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Posaconazole

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Contents

Abstract

▲ Posaconazole is a triazole antifungal agent, administered as an oral suspension, with an extended spectrum of *in vitro* activity.

▲ Posaconazole 800 mg/day demonstrated clinically relevant activity against a range of fungi in patients with invasive fungal infections who were refractory to, or intolerant of, other antifungal therapy in an open-label, multicentre, phase III study (330 patients received posaconazole and 279 patients served as external controls).

▲ In aspergillosis, the global response success rate at the end-of-therapy visit (primary endpoint) was significantly higher in posaconazole recipients than in external controls (42% vs 26%).

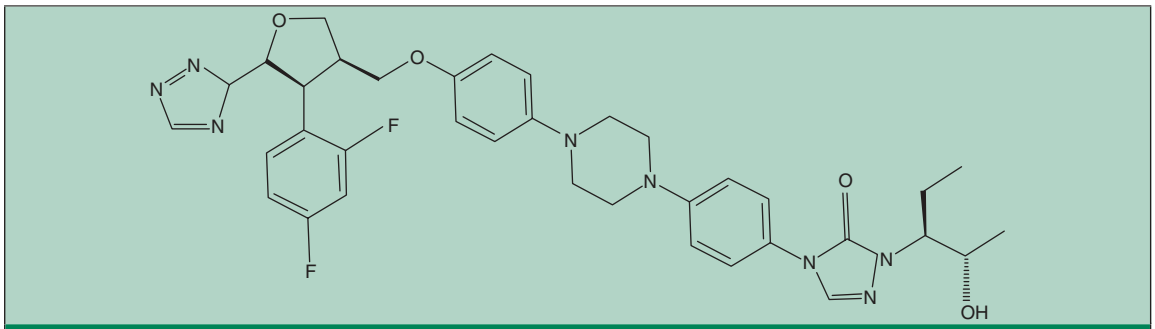
▲ Posaconazole was also associated with overall success rates of 54% in zygomycosis, 46% in fusariosis, 43% in *Pseudallescheria* infection, 80% in phaeohyphomycosis and 100% in histoplasmosis. Success rates were 48% in refractory candidiasis, 69% in refractory coccidioidomycosis, 48% in refractory cryptococcal infection and 82% in refractory chromoblastomycosis or mycetoma.

▲ Posaconazole also demonstrated potential in febrile neutropenia in an open-label phase II study (success rate of 81% 7 days after the end of treatment).

▲ In a noncomparative, multicentre, phase III study in patients with advanced HIV infection who had azole-refractory oropharyngeal and/or oesophageal candidiasis, posaconazole 400 or 800 mg/day resulted in a clinical response in 132 of 176 patients (75%).

▲ Oral posaconazole suspension was generally well tolerated in patients with invasive fungal infections, including patients who received treatment for ≥1 year.

Features and properties of posaconazole (SCH 56592; Noxafil®)	
Potential indications	
Invasive fungal infections (including aspergillosis, fusariosis and zygomycosis) in patients who are refractory to, or intolerant of, other antifungal therapy; azole-refractory oropharyngeal and/or oesophageal candidiasis; febrile neutropenia	
Mechanism of action	
Extended-spectrum triazole	Inhibits fungal ergosterol synthesis
Dosage and administration	
Usual dosage in clinical trials	800 mg/day (in divided doses)
Route of administration	Oral suspension
Pharmacokinetic profile (400mg twice daily in healthy volunteers; mean values at day 14)	
Maximum plasma concentration (C_{max})	4150 ng/mL (first dose); 3239 ng/mL (second dose)
Time to C_{max}	5h (first dose); 9h (second dose)
Area under the plasma concentration-time curve (AUC)	39 206 ng • h/mL (AUC_{12}); 33 899 ng • h/mL ($AUC_{12–24}$)
Apparent volume of distribution	486L
Total body clearance	11.5 L/h
Terminal elimination half-life	31h
Adverse events (patients with invasive fungal infections)	
Most frequent treatment-related adverse events	Nausea, vomiting, abdominal pain, headache, diarrhoea, elevated ALT or AST levels and rash



Posaconazole: structural formula

There has been a dramatic increase in the incidence of invasive fungal infections in the past few years, mainly due to the increasing number of immunosuppressed patients.[1,2] While *Candida* and *Aspergillus* are still frequently implicated in invasive mycoses, previously uncommon fungal infections such as fusariosis and zygomycosis are a growing problem.[1]

Although a number of antifungal agents are currently available, they are not without drawbacks.[2] For example, amphotericin B is associated with dose-limiting toxicity, the use of some azoles is hindered by the potential for drug-drug interactions and resistance, and the newer echinocandins are only available as intravenous formulations. Moreover, there is a lack of effective agents against emerging fungal infections such as fusariosis and zygomycosis. Thus, there is an urgent need for new antifungal agents.

