ORIGINAL RESEARCH ARTICLE

Pharmacokinetic and Exposure Response Analysis of the Double-Blind Randomized Study of Posaconazole and Voriconazole for Treatment of Invasive Aspergillosis

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Abstract

Background and Objective A double-blind phase 3 study was conducted to compare posaconazole 300 mg intravenously (IV)/300 mg orally once daily (twice daily day 1) with voriconazole 4 mg/kg IV twice daily/200 mg orally twice daily (6 mg/kg day 1) for treatment of invasive aspergillosis. This analysis was conducted to summarize the pharmacokinetics and exposure–response relationships of posaconazole and voriconazole using plasma trough concentration (C_{trough}) as a surrogate for exposure from the double-blind phase 3 study.

Methods The pharmacokinetic evaluable population included all intention-to-treat (ITT) participants with at least one plasma concentration during the treatment period. Treatment blinding was maintained without therapeutic drug monitoring. C_{trough} sampling occurred throughout treatment; efficacy and safety were evaluated using quartiles determined by mean C_{trough} concentrations. Exposure efficacy variables included day 42 all-cause mortality (primary study endpoint) and global clinical response. Exposure safety variables included all adverse events and treatment-related adverse events.

Results The pharmacokinetic analysis population included 506 of 575 ITT participants (437 with C_{trough} concentrations: 228 posaconazole, 209 voriconazole). No trend was seen across quartiles of posaconazole C_{trough} for the key efficacy endpoint of all-cause mortality through day 42. Participants in the highest quartile of voriconazole C_{trough} had higher all-cause mortality through day 42 than participants in the lower three quartiles of voriconazole C_{trough}. Similar findings were observed for global clinical response and C_{trough}. No clear exposure safety trend by quartile was seen for posaconazole or voriconazole.

Conclusions A strong exposure–response relationship was not observed across the range of exposure from the administered doses and formulations for posaconazole or voriconazole.

Trial registration: NCT01782131; registered January 30, 2013.

Key Points

A clear relationship between posaconazole exposure or voriconazole exposure and efficacy was not observed at the plasma exposures reached by the administered doses or drug formulations in the phase III randomized study.

The incidence of adverse events across plasma exposure quartiles was similar to those observed in the phase III ITT populations for both posaconazole and voriconazole.

Extended author information available on the last page of the article

1 Introduction

Patients who are immunocompromised —including those with prolonged neutropenia, those who underwent allogeneic hematopoietic stem cell transplantation or solid organ transplantation, those with inherited or acquired immunodeficiencies, and those who use corticosteroids—are at risk of invasive aspergillosis [1]. Guidelines recommend use of voriconazole or isavuconazole for the primary treatment of invasive aspergillosis [1–3].

Voriconazole is a triazole antifungal metabolized primarily by the hepatic cytochrome P450 enzymes CYP2C9, CYP2C19, and CYP3A4. CYP2C19 has genetic polymorphisms that cause large differences in the pharmacokinetics

of voriconazole across patients, and CYP450-based therapies have known drug–drug interactions with voriconazole [4–6]. When administered orally, voriconazole reaches maximum concentration in < 2 h [6]. Steady state plasma concentrations are achieved after 5–7 days of treatment, but the time to achieve steady state can be reduced with a loading dose [6]. Voriconazole has non-linear pharmacokinetics in the therapeutic range, with maximal concentration and the area under the concentration–time curve value increasing disproportionately with dose increases, possibly because of the saturation of hepatic metabolism; the half-life is also dose dependent [6]. Because of concerns about voriconazole's variable pharmacokinetics and potential drug–drug interactions, alternatives for the treatment of invasive aspergillosis are needed.

Posaconazole is a broad spectrum triazole approved as an injection, a delayed release tablet, and an oral suspension for the prevention of invasive fungal disease in selected patients who are immunocompromised [7, 8]. Posaconazole is also approved for salvage treatment of patients with invasive aspergillosis [8]. Once at steady state (by day 8), maximum concentration of posaconazole delayed release tablets is reached within 4 h of dosing, and bioavailability is superior to that of the posaconazole oral suspension (i.e., not impacted by food, gastric pH, or gastric motility) [9–12].

Adverse events (AEs) frequently reported for triazoles include nausea, vomiting, diarrhea, abdominal pain, and hepatotoxicity [13]. Voriconazole is also associated with specific drug-related AEs of visual disturbances, rashes, alopecia, periostitis, and QT prolongation; an exposure–safety relationship was observed between plasma trough concentrations (C_{trough}) of voriconazole and the risk of developing hepatotoxicity [13, 14].

In a recent randomized double-blind phase 3 study of the primary treatment of invasive aspergillosis, posaconazole [intravenous (IV) or oral 300 mg twice on day 1, then 300 mg once a day thereafter] was non-inferior to voriconazole (6 mg/kg IV or 300 mg orally twice on day 1, followed by 4 mg/kg IV or 200 mg orally twice a day thereafter) for all-cause mortality at day 42 [primary endpoint; 15% of participants in the posaconazole group, 21% in the voriconazole group; treatment difference −5.3%, 95% confidence interval (CI) (−11.6, 1.0); $p < 0.0001$] (ClinicalTrials.gov, NCT01782131) [15]. The secondary endpoint of global clinical response in the full analysis set (FAS) population was similar for posaconazole and voriconazole at week 6 in 45% of participants who received posaconazole and 46% of participants who received voriconazole [treatment difference 0.6% (95% CI −11.2, 10.1)] [15]. The overall incidence of treatment-related adverse event (TRAE) rates in the intention-to-treat (ITT) population was 30% for posaconazole and 40% for voriconazole [treatment difference −10.2% 95% CI −17.9, −2.4)] [13]. This study used the approved

formulations and dosages for both the IV and the tablet formulations of posaconazole and voriconazole. Considering the interpatient pharmacokinetic variability of both interventions, it is important to evaluate the relationship between clinical success and adequate levels of plasma exposure [6, 16]. Several previous studies used voriconazole and posaconazole plasma concentrations as surrogates for exposure to evaluate the relationship between plasma concentration and efficacy and safety [6, 16, 17]. The exposure response analyses for efficacy and safety from the current study is another key secondary objective that has not been reported.

