REVIEW ARTICLE OPEN

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Primary antifungal prophylaxis in hematological malignancies. Updated clinical practice guidelines by the European Conference on Infections in Leukemia (ECIL)

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At the 10th European Conference on Infections in Leukaemia (ECIL), the guidelines for antifungal prophylaxis in pediatric and adult patients with hematological malignancies (HM) were updated and some changes introduced. Regarding acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) patients undergoing remission induction chemotherapy, a B-II grading has been assigned to isavuconazole, micafungin, and caspofungin, based on non-randomized studies that have shown efficacy in preventing invasive fungal diseases (IFD). Regarding high-risk MDS patients treated with azacytidine, prophylaxis with posaconazole during the first four cycles of treatment is supported in the literature. Prophylaxis is not indicated in patients treated for myeloproliferative neoplasms (NPM), acute lymphoid leukemia (ALL), and Hodgkin lymphoma (HL). For patients with chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL), prophylaxis is not generally indicated. For patients with multiple myeloma (MM), prophylaxis is not indicated and the limited epidemiological data available do not support the use of prophylaxis in subjects treated with bispecific antibodies. For patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT), no substantial changes were made, apart from the addition of isavuconazole with grading B-II in the post-engraftment period. In patients undergoing auto-HSCT, antifungal prophylaxis is not indicated. Previous ECIL guidelines did not include CAR-T cells. The expert panel proposes to endorse the use of anti-mold prophylaxis in high-risk patients during pre-infusion and post-infusion, while in low-risk patients, anti-yeast prophylaxis can be recommended (B-II). For pediatric hematology patients, based on newly published data, caspofungin received a B-I grading as mold-active prophylaxis. Moreover, patients with ALL with insufficient treatment response during induction therapy, and children older than 12 y.o are now considered at high risk for IFD and are recommended to receive antifungal prophylaxis.

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INTRODUCTION

In 2005, the European Group for Blood and Marrow Transplantation (EBMT), the European Organization for Research and Treatment of Cancer (EORTC), the European Leukemia Net (ELN), and the International Immunocompromised Host Society (ICHS) inaugurated the European Conference on Infections in Leukemia (ECIL). Its main goal was to establish guidelines or recommendations for the management of infections due to bacteria, viruses, parasites, and fungi in patients with leukemia and in patients undergoing hematopoietic stem cell transplantation (HSCT) [1]. The prevention of invasive fungal disease (IFD) has been one of the key topics from the beginning [1, 2].

The ECIL committee aims to update their guidelines regularly based on current available evidence. During the fifth and sixth meetings (2013 and 2015), guidelines on antifungal prophylaxis for adults were extensively revised, and during the ninth meeting (2021) recommendations for antifungal prophylaxis in pediatrics were developed [1, 3].

An update of previous recommendations was already done in 2018 [4], but over the last few years, several new antineoplastic drugs have been introduced into clinical practice for all hematological malignancies (i.e. BCL-2 inhibitors, FLT-3 inhibitors in acute myeloid leukemias, Bruton Tyrosine Kinase inhibitors (BTKIs) other new tyrosine kinase inhibitors (TKIs), bispecific

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Table 1. Evidence-based medicine grading system according to the European Society for Clinical Microbiology and Infectious Diseases (ESCMID).

Strength of recommendation (SoR)	
Grade	Definition
A	ECIL strongly supports a recommendation for use
B	ECIL moderately supports a recommendation for use
C	ECIL marginally supports a recommendation for use
D	ECIL supports a recommendation against use
Quality of evidence (QoE)	
Level	Definition
I	Evidence from at least 1 properly designed randomized, controlled trial (orientated on the primary endpoint of the trial)
II	Evidence from at least 1 well-designed clinical trial (including secondary endpoints), without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time series; or from dramatic results of uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees
Added index for source of level II evidence	
Index	Source
r	Meta-analysis or systematic review of randomized controlled trials
t	Transferred evidence, that is, results from different patient cohorts, or similar immune-status situation
h	Comparator group: historical control
u	Uncontrolled trial
a	Published abstract (presented at an international symposium or meeting)

monoclonal antibodies). In addition, new cellular therapy procedures, such as chimeric-antigen receptor T (CAR-T) cell treatments, are now increasingly used. Therefore, at the ECIL-10 meeting in September 2024, a detailed review of the recent literature was conducted, with the agreed proposals summarized in this review.

METHODOLOGY

The methodology of the ECIL conferences has previously been reported [1, 3].

A working group of experts in the field was nominated several months in advance of the biennial conference and was charged with reviewing the literature published since the last update of the guidelines.

A literature review was performed using the PubMed database for publications up from September 2015 and the working group co-authoring this manuscript reviewed all publications identified. Recommendations drawn from data available only as abstracts were provisionally graded, pending the publication of the full papers. The quality of evidence and strength of recommendation were graded according to the EBM grading system of ESCMID (Table 1) [5].

The working group compiled a slide set discussed in several consecutive online group meetings and electronic communication until two weeks before the ECIL-10 plenary meeting held on September 20th, 2024. The final slide set, approved by all group members, was sent by email to all ECIL-10 participants before the plenary. On the day of the meeting (September 20, 2024), the slides were presented by the working group and interactively discussed during a plenary session. The comments made during the plenary discussion were reviewed by the members of the working group in a closed session and recommendations revised accordingly.

The final set of recommendations was thereafter discussed with the ECIL-10 plenary until consensus was reached.

The approved slide set was published on the ECIL website (https://ecil-leukaemia.com/en/resources/resources-ecil), with comments invited for over a month (November 2024). All members of the working group then approved the final set of recommendations.

The final manuscript has been written and revised by all co-authors.

ACUTE MYELOID LEUKEMIA (AML)

Two new major issues have been addressed since the publication of the previous ECIL guidelines on antifungal prophylaxis [4].

Oral isavuconazole has been studied for primary antifungal prophylaxis in 65 patients undergoing remission induction chemotherapy in an open-label phase II study [6]. One patient developed a proven IFD and another 3 a probable IFD. When compared with posaconazole and voriconazole in a retrospective analysis of 277 patients with newly diagnosed AML, the incidences of breakthrough IFD were 2.9% for posaconazole, 4.8% for voriconazole, and 5.7% for isavuconazole ($p = 0.55$) [7]. While isavuconazole is not approved for antifungal prophylaxis in Europe (nor in the United States), the expert panel consider that isavuconazole may be considered for antifungal prophylaxis in selected adult patients undergoing remission induction therapy for AML and for whom posaconazole is not appropriate (e.g., liver function abnormalities, QTc prolongation, drug-drug interactions, intestinal absorption issues).

The benefit from systemic antifungal prophylaxis in patients undergoing consolidation chemotherapy for AML was retrospectively analyzed in a large SEIFEM study [8]. Among 2588 adult and pediatric patients, invasive aspergillosis was diagnosed in 34/1137 (2.9%) patients receiving no antifungal prophylaxis, compared with 22/1451 (1.5%) patients who were given antifungal prophylaxis ($p = 0.01$). The number needed to treat to prevent one invasive aspergillosis was 71 patients [8]. Systemic antifungal prophylaxis has been given a B-IIu recommendation for AML patient undergoing consolidation chemotherapy.

For patients undergoing AML treatment with one of the newer systemic agents such as venetoclax, FLT3 inhibitors, or ivosidenib,

the recommendations on indications and the proper selection of agents for systemic antifungal prophylaxis, as given by the ECIL-9 guideline [9], are reinforced by the present updated guideline. Recommendations for appropriate dose adjustments in case of relevant pharmacological drug-drug interactions were thereby addressed as well.

Beyond these issues, the grading of recommendations has been modified for itraconazole (from B-I to C-I) and micafungin (from C-II to B-II), and a recommendation for "super bioavailable" (SUBA)-itraconazole has been added (C-II).

In comparison to posaconazole, itraconazole was shown to be less effective and less reliable concerning drug levels than posaconazole in AML patients [10, 11]. As SUBA-itraconazole has become available, "classic" itraconazole has been slightly downgraded (C-I).

SUBA-itraconazole has been clinically investigated for pharmacokinetics, tolerability, and safety in several cohort studies including patients with hematologic malignancies and allogeneic HSCT recipients as well as solid organ transplant recipients [12, 13].

In our former recommendations, echinocandins as a group were graded as "C-II", because of their narrower spectrum of antifungal activity when compared to amphotericin B and most triazoles, and sparse clinical data on their use as antifungal prophylaxis in patients with hematologic malignancies. As more detailed data for the efficacy and safety of micafungin are now available for AML and myelodyplastic syndromes (MDS) patients as well as for allogeneic HSCT recipients, micafungin has now been upgraded to B-II [14–16].

Table 2 shows the new recommendations compared to those suggested during ECIL-5.

Myelodysplastic Syndromes (MDS)

For patients with low-risk MDS receiving transfusion-supportive treatment or treated with growth factors (i.e. erythropoietin), no increased risk of IFD has been reported, and therefore no antifungal prophylaxis is indicated (D-I). The introduction of luspatercept does not change this recommendation. The COMMANDS study comparing luspatercept versus erythropoietin which enrolled over 600 patients, did not report any case of IFD [17].

For patients with high-risk MDS receiving intensive AML-like induction (and consolidation) chemotherapy treatment, the recommendation to administer antifungal prophylaxis has not changed (A-I) [4]. The situation is different for intermediate and high-risk patients receiving treatment with azacytidine. A review of the literature in recent years shows an increased risk of IFD, especially during the first 4 cycles of treatment with an incidence ranging from 3% to 12% [18]. When antifungal prophylaxis was administered in most patients, the rate of IFD was 3-8% [18–20], while in series where the proportion of patients receiving antifungal prophylaxis was very low, the rate of IFD rised to 8-12% [21–27]. The new recommendation for these patients is therefore to use antimold prophylaxis during the first 4 cycles of azacytidine treatment (B-IIu).

CHRONIC MYELOPROLIFERATIVE NEOPLASMS

Regarding patients with chronic myeloid leukemia treated with TKIs (imatinib, dasatinib, nilotinib, ponatinib, asciminib) and Philadelphia chromosome-negative myeloproliferative neoplasms, including those treated with ruxolitinib [28–34] an increased risk of IFD is not reported and antifungal prophylaxis is not indicated (D-I).

Table 3 shows the new recommendations compared to those suggested during ECIL-5.

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Adults with ALL are usually treated with an intensive polychemotherapy regimen inducing prolonged neutropenia and receive corticosteroids. Therefore, these patients are at risk of developing IFD. The incidence of IFD in this population varies between 4 and 18%, which is rather similar compared to that observed in AML [35]. Although TKIs (e.g. imatinib, nilotinib, ponatinib) used for the treatment of Philadelphia chromosome-positive ALL have been associated with IFD, the actual IFD incidence seems to be low (< 1%) [36]. Novel specific monoclonal antibody therapies used for ALL (e.g. blinatumomab, inotuzumab ozogamicin) have not been associated with a higher IFD incidence compared to the standard of care in randomized controlled trials [37, 38].

Antifungal prophylaxis in this population is hampered by the drug-drug interaction between triazoles and vincristine, an important component of most ALL chemotherapy regimens. Concomitant use of triazoles may result in increased vincristine-related neurotoxicity because this later drug is metabolized by the CYP3A4 cytochrome. Studies in children with ALL suggest a significantly higher risk of vincristine-related neurotoxicity with voriconazole or itraconazole, while the use of fluconazole seems to be safer [39, 40]. However, data on adults are lacking. Studies assessing the efficacy of antifungal prophylaxis in ALL adult patients for the prevention of IFD are heterogeneous and scarce [41–43]. One randomized controlled study failed to demonstrate the benefit of twice weekly intravenous liposomal amphotericin B (5 mg/kg) versus placebo with a higher incidence of drug-related adverse events in the treatment arm [44].

Antifungal prophylaxis with a mold-active triazole, such as voriconazole or posaconazole, is not recommended because of interactions which could increase the toxicity of vincristine (D-II). Although data are still lacking, isavuconazole might be considered with caution, considering its lower inhibitory effect on CYP3A4 (C-III). Similarly, fluconazole might be considered with caution for prevention of yeast infection (C-III). Alternative anti-mold prophylaxis (e.g. liposomal amphotericin B, echinocandins) might be considered in high-risk patients (i.e. prolonged chemotherapy-induced neutropenia), but no benefit has been shown to date. No antifungal prophylaxis is recommended for ALL patients receiving only TKIs (D-III) (Table 4).

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

The incidence of IFD in patients with CLL is overall low (0.5 to 3%) and varies according to the type of treatment [45–48]. These patients present with a large and diverse spectrum of immunosuppression, from untreated patients with different degrees of neutropenia, patients treated with corticosteroids, anti-BCL2 (e.g. venetoclax), or BTKIs (e.g. ibrutinib). Treatment with ibrutinib or other BTKIs is associated with the highest IFI incidence in this population (2 to 3%) [46, 49, 50]. One small retrospective analysis showed a significantly lower IFD incidence among ibrutinib-treated CLL patients receiving antifungal prophylaxis (mainly fluconazole) versus no prophylaxis [51].

Antifungal prophylaxis is not routinely recommended in CLL patients (D-III) but may be considered in selected refractory cases with prolonged neutropenia or BTKIs therapy (C-II). In the case of co-administration of venetoclax, antifungal prophylaxis should be avoided or used cautiously because of drug-drug interactions (i.e. adjustment of venetoclax dosing is needed with therapeutic drug monitoring of the antifungal agent) (Table 4).

MYELOMA

Reported IFD incidences in myeloma patients treated with conventional chemotherapy combinations have been low (< 1%) despite the presence of risk factors for IFD such as high doses of corticosteroids, disease-related comorbidities, myeloma-related innate immunodeficiency and, in treatment-experienced patients, poor marrow function [52]. Since the publication of the previous ECIL guidelines, treatment with combinations of immunomodulatory

Table 2. Recommendations for antifungal prophylaxis in patients with AML receiving intensive remission induction/reinduction chemotherapy.

Intention	Intervention	SoR	QoE	ECIL 5-6
Prevent IFD in AML patients, excluding allogeneic HSCT	posaconazole, tablet 300 mg q24h p.o. (q12h on day 1)	A	I[1]	A-I
	amphotericin B, liposomal, inhalation[*2,3] 10 mg twice weekly	B	I	B-I
	fluconazole[4] 400 mg q24h, p.o. or i.v.	B	I	B-I
	voriconazole 6 mg/kg/12 h first day then 4 mg/kg q12h, i.v. or p.o.	B	IIu	B-II
	isavuconazole[2] 200 mg q8h p.o. first 2 days then 200 mg q24h	B	IIt	NR
	micafungin 50 mg q24h i.v.	B	II u,t	NR
	amphotericin B, liposomal, i.v.[2] 1-3 mg/kg q24h	C	II	C-II
	caspofungin[2] 50 mg q24h i.v. (70 mg on day 1, 70 mg q24h in patients >80 kg)	B	IIt	NR
	itraconazole 2.5-7.5 mg/kg q24h i.v. or 200 mg q24h p.o.	C	I	B-I
	SUBA-itraconazole 200 mg q12h p.o.	C	IIt	NR

AML acute myeloid leukemia, *IFD* invasive fungal disease, *HSCT* hematopoietic stem cell transplantation, *NR* No recommendation.
1 = recommendation for AML under remission induction chemotherapy; 2 = no approval for prophylaxis of IFD; 3 = formulation not approved; 4 =Only recommended if the incidence of mold infections is low. Fluconazole may be part of an integrated care strategy together with a mold-directed diagnostic approach.
*Should be combined with systemic fluconazole.
Amphotericin deoxycholate is not approved for prophylaxis and should not be considered due to drug-related toxicity.

Table 3. Recommendations for antifungal prophylaxis in patients with MDS, CML, and MPN.

Population	Intervention	SoR	QoE	ECIL 5-6
MDS low-/intermediate No chemotherapy	Any prophylaxis	D	I	No recommendation
MDS Intermediate/High treated as AML with intensive chemotherapy	posaconazole prophylaxis 300 mg q24 p.o. (q12h on day 1)	A	I	As for AML
MDS Intermediate/High Treated with Azacytidine	posaconazole prophylaxis during the first 4 azacytidine courses	B	IIu	No recommendation
CML Treated with TKIs	Any prophylaxis	D	I	No recommendation
MPN No chemotherapy	Any prophylaxis	D	I	No recommendation
MPN Treated with Ruxolitinib	Any prophylaxis	D	I	No recommendation

MDS Myelodysplastic Syndromes, *CML* Chronic Myeloid Leukemia, *MPN* Myeloproliferative Neoplasms, *AML* acute myeloid leukemia, *TKIs* tyrosine kinase inhibitors.

drugs, proteasome inhibitors, monoclonal antibodies, and autologous HSCT have been the standard of care. While no prospective study specifically reporting on IFD in this setting has been published, retrospective studies have reported a somewhat higher IFD incidence than with conventional chemotherapy, 2.7%, 3.5%, and 5.6%, respectively [46, 53–60]. Recently, two new types of antibody treatments have been introduced, bispecific antibodies activating a T-cell response by binding to both myeloma cells and T-cells, and B-cell binding antibodies conjugated with a cytotoxic compound (antibody-drug compound, ADC). Although neither prospective trials nor retrospective studies of treatment with bispecific antibodies have reported the exact numbers of IFD, their overall incidence after excluding Pneumocystis pneumonia has been low (< 2%) [47, 61–64]. The only registered ADC is belantamab mafotidin, which has now been withdrawn as a single agent but is currently under consideration as part of a combination treatment. The incidence of IFD was not specifically reported in the treatment trials leading to its registration, but the total infection rates were low with a 3% total incidence of pulmonary infections in the largest trial including 218 patients [61]. Routine antifungal prophylaxis is thus not recommended in myeloma patients, regardless of treatment with bispecific antibodies (D-II) (Table 4). Expert panels suggest to consider mold active prophylaxis in high-risk populations such as prolonged neutropenia or prolonged steroid treatment or secondary prophylaxis (no trials).

NON-HODGKIN LYMPHOMA (NHL)

Patients with NHL have an overall low IFD incidence (0.5 to 3%) [46, 47]. The incidence among NHL patients receiving BKTIs (e.g.

Table 4. Recommendations for antifungal prophylaxis in patients with ALL, CLL, NHL, HL and MM.

Population		Intervention	SoR	QoE	ECIL 5-6
ALL	TKIs	Any prophylaxis	D	III	No data
	Chemotherapy including vincristine	posaconazole voriconazole	D	II	Against
		isavuconazole 200 mg q8h p.o. first 2 days then 200 mg q24h	C	III	No data
		Fluconazole 400 mg q24h, p.o. or i.v.	C	III	C-III
CLL	Conventional treatment	Any prophylaxis	D	III	No recommendation
	Refractory treated BTKIs and/or venetoclax	Mold-active prophylaxis	C	II	No recommendation
NHL	Treated with chemotherapy	Any prophylaxis	D	II	No recommendation
	Refractory treated BTKIs or high doses steroids	Mold-active prophylaxis	C	II	No recommendation
	Treated with Bispecific antibodies	Any prophylaxis	D	II	No data
HL	Treated with chemotherapy	Any prophylaxis	D	II	No recommendation
MM	Treated with IMiDs	Any prophylaxis	D	II	No recommendation
	Treated with Bispecific antibodies	Any prophylaxis	D	II	No data

ALL Acute Lymphoblastic Leukemia, *CLL* Chronic Lymphocytic Leukemia, *NHL* non-Hodgkin's Lymphoma, *HL* Hodgkin's Lymphoma, *MM* Multiple Myeloma, *BTKIs* Bruton tyrosine kinase inhibitors; *IMiDs* immunomodulatory drugs.

ibrutinib) is roughly similar (about 1.5%) [49]. Some factors have been associated with a higher risk of IFD, such as primary refractoriness, use of two or more previous treatment lines, and occurrence of neutropenia [62].

Antifungal prophylaxis is not routinely recommended in patients with NHL (D-II) but might be considered in selected patients with refractory lymphoma and/or repeated intensive chemotherapies with neutropenia or high dose steroids or BTKI therapy (C-II) (Table 4).

HODGKIN LYMPHOMA (HL)

The risk for IFD tends to be low in patients with Hodgkin lymphoma. Two recent nationwide epidemiological studies in hospitalized HL patients reported a total IFD incidence of 0.5% in Australia and a 0.5% incidence of pulmonary aspergillosis in Spain [47, 63]. In line with previous recommendations, routine antifungal prophylaxis is not recommended (D-II) (Table 4).

ALLOGENEIC HSCT (ALLO-HSCT)

The main practice change since the previous ECIL recommendations [4] has been the development of haplo-identical allo-HSCT using post-transplantation cyclophosphamide (haplo/PTCy) as graft-versus-host-disease (GVHD) prophylaxis. Retrospective studies on haplo/PTCy allo-HSCT report a one-year incidence rate of IFD ranging from 6 to 17% [64–68]. In two retrospective studies, the IFD incidence (especially invasive mold infections) was significantly higher in haplo/PTCy than in patients transplanted from HLA-matched related and/or unrelated donors receiving calcineurin inhibitors with or without anti-thymocyte globulin (ATG) [66, 67]. However, as the reported IFD rates remained within the range of those in post allo-HSCT outside of the haplo/PTCy setting, haplo/PTCy was still considered at low risk of IFD by the expert panel. As previously highlighted, [4] allo-HSCT centers should monitor the incidence and epidemiology of IFD and be aware that construction works may alter environmental exposure, which may warrant local adaptation of primary antifungal prophylaxis strategy.

The use of isavuconazole as primary antifungal prophylaxis in allo-HSCT recipients has been reported in two prospective open-label studies [69, 70]. The reported rates of breakthrough IFD were low (3–5%) while the treatment was well tolerated (discontinuation rate for toxicity: 2–7%). Data are insufficient to recommend isavuconazole as first-line prophylaxis; however, the expert panel proposes to endorse the ASTCT (American Society of Transplantation and Cellular Therapy) recommendations allowing the use of isavuconazole in cases of QT prolongation, or intolerance to voriconazole or posaconazole (B-II) [71].

In Tables 5 and 6, the main changes in antifungal prophylaxis recommendation are reported (with two additional references in Table 5 [72, 73]).

ANTI-CD19 CHIMERIC ANTIGEN RECEPTOR (CAR) T CELLS

Previously published ECIL guidelines did not include CAR-T cells [4]. The EBMT/JACIE (Joint Acreditation Committee International Society for Cellular Therapy (ISTC) EBMT) and EBMT/ASTCT guidelines recommend the use of an anti-*Candida* prophylaxis and suggest discussing an anti-mold prophylaxis in case of prolonged neutropenia and/or steroid use [74, 75].

Retrospective studies, along with two literature reviews, report a 1–15% incidence of IFD in patients treated with anti-CD19 CAR-T cells [76–80]. These studies highlight a significant association between the occurrence of cytokine release syndrome (CRS) and a higher incidence of infections, attributed to the use of systemic immunosuppressive agents. In the literature review by Garner et al. [80], a combination of pre-and post-infusion factors seemed to increase the risk of IFD. The panel endorses the proposal of Garner et al., published after the EBMT/ASTCT recommendations, and integrating new data not available at the time of publication of the EBMT/ASTCT recommendations. The use of anti-mold prophylaxis is thus proposed to patients with pre-infusion (such as neutropenia, previous IFD, previous allo-HSCT, refractory disease) and post-infusion (CRS/immune effector cell-associated neurotoxicity syndrome [ICANS] necessitating steroid therapy and/or tocilizumab, prolonged neutropenia, use of alternative immunosuppressive agent) risk factors for mold infections, while patients without these risk factors could receiveanti-yeast prophylaxis (B-II) [80].

AUTOLOGOUS HSCT

In the previous ECIL recommendations, patients undergoing autologous HSCT, for whatever underlying condition, were

Table 5. Recommendations for allo-HSCT recipients: pre-engraftment.

Antifungal agent	Pre-engraftment risk of mold infection		ECIL 5-6	
	low	high	low	High
Fluconazole 400 mg q24h	A-I [a]	D-III	A-I [a]	A-III against
Posaconazole tablet 300 mg q24h following a loading dose of 300 mg q12h on day 1 or oral solution 200 mg q8h	B-II	B-II	B-II	B-II
Itraconazole 2.5–7.5 mg/kg q24h i.v. or 200 mg q24h p.o	B-I	B-I	B-I	B-I
Voriconazole 6 mg/kg q12h first day then 4 mg/kg q12h i.v. or p.o.	B-I	B-I	B-I	B-I
Micafungin 50 mg q24h	B-I	C-I	B-I	C-I
Caspofungin and anidulafungin	no data	no data	no data	no data
Liposomal amphotericin B	C-II		C-II	C-II
Aerosolized liposomal amphotericin B (10 mg twice weekly) in combination with systemic fluconazole 400 mg q24h	C-III		C-III	B-II
Isavuconazole 200 mg q24h following a loading dose of 200 mg q8h on days 1 and 2 [b]	B-II	B-II	no data	no data

[a]only when combined with a mold-directed diagnostic approach (biomarker and/or CT scan-based)or a mold-directed therapeutic approach (empirical antifungal therapy).
[b]Isavuconazole can be used as second-line mold active prophylaxis, in case of intolerance to posaconazole / voriconazole, or QTc prolongation.
Pre-engraftment risk of mold infection as previously defined: high risk includes active leukemia, cord blood transplantation and unrelated donor [72]. Haplo-identical HSCT using post-transplantation cyclophosphamide should be considered at low risk (B-II) In case of prior IFD, secondary prophylaxis should be tailored according to the previous documentation [73].
HSCT hematopoietic stem cell transplantation.

Table 6. Recommendations for allo-HSCT recipients: post-engraftment.

Antifungal agent	Steroid treated acute GVHD	ECIL 5-6
Posaconazole tablet 300 mg q24h following a loading dose of 300 mg q12h on day 1, or oral solution 200 mg q8h	A-I [a, b]	A-I [a, b]
Itraconazole 2.5-7.5 mg/kg q24h i.v. or 200 mg q24h p.o	B-I [b]	B-I [b]
Voriconazole 6 mg/kg q12h first day then 4 mg/kg q12h i.v. or p.o.	B-I [b]	B-I [b]
Micafungin 50 mg q24h	C-II	C-II
Caspofungin and anidulafungin	no data	no data
Liposomal amphotericin B	C-II	C-II
Aerosolized liposomal amphotericin B (10 mg twice weekly) in combination with systemic fluconazole 400 mg q24h	no data	no data
Fluconazole 400 mg q24h	D-III	D-III
Isavuconazole 200 mg q24h following a loading dose of 200 mg q8h on days 1 and 2 [c]	B-II	no data

After engraftment, in patients without GVHD, fluconazole can be continued until D + 75.
[a] No difference compared with placebo was seen in patients with chronic GVHD.
[b] It is recommended to monitor serum drug concentration.
[c] Isavuconazole can be used as second-line mold active prophylaxis, in case of intolerance to posaconazole/voriconazole, or QTc prolongation.

considered at low risk of IFD. Primary antifungal prophylaxis is not recommended, although fluconazole (400 mg q24h) should be considered to prevent mucosal *Candida* infection during the neutropenic phase (B-III) [4]. There are no recommendations for change for autologous HSCT recipients.

PRIMARY ANTIFUNGAL PROPHYLAXIS IN PEDIATRIC HEMATOLOGICAL MALIGNANCIES

Mold-active antifungal prophylaxis is recommended for pediatric patients at high risk of IFD (incidence ≥10%), encompassing a subgroup of children with ALL, though their specific risk profile is less precisely defined [81].

A recent analysis of 6316 children with ALL enrolled in the international AIEOP-BFM ALL2009 trial reported an incidence of proven/probable IFDs at 3.8%, with a 12-week mortality rate of 11.2% [82]. In this cohort, 68% of infections were mold-related, with significant risk factors for IFD being ≥12 years of age and insufficient treatment response. A diagnoses of proven/probable IFD were associated with a elevated hazard ratio for event-free survival and overall survival [82]. Consequently, older children (≥ 12 years) with ALL and those with insufficient treatment response are identified as being at elevated risk for IFD and are now recommended to receive antifungal prophylaxis.

Since the 2021 update by ECIL, advances in pediatric antifungal development have been significant. A recent multicenter, non-randomized, open-label, phase 1b dose-escalation trial demonstrated that posaconazole intravenous solution (IV) and powder for oral suspension (PFS) were well tolerated in children, with safety profiles similar to adults [83]. Following this dose-finding trial, the European Medicines Agency (EMA) approved posaconazole IV and PFS in 2021 for high-risk patients aged ≥2 years and

weighing ≤40 kg, including those with AML/MDS or undergoing HSCT with GVHD [84]. Delayed-release tablets were approved for patients ≥2 years and >40 kg with the same conditions [84], although oral suspension remains unapproved by EMA [85].

Additionally, a prospective, randomized, open-label trial among pediatric allo-HSCT patients found caspofungin to be as effective as voriconazole and other triazoles in preventing IFD, including aspergillosis, with a 1.4% infection rate across both trial arms [86]. Hence, the caspofungin grade of recommendation has been updated to a B-I.

FUTURE PROSPECTS

The characteristics of an 'ideal' agent for antifungal prophylactic use include (a) broad spectrum of activity - covering both yeast and mold pathogens - with low risk of development of resistance, (b) availability in oral and parenteral formulations, (c) low potential for clinically problematic drug-drug interactions, (d) low risk of acute and chronic treatment-limiting toxicities, and (e) predictable pharmacokinetics. Several molecules with antifungal activity with a novel mechanism of action are currently in various stages of clinical development [87]. These new molecules tackle some of the shortcomings of the currently available aramamentarium.

- Rezafungin, a second generation echinocandin with enhanced PK/PD pharmacometrics, is active in vitro against most wild-type and azole-resistant *Candida* species (including C. auris), *Aspergillus* species (including azole-resistant A. fumigatus and cryptic species) and *Pneumocystis jirovecii*. The drug has minimal risk of drug-drug interactions and has recently been approved for the treatment of candidemia and invasive candidiasis [88]. Its prophylactic efficacy and safety, when given intravenously once weekly, is currently being tested in a phase 3 randomized double-blind study versus a standard antimicrobial regimen (including fluconazole/posaconazole plus trimethoprim-sulfamethoxazole) in allo-HSCT recipients (The ReSPECT Study) [89].
- Ibrexafungerp, a first-in-class oral glucan synthase inhibitor (a triterpenoid), is approved for the treatment of recurrent vulvovaginal *Candida* infection. The spectrum of activity is similar to the spectrum of rezafungin, but also includes *Alternaria* and *Cladosporium* species. The drug is generally well tolerated with a low risk for drug-drug interactions [90]. Ibrexafungerp has not yet been studied as prophylactic agent but has the potential for use in primary prophylaxis (similar to rezafungin).
- The fungicidal orotomide olorofim is a potent inhibitor of fungal dihydroorotate dehydrogenase. The drug is given orally, has a good tissue distribution and is generally well tolerated. Although olorofim has activity against a variety of mold pathogens (excluding Mucorales species) and dimorphic fungi, the drug displays no activity against yeast pathogens [91]. As such, olorofim is not a good candidate for primary prophylaxis, but may be used for secondary prophylaxis in patients with well documented prior mold infections (e.g., scedosporiosis or aspergillosis).
- Fosmanogepix (the active moiety is manogepix) targets fungal glycosylphosphatidylinositol-anchored cell wall transfer protein 1, inhibiting cell wall synthesis causing loss of viability. Manogepix has a very broad spectrum of activity covering most clinically important fungal pathogens. The drug is available as an oral and IV formulation, has a wide tissue distribution and displays linear pharmacokinetics. The drug has favorable drug-drug interaction and safety profiles [92]. A phase 1 safety and PK study has been performed in neutropenic leukemia patients receiving the drug prophylactically [93]. Given these characteristics, the drug has potential for being investigated as prophylactic antifungal agent.
- Opelconazole is an azole with activity against *Aspergillus* species and other fungi including various *Candida* sp. (including C. auris), *Rhizopus oryzae*, *Cryptococccus neoformans*, *Chaetomium globosum*, *Penicillium chrysogenum* and *Trichophyton rubrum*. Opelconazole was specifically designed for inhaled delivery; the drug accumulates in the lung and has a long residence time in airway cells, potentially enhancing the ability of host cells to clear the fungus, both in treatment and in prophylaxis. Systemic exposure is very low (ratio of lung: systemic concentrations is ~7000:1), resulting in a low risk for drug-drug interactions [94].

CONCLUSION

IFDs remain potentially fatal events in patients with hematological malignancies undergoing chemotherapy, transplantation or cellular therapies. Identification of the main risk factors is necessary to establish appropriate antifungal prophylaxis.

In recent years, various antineoplastic drugs directed against specific surface proteins or molecular targets have been developed for almost all hematological malignancies. This has opened new therapeutic possibilities, but has also increased the population at risk of developing IFDs. Development of cellular therapies, i.e. CAR-T therapy, and increasing use of allo-HSCT has further expanded the number of patients at risk of IFD. The main differences in this updated ECIL guidelines is the inclusion of recommendations for these new risk groups, such as venetoclax combined with azacytidine in patients with AML, treatment with bispecific antibodies, and CAR-T cell therapies.

We aimed to give solid indications based on randomized clinical trials, but in some cases, in the absence of randomized trials, clinical evidence from observational studies has been the base for a grading of recommendation (i.e. isavuconazole in AML).

New bispecific monoclonal antibodies have been introduced during the past 5 years for the treatment of myelomas and lymphomas, but current knowledge on the possible epidemiology of IFDs in these settings is still very limited and does not allow us to suggest any recommendation.

Until now, in Europe, lymphoma patients have been identified as receiving the most benefit from CAR-T cell therapies. However, the number of these procedures is constantly increasing, including myeloma and ALL patients, while their timing is changing, shifting from "the last line therapeutic change" to earlier treatment settings, and now being also used as a bridge to allo-HSCT.

The expectations for the near future are the introduction of new antineoplastic agents that will be more effective but which will also lead to increased immunosuppression. At the same time, we expect that new antifungals with greater efficacy and fewer pharmacological interactions will be available, which will hopefully have an important impact not only on the treatment of IFD but also on prophylaxis.

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AUTHOR CONTRIBUTIONS

All co-authors prepared a set of summary slides on each of the substances addressed in the manuscript, presented the slides at the ECIL-10 conference and revised the slide sets after the plenary discussion. LP prepared the manuscript, all co-authors revised the text and consented the final version.

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Livio Pagano (LP) was Board member of Gilead Science, MSD, Pfizer, Menarini-Stemline, Gentili, Jazz Pharmaceutical, Cidara and has received speaker's honoraria from Gilead Sciences, Kyowa Kirin, MSD, Pfizer Pharmaceuticals, Astellas Pharma, Novartis, Jazz Pharmaceutical, Janseen-Cilag, Astra Zeneca, F2G, Abbvie. Consultant for Menarini, Cidara. Georg Maschmeyer (GM) has received speaker's honoraria from Gilead Sciences. Frederic Lamoth (FL) reports research funding from Gilead, MSD, Pfizer and Novartis, and honoraria for conferences or advisory boards from Gilead, MSD, Pfizer, Mundipharma and Becton-Dickinson, outside of the submitted work. All contracts were made with and fees paid to his institution (CHUV). Ola Blennow has received speaker's honoraria from Gilead Sciences. Alienor Xhaard (AX) has received speaker's honoraria from Merck Sharp and Dohme and Pfizer Pharmaceuticals. Manuela spadea (MS) nothing to declare. Alessandro Busca (AB) was Board member of Gilead Science, Takeda, and has received speaker's honoraria from Gilead Kite Sciences, MSD, Pfizer Pharmaceuticals, Novartis, Jazz Pharmaceutical, Astra-Zeneca, Abbvie, Menarini Stemline, Takeda. Catherine Cordonnier (CC) has received speaker's honoraria from Gilead Science and MSD, and consulting fees from Cidara and Mundipharma. Johan Maertens (JM) reports consulting fees from Amplyx, Cidara, Gilead, Pfizer, Scynexis, F2G, Mundipharma, Takeda, and Basilea; Honoraria for lectures from Astellas, Gilead, Basilea, Mundipharma, Takeda, MedScape, Pfizer, and Shionogi; Participation on Advisory Board from Cidara, Pulmocide, Shionogi, Basilea, Sfunga.

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ADDITIONAL INFORMATION

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PLOS ONE

RESEARCH ARTICLE

A non-randomized trial to assess the safety, tolerability, and pharmacokinetics of posaconazole oral suspension in immunocompromised children with neutropenia

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Abstract

Background

Posaconazole (POS) is a potent triazole antifungal agent approved in adults for treatment and prophylaxis of invasive fungal infections (IFIs). The objectives of this study were to evaluate the pharmacokinetics (PK), safety, and tolerability of POS oral suspension in pediatric subjects with neutropenia.

Methods

This was a prospective, multicenter, sequential dose-escalation study. Enrolled subjects were divided into 3 age groups: AG1, 7 to <18 years; AG2, 2 to <7 years; and AG3, 3 months to <2 years. AG1 and AG2 were divided into 3 dosage cohorts: DC1, 12 mg/kg/day divided twice daily (BID); DC2, 18 mg/kg/day BID; and DC3, 18 mg/kg/day divided thrice daily (TID). AG3 was also divided into DC1 and DC2; however, no subjects were enrolled in DC2. Subjects received 7–28 days of POS oral suspension. PK samples were collected at predefined time points. The POS PK target was predefined as ~90% of subjects with C_{avg} (AUC /dosing interval) between 500 and 2500 ng/mL, with an anticipated mean steady state C_{avg} exposure of ~1200 ng/mL.

data; decision to publish and preparation /review of the manuscript. Authors had access to all study data upon request. A final version of the paper was approved by each co-author. The presentation also underwent formal review by the sponsor. The opinions expressed in the manuscript represent the collective views of the co-authors and do not necessarily reflect the official position of Merck. Dr. Walsh's work on this study was supported in part by the Henry Schuler Foundation.

Competing interests: The study was sponsored and funded by Merck & Co., Inc., Kenilworth, NJ, USA; the company manufactures POSACONAZOLE under the name NOXAFIL®. The authors have the following competing interests to disclose: AA and JSB received grant funds from Merck & Co., Inc., Kenilworth, NJ, USA- to conduct the study; LS has nothing to disclose; TL reports grants and from Gilead Sciences and was an Advisory Board member/Speaker at Merck, Astellas, and Basiela; AG reports consultant fee and honorarium from Merck; CMZ reports funds for the trial reimbursement; TJW received consultant fees from Allergan, Astellas, ContraFect, Drais, iCo, Medicines Company, Merck, Novartis, Pfizer, Methylgene, SigmaTau and research grants from Weill Cornell Medicine, Allergan, Astellas, Merck, Novartis, Pfizer and Scynexis. PC, DG, AJ, NK, EM, AP, and HW are employees of Merck & Co., Inc., Kenilworth, NJ, USA. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

Results

The percentage of subjects meeting the PK target was <90% across all age groups and dosage cohorts (range: 31% to 80%). The percentage of subjects that achieved the C_{avg} target of 500 to 2500 ng/mL on Day 7 ranged from 31% to 80%, with the lowest proportion in subjects 2 to <7 years receiving 12 mg/kg/day BID (AG2/DC1) and the highest proportion in subjects 7 to <18 years receiving 18 mg/kg/day TID (AG1/DC3). At all three dose levels (12 mg/kg/day BID, 18 mg/kg/day BID and 18 mg/kg/day TID), subjects in AG1 (7 to <18 years old) had higher mean PK exposures at steady state than those in AG2. High variability in exposures was observed in all groups. POS oral suspension was generally well tolerated and most of the reported adverse events were related to the subjects' underlying diseases.

Conclusion

The POS PK target of 90% of subjects with C_{avg} between 500 and 2500 ng/mL was not achieved in any of the age groups across the different dosage cohorts. New formulations of the molecule with a greater potential to achieve the established PK target are currently under investigation.

Trial registration

ClinicalTrials.gov identifier: NCT01716234

Introduction

Pediatric subjects who receive dose-intensive chemotherapy for cancer are at an increased risk of invasive fungal infections (IFIs). The pediatric population at high risk for developing IFIs includes, but is not limited to, allogeneic hematopoietic stem cell transplant (HSCT) recipients, patients with acute myeloid leukemia (AML), relapsed acute lymphoblastic leukemia (ALL), or severe aplastic anemia, and patients receiving immunosuppressant or high-dose corticosteroids for severe graft-versus-host disease (GVHD) or other conditions [1–6]. IFIs are responsible for considerable morbidity, mortality, and healthcare utilization and may prevent or delay the delivery of appropriate chemotherapy [7, 8]. Additionally, the incidence of IFIs in the pediatric population appears to have increased over the past few decades, primarily because of the prolonged survival of pediatric patients with primary or secondary immune deficiencies [9–11]. Prophylaxis for IFIs is indicated in high-risk pediatric patients, and recommended agents include fluconazole, liposomal amphotericin, and micafungin; however, more clinical data supporting use of newer antifungal agents in this population are needed, particularly with regard to appropriate pediatric dosing [12].

Posaconazole (POS) is a broad-spectrum triazole antifungal compound which exhibits potent antifungal activity against a variety of yeasts and molds, including strains that are resistant to amphotericin B, fluconazole, voriconazole, or itraconazole. The efficacy of POS in both prophylaxis and treatment has been established in adults using the oral suspension [13, 14]. Two prior prophylaxis studies in adults helped in defining the basic pharmacokinetic (ADME) and safety parameters for the pediatric study (6,14). As the pharmacokinetic (PK), safety, and efficacy data for POS in pediatric subjects are sparse, dosing recommendations for patients <13 years old has not been established. Thus, we conducted the first dedicated clinical trial of

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POS in the pediatric population. The primary objective was to evaluate the PK of POS oral suspension administered orally at three dosage levels to immunocompromised children aged 3 months to <18 years with neutropenia or expected neutropenia. The PK criteria were based on data from the adult prophylaxis and treatment studies in which doses above 800 mg per day were not found to be beneficial because of the plateau in POS exposure, which may also occur in pediatric subjects. The secondary objectives were to evaluate the safety and tolerability of POS oral suspension at these three dosage levels.

Materials and methods

Study design

This study (MK 5592–032, NCT01716234) was a prospective, non-randomized, multicenter, open-label, sequential dose-escalation study to evaluate the PK, safety, and tolerability of POS oral suspension in children aged 3 months to <18 years with neutropenia or expected neutropenia (defined as an absolute neutrophil count [ANC] $\leq 500/mm^3$). This study was conducted at centers in the US, Germany, Canada, Greece, and the Netherlands. An Institutional Review Board/independent ethics committee for each clinical site approved the study protocol, a full list can be found in the S1 Table. All clinical investigations were conducted according to principles expressed in the Declaration of Helsinki and Good Clinical Practice Guidelines. Patients were enrolled starting 06 Jun 2008 and last subject visit for follow up was 01 Apr 2015. At enrollment, informed consent was obtained from each participant and his/her legal guardian, and assent was obtained where appropriate. The authors confirm that all ongoing and related trials for this drug/intervention are now registered. An initial delay in the trial registration occurred due to the transfer of this study from Schering Plough to Merck and the differences in the trial registration requirements of the two companies.

Subjects were stratified into 3 age groups and 3 dosing cohorts as shown in **Fig 1**. Age Group 1 (AG1) consisted of subjects 7 to <18 years of age; Age Group 2 (AG2), subjects 2 to <7 years of age; and Age Group 3 (AG3), subjects 3 months to <2 years of age. AG1 and AG2 were divided into 3 sequential dosing cohorts (DCs): DC1, 12 mg/kg/day divided twice daily (BID), up to a maximum of 800 mg/day; DC2, 18 mg/kg/day divided twice daily (BID), up to a maximum of 1200 mg/day; and DC3, 18 mg/kg/day divided 3 times daily (TID), up to a maximum of 1200 mg/day.

Enrollment in AG3, the youngest subjects [3 months to <2 years], was not initiated until enrollment in the first 2 dosage cohorts in AG1 and AG2, and a preliminary review of safety and PK data was completed. The data from the subjects administered POS oral suspension at a dose of 12 mg/kg/day BID and 18 mg/kg/day BID informed which of the planned doses would be used for AG3. In AG3, the planned dosage cohorts were 12 mg/kg/day of oral POS divided TID (DC1) and 18 mg/kg/day of oral POS divided TID (DC2). All administrations in AG3 were provided orally or via enteral tube; the feasibility of administration via enteral tube was tested by the Sponsor prior to initiation of AG3. Subjects were provided a high fat meal or snack prior to dosing and most subjects did consume some food majority in the medium and high fat categories.

Each subject who enrolled in the study participated in the trial for approximately 80 days from the time the subject signed the informed consent form (ICF) through the final contact. As shown in **Fig 1**, an initial screening phase of up to 7 days was planned, during which vital signs, medical history, and blood draws for hematology and serum chemistry assessments were taken. At baseline, a physical examination with vital signs, body weight, electrocardiogram (ECG), and measurement of ANC were performed. This was followed by a treatment phase during which subjects received study drug for a minimum of 7 days and a maximum of

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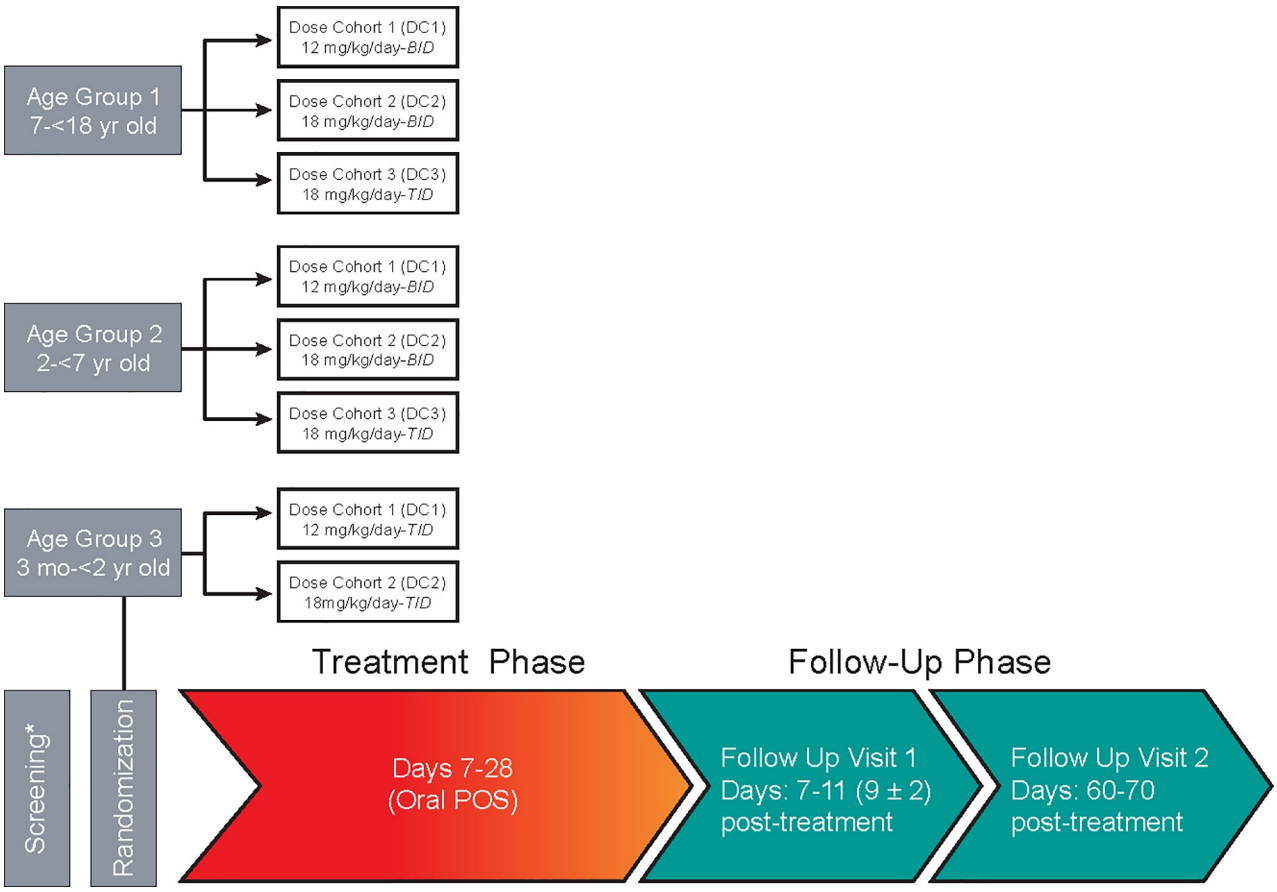


Fig 1. Study design. * Initial screening phase lasted up to 7 days; vital signs, medical history, and blood draws for hematology and serum chemistry assessments were taken.# Minimum duration of treatment was 7 days and continued until resolution of neutropenia or initiation of SOC treatment for IFI, up to a maximum of 28 days. Note: Blood draws for full PK assessments were obtained on Day1 and Day 7, immediately prior to oral administration of POS. POS trough samples were also obtained immediately prior to dosing on Days 3, 5, 8, 14, AND 28 or within 24 hours after the last dose of study drug for earlier discontinuations.

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28 days; in general, treatment continued until recovery from neutropenia (absolute neutrophil count [ANC] >500/mm^3) or until initiation of standard of care antifungal therapy. During the first 7 days of the treatment phase, vital signs and adverse events were assessed every 2 days, followed by weekly assessments for ongoing treatment through Day 28. Blood draws for serum chemistry, hematology, and PK were performed on the same schedule. At the end of the treatment phase there were two follow-up visits; a first follow-up visit performed 9 (±2) days after treatment ended, and a second follow-up visit on Day 65 (±5 days), which focused on an assessment of survival.

Patient population

Eligible subjects were required to have documented or anticipated neutropenia (ANC ≤500/mm^3) expected to last for at least 7 days. In addition, subjects were required to be recipients of an autologous or allogeneic HSCT or have an eligible cancer diagnosis. Eligible diagnoses included acute leukemia (new or relapse), myelodysplastic syndrome, severe aplastic anemia, high risk neuroblastoma, or advanced stage non-Hodgkin's lymphoma. Recipients of allogeneic HSCT were eligible during the pre-engraftment (neutropenic) period. Subjects with

proven IFIs at baseline, as defined by the European Organization for Research and Treatment of Cancer- Mycoses Study Group criteria [14], were excluded from the study. Other exclusion criteria were severe nausea and/or vomiting at screening (grade 3 or 4); study drug (POS) administration within 10 days before screening; inability to receive study drug by mouth or enteral tube; significant elevations of transaminase (>5x upper limit of normal (ULN)) and/or bilirubin levels at baseline (>2.5x upper limit of normal (ULN)); significant renal dysfunction at baseline (Calculated creatinine clearance <30 mL/min.); and history of anaphylaxis attributed to the azole class of antifungal agents. Medications known to interact with azoles and potentially leading to life-threatening adverse effects (such as astemizole, cisapride, beastie, halofantrine, pimozide, quinidine, and terfenadine) and medications known to affect the serum concentration/efficacy of triazole antifungal agents (barbiturates, carbamazepine, cimetidine, isoniazid, phenytoin, rifabutin, rifampin, and St. John's wort (*Hypericum perforatum*) were prohibited.

Assessments

Blood samples for PK assessment of POS were obtained on Days 1 and 7 immediately prior to oral administration of POS and at 3, 5, 8, and 12 hours from the time of oral administration of the morning dose. For the TID dosage cohorts, the 12-hour sample was not collected, and the 8-hour sample was drawn prior to the next dose. In addition, POS trough samples (C_{min}) were obtained immediately prior to dosing on Days 3, 5, 8, 14, and 28, or within 24 hours after the last dose of study drug for earlier discontinuations. For subjects weighing <6.5 kg, Day 1 blood samples were not collected in order to minimize blood collection in this group. Approximately 1 mL blood was collected at each PK time point for each subject and plasma samples were sent to a central laboratory for analysis. For the POS assay, a validated liquid chromatography coupled to tandem mass spectrometry detection method [15] was used, with a calibration/validation range of 5 to 5,000 ng/mL. The acceptance criteria was set at ±15%. There were minimal samples above the upper limit of quantitation, but those that exceeded 5000 ng/mL were diluted to fall within the validated range. All dilutions were validated.

PK evaluations

Subjects who received at least one dose of POS were included in the PK analysis. Key PK measures of POS were C_{avg} or the average plasma concentration; defined as the AUC (calculated using Phoenix v.6.3 software, that utilizes the linear-linear trapezoidal method for ascending concentrations up to C_{max} and log-linear trapezoidal method for descending concentrations) divided by the dosing interval on Day 7 (which was considered steady state); AUC time curve from time zero to the time of the final quantifiable sample (AUC_{tf}); maximum [peak] plasma concentration (C_{max}); time to C_{max} (T_{max}); and ratio of AUC_{tf} on Day 7 to AUC_{tf} Day 1. The POS PK target was predefined as ~90% of subjects with C_{avg} between 500 and 2500 ng/mL, with an anticipated mean steady state C_{avg} exposure of ~1200 ng/mL. All PK parameters were calculated using non-compartmental methods with Phoenix WinNonlin 6.3. AUC_{tf} was calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations. C_{max} and T_{max} were obtained by inspection of the plasma concentration data.

Safety

Safety assessments were conducted on all subjects that received at least one dose of the study drug. These assessments included reports of all adverse events (AEs). Adverse events were classified as treatment-emergent AEs (TEAEs), treatment-related (or drug-related) TR-TEAEs,

AEs leading to discontinuation of study drug, and SAEs. Treatment emergent adverse events were defined as an untoward medical occurrence in a subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment and occurred *after start of treatment* with posaconazole. TR-TEAEs were defined as TEAEs judged by the investigator to be related to treatment with posaconazole. Serious adverse events (SAE) were defined as any adverse drug experience occurring at any dose that results in any of the following outcomes: death; life-threatening AE; persistent or significant disability/incapacity; requires in-patient hospitalization or prolongs hospitalization; congenital anomaly or birth defect. Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

SAEs were captured from the time of signing of the ICF through 30 days after the administration of the last dose of study drug. All other AEs were collected from screening through the first follow-up study visit, which occurred 9 (±2) days after the last dose of study drug. A survival assessment was conducted at the second follow-up visit, on Day 65 (±5 days). TEAEs and TR-TEAEs were tabulated by body system/organ class, with summaries tabulated for each age group/dosage cohort. In addition to AE reporting, electrocardiography (ECG) was performed at baseline and Day 3; ECG summary statistics included the numbers of subjects with change from baseline in QTcF categorized as <0, 0 to 30, 31 to 60, and >60 msec and the number of subjects with a treatment-emergent QTcF interval >500 msec. Laboratory safety reporting based on hematology and serum chemistries were assessed at screening on Days 1, 3, 5, 7, 14, 21, and 28 of treatment, at end of treatment, and at the first follow-up visit.

Statistical analysis

For C_{avg}, the proportion of subjects achieving the target exposure between 500 and 2500 ng/ml was calculated for the comparison of proportions across age group and dosage cohort. A comparison between adult and pediatric subjects with respect to the proportion of PK evaluable subjects (as defined in S1 File) achieving the target exposure was also conducted. For $C_{avg,}$ the arithmetic mean and its %CV and SD) was assessed. For the other PK parameters (C_{avg}, $C_{max,}$ $T_{max,}$ and AUC_{tf}), summary statistics were provided, including medians (min, max) for each of these parameters as well as the accumulation ratio for AUC (AUC_{tf} Day 7/AUC_{tf} Day 1). Log-transformed ratio estimates with 90% confidence intervals were calculated for the differences between doses and ages. The steady-state analysis was conducted using available PK (C_{min}) trough values.

Preliminary PK data were reviewed from DC1 and DC2 in the 2 older age groups, AG1 and AG2. Subsequently, an analysis on DC1 in AG3 and DC3 in AG1 and AG2 were conducted. This manuscript summarizes the data from all of these analyses.

Results

Population

The disposition of the subjects in the study is shown in **Fig 2**. A total of 142 subjects were enrolled in the study; of these, 136 subjects received at least one dose of POS. There were a total of 86 (63%) treated subjects who completed the treatment phase of the study; i.e., they no longer required prophylaxis [having recovered from neutropenia after at least 7 days of study drug] or received up to a maximum of 28 days of study drug. Among the 50 (37%) treated subjects that discontinued in the treatment phase, the most common reason for discontinuation was an AE (35 subjects, 26%), followed by discontinuation for reasons unrelated to study

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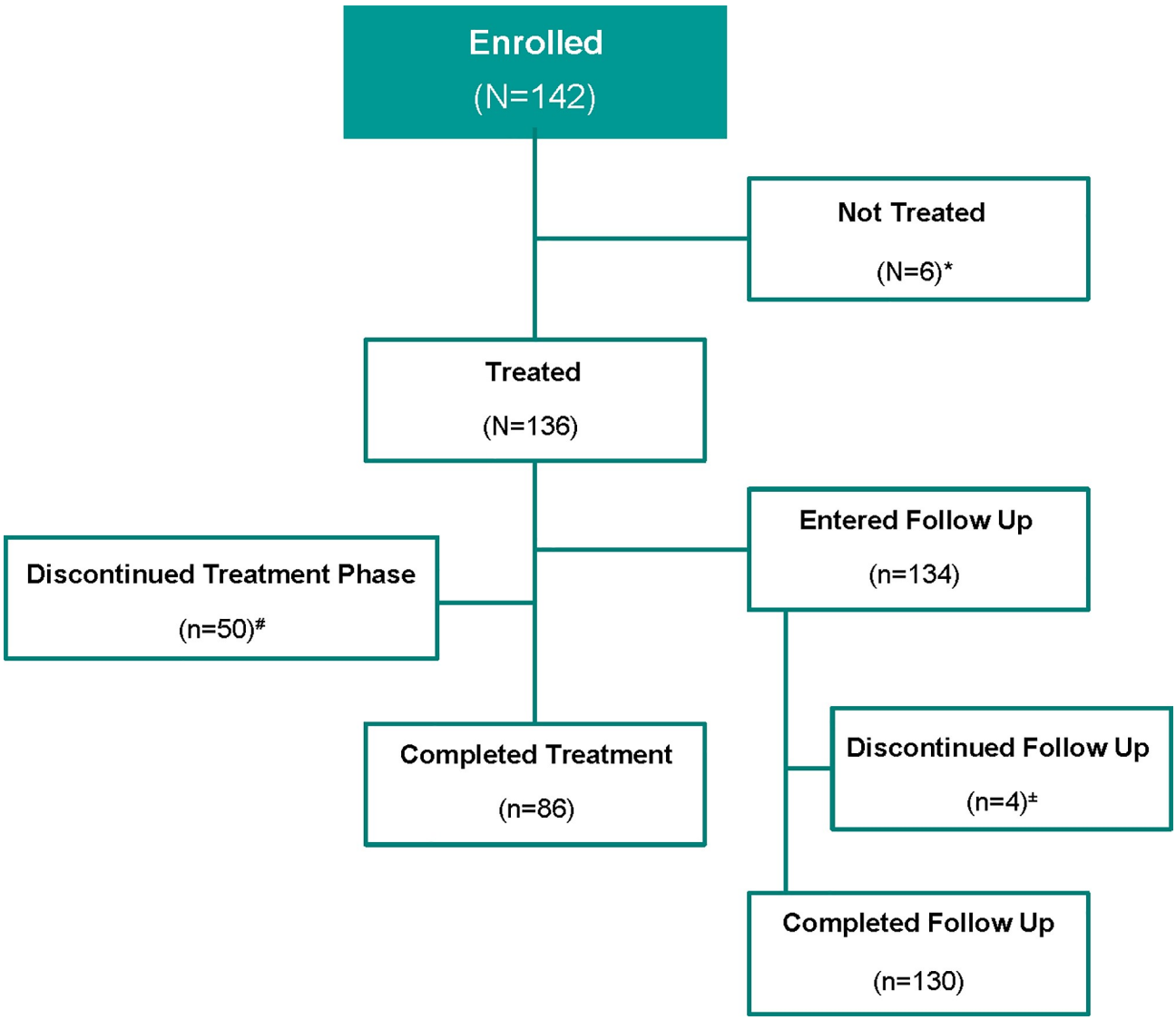


Fig 2. Subject disposition. * Of the 6 subjects not treated, 4 subjects did not wish to continue due to reasons unrelated to assigned study treatment, 1 subject did not meet protocol eligibility, and 1 subject had an adverse event (AE). # Most common reasons for discontinuation of the treatment phase were: AE (n = 35), subject not willing to continue due to reasons unrelated to treatment (n = 7), subject not meeting protocol requirement to continue therapy (due to recovery from neutropenia before 7 days of therapy, n = 4) and non-compliance with protocol (n = 3). ± Three subjects discontinued follow up due to an AE, and one subject was non-compliant with the protocol.

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treatment (7 subjects, 5%). Only 2 of the 136 treated subjects did not complete the first follow-up visit, at day 9 (±2) post-treatment. A total of 130 (97%) subjects completed the study through the second follow-up visit.

A summary of demographic data by age group and dosage cohort is provided in Table 1. Of the 136 treated subjects, the majority were male (58%) and were white (88%). The overall median age was 8.5 years, and the overall median weight was 29.8 kg. Only 1 subject was enrolled in AG3, as the study was stopped prematurely once there was evidence that the target PK could not be achieved in the 2 older age groups. Overall, slightly more than half of the subjects had a primary diagnosis of acute leukemia (52%), followed by HSCT (24%), neuroblastoma (10%), and non-Hodgkin's lymphoma (7%). Of the subjects with a primary diagnosis of

Table 1. Subject characteristics across different age groups and posaconazole dosing cohorts.

	AG1: 7 to <18 y			AG2: 2 to <7 y			AG3: 3 mo to <2 y	Total
	DC1: 12 mg/kg/d (BID) n (%)	DC2: 18 mg/kg/d (BID) n (%)	DC3: 18 mg/kg/d (TID) n (%)	DC 1: 12mg/kg/d (BID) n (%)	DC2: 18 mg/kg/d (BID) n (%)	DC3: 18mg/kg/d (TID) n (%)	DC1: 12 mg/kg/d (TID) n (%)	N(%)
Treated	21 (100)	28 (100)	30 (100)	22 (100)	19 (100)	15 (100)	1 (100)	136 (100)
Sex								
Female	11 (52)	9 (32)	14 (47)	9 (41)	8 (42)	6 (40)	0	57 (42)
Male	10 (48)	19 (68)	16 (53)	13 (59)	11 (58)	9 (60)	1 (100)	79 (58)
Race, n (%)								
White	17 (81)	22 (79)	26 (87)	20 (91)	18 (95)	15 (100)	1 (100)	119 (88)
Non-White	4 (19)	6 (21)	4 (13)	2 (9)	1 (5)	0	0	17 (13)
Asian	1 (5)	3 (11)	1 (3)	2 (9)	0	0	0	7 (5)
Black or African	1 (5)	2 (7)	2 (7)	0	1 (5)	0	0	6 (4)
Multiracial 0	2 (10)	1 (4)	1 (3)	0	0	0	0	4 (3)
Primary Diagnosis								
Acute Leukemia	11 (52)	15 (54)	20 (67)	8 (36)	9 (47)	7 (47)	1 (100)	71 (52)
ALL	5 (24)	4 (14)	5 (17)	4 (18)	2 (11)	3 (20)	0	23 (17)
AML	6 (29)	11 (39)	14 (47)	3 (14)	7 (37)	3 (20)	0	44 (32)
Unspecified	0	0	1 (3)	1 (5)	0	1 (7)	1 (100)	4 (3)
Myelodysplastic Syndrome	2 (10)	0	0	0	2 (11)	0	0	4 (3)
Aplastic Anemia	0	3 (11)	0	1 (5)	0	0	0	4 (3)
Hematopoietic Stem Cell Transplantation	5 (24)	5 (18)	6 (20)	5 (23)	7 (37)	5 (33)	0	33 (24)
Allogeneic	0	0	0	0	2 (11)	2 (13)	0	4 (3)
Autologous	1 (5)	1 (4)	0	0	1 (5)	0	0	3 (2)
Unspecified	4 (19)	4 (14)	6 (20)	5 (23)	4 (21)	3 (20)	0	26 (19)
Neuroblastoma	1 (5)	1 (4)	0	8 (36)	1 (5)	2 (13)	0	13 (10)
Non-Hodgkin's Lymphoma	1 (5)	4 (14)	4 (13)	0	0	1 (7)	0	10 (7)
Missing	1 (5)	0	0	0	0	0	0	1 (1)

ALL = acute lymphocytic leukemia; AML = acute myelogenous leukemia; BID = twice daily; TID = three times daily
n = number of subjects.

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acute leukemia, nearly twice as many subjects had AML as compared to ALL (32% versus 17%, respectively).

PK evaluations

A summary of the percentage of PK evaluable subjects who achieved the PK target (C_{avg} at steady state [Day 7] between 500 and 2500 ng/mL) is presented in Table 2 by age group and dosage cohort. Overall, 70 PK-evaluable subjects were available for assessment at steady state. None of the dosage cohorts in this study achieved the target PK of 90% of subjects with C_{avg} between 500 and 2500 ng/mL; 30 of the 70 PK-evaluable subjects (43%) had steady-state C_{avg} level <500 ng/ml, while only 3 (4%) subjects had $C_{avg} \geq 2500$ ng/mL. Furthermore, there were no data to support a trend of higher steady-state C_{avg} exposure with either increasing the dose (from 12 to 18 mg/kg) or frequency of administration (from BID to TID) of POS oral suspension.

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Table 2. Distribution of C_{avg} by age group and dose cohort in subjects with evaluable PK on day 7.

Age & Dose Cohorts			C_{avg} (ng/ml)				
Age Group	**Dose Cohorts**	**N**	**< 200 % (n/m)**	**200 to < 500 % (n/m)**	**500 to <2500 % (n/m)**	**2500 to < 3650 % (n/m)**	**>3650 % (n/m)**
AG1: (7 to 18 years)	**DC1:** 12 mg/kg/day (BID)	14	14% (2/14)	21% (3/14)	64% (9/14)	0	0
	DC2: 18 mg/kg/day (BID)	12	8% (1/12)	25% (3/12)	50% (6/12)	8% (1/12)	8% (1/12)
	DC3: 18 mg/kg/day (TID)	10	20% (2/10)	0	80% (8/10)	0	0
AG2: (2 to <7 years)	**DC1:** 12 mg/kg/day (BID)	16	19% (3/16)	44% (7/16)	31% (5/16)	6% (1/16)	0
	DC2: 18 mg/kg/day (BID)	12	25% (3/12)	25% (3/12)	50% (6/12)	0	0
	DC3: 18 mg/kg/day (TID)	5	20% (1/20)	20% (1/20)	60% (3/5)	0	0
AG3: (3 months to <2 years)	**DC1:** 12 mg/kg/day (TID)	1	0	100% (1/1)	0	0	0

Numbers in parentheses = (Number of subjects in category / Total number of subjects)

Target C_{avg} range (500-<2500 ng/ml) required for ~90% of subjects to meet criteria for study success

https://doi.org/10.1371/journal.pone.0212837.t002

The percentage of subjects that achieved the C_{avg} target of 500 to 2500 ng/mL on Day 7 ranged from 31% to 80%, with the lowest proportion in subjects 2 to <7 years receiving 12 mg/kg/day BID (AG2/DC1) and the highest proportion in subjects 7 to <18 years receiving 18 mg/kg/day TID (AG1/DC3). The one subject enrolled in the youngest age group (3 months to <2 years age, AG3) also did not meet the target.

An assessment of all the PK parameters for the various age groups and dose cohorts are summarized in **Table 3**. The combined mean (±SD) plasma concentration profiles of POS in all age groups and dose cohorts are shown in **Fig 3**. At all three dose levels (12 mg/kg/day BID, 18 mg/kg/day BID, and 18 mg/kg/day TID), subjects in AG1 (7 to <18 years old) had higher mean PK exposures at steady state than those in AG2 (2 to <7 years old). The Day 1 PK exposures were similar between the two age groups at all three dose levels. No definitive conclusions can be drawn in AG3 (3 months to <2 years) as there was only 1 subject in this group.

Safety

A total of 136 subjects received at least one dose of study drug and were included in the study safety analyses. TEAEs, treatment-related TEAEs, SAEs, treatment-related SAEs, and AEs leading to early study discontinuation are summarized in **Table 4**. Overall, TEAEs and TR-TEAEs were reported in 94% (n = 128) and 37% (n = 50) of subjects, respectively. The most common TR-TEAEs observed in ≥5% of subjects overall were nausea (13%) and vomiting (13%). Treatment-related severe/life threatening (LT) TEAEs were reported for 14 (10%) subjects. The most commonly reported treatment-related severe/LT TEAEs (representing ≥2% of subjects overall) were alanine aminotransferase increased (ALT, 4%) and aspartate aminotransferase increased (AST, 2%). Discontinuations of the study treatment due to an AE occurred in 26% of the treated subjects, with the highest rate observed with the lowest dose, (37% in those receiving POS 12 mg/kg/day BID). Serious AEs were reported for 35 subjects (26%), with the highest frequency (40%) observed at the highest dose, POS 18 mg/kg/day TID. A diverse variety of SAEs were reported, with most events pertaining to the underlying disease or complications relating to the underlying condition. The most common reported SAE was

Table 3. Pharmacokinetic parameter values of posaconazole by age group and dosing cohort following single and multiple dose administration of posaconazole oral suspension.

	AG1: 7 to 18 y						AG2: 2 to <7 y						AG3: 3 mo to <2 y	
	DC1: 12 mg/kg/d (BID)		DC2: 18 mg/kg/d (BID)		DC3: 18 mg/kg/d (TID)		DC1: 12 mg/kg/d (BID)		DC2: 18 mg/kg/d (BID)		DC3: 18 mg/kg/d (TID)		DC1: 12 mg/kg/d (TID)	
Day	1	7	1	7	1	7	1	7	1	7	1	7	1	7
n	19	14	12[d]	12	10	10	22	16[c]	12	12	5	5	1	1
C_{max} (ng/mL)	156 (78.1)	1200 (75.5)	162 (86.7)	1390 (111.4)	93.2 (60.8)	1230 (64.2)	196 (93.9)	726 (125.5)	175 (70.5)	581 (61.0)	109 (61.3)	705 (60.9)	103	520
T_{max}[a] (hr)	5.0 (2.97, 12.0)	4.58 (0, 7.75)	3.12 (2.92, 8.00)	4.03 (0.0, 28.5)	4.88 (2.92, 8.08)	2.63 (0.00, 7.62)	5.01 (2.92, 11.60)	4.13 (0.0, 11.17)	3.99 (2.98, 11.08)	3.00 (0.0, 8.08)	7.95 (2.98, 8.00)	3.00 (0.0, 5.08)	3.38	0.00
AUC_{tf} (hr*ng/mL)	1140 (93.7)	11,800 (75.4)	1270 (98.1)	13500 (115.8)	424 (49.5)	8310 (74.9)	1300 (91.4)	6770 (138.9)	1210 (76.88)	5350 (62.0)	544 (59.6)	4920 (67.1)	574	3590
tf[a] (hr)	11.88 (7.92, 12.25)	11.59 (7.95, 12.08)	11.54 (2.92, 12.08)	11.60 (7.33, 12.12)	7.92 (4.83, 8.10)	7.77 (4.67, 8.00)	11.04 (7.98, 12.15)	11.42 (8.00, 12.00)	11.23 (9.07, 12.07)	11.5 (8.0, 12.03)	7.95 (7.83, 8.00)	7.92 (7.82, 8.00)	8.38	7.92
Mean C_{avg}[b] (ng/mL)	107 (86.5, 92.5)	1050 (76.2, 789)	113 (89.1, 100)	1240 (113.4, 1400)	57.9 (52.2, 30.2)	1150 (65.4, 750)	122 (83.1, 101)	604 (129.0, 779)	112 (77.6, 86.9)	485 (63.0,306)	68.4 (59.2, 40.4)	620 (66.2, 411)	68.5	453
Median C_{avg}[a] (ng/mL)	89.7 (16.4, 398)	979 (65.4, 2420)	74.4 (33.8, 393)	698 (181, 4660)	56.2 (12.0, 105)	1300 (127, 2340)	94.7 (15.7, 437)	414 (37.8, 3350)	519 (48.3, 926)	519 (48.3, 926)	75.4 (28.10, 124)	529 (191, 1280)	68.5	453
R	–	11.2 (69.8)	–	11.7 (75.8)	–	22.0 (70.8)	–	4.42 (47.9)	–	5.33 (80.8)	–	12.0 (73.0)		6.25

n: Number of subjects; C_{max}: maximum concentration; T_{max}: time to maximum observed concentration; AUCtf: area under the concentration-time curve from time 0 to the time of the final quantifiable sample; tf: last time point with PK sample collected and concentration >LLOQ; C_{avg}: AUCtf/tf; R: accumulation ratio (AUCtf Day 7/ AUCtf Day 1).

a Median (min-max).

b Arithmetic mean (%CV, SD).

c One subject had quantifiable pre-dose concentration greater than 10% C_{max}.

d One subject had the first dose split into two and the second half of the dose was administered 3.25 hours after the first half of the dose. PK exposure was calculated based on PK sample collection time elapsed from the first half of the dose.

https://doi.org/10.1371/journal.pone.0212837.t003

febrile neutropenia in 15 subjects (11%), of which the majority (10 subjects; 22%) were in the POS 18 mg/kg/day TID group. Only 3 subjects, including 2 (5%) receiving POS 12 mg/kg/day BID (both in AG2, the 2 to <7-year age group) and 1 (2%) receiving POS 18 mg/kg/day TID (in AG1, the 7 to <18-year group), experienced SAEs considered by the investigator as treatment related. In AG2/DC1 subjects (n = 2), treatment related SAEs included: electrocardiogram T-wave inversion, increased levels of alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), and increased chemotherapeutic (methotrexate) drug levels. The single treatment-related SAE in an AG1/DC3 subject was inversion of the electrocardiogram T wave.

There were also three reported deaths across all treated subjects, including 2 in the POS 18 mg/kg/day TID group (DC3) and 1 in the POS 18 mg/kg/day BID group (DC2). In DC3, 1 death was related to Burkitt's lymphoma occurring on Day 114 (95 days after last dose of POS) and the other death was related to multi-organ failure on Day 132 (122 days after last dose of POS). In DC2, the 1 death occurred on Day 65 (58 days after the last dose of POS) as a result of

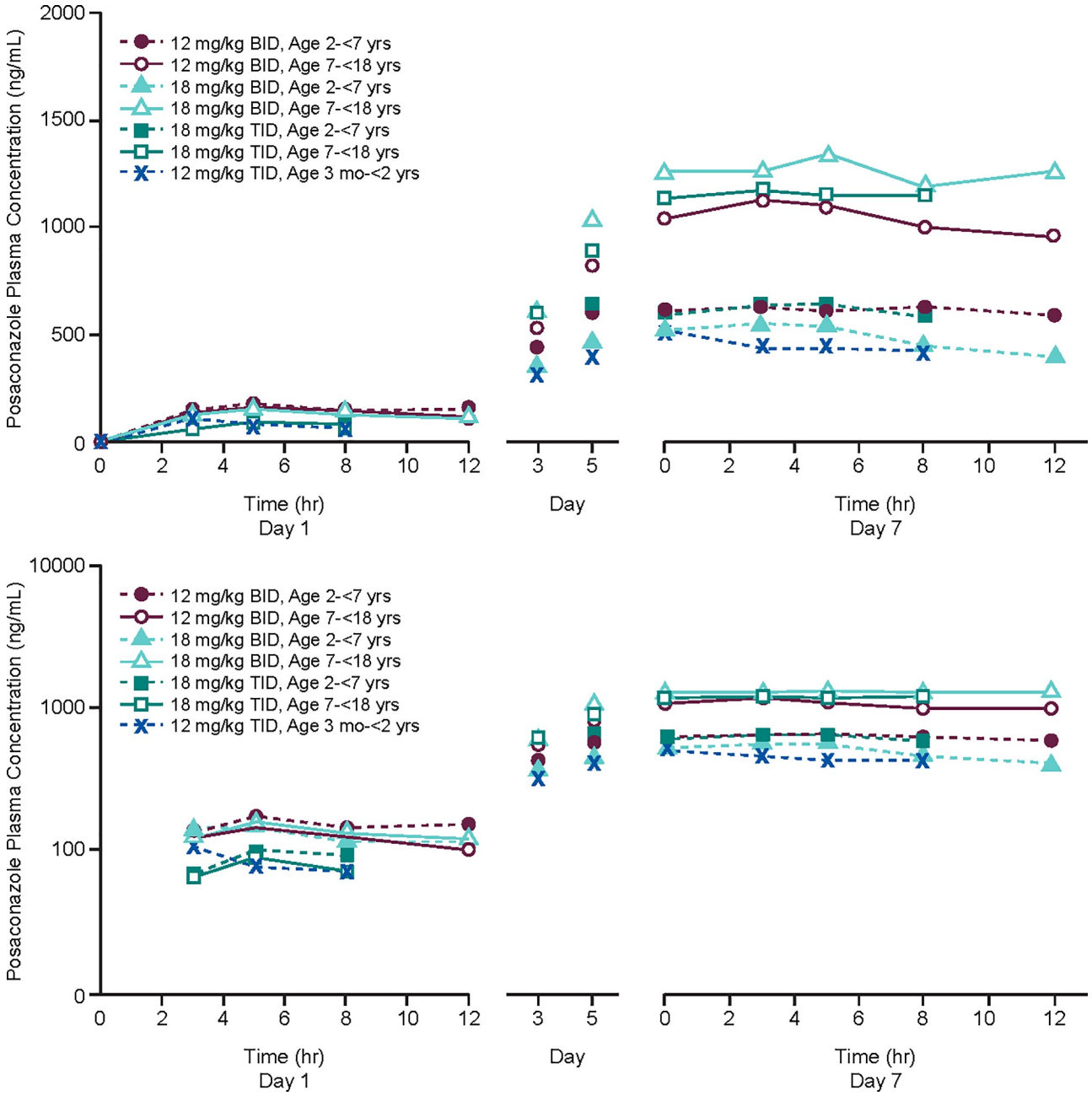


Fig 3. Combined Mean plasma concentration profile by age group and dosing cohort following single (day 1) and multiple dose (day 7) administration of posaconazole oral suspension.

https://doi.org/10.1371/journal.pone.0212837.g003

acute respiratory distress syndrome and multi-organ failure. None of the deaths were considered by the investigators as related to POS.

The frequency of TR-TEAEs reported in ≥5% of subjects within any age group was generally similar between the 2 older age groups (AG 1 [7to <18 years] and AG2 [2to <7years]). One notable exception was a higher frequency of nausea (18% vs. 7%) reported in AG1 vs. AG2. Overall, there was no apparent pattern to suggest a difference in the safety profiles among the three dosing cohorts and 2 older age groups. Safety in AG3 (3 months to <2 years) could not be assessed, with only 1 subject treated in this youngest age group.

Table 4. Summary of Safety by age group and dose cohorts and most common treatment-related adverse events by age group.

	AG1: 7 to <18 y			AG2: 2 to <7 y			AG3: 3 mo to <2 y	Total
	DC1: 12 mg/kg/d (BID) n (%)	DC2: 18 mg/kg/d (BID) n (%)	DC3: 18 mg/kg/d (TID) n (%)	DC1: 12 mg/kg/d (BID) n (%)	DC2: 18 mg/kg/d (BID) n (%)	DC3: 18 mg/kg/d (TID) n (%)	DC3: 12 mg/kg/d (BID) n (%)	
Treatment- emergent adverse event (TEAE)	21 (100)	26 (93)	30 (100)	21 (95)	16 (84)	13 (87)	1 (100)	128 (94)
Treatment-related TEAE (TR-TEAE)	5 (24)	16 (57)	10 (33)	11 (50)	5 (26)	3 (20)	0	50 (37)
Serious adverse event (SAE)	3 (14)	7 (25)	11 (37)	5 (23)	1 (5)	7 (47)	1 (100)	35 (26)
Death	0	1 (4)	1 (3)	0	0	1 (7)	0	3 (2)
Severe/life-threatening TEAE	10 (48)	16 (57)	20 (67)	14 (64)	5 (26)	7 (47)	0	72 (53)
Study drug discontinuation due to AE	9 (43)	9 (32)	6 (20)	7 (32)	2 (11)	3 (20)	0	36 (26)

Treatment-Related Treatment–Emergent Adverse Events (TR-TEAE) of >5% Frequency

	AG1: 7 to <18 y (N = 79)	AG2: 2 to <7 y (N = 56)	AG3: 3 mo to < 2 y (N = 1)	Total (N = 136)
Any Adverse Event	31 (55)	19 (24)	0	50 (37)
Nausea	14 (18)	4 (7)	0	18 (13)
Vomiting	11 (14)	6 (11)	0	17 (13)
Abdominal Pain	4 (5)	2 (4)	0	6 (4)
Diarrhea	4 (5)	1 (2)	0	5 (4)
Stomatitis	1 (1)	3 (5)	0	4 (3)
ALT increased	5 (6)	4 (7)	0	9 (7)
AST increased	3 (4)	3 (5)	0	6 (4)

n: number of subjects; POS: posaconazole; BID = two times per day; TID = three times per day

Note: Deaths are also included in serious adverse event count.

