

PRODUCT MONOGRAPH

 **NOXAFIL**[®]
posaconazole Oral Suspension



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Important Safety Information

- NOXAFIL® has been shown to interact with several medications, including drugs that suppress the immune system, and these reactions may be serious. The product label should be consulted when other drugs are prescribed with NOXAFIL®.
- Coadministration with sirolimus or ergot alkaloids is contraindicated. Coadministration with the CYP3A4 substrates terfenadine, astemizole, cisapride, pimozone, halofantrine, or quinidine, is also contraindicated since this may result in increased plasma concentrations of these medicinal products, leading to QTc prolongation and rare occurrences of torsades de pointes.
- Serious and rare fatal toxicity from cyclosporine has occurred when taken in combination with NOXAFIL® and therefore reduction of the dose of drugs like cyclosporine or tacrolimus and frequent monitoring of drug levels of these medications are necessary when taking them in combination with NOXAFIL®.
- In clinical trials, there were infrequent cases of hepatic reactions (eg, mild to moderate elevations in ALT, AST, alkaline phosphatase, total bilirubin, and/or clinical hepatitis). Rarely, more severe hepatic reactions including cholestasis or hepatic failure including fatalities were reported in patients with serious underlying medical conditions (eg, hematologic malignancies) during treatment with posaconazole. Liver function tests should be monitored at the start of and during the course of therapy. Discontinuation of NOXAFIL® must be considered in patients who experience symptoms consistent with liver disease that may be attributable to NOXAFIL®.
- The safety and effectiveness of NOXAFIL® in patients below the age of 13 years old have not been established.
- The most common treatment-related serious adverse events (1% each) in the combined prophylaxis studies were bilirubinemia, increased hepatic enzymes, hepatocellular damage, nausea, and vomiting.
- In the pooled prophylaxis safety analysis, fever, headache, anemia, diarrhea, nausea, vomiting, abdominal pain, hypokalemia, and thrombocytopenia were frequently reported treatment-emergent adverse events.
- In clinical studies of OPC and refractory OPC, adverse events were reported more frequently in the pool of patients with refractory OPC. The most commonly reported serious adverse events in refractory OPC patients included fever (13%) and neutropenia (10%).

NOXAFIL® Summary

- NOXAFIL® is indicated for prophylaxis of invasive *Aspergillus* and *Candida* infections in patients, 13 years of age and older, 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 chemotherapy¹
- NOXAFIL® is indicated for the treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole¹
- Prophylaxis of invasive fungal infections (IFIs) in neutropenic patients with acute myelogenous leukemia or myelodysplastic syndrome was assessed. The primary efficacy endpoint was the incidence of proven or probable IFI during the “while on prophylaxis” phase, which was defined as the time from randomization to 7 days after the last dose of oral study drug. As stated in the Prescribing Information, clinical efficacy was also assessed using the composite endpoint of clinical failure, defined as proven/probable IFIs, death, or use of systemic antifungal therapy for more than 3 consecutive days.¹ Patients may have been defined as a failure for more than 1 reason
 - NOXAFIL® reduced the incidence of IFIs and substantially reduced the incidence of aspergillosis compared with pooled standard azoles (fluconazole or itraconazole)¹
 - All-cause mortality was lower at 100 days for patients receiving NOXAFIL® prophylaxis compared with patients receiving pooled standard azoles¹
 - Adverse events for NOXAFIL® were comparable to fluconazole¹
- Prophylaxis of IFIs in patients who had undergone allogeneic HSCT and had GVHD also was assessed. The primary efficacy endpoint was the incidence of proven or probable IFI during the fixed time period, which was defined as the time from randomization to day 112.¹ As stated in the Prescribing Information, clinical efficacy was assessed using the composite endpoint of clinical failure, defined as proven/probable IFIs, death, or use of systemic antifungal therapy for more than 4 consecutive days.¹ Patients may have been defined as a failure for more than 1 reason
 - NOXAFIL® was non-inferior to fluconazole in preventing IFIs and substantially reduced the incidence of aspergillosis during the fixed time period. Additionally, NOXAFIL® reduced the incidence of IFIs and substantially reduced the incidence of invasive aspergillosis compared with fluconazole during the while-on-prophylaxis phase, which was defined as the time starting with the first day of treatment and ending 7 days after the last dose of oral study drug¹
 - Adverse events for NOXAFIL® were comparable to fluconazole¹

Disease Overview

Definition and Epidemiology

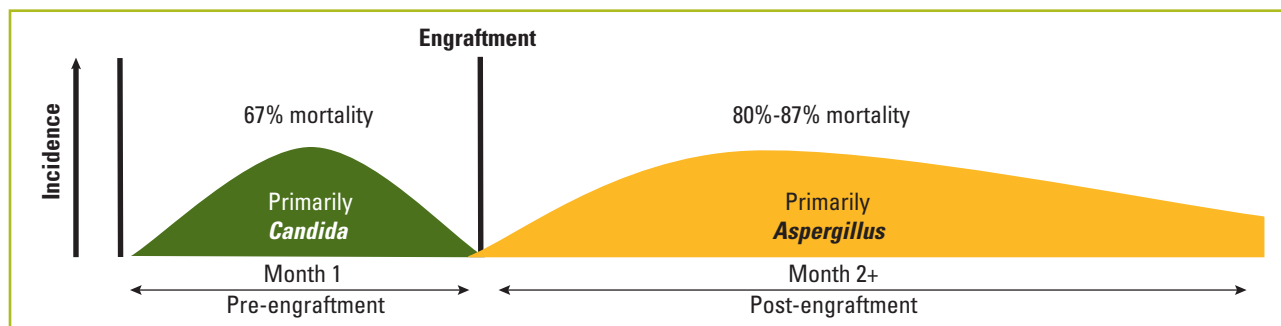
The treatment of invasive fungal infections (IFIs) presents a significant challenge to physicians managing high-risk immunocompromised patients. IFIs are defined as fungal infections that spread throughout the body to deep tissue or the bloodstream.² In 2003, it was estimated that, of 9 million patients at risk globally for IFIs, approximately 1.2 million contracted these infections, with 500,000 incidents occurring in the United States.³

IFIs are a significant cause of morbidity and mortality in high-risk patients. Patient populations that are considered at particularly high risk for developing an IFI include those who are neutropenic as a result of chemotherapy for hematologic malignancies, recipients of allogeneic hematopoietic stem cell transplants (HSCT), and recipients of immunosuppressive therapy for prevention or treatment of graft-versus-host disease (GVHD) following HSCT.^{4,5} Increased risk for fungal infections also can be attributed to the increased risk for chronic diseases and debilitation associated with longer life expectancy.⁶

IFIs are most commonly caused by members of the genus *Candida*, and *Candida albicans* accounts for almost 50%. However, more recently, moulds have become a more common cause of IFIs. Most mould infections are caused by *Aspergillus* spp; *Aspergillus fumigatus* is the most frequently isolated pathogen from mould infections.⁴ Since the early 1990s, the incidence of aspergillosis has increased from approximately 4% to approximately 10% to 20%^{7,8}; the incidence of infections caused by other opportunistic moulds also has substantially increased.⁷

The type and onset of IFIs follow a predictable pattern in select patient populations at high risk. In HSCT recipients, yeast infections such as candidiasis develop during the period before engraftment, whereas mould infections, primarily aspergillosis, account for most infections during the period after engraftment (**Figure 1**).^{9,10} Indeed, mould infections are often diagnosed more than 1 month after HSCT.⁷

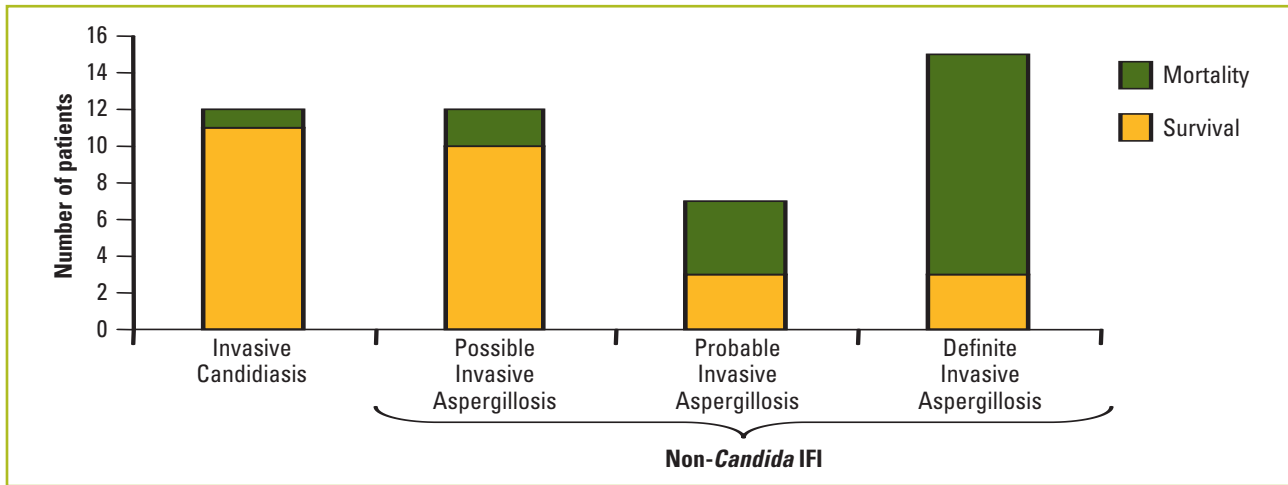
Figure 1. Schematic representation of the change in risk for fungal infection during the posttransplantation period in patients who have undergone HSCT.^{9,10}



Burden of Invasive Fungal Infections

IFIs are a source of mortality for patient populations at high risk.¹¹⁻¹⁵ Although IFIs caused by *Candida* spp are more common than moulds, the number of deaths from mould infections is greater.^{11,13} Mortality rates attributed to invasive candidiasis range from 8% to 53% in recipients of allogeneic HSCTs. A recent retrospective analysis conducted in Europe determined the incidence and risk of IFIs in 395 patients who received a peripheral blood stem cell transplant. Non-*Candida* IFIs occurred in 37 patients, the majority of which were invasive aspergillosis. Mortality rates associated with non-*Candida* IFIs, including aspergillosis, were consistently higher than those of infections caused by *Candida* spp (**Figure 2**).¹³

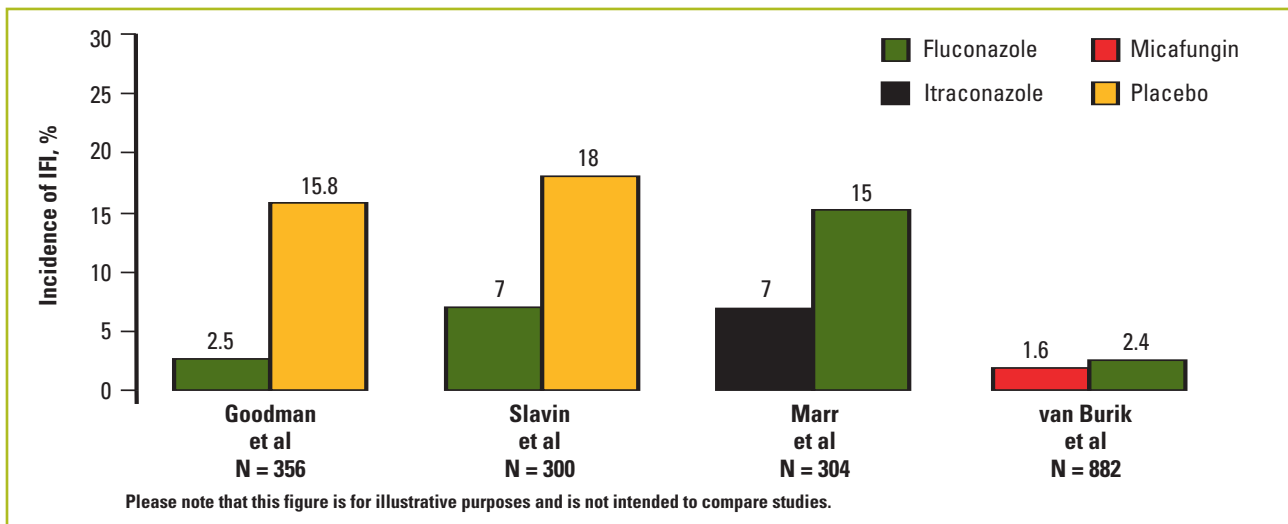
Figure 2. Incidence of IFIs and subsequent mortality rates in patients after allogeneic stem cell transplantation (N = 395).¹³



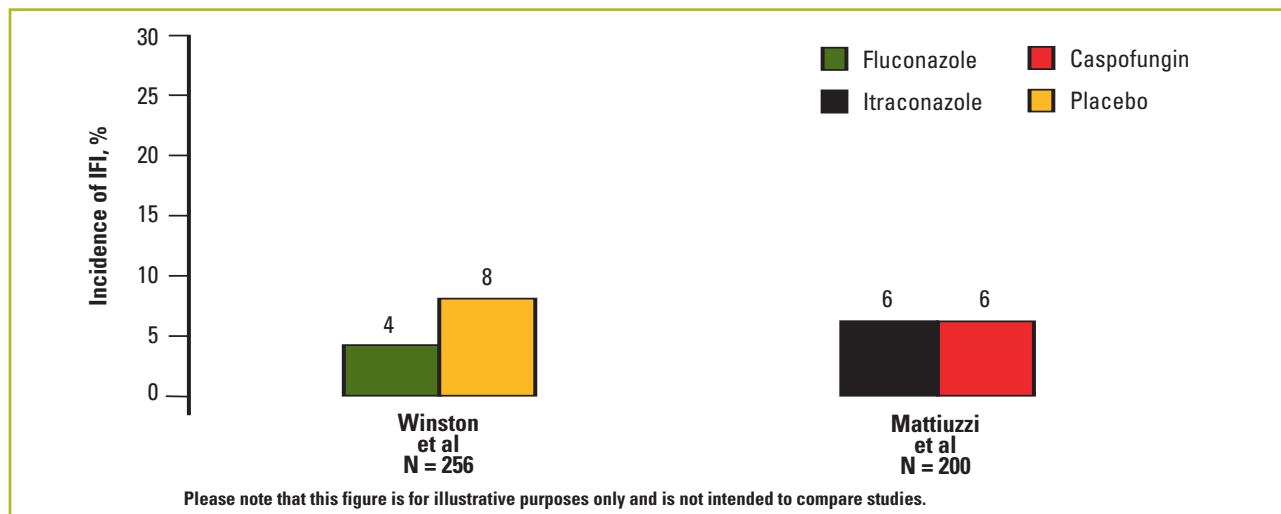
Issues in Diagnosis, Prevention, and Prophylaxis of Invasive Fungal Infection

