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Pharmacokinetics and safety results from the Phase 3 randomized, open-label, study of intravenous posaconazole in patients at risk of invasive fungal disease

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Objectives: A two-part (Phase 1B/3), sequential, open-label, multicentre study evaluated the pharmacokinetics (PK) and safety of intravenous (iv) posaconazole given as antifungal prophylaxis to neutropenic patients with AML or myelodysplastic syndrome (MDS) or to recipients at risk of invasive fungal disease (IFD) after allogeneic HSCT.

Methods: Patients ($N = 237$) received 300 mg of posaconazole iv twice daily on day 1, followed by 300 mg of posaconazole iv once daily for 4–28 days. After at least 5 days, patients were randomly assigned to receive posaconazole oral suspension, 400 mg twice daily or 200 mg three times daily, to complete a 28 day treatment course. Primary PK parameters were steady-state average concentration over the dosing interval (C_{avg}) and posaconazole trough levels (C_{min}).

Results: Mean posaconazole C_{min} was 1320 ng/mL (day 6) and 1297 ng/mL (day 8); steady-state C_{min} was 1090 ng/mL (day 10). Mean steady-state posaconazole C_{avg} was 1500 ng/mL (day 10 or 14) and was similar in HSCT recipients (1560 ng/mL) and AML/MDS patients (1470 ng/mL). The most commonly reported treatment-related adverse events were diarrhoea (8%), nausea (5%) and rash (5%). IFD was reported in 3/237 patients (1%; 2 proven, 1 probable).

Conclusions: Intravenous posaconazole at 300 mg was well tolerated, resulted in adequate steady-state systemic exposure and was associated with a low incidence of IFD in this population at high risk.

Trial registry and number: ClinicalTrials.gov, NCT01075984

Introduction

Risk factors for invasive fungal disease (IFD) include prolonged neutropenia following chemotherapy and graft-versus-host disease (GVHD) after allogeneic HSCT.[1,2] Posaconazole oral suspension is an extended-spectrum triazole with demonstrated efficacy for prophylaxis and treatment of IFD.[3–7] A limitation to any posaconazole oral formulation is that some patients at risk of IFD cannot take or absorb the formulation appropriately while experiencing mucositis, diarrhoea or nausea.[8,9]

Although an apparent association between the prophylactic efficacy of posaconazole oral suspension and that of posaconazole steady-state average concentration over the dosing interval (C_{avg}) raised debate,[10–12] this association has been shown convincingly in patients receiving salvage treatment for invasive aspergillosis.[5] In addition, data from the Phase 3 studies of posaconazole tablets suggest both C_{min} and C_{avg} can be predictive of exposure levels associated with clinical efficacy.[13]

To maximize bioavailability in patients unable to take or absorb an oral preparation, an intravenous (iv) formulation of posaconazole has been developed. A two-part study (Phase 1B/3) evaluated the pharmacokinetics (PK) and safety of iv posaconazole when given as antifungal prophylaxis to patients at high risk of IFD. Phase 1B results from this study have been reported;[14] here we present results predominantly from Phase 3, in which patients at high risk of IFD were administered an iv solution containing 300 mg of posaconazole. The aims of the study were to characterize the PK, safety and tolerability of iv posaconazole solution in a representative patient population and to compare steady-state exposures between the iv and oral suspension formulations of posaconazole.

Patients and methods

Ethics

This was an open-label, randomized, adaptive, dose-ranging, multicentre, Phase 1B/3 PK and safety study (ClinicalTrials.gov, NCT01075984; study number P05520) conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki.

Study design

The study was conducted at 34 sites worldwide (Table S1, available as Supplementary data at *JAC* Online). Patients received iv posaconazole at 300 mg twice daily on day 1, followed by 300 mg once daily thereafter, with each infusion spanning 90 min. After they completed at least 5 days of iv therapy and when they were clinically stable, patients were randomly assigned to receive an oral suspension of posaconazole at 400 mg twice daily or 200 mg three times daily for 28 days. The investigator could switch a patient back to iv therapy if the patient was unable to tolerate oral medication. This report describes the pooled data of patients who initially received 300 mg of posaconazole iv during Phase 1B of the study ($n = 24$) and patients who received the same regimen during Phase 3 ($n = 213$). Pooling of the data for the two 300 mg dose cohorts was not prespecified in the protocol.