Posaconazole (Noxafil®)[1] is a second-generation extended-spectrum triazole antifungal agent. The focus of this article is the use of oral posaconazole suspension in patients with invasive fungal infections who are refractory to, or intolerant of, other antifungal therapy, as well as its use in azole-refractory oropharyngeal and/or oesophageal candidiasis and febrile neutropenia.

1. Pharmacodynamic Profile

This section provides a brief overview of the pharmacodynamic properties of posaconazole. Some of the studies in this section are only available as abstracts and/or posters.[3-6]

Mechanism of Action

- Like other triazole antifungal agents, posaconazole blocks the synthesis of ergosterol, the primary sterol in the fungal cell membrane.[7] Posaconazole inhibits the enzyme 14α-demethylase (CYP51 or Erg11p), a cytochrome P450 (CYP) enzyme encoded by *ERG11*.[7]
- Posaconazole was a potent inhibitor of CYP51 in *Candida* spp.,[7] *Aspergillus* spp.[7] and representative pathogens from the class zygomycetes.[3] The concentration required to inhibit ergosterol synthesis by 50% in *Candida albicans* strain C43, for example, was 0.007 μg/mL for posaconazole and itraconazole, 1.5 μg/mL for fluconazole and 0.03 μg/mL for voriconazole.[7]
- Structurally, posaconazole is most similar to itraconazole.[8] The extended side chain of posaconazole may result in a tighter binding affinity to CYP51 compared with fluconazole or voriconazole, which lack this substituent, and may make it less susceptible to mutations in this enzyme.[8] Posaconazole is not a substrate for the efflux pumps encoded by *FLU1* and *MDR1*, although it is effluxed by pumps encoded by *CDR1* and *CDR2*.[8]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

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In Vitro Studies

Susceptibility testing in the studies discussed in this section was generally performed using National Committee for Clinical Laboratory Standards broth dilution methods.[4-7,9-20] It should be noted that the results of *in vitro* susceptibility testing do not necessarily correlate with clinical outcome and that interpretive breakpoints have not yet been established for posaconazole.

- Posaconazole has a broad spectrum of antifungal activity *in vitro*, as shown in table I.[4] It demonstrated activity against *Aspergillus*, zygomycetes, *Candida*, *Cryptococcus* and numerous other fungi, including *Coccidioides* and *Histoplasma* spp. The *in vitro* activity of posaconazole against *Fusarium* appeared to be species dependent. Posaconazole has shown fungicidal activity against *Trichosporon* spp., *Blastomyces dermatitidis*, *Cryptococcus neoformans* and *Aspergillus fumigatus*;[7,9-11] it has also shown fungicidal activity against some *Candida* spp. and fungistatic activity against others.[12]
- The *in vitro* antifungal activity of posaconazole was generally similar to, or greater than, that of the comparator antifungal agents itraconazole, fluconazole, voriconazole and amphotericin B (table I).[4] Notably, posaconazole was the only azole to consistently demonstrate activity against zygomycetes.[4]
- At a minimal inhibitory concentration (MIC) of ≤1 μg/mL, posaconazole inhibited 98% of *Aspergillus* isolates,[13,14] 100% of *C. neoformans* isolates[15,16] and 98–100% of *Candida* isolates (except for *C. glabrata* and *C. pelliculosa* which had susceptibilities of 80% and 44% at an MIC of ≤1 μg/mL).[15,16]
- Posaconazole had a short post-antifungal effect against *A. fumigatus* (0.75 hours) and *C. albicans* (≤0.5 hours).[21]
- In an *in vitro* study investigating the potential of combination therapy with posaconazole and caspofungin against *Aspergillus* spp., synergy was seen in 28% of posaconazole plus caspofungin interactions and an additive effect was seen in 60% of interactions; no antagonism was observed.[5] In addition, posaconazole plus caspofungin appeared to have greater activity than either agent alone against *C. glabrata*.[6]
- Multiple mutations in *ERG11* are needed for the development of reduced susceptibility of *C. albicans* to posaconazole.[18] Indeed, posaconazole demonstrated *in vitro* activity against *Candida* isolates showing reduced susceptibility to fluconazole and/or itraconazole[16-18] or voriconazole,[18] although elevated posaconazole MICs were sometimes seen against fluconazole- and/or itraconazole-resistant isolates.[15,16] Posaconazole also retained *in vitro* activity against *C. neoformans* isolates with reduced susceptibility to fluconazole.[16]
- Although the resistance of *A. fumigatus* to posaconazole has been associated with mutations in *cyp51A*, the mutations appear to be restricted to a single amino acid.[19] Isolates of *A. fumigatus* resistant to itraconazole[20,22] or voriconazole[20,23] *in vitro* showed only low level cross resistance to posaconazole. Isolates of *A. fumigatus* that were resistant to amphotericin B were susceptible to posaconazole.[20]