The objectives of the present study were to summarize the pharmacokinetics and assess the exposure response for posaconazole and voriconazole from this phase 3 study, including exposure efficacy and exposure safety relationships.

2 Methods

2.1 Ethics

All participants or their legal representatives gave written informed consent before initiation of any study procedures. The study was conducted in accordance with the principles of good clinical practice. The protocol and all amendments were reviewed and approved by the institutional review boards or independent ethics committees at all study sites before being initiated at each site.

2.2 Study Design and Participants

All participants were enrolled in the international (26 countries) 91-site double-blind phase 3 study being conducted to compare posaconazole 300 mg IV or 300 mg orally once daily (twice daily on day 1) with voriconazole 4 mg/kg IV twice daily or 200 mg orally twice daily (day 1 6 mg/kg IV or 300 mg orally twice daily) for the treatment of invasive aspergillosis (ClinicalTrials.gov, NCT01782131; Merck & Co., Inc., Rahway, NJ, USA protocol number MK-5592-069) [15]. Most participants were given initial therapy via the IV route; however, some were given initial therapy via the oral route. Azole therapy was switched from the IV route to the oral route when the participant was considered clinically stable and able to take oral medication.

The study design and inclusion and exclusion criteria are described in detail elsewhere [15]. Briefly, participants aged ≥ 13 years were eligible if they had features consistent with proven, probable, or possible invasive aspergillosis, as defined by Mycoses Study Group and European Organization for Research and Treatment of Cancer consensus criteria [18], with a likelihood to upgrade the diagnosis to proven or probable infection within the first 7 days of treatment. A subsequent protocol modification allowed for the inclusion

of individuals with neutropenia of any duration as an acceptable host factor [15].

Randomly assigned participants who received at least one dose of study drug were included in the ITT population for evaluation of safety and the primary efficacy endpoint of all-cause mortality at day 42. The secondary objective of global clinical response of success at weeks 6 and 12 was evaluated in the FAS population, which included all participants in the ITT population with proven or probable invasive aspergillosis per independent adjudication. The pharmacokinetic-evaluable population included all ITT participants for whom at least one plasma concentration was available during the treatment period, and the pharmacokinetic evaluable C_{trough} population included all participants with available plasma concentration data who met trough sample timing.

2.3 Pharmacokinetics Sampling

Steady state C_{trough} samples were collected before each dose on day 7, week 2, week 4, week 6, and week 12 [end of treatment (EOT)]. If a participant discontinued early, a trough level sample (before dose, if possible) was collected at the time of study discontinuation, and the time of sampling was noted.

Plasma posaconazole concentrations were determined by PPD, Inc. (Richmond, VA, USA) using a validated high-performance liquid chromatography–tandem mass spectrometry (HPLC–MS/MS) method. The analytical range for posaconazole was 5–5000 ng/mL in human plasma [19]. Plasma voriconazole concentrations were determined by Syneos Health Clinique, Inc. (Quebec City, PQ, Canada) using a validated HPLC–MS/MS method [20]. The analytical range for voriconazole was 5–2000 ng/mL in human plasma.

Plasma C_{trough} levels were defined as those for which the time since last dose was 16–32 h for posaconazole (administered once daily) and 8–16 h for voriconazole (administered twice daily) or for which the plasma sample of either drug was taken at the same time as the next dose. Summary statistics for the pooled posaconazole or voriconazole C_{trough} sample for each study visit were determined for three groups of participants, defined as those who received (a) IV administration only, (b) oral administration only, or (c) both IV and oral administration because of switching at least once between these. Treatment blinding was maintained without therapeutic drug monitoring.

2.4 Exposure Response Evaluations

Exposure response relationships for posaconazole and voriconazole were evaluated using summary statistics and by plotting data on a graph for efficacy and safety endpoints. For the efficacy endpoints (all-cause mortality through day 42 and global clinical response at week 6), exposure was

characterized by the within-participant arithmetic mean of plasma C_{trough} obtained through week 6 (when the endpoints were assessed). For each efficacy endpoint, participants were stratified into quartiles on the basis of the mean plasma C_{trough}, and results were determined for each quartile. For the safety endpoints (TRAEs and specific categories of tier 1 AEs) (see Sect. 2.5), exposure was characterized by the within-participant arithmetic mean of plasma C_{trough} obtained through week 12. In addition, the exposure–safety relationship for all AEs was evaluated for posaconazole using summary statistics and assessing number (percentage) of participants in each of the exposure quartiles with a particular AE or with any AE undergoing specific standard of care. For each safety endpoint, participants were stratified into quartiles on the basis of the mean plasma C_{trough}, and results were determined for each quartile.

The endpoint responses were also determined in the group of participants for whom no plasma C_{trough} was available. For the week 12 timepoint, plasma concentrations for participants who completed the week 12 visit were aggregated with those of participants who discontinued study therapy early and had an early EOT visit.

2.5 Safety

Detailed safety was previously reported [15]. Briefly, safety included the incidence of treatment emergent adverse events (TEAEs) and TRAEs and the incidence of serious AEs, summarized by treatment group. Safety analyses followed a tiered approach. Tier 1 events included hepatic laboratory changes (defined as elevated aspartate aminotransferase or alanine aminotransferase concentrations ≥ 3 times the upper limit of normal, elevated total bilirubin concentration ≥ 2 times the upper normal limit, and alkaline phosphatase concentration < 2 times the upper normal limit), central nervous system (CNS) and visual safety AEs (TEAEs related to visual and CNS disturbances), dermatological AEs (TEAEs, including rash and photosensitivity rash), and adrenal steroidogenesis and vascular AEs (TEAEs indicating adrenal insufficiency or temporally associated hypotension).