Each patient provided written informed consent. Randomization was conducted using an interactive voice response system.

Patients

Adult patients (at least 18 years old) were enrolled after they had undergone induction chemotherapy for AML, myelodysplastic syndrome (MDS) or secondary myeloid leukaemia. To be eligible, AML/MDS patients were required to have prolonged neutropenia of $<500/mm^3$ (0.5×10^9/L) likely to last $\geq$7 days or be likely to develop it within 5 days. Also eligible were recipients of allogeneic HSCT in the pre-engraftment period and patients who were receiving immunosuppressive therapy (e.g. steroids, tacrolimus, cyclosporine, mycophenolate mofetil or antithymocyte globulin) in the post-engraftment period for the prevention or treatment of GVHD. All patients were required to have a central venous catheter in place for study drug dosing to minimize the thrombophlebitis potential of iv posaconazole seen with peripheral administration in earlier studies.[15] A single iv peripheral dose was permitted as needed to bridge patients before placement of central access.

Study exclusions included history of known or suspected IFD, type 1 hypersensitivity or idiosyncratic reactions to azoles, moderate or severe liver dysfunction [defined as AST or ALT >3 times the upper limit of normal (ULN) and total bilirubin >2×ULN], QTc interval >500 ms (by either the Bazett or the Fridericia formula) or a creatinine clearance rate <50 mL/min. Patients were stratified based on underlying clinical condition (AML/MDS or HSCT).

PK sampling

Posaconazole plasma trough concentrations were measured before dose on days 3, 6 and 8, on days 15 ($\pm$3 days) and 22 ($\pm$3 days) and at the end of therapy (8–24 h from the last dose), as well as on the first and third days after step-down to oral therapy. If a step-down to oral therapy sample time coincided with another scheduled PK sample, then only one sample was taken. Patients were included in the C_{min} PK-evaluable population if they received iv posaconazole at 300 mg for at least 6–8 days and had a trough value taken during that period.

To gain additional PK data for steady-state estimation, more intensive PK sampling was conducted in 49 patients, after additional informed consent, following a minimum of 10 days of iv posaconazole therapy. Patients were considered eligible if no protocol deviations occurred that affected posaconazole levels, if they missed no doses within 7 days of PK sampling, if the time of dosing was clearly documented, if PK sampling and dosing times were reliable and if PK data were collected on day 10$\pm$2 days. Plasma samples for the expanded PK analysis were taken on day 10 ($\pm$2 days) before infusion and 1, 4, 8, 12 and 24 h after the start of infusion. Additional samples were taken at the end of the infusion and 15 min after the end of the infusion to better define the distributive phase of the drug. For patients enrolled in the Phase 1B part of the study, steady-state PK analysis was conducted on day 14. For patients enrolled in the Phase 3 part of the study, steady-state PK analysis was conducted on day 10. Days 10 and 14 were selected for PK sampling because earlier studies had shown that steady-state plasma levels are reached by the second week of treatment for oral posaconazole.[16,17]

To determine posaconazole plasma concentrations, 4 mL of whole blood was collected into dipotassium EDTA-containing tubes and processed as previously described.[18] The samples were centrifuged within 30 min of collection at 1500 **g** for 15 min at 4°C and then divided equally into two 2 mL polypropylene cryovials and stored at −20°C or lower until analysis. Plasma samples were assayed at two central laboratories [Merck & Co., Inc., Bioanalytical/Toxicokinetics, Summit, NJ, USA (October 2009 to August 2011) and PPD Analytical Laboratory, Richmond, VA, USA (September 2011 to end of study)] for posaconazole using a validated LC with tandem MS detection method[18] and a calibration range of 5–5000 ng/mL.

PK evaluations and target range

Primary PK parameters of interest were C_{avg} (AUC over the dosing interval/24 h) and trough levels (C_{min}) of posaconazole. Mean C_{min} values were calculated following iv and oral posaconazole administration in the C_{min} PK-evaluable population (patients who received $\geq$6 days of iv posaconazole at 300 mg and had a day 6 trough value) from cohort 3. The proportion of patients with steady-state C_{avg} $\geq$500 and $\leq$2500 ng/mL was also assessed in the expanded PK analysis. The lower end of the target exposure range (C_{avg} $\geq$500 ng/mL) was based on previous exposure–response analysis[5] and the observation that 500 ng/mL is the MIC_{90} for the most clinically important *Aspergillus* species.[19] The upper end of the target exposure range took into account the upper limit of exposure in previous studies of oral prophylaxis and the therapy for refractory IFD that characterized safety for approval of posaconazole oral suspension[3,4] while recognizing that dose-limiting toxicity in humans has not been observed to date.

