	41 (53.2)
Weight (kg)	64.0 (48.9–84.3)
<b>Underlying hematological diseases</b>	
Acute myeloid leukemia	35
Acute lymphoblastic leukemia	16
Myelodysplastic syndrome	11
Lymphoma	8
Chronic myeloid leukemia	1
Chronic lymphoblastic leukemia	1
Others <sup>b</sup>	5
<b>Longitudinal follow-up of POS treatment</b>	
Duration of follow-up (days)	84 (41–376)
No. of dose adjustments/patient	1 (0–2)
No. of POS C <sub>min</sub> /patient	9 (4–18)

<sup>a</sup>Data are indicated as numbers (%) or median (25th–75th percentiles).

<sup>b</sup>Others include one idiopathic medullary aplasia, two nondifferentiated acute leukemia, and two acute bichlonal leukemia.

with a PPI, and body mass index (BMI) were not associated with the POS C<sub>min</sub>. In addition, there was a trend toward an interaction (*P* = 0.07) between the presence of diarrhea and galenic formulation, suggesting a lower POS C<sub>min</sub> in the presence of diarrhea with the suspension versus the tablet formulation (Fig. S2).

**Variability of posaconazole plasma trough concentrations and its determinants.** There was a large range of POS C<sub>min</sub> among patients (Fig. 2 and 3), which translated into high intra- and interindividual variability of POS C<sub>min</sub>/dose (D), regardless of the galenic formulation (Table 2). CVs and within-subject CVs of POS-tab C<sub>min</sub>/D were slightly but not significantly lower than those of POS-susp (Table 2). Intra- and interindividual variability was not significantly associated with age, BMI, mucositis, diarrhea, or treatment with a PPI (Tables S1 and S2).

**TABLE 2** Description of plasma POS C<sub>min</sub> according to galenic formulation

Characteristic	POS-susp C <sub>min</sub>	POS-tab C <sub>min</sub>	<i>P</i> value
No. of POS C <sub>min</sub>	373	501	
<b>POS C<sub>min</sub> (mg/l)</b>			
Median <sup>a</sup> (25th–75th percentiles)	1.2 (0.7–1.6)	1.8 (1.2–2.4)	<0.0001
Minimum POS-C <sub>min</sub>	<0.1	<0.1	
Maximum POS-C <sub>min</sub>	4.7	8.2	
No. of therapeutic POS C <sub>min</sub> (%)	294 (79)	462 (92)	<0.0001
Median POS dose <sup>a</sup> (mg/day)	600 (600–800)	300 (200–300)	<0.0001
No. of POS dose adjustments (%)	39 (10.4)	48 (9.6)	0.7
<b>Coefficient of variation of POS C<sub>min</sub>/dose</b>			
Interindividual CV (%)	63.5	60.8	0.7
Within-subject CV (%)	44.9	39.7	0.3
<b>No. (%) of POS C<sub>min</sub><sup>b</sup> associated with:</b>			
<b>Mucositis</b>			
Yes	18 (5.5)	73 (17.7)	
No	307 (94.5)	338 (82.3)	
<b>Diarrhea</b>			
Yes	42 (12.9)	51 (12.7)	
No	283 (87.1)	349 (87.3)	
<b>Proton pump inhibitor</b>			
Yes	141 (78.3)	352 (92.4)	
No	39 (21.7)	29 (7.6)	

<sup>a</sup>Data are indicated as median (25th–75th percentiles).

<sup>b</sup>As indicated in Fig. 1, some data are missing. Thus, the percentage of POS-C<sub>min</sub> with these potential determinants could vary.

