

# Evaluation of the Broad-Spectrum Antimicrobial Activity of TDT 067 (Terbinafine in Transfersome®) against Dermatophytes, Yeasts, Filamentous Fungi, and Bacteria

 Mahmoud Ghannoum PhD<sup>1</sup>, Nancy Isham M(ASCP)<sup>1</sup>, William Henry PhD<sup>2</sup>, and Sam Yurdakul PhD<sup>2</sup>
<sup>1</sup>Center for Medical Mycology, Case Western Reserve University and University Hospital Case Medical Center, Cleveland, OH, US; <sup>2</sup>Celtic Pharma Development Services Europe Ltd., London, UK

## INTRODUCTION

- TDT 067 is a novel carrier-based dosage form of terbinafine in Transfersome® (1.5% spray). Transfersomes are ultra-deformable lipid-based vesicles which can cross the skin permeability barrier driven by a transcutaneous water gradient.
- TDT 067 has been formulated for topical delivery of terbinafine to the nail, nail bed, and surrounding tissue and is currently being investigated in a Phase III study for the treatment of onychomycosis.

## OBJECTIVES

- This study compared the antimicrobial activity of TDT 067 and conventional terbinafine (ie terbinafine not in Transfersome®) against dermatophytes, yeasts, filamentous fungi, and bacteria to determine the broader antimicrobial activity of TDT 067.

## METHODS

- Test isolates were obtained from the Center for Medical Mycology or from the American Type Culture Collection.
- Minimum inhibitory concentrations (MICs) of TDT 067 (serially diluted with acetate/ethanol) and terbinafine hydrochloride (dissolved in dimethyl sulfoxide and serially diluted in RPMI-1640 buffered with MOPS) were determined using CLSI M27-A3 and M38-A2 standardized methodologies.
- Minimum fungicidal concentrations (MFCs) were determined by subculturing visually clear wells from the MIC assay for colony count.

## RESULTS

### Dermatophytes

- TDT 067 demonstrated potent inhibitory activity and cidal activity against dermatophyte strains with lower MICs (mean 8-fold) and MFCs (mean 4-fold) than conventional terbinafine (Table 1; Figure 1).

Table 1. Minimum inhibitory concentrations (MICs; µg/mL) and minimum fungicidal concentrations (MFCs; µg/mL) of TDT 067 and terbinafine against dermatophytes

Organism	MIC		MFC	
	TDT 067	Terbinafine	TDT 067	Terbinafine
<i>Trichophyton rubrum</i> Range (n=5)	0.00003–0.002	0.015–0.03	0.00012–0.008	0.03–0.12
<i>Trichophyton mentagrophytes</i> Range (n=5)	0.004	0.015	0.015–0.12	0.06–0.12
<i>Epidermophyton floccosum</i> Range (n=5)*	0.004–0.015	0.015–0.06	0.015–8	0.06–0.12

\*Data not available for two strains.

### Yeasts

- TDT 067 MICs were ≤0.25 µg/mL against *Candida albicans*, *Candida parapsilosis*, and *Cryptococcus neoformans*, and were lower (mean 3-fold) than terbinafine against all yeast strains, except for *Candida glabrata* for which they were equivalent (Table 2). In contrast to terbinafine, TDT 067 was cidal against 4/5 *Cryptococcus neoformans* strains.