Safety

Safety was assessed in all treated patients and included adverse events (AEs), treatment-emergent AEs (TEAEs), treatment-related AEs, serious AEs

(SAEs), treatment-related SAEs, catheter-related AEs and infusion-site reactions, vital signs, clinical laboratory tests and electrocardiograms. In the Phase 1B study, blood samples for clinical laboratory tests were collected at baseline and on days 1, 3, 7 and 14 during iv treatment, weekly during oral treatment, and at the follow-up visit; electrocardiograms were collected at baseline and on days 1, 3, 7 and 14 during iv treatment. In the Phase 3 study, serum chemistry clinical laboratory test results were collected at baseline, days 1, 5 and 10 during iv treatment, days 6, 8, 10, 15, 22 and 28, and at the follow-up visit; electrocardiograms were collected at baseline and on days 1, 5 and 10 during iv treatment. Drug-induced liver injury using Hy's law was considered if findings of liver function tests, ALT or AST were $\geq$3×ULN, with alkaline phosphatase $\leq$2×ULN and total bilirubin $\geq$2×ULN without evidence of bilirubin obstruction. Treatment-related AEs were those judged by the study investigator to be related to study treatment. The Medical Dictionary for Regulatory Activities (MedDRA) version 15.0 was used for AE coding. TEAEs of special interest included hepatic, cardiac, adrenal/metabolic, hypersensitivity, gastrointestinal, vascular and renal TEAEs, based on the known safety profile of posaconazole oral suspension and the azole class of drugs.[20,21] Safety was assessed throughout the study during both iv and oral dosing of posaconazole, up to a maximum of 28 days and during the follow-up visit, which occurred 7 days after the last dose of study drug. Safety analyses were descriptive in nature, summarized by dose level, severity, relationship to study drug and day of onset relative to study therapy.

Efficacy and survival

Efficacy was not a primary parameter of interest in this study, but investigators were asked to report the occurrence of IFD. The study investigator was asked to classify any reported IFD as proven, probable or possible according to the 2008 European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria.[2] There was no central adjudication of reported IFDs. A final survival assessment at day 65 ($\pm$5 days) was conducted.

Sample size

The study planned to enrol ~200 patients, 150 who had neutropenia and 50 who underwent HSCT. Sample size was determined based on discussions with regulatory agencies regarding the number of patients required to constitute an adequate safety database.

Results

Patients

A total of 237 patients were enrolled between 10 March 2010 and 20 November 2012, received 300 mg of posaconazole iv twice on day 1 and thereafter once daily (213 during the Phase 3 study and 24 during the Phase 1B study) and were analysed. Table 1 describes the demographics of the study population.

Reasons for discontinuation are shown in Figure 1. The most common reason for discontinuing iv treatment was TEAEs (n = 29, 12%). The only TEAEs leading to the discontinuation of study drug that had their onset during the iv phase and that were reported by more than one patient were AML (n = 3), prolonged QT interval (n = 2) and rash (n = 2). Thirteen patients (5%) discontinued because of a treatment-related TEAE; the only treatment-related TEAE leading to discontinuation of study drug that had its onset during the iv phase and was reported by more than one patient was rash (n = 2). Mean duration of iv posaconazole therapy was 11.2 days (range, 2–28 days).

