

SF001, a Novel Micellar Polyene, Demonstrates a Prolonged Post-antifungal Effect In vitro against Yeast

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AMENDED ABSTRACT

Background: AM-2-19 is a novel polyene that selectively targets ergosterol over cholesterol, minimizing toxicity associated with this class while maintaining potency against yeast and mould. The drug product, SF001, is a micellar formulation of AM-2-19. Amphotericin B (AmB), the class representative, has demonstrated a prolonged post-antifungal effect (PAFE) of several hours against yeast. PAFE is one factor considered when designing dosing regimens. In this study, the PAFE of SF001 was evaluated against *Candida* spp. alongside comparators AmB, liposomal AmB (LAmB), and fluconazole (FLU).

Methods: The MIC of SF001, AmB, LAmB, and FLU was determined against *Candida* spp. (n=4; CLSI M27). PAFE was evaluated by exposing these isolates to drugs in RPMI medium at 0.25X, 1X, and 4X the MIC for 0.5 hr at 35°C alongside a drug-free growth control. The test agents were then removed by centrifugation and washing prior to resuspending in fresh pre-warmed RPMI for incubation at 35°C. Viable counts were then enumerated by serial dilution and plating every 2 hr out to a maximum of 14 hr, followed by a 24 hr timepoint. PAFE was calculated as the time it took for drug-exposed *Candida* to regrow 1-log post-washout minus the time it took for 1-log regrowth of the corresponding growth control as extrapolated from the resulting growth kinetic curves.

Results: At 4X the MIC, long PAFE was observed with SF001, LAmB, and AmB. As expected, no PAFE was observed with FLU. PAFE increased with increasing exposure for all polyenes.

Conclusion: The PAFE of the polyenes were comparable against *Candida*, with AmB having slightly longer PAFE than LAmB and SF001 which exhibited similar PAFE. The PAFE of the polyenes increased with increasing drug-exposure and extended out to several hours post-washout at the highest exposure concentration tested.

BACKGROUND

- Significant mortality and morbidity result from fungal infections with around 1 billion infections globally per year and 1.7 million deaths annually.^{1,2}
- SF001 is a micellar formulation of a novel analog of amphotericin B (AmB) with potentially less toxicity than AmB due to its binding specificity for ergosterol over cholesterol, the latter of which is associated with toxicity.^{3,4}
- As part of the development of effective antifungal concentrations and dosing, it is essential to understand the effects on fungal cells when the antifungal is no longer present. The PAFE of SF001, LAmB, AmB, and FLU were determined against 4 *Candida* isolates.

METHODS

- SF001, LAmB, AmB, and fluconazole were tested by broth microdilution in accordance with susceptibility testing guidelines in CLSI M27, and MIC interpretations were made based on interpretive criteria in CLSI M60.⁵
- Cultures were exposed to SF001 and comparators at 0.25, 1, and 4X the MIC for 0.5 hr. Cells were washed twice, resuspended into RPMI, and added to a culture flask. Viable cells were serially diluted and plated for viability every 2 hr until 14 hr and additionally at 24 hr.
- The PAFE was calculated as the difference in time for 1-log regrowth in the presence of drug vs. growth control.

RESULTS & CONCLUSIONS

- The SF001 MIC was 4- to 8-fold lower than the LAmB MIC and comparable to AmB MIC when tested against *Candida* spp. (**Table 1**).
- Increasing the antifungal concentration increased the length of the PAFE for all agents tested (**Figure 1, Table 2**).
- At 4X the MIC, SF001, LAmB, and AmB all showed comparable PAFE against all 4 evaluated isolates, with AmB generally having the longest PAFE of the three agents; whereas fluconazole showed minimal or no PAFE at 4X the MIC against any of the isolates (**Figure 1, Table 2**).

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- CLSI Guidelines available at www.clsi.org.

