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In Vitro Activity of a New Oral Triazole, BMS-207147 (ER-30346)

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The antifungal activity of BMS-207147 (also known as ER-30346) was compared to those of itraconazole and fluconazole against 250 strains of fungi representing 44 fungal species. MICs were determined by using the National Committee for Clinical Laboratory Standards (NCCLS)-recommended broth macrodilution method for yeasts, which was modified for filamentous fungi. BMS-207147 was about two- to fourfold more potent than itraconazole and about 40-fold more active than fluconazole against yeasts. With the NCCLS-recommended resistant MIC breakpoints of ≥1 μg/ml for itraconazole and of ≥64 μg/ml for fluconazole against *Candida* spp., itraconazole and fluconazole were inactive against strains of *Candida krusei* and *Candida tropicalis*. In contrast, all but 9 (all *C. tropicalis*) of the 116 *Candida* strains tested had BMS-207147 MICs of <1 μg/ml. The three triazoles were active against about half of the *Candida glabrata* strains and against all of the *Cryptococcus neoformans* strains tested. The three triazoles were fungistatic to most yeast species, except for BMS-207147 and itraconazole, which were fungicidal to cryptococci. BMS-207147 and itraconazole were inhibitory to most aspergilli, and against half of the isolates, the activity was cidal. BMS-207147 and itraconazole were active, though not cidal, against most hyaline *Hyphomycetes* (with the exception of *Fusarium* spp. and *Pseudallescheria boydii*), dermatophytes, and the dematiaceous fungi and inactive against *Sporothrix schenckii* and zygomycetes. Fluconazole, on the other hand, was inactive against most filamentous fungi with the exception of dermatophytes other than *Microsporum gypseum*. Thus, the spectrum and potency of BMS-207147 indicate that it should be a candidate for clinical development.

In the past two decades, the number of immunocompromised patients has increased significantly. Immunocompromised patients include patients with neoplasm on chemotherapy, organ transplant recipients on immunosuppressive therapy, and patients infected with human immunodeficiency virus (HIV). More than 95% of HIV-infected individuals suffer from oropharyngeal candidiasis (OPC) (7). Since its introduction, fluconazole (FLU) has been used extensively for the treatment of OPC. Though *Candida albicans* remains the most prevalent fungal pathogen causing human disease, other *Candida* spp. (such as *C. krusei*, *C. tropicalis*, and *C. glabrata*) have increased in frequency as causative agents of candidiasis. The increased isolation of *C. krusei* in patients on FLU therapy is likely due to its intrinsic resistance to FLU.

The only other triazole marketed for systemic fungal infections is itraconazole (ITR). Unlike FLU, the antifungal spectrum of ITR includes some strains of *C. krusei*, *C. glabrata*, *Aspergillus* spp., and other filamentous fungi. While both triazoles are generally fungistatic to yeasts, ITR is fungicidal to many strains of aspergilli. Nonetheless, aspergillosis infections treated with ITR fail in 20 to 40% of cases (1, 8).

The widespread use of triazoles in systemic fungal infections is due to their broad spectrum and improved safety profile compared to those of other marketed antifungal drugs. In this study, we report on the in vitro antifungal and fungicidal activities of the new triazole BMS-207147 (BMS). This triazole, also known as ER-30346, has been evaluated previously by Eisai Co. on 90 to 100 strains of yeasts and aspergilli using either SAAM-F (synthetic amino acid medium, fungal agar), SDA (Sabouraud dextrose agar) or the microbroth method recommended by the National Committee for Clinical Laboratory Standards (NCCLS) (4, 5). In the current study, 250 fungal strains representing 44 species were tested for their sensitivities to BMS, ITR, FLU, and amphotericin B (AMB) by the NCCLS-approved macrobroth susceptibility testing method for yeasts and modified for filamentous fungi.

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MATERIALS AND METHODS

Test organisms. A total of 250 strains from 44 fungal species were used in this study. Almost all (more than 95%) of the strains were clinical isolates; the rest were obtained from the American Type Culture Collection (Rockville, Md.).