3 Results

3.1 Pharmacokinetic Analysis Population

The overall pharmacokinetic analysis population consisted of 506 of 575 participants (88%) in the ITT population who had at least one reported posaconazole or voriconazole plasma concentration at any time during the treatment period. Sixty-nine of 575 participants (24 treated with posaconazole and 45 with voriconazole) in the ITT population had no reportable plasma concentrations. A total of 437 of

506 participants (228 who received posaconazole and 209 who received voriconazole) in the overall pharmacokinetic analysis population had at least one plasma C_{trough}. The remaining 69 of 506 participants (36 in the posaconazole arm and 33 in the voriconazole arm) had reported plasma concentrations that did not meet the timing criteria to be considered a trough concentration; of the excluded samples, > 80% could not be considered trough samples because they were drawn too soon after the next dose had been administered. The pharmacokinetic and exposure response populations are summarized in Supplementary Table S1.

3.2 Steady State Pharmacokinetic Summary

Pooled mean posaconazole plasma C_{trough} approached steady state by the end of week 1. Geometric mean posaconazole C_{trough} was approximately 1500 ng/mL through week 12 with high variability (percentage geometric mean coefficient of variation, approximately 70%–90%) (Table 1). Mean posaconazole plasma C_{trough} for participants who started and remained on posaconazole IV were 3%–53% higher than for participants who either started and remained on posaconazole tablet or transitioned between posaconazole IV and posaconazole tablet before week 12 or EOT (Fig. 1). For the week 12 timepoint, posaconazole concentrations for participants who completed the week 12 visit were aggregated with those from participants who discontinued study therapy early and had an EOT visit before week 12; therefore, these results should be interpreted with caution.

Pooled mean voriconazole plasma C_{trough} was approximately 4200 ng/mL at week 1, then decreased approximately 50% over the first 4 weeks of dosing (Table 1). Mean voriconazole plasma C_{trough} for participants who started on voriconazole IV was 2.5-fold higher for the first 2 weeks of treatment than voriconazole plasma C_{trough} for participants who started on oral voriconazole (Fig. 2). Voriconazole

Table 1 Summary statistics for trough plasma concentrations pooled across participants by drug

Week	N	Mean (ng/mL)	SD (ng/mL)	Min (ng/mL)	Median (ng/mL)	Max (ng/mL)	CV (%)	GM (ng/mL)	GM CV (%)
Posaconazole IV or tablet 300 mg once daily (twice daily on day 1)									
1	183	1658	980.6	280.0	1460	5040	59.16	1386	68.76
2	160	1867	1221	228.0	1545	7030	65.39	1521	73.98
4	146	1843	1190	184.0	1570	7310	64.54	1494	77.12
6	123	1859	1195	26.40	1570	6290	64.27	1502	82.66
12/EOT	111	2007	1263	39.10	1770	6230	62.92	1577	93.12
Voriconazole IV 4 mg/kg twice daily (6 mg/kg on day 1) or capsule 200 mg twice daily (300 mg twice daily on day 1)									
1	174	4208	3128	59.32	3335	14199	74.34	2820	149.0
2	150	3304	2882	144.0	2491	14191	87.22	2219	129.4
4	120	2204	2099	2.500	1603	14700	95.25	1300	215.4
6	104	2055	1829	2.500	1610	11991	89.02	1214	220.5
12/EOT	106	2616	3120	2.500	1869	15930	119.2	1237	352.8

CV coefficient of variation, *EOT* end of treatment, *GM* geometric mean, *IV* intravenous, *Min* minimum, *Max* maximum

Fig. 1 Mean [standard deviation (SD)] posaconazole C_{trough} for participants receiving only posaconazole tablets (grey circle, grey solid line), participants receiving posaconazole IV only (black circle, dotted line), and participants starting on posaconazole IV and switching between IV and tablet (open square, solid line). Week 12 includes EOT concentration data. C_{trough} trough concentration, *EOT* end of treatment, *IV* intravenously
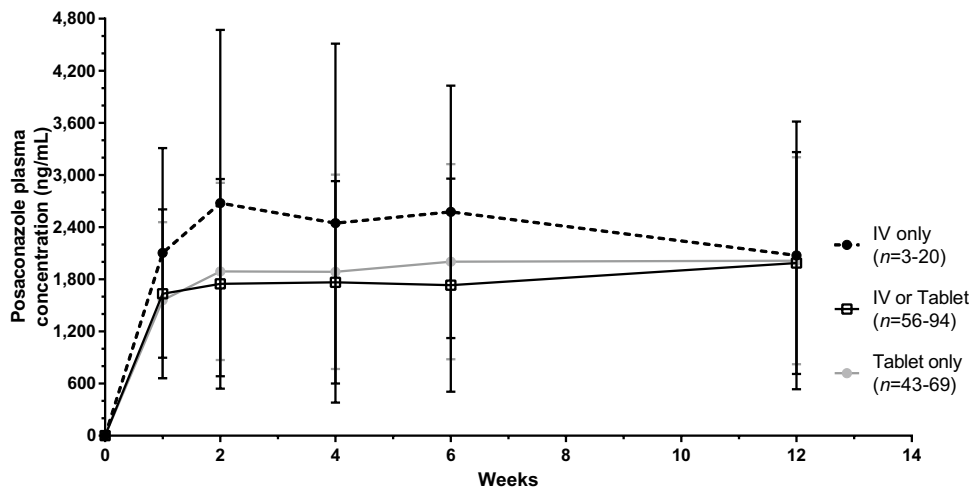
Fig. 2 Mean (SD) voriconazole C_{trough} in participants receiving only voriconazole capsules (grey circle, grey solid line), participants receiving only voriconazole IV (black circle, dotted line), and participants starting on voriconazole IV and switching between IV and capsule (open square, solid line). Week 12 includes EOT concentration data. C_{trough} trough concentration, *EOT* end of treatment, *IV* intravenous
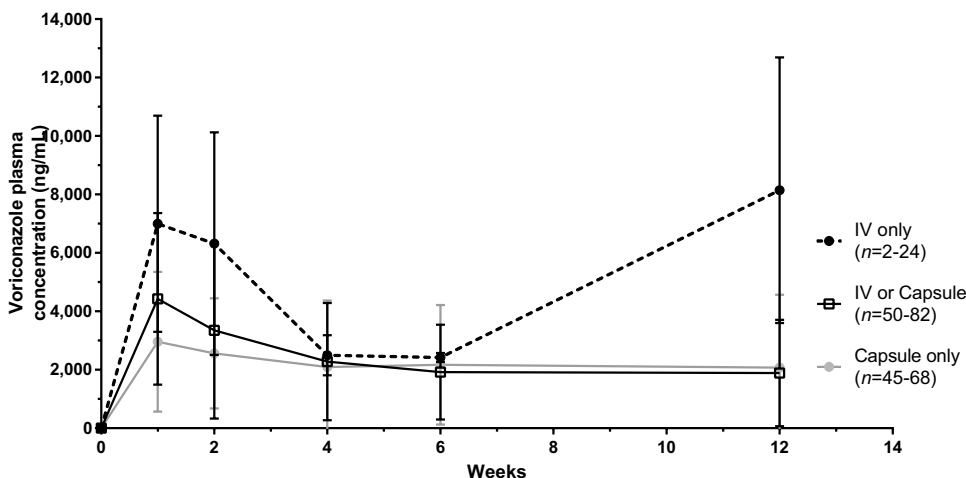
plasma concentrations were highly variable, with approximately 25% of participants having $C_{trough} > 4000$ ng/mL. Similar to posaconazole concentrations, the voriconazole concentrations for the week 12 visit and the EOT visit were aggregated and should be interpreted with caution.