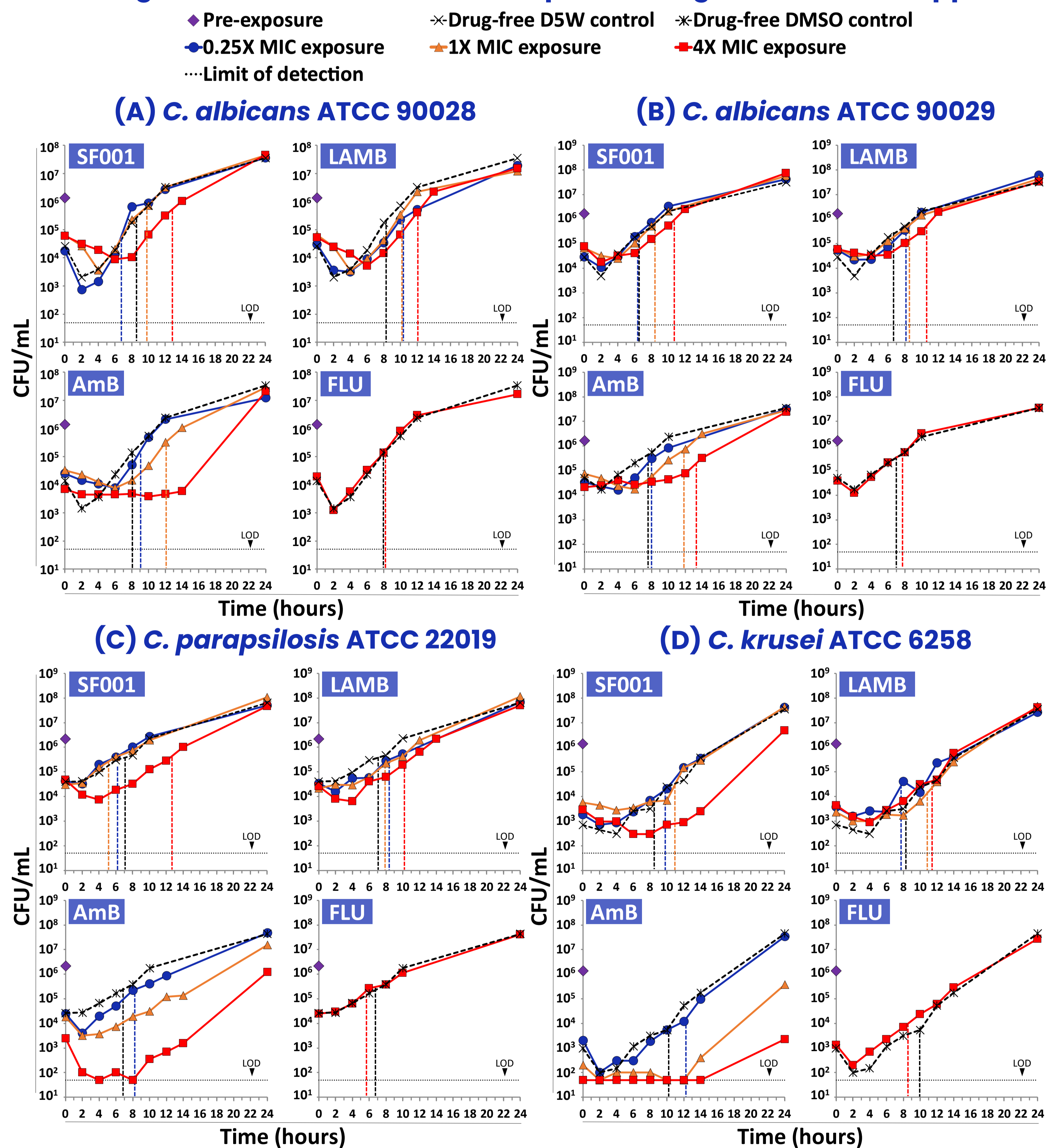
Table 1. MIC values of SF001 and comparators against the *Candida* spp. isolates evaluated by PAFE

Organism	Percent (%) inhibition	Median MIC (mg/L) n=4			
		SF001	LAmB	AmB	FLU
<i>Candida albicans</i> ATCC 90028	>50	NA	NA	NA	0.5
	100	0.25	1	0.25	NA
<i>Candida albicans</i> ATCC 90029	>50	NA	NA	NA	0.12
	100	0.25	1	0.25	NA
<i>Candida parapsilosis</i> ATCC 22019	>50	NA	NA	NA	1 (0.5-4)
	100	0.12	1	0.5 (0.25-2)	NA
<i>Candida krusei</i> ATCC 6258	>50	NA	NA	NA	16 (8-64)
	100	0.5	2	1 (0.5-2)	NA

LAmB: liposomal amphotericin-B, AmB: amphotericin-B, FLU: fluconazole, NA: not applicable; n= number of replicates for each isolate
Approved CLSI QC ranges shown in parentheses where applicable

MIC values in gray were used as the 1X MIC for PAFE test concentrations.

Figure 1. PAFE of SF001 and comparators against *Candida* spp.



CFU: colony forming units, LAmB: liposomal amphotericin-B, AmB: amphotericin-B, FLU: fluconazole, LOD: limit of detection (50 CFU/mL), D5W: 5% dextrose in water
Vertical colored lines used to indicate the time at which 1-log regrowth relative to baseline was observed.

Table 2. PAFE of SF001 and comparators against *Candida* spp.

Drug	Organism	Time to 1-log regrowth (hr)			PAFE (hr)		
		0.25X MIC	1X MIC	4X MIC	0.25X MIC	1X MIC	4X MIC
SF001	ATCC 90028	6.5	9.7	12.8	0	1.4	4.5
	ATCC 90029	6.4	8.2	10.2	0	1.5	3.5
	ATCC 22019	6.1	5.2	12.5	0	0	5.3
	ATCC 6258	9.7	10.7	>14	1.3	2.3	>5.6
LAmB	ATCC 90028	10.6	10.3	12.1	2.3	2	3.8
	ATCC 90029	8.3	8.5	10.4	1.6	1.8	3.7
	ATCC 22019	8.5	7.9	10.3	1.3	0.7	3.1
	ATCC 6258	7.8	11	11.6	0	2.6	3.2
AmB	ATCC 90028	9	12	>14	1	4	>6
	ATCC 90029	8.1	12	13.1	0.4	4.3	5.4
	ATCC 22019	8.3	>14	>14	1.4	>7.1	>7.1
	ATCC 6258	12.2	>14	>14	2	>3.8	>3.8
FLU	ATCC 90028			8.1			0.1
	ATCC 90029			7			0
	ATCC 22019			5.8			0
	ATCC 6258			8.8			0

LAmB: liposomal amphotericin-B, AmB: amphotericin-B, FLU: fluconazole, NA: not applicable

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