Mortality rates remain high in part because of the difficulties associated with diagnosing fungal infections. Appropriate treatment often is initiated late, when the fungal infection is already advanced, which reduces the likelihood of a successful outcome. To reduce the incidence of IFIs in high-risk patients, many clinicians initiate antifungal prophylaxis. Several clinical trials have evaluated the benefit of antifungal prophylaxis in patients undergoing stem cell transplantation (**Figure 3A**).^{8,16-19} The standard of care for antifungal prophylaxis in HSCT recipients has become fluconazole because it has been shown to be superior to placebo in preventing IFI and in reducing both fungal-related and overall mortality rates.^{16,18}

Figure 3A. Rationale for antifungal prophylaxis in HSCT recipients.^{8,16-18}



Several individual clinical trials have examined the efficacy of antifungal prophylaxis in patients undergoing stem cell transplantation and have shown that antifungal prophylaxis reduces the incidence of IFIs (**Figure 3B**).^{20,21}

Figure 3B. Rationale for antifungal prophylaxis in patients with hematologic malignancies.^{20,21}

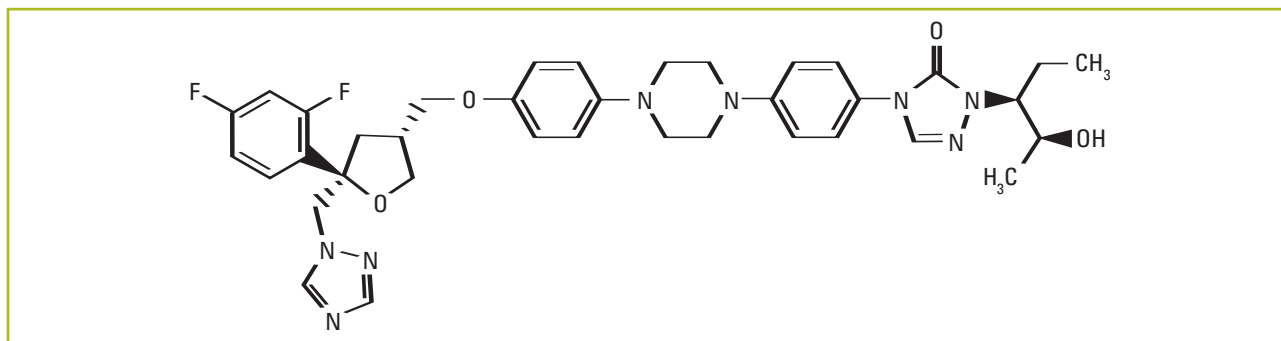
Winston et al²⁰ and Mattiuzzi et al²¹ were conducted in patients undergoing induction chemotherapy for acute myelogenous leukemia; in the Mattiuzzi study, patients with myelodysplastic syndrome were also enrolled.²¹ Results from these studies did not show a significant difference in reduction of IFI between study arms. Winston et al demonstrated a significant reduction in proven infections ($P = .02$). However, when the infections were classified as superficial or invasive, only the difference in superficial fungal infections remained statistically significant. The data from Winston et al shown in **Figure 3B** illustrates the incidence of invasive fungal infection.²⁰

This monograph provides an overview of the clinical pharmacology, pharmacokinetics, clinical efficacy, safety, and tolerability of NOXAFIL® (posaconazole), a triazole antifungal agent indicated for prophylaxis of invasive *Aspergillus* and *Candida* infections in patients, 13 years of age and older, who are at high risk of developing these infections due to being severely immunocompromised, such as HSCT recipients with GVHD or those with hematologic malignancies with prolonged neutropenia from chemotherapy. NOXAFIL® is also indicated for the treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole. Please refer to page 2 for Important Safety Information.

NOXAFIL® Pharmacologic Properties

Chemical Structure and Mechanism of Action

NOXAFIL® is a triazole antifungal agent that has a molecular weight of 700.8 Da and is available as a suspension for oral administration (**Figure 4**).¹ Similar to other triazole antifungals, NOXAFIL® inhibits the enzyme lanosterol 14 α -demethylase, which catalyzes an essential step in ergosterol biosynthesis, a key component of the fungal cell membrane.^{22,23} The depletion of ergosterol, coupled with the accumulation of methylated sterol precursors, is thought to impair membrane integrity and membrane-associated protein function, resulting in the inhibition of fungal cell growth, cell death, or both.²²

Figure 4. Chemical structure of NOXAFIL® (posaconazole).¹

Microbiology

Data from the Schering-Plough internal database of *in vitro* antifungal activity was used to assess the minimum concentration of drug necessary to inhibit 90% of the growth of a given fungal species (minimum inhibitory concentration, MIC₉₀). Based on these data, NOXAFIL[®] demonstrated potent *in vitro* activity against *C albicans* and *A fumigatus*; this activity was comparable to or better than that of voriconazole, itraconazole, and amphotericin B (Table 1).²⁴ Please note that *in vitro* activity does not necessarily correlate with clinical efficacy.²⁴

Table 1. Comparative *in vitro* activity of NOXAFIL[®] and other antifungals against *C albicans* and *A fumigatus*.²⁴

Organism	MIC ₉₀ (μg/ml)					
	N	NOX	FLU	ITZ	VOR	AMB
<i>C albicans</i>	3535	0.063	2.0	0.25	0.063	1.0
<i>A fumigatus</i>	1119	0.5	–	1.0	0.5	1.0

NOX, NOXAFIL[®]; FLU, fluconazole; ITZ, itraconazole; VOR, voriconazole; AMB, amphotericin B

In Vivo Activity

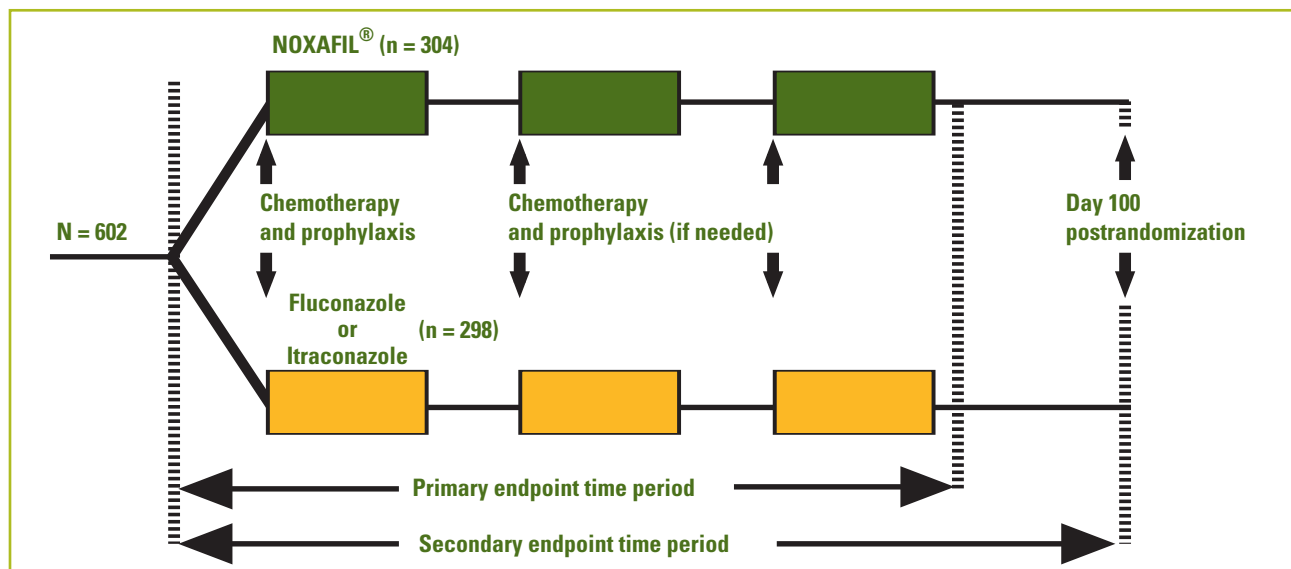
The administration of NOXAFIL[®] for *A fumigatus*, *A flavus*, or *C albicans* fungal infections in immunocompetent or immunocompromised animal models resulted in a reduction or clearance of tissue fungal burdens (suggesting fungicidal activity), increased survival, or both.²⁵⁻³⁰ NOXAFIL[®] administered prophylactically to immunocompetent and/or immunocompromised mice and rabbits with pulmonary or disseminated infection caused by *A fumigatus* was effective in prolonging survival and reducing mycologic burden. Prophylactically administered NOXAFIL[®] also prolonged survival of immunocompetent mice challenged with *C albicans* or *A flavus*.^{25,27} The clinical significance of these *in vivo* data are unknown.

NOXAFIL[®] Clinical Efficacy

NOXAFIL[®] Prophylaxis in Neutropenic Patients Receiving Chemotherapy for Acute Myelogenous Leukemia or Myelodysplastic Syndrome (Study 1899)

In a prospective, randomized, open-label, evaluator-blinded, multicenter trial, the safety, efficacy, and tolerability of NOXAFIL[®] were evaluated as prophylaxis for IFI in high-risk patients with prolonged neutropenia caused by treatment for acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) (Figure 5).^{1,31}

Figure 5. Study design details of Study 1899.³¹



Inclusion/exclusion criteria

Patients were included in this study if they were at least 13 years of age and either had neutropenia (absolute neutrophil count ≤ 500 cells/ μ L) or were anticipated to be neutropenic for more than 7 days because of intensive chemotherapy for newly diagnosed or first relapse of AML or MDS. Exclusion criteria included recent IFI, clinically significant renal or hepatic dysfunction, abnormal QTc interval, baseline Eastern Cooperative Oncology Group performance status score greater than 2, history of hypersensitivity or idiosyncratic reaction to any of the study drugs, or use of medications known to interact with azole antifungals.³²

Prophylaxis

Patients who signed an informed consent were randomly assigned (1:1 ratio) to receive either NOXAFIL® oral suspension 200 mg 3 times daily or standard azole prophylaxis of either fluconazole or itraconazole with each cycle of chemotherapy. The standard azole treatment was chosen by the investigator at each site before the start of the study and was used throughout the trial. At centers where fluconazole was selected, patients in the standard azole group received 400 mg of an oral suspension once daily; at centers where itraconazole was selected, patients in the standard azole group received 200 mg of an oral solution twice daily. Each dose of NOXAFIL® was to be administered with a full meal or, for patients who could not eat a full meal, with a liquid nutritional supplement. For patients unable to tolerate oral administration, intravenous antifungal prophylaxis at the same dose was permitted for a maximum of 3 days per cycle of chemotherapy or for a total of 10 days. Because no intravenous formulation of NOXAFIL® is currently available, amphotericin B deoxycholate (0.3-0.5 mg/kg daily) was used as the intravenous alternative for patients assigned to NOXAFIL® prophylaxis.^{31,33}

Prophylactic antifungal therapy with the study medication was initiated on the first day of chemotherapy and continued until the patient recovered from neutropenia, an IFI developed, or 84 days elapsed from randomization. Because azole antifungals can interact with anthracyclines (eg, daunorubicin, doxorubicin), patients who received this class of chemotherapeutic agents received study drug 24 hours after the final anthracycline dose. Prophylaxis was reinitiated for each additional round of chemotherapy. Two time periods of prophylaxis were defined for this study: the while-on-prophylaxis phase was defined as the time from randomization to 7 days after the final dose of study drug, and the fixed time period was defined as the time from randomization to 100 days after randomization. Prophylaxis was stopped if the patient developed a breakthrough IFI, experienced an adverse event that required discontinuation of the study drug, or died from underlying disease. Regardless of whether patients had stopped prophylaxis because of an IFI, adverse event, or because their neutropenia resolved, all patients were followed up until the end of the fixed time period and for 30 days after the last dose of study drug.^{1,31}

Study assessments

A data review committee (DRC) of infectious disease experts performed a blinded assessment of all fungal infections identified by the investigators and classified each as proven, probable, or possible, according to the European Organisation for Research and Treatment of Cancer-Mycoses Study Group (EORTC-MSG) consensus criteria. All patients were assessed for IFIs at the beginning and the end of prophylaxis, 30 days after the final dose of study medication, and at the end of the fixed time period. Patients demonstrating signs or symptoms consistent with an IFI at any time during the study were subject to a full clinical examination. In addition, plasma samples for the *Aspergillus* galactomannan assay were collected twice weekly, and throat and stool samples were cultured once weekly.³¹

Outcome definitions

The primary endpoint of this study was the DRC-determined incidence of proven or probable IFI during the while-on-prophylaxis phase. Analysis of the primary efficacy endpoint included all randomized patients (intent-to-treat population). The evaluation of efficacy for this study was assessed in 2 stages: if NOXAFIL® was shown in the first stage to be noninferior to (that is, no worse than) standard azole therapy, then additional statistical analyses were performed to assess whether NOXAFIL® was superior to standard azole therapy in this study. Secondary endpoints included the incidence of proven or probable IFI during the fixed time period and the incidence of proven or probable aspergillosis during the while-on-prophylaxis phase and the fixed time period. Finally, the incidence of all-cause mortality during the fixed time period was also calculated.^{1,31}

As stated in the Prescribing Information, the efficacy of prophylaxis was assessed using a composite endpoint of clinical success versus clinical failure. Clinical failure was defined in this study as a proven or probable IFI during the while-on-prophylaxis phase, death, or the use of systemic antifungal therapy for any reason for more than 3 consecutive days. Patient outcomes may have been defined as failures for more than 1 reason.^{1,31}

Results

In total, 602 patients were recruited from 89 centers worldwide: 304 patients were randomly assigned to the NOXAFIL® group, and 298 were randomly assigned to the standard azole group (fluconazole, 240; itraconazole, 58). Of these patients, 159 NOXAFIL® recipients and 125 standard azole recipients completed prophylaxis. Follow-up was completed for 237 (84%) of those administered NOXAFIL® and for 220 (80%) of those administered standard azole prophylaxis. The mean cumulative durations of prophylaxis with NOXAFIL® and standard azoles were 29 and 25 days, respectively, and the median cumulative durations of prophylaxis were 23 and 20 days, respectively.³¹