3.3 Exposure Efficacy

In addition to exploring efficacy relationships by quartile based on C_{trough} (Table 2), efficacy endpoint data were summarized for participants with no available C_{trough} data. For participants who received posaconazole and had evaluable C_{trough} exposure data, there was no discernible trend across quartiles of posaconazole plasma C_{trough} for the key efficacy endpoint of all-cause mortality through day 42 in the ITT population. Participants without evaluable posaconazole exposure data had higher mortality rates (Fig. 3a). Similarly, for clinical response at week 6, there was no clear trend across quartiles of posaconazole plasma C_{trough} in participants with evaluable exposure data, whereas rates of clinical

failure were two-fold higher in participants who did have evaluable exposure data (Fig. 3b).

All-cause mortality through day 42 was higher in participants in the highest quartile (Table 2) of voriconazole plasma C_{trough} than in participants in quartiles 1–3 of voriconazole plasma C_{trough} (Fig. 4a). The number of participants in the non-evaluable exposure group (approximately 28% of all voriconazole-treated participants) was higher than the number of participants in any of the exposure quartiles. As with posaconazole plasma C_{trough}, efficacy outcomes were poorer in participants who did not have voriconazole plasma C_{trough} pharmacokinetic data. A similar trend was observed for success versus failure in global clinical response at week 6 in the FAS population (Fig. 4b).

3.4 Exposure Safety

Exposure–safety relationships of posaconazole and voriconazole by quartile of exposure were evaluated for TRAEs (Fig. 5). For posaconazole, although the proportion of participants with TRAEs was highest in the maximum quartile

Table 2 C_{trough} quartile ranges for posaconazole and voriconazole (ITT population)[a]

	Q1	Q2	Q3	Q4
Posaconazole quartile				
Exposure efficacy range (ng/mL)	244–994	994–1624	1624–2323	2323–5663
	$n = 56$	$n = 55$	$n = 56$	$n = 55$
Exposure safety range (ng/mL)	244–1046	1046–1624	1625–2274	2274–5550
	$n = 57$	$n = 57$	$n = 57$	$n = 57$
Voriconazole quartile				
Exposure efficacy range (ng/mL)	59–1534	1534–2865	2865–4502	4502–14566
	$n = 52$	$n = 51$	$n = 52$	$n = 52$
Exposure safety range (ng/mL)	59–1368	1338–2607	2607–4094	4094–14566
	$n = 53$	$n = 52$	$n = 52$	$n = 52$

