

# In vitro Nail Penetration Profile Of AN2690, A Novel Broad-Spectrum Antifungal Agent In Development For The Topical Treatment Of Onychomycosis

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## AIMS

AN2690 is a new topical antifungal agent in clinical trials to treat onychomycosis. We report the following:

- Results of *In vitro* nail penetration studies
- Quantification after dosing 10% AN2690 daily for 14 days
- The effect of formulation strength on nail penetration
- Preliminary interim results of a Phase II clinical trial

## 1. INTRODUCTION

Onychomycosis, a common fungal infection of the toe and fingernails, remains difficult to treat,<sup>1</sup> probably because current therapies have poor penetration throughout the nail unit.<sup>2</sup> AN2690, a novel boron-containing small molecule designed to penetrate nails, has broad spectrum antifungal activity<sup>3</sup> and is in clinical trials to treat onychomycosis topically.

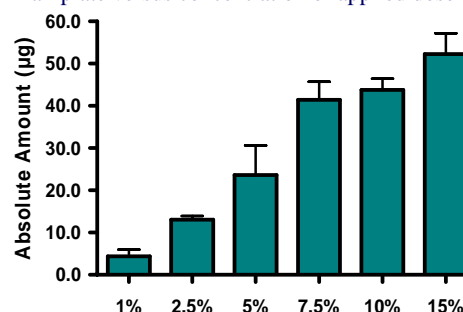
## 3. EFFECT OF CONCENTRATION VERSUS PENETRATION

AN2690 was formulated in a nail lacquer at concentrations of 1, 2.5, 5, 7.5, 10 and 15% w/v. A single dose of 2µL was applied to the top of human cadaver finger nails mounted on poloxomer gel supports and left for 24 hrs. At study end, the poloxomer gels were analyzed by LC/MS/MS for AN2690. The results are shown in Figure 4. We found the amount of AN2690 penetrating into the poloxomer support increased linearly as concentration increased to 7.5% w/v. Above this concentration, the amount of AN2690 found began to level off, indicating that 7.5% w/v is the optimal concentration delivering the greatest amount versus the applied dose.

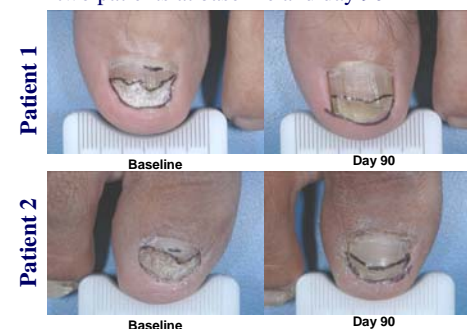
## 2. NAIL PENETRATION RESULTS

We compared the nail penetration of AN2690 to ciclopirox, the only commercial topical treatment available in the USA. Nails were mounted on a wetted cotton ball reservoir in a one-chamber diffusion cell<sup>3</sup> (Figure 1). 10 µL of radioactive AN2690 (10% w/v in ethanol/propylene glycol 4:1), or ciclopirox (8% w/w in commercial lacquer) were applied to the top of the nails over a surface area of 0.75 cm<sup>2</sup> daily for 14 days. The supporting cotton balls were replaced every three days. At study end, the top and bottom halves of the micro-dissected nails, remaining nail plate, cotton balls and surface washings were analyzed for AN2690 or ciclopirox by scintillation counting. The results are shown in Table 1. Figure 2 shows that AN2690 was almost equally distributed throughout the nail plate and Figure 3 shows the amount of AN2690 migrating into the cotton ball increased over time, with 16% of the applied dose found in the cotton balls.

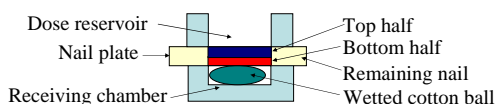
**FIGURE 4.** Amounts of AN2690 found under the nail plate versus concentration of applied dose