Antifungal susceptibility test methods. All isolates (except *Malassezia furfur*) were tested by the reference broth macrodilution method outlined by the NCCLS (6) and modified for antifungal testing of filamentous fungi (2). BMS was obtained from Eisai Co., FLU was from Pfizer, ITR was from Janssen Pharmaceutica, and AMB was from Bristol-Myers Squibb Co.

The interpretative MIC breakpoints for FLU and ITR are obtained from the NCCLS guidelines (6); these breakpoints were meant as interpretative guidelines for *Candida* spp. The NCCLS-recommended breakpoints for FLU are as follows: ≤8 μg/ml, susceptible; 16 to 32 μg/ml, susceptible-dose dependent (S-DD); and ≥64 μg/ml, resistant. For ITR, the NCCLS-recommended MIC breakpoints as follows: ≤0.13 μg/ml, susceptible; 0.25 to 0.5 μg/ml, S-DD; and ≥1 μg/ml, resistant. At this point, no interpretative MIC breakpoints for BMS have been established. For the purpose of discussion of the MIC results in this report, we will use the ITR interpretative breakpoints for BMS, given that both compounds achieve the same peak levels in plasma in dogs (4). As for AMB, no interpretative MIC breakpoints have been recommended by the NCCLS, though *Candida* isolates with AMB MICs of >1 μg/ml appear resistant in animal models (8). Thus, AMB resistance will be defined in this study as AMB MICs of ≥2 μg/ml when the NCCLS RPMI 1640 method is used.

Broth macrodilution for yeasts was performed according to the guidelines of the NCCLS (6) and modified for filamentous fungi by the method of Espinel-Ingroff and Kerkering (2). The agar dilution method used for *Malassezia furfur* was described previously (3).

The MIC endpoints by the broth macrodilution method were determined as recommended by the NCCLS (6). AMB MICs were defined as the lowest drug concentrations which inhibited all visible growth (i.e., 100% inhibition). FLU, ITR, and BMS MICs were defined as the lowest drug concentrations which inhibited 80% of the growth in the growth control tube (as determined by comparison with a 1:5 dilution of the growth control), except with *Malassezia furfur*, where 100% growth inhibition was the endpoint.

TABLE 1. Comparative in vitro activities of triazoles and AMB

Organism (no. of isolates)	MIC (μg/ml)											
	BMS			ITR			FLU			AMB		
	Range	50%	90%	Range	50%	90%	Range	50%	90%	Range	50%	90%
Candida albicans (34)	0.002–0.5	0.008	0.03	0.008–0.25	0.03	0.13	0.25–16	0.5	1	0.25–1	0.5	0.5
Candida tropicalis (34)	0.008–>16	0.12	>16	0.03–>16	0.12	>16	≤0.13–>64	1	>64	≤0.03–1	0.25	0.5
Candida krusei (16)	0.13–0.5	0.5	0.5	0.25–1	0.5	1	8–>64	32	64	0.5–1	1	1
Candida parapsilosis (11)	≤0.008–0.25	0.03	0.06	0.06–0.25	0.06	0.13	0.5–8	1	2	0.12–0.5	0.25	0.25
Candida kefyr (9)	≤0.008			≤0.008–0.06			0.25–1			0.06–1		
Candida stellatoidea (7)	≤0.008–0.015			≤0.008–0.03			≤0.13–0.25			0.06–0.12		
Candida glabrata (16)	0.12–>16	1	16	0.25–>16	1	>16	1–>64	32	>64	0.12–1	0.25	1
Cryptococcus neoformans (32)	≤0.001–0.03	0.008	0.016	≤0.001–0.06	0.008	0.008	≤0.12–8	1	2	≤0.03–0.25	0.12	0.25
Trichophyton spp. (13)[a]	≤0.008–0.13	0.06	0.06	≤0.008–0.13	0.03	0.13	0.25–32	2	16	0.25–1	0.5	1
Malassezia furfur (8)[b]	0.015–0.03			0.06–0.25			1–16			0.25–2		
Aspergillus spp. (16)[c]	0.06–2	0.25	1	0.06–1	0.25	0.5	>64			0.25–2	0.5	1
Pseudallescheria boydii (6)	0.03–>16			0.5–>16			2–>128			1–8		