Table 1. Demographic and baseline disease characteristics (all patients)

Patient characteristics	Phase 1B study (N = 24)	Phase 3 study (N = 213)
Female, *n* (%)	11 (46)	96 (45)
Race, *n* (%)		
white	24 (100)	200 (94)
American Indian or Alaskan Native	0	1 (<1)
Asian	0	3 (1)
black or African American	0	2 (1)
multiracial	0	7 (3)
Age, years, mean (SD)	52.4 (13.4)	50.7 (14.7)
ECOG PS, *n* (%)		
0	8 (33)	68 (32)
1	12 (50)	105 (49)
2	3 (13)	34 (16)
3	0	3 (1)
4	0	1 (<1)
missing	1 (4)	2 (1)
Primary diagnosis at study entry, *n* (%)		
AML	22 (92)	125 (59)
MDS	2 (8)	6 (3)
HSCT	0	82 (38)
HSCT characteristics		
stem cell source, *n* (%)[a]		
peripheral stem cell	0	61 (29)
blood marrow	0	13 (6)
peripheral blood	0	8 (4)
umbilical cord	0	1 (<1)
GVHD, *n* (%)	0	25 (12)
acute	0	22 (10)
chronic	0	3 (1)

ECOG, Eastern Cooperative Oncology Group performance status.
[a]One patient had a peripheral stem cell source and a blood marrow stem cell source, and both are captured in the table.

Pharmacokinetic analyses

The C_{min} PK-evaluable population included 108 patients who received at least 6 days of iv posaconazole at 300 mg and had a day 6 trough value; 56 patients received at least 8 days of iv posaconazole at 300 mg and had a trough value on day 8. In these patients, the mean C_{min} value was 1320 ng/mL at day 6 and 1297 ng/mL at day 8. C_{min} values were <500 ng/mL in six of 108 patients (6%) and three of 56 patients (5%) after at least 6 and 8 days, respectively, of iv posaconazole at 300 mg. None of these patients acquired suspected or proven IFD; details on these six patients are summarized in Table S2. Changing to oral suspension of 200 mg of posaconazole three times daily or 400 mg twice daily resulted in lower posaconazole exposure, with a slightly higher exposure after 200 mg three times daily compared with 400 mg twice daily (Table 2). On day 8 of iv posaconazole dosing, C_{min} was 1297 [coefficient of variation (CV) 44%] compared with 1042 (CV 71%) and 877 (CV 61%) on day 15 of oral dosing with posaconazole at 200 mg three times daily and 400 mg twice daily, respectively.

Results from the serial PK-evaluable population (at day 10$\pm$2) are shown in Tables 3 and 4 and Figure 2. Median time to maximum

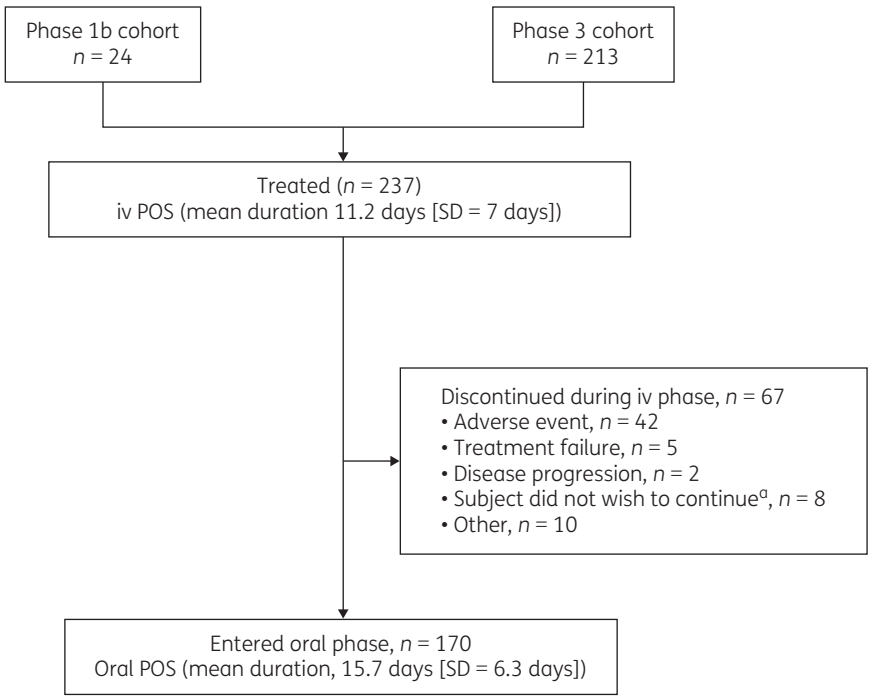

Figure 1. Patient disposition. POS, posaconazole. [a]Reasons unrelated to assigned study treatment.