**TABLE 3** Mixed-effects model of potential determinants of POS  $C_{min}$

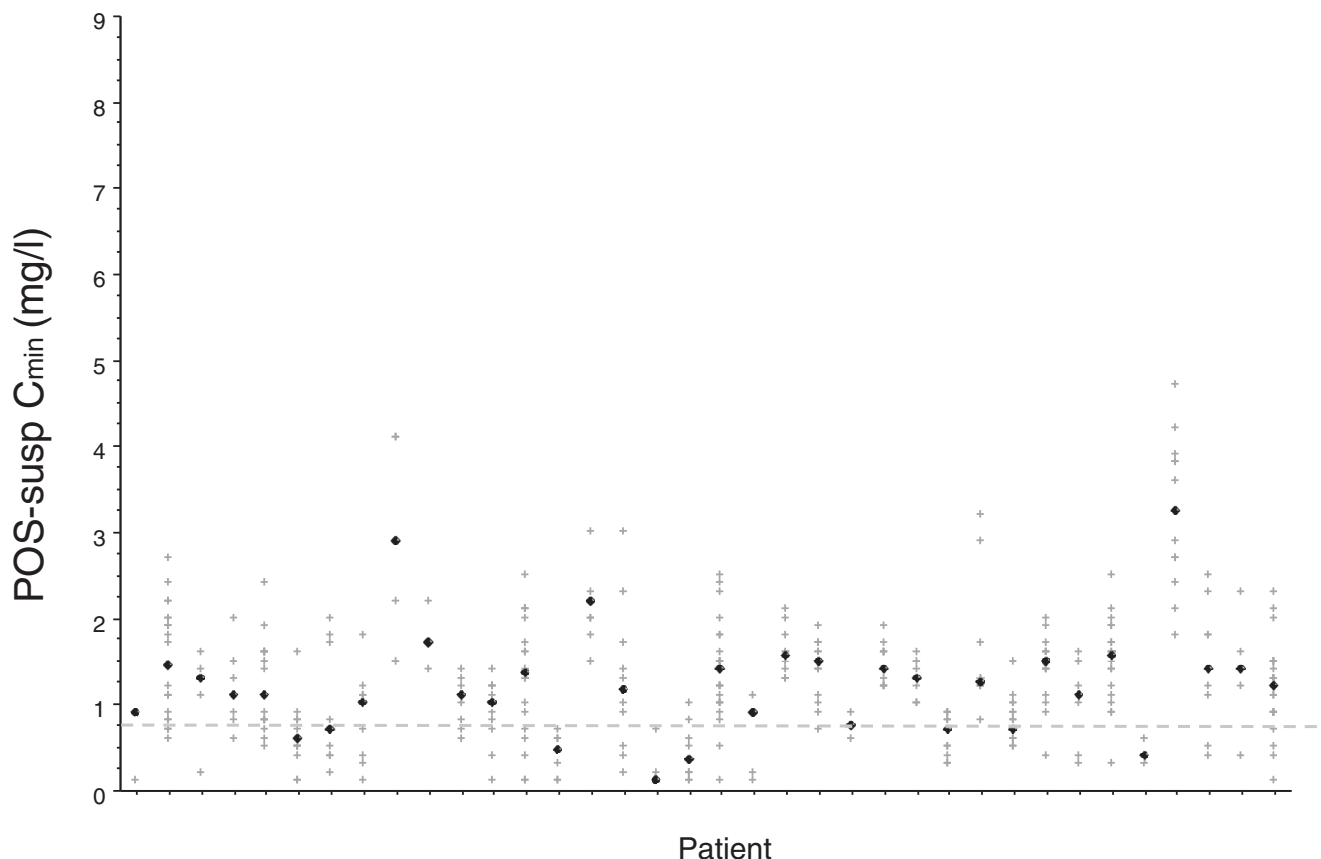
Variable	Nonmissing data (%)	Univariate analysis		Multivariate analysis	
		Estimate ± SE	P value	Estimate ± SE	P value
POS-tablet	100	0.92 ± 0.11	<0.001	1.13 ± 0.18	<0.001
Age	100	0.33 ± 0.07	<0.001	-0.19 ± 0.11	0.07
Body mass index	76	0.11 ± 0.03	0.72		
Proton pump inhibitor	76	0.14 ± 0.19	0.47		
Mucositis	82	0.11 ± 0.08	0.17		
Diarrhea	80	-0.37 ± 0.08	<0.001	-0.30 ± 0.07	<0.001