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No safety concerns were noted in other safety parameters, including ECG measurements and laboratory testing. No subject met the pre-specified protocol criteria for significant QT effect (QTc >500 msec). Laboratory abnormalities of interest were increased ALT in 14/133 subjects (11%), increased AST in 8/133 subjects (6%), and increased creatinine in 2/133 subjects (2%).

Discussion

The PK and safety of the POS oral suspension in the pediatric population was characterized in this study. POS oral suspension was administered at dosages of 12 mg/kg/day (DC1) in two divided doses, and 18 mg/kg/day in two (DC2) and three divided doses (DC3). Despite assessments at different dosages and varying dose intervals, the POS oral suspension failed to achieve the PK target for the study (i.e., >90% of pediatric subjects with a steady state C_{avg} of 500 ng/ml– 2500 ng/ml). Nonetheless, some individual subjects did attain the target levels of 500 to 2500 ng/mL on Day 7 with the lowest proportion in AG2(2y to <7 y) /DC1(12mg/kg/d, BID) subjects and the highest proportion in subjects being AG1(7y to <18 y) /DC3(18mg/kg/d, TID). At all three dose levels, subjects in AG1(7y to <18y) had higher mean PK exposures at steady state than those in AG2(2y to < 7y).

The PK target was based on previous identification of steady state C_{avg} as a key PK parameter for POS, based on data from the adult prophylaxis and treatment studies in which efficacy

was correlated with certain C_{avg} exposures (16). The target level of the steady-state POS plasma concentration was based on observations from earlier registration clinical trials conducted with the POS oral suspension in adult patients, in which POS plasma concentrations at steady state appeared to be correlated with efficacy in both the prophylaxis and treatment settings. Using data from adult pivotal trials, a mean steady state C_{avg} exposure of approximately 1200 ng/mL with approximately 90% of subjects with values between 500 and 2500 ng/mL was proposed as a target exposure for the POS pediatric program. As POS has a long terminal-phase half-life of ~35 hours, steady-state is achieved by 7 days with a relatively flat plasma concentration-time profile. Data in healthy adult volunteers [13] demonstrate that at steady-state, any concentration within a dosing interval when multiplied by the dosing interval, reliably estimates POS AUC. In addition, at steady-state, the fluctuation between POS maximum observed concentration (C_{max}) and minimum observed plasma concentration (C_{min} or trough) is relatively small. Thus, the steady-state mean trough concentrations, C_{avg}, and $C_{max,}$ are essentially the same for POS, thereby allowing for C_{avg} to be selected in clinical studies as the primary PK parameter of interest. In a controlled trial involving neutropenic adult subjects (study P01899), POS oral suspension was superior to standard triazoles (fluconazole and itraconazole) in reducing the incidence of IFI, including aspergillosis and candidiasis, and in reducing 100-day all-cause mortality. In that study, the mean plasma concentration at steady state was 583 ng/mL [6]. In another study of IFI treatment (P00041), POS oral suspension was also found to be effective for the treatment of adult subjects with refractory IFI, including aspergillosis, and for the treatment of IFI in adult subjects who were intolerant to certain antifungals, with a better response rate and survival benefit when compared to historical control cases [16]. In that study, the mean plasma concentration was 808 ng/mL. An association between POS plasma concentration achieved with POS oral suspension at steady state and efficacy in these pivotal clinical trials was identified, with adult subjects with POS steady state exposures >500 ng/mL having higher response rates than controls [16]. Hence, a minimum C_{avg} was selected for the pediatric study summarized herein.

In the current study, the percentage of subjects meeting the target C_{avg} range of 500–2500 ng/mL was low across all age groups and dose cohorts, ranging from 31% in AG2 (2y to <7 y) and DC1, (12mg/kg/d, BID) to 80% in AG1 (7y to <18 y) and DC3 (18 mg/kg/d, TID). There was no clear trend toward higher exposure with increasing the daily dose, nor with increasing the frequency of dosing. The TID regimen had higher probability of target attainment regardless of age group; this finding was more apparent in AG1 (7y to <18y) which had 80% DC3 (18mg/kg/d, TID) compared to 50% DC2 (18mg/kd/d, BID) and 64% DC1 (12 mg/kd/d, BID, thus suggesting faster, less predictable clearance in younger children. Although geometric mean C_{avg} confidence intervals were substantially wider among both age groups due to limitations in sample size (**Table 2**), there is an apparent trend of lower C_{avg} among the younger age group (AG2, 2 to <7 years). Overall, these results are not different from those seen in previously published data regarding the use of POS oral suspension in adults [6]; in one adult study, only 49% of subjects achieved steady state exposures within the target C_{avg} range [17]. The adult C_{avg} reported in the earlier study fell within the range of the younger age group included in the current pediatric study, though it is not certain that the doses are directly comparable, as the adult subjects were administered doses ranging from 600 mg to 1200 mg/day (divided TID). As with other triazole antifungals, POS is a known CYP3A4 inhibitor and is also a substrate and inhibitor for Pgp-mediated transport. However, it is unlikely that these interactions would result in the differences in PK exposure across age groups at steady-state, given the similar exposure seen across age groups in the current study on Day 1. Finally, it is worth noting that food intake has been shown to increase the PK exposure of POS oral suspension in adults by 3–4 fold [13]. The food intake of the pediatric subjects enrolled in the present study was

monitored by the subject or legal guardian and there were, as expected, slight variances between subjects. However, it is unclear if the slight differences in food intake could lead to the observed differences in PK exposures across age groups. Ultimately, due to the small sample size and early termination of the study, the cause for the higher exposures in AG 1 (7 to <18 years) compared to AG2 (2 to <7 years) is inconclusive.

Some pediatric subjects were included in the earlier POS trials, thereby helping to inform the starting dosage of 12 mg/kg/day in the current study. In the adult IFI treatment study (P00041), all adult subjects received 800 mg POS/day, corresponding to 11 mg/kg/day for a 70-kg adult. The majority of pediatric subjects (8 to 17 years of age) enrolled in this study received the full adult dosing regimen, resulting in a range of 15 mg/kg/day to 24 mg/kg/day. Despite slight differences in dose, the C_{avg} achieved in adults (844 ng/mL) was similar to the C_{avg} achieved in the pediatric subjects (776 ng/mL) in this trial. In two prior prophylaxis studies (CI98-316 and P01899) [6], all subjects received 600 mg/day, corresponding to a dose of 8.5 mg/kg/day for a 70-kg adult. This dose provided similar exposure in adults (C_{avg} = 578 ng/mL) as in pediatric subjects (13 to 17 years of age; C_{avg} = 694 ng/mL). Given that the systemic exposure to POS was similar between adolescent subjects and adults, and the exposures did not appear to be influenced by age, weight, or body surface area, it was anticipated that the starting dose of 12 mg/kg/day in the current pediatric study would result in exposures that are similar to those observed in the pediatric and adult populations at this approximate dose, and for which efficacy had already been established in adults. In adult healthy volunteers, dosing above 800 mg/day resulted in a plateau in POS exposure due to limitations in absorption of POS oral suspension. Similar limitations are also likely to occur in pediatric subjects [14]. Walsh et al found that in a group of patients treated with posaconazole for refractory aspergilosis, the group with the highest clinical response (70%), the average steady-state concentration of posaconazole was 1.25 μg/ml (1250 ng/ml; the highest concentration quartile). Patients with concentrations in the middle two quartiles (average concentrations, 0.5 to 0.7 μg/ml or 500 to 700 ng/ml) were successfully treated 53% of the time (17). Others have suggested a trough of 0.7 mcg/ml (700 ng/ml) as a target for therapeutic drug monitoring while using posaconazole (18).

POS oral suspension was generally well tolerated in pediatric subjects enrolled in this study, with a safety profile similar to that previously reported for this POS formulation [6]. As anticipated, nearly all pediatric subjects treated with POS had one or more TEAEs reported, with 26% of subjects reporting an SAE. This safety profile reflects the underlying severity of illness present in the pediatric oncology population studied. In the setting of a weakened immune system, such patients are at risk not only for a fungal infection but other infections, multi-organ failure, progression of underlying hematologic malignancy, and graft failure. Of the treated subjects, 37% (50/136) had a TEAE reported that was judged to be possibly or probably related to study drug. There was no predominant type of related TEAE, although the most commonly reported terms were those involving the gastrointestinal system. Treatment-related nausea and vomiting were reported in 13% (18/136) and 13% (17/136) of subjects, respectively. There was no apparent pattern that would indicate a clear difference among the dose cohorts or age groups; specifically, treatment-related TEAEs did not appear to be dose related.

In conclusion, the PK target (i.e., a C_{avg} at steady state [Day 7] between 500 and 2500 ng/mL in ~90% of subjects) was not achieved in any of the pediatric age groups across the different dosage cohorts receiving POS oral suspension in this study. However, it is encouraging to note that many patients individually attained target C_{avg} concentrations, while very few patients exceeded 2500 ng/ml (n = 2; 2.9%), and in the older age group an 18 mg/kg/day dose achieved C_{avg} within the desired PK parameter.

Currently, there are no approved dosing recommendations for POS oral suspension for the pediatric population. Given this, clinicians who use posaconazole based on their assessment of benefit-risk in a particular child may consider obtaining plasma concentrations and discussing results with an expert in pediatric fungal infections.

Given the potential for POS to prevent and treat IFIs in the pediatric population, and the generally favorable safety profile established in this study for POS, future pediatric development of POS will need to focus on new formulations of the molecule and dosing regimens with a greater potential to achieve the established PK target (i.e., IV formulation, oral granule) equivalent of the current adult tablet formulation. A recent report investigating the PK using a dosing regimen based on body surface area in the pediatric population has shown promising results [18]. Additional studies using new formulations and dosing regimens of the molecule are currently under investigation.

Supporting information

S1 Table. Independent ethics committee and institutional review board details.
(DOCX)

S1 File. Criteria for subjects considered to be Day 7 PK Evaluable.
(DOCX)

S2 File. TREND statement checklist.pdf.
(PDF)

S3 File. MK-5592-032-or-Prot_Final Redaction.pdf.
(PDF)

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Pharmacokinetics and safety of posaconazole intravenous solution and powder for oral suspension in children with neutropenia: an open-label, sequential dose-escalation trial

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ABSTRACT

Posaconazole is approved for use in adults as an intravenous (IV) solution and two different oral formulations (a suspension and an improved bioavailability tablet). Data on the pharmacokinetics (PK), dosing and safety of posaconazole in children are limited. A novel powder for oral suspension (PFS) offers the bioavailability of the tablet formulated for weight-based dosing in children. A non-randomised, open-label, sequential dose-escalation, phase 1b trial evaluated the PK and safety of posaconazole IV and PFS in children aged 2 to 17 years with documented or expected neutropenia (ClinicalTrials.gov, NCT02452034; MSD protocol number, MK-5592-P097). Participants received posaconazole IV 3.5, 4.5 or 6.0 mg/kg/d for ≥10 days, with an option to switch to posaconazole PFS at the identical dose for ≤18 days. The target exposure was a mean within-dose cohort average steady-state plasma concentration (C_{avg}) of ~1200 ng/mL, with ~90% of participants achieving C_{avg} between 500 and 2500 ng/mL. Doses of 4.5 and 6.0 mg/kg/d achieved the PK target of ~90% of participants with a C_{avg} ≥500 ng/mL. PFS resulted in lower posaconazole exposures than IV across age groups at all doses. Posaconazole IV and PFS were well tolerated and had safety profiles similar to those reported for adults. Posaconazole PK following IV and PFS administration was well characterised by the data and enable selection of appropriate paediatric doses. Both formulations were well tolerated without dose-, exposure- or age-related differences in the safety profiles.

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1. Introduction

Invasive fungal disease (IFD) is a leading cause of infectious disease-related morbidity and mortality in immunocompromised patients. As is found in adults, the paediatric population at risk for IFD—primarily from neutropenia and T-cell dysfunction—includes patients who have undergone allogeneic haematopoietic stem cell transplantation (HSCT), patients with myelodysplasia or severe aplastic anaemia and those with de novo or relapsed acute leukaemia or advanced-stage non-Hodgkin lymphoma undergoing dose-intensive chemotherapy [1-4]. The incidence of IFD in immunocompromised paediatric patients with these conditions ranges from 5% to 17% [1-3,5].

Posaconazole, a triazole antifungal approved for prophylaxis of IFDs in adults, is available as an intravenous (IV) solution and two oral formulations: an oral suspension and a gastro-resistant tablet with improved bioavailability [6]. Posaconazole oral suspension has been effective and generally well tolerated as IFD prophylaxis for neutropenia patients aged ≥13 years after chemotherapy for acute myelogenous leukaemia or myelodysplastic syndrome [7] and after HSCT complicated by graft-versus-host disease [8]. Posaconazole

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oral suspension has practical limitations, however, including multiple daily dosing, proton-pump inhibitors are contraindicated, and it must be taken with food (high-fat diet preferred) for adequate systemic exposure in patients [9,10]. A novel powder for oral suspension (PFS) has been developed that consists of a powder formulation of the same hot-melt extrudate intermediate of posaconazole and a pH-sensitive polymer found in the tablet formulation. PFS is combined with a liquid suspension vehicle for oral administration, offering the bioavailability of the tablet in a paediatric oral formulation and enabling weight-based dosing in children.

The objective of this trial was to characterise the pharmacokinetics (PK) and safety of posaconazole IV and posaconazole PFS in paediatric participants aged 2 to 17 years with documented or expected neutropenia to determine age-appropriate and safe dosing of both formulations in this population.

2. Methods

2.1. Study design and participants

This was a non-randomised, multicentre, open-label, sequential dose-escalation, phase1b trial of posaconazole IV solution and posaconazole PFS (ClinicalTrials.gov, NCT02452034; MSD protocol number, MK-5592-P097) in paediatric participants at high risk for IFD. The trial was conducted at 24 medical centres in 11 countries in accordance with the Declaration of Helsinki, Good Clinical Practice requirements and applicable country and/or local statutes and regulations regarding Institutional Ethics Committee review, informed consent and protection of human participants in biomedical research.

Following parental/guardian (and patient, if applicable) consent, male and female participants (aged 2-17 years) were included if they had documented or anticipated neutropenia (absolute neutrophil count $<500/mm^3$ [0.5×10^9/L]) expected to last for at least 7 days after the start of study treatment and if they had or had undergone at least one of the following clinical situations: acute leukaemia, myelodysplasia, severe aplastic anaemia, autologous HSCT, high-risk neuroblastoma, advanced-stage non-Hodgkin lymphoma, allogeneic HSCT during the pre-engraftment (neutropenic) period or haemophagocytic lymphohistiocytosis.

Participants were excluded if they had any of the following characteristics: proven or probable IFD, as defined by the 2008 European Organization for Research and Treatment of Cancer/Mycoses Study Group consensus group criteria [11], at the time of screening; posaconazole administration within the last 10 days before screening; abnormal laboratory results (such as liver function tests, including aspartate aminotransferase, alanine aminotransferase, serum total bilirubin and calculated creatinine clearance); study-defined criteria for QTc prolongation at screening (symptomatic QTc prolongation >450 ms in males or >470 ms in females or any QTc prolongation >500 ms); history of anaphylaxis attributed to the azole class of antifungal agents; or any clinically significant condition that might, in the opinion of the investigator, interfere with the trial.

2.2. Procedures

The participant population was divided into two age groups: young children aged 2 to <7 years and older children/adolescents aged 7 to 17 years. The two age groups were enrolled concurrently. The three dose cohorts (3.5, 4.5 and 6.0 mg/kg/d) were enrolled sequentially in each age group (Supplemental Figure 1). For each dose cohort (3.5, 4.5 and 6.0 mg/kg/d), at least 12 participants aged 2 to <7 years and 12 participants aged 7 to 17 years were to receive posaconazole IV solution twice daily on day 1, then posaconazole IV once daily on days 2 to 10 (maximum 300-mg/dose) by central venous catheter. Thereafter, participants proceeded to PFS at the same posaconazole once-daily dose or, if they were unable or unwilling to tolerate PFS, continued on IV solution through day 28.

2.3. Objectives

The primary objective of this trial was to evaluate the PK (area under the curve [AUC] and maximum, minimum and average plasma drug concentrations [C_{max}, C_{min} and C_{avg}, respectively]) of three doses (3.5, 4.5 and 6.0 mg/kg/d) of posaconazole (IV solution and PFS) administered to immunocompromised paediatric participants (aged 2-17 years) with neutropenia or expected neutropenia. This evaluation was used to identify a weight-based dose for both the IV and the PFS formulations that achieved posaconazole exposures comparable to those achieved in studies of adults receiving the standard 300-mg IV and gastro-resistant tablet doses, as indicated by ~90% of participants achieving C_{avg} at steady state (day 7) of 500 to 2500 ng/mL and ~1200 ng/mL mean C_{avg} concentration for the dose cohort, respectively [12,13]. Earlier studies in adults receiving posaconazole oral suspension demonstrated better clinical outcomes with increasing posaconazole exposure and no increased risk in toxicity [14]. A quartile safety analysis conducted in a clinical study of posaconazole tablet given to adults did not demonstrate an increased incidence of adverse events (AEs) with higher exposures [12]. Thus, identifying posaconazole IV and PFS doses that would result in most subjects with steady-state exposure exceeding the lower PK threshold (>500 ng/mL) was prioritised to avoid exceeding the 2500-ng/mL threshold. The secondary objective of this trial was to evaluate the safety and tolerability of posaconazole (IV solution and PFS). Additional exploratory objectives were to evaluate the palatability and acceptability of posaconazole PFS.

2.4. PK and pharmacodynamics

Serial plasma samples for the measurement of posaconazole concentrations were obtained at steady state, between days 7 and 10 of both IV and PFS dosing. Plasma posaconazole concentrations were determined using a validated high-performance liquid chromatography with tandem mass spectrometry method [15]. The lower limit of quantification (LLQ) was 5.0 ng/mL, and the analytical range was 5.0 to 5000 ng/mL. Plasma concentrations and actual elapsed plasma sampling times for each analyte relative to the corresponding time of posaconazole dosing were used to determine PK parameter values for each treatment in each participant. Concentrations below the LLQ observed before the last measurable concentration time were set to zero before the PK analysis. The PK parameters of C_{max}, time to reach C_{max} (T_{max}), AUC from time 0 to 24 hours ($AUC_{0\text{-}24}$), back-extrapolated plasma drug concentration at time 0 (C_0), C_{min}, C_{avg}, total body clearance following IV dose (CL) and apparent total body clearance following oral dose (CL/F) were calculated for posaconazole.

Intensive PK sampling for posaconazole IV and posaconazole PFS was performed between days 7 and 10 of PFS treatment. Sampling was conducted before dose (0 h), within 15 min after the end of infusion, and at 4, 6, 12 and 24 h after the start of infusion for IV administration and before dose (0 h) and at 2, 4, 6, 8 and 24 h after dose for PFS administration (participants receiving PFS as outpatients were sampled only at 0, 2 and 4 h after dose). For participants who continued posaconazole IV after day 10, C_{min} sampling for posaconazole IV was collected before dosing on day 6 and once per week thereafter. For participants who continued posaconazole PFS after day 10, C_{min} sampling for posaconazole PFS

was collected before dosing on day 6 of PFS and once per week thereafter.

2.5. Safety and tolerability

AE monitoring was required throughout the study until 14 days after the last dose of posaconazole therapy. Electrocardiography was performed at baseline and on days 6 to 8 of posaconazole IV and days 8 to 10 of posaconazole PFS treatment. Haematology and chemistry safety laboratory testing (liver function tests, including aspartate aminotransferase, alanine aminotransferase and serum bilirubin values and creatinine clearance) was required at screening, at baseline, twice per week for inpatients during treatment, once per week for outpatients during treatment and on the last day of treatment. Safety laboratory testing was required once per week for outpatients receiving posaconazole PFS. Survival was assessed between days 90 and 110.

Participants rated the palatability of the PFS formulation via questionnaire three times during the treatment phase—after the first dose, on day 5 and on the last day of therapy—to assess the taste (very good to very bad) and whether they had any problems taking the dose (refusing, spitting out, vomiting/spitting up or gagging). If a child was too young to provide verbal responses, the caregiver rated palatability based on the child's reaction to receiving the dose.

2.6. Statistical analysis

The primary PK population for each formulation included all participants who received therapy for at least 7 days and who met predefined criteria for PK evaluability, including correct dose by weight, correct dose timing, correct dose frequency, and correct timing of day 7 PK samples. The safety population included all participants who received at least 1 dose of posaconazole trial therapy. PK and safety results were tabulated by age (2-<7 years and 7-17 years), dose cohort and posaconazole treatment formulation (IV and PFS).

PK parameters were calculated using non-compartmental analysis (Phoenix WinNonlin 6.4; Certara). $AUC_{0\text{-}24}$ and $AUC_{0\text{-}12}$ were calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations. C_{max} and T_{max} were observed based on the visual inspection of the concentration data.

2.7. Role of the funding source

This trial was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. CJB, an employee of the funder, assisted the co-first authors in writing the first draft of the manuscript. Employees of the funder who were involved in study design, data acquisition and data analysis are authors on this manuscript (AP, EM, GAW, HW, CJB). All authors had full access to all the data in the study and take full responsibility for the decision to submit the manuscript for publication.

3. Results

3.1. Participant demographics and baseline characteristics

Between September 2015 and September 2018, 126 participants were screened and 118 were enrolled; of these 118, 109 (92.4%) completed the trial as per protocol. The disposition of each trial participant is summarised by age group and treatment in Table 1. The overall median (range) age was 8 years (2-17 years), and the majority of participants (58.3%) were male. The most common underlying conditions that qualified participants for enrolment were acute leukaemia (44.3%), HSCT recipient (44.3%) and high-risk neuroblastoma (13.9%). Baseline characteristics for participants by age group and treatment are listed in Table 2.

3.2. PK evaluations

Individual and geometric mean plasma steady-state C_{avg} values of posaconazole after multiple IV and PFS are shown in Fig. 1. Percentages of participants who achieved the PK target of posaconazole C_{avg} at steady state (days 7-10 of formulation dosing) between 500 and 2500 ng/mL and by dose cohort, age group and formulation are summarised in Table 3. In the 3.5-mg/kg/d posaconazole cohort, the target PK exposure of ~90% of participants with C_{avg} within 500 to 2500 ng/mL was attained for participants aged 7 to 17 years for both IV and PFS formulations but was not attained for participants aged 2 to <7 years for either formulation. In the 4.5-mg/kg/d posaconazole cohort, the target of ~90% of participants with C_{avg} within 500 to 2500 ng/mL was met for the IV and PFS formulations in both age groups. In the 6-mg/kg/d posaconazole cohort, both formulations in those aged 2 to <7 years met the target of ~90% of participants with C_{avg} within 500 to 2500 ng/mL. In those aged 7 to 17 years for the IV formulation, C_{avg} for all participants who received 6.0 mg/kg/d was above the lower target threshold of 500 ng/mL, including 6 of 24 participants (25%) who had a C_{avg} above 2500 ng/mL. For the PFS formulation, 2 of 12 participants (16%) aged 7 to 17 years who received 6 mg/kg/d had C_{avg} below the lower target threshold of 500 ng/mL; C_{avg} in another 2 of 12 participants (16%) in those aged 7 to 17 years was above 2500 ng/mL.

A summary of posaconazole PK parameters by dose cohort, age group and formulation is presented in Table 4. In the 3.5-mg/kg/d posaconazole cohort, geometric mean C_{avg} was below the target of 1200 ng/mL specified in the protocol for both IV and PFS formulations in both age groups. For both formulations in the 4.5-mg/kg/d posaconazole cohort, geometric mean C_{avg} reached or exceeded the target of 1200 ng/mL for participants aged 7 to 17 years but not for those aged 2 to <7 years. In the 6.0-mg/kg/d posaconazole cohort, geometric mean C_{avg} for the IV formulation was higher than the 1200 ng/mL target mean concentration in both age groups; in contrast, the geometric mean C_{avg} for the PFS formulation was lower than the 1200 ng/mL target mean concentration in both age groups. However, mean C_{avg} for those aged 7 to 17 years receiving PFS was substantially influenced by one participant with extremely low exposure. The geometric mean C_{avg} excluding this participant was 1420 ng/mL.

In this trial, dose was scaled by body weight up to a maximum total dose of 300 mg posaconazole, which is the recommended adult dose for both IV and oral tablet administration. The body weight above which participants received 300 mg was 85.7, 66.7 and 50.0 kg for the 3.5-, 4.5- and 6.0-mg/kg/d dose levels, respectively. No participants required dose caps at the 3.5-mg/kg/d dose level (IV or PFS), four and three participants reached the 300-mg/kg/d dose cap at the 4.5-mg/kg/d dose level (IV and PFS, respectively) and eight and three participants reached the 300-mg/kg/d dose cap at the 6.0-mg/kg/d dose level (IV and PFS, respectively). Individual and geometric mean plasma steady-state C_{avg} values of posaconazole after multiple IV and PFS are shown by weight in Supplemental Figure S2. Overall, these plots show no obvious relationship between C_{avg} and weight, particularly at the 6.0-mg/kg/d dosage.

Geometric mean CL after IV administration and CL/F after PFS administration appeared to be independent of dose level, but both were lower in participants aged 2 to <7 years than in those aged 7 to 17 years across all dose groups (Table 4). As expected, apparent clearance after PFS administration was higher than clearance after IV administration, indicating that PFS, like other oral posacona-

Table 1
Disposition by age group and dose.

Status	Posaconazole 3.5 mg/kg/d		Posaconazole 4.5 mg/kg/d		Posaconazole 6.0 mg/kg/d	
	2-<7 years n=16	7-17 years n=21	2-<7 years n=15	7-17 years n=17	2-<7 years n=20	7-17 years n=29
Trial status[a]						
Completed	14 (87.5)	20 (95.2)	14 (93.3)	16 (94.1)	19 (95.0)	26 (89.7)
Discontinued	2 (12.5)	1 (4.8)	1 (6.7)	1 (5.9)	1 (5.0)	3 (10.3)
Adverse event	0	0	0	0	0	1 (3.4)
Death	0	0	0	0	1 (5.0)	1 (3.4)
Physician decision	0	1 (4.8)	1 (6.7)	0	0	0
Protocol deviation	0	0	0	0	0	1 (3.4)
Screen failure	1 (6.3)	0	0	1 (5.9)	0	0
Withdrawal by parent/guardian	1 (6.3)	0	0	0	0	0
IV medication status[b]						
Started	14	21	15	16	20	29
Completed	9 (64.3)	15 (71.4)	15 (100.0)	12 (75.0)	18 (90.0)	20 (69.0)
Discontinued	5 (35.7)	6 (28.6)	0	4 (25.0)	2 (10.0)	9 (31.0)
Adverse event	3 (21.)	3 (14.3)	0	2 (12.5)	1 (5.0)	5 (17.2)
Physician decision	2 (14.3)	2 (9.5)	0	2 (12.5)	0	4 (13.8)
Protocol deviation	0	1 (4.8)	0	0	0	0
Withdrawal by parent/guardian	0	0	0	0	1 (5.0)	0
PFS medication status[b]						
Started	6	11	9	9	14	14
Completed	5 (83.3)	10 (90.9)	8 (88.9)	9 (100.0)	7 (50.0)	13 (92.9)
Discontinued	1 (16.7)	1 (9.1)	1 (11.1)	0	7 (50.0)	1 (7.1)
Adverse event	0	0	0	0	3 (21.4)	1 (7.1)
Physician decision	0	0	1 (11.1)	0	3 (21.4)	0
Protocol deviation	0	1 (9.1)	0	0	0	0
Withdrawal by parent/guardian	1 (16.7)	0	0	0	1 (7.1)	0

IV, intravenous; PFS, powder for oral suspension.
[a] Percentage based on the number of all enrolled participants.
[b] Percentage based on the number of participants who started the treatment period.

Table 2
Baseline characteristics by age group and treatment

Characteristics	Posaconazole 3.5 mg/kg/d		Posaconazole 4.5 mg/kg/d		Posaconazole 6.0 mg/kg/d		Total
	2-<7 years n=14	7-17 years n=21	2-<7 years n=15	7-17 years n=16	2-<7 years n=20	7-17 years n=29	N=115
Sex, n (%)							
Male	12 (86)	10 (48)	7 (47)	9 (56)	10 (50)	19 (66)	67 (58.3)
Female	2 (14)	11 (52)	8 (53)	7 (44)	10 (50)	10 (34)	48 (41.7
Age, years, median (range)	3 (2-6)	14 (10-17)	4 (2-6)	12 (7-16)	3.5 (2-7)	12 (7-17)	8 (2-17)
Race, n (%)							
Asian	4 (29)	1 (5)	2 (13)	2 (12.5)	1 (5)	1 (3)	11 (9.6)
White	10 (71)	18 (16)	12 (80)	12 (75)	18 (90)	26 (90)	96 (83.5)
Black	0	0	0	0	1 (5)	2 (7)	3 (2.6)
Native Hawaiian or other Pacific Islander	0	0	1 (7)	0	0	0	1 (0.9)
Multiple	0	2 (9)	0	2 (12.5)	0	0	4 (3.5)
Ethnicity, n (%)							
Hispanic or Latino	1 (7)	2 (10)	2 (13)	4 (25)	1 (5)	2 (7)	12 (10.4)
Not Hispanic or Latino	13 (93)	19 (90)	12 (80)	11 (69)	18 (90)	27 (93)	100 (87.0)
Not reported/unknown	0	0	1 (7)	1 (6)	1 (5)	0	3 (2.6)
Primary diagnosis, n (%)[a]							
Acute leukaemia	3 (21)	8 (38)	4 (27)	11 (69)	8 (40)	17 (59)	51 (44.3)
Myelodysplastic syndrome	0	0	1 (7)	1 (6)	0	2 (7)	4 (3.5)
Severe aplastic anaemia	3 (21)	3 (14)	3 (20)	1 (6)	2 (10)	1 (3)	13 (11.3)
HSCT recipient	7 (50)	13 (62)	9 (60)	2 (12)	7 (35)	13 (45)	51 (44.3)
High-risk neuroblastoma	2 (14)	0	5 (33)	2 (12)	5 (25)	2 (7)	16 (13.9)
Advanced state non–Hodgkin lymphoma	0	1 (5)	0	1 (6)	0	0	2 (1.7)
Hemophagocytic lymphohistiocytosis	1 (7)	0	0	0	0	1 (3)	2 (1.7)
Other	0	1 (5)	1 (7)	0	0	0	2 (1.7)

HSCT, haematopoietic stem cell transplant.
[a] It was possible for participants to have more than one condition. Participants with multiple conditions were counted once for each condition. Participants without any of the seven specific diseases were counted in the 'other' category.

zole formulations, is not fully bioavailable. There were no consistent trends in the variability of CL and CL/F across dose level, age group or formulation (Table 4).

3.3. Safety and tolerability

Across all treatment arms, AEs were reported in 113 of 115 participants (98%) (Table 5). The most common AEs in the trial population (occurring in >25% of participants) were pyrexia (44%), mucosal inflammation (28%) and vomiting (26%) (Table 6). Serious AEs were reported in 31 of 115 participants (27%; Table 5) and a drug-related serious AE (drug hypersensitivity) was reported in 1 of 115 participants (1%) aged 2 to <7 years in the 3.5-mg/kg/d cohort on day 3 of posaconazole IV. Drug-related AEs were reported in 17 of 115 participants (15%; Table 5). There was no apparent pattern to drug-related AEs that would indicate a clear difference

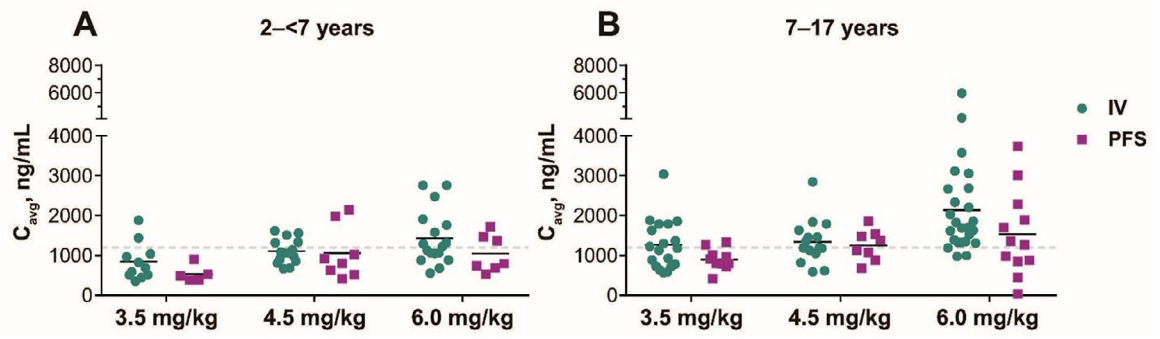


Fig. 1. Posaconazole plasma concentrations by dosage. Individual (dots) and geometric mean (solid lines) plasma steady-state C_{avg} in participants aged (**A**) 2-<7 years and (**B**) 7-17 years. Dotted line represents C_{avg} target of 1200 ng/mL. IV, intravenous; PFS, powder for oral suspension.

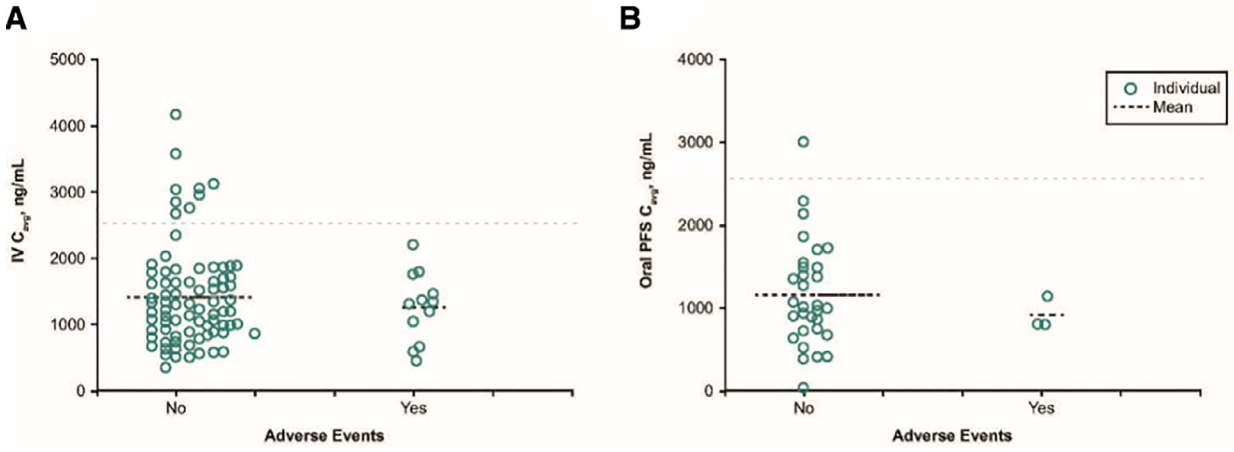


Fig. 2. Exposure/safety analysis of posaconazole by drug-related AE. Analysis of drug-related AEs by steady-state C_{avg} for the posaconazole IV and PFS groups (dosage 3.5-, 4.5-, and 6.0-mg/kg groups combined; age groups 2-<7 and 7-17 years combined). Individual C_{avg} values (open dots) and AE group means (dotted lines) are shown for (**A**) IV and (**B**) PFS treatment groups. Dotted grey line represents C_{avg} of 2500 ng/mL. IV, intravenous; PFS, powder for oral suspension.

among the dose groups, and no drug-related AEs were reported in participants who had mean C_{avg} >2500 ng/mL (Fig. 2). Overall, 18 of 115 participants (16%) discontinued study treatment because of an AE, four (4%) because of a drug-related AE (five AEs in four participants: electrocardiogram QT prolonged, epistaxis, rash and alanine aminotransferase increased and aspartate aminotransferase increased [same participant]). Four participants died during the trial and follow-up. Two deaths were attributed to underlying malignancy and occurred after the end of the AE monitoring period, and two were attributed to AEs—respiratory failure and veno-occlusive disease in one participant each—both of which occurred after the end of study treatment and were not considered related to study drug.

Most of the palatability assessment questionnaires were completed by a primary caregiver or a nurse for participants aged 2 to <7 years and by the participants themselves aged 7 to 17 years. Taste was assessed as 'average,' 'good' or 'very good' by most assessors for both age groups and all doses at all time points. Most participants in both age groups and all doses at all time points did not report any problems taking the PFS dose. A summary of responses for patient-reported palatability and acceptance measures for all participants completing the assessment is provided in Supplemental Table S1.

Table 3
Percentages of patients achieving steady-state C_{avg} range categories after multiple-dose IV and PFS administration of posaconazole

Posaconazole dose	Age group, years	Formulation	n	C_{avg}, ng/mL		
				<500, n (%)	500-<2500, n (%)	>2500, n (%)
3.5 mg/kg/d	2-<7	IV	11	2 (18)	9 (82)	0
		PFS	5	3 (60)	2 (40)	0
	7-17	IV	19	0	18 (95)	1 (5)
		PFS	10	1 (10)	9 (90)	0
4.5 mg/kg/d	2-<7	IV	14	0	14 (100)	0
		PFS	8	1 (13)	7 (88)	0
	7-17	IV	15	0	14 (93)	1 (7)
		PFS	8	0	8 (100)	0
6.0 mg/kg/d	2-<7	IV	17	0	15 (88)	2 (12)
		PFS	7	0	7 (100)	0
	7-17	IV	24	0	18 (75)	6 (25)
		PFS	12	2 (17)	8 (67)	2 (17)

C_{avg}, average steady-state plasma concentration; IV, intravenous; PFS, powder for oral suspension.

Table 4
Summary of plasma steady-state PK values of posaconazole after multiple-dose IV and PFS administration

Posaconazole dose	Age group, years	Formulation	n	PK parameter					
				C_{max}, ng/mL[a]	T_{max}, h[b]	AUC_{0-24}, h.ng/mL[a]	CL or CL/F,[c] L/h[a]	C_{min}, ng/mL[a]	C_{avg}, ng/mL[a]
3.5 mg/kg/d	2-<7	IV	11	1590 (43.1)	1.78 (1.67-5.53)	17800 (55.0)	3.39 (52.8)	400 (81.3)	743 (55.0)
		PFS	5[d]	884 (44.4)	3.83 (1.92-4.25)	12200 (36.0)	4.97 (29.1)	254 (45.6)	510 (36.0)
	7-17	IV	19	2450 (72.7)	1.77 (0-3.5)	27300 (49.7)	6.64 (38.6)	670 (65.1)	1140 (49.7)
		PFS	10[e,f]	1340 (30.8)	2.20 (1.92-6.03)	20700 (33.8)	7.67 (39.9)	579 (44.9)	861 (33.8)
4.5 mg/kg/d	2-<7	IV	18[e,f]	2320 (39.8)	1.78 (1.42-5.90)	25600 (30.0)	2.97 (36.2)	501 (56.8)	1070 (30.0)
		PFS	8[d,e,f]	1550 (40.8)	3.82 (1.88-5.92)	21600 (64.5)	3.49 (59.1)	476 (164.6)	901 (64.5)
	7-17	IV	15[e,f]	2310 (40.3)	1.75 (1.52-1.80)	29800 (42.9)	6.69 (37.3)	737 (66.0)	1240 (42.9)
		PFS	8[e,f]	1670 (28.5)	6.14 (1.98-7.98)	28700 (33.7)	7.84 (49.4)	790 (48.2)	1200 (33.7)
6.0 mg/kg/d	2-<7	IV	17	3060 (54.1)	1.75 (1.57-1.83)	31100 (48.9)	3.27 (49.3)	626 (104.8)	1300 (48.9)
		PFS	7[d,e,f]	1510 (43.4)	4.00 (2.17-7.92)	23000 (47.3)	4.60 (35.2)	542 (68.8)	960 (47.3)
	7-17	IV	24[e,f]	3340 (39.4)	1.77 (1.33-6.00)	44200 (41.5)	4.76 (55.7)	1160 (60.4)	1930 (41.5)
		PFS	12[d,e,f]	1370 (178.5)	2.78 (0-4.00)	25000 (184.3)	8.39 (190.3)	713 (300.6)	1040 (184.3)

AUC_{0-24}, area under the curve from time 0 to 24 h; C, concentration; CL, total body clearance; CL/F, clearance as a function of bioavailability; C_{max}, maximum plasma drug concentration; IV, intravenous; PFS, powder for oral suspension; PK, pharmacokinetics; T_{max}, time to reach C_{max}.

[a] Geometric mean (% geometric coefficient of variation).

[b] Median (minimum–maximum).

[c] CL is reported for those who received posaconazole IV, and CL/F is reported for those who received posaconazole PFS.

[d] As participants' conditions were at steady state, the predose value was assumed to be equal to C_{24h} for two participants aged 2-<7 years who received 3.5 mg/kg/d PFS, one participant aged 2-<7 years who received 4.5 mg/kg/d PFS and seven participants (two aged 2-<7 years and five aged 7-17 years) who received 6.0 mg/kg/d PFS without the 24-hour PK sample. This value was used to replace the missing C_{24h} to calculate C_{avg}.

[e] AUC_{0-last} was reported in place of AUC_{0-24} if C_{24h} was actually less than 24 h and AUC_{0-24} could not be calculated. This applied to one participant aged 7-17 years who received 3.5 mg/kg/d PFS, one participant aged 2-<7 years who received 4.5 mg/kg/d IV, one participant aged 2-<7 years who received 4.5 mg/kg/d PFS, four participants aged 7-17 years who received 4.5 mg/kg/d PFS, one participant aged 2-<7 years who received 6.0 mg/kg/d PFS, one participant aged 7-17 years who received 6.0 mg/kg/d IV and one participant aged 7-17 years who received 6.0 mg/kg/d PFS.

[f] Clearance (CL for IV and CL/F for PFS) calculated using AUC_{0-last} was imputed for AUC_{0-tau} if AUC_{0-tau} could not be calculated. This applied to one participant aged 7-17 years who received 3.5 mg/kg/d PFS, one participant aged 2-<7 years who received 4.5 mg/kg/d IV, one participant aged 2-<7 years who received 4.5 mg/kg/d PFS, four participants aged 7-17 years who received 4.5 mg/kg/d PFS, one participant aged 2-<7 years who received 6.0 mg/kg/d PFS, one participant aged 7-17 years who received 6.0 mg/kg/d IV and one participant aged 7-17 years who received 6.0 mg/kg/d PFS.

Table 5
Summary of AEs by category

AE category, n (%)	Posaconazole						Total
	3.5 mg/kg/d		4.5 mg/kg/d		6.0 mg/kg/d		
	2-<7 years n=14	7-17 years n=21	2-<7 years n=15	7-17 years n=16	2-<7 years n=20	7-17 years n=29	N=115
≥1 AEs	13 (93)	21 (100)	15 (100)	16 (100)	19 (95)	29 (100)	113 (98)
Drug-related AEs	2 (14)	2 (10)	3 (20)	5 (31)	2 (10)	3 (10)	17 (15)
Serious AEs	3 (21)	8 (38)	4 (27)	5 (31)	3 (15)	8 (28)	31 (27)
Serious drug-related AEs	1 (7)	0	0	0	0	0	1 (1)
Died	0	0	0	0	0	2 (7)	2 (2)
Reason for discontinuation							
AEs	3 (21)	3 (14)	0	2 (12)	4 (20)	6 (21)	18 (16)
Drug-related AEs	1 (7)	0	0	0	1 (5)	2 (7)	4 (4)
Serious AEs	2 (14)	2 (10)	0	1 (6)	2 (10)	3 (10)	10 (9)
Serious drug-related AEs	1 (7)	0	0	0	0	0	1 (1)

AE, adverse event.

4. Discussion

This trial characterised the PK, safety and tolerability of posaconazole administered as IV and PFS formulations across a range of doses in children aged 2 to 17 years who had neutropenia and were at risk for IFD, with the goal of identifying a weight-based dose that would achieve systemic exposure comparable to levels associated with efficacy in the pivotal phase 3 studies in adults. Using population PK models developed for the posaconazole IV solution and the posaconazole PFS formulation based on observed PK data in adults, simulations were conducted to project exposure in the paediatric population and to achieve a PK target C_{avg} between 500 and 2500 ng/mL in ~90% of patients aged 2 to 17 years. Based on the model results, posaconazole doses of 3.5 and 4.5 mg/kg/d were initially investigated, and an interim analysis of the data resulted in a protocol amendment to add the 6.0-mg/kg/d cohort. The results demonstrate that a once-daily dose of 6.0 mg/kg as an IV or PFS formulation achieved target exposures

Table 6
Summary of AEs by system organ class (incidence ≥5% in ≥1 treatment groups) for all treated participants

AE category, n (%)	Posaconazole			Total
	3.5 mg/kg/d 2-17 years n=35	4.5 mg/kg/d 2-17 years n=31	6.0 mg/kg/d 2-17 years n=49	N=115
≥1 AEs	34 (97)	31 (100)	48 (98)	113 (98)
Blood and lymphatic system disorders	11 (31)	9 (29)	21 (43)	41 (36)
Cardiac disorders	4 (11)	4 (13)	5 (10)	13 (11)
Ear and labyrinth disorders	1 (3)	3 (10)	1 (2)	5 (4)
Eye disorders	5 (14)	3 (10)	10 (20)	18 (16)
Gastrointestinal disorders	24 (69)	19 (61)	33 (67)	76 (66)
General disorders and administration site conditions	26 (74)	20 (65)	26 (53)	72 (63)
Hepatobiliary disorders	2 (6)	4 (13)	0 (0)	6 (5)
Immune system disorders[a]	7 (20)	5 (16)	12 (25)	24 (21)
Infections and infestations	17 (49)	15 (48)	24 (49)	56 (49)
Injury, poisoning and procedural complications	5 (14)	5 (16)	5 (10)	15 (13)
Metabolism and nutrition disorders	11 (31)	15 (48)	23 (47)	49 (43)
Musculoskeletal and connective tissue disorders	8 (23)	9 (29)	8 (16)	25 (22)
Nervous system disorders	6 (17)	7 (23)	10 (20)	23 (20)
Psychiatric disorders	3 (9)	1 (3)	5 (10)	9 (8)
Renal and urinary disorders	5 (14)	3 (10)	5 (10)	13 (11)
Reproductive system and breast disorders	2 (6)	1 (3)	4 (8)	7 (6)
Respiratory, thoracic and mediastinal disorders	11 (31)	19 (61)	15 (31)	45 (39)
Skin and subcutaneous tissue disorders	19 (54)	18 (58)	22 (45)	59 (51)
Vascular disorders	10 (29)	6 (19)	16 (33)	32 (28)

AE, adverse event.
[a] Includes AE terms drug hypersensitivity, graft-versus-host disease and graft-versus-host disease in skin.

necessary for effective antifungal prophylaxis, with a safety profile similar to the established safety profile of posaconazole oral suspension, IV and tablet in adults.

In this study, a mean steady-state C_{avg} of ~1200 ng/mL, with ~90% of participants achieving values between 500 and 2500 ng/mL, was the designated PK target based on observations from earlier registration clinical trials in adults conducted with the posaconazole oral suspension, in which posaconazole steady-state exposures >500 ng/mL were correlated with efficacy in the prophylaxis and the treatment settings [12,13]. For the IV formulation, all participants in both age groups achieved C_{avg} >500 ng/mL with both the 4.5-mg/kg/d and the 6.0-mg/kg/d doses. More participants in the 6.0-mg/kg/d dose cohort were above the upper end of the target exposure range (>2500 ng/mL)—specifically, 12% of participants aged 2 to <7 years and 25% aged 7 to 17 years. Dose-limiting toxicity has not been observed in adults in studies of the IV and tablet formulations [12,13]. In the current trial, no drug-related AEs were reported in participants with mean C_{avg} >2500 ng/mL. Given the known relationship of higher exposures with efficacy and the lack of demonstrated dose-limiting toxicity [12,13], the 6.0-mg/kg/d dose, which maximises the chance of surpassing the minimal C_{avg} threshold and approximates the average exposure achieved with a posaconazole 300-mg tablet in adults, appears to be preferable [12,16]. In the 4.5-mg/kg/d cohort, the mean C_{avg} for the younger age group was 1070 ng/mL, which was below the target C_{avg} level of ~1200 ng/mL. In the 6.0-mg/kg/d dose cohort, both age groups achieved C_{avg} levels above the target (1300 ng/mL in those aged 2-<7 years and 1930 ng/mL in those aged 7-17 years).

The PFS formulation generally resulted in lower exposures than the IV formulation when given at the same dose in both age groups and across all dose cohorts. Despite this, both the 4.5-mg/kg/d and the 6.0-mg/kg/d dose of the PFS formulation achieved the target of C_{avg} >500 ng/mL in ~90% of participants in both age groups; 17% of those in the 6.0-mg/kg/d cohort had C_{avg} levels >2500 ng/mL. In comparison, 60% of participants aged 2 to <7 years in the 3.5-mg/kg/d cohort had C_{avg} levels <500 ng/mL. In the 6.0-mg/kg/d cohort, neither age group achieved mean C_{avg} levels of 1200 ng/mL. The mean C_{avg} in the older age group was substantially lowered by a single outlier with nearly undetectable posaconazole concentrations; however, this seems physiologically improbable and likely represents spurious data. When this participant was excluded, the mean C_{avg} in the older age group was 1420 ng/mL. In the younger age group, the mean C_{avg} (960 ng/mL) was below the PK target; this level was substantially higher than the levels seen in a dose-escalation trial of the oral suspension in paediatric patients aged 2 to <7 years, in whom a maximum dose of 18 mg/kg/d divided three times daily resulted in a mean C_{avg} of 620 ng/mL [16] and in levels seen in adults in trials of the oral suspension in which steady-state C_{avg} of 583 ng/mL was associated with efficacy [7]. In paediatric participants administered the PFS formulation, mean C_{avg} did not increase substantially between the 4.5-mg/kg/d and 6.0-mg/kg/d doses, indicating a plateau in absorption that would limit the usefulness of higher doses to achieve higher mean C_{avg} concentrations.

In this study, posaconazole was generally well tolerated and had a safety profile similar to that previously reported for posaconazole in adults [7,8,12,13]. Although almost all paediatric participants treated with posaconazole experienced at least one AE and 27% of participants experienced a serious AE, the events were representative of those typically observed in neutropenia patients undergoing chemotherapy or HSCT and were similar to the rates reported in another paediatric dose-escalation trial of posaconazole PFS, with a lower rate of drug-related AEs (15% vs 37%) [16]. There was no apparent pattern to types or rates of AEs between dose cohorts to indicate increasing toxicity at higher doses; specifically, drug-related AEs did not appear to be dose-related or to be correlated with higher exposures as measured by C_{avg}. This safety profile reflects the underlying severity of illness in the paediatric oncology and transplant population studied.

In conclusion, the PK of posaconazole after IV and PFS administration at doses from 3.5 to 6.0 mg/kg/d were well characterised in paediatric participants aged 2 to 17 years. After a loading dose of 6.0 mg/kg administered twice on day 1, a once-daily dose of 6.0 mg/kg of both the IV and the PFS formulations achieved exposures comparable to those associated with efficacy in adults. This dose was generally well tolerated in participants aged 2 to 17 years, with safety profiles similar to those reported for adults. Based on these results, the IV and PFS formulations of

posaconazole may represent an improved method of administering posaconazole antifungal prophylaxis compared with the oral suspension in paediatric patients with neutropenia and at risk for IFD.

Data Sharing Statement

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymised patient-level data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. The company is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The process includes submission of data requests to the MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php). Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing the requested data.

Contributors

Conception and design of the study: AHG, HA-A, AP, EM, GAW, HW, CJB

Acquisition of data: AHG, HA-A, TL, WJS, EM

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Declarations

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HA-A reports other from Merck, during the conduct of the study; funding for costs for conducting this clinical trial.

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Ethical Approval: The trial was conducted at 24 medical centres in 11 countries in accordance with the Declaration of Helsinki, Good Clinical Practice requirements, and applicable country and/or local statutes and regulations regarding Institutional Ethics Committee review, informed consent, and protection of human participants in biomedical research.

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A population pharmacokinetic model for posaconazole intravenous solution and oral powder for suspension formulations in pediatric patients with neutropenia

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ABSTRACT The objective of this study was to support posaconazole dose regimens in pediatric patients aged ≥2 years, using a population pharmacokinetic (PK) approach with data from a phase 1b study (NCT02452034). A one-compartment model with first-order absorption was fit to pharmacokinetic data from 144 participants aged 2 to 17 years, who were administered posaconazole as intravenous (IV) and powder for oral suspension (PFS) formulations, or IV only, at dosing regimens of 3.5, 4.5, and 6 mg/kg. The influence of demographic and clinical factors on pharmacokinetic parameters was evaluated using a stepwise forward inclusion/backward exclusion procedure. The final model simulated posaconazole exposure in patients aged 2 to <7 and 7 to 17 years at dosing regimens of 4.5, 6, and 7.5 mg/kg. Plasma concentration data following IV and PFS administration were well-described by a one-compartment model with first-order absorption and estimated bioavailability, where clearance and volume were subject to allometric scaling by body weight. The 6-mg/kg dosing regimen achieved the pharmacokinetic target (90% of the pediatric population having an average steady-state plasma concentration of ≥500 and <2,000 ng/mL) for both age groups, regardless of whether patients received IV and PFS or IV only. In a virtual adolescent population (body weight >40 kg), the 300 mg/day posaconazole tablet was also predicted to achieve the pharmacokinetic target and remain within a safe range of exposure. These data informed a weight-based nomogram for PFS dosing to maximize the number of pediatric patients achieving the pharmacokinetic target across weight bands, while also maintaining a favorable benefit/risk profile.

KEYWORDS antifungal agents, invasive fungal disease, pediatrics, pharmacokinetics, posaconazole

Invasive fungal disease (IFD) is a leading cause of infectious disease morbidity and mortality in immunocompromised patients, especially in patients with severe and persistent neutropenia and T-cell dysfunction (1–3). As in adults, children at risk for IFD include allogenic hematopoietic stem cell transplant (HSCT) recipients and patients with acute leukemia, myelodysplasia, severe aplastic anemia, or advanced-stage non-Hodgkin lymphoma undergoing chemotherapy (3–6).

Posaconazole is a triazole antifungal approved in the United States and Europe for the prophylaxis of IFD resulting from *Aspergillus, Candida,* and other fungal species in severely immunocompromised patients; it is also effective in the treatment of IFDs refractory to other antifungal treatments (7–9). Like other azole antifungals, posaconazole inhibits the fungal cytochrome (CYP)-dependent enzyme, lanosterol 14 α-demethylase, thereby blocking the biosynthesis of ergosterol and impairing cell membrane stability (10). It is available in three formulations, namely, an intravenous (IV) solution, an

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oral suspension, and an oral tablet with improved bioavailability (8, 9). The recommended dosing regimen in adults is a loading dose of 300 mg twice daily (BID) on day 1, followed by 300 mg once daily (QD) as a maintenance dose. In a quartile analysis conducted by the US Food and Drug Administration, an average steady-state plasma concentration (C_{avg}) of ≥500 ng/mL was shown to be associated with an increase in clinical response in adults (11).

The goal of the posaconazole pediatric program was to utilize the established exposure–response relationship of posaconazole in adults to identify a pediatric dosing strategy that would achieve a pharmacokinetic (PK) target of a mean C_{avg} of 1,200 ng/mL, in which approximately 90% of pediatric patients would have a C_{avg} of ≥500 and <2,500 ng/mL. Furthermore, an upper exposure limit for toxicity has not been established for posaconazole. The results of a previous study on adult patients at high risk of IFD showed no correlation between high exposure levels (predicted C_{avg} of 2,304 to 9,523 ng/mL) and the occurrence of treatment-related adverse events for a posaconazole tablet formulation (12). In a previous posaconazole pediatric study, pediatric patients aged 2 to 17 years with neutropenia were treated with an oral suspension of 12 or 18 mg/kg per day (divided BID); however, population PK analyses determined that the oral suspension of posaconazole would likely not reach the defined PK targets (13), and a powder for oral suspension (PFS) formulation was developed with improved bioavailability similar to that of the marketed oral tablet (8). The PFS is a pH-controlled delayed-release formulation containing amorphous posaconazole in the form of a solid dispersion powder; it provides convenient oral administration and dosing flexibility in pediatric patients aged 2 to 17 years (14).

In a phase 1b open-label, sequential dose-escalation trial in pediatric patients aged 2 to 17 years with documented or expected neutropenia (P097; NCT02452034), the PK profiles of PFS and IV formulations were evaluated at doses of 3.5, 4.5, and 6 mg/kg (14). Data from this study suggested that both the 4.5 and 6 mg/kg dosing schedules achieved a C_{avg} of ≥500 ng/mL in approximately 90% of participants. The IV and PFS posaconazole formulations were well-tolerated in pediatric patients, and the safety profiles were comparable to those reported in adults (14). Similar to the weight-based dosing regimens, PK profiles were also simulated with the results stratified by body weight to explore fixed dosing by the weight band for simplification of administration instructions (8). Here, we report on the results of a population PK analysis of the P097 study to further support dosing recommendations in pediatric patients aged 2 to 17 years.

RESULTS

Participant characteristics

The analysis data set included 1,236 PK observations from 114 pediatric participants aged 2 to 17 years (Table 1). About 59% of the population was male, and a majority of the participants were White (83%) and not Hispanic (87%). Participants were administered posaconazole IV (*n* = 54) or IV and PFS (*n* = 60) at doses of 3.5 (*n* = 35), 4.5 (*n* = 31), or 6 mg/kg (*n* = 48) (Table S1). A total of 80 samples were excluded from the analysis, including 33 samples from 2 participants with incomplete oral PFS dose intakes. Samples for which the sampling time was not available (31 samples) or which had the same sampling time (13 samples) were also excluded.

Final model

The final structural model was described using a one-compartment model, with first-order absorption, interindividual variability (IIV) on clearance (CL), central volume of distribution (V_c) and bioavailability, correlation between CL and V_c, estimated allometric exponent on CL and V_c, estimated bioavailability using a logit function (in order to constrain its value between 0 and 1), and an additive error model in the logarithmic scale. Parameter estimates for the final structural model are shown in Table 2. All model

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TABLE 1 PK population baseline characteristics[a]

Characteristic	2 to <7 years (*n* = 48)	7 to 17 years (*n* = 66)	All (*N* = 114)
Median age (range), years	3 (2–6)	13 (7–17)	8 (2–17)
Median weight (range), kg	16 (10.2–41.7)	45.4 (18.2–102)	28.6 (10.2–102)
Median BMI (range), kg/m^2	15.5 (12.8–30.7)[b]	18 (12.6–33.7)[b]	16.5 (12.6–33.7)[c]
Median BSA (range), m^2	0.662 (0.475–1.1)[b]	1.39 (0.793–2.26)[b]	1.02 (0.475–2.26)[c]
Median eGFR (range), ml/min/1.73 m^2	154 (55.3–399)[b]	138 (12.2–314)[b]	146 (12.2–314)[c]

[a]BMI, body mass index; BSA, body surface area; eGFR, estimated glomerular filtration rate.
[b]Data missing for one patient.
[c]Data missing for two patients overall.

parameters were well-estimated, with a percentage of relative standard error (RSE) of <20% for fixed-effect parameters and <30% for random-effect parameters. The estimate of allometric exponents for body weight on CL (0.624) and V_C (0.971) approximated theoretical values (0.75 and 1, respectively). Estimates of shrinkage suggested a robust estimate of the individual values for CL (shrinkage 5%), whereas the estimates for both V_C and bioavailability were subject to shrinkage (34% and 42%, respectively) (File S1).

No significant relationships were found between covariates assessed in the stepwise analysis (age, weight, estimated glomerular filtration rate [eGFR], sex, and ethnicity) and CL, V_C, or bioavailability (File S2 for age and weight; the results were similar for eGFR, sex, and ethnicity [data not shown]); therefore, the base structural model was considered the final model.

Effect of food

The effect of food conditions on the bioavailability of the posaconazole PFS formulation was assessed after completion of the stepwise covariate analysis. The food effect was captured through different covariates and included the effect of no meal vs that of a meal and the effect of no meal vs that of a light meal, medium meal, and heavy meal, within 2 hours before dosing and up to 1-hour post-dose. None of the food covariates or categorizations showed a significant effect on bioavailability. Graphical assessments for the effect of no meal vs that of a meal did not indicate any clear trends to suggest that food had an impact on the bioavailability of posaconazole PFS (Fig. 1), and its inclusion did not result in a statistically significant improvement in the fit of the population PK model. Therefore, the food effect was not included in the final model.

TABLE 2 Parameter estimates for the final PK model[a]

Parameters	Estimate	RSE (%)	Shrinkage (%)
Fixed effects			
CL (L/h)	4.71	3.86	
V_C (L)	112	5.18	
KA (h^{-1})	0.212	17.9	
F1	0.826	5.58	
α for CL	0.624	9.86	
α for V_C	0.971	7.86	
Random effects			
IIV (CL)[b]	37.1	8.15	5
IIV (V_C)[b]	27.7	24.75	34
IIV (F1)[c]	2.02	18.9	42
Residual error, SD	0.331	4.71	8

[a]α, allometric scaling exponent; CL, clearance; F1, relative bioavailability; IIV, interindividual variability; KA, absorption rate constant; RSE, relative standard error; SD, standard deviation; Vc, central volume of distribution.
[b]Expressed as a CV%, calculated by the square root of Ω, multiplied by 100.
[c]The variability in F1 is shown as a standard deviation in the logit domain. This corresponds to 95% of patients having F1 comprising between 8% and 99%.

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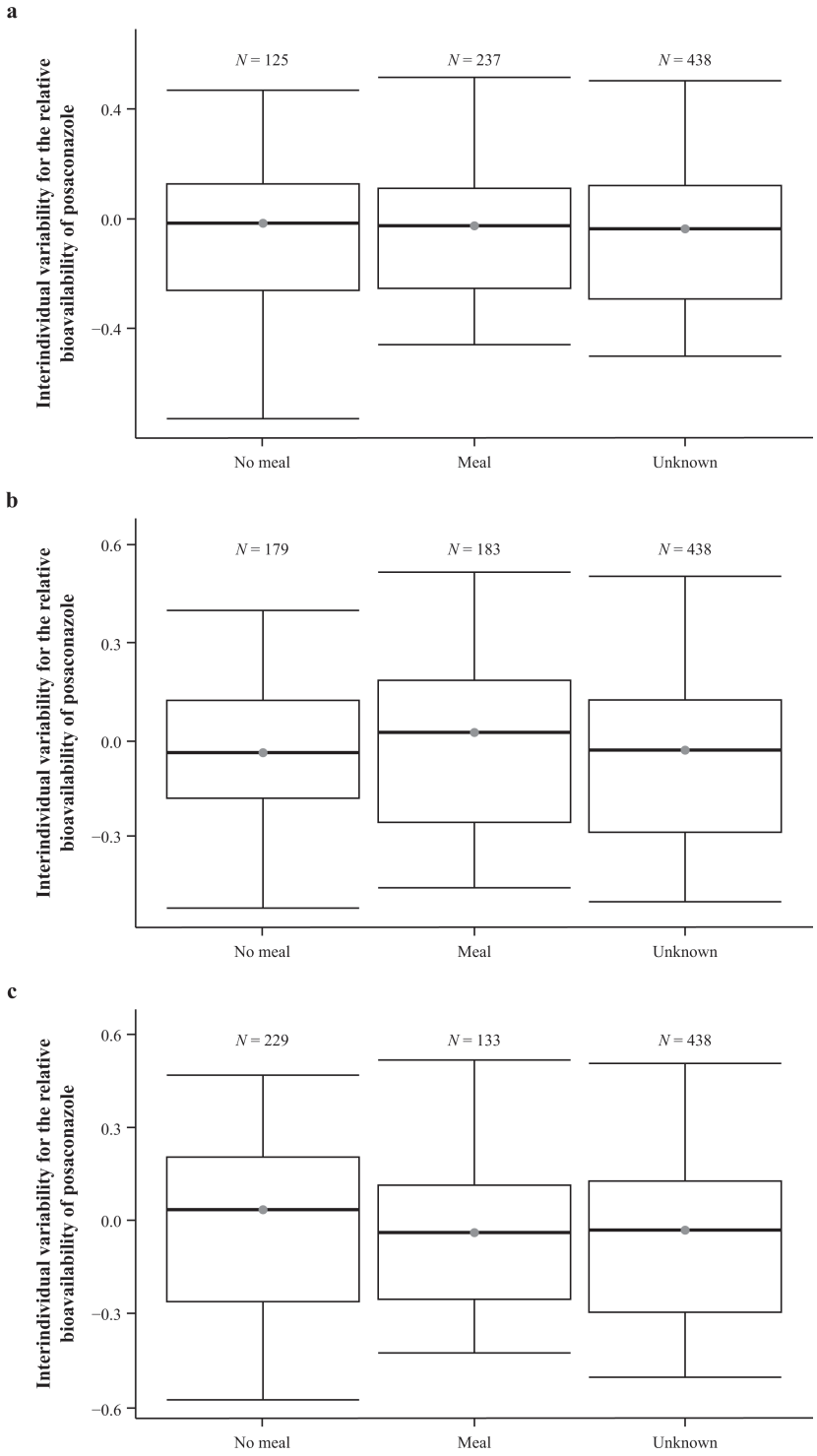


FIG 1 Correlation of interindividual variability with the relative bioavailability of the posaconazole PFS formulation vs two-category food effect covariates. Graphical assessments of the IIV of the posaconazole PFS formulation for (a) the overall food effect parameter, (b) food intake within 2 hours before dosing, and (c) food intake within 1 hour post-dose. N represents the number of observations with certain associated food information. The line in the box represents median, boxes extend to the 25th and 75th percentiles, and whiskers extend to the 5th and 95th percentiles. F1, relative bioavailability; IIV, interindividual variability; PFS, powder for oral suspension; POS, posaconazole.

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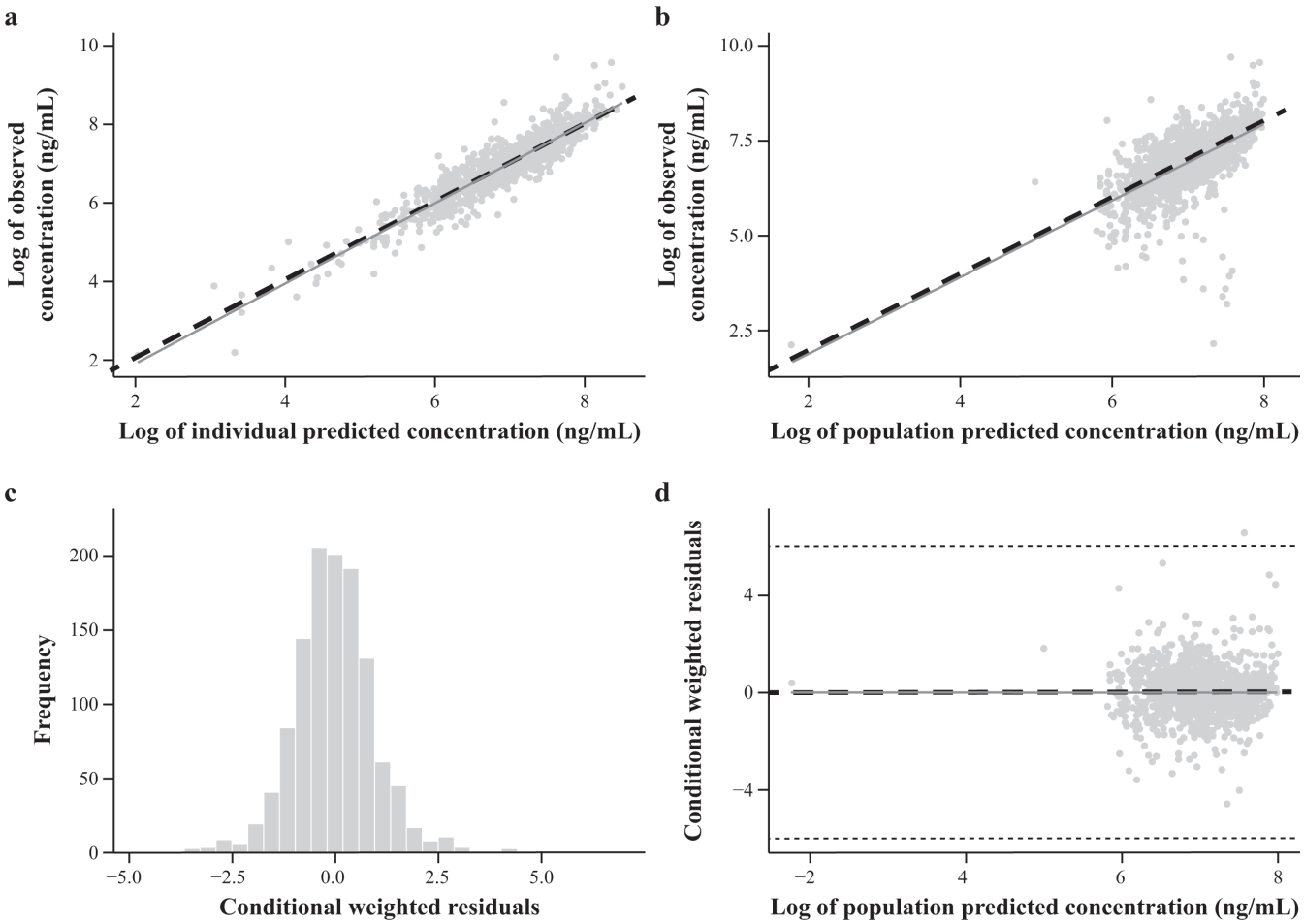


FIG 2 Goodness-of-fit analysis for the final structural pharmacokinetic model. Goodness-of-fit plots for (a) log of observed posaconazole concentrations (ng/mL) vs the log of individual predicted posaconazole concentrations (ng/mL), (b) log of observed posaconazole concentrations (ng/mL) vs the log of population predicted posaconazole concentrations (ng/mL), (c) frequency of individual conditional weighted residuals, and (d) conditional weight residuals vs the log of population-predicted posaconazole concentrations (ng/mL). Excludes outlier observations. In (a), (b), and (d), dots represent individual data and solid gray lines represent trend lines. In (a) and (b), the black dashed lines are lines of identity. In (d), the black dashed line represents a reference (zero) line.

Model validation and simulations

Reliability of the final model was confirmed with diagnostic plots, visual predictive checks, and bootstrap analysis. The predictive performance of the population PK model was confirmed by the agreement between model-predicted and observed concentration–time values across all cohorts with no obvious bias (Fig. 2).

The robustness and fidelity of the final PK model were confirmed through the comparison of C_{avg} and trough plasma concentration (C_{min}), calculated using the model-based *post hoc* parameter estimates and the corresponding noncompartmental analysis-derived PK parameters based on intensive PK sampling obtained at a steady state after approximately 10 days of IV or oral PFS administration in PN097. Overall, there was good concordance between model-predicted *post hoc* estimates of individual C_{avg} and C_{min} parameters and those calculated by noncompartmental analysis for both IV and oral PFS administration, although in the 6 mg/kg per day cohort, the model tended to overpredict C_{min} for the PFS administration (File S3).

Simulation-based visual predictive checks showed that the model accurately tracked the central tendency of the observed data (i.e., the observed data are symmetrically distributed around the median predictions, with a majority lying within the 90% prediction interval of the model predictions), providing further confirmation that the

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final model adequately described the observed data when stratified by age and route of administration (File S4). Taken together, these results support the fidelity of the model over the entire age range (2 to 17 years) following both IV and oral PFS administration and support the use of the model in confirming the appropriateness of the 6 mg/kg per day dose and exploring alternative dosing regimens using simulation approaches.

The final population PK model was used to simulate PK profiles for 2,000 virtual pediatric patients (1,000 patients aged 2 to <7 years and 1,000 patients aged 7 to 17 years) for posaconazole dose regimens of 4.5, 6, or 7.5 mg/kg IV BID on day 1, followed by IV QD dosing to day 10 and oral PFS QD dosing through day 28. Both the 6- and 7.5-mg/kg dosing regimens were predicted to achieve the PK target of >500 ng/mL steady-state C_{avg} in >90% of pediatric patients in both age groups with initial IV administration for 10 days, followed by either IV or PFS administration for a further 2 wk (Fig. 3).

Overall, the simulation results for PFS and IV posaconazole administration show that the dosing regimens of both 6 and 7.5 mg/kg achieved the required steady-state C_{avg} values of >500 ng/mL in more than 90% of pediatric patients in both age group populations, irrespective of the route of administration (Table 3). The 7.5-mg/kg dosing regimen is predicted to achieve C_{avg} > 500 ng/mL in 4% more participants aged 2 to <7 years than the 6-mg/kg dosing regimen for PFS posaconazole; however, the 7.5-mg/kg dosing regimen in participants aged 7 to 17 years is predicted to exceed the upper C_{avg} threshold of >2,500 ng/mL in 8% (PFS and IV) and 12% (IV only) more participants than the 6 mg/kg dosing regimen. C_{avg} geometric means were predicted to be above or around the target concentration of 1,200 ng/mL at the dose regimens of 6 and 7.5 mg/kg in both age groups and for both IV and PFS administration (Table S2).

Virtual pediatric population simulation

Simulations of a virtual pediatric population, generated from the National Health and Examination Survey (NHANES) database, were performed using the population PK model to assess the suitability of the posaconazole 300 mg tablet QD (BID on the first day) for pediatric patients >40 kg able to receive oral therapy. The distribution of body weight by age of the virtual pediatric population derived from the NHANES database is consistent with that previously observed in adults (12), with <5% of adolescents having a body weight of <40 kg.

For the posaconazole tablet dosing regimen of 300 mg/day, the model-predicted C_{avg} achieved the PK target of C_{avg} >500 mg/mL in 90% of pediatric patients with a body weight >40 kg (Table S3). The distribution of model-predicted C_{avg} shifted lower with increasing weight (Fig. 4). Model-predicted C_{avg} for the 300 mg tablet was 20% lower than for 300 mg PFS in patients with a body weight >50 kg, reflecting the relative bioavailability of the two formulations (PFS/tablet = 1.2).

DISCUSSION

Plasma concentration data following IV and PFS posaconazole administration across the 3.5-, 4.5-, and 6-mg/kg per day dosing regimens in a pediatric population aged 2 to 17 years with documented or expected neutropenia at risk for IFD were well-described using a one-compartment model with first-order absorption, where bioavailability was constrained from 0 to 1 using a logit function and CL and Vc were subject to allometric scaling by body weight. Simulations predict that the 6-mg/kg per day posaconazole dose regimen will provide sufficient exposure, with >90% of participants having a C_{avg} ≥500 ng/mL following IV dosing only, or with a switch from IV to PFS administration, in both the 2- to <7-year and the 7 to 17-year age groups. Extrapolation of posaconazole PK data to a 7.5-mg/kg per day posaconazole dosing regimen was predicted to result in higher exposures in all pediatric patients; however, based on previous exposure–response analyses of pivotal posaconazole trials (11), these higher exposures are unlikely to substantially improve efficacy rates relative to the 6 mg/kg per day dose

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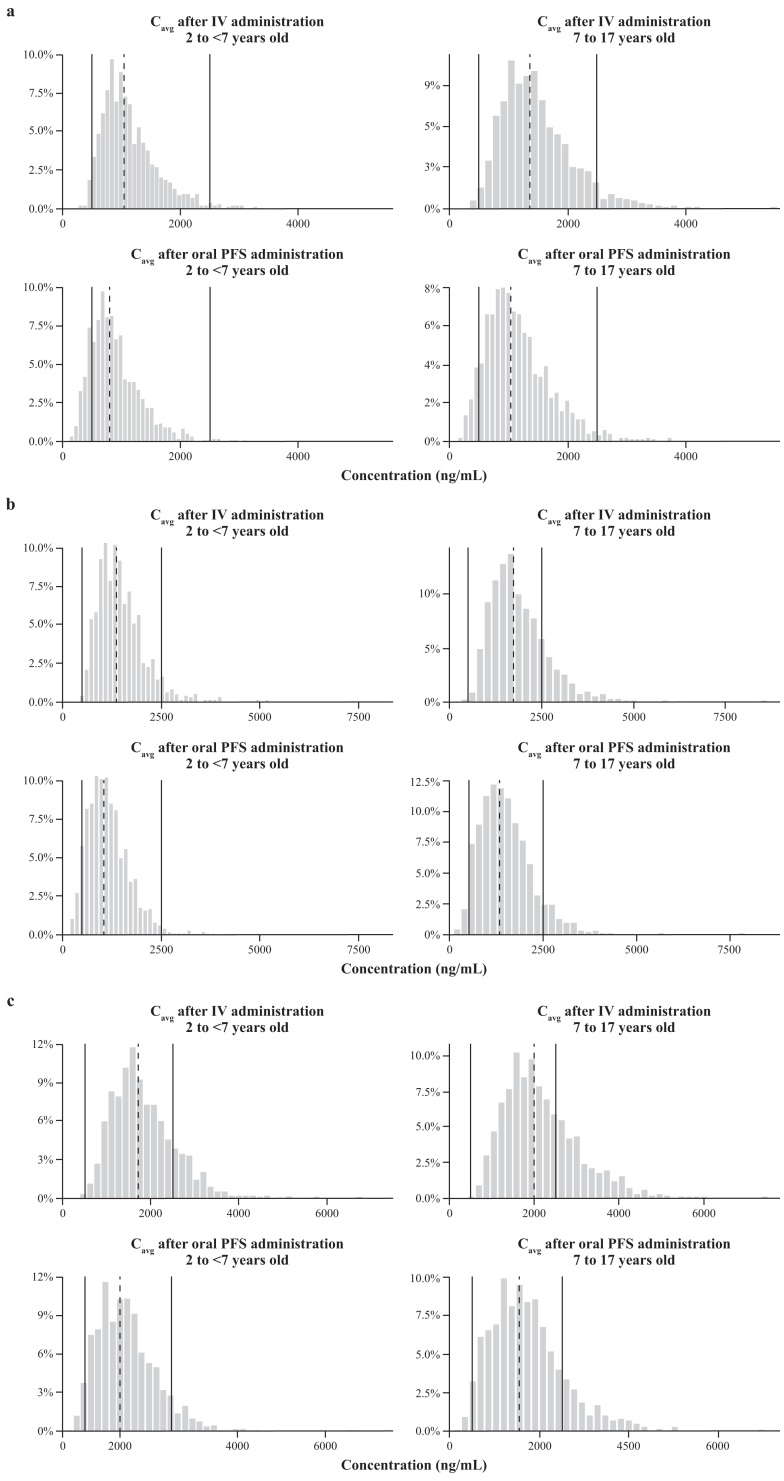


FIG 3 Distribution of simulated C_{avg} per age group and formulation. Distribution of simulated posaconazole C_{avg} per age group (2 to <7 or 7 to 17 years) and formulation (IV or PFS) at (a) 4.5, (b) 6, (c) and 7.5 mg/kg. The vertical dashed line is the geometric mean of the pharmacokinetic parameter. The left and right solid lines represent the thresholds of 500 and 2,500 ng/mL, respectively. C_{avg}, average steady-state plasma concentration; IV, intravenous; PFS, powder for oral suspension.

and would only modestly increase the number of patients with C_{avg} < 500 ng/mL. The predictive performance of the population PK model was confirmed by the agreement between model-predicted and observed concentration values across all the cohorts,

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TABLE 3 Proportions of participants achieving specific ranges of simulated C_{avg} and C_{min} across dose regimens of 4.5, 6, or 7.5 mg/kg QD by the age group[a]

Dose	Parameter	Formulation	2 to <7 years of age			7 to 17 years of age		
			Concentration ranges (ng/mL)					
			<500	≥500 to <2,500	≥2,500	<500	≥500 to <2,500	≥2,500
4.5 mg/kg	C_{avg}, %	IV	2.8	95.6	1.6	0.8	93.4	5.8
		PFS	17.2	82.1	0.7	7.6	89.9	2.5
	C_{min}, %	IV	45.3	54.6	0.1	20.7	78.2	1.1
		PFS	48.2	51.5	0.3	23.9	75.2	0.9
6 mg/kg	C_{avg}, %	IV	0.2	94.4	5.4	0.1	82.2	17.7
		PFS	6.8	91.2	2.0	3.1	89.1	7.8
	C_{min}, %	IV	30.2	69.1	0.7	9.7	85.9	4.4
		PFS	30.9	67.9	1.2	14.1	83.2	2.7
7.5 mg/kg	C_{avg}, %	IV	0	83.2	16.8	0	70.2	29.8
		PFS	2.9	89.3	7.8	1.9	82.1	16.0
	C_{min}, %	IV	20.8	77.7	1.5	6.4	85.4	8.2
		PFS	20.0	78.1	1.9	9.7	84.2	6.1

[a]C_{avg}, average plasma concentration during the dosing interval; C_{min}, trough plasma concentration; IV, intravenous; PFS, powder for oral suspension; QD, once daily.

with no obvious bias observed. Model validation approaches showed good concordance between model-predicted *post hoc* estimates of individual C_{avg} and those calculated by the noncompartmental analysis for both IV and PFS posaconazole administration as well as good concordance between model-based and observed C_{min} values. Taken together, these results support the application of the final population PK model to simulate IV and oral PFS dosing regimens in pediatric patients aged 2 to 17 years.