Demographic characteristics

Baseline demographic characteristics were similar between groups. The mean age of patients in the NOXAFIL[®] group was 49 years, and the mean age of patients in the standard azoles group was 50 years. Of the recruited patients, 72% in the NOXAFIL[®] group and 78% in the standard azoles group were white. Both groups contained slightly more men than women, and most patients were enrolled at centers in Europe (~42%), the United States (~26%), and Latin America (~20%). Disease characteristics at baseline are presented in **Table 2**.³¹ At the beginning of the study, 63% of patients in both groups were neutropenic, and 24% of patients were severely neutropenic (absolute neutrophil count of ≤100 cells/μL). The maximum number of consecutive days of neutropenia were comparable between both groups. Similar proportions of patients in each group were colonized with yeast; the primary isolate identified in most patients was *C albicans*.^{31,33}

Table 2. Baseline disease characteristics of the patient population in Study 1899.³¹

	NOXAFIL [®] (n = 304)	Standard Azoles (n = 298)
Age, years		
Mean (range)	49 (13-82)	50 (13-81)
Gender, n (%)		
Male	158 (52)	160 (54)
Primary diagnosis at study entry, n (%)		
AML (new diagnosis)	213 (70)	222 (74)
AML (first relapse)	42 (14)	38 (13)
MDS	49 (16)	38 (13)
Neutropenia severity during the prophylaxis phase, n (%)		
Nadir ANC ≤500 cells/μL	298 (98)	290 (97)
Nadir ANC ≤100 cells/μL	264 (87)	261 (88)
Total duration of neutropenia during the prophylaxis phase in days		
0-7, n (%)	21 (7)	21 (7)
>7-21, n (%)	141 (46)	143 (48)
>21, n (%)	142 (47)	134 (45)
Mean (SD)	25 (17.1)	23 (13.1)
Yeast colonization status at baseline, stool or oral, n (%)		
Positive	133 (44)	121 (41)
Negative	147 (48)	144 (48)
Missing or unknown	24 (8)	33 (11)
Use of systemic antifungals as prophylaxis before randomization		
Yes, n (%)	42 (14)	42 (14)
Mean number of days (SD)	4 (7.4)	3 (5.4)
Median number of days (range)	1 (1-45)	1 (1-31)

AML, acute myelogenous leukemia; ANC, absolute neutrophil count; MDS, myelodysplastic syndrome; SD, standard deviation

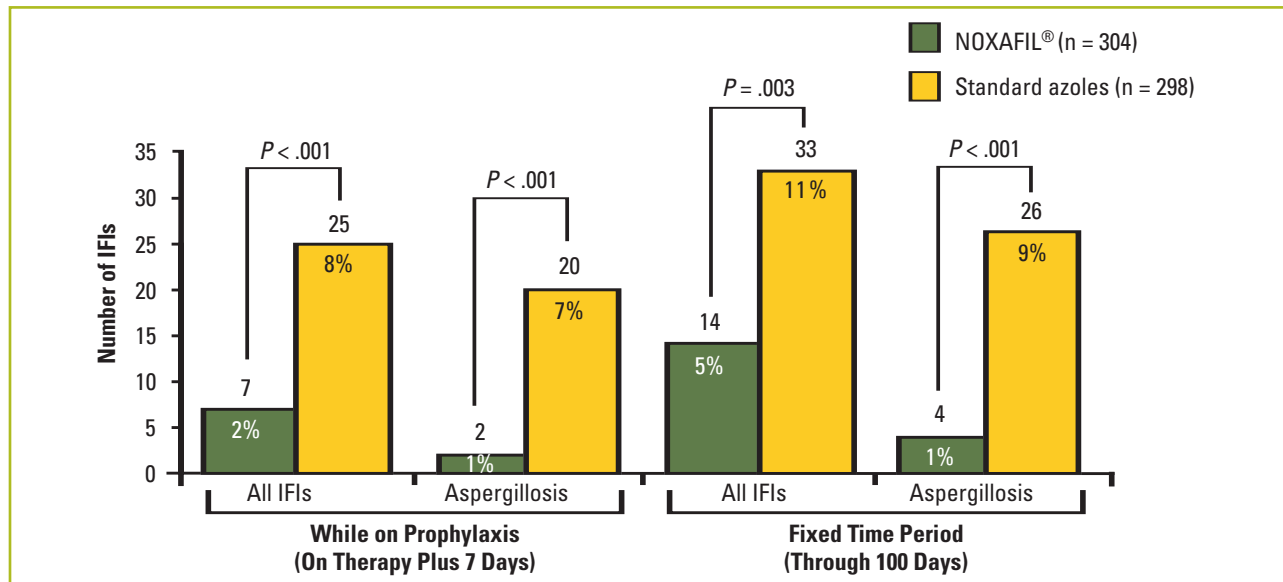
The number of chemotherapy cycles that patients underwent during the study was similar between groups. For both groups, more than half of the patients received 1 cycle of chemotherapy (57% for NOXAFIL[®], 61% for standard azoles). The percentage receiving 2 or more cycles was also similar (43% and 39% for NOXAFIL[®] and standard azoles, respectively). The use of growth factors during prophylaxis was comparable between the NOXAFIL[®] and standard azoles group (48% versus 50%, respectively), as was the mean duration of their use (14 versus 12 days, respectively).³¹

Invasive fungal infection

NOXAFIL[®] reduced the incidence of proven or probable IFI compared with prophylaxis with the standard azoles during the while-on-prophylaxis primary endpoint time period (2% [7 of 304] versus 8% [25 of 298], respectively; **Figure 6**).^{1,31} NOXAFIL[®] prophylaxis also resulted in substantially fewer infections due to *Aspergillus* species (1% [2 of 304]) compared with the standard azoles (7% [20 of 298]) in this period. Additionally, NOXAFIL[®] reduced the incidence of proven or probable IFI compared with the standard azoles during the fixed time period. During this phase, IFIs occurred in 5% (14 of 304) and 11% (33 of 298) of patients receiving NOXAFIL[®] and the standard

azoles, respectively. Furthermore, substantially fewer infections due to *Aspergillus* species were reported during this period as well; the incidence of aspergillosis was 1% (2 of 304) in the NOXAFIL® group and 9% (26 of 298) in the standard azoles prophylaxis group.^{1,31}

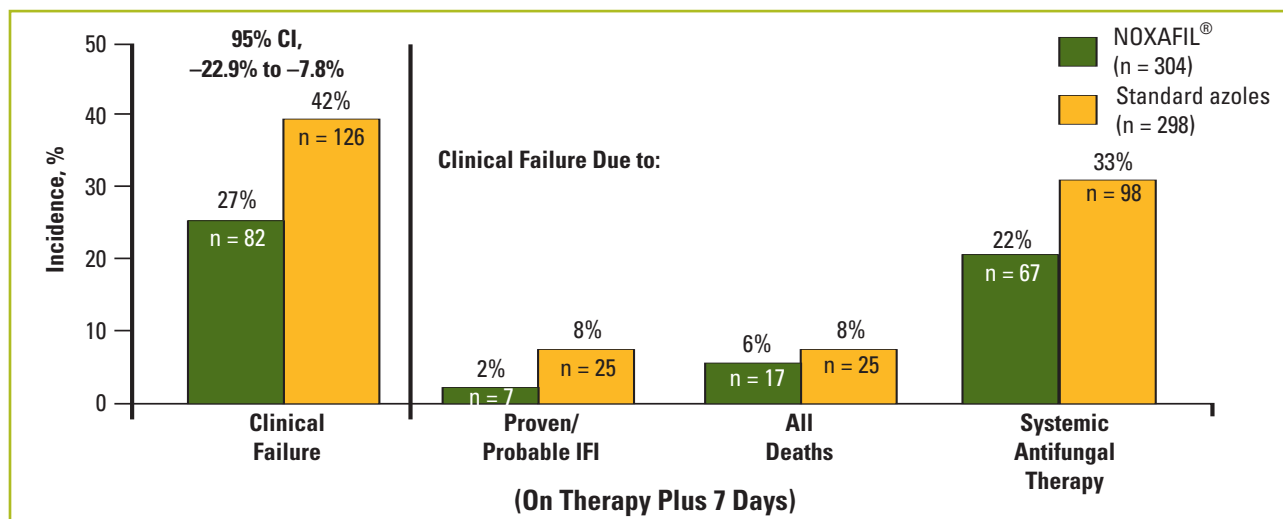
Figure 6. Incidence of proven and probable IFIs in Study 1899.^{1,31,33}



IFI, invasive fungal infection

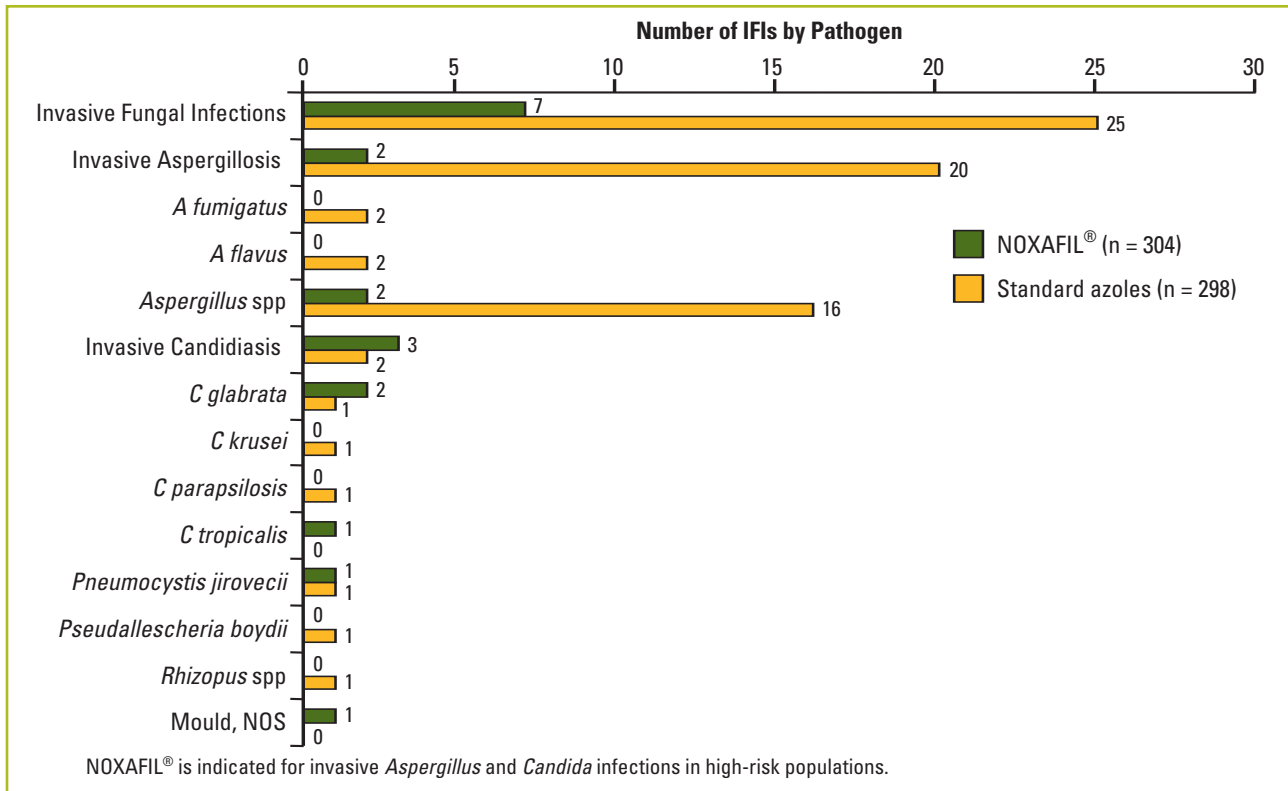
Prophylaxis with NOXAFIL® resulted in fewer clinical failures as measured by the composite endpoint during the while-on-prophylaxis phase (Figure 7A).¹ As previously stated, clinical failure was assessed as a composite score of the primary study endpoint (incidence of proven or probable IFI), death, or systemic use of prophylaxis for more than 3 consecutive days in 1 cycle of chemotherapy or more than 10 days in total. The incidence of clinical failures with NOXAFIL® was 27% (82 of 304), compared with 42% (126 of 298) in the standard azoles prophylaxis group (95% CI = -22.9% to -7.8%). Prophylaxis with NOXAFIL® also resulted in fewer IFIs (2%, 7 of 304) compared with prophylaxis with the standard azoles (8%, 25 of 298).¹ Most fungal infections in patients receiving standard azole prophylaxis were caused by *Aspergillus* spp, whereas in patients receiving NOXAFIL®, the infections were caused by various pathogens, including *Candida* and *Aspergillus* spp (Figure 7B).³¹ The percentages of deaths were similar between groups: 6% (17 of 304) and 8% (25 of 298) for prophylaxis with NOXAFIL® and the standard azoles, respectively (Figure 7A). The use of systemic antifungal therapy for more than 3 consecutive days was numerically less in patients receiving NOXAFIL® compared with patients receiving standard azole therapy (Figure 7A).^{1,31}

Figure 7A. Clinical failures during the while-on-prophylaxis phase (on therapy plus 7 days) in Study 1899.¹



CI, confidence interval; IFI, invasive fungal infection

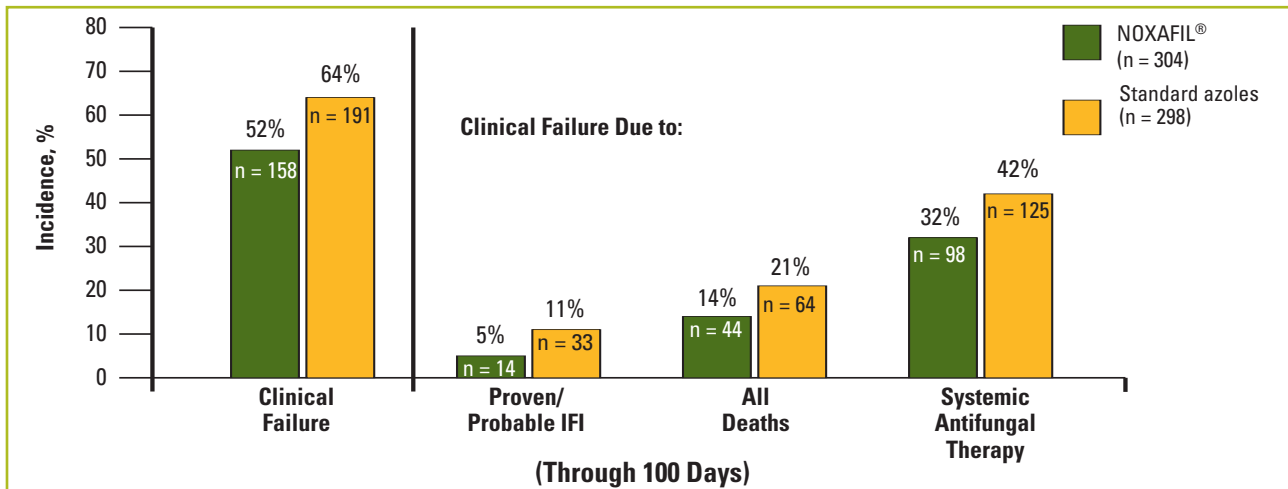
Figure 7B. Number of proven or probable IFIs by pathogen in Study 1899 during the while-on-prophylaxis period (on therapy plus 7 days).³¹