ITT intention-to-treat, *Q* quartile

[a]No evaluable exposure data: posaconazole $n = 66$, voriconazole $n = 81$

Fig. 3 Posaconazole exposure data. **a** All-cause mortality through day 42 by quartiles of within-participant mean posaconazole plasma C_{trough} (ITT population). **b** Global clinical response at week 6 by quartile of within-participant mean posaconazole plasma C_{trough} (FAS population). C_{trough} trough concentration, *FAS* full analysis set, *ITT* intention-to-treat, *Q* quartile
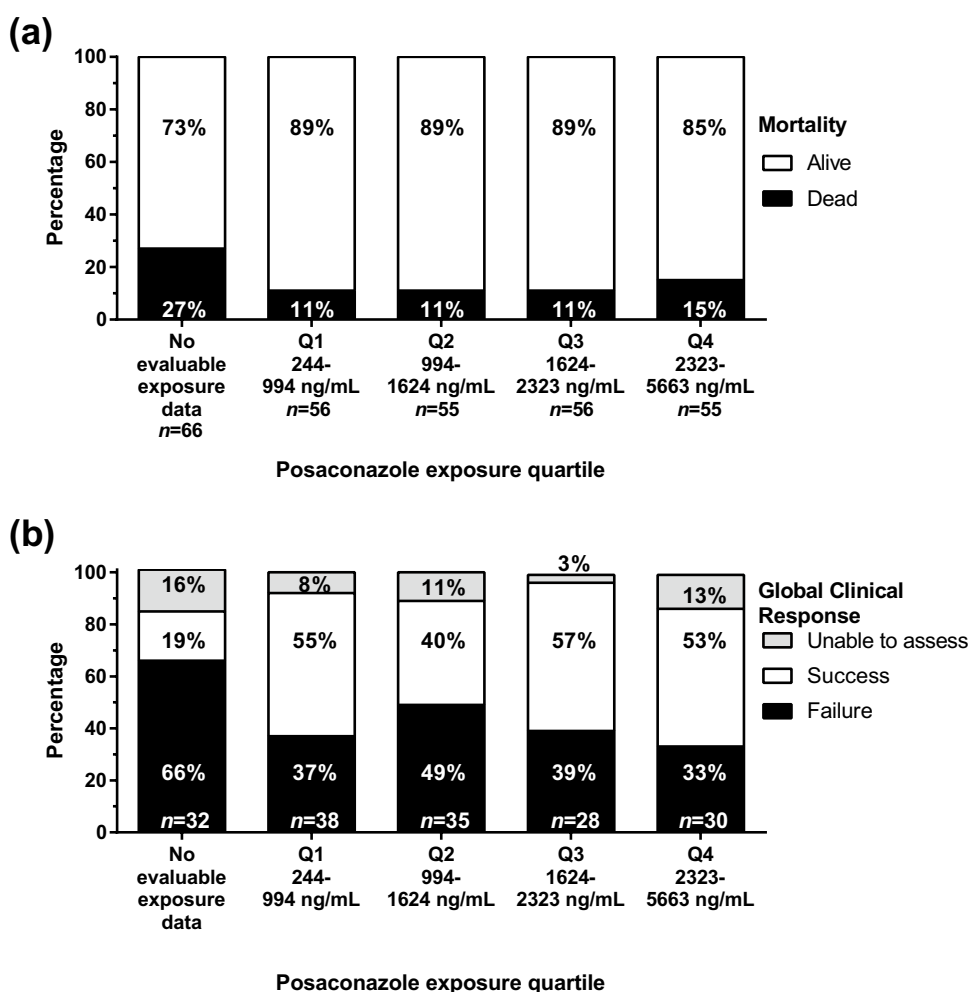
of exposure (Fig. 5a), no clear evidence of an exposure-related pattern was observed for most of the commonly reported AEs (those reported by ≥ 10% of participants) or system organ classes (Supplementary Table S2). The distributions of posaconazole C_{trough} were similar for participants with and without tier 1 CNS and visual safety AEs.

The incidence of TRAEs was similar across all quartiles of voriconazole mean C_{trough} (Fig. 5b). The distribution of voriconazole C_{trough} was similar for participants with and without tier 1 CNS and visual safety AEs and with and without tier 1 dermatological reaction AEs (data not shown).

4 Discussion

This was an exposure response analysis from the phase 3 double-blind, double-dummy study that previously showed that posaconazole was non-inferior to voriconazole with regard to the primary endpoint of all-cause mortality up to day 42 in the ITT population, and the number of TRAEs with posaconazole was 10% lower than with voriconazole

[15]. In the exposure response analyses presented here, a clear relationship was not observed between posaconazole exposure with efficacy or safety at the plasma C_{trough} reached by the administered doses or drug formulations. For voriconazole, there was also no notable relationship between exposure and efficacy outcomes for quartiles 1–3, whereas participants in the highest C_{trough} quartile of voriconazole had higher all-cause mortality through day 42 than participants in the lower three quartiles. There was no clear relationship between voriconazole exposure and safety.

Posaconazole mean plasma C_{trough} was within the concentration ranges observed previously for posaconazole IV (mean C_{trough} 1320 ng/mL) and tablet (mean C_{trough} 1720 ng/mL) formulations [9, 21]. The overall distribution of voriconazole mean plasma C_{trough} was higher than in prior clinical studies, with about 25% of participants having C_{trough} more than ~ 4000 ng/mL in the highest quartile [22].

The efficacy outcomes of all-cause mortality and global clinical response for the individual C_{trough} exposure quartiles for posaconazole and voriconazole were mostly similar to the efficacy outcomes observed for each