Table 2. Arithmetic mean (CV) of C_{min} values following administration of 300 mg of posaconazole iv and subsequent oral suspension (C_{min} PK, evaluable population)

Dose	Day[a]	Patients	C_{min}, mg/L (CV, %)
Intravenous posaconazole, 300 mg once daily	3	169	1073 (42)
	6	108	1320 (44)
	8	56	1297 (44)
Posaconazole oral suspension, 200 mg three times daily	15	48	1042 (71)
	22	59	950 (76)
	28	31	1235 (77)
Posaconazole oral suspension, 400 mg twice daily	15	61	877 (61)
	22	56	751 (49)
	28	38	789 (63)

[a]C_{min} values on days 15, 22 and 28 were combined for patients receiving posaconazole oral suspension on days 15±3, 22±3 and 28±3, respectively.

observed concentration was 1.5 h with a mean C_{avg} of 1500 ng/mL. The mean C_{min} at steady state in the serial PK-evaluable population was 1090 ng/mL (range, 295–2485 ng/mL). Most patients (46 patients, 94%) had steady-state C_{avg} exposure within the target range of ≥500 and ≤2500 ng/mL. The remaining 6% of patients had steady-state C_{avg} exposure >2500 and ≤3650 ng/mL. No subject had a steady-state C_{avg} <500 ng/mL. Steady-state C_{avg} was similar in AML/MDS patients (1470 ng/mL, $n = 30$) and allogeneic HSCT recipients (1560 ng/mL, $n = 19$). Variability in exposure (AUC/C_{avg}) at steady state was ≤35%. Figure 2 shows the arithmetic mean (± SD) steady-state plasma concentration–time profile of posaconazole after iv administration of solution containing 300 mg of posaconazole measured on or after day 10 in 49 patients.

Safety

Intravenous posaconazole at 300 mg was generally well tolerated. Table 5 documents the incidence of TEAEs. SAEs were reported for 71 (30%) patients. The most commonly reported TEAEs (≥20% of patients) with onset during the iv phase were diarrhoea (32%), hypokalaemia (22%) and pyrexia (21%). Twenty-nine (12%) patients discontinued posaconazole because of a TEAE that had its onset during the iv phase. The only TEAEs reported for more than one patient in this context were AML ($n = 3$), prolonged QT ($n = 2$) and rash ($n = 2$).

During iv treatment with posaconazole, the most commonly reported treatment-related AEs (≥5% of patients) were diarrhoea (8%), nausea (5%) and rash (5%). Infusion site reactions, including

Table 3. Steady-state (day 10[a]) PK parameters after receiving 300 mg of posaconazole twice daily by iv infusion on day 1 followed by 300 mg of posaconazole iv once daily for at least 9 additional days (serial PK-evaluable population)

	Arithmetic mean (CV, %)				
Patients	C_{max} (ng/mL)	T_{max} (h)[b]	AUC_{0-24} (ng/mL)	C_{avg} (ng/mL)[c]	C_{min} (ng/mL)
49	3280 (74)	1.50 (0.98–4.00)	36100 (35)	1500 (35)	1090 (44)

[a]For patients enrolled in the Phase 1B part of the study, steady-state PK analysis was conducted on day 14. For patients enrolled in the Phase 3 part of the study, steady-state PK analysis was conducted on day 10.
[b]Median (range).
[c]C_{avg} was calculated as AUC (interval) at steady-state/dosing interval (AUC_{24}) on day 10 (Phase 1B) or day 14 (Phase 3).

Table 4. Patients achieving prespecified C_{avg}[a] exposure target after receiving 300 mg of posaconazole twice daily by iv infusion on day 1 followed by 300 mg of posaconazole once daily for at least 9 additional days (serial PK-evaluable population)

PK steady-state C_{avg} criteria	AML/MDS ($n = 30$)	HSCT ($n = 19$)	Total ($n = 49$)
$\geq$500 and $\leq$2500 ng/mL, *n* (%)	28 (93)	18 (95)	46 (94)
>2500 and $\leq$3650 ng/mL, *n* (%)	2 (7)	1 (5)	3 (6)

[a]For patients enrolled in the Phase 1B part of the study, steady-state PK analysis was conducted on day 14. For patients enrolled in the Phase 3 part of the study, steady-state PK analysis was conducted on day 10.