Animal Studies

- Several studies have demonstrated the antifungal activity of posaconazole in animal models of invasive aspergillosis,[24-32] including pulmonary[24,26-30,32] or CNS[31] aspergillosis. Posaconazole improved survival and/or reduced the fungal tissue burden in animals infected with *A. fumigatus*,[24,25,27-29,31,32] *A. flavus*[24] or *A. terreus*.[26,30] A degree of cross resistance was seen between itraconazole and posaconazole in a study involving an itraconazole-resistant isolate of *A. fumigatus*.[28]
- Posaconazole also prolonged survival and/or reduced the fungal tissue burden in animal models of fusariosis,[33] histoplasmosis,[34,35] disseminated candidiasis[24,36] (including candidiasis caused by *C. albicans* strains with reduced susceptibility or resistance to fluconazole[24]) and cerebral[37] or disseminated[38] phaeohyphomycosis, as well as in animals systemically infected with *C. neoformans*,[39] *Pseudallescheria boydii*[40] or *Coccidioides immitis*.[41,42]

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Table I. *In vitro* activity of posaconazole (POS) and other antifungal agents against clinical strains of moulds and yeasts. Organisms were collected from >200 medical centres globally over a 10-year time period.[4]a Antifungal activity was assessed using National Committee for Clinical Laboratory Standards broth microdilution methods

Organism	Number of MICs	MIC_{90} values (μg/mL)				
		POS	ITC	FLC	VRC	AMB
***Aspergillus* spp.**						
A. fumigatus	1119	0.5	1.0		0.5	1.0
A. niger	101	0.5	2.0		2.0	1.0
A. flavus	89	0.5	1.0		1.0	2.0
A. terreus	22	0.25	0.5		0.5	2.0
Zygomycetes						
Rhizopus spp.	32	8.0	32.0		128.0	2.0
Mucor spp.	18	16.0	32.0		128.0	1.0
Absidia spp.	16	0.25	0.5		128.0	0.5
Cunninghamella spp.[b]	6	0.031–1.0	0.125–2.0		8.0–128.0	0.125–2.0
Apophysomyces spp.[b]	5	0.031–4.0	0.031–8.0		16.0–128.0	0.031–4.0
Saksenaea spp.[b]	4	0.016–2.0	0.016–0.125		0.5–4.0	0.063–0.5
Rhizomucor spp.[b]	3	0.016–0.25	0.016–0.25		2.0–16	0.063–0.125
Cokeromyces spp.[b]	2	0.25–4.0	0.25–8.0		16.0–64.0	0.125–0.5
***Fusarium* spp.**						
F. solani	39	32.0			32.0	32.0
F. oxysporum	12	4.0			32.0	16.0
***Candida* spp.**						
C. albicans	3535	0.063	0.25	2.0	0.063	1.0[c]
C. glabrata	1218	2.0	4.0	64.0	2.0	1.0[c]
C. parapsilosis	970	0.25	0.5	4.0	0.125	1.0
C. tropicalis	719	0.25	0.5	4.0	0.5	1.0
C. krusei	189	1.0	1.0	64.0	0.5	2.0
C. dubliniensis	164	0.125	0.5	32.0	0.125	1.0
C. lusitaniae	84	0.25	2.0	4.0	0.063	2.0
C. guilliermondii	26	1.0	4.0	32.0	8.0	1.0
Other organisms						
Cryptococcus spp.	271	0.25	0.5	8.0	0.125	1.0
Scedosporium prolificans	80	32.0	64.0			32.0
Histoplasma spp.	53	0.25	0.063			0.5
Pseudallescheria spp.	41	1.0	1.0			4.0
Scedosporium apiospermum	26	1.0	32.0			8.0
Coccidioides spp.	25	0.25	0.25			0.5

a Available as a poster.[4]

b The range of MIC values is shown when the number of MICs is <10.

c 3517 strains of *C. albicans* and 1192 strains of *C. glabrata* were tested against AMB.

AMB = amphotericin B; **FLC** = fluconazole; **ITC** = itraconazole; **MIC** = minimal inhibitory concentration; **MIC_{90}** = MIC at which the growth of 90% of isolates was inhibited; **VRC** = voriconazole.

● Posaconazole prolonged survival and reduced the fungal tissue burden in immunosuppressed mice infected with *Mucor* spp.[43] However, it had variable activity in zygomycosis in a second murine study, showing a dose-response effect against *Rhizopus microsporus*, partial activity against *R. corymbifera* and no activity against *R. oryzae*.[44]

● In mice infected with *A. fumigatus* or *A. flavus*, combination therapy with posaconazole and caspofungin was associated with greater survival than monotherapy with one or both drugs in 74% of cases.[5] No antagonism was seen between the two antifungal agents.

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• There did not appear to be significant antagonism between posaconazole and amphotericin B in murine models of *A. flavus* infection,[45] *C. neoformans* infection[46] or systemic *C. albicans* infection.[47]

2. Pharmacokinetic Profile

This section provides a brief overview of the pharmacokinetic properties of posaconazole, focusing on the dosage most commonly used in clinical trials (800 mg/day) where possible. Unless stated otherwise, studies were conducted in healthy volunteers (n = 8–64)[48-60] and posaconazole was administered as an oral suspension. Several studies are available only as abstracts and/or posters.[52,53,55-59,61-66]

Absorption and Distribution

• Administration of single-dose posaconazole 50–800mg to healthy volunteers resulted in a dose-proportional increase in plasma concentrations of the drug.[48] No further increase in plasma concentrations was seen with posaconazole doses above 800mg.