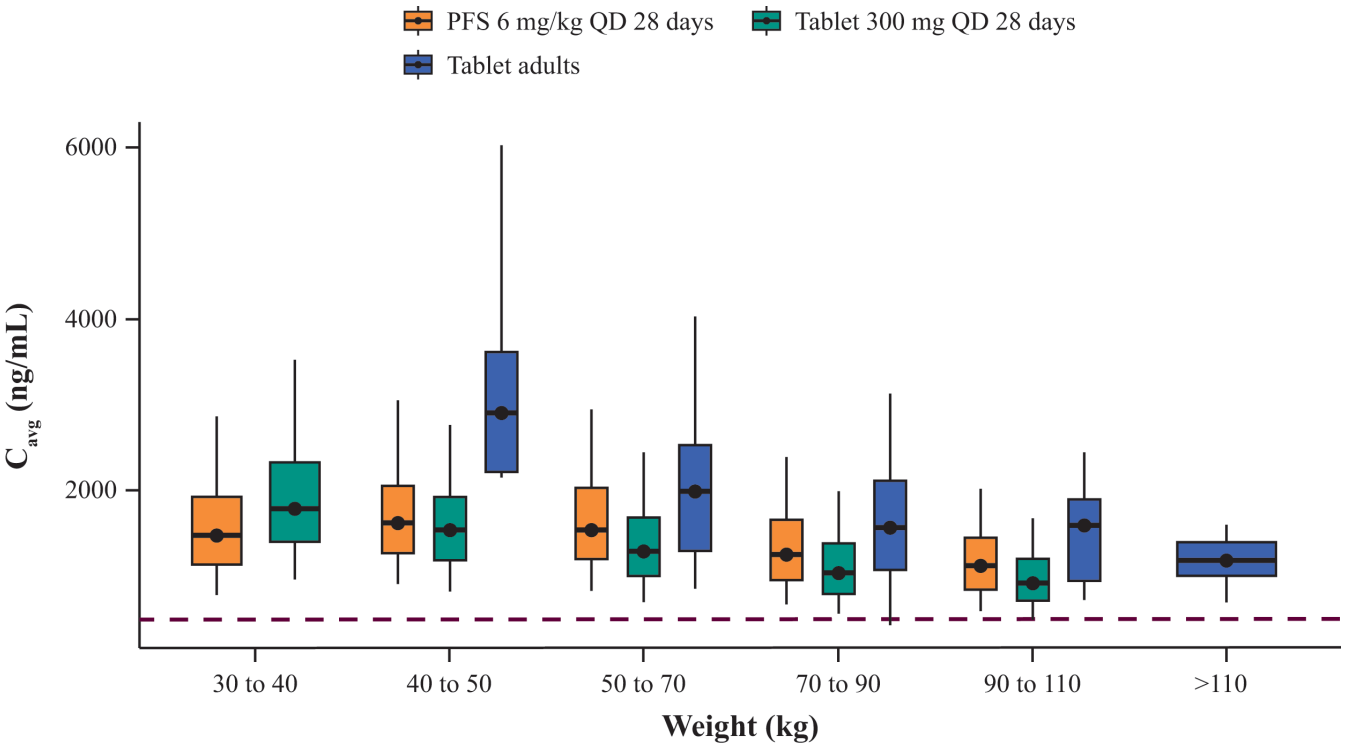


FIG 4 Distribution of model-predicted C_{avg} by body weight for posaconazole tablets and PFS in virtual pediatric subjects and observed distribution of C_{avg} for posaconazole tablets in adults. Frequency distribution of model-predicted C_{avg} by body weight for the 300 mg QD posaconazole tablet and the 6-mg/kg QD PFS dosing schedule in virtual pediatric patients vs the distribution of C_{avg} for the 300 mg QD posaconazole tablet observed in adults from a previous study (14), across 28 days of dosing. The line in the box represents the median, boxes extend to the 25th and 75th percentiles, and whiskers extend to the 5th and 95th percentiles. The dashed line represents the 500 ng/mL posaconazole C_{avg} target concentration. C_{avg}, average steady-state plasma concentration; IV, intravenous; PFS, powder for oral suspension; QD, once daily.

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The 6-mg/kg per day posaconazole dosing regimen achieved the target C_{avg} geometric mean of 1,200 ng/mL for both the IV and PFS formulation in the older age group of patients aged 7 to 17 years. In the younger age group of patients aged 2 to <7 years, the target C_{avg} geometric mean was only achieved with the IV formulation. In contrast, the 4.5-mg/kg posaconazole dosing regimen did not achieve the target C_{avg} geometric mean of 1,200 ng/mL in patients aged 2 to <7 years with either the IV or PFS formulation. These results provide further support for the current US product labeling, which recommends a dosing regimen of 6 mg/kg per day (BID on the first day and up to a maximum absolute dose of 300 mg) for IV posaconazole administration in children aged 2 to 17 years. To simplify PFS administration and allow for dosing in 1-mL increments, a weight-band dosing nomogram was ultimately applied in order to maximize the proportion of pediatric patients achieving the PK target across weight bands, while also maintaining a favorable benefit–risk profile. The weight-band dosing nomogram recommended in current US product labeling is approximately 1 to 1.5 times the 6-mg/kg per day dosing regimen used in this study.

A trend toward lower exposure with PFS compared to IV administration was observed, with higher clearance in the younger age group (2 to <7 years); however, the dosing regimen of 6 mg/kg per day of either the IV or the PFS formulation still provided sufficient exposure in this age group to achieve comparable efficacy to adults. Furthermore, age was not identified as a significant covariate, supporting the conclusion that weight-based dosing at 6 mg/kg for IV administration and the use of weight-band dosing for PFS administration (up to a maximum absolute dose of 300 mg) are appropriate in the pediatric population aged 2 to 17 years, without further adjustment for age.

No significant effect on posaconazole bioavailability was identified in the population PK analysis in this study when the PFS formulation was administered with food (between 2 hours pre-dose and 1 hour post-dose). This supports current US labeling recommendations that the PFS formulation can be administered with food to pediatric patients aged 2 to 17 years (9). These findings are consistent with previously reported findings in adults, in which a high-fat meal was reported to have a minimal effect on the overall area under the curve exposure levels with the PFS formulation (data on file), although a <50% increase in the area under the curve was previously observed for a high-fat meal compared to the fasting state in adults for the 300-mg tablet formulation (15).

Results from the virtual pediatric population simulation support the use of the adult dosing regimen of a fixed-dose 300 mg/day tablet in pediatric patients with a body weight >40 kg. More than 90% of the virtual pediatric population were predicted to achieve the PK target of C_{avg} ≥500 ng/mL while remaining within the target range of exposure for which no safety issues have been identified (12, 16). As <5% of the virtual adolescent population had a body weight of <40 kg, these results are likely to be applicable to most of the adolescent population.

A limitation of this study is that a population PK model was utilized to predict posaconazole exposure levels to a 7.5-mg/kg posaconazole dosing regimen; no clinical efficacy or safety data are available for a 7.5-mg/kg posaconazole dosing regimen in pediatric patients with neutropenia or on the weight-band dosing nomogram that was ultimately approved in the United States and the European Union for PFS administration. In the P097 study, posaconazole IV and PFS formulations were well-tolerated in dosing regimens up to 6 mg/kg and had safety profiles similar to those reported for adults (14). Although safety was not assessed in the current analysis, no dose-dependent or exposure-related toxicity was identified in the pediatric population from the P097 study (14).

In conclusion, this population PK model demonstrated that a weight-based dosing regimen of IV or PFS posaconazole (up to a 300 mg absolute dose) is appropriate for the pediatric population at risk of IFD and supports current US product labeling that the PFS formulation can safely be administered with food. The 300 mg posaconazole tablet approved for use in adults was predicted to achieve the PK target and remain within a safe range of exposure in adolescent patients with a body weight of >40 kg.

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MATERIALS AND METHODS

PK data and study population

PK data were obtained from immunocompromised patients aged 2 to 17 years, with documented or anticipated neutropenia in the setting of acute leukemia, myelodysplasia, severe aplastic anemia, autologous HSCT, high-risk neuroblastoma, advanced-stage non-Hodgkin lymphoma, allogenic HSCT during the pre-engraftment (neutropenic) period, or hemophagocytic lymphohistiocytosis, treated in the P097 study (Clinicaltrials.gov NCT02452034, Merck & Co., Inc., Rahway, NJ, USA protocol number MK-5592–097) (14). Participants received posaconazole for 10 to 28 days, initially as an IV solution, but with the option to switch to oral PFS administration between days 10 and 18 for the remainder of the treatment period. Three dose cohorts of posaconazole were assessed: 3.5, 4.5, and 6 mg/kg, administered IV BID on day 1 and IV QD on days 2 to 10, with either oral PFS or IV administration QD on days 10 to 28. The absolute maximum dose of posaconazole administered was limited to 300 mg (i.e., in patients with a high body weight in which the weight-based dosing regimen would otherwise result in an absolute dose >300 mg). The trial was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice requirements, and applicable country and/or local statutes and regulations regarding Institutional Ethics Committee review, informed consent, and protection of human participants in biomedical research. All participants or their legal representatives gave written informed consent before initiation of any study procedures.

Pharmacokinetic sampling

PK sampling during posaconazole IV administration was performed pre-dose on day 6; and pre-dose, within 15 minutes of the end of infusion; and at 4, 6, 12, and 24 hours after the start of the infusion between days 7 and 10 (14). For inpatients, PK sampling during posaconazole PFS administration was performed at pre-dose (0 hour) and 2, 4, 6, 8, and 24 hours post-dose between days 7 and 10. For outpatients, PK sampling during posaconazole PFS administration was performed at pre-dose (0 hour) and at 2 and 4 hours post-dose between days 7 and 10.

Bioanalysis and data set preparation

Plasma posaconazole concentrations were quantified using a validated high-performance liquid chromatography with tandem mass spectrometry method (17). Measurements below the lower limit of quantification (LLOQ) of 5.00 ng/mL and missing values were excluded from the analysis, with the missing concentration-dependent variable set to 1. Pre-treatment plasma concentrations above the LLOQ were also excluded from the data set. Log-transformed plasma concentrations were used as the dependent variable. Covariates were not included in the analysis if >30% of participants did not provide a covariate value. Otherwise, the value of the missing covariate observations was imputed as the median of the remaining values from an appropriate subpopulation. For categorical covariates, such as sex and race, the most frequently occurring value was imputed. All data sets were prepared using SAS V9.3 (SAS Institute, Cary, NC).

Population PK model development

PK data were analyzed using the NONMEM software (version 7.2; Globomax, Hanover, MD), and model fitting was performed in a UNIX environment with an Intel FORTRAN Compiler (version 11.1; Intel Corporation, Santa Clara, CA). The applied estimation method in NONMEN was the first-order conditional estimation, with an additive model for residual variability on log-transformed data. Xpose (http://xpose.sourceforge.net), perl speaks (PsN; http://psn.sourceforge.net), and R-project (version 3.4.3; http://www.r-project.org) were used for exploratory analysis and post-processing of NONMEM output (e.g., to assess goodness-of-fit).

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A one-compartment model with first-order absorption was fit to the PK data set of participants administered oral PFS and IV or IV-only formulations, based on the previous analyses of posaconazole PK in adults (18). The model was parameterized in terms of CL and V_c, with IV administration being assumed to be directed into the central compartment. Alternative structural models and refinements were explored to improve model fit, and allometric scaling of CL and V_c was evaluated. Residual variability in log-transformed concentrations was modeled using an additive error model, and IIV was evaluated using exponential error models. Stepwise covariate analysis assessed the influence of covariates, including age, eGFR, sex, and ethnicity, on posaconazole exposure ($p < 0.01$ for forward inclusion; $p < 0.001$ for backward deletion).

The resultant final model only contained covariates that met the pre-defined statistical criteria. As part of the final covariate selection, the clinical relevance of any relationship was also considered. The impact of food covariates on relative bioavailability was then assessed after the completion of the stepwise covariate analysis using the same statistical criteria. Information on food intake was captured within 2 hours prior to or up to 1 hour after the associated PFS dose administration and included details on whether the food intake was a light, moderate, or heavy meal. Model validation was performed using diagnostic plots, prediction-corrected visual predictive checks, and comparison of derived PK parameters (C_{avg} and C_{min}) from the noncompartmental analysis of the participants treated with 3.5, 4.5, and 6 mg/kg, with those calculated from *post hoc* estimates.

Final population PK model simulations

The final population PK model was used to simulate the distribution of posaconazole exposure in both the 2- to <7-year age group and the 7- to 17-year age group. The model was used to derive the proportion of pediatric patients achieving an exposure range of C_{avg} ≥500 ng/mL (the primary concentration target) as well as the proportion of pediatric patients achieving an exposure range of C_{min} ≥500 ng/mL (a secondary concentration target). The exposure target was a mean C_{avg} of 1,200 ng/mL, with approximately 90% of participants with C_{avg} ≥500 to <2,500 ng/mL; the critical target in this study was achieving C_{avg} ≥ 500 ng/mL in 90% of participants. The dose levels included in the simulations were 4.5, 6, or 7.5 mg/kg, with the maximum absolute dose limited to 300 mg. The 7.5-mg/kg regimen, a higher dose than was evaluated in the clinical study, was included for the purpose of confirming dose recommendations. Steady-state exposure parameters (C_{avg}; C_{min}) were calculated after the last dose of IV and PFS administration.

Simulations were performed using a combination of R and NONMEM. R was used to create the data sets (1,000 subjects aged 2 to <7 years and 1,000 subjects aged 7 to 17 years) and jointly sample the age and weight from a combined pediatric population from the P097 (14) and P032 studies. The addition of data from P032 was anticipated to enable a more robust assessment of the distribution of posaconazole exposures across a relevant pediatric population, as both studies included pediatric patients with similar diagnoses and demographics.

Virtual pediatric population analysis

As there were insufficient data in the weight range of interest in the P097 study to allow a resampling approach, a virtual pediatric population was generated using the NHANES database. The distribution of body weight by age of the virtual pediatric population derived from the NHANES database (19) was consistent with the body weight by age distribution observed in the P097 and P032 studies. The virtual pediatric population was used to predict the population PK for the posaconazole tablet formulation in pediatric patients with a body weight >40 kg.

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DATA AVAILABILITY

The data sharing policy, including restrictions, of Merck Sharp & Dohme LLC, a subsidiary of Merck & 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 the Data Access mailbox.

ADDITIONAL FILES

The following material is available online.

Supplemental Material

Supplemental tables and figures (AAC01197-23-S0001.pdf). Tables S1-S3 and Fig. S1-S4.

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Epidemiology of Candidemia in Latin America: A Laboratory-Based Survey

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Abstract

Background: The epidemiology of candidemia varies depending on the geographic region. Little is known about the epidemiology of candidemia in Latin America.

Methods: We conducted a 24-month laboratory-based survey of candidemia in 20 centers of seven Latin American countries. Incidence rates were calculated and the epidemiology of candidemia was characterized.

Results: Among 672 episodes of candidemia, 297 (44.2%) occurred in children (23.7% younger than 1 year), 36.2% in adults between 19 and 60 years old and 19.6% in elderly patients. The overall incidence was 1.18 cases per 1,000 admissions, and varied across countries, with the highest incidence in Colombia and the lowest in Chile. *Candida albicans* (37.6%), *C. parapsilosis* (26.5%) and *C. tropicalis* (17.6%) were the leading agents, with great variability in species distribution in the different countries. Most isolates were highly susceptible to fluconazole, voriconazole, amphotericin B and anidulafungin. Fluconazole was the most frequent agent used as primary treatment (65.8%), and the overall 30-day survival was 59.3%.

Conclusions: This first large epidemiologic study of candidemia in Latin America showed a high incidence of candidemia, high percentage of children, typical species distribution, with *C. albicans*, *C. parapsilosis* and *C. tropicalis* accounting for the majority of episodes, and low resistance rates.

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Introduction

Candidemia is the leading invasive mycosis occurring in hospitalized patients, with a high burden in tertiary care hospitals worldwide [1,2]. The epidemiology of candidemia has been extensively described in the Northern Hemisphere, especially in The USA, Western Europe and Asia [3–15]. In Latin America, except from Brazil [16–21] and other few reports [22–24], little is known about the epidemiology of candidemia [25]. The recognition of differences in incidence, populations at greater risk, species distribution and antifungal susceptibility patters is important in order to establish appropriate measures of infection control and for the management of this disease, including prophylaxis and empiric antifungal therapy.

In a nationwide prospective multicenter study conducted in Brazil, a high burden of candidemia was reported, with 2.49 cases per 1,000 admissions (3–10 times higher than that reported in the Northern Hemisphere) with a ~50% crude mortality rate [19]. In addition, epidemiologic studies in Brazil suggested that *Candida parapsilosis* and *Candida tropicalis* were the most frequent non-*albicans* species, and the proportion of cases due to *Candida glabrata* and *Candida krusei* was low [25].

The Latin America Invasive Mycosis Network is a group of investigators interested in invasive mycoses who met first in 2005 to identify priorities in research and educational activities in the region. In this paper we report the first multicenter prospective epidemiologic study to investigate the epidemiology of candidemia in different Latin American countries.

Patients and Methods

This is a prospective laboratory-based surveillance study conducted between November 2008 and October 2010 (24 months) in 21 tertiary care hospitals in seven Latin American countries (total 7,445 beds). They were all general hospitals with public (n = 12), private (n = 3) or public and private (n = 6) beds. Sixteen hospitals were for adults and children, one was for adults only and four were for children. All hospitals had intensive care units (ICU, 723 beds), internal medicine and surgery; 18 centers had hematology ward, 10 had solid organ transplantation and 8 had hematopoietic cell transplantation wards. The protocol was approved by ethics committees of each hospital and country without the need of written consent, because of the observational nature of the study: Comite de Etica em Pesquisa da Unifesp/EPM, Comitê de Ética em Pesquisas em Seres Humanos do Hospital de Clínicas da Universidade Federal do Parana, Comite de Etica em Pesquisa do Hospital Pequeno Principe, Comite de Etica em Pesquisa do Hospital Universitário Clementino Fraga Filho (Brazil); Comité de Ética Científico Pediátrico Servicio de Salud Metropolitano Oriente, Comité de Ética Científico Clinica Alemana, Comité de Ética Científico Facultad de Medicina, Universidad de Chile (Chile); Comite de Etica del Hospital de Clinicas Jose de San Martin, Comite de Bioetica, Hospital General de Agudos Juan A. Fernandez, Comite de Etica e Invedstigación, Hospital Pedro de Elizalde (Argentina); Hospital Vozandes Quito Bioethics Committee (Ecuador); Comité de Investigaciones y Ética Institucional (CIEI) de la Facultad De Medicina de la Pontificia Universidad Javeriana y del Hospital Universitario De San Ignacio, Comite de Investigacion, Fundacion Vele del Lili, Comité Independente de Ética en Investigación, Hospital Militar Central, Comité Ético Científico de la Empresa Social del Estado Hospital Universitario de la Samaritana (Colombia), Comite de Etica Centro Medico de Caracas, Comite de Etica Instituto Medico la Floresta (Venezuela), Comite Etica de los Postgrados de Medicina UNAH (Honduras).

Participating institutions carried out laboratory-based sentinel surveillance for candidemia. All hospitals had automated blood culture systems (either Bactec or BacT-ALERT), and an investigator designated to visit the microbiology laboratory on a daily basis in order to capture all episodes of candidemia, and trained to prospectively fill a comprehensive case report form once an episode was diagnosed. The case report form contained detailed information about demographics, underlying conditions, coexisting exposures, receipt of antifungal agents and the outcome. All clinical information was sent using a web-based system (SPSS, Inc.). Audits and query generation were carried out periodically.

All adult and pediatric patients with candidemia were eligible for inclusion in the study, and were followed for 30 days. One episode of candidemia was defined by the isolation of *Candida* species from one or more blood cultures in a patient with clinical signs of infection. If more than one blood culture was positive, a new episode was defined if more than 30 days had elapsed since the first positive blood culture (incident candidemia). Breakthrough candidemia was defined when the patient was receiving a systemic antifungal agent for >3 days once candidemia was diagnosed. Neonates were defined as patients with age ≤28 days, infants as children aged >28 days to 1 year, older children as patients 1–18 years old, adults as patients 19–60 years old, and elderly as patients >60 years.

All isolates were identified at species level in the local laboratory, but were also sent to the Special Mycology Laboratory (Universidade Federal de São Paulo) for confirmation of species, as well as antifungal susceptibility tests. Isolates were identified according to their microscopic morphology on cornmeal Tween 80 agar, complemented by biochemical tests using the ID 32C system (BioMérieux AS, Marcy l Etoile, France). Sequencing of the ITS region of ribosomal DNA was used to identify species other than *C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata* and *C. krusei*. Antifungal susceptibility tests were performed using a broth microdilution assay following the methods recommended by the Clinical and Laboratory Standards Institute (CLSI) [26]. The following antifungal drugs were tested: fluconazole (Pfizer Incorporated, New York, NY, USA), amphotericin B (Sigma Chemical Corporation, St Louis, MO, USA), voriconazole and anidulafungin (Pfizer Incorporated, New York, NY, USA). The assays were incubated at 35°C for 24 h. The minimum inhibitory concentration (MIC) breakpoints for fluconazole were: for *Candida albicans*, *C. parapsilosis* and *C. tropicalis* isolates with MIC ≤2 μg/ml were considered susceptible, those with MIC 4 μg/ml were considered susceptible dose-dependent (SDD), and those with MIC ≥8 μg/ml were considered resistant; for *C. glabrata* isolates with MIC ≤32 μg/ml were considered SDD, and MIC ≥64 μg/ml were considered resistant. All *C. krusei* isolates were considered resistant regardless of the MIC value. For voriconazole, isolates with MIC ≤2 μg/ml were considered susceptible, those with MIC 4 μg/ml were considered susceptible dose-dependent (SDD), and those with MIC ≥8 μg/ml were considered resistant. For anidulafungin, isolates of *C. albicans*, *C. tropicalis* and *C. krusei* with MIC ≤0.25 μg/ml were considered susceptible, those with MIC 0.5 μg/ml were intermediate, and isolates with MIC ≥1 μg/ml were considered resistant. For *C. parapsilosis* isolates with MIC ≤2 μg/ml were susceptible, 4 μg/ml were intermediate, and ≥8 μg/ml were resistant. For *C. glabrata* the values were as follows: ≤0.12 μg/ml susceptible, 0.25 μg/ml intermediate, and ≥0.5 μg/ml resistant. For amphotericin B, MICs ≤1 μg/ml were considered susceptible and those ≥2 μg/ml were considered resistant [27].

Incidence density of candidemia was calculated using the number of episodes of candidemia as numerators, and admissions and patients-day as denominators. Incidence rates were calculated for each hospital, each country and overall. Dichotomous variables were compared using Fisher or Chi-square test, as appropriate, and continuous variables were compared using the Wilcoxon test. All statistical analyses were performed in the SPSS software (version 15, SPSS, Inc.). P values <0.05 were considered statistically significant.

Results

During the study period 672 episodes of candidemia were reported. The median age was 26 years (0–98), and 58.9% were males. Two hundred and ninety seven episodes (44.2%) occurred in children (23.7% younger than 1 year, including 89 neonates, and 20.5% between 1 and 18 years), 36.2% in adults between 19 and 60 years old and 19.6% in elderly patients. Excluding the four children hospitals the proportion of children in the cohort was still high (31.2%). The overall incidence was 1.18 cases per 1,000 admissions and 0.23 cases per 1,000 patients-day. As shown in Table 1, the incidence differed across countries, with the highest incidence in Argentina (1.95 cases per 1,000 admissions and 0.24 cases per 1,000 patients-day) and the lowest in Chile (0.33 per 1,000 admissions and 0.09 per 1,000 patients-day). There was also a great variability in the incidence among the centers; the highest incidence was in an Argentinian hospital with 2.98 cases per 1,000 admissions, and the lowest in a Chilean center (0.21 per 1,000 admissions).

As shown in Table 2, *C. albicans* was the leading agent (37.6%), followed by *C. parapsilosis* (26.5%), *C. tropicalis* (17.6%), *C.*

Table 1. Incidence of candidemia in 20 hospitals of 7 Latin American Countries.

Country	Incidence per 1,000 admissions (range)	Incidence per 1,000 patients.day (range)
Argentina	1.95 (1.26–2.98)	0.24 (0.13–0.39)
Brazil	1.38 (0.55–2.11)	0.26 (0.14–0.30)
Chile	0.33 (0.21–0.47)	0.09 (0.06–0.16)
Colombia	1.96*	0.16 (0.12–0.24)
Ecuador	0.90 (0.30–1.10)	0.16 (0.10–0.17)
Honduras	0.90 (0.88–0.98)	0.25 (0.24–0.30)
Venezuela	1.72 (1.04–2.90)	NA
Overall	1.18	0.23

NA = not available.
*information on number of admission was available in only one hospital.
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guilliermondii (6.5%), *C. glabrata* (6.3%), and *C. krusei* (2.7%). There was a great variability in species distribution in the different countries. Ecuador had the highest proportion of episodes due to *C. albicans* (52.2%) and Honduras and Venezuela the lowest (27.4% and 26.8%, respectively). While *C. parapsilosis* was highly prevalent in most countries, it was less frequent in Honduras (14.1%). By contrast, *C. guilliermondii* was very common in this country (20.7%). The highest proportion of episodes caused by *C. glabrata* was observed in Brazil (10%) and the lowest was seen in Venezuela (1 episode, 2.4%).

Overall, cancer was the most frequent underlying condition (22.5%), and 43.8% of episodes occurred in the context of recent surgery (within 3 months of the incident candidemia). The median APACHE II score was 18 (data available in 258 episodes) and 44.6% were in an ICU at the time of the incident candidemia. The median duration of hospitalization before candidemia was 15 days (0–176).

As shown in Table 3, characteristics of the episodes of candidemia differed according to the age strata. For example, ICU admission was more frequent in neonates, elderly patients and infants, and less frequent in children ($p<0.001$); hematologic malignancies were more prevalent in children while solid tumors were more frequent in elderly ($p<0.001$). Co-morbidities like cardiac, neurologic, lung, liver disease, chronic renal failure and diabetes were more frequent in elderly patients. By contrast, the proportion of patients undergoing abdominal surgery was very similar across age strata.

Species distribution was also different (Table 4). For example, the proportion of candidemia due to *C. glabrata* was significantly higher in elderly patients (15.1% vs. 3.4% in neonates, 1.4% in infants, 3.6% in children and 4.5% in adults, $p<0.001$). No other variable besides age was associated with *C. glabrata* candidemia, including prior fluconazole use (3.5% with vs. 6.6% without prior fluconazole exposure, $p = 0.20$). For *C. guilliermondii*, the rates in children were significantly higher (11.6%) than in other age strata, whereas *C. tropicalis* was more frequent in adults. By contrast, there was no association between age and *C. parapsilosis* candidemia, with high rates in all age strata.

Information on antifungal treatment was available in all but 12 episodes (Table 4). Antifungal treatment was given in 85.4% of episodes, at a median of two days from the date of the incident candidemia (0–26). In 61 of the 86 (70.9%) episodes of candidemia in which no antifungal treatment was given, death occurred within five days from the date of the incident candidemia. Fluconazole was the most frequent agent used as primary treatment (65.8%), followed by deoxycholate amphotericin B (24.2%) and an echinocandin (6.9%). There was an inverse relationship between age strata and receipt of deoxycholate amphotericin B as primary therapy for candidemia: 54.9% in neonates, 32.8% in infants, 32% in older children, 14.1% in adults and 10.3% only in elderly patients ($p<0.001$).

The 30-day survival (data available in 583 episodes) was 59.3% (Table 4). Elderly patients had the lowest 30-day survival rate (37.7%), followed by neonates (59.7%), adults (61.9%), infants

Table 2. Species distribution of 672 episodes of candidemia.

	Argentina	Brazil	Chile	Colombia	Ecuador	Honduras	Venezuela	Overall
C. albicans	48 (42.5)	77 (40.5)	16 (42.1)	40 (36.7)	24 (52.2)	37 (27.4)	11 (26.8)	253 (37.6)
C. parapsilosis	27 (23.9)	49 (25.8)	11 (28.9)	42 (38.5)	14 (30.4)	19 (14.1)	16 (39.0)	178 (26.5)
C. tropicalis	19 (16.8)	25 (13.2)	4 (10.5)	19 (17.4)	5 (10.9)	36 (26.7)	10 (24.4)	118 (17.6)
C. guilliermondii	7 (6.2)	3 (1.6)	1 (2.6)	2 (1.8)	1 (2.2)	28 (20.7)	2 (4.9)	44 (6.5)
C. glabrata	7 (6.2)	19 (10.0)	3 (7.9)	5 (4.6)	2 (4.3)	5 (3.7)	1 (2.4)	42 (6.3)
C. krusei	2 (1.8)	9 (4.7)	3 (7.9)	–	–	4 (3.0)	–	18 (2.7)
Other*	3	8	–	1	–	6	1	19 (2.8)
Total	113	190	38	109	46	135	41	672

*Other species – Argentina: *C. lusitaniae* (2), *C. pelliculosa* (1); Brazil: *C. intermedia* (3), *C. haemulonii* (2), *C. lusitaniae*, *C. famata*, *C. norvegiensis* (1 each); Colombia: *C. lusitaniae* (1); Honduras: *C. lusitaniae* (3), *C. pelliculosa*, *C. haemulonii*, *C. albicans*+*C. glabrata* (1 each); Venezuela: *C. pelliculosa* (1).
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Table 3. Characteristics of 672 episodes of candidemia by age strata.

	Neonates N = 89	Infants N = 70	Older children N = 138	Adults N = 223	Elderly N = 152	Overall N = 672
Gender, male : female	41:48	54:16	82:56	132:91	87:65	396:276
Age*, median (range)	16 (1–28)	4 (1–11)	5 (1–18)	45 (19–60)	76 (61–98)	26 (0–98)
APACHE II score**, median (range)	15 (6–24)	13.5 (8–24)	18 (4–21)	16 (2–38)	21.5 (10–39)	18 (2–39)
Duration (days) of hospitalization before candidemia, median (range)	12 (0–28)	19 (0–146)	13 (0–176)	17 (0–162)	20 (0–130)	15 (0–176)
Admission to an ICU	70 (78.7)	34 (48.6)	36 (26.1)	83 (36.8)	78 (51.3)	300 (44.6)
Cancer	–	4 (5.7)	46 (33.3)	60 (26.9)	41 (27.0)	151 (22.5)
Hematological malignancy	–	1 (1.4)	31 (22.5)	29 (13.0)	8 (5.3)	69 (10.3)
Solid tumor	–	3 (4.3)	15 (10.9)	31 (13.9)	33 (21.7)	82 (12.2)
Cardiac disease	18 (20.2)	15 (21.4)	14 (10.1)	34 (15.2)	76 (50.0)	157 (23.4)
Neurological disease	6 (6.7)	11 (5.7)	27 (19.6)	31 (13.9)	43 (28.3)	118 (17.6)
Lung disease	27 (30.3)	19 (27.1)	15 (10.9)	46 (20.6)	60 (39.5)	167 (24.9)
Diabetes mellitus	1 (1.1)	–	4 (2.9)	33 (14.8)	38 (25.0)	76 (11.3)
Renal failure	10 (11.2)	10 (14.3)	19 (13.8)	55 (24.7)	56 (36.8)	150 (22.3)
Chronic renal failure	–	1 (1.4)	9 (6.5)	24 (10.8)	24 (15.8)	58 (8.6)
Liver disease	2 (2.2)	6 (8.6)	8 (5.8)	34 (15.2)	18 (11.8)	68 (10.1)
Surgery	26 (29.2)	27 (38.6)	58 (42.0)	105 (47.1)	78 (51.3)	294 (43.8)
Abdominal surgery	18 (20.2)	17 (24.3)	29 (21.0)	54 (24.2)	38 (25.0)	156 (23.2)
Mechanical ventilation	60 (67.4)	31 (44.3)	32 (23.2)	102 (45.7)	82 (53.9)	307 (45.7)
Parenteral nutrition	43 (48.3)	18 (25.7)	26 (18.8)	64 (28.7)	41 (27.0)	192 (28.6)
Dialysis	3 (3.4)	3 (4.3)	8 (5.8)	35 (15.7)	27 (17.8)	76 (11.3)
Neutropenia	1 (1.1)	4 (5.7)	30 (21.7)	19 (8.5)	3 (2.0)	57 (8.5)
Central venous catheter	63 (70.8)	38 (54.3)	91 (65.9)	167 (74.9)	124 (81.6)	483 (71.9)
Receipt of antibiotic	85 (95.5)	68 (97.1)	131 (94.9)	211 (94.6)	140 (92.1)	635 (94.5)
Receipt of corticosteroids	12 (13.5)	16 (22.9)	48 (34.8)	87 (39.0)	62 (40.8)	225 (33.5)
Previous use of fluconazole	15 (16.9)	3 (4.3)	22 (15.9)	48 (21.5)	19 (12.5)	107 (15.9)

NOTE: Numbers are no. (%) of patients, unless otherwise indicated. APACHE = Acute Physiologic and Chronic Health Evaluation; Infants defined as children older than 28 days and younger than 1 year; Elderly defined as patients older than 60 years.
*days for neonates, months for infants and years for the other age strata and overall.
**data available for 258 episodes.
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(73.3%) and older children (73.7%). The 30-day survival among treated patients was 65.3%, and was not different according to the antifungal agent used as primary treatment.

Table 5 summarizes the antifungal susceptibility tests of the most frequent *Candida* bloodstream isolates. For fluconazole, resistance was observed only in *C. krusei* (all resistant by definition) and *C. glabrata* (7.1%). In addition, SDD was observed in one *C. albicans* (0.4%), two *C. parapsilosis* (1.1%), and 39 (92.9%) *C. glabrata* isolates. All isolates were susceptible to voriconazole and amphotericin B. For anidulafungin, there were two (4.8%) *C. glabrata* isolates, one (0.4%) *C. albicans* and two (1.7%) *C. tropicalis* isolates with intermediate susceptibility.

Discussion

In this first multi-country epidemiologic study of candidemia in Latin America we confirmed some unique epidemiologic features reported in multicenter studies in Brazil: high incidence, a large proportion of children (not only neonates), the typical species distribution with high rates of *C. tropicalis* and *C. parapsilosis* and low rate of *C. glabrata* candidemia, and low resistance rates. In addition, we observed some important differences in the epidemiology across countries.

The proportion of children in this cohort was very high (44.2%). This is in sharp contrast with series from Europe and the USA. For example, a 28-month prospective study in six European countries reported 7.6% of children in a cohort of 2,089 episodes of candidemia [28]. Other European series reported rates between 2 and 9% [11,12,29,30], and a large prospective study in the USA reported 9% of children among 1,591 episodes of candidemia [14]. Another important difference is that while in those series the majority of children were neonates, in the present series there was a high proportion of infants (23.6% of the pediatric population).

We observed a high burden of candidemia in the region, with 1.19 cases per 1,000 admissions. The incidence rates were higher than those reported in the Northern Hemisphere [11,13,15,28,31–33], but lower compared to Brazilian studies. A multicenter study reported 2.49 cases per 1,000 admissions [19], but the rates were even higher in more recent single-center studies (3.6 to 6.0 in one study [34] and 1.54 to 2.99 in another [35]). However, lower incidence rates (0.74–0.91 cases per 1,000 admissions) were observed in private hospitals in this country [36,37]. In the present study, three hospitals were private and six had both public

Table 4. Species distribution and treatment of 672 episodes of candidemia by age strata.

	Neonates N = 89	Infants N = 70	Older children N = 138	Adults N = 223	Elderly N = 152	Overall N = 672
Species distribution						
Candida albicans	39 (43.8)	34 (48.6)	41 (29.7)	75 (33.6)	64 (42.1)	253 (37.6)
Candida parapsilosis	24 (27.0)	17 (24.3)	39 (28.3)	67 (30.0)	31 (20.4)	178 (26.5)
Candida tropicalis	13 (14.6)	6 (8.6)	22 (15.9)	49 (22.0)	28 (18.4)	118 (17.6)
Candida guilliermondii	4 (4.5)	11 (15.7)	16 (11.6)	9 (4.0)	4 (2.6)	44 (6.5)
Candida glabrata	3 (3.4)	1 (1.4)	5 (3.6)	10 (4.5)	23 (15.1)	42 (6.3)
Candida krusei	4 (4.5)	–	5 (3.6)	9 (4.0)	–	18 (2.7)
Received antifungal therapy	71 (79.8)	64 (91.4)	122 (88.4)	191 (85.6)	126 (82.9)	574 (85.4)
Primary treatment*						
Fluconazole	25/71 (35.2)	37/64 (57.8)	76/122 (62.3)	141/191 (73.8)	99/126 (78.6)	378/574 (65.8)
d-AMB	39/71 (54.9)	21/64 (32.8)	39/122 (32.0)	27/191 (14.1)	13/126 (10.3)	139/574 (24.2)
Caspofungin	4/71 (5.6)	–	3/122 (2.4)	14/191 (7.3)	8/126 (6.3)	29/574 (5.0)
Anidulafungin	–	3/64 (4.7)	1/122 (0.8)	3/191 (1.6)	4/126 (3.2)	11/574 (1.9)
Voriconazole	2/71 (2.8)	1/64 (1.6)	1/122 (0.8)	6/191 (3.1)	2/126 (1.6)	12/574 (2.1)
l-AMB	1/71 (1.4)	2/64 (3.1)	2/122 (1.6)	–	–	5/574 (0.9)
15-day survival**	56 (64.4)	47 (74.6)	95 (76.0)	137 (64.9)	56 (39.4)	391 (62.3)
30-day survival***	46 (59.7)	44 (73.3)	84 (73.7)	120 (61.9)	52 (37.7)	346 (59.3)

NOTE: Numbers are no. (%) of patients; d-AMB = deoxycholate amphotericin B; l-AMB = lipid formulation of amphotericin B.
Infants defined as children older than 28 days and younger than 1 year; Elderly defined as patients older than 60 years.
*In 12 episodes no information was available regarding antifungal treatment.
**Data available in 628 episodes.
***Data available in 583 episodes.
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and private coverage. Therefore, it is possible that these differences may partly explain the great variety in the incidence of candidemia observed across countries and across centers within a country. Although speculative, other factors that may have contributed to this variation include the characteristics of the hospitals, with different patient populations and standards of prophylaxis and empiric therapy.

In our study, species distribution confirmed that in Latin America, *C. albicans*, *C. parapsilosis* and *C. tropicalis* account for more than 80% of episodes of candidemia, *C. parapsilosis* is not clustered in children, and the frequency of *C. glabrata* candidemia is lower than that reported in the Northern Hemisphere [25]. However, there were some important differences across countries. For example, Brazil had the highest proportion of candidemia due to *C. glabrata* (10%). A trend for an increase in the incidence of *C. glabrata* candidemia in Brazilian hospitals has been recently reported in two studies. In a single-center study, the proportion of *C. glabrata* increased from 4.8% in 2008 to 23.5% in 2010. No association between fluconazole use and the increase in *C. glabrata* candidemia was observed [34]. By contrast, another study observed a higher proportion of candidemia due to *C. glabrata* in private hospitals compared to public hospitals. Patients from private hospitals were more likely to have been exposed to fluconazole, and *C. glabrata* isolates from private hospitals were less susceptible to fluconazole [37]. In the present study, we did not observe an association between fluconazole exposure and candidemia due to *C. glabrata*. On the other hand, *C. glabrata* candidemia was more frequent in elderly patients, as reported elsewhere [38]. Interestingly, Brazilian patients (the country with the highest proportion of *C. glabrata*) were significantly older than patients from other countries (median age 45 years vs. 20 years, $p<0.001$). Furthermore, the proportion of isolates with resistance to fluconazole was low (6.5% only). Taken together, it seems that there are two epidemiologic scenarios of candidemia due to *C. glabrata*: one that is driven by older age, typically with more fluconazole-susceptible isolates, and other driven by selective pressure of fluconazole use, with less-susceptible isolates. More studies are needed to confirm this hypothesis.

Our study confirmed that *C. parapsilosis* is very prevalent in Latin America, and is distributed in all age strata, contrasting to studies from other parts of the globe, in which this species is more frequent among neonates [39]. We also observed a high proportion of candidemia episodes caused by *C. guilliermondii*. The majority of cases occurred in Honduras, mostly in children. A pseudo-outbreak of *C. guilliermondii* candidemia was reported in a center in Brazil, with most cases occurring in pediatric patients [40]. The pseudo-outbreak was suspected because of the cluster of cases in time and place, and also because the large majority of patients did not have the typical risk factors for candidemia or had clinical manifestations of infection. In the present study, we performed a careful review of the clinical characteristics of the cases, including risk factors, antifungal treatment and outcome, and did not find any feature suggestive of a pseudo-outbreak.

The antifungal susceptibility tests confirmed previous studies [25], with very low rates of resistance, except for *C. glabrata* and *C. krusei* and fluconazole. In addition, we observed two *C. glabrata* isolates (4.3%) exhibiting higher MICs to anidulafungin. The clinical relevance of these findings is unknown because although epidemiologic breakpoints for the echinocandins have been proposed [26], the correlation between MIC and the outcome is still uncertain. However, caution should be taken since sporadic cases of therapeutic failure with echinocandins have been reported in candidemia due to *C. glabrata* [41], and data on an animal model

Table 5. *In vitro* susceptibility of *Candida* species to four antifungal agents.

Species (N)	Antifungal agent	MIC* (μg/ml)			SDD or I, n (%)	Resistant, n (%)
		Range	MIC 50	MIC 90		
C. albicans (253)	Amphotericin B	0.125–1.0	0.5	1.0	NA	0
	Fluconazole	0.125–4.0	0.125	0.5	1 (0.4)	0
	Voriconazole	0.03–0.125	0.03	0.03	0	0
	Anidulafungin	0.03–0.5	0.03	0.125	1 (0.4)	0
C. parapsilosis (178)	Amphotericin B	0.25–1.0	0.5	1.0	NA	0
	Fluconazole	0.125–4.0	0.25	1.0	2 (1.1)	0
	Voriconazole	0.03–0.25	0.03	0.25	0	0
	Anidulafungin	0.03–2.0	1.0	2.0	0	0
C. tropicalis (118)	Amphotericin B	0.25–1.0	0.5	1.0	NA	0
	Fluconazole	0.125–1.0	0.25	0.5	0	0
	Voriconazole	0.03–0.125	0.03	0.03	0	0
	Anidulafungin	0.03–0.5	0.03	0.25	2 (1.7)	0
C. guilliermondii (44)	Amphotericin B	0.25–1,0	0.5	1.0	NA	0
	Fluconazole	0.125–16	2.0	8.0	ND	ND
	Voriconazole	0.03–0.5	0.06	0.25	0	0
	Anidulafungin	0.03–2.0	1.0	2.0	ND	ND
C. glabrata (42)	Amphotericin B	0.25–1.0	0.5	1.0	NA	0
	Fluconazole	0.25–64	4.0	16	39 (92.9)	3 (7.1)
	Voriconazole	0.03–2.0	0.125	0.5	0	0
	Anidulafungin	0.03–0.25	0.06	0.125	2 (4.8)	0
C. krusei (18)	Amphotericin B	0.5–1.0	0.5	1.0	NA	0
	Fluconazole	8.0–32	16	32	0	18 (100)
	Voriconazole	0.03–0.25	0.125	0.25	0	0
	Anidulafungin	0.03–0.125	0.06	0.125	0	0

MIC = minimal inhibitory concentration; SDD = susceptible, dose-dependent; I = intermediate; NA = not applicable; ND = not defined.
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suggested that the echinocandins have a fungistatic effect against this species [42].

In the present study, almost 15% of patients did not receive treatment. The most likely reason was late diagnosis, since the majority of such patients died very early after the incident candidemia. Fluconazole was the leading agent given as primary treatment. Echinocandins were used infrequently despite their excellent attributes for the treatment of candidemia, probably because of its high price compared with deoxycholate amphotericin B and fluconazole. Another interesting observation was that elderly patients were much less likely to have received deoxycholate amphotericin B as primary therapy.

A limitation of our study is that although 21 centers from seven Latin American countries participated, this may not be representative of each country, especially those with higher population and bigger territory, such as Argentina and Brazil. Nevertheless, this is the first attempt to estimate the burden and to characterize the epidemiology of candidemia in the region. Additional studies are needed to expand the epidemiology of candidemia in individual countries, especially those with no data. In addition, a better characterization of the epidemiology of candidemia in the pediatric population is warranted, considering the high burden and consequences of candidemia in these patients.

In conclusion, this first large epidemiologic study of candidemia in Latin America showed similar findings as studies conducted in Brazil: high incidence, high percentage of children, typical species distribution, with *C. albicans*, *C. parapsilosis* and *C. tropicalis* accounting for the majority of episodes, and low resistance rates.

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Reviewed the manuscript, significantly contributed to its scientific content and approved the final version of it: MN FQT TAM INT JC JZ MGB MES LT JIE JSO ALC. Conceived and designed the experiments: MN ALC. Performed the experiments: MN FQT TAM INT JC JZ MGB MES LT ALC. Analyzed the data: MN ALC. Contributed reagents/materials/analysis tools: MN FQT TAM INT JC JZ MGB MES LT JIE JSO ALC. Wrote the paper: MN.

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Infecciones fúngicas invasivas en niños hospitalizados en un centro de referencia de Uruguay

Invasive fungal infections in children hospitalized at a Pediatric Reference Hospital in Uruguay

Infecções fúngicas invasivas em crianças internadas em um Centro Hospitalar de Referência no Uruguai

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Resumen

Introducción: las infecciones fúngicas invasivas (IFI) son un problema de salud en creciente aumento.
Objetivo: describir las características epidemiológicas, microbiológicas y clínicas de los menores de 15 años con IFI hospitalizados en el Hospital Pediátrico, Centro Hospitalario Pereira Rossell entre 2010- 2019.
Metodología: estudio retrospectivo, mediante revisión de historias clínicas. Variables: edad, sexo, comorbilidades, factores de riesgo, clínica, patógenos, tratamiento y evolución.
Resultados: se registraron 26 casos de IFI en 23 niños. La mediana de edad fue 8 años, de sexo femenino 17, con comorbilidades 17: infección por VIH 5, enfermedad hematooncológica 4. Todos presentaban factores de riesgo para IFI. Las manifestaciones clínicas de sospecha fueron: fiebre en 19, síntomas neurológicos 11, respiratorios 9, gastrointestinales 6, urinarios 2, sepsis/shock en 3. Los agentes identificados fueron: *Candida spp* en 14, *Cryptococcus neoformans complex* 8 y *Aspergillus fumigatus complex* 4.
Tratamiento: se indicó fluconazol en 15, asociado a anfotericina B 11. Todas las infecciones por candida fueron sensibles a los azoles. Fallecieron 7 niños, la mediana de edad fue 1 año. En 4 se identificó *Candida spp*, *Aspergillus fumigatus complex* 2 y *Cryptococcus neoformans complex* 1.
Conclusiones: las IFI son poco frecuentes, afectan en su mayoría a niños inmunocomprometidos asociando elevada mortalidad. El diagnóstico requiere alto índice de sospecha. *Candida spp* y *Cryptococcus spp* fueron los agentes más involucrados. El inicio precoz del tratamiento acorde a la susceptibilidad disponible se asocia a menor mortalidad.

Palabras clave: Infecciones fúngicas invasoras
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Summary

Introduction: invasive fungal infections (IFI) are an increasing health problem.

Objective: describe the epidemiological, microbiological and clinical characteristics of children under 15 years of age with IFI hospitalized at the Pereira Rossell Hospital Center between 2010-2019.

Methodology: retrospective study, review of medical records. Variables: age, sex, comorbidities, risk factors, symptoms, pathogens, treatment and evolution.

Results: 26 cases of IFI were recorded involving 23 children. Median age 8 years, female 17, comorbidities 17, HIV infection 5, hematological-oncological disease 4. All with risk factors. Suspicion symptoms: fever 19, neurological symptoms 11, respiratory 9, gastrointestinal 6, urinary 2, sepsis / shock 3. Identified agents: *Candida* spp 14, *Cryptococcus neoformans complex* 8 and *Aspergillus fumigatus complex* 4.

Treatment: fluconazole 15, associated with amphotericin B 11. All candida infections were sensitive to azoles. 7 died, median age 1 year. In 4, *Candida spp* was isolated, *Aspergillus fumigatus complex* in 2 and *Cryptococcus neoformans complex* in 1.

Conclusions: IFI are rare, mostly affecting immunocompromised children, associated with high mortality. The diagnosis requires a high index of suspicion. Candida spp and Cryptococcus spp were the most involved agents. Early treatment according to available susceptibility is associated with lower mortality

Key words: Invasive fungal infections
Child

Resumo

Introdução: as infecções fúngicas invasivas (IFI) são um problema de saúde crescente.

Objetivo: descrever as características epidemiológicas, microbiológicas e clínicas de crianças menores de 15 anos com IFI internadas no Centro Hospitalar Pereira Rossell entre 2010 e 2019.

Metodologia: estudo retrospectivo, revisão de prontuários. Variáveis: idade, sexo, comorbidades, fatores de risco, sintomas, patógenos, tratamento e evolução.

Resultados: foram registrados 26 casos de IFI em 23 crianças. Idade mediana 8 anos, sexo feminino 17, comorbidades 17, infecção por HIV 5, doença hemato-oncológica 4. Todos com fatores de risco. Suspeita clínica: febre 19, sintomas neurológicos 11, respiratórios 9, gastrointestinais 6, urinários 2, sepse/choque 3. Agentes identificados: *Candida spp* 14, *Cryptococcus neoformans complexo* 8 e *Aspergillus fumigatus complexo* 4.

Tratamento: fluconazol 15, associado à anfotericina B 11. Todas as infecções por cândida foram sensíveis aos azóis. 7 morreram, idade média de 1 ano. Em 4 das crianças *Cândida spp* foi isolada, *Aspergillus fumigatus complexo* em 2 e *Cryptococcus neoformans complexo* em 1.

Conclusões: IFIs são raras, afetando principalmente crianças imunocomprometidas, associadas a alta mortalidade. O diagnóstico requer alto índice de suspeita. *Cândida spp* e *Cryptococcus spp* são os agentes mais envolvidos. O tratamento precoce de acordo com a suscetibilidade disponível está associado a menor mortalidade.

Palavras chave: Infecções fúngicas invasivas,
Criança

Introducción

Las infecciones fúngicas invasivas (IFI) en la infancia constituyen un problema de salud en creciente aumento[1-4]. Dado que sus manifestaciones clínicas son inespecíficas, en ocasiones el diagnóstico puede ser tardío, provocando una elevada morbimortalidad[1-7].

La prevalencia de las IFI no es del todo conocida, las series pediátricas incluyen definiciones operativas diferentes[1-10]. En Uruguay el espectro de especies de hongos no es tan amplio como en otros países de Latinoamérica. La notificación de infecciones fúngicas no es obligatoria, por lo que no existen registros completos[11].

Algunas de las IFI probablemente se encuentren en crecimiento, vinculadas al aumento de la población inmunodeprimida, secundarias a la infección del virus de la inmunodeficiencia humana (VIH), al trasplante de órganos sólidos, médula ósea y al uso prolongado de fármacos inmunodepresores[1-10]. En 2018 Macedo-Viñas y colaboradores estimaron que en Uruguay cerca de 127.968 adultos y niños (3.716/100.000) padecían infecciones fúngicas graves al año[11].

La epidemiología y el agente fúngico involucrado varían según la comorbilidad subyacente, la presencia de factores de riesgos, existencia de profilaxis, sensibilidad de los estudios diagnósticos utilizados y la adherencia a los tratamientos específicos para cada situación clínica[1-5].

Los principales agentes responsables de IFI en la infancia son *Candida* spp*, Aspergillus* spp*, Cryptococcus* spp*, Histoplasma capsulatum, Coccidioides immitis, Paracoccidioides* spp*. y Fusarium* spp[1-10].

La literatura describe la existencia de diversos factores de riesgo para presentar IFI, algunos son compartidos por los diferentes agentes fúngicos, otros son característicos a una IFI en particular[1-7]. En las IFI por *Candida* spp se describen como factores de riesgo los recién nacidos prematuros con muy bajo o extremo bajo peso al nacer sometidos a procedimientos invasivos, niños con inmunodeficiencias primarias o adquiridas, enfermedades hematooncológicas con neutropenias severas persistentes, el paciente crítico con estadías prolongadas en cuidados intensivos, que requieren: procedimientos invasivos (catéteres venosos profundos, sonda endotraqueal, sonda vesical); cirugías abdominales, gastrointestinales o genitourinarias; alimentación parenteral; uso prolongado de antibioticoterapia de amplio espectro, glucocorticoides, inmunosupresores, inhibidores de la bomba de protones[1-7].

Para la IFI por *Aspergillus* spp se reportan como factores de riesgo la presencia de alguna inmunodeficiencia primaria, sobre todo la enfermedad granulomatosa crónica, y las enfermedades hematooncológicas como leucemias y tumores sólido con neutropenias persistentes, necesidad de uso de catéteres venosos profundos, alimentación parenteral, y la presencia de complicaciones vinculadas a la inmunodepresión como el uso de corticoides, la enfermedad injerto contra huésped y la infección por citomegalovirus[1-7]. Se describen como factores de riesgo para IFI por *Cryptococcus* spp la presencia de una inmunodeficiencia primaria o secundaria moderada a severa, sobre todo secundaria a infección por VIH. La baja adherencia al tratamiento antirretroviral y a la profilaxis con fluconazol, así como la desnutrición proteico calórica y la exposición a excretas de palomas y otras aves de corral son otros factores de riesgo[1-5,8,9].

La mayoría de los estudios de IFI en niños han analizado la incidencia y prevalencia de candidiasis invasivas (CI), otros únicamente las candidemias. La incidencia de CI en series internacionales es de 35-52 casos/100.000 niños hospitalizados[12,13]. En Uruguay Decia y colaboradores reportaron en la unidad de cuidados intensivos de niños del Centro Hospitalario Pereira Rossell (CHPR), una incidencia de CI de 0,23 casos cada 1.000 días/paciente, con una prevalencia de 0,18%[6].

Algunas características epidemiológicas, clínicas y terapéuticas de las IFI son comparables con los pacientes adultos, pero existen particularidades que deben ser reconocidas por los pediatras, sobre todo sus manifestaciones clínicas. Otro punto desafiante constituye el abordaje terapéutico. La mayoría de los azoles requieren monitorización de sus niveles terapéuticos para optimizar la eficacia y seguridad. Las recomendaciones de profilaxis y tratamiento se encuentran en continua actualización[5,6].

Son escasas las publicaciones sobre IFI en pediatría en nuestro medio, por lo que caracterizar este problema de salud podría contribuir a mejorar las prácticas asistenciales en una patología poco frecuente, pero de elevada morbimortalidad.

Objetivos

Describir las características epidemiológicas, microbiológicas y clínicas de los menores de 15 años con IFI hospitalizados en el Hospital Pediátrico-CHPR (HP-CHPR)entre 2010 y 2019.

Material y métodos

Se realizó un estudio observacional, descriptivo, retrospectivo en el que se incluyeron todos los menores de 15 años con diagnóstico de IFI confirmada por estudio micológico (examen directo en fresco, examen

directo con tinta china, coloraciones y cultivos), ingresados en el HP-CHPR, entre 2010 y 2019.

Se excluyeron los recién nacidos hospitalizados en el Servicio de Neonatología del Hospital de la Mujer, CHPR.

Se consideraron como dispositivos invasivos que favorecen a la IFI: vías venosas profundas, sonda endotraqueal, sonda vesical, catéter de Tenckhoff, dispositivos de diálisis peritoneal, dispositivos de drenaje torácico, sistema de derivación ventricular externo, dispositivo de alimentación parenteral, y otros.

Los casos se enrolaron a través de la base de datos informatizada del laboratorio de Parasitología y Micología del CHPR. La fuente de datos fueron las historias clínicas y los registros de laboratorio.

Se registraron las siguientes variables: edad, sexo, comorbilidades (inmunodepresión congénita o adquirida, enfermedades crónicas), factores de riesgo de IFI según agente fúngico, manifestaciones clínicas al momento del diagnóstico (fiebre, síntomas respiratorios, digestivos, urinarios, neurológicos, sepsis, otros), estudios diagnósticos (estudio micológico, agente identificado), días de hospitalización, tratamientos (fármacos, efectos adversos), y evolución (complicaciones, fallecimientos).

En el laboratorio de Parasitología y Micología del CHPR se procesaron muestras biológicas para estudio micológico e identificación de hongos aislados en el laboratorio de microbiología a partir de hemocultivos y punta de catéter a los cuales se les había realizado estudios bacteriológicos.

A las muestras biológicas se les realizó examen directo en fresco con solución fisiológica, examen directo en fresco con tinta china, tinciones permanentes y cultivos en agar Sabouraud (AS), AS con cloranfenicol y medio selectivos con cicloheximida. La identificación de los mohos se realizó por los métodos fenotípicos clásicos (microscopía y macroscopía); la identificación de levaduras también se hizo por las características fenotípicas y fisiológicas (pruebas bioquímicas) disponibles en nuestro laboratorio al momento de aislar las cepas.

El mayor porcentaje de las especies de levaduras se identificó y se valoró la susceptibilidad a los antifúngicos (ATF) con el equipo VITEK 2 (bioMérieux, Marcy-L'Etoile, France, database v.3.01), los antifúngicos testeados fueron: anfotericina B, fluconazol, 5-flucitosina, voriconazol, caspofungina y micafungina. En nuestro país los métodos de microdilución en placa para ATF, se realizan en centros de referencia y control epidemiológico, otras técnicas como la espectrometría de masas (MALDI), no está disponible en este centro asistencial.

Las variables continuas se describieron mediante mediana y rangos, y las discretas con frecuencias absolutas y relativas. El análisis de datos se realizó con el programa Epi Info 7.

Los datos de los usuarios se manejaron con total anonimato, salvaguardando la confidencialidad y el secreto médico. Se contó con la aprobación del Comité de Ética de investigación de la institución.

Resultados

Durante el período de estudio se registraron 26 casos de IFI en 23 niños; tasa 2,21/10.000 egresos. La mediana de edad al ingreso fue 8 años (1 mes-15 años), 17 eran de sexo femenino. Presentaban comorbilidades previas 17 casos, las más frecuentes inmunodepresión secundaria a infección por VIH 5 y enfermedades hematooncológicas 4. Los 5 niños con VIH adquirieron la infección por transmisión vertical. Al ingreso hospitalario 3 presentaban inmunodepresión severa y 2 inmunodepresión moderada.

Presentaban factores de riesgo para desarrollar IFI los 23 niños incluidos. Al analizar la presencia de factor de riesgo según agente fúngico involucrado, se encontró que los niños con IFI por *Candida* spp habían presentado ingreso a cuidados intensivos (UCI) 14/14; utilizado dispositivos invasivos 14/14 (vías venosas profundas 14, sonda endotraqueal 10, sonda vesical 7, alimentación parenteral 6, catéter de Tenckhoff 3, tubo de tórax 3); utilizados antibióticos de amplio espectro 14/14; inhibidores de la bomba de protones 12/14; corticoides 6/14; inmunosupresores 3/14; y requirieron cirugías mayores abdomino- pélvicas 5/14.

En los niños con IFI secundarias a *Aspergillus* spp se encontró como factor de riesgo la presencia de una enfermedad hematooncológica en 4/4; neutropenia severa prolongada en 4/4, uso de catéter venoso profundo en 3/4, y uso de corticoides o inmunosupresores 2/4.

En los casos con IFI secundarias a *Cryptococcus* spp 4/5 presentaban inmunodeficiencias moderadas a severas secundarias a infección por VIH con baja adherencia a la terapia antirretroviral y a la profilaxis con fluconazol, un niño presentaba inmunodeficiencia primaria combinada severa. En la tabla 1 se expresan las características de la población de niños incluidos.

La fiebre fue la manifestación clínica que orientó la sospecha diagnóstica de IFI en 19/23 casos. En la tabla 2 se presentan las manifestaciones clínicas según agente fúngico identificado.

Las IFI se confirmaron mediante estudio de líquido cefalorraquídeo en 8, líquido peritoneal 6, hemocultivo 6, cultivo de lavado bronquioloalveolar (LBA) 3, biopsia esofágica 2, urocultivo uno. En los casos que se obtuvo cultivo de LBA, los tres presen-

Tabla 1. Infecciones fúngicas invasivas en menores de 15 años hospitalizados en el CHPR, 2010- 2019. Características epidemiológicas y clínicas (N=23).

Variable	Frecuencia absoluta
Sexo	
Femenino	17
Masculino	6
Comorbilidades	17
Infección por virus de la inmunodeficiencia humana	5
Enfermedad hemato oncológica	4
Leucemia linfoide aguda	2
Leucemia mieloide aguda	2
Enfermedad renal crónica	3
GNRP primaria.	1
HFS corticorresistente y sin respuesta a inmunosupresores	1
Síndrome urémico hemolítico.	1
Inmunodeficiencia primaria combinada severa	1
Cardiopatía congénita	1
Comunicación interventricular perimembranosa	1
Hiperinsulinismo congénito	1
Prematurez	1
Atresia de la vía biliar	1

Los tres casos de enfermedad renal crónica no presentaban tratamiento de sustitución de la función renal.
GNRP: glomerulonefritis rápidamente progresiva; HFS: hialinosis focal y segmentaria.

Tabla 2. Manifestaciones clínicas según agente fúngico identificado (N=23).

Síntomas y signos	Infección por *Candida* spp Frecuencia absoluta	Infección por *Cryptococcus neoformans complex** Frecuencia absoluta	Infección por *Aspergillus fumigatus complex* Frecuencia absoluta
Fiebre	12	5	2
Síntomas respiratorios Rinorrea, tos, polipnea	2	0	4
Síntomas gastrointestinales Vómitos, diarrea, dolor abdominal	4	2	0
Síntomas neurológicos* Cefaleas, alteraciones visuales, vómitos, focalidad neurológica	0	8	0
Sepsis y/o shock séptico	2	0	1
Síntomas urinarios Disuria, polaquiuria, tenesmo, dolor lumbar.	1	0	0

*Se registraron 3 casos de nueva IFI durante el periodo de estudio, todos a forma de meningoencefalitis por *Cryptococcus neoformans*.

taban muguet oral, imágenes compatibles con neumonitis fúngica, ventilación mecánica prolongada, un caso presentaba infección por VIH y en dos se sospechaba inmunodeficiencia primaria no confirmada. En el niño en que la IFI se confirmó por urocultivo, la muestra se tomó mientras presentaba cateterismo vesical a permanencia, pero junto a la candiduria se identificaron imágenes ecográficas intrarrenales ovales, móviles y ecogénicas interpretadas como nidos fúngicos o fungomas que no se puncionaron. El niño presentó múltiples urocultivos sin desarrollo de agentes bacterianos.

Los agentes de IFI identificados fueron *Candida* en 14 casos (*Candida albicans* 5, *Candida parapsilosis* 3, *Candida* sp *3, Candida lusitaniae* 1, *Candida tropicalis 1, Candida glabrata 1*), *Cryptococcus neoformans complex* en 8 y *Aspergillus fumigatus complex* en 4. En la tabla 3 se muestran los agentes

Tabla 3. Agentes fúngicos y tipo de muestra analizada. (N=23)

Agente fúngico y muestra analizada	Frecuencia absoluta
Candida spp	14
Hemocultivo	6
Cultivo de líquido peritoneal	5
Biopsia esofágica	2
Urocultivo	1
*Cryptococcus neoformans complex**	8
Cultivo de líquido cefalorraquídeo	8
Aspergillus fumigatus complex	4
Cultivo de lavado bronquiolo alveolar	3
Cultivo de líquido peritoneal	1

*Se registraron 3 casos de nueva IFI durante el periodo de estudio, todos a forma de meningoencefalitis por *Cryptococcus neoformans*.

Tabla 4. Tratamientos y agente de infecciones fúngicas invasivas identificados. (N=23)

Agente etiológico	Antifúngico	Frecuencia absoluta
Candida spp	Fluconazol	5
	Anfotericina B	3
	Fluconazol y anfotericina B	2
	Anfotericina B y caspofungina	2
	Caspofungina	1
	Voriconazol	1
Cryptococcus neoformans complex	Fluconazol y anfotericina B	8
Aspergillus fumigatus complex	Caspofungina	2
	Fluconazol y anfotericina B	1
	Fluconazol y voriconazol	1

fúngicos identificados en función del tipo de muestra analizada.

Se indicaron antifúngicos endovenosos en todos los casos, recibieron fluconazol 16, asociado a anfotericina B 11/16, caspofungina 5, anfotericina B sola 3 y voriconazol 2 niños. La mediana de duración de los tratamientos fue 20 días (1-90). Con el método de susceptibilidad a los ATF, utilizado, no se encontraron cepas resistentes a los azoles, anfotericina B ni a caspofungina.

Se encontró registro de dos casos de hipopotasemias leves, durante el uso combinado de fluconazol y anfotericina B. En la tabla 4 se muestran los tratamientos antifúngicos indicados según el agente.

La mediana de días de hospitalización fue 35 (rango 1–176 días), la mediana de días en UCI fue de 20 (rango 1-150 días). Durante el periodo de estudio tres niños presentaron una nueva IFI, todos a forma de meningoencefalitis criptococócica, dos de ellos eran portadores de VIH, y el tercero presentaba inmunodeficiencia combinada severa. En los dos casos portadores de VIH, la nueva infección se asoció a abandono de tratamiento de profilaxis secundaria con fluconazol y al tratamiento antirretroviral.

Fallecieron 7 niños (letalidad 30%), todos en UCI, mediana de edad 1 año (rango 3 meses- 14 años), de sexo femenino 5. En 4 casos se aisló *Candida* spp, en líquido peritoneal 2 (*C albicans y C parapsilosis*) y 2 en hemocultivo (*C albicans y C tropicalis*). En 2 niños se identificó *Aspergillus fumigatus complex*, en líquido peritoneal 1 y el otro en secreciones respiratorias. El séptimo niño presentó meningitis por *Cryptococcus neoformans complex*. En la tabla 5 se expresan las características de los niños fallecidos con IFI.

Discusión

La literatura describe como poblaciones más vulnerables a IFI en especial a la infección por *Candida* spp a los neonatos prematuros, especialmente menores de 1000 gramos y a niños portadores de inmunodeficiencias primarias o adquiridas. Otros grupos de riesgo son los desnutridos y los gravemente enfermos que requieren estadías prolongadas en UCI[1-7]. Esta serie no incluyó neonatos, por razones de organización estos se hospitalizan en el Servicio de Neonatología perteneciente al Hospital de la Mujer, que cuenta con salas de cuidados moderados y UCI neonatal.

La comorbilidad más frecuente identificada fue la inmunodepresión secundaria a infección por VIH, seguida por enfermedades hematooncológicas. En estos grupos particulares de niños pueden identificarse la existencia de factores favorecedores al desarrollo de IFI, estos factores varían según el agente fúngico involucrado, como se mencionó previamente[1-10,12,14-20].

En niños con infección por VIH son factores de riesgo para desarrollar IFI y sobre todo para infección por *Cryptococcus* spp la presencia de: inmunosupresión moderada a severa y la mala adherencia a la terapia antirretroviral como ocurrió en esta serie[8,9,18,19]. Es rara la presentación de esta infección en niños previamente sanos[8,9,18,19].

En niños con enfermedades hematooncológicas, segunda comorbilidad más frecuente en esta serie, las neoplasias que más se asocian a IFI sobre todo a infecciones secundarias a *Aspergillus* spp son las leucemias, seguidas por los tumores sólidos[1-5,14-17,20]. Se describen factores asociados vinculados al huésped como presencia de mucositis (mayoritariamente en relación a candidiasis) y colonización previa por agentes fúngicos; y factores relacionados a la enfermedad y sus tratamientos. Entre estos últimos la presencia de neutropenia prolongada, necesidad de procedimientos invasivos, cirugías, quimioterapia y

Tabla 5. Características de los niños fallecidos con infecciones fúngicas invasivas (N=7).

Caso	Edad	Sexo	Comorbilidad	Factores de riesgo	Agente de MP y topografía	Tratamiento y duración
1	1 año	Masculino	Leucemia mieloide aguda	Dispositivos invasivos Inhibidores secreción gástrica	*Aspergillus fumigatus complex* (secreciones respiratorias)	Anfotericina B y fluconazol (10 días)
2	3 meses	Femenino	Hiperinsulinismo congénito	Dispositivos invasivos Antibióticos de amplio espectro	*Candida* spp (hemocultivo)	Caspofungina (3 días)
3	6 meses	Femenino	Atresia de la vía biliar	Dispositivos invasivos Antibióticos de amplio espectro Corticoides Alimentación parenteral Cirugía abdominal	*Candida* spp (líquido peritoneal)	Anfotericina B y caspofungina (15 días)
4	13 años	Femenino	Ninguna	Dispositivos invasivos Antibióticos de amplio espectro Corticoides	*Candida* spp (hemocultivo)	Fluconazol (20 días)
5	1 año	Femenino	Síndrome uremico hemolítico	Dispositivos invasivos Inhibidores secreción gástrica	*Aspergillus fumigatus complex* (líquido peritoneal)	Caspofungina (22 días)
6	14 años	Femenino	Herida de arma de fuego abdominal	Dispositivos invasivos Antibióticos de amplio espectro Inhibidores secreción gástrica Corticoides Alimentación parenteral Cirugía abdominal	*Candida* spp (líquido peritoneal)	Caspofungina (6 días)
7	7 años	Masculino	Virus de la inmunodeficiencia humana	Dispositivos invasivos Antibióticas de amplio espectro Inhibidores secreción gástrica	*Cryptococcus neoformans complex* (líquido cefalorraquídeo)	Anfotericina B y fluconazol (42 días)

las complicaciones vinculadas a la inmunosupresión, similar a los datos presentados en esta serie[1-5,14-17,20].

La sintomatología de presentación de las diversas IFI son variadas e inespecíficas, lo que determina retraso diagnóstico. Los síntomas varían según el agente fúngico involucrado y la localización de la IFI. En este grupo particular de niños y adolescentes la fiebre fue el síntoma que más frecuentemente guió la sospecha diagnóstica, siendo acompañada en algunos casos por otros síntomas según la localización[1-7,14-17].

La infección por *Candida spp* suele presentarse la mayoría de las veces con fiebre, sola o acompañada de vómitos, deposiciones líquidas y/o síntomas respiratorios como ocurrió en esta serie. En neonatos y lactantes pequeños la fiebre puede estar ausente. La candidiasis sistémica puede acompañarse de shock en 30%[5,12-16].

En la infección por *Cryptococcus* spp, la manifestación clínica más frecuente fue la fiebre acompañada de cefalea y vómitos. Esta levadura capsulada tiene

predilección por el sistema nervioso central (SNC), siendo la meningoencefalitis su principal forma de presentación[9,14-19].

La infección por *Aspergillus* spp, sobre todo la aspergilosis invasiva suele cursar con fiebre persistente en el contexto de neutropenia prolongada. La afectación pulmonar (50%), se presenta con tos, disnea y dolor pleurítico, en oportunidades los síntomas son inespecíficos y la fiebre puede faltar, al igual que lo encontrado en este trabajo[1-5,7,14-17,20,21]. En niños suele ser menos frecuente la presentación cerebral, rinosinusal e intestinal[5,7,20,21].

La confirmación diagnóstica representa un gran desafío. El cultivo, la microscopía y la histopatología continúan siendo el patrón de oro para el diagnóstico microbiológico pero con frecuencia no identifican ningún agente fúngico. Los hemocultivos presentan baja sensibilidad para identificar agentes fúngicos, reportándose sensibilidades menores a 50% para *Candida* spp y menor a 5% para *Aspergillus* spp[5,14-17].

En los casos de sospecha de IFI con compromiso del SNC será necesario el estudio del líquido cefalorraquídeo en fresco con tinta china, siendo este método de baja sensibilidad pero específico para confirmar la meningitis criptococócica[8,9,14-19].

Es posible que estas dificultades diagnósticas y el excluir a los neonatos pudieran contribuir en haber identificado únicamente 26 casos de IFI en los últimos 10 años en este centro de referencia de Uruguay.

Es importante en niños con factores de riesgo para desarrollar IFI mantener un alto índice de sospecha e interpretar adecuadamente alteraciones analíticas inespecíficas como hiperglucemia, trombocitopenia o acidosis metabólica, complementados con estudios imagenológicos según el agente fúngico y topografía de la afectación sospechada[5,6,14-17,21].

En esta serie, al tratarse de un estudio retrospectivo, no se pudo relevar información sobre el uso de biomarcadores de infección micótica en este centro asistencial. Las pruebas no invasivas basadas en biomarcadores, como el beta-D-glucano (BDG), manano, antimanano y galactomanano, son los métodos sin cultivo más convenientes para el diagnóstico de IFI en pacientes sintomáticos, y en asintomáticos de alto riesgo así como también para monitorear la respuesta terapéutica[1-4]. En la aspergilosis pulmonar invasiva la sensibilidad del galactomanano en suero y LBA es similar al adulto para niños con enfermedad hemato-oncológica, pero varía en niños con inmunodeficiencias primarias y adquiridas. Ante la presencia de factores de riesgo y un cuadro clínico compatible para IFI estos biomarcadores podrían ser de utilidad para decidir el inicio de un antifúngico[4,22,23].

La reacción en cadena de la polimerasa (PCR) multiplex obtenida de sangre, LBA o líquido cefalorraquídeo, podría ser útil para el diagnóstico de IFI grave, si bien la sensibilidad para *Cryptococcus neoformans* suele ser baja. Los resultados respecto a sensibilidad y especificidad para los diferentes agentes fúngicos necesitan ser validados en niños [14-17,24,25].

Si bien no todas las series pediátricas incluyen el análisis de IFI o profundas por mohos y levaduras de forma simultánea, la literatura refiere como los principales agentes patógenos a especies del género *Candida* seguida por *Aspergillus*[1-5,7,8,14-17]. En los casos de candidiasis invasora la especie aislada con más frecuencia al igual que en adultos es *C. albicans*, seguida por *C. parapsilosis* y *C. tropicalis* al igual que lo identificado en esta serie[5,6,25,26,27].

Cryptococcus neoformans complex fue el segundo agente fúngico más identificado. En Uruguay se realiza en forma sistemática la identificación de la especie de *Cryptococcus*. Carbia y colaboradores analizaron 147 aislamientos de *Cryptococcus* entre los años 2006-2012, en distintos centros asistenciales de Uruguay aislados en muestras de pacientes con VIH en 91,8%. *C. neoformans* variante *grubii* fue la especie más identificada (74,1%), seguida de *C. neoformans* var. *neoformans* (23,1%). Este dato coincide con estudios internacionales previos. En esta serie los 5 casos en que se identificó *Cryptococcus neoformans complex* eran portadores de VIH[20,28].

En relación a la elección del tratamiento antifúngico, fluconazol es el tratamiento de primera elección para la mayoría de las IFI por *Candida* spp, se trata de un fármaco con cinética conocida, buena penetrancia al SNC, adecuada tolerancia siendo el antifúngico más indicado en esta serie. Recientes revisiones sugieren en pacientes graves, con inestabilidad hemodinámica y sospecha de alta inoculación fúngica iniciar tratamiento con equinocandinas (caspofungina, micafungina). Después del curso inicial de la terapia con antifúngicos de amplio espectro, se puede recomendar una terapia de reducción con fluconazol, considerando la evolución clínica y la sensibilidad del agente fúngico. No se recomienda el tratamiento con fluconazol para infecciones por *Candida krusei y Candida glabrata*, ya que *C. krusei* es inherentemente resistente y *C. glabrata* tiene baja susceptibilidad a este fármaco[2,3,13,16]. Anfotericina B es el antifúngico de elección en las candidiasis urinarias y en la criptococosis. Se puede administrar como monoterapia o asociada a un azol en la criptococosis[8,9,18,19]. Como tratamiento empírico en la aspergilosis invasiva se encuentra indicado voriconazol. Anfotericina B liposomal es una alternativa aceptable para menores de dos años o que tienen contraindicado la utilización de voriconazol. No hay pruebas que apoyen el uso de la

terapia antimicótica combinada para el tratamiento de niños con aspergilosis[2].

En cuanto a la duración del tratamiento se encontró una gran disparidad en la mediana de días de tratamiento. La mayoría de ellos se trataron de pacientes críticos en los que se prolongó el uso de antifúngicos pudiendo esto sobrestimar la mediana de días de tratamiento[2,3,13,16,18,19,29].

En serie la letalidad fue elevada y vinculada a algún tipo de inmunodeficiencia. Estos hallazgos son similares a lo comunicado en la literatura con tasas de letalidad en candidiasis invasivas de 35%-66%. En la aspergilosis invasiva se describe una mortalidad de 10-52% dependiendo del órgano afectado, la inmunidad del paciente y el tratamiento utilizado[5,14-17].

Conclusiones

Las IFI en la infancia son una patología poco frecuente, que afecta en su mayoría en niños inmunocomprometidos o gravemente enfermos, asociadas a una elevada mortalidad.

Es necesario identificar los pacientes con factores de riesgo y tener un alto índice de sospecha dado que la presentación clínica es variada e inespecífica y se encuentra relacionada con el agente y la localización. La confirmación puede requerir el empleo simultáneo de varias técnicas diagnósticas. *Candida* spp *y Cryptococcus* spp son los agentes fúngicos más involucrados. El inicio precoz del tratamiento y acorde a los datos de susceptibilidad disponibles se asocia a menor mortalidad.