**Onset of invasive aspergillosis.** Invasive aspergillosis (IA) occurred in three patients treated with POS-tab (3/48) and four treated with POS-susp (4/36). The characteristics of these patients and their POS  $C_{min}$  are shown in the supplemental material (Table S3). The mean POS  $C_{min}$  per patient before IA diagnosis was 2.3 mg/liter for patients treated with POS-tab and 0.65 mg/liter for those treated with POS-susp.

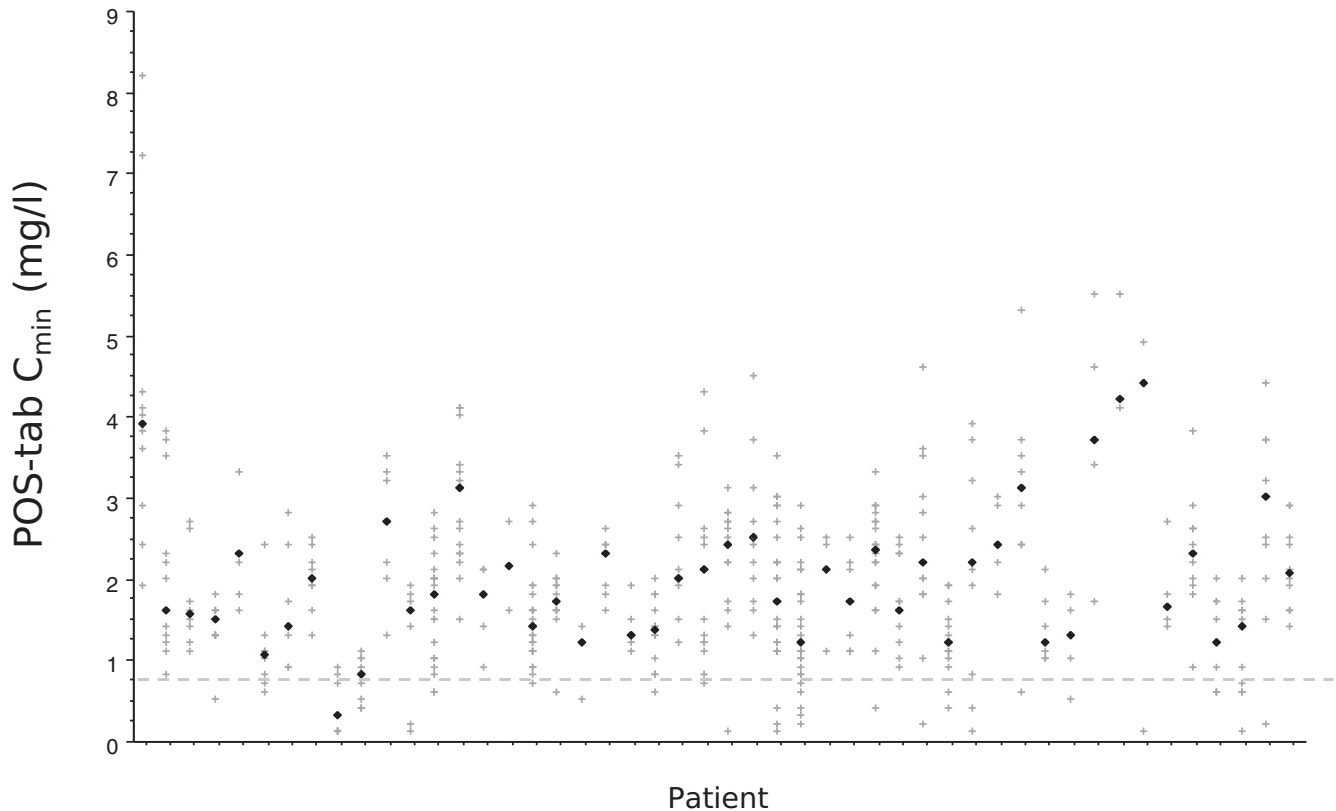
**DISCUSSION**

Retrospective analysis of 874 POS  $C_{min}$  measured in 77 AHST patients demonstrates that the POS tablet formulation results in higher POS exposure than the POS oral suspension, without reducing either inter- or intraindividual variability of the POS  $C_{min}$ .

**Enhanced exposure with posaconazole tablets.** POS  $C_{min}$  determined during longitudinal TDM of AHST patients were significantly higher during POS-tab treatment than those obtained with POS-susp, in accordance with the results of a phase III study



**FIG 2** Variability of plasma posaconazole (POS) trough concentration ( $C_{min}$ ) in 36 patients treated with POS suspension. Each vertical series of crosses corresponds to repetitive POS trough concentrations in one patient, with the black diamond indicating the median POS  $C_{min}$  per patient. The dotted line indicates the prophylactic threshold of POS  $C_{min}$  (5).



**FIG 3** Variability of plasma posaconazole (POS) trough concentration ( $C_{\min}$ ) in 48 patients treated with POS tablet. Each vertical series of crosses corresponds to repetitive POS trough concentrations in one patient, with the black diamond indicating the median POS  $C_{\min}$  per patient. The dotted line indicates the prophylactic threshold of POS  $C_{\min}$  (5).

of POS-tab (4) and several other retrospective studies (2, 3, 6, 11, 13, 16). Logically, this increased POS exposure resulted in a higher percentage of therapeutic POS  $C_{\min}$  with POS-tab but did not reduce the number of POS dose adjustments. The magnitude of the increase in POS  $C_{\min}$  that we observed (mean increase of 0.6 mg/liter, which represents a 1.5-fold increase) for POS-tab is close to that previously reported by Pham et al. (1.4-fold increase) (6) and Jung et al. (2.5-fold increase) (2).

