

# Nail Penetration Of AN2690: Efficacy Coefficient And Effect of Formulation

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## Aims

AN2690 is a new topical antifungal agent in Phase II clinical trials to treat onychomycosis. This poster reports the following studies:

- The *in vitro* efficacy coefficient of AN2690 compared to ciclopirox.
- The *in vitro* nail penetration of AN2690 formulated in four different vehicles.

## Definition Of Efficacy Coefficient (EC)<sup>1</sup>

Efficacy coefficient (EC) is the ratio of flux of an antifungal agent through the nail plate to the minimum inhibitory concentration (MIC) of the drug.

When the EC = 1, the amount of material penetrating out of a 1 cm<sup>2</sup> area in one day, diluted in 1mL volume is 1x MIC. As EC increases, the potential for clinical efficacy should also increase.

## Nail Penetration Study Design

Nail penetration was measured using human cadaver nails mounted on a wetted cotton ball reservoir in a one-chamber diffusion cell<sup>5</sup> (Figure 2). A dose of 10 μL of a test formulation was applied to the top of the nails over a surface area of 0.75 cm<sup>2</sup> daily for 14 days. For the EC study, the supporting cotton balls were replaced every three days. For the vehicle comparison study the cotton balls were replaced every 5 days. At study end, the top and bottom section of the micro-dissected nails, remaining nail plate, cotton balls and surface washings were analyzed for AN2690 or ciclopirox.

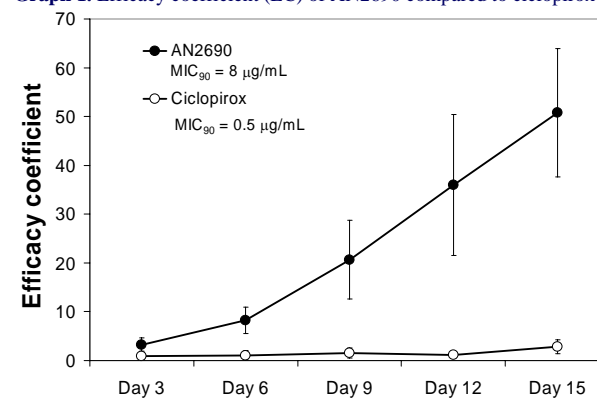
## Result of Efficacy Coefficient Analysis

We previously reported the *in vitro* nail penetration results of AN2690 compared to ciclopirox.<sup>6</sup> In this analysis, the amounts of AN2690 or ciclopirox found in the cotton ball samples were used to calculate flux (Flux = amount found/dosing area/time). Flux and MIC<sub>90</sub> values against *T. rubrum* for AN2690 (8 μg/mL) and ciclopirox (0.5 μg/mL) were used to calculate the efficacy coefficient (EC) of each drug (EC = Flux/MIC<sub>90</sub>). These results are shown in Table 1 and Graph 1. The efficacy coefficient for AN2690 increased significantly, reaching 50 times the MIC<sub>90</sub> by the end of 14 days, while the efficacy coefficient for ciclopirox was very low and flat, only 0.8 – 1.6 times the MIC<sub>90</sub> value throughout the 14-day period.

TABLE 1. Flux and efficacy coefficient (EC) for AN2690 and ciclopirox

	Flux (μg eq/cm <sup>2</sup> /d)		Efficacy Coefficient	
	AN2690	Ciclopirox	AN2690	Ciclopirox
Days 0-3	26 ± 10	0.5 ± 0.35	3.2 ± 1.4	0.9 ± 0.71
Days 4-6	66 ± 23	0.5 ± 0.47	8.2 ± 2.7	1.1 ± 0.93
Days 7-9	165 ± 64	0.8 ± 0.52	21 ± 8.1	1.6 ± 1.03
Days 10-12	288 ± 115	0.6 ± 0.32	36 ± 14	1.2 ± 0.64
Days 13-15	407 ± 106	1.4 ± 0.70	51 ± 13	2.8 ± 1.40
Mean	204 ± 64	0.8 ± 0.49	25 ± 7.9	1.6 ± 0.97

Graph 1. Efficacy coefficient (EC) of AN2690 compared to ciclopirox



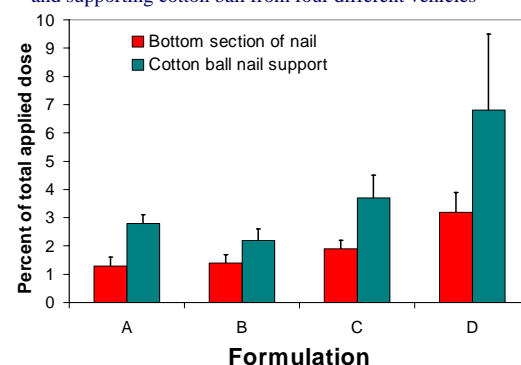
## The Effect Of Vehicle On Nail Penetration

Nail lacquer formulations are a popular choice for topical antifungal treatment. They typically contain a film-forming agent, solvent, antifungal drug, and possibly a penetration enhancer. In this experiment, the facilitating role of the vehicle on the permeation of AN2690, into and through the nail plate was investigated. Four different vehicles, A-D, containing 10% w/w AN2690 were examined for deeper nail penetration. Three formulations, A-C, were nail lacquers with different compositions. Formulation D was a simple solution. These were tested for nail penetration and the results of this study are shown in Table 2 and Graph 2. There was no statistical difference between any of the vehicles, although formulation D did appear to show the highest penetration.

TABLE 2. Flux and amount of AN2690 found in the deep layers from four vehicles

Vehicle	Flux (μg eq/cm <sup>2</sup> /d)	AN2690 in deeper nail/nail bed (% of total applied dose)	
		Bottom Section of Nail	Cotton ball nail supporting bed
A 70% ethanol, 20% poly (vinyl methyl ether alt maleic acid monobutyl ester)	32.8 ± 4.4	1.3 ± 0.3	2.8 ± 0.3
B 56% ethanol, 14% water, 15% poly (2-hydroxyethyl methacrylate), 5% dibutyl sebacate	29.9 ± 5.7	1.4 ± 0.3	2.2 ± 0.4
C 55% ethanol, 15% ethyl acetate, 15% poly (vinyl acetate), 5% dibutyl sebacate	38.7 ± 7.4	1.9 ± 0.3	3.7 ± 0.8
D 20%propylene glycol, 70% ethanol	78.8 ± 31.1	3.2 ± 0.7	6.8 ± 2.7
P value (ANOVA)	> 0.05	> 0.05	> 0.05

Graph 2. Amount of AN2690 found in bottom section of nail and supporting cotton ball from four different vehicles



## CONCLUSIONS

AN2690, a novel boron-containing compound in clinical trials for the topical treatment of onychomycosis, exhibits excellent ability to penetrate full thickness human nails.

- The efficacy coefficient of AN2690 reached 50x MIC<sub>90</sub> after 14 days, and was still increasing.
- The high penetration of AN2690 is vehicle independent.

FIGURE 1. Structure of AN2690 (5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole)

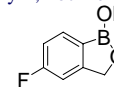
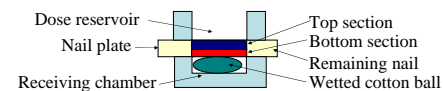


FIGURE 2. Diagram of quantitative nail penetration cell design including layers analyzed for drug



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