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CARACTERIZACIÓN CLÍNICA Y MICROBIOLÓGICA DE LAS INFECCIONES FÚNGICAS INVASORAS EN NIÑOS MENORES DE 14 AÑOS DE MEDELLÍN (COLOMBIA) DURANTE LOS AÑOS 2013 A 2017: ESTUDIO MULTICÉNTRICO

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RESUMEN

Introducción. Las infecciones fúngicas invasoras (IFI) son causa importante de morbilidad y mortalidad en niños hospitalizados, con un incremento significativo de casos en los últimos años debido a un aumento en la complejidad de las patologías de base de los pacientes. Las infecciones por *Candida spp*. son la principal IFI en pediatría. Los factores de riesgo descritos en la literatura son principalmente los relacionados con la alteración del sistema inmunológico como en cáncer y quimioterapia, trasplante de células madre hematopoyéticas e inmunodeficiencias. La mayoría de las estrategias terapéuticas en pediatría son extrapoladas de estudios en población de adultos. El conocimiento local sobre características clínicas y microbiológicas de las IFI en niños es limitado.

Objetivo: describir las características clínicas y microbiológicas de las infecciones fúngicas invasoras presentadas en niños atendidos en hospitales de alta complejidad de Medellín, Colombia, entre los años 2013 y 2017.

Metodología: estudio observacional descriptivo de corte transversal y multicéntrico que incluyó pacientes menores de 14 años con diagnóstico de infección fúngica invasora e Histoplasmosis que fueron atendidos en hospitales de alta complejidad en Medellín, Colombia entre los años 2013 y 2017.

Resultados: la muestra final fue de 186 pacientes con IFI e histoplasmosis (114 hombres y 72 mujeres, mediana de edad 2.3 años (RIQ 0.3-0.7). Los lactantes (32.2%) fueron los más afectados. Las infecciones más frecuentes fueron en orden de frecuencia candidiasis (56.9%), aspergilosis (24.1%) e histoplasmosis (20%), otras 7.8%. Las neoplasias, entre ellas las hematolinfoides y tumores sólidos, fueron la condición de base más común (36%). Los factores de riesgo descritos más

frecuentes entre los pacientes fueron el uso previo de antibióticos (94.3%), catéter venoso central (70.3%) y la estancia en UCI (51.3%). La presentación clínica más común en la candidiasis fue la infección diseminada con candidemia (66%), en aspergilosis la forma pulmonar invasiva (95.5%) y para histoplasmosis la forma diseminada (55%). Los antifúngicos más usados fueron fluconazol 68% (candidiasis), voriconazol 62% (aspergilosis) y anfotericina B deoxicolato 55% (histoplasmosis).

Conclusión: las IFI se presentan de forma heterogénea e inespecífica en pacientes pediátricos con factores de riesgo; al tratarse de infecciones que amenazan la vida, se deben sospechar y realizar una búsqueda activa para ofrecer un tratamiento oportuno y disminuir la morbimortalidad.

PALABRAS CLAVE: candidemia, aspergilosis, histoplasmosis, micosis, infección fúngica invasiva, inmunosupresión, infección oportunista, niños.

INTRODUCCIÓN

Las infecciones fúngicas invasoras (IFI) son una causa importante de morbilidad y mortalidad entre pacientes pediátricos hospitalizados principalmente aquellos con alteración del sistema inmunológico. En los últimos 15 años ha ocurrido un aumento significativo de casos explicado por el incremento de factores de riesgo para IFI en la población pediátrica especialmente por el avance en el tratamiento del cáncer , el aumento de los trasplantes (hematopoyéticos y órganos sólidos), el aumento de terapias inmunosupresoras, así como por un aumento en el diagnóstico gracias a los avances en nuevas herramientas diagnósticas, modificando su epidemiología(1).

Las principales condiciones de riesgo para IFI son el cáncer especialmente hematolinfoide, la quimioterapia , la inmunosupresión para los trasplantes de células madre hematopoyéticas (TCMH) y las inmunodeficiencias primarias (IDP) o adquiridas (2)(3). Entre otros factores de riesgo descritos en niños se encuentran la presencia de catéter venoso central (OR 13.4 IC 95% 4.8-37.42), neutropenia mayor o igual a 15 días (OR 5.58 IC 95% 1.12-27.79), uso prolongado de antibióticos (OR 5.44 IC 95% 1.87-15.77) y la nutrición parenteral (OR 5.3 IC 95% 2.8-10). Al sumar factores de riesgo, la posibilidad de presentar una IFI aumenta, como se ha descrito en candidiasis invasora pasando del 10% a 46% en presencia de tres factores de riesgo. (1) (2).

Se estima que *Candida spp.* es la causa principal de IFI y es el cuarto patógeno más comúnmente detectado en las infecciones pediátricas del torrente sanguíneo en Estados Unidos y Europa (2) (3). La candidiasis junto con la aspergilosis invasiva se asocia a un aumento significativo de la estancia hospitalaria y de la mortalidad en pacientes pediátricos. Con menor frecuencia, pero mayor morbimortalidad se describen infecciones por *Cryptococcus spp*., *P. jiroveci*, *Mucor spp*. y *Fusarium spp* (3)(4). *Histoplasma capsulatum* es una micosis endémicas que también se comporta como IFI (5); esta micosis tiene el mayor número de casos reportados en el

continente americano principalmente en algunas áreas de Estados Unidos, Centro y Sur América.(6)(7)(8).

La detección rápida y precisa de los niños que requieren terapia antifúngica en etapa temprana de la infección es uno de los objetivos más importantes del tratamiento. Sin embargo, el diagnóstico de la mayoría de IFI sigue siendo difícil porque los métodos convencionales no tienen adecuada sensibilidad y especificidad, y en los niños con frecuencia la presentación clínica e imágenes se asocian con signos inespecíficos que conducen a retraso diagnóstico (9). En relación al tratamiento antifúngico en pediatría la evidencia científica es limitada; en la clínica se emplean estrategias similares a las usadas en adultos, aun sabiendo que existen diferencias significativas en farmacocinética y farmacodinamia (10)(11).

En Colombia encontramos varios reportes en la literatura enfocados específicamente en un tipo de IFI, la mayoría sobre candidiasis invasiva. Se han publicado pocos estudios que describen varias IFI, estos incluyen tanto población pediátrica como adulta con mayor énfasis en esta última. Dentro de estos están el realizado por Álvarez et al cuyo objetivo fue estimar la carga de las IFI en este país (12) y el realizado por Cortés et al. donde muestran la frecuencia y especies de hongos responsables de fungemia que ocurrieron en una red de hospitales de tercer nivel (13). En la revisión bibliográfica no se encontró ningún estudio que agrupe varias IFI en población pediátrica de Colombia, exclusivamente. En este estudio, describimos cuáles son las características clínicas y microbiológicas de las IFI en la población pediátrica de 0 a 14 años en 4 hospitales de tercer nivel de Medellín durante los años 2013 a 2017.

MÉTODOS

Se trata de un estudio observacional descriptivo de corte transversal y multicéntrico. La población estudiada fueron pacientes con edad igual o menor a 14 años, incluyendo recién nacidos pretérmino y a término con diagnóstico de infección fúngica invasiva que fueron atendidos en los servicios de pediatría de 4 instituciones de salud de alta complejidad (Hospital San Vicente Fundación, Hospital Pablo Tobón Uribe, Hospital General de Medellín y Clínica Las Américas) en la ciudad de Medellín, Colombia, durante los años 2013 y 2017.

El proyecto fue aprobado por los comités de investigación y ética médica de cada una de las instituciones mencionadas. La fuente de información fue secundaria, basada en las historias clínicas de los pacientes con diagnóstico de IFI filtrados por código diagnóstico CIE – 10 (anexo 1) y a partir de reportes de laboratorio positivos para estos microorganismos, realizando verificación respectiva de las historias.

Se clasificaron como posible, probable o confirmada según criterios clínicos, imagenológicos, micológicos y microbiológicos teniendo en cuenta la clasificación internacional de la EORTC (European Organization for Research and Treatment of Cancer)/MSG (Mycoses Study Group) (anexo 2) (14). Se incluyó también la

infección por *Histoplasma* spp. teniendo en cuenta los criterios de la EORTC/MSG para micosis endémicas (anexo 3) (14). Se excluyeron pacientes con historia clínica incompleta o con información deficiente para la aplicación del instrumento y se correlacionaron los hallazgos descritos con los del laboratorio, con el fin de reducir los sesgos de información. En cuanto al control de los sesgos de selección se elaboró una lista de diagnósticos con códigos CIE 10 y teniendo en cuenta la posibilidad de pérdida de casos por la no actualización de los códigos, se realizó búsqueda a través de los aislamientos microbiológicos en los laboratorios; adicionalmente se incluyeron pacientes de todos los servicios de atención pediátricos de cuatro instituciones de salud de alta complejidad. Para la recolección de la información, se realizó por medio de preguntas cerradas en el instrumento de medición y se diseñó una base de datos única en Microsoft Excel que fue diligenciada por personal previamente entrenado en la que se unificaron los resultados de cada institución.

Los análisis se realizaron con el software estadístico SPSS versión 20. Se utilizaron medidas de tendencia central para las variables cuantitativas que se resumieron en forma de media o mediana según su distribución normal, se calcularon las desviaciones estándar o los valores de cuartil 1 y 3 según correspondan. Las variables cualitativas se resumieron como frecuencias absolutas o proporciones.
Se realizó un análisis diferenciado por cada centro de atención, edad, sexo y condición de base.

RESULTADOS

Se analizaron un total de 384 historias clínicas de las bases de datos suministradas por las instituciones participantes, de los cuales se excluyeron 198, obteniendo una muestra final de 186 pacientes. El hospital con mayor número de casos fue el HUSVF (45,2%). En la tabla 1 se describen las características generales de la población.

Tabla 1. Características generales de los pacientes menores de 14 años con IFI e histoplasmosis en la ciudad de Medellín.

Características	N.º pacientes (%)
Género	
Masculino	114 (61.3)
Femenino	72 (38.7)
Edad	
Neonatos (días), media	18.2 (+/- 61.9)

Niños (años) , mediana	3.3 (RIQ 0.9-8.5)
Grupos por edades	
Neonatos	28 (15.05)
Prematuro (EG < 37 semanas)	19 (67.8)
Prematuro extremo (EG < 28 semanas)	6 (24)
A término (EG > o igual 37 semanas)	3 (8.2)
Lactantes	60 (32.25)
Preescolares	28 (15.05)
Escolares	45 (24.19)
Adolescentes	25 (13.44)
Hospital	
Hospital Universitario San Vicente Fundación	84 (45.2)
Hospital Pablo Tobón Uribe	64 (34.4)
Hospital General de Medellín	21 (11.3)
Clínica Las Américas	17 (9.1)
Diagnóstico	
Candidiasis	106 (56.9)
Aspergilosis	45 (24.1)
Histoplasmosis	20 (10.7)
Infección por *P. jiroveci*	5 (2.6)
Criptococosis	3 (1.6)
Fusariosis	2 (1)
Mucormicosis	2 (1)
Otras	3 (1.6)

EG: Edad gestacional

La condición de base más frecuente fue el cáncer hematolinfoide, en un 42.4% de los pacientes, de los cuales el 55.1% se encontraba en fase de inducción de

quimioterapia; seguida por estado posoperatorio de cirugía intra abdominal (10.7%) e inmunodeficiencia primaria (7.5%). En el 8.2% de los casos no se encontró ninguna condición de base (Tabla 2).

El 91.8% de los neonatos eran prematuros (menores de 37 semanas de EG) y de estos el 24% eran prematuros extremos (menores de 28 semanas de EG). Dentro de las condiciones de riesgo descritas se encontró que todos los neonatos recibieron antibióticos de amplio espectro previo a la IFI, la mayoría estuvieron en UCIN (92.8%), portaban CVC y recibieron nutrición parenteral (85.7%).

Al evaluar el tipo de infección en neonatos se encontró candidiasis en 27 (96.4%) pacientes y un caso de infección por *Kodamaea ohmeri.* Con respecto a las infecciones por *Candida spp.* en esta población la mayoría fueron por el género *albicans* (70.3%), seguida por *C. parapsilosis* (18.5%) y en menor porcentaje *C. glabrata* y *C. famata* con 3.6% cada uno. En el 96.2% de los pacientes se confirmó el diagnóstico por aislamiento microbiológico, en el 80.7% por hemocultivo, de estos el 23% tenían urocultivo positivo y se realizó aislamiento por cultivo de LCR en el 7.6%. De los pacientes con fungemia, 3 presentaron compromiso de otros órganos (endocarditis infecciosa, ITU/meningitis e infección intra-abdominal). Sólo un caso fue catalogado como posible, recibió tratamiento con fluconazol con adecuada respuesta clínica, se presentó como sepsis neonatal tardía.

Por fuera del periodo neonatal la terapia previa con antibióticos fue la condición de riesgo más frecuentemente encontrada (94.3%), sólo el 19.4% de los niños expuestos a antibiótico tenían monoterapia, en su mayoría con betalactámicos, el resto recibieron combinación de 2 a 4 antibióticos de amplio espectro. En orden de frecuencia se encontró en los pacientes presencia de CVC (70.3%), seguido de estancia en UCIP (51.3%) y neutropenia (45.6%), la cual era profunda (RAN < 100/ mm^3) en 32.3% de los pacientes, la mediana de días de neutropenia previa al diagnóstico fue de 10 (RIQ 7 - 20).

La nutrición parenteral fue usada en el 39.2% con una mediana de 19 días (RIQ 10 - 39.5 días). Se encontró reporte de desnutrición aguda grave (definida por índices antropométricos según OMS) en el 12.7% de los casos. En pacientes no oncológicos se encontró que 7.6% recibieron esteroide a dosis alta (mayor 1 mg/kg/día) y 4.4% recibieron otro tipo de terapia inmunosupresora 2 semanas previas al inicio de los síntomas. Sólo un paciente recibió terapia biológica con Omalizumab previo a la infección (Tabla 2).

Tabla 2. Condiciones de base y factores de riesgo en mayores de 1 mes de EGC

	Nº pacientes (%)
Condiciones de base	n = 158
Cáncer (hematolinfoide y tumor sólido)	67 (42.4%)

Posoperatorio de cirugía intra-abdominal	17 (10.7)
Inmunodeficiencia primaria*	12 (7.5%)
Pos trasplante	5 (3.1%)
VIH	1 (0.6%)
Otras	60 (37.9%)
Ninguna	13 (8.2%)
Factores de riesgo descritos	
Uso previo de antibiótico intravenoso	149 (94.3)
Catéter venoso central	111 (70.3)
Estancia en UCIP	81 (51.3)
Neutropenia	72 (45.6)
Nutrición parenteral	62 (39.2)
Desnutrición aguda grave	20 (12.7)
Uso de esteroide > 1 mg/kg/dosis**	12 (7.6)
Terapia inmunosupresora*┼	7 (4.4)
Terapia biológica	1 (0.6%)

*Inmunodeficiencias primarias encontradas: agammaglobulinemia, inmunodeficiencia común variable, inmunodeficiencia combinada grave, otras inmunodeficiencias no especificadas
**En últimas 2 semanas, diferente a quimioterapia

┼Diferente a esteroide

Así mismo por fuera del periodo neonatal la IFI más frecuente fue Candidiasis en 79 (51%) pacientes, seguida por Aspergilosis con 45 (24.1%) e Histoplasmosis con 20 (10.7%) casos. En menor frecuencia se encontraron casos de infección por *P. jirovecii* en 5 (2.6%), Criptococosis en 3 (1.6%), Mucormicosis y Fusariosis en 2 (1%) de los casos respectivamente.

Incluyendo todos los grupos de edad, en las infecciones por *Candida spp*. la presentación clínica más frecuente fue la sepsis en el 66% de los casos, seguido de ITU e infección intraabdominal en el 32% y 13.2% respectivamente. De los pacientes con fungemia el 24.2% presentaron otro compromiso, la mayoría ITU (58%), seguido por infección intra abdominal (23.5%) y en menor proporción infección osteoarticular, meningitis y endocarditis infecciosa (11.7% cada una).

Se obtuvo aislamiento microbiológico en el 93,6% de los casos, en el 5% se consideró diagnóstico probable y 1.4% posible. El sitio de aislamiento más frecuente fue en sangre (69%), seguido por líquidos no estériles (28%), líquidos estériles (12%) y tejidos (4%).

Las especies de Candida no *albicans* fueron más frecuentes por fuera del periodo neonatal (67.5%), principalmente *C. parapsilosis* (35.7%) y *C. tropicalis* (28.5%), cabe resaltar que se encontró un aislamiento de *C. krusei.* Sólo el 32,4% de las candidiasis invasoras fueron causadas por *C. albicans.* Se encontró reporte de antifungigrama en el 87% de los pacientes con diagnóstico confirmado reportando sensibilidad a fluconazol en el 89.6% de los casos y resistencia en el 10.4% en la mayoría para especies no albicans con predominio de *C. glabrata* (3 casos) y *C. parapsilosis* (2 casos) seguido por *C. krusei*, *C. albicans* y *C. intermedia* con 1 caso respectivamente.

El antifúngico usado con mayor frecuencia como terapia inicial fue el fluconazol en el 68.8% de los casos, seguido de caspofungina (11.3%). De los pacientes que iniciaron terapia con fluconazol en el 16,4% se cambió la terapia a anfotericina B, 15% a caspofungina y 5.4% a voriconazol. En el 63% no se realizó cambio de antifúngico. La razón más frecuente de cambio fue fracaso clínico (32.1%) seguido por fungemia persistente (28.5%), resistencia (10.4%) y toxicidad (10.7%). Entre los pacientes con *Candida spp*. sensible al fluconazol se realizó cambio a otro antifúngico en el 34.6% de los casos. Los antifúngicos usados como tratamiento definitivo con mayor frecuencia fueron fluconazol (62.2%), anfotericina B liposomal y caspofungina (14.1% cada uno). La mediana en días de tratamiento fue de 19 (RIQ 14 - 25).

En los pacientes con Aspergilosis (n=45) la presentación clínica predominante fue la pulmonar invasiva en el 95.5%, en uno de estos pacientes hubo infección asociada en tejidos blandos; se encontró también presentación diseminada y sinusitis en 2.2% de casos respectivamente. El diagnóstico se clasificó como posible en el 20% de los casos, probable en el 73.3% y se confirmó solo en el 6.6% (3 casos). Se obtuvo aislamiento en tejidos en los 3 casos confirmados y en 1 de estos pacientes también en lavado broncoalveolar. El aislamiento más frecuente fue *A. fumigatus* en 2 pacientes y en uno se aisló *A. flavus.* No se obtuvo antifungigrama de ninguna muestra. El 82.2% de los pacientes tenía hallazgos patológicos en la TAC de tórax. Se realizó galactomanan en 41 pacientes con positividad en 28 (68.8%), de estos el 87% fue positivo en sangre y el 12.9% en lavado broncoalveolar. Así mismo un 12.9% de los pacientes presentaron positividad las 2 muestras (sangre y LBA).

El voriconazol fue el antifúngico instaurado con mayor frecuencia como tratamiento inicial en 28 (62.2%) pacientes, seguido por anfotericina B en 9 (19.9%) pacientes. Se realizó cambio de antifúngico en el 40% de los pacientes por fracaso clínico en 7 casos, de los cuales 3 estaban recibiendo voriconazol, 3 anfotericina B y 1 caspofungina. En igual número de pacientes se realizó el cambio para redireccionar el espectro donde 4 de los 7 pacientes recibían anfotericina B, 2 caspofungina y 1

fluconazol. El antifúngico definitivo más frecuente fue el voriconazol en 86.6% de los casos. La mediana de duración del tratamiento intrahospitalario fue de 30 días (RIQ 18 - 49).

En los pacientes con diagnóstico de histoplasmosis (n=20) el 50% presentaron compromiso diseminado, el 20% meningitis, 15% linfadenitis y 10% compromiso pulmonar. El diagnóstico se confirmó en 12 pacientes (60%), 10 casos por aislamiento microbiológico y 2 por prueba molecular en líquido cefalorraquídeo. En los pacientes que se obtuvo aislamiento microbiológico la mayoría fue en muestra de tejido de ganglio linfático (41.6%), seguido por hemocultivo (25%), cultivo de líquido cefalorraquídeo y mielocultivo (10% cada uno). Se identificó *H. capsulatum* en todos los casos confirmados. No se obtuvieron datos de antifungigrama.
A 18 de los 20 pacientes con histoplasmosis se realizaron marcadores micológicos, principalmente serología (fijación de complemento e inmunodifusión) en 11 pacientes (61.1%) la cual fue positiva en 9 casos (81%) principalmente en muestras tomadas de sangre (n=8) y líquido cefalorraquídeo (n=3) con datos no excluyentes. El antígeno urinario fue el segundo marcador micológico realizado con mayor frecuencia, en 9 de los 18 pacientes con positividad en 4 de éstos. Se realizó panfungal en 2 pacientes ambos con resultado negativo. En 9 pacientes (45%) se encontraron alteraciones en imágenes diagnósticas.

La anfotericina B fue el tratamiento inicial en el 70% de los casos. Se realizó cambio de antifúngico en el 42,1% de los pacientes (cambio a terapia oral en el 75% y toxicidad en 12.5%). El antifúngico definitivo más común fue el itraconazol (60%) seguido de anfotericina (35%). En 1 caso no se dio tratamiento por histoplasmosis ganglionar en paciente inmunocompetente. La mediana de duración del tratamiento fue de 28 días RIQ (11 - 76).

Tabla 3. Presentación clínica de Infecciones más frecuentes

Tipo de infección	Presentación clínica	Nº pacientes (%)
Candidiasis n= 106	Sepsis	70 (66.03)
	Infección de tracto urinario	34 (32)
	Infección intra-abdominal	14 (13.2)
	Meningitis	4 (3.7)
	Infección osteoarticular	3 (2.8)
	Endocarditis infecciosa	2 (1.8)

	Infección de piel y tejidos blandos	2 (1.8)
Aspergilosis n= 45	Infección pulmonar	43 (95.5)
	Infección diseminada*	1 (2.2)
	Sinusitis	1 (2.2)
	Infección en piel y tejidos blandos	1 (2.2)
Histoplasmosis n= 20	Diseminada	11 (55)
	Meningitis	4 (20)
	Linfadenitis	3 (15)
	Neumonía	1 (5)
	Nódulo pulmonar	1 (5)
	Infección de piel y tejidos blandos	1 (5)

Datos no excluyentes, algunos pacientes tuvieron aislamiento y compromiso de varios sitios.
*Compromiso pulmonar, esplácnico y endocarditis infecciosa

Tabla 4. Tratamiento según tipo de IFI

Tipo de infección	Antifúngico inicial (%)	Antifúngico definitivo (%)
	Fluconazol (68.8)	Fluconazol (62.2)

Candidiasis	Caspofungina (11.3)	Anfotericina B liposomal (14.1)
	Anfotericina B deoxicolato (3.7)	Caspofungina (14.1)
	Anfotericina B liposomal (1.8)	Voriconazol (4.7)
	Micafungina (1.8)	Anfotericina B deoxicolato (2.8)
	Anidulafungina (0.9)	Anidulafungina (1.8)
	Anfotericina B (0.9)	Micafungina (0.9)
Aspergilosis	Voriconazol (62.2)	Voriconazol (86.6)
	Anfotericina B deoxicolato (13.3)	Anfotericina B deoxicolato (6.6)
	Anfotericina B liposomal (6.6)	Anfotericina B liposomal (4.4)
	Caspofungina (6.6)	Caspofungina (2.2)
	Fluconazol (6.6)	Voriconazol (2.2)
	Anidulafungina (2.2)	Voriconazol (2.2)
Histoplasmosis	Anfotericina B deoxicolato (55)	Itraconazol (60)
	Anfotericina B liposomal (15)	Anfotericina B deoxicolato (30)
	Itraconazol (15)	Anfotericina B liposomal (5)
	Ninguno (15)	Ninguno (5)

DISCUSIÓN

En este estudio se investigaron las características clínicas y microbiológicas de las IFI en pediatría en cuatro centros de alta complejidad de la ciudad de Medellín.

sólo se discutirán en orden de frecuencia la candidiasis, aspergilosis e histoplasmosis por ser las IFI más frecuentes en nuestra población pediátrica.

Los pacientes del género masculino fueron los más afectados en concordancia con estudios descritos en la literatura (15) (16), pero la edad media de presentación de los pacientes por fuera del periodo neonatal fue 3.3 años discordante con otros en los que predomina la edad escolar (15)(17)(18). La edad como factor de riesgo adicional para IFI ha sido estudiada sobre todo en niños con neoplasia maligna y en histoplasmosis diseminada progresiva (19)(20). Kobayashi et al. describen que los niños mayores de 10 años tenían un HR de 8.4 (IC 1.573-10.223) para presentar IFI pero este estudio no es comparable con el nuestro ya que sólo se incluyeron niños con neoplasia maligna, anormalidades metabólicas, inmunodeficiencias expuestos a quimioterapia, terapia inmunosupresora o trasplante de células madre (20).

Se ha reportado en el periodo neonatal una frecuencia más alta de IFI especialmente candidiasis, este riesgo es inversamente proporcional a la edad gestacional y peso al nacer. En nuestro estudio hubo una proporción de neonatos prematuros considerable 91.8%, de estos 24% prematuros extremos, en otros estudios poblacionales, como el de Blyth et al. se encontró una mayor incidencia de IFI dentro de este grupo de edad al ser comparado con niños mayores (4.4 versus vs 0.9 y 1.8/100.000 en niños mayores) (21) (22). Sin embargo, otras condiciones como la exposición a antibiótico de amplio espectro, la presencia de CVC, la nutrición parenteral y cirugías intrabdominales, son los más relevantes en los neonatos (23)(24). Estos factores estuvieron presentes en casi la totalidad de los neonatos de nuestro estudio. Benjamin et al. en una cohorte prospectiva observacional de recién nacidos de peso extremadamente bajo encontró que los cuatro factores descritos, se asociaron fuertemente con candidiasis invasiva (25).

Dentro de las IFI en el periodo neonatal la mayoría de los pacientes presentaron candidiasis por especies *C. albicans* (70%), seguido por *C. parapsilosis* de forma similar a lo reportado por Santolaya y colaboradores, donde las especies *C. albicans* se aislaron en el 60% de los casos, 40% *C. no albicans* de estas principalmente *C. parapsilosis* en un 24% (26). El sitio de aislamiento más frecuente fue en sangre en el 80%, en porcentaje similar al reportado por Steinbach et al y Hsu et al (80 al 91%) (15) (24).

En el periodo neonatal, solo encontramos un caso de IFI diferente a candidiasis, que fue una infección por *Kodamaea ohmeri* en un paciente prematuro con clínica de enterocolitis y sepsis, la mayoría de reportes de caso son de Asia, algunos en Estados Unidos y Brasil, este es el único caso reportado en Colombia (27). En una serie reportada en India que incluyó 38 pacientes el 78.9% eran neonatos (28). Se han descrito factores de riesgo como prematuridad, enterocolitis, bajo peso, estancia prolongada en UCI, uso previo de antibióticos, dispositivos médicos, neutropenia e inmunosupresión (29).

Fuera de la población neonatal, los factores de riesgo descritos son principalmente los asociados a trastornos de la inmunidad (11)(12)(22)(23)(24) que también fueron comunes en nuestro estudio, resaltando las neoplasias hematológicas, sin embargo, el uso previo de antibióticos de amplio espectro fue el más frecuentemente encontrado en nuestra serie de pacientes, reportándose un porcentaje similar al reportado por Hsu et al. en un estudio de cohorte de 12 años que incluyó 342 pacientes con candidemia aunque para ellos no fue el factor más importante (24). En el estudio Alemán observacional retrospectivo de 10 años realizado por Tragiannidis et al. encontraron que el principal factor asociado a la ocurrencia de candidemia fue también el uso de antibióticos de amplio espectro en la presentación (93%) o dentro de las 2 semanas previas a esta (69.7%) y como segundo factor la presencia de catéter venoso central al igual que en nuestros pacientes pero en mayor porcentaje (17). En neoplasias hematológicas, el riesgo más alto para IFI para estos pacientes reportado en la literatura ocurre en la fase de inducción aproximadamente 10% vs 6% comparado con otras fases de quimioterapia (30)(31) lo que concuerda con los datos obtenidos donde la mitad de los pacientes se encontraba en esta fase.

El estado postoperatorio de cirugía intra – abdominal se encontró como segunda condición de base más común, superando patologías como inmunodeficiencias primarias o adquiridas de manera similar a lo reportado por Steinbach et al. en un estudio prospectivo de 196 pacientes pediátricos y neonatos con candidiasis invasiva en Estados Unidos donde 15% de los pacientes tenían trauma/cirugía en su mayoría de origen gastrointestinal (15). Diferentes estudios en población pediátrica y adultos también lo han reportado como factor de riesgo frecuente para IFI asociado a translocación bacteriana o daño en integridad de la mucosa gastrointestinal (18)(32)(33)(34).

Más de la mitad de los pacientes tuvieron estancia en UCIP que se ha descrito como factor de riesgo independiente para infección por *Candida* spp pero también se asocia con el uso de dispositivos invasivos, nutrición parenteral y uso de medicamentos como antibióticos y corticoides que aumentan la susceptibilidad a contraer candidiasis y aspergilosis, (2)(35).

En cuanto a la desnutrición aguda grave presente en un 12.6% de nuestra población no encontramos reportes de ésta como factor de riesgo en estudios de IFI en pediatría(36),por el contrario en estudios en población adulta se ha descrito como factor de riesgo para aspergilosis invasiva (37) (38).

En cuanto a la etiología de IFI, la candidiasis por fuera del periodo neonatal se presentó en el 50% de los pacientes del estudio, con predominio de especies no albicans 70.8%, las más frecuentes *C. parapsilosis* y *C. tropicalis,* reportándose de igual forma que en otros estudios como el de Rodrigues et al. en Brasil (71% no albicans), y Santolaya en Chile (69.5% no albicans)(26)(39). El sitio de aislamiento microbiológico más frecuente fue en sangre 69% seguido de líquidos no estériles 28%, resultados similares a los encontrados por Mesini et al. en un estudio de

cohorte, al igual que Santolaya y Rodrigues et al. donde el 71% de los aislamientos fueron en sangre (39)(40).

En los pacientes con infección por *Candida* spp la presentación clínica más frecuente fue la sepsis, seguido de ITU e infección intrabdominal, de los pacientes con fungemia el 24.2% presentaron diseminación principalmente a sistema nervioso central, osteoarticular y cardiaca, hallazgos similares a los descritos en la literatura en donde el compromiso meníngeo se observa en 10% de los pacientes con candidemia (principalmente en neonatos), la osteomielitis afecta principalmente la metáfisis femoral y la endocarditis descrita más frecuentemente en pacientes con cardiopatías o neoplasias hematológicas (30)(41). Se encontró un único aislamiento de *C. krusei* en un paciente masculino de 3 años con ITU sin factores de riesgo. Se ha descrito en diferentes trabajos una frecuencia de 2-5% para la especie *C. krusei* con aislamiento principalmente en sangre y líquidos estériles, con resistencia intrínseca al fluconazol (42) (43).

La sensibilidad antifúngica de las especies de Candida analizadas es similar a lo reportado en la literatura (10% resistencia a fluconazol). Cabe resaltar que el 13% de los aislamientos de *Candida* spp, no tienen antifungigrama, lo cual es una recomendación actual para todos los aislamientos de esta especie por el aumento progresivo de la resistencia para así definir de forma adecuada la terapia antifúngica definitiva, además teniendo en cuenta que en nuestro medio el fluconazol fue la terapia empírica más usada(24)(43)(44).

El tratamiento de las infecciones por *Candida spp* sigue siendo un reto, con alto porcentaje de fracaso terapéutico, 31% de los pacientes que recibieron tratamiento empírico con fluconazol requirieron cambio de antifúngico a anfotericina B y caspofungina, por fracaso clínico definido como la falta de respuesta clínica a las 72 horas de iniciado el tratamiento antifúngico (32%), fungemia persistente (28%) o resistencia a los antifúngicos (21%), comportamiento similar a lo reportado en otros estudios (15). Los grupos de expertos recomiendan ante fungemia o compromiso clínico grave iniciar tratamiento con medicamentos fungicidas (equinocandinas) como primera línea, más aun teniendo en cuenta que la mayoría de los pacientes tienen condiciones de base graves predominantemente neoplasia hematológica, trasplantes o son neonatos como en este estudio. El fluconazol puede usarse como primera línea en candiduria y cepa sensibles, siempre y cuando haya estabilidad clínica; adicionalmente para tener la opción de dar continuidad al tratamiento antifúngico vía oral si la sensibilidad lo permite (45).

La segunda IFI en frecuencia fue la Aspergilosis en 28.4%. *A. fumigatus* fue la especie más comúnmente aislada, similar a otros reportes de la literatura (16). La presentación clínica más frecuente fue la pulmonar, seguida de sinusitis, hallazgos similares a los reportados en la literatura, donde la neumonía y la rinosinusitis son las manifestaciones más comunes, seguidas del compromiso cerebral. Uno de los pacientes con aspergilosis pulmonar presentó también lesión cutánea, se ha reportado afectación en piel y tejidos blandos en 8-41% generalmente secundario a trauma o diseminación hematógena (30).

La mayoría de los casos fueron aspergilosis probables, sólo se confirmaron en el 6.6% de los casos lo que refleja la limitación diagnóstica que existe y la necesidad de sumar pruebas diagnósticas ante un paciente con alta sospecha clínica teniendo en cuenta los factores de riesgo. La tomografía (TAC) de tórax contrastado o la tomografía de tórax de alta resolución (TACAR) y el galactomanan fueron los marcadores complementarios más utilizados, con hallazgos positivos en 82.2% y 68.8% respectivamente, similar a lo encontrado en el trabajo de Ferreras et al. donde en el 74% de los pacientes tenían alteraciones en la TAC de tórax y 63% de los pacientes tenían galactomanano positivo (46)(47).

El voriconazol fue el tratamiento inicial en el 62% de los pacientes seguido por anfotericina B, igualmente como antifúngicoiótico definitivo se usó en el 86.6% de los casos, hallazgos correspondientes a lo encontrado en otros estudios y la literatura donde el voriconazol constituye la primera línea de tratamiento en 82% de los casos (47)(48).

La histoplasmosis, se incluyó en el presente estudio ya que, entre las micosis endémicas, ésta tiene el mayor número de casos reportados en el continente americano principalmente en algunas áreas de Estados Unidos, Centro y Sur América. En nuestro estudio se encontró en el 12.7% de los pacientes, la forma diseminada fue la manifestación más frecuente (50%), el compromiso medular se ha observado en el 60-100% de los pacientes en las diferentes series de Argentina y Colombia, en relación con la inmadurez de la respuesta inmune celular principalmente en los menores de dos años, sin embargo en el presente estudio solo fue del 15% (49)(50).

En nuestro estudio, el compromiso meníngeo ocurrió en el 20% de los pacientes, en otros trabajos se ha encontrado frecuencias del 48% y cultivo de LCR positivo hasta 80% de los pacientes, como señalan López et al en un estudio retrospectivo realizado en Colombia de 45 niños con histoplasmosis (49).

A diferencia de aspergilosis, en la mayoría de pacientes con histoplasmosis el diagnóstico fue confirmado, el principal sitio de aislamiento fue del tejido ganglionar, seguido de sangre, LCR y médula ósea, importante resaltar que en el 10% el diagnóstico se realizó por prueba molecular, método que puede ser útil en casos seleccionados, como pacientes con compromiso inmunitario y sospecha de enfermedad diseminada (51).

Entre los marcadores micológicos, la serología fue el de mayor positividad. El antígeno urinario fue positivo en el 40% de los casos, similar a lo descrito en otros estudios. La sensibilidad del antígeno urinario se ha reportado en 81.4% y especificidad del 98.3% (52)(53), siendo una herramienta que debe ser considerada para el diagnóstico de la enfermedad aguda y en pacientes inmunosuprimidos. Entre sus limitaciones está la reacción cruzada en presencia de otras micosis (blastomicosis, peniciliosis, coccidioidomicosis) (54)(55).

Las imágenes diagnósticas también son una herramienta útil a la hora de definir el diagnóstico. Hasta en el 45% de los pacientes con compromiso pulmonar se encontraron hallazgos patológicos en las imágenes diagnósticas lo que se ha observado en otros estudios (54-83%) (49)(50)(56), , los hallazgos más comúnmente encontrados en orden de frecuencia son la linfadenopatía intratorácica principalmente en los pacientes inmunocomprometidos seguido de nódulos pulmonares y consolidaciones lobares (53)(54).

La terapia antifúngica está indicada en pacientes con histoplasmosis diseminada, cerebral y pulmonar con cavitaciones o síntomas moderados a severos, 95% de los pacientes del presente estudio recibieron tratamiento, principalmente anfotericina B (70%) seguido de itraconazol, hallazgos compatibles con los trabajos de Ouellete y colaboradores donde la anfotericina B fue el principal antifúngico durante las primeras 1-2 semanas, seguido por itraconazol durante 12 semanas (53)(55). Se cambió el antifúngico en menos de la mitad de los pacientes, para continuar terapia oral en el 75% de los casos y en un caso por toxicidad, el antifúngico definitivo en la mayoría fue el itraconazol, como en otras series (53)(55). El 5 % de los pacientes no recibieron tratamiento antifúngico ya que presentaron histoplasmosis ganglionar sin antecedente de inmunosupresión.

Entre las limitaciones del estudio son las propias de un estudio retrospectivo, en la cual los registros clínicos pueden contener información errónea e incompleta, algunos de los pacientes pudieron no tener reportes del aislamiento microbiológico y tampoco tener el código diagnóstico actualizado por lo cual se pueden perder del universo de los datos.

En conclusión, las IFI de nuestra cohorte de niños tienen un comportamiento similar a lo reportado en la literatura, principalmente asociado a escenarios de inmunosupresión como aquellos con neoplasias hematológicas, sin embargo, fue muy frecuente el antecedente de uso de antibiótico de amplio espectro y la presencia de catéter venoso central, que pueden ser factores de riesgo modificables en la práctica médica. Las manifestaciones clínicas de las IFI encontradas son heterogéneas e inespecíficas, lo cual representa un reto para el clínico y con frecuencia da lugar al retraso diagnóstico y terapéutico. Para hacer un diagnóstico oportuno es indispensable la suma de criterios y pruebas: la sospecha clínica, los factores de riesgo, imágenes como escanografía en el caso de micosis pulmonares, marcadores micológicos y estudios microbiológicos en muestras adecuadas que incluyan antifungigrama .

Este estudio describe de forma amplia y general datos poblacionales de las IFI en población pediátrica no reportados previamente en Colombia, lo que sirve como base para evaluar la adherencia a guías de diagnóstico y manejo internacionales. Así mismo da pié al desarrollo de investigaciones futuras dirigidas a una comprensión más profunda y específica de estas patologías que contribuyan a mejorar la morbilidad y mortalidad asociada a estas en la población pediátrica.

Anexo 1. Códigos CIE 10 Diagnósticos	
Micosis B205: Enfermedad por VIH, resultante en otras micosis B431: Absceso cerebral feomicótico B487: Micosis oportunistas B488: Otras micosis especificadas G021: Meningitis por micosis J172: Neumonía en micosis M016: Artritis en micosis ***Aspergillus spp*** B440: Aspergilosis pulmonar invasiva B441: Otras aspergilosis pulmonares B447: Aspergilosis Diseminada B448: Otras formas de aspergilosis B449: Aspergilosis no especificada ***Candida spp*** B371: Candidiasis pulmonar B374: Candidiasis de otras localizaciones urogenitales B375: Meningitis debida a *Candida* B376: Endocarditis debida a *Candida* (I398) B377: Septicemia debida a *Candida* B378: Candidiasis de otros sitios B379: Candidiasis no especificada P375: Candidiasis neonatal ***P. jiroveci*** B206: Enfermedad por VIH, resultante en neumonía por P. carinii	***Criptococcus spp*** B450: Criptococosis pulmonar B451: Criptococosis cerebral B452: Criptococosis cutánea B453: Criptococosis ósea B457: Criptococosis diseminada B458: Otras formas de Criptococosis B459: Criptococosis, no especificada ***Histoplasma spp*** B390: Infección pulmonar aguda por H. capsulatum B391: Infección pulmonar crónica por H. capsulatum B392: Infección pulmonar por H. capsulatum, sin otra especificación B393: Infección diseminada por H. capsulatum B394: Histoplasmosis debida a H. capsulatum, sin otra especificación B399: Histoplasmosis, no especificada ***Mucor spp*** B460: Mucormicosis pulmonar B461: Mucormicosis rinocerebral B462: Mucormicosis gastrointestinal B463: Mucormicosis cutánea B464: Mucormicosis diseminada B465: Mucormicosis, sin otra especificación

Anexo 2. Criterios de la EORTC y MSG para el diagnóstico de IFI probable, excepto micosis endémicas
Factores del huésped
• Neutropenia de < 500 neutrófilos/mm3 durante más de 10 días • Trasplante alogénico de progenitores hematopoyéticos • Corticoides a dosis de ≥ 0,3 mg/kg/día (equivalentes a prednisona) durante > de 3 semanas • Inmunosupresores anti-linfocitos T como ciclosporina, anti-TNF, alemtuzumab o análogos nucleósidos durante los 3 meses previos • Inmunodeficiencia grave congénita (IDSC, enfermedad granulomatosa crónica)
Criterios clínicos
• Enfermedad fúngica del tracto respiratorio inferior: Presencia de 1 de los 3 signos en el TAC torácico: – Lesión densa bien definida con o sin signo del halo – Signo de la media luna *(air crescent sign)* – Cavitación • Traqueobronquitis: – Ulceración traqueobronquial, nódulos, pseudomembranas, placas o escaras observadas en broncoscopia - Infección sinonasal • Imagen de sinusitis más 1 de los 3 signos siguientes: – Dolor agudo localizado – Úlcera nasal con escara negruzca – Invasión ósea, incluida la órbita • Infección del SNC: – 1 de los 2 signos: - Lesiones focales en la radiología - Refuerzo meníngeo en la RMN o TAC • Candidiasis diseminada: – Uno de los 2 hallazgos después de un episodio de candidemia en las 2 semanas previas: - Pequeños abscesos (en ojo de buey) en hígado o bazo - Exudados retinianos
Criterios micológicos
Tests directos (citología, examen microscópico directo, cultivos) Hongos filamentosos en esputo, LBA, cepillado bronquial o aspirado sinusal • Tests indirectos (detección de Ag o constituyentes de la pared celular) Aspergilosis: galactomanano + en plasma, suero, BAL o LCR IFI (excepto criptococosis y zigomicosis): ß glucano + en suero
Términos
IFI: infecciones causadas por levaduras o mohos que producen compromiso sistémico **Neutropenia profunda:** RAN < 100 céls/$mm^{3.}$ **Caso confirmado:** evidencia de levaduras u hongo filamentoso por tinción y/o cultivo en sangre o muestra clínica de cavidad estéril o estudio histológico con evidencia de invasión fúngica. **Caso probable:** factor del hospedero más criterios clínicos y criterio micológico. **Caso posible:** factor del hospedero más criterios clínicos sin criterio micológico.

Anexo 2. Criterios de la EORTC y MSG para IFI confirmada excepto para micosis endémicas		
Análisis y especimen	**Mohos**	**Levaduras**
Análisis microscópico: material estéril	Histopatológico, citopatológico o examen microscópico directo de un especimen obtenido por aspiración con aguja o biopsia en el cual las hifas o formas similares a levaduras melanizadas son vistas asociadas a daño tisular asociado	Histopatológico, citopatológico o examen microscópico directo de un espécimen obtenido por aspiración con aguja o biopsia de un sitio normalmente estéril mostrando levaduras
Cultivo de material estéril	Recuperación de un moho o "levadura negra" por cultivo de una muestra obtenida por procedimiento estéril de un sitio normalmente estéril y clínica o radiológicamente anormal consistente con un proceso infeccioso, excluyendo LBA, muestra de cavidad de seno craneal y orina.	Recuperación de levaduras por cultivo de muestra obtenida de un procedimiento estéril de un sitio normalmente estéril mostrando una anormalidad clínica o radiológica consistente con proceso infeccioso.
Sangre	Hemocultivo con crecimiento de moho en contexto de un proceso infeccioso compatible	Hemocultivo con crecimiento de levaduras (*Cryptococcus o Candida spp*.) u hongos similares a levaduras (*Trichosporon spp*.)
Análisis serológico: LCR	No aplica	Antígeno para *Cryptococcus spp* en LCR indica infección diseminada

Anexo 3. Criterios de la EORTC y MSG para el diagnóstico de micosis endémicas
Micosis endémica confirmada
En un huésped con una enfermedad compatible con una micosis endémica 1 de los siguientes: • Recuperación en un cultivo de un espécimen obtenido de un sitio afectado o de sangre • Demostración histopatológica o microscópica directa de formas morfológicas apropiadas con una apariencia verdaderamente distintiva y característica de hongo dimórfico como las esférulas de *Coccidioides spp*, levaduras en crecimiento de base ancha y paredes gruesas de *Blastomyces dermatitidis*, las células en levadura múltiple de *Paracoccidioides brasiliensis* y en caso de histoplasmosis la presencia de levaduras intracelulares características en un fagocito en un extendido de sangre periférica o en macrófagos de tejido. • Para coccidiodomicosis, demostración de anticuerpo coccidioidal en LCR o un aumento en 2 diluciones medido en 2 muestras de sangre consecutivas analizadas simultáneamente en el contexto de un proceso infeccioso • Para paracoccidioidomicosis, demostración en 2 muestras consecutivas de suero de bandas de precipitina paracoccidioidina en el contexto de proceso infeccioso.
Micosis endémica probable
Presencia de un factor del huésped incluyendo, pero no limitado a los especificados en la tabla de IFI más un cuadro clínico consistente con micosis endémica y evidencia micológica como un antígeno positivo para Histoplasma en orina, sangre o LCR.

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Artículo original

Características epidemiológicas de pacientes pediátricos con candidiasis invasora en una unidad de cuidados intensivos del suroccidente colombiano

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Introducción. Las especies de *Candida* son el principal agente etiológico de infecciones fúngicas en la población pediátrica, especialmente en neonatos y pacientes atendidos en la unidad de cuidados intensivos. La candidiasis invasiva se relaciona con desenlaces clínicos desfavorables como tiempo de hospitalización prolongado y mortalidad.
Objetivo. Describir las características demográficas, clínicas y microbiológicas de los pacientes pediátricos (mayores de un mes y menores de 18 años) hospitalizados en una unidad de cuidados intensivos pediátricos con diagnóstico de candidiasis invasora entre el 2012 y el 2020.
Materiales y métodos. Se adelantó un estudio observacional, retrospectivo, de tipo cohorte, en un centro de alta complejidad del suroccidente colombiano.
Resultados. Se incluyeron 100 pacientes pediátricos con diagnósticos de candidiasis invasora, el 51 % de sexo femenino con una mediana de edad de 6,5 años (RIC = 2-11,5). Se obtuvieron 114 aislamientos de *Candida* spp. La mediana de estancia hospitalaria fue de 51 días (RIC = 29-77) y de estancia en la unidad de cuidados intensivos pediátricos de 27 días (RIC = 16-58). El 85 % de los pacientes presentó taquicardia 24 horas antes del aislamiento de *Candida* spp. El 49,1 % de los aislamientos se encontró en las muestras de sangre (49,1 %), el lavado broncoalveolar (21,9 %) y el líquido peritoneal (20,2 %). La especie aislada más frecuente fue *Candida albicans* (36,8 %), seguida de *C. parapsilosis* (22,8 %) y *C. tropicalis* (21,1 %). El 36 % de los pacientes falleció.
Conclusiones. La candidiasis invasora es una entidad común en las unidades de cuidados intensivos pediátricos y es un desafío por su alta morbilidad, prolongación de la estancia hospitalaria y tasa de mortalidad elevada. Aunque *C. albicans* sigue siendo la especie predominante, las especies de *C.* no *albicans* han mostrado una tendencia creciente, lo que plantea nuevos retos diagnósticos y terapéuticos.

Palabras clave: *Candida*; candidiasis; candidemia; candidiasis invasiva; unidades de cuidados intensivos pediátricos; pediatría.

Epidemiological characteristics of pediatric patients with invasive candidiasis in an intensive care unit in southwestern Colombia

Introduction. *Candida* species are the main etiological agent of fungal infections in the pediatric population, especially in neonates and in intensive care unit patients. Invasive candidiasis is associated with unfavorable clinical outcomes, such as prolonged hospitalization time, and mortality.
Objective. To describe demographic, clinical and microbiological characteristics of pediatric patients (older than one month and younger than 18 years) hospitalized in a pediatric intensive care unit with a diagnosis of invasive candidiasis between 2012 and 2020.
Materials and methods. A retrospective, observational, cohort study was conducted at a high-complexity center in southwestern Colombia.
Results. We included 100 pediatric patients diagnosed with invasive candidiasis, 51% female with a median age of 6.5 years (IQR = 2-11.5). We obtained 114 isolates of *Candida* spp. The median hospital stay was 51 days (IQR = 29-77), with a pediatric intensive care unit stay of 27 days (IQR = 16-58). Tachycardia was present in 85% of the patients 24 hours before *Candida* spp. isolation. Nearly half of the isolates were found in bloodstream samples (49.1%), respiratory samples (21.9%), and peritoneal fluid (20.2%). The most frequently isolated species were *C. albicans* (36.8%), followed by non-albicans species, such as *C. parapsilosis* (22.8%), and *C. tropicalis* (21.1%). The overall mortality rate at discharge was 36%.

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Contribución de los autores:
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Camila Ariza-Insignares, Paula Solís-Núñez, Juliana V. Cedeño-Castaño, Ana M. Aguilar-González, Lina M. Sandoval-Calle e Inés Elvira Gómez Hernández: recolección de datos
Paola Marsela Pérez-Camacho, Jaime Alberto Patiño-Niño, Camila Ariza-Insignares, Lina M. Sandoval-Calle e Inés Elvira Gómez Hernández: escritura del manuscrito
Carmen Vargas-Moran y Laura Torres-Cánchala participaron en el análisis de los datos y en todas las etapas del estudio.

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Conclusions. In pediatric intensive care units, invasive candidiasis is a common condition representing a significant threat due to its high morbidity, prolonged hospital stay, and considerable mortality rate. While *C. albicans* remains as the predominant species, non-*albicans Candida* species exhibit a growing trend, posing new diagnostic and therapeutic challenges.

Key words: *Candida*; candidiasis; candidemia; candidiasis, invasive; intensive care units, pediatric; pediatrics.

La Organización Mundial de la Salud reportó que en el 2022 fallecieron 2,3 millones de neonatos en el mundo. Las infecciones son la tercera causa de muerte más frecuente, después de las complicaciones clínicas asociadas con la prematuridad y el parto. La mayoría de las infecciones neonatales son causadas por especies de *Candida* y las tasas de infección varían según la ubicación geográfica, las características clínicas que aumentan la susceptibilidad de los pacientes y las prácticas de asepsia y antisepsia de los servicios de salud (1-4). Por ejemplo, los pacientes inmunocomprometidos o aquellos que requieren catéter venoso central o sonda urinaria presentan infecciones por *Candida* spp. del torrente sanguíneo con una prevalencia del 10 al 20 % (5-7).

La infección invasora por *Candida* spp., conocida también como candidiasis invasora, incluye la presencia de levaduras en la sangre (candidemia) y la diseminación del hongo a órganos profundos, con candidemia asociada o sin ella (8). A nivel mundial, se reportan aproximadamente 700.000 casos anuales de candidiasis invasora (4). En los países de altos ingresos, la tasa bruta de mortalidad por candidiasis invasora se estima entre el 12 y el 37 %, mientras que en los países de bajos y medianos ingresos, la mortalidad varía entre el 8,9 y el 75 %. En la población pediátrica, las infecciones por especies de *Candida* son la tercera causa de infecciones sanguíneas en unidades de cuidados intensivos pediátricos y neonatales (6,7,9,10). Además, estas infecciones están asociadas con una mayor estancia hospitalaria –estimada en un promedio de 21 días adicionales a lo que la enfermedad de base requiere–, lo que también incrementa los costos hospitalarios (11,12).

El desarrollo de candidiasis invasora está asociado con múltiples factores de riesgo, que se pueden clasificar en dos categorías principales: aquellos relacionados con el huésped (como diagnósticos de malignidad o inmunosupresión, neutropenia y edad) y aquellos relacionados con la atención médica (medidas de asepsia y antisepsia, uso de catéter venoso central o accesos sanguíneos, nutrición parenteral, uso prolongado de antibióticos intravenosos, corticoesteroides, administración previa de antifúngicos o cirugías recientes, especialmente abdominales) (7,9,11-13). En los países de altos ingresos, la mortalidad por candidiasis invasora es particularmente alta en los neonatos con un peso inferior a los 1.000 g o una edad gestacional menor de 28 semanas. En contraste, en los países de bajos y medianos ingresos, la candidiasis invasora afecta a una población más amplia y se ha observado un aumento en la incidencia de especies de *Candida* no *albicans*, como *C. parapsilosis*, *C. krusei* y *C.auris*, las cuales presentan menor sensibilidad al fluconazol (3).

En la última década, se ha reportado un cambio en la incidencia de candidiasis invasora y en la distribución de especies. Por ejemplo, los *Centers for Disease Control and Prevention* (CDC) reportaron una disminución de la candidemia en niños mayores de cinco años en Estados Unidos, de 1,8 casos por 100.000 nacidos en el 2009 a 0,8 casos por 100.000 nacidos en el 2014 (14). Como se mencionó, aunque *C. albicans*

sigue siendo la especie más aislada, la incidencia de las especies no *albicans* ha aumentado (7,11,15). Esto es relevante porque algunas especies de *C.* no *albicans*, como *C. parapsilosis* y *C. tropicalis*, presentan patrones de resistencia a antifúngicos, lo que genera un desafío terapéutico (10).

En Latinoamérica, diversos estudios han abordado la candidiasis en la población neonatal, pero las demás edades pediátricas no suelen ser comúnmente incluidas a pesar de su relevancia clínica. Nucci *et al.* describieron que el 44,2 % de los casos de candidiasis invasora –en los 21 hospitales latinoamericanos evaluados– correspondía a niños mayores de un mes y menores de 18 años. La especie más comúnmente aislada fue *C. albicans*, presente en el 37,2 % de los individuos estudiados, seguida de *C. parapsilosis* (26,5 %) y *C. tropicalis* (17,6 %) (16). En el 2021, México reportó una incidencia de candidiasis invasora de 2,27 por cada 1.000 recién nacidos vivos, y *C. albicans* fue la especie más prevalente (35,3 %). También se documentaron factores de riesgo asociados a candidiasis invasora como: necesidad de respiración mecánica asistida (OR = 3,04; IC $_{95\,\%}$: 1,13-8,14), terapia antibiótica sistémica (OR = 7,48; IC $_{95\,\%}$: 1,30-42,9), el número de esquemas antimicrobianos (OR = 2,02; IC $_{95\,\%}$: 1,01-4,03) y los días con nutrición parenteral total (OR = 1,14; IC $_{95\,\%}$: 1,04-1,25) o con catéter venoso central (OR = 1,11; IC $_{95\,\%}$: 1,02-1,20) (17).

En 2012, en Colombia se estimó una incidencia de candidemia de 1,98 casos por cada 1.000 hospitalizaciones (18). Sin embargo, dicha cifra puede variar dependiendo del área geográfica y del servicio de hospitalización que esté tratando al paciente. Varios estudios del país han evidenciado una disminución de la frecuencia relativa de *C. albicans* y un aumento de otras especies como *C. parapsilosis* y *C. glabrata*, lo cual tiene implicaciones en el manejo farmacológico debido a su menor sensibilidad al fluconazol (18).

El diagnóstico de candidiasis invasora es un reto para el personal de salud, ya que los cultivos de sangre son poco sensibles y específicos para la detección de *Candida* spp. Por ello, se ha implementado el uso de otros métodos diagnósticos, como el sistema T2Candida™ Panel, la amplificación de ácidos nucleicos y la detección enzimática de glucano (14). Además, el tratamiento de las infecciones fúngicas invasivas sigue siendo un desafío, especialmente por la resistencia a los antifúngicos, lo que ha llevado a la incorporación y el estudio de medicamentos como la anfotericina B liposómica, la micafungina y la anidulafungina en la población pediátrica y neonatal (19-22).

Dada la importancia clínica y epidemiológica de la candidiasis invasora y la escasa información publicada hasta el momento en población pediátrica (diferente al periodo neonatal), el objetivo de este estudio fue describir las características demográficas y clínicas, y la mortalidad de pacientes pediátricos con diagnóstico de candidiasis invasora. La población estudiada estuvo hospitalizada en una unidad de cuidados intensivos pediátricos de una institución de alta complejidad del suroccidente colombiano entre el 2012 y el 2020.

Materiales y métodos

Se llevó a cabo un estudio descriptivo y retrospectivo en el que se recolectaron datos de las historias clínicas del sistema de registro de la Fundación Valle del Lili de *Systems, Applications & Products in Data Processing,* SAP. Con ayuda del Departamento de Estadística y del Comité Institucional de Infecciones, se hizo la búsqueda de los pacientes

pediátricos con aislamiento microbiológico de *Candida* spp. a partir de muestras estériles (hemocultivos, líquido peritoneal, cefalorraquídeo o de lavado broncoalveolar), hospitalizados en la unidad de cuidados intensivos pediátricos incluida la de cuidados cardiovasculares entre enero del 2012 y diciembre del 2020. En este periodo se atendieron 8.394 pacientes en la unidad de cuidados intensivos pediátricos y 2.513 en la de cuidados cardiovasculares, para un total de 10.907 pacientes pediátricos. En promedio, a cada unidad de cuidados intensivos ingresaron 1.211 pacientes por año.

Se excluyeron los pacientes menores de 30 días (un mes) o mayores de 18 años, hospitalizados en la unidad de cuidados intensivos neonatales o con ingresos previos en esta unidad, con aislamientos asociados a infecciones de las vías urinarias o aislamientos microbiológicos de especies de *Candida* de muestras no estériles y estancia hospitalaria menor de siete días.

Las muestras fueron cultivadas en el laboratorio de la institución, en medios selectivos como agar Sabouraud dextrosa y agar cromogénico para levaduras. Las placas se incubaron a 35-37 °C durante 48 a 72 horas. Posteriormente, se hizo la identificación de las especies de *Candida* mediante la observación de las características morfológicas y de su color en el agar cromogénico. Mediante el sistema Vitek 2™ se determinó la identificación microbiana y la prueba de sensibilidad antimicrobiana de forma automatizada. Se calculó la concentración inhibitoria mínima para cada antifúngico según los manuales M27M44S y M57S del *Clinical and Laboratory Standards Institute* (CLSI). La cepa se consideró sensible (S) cuando la concentración inhibitoria mínima era igual o menor del punto de corte establecido, intermedia (I) cuando dicho valor se encontraba en un rango en el cual el éxito del tratamiento era incierto, y resistente (R) cuando superaba el punto de corte.

Entre las variables del estudio se incluyeron características epidemiológicas (edad y sexo); clínicas (signos y síntomas, antecedentes de importancia, sitio de la infección, diagnósticos de sepsis grave o choque séptico, según los criterios diagnósticos propuestos por la Conferencia Internacional de Consenso sobre Sepsis Pediátrica del 2005 (23)); motivo de ingreso a la unidad de cuidados intensivos pediátricos o a la unidad cardiovascular, y microbiológicas (identificación de la especie de *Candida* y el antifungigrama cuando estaba disponible). Además, se incluyeron variables que describen factores de riesgo reconocidos como: tiempo de estancia hospitalaria, tratamientos antibióticos previos, uso de catéteres intravasculares, cirugía abdominal, criterios para sepsis grave y características microbiológicas del aislamiento de las especies de *Candida*, incluyendo el patrón de sensibilidad, en los casos donde se reportaba.

Las variables continuas se representaron con medianas y rangos intercuartílicos (RIC) y las variables categóricas, con tablas de frecuencias y porcentajes. El análisis se realizó con el paquete estadístico Stata™, versión 14.0 (Stata Corp., TX). Esta investigación se acogió a las normas internacionales sobre investigación biomédica, la Declaración de Helsinki y del *Council for International Organizations of Medical Sciences* (CIOMS). Dado que los datos se obtuvieron para la práctica clínica habitual, no se exigió el consentimiento informado. Este estudio fue aprobado por el Comité en Investigación Biomédica de la Fundación Valle del Lili, Cali, Colombia (Protocolo No. 1277).

Resultados

Se identificaron 498 pacientes con infecciones por *Candida* spp. según la Clasificación Internacional de Enfermedades (códigos CIE-10). Al aplicar los criterios de inclusión del estudio, se obtuvieron 100 pacientes pediátricos con diagnósticos de candidiasis invasora de quienes se obtuvieron 114 aislamientos de *Candida* spp.

La mediana de edad fue de 6,5 años (RIC = 2-11,5) y no se identificó una diferencia significativa en la distribución por sexo. El 76 % de los pacientes tenía una enfermedad de base al momento de su ingreso a la unidad de cuidados intensivos pediátricos o a la cardiovascular, siendo las cardiopatías (35,5 %) las más frecuentes. No hubo ningún paciente que tuviera como antecedente trasplante de médula ósea. La mediana de estancia hospitalaria fue de 51 días (RIC = 29-7) y en unidad de cuidados intensivos fue de 27 días (RIC = 16-8). Se registró una mortalidad general del 36 % (cuadro 1).

Cuadro 1. Características demográficas y clínicas de pacientes con diagnóstico de candidiasis invasiva (N = 100)

	n	%
Sexo		
Femenino	51	51,0
Masculino	49	49,0
Edad (años), mediana	6.5 (2-11.5)	
Procedencia del paciente		
Urgencias	25	25,0
Hospitalización	30	30,0
Unidad de cuidados intensivos pediátricos de otra institución	7	7,0
Otra institución	38	38,0
Enfermedad de base	76	100
Cardiopatía	27	35,5
Patología neurológica	19	25,0
Trastorno hepático	17	22,4
Enfermedad gastrointestinal	14	18,4
Trastorno hematooncológico	10	13,2
Patología metabólica	10	13,2
Nefropatía	9	11,8
Trasplante hepático	8	10,5
Patología respiratoria	6	7,9
Inmunodeficiencia	5	6,6
Patología autoinmunitaria	5	6,6
Trasplante renal	2	2,6
Trastorno musculoesquelético	1	1,3
Trasplante de médula ósea	0	0,0
Días de hospitalización**	51 (29-77)	
Días en UCI, mediana**	27 (16-58)	
Razón de ingreso a la unidad de cuidados intensivos		
Infección asociada a los cuidados de la salud	30	30,0
Infección adquirida en la comunidad	23	23,0
Cirugía	24	24,0
Cardiopatía	18	18,0
Trasplante hepático	10	10,0
Trauma	8	8,0
Enfermedad hematooncológica	5	5,0
Tumores sólidos	2	2,0
Trasplante renal	2	2,0
Trasplante de médula ósea	0	0,0
Muerte al egreso	36	36,0

* Mediana (RIC)

En cuanto a los datos de laboratorio, durante el episodio de candidiasis invasora, el 11 % (n = 11) de los pacientes desarrolló neutropenia por más de 10 días. De estos, 4 pacientes tenían enfermedad hematooncológica de base (3 padecían leucemia linfoblástica aguda y 1 tenía aplasia medular) y presentaron una mediana de 1.010 neutrófilos en el día uno de la neutropenia (RIC = 270-1.380) y de 80 neutrófilos en el día 10 de la neutropenia (RIC = 10-960).

En cuanto a la presencia de factores de riesgo asociados al desarrollo de candidiasis invasora, se encontró que 15 días antes del diagnóstico el 88 % de los pacientes había tenido un catéter venoso central o había sido sometido a otros procedimientos invasivos como respiración mecánica asistida (65 %), nutrición parenteral (58 %) o transfusiones sanguíneas (60 %). Además, entre los pacientes que habían sido intervenidos quirúrgicamente (n = 46), en más de la mitad, la cirugía fue abdominal (n = 25). Se evidenció que el uso de antibióticos, corticoesteroides e inhibidores de la bomba de protones tenía una asociación con el desarrollo de candidiasis invasora (cuadro 2).

Cuadro 2. Factores de riesgo documentados 15 días antes de la infección por *Candida* spp. (N = 100)

	n	%
Uso de antibióticos dos semanas antes del diagnóstico	95	95,0
Uso de catéter venoso central	88	88,0
Uso de inhibidores de la bomba de protones o bloqueadores de H^2	67	67,0
Respiración mecánica invasiva	65	65,0
Uso de catéteres vesicales	63	63,0
Infección documentada los últimos 15 días*	61	61,0
Trasfusiones de hemoderivados	60	60,0
Uso de nutrición parenteral	58	58,0
Algún tipo de cirugía	46	46,0
Abdominal	25	25,0
Cardiovascular	15	15,0
Ortopédica	4	4,0
Oftalmológica	2	2,0
Uso de corticoesteroides	44	44,0
Uso de antifúngicos	26	26,0
Bacteriemia durante el uso de antifúngicos	9	9,0
Días de antibiótico antes del diagnóstico**	9 (6-14)	
Vancomicina	55	55,0
Meropenem	49	49,0
Piperacilina-tazobactam	49	49,0
Cefalosporina	17	17,0
Cefepime	17	17,0
Hemodiálisis	8	8,0
Días de nutrición parenteral**	7 (4-16)	
Días de uso de corticoesteroides**	6 (3-10)	
Días de uso de antifúngicos**	5 (3-14)	
Finalidad del uso del antifúngico	5	5,0
Profilaxis	19	19,0
Tratamiento	2	2,0
Sin datos		12,0
Tipo de antifúngico recibido	12	12,0
Fluconazol	12	4,0
Caspofungina	4	4,0
Anfotericina B	4	
Voriconazol		

* Se incluyeron todas las infecciones previas de cualquier etiología.
** Mediana (RIC)

Veinticuatro horas antes del diagnóstico de candidiasis se recolectaron datos de los parámetros clínicos y paraclínicos que hacen parte de los criterios de sepsis grave (cuadro 3). La taquicardia fue el signo más común (87 %) junto con la fiebre (51 %). En cuanto a las alteraciones de laboratorio, el 65,6 % de los pacientes presentó alguna anomalía en el conteo de leucocitos (leucopenia y leucocitosis). También se evaluó la presencia de disfunciones orgánicas: disfunción cardiovascular (definida como la presencia de hipotensión resistente a la reanimación hídrica) en el 22 % y necesidad de vasoactivos en el 42 %; disfunción respiratoria por la necesidad de respiración mecánica invasiva y no invasiva (76 %) y necesidad de una fracción inspirada de oxígeno (FiO_2) mayor del 50 % (55 %). Con relación a la disfunción neurológica, la escala de Glasgow fue menor de 11 puntos en 7 pacientes. Sin embargo, no fue posible recolectar este dato en todos los casos, ya que la mayoría requirió respiración mecánica. Este procedimiento implica sedación y analgesia y, por lo tanto, no permite una valoración neurológica adecuada.

En cuanto a las características microbiológicas de los aislamientos (n = 114), casi la mitad de los que resultaron positivos se obtuvieron de muestras de sangre (49,1 %), seguidas del lavado broncoalveolar (21,9 %) y del líquido peritoneal (20,2 %). Se identificó que la especie aislada más frecuente fue *C. albicans* (36,8 %), seguida por especies de *C.* no *albicans* como C. *parapsilosis* (22,8 %) y *C. tropicalis* (21,1 %) (cuadro 4).

De los 114 aislamientos positivos, 14 correspondieron a episodios con segundos aislamientos de *Candida* spp.: 8 fueron coinfecciones (dos especies diferentes de *Candida* en el mismo cultivo) y los 6 restantes fueron cultivos positivos para especies de *Candida* en dos tiempos diferentes durante la misma hospitalización (cuadro 5).

El patrón de sensibilidad y resistencia a los antifúngicos de las especies identificadas en todos los aislamientos (n = 114) se resume en el cuadro 6. Es importante aclarar que no en todos los casos se realizaron pruebas de sensibilidad para todos los antifúngicos: el 62 % (71/114) fue evaluado para fluconazol, el 50,8 % (58/114) para voriconazol, el 9,6 % (11/114) para anfotericina B y el 55 % (63/114) para caspofungina.

Cuadro 3. Criterios de sepsis grave 24 horas antes del diagnóstico confirmado de *Candida* spp., según la Conferencia Internacional de Consenso sobre Sepsis Pediátrica del 2005

	n	%
Temperatura mayor de 38 °C o menor de 36 °C	51	51,0
Taquicardia	87	87,0
Taquipnea	76	76,0
Número de leucocitos en el momento de la toma del cultivo	10.490 (7.090 a 16.250)	
Hipotensión después de reanimación hídrica	22	22,0
Necesidad de vasoactivos	42	42,0
Base exceso < -5	27	27,0
Ácido láctico > 2	19	19,0
Oliguria	14	14,0
Llenado capilar > 5 s	10	10,0
INR (International Normalized Ratio) > 2	6	6,0
Número de plaquetas en el momento de la toma del cultivo	122.000 (46.000 a 226.500)	
Niveles de alanina aminotransferasa**	27,2 (13,4 a 57)	
Necesidad de respiración mecánica invasiva o no invasiva	76	76,0
Oxigeno suplementario con FiO2 > 50 %	55	55,0
Glasgow < 11	7	7,0
Primera creatinina tomada después del ingreso**	0,37 (0,25 a 0,67) mg/dl	
Creatinina más alta durante la hospitalización**	0,34 (0,24 a 0,57) md/dl	

* Plaquetas < 150.000 por ml

** Mediana (RIC)

Cuadro 4. Características microbiológicas de aislamientos positivos para *Candida* spp. (N = 114)

Tipo de muestra	n	%
Sangre	56	49,1
Respiratoria	25	21,9
Líquido peritoneal	23	20,2
Líquido pleural	2	1,8
Otros*	8	7,0
Especies aisladas		
Candida albicans	42	36,8
Candida parapsilosis	26	22,8
Candida tropicalis	24	21,1
Candida glabrata	8	7,0
Candida lusitaniae	6	5,3
Candida guilliermondii	4	3,5
Candida auris	2	1,8
Candida krusei	1	0,9
Candida intermedia	1	0,9

* otros: Colección intrabdominal, secreción mediastinal

Cuadro 5. Características microbiológicas de los segundos aislamientos de *Candida* spp. (n = 14)

Lugar del primer aislamiento	Especie de Candida	Fecha (DD.MM.AA)	Lugar del segundo aislamiento	Especie	Fecha (DD.MM.AA)	Tipo del segundo aislamiento
Líquido peritoneal	*C. krusei*	06.01.17	Líquido peritoneal	*C. tropicalis*	06.01.17	Coinfección
Vías respiratorias	*C. albicans*	14.09.15	Lavado broncoalveolar	*C. tropicalis*	14.09.15	Coinfección
Líquido peritoneal	*C. albicans*	30.03.18	Sangre	*C. guilliermondii*	13.04.18	Segunda infección
Sangre	*C. glabrata*	13.06.21	Lavado broncoalveolar	*C. tropicalis; C. glabrata*	13.06.21	Coinfección
Vías respiratorias	*C. albicans*	14.08.14	Lavado broncoalveolar	*C. tropicalis*	14.08.14	Coinfección
Líquido peritoneal	*C. parapsilosis*	26.03.16	Líquido peritoneal	*C. tropicalis*	26.03.16	Coinfección
Líquido peritoneal	*C. albicans*	05.06.16	Líquido peritoneal	*C. parapsilosis*	05.06.21	Coinfección
Sangre	*C. auris*	09.03.18	Secreción del mediastino	*C. auris*	20.03.18	Segunda infección
Sangre	*C. glabrata*	03.08.15	Líquido peritoneal	*C. albicans*	03.08.15	Coinfección
Líquido peritoneal	*C. tropicalis*	19.02.17	Líquido peritoneal	*C. albicans*	19.02.17	Coinfección
Sangre	*C. parapsilosis*	05.02.12	Sangre	*C. albicans*	29.02.12	Segunda infección
Vías respiratorias	*C. tropicalis*	27.11.12	Sangre	*C. parapsilosis*	13.12.12	Segunda infección
Colección suprahepática	*C. albicans*	25.09.12	Absceso peritoneal	*C. parapsilosis*	26.12.12	Segunda infección
Líquido peritoneal	*C. glabrata*	29.07.16	Sangre	*C. glabrata*	22.08.16	Segunda infección

Cuadro 6. Antifungigrama según la especie de *Candida* de los primeros y segundos aislamientos

Antifúngico*	Fluconazol (n = 71)				Voriconazol (n = 58)				Anfotericina B (n = 11)				Caspofungina (n = 63)			
Especie de Candida**	**S**	**I**	**R**	**Sd**	**S**	**I**	**R**	**Sd**	**S**	**I**	**R**	**Sd**	**S**	**I**	**R**	**Sd**
Candida albicans (n = 82)	26	0	1	15	28	0	0	14	0	0	0	42	27	0	0	15
Candida parapsilosis (n = 40)	3	0	14	9	8	1	0	17	0	0	2	24	12	0	0	14
Candida tropicalis (n = 43)	14	0	1	9	14	0	0	10	0	0	0	24	14	0	0	10
Candida glabrata (n = 16)	2	3	2	1	2	0	0	6	2	0	0	6	3	2	0	3
Candida lusitaniae (n = 11)	2	0	0	4	2	0	0	4	2	0	3	1	2	0	0	4
Candida guilliermondii (n = 6)	2	0	0	2	2	0	0	2	0	0	0	4	2	0	0	2
Candida auris (n = 4)	0	0	1	1	1	0	0	1	0	0	1	1	1	0	0	1
Candida krusei (n = 1)	0	0	0	1	0	0	0	1	0	0	1	0	0	0	0	1
Candida Intermedia (n = 0)	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	1

S: sensible, I: intermedio, R: resistente, Sd: sin datos (No se hizo antifungigrama.)

* Se señala el número de aislamientos por columna para cada antifúngicos utilizado en los antifungigramas.

** Se señala el número de aislamientos por fila por especie de Candida evaluada en los antifungigramas.

Durante el periodo del estudio se documentó la muerte de 36 pacientes: 27 murieron en los 30 días posteriores al diagnóstico de candidiasis y, de estos, 16 se atribuyeron a la infección por *Candida* spp. según criterio médico. De los 36 fallecidos, el 44,4 % (n = 16) tuvo infección por *C. albicans*, el 22,2 % (n = 8) por *C. parapsilosis*, el 22,2 % (n = 8) por *C. tropicalis* y el 11,1 % (n = 4) por *C. glabrata*. Solamente uno de estos pacientes tuvo una

coinfección, confirmada por el aislamiento de *C. glabrata* en el hemocultivo y de *C. glabrata* y *C. tropicalis* en la muestra de lavado broncoalveolar.

Discusión

Este es el primer estudio de candidiasis invasora en Colombia de pacientes pediátricos hospitalizados en la unidad de cuidados intensivos pediátricos o en la cardiovascular, en el cual se describen las características demográficas, clínicas y microbiológicas de 100 pacientes con diagnóstico de candidiasis invasora del 2012 al 2020.

Las especies de *Candida* son el principal agente causal de las infecciones fúngicas invasoras en las unidades de cuidados intensivos pediátricos o de adultos. En el presente estudio, se encontró que el aislamiento de *Candida* spp. fue más común en las muestras de sangre (49,1 %), el lavado broncoalveolar (21,9 %) y el líquido peritoneal (20,2 %). Esto se asemeja a los resultados de un estudio multicéntrico realizado en Turquía, en el que se incluyeron pacientes pediátricos de todos los servicios (no exclusivamente de la unidad de cuidados intensivos pediátricos), y reportaron que cerca del 51 % de los aislamientos fueron de casos de candidemia versus el 49,3 % de casos sin candidemia, sino infecciones urinarias o intraabdominales, entre otras (24).

Es importante recordar que, aunque los hemocultivos continúan siendo los pilares para el diagnóstico de la candidemia, su sensibilidad es baja, cerca del 40 al 70 % (25). Sin embargo, cuando el resultado es positivo, se puede identificar la especie y, si se solicita, la evaluación de la sensibilidad antifúngica para detectar aislamientos resistentes. En este estudio solo se incluyeron aquellos casos con aislamientos positivos que, por definición, correspondían a una infección por *Candida* spp. confirmada según los criterios del grupo de consenso de la *European Organization for Research and Treatment of Cancer* y del *Mycoses Study Group Education and Research Consortium* (25) . Sin embargo, es posible que existan otros casos –no incluidos en este estudio– clasificados como candidiasis probable o posible en el consenso mencionado. Sería necesario adelantar otro estudio que incluya todos los pacientes con sospecha de infección por *Candida* spp. para evaluar la sensibilidad de los cultivos realizados.

Otro aspecto por resaltar es el porcentaje alto de aislamientos positivos para *Candida* spp. a partir de muestras del lavado broncoalveolar, pues esto ya indica colonización del hongo. Sin embargo, existen algunas situaciones excepcionales en las que la infección se trata como una candidiasis: cuando hay otro aislamiento positivo para *Candida* spp. en sangre, como en el caso de dos pacientes (uno con coinfección y el otro con segunda infección como se muestra en el cuadro 5); o cuando se sospecha que el paciente tiene neumonía, con una imagen compatible, y sin ningún otro aislamiento que explique la clínica, como ocurrió en otros aislamientos (n = 23).

Se ha documentado que la candidiasis es más frecuente en la población pediátrica hospitalizada que en la adulta (9,11,21). En este estudio se calculó una incidencia acumulada de 10,6 casos por cada 1.000 pacientes pediátricos admitidos a las unidades de cuidados intensivos pediátricos o la cardiovascular de la institución. Estos hallazgos difieren de los reportados en un estudio multicéntrico realizado por Nucci *et al.* sobre candidemia en la población general de Latinoamérica. En tal estudio, Colombia tuvo la mayor incidencia reportada entre los países evaluados con 1,96 casos por cada 1.000 hospitalizados versus la incidencia general de 1,18 casos por cada

1.000 hospitalizados (16). Cabe destacar que dicho estudio multicéntrico no se centró exclusivamente en población pediátrica, mientras que el presente trabajo sí, de hecho, se enfoca en una población muy susceptible: pacientes de una unidad de cuidados intensivos hospitalizados en un centro de alta complejidad y una afluencia elevada de pacientes.

La literatura es congruente en demostrar que la incidencia de candidemia es mayor en los países en desarrollo que en los desarrollados. Por ejemplo, para Argentina y Venezuela se han reportado incidencias de 1,95 y de 1,72 por cada 1.000 hospitalizados, respectivamente (16), mientras que para Estados Unidos, la incidencia varía entre 0,3 y 0,9 por cada 1.000 hospitalizados y entre 0,2 y 0,4 en las unidades de cuidados intensivos de Europa (11,25).

La distribución de las especies de *Candida* varía según la región, la institución y la subpoblación. En la cohorte estudiada, la especie más aislada fue *C. albicans* (40 %), seguida por *C. parapsilosis* (25 %) y *C. tropicalis* (20 %). En su artículo de candidemia en Colombia, Cortés *et al.* reportaron diferentes estudios en los que *C. albicans* fue la especie predominante en la población general, seguida por *C. tropicalis* y *C. parapsilosis* (18). De estos resultados se puede concluir que las tres especies mencionadas son las más frecuentes en la población. Sin embargo, el cambio del orden entre las dos especies no *albicans* puede deberse a que el presente estudio se enfoca en la población pediátrica. Algunos estudios que apoyan esta hipótesis se mencionan a continuación: Jordan *et al.* realizaron un estudio multicéntrico sobre los factores de riesgo y predictores de infección invasora por *Candida* spp. en las unidades de cuidados intensivos pediátricos de España y reportaron que las especies más frecuentes habían sido: *C. albicans* (37,6 %), *C. parapsilosis* (29,6 %) y *C. tropicalis* (15,2 %) (21); por otro lado, en el estudio multicéntrico y multinacional de Steinbach *et al.* se reportaron porcentajes similares, ya que *C. albicans* fue la especie más prevalente (44 %), seguida por *C. parapsilosis* (22 %) (15); y, en general, esta es la tendencia mundial reportada por los estudios que se centran en pacientes pediátricos (5,6,24).

Algunos de los factores que podrían contribuir a la alta incidencia de *C. parapsilosis* en la población pediátrica son el uso frecuente de catéteres y otros dispositivos en las unidades de cuidados intensivos pediátricos, pues esta especie tiene una alta afinidad por estos dispositivos y termina adhiriéndose a ellos. Esta adhesión se asocia con la colonización gastrointestinal, más común en niños pequeños, y se ha documentado transmisión horizontal entre las manos de los trabajadores de la salud y los pacientes pediátricos (26-28).