NOS, not otherwise specified

The composite endpoint of clinical outcome during the fixed time period was also assessed and is presented in **Figure 8A**.¹ Although they are not statistically significant, fewer clinical failures were reported during this time period in patients receiving NOXAFIL® than in patients receiving the standard azole prophylaxis (52% [158 of 304] versus 64% [191 of 298], respectively). Proven or probable IFIs were also lower in the NOXAFIL® group (5%, 14 of 304) than in the standard azoles group (11%, 33 of 298). The percentages of deaths were 14% (44 of 304) and 21% (64 of 298) with NOXAFIL® prophylaxis and standard azoles, respectively. Systemic antifungal therapy use for more than 3 consecutive days was numerically less in patients receiving NOXAFIL® compared with prophylaxis with the standard azoles (32% versus 42%, respectively; **Figure 8A**).¹

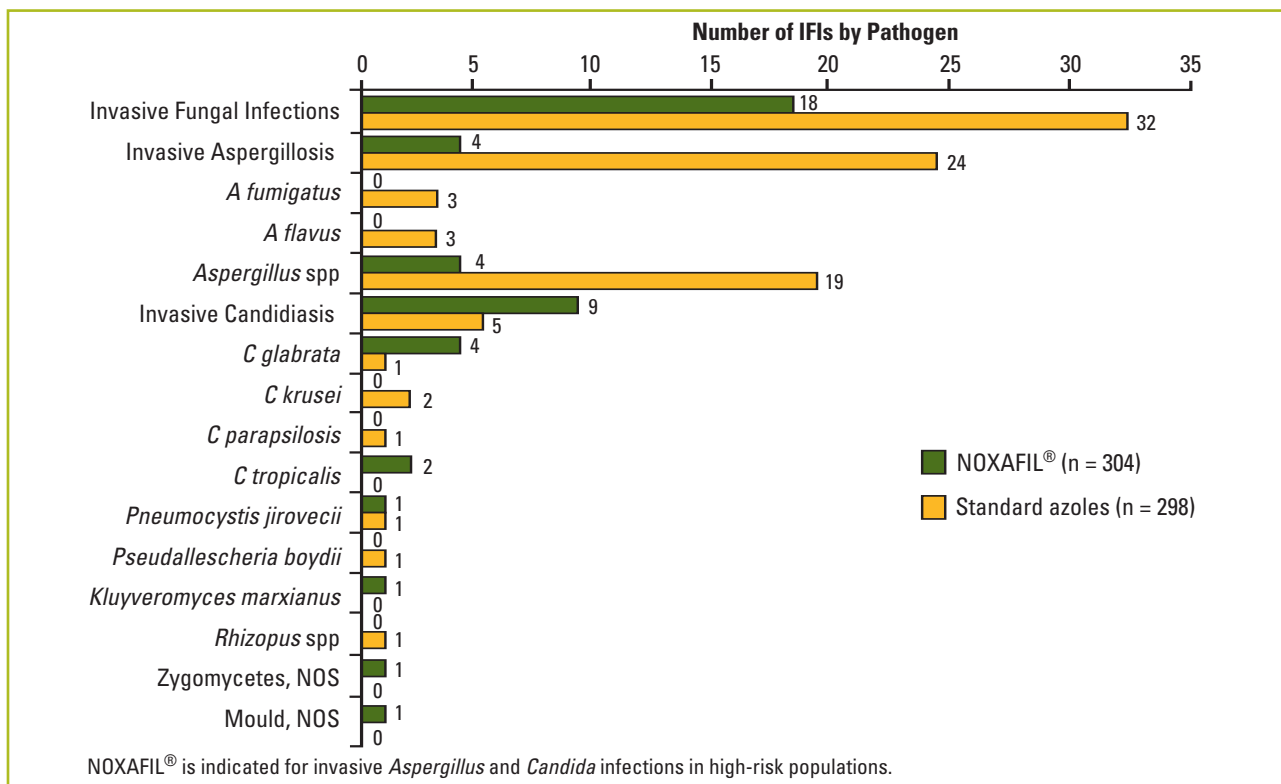
Figure 8A. Clinical failures during the fixed time period (through 100 days) in Study 1899.¹



IFI, invasive fungal infection

The incidence of each pathogen causing a breakthrough IFI during the fixed time period is shown in **Figure 8B**.³³ As was observed during the while-on-prophylaxis phase, most fungal infections in patients receiving standard azole prophylaxis were caused by *Aspergillus* spp, whereas in patients receiving NOXAFIL®, the infections were caused by various pathogens, including *Candida* and *Aspergillus* spp.

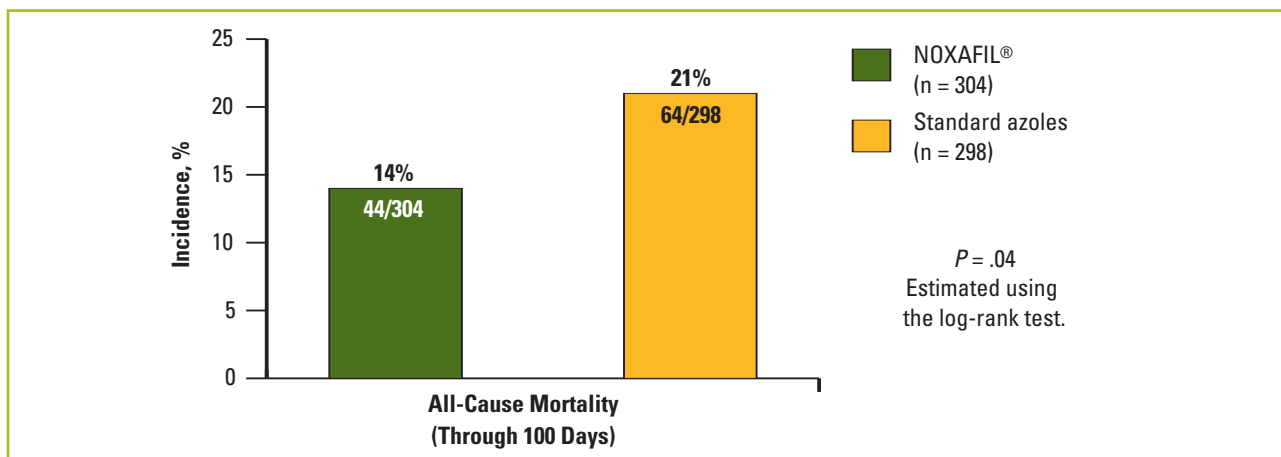
Figure 8B. Number of proven or probable IFIs by pathogen in Study 1899 during the fixed time period (through 100 days).³³



NOS, not otherwise specified

An additional secondary endpoint assessed was all-cause mortality. A decrease in all-cause mortality at day 100 was observed in favor of NOXAFIL® (14%, 44 of 304) compared with standard azoles (21%, 64 of 298; **Figure 9**).^{1,31}

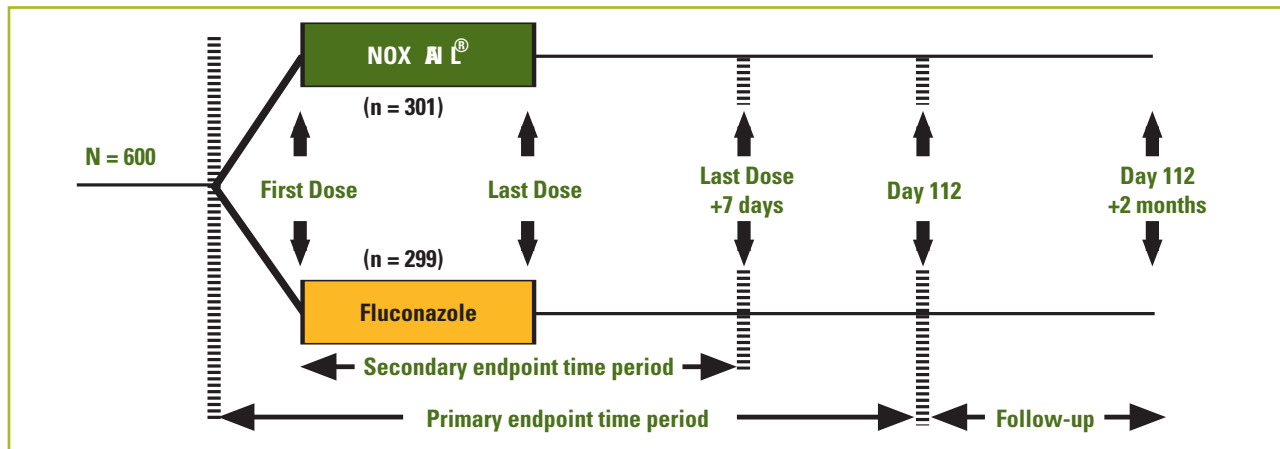
Figure 9. All-cause mortality during the fixed time period (through 100 days) in Study 1899.^{1,31}



NOXAFIL® Prophylaxis in Allogeneic HSCT Patients With GVHD (Study 316)

In a randomized, multicenter, double-blind, double-dummy, parallel-group, multicenter trial, the safety, efficacy, and tolerability of NOXAFIL® were evaluated as prophylaxis therapy for IFIs in HSCT recipients with acute or chronic GVHD (Figure 10).^{1,34}

Figure 10. Study design details of Study 316.³⁴



Inclusion/exclusion criteria

Patients were enrolled in this study if they were allogeneic HSCT recipients at least 13 years of age and weighed more than 34 kg. In addition, all patients had either acute (grades II-IV) or chronic extensive GVHD and/or were receiving 1 of the following intensive immunosuppression regimens³⁴:

- High-dose corticosteroids (≥ 1 mg/kg per day for acute disease or ≥ 0.8 mg/kg every other day for chronic disease)
- Antithymocyte globulin
- A steroid-sparing combination regimen consisting of at least 2 immunosuppressive agents or modalities

All patients who signed an informed consent and were randomized were included in the intent-to-treat population. Patients were ineligible for this study if they were previously diagnosed with a mould infection requiring secondary prophylaxis or were suspected of having an IFI at baseline (excluding *Pneumocystis pneumonia*). Other exclusion criteria included a prolonged QTc interval, hypersensitivity to azole drugs, concomitant treatment with drugs known to react with azoles, and concomitant therapy with other antifungals or investigational agents. Patients with hepatic dysfunction (alanine aminotransferase and/or aspartate aminotransferase levels >10 times the upper limit of normal) or renal dysfunction (estimated creatinine clearance <20 mL/min or patients who required dialysis) also were excluded.^{34,35}

Prophylaxis

At baseline, patients were stratified by GVHD status and were randomly assigned to receive either NOXAFIL® oral suspension 200 mg 3 times daily taken with a placebo capsule once daily or a fluconazole capsule 400 mg once daily plus placebo suspension 3 times daily.³⁴ Study medications were administered with food or with a nutritional supplement. If at any time during the study patients developed a condition that made them unable to tolerate or swallow the oral study drug, the study medication was withheld and intravenous prophylaxis with a nonazole antifungal was permitted for no more than 5 days.³³

Two time periods of prophylaxis were defined for this study: the fixed time period was defined as the time from randomization to 112 days after randomization or until a protocol-designated endpoint was reached (breakthrough IFI, discontinuation because of adverse event, or death due to the underlying disease or GVHD), and the while-on-prophylaxis phase was defined as the time from the first day of prophylaxis to 7 days after the final dose of study drug. Patients were followed up for an additional 2 months after their last dose of study medication.³⁴

Outcome definitions

The primary efficacy endpoint was the adjudicated incidence of proven or probable IFIs as defined by the EORTC-MSG criteria during the fixed time period. All suspected cases of IFI were evaluated by a blinded DRC. Susceptibility testing of all fungal isolates was performed every 2 weeks at 1 designated laboratory. *Aspergillus* galactomannan assays were also conducted every 2 weeks at a central laboratory; the results of these assays were available only to the DRC.^{33,34}

Similar to the previous study, the evaluation of efficacy for this study was assessed in 2 stages. If prophylaxis with NOXAFIL® was shown in the first stage to be noninferior to (that is, no worse than) prophylaxis with fluconazole, then additional statistical analyses

were performed to assess whether NOXAFIL® was superior to fluconazole in this study. Secondary endpoints in this trial include the incidence of proven or probable IFI during the while-on-prophylaxis period, the incidence of IFI due to *Aspergillus* species during the while-on-prophylaxis and fixed time periods, and the all-cause mortality rate.³⁴ As stated in the Prescribing Information, clinical outcome (success versus failure) was also assessed in this study using a composite endpoint.¹ Clinical failure was defined as proven or probable IFI during the primary study endpoint, death, or the use of systemic antifungal therapy for any reasons for more than 4 consecutive days. Patient outcomes may have been defined as failures for more than 1 reason.^{1,34}

Results

Six hundred patients (NOXAFIL®, 301; fluconazole, 299) were enrolled at 90 centers worldwide and were included in the intent-to-treat population. Approximately 60% of these patients were enrolled at centers in Canada, Mexico, Europe, Australia, Taiwan, Singapore, and Central and South America; the remaining patients were enrolled within the United States. The while-on-prophylaxis group consisted of 291 patients in the NOXAFIL® group and 288 in the fluconazole group. Mean durations of prophylaxis with NOXAFIL® and fluconazole were 80 and 77 days, respectively, and the median durations of prophylaxis were 111 and 108 days, respectively.³⁴