**Determinants of posaconazole trough concentrations.** Among the potential determinants of POS  $C_{\min}$ , we explored diarrhea, mucositis, age, BMI, and concomitant treatment with a PPI. We found a significant impact of diarrhea, which decreased the POS  $C_{\min}$  in both univariate and multivariate analyses. This finding is in accordance with the previously described negative impact of diarrhea on POS-susp  $C_{\min}$  (7, 9) but also with several retrospective studies conducted in hematological patients treated with POS-tab (11, 12, 15). However, the impact of diarrhea appeared to be lower during POS-tab therapy than POS-susp treatment (Figure S2), even if the interaction did not reach statistical significance. The lower magnitude of the effect of diarrhea with the tablet might explain why other studies did not find an influence of diarrhea on POS-tab  $C_{\min}$  (13, 16). However, other factors could be involved, such as heterogeneous study populations, i.e., lung-transplant recipients and hematological patients (16) or hematological patients without a distinction between allografted or nonallografted patients (13).

In addition, we found a positive association between age and POS  $C_{\min}$  in univariate analyses, which is in accordance with previous studies performed in hematological patients treated with POS-susp (7, 17) or POS-tab (18). However, this association did not reach significance in multivariate analyses, suggesting that the influence of age on POS  $C_{\min}$  was dependent on another variable in our cohort.

Conversely, we found no effect of BMI, mucositis, or PPI cotreatment on the POS  $C_{\min}$ , whereas several studies did (3, 11, 19). However, these studies were not all comparable in terms of sample size and patient inclusion criteria, which could explain, at least in part, these discrepancies.