Fig. 4 Voriconazole exposure data. **a** All-cause mortality through day 42 by quartiles of within-participant mean voriconazole plasma C_{trough} (ITT population). **b** Global clinical response at week 6 by quartile of within-participant mean voriconazole plasma C_{trough} (FAS population). C_{trough} trough concentration, *FAS* full analysis set, *ITT* intention-to-treat, *Q* quartile
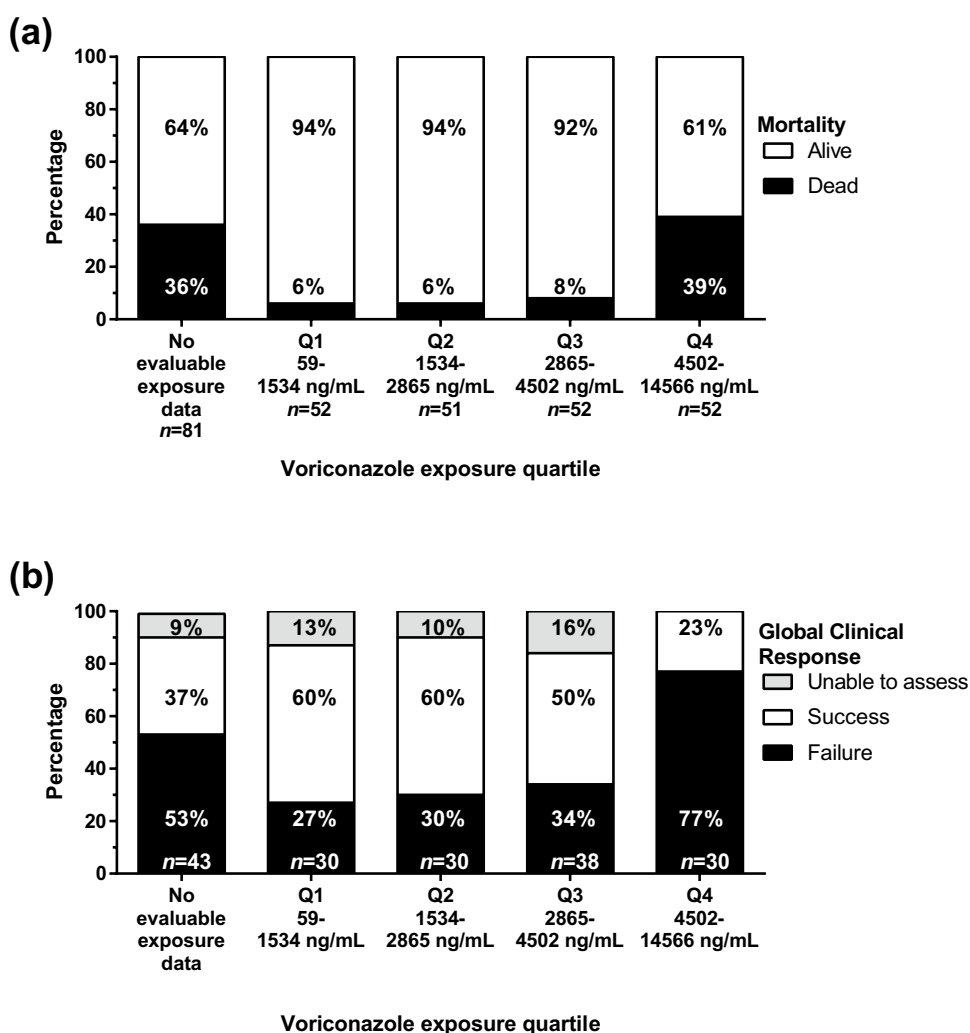

ITT population [15]. Seeing no discernible relationship between C_{trough} exposure quartiles and efficacy outcomes for posaconazole suggests that posaconazole exposures generated from the administered doses and formulations used in the primary phase 3 study were on the plateau of the exposure–efficacy curve, where efficacy is relatively insensitive to exposure (e.g., the lowest quartile of exposure was at or above the concentration threshold needed for efficacy).

For voriconazole, higher all-cause mortality and global clinical response failures were observed in participants in the highest quartile of voriconazole plasma C_{trough}, which may be attributable to more seriously ill participants needing to be on IV voriconazole and as a result having higher voriconazole concentrations. Additionally, genotypic and phenotypic variability of hepatic enzymes that metabolize voriconazole can lead to higher than normal voriconazole plasma concentrations and toxicity [5]. An exploratory pharmacogenetic analysis indicated a low likelihood that the CYP2C19 poor metabolizer phenotype contributed to

variability in the voriconazole efficacy or safety findings, but the sample size was relatively small [15].

The incidence of TRAEs across C_{trough} exposure quartiles was mostly similar to observed TRAEs from the ITT populations for both posaconazole and voriconazole [15]. For the posaconazole exposure safety analysis, the relationship of posaconazole to safety by quartile of exposure was evaluated for all AEs and for drug-related AEs. A higher incidence of TRAEs was observed in the highest exposure quartile, but there were no observed relationships between exposures and the incidence of individual-reported AEs (regardless of investigator-reported relationship), including tier 1 AEs. Similarly, no exposure–safety relationships were observed in prior studies of posaconazole in the IV or tablet formulation, in which similar or higher exposures were achieved [9, 21]. An exposure–safety relationship was also not observed with posaconazole oral suspension, although exposures with the oral suspension were generally lower than those achieved with the IV or tablet formulations [7]. A potential contributing factor to the observed association in the current study is

Fig. 5 Proportion of participants with TRAEs by quartile of within-participant mean **a** posaconazole C_{trough} and **b** voriconazole C_{trough}. C_{trough} trough concentration, *Q* quartile, *TRAE* treatment-related adverse event
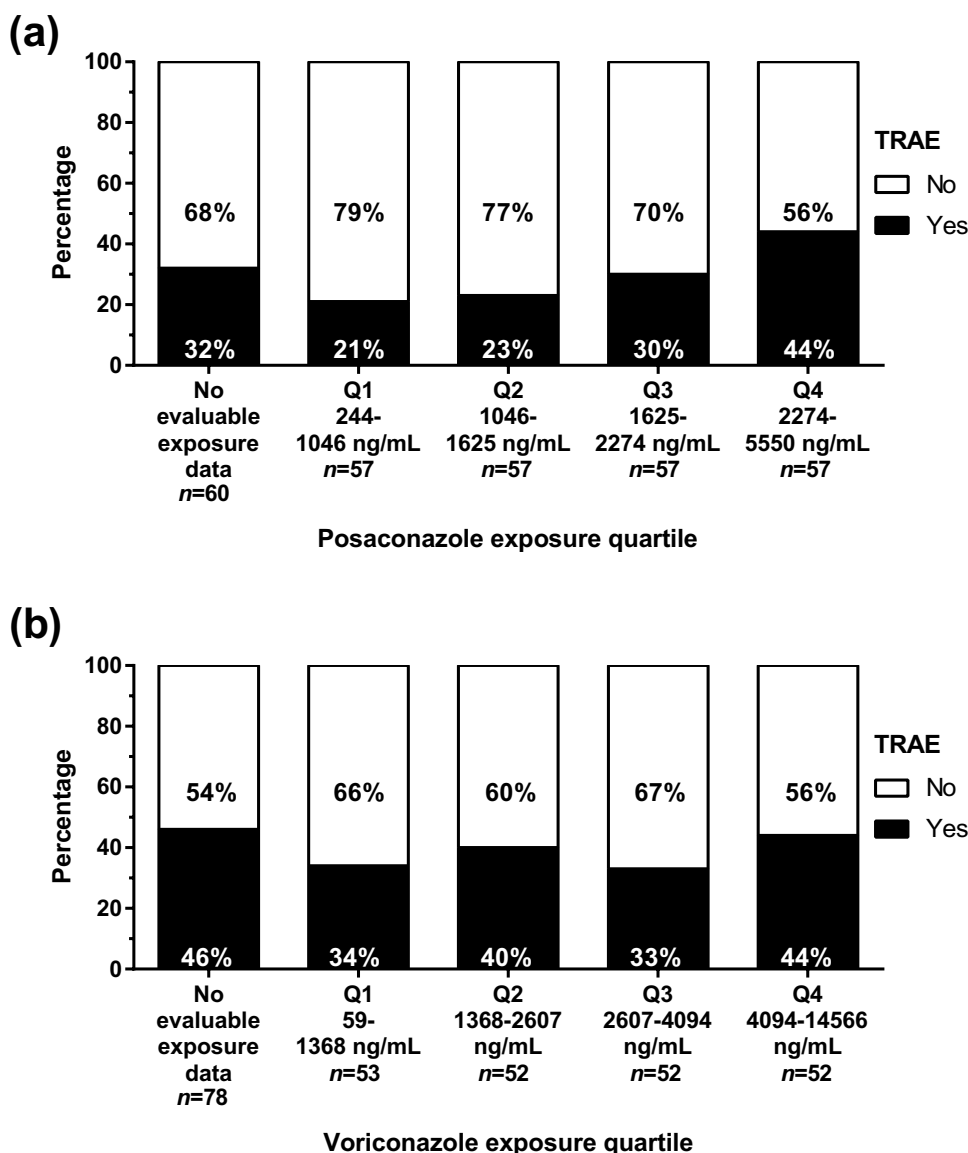
that a larger proportion of participants who were more seriously ill were likely to have been receiving the IV formulation rather than the tablet formulation and therefore would likely have had higher exposures. Furthermore, the severity of illness would have led to a higher incidence of AEs.