• Following administration of posaconazole 400mg twice daily, mean maximum plasma concentration (C_{max}) values on day 14 were 4150 ng/mL after the first dose and 3239 ng/mL after the second dose, with mean times to C_{max} of 5 and 9 hours.[48] The mean area under the plasma concentration-time curve from 0–12 hours (AUC_{12}) was 39 206 ng • h/mL and the $AUC_{12–24}$ was 33 899 ng • h/mL. Steady-state plasma posaconazole concentrations were reached by day 10.

• Exposure following a single dose of posaconazole 200mg increased when the drug was administered as a suspension rather than a tablet, and in the fed rather than the fasted state.[50] The mean posaconazole AUC_{72} increased by 37% with the suspension versus the tablet formulation, and was 4- and 2.6-fold higher when the suspension was administered with a high-fat or nonfat meal versus the fasting state.

• Administering posaconazole in divided doses significantly ($p < 0.0001$) increased its oral bioavailability.[49] Compared with a single dose, the relative bioavailability of posaconazole 800mg increased by 98% when it was administered in two divided doses 12 hours apart and by 220% when it was administered in four divided doses 6 hours apart, in the fasted state.

• The pharmacokinetics of posaconazole in patients with invasive fungal infections may differ to those in healthy volunteers.[64] For example, an ≈3-fold higher mean AUC_{12} for posaconazole has been reported in healthy volunteers versus patients (29 500 vs 8620 ng • h/mL).

• Posaconazole has a large volume of distribution (486L)[48] and is highly protein bound (>95%).[67]

Metabolism and Elimination

• Metabolism plays only a minor role in the elimination of posaconazole.[51] Most of the detected metabolites were glucuronide conjugates, suggesting that posaconazole metabolism is mainly mediated via UDP-glucuronosyltransferase (UGT) enzyme pathways.[51] Indeed, an *in vitro* study found that the formation of posaconazole metabolites in human liver microsomes was mediated by the enzyme UGT1A4.[68]

• Following administration of a single radiolabelled dose of posaconazole 400mg, the majority of the radioactivity (77%) was recovered in faeces, with 14% recovered in urine.[51] Unchanged posaconazole was present in only trace amounts in the urine, whereas the parent drug accounted for ≈66% of the dose in the faeces.[51]

• The mean total body clearance of posaconazole was 11.5 L/h, with a mean terminal elimination half-life of 31 hours.[48]

Special Patient Populations

• Mean plasma posaconazole concentrations were similar in young patients aged <18 years (n = 12) and adults aged 18–64 years (n = 194) [776 vs 817 ng/mL], according to results of a study in patients with invasive fungal infections.[61] All patients received oral posaconazole 800 mg/day, except for one patient in the younger group who received 400

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mg/day on the days that pharmacokinetic samples were collected.

- Age,[52,62] sex[52,62] and ethnicity[53,62] did not have clinically relevant effects on the pharmacokinetics of oral posaconazole in healthy volunteers[52,53] or patients with HIV infection (n = 46).[62] Moreover, renal[66] or hepatic[65] impairment did not have clinically significant effects on the pharmacokinetics of posaconazole (n = 18[66] and 12[65]), meaning that dosage adjustment is not needed in these patient groups.

Potential Drug Interactions

Unless stated otherwise, oral posaconazole 200 mg/day was administered in studies examining potential drug interactions.

- Posaconazole did not inhibit the CYP enzymes CYP1A2, CYP2C8/9, CYP2D6 or CYP2E1 following administration of the antifungal and a drug cocktail containing several probe substrates.[54] However, the AUC for midazolam was almost 2-fold higher after coadministration with posaconazole, compared with midazolam alone, indicating inhibition of CYP3A4.
- Monitoring of tacrolimus[55] and ciclosporin[63] concentrations is recommended when posaconazole is administered in combination with these immunosuppressants (which are metabolised by CYP3A4). Coadministration of posaconazole 400mg twice daily significantly increased tacrolimus C_{max} and AUC_{∞} by 121% and 358% ($p = 0.001$ vs tacrolimus alone).[69] In addition, at steady-state, ciclosporin clearance decreased by 16–33% with concomitant posaconazole, necessitating a reduction in the ciclosporin dosage of 14–29% in three of four heart transplant patients.[63]
- Coadministration of posaconazole with phenytoin[56] or rifabutin[57] is not recommended (both are inducers of CYP3A4). Clinically significant increases in phenytoin exposure occurred with concomitant administration of posaconazole,[56] and coadministration of posaconazole and rifabutin resulted in a 2-fold increase in posaconazole clearance with reductions in posaconazole C_{max} and AUC during the dosing interval (AUC_{τ}) of 57% and 51%, and increases in rifabutin C_{max} and AUC_{τ} of 31% and 72%.[57]
- Concomitant administration of cimetidine (an inducer of CYP enzymes) decreased the C_{max} and AUC_{τ} of posaconazole by ≈40%, compared with posaconazole alone.[58]
- Coadministration of posaconazole 800 mg/day and glipizide did not result in any clinically significant pharmacokinetic interaction.[59] Similarly, there was no clinically significant interaction between a single dose of posaconazole 200mg and an aluminium/magnesium-containing antacid, under both fasting and nonfasting conditions.[60]