**Variability of posaconazole trough concentrations.** The originality of our study consists of the comparison of intra- and interindividual variability of POS  $C_{\min}/D$  for both galenic formulations. As dose adjustments occurred during longitudinal TDM (Table 1 and 2), we adjusted the POS  $C_{\min}$  for the POS dose to overcome this factor of variability. Although the interindividual CV and within-subject CV of the POS  $C_{\min}/D$  were lower for the POS-tab than for the POS-susp (Table 2 and Fig. 2 and 3), the difference was small and neither clinically relevant nor statistically significantly different, suggesting that the variability of POS-tab  $C_{\min}$  is still as large as that of POS-susp  $C_{\min}$  (20). Aside from one study, which reported lower POS  $C_{\min}$  variability with the tablet regimen in 24 lung-transplant patients (8), such a comparison of the intra- and interpatient variability of POS  $C_{\min}$  between the two oral galenic formulations of POS has never been performed. Several studies reported CVs for the POS-tab  $C_{\min}$ , but comparing CV values is problematic since calculation methods of CV differ. Here, we used the method described by Bland (21) to calculate within-subject CV, whereas a different approach was used in other studies, i.e., the ratio between standard error and the mean POS  $C_{\min}$  in each patient (18, 22). Finally, as explained above, we adjusted the POS  $C_{\min}$  for the POS dose in our cohort, which was not done in the other studies (18, 22). Moreover, differences in study populations may also account for the differences observed between the studies. For example, the within-subject CV of the POS-tab  $C_{\min}$  was 39.7% in AHST patients in our study, whereas it was estimated to be 16% in 24 lung transplant recipients and 48% in 15 patients with hematological malignancies (18). Despite the significant variability of POS  $C_{\min}$ , we did not identify any variable associated with such variability in our cohort, suggesting that factors other than those studied here, such as genetic variants of UGT1A4 (23) or reduced hepatic function, still need to be investigated.

**Efficacy of posaconazole.** Finally, the central question is probably the efficacy of POS-tab relative to that of POS-susp. In our study, we could not perform any statistical analysis to compare the number of treatment failures between groups, because episodes of IA were very rare during POS therapy, regardless of the galenic formulation used. In addition, the retrospective design of our study and heterogeneity in follow-up enhance the risk of bias. To date, only one study has demonstrated a lower number of IA episodes during treatment with POS-tab than POS-susp (15), whereas others have reported similar rates of invasive fungal infections between the two galenic formulations (3, 13, 24, 25). In our cohort, we reported treatment failure in 6.3% of patients receiving POS-tab (3/48), although all these patients had a therapeutic POS  $C_{\min}$ . Such findings have already been described for POS-susp (13, 18), which suggests that some therapeutic failures may not be related to insufficient POS exposure.

**Limitations.** Our study had several limitations. First, this study was retrospective and performed in a single center. Thus, some data were missing, especially for potential factors influencing the POS-tab  $C_{\min}$  (allograft-versus-host disease, PPI, weight, and gradation of diarrhea and mucositis). In the same vein, POS safety was not evaluated, while high POS  $C_{\min}$  could be associated with occurrence of adverse events as recently described in several case reports (14, 18, 26, 27). Despite these limitations, our study also had several strengths, since it is notably the first study to compare the variability of the POS  $C_{\min}$  between POS-susp and POS-tab. In addition, our study was conducted in a homogeneous and large population of recipients of allograft stem-cell transplantation (77 patients and 874 POS  $C_{\min}$ ), which is not true of several previous studies (3, 11, 12, 16).

**Conclusion.** Although the tablet formulation increased POS exposure, variability of the POS  $C_{\min}$  was still high and not significantly lower than that observed with the oral

suspension. Therefore, these results suggest that TDM may still be useful for AHSCT patients treated with POS-tab.