En las últimas décadas, la incidencia de las especies no *albicans* en el mundo ha ido en aumento, como se evidencia en diferentes series y estudios de pediatría (5,7,15). Los resultados del presente estudio concordaron con lo anterior, pues el 60 % de los aislamientos fueron de especies no *albicans*. Esta tendencia es de importancia clínica para decidir el tratamiento empírico y evaluar la resistencia a los antifúngicos, especialmente al fluconazol, que es mayor en las especies de *C.* no *albicans* (7,28).

Un estudio futuro podría plantear una comparación entre las diferentes especies para evaluar si hay diferencias significativas entre los factores de riesgo o en su prevalencia respecto a otras subpoblaciones. Esto permitiría elaborar recomendaciones más concisas sobre el tratamiento empírico.

En el periodo del estudio se evaluó la resistencia a los antifúngicos en 71 aislamientos. Se resalta que, en ocasiones, se evaluó la resistencia solamente a uno o dos antifúngicos, según los perfiles de resistencia conocidos de la especie aislada. De forma general, las tasas de resistencia son muy bajas, con excepción de los aislamientos de especies como *C. parapsilosis*, *C. lusitaniae* y *C. auris,* que presentaron porcentajes de resistencia altos, por lo menos, a un antifúngico (cuadro 6). Se detectaron dos aislamientos de la especie emergente *C. auris* de un mismo paciente, quien tuvo un desenlace fatal por sepsis causada por este microorganismo. No se observó resistencia en los aislamientos identificados (16,29).

Los factores de riesgo para la candidiasis invasora están bien descritos, entre ellos se encuentran: hospitalización prolongada en una unidad de cuidados intensivos, diagnóstico de neoplasia maligna, uso de antibióticos, catéter venoso central y nutrición parenteral (9,12,21). Todos los anteriores fueron predominantes en el presente estudio, lo que confirma nuevamente su asociación con el desarrollo de candidiasis invasiva.

En la cohorte evaluada, el 76 % (n = 76) de los pacientes tenía una enfermedad de base, las más frecuentes fueron las cardiopatías en 27 de los pacientes. Esto difiere de lo usualmente reportado en otros estudios, donde la enfermedad más común suele ser oncológica (9,12). En este caso, la mayoría de los pacientes con cardiopatías consultan a la Fundación Valle del Lili porque es un hospital de referencia para cardiopatías congénitas pediátricas, que son atendidas en la unidad de cuidados intensivos pediátricos cardiovasculares.

El uso de antibióticos en las dos semanas anteriores al diagnóstico de candidiasis invasora fue el factor de riesgo más común en el presente estudio. Una media de nueve días (RIC = 6 a 14) de tratamiento antibiótico podría considerarse –según el tipo de infección– como prolongado. Está descrito que el uso prolongado de antibióticos, sobre todo los de amplio espectro, altera la flora gastrointestinal y permite el sobrecrecimiento de especies de *Candida* spp.*,* lo que facilita el desarrollo de candidiasis invasora (9). Otro mecanismo que puede alterar la flora gastrointestinal son las intervenciones quirúrgicas abdominales: el 25 % de nuestros pacientes había tenido una cirugía abdominal. Un resultado interesante de la cohorte estudiada fue que solo el 11 % de los pacientes tuvo neutropenia (documentada) en el momento del aislamiento de *Candida* spp.*,* a diferencia de otras series (9).

En cuanto a las manifestaciones clínicas de los pacientes con candidiasis invasora, no hay un signo patognomónico para esta entidad, su clínica es inespecífica, por lo que requiere un alto grado de sospecha. La presentación usual de estos casos incluye un cuadro de sepsis o choque séptico, por lo que usualmente se piensa en una etiología bacteriana. Solo cuando hay un fracaso terapéutico con la antibioticoterapia o cuando el paciente presenta factores de riesgo para candidiasis invasora, se sospecha de la misma (28).

Por lo anterior, en este estudio se decidió clasificar a los pacientes según los criterios de sepsis pediátrica. La mayoría presentaba choque séptico (30 %) o sepsis grave (30 %) y, en menor proporción, sepsis (10 %) y sin respuesta inflamatoria (7 %). Sin embargo, es preciso resaltar que el 23 % de los pacientes presentaba disfunciones orgánicas sin desarrollar una respuesta inflamatoria sistémica (23 %). Cabe aclarar que el tipo de población en estudio se encuentra críticamente enferma, en su mayoría por causas diferentes a la candidiasis invasora, por lo tanto, la morbimortalidad

de estos pacientes es difícil de atribuir únicamente a la candidiasis invasora. Es importante enfatizar el gran reto diagnóstico que representa la candidiasis dadas sus manifestaciones clínicas inespecíficas.

En el presente estudio, el 36 % (n = 36) de los pacientes murió en la misma hospitalización en la que se documentó la candidiasis invasora. Sin embargo, solo 16 casos podrían ser atribuidos a la infección por *Candida* spp., según criterio médico. La mortalidad durante los primeros 30 días después del aislamiento de *Candida* spp. fue del 27 % (n = 27). Las tasas de mortalidad reportadas en los diferentes estudios varían del 7,7 al 26 % dependiendo de la subpoblación estudiada y sus enfermedades de base (11,12).

Según el conocimiento de los autores, este es el estudio con mayor número de pacientes y el más grande realizado en Colombia sobre candidiasis invasiva en una unidad de cuidados intensivos pediátricos. No obstante, su principal limitación radica en su diseño retrospectivo y monocéntrico, aunque fue desarrollado en un centro de alta complejidad (cuarto nivel de atención), que cuenta con una unidad de cuidados intensivos pediátricos y una unidad cardiovascular. Finalmente, es preciso anotar que solo a partir del 2015 se realizan, de forma rutinaria, pruebas de sensibilidad a antifúngicos de los diferentes aislamientos obtenidos.

En conclusión, la candidiasis invasora es una entidad común en las unidades de cuidados intensivos pediátricos y cardiovasculares, y constituye un desafío dada su alta morbilidad, prolongación de la estancia hospitalaria y tasas de mortalidad elevadas. Aunque *C. albicans* sigue siendo la especie predominante, las especies de *C.* no *albicans* han mostrado una tendencia creciente, lo que plantea nuevos retos diagnósticos y terapéuticos. La población pediátrica que ingresa a las unidades de cuidados intensivos es particularmente sensible a las infecciones por *Candida* spp. no solo por sus múltiples enfermedades de base, sino también porque es sometida a procedimientos invasores, lo que aumenta significativamente el riesgo de desarrollar candidiasis invasora.

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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Efficacy, safety and feasibility of antifungal prophylaxis with posaconazole tablet in paediatric patients after haematopoietic stem cell transplantation

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Abstract

Purpose Paediatric recipients of haematopoietic stem cell transplantation (HSCT) have a high risk for invasive fungal infections. Posaconazole oral suspension has proven to be effective in antifungal prophylaxis in adult and paediatric patients. A new posaconazole tablet formulation with absorption independent of the gastric conditions was approved by the FDA in 2013. This is the first report on the use of posaconazole tablets in paediatric patients.

Methods This single-centre study included 63 paediatric patients with haemato-oncological malignancies who received posaconazole for antifungal prophylaxis after HSCT. They were analysed for efficacy, feasibility and the safety of posaconazole. Out of 63 patients, 31 received posaconazole oral suspension and 32 received posaconazole tablets up to 200 days after transplantation. Analyses of the posaconazole trough levels were determined.

Results No possible, probable or proven invasive fungal infection was observed in either group. Posaconazole trough levels were significantly higher in the tablet group than in the suspension group at all analysed time points. Drug-related adverse events were similarly low in both groups.

Conclusions Posaconazole tablets are effective in preventing invasive fungal infections in paediatric patients. As early as day 3 after starting posaconazole tablets, over 50% of the posaconazole trough levels were >500 ng/mL, while this was observed on day 14 after start with posaconazole suspension. The administration of posaconazole tablets was

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safe, effective and feasible as antifungal prophylaxis in paediatric patients after HSCT.

Keywords Antifungal prophylaxis · Invasive fungal infections · Azole antifungals · Haematopoietic stem cell transplantation · Paediatric patients

Abbreviations

ALL	Acute lymphoblastic leukaemia
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
AST	Aspartate aminotransferase
BID	Bis in die, twice a day
CA	Carboplatin
CsA	Cyclosporine A
ETO	Etoposide
FLU	Fludarabine
GvHD	Graft-versus-host disease
HSCT	Haematopoietic stem cell transplantation
JMML	Juvenile myelomonocytic leukaemia
MAC	Myeloablative conditioning regimen
MDS	Myelodysplastic syndromes
MFD	Matched family donor
mg kg BW^{-1}	Milligram per kilogram bodyweight
MTX	Methotrexate
MUD	Matched unrelated donor
n	Sample size
NHL	Non-Hodgkin's lymphoma
QD	Quaque die, once a day
RIC	Reduced-intensity conditioning regimen
SD	Standard deviation
TBI	Total body irradiation
TID	Ter in die; three times daily
TLI	Total lymphoid irradiation
TT	Thiotepa

Introduction

The early post-transplant period after haematopoietic stem cell transplantation (HSCT) is accompanied by a substantial immunodeficiency. Thus, these patients are at high risk not only for viral and bacterial infections but also for invasive fungal infections (Abbasi et al. 1999; Castagnola et al. 2006; Denning et al. 1997; Fisher and Zaoutis 2008; Groll et al. 1996; Hale et al. 2010; Lass-Flörl 2009; Maertens et al. 2001; Meyers 1990; Rosen et al. 2005; Zaoutis 2010; Zaoutis et al. 2004, 2006). The most common causes of invasive fungal infections in immunocompromised paediatric patients after HSCT are *Aspergillus* spp. and *Candida* spp. (Abbasi et al. 1999; Dornbusch et al. 2009; Lass-Flörl 2009; Lehrnbecher et al. 2010b; Lin et al. 2001; Nucci et al. 1997). In addition, rare but difficult to treat infections caused by *Mucormycetes* spp. or *Fusarium* spp. may occur (Lehrnbecher et al. 2010b; Malani and Kauffman 2007; Nucci et al. 1997; Rekha et al. 2008; Zirak et al. 2005). Posaconazole is a broad-spectrum triazole and shows clinical activity against *Aspergillus* spp., *Candida* spp., *Fusarium* spp., *Mucormycetes* and other yeasts and filamentous fungi (Barchiesi et al. 2001; Bennett et al. 2006; Groll and Walsh 2005, 2006, MSD & DOHME 09/2013; Sabatelli et al. 2006; Sun et al. 2002).

The first approved formulation of posaconazole was the oral suspension. However, the absorption rate of the posaconazole suspension is highly variable and mainly depends on gastrointestinal conditions. Many factors, including reduced gastric acidity, e.g. caused by concomitant medication of proton pump inhibitors, fasting, low fat content in food, or intestinal graft-versus-host disease (GvHD) may all impair the bioavailability of this azole (Krishna et al. 2009; Ullmann et al. 2007). Clinical investigations have shown that the consumption of high fat meals prior to posaconazole administration significantly improved posaconazole uptake. However, these results were obtained after the intake of food containing approximately 50 g fat, which is an extremely difficult amount to achieve in paediatric patients (Krishna et al. 2009). Especially after HSCT, paediatric patients often experience nausea and loss of appetite and thus eat significantly less than healthy children do.

Owing to the data published on posaconazole suspension as an effective oral antifungal prophylaxis in adults with neutropenia and GvHD, we have changed our antifungal prophylaxis after HSCT from fluconazole or voriconazole to a posaconazole suspension in 2007 (Cornely et al. 2007; Ullmann et al. 2007). For 60 paediatric patients under 12 years of age using posaconazole suspension in a dosage of 3×4 mg/kg bodyweight per day we already have shown good efficacy, safety and limited side effects (Döring et al. 2012).

In addition to the oral suspension formulation of posaconazole, a new posaconazole formulation of a delayed-release tablet was approved by the Food and Drug Administration in November 2013 (MSD SHARP & DOHME GMBH 09/2013). This tablet formulation provides a consistent absorption independent of the gastrointestinal conditions listed above or concomitant medication and thus offers an improved bioavailability compared to the posaconazole suspension (Courtney et al. 2003; Guarascio and Slain 2015; Kersemaekers et al. 2015; Kraft et al. 2014; Krishna et al. 2012a, b). Posaconazole suspension should be administered for prophylaxis three times daily in order to reach the target plasma concentration (Krishna et al. 2007b, 2009). In contrast, the recommended dose of posaconazole tablets for prophylaxis or treatment for adolescents of 13 years of age and older is a single dose of 300 mg per day,

after an initial dose of 300 mg BID on the first day (MSD SHARP & DOHME GMBH 09/2013).

To our knowledge, this is the first survey to analyse the plasma concentrations, safety, feasibility and efficacy of posaconazole tablets in comparison to posaconazole suspension in paediatric patients after HSCT.

Materials and methods

This analysis was conducted in accordance with the Declaration of Helsinki and performed with approval from the University Children's Hospital Tübingen's Institutional Review Board.

Study design and patients

The present survey is a single centre, non-randomized analysis of 63 paediatric patients who received either posaconazole suspension or tablets as an oral antifungal monoprophylaxis after HSCT. The analysis was performed at the Department of Paediatric Haematology and Oncology, University Children's Hospital Tübingen, Germany. Baseline demographics, clinical factors, treatment-related adverse events, and survival were abstracted from the clinical and research records of all patients and maintained on a prospective basis. Patients with invasive fungal infections prior to the planned allogeneic HSCT were excluded. The patient cohorts consisted of patients with haemato-oncological malignancies or non-malignant diseases receiving autologous ($n=6$) or allogeneic HSCT ($n=57$) between August 2013 and December 2015 (Table 1). All patients enrolled in this analysis stayed in laminar air flow rooms from the first day of conditioning, during and after HSCT until inpatient discharge. During the conditioning liposomal amphotericin B (1 mg/(kg · day)) was given as an antifungal prophylaxis. Beginning on day +1 after HSCT patients received antifungal prophylaxis with caspofungin of 50 mg/m^2 (maximum 50 mg/day). The antifungal prophylaxis was changed to posaconazole at a median of 7 days (range 5–8 days) before inpatient discharge to prevent severe infections with *Aspergillus* spp., *Candida* spp., *Mucor* spp. or other fungal species as good as possible. Given the treatment difficulties and the distinct susceptibility for fungal infections in particular in paediatric patients after HSCT or during neutropenia after high-dose chemotherapy and the favorable side-effect profile of posaconazole in adult patients, we believe that a clear indication is given for an antifungal prophylaxis with posaconazole. Patients received cotrimoxazole, penicillin V, acyclovir or foscarnet simultaneously with posaconazole. At the time

Table 1 Patient characteristics

Characteristic	Posaconazole		*p* value
	Suspension	Tablets	
	No. of patients (%)		
	$n=31$	$n=32$	
Gender			
Male	19 (61.3)	22 (68.8)	0.7214
Female	12 (38.7)	10 (31.3)	0.7214
Age group			
≤6 years	16 (51.6)	4 (12.5)	0.0022
7–12 years	9 (29.0)	9 (28.1)	1.0
13–17 years	6 (19.4)	19 (59.4)	0.0028
Type of transplantation			
Allogeneic MUD	14 (45.2)	13 (40.6)	0.913
Allogeneic MMFD	11 (35.5)	10 (31.3)	0.929
Allogeneic MFD	4 (12.9)	6 (18.8)	0.772
Autologous	2 (6.5)	3 (9.4)	1.0
Diagnosis			
ALL	3 (9.7)	5 (15.6)	0.741
ALL relapse	2 (6.5)	6 (18.8)	0.277
AML	3 (9.7)	0 (0.0)	0.226
AML relapse	2 (6.5)	1 (3.1)	0.977
JMML	1 (3.2)	0 (0.0)	0.987
MDS	1 (3.2)	2 (6.3)	1.0
NHL	0 (0.0)	2 (6.3)	0.487
Gray zone lymphoma	0 (0.0)	1 (3.1)	1.0
Hodgkin's lymphoma	0 (0.0)	0 (0.0)	1.0
Thalassemia major	4 (12.9)	3 (9.4)	0.964
Aplastic anaemia	1 (3.2)	0 (0.0)	0.987
Sickle cell anaemia	1 (3.2)	1 (3.1)	1.0
Brain tumour	1 (3.2)	4 (12.5)	0.371
Solid tumour	7 (22.6)	7 (21.9)	1.0
Immunodeficiency disorders	4 (12.9)	0 (0.0)	0.113
Neurometabolic disease	1 (3.2)	0 (0.0)	0.987
Radiation			
TBI	4 (12.9)	6 (18.8)	0.772
TLI	3 (9.7)	0 (0.0)	0.226
Conditioning regimen			
MAC	29 (93.5)	26 (81.3)	0.277
RIC	2 (6.5)	2 (6.3)	1.0
CA/TT/FLU	0 (0.0)	1 (3.1)	1.0
CA/TT/ETO	0 (0.0)	3 (9.4)	0.248
GvHD prophylaxis			
Thmyoglobulin Sangstadt	6 (19.4)	6 (18.8)	1.0
ATG	23 (74.2)	23 (71.9)	1.0
Mycophenolate mofetil	11 (35.5)	10 (31.3)	0.929
CsA	4 (12.9)	6 (18.8)	0.772
CsA + MTX	14 (45.2)	14 (43.8)	1.0
GvHD Grade			
I	7 (22.5)	4 (12.5)	0.4704
II	1 (3.2)	1 (3.1)	1.0

Table 1 (continued)

Characteristic	Posaconazole		*p* value
	Suspension	Tablets	
	No. of patients (%)		
	n = 31	*n* = 32	
III	0 (0.0)	1 (3.1)	1.0
IV	0 (0.0)	0 (0.0)	1.0
Skin GvHD			
Stage I	6 (19.4)	3 (9.4)	0.4403
Stage II	1 (3.2)	1 (3.1)	1.0
Stage III	1 (3.2)	2 (6.3)	1.0
Stage IV	0 (0.0)	0 (0.0)	1.0
Intestinal GvHD			
Stage I	0 (0.0)	0 (0.0)	1.0
Stage II	0 (0.0)	1 (3.1)	1.0
Stage III	0 (0.0)	0 (0.0)	1.0
Stage IV	0 (0.0)	0 (0.0)	1.0

ALL acute lymphoblastic leukaemia, *AML* acute myeloid leukaemia, *ATG* anti-thymocyte globulin, *CA* Carboplatin, *CsA* Cyclosporine A, *ETO* Etoposide, *FLU* fludarabine, *GvHD* graft-versus-host disease, *JMML* juvenile myelomonocytic leukaemia, *MAC* myeloablative conditioning regimen, *MDS* myelodysplastic syndromes, *MFD* matched family donor, *MMFD* mismatched family donor, *MTX* methotrexate, *MUD* matched unrelated donor, *n* sample size, *NHL* non-Hodgkin's lymphoma, *RIC* reduced-intensity conditioning regimen, *TBI* total body irradiation, *TLI* total lymphoid irradiation, *TT* thiotepa

of inpatient discharge foscarnet was changed to oral valganciclovir. All patients received a regular balanced diet without coliquid supplements or high-fat nutrition during the observation period.

Administration of posaconazole suspension and tablets

Out of 63 patients, 31 (49.2%) received posaconazole as an oral suspension at a dosage of 4 mg per kg bodyweight three times daily (mg kg BW^{-1} TID) approximately 10–20 min after a meal and 32 patients (50.8%) received posaconazole as tablets. Administration of posaconazole tablets was 5–7 mg kg BW^{-1} twice a day (BID) on the initial day as loading dose and then 5–7 mg kg BW^{-1} once a day (QD). Administration of the posaconazole tablets was adapted to the patients' bodyweight with 100 mg per day (2 × 100 mg on the first day) for patients between >15 and 21 kg, 150 mg per day (2 × 150 mg initially) for patients weighing between 22 and 30 kg, 200 mg per day (2 × 200 mg initially) for patients weighing between 31 and 35 kg, 250 mg per day (2 × 250 mg initially) for patients weighing between 36 and 40 kg and 300 mg per day (2 × 300 mg initially) for patients weighing >40 kg or older than 13 years.

Analysis of posaconazole plasma concentrations

Due to its CYP_{450}-dependent metabolization, drug monitoring of posaconazole is recommended, especially during concomitant medication with other CYP_{450}-dependent agents such as antacids (Sanchez-Ortega et al. 2012). Excess material from routine blood analyses that had been routinely cryopreserved was analysed for posaconazole plasma concentrations for all 63 paediatric patients. The analyses were performed using blood samples taken in the morning between 7 and 10 a.m. on days 2, 3, 5, 7, 10, 14 ± 2 and 28 ± 2 shortly before drug administration including posaconazole. EDTA-anti-coagulated peripheral blood was centrifuged for 2 min at 2000 relative centrifugal force and the supernatant plasma was cryopreserved at −80 °C. Posaconazole plasma concentration was determined using high-performance liquid chromatography on a ReproSil-Pur Basic C_{18} column (150 mm by 2 mm by 5 µm; Dr. Maisch GmbH, Ammerbuch, Germany) and a mobile phase consisting of 0.09 M aqueous ammonium phosphate monobasic (Riedel-de-Haën, Seelze, Germany) and acetonitrile (Merck, Darmstadt, Germany) (50%:50%, (v/v). Posaconazole was detected at 260 nm with a UV–VIS diode array detector as previously described (Kahle et al. 2009).

Efficacy analysis

The efficacy analysis was carried out by observing the clinical signs of an invasive fungal infection and using computed tomography when indicated. In addition, body temperature and CRP (C-reactive protein) were measured daily. Invasive fungal infections were classified according to the EORTC/MSG criteria (De Pauw et al. 2008). Successful treatment was regarded as having no more symptoms related to an invasive fungal infection such as fever, coughing, and normal values of *aspergillus* galactomannan antigen in the absence of increasing infiltrates in radiological imaging, if available. The galactomannan antigen was determined using the PLATELIA™ *Aspergillus* enzyme-linked immunosorbent assay according to the manufacturer's protocol (Bio-Rad Laboratories, Munich, Germany) at least once a week up to 100 days after HSCT or up to a maximum of 200 days after HSCT until $CD3^+$ T-cells were ≥200/µL and $CD4^+$ cells were ≥100/µL.

Assessment of safety and tolerance

Adverse events were graded according to current United States National Cancer Institute's Common Terminology Criteria for Adverse Events (National Cancer Institute 2009). During the observation period, an analysis of liver values, kidney parameters and potassium was performed

daily during inpatient stay and at least twice a week after discharge. The analysis of hepatic toxicity included transaminases alanine aminotransferase (ALT, normal range ≤39 U/L) and aspartate aminotransferase (AST, normal range ≤39 U/L), as well as cholestasis parameters of total bilirubin (normal range ≤1.1 mg/dL), and direct bilirubin (normal range ≤0.3 mg/dL). The evaluation of kidney toxicity involved an examination of serum creatinine (normal range ≤0.7 mg/dL), urea (normal range ≤46 mg/dL), and potassium (normal range ≥3.4 mmol/L). We assessed clinically relevant elevations of >1.5 and >2.5 times the normal values of hepatic and renal parameters, and decreases of potassium values <3.4 mmol/L or <2.4 mmol/L. Blood analyses were documented the day before starting oral monoprophylaxis with posaconazole (baseline), along with the maximum (ALT, AST, total and direct bilirubin, creatinine, and urea) or minimum (potassium) values during and at the end of posaconazole prophylaxis, defined as the last day of posaconazole intake.

Statistical analysis

None of the patients was excluded from the statistical analyses. In case of discontinuation of posaconazole prophylaxis ($n=4$) for reasons other than an adverse event or fungal infection, only the time period until the termination of posaconazole application was used for analyses. The analysed posaconazole levels were measured at 2, 3, 5, 7, 10, 14 ± 2 and 28 ± 2 days after HSCT. The posaconazole plasma concentration data are presented as mean ± standard deviation (SD), as mean ± 95% confidence interval, or as box plots with Tukey whiskers as indicated in the figure legends. Non-parametric statistical tests were applied because of the frequent non-normality of data sets as tested by the Shapiro–Wilk normality test. The Mann–Whitney test was used for statistical comparisons of serum levels in dependence of age and gender in the suspension and tablet group (unpaired samples). Chi square tests were used for testing on equal proportions in the analysis of patient characteristics (Tables 1, 2). The comparison of age differences took place between the three age groups of <6, 7–12, and 13–17 years by applying the Kruskal–Wallis Test. The comparison of posaconazole trough levels within the suspension and the tablet group was performed using the Mann–Whitney test. The levels of ALT, AST, total and direct bilirubin, creatinine and potassium of all patients were analysed at baseline, defined as the day before starting posaconazole monoprophylaxis, along with the maximum or minimum (minimum only for potassium) values during the antifungal treatment, and at the end of posaconazole administration. The Wilcoxon Signed Rank Test was used for comparison with clinical normal values. Statistically significant values were reported depending on their clinical relevance, i.e. only if data were significantly higher or lower than the age-adjusted normal values (=horizontal dotted lines in bar charts). The Wilcoxon matched-pairs signed-ranks test was used for inferential statistical comparisons of the baseline and maximum or minimum values. Graphs and statistical tests were created with GraphPad Prism 6 for Windows, version 6.05 (GraphPad Software. Inc., La Jolla, CA, USA). *P* values of $p<0.05$ (*), $p<0.01$(**), $p<0.001$ (***), and $p<0.0001$ (****) were defined as statistically significant and are symbolized in the bar charts. Study design, data analysis and interpretation were performed under the instruction of a professional biostatistician of the Institute of Clinical Epidemiology and Applied Biometry of the University of Tübingen.

Results

Patient characteristics

This analysis investigates the safety, feasibility, and efficacy of posaconazole as an antifungal prophylaxis after HSCT. A total of 63 paediatric patients were included, with 5 patients after autologous and 58 patients after allogeneic HSCT. Out of 63 patients, 31 (12 females, 19 males) with a median age of 6 years (range 0.6–17 years) received posaconazole suspension (49.2%). The other 32 patients (10 females, 22 males) with a median age of 14 years (range 3–17 years) received posaconazole tablets. In both groups, the percentage of patients with leukaemia, myelodysplastic syndromes (MDS) and non-Hodgkin's lymphoma (NHL) was about 40%. The only detected significant difference between both treatment groups was the rate for the age groups of patients ≤6 years ($p=0.005$) and patients between 13 and 17 years ($p<0.001$) of age. A myeloablative-conditioning regimen (MAC) based on busulfan, treosulfan, melphalan or total body irradiation (TBI) was used in 55 of the 63 patients (87.3%). A reduced-intensity conditioning regimen (RIC) with fludarabine and thiotepa, carboplatin and thiotepa or cyclophosphamide was used in 4 of the 63 patients (6.3%). Patients receiving a graft from a matched unrelated donor (MUD) were given short course methotrexate (MTX) and cyclosporine A (CsA). Patients receiving a graft from a matched family donor (MFD) were given MTX and CsA or CsA only. Patients undergoing haploidentical transplantation received a T cell depleted graft and mycophenolate mofetil only. The median duration of neutropenia (granulocytes <500/µl) was 14 days (range 9–28 days) in the suspension group and 15 days (range 9–22 days) in the tablet group. GvHD occurred in 14 of 63 patients (22.2%), of whom 8 were in the suspension group and 6 were in the tablets group.

Table 2 Clinical and laboratory adverse events during antifungal prophylaxis with posaconazole

Variable	Posaconazole		*p* value
	Suspension	Tablets	
	No. of patients (%)		
	n = 31	*n* = 32	
Drug-related adverse event			
Clinical (total)	3 (9.7)	2 (6.3)	0.971
Nausea	2 (6.5)	1 (3.1)	0.977
Exanthema	0 (0.0)	1 (3.1)	1.0
Lack of appetite	1 (3.2)	0 (0.0)	0.987
Laboratory			
Increase in alanine aminotransferase (ALT)			
>1.5 × upper normal limit (39 U/L)	9 (29.0)	10 (31.3)	0.934
>2.5 × upper normal limit (39 U/L)	11 (35.5)	13 (40.6)	0.872
Increase in aspartate aminotransferase (AST)			
>1.5 × upper normal limit (39 U/L)	7 (22.6)	11 (34.4)	0.449
> 2.5 × upper normal limit (39 U/L)	11 (35.5)	10 (31.3)	0.929
Increase in total bilirubin			
>1.5 × upper normal limit (1.1 mg/dL)	0 (0.0)	0 (0.0)	1.00
>2.5 × upper normal limit (1.1 mg/dL)	0 (0.0)	0 (0.0)	1.00
Increase in direct bilirubin			
>1.5 × upper normal limit (0.3 mg/dL)	2 (6.5)	3 (9.4)	0.971
>2.5 × upper normal limit (0.3 mg/dL)	0 (0.0)	0 (0.0)	1.00
Increase in creatinine			
>1.5 × upper normal limit (0.7 mg/dL)	0 (0.0)	0 (0.0)	1.00
>2.5 × upper normal limit (0.7 mg/dL)	0 (0.0)	0 (0.0)	1.00
Increase of urea			
>1.5 × upper normal limit (46 mg/dL)	0 (0.0)	0 (0.0)	1.00
>2.5 × upper normal limit (46 mg/dL)	2 (6.5)	0 (0.0)	0.458
Decrease of potassium			
<3.4 mmol/L	7 (22.6)	4 (12.5)	0.470
<2.4 mmol/L	0 (0.0)	0 (0)	1.00

Statistical tests: χ^2 test with Yates' correction with GraphPad Prism Version 6.05 on contingency tables
mg/dL Milligram per decilitre, *mmol/L* Millimol per litre, *n* sample size, *U/L* Units per litre

No significant differences were found in the proportions of patient characteristics (Table 1). The majority of patient characteristics were similar in both groups. All patients received a regular balanced diet without coliquid supplements or high-fat nutrition during the observation period.

Treatment and observation period

The median observation period was 108 days (range 41–206 days) for the suspension group, and 106 days (range 45–203 days) in the tablet group. The median treatment period was 98 days (range 27–192 days) for the suspension group, and 91 days (31–189 days) in the tablet group.

Efficacy analysis

None of the patients included in this analysis had a proven, probable or possible fungal infection after HSCT according to the EORTC guidelines (De Pauw et al. 2008). For all 63 patients, the galactomannan antigen showed normal values during the observation period.

Clinical adverse events

In both groups the spectrum of drug-related adverse events was mainly ascribed to gastrointestinal symptoms. In the suspension group 3 of 31 patients (9.7%) experienced adverse events, two with nausea, and one with a short-term loss of appetite. In the tablet group, 2 of 32 patients (6.3%) experienced drug-related adverse events. One experienced

exanthema in the face, and the other experienced nausea. The differences between these two groups were not significant ($p = 1.0$ resp. $p = 0.977$, χ^2 Test with Yates' correction; Table 2). Posaconazole was continued for four of these patients.

Mortality and discontinuation of the drug

Out of 63 patients, 2 (3.2%), both of which were in the suspension group, died during the observation period. One died from an invasive adenovirus infection, and the other from a relapse of the underlying disease. None of the patients died from an invasive fungal infection. In 2 of the 32 patients (6.3%), both of which were in the tablet group, the oral prophylaxis had to be stopped earlier than planned and changed to an intravenous antifungal prophylaxis. The discontinuation was indicated for one patient because of the occurrence of a sepsis 25 days after HSCT. For the other patient, discontinuation was indicated because of a graft rejection and subsequent reconditioning on day 54 after HSCT. Data for all four of the aforementioned patients were kept in the analysis until posaconazole was discontinued.

Safety and tolerance

In the suspension group, the maximum values for liver parameters ALT and AST (ALT mean 100.8 ± 72.06 U/L, AST mean 86.60 ± 52.57 U/L) were significantly higher than the baseline values (ALT mean 32.13 ± 21.06 U/L; $p < 0.0001$; AST mean 33.09 ± 17.54 U/L; $p < 0.0001$). Similar observations were made in the tablet group with significantly higher maximum ALT and AST values (ALT mean 89.97 ± 60.98 U/L; AST mean 75.47 ± 35.51 U/L) than the baseline values ($p < 0.0001$). An increase in ALT of >1.5 and >2.5 times the upper normal limit was observed in 20 out of 31 patients (66.7%) in the suspension group, and in 23 out of 32 patients (71.9%) in the tablet group. An increase in AST of >1.5 and >2.5 times the upper normal limit was observed in 18 of 31 patients (58.1%) in the suspension group and in 21 of 32 patients (65.6%) in the tablet group. Increases of ALT and AST were not significantly higher in the tablet group as compared to the increases of ALT and AST in the suspension group (Table 2). Direct and total bilirubin levels did not significantly change during the observation period. The kidney parameters of creatinine and urea did not significantly increase above the standard value during the study in either of the two groups. Mean minimum potassium values in both groups did not decrease below 3.4 mmol/L. However, hypokalaemia ≤3.4 mmol/L occurred in both the suspension and the tablet group in 7 of 31 patients (29.0%) and in 4 of 32 patients (28.1%), respectively (Table 2).

Posaconazole plasma trough levels

The analysis of posaconazole plasma trough concentrations was performed for all 63 patients enrolled in this analysis. A total of 334 posaconazole trough levels were determined. In the suspension group ($n = 31$) and in the tablet group ($n = 32$), 158 (45.9%) and 176 (51.2%) posaconazole levels were analysed, respectively. Table 3 shows median, mean ± standard deviation (SD), range and sample

Table 3 Posaconazole trough levels after application of suspension or tablets

Treatment group	Day after start	Median [ng/mL]	Mean ± SD [ng/mL]	Range [ng/mL]	Sample size *n*	*n*-fold median*	*p* value**
Suspension	2	71	79 ± 50	28–198	18		<0.0001
	3	133	156 ± 81	45–312	25		<0.0001
	5	209	259 ± 184	41–742	28		<0.0001
	7	252	390 ± 460	54–2441	28		<0.0001
	10	324	447 ± 351	104–1581	22		<0.0001
	14 ± 1	529	643 ± 493	115–2081	19		0.0006
	28 ± 2	634	732 ± 408	290–1664	28		<0.0001
Tablets	2	434	565 ± 348	219–1489	29	6.1	<0.0001
	3	516	607 ± 308	224–1383	26	3.9	<0.0001
	5	662	689 ± 257	355–1555	26	3.2	<0.0001
	7	874	912 ± 422	329–2227	27	3.5	<0.0001
	10	889	888 ± 204	628–1462	19	2.7	<0.0001
	14 ± 1	978	1111 ± 556	404–3060	25	1.8	0.0006
	28 ± 2	1541	1770 ± 815	582–4066	24	2.4	<0.0001

ng/mL nanogram per millilitre, *n* sample size

**n*-fold median values of the suspension group compared to the respective days of the tablet group after starting antifungal prophylaxis

**Comparison of the plasma levels of the treatment groups suspension versus tablets of the respective days after starting antifungal prophylaxis

size for the analysed trough levels in both groups. As displayed in Fig. 1, the trough levels in the tablet group were significantly higher at all analysed time points after starting antifungal prophylaxis compared to the suspension group. The median posaconazole trough levels in the tablet group were 1.8–6.1-fold (median 3.2-fold) higher compared to the suspension group. The biggest difference was found 2 days after starting antifungal prophylaxis with 6.1-fold higher values in the tablet group. The majority of samples and the average concentration per patient showed a sufficient posaconazole concentration of >500 ng/mL in the suspension group on day 14 ± 1 and in the tablet group on day 3 after starting antifungal prophylaxis. Until day 14, 9 patients (0 patients) in the suspension (tablet) group had a posaconazole serum level below 200 ng/mL, respectively. On day 28, 6 patients (0 patients) of the suspension (tablets) group had a posaconazole serum level below the target concentration of 500 ng/mL, respectively. After 14 days of prophylaxis, 22 out of 31 patients (70.9%) in the suspension group but only 1 out of 32 patients (3.1%) in the tablet group had a posaconazole trough concentration below 500 ng/mL (Table 3).

Influence of age on posaconazole plasma levels

In the suspension group, the mean posaconazole plasma concentrations of patients ≤6 years of age were not significantly different from those of patients aged 7–12 years or 13–17 years on day 2 ($p=0.147$), day 3 ($p=0.769$), day 5 ($p=0.456$), day 7 ($p=0.215$), and day 10 ($p=0.485$) after starting antifungal prophylaxis (Fig. 2a). Likewise, no statistically significant differences could be detected on days 14 or 28 for all three age groups (Fig. 2a). In the tablet group, the mean posaconazole plasma concentrations of patients aged ≤6 years were not significantly different from patients aged either 7–12 years or 13–17 years on day 2 ($p=0.177$), day 3 ($p=0.534$), day 5 ($p=0.448$), day 7 ($p=0.986$), day 14 ($p=0.612$) and day 28 ($p=0.214$) after starting antifungal prophylaxis (Fig. 2b).

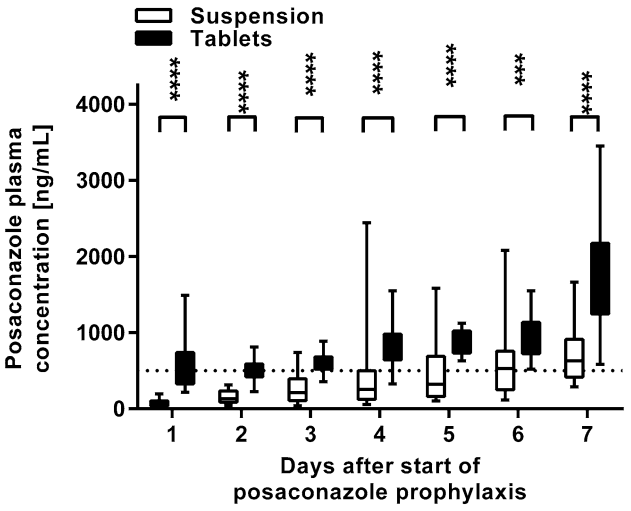


Fig. 1 Posaconazole plasma trough concentration after oral administration of posaconazole suspension or tablets in paediatric patients. A *Graph* shows *boxplots* with whiskers min to max of posaconazole trough plasma concentrations of patients receiving posaconazole suspension or tablets on several points in time after start with antifungal prophylaxis. Comparison of the plasma levels of the suspension group ($n=31$ patients) with the tablet group ($n=32$ patients) shows significantly higher plasma levels in the tablet group at all analysed time points

Influence of gender on posaconazole plasma levels

In the suspension group, the posaconazole plasma concentrations of male patients ($n=19$) were not significantly different from the plasma concentrations of female patients ($n=10$) on day 7 ($p=0.4908$), day 14 ($p=0.7267$) or day 28 ($p=0.2111$) after starting antifungal prophylaxis. After analysing the entire data collective of the observation period no significant differences between male and female patients were detected in the suspension group ($p=0.46$, two-way ANOVA for factor gender; Fig. 2c). In the tablet group, the posaconazole plasma concentrations of male patients ($n=22$) were not significantly different from those of female patients ($n=10$) on day 14 ($p=0.246$) or day 28 ($p=0.715$) after starting antifungal prophylaxis. However, comparison of the plasma concentration of male versus female patients showed a significant difference ($p=0.011$) on day 7 in the tablet group. After analysing the entire data collective of the observation period no significant difference between male and female patients was found in the tablet group ($p=0.183$, two-way ANOVA for factor gender; Fig. 2d).

Discussion

The present analysis addresses the safety, efficacy and pharmacokinetics of posaconazole suspension or tablets for antifungal prophylaxis in paediatric patients up to 200 days after HSCT.

No evidence-based therapeutic target plasma level has been determined yet for paediatric patients. Therapeutic drug monitoring and a posaconazole plasma target concentration of ≥500 ng/mL are recommended according to the guidelines formulated by the 4th European Conference on Infections in Leukaemia (ECIL-4) (Groll et al. 2014). Jang et al. suggest plasma concentrations of at least 500 to 700 ng/mL for protection against fungal infection (Jang et al. 2010). Posaconazole is a highly lipophilic agent with low gastrointestinal absorption rates. Until recently posaconazole was usually formulated as an oral suspension with

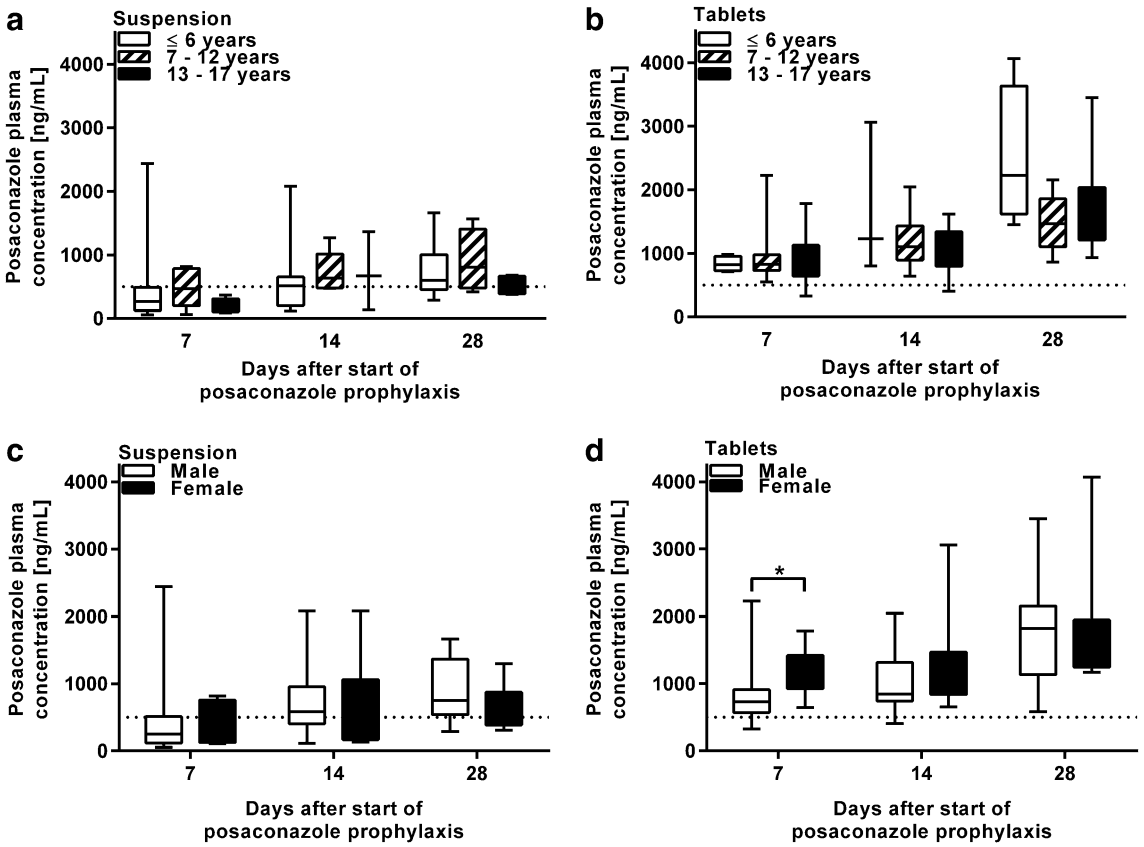


Fig. 2 Posaconazole plasma trough concentration after oral administration of posaconazole suspension or tablets in dependence of age and gender. **a***Graph* shows *boxplots* with min to max of posaconazole trough concentrations of patients in different age groups at 7, 14 or 28 days after starting antifungal prophylaxis with posaconazole suspension. No significant difference could be detected between the age groups. **b***Graph* shows *boxplots* with min to max posaconazole trough concentrations of patients in different age groups at 7, 14 or 28 days after starting antifungal prophylaxis with posaconazole tablets. No significant difference could be detected between the age groups on days 7, 14 and 28 days after starting antifungal prophylaxis. **c** Graph shows *boxplots* with min to max posaconazole trough concentrations of male and female patients at 7, 14 or 28 days after starting antifungal prophylaxis with posaconazole suspension. No significant difference could be detected between male and female patients. **d** Graph shows *boxplots* with minimum to maximum posaconazole trough concentrations of male and female patients at 7, 14 or 28 days after starting antifungal prophylaxis with posaconazole tablets. No significant difference could be detected between male and female patients at 7 or 14 days after starting with posaconazole. On day 7, a significant difference ($p = 0.011$) could be found between male and female patients. *Dotted lines* indicate target posaconazole plasma concentration of 500 ng/mL. Symbols indicate $*p < 0.05$; $**p < 0.01$; $***p < 0.001$; $****p < 0.0001$

an intestinal absorption that is highly sensitive to gastric conditions. Thus, the fat content of food, gastric pH, gastrointestinal passage time, or special gastric conditions such as intestinal GvHD all have a major influence on the achievable plasma concentrations (Krishna et al. 2009; Ullmann et al. 2007). A newly formulated tablet, produced in a hot-melt extrusion process, achieves higher plasma concentrations in adults and its intestinal absorption is mostly independent of gastrointestinal or dietary conditions (Krishna et al. 2012a, b). Data on the administration of posaconazole tablets in children are not available as of yet. To our knowledge, this is the first report on the administration of posaconazole tablets in paediatric patients.

The efficacy of the posaconazole suspension or tablets in the present analysis was comparable. Thus, no possible, probable or proven invasive fungal infection was observed in either treatment group.

Posaconazole suspension

For adult haemato-oncological patients the efficacy, safety and pharmacokinetics of prophylactic or therapeutic posaconazole with respect to different gastric, dietary or clinical conditions, have all been widely investigated in prospective and randomized clinical trials (Cornely et al. 2007; Krishna et al. 2007a; Ullmann et al. 2007). In contrast, the evidence for paediatric patients receiving posaconazole suspension is less pronounced. Thus far, only a few clinical trials with low patient numbers have been carried out, regarding the therapeutic (Cesaro et al. 2011; Krishna et al. 2007b;

Lehrnbecher et al. 2010a) or prophylactic (Cesaro et al. 2011; Döring et al. 2012) use of a posaconazole in immunocompromised paediatric patients. All of these trials show excellent results in terms of the treatment and prevention of invasive fungal infections.

In the present analysis, administration of posaconazole suspension resulted in sufficient plasma concentrations with mean values of >500 ng/mL after approximately 14 days and >700 ng/mL approximately 28 days after starting antifungal prophylaxis which is comparable to the reported plasma concentrations of patients with acute myeloid leukaemia (AML) and MDS receiving 200 mg posaconazole three times a day in a prospective trial (Krishna et al. 2008). In a single centre analysis of 60 paediatric patients after allogeneic HSCT under 12 years of age who received 4 mg/kg bodyweight of posaconazole suspension three times a day, the mean trough concentrations were substantially lower with only 434 ± 241 ng/mL (Döring et al. 2012). An analysis of 15 paediatric patients under 13 years of age who were receiving therapeutic dosages of median 22 mg kg BW^{-1} day^{-1} revealed mean plasma concentrations of 800 ng/mL, which is comparable to the values achieved in the present analysis after 28 days with prophylactic dosages (12 mg kg BW^{-1} day^{-1}) of posaconazole suspension with mean plasma levels of approximately 730 ng/mL (Bernardo et al. 2013). According to our experience, the relatively high plasma concentrations achieved in this analysis, when compared to previously performed studies might be a result of improved training of the nursing staff and health professionals in the administration of posaconazole and the importance of dietary behaviour.

Posaconazole tablets

To date, the use of posaconazole tablets in paediatric patients under 13 years of age has not yet been analysed. Only few analyses address posaconazole trough levels in adolescent and adult patients and healthy volunteers (Durani et al. 2015; Krishna et al. 2012a, b). In a retrospective comparison of posaconazole levels in 93 adult patients taking either the delayed-release tablet or the oral suspension the median posaconazole serum level of the tablet cohort (1655 ng/mL) was significantly higher ($p = 0.004$) than in the suspension cohort (798 ng/mL) (Krishna et al. 2012a). During the present analysis, similar plasma levels were achieved on day 28 in the suspension cohort (median 634 ng/mL) and the tablet cohort (median 1367 ng/mL).

In a prospective trial of a total of 54 high-risk AML and MDS patients with prolonged neutropenia, 20 out of 54 received a dosage of 1 × 200 mg, and 34 out of 54 patients received 1 × 300 mg posaconazole tablet daily as an antifungal prophylaxis. The achieved posaconazole plasma concentrations of these adult patients were comparable to the results achieved in the present analysis (Duarte et al. 2014).

Compared to the suspension group of the present analysis, the tablet group achieved significantly higher posaconazole plasma concentrations from the very beginning of the drug administration as well as on every analysed day after starting posaconazole prophylaxis. More importantly, the tablet group had already reached the target plasma concentration of 500 ng/mL by day 2–3 of posaconazole prophylaxis. The suspension group did not reach this value until day 10. A median posaconazole trough level of 700 ng/mL was achieved on days 7 and 28, respectively. On day 28, all analysed trough levels for the tablet group were >500 ng/mL. This significant improvement of the plasma concentration using posaconazole tablets is of critical importance in avoiding fungal infections in the early and neutropenic phases after HSCT. This represents a substantial advantage for the clinical situation.

Adverse events

Despite the significantly higher plasma levels in the posaconazole tablet group, the incidence of clinical adverse events with gastrointestinal problems such as nausea and vomiting was comparable to those shown in the posaconazole tablet and suspension group, and generally very low. Similar observations were made in clinical trials during prophylaxis with posaconazole suspension (Cornely et al. 2007; Döring et al. 2012, 2014; Schrenk et al. 2015; Ullmann et al. 2007) and tablets (Duarte et al. 2014, MSD & DOHME 09/2013) in adult and paediatric patients. In the present analysis, the transaminases ALT and AST increased significantly beyond the normal range during antifungal prophylaxis with both the suspension and tablets. This was also confirmed in the analysis of paediatric patients treated with posaconazole suspension (Döring et al. 2012, 2014), and adults treated with posaconazole tablets (Krishna et al. 2012b).

Conclusions

Antifungal prophylaxis with posaconazole tablets and suspension showed comparable excellent efficacy. No possible, probable or proven invasive fungal infections occurred in either treatment group during the observation period. The posaconazole trough levels were significantly higher in the tablet group than in the suspension group at all analysed time points after starting antifungal prophylaxis. As early as day 3 after starting posaconazole tablets, over 50% of the posaconazole trough levels were >500 ng/mL, while this was observed on day 14 after start with posaconazole suspension. Thus, in view of safety, efficacy, and feasibility, the posaconazole tablets proved to be a very good

alternative to antifungal prophylaxis using a posaconazole suspension in paediatric patients after HSCT. However, larger prospective trials are required in order to further evaluate these findings.

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Compliance with ethical standards

Conflict of interest WJH received research grants from Merck and Pfizer; serves on the speakers' bureaus of Alexion, Astellas, Bristol-Myers Squibb, Chugai Pharma, Gilead, Janssen, MSD/Merck, and Pfizer; and received travel grants from Alexion, Astellas, MSD/Merck, Novartis, and Pfizer. All other authors declare that they have no conflicts of interest.

This retrospective analysis was performed in accordance with the declaration of Helsinki and under the waiver for retrospective anonymized studies in accordance with the institutional ethics regulations.Data were collected retrospectively, entered in a standardized case report form and anonymized. Informed consent was obtained from all individual participants included in the study or their legal representatives.

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Full Length Article
Pediatric

Utilization of Intravenous Posaconazole in Pediatric Patients Undergoing Hematopoietic Stem Cell Transplant

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A B S T R A C T

Pediatric patients undergoing hematopoietic stem cell transplant (HSCT) are at high risk for fungal infections, including *Candida, Aspergillus*, and Mucorales, necessitating the use of broad-spectrum antifungal agents such as posaconazole for prophylaxis and at times for treatment of invasive fungal infections. When first approved, posaconazole was limited to an immediate-release oral suspension, which exhibited unreliable absorption dependent on co-administration with high-fat meals. During HSCT, patients commonly have significant nausea, vomiting, and decreased enteral intake, making this formulation particularly challenging. In 2014, intravenous (IV) posaconazole became available with its first approval only for adult patients, as there were no data on its use in pediatric patients. This approval has since been expanded to include pediatric patients as young as 2 yr of age. In terms of dosing, however, clinical practice experience supports a significantly higher starting dose than the manufacturer-recommended 6 mg/kg/dose. Current literature involving the use of IV posaconazole in pediatric HSCT patients is limited to studies with small sample sizes and varying dose ranges recommended to achieve posaconazole target levels. Describe the safety and efficacy of IV posaconazole for prophylaxis and treatment of invasive fungal infections in pediatric HSCT patients. This was a single-center, retrospective chart review of pediatric HSCT patients who received IV posaconazole from January 1, 2015, to August 1, 2023. One hundred eighty-two patients were identified as receiving at least one dose of IV posaconazole, and 109 were included in the final analysis. Of these, 105 (96.3%, 95% confidence interval [0.924, 1.01]) patients were able to achieve their target level within a single course of IV posaconazole, defined as continuous treatment with an interruption of no more than 5 days. The median weight-based dose after therapeutic dose adjustments (if necessary), achieving their target level was 10 mg/kg for both prophylaxis and treatment. Additionally, a median fixed dose of 300 mg for prophylaxis (patients weighing ≥30 kg) and 400 mg (patients weighing

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≥40 kg) for treatment were able to achieve target levels. Seventy-eight patients received IV posaconazole for prophylaxis, with three patients (3.8%) requiring an escalation to treatment dosing of an antifungal. Thirty-one patients received IV posaconazole for treatment of either probable (n = 21, 19.3%) or proven fungal infection (n = 10, 9.2%). A total of 22 patients discontinued IV posaconazole due to an adverse event, with hepatic dysfunction being the most common reason (n = 19, 86%). Thirteen patients were able to restart posaconazole after resolution of liver function tests. There was not an association between high levels and discontinuation due to an adverse event. Administration of a loading dose of IV posaconazole at 10 mg/kg every 12 h for two doses, followed by a maintenance dose of 10 mg/kg every 24 h was an effective starting dose for achieving target levels for prophylaxis and treatment in pediatric HSCT recipients. The most common adverse event leading to discontinuation of IV posaconazole was hepatic dysfunction, but a substantial portion of these patients were able to restart posaconazole without repeated issue. To our knowledge, this was the largest study to date evaluating the efficacy of IV posaconazole in pediatric HSCT patients.

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INTRODUCTION

Pediatric hematopoietic stem cell transplant (HSCT) patients are at high risk of invasive fungal infections and therefore require fungal prophylaxis and sometimes treatment with antifungal agents [1]. Posaconazole is an extended-spectrum triazole antifungal agent [1]. Compared with other agents in the same class, posaconazole exhibits enhanced activity against *Candida* sp., *Aspergillus* sp., and Mucorales. When first approved, posaconazole was only available as an immediate-release oral suspension, which is known to exhibit unreliable absorption dependent on co-administration with high-fat enteral nutrition or acidic beverages. Despite the favorable spectrum of activity, the practical utility of posaconazole suspension in the pediatric HSCT population is usually limited by significant nausea, vomiting, and decreased enteral intake. In 2014, intravenous (IV) posaconazole became available and received Food and Drug Administration approval for use in adult patients for prophylaxis of invasive *Aspergillus* and *Candida* infections [2].

Approval has since been expanded to include patients as young as 2 yr of age, but the starting dose recommendation of 6 mg/kg/dose in the package insert is significantly below what is needed to reach optimal exposure per previous studies [1,3–6].

Our initial experience in 24 patients showed that patients required posaconazole dosing as described in our Institutional Dosing Strategy section. Since our initial report, we have continued to dose posaconazole following this dosing scheme and have gathered extensive experience with this dosing and therapeutic drug monitoring. However, there is still a paucity of published data to support this dosing practice. The objective of this study is to describe the safety and efficacy of IV posaconazole in a large cohort of pediatric HSCT patients.

MATERIALS AND METHODS

This was a single-center, retrospective chart review of pediatric HSCT patients during a single course of IV posaconazole at Cincinnati Children's Hospital Medical Center from January 1, 2015, to August 1, 2023. Patients were included in the final analysis if they were less than 18 yr of age at time of initiation of IV posaconazole and had at least one measured posaconazole level associated with the included course of IV posaconazole. Patients were excluded if IV posaconazole was initiated after transplant day +200 due to the complexity of these patients' post-transplant course and potential confounding factors at that point.

A course of posaconazole was defined as continuous treatment with no more than 5 days of interruption in therapy [1,2]. Only the first course of IV posaconazole for a given patient within our study period was included for evaluation. This was done to limit confounders on the clinical effect of IV posaconazole with changes to other formulations or antifungal agents. All posaconazole levels were assessed for appropriate timing such that the patient was at steady-state, defined as at least 5 days of therapy, and the level was reflective of a trough concentration (drawn no more than 3 h prior to the next scheduled dose). Individual levels were excluded if the timing of the lab draw was inappropriate. Posaconazole levels were evaluated once weekly at our institution.

Mass Spectrometry Assay for Serum Posaconazole

Serum posaconazole concentration was measured by a lab-developed test that was fully validated (SOP PATH. CMS.1062, available on request) to meet CAP/CLIA requirements. The assay was based on a stable-isotope dilution electrospray ionization liquid chromatography tandem

mass spectrometry method. Posaconazole, and the added internal standard, [$^2H_4$]posaconazole were extracted from serum by protein precipitation with methanol, chromatographed by reverse phase chromatography, and analyzed on an Acquity UPLC-H Class—Xevo TQ-S triple quadrupole mass spectrometry system. Quantification of posaconazole was accurate and linear over the dynamic range of 0.05 to 10.0 mcg/mL. The inter-run precision (%CV) and accuracy (%bias) for spiked quality control samples prepared at concentrations 0.1, 0.8, 2.0, and 8.0 mcg/mL were 4.13%, 3.02%, 2.24%, and 3.43% and −2.50%, 6.44%, −3.88%, and 6.54%, respectively. The corresponding intra-run precision (%CV) and accuracy (%bias) were 3.66%, 1.54%, 1.51%, and 1.41%, and −6.94%, 2.87%, −6.23%, and 3.37%, respectively. The lower limit of quantification was 0.1 mcg/mL.

Institutional Dosing Strategy

At Cincinnati Children's Hospital Medical Center, IV posaconazole is administered with a loading dose of 10 mg/kg every 12 h for two doses, followed by 10 mg/kg once daily, and may reach the maximum starting dose based on indication from historical data within our institution [7]. Patients receiving IV posaconazole for prophylaxis receive a recommended maximum starting dose of 300 mg. Patients receiving IV posaconazole for treatment receive a maximum starting dose of 400 mg. Dosing described are starting doses and may be adjusted based on therapeutic drug monitoring by levels. Weight-based dosing is done by actual body weight, and no dose adjustments are recommended for renal or hepatic function. Clinical decision-making guides conversion from enteral dosage forms of posaconazole to the IV formulation if the patient was previously therapeutic on an enteral dose.

Safety Assessment

Safety was assessed by reviewing documented reasons for drug discontinuation as well as assessing significant changes in serum creatinine (SCr), cystatin C glomerular filtration rate (GFR), bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), and corrected QT (QTc) interval at any time point from initiation of IV posaconazole and for 3 days after its discontinuation. Baseline organ function was defined as the value most proximal to posaconazole initiation. Changes in SCr > 1.5× baseline, cystatin C GFR > 50% decrease from baseline, bilirubin >2 mg/dL, ALT and/or AST > 3× upper limit of normal (ULN), and prolonged QTc prolongation as defined by age and pubertal status [8] were considered significant and classified as an adverse drug event when IV posaconazole was discontinued due to one of these. Clinical notes were reviewed to record the documented reason for discontinuation. A patient's medication list at the time of posaconazole discontinuation was reviewed for concomitant medications with overlapping toxicity that may have contributed to the adverse event leading to posaconazole discontinuation [9–11].

Target Level Achievement—Prophylaxis

A retrospective chart review was conducted to determine the indication for posaconazole therapy in each patient (treatment or prophylaxis); achievement of their target level was assessed based on the determined indication. The target level for a prophylaxis indication was ≥0.7 mcg/mL. The doses associated with the first achievement of the target levels are reported.

Efficacy Assessment—Prophylaxis

To determine the efficacy of patients receiving IV posaconazole for prophylaxis, we assessed the incidence of breakthrough fungal infection. Patients were categorized as having a probable or proven breakthrough fungal infection if the patient's posaconazole indication changed from prophylaxis to treatment, or if an alternative antifungal agent was added for a treatment indication determined by chart review. Probable fungal infection was defined as clinical worsening requiring escalation of antifungal therapy for treatment purposes, with no histopathologic confirmation, while proven fungal infection was a histopathologic confirmation of a fungal species from a sterile sample. Only proven fungal infections were classified as a true breakthrough fungal infection, as clinical endpoints of proven infection is more clearly defined than probable infections.

Target Level Achievement—Treatment

The target level for a treatment indication was ≥1 mcg/mL. The doses associated with the first achievement of the target levels are reported.

Efficacy Assessment—Treatment

Due to the retrospective nature of this study, it is difficult to assess treatment success in this complex patient population. We utilized the achievement of target levels as a surrogate for efficacy. However, this does not fully capture treatment outcomes; therefore, a description of the patients utilizing IV posaconazole for treatment of a proven fungal infection is also provided.

Statistical Analysis

Descriptive statistics were reported for patient demographics, dosing, and frequency of adverse events. Data is presented as median, range, interquartile range (IQR), frequency, percentages, and 95% confidence interval (CI) where appropriate. Patients were stratified based on the dosing strategy of a weight-based dose or a fixed dose and based on posaconazole indication.

RESULTS

Patient Characteristics

One hundred and eighty-two HSCT patients received IV posaconazole, and 109 were included in the final analysis. Reasons for exclusion are indicated in Figure 1. Patient characteristics are described in Table 1.

Safety

Available results of baseline organ function testing for all patients are described in Table 2. Baseline SCr, bilirubin, ALT, and AST were available for all patients. Baseline cystatin C GFR and QTc were available in 93 (85.3%) and 61 (56%) patients, respectively. Rates and details of adverse events are listed in Table 3.

Overall, 22 (20.2%, 95% CI [0.127, 0.277] patients discontinued IV posaconazole due to an adverse event, but 13 (60%) of these patients were later restarted on posaconazole without any issue. Nineteen patients experienced hepatic dysfunction, one experienced renal dysfunction, one

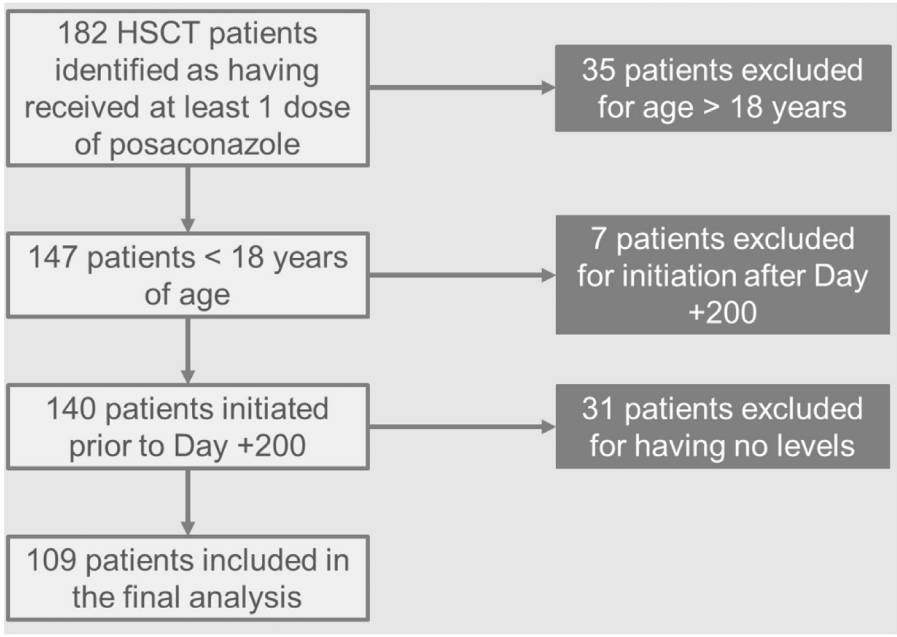


Figure 1. Inclusion and exclusion flowchart.

Table 1
Patient Characteristics

Patient Characteristics, *n* = 109	
	Median (range)/*n* (%)
Age, yr	8 (0.3-17.8)
Dosing weight, kg	26 (6.5-130)
Gender	
Male	71 (65.1)
Race	
African American	11 (10.1)
Asian	5 (4.6)
Caucasian	79 (72.5)
Other	14 (12.8)
Primary diagnosis	
Bone marrow failure	29 (26.6)
Immunodeficiency/metabolic disorder	30 (27.5)
Malignancy	50 (45.9)
Source of graft	
Bone marrow	57 (52.3)
CAR-T	2 (1.8)
Cord	7 (6.4)
Peripheral blood stem cells	43 (39.4)
Conditioning regimen	
Myeloablative	74 (67.9)
Reduced intensity	35 (32.1)
IV posaconazole course duration, days	23 (3-148)
Indication	
Prophylaxis	78 (71.6)
Probable fungal infection*	21 (19.3)
Proven fungal infection†	10 (9.2)

CAR-T indicates chimeric antigen receptor T-cell; IQR, interquartile range.
* Presence of at least 1 host factor, clinical feature, and mycologic evidence in immunocompromised patients.
† Detection of fungal species by histology or culture.

Table 2
Baseline Organ Function

	Patients with Available Data	Median (IQR)
Baseline renal function		
SCr, mg/dL	109	0.33 (0.24-0.47)
Cystatin C GFR, mL/min/1.73 m^2	93	116 (80-148)
Baseline hepatic function		
Bilirubin, mg/dL	109	0.5 (0.3-0.9)
ALT, U/L	109	27 (15-52)
AST, U/L	109	27 (18-47)
Baseline QTc		
QTc, ms	61	432 (409-437)

Table 3
Frequency of Adverse Events

	Total Evaluable Patients	Patients with Adverse Events (%)
Renal function		
SCr > 1.5× baseline	109	49 (45)
Cystatin C GFR > 50% decrease from baseline	93	24 (25.8)
Hepatic function		
Bilirubin > 2 mg/dL	109	43 (39.4)
ALT > 3× ULN	109	50 (45.9)
AST > 3× ULN	109	41 (37.6)
QTc		
Prolonged QTc	61	13 (21.3)

experienced an infusion-related reaction, and one experienced diarrhea. No patients discontinued IV posaconazole due to prolonged QTc. One patient died due to cytomegalovirus viremia before being able to retrial IV posaconazole. Of the patients who discontinued posaconazole (n = 19) due to hepatic dysfunction, three had concomitant diagnosis of liver sinusoidal obstruction syndrome, and six were receiving treatment for graft versus host disease, including liver graft versus host disease in two of these patients. A list of hepatotoxic medications that patients received at the time of posaconazole discontinuation are listed in Table 4, with an average of 2.5 concomitant hepatotoxic medications per patient. The median level of posaconazole drawn prior to discontinuation due to an adverse event was 1.73 mcg/mL (IQR 1.13 to 2.42 mcg/mL), with the highest reported level of 8.3 mcg/mL in one patient. Patients who discontinued due to an adverse event were on IV posaconazole for a median of 23 days (IQR 12 to 30 days) at time of discontinuation.

Target Level Achievement—Overall

For the 109 patients included in the study, a total of 361 levels were drawn appropriately. Ninety-four patients (86.2%, 95% CI [0.797, 0.927]) reached the goal target level on the first level assessment. An additional 11 patients underwent dose adjustments and were able to achieve their target level within this course of IV posaconazole. Sixty (96.8%, 95% CI [0.924, 1.01]) of patients utilizing our weight-based dosing and 45 (93.8%, 95% CI [0.87, 1.01]) of patients utilizing our fixed

Table 4
Concomitant Hepatotoxic Medications for Patients who Discontinued IV Posaconazole due to Hepatotoxicity

Medication	n (%)
TPN/ILE	17 (89)
Cyclosporine	7 (37)
Olanzapine	6 (32)
Infliximab	4 (21)
Mycophenolate	3 (16)
Rituximab	3 (16)
Decitabine	2 (10)
Ruxolitinib	2 (10)
Tacrolimus	2 (10)
Busulfan	1 (5)

ILE indicates injectable lipid emulsion; TPN, total parenteral nutrition.

Table 5
IV Posaconazole Dose Associated with Achievement of Target Level by Indication

	n	Median (IQR)	Minimum	Maximum
Weight-based dosing—mg/kg				
Prophylaxis	46	10 (9.7-10.1)	3.7	16.5
Treatment	16	10 (9.6-10.1)	9.1	13.7
Fixed dosing—mg				
Prophylaxis	30	300 (300)	300	400
Treatment	13	400 (400)	300	600

dosing strategy achieved target levels. Four patients were not able to achieve their target level; one patient stopped posaconazole due to an anticipated drug interaction, and three patients were eventually successfully switched to oral posaconazole.

For further analysis, patients were stratified based on the dosing strategy of a weight-based dose or a fixed dose and based on posaconazole indication (Table 5). For all patients achieving target, the median posaconazole level was well within safe limits of 1.9 mcg/mL (IQR 1.2 to 2.6 mcg/mL), with a minimum level of 0.72 mcg/mL and highest reported level of 8.3 mcg/mL. Median time to first target level for all patients was 7.5 days (IQR 6 to 12 days).

Target Level Achievement—Prophylaxis

Seventy-eight patients received IV posaconazole for fungal prophylaxis. Table 5 describes the median doses associated with the achievement of target levels by indication. Figures 2 and 3 demonstrate the distribution of doses associated with achievement of target levels for weight-based dosing and fixed-dosing, respectively (Figure 4).

Efficacy—Prophylaxis

Of the 78 patients receiving posaconazole for prophylaxis, 75 (96%, 95% CI [0.917, 1]) were never escalated to treatment dosing. Three patients (3.8%, 95% CI [−0.004, 0.08]) were escalated to treatment dosing of an antifungal. One patient (1.3%, 95% CI [−0.012, 0.038]) had a proven breakthrough fungal infection, requiring a switch to an alternative antifungal agent due to growth of a resistant *Candida* sp. The other two patients required a temporary escalation in their target levels for posaconazole due to acute decompensation for a probable fungal infection and were later transitioned back to prophylactic targets. The median time to target level for prophylaxis patients was 7.7 days (IQR 6.8 to 12 days).

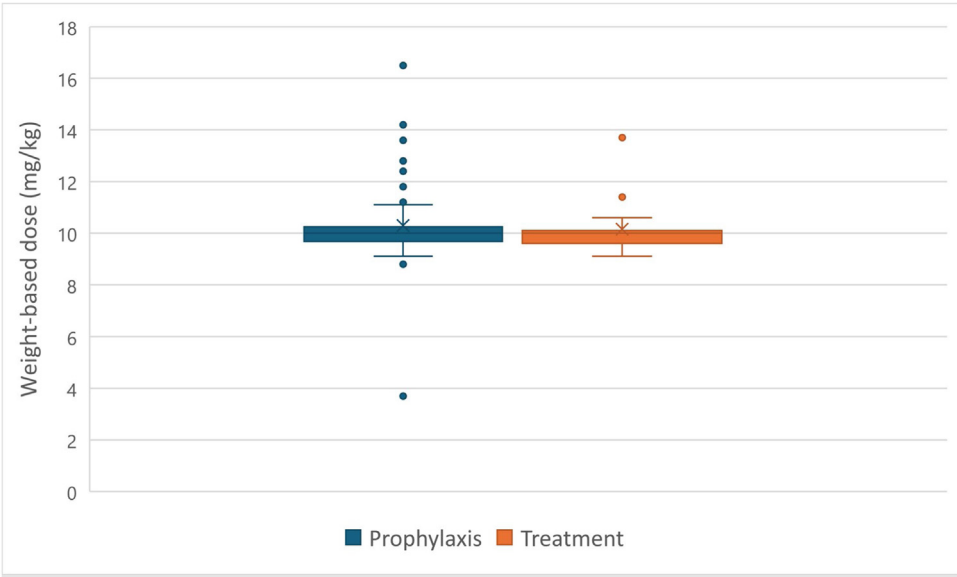


Figure 2. Weight-based IV posaconazole dosing leading to achievement of target level.

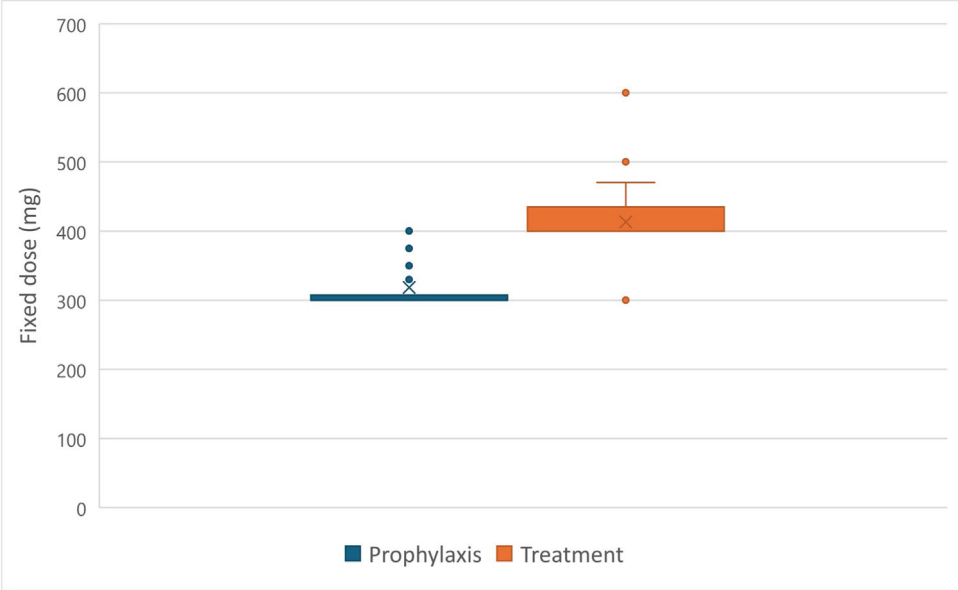


Figure 3. Fixed IV posaconazole dosing leading to achievement of target level.

Target Level Achievement—Treatment

Thirty-one patients received posaconazole for treatment of probable (n = 21, 19.3%) and proven (n = 10, 9.2%) fungal infections. Table 5 describes the median doses associated with target level achievement by indication. The median time to target level for these patients who were determined to be at steady state with IV posaconazole was 6 days (IQR 5.5 to 9.6 days).

Efficacy—Treatment

Patients treated for a probable fungal infection were committed to a treatment course without clearly defined endpoints for resolution of infection driven by clinical improvement (rather than by microbial clearance or imaging) and therefore could not be definitively assessed for treatment efficacy. The 10 patients treated for a proven fungal infection are described in Table 6. No patients included in this study died of fungal infection.

DISCUSSION

To our knowledge, this is the largest study evaluating the safety and efficacy of IV posaconazole in pediatric patients undergoing HSCT. Posaconazole dosed according to our algorithm resulted in

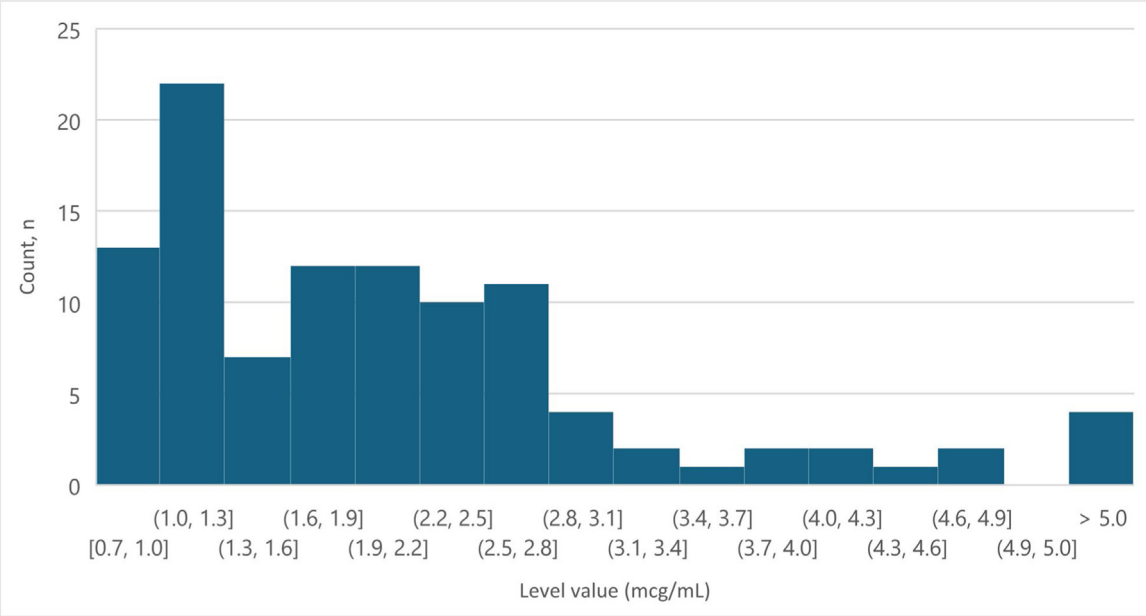


Figure 4. Distribution of target levels.

Table 6
Patient Demographics and Details for Treatment of Proven Fungal Infections

Patient ID	Age (Yr)	Pre or Post HSCT	Underlying Diagnosis	Culture Source	Organism	Prior Antifungal	Time to Target Level (Days)	Dose Achieving Target level		Duration of IV Posaconazole (Days)	Outcome
								Fixed	Weight-Based		
1	16	Pre	ALL	Tissue (ear canal)*	*Aspergillus* sp.	Micafungin ppx	4.1	400 mg	-	98	Adequate response; switch to enteral posaconazole
2	15.5	Pre	AML	BAL	*Candida glabrata*	Enteral posaconazole treatment	4	400 mg	-	13	Adequate response; switch to enteral posaconazole
3	15.7	Post	ALL	BAL	*Scedosporium apiospermum*	Micafungin ppx	3.5	400 mg	-	42	Adequate response; switch to enteral posaconazole
4	2.1	Post	Aplastic anemia	Blood*	*Fusarium* sp.	Enteral posaconazole treatment	6	-	10 mg/kg	22	Adequate response; switch to enteral posaconazole
5	0.8	Post	WAS	Blood	*Malassezia pachydermatis*	Amphotericin treatment	14.1	-	9.1 mg/kg	28	Hepatic dysfunction (hyperbilirubinemia)
6	5.8	Pre	AML	Unknown*	*Aspergillus* sp.	Enteral posaconazole treatment	2		18.2 mg/kg	9	Adequate response; switch to enteral posaconazole
7	12	Pre	DOCK8 def	Tissue (chest cavity)	*Histoplasmosis capsulatum*	Itraconazole treatment	6		10.1 mg/kg	5	Adequate response; switch to enteral posaconazole
8	17.1	Post	AML	Tissue (sinus)	Zygomycetes	Enteral isavuconazole	14	400 mg	-	73	Patient transferred to outside hospital for oncologic clinical trial
9	15.1	Post	AML	Tissue (sinus)*	*Aspergillus* sp.	Enteral posaconazole treatment	4.1	600 mg	-	26	Adequate response; switch to enteral posaconazole
10	16.5	Post	ALL	Tissue (sinus and thigh)	*Candida parapsilosis*	Micafungin ppx	7.9	400 mg	-	129	New lesions >3 mo on therapeutic posaconazole; switched to micafungin treatment for presumed resistance

ALL indicates acute lymphoblastic leukemia; AML, acute myeloblastic lymphoma; ppx, prophylaxis; WAS, Wiskott–Aldrich syndrome.
* Reported positive from outside hospital.

the majority of patients reaching their desired target level within the first course.

The majority of our doses were concentrated around the reported medians, but we did note a few outliers. There was no correlation between patient characteristics and need for a significantly higher or lower dose. We hypothesize a potential role of CYP3A4 polymorphisms or even phenoconversion while in a hyperinflammatory state in these select patients. Further investigation is warranted to investigate this.

While our standard practice is to administer loading doses of posaconazole, only 54.1% of patients received loading doses. This was in large part due to transitioning from therapeutic enteral posaconazole to IV, which is viewed as the only clinical reason to not recommend loading doses of IV posaconazole. Two-thirds of the patients who did not receive loading doses were transitioned from therapeutic enteral posaconazole.