**FIGURE 5.** Photos of the target toenail of two patients at baseline and day 90



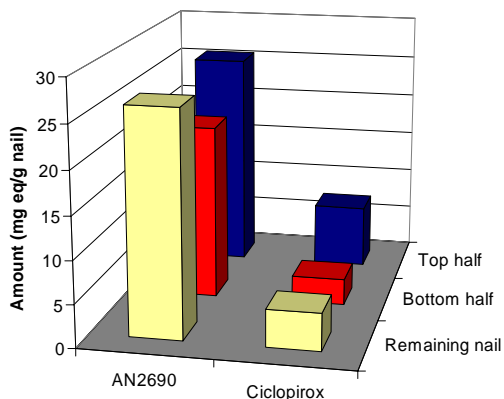
**FIGURE 1.** Diagram of quantitative nail penetration cell design including layers analyzed for drug



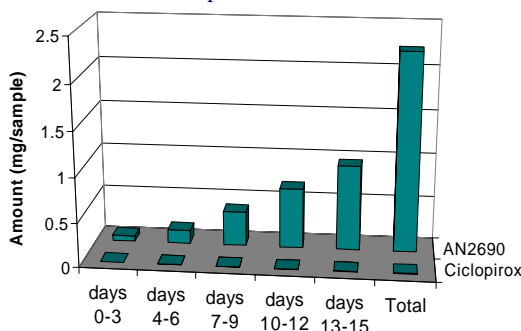
**TABLE 1.** Amount of AN2690 and ciclopirox found within the nail plate and in supporting cotton balls

	AN2690	Ciclopirox	P-value (t-test)
Top half (mg eq/g nail)	25.6 ± 8.8	7.4 ± 3.5	0.0008
Bottom half (mg eq/g nail)	20.5 ± 4.7	3.1 ± 2.1	0.0001
Remaining nail (mg eq/g nail)	26.06 ± 12.41	4.38 ± 2.73	0.0022
Supporting cotton ball (mg eq/sample)			
days 0-3	0.0609 ± 0.0605	0.0011 ± 0.0020	0.004
days 4-6	0.1551 ± 0.1314	0.0013 ± 0.0027	0.002
days 7-9	0.3892 ± 0.3714	0.0018 ± 0.0030	0.002
days 10-12	0.6775 ± 0.6663	0.0014 ± 0.0019	0.002
days 13-15	0.9578 ± 0.6106	0.0033 ± 0.0041	0.002
Total	2.2405 ± 1.7325	0.0089 ± 0.0131	0.002
Mass balance (%)	88 ± 9 %	89 ± 2 %	0.06

**FIGURE 2.** Amounts of AN2690 and ciclopirox found within the nail plate



**FIGURE 3.** Amounts of AN2690 and ciclopirox found under the nail plate



## 4. PRELIMINARY CLINICAL DATA

An open-label two-arm clinical trial to treat onychomycosis using 5% and 7.5% AN2690 is underway. Drug is applied topically to a designated great nail and all other affected nails once-daily for 180 days. Inclusion criteria for the targeted nail include area involvement of 20-60% and KOH positive mycology. Samples for mycology are taken at baseline, 30, 60, 90, 180, 240 and 360 days. We present preliminary interim 90 day efficacy data on the first 24 patients in the 5% group. For this interim analysis, efficacy is determined by reduction in culture positive and KOH positive results and new unaffected nail growth (Table 2 and Figure 5). By day 90, mycology samples were 100% culture negative and 70% KOH negative, average unaffected nail growth was 2.6 mm (13/24 patients had >2.5 mm unaffected nail growth). Photos show improvement in the appearance of the nail plate.

**TABLE 3.** Preliminary data from the first 90 days of treatment with 5% AN2690 in the first 24 patients

	Average unaffected nail growth, mm (range)	Culture positive	KOH positive
Baseline	0	50%	100%
30 days	1.8 (-0.8-6.1)	0%	88%
60 days	N/A	0%	66%
90 days	2.6 (-1.7-6.6)	not yet available	30%

## CONCLUSIONS

AN2690, a novel boron-containing compound in clinical trials to treat onychomycosis topically, exhibits excellent ability to penetrate full thickness human nail plates.

- AN2690 achieves amounts under the nail plate over 200x that of ciclopirox in its commercial vehicle
- 7.5% w/v AN2690 was found to give the optimal ratio of amount delivered to strength applied.
- Preliminary interim 90 day clinical data using 5% AN2690 shows a good clinical response

References  
1. J.E. Arrese and G.E. Piérard. *Dermatology*, 2003, 207, 255.  
2. S. Murrain. *Int. J. Pharmaceutics*, 2002, 236, 1.  
3. SID poster 775