3. Therapeutic Efficacy

Invasive Fungal Infections

The efficacy of oral posaconazole suspension in patients with proven or probable invasive fungal infections who were intolerant of, or refractory to, other antifungal therapy has been examined in a large, open-label, multicentre, phase III study.[70] In this study, 330 patients received posaconazole 800 mg/day (in divided doses) as an oral suspension for an initial period of up to 12 months, with an additional 279 patients serving as the external control group; the majority of patients (86%) were refractory to prior therapy (mainly amphotericin B).[70] All study data were reviewed by an external blinded data review committee who determined eligibility and global response.[70]

The primary endpoint was the global response rate (based on clinical, mycological and radiological data) at the end-of-therapy (EOT) visit.[70] Success was defined as a complete response (resolution of attributable symptoms, signs and radiographic or bronchoscopic abnormalities) or a partial response (clinically meaningful improvement in attributable symptoms, signs and radiographic or bronchoscopic abnormalities).[70] The modified intent-to-treat (ITT) analysis included 238 posaconazole recipients and 218 patients from the external control group.[70]

Among patients receiving posaconazole and those acting as controls, 45% and 40% were infected

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with *Aspergillus*, 10% and 14% were infected with *Candida*, 8% and 2% were infected with *Fusarium*, 13% and 29% were infected with *Cryptococcus*, 5% and 4% were infected with zygomycetes, 5% and 0.5% were infected with other filamentous fungi, 16% and 12% had endemic infections, and 4% and 1% were infected with multiple organisms.[69] Several subgroup analyses of trial data are also available and are briefly discussed.[71-79]

The results of an open-label phase II[80] and a pilot[81] trial are also discussed. The multicentre, phase II study included patients with proven, probable or possible refractory invasive fungal infections (n = 21 evaluable patients) or febrile neutropenia (n = 53) [results in the latter group of patients are discussed in the next section].[80] Patients were randomised to one of three treatment regimens: oral posaconazole suspension 200mg four times daily for 2 days followed by 400mg twice daily; 400mg four times daily for 2 days followed by 600mg twice daily; or 800mg twice daily for 2 days followed by 800mg once daily.[80] The single-centre pilot study included patients with chronic granulomatous disease and invasive filamentous fungal infection; seven patients had proven invasive fungal infections and one had possible fungal pneumonia.[81] Of the seven patients with proven invasive fungal infections, six had pneumonia (isolated pathogens included *A. fumigatus* [n = 2], *Phaeoacremonium parasiticum* [n = 2], *Paecilomyces variotii* [n = 1] and *Scedosporium apiospermum* [n = 1]), and one had cervical adenitis confirmed by histopathology. Six patients were refractory to voriconazole and one was intolerant of voriconazole. Patients received salvage therapy with oral posaconazole suspension 400mg twice daily (n = 7; duration of therapy 4–19 months) or 200mg three times daily (n = 1; duration of therapy 6 months).[81]

An additional retrospective analysis compared the use of posaconazole as salvage therapy in patients with haematological malignancy and definite or probable invasive aspergillosis (n = 46) with that of liposomal amphotericin B plus caspofungin (n = 42) [drug dosages not reported].[82]

Except for one fully published study,[81] all data are available as abstracts and/or posters.[70-80,82,83]

Phase III Trial

- Oral posaconazole 800 mg/day demonstrated clinically relevant activity against a range of fungi in patients with invasive fungal infections who were refractory to, or intolerant of, other antifungal therapy in the phase III study.[70]
- In patients with aspergillosis, the global response success rate at the EOT visit was significantly higher in posaconazole recipients than in the control group (42% vs 26%; p = 0.006), with a corresponding odds ratio of 4.06 (95% CI 1.5, 11.04) [107 posaconazole recipients and 86 patients assigned to the control group comprised the modified ITT population].[70] Kaplan-Meier analysis showed a significant survival benefit in posaconazole recipients (p < 0.001 vs controls).[83] Six posaconazole recipients had invasive aspergillosis refractory to voriconazole; a successful outcome was seen in three of these patients (50%) after 152–585 days' treatment.[76]
- When analysed according to the infecting *Aspergillus* spp., a successful outcome occurred in 12 of 29 posaconazole recipients (41%) versus 12 of 34 controls (35%) infected with *A. fumigatus*, in 10 of 19 posaconazole recipients (53%) versus 3 of 16 controls (19%) infected with *A. flavus*, in 4 of 14 posaconazole recipients (29%) versus 2 of 13 controls (15%) infected with *A. terreus* and in three of five posaconazole recipients (60%) versus two of seven controls (29%) infected with *A. niger*.[70]
- Posaconazole was associated with overall success rates of 54% in patients with zygomycosis, 46% in patients with fusariosis (11 of 24 patients), 43% in patients infected with *Pseudallescheria* (3 of 7 patients), 80% in patients with phaeohyphomycosis (4 of 5 patients) and 100% in patients with histoplasmosis (7 of 7 patients).[70] One of the patients with histoplasmosis who responded to posaconazole had been refractory to treatment with voriconazole.[76]
- Success rates with posaconazole 800 mg/day were 48% in patients with refractory candidiasis (11 of 23 patients), 69% in patients with refractory coccidioidomycosis (11 of 16 patients), 48% in pa-