Table 2. Minimum inhibitory concentrations (MICs; µg/mL) and minimum fungicidal concentrations (MFCs; µg/mL) of TDT 067 and terbinafine against yeasts

Organism	MIC		MFC	
	TDT 067	Terbinafine	TDT 067	Terbinafine
<i>Candida albicans</i> Range (n=5)	0.06–0.25	0.12–15	469–7500	1875–7500
<i>Candida glabrata</i> Range (n=6)	0.5–2	0.5–8	7500–7500	1875–3750
<i>Candida krusei</i> Range (n=6)	0.5–1	8–30	1875–7500	1875–7500
<i>Candida parapsilosis</i> Range (n=6)	0.06–0.12	0.5–1	15–117	59–1875
<i>Cryptococcus neoformans</i> Range (n=5)	0.00001–0.06	0.25–0.5	0.0002–15	4–1875

### Filamentous fungi

- TDT 067 MICs were ≤0.12 µg/mL against 9/10 *Aspergillus* strains, and were up to 60-fold lower than terbinafine against nine *Aspergillus* strains, up to 117-fold lower against all *Rhizopus* strains, and up to 30-fold lower against one *Pseudallescheria boydii* and three *Fusarium solani* strains (Table 3).

Table 3. Minimum inhibitory concentrations (MICs; µg/mL) and minimum fungicidal concentrations (MFCs; µg/mL) of TDT 067 and terbinafine against filamentous fungi

Organism	MIC		MFC	
	TDT 067	Terbinafine	TDT 067	Terbinafine
<i>Aspergillus fumigatus</i> Range (n=5)	0.06–1	0.5–4	234–3750	1875–12875
<i>Aspergillus flavus</i> Range (n=5)	0.002–0.004	0.00001–0.25	0.03–1	0.03–2
<i>Rhizopus</i> Range (n=5)	4–8	469	>7500	7500–7500
<i>Pseudallescheria boydii</i> Range (n=6)*	15–469	469	7500–7500	7500–7500
<i>Fusarium solani</i> Range (n=5)	1–234	8–234	7500–7500	3750–7500

\*Terbinafine MIC data available for five strains.

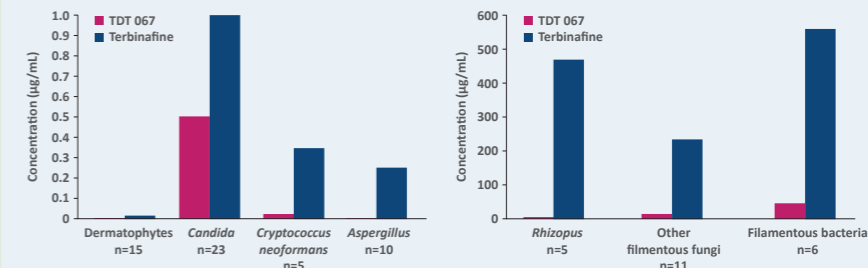
### Filamentous bacteria

- TDT 067 MICs were 2–234-fold lower than terbinafine against 5/6 strains of bacteria (Table 4).

Table 4. Minimum inhibitory concentrations (MICs; µg/mL) and minimum fungicidal concentrations (MFCs; µg/mL) of TDT 067 and terbinafine against filamentous bacteria

Organism	MIC		MFC	
	TDT 067	Terbinafine	TDT 067	Terbinafine
<i>Nocardia asteroides</i> Range (n=5)	4–120	2–938	1875–7500	938–3750
<i>Actinomyces madurae</i> Range (n=1)	8	1875	234	>5000

Figure 1. Minimum inhibitory concentrations at which 50% of strains are inhibited by TDT 067 are lower than those of terbinafine against a broad spectrum of organisms



Note: data presented on two graphs due to difference in range/scale; values for *Cryptococcus neoformans*, *Rhizopus*, and filamentous bacteria are presented as means.

## CONCLUSIONS

- TDT 067 has potent antifungal activity against dermatophyte and non-dermatophyte pathogens of onychomycosis.
- The antimicrobial activity of TDT 067 extends to other fungi and filamentous bacteria, indicating that TDT 067 may have broader clinical utility than onychomycosis.
- The Transfersome® in TDT 067 appears to potentiate the activity of terbinafine. These data support our published *in vitro* data which suggest that the Transfersome® enhances the antifungal activity of terbinafine and accelerates its delivery to its site of action in the fungus.<sup>1,2</sup>

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## REFERENCES

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