[a] *Trichophyton* spp. were represented by four strains each of *T. rubrum* and *T. mentagrophytes*, three strains of *T. tonsurans*, and two strains of *T. verrucosum*.
[b] Antimycotic testing of *M. furfur* was done on SDA containing 2% olive oil, and an inoculum size of 3×10^3 CFU per spot was used. Plates were incubated at 30°C for 5 days. MIC endpoints, including those for triazoles, were the lowest drug concentrations inhibiting all (100%) growth.
[c] *Aspergillus* spp. were represented by six strains of *A. fumigatus*, five strains of *A. flavus*, four strains of *A. niger*, and one strain of *A. nidulans.*

MFCs. Minimum fungicidal concentrations (MFCs) were determined by subculturing 0.1 ml from each tube with no visible growth in the MIC broth macrodilution series onto drug-free SDA plates, as previously described (3). Colony counts were determined, and the MFCs were defined in accordance with the level of decrease in the number of CFU per milliliter, i.e., MFC_{99} means a 99% reduction in the number of CFU of the final inoculum size per milliliter, MFC_{95} means a 95% reduction, and MFC_{90} means a 90% reduction.

RESULTS

Comparative in vitro antifungal spectra of BMS, ITR, and FLU. Of the 116 *Candida* strains tested, all but 9 strains of *C. tropicalis* were susceptible to BMS at MICs of ≤0.5 μg/ml (Table 1). Likewise, eight strains of *C. tropicalis* and four strains of *C. krusei* were resistant to ITR (MICs of ≥1 μg/ml) compared to eight *C. tropicalis* and six *C. krusei* strains being resistant to FLU (MICs of ≥64 μg/ml). Based on MIC_{90}s, only *C. tropicalis* strains were considered resistant to BMS, whereas *C. tropicalis* and *C. krusei* were resistant to ITR and FLU. Nonetheless, whereas the MIC_{90}s of BMS to *C. albicans* and *Candida parapsilosis* were 0.03 to 0.06 μg/ml, the BMS MIC_{90} for *C. krusei* was 10-fold higher (at 0.5 μg/ml). This suggests that while BMS was active against *C. krusei*, it was intrinsically less active against this species. *C. krusei* is considered intrinsically resistant to FLU. All of the yeast strains tested were susceptible to AMB.

TABLE 2. MICs of triazoles and AMB for species represented by five or fewer clinical isolates each

Organism	MICs (μg/ml) for individual isolates[a]			
	BMS	ITR	FLU	AMB
Candida guilliermondii	0.015, 0.06	0.13, 0.25	2_2	0.13_2
Candida lusitaniae	0.004_2, 0.008	0.03_2, 0.06	≤0.13, 0.25, 0.5	$0.13, 0.25_2$
Rhodotorula spp.	0.25, 2	4, >16	$>64_2$	0.25, 0.5
Trichosporon beigelii	≤0.008, 0.13	0.015, 0.06	≤0.13, 4	0.06, 1
Microsporum canis	$≤0.008_3$, 0.03	$≤0.008_3$, 0.06	$0.5, 4_3$	$0.13, 0.25, 0.5_2$
Microsporum gypseum	$0.015, 0.03_2$, 0.06	$0.03, 0.06_3$	$32_2, >64_2$	$0.5_2, 1_2$
Epidermophyton floccosum	$0.015, 0.03_3$	$≤0.008_2, 0.015_2$	$1, 2_2, 4$	$0.06_2, 0.13_2$
Acremonium strictum	0.06	0.25	8	1
Fusarium spp.	$2, >16_3$	$>16_4$	$>64_4$	$0.5, 1_2, 2$
Paecilomyces variotii	0.03, 0.06, 0.25	$≤0.008_3$	16_2, 64	$0.06, 0.13_2$
Penicillium spp.	≤0.008	≤0.008	4	0.13
Alternaria spp.	1, 2	0.13, 0.25	32, >128	0.5_2
Curvularia spp.	1, 2	0.25, 0.5	8, 32	0.13, 0.5
Cladosporum carrionii	0.13	0.13	8	4
Exophiala jeanselmei	0.25	0.13	>64	0.5
Exserohilum mcginnisii	0.06	0.03	16	0.5
Fonsecaea pedrosoi	$0.015, 0.13_2$	$0.015, 0.13_2$	16, 32, 64	$2, 4_2$
Phialophora verrucosa	0.06, 0.13	0.015, 0.06	32, 64	1, 2
Rhinocladiella atrovirens	0.06	0.06	16	1
Sporothrix schenckii	1, 2, 4	0.5, 1, 2	$64, >64_2$	1_3
Mucor spp.	8	4	>64	0.25
Rhizopus strain	1	1	>64	0.5
Absidia strain	1	0.5	>64	0.5