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tients with refractory *Cryptococcus* infection (15 of 31 patients) and 82% in patients with refractory chromoblastomycosis or mycetoma (9 of 11 patients).[70]

Additional Trials and Analyses

- The results of the phase III study[70] confirm the findings of earlier studies[80,81] in patients with invasive fungal infections. In the phase II study, the overall clinical success rate was 43% (9 of 21 patients), with a clinical success rate of 56% (5 of 9 patients) in those receiving maintenance therapy with posaconazole 400mg twice daily.[80] Success rates were 20% (2 of 10 patients) in aspergillosis, 100% (2 of 2 patients) in fusariosis, and 33% (1 of 3 patients) in zygomycosis.[80]
- A complete response occurred in seven of the eight patients (88%) with chronic granulomatous disease and invasive filamentous fungal infection who received posaconazole 600–800 mg/day in the pilot study.[81]
- Several small subgroup analyses of trial data also yielded similar results to those seen in the large phase III study.[71-73,77,79] Some of the patients summarised in the subgroup analyses were part of the phase III trial, whereas others were patients treated outside of that protocol. Salvage therapy with posaconazole 800 mg/day resulted in success rates of 45% (9 of 20 patients) in fusariosis,[79] 65% (17 of 26 patients) in zygomycosis,[72] 67% (4 of 6 patients) in coccidioidomycosis,[71] 86% (6 of 7 patients) in histoplasmosis[73] and 83% (5 of 6 patients) in chromoblastomycosis.[77] A successful outcome was seen in four of seven patients (57%) with mycetoma after the initial course of posaconazole, with a further two patients responding to retreatment.[77]
- Posaconazole was associated with a success rate of 74% in elderly patients (aged ≥65 years) with proven or probable invasive fungal infections (n = 31).[78] In this subgroup analysis of the phase III trial, 19 of 25 patients (76%) who were intolerant of or refractory to other antifungal therapy experienced treatment success.
- Posaconazole has potential in the treatment of fungal CNS infections.[74,75] In patients with such infections (most of whom were refractory to, or intolerant of, other antifungal therapy), therapy with posaconazole 800 mg/day was associated with a success rate of 50% (5 of 10 patients) in CNS infections due to organisms other than *Cryptococcus* (successful against *Aspergillus* spp., *Histoplasma capsulatum*, *S. apiospermum*, *Ramichloridium mackenziei* and *Coccidioides* spp.)[75] and 59% (23 of 39 patients) in patients with HIV-related cryptococcal meningitis.[74]
- Salvage therapy with posaconazole had similar efficacy to liposomal amphotericin B plus caspofungin in patients with invasive aspergillosis associated with haematological malignancy.[82] The response rate was 37% with posaconazole versus 21% with liposomal amphotericin B plus caspofungin.[82] Significantly fewer posaconazole than liposomal amphotericin B plus caspofungin recipients required admission to the intensive care unit (20% vs 50%; $p < 0.01$) or mechanical ventilation (9% vs 41%; $p < 0.01$).[82]
- Numerous case reports (some only available as abstracts or posters)[84-94] have also described the efficacy of posaconazole in invasive fungal infections caused by various organisms (e.g. *Absidia* spp.,[84] *Acremonium strictum*,[95] *Aspergillus* spp.,[85,86,96] *Alternaria* spp.,[87] *C. glabrata*,[88] *C. immitis*,[89] *Exophiala spinifera*,[97] *Fusarium* spp.,[90,98,99] *Mucor* spp.,[91-93] *R. mackenziei*,[100] *Rhizopus* spp.[85,94,101] and *S. apiospermum*[102]).

Febrile Neutropenia

As previously mentioned, the phase II trial included patients with febrile neutropenia (53 evaluable patients) as well as patients with refractory invasive fungal infections.[80]

- Oral posaconazole suspension shows potential in the empirical treatment of patients with febrile neutropenia.[80] The overall success rate at the EOT visit was 77% (41 of 53 patients), with 14 of 19 patients (74%) who received maintenance therapy with posaconazole 400mg twice daily achieving success.[80] Seven days after the end of treatment, the success rate was 81% (38 of 47 patients) in the overall population and 76% (13 of 17 patients) in recipients of posaconazole 400mg twice daily.