One limitation to this analysis is that plasma C_{trough} data for the exposure efficacy analyses were not available for 21%–25% of participants, and there was a marked difference in mortality rate and clinical response rate for participants with and without exposure data. Efficacy was lower in participants who did not have evaluable exposure data for posaconazole and voriconazole, suggesting that participants who died or who remained seriously ill were more likely not to have evaluable exposure data, potentially introducing bias in the exposure efficacy analysis. Additionally, the enrollment of adolescents was limited to five participants;

therefore, generalizing study conclusions to the adolescent population should be done with caution. A separate clinical study is ongoing to evaluate posaconazole for the primary treatment of invasive aspergillosis in pediatric patients.

5 Conclusion

No significant associations were observed between efficacy or safety and the plasma levels of voriconazole or posaconazole reached from the administered doses and formulations evaluated in this phase 3 trial for the primary treatment of invasive aspergillosis.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40261-023-01282-7.

Conflicts of Interest J.A.M. reports personal fees and non-financial support from MSD, grants, personal fees and non-financial support from Pfizer Inc., grants, personal fees and non-financial support from Gilead Sciences, personal fees and non-financial support from F2G, and personal fees and non-financial support from Cidara. G.R., S. Haider, I.C.R. and A.P. have nothing to disclose. D.-G.L. has received grants and personal fees from Pfizer, Gilead Sciences, and Yuhan. N.K. has received research grants or honoraria as a speaker or advisor from Astellas, Gilead, MSD, and Pfizer. R.W. is an employee of Merck Sharp and Dohme LLC, a subsidiary of Merck and Co., Inc., Rahway, NJ, USA, and has stock in Merck and Co., Inc., Rahway, NJ, USA. G.A.W. is working under contract with Certara USA, Inc., Princeton, NJ, USA. S. Han, A.G., and H.W. are employees of Merck Sharp and Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Ethics Approval The study was conducted in accordance with the principles of good clinical practice. The protocol and all amendments were reviewed and approved by the institutional review boards or independent ethics committees at all study sites before being initiated at each site.

Consent to Participate All participants or their legal representatives gave written informed consent before initiation of any study procedures.

Consent to Publish Not applicable.

Data Availability The data sharing policy, including restrictions, of Merck Sharp and Dohme LLC, a subsidiary of Merck and Co., Inc., Rahway, NJ, USA is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the Engage Zone site or via email to dataaccess@merck.com.

Code Availability Not applicable.

Author Contributions All authors approved the final version of the manuscript to be submitted. Additional specific contributions are detailed by author. J.A.M. contributed to the acquisition and analysis of data and the interpretation of results and drafted, reviewed, and revised the manuscript. G.R. contributed to the acquisition of data and reviewed and revised the manuscript. D.-G.L. contributed to design of the study, acquisition and analysis of data, and the interpretation of results and drafted, reviewed, and revised the manuscript. S. Haider contributed to acquisition of the data and interpretation of results and reviewed and revised the manuscript. I.C.R. contributed to the acquisition of data and reviewed and revised the manuscript. N.K. contributed to the acquisition of data and reviewed and revised the manuscript. A.P. contributed to the acquisition of data and reviewed and revised the manuscript. S. H was involved in study design and reviewed and revised the manuscript. R.W. contributed to the study design, analysis of data, the interpretation of results, and drafting of the manuscript. G.A.W. contributed to the analysis of data and the interpretation of results and reviewed and revised the manuscript. A.G. contributed to the study design, acquisition and analysis of data, and the interpretation of results and reviewed and revised the manuscript. H.W. contributed to the study design, analysis of data, and the interpretation of results and drafted, reviewed, and revised the manuscript.