[a] The subscript numbers indicate the number of isolates for which the MIC was as indicated.

TABLE 3. Fungicidal activities of triazoles and AMB for yeast strains

Organism	Drug	MIC (μg/ml)	MFC_{99} (μg/ml)
Candida albicans A28235	BMS	≤0.007	>16
	ITR	0.03	>16
	FLU	0.25	>128
	AMB	0.25	0.5
Candida albicans A28200	BMS	≤0.007	>16
	ITR	0.015	>16
	FLU	0.25	>128
	AMB	0.25	0.5
Candida tropicalis A26003	BMS	0.25	16
	ITR	0.25	>16
	FLU	1	>128
	AMB	0.25	0.5
Candida krusei A25819	BMS	0.06	16
	ITR	0.06	16
	FLU	32	64
	AMB	0.5	0.5
Candida lusitaniae A25882	BMS	≤0.007	>16
	ITR	0.015	>16
	FLU	0.13	1
	AMB	1	1
Candida glabrata A25989	BMS	0.12	>16
	ITR	0.25	>16
	FLU	16	>128
	AMB	0.5	0.5
Cryptococcus neoformans A28201	BMS	0.015	4 (MIC_{95} = 0.25)
	ITR	≤0.007	4 (MIC_{95} = 0.25)
	FLU	1	>128 (MIC_{95} > 128)
	AMB	0.25	0.5
Cryptococcus neoformans A25838	BMS	0.06	0.5
	ITR	0.06	0.25
	FLU	1	>128 (MFC_{95} > 128)
	AMB	0.13	0.25
Cryptococcus neoformans A26037	BMS	0.008	0.06 (MFC_{95} = 0.06)
	ITR	0.008	>2 (MFC_{95} > 2)
Cryptococcus SC15116	BMS	0.002	1 (MFC_{95} = 1)
	ITR	0.002	1 (MFC_{95} = 0.5)

Another yeast species often resistant to FLU is *C. glabrata*. Of the 16 *C. glabrata* strains tested, 9 (or 56%) have FLU MICs of <64 μg/ml (Table 1). Compared to other yeast species, BMS and ITR were also less active against *C. glabrata*; 44 and 38% of the *C. glabrata* strains tested had BMS and ITR MICs of <1 μg/ml, respectively.

All 32 *C. neoformans* strains tested were susceptible to the three azoles, as were the two *Trichosporon beigelii* strains (Tables 1 and 2). While one of the two *Rhodotorula* strains was susceptible to BMS, they were both less susceptible to ITR and FLU than to BMS (Table 2).

TABLE 4. Antifungal activities of triazoles and AMB against *Aspergillus* spp.