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● Resolution of fever and neutropenia occurred in 86% (25 of 29 patients) and 67% (40 of 60 patients) of patients in the overall population.[80] Among patients who received maintenance therapy with posaconazole 400mg twice daily, resolution of fever occurred in 92% (11 of 12 patients) and resolution of neutropenia occurred in 64% (14 of 22 patients) of patients.

Oropharyngeal and Oesophageal Candidiasis

A noncomparative, multicentre, phase III study examined the efficacy of oral posaconazole suspension in 199 patients with advanced HIV infection who had azole-refractory oropharyngeal and/or oesophageal candidiasis.[103] Patients were aged ≥18 years and had microbiological resistance, or had not responded clinically, to fluconazole and/or itraconazole. Patients received an oral suspension of posaconazole 400mg twice daily for 28 days or 400mg twice daily for 3 days followed by 400 mg/day for 25 days. The primary endpoint was the clinical response rate at 4 weeks. Clinical response was defined as cure (absence of plaques and ulcers and no, or minimal, symptoms) or improvement (partial resolution of signs and symptoms).

● At day 29, posaconazole therapy resulted in a clinical response in 132 of 176 patients (75%) in the modified ITT population.[103] A clinical response occurred in 67 of 92 patients (73%) with fluconazole-resistant infection, in 34 of 46 patients (74%) with itraconazole-resistant infection, and in 32 of 44 patients (73%) with infections resistant to both fluconazole and itraconazole.

● In addition, negative cultures were obtained in 46 of the 126 posaconazole recipients in whom mycological assessment was performed (37%).[103] Mycological response occurred in 47 of 117 patients (40%) infected with *C. albicans* and in 18 of 36 patients (50%) infected with other *Candida* spp.

● Several case reports (available as posters) have also described the efficacy of posaconazole in patients with refractory oropharyngeal candidiasis[104] or chronic refractory oesophageal candidiasis[105,106] associated with *C. albicans*[104-106] and *C. glabrata*.[106]

4. Tolerability

Data concerning the tolerability of oral posaconazole suspension in patients with invasive fungal infections or oropharyngeal and/or oesophageal candidiasis are available from the phase III trials discussed in section 3,[70,103] and a related tolerability analysis.[107] A pooled analysis of healthy volunteer studies (449 posaconazole recipients and 48 placebo recipients) was conducted to examine the tolerability of posaconazole 50–1200mg in a population without the confounding factors of underlying serious illness or concomitant drugs.[108] Moreover, the effect of posaconazole on the corrected QT (QTc) interval in healthy volunteers (173 posaconazole recipients and 16 placebo recipients) is also discussed.[64]

● Oral posaconazole was generally well tolerated in patients with invasive fungal infections.[107] In the phase III trial, the most commonly reported treatment-related adverse events in the overall study population (n = 330) included nausea (9% of posaconazole recipients), vomiting (6%), abdominal pain (5%), headache (5%) and diarrhoea, elevated ALT or AST levels and rash (3% each).[107] The adverse event profile (i.e. type and incidence of treatment-related adverse events) in patients receiving posaconazole for ≥6 months (n = 102; figure 1) was similar to that reported in the overall study group.[107]

● Among patients treated for ≥6 months, 19 serious treatment-related adverse events were reported in 12 of 102 posaconazole recipients.[107] Serious treatment-related adverse events included adrenal insufficiency, nausea/vomiting, nephrotoxicity and QTc-interval prolongation. Altered drug concentrations (e.g. increased tacrolimus, ciclosporin or digitalis concentrations) were reported in four posaconazole recipients, and necessitated interruption of posaconazole therapy in two patients. However, discontinuation because of a serious treatment-related adverse event occurred in only one patient (relapsed oesophageal candidiasis).