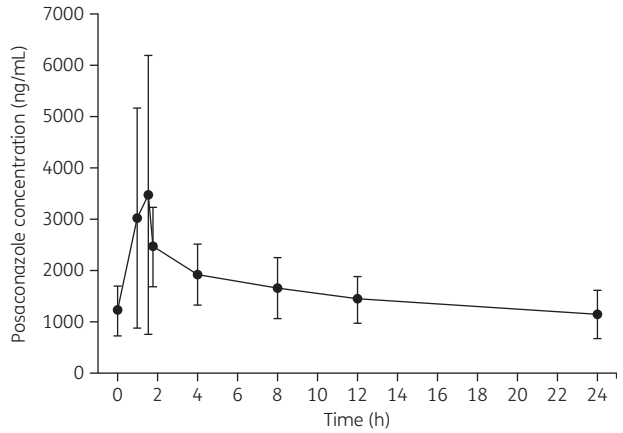

Figure 2. Arithmetic mean (±SD) steady-state plasma concentration–time profile of posaconazole after iv administration of solution containing 300 mg of posaconazole, measured on or after day 10 (serial PK-evaluable population; $n = 49$).

pain, phlebitis and thrombosis, were each reported by $\leq$1% of patients during iv posaconazole dosing. Serious TEAEs that had their onset during the iv phase were sepsis ($n = 3$), acute renal failure ($n = 3$), respiratory distress ($n = 2$), respiratory failure ($n = 2$) and subarachnoid haemorrhage ($n = 2$). Three treatment-related SAEs occurred: two patients reported treatment-related SAEs that had their onset during the iv phase (hyperbilirubinaemia and pulmonary mycosis not otherwise specified), and one patient reported a treatment-related SAE of nausea and vomiting during the oral phase.

Nineteen (8%) patients died during the study, 16 during the treatment period and 3 during follow-up after day 70. None of the deaths was due to IFD or was considered study drug related. Most deaths were due to sepsis ($n = 7$) and disease progression ($n = 4$).

AEs of special interest during the iv phase included cardiac, renal, adrenal and hepatic findings. One (<1%) patient had a QTc >500 ms on day 5 and a corresponding posaconazole C_{min} of 1050 ng/mL on day 3. Three (1%) patients experienced hypertension (moderate, $n = 1$; severe, $n = 2$). Renal impairment according to MedDRA preferred terms occurred in 11 (5%) patients (renal failure/acute renal failure, $n = 10$; renal impairment, $n = 1$). Two patients each had a treatment-related TEAE of acute renal failure that had its onset during the iv phase. One patient received reports of elevated creatinine and blood urea nitrogen levels ~1 month before the event, and the other patient had a history of hypertension and previous acute renal failure. Hyperbilirubinaemia was reported in two (1%) subjects, but no significant changes in liver enzyme levels occurred during treatment. Mean AST levels were 25.8 U/L at baseline, 36.9 U/L at day 10 and 31.6 U/L at day 28; respective mean ALT levels were 36.2, 46.3 and 45.7 U/L.

Efficacy

Proven or probable IFD as classified by the study investigator was reported in three (1%) patients, all with AML. There was no central adjudication of the classification or diagnosis of IFD. One patient with a history of AML had a proven pulmonary IFD diagnosed by histopathological examination of bronchoalveolar lavage on day 29 of treatment; oral posaconazole was discontinued on day 24 because of probable pulmonary IFD diagnosed on day 21 and was replaced by caspofungin and then by amphotericin B. The patient experienced hypotension, suspected bloodstream infection and presumed septic shock on days 39–41 and recovered on day 41. Another patient had a history of AML, and the investigator suspected pulmonary IFD on day 13 of treatment based on CT of the

Table 5. Summary of adverse events (all treated patients)