References

1. Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;63:e1–60. https://doi.org/10.1093/cid/ciw326.
2. Tissot F, Agrawal S, Pagano L, Petrikkos G, Groll AH, Skiada A, et al. ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. Haematologica. 2017;102:433–44. https://doi.org/10.3324/haematol.2016.152900.
3. Ullmann AJ, Aguado JM, Arikan-Akdagli S, Denning DW, Groll AH, Lagrou K, et al. Diagnosis and management of aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clin Microbiol Infect. 2018;24(suppl 1):e1–38. https://doi.org/10.1016/j.cmi.2018.01.002.
4. VFEND (voriconozole) tablets, for oral use. VFEND (voriconazole) for oral suspension. VFEND (voriconazole) for injection, for intravenous use [package insert]. New York: Pfizer, Inc.; 2022.
5. Pasqualotto AC, Xavier MO, Andreolla HF, Linden R. Voriconazole therapeutic drug monitoring: focus on safety. Expert Opin Drug Saf. 2010;9:125–37. https://doi.org/10.1517/14740330903485637.
6. Bruggemann RJM, Donnelly JP, Aarnoutse RE, Warris A, Blijlevens NMA, Mouton JW, et al. Therapeutic drug monitoring of voriconazole. Ther Drug Monit. 2008;30:403–11. https://doi.org/10.1097/FTD.0b013e31817b1a95.
7. NOXAFIL (posaconazole) tablets and oral suspension 40 mg/mL. Rahway, NJ, USA: Merck Sharp & Dohme LLC, 2022.
8. Noxafil 40 mg/mL oral suspension (summary of product characteristics). Netherlands: MSD; 2019.
9. Cornely OA, Duarte RF, Haider S, Chandrasekar P, Helfgott D, Jimenez JL, et al. Phase 3 pharmacokinetics and safety study of a posaconazole tablet formulation in patients at risk for invasive

fungal disease. J Antimicrob Chemother. 2016;71:718–26. https://doi.org/10.1093/jac/dkv380.

10. Duarte RF, Lopez-Jimenez J, Cornely OA, Laverdiere M, Helfgott D, Haider S, et al. Phase 1b study of new posaconazole tablet for prevention of invasive fungal infections in high-risk patients with neutropenia. Antimicrob Agents Chemother. 2014;58:5758–65. https://doi.org/10.1128/AAC.03050-14.

11. Krishna G, Ma L, Martinho M, O'Mara E. Single-dose phase 1 study to evaluate the pharmacokinetics of posaconazole in new tablet and capsule formulations relative to oral suspension. Antimicrob Agents Chemother. 2012;56:4196–201. https://doi.org/10.1128/AAC.00222-12.

12. Kersemaekers WM, Dogterom P, Xu J, Marcantonio EE, de Greef R, Waskin H, et al. Effect of a high-fat meal on the pharmacokinetics of 300-milligram posaconazole in a solid oral tablet formulation. Antimicrob Agents Chemother. 2015;59:3385–9. https://doi.org/10.1128/AAC.05000-14.

13. Mourad A, Perfect JR. Tolerability profile of the current antifungal armoury. J Antimicrob Chemother. 2018;73(suppl 1):i26–32. https://doi.org/10.1093/jac/dkx446.

14. Jin H, Wang T, Falcione BA, Olsen KM, Chen K, Tang H, et al. Trough concentration of voriconazole and its relationship with efficacy and safety: a systematic review and meta-analysis. J Antimicrob Chemother. 2016;71:1772–85. https://doi.org/10.1093/jac/dkw045.

15. Maertens JA, Rahav G, Lee DG, Ponce-de-León A, Ramírez Sánchez IC, Klimko N, et al. Posaconazole versus voriconazole for primary treatment of invasive aspergillosis: a phase 3, randomised, controlled, non-inferiority trial. Lancet. 2021;397:499–509. https://doi.org/10.1016/S0140-6736(21)00219-1.

16. Jang SH, Colangelo PM, Gobburu JVS. Exposure-response of posaconazole used for prophylaxis against invasive fungal infections: evaluating the need to adjust doses based on drug concentrations in plasma. Clin Pharmacol Ther. 2010;88(1):115–9. https://doi.org/10.1038/clpt.2010.64.

17. Walsh TJ, Raad I, Patterson TF, Chandrasekar P, Donowitz GR, Graybill R, et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: An externally controlled trial. Clin Infect Dis. 2007;44:2–12. https://doi.org/10.1086/508774.

18. Segal BH, Herbrecht R, Stevens DA, Ostrosky-Zeichner L, Sobel J, Viscoli C, et al. Defining responses to therapy and study outcomes in clinical trials of invasive fungal diseases: mycoses study group and european organization for research and treatment of cancer consensus criteria. Clin Infect Dis. 2008;47:674–83. https://doi.org/10.1086/590566.

19. Cunliffe JM, Noren CF, Hayes RN, Clement RP, Shen JX. A high-throughput LC–MS/MS method for the quantitation of posaconazole in human plasma: implementing fused core silica liquid chromatography. J Pharm Biomed Anal. 2009;50(1):46–52. https://doi.org/10.1016/j.jpba.2009.03.034.

20. Kahle K, Langmann P, Schirmer D, Lenker U, Keller D, Helle A, et al. Simultaneous determination of voriconazole and posaconazole concentrations in human plasma by high-performance liquid chromatography. Antimicrob Agents Chemother. 2009;53(7):3140–2. https://doi.org/10.1128/AAC.00213-09.

21. Cornely OA, Robertson MN, Haider S, Grigg A, Geddes M, Aoun M, et al. Pharmacokinetics and safety results from the Phase 3 randomized, open-label, study of intravenous posaconazole in patients at risk of invasive fungal disease. J Antimicrob Chemother. 2017;72:3406–13. https://doi.org/10.1093/jac/dkx382.

22. Andes D, Pascual A, Marchetti O. Antifungal therapeutic drug monitoring: established and emerging indications. Antimicrob Agents Chemother. 2009;53:24–34. https://doi.org/10.1128/AAC.00705-08.

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