Demographic characteristics

Prophylaxis group populations were similar with respect to their demographic characteristics and risk factors for IFI. Most patients had at least 2 risk factors for IFI. In the intent-to-treat population, mean age was 42 years in the NOXAFIL® group and 40 years in the fluconazole group. Most patients were men (67% and 63% for NOXAFIL® and fluconazole, respectively) between 18 and 65 years of age (97%). The most common primary underlying diagnoses (all comparisons are for the NOXAFIL® and fluconazole groups, respectively) were chronic myelogenous leukemia (33% and 35%), AML (27% and 22%), non-Hodgkins lymphoma (13% and 12%), acute lymphoblastic leukemia (8% and 12%), and MDS (6% and 4%). At baseline, most patients had acute grade 2 or 3 (62% and 63%) or chronic extensive GVHD (32% and 33%). In 40% of patients, the interval between transplantation and study baseline was greater than 101 days; the median interval was 63 days and 64 days in the NOXAFIL® and fluconazole groups, respectively. Similar percentages of patients in each group were colonized with yeast (**Table 3**).³⁴

Table 3. Baseline demographic and disease characteristics of the patient population in Study 316.³⁴

	NOXAFIL® (n = 301)	Fluconazole (n = 299)
Age, years		
Mean (range)	42 (13-72)	40 (13-70)
Gender, n (%)		
Male	203 (67)	187 (63)
Primary underlying diagnosis, n (%)		
Chronic myelogenous leukemia	98 (33)	104 (35)
AML	81 (27)	66 (22)
Non-Hodgkins lymphoma	40 (13)	35 (12)
Acute lymphoblastic leukemia	25 (8)	36 (12)
MDS	19 (6)	13 (4)
GVHD class at baseline, n (%)		
Acute Grade I	3 (1)	1 (<1)
Acute Grade II	135 (45)	136 (45)
Acute Grade III	52 (17)	54 (18)
Acute Grade IV	12 (4)	6 (2)
Chronic limited	2 (1)	1 (<1)
Chronic extensive	96 (32)	99 (33)
Missing	1 (<1)	2 (1)
Days from transplant to baseline, n (%)		
<30	45 (15)	37 (12)
30-60	98 (33)	103 (34)
61-100	32 (11)	37 (12)
≥101	124 (41)	121 (40)
Median, days	63	64

AML, acute myelogenous leukemia; GVHD, graft-versus-host disease; MDS, myelodysplastic syndrome

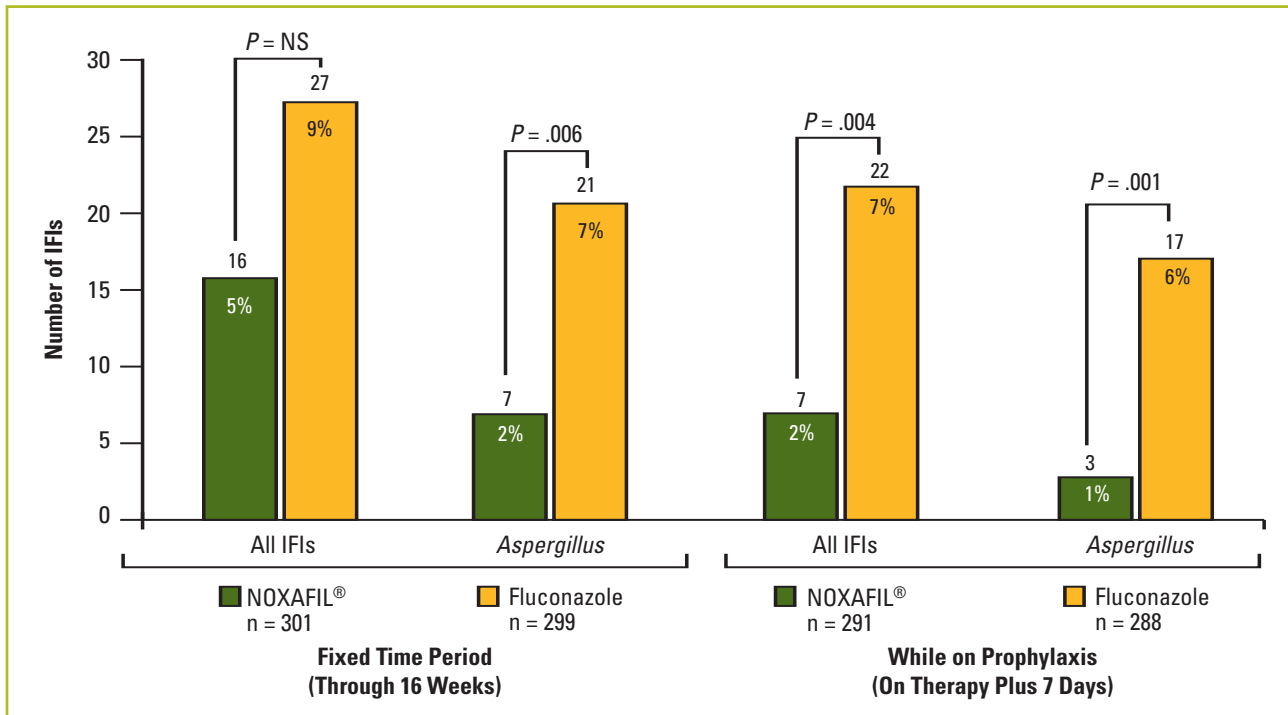
All enrolled patients received at least 1 immunosuppressive agent at baseline with the exception of 2 patients (1 in the NOXAFIL[®] prophylaxis group and 1 in the fluconazole prophylaxis group). More than 50% of patients in each group received 2 immunosuppressive agents (50% and 56% for NOXAFIL[®] and fluconazole, respectively), and more than 25% of patients in each group received 3 or more immunosuppressive agents (28% and 27% for NOXAFIL[®] and fluconazole, respectively).³⁴

Patients were permitted to have received courses of antifungal prophylaxis prior to enrollment. The mean duration of prior antifungal prophylaxis was 26 days and 35 days for the NOXAFIL[®] and fluconazole groups, respectively; the median number of days was 16 days and 19 days, respectively. In both groups, most patients were not neutropenic (92% for NOXAFIL[®] and 94% for fluconazole) and only a small percentage received a T-cell-depleted stem cell transplant prior to entry in the study (12% for NOXAFIL[®] and 11% for fluconazole).³⁵

Invasive fungal infection

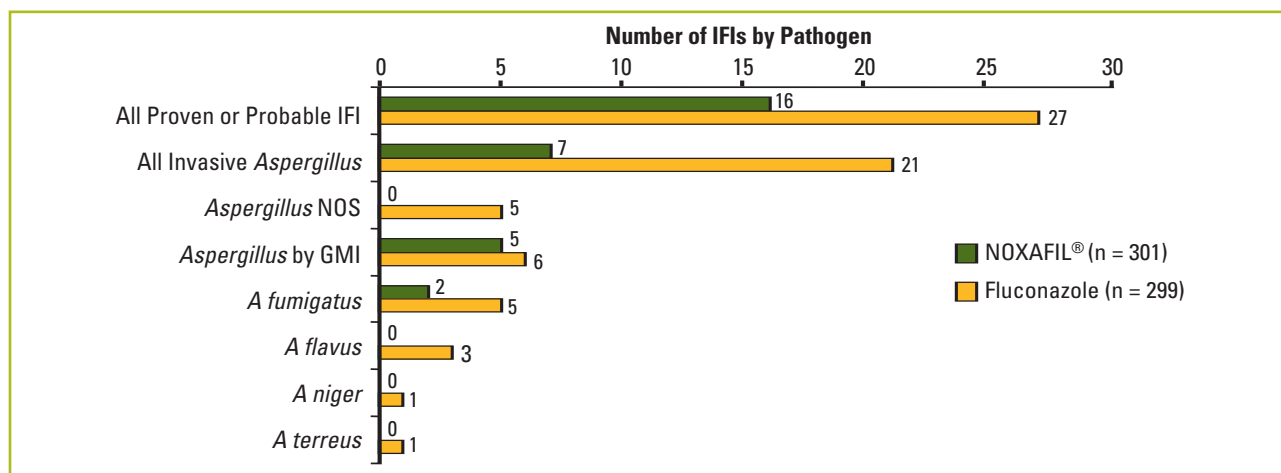
NOXAFIL[®] reduced the incidence of proven or probable IFI compared with fluconazole during the fixed time period (5% [16 of 301] versus 9% [27 of 299]; **Figure 11A**).^{1,34} NOXAFIL[®] prophylaxis also resulted in substantially fewer infections due to *Aspergillus* spp (2% [7 of 301]) compared with fluconazole (7% [21 of 299]) in the fixed time period. In addition, NOXAFIL[®] reduced the incidence of proven or probable IFI compared with fluconazole during the while-on-prophylaxis phase. During this time period, IFIs occurred in 2% (7 of 301) and 7% (22 of 299) of patients receiving NOXAFIL[®] and fluconazole, respectively. The incidence of aspergillosis was also substantially lower in the NOXAFIL[®] group compared with the fluconazole group during this period (1% [3 of 301] versus 6% [17 of 299], respectively).^{1,34}

Figure 11A. Incidence of proven and probable IFIs in Study 316.^{1,33,34}



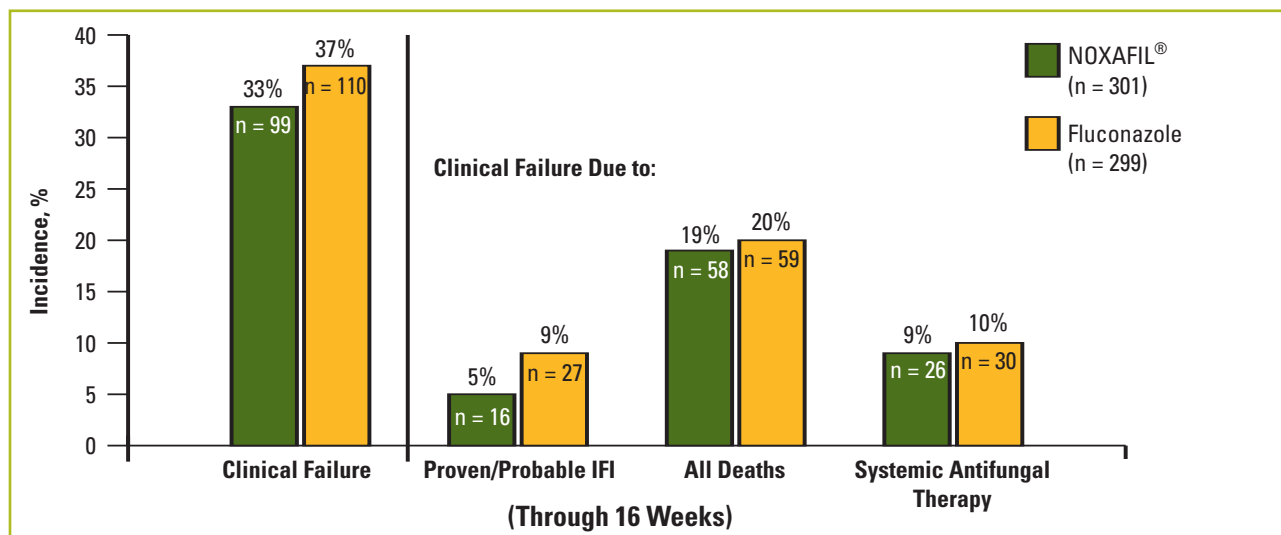
IFI, invasive fungal infection; NS, not significant

The incidence of each causative pathogen occurring during the fixed time period is presented in **Figure 11B**.³⁴ Most fungal infections in patients receiving fluconazole prophylaxis were caused by invasive aspergillosis, whereas in patients receiving NOXAFIL[®], the infections were caused by various pathogens, including *Candida* and *Aspergillus* spp (**Figure 11B**).³⁴

Figure 11B. Number of proven or probable IFIs by pathogen during the fixed period (through 16 weeks) of Study 316.^{3a}

GMI, galactomannan index; IFI, invasive fungal infection; NOS, not otherwise specified

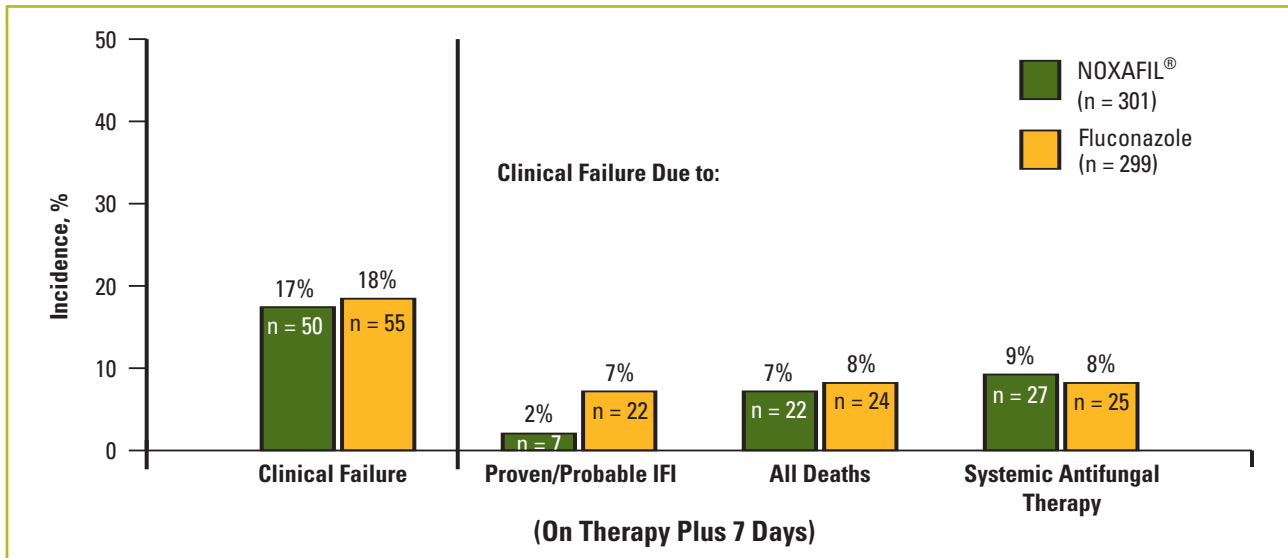
The overall incidence of clinical failure was similar between the NOXAFIL® and fluconazole prophylaxis groups during the fixed time period (33% [99 of 301] versus 37% [110 of 299], respectively; **Figure 12**).¹ NOXAFIL® reduced the incidence of proven or probable IFIs compared with fluconazole (5% [16 of 301] versus 9% [27 of 299], respectively) and substantially reduced the incidence of aspergillosis (2% [7 of 301] versus 7% [21 of 299]). The incidence of death was similar between groups (19% [58 of 301] versus 20% [59 of 299], respectively), as was the use of systemic antifungal therapy for more than 4 consecutive days (9% [26 of 301] versus 10% [30 of 299], respectively).¹