	Iv phase ($N = 237$)	Oral phase ($N = 170$)	Entire treatment duration ($N = 237$)
All TEAEs, *n* (%)	220 (93)	157 (92)	235 (99)
Most common TEAEs (≥20% of patients with onset during iv phase), *n* (%)			
diarrhoea	75 (32)	27 (16)	93 (39)
hypokalaemia	51 (22)	16 (9)	67 (28)
pyrexia	49 (21)	32 (19)	73 (31)
nausea	46 (19)	27 (16)	70 (30)
Treatment-related TEAEs,[a] *n* (%)	72 (30)	33 (19)	90 (38)
diarrhoea	19 (8)	4 (2)	21 (9)
nausea	12 (5)	6 (4)	18 (8)
rash	11 (5)	3 (2)	14 (6)
vomiting	9 (4)	4 (2)	13 (5)
hypokalaemia	9 (4)	2 (1)	11 (5)
Serious AEs, *n* (%)	27 (11)	41 (24)	71 (30)
Death, *n* (%)	10 (4)	7 (4)	19[b] (8)
Serious drug-related AEs, *n* (%)	2 (1)	1 (<1)	3 (1)
Study drug discontinuation because of AEs, *n* (%)	29[c] (12)	14 (8)	45 (19)

[a]Occurring in at least 5% of patients over the entire treatment phase.
[b]Causes of death were sepsis ($n = 7$), disease progression ($n = 4$), multiple organ failure ($n = 2$), acute liver failure, acute pulmonary oedema, acute renal failure, acute respiratory distress, gastrointestinal bleeding and subarachnoid haemorrhage ($n = 1$ each). None of the deaths was considered drug related.
[c]In total, 29 patients reported a total of 33 AEs leading to discontinuation during the iv phase: acute myeloid leukaemia ($n = 3$), prolonged QT interval ($n = 2$), rash ($n = 2$), abdominal pain, diarrhoea, nausea, catheter site inflammation, drug-induced liver injury, hepatitis, hyperbilirubinaemia, GVHD, aspergillosis, bacterial sepsis, bronchopulmonary aspergillosis, fungal infection, bacterial meningoencephalitis, fungal pneumonia, pulmonary mycosis, systemic mycosis, increased bilirubin, decreased creatinine clearance, increased hepatic enzyme, dizziness, subarachnoid haemorrhage, acute renal failure, acute pulmonary oedema, pulmonary haemorrhage, respiratory distress and veno-occlusive disease.

chest; oral posaconazole was discontinued and replaced with voriconazole. The aetiology of mycosis was not worked up. A third patient who had a history of AML acquired probable aspergillosis on day 11 of treatment. Diagnosis was based on positive galactomannan in bronchoalveolar lavage and a new nodular infiltrate with a halo sign detected on CT of the chest. Oral posaconazole was ceased on day 13, and amphotericin B was administered. The patient died of *Pseudomonas aeruginosa* sepsis on day 44. In these patients, day 8 posaconazole trough concentrations were 1280, 754 and 991 ng/mL, respectively. One additional patient with AML received empirical antifungal therapy with micafungin for persistent fever while on study drug.

At the day 65 survival assessment, 210 (89%) patients were confirmed alive and 16 were confirmed to have died during the survival assessment period; data were missing for 11 patients. None of the deaths was considered treatment related.

Discussion

Data from this pivotal study targeting a patient population at high risk of IFD confirm that a once-daily iv dose of 300 mg of posaconazole is effective at achieving target exposures necessary for effective antifungal prophylaxis, with a safety profile similar to that of posaconazole oral suspension. Most (94%) patients attained the target PK exposure of C_{avg} between 500 and 2500 ng/mL while receiving iv posaconazole, which is in line with the mean C_{avg} of >1300 ng/mL reported with once-daily oral posaconazole at 200 mg.[22] The remaining 6% of patients attained a steady-state C_{avg} between 2500 and 3650 ng/mL without signs of toxicity. Steady-state C_{avg} was similar in AML/MDS patients and allogeneic HSCT recipients. Additionally, in the C_{min} PK-evaluable population, the mean C_{min} at day 6 was 1320 ng/mL, which is well beyond the C_{min} regarded as necessary to prevent IFD reliably.[10,11] C_{min} values were <500 ng/mL in six of 108 patients (6%) and in three of 56 patients (5%) after at least 6 and 8 days, respectively, of iv administration of 300 mg of posaconazole.