Organism	Drug	MIC (μg/ml)	MFC_{99} (μg/ml)	MFC_{95} (μg/ml)	MFC_{90} (μg/ml)
A. fumigatus					
SC2164	BMS	0.13	16	1	0.5
	FLU	>64			
	ITR	0.25	16	1	0.5
	AMB	1	1		
A9381	BMS	0.13	16	1	0.5
	FLU	>128			
	ITR	0.13	1	0.5	0.5
	AMB	1	1		
A15054	BMS	0.13	>16	>16	>16
	FLU	>128			
	ITR	0.13	>16	>16	8
	AMB	0.5	0.5		
A25935	BMS	0.13	16	8	2
	FLU	>128			
	ITR	0.13	16	4	1
	AMB	1	1		
A. flavus					
A28339	BMS	0.5	2	2	2
	FLU	>128			
	ITR	0.25	0.5	0.5	0.5
	AMB	1	1		
A15197	BMS	0.5	1	1	1
	FLU	>128			
	ITR	0.25	0.5	0.25	0.25
	AMB	0.5	0.5		
A21323	BMS	0.13	1	0.5	0.25
	FLU	>16	>16	16	16
	ITR	0.06	0.5	0.25	0.25
	AMB	NT[a]			
A21437	BMS	0.25	1	1	0.5
	FLU	>16	>16	>16	>16
	ITR	0.5	0.5	0.25	0.25
	AMB	NT			
A27718	BMS	0.13	1	1	0.5
	FLU	>16	>16	>16	>16
	ITR	0.13	0.25	0.25	0.25
	AMB	NT			
A. niger					
SC2164	BMS	0.5	1	1	1
	FLU	>128			
	ITR	0.5	0.5	0.5	0.5
	AMB	0.25	0.25		
A25717	BMS	1	>16	8	8
	FLU	>128			
	ITR	0.5	>16	4	4
	AMB	0.13	0.25		
A22136	BMS	0.5	2	2	1
	FLU	>16	>16	>16	>16
	ITR	0.25	1	1	0.5
	AMB	NT			
A24199	BMS	0.25	1	0.5	0.5
	FLU	>16	>16	>16	>16
	ITR	0.25	1	1	1
	AMB	NT			
A. nidulans SC2385	BMS	0.06	1	0.25	0.25
	FLU	128			
	ITR	0.13	1	0.5	0.25
	AMB	0.5	0.5		

[a] NT, not tested.

TABLE 5. Fungicidal activities of triazoles and AMB against filamentous fungi other than *Aspergillus* spp.

Organism	Drug	MIC (μg/ml)	MFC_{99} (μg/ml)	MFC_{95} (μg/ml)	MFC_{90} (μg/ml)
Trichophyton rubrum A26761	BMS	0.13	>16	>16	>16
	FLU	2	>128	>128	>128
	ITR	0.25	>16	>16	>16
	AMB	0.5	0.25		
Trichophyton mentagrophytes A27979	BMS	0.03	>2	>2	>2
	FLU	2	>128	>128	>128
	ITR	0.06	>2	>2	>2
Microsporum gypseum A26835	BMS	0.13	>2	>2	>2
	FLU	128	>128	>128	>128
	ITR	0.5	>2	>2	>2
Epidermophyton floccosum A26765	BMS	0.03	>2	1	1
	FLU	4	>128	>128	>128
	ITR	0.06	0.5	0.5	0.5
Curvularia sp. strain SC8156	BMS	2	16	8	8
	FLU	8	>128	>128	>128
	ITR	0.5	>16	4	4
	AMB	0.5	32	16	16
Curvularia sp. strain SC2475	BMS	1	>16	>16	>16
	FLU	32	64		
	ITR	0.25	8	4	4
	AMB	0.13	4	1	1
Cladosporium carrionii ATCC 22864	BMS	0.13	>16	>16	>16
	FLU	8	>128	>128	>128
	ITR	0.13	>16	>16	>16
	AMB	4	>32	>32	4
Fonsecaea pedrosi A26042	BMS	0.13	>16	>16	>16
	FLU	64	>128		
	ITR	0.13	>32	32	8
	AMB	4	>16	>16	>16
Phialophora verrucosa ATCC 4806	BMS	0.06	4	4	4
	FLU	32	>128		
	ITR	0.06	0.5	0.5	0.5
	AMB	2	4		
Pseudallescheria boydii A25933	BMS	>16	>16	>16	>16
	FLU	>128	>128	>128	>128
	ITR	>16	>16	>16	>16
	AMB	8	>32	>32	>32
Sporothrix schenckii A25976	BMS	1	>16	>16	>16
	FLU	>128	>128		
	ITR	0.5	>16	>16	>16
	AMB	1	1		