Figure 12. Clinical failures during the fixed time period (through 16 weeks) in Study 316.¹

IFI, invasive fungal infection

Similar to the results from the fixed time period, the incidence of clinical failure was similar between the NOXAFIL® and fluconazole prophylaxis groups during the while-on-prophylaxis phase (17% [50 of 301] versus 18% [55 of 299], respectively; **Figure 13A**).¹ During this phase, NOXAFIL® reduced the incidence of proven or probable IFIs compared with fluconazole (2% [7 of 301] versus 7% [22 of 299], respectively) and substantially reduced the incidence of invasive aspergillosis (1% [3 of 301] versus 6% [17 of 299], respectively). The rate of death was similar between the NOXAFIL® and fluconazole prophylaxis groups (7% [22 of 301] versus 8% [24 of 299], respectively) as was the use of systemic antifungal therapy for more than 4 consecutive days (9% [27 of 301] versus 8% [25 of 299], respectively).¹

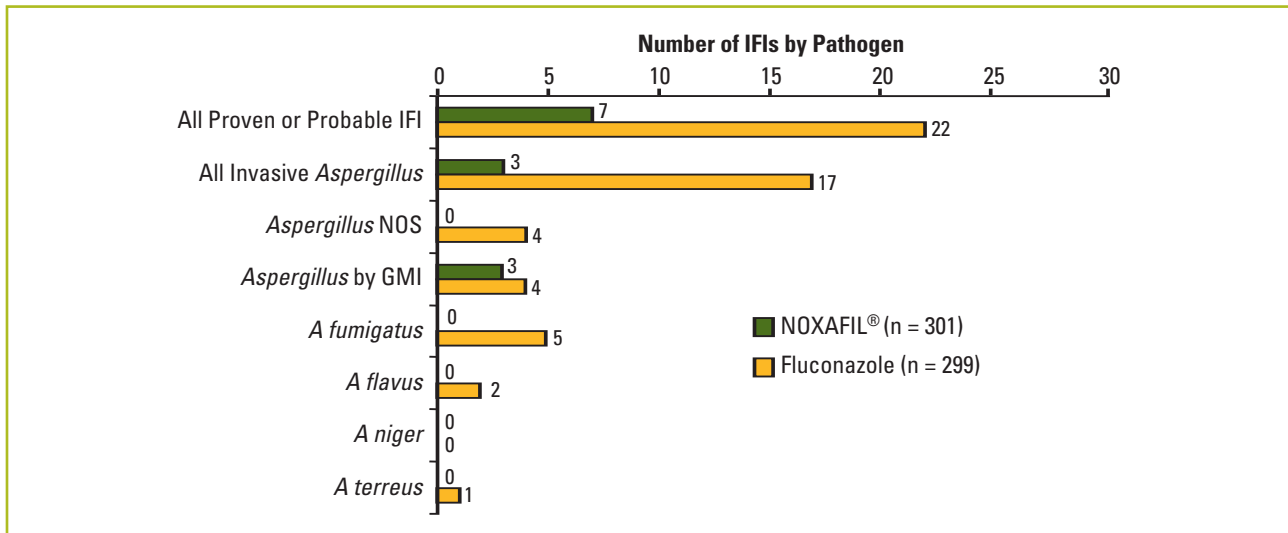
Figure 13A. Clinical failures during the while-on-prophylaxis phase (on therapy plus 7 days) in Study 316.¹



IFI, invasive fungal infection

The incidence of each pathogen causing a breakthrough IFI during the while-on-prophylaxis phase is presented in **Figure 13B**.³⁴ Substantially fewer breakthrough invasive *Aspergillus* spp infections occurred during prophylaxis with NOXAFIL® compared with fluconazole.³⁴

Figure 13B. Number of proven or probable IFIs by pathogen in Study 316 during while-on-prophylaxis phase (on therapy plus 7 days).³⁴



GMI, galactomannan index; IFI, invasive fungal infection; NOS, not otherwise specified

NOXAFIL® Safety and Tolerability

The safety of NOXAFIL® therapy has been assessed in 1844 patients. This includes 605 patients in the prophylaxis studies and 1239 patients treated for other indications. NOXAFIL® therapy was given to 171 patients for 6 months or longer, and 58 patients received NOXAFIL® therapy for 12 months or longer.¹

Prophylaxis Study 1899

The safety and tolerability of the study drugs were evaluated in all 602 patients treated in the prophylaxis study of patients with neutropenia due to chemotherapy for the treatment of AML or MDS. In both groups, 34% of patients experienced an adverse event considered by the investigators to be possibly or probably related to the study drug. Treatment-related adverse events that occurred in at least 2% of patients in either group are presented in **Table 4**.¹ The most frequently reported treatment-related adverse events for both regimens were gastrointestinal in nature and included nausea, diarrhea, and vomiting. Other common adverse events included QT or corrected QT (QTc) interval prolongation and rash. For both NOXAFIL® and the standard azoles prophylaxis, most adverse events were considered mild to moderate in severity (88% and 93%, respectively).^{1,33} In this study, the adverse event profile for NOXAFIL® was comparable to that of fluconazole.

Table 4. Treatment-related adverse events with a 2% or greater incidence in patients receiving NOXAFIL® or overall standard azole therapy (Study 1899).¹

	Number (%) of Patients			
	NOXAFIL® (n = 304)	Fluconazole/ Itraconazole (n = 298)	Fluconazole (n = 240)	Itraconazole (n = 58)
Body System/Preferred Term				
Subjects reporting any adverse event	102 (34)	101 (34)	71 (30)	30 (52)
Body as a whole: general disorders				
Headache	5 (2)	1 (<1)	0	1 (2)
Gastrointestinal system disorders				
Nausea	22 (7)	25 (8)	17 (7)	8 (14)
Diarrhea	20 (7)	21 (7)	12 (5)	9 (16)
Vomiting	14 (5)	20 (7)	14 (6)	6 (10)
Abdominal pain	9 (3)	9 (3)	8 (3)	1 (2)
Mucositis NOS	7 (2)	0	0	0
Dyspepsia	5 (2)	3 (1)	3 (1)	0
Constipation	3 (1)	7 (2)	7 (3)	0
Heart rate and rhythm disorders				
QT/QTc prolongation	12 (4)	9 (3)	5 (2)	4 (7)
Liver and biliary system disorders				
Bilirubinemia	7 (2)	8 (3)	5 (2)	3 (5)
Hepatic enzymes increased	7 (2)	3 (1)	3 (1)	0
SGPT increased	7 (2)	5 (2)	4 (2)	1 (2)
SGOT increased	6 (2)	5 (2)	4 (2)	1 (2)
GGT increased	5 (2)	2 (1)	1 (<1)	1 (2)
Metabolic and nutritional disorders				
Hypokalemia	9 (3)	6 (2)	5 (2)	1 (2)
Skin and subcutaneous tissue disorders				
Rash	9 (3)	11 (4)	10 (4)	1 (2)

GGT, γ -glutamyl transpeptidase; NOS, not otherwise specified; QTc, corrected QT interval; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase

Prophylaxis Study 316

The safety and tolerability of NOXAFIL® and fluconazole were evaluated in all 600 patients treated in the prophylaxis study of HSCT recipients with GVHD during the 112 days of prophylaxis and for 2 additional months. Treatment-related adverse events were observed in 36% of patients in the NOXAFIL® group and in 38% of patients in the fluconazole group; the most frequently occurring (≥2% of either prophylaxis group) are reported in **Table 5**.¹ Similar to the previous study, the most frequently reported treatment-related adverse events for both regimens were gastrointestinal in nature and included nausea, diarrhea, and vomiting. The only cardiovascular disorder occurring at a frequency of ≥2% in either prophylaxis group was hypertension (1% for NOXAFIL®, 2% for fluconazole); the only nervous system disorder occurring with the same frequency was tremor (1% for NOXAFIL®, 2% for fluconazole). Sensory disturbances such as blurred vision and taste perversion were also reported for the NOXAFIL® and fluconazole prophylaxis groups (1% and 2% for both adverse events, respectively).¹

Table 5. Treatment-related adverse events with a 2% or greater incidence in patients receiving NOXAFIL® or fluconazole (Study 316).¹

	NOXAFIL® (n = 301) n (%)	Fluconazole (n = 299) n (%)
Body System/Preferred Term		
Subjects reporting any adverse event	107 (36)	115 (38)
Body as a whole: general disorders		
Drug level altered	5 (2)	2 (1)
Dizziness	4 (1)	5 (2)
Fatigue	4 (1)	6 (2)
Anorexia	3 (1)	7 (2)
Headache	3 (1)	8 (3)
Weakness	3 (1)	5 (2)
Cardiovascular disorders, general		
Hypertension	2 (1)	5 (2)
Central and peripheral nervous system disorders		
Tremor	4 (1)	6 (2)
Disorders of the eye		
Vision blurred	3 (1)	5 (2)
Gastrointestinal system disorders		
Nausea	22 (7)	28 (9)
Vomiting	13 (4)	15 (5)
Diarrhea	8 (3)	12 (4)
Abdominal pain	4 (1)	7 (2)
Dyspepsia	3 (1)	6 (2)
Constipation	1 (<1)	5 (2)
Liver and biliary system disorders		
SGOT increased	9 (3)	4 (1)
GGT increased	9 (3)	7 (2)
Bilirubinemia	8 (3)	5 (2)
Hepatic enzymes increased	8 (3)	7 (2)
SGPT increased	8 (3)	3 (1)
Metabolic and nutritional disorders		
Alkaline phosphatase increased	5 (2)	5 (2)
Renal and urinary system disorders		
Blood creatinine increased	6 (2)	5 (2)
Special senses, other disorders		
Taste perversion	3 (1)	5 (2)

GGT, γ -glutamyl transpeptidase; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase

Discontinuation rates because of adverse events also were similar between the 2 groups. In total, 103 patients receiving NOXAFIL® and 114 patients receiving fluconazole discontinued prophylaxis because of an adverse event (34% versus 38%, respectively). The high rates of discontinuation in this study were attributed to the severity of the underlying disease in many patients: only 46% of patients receiving NOXAFIL® and 41% of those receiving fluconazole completed the entire 16-week study. Serious adverse events were reported in 2% or less of patients in each group.³⁴

When considering the combined safety data from the prophylaxis studies (316 and 1899), the most common treatment-related serious adverse events associated with NOXAFIL® prophylaxis were bilirubinemia, increased hepatic enzyme levels, hepatocellular damage, nausea, and vomiting (1% each). Uncommon and rare treatment-related serious or medically significant adverse events reported during clinical trials with NOXAFIL® have included adrenal insufficiency and allergic and/or hypersensitivity reactions. Rare cases of hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and pulmonary embolus have been reported primarily among patients who had been receiving concomitant cyclosporine or tacrolimus for management of transplant rejection or GVHD.

Clinical Laboratory Tests

In healthy volunteers and patients, elevation in liver function test results did not appear to be associated with higher plasma concentrations of NOXAFIL®. The majority of abnormal liver function tests were minor and transient and did not lead to discontinuation of therapy.¹ Liver function tests were performed at scheduled intervals during the aforementioned clinical trials. In these studies, changes in liver function test results were described by using the Common Toxicity Criteria. Data for patients for whom Common Toxicity Criteria grade changed from 0, 1, or 2 at baseline to grade 3 or 4 during these studies are presented in **Table 6**.¹

Table 6. Patients with change from common toxicity criteria Grade 0, 1, or 2 to Grade 3 or 4 during prophylaxis in Studies 316 and 1899.¹

Laboratory Parameter	Study 1899	
	NOXAFIL® n = 304 (%)	Standard Azole Therapy 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)
Laboratory Parameter	Study 316	
	NOXAFIL® 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)

ALT, alanine aminotransferase; AST, aspartate aminotransferase

In clinical trials, there were infrequent cases of hepatic reactions (eg, mild to moderate elevations in ALT, AST, alkaline phosphatase, total bilirubin, and/or clinical hepatitis). The elevations in liver function tests were generally reversible on discontinuation of therapy, and in some instances these tests normalized without drug interruption and rarely required drug discontinuation. Rarely, more severe hepatic reactions, including cholestasis or hepatic failure with fatalities, were reported in patients with serious underlying medical conditions (eg, hematologic malignancy) during prophylaxis with NOXAFIL®. These severe hepatic events were seen primarily in subjects receiving the 800-mg daily dose (400 mg twice daily or 200 mg 4 times daily) in another indication.

Liver function tests should be evaluated at the start of and during the course of NOXAFIL® therapy. Patients who develop abnormal liver function 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 function 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®.

Adverse Events in Special Populations

Pediatric and adolescent patients

Twelve adolescent patients between 13 and 17 years of age received NOXAFIL® 600 mg/day (200 mg 3 times daily) for prophylaxis of IFIs. The safety profile in these patients appears similar to the safety profile observed in adults.¹

Sixteen pediatric/adolescent patients aged 8 to 17 years were treated with NOXAFIL® 800 mg/day (400 mg twice daily or 200 mg 4 times daily) in a study for another indication. The occurrence of treatment-emergent adverse events was similar to that observed in adult patients.^{1,36} Gastrointestinal events, fever, and headache were the most commonly reported events in both age groups.³⁶ The safety and effectiveness of NOXAFIL® in pediatric patients below the age of 13 years have not been established.

Geriatric patients

Of the 605 patients randomized to NOXAFIL® in the aforementioned prophylaxis clinical trials, 63 (10%) were ≥65 years of age. In addition, 48 patients treated with ≥800 mg/day of NOXAFIL® in another indication were ≥65 years of age. No overall differences in safety were observed between the geriatric patients and younger patients; therefore, no dosage adjustment is recommended for geriatric patients.

Electrocardiogram Evaluation

Some azoles, including NOXAFIL®, have been associated with prolongation of the QT interval on the electrocardiogram (ECG). In one study, multiple time-matched electrocardiograms 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® 400 mg twice daily with a high-fat meal for 7 to 8 days (ie, at steady state),³⁷ which were then read by a blinded third party. In this study, the mean QTc (Fridericia) [QTc(F)] interval change from baseline was –5 milliseconds following administration of the recommended clinical dose. A decrease in the QTc(F) interval (–3 milliseconds) 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 milliseconds (–8 milliseconds). No healthy subject administered NOXAFIL® had a QTc(F) interval ≥500 milliseconds or an increase ≥60 milliseconds in their QTc(F) interval from baseline.