Mean C_{avg} at steady state was 1500 ng/mL. Posaconazole plasma levels decreased after patients transitioned from iv treatment to dosing with posaconazole oral suspension, regardless of the dose of suspension or regimen. Mean C_{min} values were 1297 ng/mL at day 8 of iv dosing compared with 1042 and 877 ng/mL at day 15 in patients receiving oral posaconazole at 200 mg three times a day and 400 mg twice daily, respectively. C_{avg} values observed in this study during the iv study phase were greater than those reported in previous studies of posaconazole oral suspension, in which steady-state C_{avg} was 582 ng/mL in neutropenic patients with AML/MDS[16] and 922 ng/mL in patients with GVHD who did not have IFD.[23] In these studies, posaconazole oral suspension was also shown to have lower steady-state median C_{avg} and C_{max} in neutropenic patients with AML/MDS[16] and in patients with GVHD who were experiencing diarrhoea;[23] among patients with AML/MDS, the median C_{avg} and C_{max} of posaconazole did not reach the minimum inhibitory plasma concentration

required for most fungi.[16] The higher mean C_{avg} steady-state posaconazole plasma levels observed in the current study suggest that the posaconazole iv formulation could be considered for patients with AML/MDS and diarrhoea or HSCT and acute GVHD.

The Phase 3 portion of this study supports the safety of iv posaconazole at 300 mg in a representative patient population. Overall, patients treated iv with solution containing 300 mg of posaconazole once daily demonstrated a safety profile similar to that previously reported for posaconazole oral suspension.[3,4] Although almost all patients (99%) had at least one TEAE and 30% of patients reported an SAE, the spectrum of events reflects those typically observed in patients who experience neutropenia after chemotherapy and HSCT rather than specific AEs attributable to the study medication. Treatment-related TEAEs were reported in 38% of patients.

In addition to the most commonly observed AEs, several categories of AEs common to the azole class of medications and previously reported for posaconazole oral suspension were closely evaluated. There was no evidence of an increased risk of cardiac, adrenal or hepatic AEs in patients treated with the iv solution. Two patients (<1%) reported prolonged QTc; this is less than the 12/304 (4%) reported in the Phase 3 study of posaconazole prophylaxis versus fluconazole or itraconazole in patients with neutropenia.[3] Of the nine patients who received iv posaconazole through a peripheral line, only one patient reported a local tolerability reaction of moderate pain, but this was not judged to be related to treatment.

Although evaluation of efficacy in this study was only descriptive in nature and no adjudication of fungal diagnoses was performed, the incidence of proven/probable IFD and the requirement for empirical antifungal therapy was very low, consistent with previous controlled studies of posaconazole oral suspension for prophylaxis.[3,4] In a Phase 3 study of patients with neutropenia, posaconazole oral suspension (200 mg three times daily) resulted in a lower incidence of IFDs than fluconazole or itraconazole, with a mean posaconazole plasma concentration of 583±381 ng/mL.[4] Our data also confirm findings from a multicentre, retrospective study across seven Australian tertiary teaching hospitals that showed prophylactic iv posaconazole at 300 mg in patients ($n = 60$) with haematological malignancies prevented IFD in these patients.[24]

Conclusions

Results of this pivotal study in patients at high risk of IFD indicate that an iv posaconazole solution dose of 300 mg/day provides an exposure profile in the upper range of previously studied exposures. Intravenous posaconazole at 300 mg resulted in adequate steady-state systemic exposure in patients at risk of IFD, with 94% of patients in the serial PK-evaluable population achieving the prespecified exposure target of C_{avg} ≥500 and ≤2500 ng/mL. No apparent difference was observed in exposure between patients with AML/MDS and recipients of allogeneic HSCT. Intravenous administration of 300 mg of posaconazole through a central venous catheter was well tolerated in patients at risk of IFD. In patients requiring bridging therapy before placement of central access, plasma posaconazole concentrations in this range should provide effective antifungal prophylaxis. Intravenous posaconazole solution may also be beneficial for critically ill patients who require antifungal prophylaxis to prevent life-threatening IFD, at least in those who are unable to tolerate or absorb oral therapy.

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Author contributions

All authors approved the final version of the manuscript to be submitted. Additional specific contributions are detailed by author. O. A. C. provided study patients, contributed to the acquisition of data and the interpretation of results and drafted, reviewed and revised the manuscript. M. N. R. contributed to the study design and the interpretation of results and drafted, reviewed and revised the manuscript. S. H. contributed to

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Supplementary data

Tables S1 and S2 appear as Supplementary data at *JAC* Online.

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