Sixteen *Aspergillus* strains were tested. All but one strain each of *Aspergillus niger* and *Aspergillus fumigatus* had MICs of <1 μg/ml to BMS and ITR, respectively (Table 1). In contrast, all 16 strains of *Aspergillus* were resistant to FLU. BMS and ITR were active against other hyaline *Hyphomycetes* (*Acremonium strictum*, *Paecilomyces variotii*, and *Penicillium* sp.) but inactive (MICs >16 μg/ml) against *Fusarium* spp. and 4 of the 6 *Pseudallescheria boydii* strains (Tables 1 and 2). FLU MICs were ≥64 μg/ml for *Fusarium* spp., one of the four *P. variotii* strains, and one of the six *P. boydii* strains tested. AMB MICs that were ≥2 μg/ml were observed with one strain of *Fusarium* spp. and in five of the six strains of *P. boydii*.

The 25 dermatophytes were highly susceptible (MICs of ≤0.13 μg/ml) to BMS and ITR. The four dermatophytic strains with FLU MICs of ≥64 μg/ml belonged to the species *Microsporum gypseum.*

ITR MICs were ≤0.13 μg/ml against all of the dematiaceous fungi tested (Table 2). BMS, on the other hand, was less active than ITR against *Alternaria* and *Curvularia* spp., with MICs of 1 to 2 μg/ml. FLU MICs of ≥64 μg/ml were observed with strains of *Alternaria* spp., *Exophiala jeanselmei*, *Fonsecaea pedrosoi*, and *Phialophora verrucosa. Cladosporium carrionii*, *F. pedrosoi*, and *P. verrucosa* strains had AMB MICs of ≥2 μg/ml.

For the most part, BMS and ITR MICs of ≥1 μg/ml were

TABLE 6. MIC distribution of BMS and ITR strains to NCCLS-recommended quality control

Drug	Quality control strain	No. of tests with the following drug MIC (μg/ml)[a]:					
		0.5	0.25	0.13	0.06	0.03	0.015
BMS	*C. parapsilosis* ATCC 22019				[1	16	5]
	C. krusei ATCC 22492	[0	5	13]			
ITR	*C. parapsilosis* ATCC 22019		(2	5	16)	1	
	C. krusei ATCC 22492	(0	12	8)	1		

[a] Brackets represent proposed acceptable quality control range for BMS. Parentheses represent NCCLS-recommended acceptable quality control range for ITR.

inactive against *Sporothrix schenckii* and the zygomycetes (*Mucor* spp., an *Absidia* strain, and a *Rhizopus* strain) (Table 2). AMB MICs to *S. schenckii* and the zygomycetes were ≤1 μg/ml.

Fungicidal activities of BMS, ITR, FLU, and AMB. For the five strains of *Candida* spp. and one *C. glabrata* strain tested, AMB MFC_{99}s were no more than twofold greater than the MICs (Table 3). The three triazoles were not fungicidal to *Candida* spp. One strain of *Candida lusitaniae* had a FLU MFC_{99} of 1 μg/ml.

FLU was not fungicidal to *Cryptococcus neoformans* (Table 3). Even though the MFC_{99} and MIC_{95}s of BMS and ITR were much higher than the MICs of these drugs, the MFC_{95} values were often <1 μg/ml. Thus, it appears that ITR and BMS were often fungicidal to cryptococci at achievable levels of drug in serum.

BMS and ITR were often fungicidal to aspergilli (Table 4). The MFC_{99}s, MFC_{95}s, and MFC_{90}s were usually the same, though these values differed by 4- to 32-fold in four strains. The BMS MFC_{90}s were <1 μg/ml for 7 of 14 *Aspergillus* strains compared to 10 of the 14 strains with this level of fungicidal activity with ITR.

The three triazoles were not fungicidal to non-*Aspergillus* filamentous fungi (Table 5).