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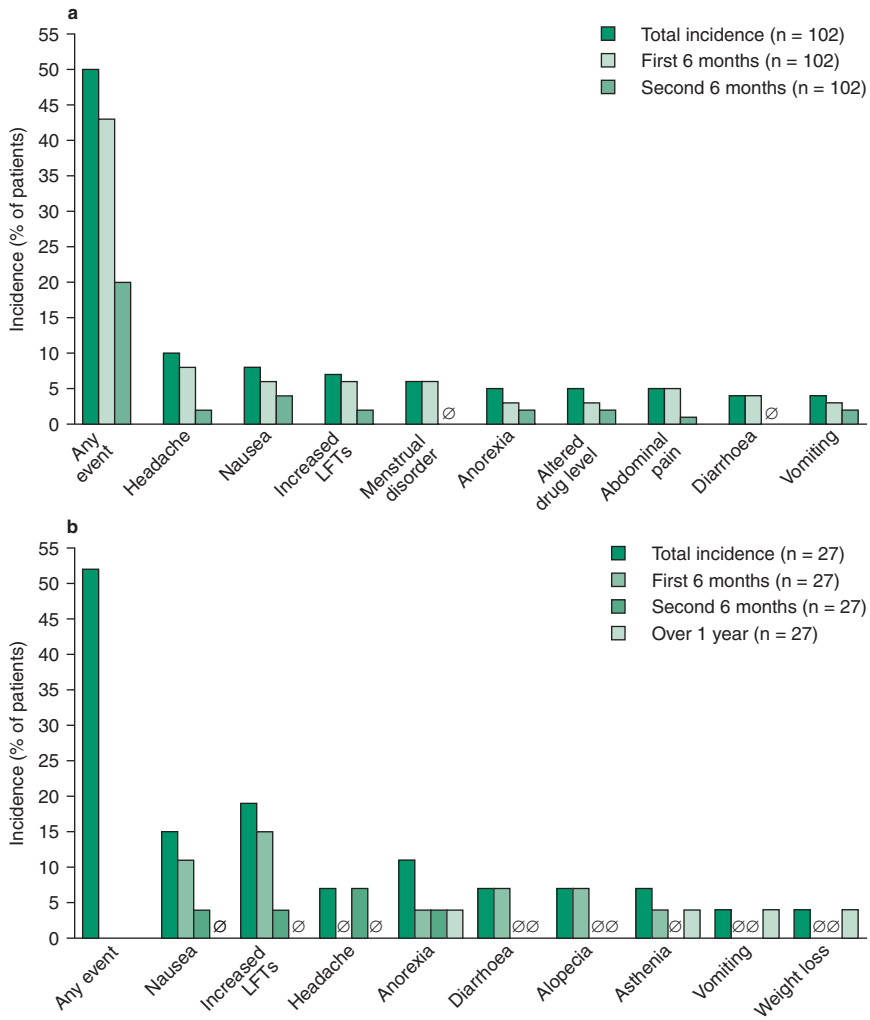

Fig. 1. Emergence of treatment-related adverse events in patients receiving posaconazole (POS). Results of an open-label, multicentre, phase III study in patients with invasive fungal infections who were refractory to, or intolerant of, other antifungal therapy and received oral POS 800 mg/day (in divided doses) [n = 330].[107] Figure shows (**a**) the incidence of treatment-related adverse events (occurring in ≥4% of patients) throughout the course of POS therapy and during the first and second 6 months of POS therapy in patients receiving POS for ≥6 months (n = 102) and (**b**) the incidence of treatment-related adverse events (occurring in >2 patients overall or in any patient reporting a new event after 1 year of POS) throughout the course of POS therapy, during the first or second 6 months of POS therapy and after the first year of POS therapy in patients receiving POS for ≥1 year (n = 27). **LFTs** = liver function tests.

● The incidence of treatment-related adverse events in patients who received posaconazole for ≥1 year is also shown in figure 1.[107] It should be noted that this analysis included only a small number of patients (n = 27).

● Posaconazole was generally well tolerated in elderly patients (aged ≥65 years) with invasive fungal infections, according to the results of a subgroup analysis[78] of the phase III trial.[70] The tolerability profile of posaconazole in elderly patients was similar to that seen in the overall study population.

● The most commonly occurring treatment-related adverse events in patients with HIV infection and azole-refractory oropharyngeal and/or oesophageal

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candidiasis included diarrhoea (11% of posaconazole recipients), neutropenia (7%), flatulence (6%), nausea (6%) and abdominal pain, headache and vomiting (5% each).[103]

- In healthy volunteers, treatment-related adverse events were reported in 44% of posaconazole recipients and 33% of placebo recipients.[108] Treatment-related adverse events occurred in the following body systems/organ classes: CNS and peripheral nervous system (9% of posaconazole recipients vs 8% of placebo recipients); gastrointestinal (18% vs 2%); infections and infestations (1% vs 0%); musculoskeletal (7% vs 0%); respiratory (2% vs 2%); and skin and subcutaneous tissues (6% vs 4%).
- Posaconazole 400mg twice daily was not associated with any clinically significant cardiovascular adverse effects in healthy volunteers.[64] A mean reduction from baseline in the QTc (Fridericia) interval of 5.6 msec occurred with posaconazole versus 3.2 msec with placebo.[64]
- As of October 2004, >2200 individuals have received oral posaconazole, with >1000 individuals receiving a posaconazole dosage of ≥800 mg/day.[70] No visual abnormalities and only mild-to-moderate abnormalities in liver function tests (even with maximal posaconazole exposure) have been reported.[70,107]

5. Dosage and Administration

In clinical trials in patients with invasive fungal infections, oral posaconazole suspension was generally administered at a dosage of 800 mg/day (in divided doses) with food.[70] Formal prescribing information is not yet available.

6. Posaconazole: Current Status

Posaconazole is awaiting approval in the US and the EU. Posaconazole, administered as an oral suspension, demonstrates clinically relevant activity against a range of fungi in patients with invasive fungal infections (including aspergillosis, zygomycosis and fusariosis) who are refractory to, or intolerant of, other antifungal therapy. The drug also demonstrates efficacy in patients with azole-refractory oropharyngeal and oesophageal candidiasis, and febrile neutropenia. Posaconazole is generally well tolerated.

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