During clinical development there was 1 case of torsades de pointes in a patient taking NOXAFIL®. This patient was seriously ill with multiple confounding risk factors including a history of cardiotoxic chemotherapy, hypokalemia, and concomitant medications that may have been contributory. NOXAFIL® should be administered with caution to patients with potentially proarrhythmic conditions and should not be administered with drugs that are known to prolong the QTc interval and are metabolized through CYP3A4. Rigorous attempts to correct potassium, magnesium, and calcium should be made before starting NOXAFIL®.

How Supplied

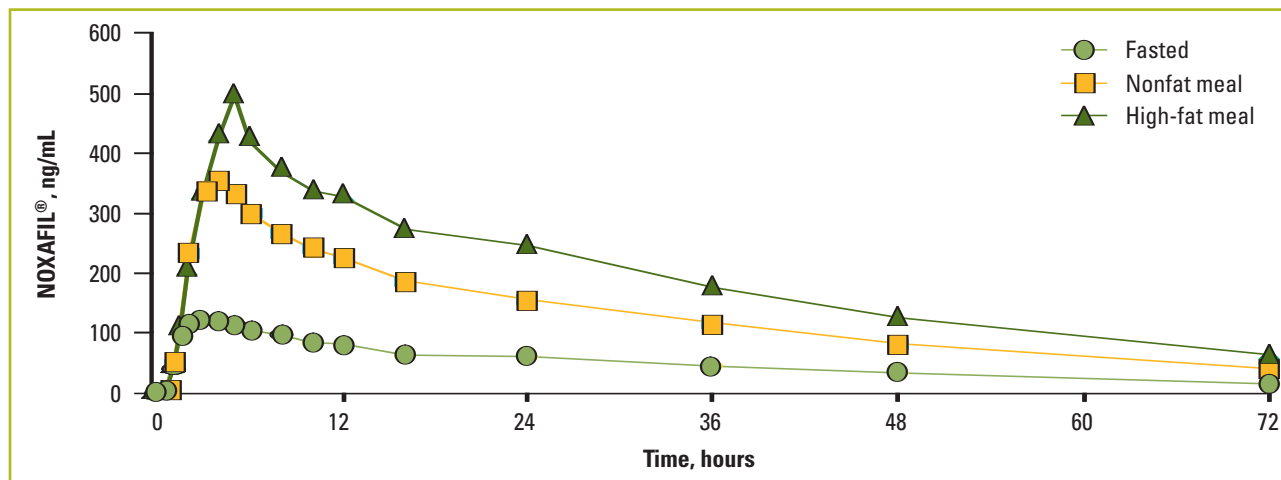
NOXAFIL® Oral Suspension is available in 4-oz amber glass bottles with child-resistant closures containing 105 mL of suspension (40 mg of NOXAFIL® per mL). Supplied with each bottle is a plastic dosing spoon calibrated for measuring 2.5-mL and 5-mL doses. NOXAFIL® suspension should be stored at 25°C (77°F) and should not be frozen. Excursions to 15°C-30°C (59°F-86°F) are permitted.¹

NOXAFIL® Pharmacokinetic Properties

Absorption

NOXAFIL® is absorbed slowly; median time to peak plasma concentration is achieved approximately 5 hours after oral administration.³⁸ The absorption of NOXAFIL® is dose proportional (ie, linear) after the administration of single or multiple oral doses up to 800 mg when taken with a high-fat meal.³⁸ Doses higher than 800 mg/day in patients and healthy volunteers were not associated with a further increased exposure to the drug.³⁹ Dividing the total daily dose of NOXAFIL® (800 mg) into 200 mg 4 times daily increased NOXAFIL® exposure by 58% over 48 hours in fasted healthy volunteers compared with 400 mg twice daily.³⁹ For the prophylaxis of IFIs, NOXAFIL® should be administered at 200 mg (5 mL) 3 times a day.

The absorption of NOXAFIL® after oral administration is influenced by food intake. In a randomized, open-label, single-dose, crossover study, the exposure (assessed as area under the plasma concentration–time curve) of NOXAFIL® when given with a high-fat meal was approximately 4 times greater compared with exposure in the fasting state (**Figure 14**).⁴⁰ Administering NOXAFIL® with a nonfat meal also increased exposure to the drug, albeit to a lesser extent (2.6-fold exposure increase with the nonfat meal compared with the fasting state).⁴⁰ Similarly, administering NOXAFIL® with a liquid nutritional supplement resulted in an approximately 2.6-fold bioavailability increase compared with administration under fasting conditions.⁴¹ As a result of these findings, it is recommended that each dose of NOXAFIL® should be administered with a full meal or with a nutritional liquid supplement in patients who cannot eat a full meal. For patients who cannot eat a full meal or tolerate an oral supplement, alternative antifungal therapy should be considered or patients should be monitored closely for breakthrough fungal infections.¹

Figure 14. Effect of food on the absorption of NOXAFIL®.⁴⁰

In a randomized, open-label, crossover study, coadministration of NOXAFIL® with an antacid (Mylanta®, Johnson & Johnson, New Brunswick, NJ) had no significant effect on exposure in the fasted or nonfasted state in healthy volunteers.⁴² NOXAFIL® exposure was decreased by 15% and 12% when administered with the antacid in fasted and nonfasted healthy subjects, respectively.⁴² No clinically relevant effect on NOXAFIL® was observed when administered with H₂-receptor antagonists other than cimetidine (see “Drug Interactions”) or proton pump inhibitors.

Distribution/Exposure

NOXAFIL® has an apparent volume of distribution of 1774 L, suggesting extensive extravascular distribution and penetration into the body tissues.¹ NOXAFIL® is highly bound to plasma proteins (>98%), predominantly to albumin.⁴³ Steady-state concentrations of NOXAFIL® are achieved after approximately 7 to 10 days of multiple-dose therapy.^{38,43}

Metabolism and Excretion

NOXAFIL® does not undergo significant metabolism and circulates in the plasma primarily as the parent compound.⁴³ The majority of circulating metabolites are glucuronide conjugates formed via phase 2 metabolism.⁴⁴ NOXAFIL® does not have any major circulating oxidative metabolites, suggesting that the drug is not extensively metabolized by the cytochrome P450 enzyme system.⁴⁴ After administration of radiolabeled NOXAFIL® in healthy volunteers, approximately 17% of the dose was excreted as metabolites in the urine and feces.⁴³

NOXAFIL® is eliminated slowly; its mean half-life is 35 hours (range, 20-66 hours).¹ It is eliminated primarily through the feces (71% of the administered dose), with most excreted as the parent drug (66% of the dose).⁴³ Renal elimination is a minor excretion pathway, and 13% of the administered dose is excreted in the urine, generally as glucuronide conjugates.⁴³ Less than 0.2% of the radiolabeled dose is excreted in the urine as the parent drug.

Despite the observation that the majority of an administered dose of NOXAFIL® is recovered unchanged in the feces, it is unlikely that this represents only unabsorbed drug.⁴³ Like other triazole antifungal agents (eg, ketoconazole, itraconazole),⁴⁵ NOXAFIL® is a substrate for intestinal P-glycoprotein, an adenosine triphosphate-dependent plasma membrane transporter responsible for drug efflux from cells.⁴⁶ In some clinical trials, multiple peaks in NOXAFIL® plasma concentrations have been observed, suggesting that NOXAFIL® efflux by the transporter is reabsorbed into the systemic circulation.^{43,46}

Pharmacokinetics in Special Populations

HSCT Recipients With GVHD and Neutropenic Patients With Acute Myelogenous Leukemia or Myelodysplastic Syndrome

Mean steady-state plasma concentrations of NOXAFIL® have been measured during clinical trials. In Study 316, patients with GVHD were treated with NOXAFIL® 200 mg 3 times daily resulting in mean plasma concentrations of 1470 ng/mL (n = 82) and 958 ng/mL (n = 158) in patients with chronic and acute disease, respectively. Similarly, in Study 1899, neutropenic patients undergoing chemotherapy and receiving NOXAFIL® 200 mg 3 times each day achieved a mean plasma concentration of 583 ng/mL (n = 215) at steady-state dosing.³³

Gender

There was no significant effect of gender on the pharmacokinetics of NOXAFIL[®] among 64 healthy volunteers (32 men, 32 women) randomly assigned (3:1) to receive NOXAFIL[®] 800 mg/day or placebo in divided doses with a high-fat meal for 8 days.⁴⁷ There was no significant difference in maximum plasma concentration, time to maximum plasma concentration, or area under the plasma concentration–time curve values between male and female patients.⁴⁷

Pediatric and Adolescent Patients

The mean steady state concentration of NOXAFIL[®] was similar in the 10 adolescent patients (aged 13-17 years) in the prophylaxis studies and in adults (≥ 18 years of age).¹ Of the 16 patients 8 to 17 years of age enrolled in the open-label study evaluating NOXAFIL[®] in the treatment of IFIs, 12 were deemed evaluable for pharmacokinetic analysis.⁴⁸ These patients received NOXAFIL[®] 800 mg/day in divided doses, except for 1 patient who received 400 mg/day in divided doses. Mean trough plasma NOXAFIL[®] concentrations were similar among pediatric/adolescent patients (776 ± 769 ng/mL) and adult patients aged 18 to 64 years (817 ± 689 ng/mL).⁴⁸

Geriatric Patients

Among healthy volunteers aged 18 to 45 years ($n = 32$) or 65 years or older ($n = 32$) randomly assigned (3:1) to receive NOXAFIL[®] 800 mg/day or placebo in divided doses with a high-fat meal for 8 days, elderly subjects had a slightly higher exposure to NOXAFIL[®] than younger subjects at steady state.⁴⁷ Values for maximum plasma concentration and area under the plasma concentration–time curve from 0 to 12 hours were 26% ($P = .034$) and 29% ($P = .022$) higher among elderly subjects than among younger subjects.⁴⁷ A similar trend was observed in a clinical program involving a small number of patients 65 years or older ($n = 25$) compared with patients aged 18 to 64 years ($n = 194$).⁴⁸ These small differences do not appear to be of clinical significance, and no dose adjustment is required for elderly patients.¹

Race

In a multiple-dose study of healthy volunteers ($n = 56$), there was a small (16%) decrease in area under the plasma concentration–time curve and maximum plasma concentration values in black subjects compared with those in white subjects.⁴⁷ However, the safety profile of NOXAFIL[®] in black subjects and white subjects was similar. This difference is considered clinically insignificant, and no dose adjustment for race is required.¹

Renal Insufficiency

Among 18 patients with mild to moderate renal insufficiency (creatinine clearance 20-80 mL/min/1.73 m²), the pharmacokinetics of NOXAFIL[®] were not altered after single-dose administration.⁵⁰ No dose adjustment is recommended for patients with renal dysfunction.¹ Among 6 subjects with severe renal insufficiency (creatinine clearance < 20 mL/min/1.73 m²), exposure to NOXAFIL[®] was highly variable (coefficient of variation, 96%) compared with subjects in other renal impairment groups (coefficient of variation, $< 40\%$). Due to the variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough fungal infections. NOXAFIL[®] is not removed by hemodialysis.⁵⁰

Hepatic Insufficiency

The pharmacokinetics of NOXAFIL[®] in 12 patients with Child-Pugh class A, B, or C hepatic insufficiency (4 subjects each) were compared with those of 4 subjects with normal hepatic function after the administration of a single 200-mg dose of NOXAFIL[®].⁵¹ Mean maximum plasma concentrations were 545, 414, and 347 ng/mL for patients with mild, moderate, and severe hepatic impairment, respectively, compared with 508 ng/mL for healthy subjects. The mean half-life of NOXAFIL[®] was prolonged in subjects with mild, moderate, or severe hepatic impairment (26.6, 35.3, and 46.1 hours, respectively) compared with healthy subjects (22.1 hours).⁵¹ There also was a trend toward greater drug exposure among patients with hepatic impairment, as evidenced by higher area under the plasma concentration–time curve values extrapolated to infinity among subjects with mild, moderate, and severe hepatic impairment (25,805, 23,535, and 30,521 (ng·h)/mL, respectively) compared with subjects with normal hepatic function (18,944 (ng·h)/mL). Because of substantial intersubject variability and limited numbers of subjects, these differences were not statistically significant.⁵¹ The pharmacokinetic data in subjects with hepatic impairment were not sufficient to determine if dose adjustment was necessary in patients with hepatic dysfunction. It is recommended that NOXAFIL[®] be used with caution in patients with hepatic impairment.

Drug Interactions

NOXAFIL[®] is metabolized primarily through phase 2 biotransformations by uridine diphosphate glucuronidation and is a substrate for P-glycoprotein efflux.⁴⁴⁻⁴⁶ Therefore, inhibitors or inducers of these clearance pathways may increase or decrease plasma concentrations of NOXAFIL[®], respectively.¹ Studies of healthy humans and *in vitro* models have demonstrated that NOXAFIL[®] does not significantly alter most cytochrome P450 isozymes that affect the metabolism of drugs in humans, including the isozymes 1A2, 2C8/9, 2D6, 2E1, and 2C19.⁵²

However, because NOXAFIL® inhibits the cytochrome P450 3A4 isozyme, plasma concentrations of drugs metabolized by cytochrome P450 enzyme 3A4 may be increased by this drug.¹

The effects of the coadministration of other drugs on the pharmacokinetics of NOXAFIL® and the effects of NOXAFIL® on the pharmacokinetics of other drugs are summarized in **Tables 7** and **8**.¹ **Table 7** summarizes the effect of coadministered drugs on NOXAFIL®, and **Table 8** summarizes the effect of NOXAFIL® on coadministered drugs.