Susceptibility testing of BMS. Since test factors can influence the MICs to azoles, we examined a number of test factors (temperature, inoculum size, pH, duration of incubation, and human serum) on three yeast strains (data not shown). The MICs of BMS, ITR, and FLU were not affected by incubation temperature (30, 35, or 37°C) or pH (3, 4, 5, 6, or 7). The MICs increased no more than fourfold with an additional 24 h of incubation. Increasing the inocula from 10^2 to 10^5 CFU/ml affected BMS MIC the least (up to 2-fold increase), while up to 16- and 8-fold increases were observed in ITR MICs and FLU MICs, respectively. In the presence of 50% human serum, the MICs of the three azoles remained essentially unchanged (≤4-fold increase) against two strains of *C. albicans*. Interestingly, with the *C. tropicalis* strain, the MICs of the azoles decreased by 8- to 16-fold in the presence of human serum.

The MIC distribution of BMS and ITR are listed in Table 6. Only 1 of the 24 ITR MICs with *C. parapsilosis* ATCC 22019 was outside the acceptable quality control range recommended by the NCCLS. The ITR MICs for *C. krusei* ATCC 22492 was within the NCCLS-recommended, acceptable quality control range. The recommended acceptable quality control MIC ranges for BMS are 0.015 to 0.06 μg/ml for *C. parapsilosis* ATCC 22019 and 0.13 to 0.5 μg/ml for *C. krusei* ATCC 22492.

DISCUSSION

BMS appears to have a broader anticandidal spectrum than ITR and FLU do. Based on their MIC_{90}s, ITR and FLU were inactive against some strains of *C. krusei* and *C. tropicalis*, compared to BMS, which was active against all of the *C. krusei* strains tested but was inactive against some strains of *C. tropicalis*. Only 40 to 60% of the *C. glabrata* strains were susceptible or S-DD to the three triazoles. With the exception of the MIC_{90}s reported by Hata et al. (4, 5) against *C. tropicalis* and *C. glabrata*, our results confirmed their findings. Hata et al. reported MIC_{90}s in the 0.03- to 0.4-μg/ml range for the three triazoles against *C. tropicalis* when SAAM-F medium was used (5) but in the 12.5- to >100-μg/ml range when RPMI 1640 medium was used (4). In both studies by Hata et al. (4, 5), the BMS MIC_{90}s to *C. glabrata* were 0.4 μg/ml versus the >16 μg/ml result obtained in this study.

The three triazoles were active against *C. neoformans*, though only BMS and ITR were fungicidal to this yeast species. In this study and the Hata et al. studies (4, 5), BMS was 2- to 4-fold more active than ITR and 40-fold more active than FLU against yeast species.

In this study, BMS and ITR were inhibitory at 1 μg/ml to all but one of the 16 strains of *Aspergillus* spp. Similarly, Hata et al. observed the consistent activity of BMS and ITR against *Aspergillus* spp. (4, 5). The antiaspergillus potencies of BMS and ITR are comparable. FLU was inactive against aspergilli. BMS and ITR were also fungicidal to 50 to 74% of the *Aspergillus* strains tested.

The activities of BMS and ITR against other filamentous fungi are variable compared to FLU, which was inactive against most filamentous fungi. ITR and BMS were uniformly active against dermatophytes, while FLU was less active against *Microsporum gypseum. Acremonium strictum*, *Paecilomyces variotii*, and *Penicillium* sp. were susceptible to BMS and ITR. Though both ITR and BMS were active against most dematiaceous fungi, ITR appeared to be somewhat more active than BMS. BMS and ITR were less active against most strains of *Pseudallescheria boydii*, *Sporothrix schenckii*, and the zygomycetes, and both were generally inactive against *Fusarium* spp. Unlike *Aspergillus* spp., BMS and ITR were not fungicidal to the other filamentous fungi.

In summary, BMS is a new triazole that is two- to fourfold more potent than ITR and up to 40-fold more active than FLU against many species of fungi. Its spectrum includes some yeast strains that are resistant to FLU. BMS is like ITR in that it is fungicidal to cryptococci and many strains of aspergilli. The in vitro profile of BMS warrants its development as a therapeutic agent in humans.

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ERRATUM

In Vitro Activity of a New Oral Triazole, BMS-207147 (ER-30346)

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Volume 42, no. 2, p. 317, column 1, lines 43 and 48, and Table 6, column 2, lines 2 and 4: "*C. krusei* ATCC 22492" should read "*C. krusei* ATCC 6258."