As the primary evaluation of efficacy for prophylaxis, we measured the rate of breakthrough fungal infections in our patient population. Our rate of breakthrough proven fungal infection occurred in only 1.3% of patients receiving posaconazole for prophylaxis. This rate is lower than the currently reported rates of 5% to 12% breakthrough invasive fungal infection (IFI) in pediatric HSCT patients [12]. Although only a surrogate marker for efficacy, blood concentrations of posaconazole are regularly used to assess the efficacy of the medication regimen. Target levels vary according to indication, with a higher target level desired for treatment compared to prophylaxis. Studies have established the clinically accepted practice of target levels of $\geq$0.7 mcg/mL for prophylaxis and $\geq$1.0 mcg/mL for treatment [13,14]. Although there is not a definitive upper limit, posaconazole levels $>$5 mcg/mL are variably reported to be associated with greater adverse events with no additional clinical benefit. Additionally, emerging adult studies suggest a possible dose-dependent toxicity of pseudo-hyperaldosteronism with concentrations greater than 3 mcg/mL; symptoms of this complication can be difficult to identify in pediatrics [15]. A total of eight patients had a measured posaconazole level $>$5 mcg/mL in this cohort; only one discontinued experienced hyperbilirubinemia, and this was associated with a level of 8.3 mcg/mL. The remaining patients did not undergo further dose adjustments while on the IV formulation, despite these high levels, did not discontinue due to an adverse event, and were transitioned to enteral posaconazole.

Bernardo et al. [4] reported their experience in 54 patients, with 81% of patients achieving their target level with a median weight-based dose of 9.8 mg/kg/day, with a maximum of 300 mg. Our data demonstrate a higher rate of success with achieving the target level with a similar weight-based dosing of 10 mg/kg/day. Our higher success rates could be explained, at least in part, by the fact that we utilized a maximum starting dose of 400 mg for the treatment of fungal infections, whereas they used a maximum starting dose of 300 mg regardless of indication. Lambrix et al. [1], reported their experience with 25 patients utilizing treatment dosing of 9 to 12 mg/kg/day. In this small study, a median dose of 8.3 mg/kg/day achieved a treatment posaconazole level of 1 to 5 mcg/mL. In contrast to ours and other studies, Nickless and colleagues reported that a median dose of 6.5 mg/kg was needed to achieve their target level. Reasons for this lower dose requirement is likely because they aimed for concentrations $>$0.7 mcg/mL for both treatment and prophylaxis. Additionally, they calculated the weight-based dose for older, larger patients that we analyzed separately as our "fixed-dosing group," thus lowering their overall median weight-based dose. Unfortunately, the current literature does not report time to a target level, but we found that the median time to target level in our cohort was 7.7 and 6 days for prophylaxis and treatment, respectively. This aligns with the estimated time to steady-state of posaconazole and is important to ensure adequate prophylactic coverage or treatment in these high-risk patients.

Twenty-two patients (20%) discontinued posaconazole due to an adverse event. The rates of adverse effects described in our study are higher than seen in manufacturer-sponsored clinical trials, but our discontinuation rates due to an adverse event were similar to those reported at about 20% [16]. Additionally, rates of increased transaminases are similar to those reported in previous studies [4]. It should be noted that it is difficult to assess the safety of IV posaconazole in this patient population, as some of the post-transplant complications can mimic adverse effects from posaconazole, and most are receiving concomitant medications with overlapping toxicity. Additionally, varying degrees of toxicities may be tolerated, dependent on patient-specific factors such as treatment of a proven fungal infection, for example. The adverse events we selected are well-established class effects related to hepatotoxicity and QTc prolongation of azole antifungals, with the addition of renal function due to the

manufacturer warning for use of IV posaconazole in renal impairment due to the excipient cyclodextrin [2]. While we did note high rates of renal impairment, we postulate it is unlikely to be caused by the use of IV posaconazole but rather due to the complex clinical status of these patients. We support this by the identification that only one patient discontinued IV posaconazole due to severe renal impairment. Hyperaldosteronism was not evaluated as part of this study due to the exceptional difficulty in differentiating this as a posaconazole-related adverse event in this patient population. Hyperaldosteronism would most commonly present as hypertension and hypokalemia. Hypertension is a shared effect of calcineurin inhibitors and corticosteroids, commonly co-administered in HSCT patients receiving posaconazole, and can be a sign of uncontrolled thrombotic microangiopathy, which is also not an uncommon comorbidity in HSCT patients.

The median level of posaconazole drawn nearest to the time of discontinuation due to an adverse event was 1.73 mcg/mL (IQR 1.13 to 2.42 mcg/mL), which did not differ greatly from the median initial target posaconazole levels of 1.9 mcg/mL (IQR 1.2 to 2.6 mcg/mL) for all patients. The patient with a posaconazole level of 8.3 mcg/mL was being treated for a probable fungal infection, and we discontinued IV posaconazole due to hyperbilirubinemia of 14.4 mg/dL. We did not find a clear association between elevated levels and rates of adverse events leading to discontinuation; this relationship warrants further investigation in future studies.

There were four patients who did not achieve a target level during the evaluated IV posaconazole course. No correlation between age or weight was identified for these patients that could suggest a difficulty in achieving target levels in a specific patient subpopulation. Ages of these four patients ranged from 3.3 to 15.8 yr, with one female and three males. We suspect that a patient with a high weight and/or body mass index may contribute to the difficulty in achieving target levels. The weights, weight percentile, and body mass index of the patients unable to achieve target levels were 19.8 kg (88th percentile, 16.4 kg/m^2), 55.7 kg (29th percentile, 18.62 kg/m^2), 68.8 kg (98th percentile, 25.18 kg/m^2), and 72.6 kg (88th percentile, 27 kg/m^2). Three of these patients were transitioned to enteral posaconazole after relatively short courses of IV posaconazole (durations of 5, 6, and 15 days); it's postulated that they may have been able to achieve target levels if they had a longer course for further dose adjustments to be made.

The primary limitation of this study is its retrospective nature. We relied on clinical documentation to determine the reason for drug discontinuation, and the retrospective nature of the study prevented us from being able to accurately assess for side effects such as hyperaldosteronism. Further, utilization of posaconazole levels as a surrogate marker for efficacy does not fully capture the clinical effectiveness of IV posaconazole for treatment of fungal infections. Posaconazole levels are also only evaluated once per week at our institution, making time to target levels limited by this constraint.

Despite these limitations, to our knowledge, this is the largest published study describing the safety and efficacy of IV posaconazole in pediatric HSCT patients. This study is not intended to alter recommendations for selection of antifungal agents, but rather to serve as guidance for those utilizing IV posaconazole. Our study confirms that posaconazole dosing by our described algorithm is safe and effective for the prophylaxis and treatment of invasive fungal infections in pediatric HSCT patients. The results of this study support our standard clinical practice, although our dosing exceeds the package insert recommendations in order to obtain the desired target levels associated with posaconazole efficacy, and may be used as a model for other institutions serving pediatric patients. Additionally, the rate of adverse events in our study is consistent with previous literature and suggests that the recommended posaconazole dosing is safe for pediatric HSCT population. Larger, prospective, multi-institutional studies should be conducted to confirm these findings.

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Ethic Approval Statement: Our local Institutional Review Board determined that this project was exempt from review in accordance with applicable regulations and institutional policy.

Conflict of Interest Statement: There are no conflicts of interest to report.

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Plasma exposures following posaconazole delayed-release tablets in immunocompromised children and adolescents

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Background: Posaconazole is a recommended option for antifungal prophylaxis in paediatric patients >12 years of age. However, little is known about plasma exposures and safety following administration of the delayed-release tablets (DRTs) in children and adolescents.

Methods: In a retrospective observational study, we analysed steady-state trough concentrations of posaconazole in all paediatric patients who had received the DRT formulation between May 2015 and December 2018 for antifungal prophylaxis. Dosing was guided by a published population pharmacokinetic model with weight-based dosing. Drug concentrations in plasma were measured by a validated tandem MS method. Liver function and drug discontinuations due to adverse effects were also assessed.

Results: A total of 34 patients (21 male, 13 female; median age 12 years, range 5–17 years; median body weight 43.5 kg, range 16–84 kg) undergoing treatment for haemato-oncological disorders (n=23) or immunosuppression for polyarthritis (n=1) or post-allogeneic HSCT (n=11) received posaconazole DRTs for a median of 70 days (range 9–391 days). The median first steady-state trough plasma concentration following model-derived dosing was 1607 ng/mL (range 501–8485 ng/mL) with trough concentrations being above the dosing target of ≥700 ng/mL in 32/34 patients (94%). Considering all (first and subsequent) trough concentrations, target attainment was 90% (63/70 samples). Posaconazole was well tolerated without adverse event-related discontinuations or breakthrough infections.

Conclusions: Administration of posaconazole DRTs to paediatric patients guided by a population pharmacokinetic-derived dosing algorithm resulted in predictable and potentially effective exposures and was well tolerated over prolonged time periods.

Introduction

Invasive fungal diseases (IFDs) remain important causes of morbidity and mortality in immunocompromised children and adolescents receiving treatment for haematological malignancies and in those undergoing allogeneic HSCT.[1] Using a risk-based approach and internationally acknowledged concepts of paediatric drug development, paediatric-specific guidelines developed by the European Conference on Infections in Leukemia (ECIL) strongly recommend antifungal prophylaxis in children and adolescents with acute and recurrent acute leukaemia and in those undergoing allogeneic HSCT. Referring to pivotal clinical trials conducted in adults, mould-active, azole-based prophylaxis with a preference for posaconazole is recommended in all circumstances where it is not contraindicated owing to age, organ impairment or clinically relevant drug–drug interactions.[2,3]

Posaconazole is a lipophilic antifungal triazole with potent and broad-spectrum antifungal activity *in vitro* and efficacy in clinically relevant animal models of opportunistic and endemic fungal infections.[4,5] Apart from indications for antifungal treatment, posaconazole is approved in the USA, Canada, the EU and other countries for antifungal prophylaxis in adult patients at high risk of developing IFDs.[6,7] This indication is based on two milestone clinical trials in adult patients with AML or the myelodysplastic syndrome (MDS) and in allogeneic HSCT patients, respectively, that have demonstrated a reduction in invasive fungal infections and in invasive aspergillosis[8,9] and improved overall survival versus the active comparator.[8] Posaconazole was well tolerated in these two pivotal

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trials[8,9] and the compound's favourable safety profile has now been corroborated in more than 10 years of clinical use.[10–12]

Posaconazole is available as an oral suspension, as a solid delayed-release tablet (DRT) formulation and as an intravenous solution in sulfobutylether-β-cyclodextrin.[6,7] In both adults[13,14] and children,[15–17] the oral suspension has been demonstrated to have unpredictable absorption that depends on administration with a high-fat meal or nutritional supplement, gastric pH, mucosal health and frequency of administration.[18,19] As a consequence, the development of the suspension for children has been discontinued by the manufacturer for reasons of poor oral bioavailability.[17] The solid oral DRT formulation, in contrast, contains a pH-sensitive polymer matrix that inhibits the release of posaconazole prior to reaching the small intestine and has been shown in studies conducted in adults to confer enhanced oral bioavailability that is independent of gastric physiology, and less variability in exposure.[20–22]

While the oral posaconazole formulations are approved in the USA in patients >12 years of age[6] on the basis of very limited data, they are not approved for paediatric age groups in the EU[7] and little is known about plasma exposure and safety in the paediatric population, particularly after administration of the DRT formulation. We therefore analysed plasma exposure and safety of posaconazole in all children and adolescents who received the DRT formulation as primary or secondary prophylaxis at our department between May 2015 and December 2018.

Patients and methods

In a retrospective observational single-centre cohort study, we analysed steady-state trough plasma concentrations and key safety endpoints of posaconazole in all children and adolescents (<18 years old) with cancer or following allogeneic HSCT who had received the DRT formulation between May 2015 and December 2018 for primary or secondary antifungal prophylaxis and in whom therapeutic drug monitoring (TDM) was performed.

The Department of Pediatric Hematology and Oncology of the University Children's Hospital of Muenster is one of the largest paediatric cancer centres in Germany. Each year, 140 to 160 patients with a new diagnosis of cancer, 20 to 40 patients with recurrent cancer and ∼35 patients scheduled to undergo allogeneic HSCT are admitted.[23] Posaconazole prophylaxis is an established institutional standard of care for patients >12 years old with high-risk or recurrent leukaemia, high-risk lymphomas and those undergoing allogeneic HSCT; patients ≤12 years old may receive the compound after careful risk/benefit evaluation, and TDM is recommended if the suspension is used.[24] Dosing of the DRT formulation in high-risk patients was guided by a non-parametric population pharmacokinetic model that aimed to derive dosage regimens to maintain 24 h trough concentrations of >1000 ng/mL for paediatric patients with body weights between 10 and 50 kg, in 10 kg increments. Dosing regimens obtained by the model included 300 mg twice-daily loading doses on day 1 and 300 mg once daily for maintenance for >30–50 kg body weight; a 300 mg loading dose, then 300/200 mg alternating daily maintenance doses for >20–30 kg body weight; and a 200 mg loading dose and 200 mg daily maintenance doses for 10–20 kg body weight, respectively.[25] Drug concentrations in plasma were measured by a validated tandem MS method.[26] A trough concentration in plasma of ≥700 ng/mL was considered as the dosing target in the setting of primary or secondary antifungal prophylaxis.[22,27,28]

Patients were included in the study if they fulfilled the following criteria: aged <18 years; receipt of DRT formulation of posaconazole for primary or secondary prophylaxis with weight-based dosing as outlined above; no use of posaconazole in oral or intravenous formulation for prophylaxis or treatment in the last 7 days; and at least one plasma concentration after the fourth day following the start of posaconazole DRTs to permit adequate time to achieve steady-state concentrations. Samples were drawn 1–2 h prior to administration of posaconazole, centrifuged and kept at −20°C until assay. For all patients, demographic data, underlying disease, body weight and height, and laboratory parameters of hepatic function immediately before, during and after cessation of posaconazole were collected in pseudonymized form and analysed. The rates of drug discontinuations due to Common Toxicity Criteria (CTC) grade III or IV adverse effects or intolerance to posaconazole and proven or probable breakthrough infections[29] were also assessed.

All statistical analyses were performed using SPSS, version 23.0 (SPSS, Chicago, IL, USA). For non-descriptive statistics, a two-tailed *P* value of <0.05 was considered significant.

Ethics

Written informed consent for use of the patient's pseudonymized medical data for scientific or auditing purposes and the possible use of medications that are not approved for paediatric use was obtained within the consent procedure for cancer treatment, HSCT and specialized medical care at the Department of Pediatric Hematology and Oncology.

Results

A total of 34 patients (21 male/13 female) were eligible for the analysis. Underlying conditions included *de novo* or recurrent acute leukaemia (23 patients), *de novo* or recurrent non-Hodgkin lymphoma (3 patients), bone marrow failure syndrome (3 patients), Langerhans cell histiocytosis, chronic granulomatous disease, recurrent nephroblastoma, synovial sarcoma and polyarthritis treated with immunosuppressive therapy (1 patient each). Eleven patients were status post-allogeneic HSCT and receiving immunosuppressive therapy. The median age was 12 years (range 5–17 years; 18 patients ≤12 years) and the median body weight was 43.5 kg (range 16–84 kg) (Table 1).

Based on body weight and the corresponding model-derived dosing recommendation, posaconazole DRTs were started at the adult dose of 300 mg once daily (300 mg twice daily on day 1) in 25 patients and at a modified, reduced dose in 9 patients. The dosage was subsequently decreased in three patients receiving 300 mg once daily who exhibited trough concentrations exceeding 5000 ng/mL, and increased in two patients receiving alternating doses of 200 and 300 mg once daily who exhibited trough concentrations below 1000 ng/mL. These dosage modifications were made pre-emptively by the attending physician to avoid potential toxicity and inadequate exposure, respectively. The median duration of posaconazole treatment in the 34 patients was 70 days (mean 105 days) with a range of 9–391 days.

A total of 70 trough concentrations were obtained: 19 patients had at least 2 concentration values and 10 patients had either 3 (n=4), 4 (n=1), 5 (n=3) or 6 (n=1) concentration values, respectively. The median first steady-state trough plasma concentration of the entire cohort following model-derived dosing was 1607 ng/mL (mean 2308 ng/mL; range 501–8485 ng/mL) with trough concentrations above the dosing target of ≥700 ng/mL observed in 32/34 patients (94%). Considering all (first and subsequent) trough concentrations, target attainment was 90% (63/70 samples). Of note, concentrations above 4000 ng/mL were observed in 9/70 trough concentration measurements (12.9%; eight patients) (Figure 1).

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Table 1. Demographics of patients receiving the DRT formulation of posaconazole for primary or secondary antifungal prophylaxis

Patient characteristic	Value
Total number of patients	34
Age, years, median (range)	12 (5–17)
Gender (male; female)	21; 13
No. patients ≤12 years old	18
Body weight, kg, median (range)	43.5 (16–84)
Underlying condition (*n*)	
de novo/recurrent acute leukaemia	23
de novo/recurrent non-Hodgkin lymphoma	3
bone marrow failure syndrome	3
Langerhans cell histiocytosis	1
chronic granulomatous disease	1
recurrent nephroblastoma	1
synovial sarcoma	1
polyarthritis[a]	1
status post-allogeneic HSCT	11

[a]Receiving immunosuppressive therapy with mycophenolate mofetil and methylprednisolone.

Consistent with the model-derived, weight-based dosing approach, posaconazole exposure did not differ between children and adolescents: mean trough [±standard error of the mean (SEM)] concentrations in patients ≤12 years old and in those 13 years and older were 2416±311 and 1871±231 ng/mL, respectively ($P > 0.05$). Target attainment rates were also similar: 34 of 37 samples in children ≤12 years (92%) and 29 of 33 samples in adolescents ≥13 years old (88%) revealed posaconazole trough concentrations ≥700 ng/mL ($P > 0.05$). Furthermore, no differences in mean (±SEM) posaconazole trough concentrations were observed between children and adolescents weighing <50 kg and ≥50 kg at the start of treatment (2262±267 versus 1942±263 ng/mL, $P > 0.05$).

Posaconazole was well tolerated without adverse event-related discontinuations or signals of clinical or laboratory hepatic toxicity [baseline versus end of therapy, mean±SEM: serum bilirubin 0.86±0.11 versus 0.95±0.15 mg/dL; serum glutamic oxaloacetic transaminase 52.7±11 versus 52.4±8 IU/L; serum glutamate-pyruvate transaminase 89.8±19 versus 81.6±13 IU/L; alkaline phosphatase (ALP) 153.9±29 versus 216.9±50 IU/L); $P > 0.05$ for all comparisons with the exception of ALP ($P = 0.044$)]. There was no apparent correlation between patient age or posaconazole exposure with laboratory values at the end of therapy. No invasive fungal breakthrough infection or disease progression was observed among the 34 patients while on posaconazole prophylaxis.

Discussion

In this retrospective cohort study in severely immunocompromised children and adolescents at high risk of IFDs, administration of posaconazole DRTs using a population pharmacokinetic model-based dosing algorithm and a dosing target of trough concentrations ≥700 ng/mL yielded target attainment rates exceeding 90% after the first and subsequent measurements. The DRT formulation was well tolerated over prolonged periods of time and no breakthrough IFD or IFD progression was observed while on treatment with posaconazole.

The pharmacokinetics of posaconazole in children and adolescents <18 years old have not been conclusively studied to date. Early data obtained in 12 paediatric patients >8 years old receiving the oral suspension formulation at the adult dosage suggested no fundamental differences in trough plasma concentrations relative to those observed in adults;[30] in similarly small numbers of children, a twice-daily dosing algorithm based on allometric scaling[31] and dosing according to body surface area[32] appeared to result in adequate exposures. However, reflecting published clinical experience,[15,16] a large, international paediatric Phase Ib dose-escalation trial of the oral suspension initiated by the manufacturer to define paediatric doses was discontinued for failure to achieve the pharmacokinetic target in any of the age groups across the different dosage cohorts.[17] Similar to the situation in adults,[33] decreasing bioavailability with increasing dose was observed in this and other large analyses.[17,34] New formulations of posaconazole with greater potential to achieve the established pharmacokinetic target, including the intravenous solution in sulfobutylether-β-cyclodextrin and a new oral delayed-release suspension are currently under clinical investigation to provide pharmacokinetic and safety data in paediatric patients <2 to 18 years old.[35] Whereas the DRT formulation of posaconazole is formally approved in the USA in adolescents >12 years of age at the adult dose of 300 mg once daily (300 mg twice daily on day 1), the population pharmacokinetic model used for dosing in our patients was the first to suggest dosing in children ≤12 years of age by simulating the probability of different dosage regimens to maintain 24 h trough concentrations of >1000 ng/mL for patients weighing 10 to 50 kg in 10 kg increments.[25] Using loading on the first day with two doses, followed by maintenance once-daily dosing, simulations of 1000 profiles for each dosage cohort provided a 70% to 90% target attainment. These doses represent a reasonable alternative to the suspension for children who can swallow unaltered tablets and the data generated in our cohort of 34 immunocompromised children provide a first confirmation of their clinical usefulness. However, similar to the authors of the population pharmacokinetic study,[25] and despite a target attainment rate of ≥90% in our study, we would strongly advise TDM owing to the limited clinical experience in the paediatric population.

Apart from a case report,[36] a single study has been published on the use of posaconazole DRTs in paediatric patients.[37] In that study, posaconazole DRTs were administered as antifungal prophylaxis after neutrophil engraftment following allogeneic HSCT at a dose of 5–7 mg/kg once daily (day 1, 5–7 mg/kg twice daily) with a dosing scheme that required tablet fractions of 50 mg in children weighing 22–30 kg (150 mg once daily) and 36–40 kg (250 mg twice daily), respectively. Posaconazole DRTs were well tolerated and effective in the 32 patients analysed; median trough concentrations of posaconazole in plasma were below 700 ng/mL on days 2, 3 and 5 after the start of treatment, and exceeded 700 ng/mL from day 7 to day 28. Median trough concentrations were 2- to 6-fold higher relative to those observed in a non-randomized comparator group of 31 children receiving the suspension formulation at 4 mg/kg three times daily.[37] While plasma exposure with the selected dosing regimens was improved for children who received the DRT formulation, the selected dosing regimen for DRTs was not based on

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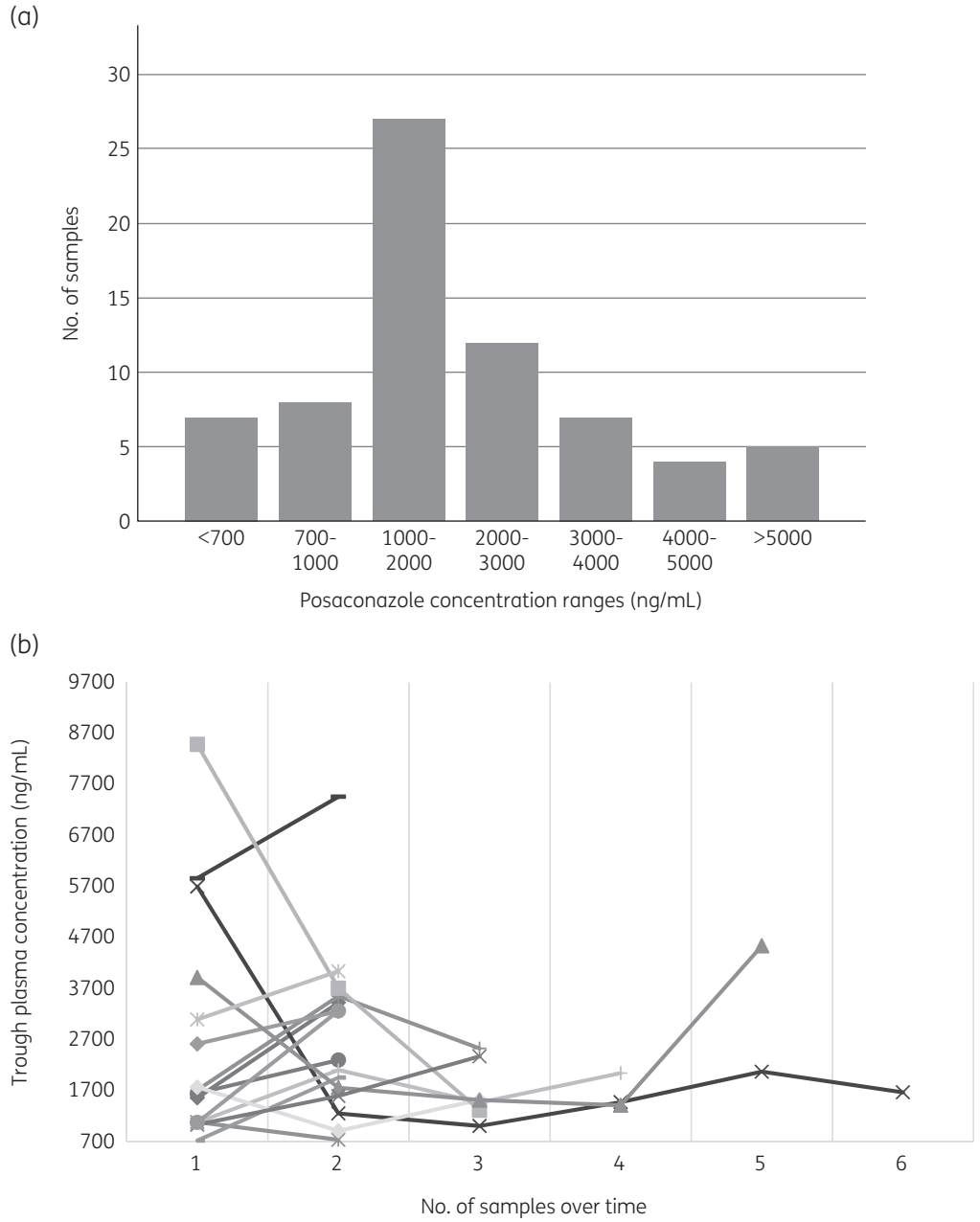


Figure 1. (a) Distribution of 70 individual trough concentration values of posaconazole after administration of the DRT formulation in 34 patients. (b) Trough concentration values of posaconazole over time after administration of the DRT formulation in 19 patients with two or more samples.

pharmacokinetic/pharmacodynamic modelling, exposures were suboptimal based on the currently recommended dosing target and the use of fractions of the tablet is ultimately prohibitive as the integrity of the DRTs should not be altered.[6,7]

Using a rationally developed dosing algorithm, target attainment rates in our paediatric cohort are consistent with those reported for adult patients receiving the DRT formulation at the recommended adult dose of 300 mg once daily: in a Phase 3 pharmacokinetics and safety study in adult patients at risk of IFD, the steady-state trough concentration was ≥700 ng/mL in 90% of 186 evaluable subjects with 5% <500 ng/mL and 5% between 500 and 700 ng/mL.[22] In a retrospective study in 64 adult patients with AML or MDS undergoing induction chemotherapy, 62 patients (97%) achieved target steady-state trough concentrations of posaconazole in plasma of >700 ng/mL; the median plasma concentration was 1.665 ng/mL with a range of 522–3830 ng/mL.[38] Among 32 immunocompromised adults, 29 (91%) achieved an initial trough concentration of >700 ng/mL; on measurement performed 5 to 14 days after the start of treatment, the target attainment rate was 90%. The median posaconazole trough concentration was 1655 ng/mL.[39] In 28 adults with haematological malignancies, the mean trough concentration was

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1190±630 ng/mL and 71% of patients had trough concentrations >700 ng/mL;[40] and lastly, target attainment rate was 100% with median plasma concentrations of 1550 ng/mL (range 1080–2500 ng/mL) in a small study including 14 adult patients.[41] Of note, diarrhoea was significantly associated with decreased exposure in one of the analyses,[40] emphasizing the continued need for TDM in selected situations also in adults.[28]

Posaconazole in the form of the DRT formulation was well tolerated in our patients without adverse event-related discontinuations or clinical or laboratory toxicities despite prolonged administration. Similar observations were made in the retrospective cohort study cited above[37] and in larger paediatric cohort studies with the oral suspension that revealed no signals for increased or unexpected toxicities relative to the adult population.[17,42–45]

Despite the limitations of a retrospective single-centre analysis and the inclusion of only a few children ≤6 years of age, the results of our study provide evidence that administration of posaconazole DRTs to children and adolescents using a population pharmacokinetic weight-based dosing algorithm is safe and achieves the pharmacokinetic/pharmacodynamic concentration target in plasma of ≥700 ng/mL at trough in ≥90% of measurements. The improved target attainment of the DRT formulation supports its preferential use in immunocompromised children and adolescents with an indication for antifungal prophylaxis who can swallow unaltered tablets. Owing to the limited experience in this population and the complex medical conditions and treatments of affected patients, however, we strongly advocate TDM with a dosing target at trough of ≥700 ng/mL and a suggested upper limit of trough concentrations of 4000 ng/mL.[25]

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Therapeutic drug monitoring of posaconazole delayed-release tablets and injections in pediatric patients

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ABSTRACT This study aimed to investigate the dose and trough concentration (C_{min}) of posaconazole delayed-release tablets and injections, and their correlation with efficacy and safety in pediatric patients. Patients younger than 18 years old received posaconazole delayed-release tablets or injections for prophylaxis or treatment of invasive fungal disease (IFD). Blood samples were collected to determine the plasma C_{min}s, and dose regimen adjustments were made if necessary. Clinical data were collected. A total of 210 C_{min}s of 113 pediatric patients were detected. The median C_{min}s were 1.0 and 1.3 mg/L for tablets and injections, respectively ($P < 0.05$). The median doses required to achieve the target C_{min} were about 6.0 mg/kg of body weight/day, and no statistical difference was observed between different age groups, formulations, or indications ($P > 0.05$). Concomitant treatment of tacrolimus and diarrhea were found to affect C_{min}s of tablets, while age, gender, and BMI were found to be correlated with C_{min}s of injections. IFD breakthrough occurred in 9.2% of patients with a median C_{min}s of 0.74 mg/L for prophylaxis, and infection progression occurred in 43.2% of patients with a median C_{min}s of 0.97 mg/L for treatment, respectively. Transaminitis was the most common adverse event. Posaconazole delayed-release tablets and injections are safe for prophylaxis and treatment of IFD in pediatric patients. An empirical initial dose of 6.0 mg/kg of body weight/day is appropriate for prophylaxis, while a higher dose should be required for the treatment of IFD. It is necessary to adjust the dose regimen according to the results of therapeutic drug monitoring.

CLINICAL TRIALS This study is registered with chictr.gov.cn under identifier ChiCTR2300070008.

KEYWORDS posaconazole, therapeutic drug monitoring, pediatric patients, delayed-release tablet, injection

Invasive fungal disease (IFD) remains an important cause of morbidity and mortality in immunocompromised children (1). Posaconazole is a triazole antifungal agent with an expanded-spectrum activity that blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of enzyme lanosterol 14α-demethylase (2, 3). Posaconazole was approved by the FDA for the treatment of invasive aspergillosis in adults and pediatric patients above 13 years old and for the prophylaxis of invasive *Aspergillus* and *Candida* infections in patients above 2 years old who are severely immunocompromised (4).

Due to its better absorption profile and more effectiveness in achieving therapeutic concentration than suspension (5–7), posaconazole delayed-release tablet is prescribed more commonly by clinicians. However, the delayed-release tablet is only recommended for children weighing greater than 40 kg with a dose of 300 mg (three 100 mg tablets) (4). For patients with lower body weight or those who are unable to swallow a tablet whole, giving a weight-based dose of the tablet or IV formulation off-label is an

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alternative (8, 9). Recent studies described a wide range of doses: 3.5–12 mg/kg of body weight/day, and very limited pediatric data have been reported (10–12).

Individual variations of posaconazole in children are greater than adults, and there are potential drug-drug interactions (13). Therefore, therapeutic drug monitoring (TDM) is very important for the efficacy and safety of posaconazole in pediatric patients. There has been an agreement that the target trough concentration (C_{min}) of posaconazole for prophylaxis and treatment of IFD should be greater than 0.7 and 1.0 mg/L, respectively, and the upper limit for toxicity has not yet been defined (14).

This study was conducted to evaluate the C_{min} of posaconazole delayed-release tablet and injection and their correlation with efficacy and safety in pediatric patients in order to suggest more appropriate dose regimens as well as the potential factors influencing posaconazole C_{min}.

RESULTS

Patient characteristics

A total of 113 pediatric patients participated in this study, and 210 posaconazole C_{min}s were detected (Fig. 1). Patient characteristics are shown in Table 1. This study included 71 (62.8%) males and 42 (37.2%) females. The median age was 8.4 years old (range 0.3–18.0 years old). The most common underlying conditions were acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). Posaconazole was administered in 76 (67.3%) patients for prophylaxis and 37 (32.7%) patients for treatment. Among the 37 patients for treatment, there were 2 (5.4%) cases of proven IFD (*Candida*), 7 (18.9%) cases of probable IFD (2 cases of *Candida* and 5 cases of *Aspergillus*), 14 (37.8%) cases of possible IFD, and 14 (37.8%) cases of empirical treatment, respectively.

Posaconazole trough concentrations

Delayed-release tablets were given to 63 (55.8%) patients and injections were given to 50 (44.2%) patients initially. The median therapy duration was 33 days (range 7–360 days). Dose information is presented in Table 2. In addition, due to the weight-based dosing regimen in younger patients, a total of 31 of them were given cut tablets.

A total of 113 initial and 97 subsequent posaconazole plasma C_{min}s were achieved. The median C_{min} for all was 1.2 mg/L (range BQL [below the quantification limit] –14.6 mg/L). The distribution of posaconazole C_{min}s is shown in Fig. 2.

Of the patients who received posaconazole delayed-release tablets, 126 C_{min}s were measured. The median C_{min} was 1.0 mg/L (range BQL—14.6 mg/L). C_{min}s were 0.5 mg/L (range 0.2–1.5 mg/L), 1.2 mg/L (range BQL—14.6 mg/L), and 1.2 mg/L (range BQL—3.7 mg/L) in patients who were <2 years old, 2–13 years old, and >13 years old, respectively. No significant difference was observed among these three groups ($H = 4.412$, $P = 0.095$). For patients given cut tablets, the median C_{min} was 1.3 mg/L (range BQL—5.6 mg/L, 47 C_{min}s measured). There was no statistical difference between C_{min}s of this group and those of whole tablets administered (median 0.9 mg/L, range BQL—14.6 mg/L, 79 C_{min}s measured) ($Z = 1.341$, $P = 0.180$).

Of the patients who received posaconazole injections, 84 C_{min}s were measured. The median C_{min} was 1.3 mg/L (range BQL—5.0 mg/L). C_{min}s were 1.2 mg/L (range 0.9–3.8 mg/L), 1.3 mg/L (range 0.2–5.0 mg/L), and 2.1 mg/L (range 0.7–4.5 mg/L) in patients who were <2 years old, 2–13 years old, and >13 years old, respectively. No significant difference was observed among these three groups ($H = 4.602$, $P = 0.100$). C_{min}s of patients treated by injection were significantly higher than those of patients treated by delayed-release tablets ($Z = 2.815$, $P < 0.05$).

Dose regimen adjustment

The initial C_{min}s of 38 (33.6%) patients did not reach the target, of whom 28 (73.7%) received delayed-release tablets and 10 (26.3%) received injections, including 20 (52.6%) in the prophylaxis group and 18 (47.4%) in the treatment group. Dose regimen

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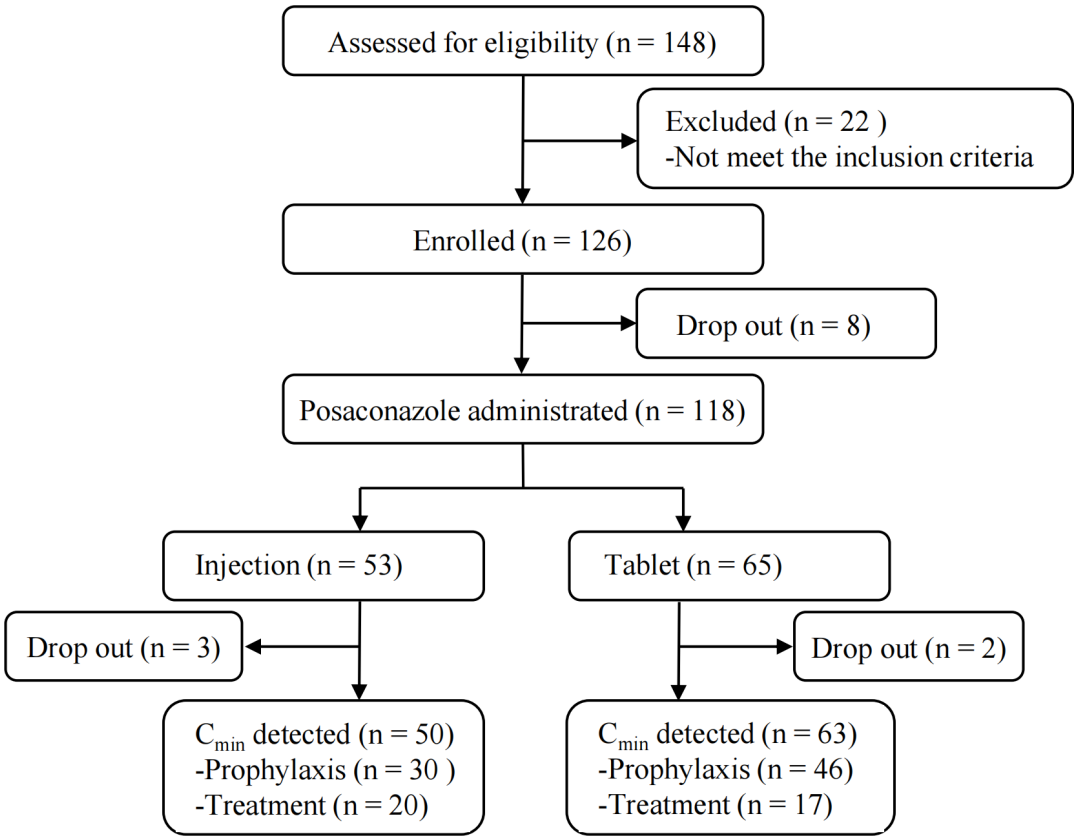


FIG 1 Study flowchart diagram.

adjustment was performed in 25 (65.8%) patients, including switching from delayed-release tablet to injection or/and increasing the dose. The results of adjustment are shown in Table 3. For the 13 (34.2%) patients who did not receive dose adjustment, five of them were treated with other antifungal agents (e.g., fluconazole, amphotericin B, voriconazole, and caspofungin).

There was one patient (31.2 kg) treated with 200 mg posaconazole delayed-release tablets whose initial C_{min} was 14.6 mg/L. This patient was given tacrolimus in combination. Considering the safety, posaconazole was discontinued for 3 days, and the C_{min} was reduced to 6.1 mg/L. After a continuous TDM and dose adjustment, the final dose was 50 mg/day with a C_{min} range of 1.8–2.6 mg/L.

Dose to achieve the target trough concentrations

Doses of different formulations required to achieve target C_{min}s of prophylaxis and treatment for different age groups are shown in Fig. 3.

Patients aged <2 years, 2–13 years, and >13 years who received posaconazole delayed-release tablets for prophylaxis required median doses of 6.3 mg/kg of body weight/day (range 4.0–11.8 mg/kg of body weight/day), 5.9 mg/kg of body weight/day (range 4.3–11.4 mg/kg of body weight/day), and 5.9 mg/kg of body weight/day (range 4.7–9.5 mg/kg of body weight/day), respectively, to achieve the target C_{min}. No significant difference was observed between the three groups ($H = 1.434$, $P > 0.05$).

Patients aged 2–13 years who received posaconazole delayed-release tablets for treatment required a median dose of 5.8 mg/kg of body weight/day (range 1.6–8.3 mg/kg of body weight/day) to achieve the target C_{min}. No patient <2 years old achieving the target C_{min} was enrolled, and only one patient >13 years old was enrolled (dose 5.9 mg/kg of body weight/day). No significant difference was observed between groups ($Z = 0.331$, $P > 0.05$).

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TABLE 1 Patient characteristics[a]

Characteristic	Total (*n* = 113)	<2 years old *n* = 11 (9.7%)	2–13 years old *n* = 81 (71.7%)	>13 years old *n* = 21 (18.6%)
Age (years)	8.4 (0.3–18.0)	1.1 (0.3–1.8)	7.7 (2.9–13.0)	14.2 (13.1–18.0)
Weight (kg)	25.0 (5.7–66.0)	8.0 (5.7–11.0)	24.0 (10.9–66.0)	46.4 (20.0–66.0)
BMI (kg/m^2)	15.3 (9.3–25.2)	15.1 (12.7–18.9)	15.2 (10.2–25.2)	17.5 (9.3–23.3)
Gender				
Male	71 (62.8%)	6 (54.5%)	50 (61.7%)	15 (71.4%)
Female	42 (37.2%)	5 (45.5%)	31 (38.3%)	6 (28.6%)
Primary diagnosis				
ALL	56 (49.6%)	2 (18.2)	47 (58.0%)	7 (33.3%)
AML	23 (20.4%)	3 (27.3%)	12 (14.8%)	8 (38.1%)
Lymphoma	12 (10.6%)	0 (0.0%)	9 (11.1%)	3 (14.3%)
Solid organ malignancy	5 (4.4%)	2 (18.2%)	3 (3.7%)	0 (0.0%)
AA	3 (2.7%)	0 (0.0%)	1 (1.2%)	2 (9.5%)
MDS	3 (2.7%)	0 (0.0%)	3 (3.7%)	0 (0.0%)
Other	11 (9.7%)	4 (36.4%)	6 (7.4%)	1 (4.8%)
Medical condition				
HSCT	40 (35.4%)	3 (27.3%)	28 (34.6%)	9 (42.9%)
Chemotherapy	41 (36.3%)	7 (63.6%)	26 (32.1%)	8 (38.1%)
CAR-T	32 (28.3%)	1 (9.1%)	27 (33.3%)	4 (19.0%)
Indication				
Prophylaxis	76 (67.3%)	10 (90.9%)	47 (58.0%)	19 (90.5%)
Treatment	37 (32.7%)	1 (9.1%)	34 (42.0%)	2 (9.5%)

[a]Data are given as absolute number (percent) and median (range). AA, aplastic anemia; MDS, myelodysplastic syndrome; HSCT, hematopoietic stem cell transplantation; and CAR-T, chimeric antigen receptor T-cell immunotherapy.

Patients aged <2 years, 2–13 years, and >13 years who received posaconazole injections for prophylaxis required median doses of 6.1 mg/kg of body weight/day (range 4.6–6.6 mg/kg of body weight/day), 6.0 mg/kg of body weight/day (range 3.5–11.8 mg/kg of body weight/day), and 6.1 mg/kg of body weight/day (range 4.5–8.1 mg/kg of body weight/day), respectively, to achieve the target C_{min}. No significant difference was observed between the three groups ($H = 1.182$, $P > 0.05$).

Patients aged 2–13 years who received posaconazole injections for treatment required median doses of 6.0 mg/kg of body weight/day (range 3.8–11.8 mg/kg of body weight/day) to achieve the target C_{min}. No patient <2 years old was enrolled, and only one patient >13 years old was enrolled (dose 5.7 mg/kg of body weight/day). No significant difference was observed between groups ($Z = 0.806$, $P > 0.05$).

TABLE 2 Posaconazole dose regimen[a]

	Total (*n* = 113)	<2 years old *n* = 11 (9.7%)	2–13 years old *n* = 81 (71.7%)	>13 years old *n* = 21 (18.6%)
Initial formulation				
PO	63 (55.8%)	4 (36.4%)	45 (55.6%)	14 (66.7%)
IV	50 (44.2%)	7 (63.6%)	36 (44.4%)	7 (33.3%)
Therapy duration (days)	33 (7–360)	15 (8–176)	36 (7–360)	25 (8–147)
Initial prophylaxis dose (mg/kg of body weight/day)				
PO	5.7 (4.3–9.5)	6.0 (5.4–6.4)	5.7 (4.3–7.8)	5.9 (4.6–9.5)
IV	6.0 (4.5–8.8)	6.1 (4.6–6.6)	5.9 (4.5–8.8)	5.9 (4.5–6.5)
Initial treatment dose (mg/kg of body weight/day)				
PO	5.8 (4.2–6.9)	6.4 (6.4–6.4)	5.8 (4.2–6.9)	5.9 (5.9–5.9)
IV	5.9 (5.0–6.5)	NA[b]	5.9 (5.0–6.5)	5.7 (5.7–5.7)

[a]Data are given as absolute number (percent) and median (range).
[b]NA, not available.

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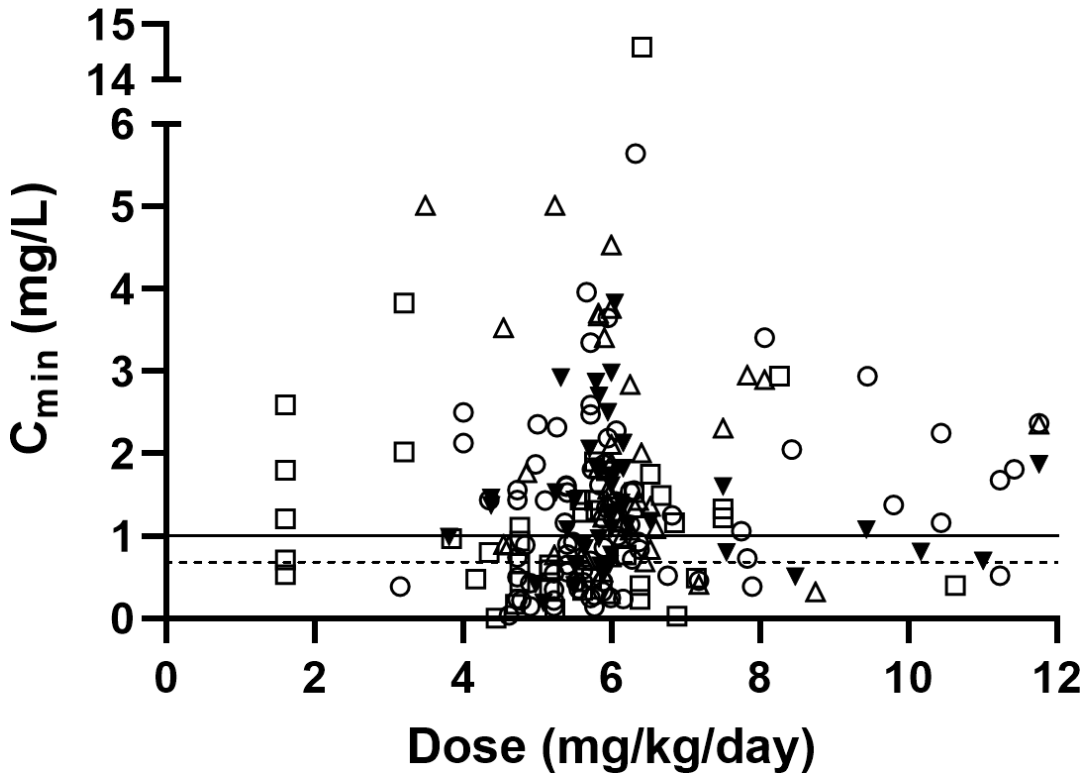


FIG 2 Distribution of posaconazole C_{min}s. Hollow circle: delayed-release tablet for prophylaxis; hollow square: delayed-release tablet for treatment; hollow triangle: injection for prophylaxis; solid triangle: injection for treatment; dotted line: the target C_{min} for prophylaxis (0.7 mg/L); solid line: the target C_{min} for treatment (1.0 mg/L).

Influencing factors of posaconazole trough concentrations

Results of multiple linear regression analysis performed to investigate influencing factors of posaconazole C_{min}s are shown in Table 4. For delayed-release tablet, dose-normalized posaconazole C_{min} was found to be positively correlated with concomitant treatment of tacrolimus, whereas negatively correlated with diarrhea. For injection, dose-normalized posaconazole C_{min} was found to be positively correlated with age, gender (female), and BMI.

Clinical outcome

Of the 76 patients receiving posaconazole for prophylaxis, 7 patients (9.2%) developed IFD breakthrough (two cases of probable *Aspergillus* infection and five cases of possible

TABLE 3 Dose regimen adjustment and results[a]

Dose regimen adjustment	Target C_{min} achieved			
	Total (n = 25)	Yes n = 14 (56.0%)	No n = 6 (24.0%)	ND[b] n = 5 (20.0%)
PO (n = 17)				
Switching to IV	4 (23.5%)	3 (75.0%)	0 (0.0%)	1 (25.0%)
Increasing the dose	10 (58.8%)	4 (40.0%)	3 (30.0%)	3 (30.0%)
Switching to IV and increasing the dose	3 (17.6%)	1 (33.3%)	2 (66.7%)	0 (0.0%)
IV (n = 8)				
Increasing the dose	8 (100.0%)	6 (75.0%)	1 (12.5%)	1 (12.5%)

[a]Data are given as absolute number (percent).
[b]ND, not detected.

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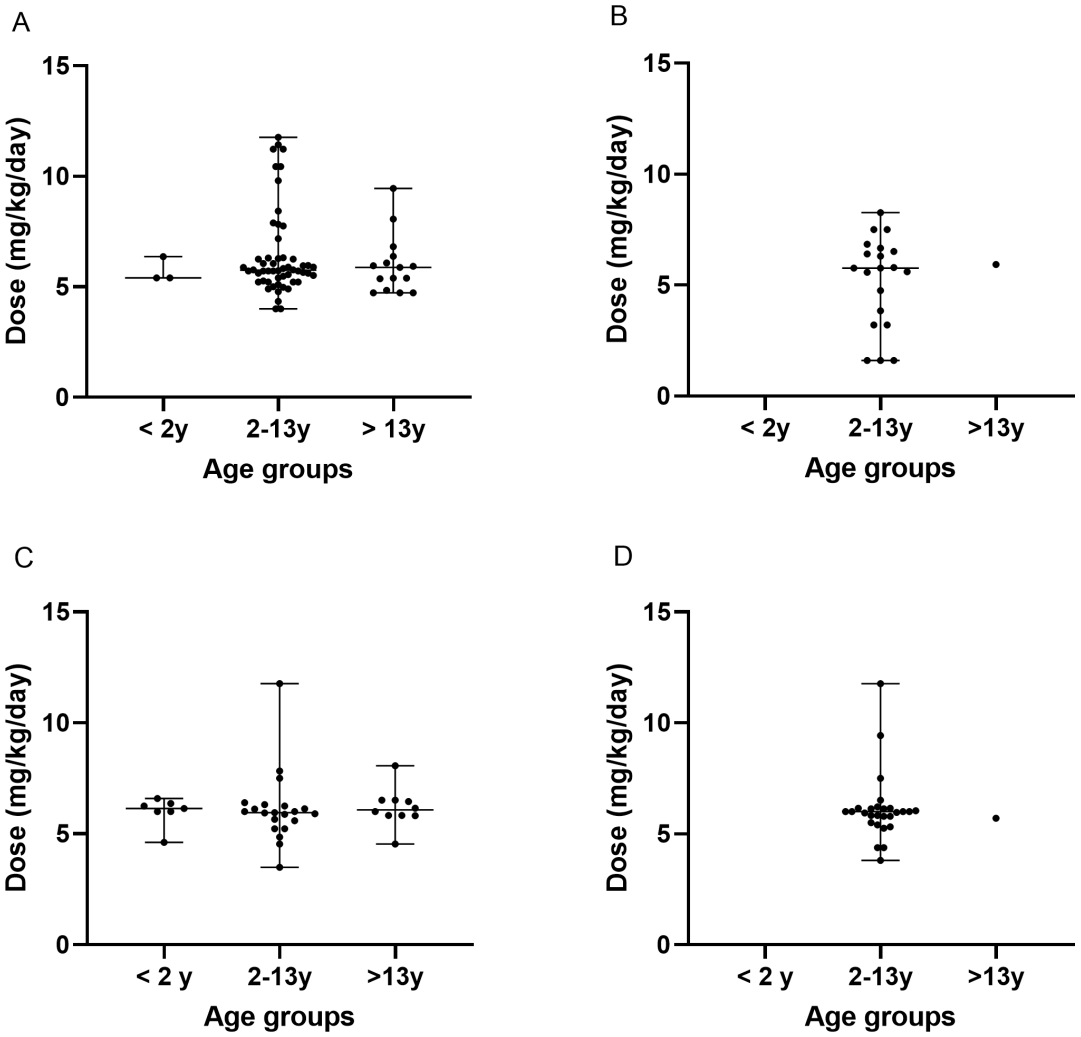


FIG 3 Dose to achieve the target C_{min}s. (A) Delayed-release tablet for prophylaxis. (B) Delayed-release tablet for treatment. (C) Injection for prophylaxis. (D) Injection for treatment.

IFD) with a median C_{min} of 0.74 mg/L (range BQL—2.36 mg/L). The median C_{min} of patients without IFD breakthrough was 1.23 mg/L (range BQL—5.64 mg/L). However, there is no significant difference between the two groups ($Z = 1.512$, $P = 0.131$).

Of the 37 patients receiving posaconazole for treatment, 16 patients (43.2%) had disease progression with a median C_{min} of 0.97 mg/L (range BQL—3.83 mg/L). The median C_{min} of patients without progression was 1.15 mg/L (range BQL—14.59 mg/L). However, there is no significant difference between the two groups ($Z = 0.502$, $P = 0.615$).

Safety evaluation

Transaminitis was observed in 35 (31.0%) patients: 14 (40.0%) patients were CTCAE grade 1, 12 (34.3%) were grade 2, and 9 (25.7%) were grade 3. However, all of these patients were given other concomitant medications that could cause transaminitis. Only one patient was given a lower dose due to this adverse event. In 16 (45.7%) patients, transaminase returned to baseline in follow-up assessment. One (0.9%) patient experienced bradycardia, CTCAE grade 2, who discontinued posaconazole treatment and had recovered by the end of the study. No statistically significant association between C_{min}s and the occurrence of adverse events (AEs) ($Z = -1.127$, $P = 0.260$).

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TABLE 4 Multiple linear regression to investigate influencing factors of dose-normalized posaconazole C_{min}s[a]

Variable	Delayed-release tablet		Injection	
	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*
Age	0.012 (0.000, 0.024)	0.056	0.018 (0.008, 0.028)	0.001
Gender	0.067 (−0.026, 0.159)	0.155	0.109 (0.023, 0.195)	0.014
BMI	0.005 (−0.012, 0.021)	0.575	0.029 (0.016, 0.041)	<0.001
Medical condition	−0.003 (−0.062, 0.057)	0.931	−0.019 (−0.087, 0.049)	0.584
Nausea/emesis	−0.029 (−0.214, 0.155)	0.753	NA	NA
Diarrhea	−0.113 (−0.221,−0.004)	0.042	NA	NA
Mucositis	−0.143 (−0.313, 0.027)	0.099	NA	NA
Concomitant medications				
Proton pump inhibitor	0.014 (−0.111, 0.139)	0.823	NA	NA
Cyclosporin	−0.064 (−0.182, 0.054)	0.286	−0.083 (−0.187, 0.021)	0.115
Tacrolimus	0.574 (0.399, 0.748)	<0.001	0.155 (−0.009, 0.319)	0.063
Ruxolitinib	0.003 (−0.170, 0.175)	0.976	−0.086 (−0.272, 0.100)	0.359
Venetoclax	−0.043 (−0.287, 0.202)	0.731	0.147 (−0.110, 0.404)	0.257

[a]NA, not available.

DISCUSSION

At present, the study of posaconazole pharmacokinetics in pediatric patients, especially in early-age patients, is still insufficient. Limited data are available on the use of delayed-release tablets and injections in pediatric patients.

A retrospective study involving 34 patients (5–17 years old, 16–84 kg) who were treated with posaconazole delayed-release tablets with maintenance doses of 300, 200–300, and 200 mg for patients weighing 31–50, 21–30, and 10–20 kg, respectively (5). In total, 94% of patients achieved the target C_{min} (0.7 mg/L) with a median C_{min} of 1.607 mg/L (range 0.501–8.485 mg/L). Another study of 33 patients receiving posaconazole delayed-release tablet treatment with the median dose of 7.3 mg/kg of body weight/day for patients <13 years of age and 4.6 mg/kg of body weight/day for patients 13 years of age or older achieved a median C_{min} of 1.7 (1.3–2.1 mg/L) (15). In our study, with a median dose around 6.0 mg/kg of body weight/day of posaconazole delayed-release tablet in all age groups, the median C_{min} was 1.0 mg/L and markedly individual variation was observed (range BQL—14.6 mg/L). Due to the inability to swallow the tablet in a whole and weight-based dose, tablets were cut to administer to children of young age or low weight. In our study, cutting had no significant effect on the C_{min} of posaconazole delayed-release tablets, which is consistent with the conclusions of previous studies conducted in adults and children (8, 16). Therefore, it can be inferred that the solubilization effect of the pH-sensitive polymer matrix containing amorphous posaconazole by hot-melt extrusion technology can lead to better drug absorption in young children, as in adults or adolescents (17–20).

Nickless et al. (11) evaluated dosing and C_{min}s of posaconazole injection in 10 pediatric patients (aged 1.5–11 years old). A median minimum effective dose of 6.55 mg/kg of body weight was found to achieve the therapeutic plasma concentrations (>0.7 mg/L) 95% of the time. A study conducted in 57 pediatric patients receiving posaconazole injection with doses of 3.5, 4.5, and 6 mg/kg of body weight showed that younger patients (<7 years old) had lower posaconazole concentrations than older patients (≥7 years old) at all doses evaluated. A dose of 6 mg/kg of body weight/day may achieve the target concentrations in patients younger than 7 years of age (12). Lambrix et al. suggested a body surface area-based dosing approach (225 mg/m^2/day) may allow a consistent empirical dose for all patients <18 years of age (9). In our study, a median dose of around 6.0 mg/kg of body weight/day of posaconazole injection was administered. The median C_{min} of posaconazole injection was 1.3 mg/L (range BQL—5.0 mg/L), and

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no significant difference was observed among the three age groups. However, consistent with previous studies, multiple linear regression analysis indicated that age was one of the influencing factors of posaconazole C_{min}.

Recent studies described a wide range of doses (3.5–12 mg/kg of body weight/day) for the use of posaconazole delayed-release tablets and injections in pediatric patients (10–12). In our study, a dose of 6.0 mg/kg of body weight seems to be an appropriate initial dose for children of different ages. However, due to individual variation, TDM is very important for dose regimen adjustment to achieve the therapeutic concentration.

As found in previous studies, multiple linear regression analysis indicated that diarrhea rather than concomitant administration of proton pump inhibitor may significantly reduce the C_{min}s of posaconazole delayed-release tablet (15, 21). One possible explanation is that individual gastrointestinal conditions, especially the absorption capacity of the small intestine, are one of the most important factors affecting tablet concentrations. It is known that posaconazole increases tacrolimus exposure by inhibiting CYP3A4 (22). However, the mechanism by which tacrolimus affects posaconazole concentration remains unknown. It is supposed to be related to the competitive binding to plasma proteins and the competitive efflux of the P-glycoprotein of these two compounds. The effect of posaconazole on the pharmacokinetic properties of ruxolitinib and venetoclax by inhibiting CYP3A was evaluated in a previous study (23, 24). The potential effect of ruxolitinib or venetoclax, P-glycoprotein (P-gp) inhibitors, on the exposure of posaconazole, a P-gp substrate, remains unestablished. Our study suggested that both ruxolitinib and venetoclax had no significant effect on posaconazole concentrations. However, due to the limited sample size of our study, further studies should be carried out to assess the drug-drug interaction of posaconazole.

A previous study involving 81 Chinese adult patients reported that C_{min} values of 0.76 and 1.0 mg/L were both associated with over an 80% probability of successful response to prophylaxis and treatment of IFD, respectively (25). A study in pediatric patients found that 88.0% of patients successfully responded to prophylaxis with a median C_{min} of 1.20 mg/L and 79.2% of patients successfully responded to treatment with a median C_{min} of 1.06 mg/L (26). Our study found a similar success rate (91.8%) of prophylaxis but a lower success rate (56.8%) of treatment, which indicated that higher doses should be given to achieve adequate C_{min}s for the treatment of IFD.

Findings from the safety evaluation were similar to previous studies (9, 15). Posaconazole was well tolerated and only one patient was given a lower dose due to transaminitis and one patient discontinued treatment due to bradycardia. The safety of posaconazole was acceptable to all age groups in this study.

There were several limitations in this study that should be clarified. First, this study was conducted in a single center, and the number of subjects is relatively small. It is not possible to draw the final conclusions. Second, laboratory tests were not specified in this study; therefore, the correlation between laboratory values and C_{min}s was not analyzed due to the presence of some missing values. Third, the final survival assessment and IFD assessment were not carried out due to the relatively short observation time. Finally, this study was unable to thoroughly evaluate the exact role of posaconazole in patients' outcomes because of concurrent or sequential treatment with other antifungal agents.

Conclusions

Overall, posaconazole delayed-release tablets and injections are safe in pediatric patients, including patients <2 years old. The recommended initial dose for prophylaxis is 6.0 mg/kg of body weight/day for all age groups, while the dose for treatment should be higher. Therefore, it is very important to adjust the dose regimen according to the results of therapeutic drug monitoring.

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MATERIALS AND METHODS

Patient enrollment

This study was conducted in Shanghai Children's Medical Center, Shanghai, from April 2023 to June 2024, in accordance with the Declaration of Helsinki. Eligible subjects were patients <18 years old who intended to take posaconazole delayed-release tablets or injections for the prophylaxis or treatment of IFD. Exclusion criteria included allergies to any component of the study drug or similar drugs; conditions may interfere with study participation.

Treatment and therapeutic drug monitoring

All patients received posaconazole delayed-release tablets or injections as prescribed, with an empirical initial dosing of approximately 6.0 mg/kg of body weight/day for patients <13 years old and 300 mg/day for patients ≥13 years old. For patients whose dose was not an integral multiple of 100 mg, the tablet was cut into halves, thirds, or quarters before administration. One milliliter of peripheral venous blood was collected into an EDTA vacutainer 30 min before administration when plasma posaconazole concentration was considered to have achieved a steady state (after about 7 days of dosing) (27). Plasma C_{min}s were determined using a validated HPLC-UV method described in a previous study (28). The analytical range was 0.05–10.00 mg/L. Dose adjustments were made when C_{min}s were lower than 0.7 and 1.0 mg/L for prophylaxis and treatment purposes, respectively (15). Other interventions (e.g., laboratory tests, and concomitant medications) were determined by clinicians based on routine. All patients were followed up for 30 days after discontinuation of posaconazole.

Clinical data collection

Data were collected, including patient demographics (e.g., age, gender, weight, and height), primary diagnosis, indications, dosing information, laboratory values (e.g., liver function tests and serum creatinine), concomitant medications that could potentially interfere with posaconazole as well as the addition of antifungal medications. Adverse events were assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events. Diagnosis of IFD and outcome evaluation were in accordance with the guidelines of the Chinese Invasive Fungal Infection Working Group (29).

Statistical analysis

SPSS Statistics version 25 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Descriptive statistics were reported by means, medians, frequencies, and percentages. Continuous data were analyzed by Mann-Whitney *U* test or Kruskal-Wallis *H* test. Categorical data were analyzed by Chi-square test or Fisher's exact test. Influencing factors of C_{min} were analyzed using multiple linear regression. *P* values < 0.05 were considered statistically significant.

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J.W. designed and performed the research, and wrote the manuscript; C.C., C.L., B.N., and Y.L. performed the research and edited the manuscript; Z.L. analyzed the data; S.Z. and Z.L. designed the research and edited the manuscript. All authors read and approved the final manuscript.

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Juan Wu, Conceptualization, Funding acquisition, Investigation, Methodology, Writing – original draft | Changcheng Chen, Investigation, Writing – review and editing | Chengjuan Luo, Investigation, Writing – review and editing | Botao Ning, Investigation, Writing – review and editing | Yue Liu, Investigation, Writing – review and editing | Zhuo Li, Data curation, Formal analysis | Shunguo Zhang, Project administration, Writing – review and editing | Zhiling Li, Project administration, Writing – review and editing

DATA AVAILABILITY

The original contributions presented in the study are included in the article, and further inquiries can be directed to the authors.

ETHICS APPROVAL

The study protocol was approved by the Ethics Committee of Shanghai Children's Medical Center. All guardians of the patients provided written informed consent before enrollment.

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NOXAFIL safely and effectively. See full prescribing information for NOXAFIL.

NOXAFIL® (posaconazole) injection, for intravenous use
NOXAFIL® (posaconazole) delayed-release tablets, for oral use
NOXAFIL® (posaconazole) oral suspension
NOXAFIL® POWDERMIX (posaconazole) for delayed-release oral suspension
Initial U.S. Approval: 2006

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.1, 1.2)	1/2026
Dosage and Administration (2)	1/2026

----------INDICATIONS AND USAGE----------

Noxafil is an azole antifungal indicated as follows:

- Noxafil is indicated for the treatment of invasive aspergillosis as follows: (1.1)
  - Noxafil injection: adults and pediatric patients 2 years of age and older who weigh 10 kg or greater.
  - Noxafil delayed-release tablets: adults and pediatric patients 2 years of age and older who weigh greater than 40 kg
  - Noxafil PowderMix for delayed-release oral suspension: pediatric patients 2 years of age and older who weigh 10 kg to 40 kg
- Noxafil is indicated for the prophylaxis of invasive *Aspergillus* and *Candida* infections in patients who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy as follows: (1.2)
  - Noxafil injection: adults and pediatric patients 2 years of age and older who weigh 10 kg or greater.
  - Noxafil delayed-release tablets: adults and pediatric patients 2 years of age and older who weigh greater than 40 kg
  - Noxafil oral suspension: adults and pediatric patients 13 years of age and older
  - Noxafil PowderMix for delayed-release oral suspension: pediatric patients 2 years of age and older who weigh 10 kg to 40 kg
- Noxafil oral suspension is indicated for the treatment of oropharyngeal candidiasis (OPC), including OPC refractory (rOPC) to itraconazole and/or fluconazole in adults and pediatric patients 13 years of age and older (1.3)

----------DOSAGE AND ADMINISTRATION----------

- Noxafil formulations are supplied in different dose strengths of posaconazole, are approved for different indications, age groups, and weights, have different dosages and duration of therapy; and have different preparation and administration instructions. (2.1)
- Noxafil oral suspension is not substitutable with Noxafil delayed-release tablets or Noxafil PowderMix for delayed-release oral suspension due to the differences in the dosing of each formulation. Therefore, follow the specific dosage recommendations for each of the formulations. (2.1, 2.2, 2.3)
- Noxafil injection must be administered through an in-line filter. (2.6)
- Administer Noxafil injection by intravenous infusion over approximately 90 minutes via a central venous line. (2.1, 2.6)
- Do NOT administer Noxafil injection as an intravenous bolus injection. (2.1)
- Administer Noxafil delayed-release tablets with or without food. (2.1)
- Administer Noxafil oral suspension with a full meal. (2.1)
- Administer Noxafil PowderMix for delayed-release oral suspension with food. (2.1)
- Administer Noxafil PowderMix for delayed-release oral suspension with the provided notched tip syringes only. (2.1)
- See the full prescribing information for important administration instructions and preparation instructions for Noxafil (injection, delayed -release tablets, and oral suspension) and Noxafil PowderMix delayed-release oral suspension (2.5, 2.6, 2.7, 2.8, 2.9, 2.10)
- For adult and pediatric patients aged 2 years of age and older, see the Full Prescribing Information for dosing recommendations for Noxafil injection, Noxafil delayed-release tablets, Noxafil oral suspension, and/or Noxafil PowderMix for delayed-release oral suspension based on the indication, age, and weight associated with the dosage form (1.1, 1.2, 1.3, 2.1, 2.2, 2.3, 2.4)

----------DOSAGE FORMS AND STRENGTHS----------

- Noxafil injection: 300 mg per vial (18 mg per mL) in a single-dose vial (3)
- Noxafil delayed-release tablet: 100 mg (3)
- Noxafil oral suspension: 40 mg per mL (3)
- Noxafil PowderMix for delayed-release oral suspension: 300 mg (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to posaconazole or other azole antifungal agents. (4.1)
- Coadministration of Noxafil with the following drugs is contraindicated; Noxafil increases concentrations and toxicities of:
  - Sirolimus (4.2, 7.2)
  - CYP3A4 substrates (pimozide, quinidine): can result in QTc interval prolongation and cases of torsades de pointes (TdP) (4.3, 5.2, 7.2)
  - HMG-CoA Reductase Inhibitors Primarily Metabolized through CYP3A4 (4.4, 7.2)
  - Ergot alkaloids (4.5, 7.2)
  - Venetoclax: In patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) at initiation and during the ramp-up phase (4.6, 5.11, 7.2)
- Noxafil PowderMix for delayed-release oral suspension is contraindicated in patients with known or suspected Hereditary Fructose Intolerance (HFI). (4.7, 5.9, 8.4)

---------- WARNINGS AND PRECAUTIONS ----------

- Calcineurin-Inhibitor Toxicity: Noxafil increases concentrations of cyclosporine or tacrolimus; reduce dose of cyclosporine and tacrolimus and monitor concentrations frequently. (5.1)
- Arrhythmias and QTc Prolongation: Noxafil has been shown to prolong the QTc interval and cause cases of TdP. Administer with caution to patients with potentially proarrhythmic conditions. Do not administer with drugs known to prolong QTc interval and metabolized through CYP3A4. (5.2, 7.2)
- Electrolyte Disturbances: Monitor and correct, especially those involving potassium (K^+), magnesium (Mg^{++}), and calcium (Ca^{++}), before and during Noxafil therapy. (5.3)
- Pseudoaldosteronism: Manifested by the onset or worsening of hypertension, and abnormal laboratory findings. Monitor blood pressure and potassium levels, and manage as necessary. (5.4)
- Hepatic Toxicity: Elevations in liver tests may occur. Discontinuation should be considered in patients who develop abnormal liver tests or monitor liver tests during treatment. (5.5)
- Renal Impairment: Noxafil injection should be avoided in patients with moderate or severe renal impairment (eGFR less than 50 mL/min/1.73 m^2), unless an assessment of the benefit/risk to the patient justifies the use of Noxafil injection. (5.6, 8.6)
- Concomitant Use with Midazolam: Noxafil can prolong hypnotic/sedative effects. Monitor patients and benzodiazepine receptor antagonists should be available. (5.7, 7.2)
- Vincristine Toxicity: Concomitant administration of azole antifungals, including Noxafil, with vincristine has been associated with neurotoxicity and other serious adverse reactions; reserve azole antifungals, including Noxafil, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options. (5.8, 7.2)
- Risk in Patients with Hereditary Fructose Intolerance (HFI): Noxafil PowderMix for delayed-release oral suspension contains sorbitol. Risk of metabolic crisis with life-threatening hypoglycemia, hypophosphatemia, lactic acidosis, and hepatic failure. Obtain history of HFI symptoms in pediatric patients before Noxafil PowderMix for delayed-release oral suspension administration. (5.9, 8.4)
- Breakthrough Fungal Infections: Monitor patients with severe diarrhea or vomiting when receiving Noxafil delayed-release

tablets, Noxafil oral suspension, and Noxafil PowderMix for delayed-release oral suspension. (5.10)
- Venetoclax Toxicity: Concomitant administration of Noxafil with venetoclax may increase venetoclax toxicities, including the risk of tumor lysis syndrome, neutropenia, and serious infections; monitor for toxicity and reduce venetoclax dose. (4.6, 5.11, 7.2)

---------- ADVERSE REACTIONS ----------

- Adult Patients: Common adverse reactions in studies with Noxafil in adults are diarrhea, nausea, fever, vomiting, headache, coughing, and hypokalemia. (6.1)
- Pediatric Patients: Common adverse reactions (incidence >20% receiving 6 mg/kg Noxafil injection and Noxafil PowderMix for delayed-release oral suspension) in a study in pediatric patients are pyrexia, febrile neutropenia, vomiting, mucosal inflammation, pruritus, hypertension, hypokalemia, and stomatitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme LLC at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch .

----------DRUG INTERACTIONS----------

Interaction Drug	***Interaction***
Rifabutin, phenytoin, efavirenz, cimetidine, esomeprazole*	*Avoid coadministration unless the benefit outweighs the risks (7.1, 7.2)*
Other drugs metabolized by CYP3A4	*Consider dosage adjustment and monitor for adverse effects and toxicity (7.2)*
Digoxin	*Monitor digoxin plasma concentrations (7.2)*
Fosamprenavir, metoclopramide*	*Monitor for breakthrough fungal infections (7.1)*
*The drug interactions with esomeprazole and metoclopramide do not apply to Noxafil tablets or Noxafil PowderMix *(7.3, 12.3)*.	

---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Pediatrics: Safety and effectiveness in patients younger than 2 years of age have not been established. (8.4)
- Severe Renal Impairment: Monitor closely for breakthrough fungal infections. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 1/2026

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Invasive Aspergillosis

Noxafil is indicated for the treatment of invasive aspergillosis as follows:

- **Noxafil injection:** adults and pediatric patients 2 years of age and older who weigh 10 kg or greater
- **Noxafil delayed-release tablets:** adults and pediatric patients 2 years of age and older who weigh greater than 40 kg
- **Noxafil PowderMix for delayed-release oral suspension:** pediatric patients 2 years of age and older who weigh 10 to 40 kg

1.2 Prophylaxis of Invasive *Aspergillus* and *Candida* Infections

Noxafil is indicated for the prophylaxis of invasive *Aspergillus* and *Candida* infections in patients who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy as follows:

- **Noxafil injection:** adults and pediatric patients 2 years of age and older who weigh 10 kg or greater
- **Noxafil delayed-release tablets:** adults and pediatric patients 2 years of age and older who weigh greater than 40 kg
- **Noxafil oral suspension:** adults and pediatric patients 13 years of age and older
- **Noxafil PowderMix for delayed-release oral suspension:** pediatric patients 2 years of age and older who weigh 10 kg to 40 kg

1.3 Treatment of Oropharyngeal Candidiasis Including Oropharyngeal Candidiasis Refractory to Itraconazole and/or Fluconazole

Noxafil oral suspension is indicated for the treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole in adults and pediatric patients 13 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

Noxafil injection, Noxafil delayed-release tablets, Noxafil oral suspension and Noxafil PowderMix for delayed-release oral suspension are supplied in different dose strengths of posaconazole, are approved for different indications, age groups and weights; have different dosages and duration of therapy; and have different preparation and administration instructions.

Therefore, select the recommended dosage form based on the indication, age group, and weight and carefully follow the recommended dosage, preparation and administration instructions described for each product *[see Dosage and Administration (2.2 to 2.11)]*, and the following important administration instructions described below.

Non-substitutable

Noxafil oral suspension is not substitutable with Noxafil delayed-release tablets or Noxafil PowderMix for delayed-release oral suspension due to the differences in the dosing of each formulation. Therefore, follow the specific dosage recommendations for each of the formulations *[see Dosage and Administration (2.2, 2.3)]*.

Noxafil injection

- Administer via a central venous line, including a central venous catheter or peripherally inserted central catheter (PICC), by slow intravenous infusion over approximately 90 minutes *[see Dosage and Administration (2.6)]*.
- Do NOT administer Noxafil injection as an intravenous bolus injection.

Noxafil delayed-release tablets

- Swallow tablets whole. Do not divide, crush, or chew.
- Administer with or without food *[see Dosage and Administration (2.7) and Clinical Pharmacology (12.3)]*.
- For patients who cannot eat a full meal, Noxafil delayed-release tablets should be used instead of Noxafil oral suspension for the prophylaxis indication. Noxafil delayed-release tablets generally provide higher plasma drug exposures than Noxafil oral suspension under both fed and fasted conditions *[see Dosage and Administration (2.8)]*.

Noxafil oral suspension

- Administer with a full meal or with a liquid nutritional supplement or an acidic carbonated beverage (e.g., ginger ale) in patients who cannot eat a full meal *[see Dosage and Administration (2.8)]*.

Noxafil PowderMix for delayed-release oral suspension

- Administer with food *[see Clinical Pharmacology (12.3)]*.
- To ensure delivery of the correct dose, ONLY the provided notched tip syringes must be used for preparation and administration. The design of the notched tip syringe prevents aggregation of the suspension during preparation and administration *[see Dosage and Administration (2.10)]*.

2.2 Recommended Dosage of Noxafil in Adult Patients

The recommended dosage of Noxafil (injection, delayed-release tablets, and oral suspension) in adult patients for the treatment of invasive aspergillosis, prophylaxis of invasive *Aspergillus* and *Candida* infections in patients who are at high risk of developing these infections due to being severely immunocompromised, or for the treatment of oropharyngeal candidiasis (OPC) is shown in Table 1 *[see Dosage and Administration (2.5, 2.6, 2.7,2.8, 2,9) and Clinical Pharmacology (12.3)]*.

Noxafil PowderMix for delayed-release oral suspension is not recommended for use in adults *[see Indications and Usage (1.1, 1.2)]*.

Table 1: Recommended Dosage of Noxafil Injection, Noxafil Delayed-Release Tablets, and Noxafil Oral Suspension in Adult Patients

Dosage	Duration of Therapy
Treatment of Invasive Aspergillosis*	
Noxafil Injection: Loading dose: 300 mg Noxafil injection intravenously twice a day on the first day. Maintenance dose: 300 mg Noxafil injection intravenously once a day, starting on the second day. **Noxafil Delayed-Release Tablets:** Loading dose: 300 mg (three 100 mg delayed-release tablets) twice a day on the first day. Maintenance dose: 300 mg (three 100 mg delayed-release tablets) once a day, starting on the second day.	Loading dose: 1 day Maintenance dose: Recommended total duration of therapy is 6 to 12 weeks.
Prophylaxis of Invasive *Aspergillus* and *Candida* Infections	
Noxafil Injection:	Loading dose: 1 day

Loading dose: 300 mg Noxafil injection intravenously twice a day on the first day. Maintenance dose: 300 mg Noxafil injection intravenously once a day thereafter. **Noxafil Delayed-Release Tablets:** Loading dose: 300 mg (three 100 mg delayed-release tablets) twice a day on the first day. Maintenance dose: 300 mg (three 100 mg delayed-release tablets) once a day, starting on the second day. **Noxafil Oral Suspension:** 200 mg (5 mL) three times a day.	Maintenance dose: Duration of therapy is based on recovery from neutropenia or immunosuppression
Oropharyngeal Candidiasis (OPC)	
Noxafil Oral Suspension: Loading dose: 100 mg (2.5 mL) twice a day on the first day. Maintenance dose: 100 mg (2.5 mL) once a day thereafter.	Loading dose: 1 day Maintenance dose: 13 days
OPC Refractory (rOPC) to Itraconazole and/or Fluconazole	
Noxafil Oral Suspension: 400 mg (10 mL) twice a day.	Duration of therapy is based on the severity of the patient's underlying disease and clinical response.
* Switching between the Noxafil injection and delayed-release tablets is acceptable. A loading dose is not required when switching between dosage forms.	

2.3 Recommended Dosage of Noxafil for the Treatment of Invasive Aspergillosis and Prophylaxis of Invasive *Aspergillus* and *Candida* Infections in Pediatric Patients 2 Years of Age and Older

Noxafil injection and Noxafil delayed-release tablets

The recommended dosage of (1) Noxafil injection in pediatric patients 2 years of age and older who weigh 10 kg or greater, and (2) Noxafil delayed-release tablets in pediatric patients 2 years of age and older who weigh greater than 40 kg for the treatment of invasive aspergillosis and prophylaxis of invasive *Aspergillus and Candida* infections is shown in Table 2 *[see Dosage and Administration (2.5, 2.6, 2.7, 2.9) and Clinical Pharmacology (12.3)].*

Noxafil delayed-release tablets are not recommended for use in pediatric patients who weigh 40 kg or less because the recommended dosage cannot be achieved with this dosage form.