## MATERIALS AND METHODS

**Study design.** This retrospective study was conducted at the Grenoble University Hospital, France. Adult (>18 years old) AHSCT patients with graft-versus-host disease, treated with POS according to the European Conference on Infections in Leukemia 6 guidelines (5), with longitudinal TDM (defined by at least three POS  $C_{\min}$  determinations per patient and per galenic form) from January 2014 to December 2016 were eligible (see Fig. 1 for details). Demographic (age, sex) and clinical data (diarrhea, mucositis, and weight), as well as records concerning POS therapy (daily dose, galenic form, and POS  $C_{\min}$ ) and concomitant PPI treatment were collected retrospectively. Concerning the factors that could potentially affect the POS  $C_{\min}$ , we considered only those that are concomitant to the determination of the POS  $C_{\min}$ . For clinical events (diarrhea, mucositis), we considered only those that occurred within 7 days before the POS  $C_{\min}$  determination. Similarly, only PPI therapy initiated at least 7 days before measuring the POS  $C_{\min}$  was considered. Due to the retrospective design of our study, some data are missing, especially for potential determinants of the POS-tab  $C_{\min}$  (see Fig. 1 for details). Concerning comedications, only PPIs were considered to be a risk factor in our model, but the absence of any other drug that could interact with POS was carefully checked. All patients gave written consent for collection and use of their data.

**Posaconazole therapeutic drug monitoring.** All patients received POS for prophylaxis of invasive fungal infection. Patients treated with POS-susp were asked to take their POS with an acidic beverage to improve POS absorption. All patients treated with POS received regular POS TDM. Blood samples were drawn just before drug intake or at least 20 h after intake for the POS-tab. After treatment initiation or dose adjustment, a 7-day period was considered necessary to obtain a pharmacokinetic steady state. POS  $C_{\min}$  were excluded in case of inappropriate blood collection time (sample handled before pharmacokinetic steady state or less than 20 h after POS-tab intake) (see Fig. 1 for details). Plasma POS  $C_{\min}$  were measured by validated liquid chromatography tandem-mass spectrometry, as previously described (28). The plasma drug standard curve ranged from 0.1 to 20 mg/liter with adequate between-day and within-day variabilities ( $CV < 15\%$ ) and accuracy. A therapeutic threshold of 0.7 mg/liter defined for prophylaxis was considered (5).

**Evaluation of efficacy.** The efficacy of POS was assessed by the absence of invasive fungal infections (especially infections due to *Aspergillus* spp.) during the follow-up period for each patient. The follow-up period was defined as the time elapsed between the initiation of POS therapy and the last determination of the POS  $C_{\min}$ . All cases were prospectively reviewed monthly by a multidisciplinary team including chest physicians, a microbiologist, a hygienist, and a pharmacologist (29). Cases were classified according to guidelines from the European Organization for Research and Treatment of Cancer/European Invasive Infections Cooperative Group and the criteria of the National Institute of Allergy and Infectious Diseases-Mycoses Study Group (EORTC/MSG) (30).

**Statistical analysis.** Categorical variables are expressed as frequencies (and percentages) and quantitative variables, as medians (with the 25th to 75th percentiles). The analysis of POS exposure, depending on galenic formulation or potential determinants, was performed for the POS  $C_{\min}$ , whereas the study of variability was performed on the POS  $C_{\min}$  adjusted for dose ( $C_{\min}/D$ ) to overcome the influence of dosage adjustments occurring during longitudinal follow-up. CVs and within-subject CVs were calculated as previously described (21) for each POS formulation to assess inter- and intraindividual variability, respectively. They were subsequently compared using a method adapted from Levene's test. As some patients received both formulations, we used mixed effects models, in which the formulation was a fixed factor and the patient a random factor. We performed a log transformation of the  $C_{\min}/D$  ratio because the data were not normally distributed. A  $P$  value of 0.05 was considered statistically significant. Statistical analyses were performed with SPSS Statistics version 21 (IBM, Armonk, NY, USA).

## SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at <https://doi.org/10.1128/AAC.00484-19>.

**SUPPLEMENTAL FILE 1**, PDF file, 0.1 MB.

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We declare no conflict of interest.

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