Table 7. Summary of the effect of coadministered drugs on NOXAFIL® in healthy volunteers.¹

Drugs (Schedule)	NOXAFIL® Dose/Schedule	Effect on Bioavailability of NOXAFIL® C _{max}	Effect on Bioavailability of NOXAFIL® AUC	Recommendation
Rifabutin 300 mg QD × 17 days	200 mg (tablets) QD × 10 days	↓43%	↓49%	Avoid concomitant use unless benefit outweighs risk
Phenytoin 200 mg QD × 10 days	200 mg (tablets) QD × 10 days	↓41%	↓50%	Avoid concomitant use unless benefit outweighs risk
Cimetidine 400 mg BID × 10 days	200 mg (tablets) QD × 10 days	↓39%	↓39%	Avoid concomitant use unless benefit outweighs risk
Efavirenz 400 mg QD × 10 and 20 days	400 mg (oral suspension) BID × 10 and 20 days	↓45%	↓50%	Avoid concomitant use unless benefit outweighs risk

C_{max}, maximum plasma concentration; AUC, area under the plasma concentration–time curve; QD, once daily; BID, twice daily

Table 8. Summary of the effects of NOXAFIL® on coadministered drugs in healthy volunteers and patients.¹

Coadministered Drug	Coadministered Drug Dose/Schedule	NOXAFIL® Dose/Schedule	Effect on Bioavailability of Coadministered Drug		Recommendations
			C _{max}	AUC	
Sirolimus	2 mg single oral dose	400 mg (oral suspension) BID × 16 days	↑572%	↑788%	Coadministration of NOXAFIL® with sirolimus is contraindicated
Cyclosporine	Stable maintenance dose in heart transplant recipients	200 mg (tablets) QD × 10 days	↑Cyclosporine concentrations required cyclosporine dose reductions of up to 29%		At initiation of NOXAFIL® treatment, reduce the cyclosporine dose to approximately three fourths of the original dose Frequent monitoring of cyclosporine whole-blood trough concentrations should be performed during and at discontinuation of NOXAFIL® treatment and the cyclosporine dose adjusted accordingly
Tacrolimus	0.05 mg/kg single oral dose	400 mg (oral suspension) BID × 7 days	↑121%	↑358%	At initiation of NOXAFIL® treatment, reduce the tacrolimus dose to approximately one third of the original dose Frequent monitoring of tacrolimus whole-blood trough concentrations should be performed during and at discontinuation of NOXAFIL® treatment and the tacrolimus dose adjusted accordingly
Rifabutin	300 mg QD × 17 days	200 mg (tablets) QD × 10 days	↑31%	↑72%	Avoid concomitant use unless the benefit outweighs the risks. If the drugs are coadministered, frequent monitoring of rifabutin adverse events (eg, uveitis, leukopenia) should be performed
Midazolam	Single IV infusion of 0.05 mg/kg	200 mg (tablets) QD × 10 days	NA	↑83%	Frequent monitoring of adverse events of benzodiazepines metabolized by CYP3A4 should be performed and dose reduction of these benzodiazepines should be considered during coadministration with NOXAFIL®. A clinical study in healthy volunteers demonstrated a >5-fold increase in midazolam AUC
	0.4 mg single IV dose*	200 mg (oral suspension) BID × 7 days	↑30%	↑362%	
	2 mg single oral dose*	200 mg (oral suspension) BID × 7 days	↑126%	↑362%	
	0.4 mg single IV dose*	400 mg (oral suspension) BID × 7 days	↑62%	↑524%	
Phenytoin	200 mg QD × 10 days	200 mg (tablets) QD × 10 days	↑16%	↑16%	Frequent monitoring of phenytoin concentrations should be performed while coadministered with NOXAFIL® and dose reductions of phenytoin should be considered
Ritonavir	100 mg QD × 14 days	400 mg (oral suspension) BID × 7 days	↑49%	↑80%	Frequent monitoring of adverse effects and toxicity of ritonavir should be performed during coadministration with NOXAFIL®
Atazanavir	300 mg QD × 14 days	400 mg (oral suspension) BID × 7 days	↑155%	↑268%	Frequent monitoring of adverse effects and toxicity of atazanavir should be performed during coadministration with NOXAFIL®
Atazanavir/ritonavir boosted regimen	300 mg/100 mg QD × 14 days	400 mg (oral suspension) BID × 7 days	↑53%	↑146%	

IV, intravenous; NA, not applicable if administered as an IV; C_{max}, maximum plasma concentration; AUC, area under the plasma concentration–time curve; QD, once daily; BID, twice daily; CYP, cytochrome P450

*The mean terminal half-life of midazolam was increased from 3 hours to 8 to 10 hours during coadministration with NOXAFIL®

Effects of Other Drugs on NOXAFIL®

Coadministration of rifabutin, phenytoin, cimetidine, and efavirenz with NOXAFIL® produces significant decreases in NOXAFIL® exposure, evidenced by an approximate 40% to 50% decrease in NOXAFIL® maximum plasma concentration and area under the plasma concentration–time curve values.^{38,40,53} Therefore, avoiding the concomitant use of NOXAFIL® with these medications is recommended unless the benefit of combined therapy outweighs the risk (**Table 7**).^{1,38,41,53} There were no clinically relevant effects on the bioavailability of NOXAFIL® when it was administered with an antacid, glipizide, H₂-receptor antagonists other than cimetidine, or proton pump inhibitors. No dose adjustments are required for these products when coadministered with NOXAFIL® 200 mg QD.¹

Effects of NOXAFIL® on Other Drugs

Coadministration of NOXAFIL® with the cytochrome P450 substrates terfenadine, astemizole, cisapride, pimozide, halofantrine, or quinidine is contraindicated, as it may result in increased plasma concentrations of these medicinal products and potentially lead to prolongation of the QT interval and rare occurrences of torsades de pointes. Coadministration of NOXAFIL® and ergot alkaloids also is contraindicated because NOXAFIL® may increase the plasma concentration of these agents, leading to ergotism.¹ Coadministration of NOXAFIL® and the immunosuppressive agent sirolimus is contraindicated because NOXAFIL® may increase the plasma concentration of this agent, leading to nephrotoxicity and neurotoxicity.

Cyclosporine

In 4 heart transplant patients receiving stable maintenance doses of cyclosporine, the administration of NOXAFIL® 200 mg/day for 10 days produced decreases in cyclosporine clearance such that 3 of 4 patients required dose reductions of cyclosporine ranging from 14% to 29% (**Table 8**).⁵⁴ Cases of elevated cyclosporine levels resulting in rare serious adverse events, including nephrotoxicity and leukoencephalopathy, and death were reported in clinical efficacy studies. When NOXAFIL® treatment is initiated in a patient receiving cyclosporine, the cyclosporine dose should be reduced to about three-fourths of the original dose¹ and cyclosporine whole blood trough concentrations should be monitored frequently during and at discontinuation of NOXAFIL® therapy, with cyclosporine doses adjusted as necessary.⁵⁴

Tacrolimus

In healthy volunteers, multiple-dose administration of NOXAFIL® increased mean maximum plasma concentration and area under the plasma concentration–time curve values of tacrolimus by 121% and 358%, respectively (**Table 8**).^{1,50} This interaction is presumed to be mediated via NOXAFIL®-mediated inhibition of cytochrome P450 enzyme 3A4 metabolism and P-glycoprotein transport of tacrolimus. When NOXAFIL® treatment is initiated in patients already receiving tacrolimus, the dose of tacrolimus should be reduced to about one-third of the original dose.¹ Thereafter, blood levels of tacrolimus should be monitored carefully during coadministration and upon discontinuation of NOXAFIL®; the dose of tacrolimus should be adjusted as necessary.^{1,50}

Rifabutin

In addition to reductions in NOXAFIL® exposure, coadministration of multiple doses of NOXAFIL® and rifabutin resulted in increases in rifabutin maximum plasma concentration (31%) and area under the plasma concentration–time curve (72%) values in healthy volunteers (**Table 8**).³⁸ Concomitant administration of NOXAFIL® and rifabutin should be avoided unless the benefit to the patient outweighs the risk. If these medicinal products are coadministered, careful monitoring of full blood counts and adverse events related to increased rifabutin levels (eg, uveitis, leukopenia) is recommended.¹

Midazolam

NOXAFIL® 200 mg orally once daily increased the area under the plasma concentration–time curve of midazolam by 83% after intravenous administration (**Table 8**).^{1,52} Administration of NOXAFIL® 200 mg and 400 mg twice daily with a single intravenous dose of midazolam 0.4 mg increased the area under the concentration–time curve of midazolam by 362% and 524%, respectively.¹ Finally, administration of NOXAFIL® 200 mg twice daily with a single oral dose of midazolam 2 mg increased the area under the concentration–time curve of midazolam by 362%.¹ Dose adjustments should be considered for all benzodiazepines metabolized through cytochrome P450 enzyme 3A4 (eg, midazolam, triazolam, alprazolam) during coadministration with NOXAFIL®.^{1,52}

Ritonavir

In healthy subjects, coadministration of NOXAFIL® 400 mg orally twice daily with ritonavir 100 mg once daily for 7 days resulted in an increase of the C_{max} and AUC of ritonavir by 49% and 80%, respectively (**Table 8**).^{1,55} Frequent monitoring for adverse events and toxicity related to ritonavir is recommended during coadministration with NOXAFIL®.¹

Atazanavir

In healthy subjects, coadministration of NOXAFIL® 400 mg orally twice daily with atazanavir 300 mg once daily for 7 days resulted in an increase of the C_{max} and AUC of atazanavir by 155% and 268%, respectively (Table 8).^{1,55} Coadministration of NOXAFIL® 400 mg orally twice daily with atazanavir/ritonavir 300/100 mg once daily for 7 days resulted in an increase of the C_{max} and AUC of atazanavir by 53% and 146%, respectively (Table 8).^{1,55} Clinically significant increases in bilirubin levels occurred in 5 subjects receiving atazanavir with NOXAFIL® and in 6 subjects receiving atazanavir/ritonavir with NOXAFIL®.⁵⁵ Frequent monitoring for adverse events and toxicity related to atazanavir is recommended during coadministration with NOXAFIL®.¹

Glipizide

Glucose concentrations decreased in some healthy volunteers when glipizide was coadministered with NOXAFIL®. Dose adjustments are not required with either drug; however, glucose concentrations should be monitored in accordance with the current standard of care for patients with diabetes when NOXAFIL® is coadministered with glipizide.¹ No clinically relevant effect on NOXAFIL® bioavailability and/or plasma concentrations was observed when administered with an antacid, ritonavir, H₂-receptor antagonists other than cimetidine, or proton pump inhibitors; therefore, no NOXAFIL® dose adjustments are required when used concomitantly for these drug combinations.¹

Drugs that NOXAFIL® coadministration may potentially affect (but that have not been specifically studied) include vinca alkaloids, calcium channel blockers metabolized via cytochrome P450, and 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) inhibitors (ie, statins) metabolized through cytochrome P450 (Table 9).¹ If NOXAFIL® is coadministered with these agents, patients should be monitored closely for increased plasma concentrations of the concomitant drug, for drug toxicity, or for both. Dose adjustments of the coadministered drug may be required.¹

Table 9. Drugs not studied that likely will result in significant drug interactions with NOXAFIL®.¹

Drug or Drug Class (CYP3A4 Substrates)	Recommendations
Vinca alkaloids	NOXAFIL® may increase plasma concentrations of vinca alkaloids (eg, vincristine and vinblastine), which may lead to neurotoxicity. Therefore, it is recommended that dose adjustment of the vinca alkaloid be considered
HMG-CoA reductase inhibitors (statins) metabolized through CYP3A4	It is recommended that dose reduction of statins be considered during coadministration. Increased statin concentrations in plasma can be associated with rhabdomyolysis
Calcium channel blockers (CCBs) metabolized through CYP3A4	Frequent monitoring for adverse events and toxicity related to CCBs is recommended during coadministration. Dose reduction of CCBs may be needed
Digoxin	Increased plasma concentrations of digoxin have been reported in patients receiving digoxin and NOXAFIL®. Therefore, monitoring of digoxin plasma concentrations is recommended during coadministration

HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; CYP, cytochrome P450; CCBs, calcium channel blockers

NOXAFIL® Dosage and Administration

Each dose of NOXAFIL® should be administered with a full meal or a liquid nutritional supplement. For patients who cannot eat a full meal or tolerate an oral nutritional supplement, alternative antifungal therapy should be considered or patients should be monitored closely for breakthrough fungal infections.¹ Patients who have severe diarrhea or vomiting should also be monitored for breakthrough fungal infections. The duration of therapy is based on recovery from neutropenia or immunosuppression.

Age, gender, race, and renal dysfunction do not appear to produce clinically significant changes in the pharmacokinetics of NOXAFIL®; therefore, no dose adjustment is recommended for these groups.^{1,47-50} Please see Important Safety Information on Page 2.

Prophylaxis

NOXAFIL® Oral Suspension is indicated for prophylaxis of invasive *Aspergillus* and *Candida* infections in patients, 13 years of age and older, who are at high risk of developing these infections due to being severely immunocompromised, such as HSCT recipients with GVHD or those with hematologic malignancies with prolonged neutropenia from chemotherapy. For the prophylaxis of IFIs in high-risk patients, NOXAFIL® should be administered 200 mg 3 times a day.

Oropharyngeal Candidiasis

NOXAFIL® Oral Suspension is indicated for the treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole. For oropharyngeal candidiasis, NOXAFIL® should be administered at a loading dose of 200 mg once a day on the first day, then 100 mg once a day for 13 days. For refractory oropharyngeal candidiasis, NOXAFIL® should be administered at 400 mg twice a day, and the duration of therapy should be based on the severity of the patient's underlying disease and clinical response.

Summary

In the past several decades, the incidence of IFIs has increased substantially, and the spectrum of pathogens causing these infections has shifted such that *Aspergillus* is being isolated with greater frequency.

After oral administration, NOXAFIL® is well absorbed and is distributed extensively to many tissue sites. It has a long half-life (mean, 35 hours) and large apparent volume of distribution (1774 L), suggesting its sustained exposure to the body tissues. Co-administering NOXAFIL® with solid food or with a liquid nutritional supplement and splitting the daily dose significantly increases its exposure.³⁹⁻⁴¹ Age, gender, race, and renal function do not influence the pharmacokinetics of NOXAFIL®.⁴⁷⁻⁵⁰

The efficacy of NOXAFIL® prophylaxis for IFIs was studied in 2 populations at high risk: neutropenic patients who were receiving chemotherapy for AML or MDS and HSCT patients with GVHD. NOXAFIL® prophylaxis in neutropenic patients with AML or MDS reduced the number of IFIs and substantially reduced the incidence of IFIs due to *Aspergillus*.¹ Fewer clinical failures were observed in this population and a benefit in overall mortality at day 100 was observed in favor of NOXAFIL®. In this study, the adverse event profile of NOXAFIL® was comparable to fluconazole.¹ In HSCT recipients with GVHD, NOXAFIL® reduced the number of IFIs and substantially reduced the incidence of IFIs due to *Aspergillus*, compared with fluconazole.¹ The adverse event profile of NOXAFIL® was comparable to fluconazole in this study as well.¹ Gastrointestinal adverse events were the most frequently reported class of adverse events.¹

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