Table 2: Recommended Dosage of Noxafil Injection and Noxafil Delayed-Release Tablets for the Treatment of Invasive Aspergillosis* and Prophylaxis of Invasive *Aspergillus* and *Candida* Infections in Pediatric Patients (2 Years of Age and Older)

Recommended Pediatric Dosage by Formulation	Duration of Therapy
Noxafil Injection (patients weighing 10 kg or greater): Loading dose: 6 mg/kg up to a maximum of 300 mg twice daily on the first day Maintenance dose:	Treatment of invasive aspergillosis: Recommended total duration of therapy is 6 to 12 weeks

6 mg/kg up to a maximum of 300 mg once daily, starting on the second day. **Noxafil Delayed-Release Tablets (patients weighing greater than 40 kg):** Loading dose: 300 mg (three 100 mg delayed-release tablets) twice a day on the first day. Maintenance dose: 300 mg (three 100 mg delayed-release tablets) once a day, starting on the second day.	Prophylaxis of invasive *Aspergillus* and *Candida* infections: Duration of therapy is based on recovery from neutropenia or immunosuppression.

* Switching between the intravenous and delayed-release tablets is acceptable. A loading dose is not required when switching between formulations.

Noxafil Oral Suspension

The recommended dosage of Noxafil oral suspension in pediatric patients 13 years of age and older for the prophylaxis of invasive *Aspergillus and Candida* Infections is shown in Table 3.

Table 3: Recommended Dosage of Noxafil Oral Suspension for the Prophylaxis of Invasive *Aspergillus* and *Candida* Infections in Pediatric Patients (13 Years of Age and Older)

Recommended Pediatric Dosage of Noxafil Oral Suspension	Duration of Therapy
200 mg (5 mL) three times a day	Duration of therapy is based on recovery from neutropenia or immunosuppression.

Noxafil PowderMix

The recommended dosage of Noxafil PowderMix for delayed-release oral suspension in pediatric patients 2 years of age and older who weigh 10 kg to 40 kg, for the treatment of invasive aspergillosis, and the prophylaxis of invasive *Aspergillus* and *Candida* infections, is shown in Table 4 and Table 5. The dosing for these indications is the same, except for patients weighing 10 to less than 12 kg *[see Dosage and Administration (2.9, 2.10) and Clinical Pharmacology (12.3)].*

Noxafil PowderMix for delayed-release oral suspension is not recommended for use in pediatric patients who weigh greater than 40 kg because the recommended dosage cannot be achieved with this dosage form.

Table 4: Recommended Dosage for Noxafil PowderMix for Delayed-Release Oral Suspension for the Treatment of Invasive Aspergillosis in Pediatric Patients (2 Years of Age and Older)

Weight (kg)	Recommended Pediatric Dosage of Noxafil PowderMix for Delayed-Release Oral Suspension	Duration of Therapy
10 to less than 17	Loading Dose: 120 mg (4 mL) twice daily on the first day Maintenance Dose: 120 mg (4 mL) once daily	Recommended total duration of therapy is 6 to 12 weeks.
17 to less than 21	Loading Dose: 150 mg (5 mL) twice daily on the first day Maintenance Dose: 150 mg (5 mL) once daily	
21 to less than 26	Loading Dose: 180 mg (6 mL) twice daily on the first day Maintenance Dose: 180 mg (6 mL) once daily	
26 to less than 36	Loading Dose: 210 mg (7 mL) twice daily on the first day Maintenance Dose: 210 mg (7 mL) once daily	
36 to 40	Loading Dose: 240 mg (8 mL) twice daily on the first day Maintenance Dose: 240 mg (8 mL) once daily	

Table 5: Recommended Dosage for Noxafil PowderMix for Delayed-Release Oral Suspension for the Prophylaxis of Invasive *Aspergillus* and *Candida* infections in Pediatric Patients (2 Years of Age and Older)

Weight (kg)	Recommended Pediatric Dosage of Noxafil PowderMix for Delayed-Release Oral Suspension	Duration of Therapy
10 to less than 12	Loading Dose: 90 mg (3 mL) twice daily on the first day Maintenance Dose: 90 mg (3 mL) once daily	Duration of therapy is based on recovery from neutropenia or immunosuppression.
12 to less than 17	Loading Dose: 120 mg (4 mL) twice daily on the first day Maintenance Dose: 120 mg (4 mL) once daily	

17 to less than 21	Loading Dose: 150 mg (5 mL) twice daily on the first day Maintenance Dose: 150 mg (5 mL) once daily	
21 to less than 26	Loading Dose: 180 mg (6 mL) twice daily on the first day Maintenance Dose: 180 mg (6 mL) once daily	
26 to less than 36	Loading Dose: 210 mg (7 mL) twice daily on the first day Maintenance Dose: 210 mg (7 mL) once daily	
36 to 40	Loading Dose: 240 mg (8 mL) twice daily on the first day Maintenance Dose: 240 mg (8 mL) once daily	

2.4 Recommended Dosage of Noxafil Oral Suspension for the Treatment of Oropharyngeal Candidiasis in Pediatric Patients 13 Years of Age and Older

The recommended dosage of Noxafil oral suspension for the treatment of oropharyngeal candidiasis (OPC) and OPC refractory (rOPC) to itraconazole and/or fluconazole in pediatric patients 13 years of age and older is shown in Table 6.

The Noxafil injection, Noxafil delayed-release tablets, and Noxafil PowderMix for delayed-release oral suspension products are not approved for the treatment of oropharyngeal candidiasis in pediatric patients.

Table 6: Recommended Dosage of Noxafil Oral Suspension for the Treatment of OPC and rOPC in Pediatric Patients (13 Years of Age and Older)

Recommended Pediatric Dosage of Noxafil Oral Suspension	Duration of Therapy
Oropharyngeal Candidiasis (OPC)	
Loading Dose: 100 mg (2.5 mL) twice daily on the first day Maintenance Dose: 100 mg (2.5 mL) once daily	Loading dose: 1 day Maintenance dose: 13 days
OPC Refractory (rOPC) to Itraconazole and/or Fluconazole	
400 mg (10 mL) twice daily	Duration of therapy is based on the severity of the patient's underlying disease and clinical response.

2.5 Preparation of Noxafil Injection

Preparation of Noxafil Injection:

- Remove the vial of Noxafil injection from the refrigerator and allow to equilibrate to room temperature prior to use.
- To prepare the required dose, aseptically transfer one vial of Noxafil injection (containing 300 mg of posaconazole in 16.7 mL of solution) to an intravenous bag or bottle of one of the following compatible diluents to achieve a final posaconazole concentration between 1 mg/mL and 2 mg/mL:
  - 0.45% Sodium Chloride Injection
  - 0.9% Sodium Chloride Injection
  - 5% Dextrose Injection
  - 5% Dextrose and 0.45% Sodium Chloride Injection
  - 5% Dextrose and 0.9% Sodium Chloride Injection
  - 5% Dextrose and 20 mEq Potassium Chloride Injection

  Use of other diluents is not recommended because they may result in particulate formation.
- Discard any unused Noxafil injection from the vial.
- Parenteral drug products should be inspected visually for particulate matter prior to administration, whenever solution and container permit. Once admixed, the diluted Noxafil infusion solution ranges from colorless to yellow (variations of color within this range do not affect the quality of the product).
- Immediately use the diluted Noxafil infusion solution, once admixed. If not used immediately, refrigerate (2 to 8°C (36 to 46°F)) the diluted Noxafil infusion solution up to 24 hours. Discard any unused portion.

Incompatible Diluents

Co-administration of drug products besides the infusion solutions or products stated above are not recommended because this may result in particulate formation. The following diluents were determined to be incompatible with Noxafil injection; thus, do **not** dilute Noxafil injection with them:

- Lactated Ringer's Injection
- Lactated Ringer's and 5% Dextrose Injection
- 4.2% Sodium Bicarbonate Injection

2.6 Administration of Diluted Noxafil Infusion Solution

See *Dosage and Administration (2.5)* for the preparation instructions for the diluted Noxafil Solution.

Important Administration Instructions for the Diluted Noxafil Infusion Solution

- Must administer diluted Noxafil Infusion Solution through a 0.22-micron polyethersulfone (PES) or polyvinylidene difluoride (PVDF) filter.
- Administer diluted Noxafil infusion solution via a central venous line, including a central venous catheter (CVC) or peripherally inserted central catheter (PICC), by slow intravenous infusion over approximately 90 minutes *[see Adverse Reactions (6.1)]*
- If a CVC or PICC are not available, may administer diluted Noxafil solution **once** through a peripheral venous catheter by intravenous infusion over approximately 30 minutes to bridge the period during which a CVC or PICC are replaced, inserted, or unavailable for use (e.g., the CVC is being used for intravenous treatment with another product). However, do not administer diluted Noxafil infusion solution more than once via peripheral venous catheter because in clinical trials, multiple peripheral infusions given through the same vein resulted in infusion site reactions *[see Adverse Reactions (6.1)]*.
- When multiple dosing is required, the infusion should be done via a central venous line.

Additional Administration Instructions for the Diluted Noxafil Infusion Solution

- Administer diluted Noxafil infusion solution intravenously through the same intravenous line (or cannula) with the following compatible infusion solutions:
  - 0.45% Sodium Chloride Injection
  - 0.9% Sodium Chloride Injection
  - 5% Dextrose Injection

- 5% Dextrose and 0.45% Sodium Chloride Injection
- 5% Dextrose and 0.9% Sodium Chloride Injection
- 5% Dextrose and 20 mEq potassium chloride Injection

- Administer diluted Noxafil infusion solution intravenously at the same time through the same intravenous line (or cannula) with the following intravenous drug products prepared in 5% Dextrose Injection or 0.9% Sodium Chloride Injection:
  - Amikacin Sulfate Injection
  - Caspofungin Acetate for Injection
  - Ciprofloxacin Injection
  - Daptomycin for Injection
  - Dobutamine Injection
  - Famotidine Injection
  - Filgrastim Injection
  - Gentamicin Injection
  - Hydromorphone Hydrochloride Injection
  - Levofloxacin Injection
  - Lorazepam Injection
  - Meropenem for Injection
  - Micafungin for Injection
  - Morphine Sulfate Injection
  - Norepinephrine Bitartrate Injection
  - Potassium Chloride Injection
  - Vancomycin Hydrochloride for Injection

2.7 Administration Instructions for Noxafil Delayed-Release Tablets

- Swallow the Noxafil delayed-release tablets whole. Do not divide, crush, or chew.
- Administer Noxafil delayed-release tablets orally with or without food *[see Clinical Pharmacology (12.3)]*.

2.8 Administration Instructions for Noxafil Oral Suspension

Administer Noxafil oral suspension with a full meal or with a liquid nutritional supplement or an acidic carbonated beverage (e.g., ginger ale) in patients who cannot eat a full meal.

For patients who cannot eat a full meal, use Noxafil delayed-release tablets instead of the Noxafil oral suspension for the prophylaxis of invasive *Aspergillus* and *Candida* infections in those who are at high risk of developing these infections due to being severely immunocompromised. This is because Noxafil delayed-release tablets provide higher plasma drug exposures than Noxafil oral suspension under fasted condition *[see Dosage and Administration (2.1)]*.

For those patients using the Noxafil oral suspension:

- Shake Noxafil oral suspension well before use.
- Administer with measured dosing spoon provided in the package (see Figure 1).

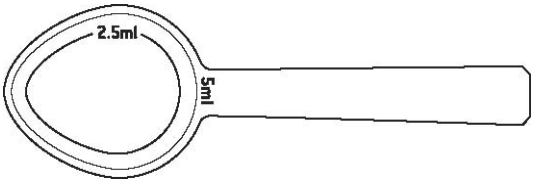


Figure 1: Measured dosing spoon provided in the package marked for doses of 2.5 mL and 5 mL.

- Administer each dose of Noxafil oral suspension during or immediately (i.e., within 20 minutes) following a full meal *[see Clinical Pharmacology (12.3)]*.
- In patients who cannot eat a full meal and for whom Noxafil delayed-release tablets or Noxafil injection are not options, administer each dose of Noxafil oral suspension with a liquid nutritional supplement or an acidic carbonated beverage (e.g., ginger ale). If these patients cannot tolerate an oral nutritional supplement or an acidic carbonated beverage either use:

- An alternative antifungal therapy, or
- Noxafil oral suspension and closely monitor patients for breakthrough fungal infections.

- Rinse the spoon with water after each administration and before storage.

2.9 Non-substitutability between Noxafil Oral Suspension and Other Formulations

Noxafil oral suspension is not substitutable with Noxafil delayed-release tablets or Noxafil PowderMix for delayed-release oral suspension due to the differences in the dosing of each formulation. Therefore, follow the specific dosage recommendations for each of the formulations *[see Dosage and Administration (2.2, 2.3)]*.

2.10 Preparation and Administration Instructions for Noxafil PowderMix for Delayed-Release Oral Suspension

For details on preparation and administration of Noxafil PowderMix for delayed-release oral suspension, see Instructions for Use.

Preparation Instructions for Noxafil PowderMix for Delayed-Release Oral Suspension

- Do not open the Noxafil PowderMix packet until ready to prepare the drug.
- Remove cap from the mixing liquid and push the bottle adapter into the neck of the bottle. Once in place, the bottle adapter stays in the bottle.
- Remove 9 mL of mixing liquid using the provided **blue** syringe. Put the cap back on the bottle. **Only use the mixing liquid in the kit to prepare Noxafil PowderMix.**
- Using the provided mixing cup, combine 9 mL of mixing liquid and the entire contents of one packet in the Noxafil PowderMix kit and mix (containing 300 mg of posaconazole).
- Shake the mixing cup vigorously for 45 seconds to mix the powder and mixing liquid from the Noxafil PowderMix kit. The final concentration of the reconstituted Noxafil PowderMix delayed-release suspension is approximately 30 mg/mL of posaconazole. Check to make sure the powder is mixed (the mixture should look cloudy and free of clumps).
- Must use the reconstituted Noxafil PowderMix delayed-release suspension within 1 hour of reconstitution. Discard unused portion of the reconstituted Noxafil PowderMix delayed-release suspension.

Administration Instructions for Noxafil PowderMix Delayed-Release Reconstituted Suspension

- To ensure delivery of the correct reconstituted Noxafil PowderMix Delayed-release dose, **only** use the provided notched tip syringes for preparation and administration because its design reduces the risk of aggregation of the product during preparation and administration.
- Choose the correct syringe based on the prescribed Noxafil PowderMix dose:
  - Use 3 mL (**green**) notched tip syringe (provided with the kit) if dose is 3 mL or less.
  - Use 10 mL (**blue**) notched tip syringe (provided with the kit) if dose is more than 3 mL.
- Administer reconstituted Noxafil PowderMix suspension orally with food within 1 hour of reconstitution *[see Clinical Pharmacology (12.3)]*.
- The maximum dose that can be accurately withdrawn from the mixing cup after reconstitution is 240 mg (8 mL).

Discarding Unused Reconstituted Noxafil PowderMix Suspension and Reuse of Syringes

- Not all the reconstituted Noxafil PowderMix suspension in the mixing cup will be used; there will be some left over in the mixing cup.
- Discard any remaining reconstituted Noxafil PowderMix suspension.
- The mixing cup may be hand washed and reused. Alternatively, the mixing cup may be discarded, and a similar mixing cup with a lid may be used for subsequent doses.
- The notched tip syringes may be hand washed and reused.

2.11 Dosage Modifications in Patients with Renal Impairment

The recommended dosage of Noxafil oral suspension, Noxafil delayed-release tablets, and Noxafil PowderMix for delayed-release oral suspension is the same in patients with renal impairment compared to those with normal renal function.

Avoid the use of Noxafil injection in patients with eGFR less than 50 mL/minute/1.73 m^2, unless an assessment of the benefit/risk to the patient justifies its use. If the decision is made to use Noxafil

injection in patients with eGFR less than 50 mL/minute/1.73 m^2, closely monitor serum creatinine levels, and, if increases occur, consider changing to oral Noxafil therapy. The recommended dosage of Noxafil injection in patients with eGFR 50 to 90 mL/minute/1.73 m^2 is the same as those with normal renal function.

3 DOSAGE FORMS AND STRENGTHS

Noxafil injection
300 mg/16.7 mL (18 mg/mL) of posaconazole: Clear, colorless to yellow sterile liquid in a single-dose vial.

Noxafil Delayed-Release Tablets
100 mg of posaconazole: Yellow, coated, oblong tablets, debossed with "100" on one side.

Noxafil Oral Suspension
4,200 mg/105 mL (40 mg/mL) of posaconazole: White, cherry-flavored suspension in amber glass bottles with child-resistant closures.

Noxafil PowderMix for Delayed-Release Oral Suspension
300 mg: Off-white to yellowish powder for delayed-release oral suspension and a mixing liquid in a kit. The kit contains (1) Package A that contains single-use packets of Noxafil PowderMix, green notched tip syringes, blue notched tip syringes, mixing cups, mixing liquid bottle, and one bottle adapter for the mixing liquid bottle; and (2) Package B that contains green and blue notched tip syringes for additional supply *[see How Supplied/Storage and Handling (16.1)]*.

4 CONTRAINDICATIONS

4.1 Hypersensitivity
Noxafil is contraindicated in persons with known hypersensitivity to posaconazole or other azole antifungal agents.

4.2 Use with Sirolimus
Noxafil is contraindicated with sirolimus. Concomitant administration of Noxafil with sirolimus increases the sirolimus blood concentrations by approximately 9-fold and can result in sirolimus toxicity *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

4.3 QT Prolongation with Concomitant Use with CYP3A4 Substrates
Noxafil is contraindicated with CYP3A4 substrates that prolong the QT interval. Concomitant administration of Noxafil with the CYP3A4 substrates, pimozide and quinidine may result in increased plasma concentrations of these drugs, leading to QTc prolongation and cases of torsades de pointes *[see Warnings and Precautions (5.2) and Drug Interactions (7.2)]*.

4.4 HMG-CoA Reductase Inhibitors Primarily Metabolized Through CYP3A4
Coadministration with the HMG-CoA reductase inhibitors that are primarily metabolized through CYP3A4 (e.g., atorvastatin, lovastatin, and simvastatin) is contraindicated since increased plasma concentration of these drugs can lead to rhabdomyolysis *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

4.5 Use with Ergot Alkaloids
Noxafil may increase the plasma concentrations of ergot alkaloids (ergotamine and dihydroergotamine) which may lead to ergotism *[see Drug Interactions (7.2)]*.

4.6 Use with Venetoclax
Coadministration of Noxafil with venetoclax at initiation and during the ramp-up phase is contraindicated in patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) due to the potential for increased risk of tumor lysis syndrome *[see Warnings and Precautions (5.11) and Drug Interactions (7.2)]*.

4.7 Use of Noxafil PowderMix for Delayed-Release Oral Suspension in Patients with Hereditary Fructose Intolerance

Noxafil PowderMix for delayed-release oral suspension is contraindicated in patients with known or suspected hereditary fructose intolerance (HFI) *[see Warnings and Precautions (5.9) and Use in Specific Populations (8.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Calcineurin-Inhibitor Toxicity

Concomitant administration of Noxafil with cyclosporine or tacrolimus increases the whole blood trough concentrations of these calcineurin-inhibitors *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*. Nephrotoxicity and leukoencephalopathy (including deaths) have been reported in clinical efficacy studies in patients with elevated cyclosporine or tacrolimus concentrations. Frequent monitoring of tacrolimus or cyclosporine whole blood trough concentrations should be performed during and at discontinuation of Noxafil treatment and the tacrolimus or cyclosporine dose adjusted accordingly.

5.2 Arrhythmias and QT Prolongation

Some azoles, including Noxafil, have been associated with prolongation of the QT interval on the electrocardiogram. In addition, cases of torsades de pointes have been reported in patients taking Noxafil.

Results from a multiple time-matched ECG analysis in healthy volunteers did not show any increase in the mean of the QTc interval. Multiple, time-matched ECGs collected over a 12-hour period were recorded at baseline and steady-state from 173 healthy male and female volunteers (18-85 years of age) administered Noxafil oral suspension 400 mg twice daily with a high-fat meal. In this pooled analysis, the mean QTc (Fridericia) interval change from baseline was –5 msec following administration of the recommended clinical dose. A decrease in the QTc(F) interval (–3 msec) was also observed in a small number of subjects (n=16) administered placebo. The placebo-adjusted mean maximum QTc(F) interval change from baseline was <0 msec (–8 msec). No healthy subject administered Noxafil had a QTc(F) interval ≥500 msec or an increase ≥60 msec in their QTc(F) interval from baseline.

Noxafil should be administered with caution to patients with potentially proarrhythmic conditions. Do not administer with drugs that are known to prolong the QTc interval and are metabolized through CYP3A4 *[see Contraindications (4.3) and Drug Interactions (7.2)]*.

5.3 Electrolyte Disturbances

Electrolyte disturbances, especially those involving potassium, magnesium or calcium levels, should be monitored and corrected as necessary before and during Noxafil therapy.

5.4 Pseudoaldosteronism

Pseudoaldosteronism, manifested by the onset of hypertension or worsening of hypertension, and abnormal laboratory findings (hypokalemia, low serum renin and aldosterone, and elevated 11-deoxycortisol), has been reported with posaconazole use in the postmarket setting. Monitor blood pressure and potassium levels and manage as necessary. Management of pseudoaldosteronism may include discontinuation of Noxafil, substitution with an appropriate antifungal drug that is not associated with pseudoaldosteronism, or use of aldosterone receptor antagonists.

5.5 Hepatic Toxicity

Hepatic reactions (e.g., mild to moderate elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, and/or clinical hepatitis) have been reported in clinical trials. The elevations in liver tests were generally reversible on discontinuation of therapy, and in some instances these tests normalized without drug interruption. Cases of more severe hepatic reactions including cholestasis or hepatic failure including deaths have been reported in patients with serious underlying medical conditions (e.g., hematologic malignancy) during treatment with Noxafil. These severe hepatic reactions were seen primarily in subjects receiving the Noxafil oral suspension 800 mg daily (400 mg twice daily or 200 mg four times a day) in clinical trials.

Liver tests should be evaluated at the start of and during the course of Noxafil therapy. Patients who develop abnormal liver tests during Noxafil therapy should be monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function

(particularly liver tests and bilirubin). Discontinuation of Noxafil must be considered if clinical signs and symptoms consistent with liver disease develop that may be attributable to Noxafil.

5.6 Renal Impairment

Due to the variability in exposure with Noxafil delayed-release tablets, Noxafil oral suspension, and Noxafil PowderMix for delayed-release oral suspension, patients with severe renal impairment should be monitored closely for breakthrough fungal infections *[see Dosage and Administration (2.11) and Use in Specific Populations (8.6)].*

Noxafil injection should be avoided in patients with moderate or severe renal impairment (eGFR <50 mL/min/1.73 m^2), unless an assessment of the benefit/risk to the patient justifies the use of Noxafil injection. In patients with moderate or severe renal impairment (eGFR <50 mL/min/1.73 m^2), receiving the Noxafil injection, accumulation of the intravenous vehicle, SBECD, is expected to occur. Serum creatinine levels should be closely monitored in these patients, and, if increases occur, consideration should be given to changing to oral Noxafil therapy *[see Dosage and Administration (2.11) and Use in Specific Populations (8.6)]*.

5.7 Midazolam Toxicity

Concomitant administration of Noxafil with midazolam increases the midazolam plasma concentrations by approximately 5-fold. Increased plasma midazolam concentrations could potentiate and prolong hypnotic and sedative effects. Patients must be monitored closely for adverse effects associated with high plasma concentrations of midazolam and benzodiazepine receptor antagonists must be available to reverse these effects *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

5.8 Vincristine Toxicity

Concomitant administration of azole antifungals, including Noxafil, with vincristine has been associated with neurotoxicity and other serious adverse reactions, including seizures, peripheral neuropathy, syndrome of inappropriate antidiuretic hormone secretion, and paralytic ileus. Reserve azole antifungals, including Noxafil, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options *[see Drug Interactions (7.2)]*.

5.9 Risk in Patients with Hereditary Fructose Intolerance (HFI)

Noxafil PowderMix for delayed-release oral suspension contains sorbitol, an inactive ingredient, and may precipitate a metabolic crisis that may include, but is not limited to life-threatening hypoglycemia, hypophosphatemia, lactic acidosis, and hepatic failure in patients with HFI. Obtain careful history of HFI symptoms (nausea, vomiting, abdominal pain) with sorbitol/fructose/sucrose exposure prior to Noxafil PowderMix for delayed-release oral suspension administration because a diagnosis of HFI may not yet be established in pediatric patients *[see Contraindications (4) and Use in Specific Populations (8.4)]*.

5.10 Breakthrough Fungal Infections

Patients who have severe diarrhea or vomiting should be monitored closely for breakthrough fungal infections when receiving Noxafil delayed-release tablets, Noxafil oral suspension, or Noxafil PowderMix for delayed-release oral suspension.

5.11 Venetoclax Toxicity

Concomitant administration of Noxafil, a strong CYP3A4 inhibitor, with venetoclax may increase venetoclax toxicities, including the risk of tumor lysis syndrome (TLS), neutropenia, and serious infections. In patients with CLL/SLL, administration of Noxafil during initiation and the ramp-up phase of venetoclax is contraindicated *[see Contraindications (4.6)]*. Refer to the venetoclax labeling for safety monitoring and dose reduction in the steady daily dosing phase in CLL/SLL patients.

For patients with acute myeloid leukemia (AML), dose reduction and safety monitoring are recommended across all dosing phases when coadministering Noxafil with venetoclax *[see Drug Interactions (7.2)]*. Refer to the venetoclax prescribing information for dosing instructions.

6 ADVERSE REACTIONS

The following serious and otherwise important adverse reactions are discussed in detail in another section of the labeling:

- Arrhythmias and QT Prolongation *[see Warnings and Precautions (5.2)]*
- Electrolyte Disturbances *[see Warnings and Precautions (5.3)]*
- Pseudoaldosteronism *[see Warnings and Precautions (5.4)]*
- Hepatic Toxicity *[see Warnings and Precautions (5.5)]*

6.1 CLINICAL TRIALS EXPERIENCE

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of Noxafil cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Treatment of Invasive Aspergillosis in Adults and Adolescents (Noxafil injection and Noxafil Delayed-Release Tablets)

The safety of Noxafil injection and Noxafil delayed-release tablets was assessed in a randomized, double-blind, active-controlled clinical study of Noxafil injection and Noxafil delayed-release tablets versus voriconazole for treatment of invasive aspergillosis (Aspergillosis Treatment Study). A total of 575 adult and pediatric patients 14 years of age and older (288 in the Noxafil group, 287 in voriconazole group (voriconazole for injection or voriconazole tablets)) with proven, probable or possible invasive aspergillosis were included. The median duration of treatment was 67 days for Noxafil injection or Noxafil delayed-release tablets and 64 days for voriconazole. In this study, 55% to 60% of patients started intravenous treatment with Noxafil (Noxafil injection) or voriconazole (voriconazole for injection). The median duration of the first instance of intravenous treatment (before switching to oral treatment or discontinuing or completing study treatment) was 9 days for both groups. Table 7 presents adverse reactions reported at an incidence of ≥10% in either one of the treatment groups in the Aspergillosis Treatment Study.

Adverse reactions leading to treatment discontinuation were reported for 34% of patients. The most commonly reported adverse reactions (>2% of patients) leading to treatment discontinuation were septic shock, respiratory failure, and bronchopulmonary aspergillosis in the Noxafil group, and septic shock and acute myeloid leukemia in the voriconazole group. The most frequently reported adverse reactions in the Noxafil-treated group were pyrexia (28%), hypokalemia (28%), and nausea (23%).

Table 7: Adverse Reactions in at least 10% of Adults and Adolescents Receiving Noxafil Injection or Noxafil Delayed-Release Tablets for the Treatment of Invasive Aspergillosis

Adverse Reactions	Noxafil injection or Noxafil delayed-release tablets n = 288 (%)	Voriconazole for injection or Voriconazole tablets n = 287 (%)
Percentage of Patients Reporting any Adverse Reaction	97.6	97.6
Hypokalemia	28.5	17.1
Pyrexia	28.1	25.1
Nausea	22.6	17.8
Diarrhea	18.1	18.1
Vomiting	18.1	13.6
Alanine aminotransferase increased	14.6	12.9
Febrile neutropenia	14.6	13.2
Aspartate aminotransferase increased	13.2	12.5
Pneumonia	12.5	9.1
Headache	12.2	8.7
Constipation	11.1	8.0
Edema peripheral	11.1	8.4
Epistaxis	11.1	5.9
Cough	10.4	8.4
Abdominal pain	10.1	8.4
Hypomagnesemia	10.1	6.3

Clinical Trial Experience with Noxafil Injection for Prophylaxis of Invasive *Aspergillus* and *Candida* Infections

Administration of multiple doses of Noxafil injection via a peripheral venous catheter were associated with thrombophlebitis (60% incidence). Therefore, in subsequent studies, Noxafil injection was administered via central venous catheter *[see Dosage and Administration (2.6)].*

The safety of Noxafil injection has been assessed in 268 patients in a clinical trial. Patients were enrolled in a non-comparative pharmacokinetic and safety trial of Noxafil injection when given as antifungal prophylaxis (Noxafil Injection Study). Patients were immunocompromised with underlying conditions including hematological malignancy, neutropenia post-chemotherapy, GVHD, and post HSCT. This patient population was 55% male, had a mean age of 51 years (range 18-82 years, 19% of patients were ≥65 years of age), and were 95% White and 8% Hispanic. In this study, 10 patients received a single dose of 200 mg Noxafil injection, 21 patients received 200 mg daily dosage for a median of 14 days, and 237 patients received 300 mg daily dosage for a median of 9 days (the 200 mg dosage is not a recommended dosage for prophylaxis of invasive *Aspergillus* and *Candida* infections in adults *[see Dosage and Administration (2.2)].* In the 300 mg daily dosage group each patient received a loading intravenous dose of Noxafil injection 300 mg twice on Day 1, then intravenous Noxafil injection therapy, and finally Noxafil oral suspension to complete 28 days of total Noxafil therapy.

Table 8 presents adverse reactions observed in patients treated with the Noxafil injection 300 mg daily dosage group in the Noxafil Injection Study.

The most frequently reported adverse reactions with an onset during the intravenous Noxafil injection phase of dosing with 300 mg once daily were diarrhea (32%), hypokalemia (22%), pyrexia (21%), and nausea (19%). These adverse reactions were consistent with those seen in studies with Noxafil oral suspension.

Table 8: Adverse Reactions in at least 10% of Adults Receiving Noxafil Injection for the Prophylaxis of Invasive *Aspergillus* and *Candida* infections

Adverse Reactions	Noxafil Injection Treatment Phase n=237* (%)	Noxafil Injection Treatment Phase or Subsequent Noxafil Oral Suspension Treatment Phase n=237† (%)
Percentage of Patients Reporting any Adverse Reaction	93	99
Diarrhea	32	39
Hypokalemia	22	28
Pyrexia	21	31
Nausea	19	30
Rash	15	24
Headache	14	21
Epistaxis	14	17
Abdominal Pain	13	17
Chills	12	16
Edema Peripheral	12	15
Vomiting	12	19
Hypomagnesemia	11	13
Decreased appetite	10	12
Cough	9	13
Constipation	8	13
Fatigue	8	10
Hypertension	8	11
Petechiae	8	10
Anemia	7	10
Dyspnea	7	10
Thrombocytopenia	7	11
Abdominal Pain Upper	6	11

* Adverse reactions reported in patients with an onset during the Noxafil intravenous dosing phase of the study.
† Adverse reactions reported with an onset at any time during the study in patients who were treated for up to 28 days of Noxafil therapy.

Clinical Trial Experience with Noxafil Delayed-Release Tablets for Prophylaxis of Invasive *Aspergillus* and *Candida* Infections

The safety of Noxafil delayed-release tablets has been assessed in 230 patients in clinical trials. Patients were enrolled in a non-comparative pharmacokinetic and safety trial of Noxafil delayed-release tablets when given as antifungal prophylaxis (Noxafil Delayed-Release Tablet Study). Patients were immunocompromised with underlying conditions including hematological malignancy, neutropenia post-chemotherapy, GVHD, and post HSCT. This patient population was 62% male, had a mean age of 51 years (range 19-78 years, 17% of patients were ≥65 years of age), and were 93% White and 16% Hispanic. Noxafil delayed-release tablets were given for a median duration of 28 days. In this study, 20 adult patients received 200 mg daily dosage (this is not a recommended dosage *[see Dosage and Administration (2.2)]*) and 210 adult patients received 300 mg daily dosage (following twice daily dosing on Day 1 in each cohort). Table 9 presents adverse reactions (incidence of ≥10%) observed in patients treated with the Noxafil delayed-release tablets 300 mg daily dosage in the Noxafil Delayed-Release Tablet Study.

The most frequently reported adverse reactions (>25%) in patients treated with Noxafil delayed-release tablets 300 mg once daily were diarrhea, pyrexia, and nausea. The most common adverse reaction leading to discontinuation of Noxafil delayed-release tablets 300 mg once daily was nausea (2%).

Table 9: Adverse Reactions in at least 10% of Adults Receiving Noxafil Delayed-Release Tablets (300 mg Daily Dosage) for the Prophylaxis of Invasive *Aspergillus* and *Candida* infections

Adverse Reactions	Noxafil delayed-release tablet (300 mg) n=210 (%)
Percentage of Patients Reporting any Adverse Reaction	99
Diarrhea	29
Pyrexia	28
Nausea	27
Hypokalemia	22
Cough	17
Edema Peripheral	16
Rash	16
Epistaxis	14
Headache	14
Mucosal Inflammation	14
Thrombocytopenia	14
Vomiting	13
Abdominal Pain	11
Hypertension	11
Anemia	10
Asthenia	10
Chills	10
Constipation	10
Hypomagnesemia	10

Clinical Trials Safety Experience with Noxafil Oral Suspension

The safety of Noxafil oral suspension has been assessed in 1,844 patients, including:

- 605 patients in the active-controlled studies for the prophylaxis of invasive *Aspergillus* and *Candida* infections
- 557 patients in the active-controlled OPC studies (not refractory to itraconazole or fluconazole)
- 239 patients in refractory OPC studies (refractory to itraconazole or fluconazole) (rOPC), and
- 443 patients in other patient populations

These studies included immunocompromised patients (e.g., patients with hematological malignancy, neutropenia post-chemotherapy, GVHD post HSCT, and HIV infection), as well as non-neutropenic patients. This patient population was 71% male, had a mean age of 42 years (range 8-84 years, 6% of patients were ≥65 years of age and 1% was <18 years of age), and were 64% White, 14% Black, 16% Hispanic. Noxafil oral suspension therapy was given to 171 patients for ≥6 months, including 58 patients who received Noxafil oral suspension therapy for ≥12 months. Table 10 presents adverse reactions observed at an incidence of >10% in the studies for prophylaxis of invasive *Aspergillus* and *Candida* infections. Table 11 presents adverse reactions observed at an incidence of at least 10% in the OPC/rOPC studies.

Prophylaxis of Invasive *Aspergillus* and *Candida* Infections (Noxafil oral suspension)

In the two randomized, comparative studies for prophylaxis of invasive *Aspergillus* and *Candida* infections in those at high risk of developing these infections due to being severely immunocompromised (Noxafil Oral Suspension Study 1 and 2), the safety of Noxafil oral suspension 200 mg three times a day was compared to fluconazole 400 mg once daily or itraconazole 200 mg twice a day in severely immunocompromised patients. The most frequently reported adverse reactions (>30%) in these trials

were fever, diarrhea, and nausea. The most common adverse reactions leading to discontinuation of Noxafil oral suspension were GI adverse reactions, specifically, nausea (2%), vomiting (2%), and increased hepatic enzymes (2%).

Table 10: Adverse Reactions in at least 10% of Patients Receiving Noxafil Oral Suspension for the Prophylaxis of Invasive *Aspergillus* and *Candida* Infections

Adverse Reactions	Noxafil Oral Suspension n=605 (%)	Fluconazole n=539 (%)	Itraconazole n=58 (%)
Percentage of Patients Reporting any Adverse Reaction	98	99	100
Fever	45	47	55
Diarrhea	42	39	60
Nausea	38	37	52
Hypokalemia	30	26	52
Thrombocytopenia	29	27	34
Vomiting	29	32	41
Headache	28	26	40
Abdominal Pain	27	27	36
Anemia	25	23	28
Coughing	24	24	24
Neutropenia	23	23	40
Constipation	21	17	17
Dyspnea	20	22	26
Rigors	20	16	29
Rash	19	18	43
Hypertension	18	16	5
Hypomagnesemia	18	16	19
Fatigue	17	18	9
Insomnia	17	17	19
Musculoskeletal Pain	16	15	16
Anorexia	15	17	28
Edema Legs	15	12	19
Epistaxis	14	14	21
Hypotension	14	15	17
Pharyngitis	12	11	21
Tachycardia	12	14	5
Arthralgia	11	12	9
Dizziness	11	10	9
Hyperglycemia	11	14	3
Petechiae	11	10	16
Pruritus	11	12	19
Back Pain	10	12	7
Bilirubinemia	10	9	19
Dyspepsia	10	9	10
Vaginal Hemorrhage*	10	9	12

* Percentages of sex-specific adverse reactions are based on the number of males/females.

Treatment of Nonrefractory OPC and Refractory OPC (Noxafil oral suspension)

In two randomized comparative studies for the treatment of nonrefractory OPC, the safety of Noxafil oral suspension (less than or equal to 400 mg once daily) in 557 HIV-infected patients was compared to the safety of fluconazole (100 mg once daily) in 262 HIV-infected patients.

An additional 239 HIV-infected patients with refractory OPC (rOPC) received Noxafil oral suspension in two non-comparative trials for rOPC. Of these patients, 149 received the 800 mg/day dosage and the remainder received the less than or equal to 400 mg once daily dosage.

In the nonrefractory OPC and rOPC studies, the most common adverse reactions in patients treated with Noxafil oral suspension were fever, diarrhea, nausea, headache, vomiting, and coughing.

Adverse reactions were reported more frequently in the studies of patients with refractory OPC. Among these highly immunocompromised patients with advanced HIV disease, serious adverse reactions were reported in 55% (132/239) of Noxafil oral suspension-treated patients. The most commonly reported serious adverse reactions were fever (13%) and neutropenia (10%).

Table 11: Adverse Reactions in at least 10% of Patients Receiving Noxafil Oral Suspension for the Treatment of Nonrefractory and Refractory OPC

Adverse Reactions	Controlled OPC Pool		Refractory OPC Pool
	Noxafil Oral Suspension	Fluconazole	Noxafil Oral Suspension
	n=557 (%)	n=262 (%)	n=239 (%)
Percentage of Patients that Reported any Adverse Reaction*	64	67	92
Diarrhea	10	13	29
Nausea	9	11	29
Headache	8	9	20
Vomiting	7	7	28
Fever	6	8	34
Abdominal Pain	5	6	18
Neutropenia	4	3	16
Coughing	3	4	25
Fatigue	3	5	13
Herpes Simplex	3	3	11
Pneumonia	3	2	10
Rash	3	4	15
Anemia	2	2	14
Anorexia	2	2	19
Asthenia	2	2	13
Sweating Increased	2	2	10
Candidiasis, Oral	1	<1	12
Dehydration	1	3	11
Dyspnea	1	3	12
Insomnia	1	1	16
Pain	1	1	11
Weight Decrease	1	<1	14
Rigors	<1	2	12

OPC=oropharyngeal candidiasis

* Based on patients reporting adverse reactions at least once during the study, without regard to relationship to treatment. Patients may have reported more than 1 adverse reaction.

Additional Adverse Reactions Reported in Less Than 5% of Noxafil-Treated Patients in Clinical Trials

Other clinically significant adverse reactions reported in less than 5% of patients in clinical trials of Noxafil are listed below:

- *Blood and lymphatic system disorders:* hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, neutropenia aggravated
- *Endocrine disorders:* adrenal insufficiency
- *Nervous system disorders:* paresthesia

- *Immune system disorders: allergic reaction [see Contraindications (4.1)]*
- *Cardiac disorders: torsades de pointes [see Warnings and Precautions (5.2)]*
- *Vascular disorders: pulmonary embolism*
- *Gastrointestinal disorders: pancreatitis*
- *Liver and Biliary System Disorders: hepatic enzymes increased, hepatic function abnormal, hepatitis, hepatomegaly, jaundice*
- *Renal & Urinary System Disorders: renal failure acute*

Liver Test Abnormalities in the Clinical Trials of Noxafil Oral Suspension

Liver Test Abnormalities in the Clinical Trials with Noxafil Oral Suspension for Prophylaxis of Invasive *Aspergillus* and *Candida* Infections

In the prophylaxis of invasive *Aspergillus* and *Candida* infections studies, the number and percentage of patients with changes in liver tests from Common Toxicity Criteria (CTC) Grade 0, 1, or 2 at baseline to Grade 3 or 4 at the end of the studies is presented in Table 12.

Table 12: Changes in Liver Test Results from CTC Grade 0, 1, or 2 at Baseline to Grade 3 or 4 in Prophylaxis of Invasive *Aspergillus* and *Candida* Infections Studies (Noxafil Oral Suspension Studies 1 and 2)

Number (%) of Patients with Change*		
Noxafil Oral Suspension Study 1		
Laboratory Parameter	**Noxafil Oral Suspension n=301**	**Fluconazole n=299**
AST	11/266 (4)	13/266 (5)
ALT	47/271 (17)	39/272 (14)
Bilirubin	24/271 (9)	20/275 (7)
Alkaline Phosphatase	9/271 (3)	8/271 (3)
Noxafil Oral Suspension Study 2		
Laboratory Parameter	**Noxafil Oral Suspension (n=304)**	**Fluconazole/Itraconazole (n=298)**
AST	9/286 (3)	5/280 (2)
ALT	18/289 (6)	13/284 (5)
Bilirubin	20/290 (7)	25/285 (9)
Alkaline Phosphatase	4/281 (1)	1/276 (<1)

* Change from Grade 0 to 2 at baseline to Grade 3 or 4 during the study. These data are presented in the form X/Y, where X represents the number of patients who met the criterion as indicated, and Y represents the number of patients who had a baseline observation and at least one post-baseline observation.

CTC = Common Toxicity Criteria; AST= Aspartate Aminotransferase; ALT= Alanine Aminotransferase.

Liver Test Abnormalities in the Clinical Trials with Noxafil Oral Suspension for the Treatment of OPC

The number and percentage of patients treated for OPC with clinically significant liver test abnormalities at any time during the studies is provided in Table 13 (liver test abnormalities were present in some of these patients prior to initiation of the study drug).

Table 13: Clinically Significant Liver Test Abnormalities without Regard to Baseline Value (Noxafil Oral Suspension Studies for the Treatment of OPC)

	Nonrefractory OPC		Refractory OPC
	Noxafil Oral Suspension	Fluconazole	Noxafil Oral Suspension
Laboratory Test	**n=557 (%)**	**n=262 (%)**	**n=239 (%)**
ALT > 3.0 x ULN	16/537 (3)	13/254 (5)	25/226 (11)
AST > 3.0 x ULN	33/537 (6)	26/254 (10)	39/223 (17)
Total Bilirubin > 1.5 x ULN	15/536 (3)	5/254 (2)	9/197 (5)
Alkaline Phosphatase > 3.0 x ULN	17/535 (3)	15/253 (6)	24/190 (13)

ALT= Alanine Aminotransferase; AST= Aspartate Aminotransferase.

Liver Test Abnormalities in the Clinical Trials with Noxafil Oral Suspension for the Treatment of Invasive Aspergillosis

The number and percentage of patients treated for invasive aspergillosis with clinically significant liver test abnormalities at any time during the Aspergillosis Treatment Study is provided in Table 14. Liver test abnormalities present prior to the initiation of study drug included: ALT (22% of the patients), AST (13% of the patients), and bilirubin (13% of the patients).

Table 14: Changes in Liver Test Results from CTC Grade 0, 1, or 2 at Baseline to Grade 3 or 4 (Aspergillosis Treatment Study)

	Number (%) of Patients with Change*	
Laboratory Parameter	**Noxafil n/N (%)**	**Voriconazole n/N (%)**
AST	22/281 (8)	21/285 (7)
ALT	29/281(10)	23/282 (8)
Bilirubin	26/280 (9)	25/284 (9)
Alkaline Phosphatase	12/282 (4)	20/284 (7)

* Change from Grade 0 to 2 at baseline to Grade 3 or 4 during the study. These data are presented in the form n/N, where n represents the number of patients who met the criterion as indicated, and N represents the number of patients who had a baseline observation and at least one post-baseline observation.

N=Number of patients for a given laboratory test with a baseline value of CTC Grade 0, 1, or 2 and at least one post-baseline value.

CTC = Common Toxicity Criteria; AST= Aspartate Aminotransferase; ALT= Alanine Aminotransferase.

In healthy volunteers and patients, elevation of liver test values did not appear to be associated with higher plasma posaconazole concentrations.

Clinical Trials in Pediatric Patients 2 Years of Age and Older

The safety of Noxafil injection and Noxafil PowderMix (for delayed-release oral suspension) for prophylaxis of invasive fungal infections was evaluated in an open-label uncontrolled dose-ranging pharmacokinetic and safety study of Noxafil injection and Noxafil PowderMix (Pediatric Study 1, NCT02452034). In this study, 115 immunocompromised pediatric patients 2 to less than 18 years of age with known or expected neutropenia initially received Noxafil injection (up to 6 mg/kg twice daily for the first day and then up to 6 mg/kg for at least 7 days), and then 63 patients were transitioned to Noxafil PowderMix(up to 6 mg/kg once daily). The mean overall treatment duration was 21 days including a mean duration of 14 days (range: 1 to 28 days) on Noxafil injection and a mean duration of 12 days (range: 2 to 18 days) on Noxafil PowderMix *[see Clinical Pharmacology (12.3)]*. In this study, the reported adverse reaction profile of Noxafil injection and Noxafil PowderMix in pediatric patients was consistent with the safety profile of Noxafil in adults. The most common adverse reactions that occurred in greater than 20% of pediatric patients who received Noxafil injection and Noxafil PowderMix were pyrexia, febrile neutropenia, vomiting, mucosal inflammation, pruritus, hypertension, hypokalemia, and stomatitis.

The safety of Noxafil injection, Noxafil delayed-release tablets, and Noxafil PowderMix for delayed-release oral suspension for the treatment of invasive aspergillosis was evaluated in an open-label, non-comparative clinical study in 31 pediatric patients 2 to less than 18 years of age with a diagnosis of possible, probable, or proven invasive aspergillosis (Pediatric Study 2, NCT04218851). In this study, all 31 pediatric patients initially received Noxafil injection (6 mg/kg twice daily on the first day and then 6 mg/kg once daily) for the treatment of invasive aspergillosis; 12 patients were transitioned to Noxafil delayed-release tablets (300 mg once daily) if they weighed ≥40 kg, and 10 patients were transitioned to Noxafil PowderMix (based on weight) if they weighed 10 to 40 kg *[see Dosage and Administration (2.3)]*. The mean overall treatment duration was 50 days including 15 days (range 2 to 78 days) on Noxafil injection, 54 days (range: 6 to 80 days) on Noxafil delayed-release tablets, and 44 days (range 7 to 76 days) on Noxafil PowderMix. The reported adverse reaction profile of Noxafil injection, Noxafil delayed-release tablets, and Noxafil PowderMix in pediatric patients was consistent with the known safety profile of Noxafil in adults. The most common adverse reactions that occurred in greater than 20% of pediatric patients who received any of the three formulations of Noxafil were vomiting, pyrexia, abdominal pain, liver test abnormalities, and hypertension.

6.2 Postmarketing Experience

The following adverse reaction has been identified during the post-approval use of Noxafil. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Endocrine Disorders: Pseudoaldosteronism

7 DRUG INTERACTIONS

Table 15 and Table 17 include drugs with clinically important drug interactions when administered concomitantly with Noxafil and Noxafil PowderMix and instructions for preventing or managing them. Table 16 includes important drug interactions specific to the absorption of posaconazole administered as either Noxafil oral suspension or Noxafil PowderMix.

These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious adverse reactions or loss of efficacy *[see Clinical Pharmacology (12.3)]*.

The following information was derived from data with Noxafil oral suspension or another posaconazole tablet formulation unless otherwise noted. All clinically important drug interactions with Noxafil oral suspension, except for those that affect the absorption of posaconazole (via gastric pH and motility), are considered relevant to clinically important drug interactions with Noxafil injection, Noxafil delayed-release tablets, and Noxafil PowderMix for delayed-release oral suspension *[Clinical Pharmacology (12.3)]*.

Consult the labeling of concomitantly used drugs to obtain further information about interactions with posaconazole.

7.1 Effects of Other Drugs on Noxafil and Noxafil PowderMix

Posaconazole is primarily metabolized via UDP-glucuronosyltransferase and is a substrate of p-glycoprotein (P-gp) efflux. Therefore, inhibitors or inducers of these clearance pathways may affect posaconazole plasma concentrations. Concomitant use of Noxafil with drugs that can decrease the plasma posaconazole concentrations should generally be avoided unless the benefit outweighs the risk. If such drugs are necessary, patients should be monitored closely for breakthrough fungal infections.

Table 15: Drug Interactions Affecting Noxafil and Noxafil PowderMix When Administered Concomitantly with Other Drugs

UDP-Glucuronidase Inducers		
Mechanism and Clinical Effect(s)		Posaconazole is a UDP-glucuronosyltransferase substrate. Concomitant use of Noxafil with UDP-glucuronidase inducers may decrease posaconazole exposure *[see Clinical Pharmacology (12.3)],* which may reduce the effectiveness of posaconazole.
Prevention or Management	*Efavirenz*	Avoid concomitant use of posaconazole with efavirenz, unless the benefit outweighs the risks.
	Rifabutin	Avoid concomitant use of posaconazole with rifabutin unless the benefit to the patient outweighs the risk. If concomitant use is needed, monitor closely for breakthrough fungal infections. *See Table 17 for rifabutin monitoring considerations when posaconazole affects rifabutin via CYP3A4 inhibition.*
	Phenytoin	Avoid concomitant use of posaconazole with phenytoin unless the benefit to the patient outweighs the risk. If concomitant use is needed, monitor for breakthrough fungal infections. *See Table 17 for phenytoin monitoring considerations when posaconazole affects phenytoin via CYP3A4 inhibition.*
Fosamprenavir		
Mechanism and Clinical Effect(s)		Concomitant use of Noxafil with fosamprenavir may lead to decreased posaconazole plasma concentrations *[see Clinical Pharmacology (12.3)],* which may reduce effectiveness of posaconazole.
Prevention or Management		If concomitant use of posaconazole with fosamprenavir is needed, monitor closely for breakthrough fungal infections.

Table 16: Drug Interactions Affecting Noxafil Oral Suspension and Noxafil PowderMix Absorption When Administered Concomitantly with Other Drugs

Noxafil Oral Suspension	
Cimetidine and Esomeprazole	
Mechanism and Clinical Effect(s)	Concomitant use of Noxafil oral suspension with cimetidine or esomeprazole resulted in decreased posaconazole plasma concentrations *[see Clinical Pharmacology (12.3)],* which may reduce effectiveness of Noxafil.
Prevention or Management	Avoid concomitant use of Noxafil oral suspension with cimetidine or esomeprazole unless the benefit outweighs the risks. If concomitant use is needed, monitor closely for breakthrough fungal infections.
Metoclopramide	
Mechanism and Clinical Effect(s)	Concomitant use of Noxafil oral suspension with metoclopramide decreased posaconazole plasma concentrations *[see Clinical Pharmacology (12.3)],* which may reduce effectiveness of Noxafil oral suspension.
Prevention or Management	If Noxafil oral suspension is concomitantly administered with metoclopramide, closely monitor for breakthrough fungal infections.

Noxafil Oral PowderMix	
Alcohol	
Mechanism and Clinical Effect(s)	Posaconazole releases faster from Noxafil PowderMix in the presence of alcohol, which may interfere with Noxafil PowderMix's delayed-release characteristics *[see Clinical Pharmacology (12.3)]*.
Prevention or Management	Administration of Noxafil PowderMix with alcohol is not recommended.

7.2 Effects of Noxafil and Noxafil PowderMix on Other Drugs

Posaconazole is a strong CYP3A4 inhibitor. Therefore, concomitant use of Noxafil may increase plasma concentrations of drugs that are CYP3A4 substrates *[see Clinical Pharmacology (12.3)]*.

Table 17: Drug Interactions Affecting Drugs Administered Concomitantly with Noxafil and Noxafil PowderMix

Digoxin		
Clinical Effect(s)	Increased digoxin plasma concentrations have been reported in patients who received concomitant posaconazole and digoxin.	
Prevention or Management	Monitor digoxin plasma concentrations during concomitant use of posaconazole .	
Glipizide		
Clinical Effect(s)	No dosage modification of glipizide is needed when used concomitantly with Noxafil. However, glucose concentrations decrease in some patients concomitantly administered posaconazole and glipizide.	
Prevention or Management	Increase monitoring of glucose concentrations when used concomitantly.	
CYP3A Substrates		
Immunosuppressants that are CYP3A4 Substrates		
Mechanism and Clinical Effect(s)	Posaconazole is a strong CYP3A4 inhibitor. Therefore, plasma concentrations of CYP3A4 substrates may be increased by posaconazole use *[see Clinical Pharmacology (12.3)]*.	
Prevention or Management	Sirolimus	Posaconazole is contraindicated with sirolimus *[see Clinical Pharmacology (12.3)]*.
	Tacrolimus	• At initiation of posaconazole treatment, reduce the tacrolimus dosage to approximately one-third of the original tacrolimus dosage. • Frequent monitoring of tacrolimus whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the tacrolimus dosage should be modified accordingly *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.
	Cyclosporine	• At initiation of posaconazole treatment reduce the cyclosporine dosage to approximately three-fourths of the original dosage. • Frequent monitoring of cyclosporine whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the cyclosporine dosage should be modified accordingly *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.
CYP3A4 Substrates that Prolong QTc Interval		
Mechanism and Clinical Effect(s)	Concomitant use of posaconazole with CYP3A4 substrates such as pimozide and quinidine may result in increased plasma concentrations of the CYP3A4 substrates leading to QTc interval prolongation and torsades de pointes *[see Warnings and Precautions (5.2)]*.	

Prevention or Management	Pimozide Quinidine	Concomitant use with posaconazole is contraindicated.
HMG-CoA Reductase Inhibitors (Statins) that are CYP3A4 Substrates		
Mechanism and Clinical Effect(s)	Concomitant use of posaconazole with simvastatin increased simvastatin plasma concentrations which can lead to rhabdomyolysis *[see Clinical Pharmacology (12.3)]*.	
Prevention or Management	Atorvastatin, Lovastatin, Simvastatin	Concomitant use with posaconazole is contraindicated.
Benzodiazepines that are CYP3A4 Substrates		
Mechanism and Clinical Effect(s)	Concomitant use of posaconazole with midazolam increased midazolam plasma concentrations which could potentiate and prolong hypnotic and sedative effects *[see Clinical Pharmacology (12.3)]*.	
Prevention or Management	Midazolam, Alprazolam, Triazolam	Closely monitor for adverse reactions associated with high plasma concentrations of benzodiazepines that are CYP3A4 substrates during concomitant use, and a benzodiazepine receptor antagonist should be available to reverse effects *[see Warnings and Precautions (5.7)]*.
Calcium Channel Blockers that are CYP3A4 Substrates		
Mechanism and Clinical Effect(s)	Posaconazole may increase the plasma concentrations of calcium channel blockers that are substrates of CYP3A4.	
Prevention or Management	Verapamil, Diltiazem, Nifedipine, Nicardipine, Felodipine	Monitor frequently for adverse reactions and toxicity with concomitant use of posaconazole with calcium channel blockers that are CYP3A4 substrates. Dosage reduction of the calcium channel blocker may be needed.
Anti-HIV Drugs that are CYP3A4 Substrates		
Mechanism and Clinical Effect(s)	Ritonavir and atazanavir are CYP3A4 substrates and posaconazole increased plasma concentrations of these drugs *[see Clinical Pharmacology (12.3)]*.	
Prevention or Management	Ritonavir and Atazanavir	Monitor frequently for adverse reactions and toxicity of ritonavir and atazanavir during concomitant use.
Antineoplastic Drugs that are CYP3A4 Substrates		
Mechanism and Clinical Effect(s)	Posaconazole may increase plasma concentrations of oncology drugs that are CYP3A4 substrates, which may increase the risk of serious adverse reactions.	
Prevention or Management	Venetoclax	*CLL/SLL patients:* Concomitant use of posaconazole with venetoclax during initiation and ramp-up phase is contraindicated. *AML patients:* With concomitant use, venetoclax dosage reduction and safety monitoring is recommended across all dosing phases *[see Warnings and Precautions (5.11)]*.
	Vinca alkaloids (e.g., vincristine, vinblastine)	Reserve concomitant use for patients with no alternative antifungal treatment options *[see Warnings and Precautions (5.8)]*.
Ergot Alkaloids		
Mechanism and Clinical Effect(s)	Most of the ergot alkaloids are CYP3A4 substrates. Posaconazole may increase the plasma concentrations of ergot alkaloids (ergotamine and dihydroergotamine) which may lead to ergotism.	
Prevention or Management	Ergotamine, Dihydroergotamine	Concomitant use with posaconazole is contraindicated.
Phenytoin		
Mechanism and Clinical Effect(s)	Phenytoin is a CYP3A4 substrate. Concomitant use of posaconazole with phenytoin increased phenytoin plasma concentrations *[see Clinical Pharmacology (12.3)]*.	

Prevention or Management	Avoid concomitant use of posaconazole with phenytoin unless the benefit outweighs the risk. frequently monitor phenytoin concentrations and consider a dosage reduction of phenytoin. *See Table 15 for additional monitoring considerations when phenytoin affects posaconazole via UDP-glucuronosyltransferase inhibition.*
Rifabutin	
Mechanism and Clinical Effect(s)	Rifabutin is a CYP3A4 substrate. Concomitant use of posaconazole with rifabutin increased rifabutin plasma concentrations *[see Clinical Pharmacology (12.3)].*
Prevention or Management	Avoid concomitant use of posaconazole with rifabutin unless the benefit outweighs the risk. Frequent monitoring of full blood counts and adverse reactions due to increased rifabutin plasma concentrations (e.g., uveitis, leukopenia) during concomitant use are recommended. *See Table 15 for additional monitoring considerations when rifabutin affects posaconazole via UDP-glucuronosyltransferase inhibition.*

7.3 Absence of Clinically Important Interaction with Noxafil and Noxafil PowderMix

Additional clinical studies demonstrated that no clinically important effects on zidovudine, lamivudine, indinavir, or caffeine were observed when administered with Noxafil 200 mg once daily; therefore, no dose adjustments are required for these drugs when coadministered with Noxafil 200 mg once daily.

No clinically relevant effects on the pharmacokinetics of Noxafil delayed-release tablets were observed during concomitant use with antacids, H_2-receptor antagonists and proton pump inhibitors, and metoclopramide *[see Clinical Pharmacology (12.3)]*. No dosage adjustment of Noxafil delayed-release tablets or Noxafil PowderMix for delayed-release oral suspension is required during concomitant use with these drugs.

No clinically relevant effects on the pharmacokinetics of Noxafil oral suspension were observed during concomitant use with antacids, H_2-receptor antagonists (other than cimetidine), and loperamide *[see Clinical Pharmacology (12.3)]*. No dosage adjustment of Noxafil oral suspension is required during concomitant use with these drugs (other than cimetidine).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal data, Noxafil may cause fetal harm when administered to pregnant women. Available data for use of Noxafil in pregnant women are insufficient to establish a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, skeletal malformations were observed when posaconazole was dosed orally to pregnant rats during organogenesis at doses ≥1.4 times the 400 mg twice daily oral suspension regimen based on steady-state plasma concentrations of Noxafil in healthy volunteers. In pregnant rabbits dosed orally during organogenesis, doses of ≥ 3 times the clinical exposure caused an increase in resorptions *(see Data)*. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data: Posaconazole resulted in maternal toxicity (reduced food consumption and reduced body weight gain) and skeletal malformations (cranial malformations and missing ribs) when given orally to pregnant rats during organogenesis (Gestational Days 6 through 15) at doses ≥27 mg/kg (≥1.4 times the 400 mg twice daily oral suspension regimen based on steady-state plasma concentrations of drug in healthy volunteers). The no-effect dose for malformations and maternal toxicity in rats was 9 mg/kg, which is 0.7 times the exposure achieved with the 400 mg twice daily oral suspension regimen. No malformations were seen in rabbits dosed during organogenesis (Gestational Days 7 through 19) at doses up to 80 mg/kg (5 times the exposure achieved with the 400 mg twice daily oral suspension

regimen). In the rabbit, the no-effect dose was 20 mg/kg, while high doses of 40 mg/kg and 80 mg/kg (3 or 5 times the clinical exposure) caused an increase in resorptions. In rabbits dosed at 80 mg/kg, a reduction in body weight gain of females and a reduction in litter size were seen.

8.2 Lactation

Risk Summary

There are no data on the presence of posaconazole in human milk, the effects on the breastfed infant, or the effects on milk production. Posaconazole is excreted in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Noxafil and any potential adverse effects on the breastfed child from Noxafil or from the underlying maternal condition.

8.4 Pediatric Use

The three Noxafil dosage forms (injection, delayed-release tablets, oral suspension) and one Noxafil PowderMix (for delayed-release oral suspension) dosage form are different products; are approved for different pediatric indications, age groups, and weights; have different dosing regimens; and have different preparation and administration instructions. Therefore, select the recommended dosage form based on the pediatric indication, age group, and weight *[see Dosage and Administration (2.1)].*

Noxafil PowderMix for delayed-release oral suspension is contraindicated in patients with HFI. Because a diagnosis of HFI may not yet be established in pediatric patients, obtain a careful history of HFI symptoms with sorbitol/fructose/sucrose exposure prior to administration of Noxafil PowderMix *for delayed-release oral suspension [see Warnings and Precautions (5.9)].*

Treatment of Invasive Aspergillosis

The safety and effectiveness of Noxafil (injection and delayed-release tablets) have been established for the treatment of invasive aspergillosis in pediatric patients 2 years of age and older .

The safety and effectiveness of Noxafil PowderMix have been established for the treatment of invasive aspergillosis in pediatric patients 2 years of age and older who weigh 10 kg to 40 kg.

Use of Noxafil and Noxafil PowderMix for these pediatric indications is supported by evidence from adequate and well-controlled studies of Noxafil in adults and safety and pharmacokinetic (PK) data from two pediatric studies *[see Adverse Reactions (6.1*) and *Clinical Pharmacology (12.3)]*. The safety of Noxafil and Noxafil PowderMix in pediatric patients for these pediatric indications was consistent with the known safety profile of Noxafil in adults *[see Adverse Reactions (6.1)].*

Noxafil PowderMix for delayed-release oral suspension is not recommended for use in patients who weigh greater than 40 kg because the recommended dosage cannot be achieved with this dosage form.

The safety and effectiveness of Noxafil and Noxafil PowderMix have not been established in pediatric patients less than 2 years of age**.**

Prophylaxis of Invasive *Aspergillus* and *Candida* Infections

The safety and effectiveness of Noxafil (injection and delayed-release tablets) have been established for the prophylaxis of invasive *Aspergillus* and *Candida* infections in pediatric patients 2 years of age and older who are at high risk of developing these infections due to being severely immunocompromised. The safety and effectiveness of Noxafil oral suspension have been established for the prophylaxis of invasive *Aspergillus* and *Candida* infections in pediatric patients 13 years of age and older who are at high risk of developing these infections due to being severely immunocompromised.

The safety and effectiveness of Noxafil PowderMix have been established for the prophylaxis of invasive *Aspergillus* and *Candida* infections in pediatric patients 2 years of age and older who weigh 10 kg to 40 kg who are at high risk of developing these infections due to being severely immunocompromised.

Use of Noxafil and Noxafil PowderMix for these pediatric indications is supported by adequate and well controlled studies of Noxafil in adults and pediatric patients aged 13 years of age and older and additional PK and safety data in pediatric patients 2 years of age and older *[see Clinical Pharmacology (12.3) and Clinical studies (14)*].

Noxafil PowderMix is not recommended for use in patients who weigh greater than 40 kg because the recommended dosage cannot be achieved with this dosage form.

The safety and effectiveness of Noxafil and Noxafil PowderMix have not been established in pediatric patients less than 2 years of age.

Treatment of Oropharyngeal Candidiasis, including Refractory to Itraconazole and/or Fluconazole

The safety and effectiveness of Noxafil oral suspension have been established for the treatment of oropharyngeal candidiasis (OPC), including OPC refractory (rOPC) to itraconazole and/or fluconazole in pediatric patients 13 years of age and older.

Use of Noxafil oral suspension for this pediatric indication is supported by adequate and well controlled studies in adults and pediatric patients 13 years of age and older *[see Clinical studies (14.4)]*.

The Noxafil injection, Noxafil delayed-release tablets, and Noxafil PowderMix products are not approved for the treatment of oropharyngeal candidiasis in pediatric patients. Noxafil Oral Suspension is the only dosage form approved for the treatment of OPC and rOPC in pediatric patients *[see Dosage and Administration (2.4)]*.

The safety and effectiveness of Noxafil oral suspension for the treatment of OPC and rOPC have not been established in pediatric patients less than 13 years of age.

8.5 Geriatric Use

No overall differences in the safety or effectiveness of Noxafil injection, Noxafil delayed-release tablets, and Noxafil oral suspension have been observed between geriatric patients and younger adult patients in the clinical trials; therefore, the recommended dosage in geriatric patients is the same as that for younger adult patients. No clinically meaningful differences in posaconazole pharmacokinetics were observed in Noxafil-treated geriatric patients compared to Noxafil-treated younger adult patients during clinical trials *[see Clinical Pharmacology (12.3)]*.

- Of the 279 patients treated with Noxafil injection in the Noxafil Injection Study (prophylaxis of invasive *Aspergillus* and *Candida* infections in those at high risk of developing these infections due to being severely immunocompromised), 52 (19%) patients were >65 years of age.
- Of the 230 patients treated with Noxafil delayed-release tablets, 38 (17%) patients were >65 years of age.
- Of the 605 patients treated with Noxafil oral suspension in Noxafil Oral Suspension Study 1 and Study 2 (prophylaxis of invasive *Aspergillus* and *Candida* infections in those at high risk of developing these infections due to being severely immunocompromised), 63 (10%) patients were ≥65 years of age.
- In studies of Noxafil for an unapproved indication, 48 patients treated with Noxafil oral suspension (greater than or equal to 800 mg/day (eight times the maximum recommended maintenance dosage for the treatment of OPC)) were ≥65 years of age.
- Of the 288 patients treated with Noxafil injection or Noxafil delayed-release tablets in the Aspergillosis Treatment Study, 85 (29%) patients were ≥65 years of age.

8.6 Renal Impairment

Noxafil Oral Suspension and Noxafil Delayed-Release Tablets

No dosage adjustment is required for patients with eGFR 20 mL/minute/1.73 m^2 or higher. Due to variability in posaconazole exposure, closely monitor patients with eGFR less than 20 mL/minute/1.73 m^2 for breakthrough fungal infections. *[see Clinical Pharmacology (12.3)]*.

Noxafil Injection

Avoid use of Noxafil injection in patients with eGFR less than 50 mL/minute/1.73 m^2 unless the benefit/risk to the patient justifies its use. The inactive ingredient in Noxafil injection, Betadex Sulfobutyl Ether Sodium (SBECD) is expected to accumulate in patients with reduced renal function. Safety and effectiveness of Noxafil injection have not been established in patients with less than 50 mL/minute/1.73 m^2.

If treatment with Noxafil injection is unavoidable in patients with eGFR less than 50 mL/minute/1.73 m^2, monitor serum creatinine levels. If serum creatinine increases, consider changing to oral Noxafil therapy .

8.7 Hepatic Impairment

No dosage adjustment is recommended for Noxafil oral suspension, Noxafil delayed-release tablets, Noxafil PowderMix for delayed-release oral suspension, and Noxafil injection in patients with mild,

moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C, respectively) *[see Clinical Pharmacology (12.3)]*.

However, a specific hepatic impairment study has not been conducted with the Noxafil delayed-release tablets, Noxafil PowderMix for delayed-release oral suspension, or Noxafil injection.

8.8 Sex

No adjustment in the dosage of Noxafil is necessary based on sex.

8.9 Race

No adjustment in the dosage of Noxafil is necessary based on race.

8.10 Weight

Pharmacokinetic modeling suggests that patients who weigh greater than 120 kg may have lower posaconazole plasma drug exposure. Therefore, consider closely monitoring for breakthrough fungal infections particularly when using Noxafil oral suspension in patients weighing greater than 120 kg *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There is no experience with overdosage of Noxafil injection and Noxafil delayed-release tablets.

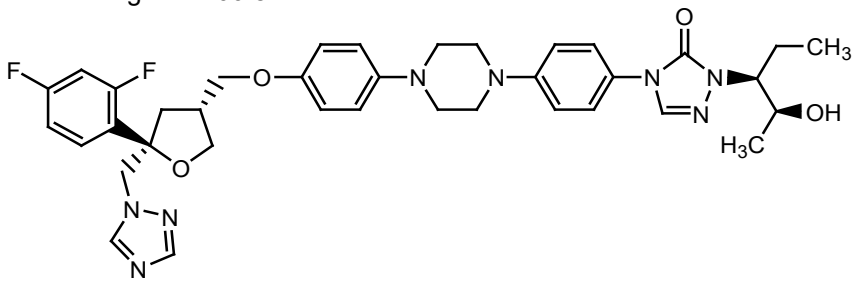
During the clinical trials, some patients received Noxafil oral suspension up to 1,600 mg/day with no adverse reactions noted that were different from the lower doses. In addition, accidental overdose was noted in one patient who took 1200 mg twice daily Noxafil oral suspension for 3 days. No related adverse reactions were noted by the investigator.

Posaconazole is not removed by hemodialysis.

11 DESCRIPTION

Noxafil and Noxafil PowderMix contain posaconazole, an azole antifungal agent.

Posaconazole is designated chemically as 4-[4-[4-[4-[[(3*R*,5*R*)-5- (2,4-difluorophenyl)tetrahydro-5-(1*H*-1,2,4-triazol-1-ylmethyl)-3-furanyl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[(1*S*,2*S*)-1-ethyl-2-hydroxypropyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one with an empirical formula of $C_{37}H_{42}F_2N_8O_4$ and a molecular weight of 700.8. The chemical structure is:



Posaconazole is a white powder with a low aqueous solubility.

Noxafil (posaconazole) Injection

Noxafil injection, for intravenous use, is a clear colorless to yellow, without preservatives sterile liquid essentially free of foreign matter. Each vial contains 300 mg of posaconazole and the following inactive ingredients: 6.68 g Betadex Sulfobutyl Ether Sodium (SBECD), 0.0033 g edetate disodium, hydrochloric acid and sodium hydroxide to adjust the pH to 2.6, and water for injection.

Noxafil (posaconazole) Delayed-Release Tablets

Noxafil delayed-release tablet, for oral use, is yellow, coated, and oblong and contains 100 mg of posaconazole. Each delayed-release tablet contains the following inactive ingredients: croscarmellose sodium, hydroxypropylcellulose, hypromellose acetate succinate, iron oxide yellow, Macrogol/PEG 3350,

magnesium stearate, microcrystalline cellulose, polyvinyl alcohol partially hydrolyzed, silicon dioxide, talc, and titanium dioxide.

Noxafil (posaconazole) Oral Suspension

Noxafil oral suspension is a white, cherry-flavored immediate-release suspension that contains 40 mg of posaconazole per mL and the following inactive ingredients: artificial cherry flavor, citric acid monohydrate, glycerin, liquid glucose, polysorbate 80, purified water, simethicone, sodium benzoate, sodium citrate dihydrate, titanium dioxide, and xanthan gum.

Noxafil PowderMix (posaconazole) for Delayed-Release Oral Suspension

Noxafil PowderMix for delayed-release oral suspension is supplied as a component of a kit. Each kit contains Noxafil as an off-white to yellowish powder for delayed-release oral suspension, a bottle of mixing liquid, two 3 mL (green) notched tip syringes, two 10 mL (blue) notched tip syringes, two mixing cups, and one bottle adapter for the mixing liquid bottle.

- Noxafil PowderMix for delayed-release oral suspension contains 300 mg of posaconazole and the following inactive ingredient: hypromellose acetate succinate.
- The mixing liquid contains: anhydrous citric acid, antifoam Af emulsion, berry citrus sweet flavor, carboxymethylcellulose sodium, carrageenan calcium sulfate trisodium phosphate, glycerin, methylparaben, microcrystalline cellulose, potassium sorbate, propylparaben, purified water, sodium citrate, sodium phosphate monobasic monohydrate, sodium saccharin, sorbitol solution, and xanthan gum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Posaconazole is an azole antifungal agent *[see Clinical Pharmacology (12.4)]*.

12.2 Pharmacodynamics

Exposure Response Relationship: Prophylaxis of invasive *Aspergillus* and *Candida* Infections in Adults Who Are at High Risk of Developing These Infections Due to Being Severely Immunocompromised

In clinical studies of neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) or hematopoietic stem cell transplant (HSCT) recipients with Graft versus Host Disease (GVHD), a wide range of plasma posaconazole exposures was noted following administration of Noxafil oral suspension. A pharmacokinetic-pharmacodynamic analysis of patient data revealed an apparent association between average posaconazole concentrations (Cavg) and prophylactic efficacy (Table 18). A lower Cavg may be associated with an increased risk of treatment failure, defined as treatment discontinuation, use of empiric systemic antifungal therapy (SAF), or occurrence of breakthrough invasive fungal infections.

Table 18: Noxafil Oral Suspension Exposure Analysis (Cavg) in Prophylaxis Trials

	Prophylaxis in AML/MDS*		**Prophylaxis in GVHD†**	
	Cavg Range (ng/mL)	Treatment Failure‡ (%)	Cavg Range (ng/mL)	Treatment Failure‡ (%)
Quartile 1	90-322	54.7	22-557	44.4
Quartile 2	322-490	37.0	557-915	20.6
Quartile 3	490-734	46.8	915-1563	17.5
Quartile 4	734-2200	27.8	1563-3650	17.5

Cavg = the average posaconazole concentration when measured at steady state
* Neutropenic patients who were receiving cytotoxic chemotherapy for AML or MDS
† HSCT recipients with GVHD
‡ Defined as treatment discontinuation, use of empiric systemic antifungal therapy (SAF), or occurrence of breakthrough invasive fungal infections

Exposure Response Relationship: Treatment of Invasive Aspergillosis in Adult and Adolescent Patients:

Across a range of posaconazole plasma minimum concentrations (C_{min}, range: 244 to 5663 ng/mL) following administration of Noxafil injection and Noxafil delayed-release tablets in adult and pediatric patients aged 14 years and older treated for invasive aspergillosis in Aspergillosis Treatment Study, there was no association between posaconazole C_{min} and treatment efficacy *[see Clinical Pharmacology (12.3) and Clinical Studies (14.1)]*. Similarly, across a range of population pharmacokinetic model-predicted steady-state plasma average concentrations (Cavg, range: 589 to 6315 ng/mL), there was no association between posaconazole Cavg and treatment efficacy.

12.3 Pharmacokinetics

General Pharmacokinetic Characteristics

General Pharmacokinetic Characteristics of Noxafil Injection

Noxafil injection exhibits dose proportional pharmacokinetics after single doses between 200 and 300 mg in healthy volunteers and patients. The mean pharmacokinetic parameters after single doses with Noxafil injection in healthy volunteers and patients are shown in Table 19.

Table 19: Summary of Mean Pharmacokinetic Parameters (%CV) in Healthy Volunteers (30 minute infusion via peripheral venous line) and Patients (90 minute infusion via central venous line) after Dosing with Noxafil Injection on Day 1

	Dose (mg)	n	$AUC_{0-\infty}$ (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	C_{max} (ng/mL)	$t_{1/2}$ (hr)	CL (L/hr)
Healthy Volunteers	200	9	35400 (50)	8840 (20)	2250 (29)	23.6 (23)	6.5 (32)
	300	9	46400 (26)	13000 (13)	2840 (30)	24.6 (20)	6.9 (27)
Patients	200	30	N/D	5570 (32)	954 (44)	N/D	N/D
	300	22	N/D	8240 (26)	1590 (62)	N/D	N/D

AUC0-∞ = Area under the plasma concentration-time curve from time zero to infinity; AUC0-12 = Area under the plasma concentration-time curve from time zero to 12 hr after the first dose on Day 1; Cmax = maximum observed concentration; t½ = terminal phase half-life; CL = total body clearance; N/D = Not Determined

Table 20 displays the pharmacokinetic parameters of posaconazole in patients following administration of Noxafil injection 300 mg taken once a day for 10 or 14 days following twice daily dosing on Day 1.

Table 20: Arithmetic Mean (%CV) of PK Parameters in Serial PK-Evaluable Patients Following Dosing of Noxafil Injection (300 mg)*

Day	N	C_{max} (ng/mL)	T_{max}† (hr)	AUC_{0-24} (ng*hr/mL)	Cav (ng/mL)	C_{min} (ng/mL)
10/14	49	3280 (74)	1.5 (0.98-4.0)	36100 (35)	1500 (35)	1090 (44)

AUC0-24 = area under the concentration-time curve over the dosing interval (i.e. 24 hours); Cav= time-averaged concentrations (i.e., AUC0-24h/24hr);
Cmin = POS trough level immediately before a subject received the dose of POS on the day specified in the protocol; Cmax = observed maximum plasma concentration; CV = coefficient of variation, expressed as a percent (%); Day = study day on treatment; Tmax = time of observed maximum plasma concentration.
* 300 mg dose administered over 90 minutes once a day following twice daily dosing on Day 1
† Median (minimum-maximum)

General Pharmacokinetic Characteristics of Noxafil Delayed-Release Tablets

Noxafil delayed-release tablets exhibit dose proportional pharmacokinetics after single and multiple dosing up to 300 mg. The mean pharmacokinetic parameters of posaconazole at steady state following administration of Noxafil delayed-release tablets 300 mg twice daily on Day 1, then 300 mg once daily

thereafter in healthy volunteers and in neutropenic patients who are receiving cytotoxic chemotherapy for AML or MDS or HSCT recipients with GVHD are shown in **Table 21**.

Table 21: Arithmetic Mean (%CV) of Steady State PK Parameters in Healthy Volunteers and Patients Following Administration of Noxafil Delayed-Release Tablets (300 mg)*

	N	$AUC_{0\text{-}24\ hr}$ (ng·hr/mL)	Cav† (ng/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)	T_{max}‡ (hr)	$t_{1/2}$ (hr)	CL/F (L/hr)
Healthy Volunteers	12	51618 (25)	2151 (25)	2764 (21)	1785 (29)	4 (3-6)	31 (40)	7.5 (26)
Patients	50	37900 (42)	1580 (42)	2090 (38)	1310 (50)	4 (1.3-8.3)	-	9.39 (45)

CV = coefficient of variation expressed as a percentage (%CV); AUC0-T = Area under the plasma concentration-time curve from time zero to 24 hr; Cmax = maximum observed concentration; Cmin = minimum observed plasma concentration; Tmax = time of maximum observed concentration; t½ = terminal phase half-life; CL/F = Apparent total body clearance

* 300 mg twice daily on Day 1, then 300 mg once daily thereafter

† Cav = time-averaged concentrations (i.e., AUC0-24 hr/24 hr)

‡ Median (minimum-maximum)

General Pharmacokinetic Characteristics of Noxafil Oral Suspension

Dose-proportional increases in plasma exposure (AUC) to Noxafil oral suspension were observed following single oral doses from 50 mg to 800 mg and following multiple-dose administration from 50 mg twice daily to 400 mg twice daily in healthy volunteers. No further increases in exposure were observed when the dose of the oral suspension increased from 400 mg twice daily to 600 mg twice daily in febrile neutropenic patients or those with refractory invasive fungal infections.

The mean (%CV) [min-max] Noxafil oral suspension average steady-state plasma concentrations (Cavg) and steady-state pharmacokinetic parameters in patients following administration of 200 mg three times a day and 400 mg twice daily of the oral suspension are provided in **Table 22.**

Table 22: The Mean (%CV) [min-max] Posaconazole Steady-State Pharmacokinetic Parameters in Patients Following Oral Administration of Noxafil Oral Suspension 200 mg Three Times a Day and 400 mg Twice Daily

Dose*	Cavg (ng/mL)	AUC† (ng·hr/mL)	CL/F (L/hr)	V/F (L)	t½ (hr)
200 mg three times a day‡ (n=252)	1103 (67) [21.5-3650]	ND§	ND§	ND§	ND§
200 mg three times a day¶ (n=215)	583 (65) [89.7-2200]	15,900 (62) [4100-56,100]	51.2 (54) [10.7-146]	2425 (39) [828-5702]	37.2 (39) [19.1-148]
400 mg twice daily# (n=23)	723 (86) [6.70-2256]	9093 (80) [1564-26,794]	76.1 (78) [14.9-256]	3088 (84) [407-13,140]	31.7 (42) [12.4-67.3]

Cavg = the average posaconazole concentration when measured at steady state

* Oral suspension administration

† AUC (0-24 hr) for 200 mg three times a day and AUC (0-12 hr) for 400 mg twice daily

‡ HSCT recipients with GVHD

§ Not done

¶ Neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes

Febrile neutropenic patients or patients with refractory invasive fungal infections, Cavg n=24

The variability in average plasma posaconazole concentrations in patients was relatively higher than that in healthy subjects.

Absorption:

Absorption of Noxafil Delayed-Release Tablets

When given orally in healthy volunteers, Noxafil delayed-release tablets are absorbed with a median T_{max} of 4 to 5 hours. Steady-state plasma concentrations are attained by Day 6 at the 300 mg dose (once daily after twice daily loading dose at Day 1). The absolute bioavailability of the oral delayed-release tablet is approximately 54% under fasted conditions. The C_{max} and AUC of posaconazole following administration of Noxafil delayed-release tablets are increased 16% and 51%, respectively, when given with a high fat meal compared to a fasted state (see **Table 23**).

Table 23: Statistical Comparison of Plasma Pharmacokinetics of Posaconazole Following Single Oral Dose Administration of 300 mg Noxafil Delayed-Release Tablet to Healthy Subjects under Fasting and Fed Conditions

	Fasting Conditions		**Fed Conditions (High Fat Meal)***		**Fed/Fasting**
Pharmacokinetic Parameter	**N**	**Mean (%CV)**	**N**	**Mean (%CV)**	**GMR (90% CI)**
C_{max} (ng/mL)	14	935 (34)	16	1060 (25)	1.16 (0.96, 1.41)
$AUC_{0\text{-}72hr}$ (hr·ng/mL)	14	26200 (28)	16	38400 (18)	1.51 (1.33, 1.72)
T_{max}† (hr)	14	5.00 (3.00, 8.00)	16	6.00 (5.00, 24.00)	N/A

GMR=Geometric least-squares mean ratio; CI=Confidence interval
* 48.5 g fat
† Median (Min, Max) reported for Tmax

Absorption of Noxafil PowderMix for Delayed-Release Oral Suspension

The absolute bioavailability of the Noxafil PowderMix for delayed-release oral suspension is approximately 70-80%. The effect of food on the pharmacokinetics of the Noxafil PowderMix for delayed-release oral suspension has not been determined.

Absorption of Noxafil Oral Suspension

Noxafil oral suspension is absorbed with a median T_{max} of ~3 to 5 hours. Steady-state plasma concentrations are attained at 7 to 10 days following multiple-dose administration.

Following single-dose administration of 200 mg, the mean AUC and C_{max} of posaconazole are approximately 3 times higher when the oral suspension is administered with a nonfat meal and approximately 4 times higher when administered with a high-fat meal (~50 gm fat) relative to the fasted state. Following single-dose administration of Noxafil oral suspension 400 mg, the mean AUC and C_{max} of posaconazole are approximately 3-times higher when administered with a liquid nutritional supplement (14 gm fat) relative to the fasted state (see **Table 24**). In addition, the effects of varying gastric administration conditions on the C_{max} and AUC of Noxafil oral suspension in healthy volunteers have been investigated and are shown in **Table 25**.

To assure attainment of adequate plasma concentrations, it is recommended to administer Noxafil oral suspension during or immediately following a full meal. In patients who cannot eat a full meal, Noxafil oral suspension should be taken with a liquid nutritional supplement or an acidic carbonated beverage (e.g., ginger ale).

Table 24: The Mean (%CV) [min-max] Posaconazole Pharmacokinetic Parameters Following Single-Dose Noxafil Oral Suspension Administration of 200 mg and 400 mg Under Fed and Fasted Conditions

Dose (mg)	C_{max} (ng/mL)	T_{max}* (hr)	AUC (I) (ng·hr/mL)	CL/F (L/hr)	$t_{½}$ (hr)
200 mg fasted (n=20)†	132 (50) [45-267]	3.50 [1.5-36‡]	4179 (31) [2705-7269]	51 (25) [28-74]	23.5 (25) [15.3-33.7]
200 mg nonfat (n=20)†	378 (43) [131-834]	4 [3-5]	10,753 (35) [4579-17,092]	21 (39) [12-44]	22.2 (18) [17.4-28.7]
200 mg high fat (54 gm fat) (n=20)†	512 (34) [241-1016]	5 [4-5]	15,059 (26) [10,341-24,476]	14 (24) [8.2-19]	23.0 (19) [17.2-33.4]
400 mg fasted (n=23)§	121 (75) [27-366]	4 [2-12]	5258 (48) [2834-9567]	91 (40) [42-141]	27.3 (26) [16.8-38.9]
400 mg with liquid nutritional supplement (14 gm fat) (n=23)§	355 (43) [145-720]	5 [4-8]	11,295 (40) [3865-20,592]	43 (56) [19-103]	26.0 (19) [18.2-35.0]

* Median [min-max].
† n=15 for AUC (I), CL/F, and t½
‡ The subject with Tmax of 36 hrs had relatively constant plasma levels over 36 hrs (1.7 ng/mL difference between 4 hrs and 36 hrs).
§ n=10 for AUC (I), CL/F, and t½

Table 25: The Effect of Varying Gastric Administration Conditions on the C_{max} and AUC of Noxafil Oral Suspension in Healthy Volunteers*

Study Description	Administration Arms	Change in C_{max} (ratio estimate†; 90% CI of the ratio estimate)	Change in AUC (ratio estimate†; 90% CI of the ratio estimate)
400 mg single dose with a high-fat meal relative to fasted state (n=12)	5 minutes before high-fat meal	↑96% (1.96; 1.48-2.59)	↑111% (2.11; 1.60-2.78)
	During high-fat meal	↑339% (4.39; 3.32-5.80)	↑382% (4.82; 3.66-6.35)
	20 minutes after high-fat meal	↑333% (4.33; 3.28-5.73)	↑387% (4.87; 3.70-6.42)
400 mg twice daily and 200 mg four times daily for 7 days in fasted state and with liquid nutritional supplement (BOOST®) (n=12)	400 mg twice daily with BOOST	↑65% (1.65; 1.29-2.11)	↑66% (1.66; 1.30-2.13)
	200 mg four times daily with BOOST	No Effect	No Effect
Divided daily dose from 400 mg twice daily to 200 mg four times daily for 7 days regardless of fasted	Fasted state	↑136% (2.36; 1.84-3.02)	↑161% (2.61; 2.04-3.35)
	With BOOST	↑137%	↑157%

conditions or with BOOST (n=12)		(2.37; 1.86-3.04)	(2.57; 2.00-3.30)
400 mg single dose with carbonated acidic beverage (ginger ale) and/or proton pump inhibitor (esomeprazole) (n=12)	Ginger ale	↑92% (1.92; 1.51-2.44)	↑70% (1.70; 1.43-2.03)
	Esomeprazole	↓32% (0.68; 0.53-0.86)	↓30% (0.70; 0.59-0.83)
400 mg single dose with a prokinetic agent (metoclopramide 10 mg three times a day for 2 days) + BOOST or an antikinetic agent (loperamide 4 mg single dose) + BOOST (n=12)	With metoclopramide + BOOST	↓21% (0.79; 0.72-0.87)	↓19% (0.81; 0.72-0.91)
	With loperamide + BOOST	↓3% (0.97; 0.88-1.07)	↑11% (1.11; 0.99-1.25)
400 mg single dose either orally with BOOST or via an NG tube with BOOST (n=16)	Via NG tube‡	↓19% (0.81; 0.71-0.91)	↓23% (0.77; 0.69-0.86)

* In 5 subjects, the Cmax and AUC decreased substantially (range: -27% to -53% and -33% to -51%, respectively) when Noxafil was administered via an NG tube compared to when Noxafil was administered orally. It is recommended to closely monitor patients for breakthrough fungal infections when Noxafil is administered via an NG tube because a lower plasma exposure may be associated with an increased risk of treatment failure.
† Ratio Estimate is the ratio of coadministered drug plus Noxafil to coadministered drug alone for Cmax or AUC.
‡ NG = nasogastric

Distribution:

The mean volume of distribution of posaconazole after intravenous solution administration was 261 L and ranged from 226-295 L between studies and dose levels.

Posaconazole is highly bound to human plasma proteins (>98%), predominantly to albumin.

Metabolism:

Posaconazole primarily circulates as the parent compound in plasma. Of the circulating metabolites, the majority are glucuronide conjugates formed via UDP glucuronidation (phase 2 enzymes). Posaconazole does not have any major circulating oxidative (CYP450 mediated) metabolites. The excreted metabolites in urine and feces account for ~17% of the administered radiolabeled dose. Posaconazole is a substrate for p-glycoprotein (P-gp) efflux.

In vitro studies with human hepatic microsomes and clinical studies indicate that posaconazole is an inhibitor primarily of CYP3A4.

Excretion:

Following administration of Noxafil oral suspension, posaconazole is predominantly eliminated in the feces (71% of the radiolabeled dose up to 120 hours) with the major component eliminated as parent drug (66% of the radiolabeled dose). Renal clearance is a minor elimination pathway, with 13% of the radiolabeled dose excreted in urine up to 120 hours (<0.2% of the radiolabeled dose is parent drug). Noxafil injection is eliminated with a mean terminal half-life ($t_{½}$) of 27 hours and a total body clearance (CL) of 7.3 L/h.

Noxafil delayed-release tablet is eliminated with a mean half-life ($t_{½}$) ranging between 26 to 31 hours.

Noxafil oral suspension is eliminated with a mean half-life ($t_{½}$) of 35 hours (range: 20-66 hours).

Specific Populations:

No clinically significant differences in the pharmacokinetics of posaconazole were observed based on age, sex, renal impairment, and indication (prophylaxis or treatment).

Patients with Renal Impairment:

After Noxafil oral administration, there were no significant differences in the posaconazole pharmacokinetics in patients with eGFR 20 mL/minute/1.73 m^2 or higher compared to those with eGFR>80 mL/minute/1.73 m^2. Although the mean posaconazole plasma exposure (AUC) was similar in patients with eGFR less than 20 mL/minute/1.73 m^2 treated with Noxafil oral suspension to those with eGFR >80 mL/minute/1.73 m^2 treated with Noxafil oral suspension, the range of the AUC estimates was highly variable (CV=96%) in patients with eGFR less than 20 mL/minute/1.73 m^2 compared to those with eGFR>80 mL/minute/1.73 m^2 (CV<40%).Similar posaconazole pharmacokinetic results are expected after administration of Noxafil delayed-release tablets *[see Use in Specific Populations (8.6)].*

Patients with Hepatic Impairment:

After a single oral dose of Noxafil oral suspension 400 mg, the mean AUC was 43%, 27%, and 21% higher in subjects with mild (Child-Pugh Class A, N=6), moderate (Child-Pugh Class B, N=6), or severe (Child-Pugh Class C, N=6) hepatic impairment, respectively, compared to subjects with normal hepatic function (N=18). Compared to subjects with normal hepatic function, the mean C_{max} was 1% higher, 40% higher, and 34% lower in subjects with mild, moderate, or severe hepatic impairment, respectively *[see Use in Specific Populations (8.7)].*

Race/Ethnicity:

In a population pharmacokinetic analysis of posaconazole, AUC was found to be 25% higher in Chinese patients relative to patients from other races/ethnicities. This higher exposure is not expected to be clinically relevant given the expected variability in posaconazole exposure *[see Use in Specific Populations (8.9)]*.

Patients Weighing More Than 120 kg:

Weight has a clinically significant effect on posaconazole clearance. Relative to 70 kg patients, the Cavg is decreased by 25% in patients greater than 120 kg. Patients administered Noxafil weighing more than 120 kg may be at higher risk for lower posaconazole plasma concentrations compared to lower weight patients *[see Use in Specific Populations (8.10)]*.

Pediatric Patients:

Prophylaxis of invasive Aspergillus and Candida infections in pediatric patients 2 years of age and older: A total of 12 patients 13 to 17 years of age received 600 mg/day (200 mg three times a day) of Noxafil oral suspension for prophylaxis of invasive fungal infections. Based on pharmacokinetic data in 10 of these pediatric patients, the mean steady-state Cav was similar between these patients and adults (≥18 years of age). In a study of 136 neutropenic pediatric patients 11 months to less than 18 years treated with Noxafil oral suspension, the exposure target of steady-state posaconazole Cavg between 500 ng/mL and less than 2500 ng/mL was attained in approximately 50% of patients instead of the pre-specified 90% of patients.

The mean pharmacokinetic parameters after multiple-dose administration of Noxafil injection and Noxafil PowderMix for delayed-release oral suspension in neutropenic pediatric patients 2 to less than 18 years of age (Pediatric Study 1) are shown in **Table 26**. Patients were enrolled into 2 age groups and received Noxafil injection and Noxafil PowderMix for delayed-release oral suspension doses at 6 mg/kg (0.6 to 1 times the recommended dose) with a maximum 300 mg dose once daily (twice daily on Day 1) *[see Adverse Reactions (6.1)]*.

Table 26: Summary of Steady-State Geometric Mean Pharmacokinetic Parameters (% Geometric CV) After Multiple Dosing with Noxafil Injection and Noxafil PowderMix for Delayed-Release Oral Suspension 6 mg/kg* in Pediatric Patients with Neutropenia or Expected Neutropenia

Age Group	Dose Type	N	$AUC_{0\text{-}24\ hr}$ (ng·hr/mL)	Cav† (ng/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)	T_{max}‡ (hr)	CL/F§ (L/hr)
2 to <7 years	IV	17	31100 (48.9)	1300 (48.9)	3060 (54.1)	626 (104.8)	1.75 (1.57-1.83)	3.27 (49.3)
	PFS	7	23000 (47.3)	960 (47.3)	1510 (43.4)	542 (68.8)	4.00 (2.17-7.92)	4.60 (35.2)
7 to 17 years	IV	24	44200 (41.5)	1840 (41.5)	3340 (39.4)	1160 (60.4)	1.77 (1.33-6.00)	4.76 (55.7)
	PFS	12	25000 (184.3)	1040 (184.3)	1370 (178.5)	713 (300.6)	2.78 (0.00-4.00)	8.39 (190.3)

IV= Noxafil injection; PFS= Noxafil PowderMix for delayed-release oral suspension; AUC0-24 = Area under the plasma concentration-time curve from time zero to 24 hr; Cmax = maximum observed concentration; Cmin = minimum observed plasma concentration; Tmax = time of maximum observed concentration; CL/F = apparent total body clearance

* 0.6 to 1 times the recommended dose

† Cav = time-averaged concentrations (i.e., AUC0-24 hr/24 hr)

‡ Median (minimum-maximum)

§ Clearance (CL for IV and CL/F for PFS)

Based on a population pharmacokinetic model evaluating posaconazole pharmacokinetics and predicting exposures in pediatric patients, the exposure of steady-state posaconazole average concentration greater than or equal to 700 ng/mL in approximately 90% of patients is attained with the recommended dose of Noxafil injection and Noxafil PowderMix for delayed-release oral suspension. The population pharmacokinetic analysis of posaconazole in pediatric patients from Pediatric Study 1 suggests that age, sex, renal impairment and ethnicity have no clinically meaningful effect on the pharmacokinetics of posaconazole.

Treatment of invasive aspergillosis in pediatric patients 2 years of age and older: A total of 31 patients 2 to less than 18 years of age (body weight of ≥12 kg) received pediatric dosing based on body weight of Noxafil delayed-release tablets, Noxafil Injection, and Noxafil PowderMix for delayed-release oral suspension *[see Dosage and Administration (2.3].*

The mean population pharmacokinetic model parameters after multiple dose administration of Noxafil delayed-release tablets, Noxafil Injection, and Noxafil PowderMix for delayed-release oral suspension in pediatric patients 2 to less than 18 years of age for the treatment of invasive aspergillosis (Pediatric Study 2) are shown in **Table 27**. *[see Adverse Reactions (6.1)]*.

Table 27: Summary of Steady-State Geometric Mean Pharmacokinetic Parameters* (% Geometric CV) After Multiple Dosing with Noxafil Injection, Noxafil PowderMix for Delayed-Release Oral Suspension, and Noxafil Delayed-Release Tablets in Pediatric Patients being Treated for Invasive Aspergillosis

Age Group	Dose Type	N†	$AUC_{0\text{-}24\ hours}$ (ng·hr/mL)	C_{av}‡ (ng/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)	T_{max}§ (hr)	CL/F¶ (L/hr)
2 to <12 years	IV	9	61900 (49.8)	2580 (49.8)	3630 (30.8)	1710 (82.2)	1.50 (1.25-1.77)	2.56 (47.8)
	PFS	6	45200 (30.2)	1880 (30.2)	2220 (26.5)	1370 (41.8)	7.00 (6.40-7.20)	3.25 (34.6)
12 to <18 years	IV	13	60800 (35.6)	2530 (35.6)	3510 (26.8)	1740 (48.5)	1.50 (1.30-1.63)	4.41 (41.8)
	Tablet	10	47800 (52.7)	1990 (52.7)	2250 (48.3)	1580 (62.6)	7.15 (6.70-7.30)	6.27 (52.7)

IV= Noxafil injection; PFS= Noxafil PowderMix for delayed-release oral suspension, Tablet= Noxafil delayed-release tablets; AUC0-24 hours = Area under the plasma concentration-time curve from time zero to 24 hr; Cmax = maximum observed concentration; Cmin = minimum observed plasma concentration; Tmax = time of maximum observed concentration; CL/F = apparent total body clearance

* Parameter estimates reported only for N>2 (excludes a single patient ≥2 to <12 receiving tablet and 2 patients ≥12 to <18 years receiving PFS)

† Some patients had 2 values (1 for IV dosing and 1 for oral dosing)

‡ Cav = time-averaged concentrations (i.e., AUC0-24 hours/24hr)

§ Median (minimum-maximum)

¶ Clearance (CL for IV and CL/F for PFS or Tablet)

The population pharmacokinetic analysis of posaconazole in pediatric patients, including Pediatric Study 2, suggests that age, sex, ethnicity, and disease status have no clinically meaningful effect on the pharmacokinetics of posaconazole

Drug Interaction Studies:

Posaconazole is primarily metabolized via UDP glucuronidation (phase 2 enzymes) and is a substrate for p-glycoprotein (P-gp) efflux. Therefore, inhibitors or inducers of these clearance pathways may affect posaconazole plasma concentrations. A summary of drugs studied clinically with the oral suspension or another tablet formulation, which affect posaconazole concentrations, is provided in **Table 28**.

Table 29 and **Table 30** include a summary of the drug effects of concomitant medications that may impact the absorption of posaconazole when administered as either the oral suspension or delayed-release tablets.

A clinical study in healthy volunteers also indicates that posaconazole is a strong CYP3A4 inhibitor as evidenced by a >5-fold increase in midazolam AUC. Therefore, plasma concentrations of drugs predominantly metabolized by CYP3A4 may be increased by posaconazole. A summary of the drugs studied clinically, for which plasma concentrations were affected by posaconazole, is provided in **Table 31** *[see Contraindications (4)* and *Drug Interactions (7.2) including recommendations]*.

Effects of Other Drugs on Noxafil and Noxafil PowderMix:

Table 28: Summary of the Effects of Coadministered Drugs on Noxafil in Healthy Volunteers

Coadministered Drug (Postulated Mechanism of Interaction)	**Coadministered Drug Dose/Schedule**	**Noxafil Dose/Schedule**	**Effect on Bioavailability of Posaconazole**	
			Change in Mean C_{max} (ratio estimate*; 90% CI of the ratio estimate)	**Change in Mean AUC** (ratio estimate*; 90% CI of the ratio estimate)
Efavirenz (UDP-G Induction)	400 mg once daily × 10 and 20 days	400 mg (oral suspension) twice daily × 10 and 20 days	↓45% (0.55; 0.47-0.66)	↓ 50% (0.50; 0.43-0.60)
Fosamprenavir (unknown mechanism)	700 mg twice daily x 10 days	200 mg once daily on the 1st day, 200 mg twice daily on the 2nd day, then 400 mg twice daily x 8 Days	↓21% 0.79 (0.71-0.89)	↓23% 0.77 (0.68-0.87)
Rifabutin (UDP-G Induction)	300 mg once daily x 17 days	200 mg (tablets) once daily × 10 days†	↓ 43% (0.57; 0.43-0.75)	↓ 49% (0.51; 0.37-0.71)
Phenytoin (UDP-G Induction)	200 mg once daily x 10 days	200 mg (tablets) once daily × 10 days†	↓ 41% (0.59; 0.44-0.79)	↓ 50% (0.50; 0.36-0.71)

* Ratio Estimate is the ratio of coadministered drug plus Noxafil to Noxafil alone for Cmax or AUC.
† The tablet refers to a non-commercial tablet formulation without polymer.

Noxafil Oral Suspension: Concomitant administration of Noxafil oral suspension with drugs affecting gastric pH or gastric motility results in lower posaconazole exposure. (see **Table 29**.)

Table 29: The Effects of Concomitant Medications that Affect the Gastric pH and Gastric Motility on the Pharmacokinetics of Noxafil Oral Suspension in Healthy Volunteers

Coadministered Drug (Postulated Mechanism of Interaction)	**Coadministered Drug Dose/Schedule**	**Noxafil Dose/Schedule**	**Effect on Bioavailability of Posaconazole**	
			Change in Mean C_{max} (ratio estimate*; 90% CI of the ratio estimate)	**Change in Mean AUC** (ratio estimate*; 90% CI of the ratio estimate)
Cimetidine (Alteration of gastric pH)	400 mg twice daily × 10 days	200 mg (tablets) once daily × 10 days†	↓ 39% (0.61; 0.53-0.70)	↓ 39% (0.61; 0.54-0.69)
Esomeprazole (Increase in gastric pH)‡	40 mg every morning × 3 days	400 mg (oral suspension) single dose	↓ 46% (0.54; 0.43-0.69)	↓ 32% (0.68; 0.57-0.81)
Metoclopramide (Increase in gastric motility)‡	10 mg three times a day × 2 days	400 mg (oral suspension) single dose	↓ 21% (0.79; 0.72-0.87)	↓ 19% (0.81; 0.72-0.91)

* Ratio Estimate is the ratio of coadministered drug plus Noxafil to coadministered drug alone for Cmax or AUC.
† The tablet refers to a non-commercial tablet formulation without polymer.
‡ The drug interactions associated with the oral suspension are also relevant for the delayed-release tablet with the exception of Esomeprazole and Metoclopramide.

Noxafil Delayed-Release Tablets: Concomitant administration of Noxafil delayed-release tablets with drugs affecting gastric pH or gastric motility did not demonstrate any significant effects on posaconazole pharmacokinetic exposure (see **Table 30**).

Table 30: The Effects of Concomitant Medications that Affect the Gastric pH and Gastric Motility on the Pharmacokinetics of Noxafil Delayed-Release Tablets in Healthy Volunteers

Coadministered Drug	**Administration Arms**	**Change in C_{max}** (ratio estimate*; 90% CI of the ratio estimate)	**Change in $AUC_{0\text{-last}}$** (ratio estimate*; 90% CI of the ratio estimate)
Mylanta® Ultimate strength liquid (Increase in gastric pH)	25.4 mEq/5 mL, 20 mL	↑6% (1.06; 0.90 -1.26)↑	↑4% (1.04; 0.90 -1.20)
Ranitidine (Zantac®) (Alteration in gastric pH)	150 mg (morning dose of 150 mg Ranitidine twice daily)	↑4% (1.04; 0.88 -1.23)↑	↓3% (0.97; 0.84 -1.12)
Esomeprazole (Nexium®) (Increase in gastric pH)	40 mg (every morning for 5 days, Day -4 to 1)	↑2% (1.02; 0.88-1.17)↑	↑5% (1.05; 0.89 -1.24)
Metoclopramide (Reglan®) (Increase in gastric motility)	15 mg four times daily for 2 days (Day -1 and 1)	↓14% (0.86, 0.73,1.02)	↓7% (0.93, 0.803,1.07)

* Ratio Estimate is the ratio of coadministered drug plus Noxafil to Noxafil alone for Cmax or AUC0-last.

Noxafil PowderMix for Delayed-Release Oral Suspension: Concomitant administration of Noxafil PowderMix for delayed-release oral suspension with drugs affecting gastric pH or gastric motility would not be expected to demonstrate any significant effects on posaconazole pharmacokinetic exposure based on similarity to the delayed-release tablets.

An *in vitro* dissolution study was conducted to evaluate the impact of alcohol (5, 10, 20, and 40%) on the dissolution of Noxafil PowderMix delayed-release oral suspension. The study showed alcohol-induced dose-dumping potential with the Noxafil PowderMix delayed-release oral suspension *[see Drug Interactions (7.1)]*.

Effects of Noxafil and Noxafil PowderMix on Other Drugs:

Table 31: Summary of the Effects of Noxafil on Coadministered Drugs in Healthy Adult Volunteers and Patients

Coadministered Drug (Postulated Mechanism of Interaction is Inhibition of CYP3A4 by posaconazole)	**Coadministered Drug Dose/Schedule**	**Noxafil Dose/ Schedule**	**Effect on Bioavailability of Coadministered Drugs**	
			Change in Mean C_{max} (ratio estimate*; 90% CI of the ratio estimate)	**Change in Mean AUC** (ratio estimate*; 90% CI of the ratio estimate)
Sirolimus	2-mg single oral dose	400 mg (oral suspension) twice daily x 16 days	↑ 572% (6.72; 5.62-8.03)	↑ 788% (8.88; 7.26-10.9)
Cyclosporine	Stable maintenance	200 mg (tablets) once daily x 10 days†	↑ Cyclosporine whole blood trough concentrations	

	dose in heart transplant recipients		Cyclosporine dose reductions of up to 29% were required	
Tacrolimus	0.05-mg/kg single oral dose	400 mg (oral suspension) twice daily × 7 days	↑ 121% (2.21; 2.01-2.42)	↑ 358% (4.58; 4.03-5.19)
Simvastatin	40-mg single oral dose	100 mg (oral suspension) once daily x 13 days 200 mg (oral suspension) once daily x 13 days	Simvastatin ↑ 841% (9.41, 7.13-12.44) Simvastatin Acid ↑ 817% (9.17, 7.36-11.43) Simvastatin ↑ 1041% (11.41, 7.99-16.29) Simvastatin Acid ↑851% (9.51, 8.15-11.10)	Simvastatin ↑ 931% (10.31, 8.40-12.67) Simvastatin Acid ↑634% (7.34, 5.82-9.25) Simvastatin ↑ 960% (10.60, 8.63-13.02) Simvastatin Acid ↑ 748% (8.48, 7.04-10.23)
Midazolam	0.4-mg single intravenous dose‡ 0.4-mg single intravenous dose‡ 2-mg single oral dose‡ 2-mg single oral dose‡	200 mg (oral suspension) twice daily x 7 days 400 mg (oral suspension) twice daily x 7 days 200 mg (oral suspension) once daily x 7 days 400 mg (oral suspension) twice daily x 7 days	↑ 30% (1.3; 1.13-1.48) ↑62% (1.62; 1.41-1.86) ↑ 169% (2.69; 2.46-2.93) ↑ 138% (2.38; 2.13-2.66)	↑ 362% (4.62; 4.02-5.3) ↑524% (6.24; 5.43-7.16) ↑ 470% (5.70; 4.82-6.74) ↑ 397% (4.97; 4.46-5.54)
Rifabutin	300 mg once daily x 17 days	200 mg (tablets) once daily × 10 days†	↑ 31% (1.31; 1.10-1.57)	↑ 72% (1.72;1.51-1.95)
Phenytoin	200 mg once daily PO x 10 days	200 mg (tablets) once daily x 10 days†	↑ 16% (1.16; 0.85-1.57)	↑ 16% (1.16; 0.84-1.59)
Ritonavir	100 mg once daily x 14 days	400 mg (oral suspension) twice daily x 7 days	↑ 49% (1.49; 1.04-2.15)	↑ 80% (1.8;1.39-2.31)
Atazanavir Atazanavir/ ritonavir boosted regimen	300 mg once daily x 14 days	400 mg (oral suspension) twice daily x 7 days	↑ 155% (2.55; 1.89-3.45) ↑ 53% (1.53; 1.13-2.07)	↑ 268% (3.68; 2.89-4.70) ↑ 146% (2.46; 1.93-3.13)

	300 mg/100 mg once daily x 14 days	400 mg (oral suspension) twice daily x 7 days		

* Ratio Estimate is the ratio of coadministered drug plus Noxafil to coadministered drug alone for Cmax or AUC.
† The tablet refers to a non-commercial tablet formulation without polymer.
‡ The mean terminal half-life of midazolam was increased from 3 hours to 7 to 11 hours during coadministration with Noxafil.

12.4 MICROBIOLOGY

Mechanism of Action

Posaconazole blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14α-demethylase responsible for the conversion of lanosterol to ergosterol in the fungal cell membrane. This results in an accumulation of methylated sterol precursors and a depletion of ergosterol within the cell membrane thus weakening the structure and function of the fungal cell membrane. This may be responsible for the antifungal activity of posaconazole.

Resistance

Clinical isolates of *Candida albicans* and *Candida glabrata* with decreased susceptibility to posaconazole were observed in oral swish samples taken during prophylaxis with posaconazole and fluconazole, suggesting a potential for development of resistance. These isolates also showed reduced susceptibility to other azoles, suggesting cross-resistance between azoles. The clinical significance of this finding is not known.

Antimicrobial Activity

Posaconazole has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections *[see Indications and Usage (1)]*.

Microorganisms

Aspergillus spp. and *Candida spp.*

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC**.**

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No drug-related neoplasms were recorded in rats or mice treated with posaconazole for 2 years at doses higher than the clinical dose. In a 2 year carcinogenicity study, rats were given posaconazole orally at doses up to 20 mg/kg (females), or 30 mg/kg (males). These doses are equivalent to 3.9- or 3.5 times the exposure achieved with a 400 mg twice daily oral suspension regimen, respectively, based on steady-state AUC in healthy volunteers administered a high-fat meal (400 mg twice daily oral suspension

regimen). In the mouse study, mice were treated at oral doses up to 60 mg/kg/day or 4.8 times the exposure achieved with a 400 mg twice daily oral suspension regimen.

Mutagenesis

Posaconazole was not genotoxic or clastogenic when evaluated in bacterial mutagenicity (Ames), a chromosome aberration study in human peripheral blood lymphocytes, a Chinese hamster ovary cell mutagenicity study, and a mouse bone marrow micronucleus study.

Impairment of Fertility

Posaconazole had no effect on fertility of male rats at a dose up to 180 mg/kg (1.7 x the 400 mg twice daily oral suspension regimen based on steady-state plasma concentrations in healthy volunteers) or female rats at a dose up to 45 mg/kg (2.2 x the 400 mg twice daily oral suspension regimen).

14 CLINICAL STUDIES

14.1 Treatment of Invasive Aspergillosis with Noxafil Injection and Noxafil Delayed-Release Tablets

Aspergillosis Treatment Study (NCT01782131) was a randomized, double-blind, controlled trial which evaluated the safety and efficacy of Noxafil injection and Noxafil delayed-release tablets versus voriconazole for primary treatment of invasive fungal disease caused by *Aspergillus* species. Eligible patients had proven, probable, or possible invasive fungal infections per the European Organization for Research and Treatment of Cancer/Mycoses Study Group, EORTC/MSG criteria. Patients were stratified by risk for mortality or poor outcome where high risk included a history of allogeneic bone marrow transplant, liver transplant, or relapsed leukemia undergoing salvage chemotherapy. The median age of patients was 57 years (range 14-91 years), with 27.8% of patients aged ≥65 years; 5 patients were pediatric patients 14-16 years of age, of whom 3 were treated with Noxafil and 2 with voriconazole. The majority of patients were male (59.8%) and white (67.1%). With regard to risk factors for invasive aspergillosis, approximately two-thirds of the patients in the study had a recent history of neutropenia, while approximately 20% with a history of an allogeneic stem cell transplant. Over 80% of subjects in each treatment group had infection limited to the lower respiratory tract (primarily lung), while approximately 11% to 13% also had infection in another organ. Invasive aspergillosis was proven or probable in 58.1% of patients as classified by independent adjudicators blinded to study treatment assignment. At least one *Aspergillus* species was identified in 21% of the patients; *A. fumigatus* and *A. flavus* were the most common pathogens identified.

Patients randomized to receive Noxafil were given a dose of 300 mg once daily (twice daily on Day 1) IV or tablet. Patients randomized to receive voriconazole were given a dose of 6 mg/kg twice daily Day 1 followed by 4 mg/kg twice daily IV, or oral 300 mg twice daily Day 1 followed by 200 mg twice daily. The recommended initial route of administration was IV; however, patients could begin oral therapy if clinically stable and able to tolerate oral dosing. The transition from IV to oral therapy occurred when the patient was clinically stable. The protocol recommended duration of therapy was 84 days with a maximum allowed duration of 98 days. Median treatment duration was 67 days for Noxafil patients and 64 days for voriconazole patients. Overall, 55% to 60% of patients began treatment with the IV formulation with a median duration of 9 days for the initial IV dosing.

The Intent to Treat (ITT) population included all patients randomized and receiving at least one dose of study treatment. All-cause mortality through Day 42 in the overall population (ITT) was 15.3% for Noxafil patients compared to 20.6% for voriconazole patients for an adjusted treatment difference of -5.3% with a 95% confidence interval of -11.6 to 1.0%. Consistent results were seen in patients with proven or probable invasive aspergillosis per EORTC criteria (see **Table 32**).

Table 32: Noxafil Injection and Noxafil Delayed-Release Tablets Invasive Aspergillosis Treatment Study: All-Cause Mortality Through Day 42

	Noxafil Injection and Delayed-Release Tablets		Voriconazole		
Population	N	n (%)	N	n (%)	Difference* (95% CI)
Intent to Treat	288	44 (15.3)	287	59 (20.6)	-5.3 (-11.6, 1.0)
Proven/Probable Invasive Aspergillosis	163	31 (19.0)	171	32 (18.7)	0.3 (-8.2, 8.8)

* Adjusted treatment difference based on Miettinen and Nurminen's method stratified by randomization factor (risk for mortality/poor outcome), using Cochran-Mantel-Haenszel weighting scheme.

Global clinical response at Week 6 was assessed by a blinded, independent adjudication committee based upon prespecified clinical, radiologic, and mycologic criteria. In the subgroup of patients with proven or probable invasive aspergillosis per EORTC criteria, the global clinical response of success (complete or partial response) at Week 6 was seen in 44.8% for Noxafil-treated patients compared to 45.6% for voriconazole-treated patients (see **Table 33**).

Table 33: Noxafil Injection and Noxafil Delayed-Release Tablets Invasive Aspergillosis Treatment Study: Successful Global Clinical Response* at Week 6

	Posaconazole		Voriconazole		
Population	N	Success	N	Success	Difference† (95% CI)
Proven/Probable Invasive Aspergillosis	163	73 (44.8)	171	78 (45.6)	-0.6 (-11.2, 10.1)

* Successful Global Clinical Response was defined as survival with a partial or complete response.
† Adjusted treatment difference based on Miettinen and Nurminen's method stratified by randomization factor (risk for mortality/poor outcome), using Cochran-Mantel-Haenszel weighting scheme.

14.2 Prophylaxis of *Aspergillus* and *Candida* Infections with Noxafil Oral Suspension

Two randomized, controlled studies were conducted using Noxafil as prophylaxis for the prevention of invasive fungal infections (IFIs) among patients at high risk due to severely compromised immune systems.

The first study (Noxafil Oral Suspension Study 1) was a randomized, double-blind trial that compared Noxafil oral suspension (200 mg three times a day) with fluconazole capsules (400 mg once daily) as prophylaxis against invasive fungal infections in allogeneic hematopoietic stem cell transplant (HSCT) recipients with Graft versus Host Disease (GVHD). Efficacy of prophylaxis was evaluated using a composite endpoint of proven/probable IFIs, death, or treatment with systemic antifungal therapy (patients may have met more than one of these criteria). This assessed all patients while on study therapy plus 7 days and at 16 weeks post-randomization. The mean duration of therapy was comparable between the 2 treatment groups (80 days, Noxafil oral suspension; 77 days, fluconazole). **Table 34** contains the results from Noxafil Oral Suspension Study 1.

Table 34: Results from Blinded Clinical Study in Prophylaxis of IFI in All Randomized Patients with Hematopoietic Stem Cell Transplant (HSCT) and Graft-vs.-Host Disease (GVHD): Noxafil Oral Suspension Study 1

	Posaconazole n=301	**Fluconazole n=299**
On therapy plus 7 days		
Clinical Failure*	50 (17%)	55 (18%)
Failure due to:		
Proven/Probable IFI	7 (2%)	22 (7%)
(*Aspergillus*)	3 (1%)	17 (6%)
(*Candida*)	1 (<1%)	3 (1%)
(Other)	3 (1%)	2 (1%)
All Deaths Proven/probable fungal infection prior to death	22 (7%) 2 (<1%)	24 (8%) 6 (2%)
SAF†	27 (9%)	25 (8%)
Through 16 weeks		
Clinical Failure*,‡	99 (33%)	110 (37%)
Failure due to:		
Proven/Probable IFI	16 (5%)	27 (9%)
(*Aspergillus*)	7 (2%)	21 (7%)
(*Candida*)	4 (1%)	4 (1%)
(Other)	5 (2%)	2 (1%)
All Deaths Proven/probable fungal infection prior to death	58 (19%) 10 (3%)	59 (20%) 16 (5%)
SAF†	26 (9%)	30 (10%)
Event free lost to follow-up§	24 (8%)	30 (10%)

* Patients may have met more than one criterion defining failure.
† Use of systemic antifungal therapy (SAF) criterion is based on protocol definitions (empiric/IFI usage >4 consecutive days).
‡ 95% confidence interval (posaconazole-fluconazole) = (-11.5%,+3.7%).
§ Patients who are lost to follow-up (not observed for 112 days), and who did not meet another clinical failure endpoint. These patients were considered failures.

The second study (Noxafil Oral Suspension Study 2) was a randomized, open-label study that compared Noxafil oral suspension (200 mg 3 times a day) with fluconazole suspension (400 mg once daily) or itraconazole oral solution (200 mg twice a day) as prophylaxis against IFIs in neutropenic patients who were receiving cytotoxic chemotherapy for AML or MDS. As in Noxafil Oral Suspension Study 1, efficacy of prophylaxis was evaluated using a composite endpoint of proven/probable IFIs, death, or treatment with systemic antifungal therapy (Patients might have met more than one of these criteria). This study assessed patients while on treatment plus 7 days and 100 days post-randomization. The mean duration of therapy was comparable between the 2 treatment groups (29 days, posaconazole; 25 days, fluconazole or itraconazole). **Table 35** contains the results from Noxafil Oral Suspension Study 2.

Table 35: Results from Open-Label Clinical Study 2 in Prophylaxis of IFI in All Randomized Patients with Hematologic Malignancy and Prolonged Neutropenia: Noxafil Oral Suspension Study 2

	Posaconazole n=304	**Fluconazole/Itraconazole n=298**
On therapy plus 7 days		
Clinical Failure*,†	82 (27%)	126 (42%)
Failure due to:		
Proven/Probable IFI	7 (2%)	25 (8%)
(*Aspergillus*)	2 (1%)	20 (7%)
(*Candida*)	3 (1%)	2 (1%)
(Other)	2 (1%)	3 (1%)
All Deaths Proven/probable fungal infection prior to death	17 (6%) 1 (<1%)	25 (8%) 2 (1%)
SAF‡	67 (22%)	98 (33%)
Through 100 days post-randomization		
Clinical Failure†	158 (52%)	191 (64%)
Failure due to:		
Proven/Probable IFI	14 (5%)	33 (11%)
(*Aspergillus*)	2 (1%)	26 (9%)
(*Candida*)	10 (3%)	4 (1%)
(Other)	2 (1%)	3 (1%)
All Deaths Proven/probable fungal infection prior to death	44 (14%) 2 (1%)	64 (21%) 16 (5%)
SAF‡	98 (32%)	125 (42%)
Event free lost to follow-up§	34 (11%)	24 (8%)

* 95% confidence interval (posaconazole-fluconazole/itraconazole) = (-22.9%, -7.8%).
† Patients may have met more than one criterion defining failure.
‡ Use of systemic antifungal therapy (SAF) criterion is based on protocol definitions (empiric/IFI usage >3 consecutive days).
§ Patients who are lost to follow-up (not observed for 100 days), and who did not meet another clinical failure endpoint. These patients were considered failures.

In summary, 2 clinical studies of prophylaxis were conducted with the Noxafil oral suspension. As seen in the accompanying tables (**Table 34 and Table 35**), clinical failure represented a composite endpoint of breakthrough IFI, mortality and use of systemic antifungal therapy. In Noxafil Oral Suspension Study 1 (**Table 34**), the clinical failure rate of posaconazole (33%) was similar to fluconazole (37%), (95% CI for the difference posaconazole–comparator -11.5% to 3.7%) while in Noxafil Oral Suspension Study 2 (**Table 35**) clinical failure was lower for patients treated with posaconazole (27%) when compared to patients treated with fluconazole or itraconazole (42%), (95% CI for the difference posaconazole–comparator -22.9% to -7.8%).

All-cause mortality was similar at 16 weeks for both treatment arms in Noxafil Oral Suspension Study 1 [POS 58/301 (19%) vs. FLU 59/299 (20%)]; all-cause mortality was lower at 100 days for Noxafil-treated patients in Noxafil Oral Suspension Study 2 [POS 44/304 (14%) vs. FLU/ITZ 64/298 (21%)]. Both studies demonstrated fewer breakthrough infections caused by *Aspergillus* species in patients receiving Noxafil prophylaxis when compared to patients receiving fluconazole or itraconazole.

14.3 Treatment of Oropharyngeal Candidiasis with Noxafil Oral Suspension

Noxafil Oral Suspension Study 3 was a randomized, controlled, evaluator-blinded study in HIV-infected patients with oropharyngeal candidiasis. Patients were treated with Noxafil or fluconazole oral

suspension (both Noxafil and fluconazole were given as follows: 100 mg twice a day for 1 day followed by 100 mg once a day for 13 days).

Clinical and mycological outcomes were assessed after 14 days of treatment and at 4 weeks after the end of treatment. Patients who received at least 1 dose of study medication and had a positive oral swish culture of *Candida* species at baseline were included in the analyses (see **Table 36**). The majority of the subjects had *C. albicans* as the baseline pathogen.

Clinical success at Day 14 (complete or partial resolution of all ulcers and/or plaques and symptoms) and clinical relapse rates (recurrence of signs or symptoms after initial cure or improvement) 4 weeks after the end of treatment were similar between the treatment arms (see **Table 36**).

Mycologic eradication rates (absence of colony forming units in quantitative culture at the end of therapy, Day 14), as well as mycologic relapse rates (4 weeks after the end of treatment) were also similar between the treatment arms (see **Table 36**).

Table 36: Noxafil Oral Suspension Clinical Success, Mycological Eradication, and Relapse Rates in Oropharyngeal Candidiasis

	Noxafil	**Fluconazole**
Clinical Success at End of Therapy (Day 14)	155/169 (91.7%)	148/160 (92.5%)
Clinical Relapse (4 Weeks after End of Therapy)	45/155 (29.0%)	52/148 (35.1%)
Mycological Eradication (absence of CFU) at End of Therapy (Day 14)	88/169 (52.1%)	80/160 (50.0%)
Mycological Relapse (4 Weeks after End of Treatment)	49/88 (55.6%)	51/80 (63.7%)

Mycologic response rates, using a criterion for success as a posttreatment quantitative culture with ≤20 colony forming units (CFU/mL) were also similar between the two groups (Noxafil 68.0%, fluconazole 68.1%). The clinical significance of this finding is unknown.

14.4 Noxafil Oral Suspension Treatment of Oropharyngeal Candidiasis Refractory to Treatment with Fluconazole or Itraconazole

Noxafil Oral Suspension Study 4 was a noncomparative study of Noxafil oral suspension in HIV-infected subjects with OPC that was refractory to treatment with fluconazole or itraconazole. An episode of OPC was considered refractory if there was failure to improve or worsening of OPC after a standard course of therapy with fluconazole greater than or equal to 100 mg/day for at least 10 consecutive days or itraconazole 200 mg/day for at least 10 consecutive days and treatment with either fluconazole or itraconazole had not been discontinued for more than 14 days prior to treatment with Noxafil. Of the 199 subjects enrolled in this study, 89 subjects met these strict criteria for refractory infection.

Forty-five subjects with refractory OPC were treated with Noxafil oral suspension 400 mg twice daily for 3 days, followed by 400 mg once daily for 25 days with an option for further treatment during a 3-month maintenance period. Following a dosing amendment, a further 44 subjects were treated with posaconazole 400 mg twice daily for 28 days. The efficacy of Noxafil was assessed by the clinical success (cure or improvement) rate after 4 weeks of treatment. The clinical success rate was 74.2% (66/89). The clinical success rates for both the original and the amended dosing regimens were similar (73.3% and 75.0%, respectively).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Noxafil Injection

Noxafil injection is a clear, colorless to yellow sterile liquid in single-dose Type I glass vials closed with bromobutyl rubber stopper and aluminum seal containing 300 mg of posaconazole in 16.7 mL of solution (18 mg of posaconazole per mL) (NDC 0085-4331-01).

Noxafil Delayed-Release Tablets

Noxafil delayed-release tablets are yellow, coated, oblong, debossed with "100" on one side containing 100 mg of posaconazole. Bottles with child-resistant closures of 60 delayed-release tablets (NDC 0085-4324-02).

Noxafil Oral Suspension

Noxafil oral suspension is a white, cherry-flavored oral suspension in 4-ounce (123 mL) amber glass bottles with child-resistant closures containing 105 mL of suspension (40 mg of posaconazole per mL). Supplied with each oral suspension bottle is a plastic dosing spoon calibrated for measuring 2.5 mL and 5 mL doses (NDC 0085-1328-01).

Noxafil PowderMix for Delayed-Release Oral Suspension

Noxafil PowderMix for delayed-release oral suspension is supplied as:

- Package A: a kit with 8 child-resistant single-use packets of Noxafil PowderMix for delayed-release oral suspension 300 mg, two 3 mL (green) notched tip syringes, two 10 mL (blue) notched tip syringes, two mixing cups, one mixing liquid bottle, one bottle adapter for the mixing liquid bottle and Instructions for Use.
- Package B: a box of six 3 mL (green) and six 10 mL (blue) notched tip syringes for additional supply.
- Packages A and B are supplied separately.

NDC 0085-2224-02 unit of use carton with 8 packets.
NDC 0085-2224-01 individual packet.

16.2 Storage and Handling

Noxafil Injection

Store Noxafil injection vial refrigerated at 2 to 8°C (36 to 46°F). Storage conditions for the diluted Noxafil infusion solution are presented in another section of the prescribing information *[see Dosage and Administration (2.5)].*

Noxafil Delayed-Release Tablets

Store at 20 to 25°C (68 to 77°F), excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

Noxafil Oral Suspension

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]. **DO NOT FREEZE.**

Noxafil PowderMix for Delayed-Release Oral Suspension

Store the entire kit at 20 to 25°C (68 to 77°F), excursions permitted to 15 to 30°C (59 to 86°F) in a clean, dry place. Do not open foil packet containing Noxafil PowderMix for delayed-release oral

suspension until ready for use. Storage conditions for the reconstituted solution are presented in another section of the prescribing information *[see Dosage and Administration (2.10)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Important Administration Instructions

Noxafil Delayed-Release Tablets

Advise patients that Noxafil delayed-release tablets must be swallowed whole and not divided, crushed, or chewed.

Instruct patients that if they miss a dose, they should take it as soon as they remember. If they do not remember until it is within 12 hours of the next dose, they should be instructed to skip the missed dose and go back to the regular schedule. Patients should not double their next dose or take more than the prescribed dose.

Noxafil Oral Suspension

Advise patients to take each dose of Noxafil oral suspension during or immediately (i.e., within 20 minutes) following a full meal. In patients who cannot eat a full meal, each dose of Noxafil oral suspension should be administered with a liquid nutritional supplement or an acidic carbonated beverage (e.g., ginger ale) in order to enhance absorption.

Instruct patients that if they miss a dose, they should take it as soon as they remember. However, if it is almost time for the next dose, they should be instructed to skip the missed dose and go back to the regular schedule. Patients should not double their next dose or take more than the prescribed dose.

Noxafil PowderMix for Delayed-Release Oral Suspension

Instruct parents and/or caregivers that ONLY the provided notched tip syringes can be used to administer Noxafil PowderMix for delayed-release oral suspension to pediatric patients.

Advise patients to take Noxafil PowderMix for delayed-release oral suspension with food.

Drug Interactions

Advise patients to inform their physician immediately if they:

- develop severe diarrhea or vomiting.
- are currently taking drugs that are known to prolong the QTc interval and are metabolized through CYP3A4.
- are currently taking a cyclosporine or tacrolimus, or they notice swelling in an arm or leg or shortness of breath.
- are taking other drugs or before they begin taking other drugs as certain drugs can decrease or increase the plasma concentrations of posaconazole.

Serious and Potentially Serious Adverse Reactions

Advise patients to inform their physician immediately if they:

- notice a change in heart rate or heart rhythm or have a heart condition or circulatory disease. Noxafil can be administered with caution to patients with potentially proarrhythmic conditions.
- are pregnant, plan to become pregnant, or are nursing.
- have liver disease or develop itching, nausea or vomiting, their eyes or skin turn yellow, they feel more tired than usual or feel like they have the flu.
- have ever had an allergic reaction to other antifungal medicines such as ketoconazole, fluconazole, itraconazole, or voriconazole.

Hereditary Fructose Intolerance (HFI)

Inform patients and caregivers that Noxafil PowderMix for delayed-release oral suspension contains sorbitol and can be life-threatening when administered to patients with hereditary fructose intolerance (HFI) *[see Warnings and Precautions (5.9)]*. Inquire for symptoms of sorbitol/fructose and/or sucrose intolerance before administration.

Manuf. for: Merck Sharp & Dohme LLC
Rahway, NJ 07065, USA

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Patient Information
NOXAFIL® (**NOX**-a-fil)
(posaconazole) injection
NOXAFIL® (**NOX**-a-fil)
(posaconazole) delayed-release tablets
NOXAFIL® (**NOX**-a-fil)
(posaconazole) oral suspension
NOXAFIL® (**NOX**-a-fil) POWDERMIX
(posaconazole) for delayed-release oral suspension

What is Noxafil and Noxafil PowderMix?

Noxafil (which refers to injection, delayed-release tablets, and oral suspension) and Noxafil PowderMix (for delayed-release oral suspension) are prescription medicines used in adults and children to help prevent or treat fungal infections that can spread throughout your body (invasive fungal infections). These infections are caused by fungi called *Aspergillus* or *Candida*. Noxafil and Noxafil PowderMix are used in people who have an increased chance of getting these infections due to a weak immune system. These include people who have had a hematopoietic stem cell transplantation (bone marrow transplant) with graft versus host disease or those with a low white blood cell count due to chemotherapy for blood cancers (hematologic malignancies).

Noxafil injection is used for:

- prevention of fungal infections in adults and children 2 years of age and older who weigh 22 lbs (10 kg) or greater.
- treatment of fungal infections in adults and children 2 years of age and older who weigh 22 lbs (10 kg) or greater.

Noxafil delayed-release tablets are used for:

- prevention of fungal infections in adults and children 2 years of age and older who weigh greater than 88 lbs (40 kg).
- treatment of fungal infections in adults and children 2 years of age and older who weigh greater than 88 lbs (40 kg).

Noxafil oral suspension is used for:

- prevention of fungal infections in adults and children 13 years of age and older.

Noxafil PowderMix for delayed-release oral suspension is used for:

- prevention of fungal infections in children 2 years of age and older who weigh 22 lbs to 88 lbs (10 kg to 40 kg).
- treatment of fungal infections in children 2 years of age and older who weigh 22 lbs to 88 lbs (10 kg to 40 kg).

Noxafil oral suspension is also used to treat a fungal infection called “thrush” caused by *Candida* in your mouth or throat area. **Noxafil oral suspension** can be used as the first treatment for thrush, or as another treatment for thrush after itraconazole or fluconazole treatment has not worked.

Noxafil oral suspension is for adults and children 13 years of age and older.
It is not known if Noxafil oral suspension is safe and effective in children under 13 years of age for the treatment of thrush as the first treatment for thrush, or as another treatment for thrush after itraconazole or fluconazole treatment has not worked.

It is not known if Noxafil or Noxafil PowderMix is safe and effective in children under 2 years of age.

Do not take Noxafil or Noxafil PowderMix if you:

- are allergic to posaconazole, any of the ingredients in Noxafil or Noxafil PowderMix, or other azole antifungal medicines. See the end of this Patient Information leaflet for a complete list of ingredients in Noxafil and Noxafil PowderMix.
- are taking any of the following medicines:
  - sirolimus
  - pimozide
  - quinidine
  - certain statin medicines that lower cholesterol (atorvastatin, lovastatin, simvastatin)
  - ergot alkaloids (ergotamine, dihydroergotamine)
- have chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) and you have just started taking venetoclax or your venetoclax dose is being slowly increased.
- are taking **Noxafil PowderMix for delayed-release oral suspension** and have hereditary fructose intolerance.

Ask your healthcare provider or pharmacist if you are not sure if you are taking any of these medicines.
Do not start taking a new medicine without talking to your healthcare provider or pharmacist.

Before you take Noxafil or Noxafil PowderMix, tell your healthcare provider about all of your medical conditions, including if you:

- are taking certain medicines that lower your immune system like cyclosporine or tacrolimus.
- are taking certain drugs for HIV infection, such as ritonavir, atazanavir, efavirenz, or fosamprenavir. Efavirenz and fosamprenavir can cause a decrease in the Noxafil levels in your body. Efavirenz and fosamprenavir should not be taken with Noxafil or Noxafil PowderMix.
- are taking midazolam, a hypnotic and sedative medicine.
- are taking vincristine, vinblastine and other "vinca alkaloids" (medicines used to treat cancer).
- are taking venetoclax, a medicine used to treat cancer.
- have or had liver problems.
- have or had kidney problems.
- have or had an abnormal heart rate or rhythm, heart problems, or blood circulation problems.
- are pregnant or plan to become pregnant. It is not known if Noxafil will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if Noxafil passes into your breast milk. You and your healthcare provider should decide if you will take Noxafil or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Noxafil and Noxafil PowderMix can affect the way other medicines work, and other medicines can affect the way Noxafil and Noxafil PowderMix work, and can cause serious side effects.
Especially tell your healthcare provider if you take:

- rifabutin or phenytoin. If you are taking these medicines, you should not take **Noxafil delayed-release tablets**, **Noxafil oral suspension**, or **Noxafil PowderMix for delayed-release oral suspension**.
- cimetidine or esomeprazole. If you are taking these medicines, you should not take **Noxafil oral suspension**.

Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure.

Know the medicines you take. Keep a list of them with you to show your healthcare provider or pharmacist when you get a new medicine.

How should I take Noxafil or Noxafil PowderMix?

- **Do not switch between Noxafil oral suspension and Noxafil delayed-release tablets or Noxafil PowderMix for delayed-release oral suspension**.
- Take Noxafil or Noxafil PowderMix exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much Noxafil or Noxafil PowderMix to take and when to take it.
- Take Noxafil or Noxafil PowderMix for as long as your healthcare provider tells you to take it.
- If you take too much Noxafil or Noxafil PowderMix, call your healthcare provider or go to the nearest hospital emergency room right away.
- Noxafil injection is usually given over 30 to 90 minutes through a plastic tube placed in your vein.
- **Noxafil delayed-release tablets:**
  - Take Noxafil delayed-release tablets with or without food.
  - Take Noxafil delayed-release tablets whole. Do not break, crush, or chew Noxafil delayed-release tablets before swallowing. If you cannot swallow Noxafil delayed-release tablets whole, tell your healthcare provider. You may need a different medicine.
  - If you miss a dose, take it as soon as you remember and then take your next scheduled dose at its regular time. If it is within 12 hours of your next dose, do not take the missed dose. Skip the missed dose and go back to your regular schedule. Do not double your next dose or take more than your prescribed dose.
- **Noxafil oral suspension:**
  - Shake Noxafil oral suspension well before use.
  - Take each dose of Noxafil oral suspension during or within 20 minutes after a full meal. If you cannot eat a full meal, take each dose of Noxafil oral suspension with a liquid nutritional supplement or an acidic carbonated beverage, like ginger ale.
  - A measured dosing spoon comes with your Noxafil oral suspension and is marked for doses of **2.5 mL** and **5 mL**. **See Figure A.**

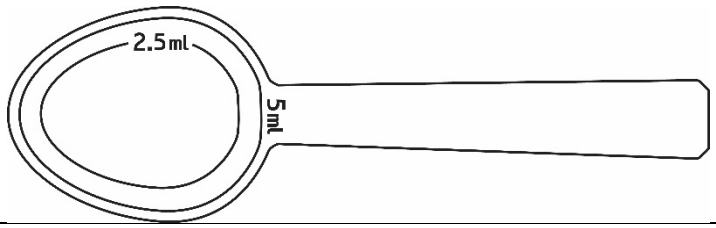


Figure A

- Rinse the spoon with water after each dose of Noxafil oral suspension and before you store it away.
- If you miss a dose, take it as soon as you remember. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not take a double dose to make up for the missed dose or take more than your prescribed dose.

- **Noxafil PowderMix for delayed-release oral suspension:**
  - Before giving the first dose of Noxafil PowderMix for delayed-release oral suspension, **read the Instructions for Use booklet that comes with Noxafil PowderMix for delayed-release oral suspension** for information about the correct way to mix and give a dose of Noxafil PowderMix for delayed-release oral suspension to your child. **Keep the booklet and follow it each time you prepare the medicine. Bring this booklet to your child's appointments.**
  - If you have questions about how to mix or give Noxafil PowderMix, talk with your healthcare provider or pharmacist.
  - Only use the mixing liquid that comes with the kit to prepare Noxafil PowderMix.
  - After mixing, measure the prescribed dose with notched tip syringe provided with the kit. **Only use the notched tip syringes that come with the kit to prepare and give the medicine.**
  - **Give the dose within 1 hour of mixing the suspension. Give with food.**
  - **If your child does not take all of the prescribed dose or spits some of it out, call your healthcare provider to find out what to do.**

Follow the instructions from your healthcare provider on how much Noxafil or Noxafil PowderMix you should take and when to take it.

What are the possible side effects of Noxafil or Noxafil PowderMix?

Noxafil or Noxafil PowderMix may cause serious side effects, including:

- **drug interactions with cyclosporine or tacrolimus.** If you take Noxafil or Noxafil PowderMix with cyclosporine or tacrolimus, your blood levels of cyclosporine or tacrolimus may increase. Serious side effects can happen in your kidney or brain if you have high levels of cyclosporine or tacrolimus in your blood. Your healthcare provider should do blood tests to check your levels of cyclosporine or tacrolimus if you are taking these medicines while taking Noxafil or Noxafil PowderMix. Tell your healthcare provider right away if you have swelling in your arm or leg or shortness of breath.
- **problems with the electrical system of your heart (arrhythmias and QTc prolongation).** Certain medicines used to treat fungus called azoles, including posaconazole, the active ingredient in Noxafil and Noxafil PowderMix, may cause heart rhythm problems. People who have certain heart problems or who take certain medicines have a higher chance for this problem. Tell your healthcare provider right away if your heartbeat becomes fast or irregular.
- **changes in body salt (electrolytes) levels in your blood.** Your healthcare provider should check your electrolytes while you are taking Noxafil or Noxafil PowderMix.
- **new or worsening high blood pressure and low potassium levels in your blood (pseudoaldosteronism).** Your healthcare provider should check your blood pressure and potassium levels.
- **liver problems.** Some people who also have other serious medical problems may have severe liver problems that may lead to death, especially if you take certain doses of Noxafil or Noxafil PowderMix. Your healthcare provider should do blood tests to check your liver while you are taking Noxafil or Noxafil PowderMix. Call your healthcare provider right away if you have any of the following symptoms of liver problems:
  - itchy skin
  - nausea or vomiting
  - yellowing of your eyes or skin
  - feeling very tired
  - flu-like symptoms
- **increased amounts of midazolam in your blood.** If you take Noxafil or Noxafil PowderMix with midazolam, Noxafil or Noxafil PowderMix increases the amount of midazolam in your blood. This can make your sleepiness last longer. Your healthcare provider should check you closely for side effects if you take midazolam with Noxafil or Noxafil PowderMix.

The most common side effects of Noxafil in adults include:

- diarrhea
- nausea
- fever
- vomiting
- headache
- coughing
- low potassium levels in the blood

The most common side effects of Noxafil injection and Noxafil PowderMix in children include:

- fever
- fever with low white blood cell count (febrile neutropenia)
- vomiting
- redness and sores of the lining of the mouth, lips, throat, stomach, and genitals (mucositis or stomatitis)
- itching
- high blood pressure
- low potassium levels in the blood

If you take Noxafil delayed-release tablets, Noxafil oral suspension, or Noxafil PowderMix for delayed-release oral suspension, tell your healthcare provider right away if you have diarrhea or vomiting.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Noxafil or Noxafil PowderMix. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Noxafil or Noxafil PowderMix?

Noxafil injection

- Store Noxafil injection refrigerated between 36°F to 46°F (2°C to 8°C).

Noxafil delayed-release tablets

- Store Noxafil delayed-release tablets at room temperature between 68°F to 77°F (20°C to 25°C).

Noxafil oral suspension

- Store Noxafil oral suspension at room temperature between 68°F to 77°F (20°C to 25°C).
- Do **not** freeze Noxafil oral suspension.

Noxafil PowderMix for delayed-release oral suspension

- Store the entire kit at room temperature between 68°F to 77°F (20°C to 25°C) in a clean, dry place.
- Do not open the foil packet until ready for use.

Safely throw away medicine that is out of date or no longer needed.

Keep Noxafil and Noxafil PowderMix and all medicines out of the reach of children.

General information about the safe and effective use of Noxafil and Noxafil PowderMix.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use Noxafil or Noxafil PowderMix for a condition for which it was not prescribed. Do not give Noxafil or Noxafil PowderMix to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about Noxafil or Noxafil PowderMix that is written for health professionals.

What are the ingredients in Noxafil and Noxafil PowderMix?

Active ingredient: posaconazole

Inactive ingredients:

Noxafil injection: Betadex Sulfobutyl Ether Sodium (SBECD), edetate sodium, hydrochloric acid, sodium hydroxide, and water for injection.

Noxafil delayed-release tablets: croscarmellose sodium, hydroxypropylcellulose, hypromellose acetate succinate, iron oxide yellow, Macrogol/PEG 3350, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol partially hydrolyzed, silicon dioxide, talc, and titanium dioxide.

Noxafil oral suspension: artificial cherry flavor, citric acid monohydrate, glycerin, liquid glucose, polysorbate 80, purified water, simethicone, sodium benzoate, sodium citrate dihydrate, titanium dioxide, and xanthan gum.

Noxafil PowderMix for delayed-release oral suspension: hypromellose acetate succinate. The mixing liquid contains: anhydrous citric acid, antifoam Af emulsion, berry citrus sweet flavor, carboxymethylcellulose sodium, carrageenan

calcium sulfate trisodium phosphate, glycerin, methylparaben, microcrystalline cellulose, potassium sorbate, propylparaben, purified water, sodium citrate, sodium phosphate monobasic monohydrate, sodium saccharin, sorbitol solution, and xanthan gum.

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usppi-mk5592-mf-2601r024

For more information, go to www.noxafil.com or call 1-800-672-6372.
This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 1/2026

Important: Read This Booklet First

Noxafil PowderMix (posaconazole)

for delayed-release oral suspension

Instructions for Use

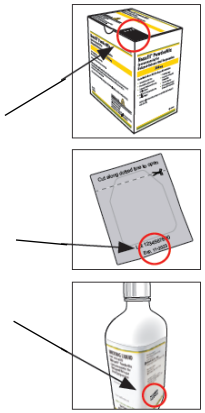
for caregivers and healthcare providers of toddlers and children



Reference ID: 5734740

Before You Start

- Before you start, be sure that you read and understand all of these instructions. They may be different than those for medicines that you have used in the past.
- It is important that you make all measurements very carefully.
- Before you give Noxafil PowderMix, check all 3 expiration dates. The expiration date is printed on the box, the Noxafil PowderMix packets, and the mixing liquid.
- Do not open the Noxafil PowderMix packets until you are ready to mix the dose.
- Give Noxafil PowderMix with food.



Note: Put your child in a safe place. You will need both hands to prepare Noxafil PowderMix. Wash your hands with soap and water before preparing Noxafil PowderMix.

Reference ID: 5734740

Before You Start

- The amount of Noxafil PowderMix you give depends on your child's weight. Your healthcare provider will tell you the right dose to give your child. Be sure to keep your healthcare provider's appointments so you get new dosing information as your child grows.

- This booklet tells you how to:
  - Make the Noxafil PowderMix into a liquid form.
  - Measure the right dose using the included notched-tip oral syringe. Only use the notched-tip syringes supplied with the kit. Do not use other oral syringes.
  - Give the Noxafil PowderMix to your child.
  - Clean up.

Note before adding Noxafil PowderMix: Make sure you and your child are ready! If you do not use Noxafil PowderMix within **1 hour**, you will need to throw it away and start over.

Note: If you have any questions, call your healthcare provider.

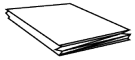
Reference ID: 5734740

Kit Contents

- Prescription (on Noxafil PowderMix box)



- Instructions for Use (this booklet)
- Package insert



- 4 syringes (shown below)

- 2 mixing cups

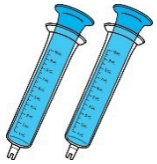


- 8 packets of Noxafil PowderMix
- Bottle adapter

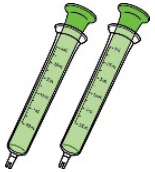


- Bottle of Mixing Liquid for use with Noxafil PowderMix





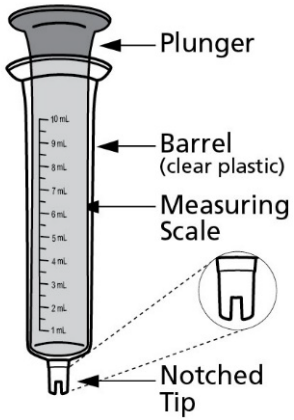
2 blue (10 mL) syringes



2 green (3 mL) syringes

The kit has an extra cup and set of syringes in case one is lost or damaged.
Do not use any damaged cups or syringes.

Get to Know the Oral Syringes



- Before you prepare a dose, review the parts of the syringe and how to use them.
- If you have any questions about measuring with a syringe, call your healthcare provider.
- Make sure the plunger is pushed all the way into the barrel before you start to measure the dose.

- Look for the number on the measuring scale that matches the amount of mixing liquid or Noxafil PowderMix that you need.
- Be sure to follow the directions in this booklet to remove air bubbles from the syringe. **Air bubbles can affect the amount of medicine that the child gets.**

Reference ID: 5734740

Step 1. Get the mixing liquid ready.

Important: Noxafil PowderMix needs to be prepared using the mixing liquid. **Do not** mix Noxafil PowderMix with milk, juice, or water.







When you use the mixing liquid for the first time:

- Open the bottle and remove the safety seal.
- Place the bottle adapter on top of the bottle with the small hole facing up.
- **Push the bottle adapter all the way down.**
- After it is in place, the bottle adapter stays in the bottle.
- Put the cap back on the bottle.

Reference ID: 5734740

Step 2. Gather all your supplies and put on a clean surface.

Note: Put your child in a safe place. You will need both hands to prepare Noxafil PowderMix. Wash your hands with soap and water before preparing Noxafil PowderMix.



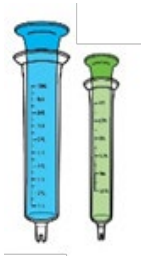
1 mixing cup
(Using the tab on the mixing cup, pull open the lid.)



1 packet of Noxafil PowderMix powder



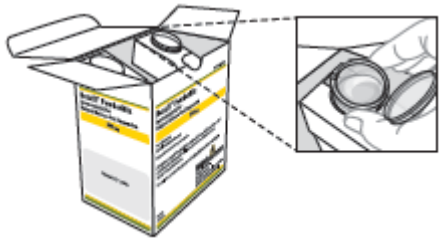
Mixing liquid



2 syringes
(Have 1 of each size ready, but you may only use 1, depending on the dose.)



Scissors
(not included with kit: use sharp household scissors or kitchen scissors)



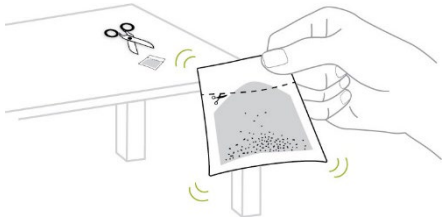
The Noxafil PowderMix box has a mixing cup holder inside to help tilt the cup when you are measuring the dose.

Reference ID: 5734740

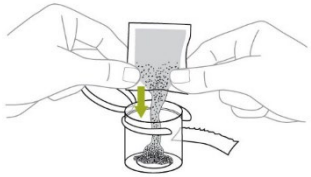
Step 3. Add Noxafil PowderMix to the mixing cup.

Note before adding Noxafil PowderMix:
Make sure you and your child are ready! If you do not use Noxafil PowderMix within **1 hour**, you will need to throw it away and start over.

- Take **1 packet** of Noxafil PowderMix and shake the powder to the bottom of the packet.



- Cut open the packet of Noxafil PowderMix at the dotted line and add all of the Noxafil PowderMix to the mixing cup. Make sure the packet of Noxafil PowderMix is completely empty.



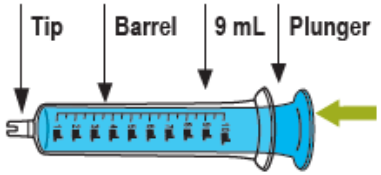
Reference ID: 5734740

Step 4. Shake the mixing liquid bottle.

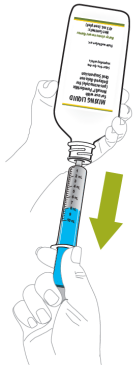


- Shake the mixing liquid well before each time you prepare Noxafil PowderMix.

Step 5. Fill the blue syringe with 9 mL of mixing liquid.



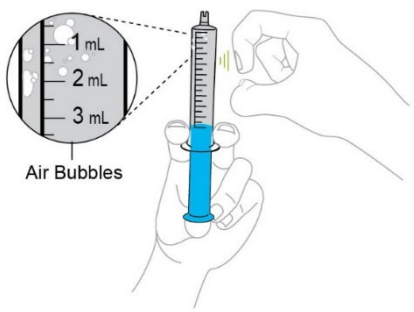
- Push the plunger of the **blue** syringe into the syringe barrel as far as it goes.
- Remove the cap from the bottle of mixing liquid.
- Push the notched tip of the syringe into the bottle adapter.
- With the syringe attached to the bottle, turn the bottle and syringe upside down. With your other hand, pull back the plunger to draw the mixing liquid back into the syringe.
- Stop when you get to the 9 mL line.
- Turn the bottle back over and remove the syringe to check your measurement.

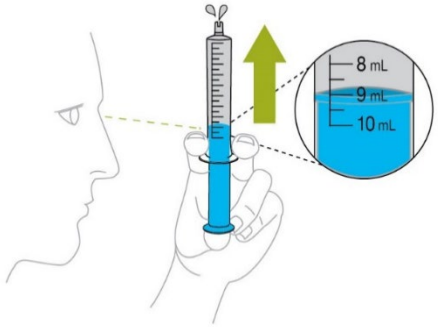


Reference ID: 5734740

Step 6. Check for air bubbles.

- Hold the syringe with notched tip up. Tap it with your finger to move any air bubbles up.
- Slowly push the plunger to make the air come out.





- Re-check the measurement of mixing liquid in the syringe. If it is less than 9 mL, put the notched tip back into the mixing liquid and pull the plunger back until you get to the 9 mL mark.

Reference ID: 5734740

Step 7. Add the 9 mL of mixing liquid to the Noxafil PowderMix.



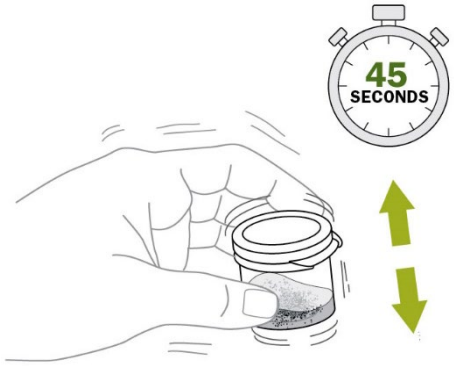
- Add the 9 mL of mixing liquid to the Noxafil PowderMix in the mixing cup by pushing all the way down on the plunger.

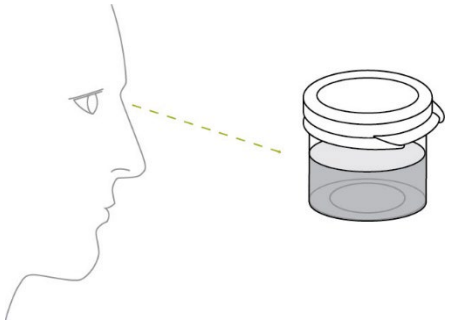
Reference ID: 5734740

Step 8. Mix the Noxafil PowderMix.

- Snap the lid of the mixing cup shut.

- Shake the mixing cup really hard for 45 seconds to mix the Noxafil PowderMix.





- Check to make sure the Noxafil PowderMix powder is mixed. If it is not mixed, shake the mixing cup some more. Noxafil PowderMix should look cloudy and free of clumps.

Reference ID: 5734740

Step 9. Check your prescription label.

- Find the dose amount (look for the 'mL' written on the prescription label on the box from your healthcare provider).



Note: The dose may change each time you go to the healthcare provider, so make sure you have all the recent information. Be sure to go to all of your child's healthcare provider appointments so your child gets the right dose.

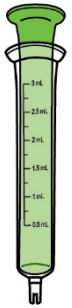
Reference ID: 5734740

Step 10. Choose the syringe you need.

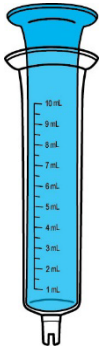
Note: Only use the syringes provided in the kit.

Choose the correct syringe for your child's dose:

For **1 mL** to **3 mL** **Green**



For **3 mL** to **10 mL** **Blue**

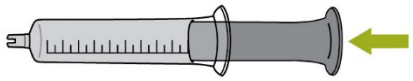


- Then find the mL mark on the syringe that matches your child's dose.

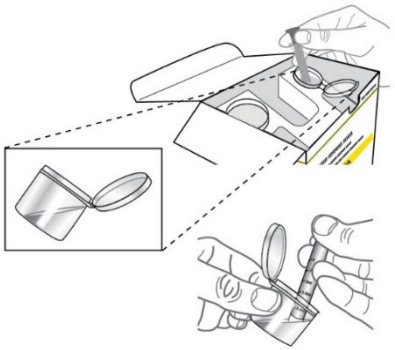
Reference ID: 5734740

Step 11. Measure the Noxafil PowderMix.

- Push the plunger into the dosing syringe as far as it goes.



- Tilt the cup by hand or use the mixing cup holder inside the Noxafil PowderMix box.



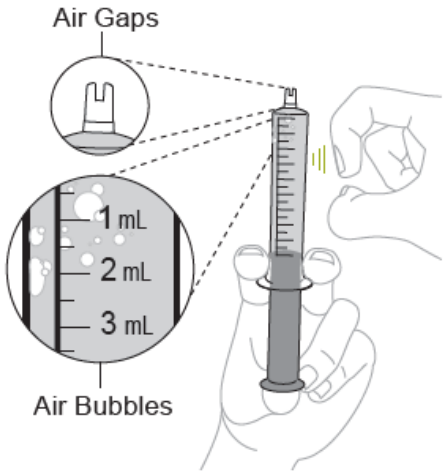
- Put the notched tip of the dosing syringe into the lowest part of the cup with the Noxafil PowderMix and pull back the plunger.
- Stop when you get to the line showing the prescribed dose.

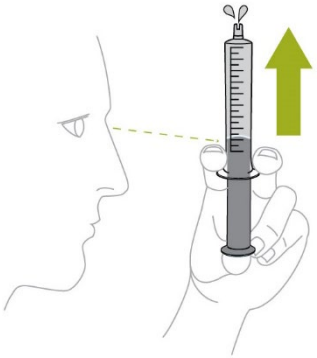
Important: You will not use all of the Noxafil PowderMix. There will be some left over in the mixing cup.

Reference ID: 5734740

Step 12. Check for air bubbles.

- Be sure to follow the directions to remove air bubbles from the syringe. Air bubbles can affect the amount of medicine that the child gets.
- Hold the syringe with notched tip up. Tap it with your finger to move any air bubbles up. Check for air gaps in the tip of the syringe. Slowly push the plunger to make the air bubbles or air gaps come out.





- Re-check the measurement of Noxafil PowderMix in the syringe. If it is less than the prescribed dose, put the notched tip back into the mixing cup with the Noxafil PowderMix and pull the plunger back until you get to the right dose mark.

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Step 13. Give the Noxafil PowderMix to your child.

- Gently place the syringe inside your child's mouth so that the notched tip touches one of his or her cheeks.



- Slowly push down on the plunger to give the dose of Noxafil PowderMix. It is important that your child takes all of the dose of Noxafil PowderMix (a little left in the syringe notched tip is ok).

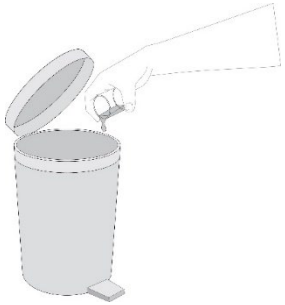
Important:

- If your child does not take the whole dose or spits some of it out, call your healthcare provider to find out what to do.
- Only use the mixing liquid from the kit. Do not mix Noxafil PowderMix with milk, juice, or water.

Reference ID: 5734740

Step 14. Clean the cup and syringes.

Note: Syringes and mixing cups should be reused. Do not throw away syringes and mixing cups provided until all the Noxafil PowderMix packets are used.



- Pour the leftover Noxafil PowderMix from the mixing cup into the trash.
  Do not pour it into the sink.
- Pull the plungers out of any syringes you used.
- Hand wash the syringes, plungers, and mixing cup with warm water and dish soap. **Do not wash in the dishwasher.**
- Rinse with water and air dry.
- Put everything in a clean, dry place.



Reference ID: 5734740

Step 15. After all packets of Noxafil PowderMix have been used.

- After you have used the last Noxafil PowderMix packet in this box, you will have leftover mixing liquid in the bottle. Throw away the leftover mixing liquid and all components of the kit.

Reference ID: 5734740

How should I store Noxafil PowderMix?

- Store the entire kit at room temperature between 68ºF to 77ºF (20ºC to 25ºC) in a clean, dry place.
- Keep the mixing liquid at room temperature.
- Do not open the Noxafil PowderMix packet until you are ready to mix a dose.

Reference ID: 5734740

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Keep NOXAFIL PowderMix and all medicines out of the reach of children.

For more information go to www.Noxafil.com or call 1-800-622-4477.

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This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: September 2022