

An Open-Label, Multiple-Dose Study of the Absorption and Systemic Pharmacokinetics of AN2690 Applied as a 7.5% Solution to All Toenails of Adult Patients with Moderate to Severe Onychomycosis

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ABSTRACT

AN2690 is a new novel antifungal being developed for the treatment of onychomycosis. AN2690 has demonstrated excellent nail plate penetration in *ex vivo* studies as well as favorable early clinical efficacy results. In pre-clinical studies, the plasma half life of AN2690 in rats was 11 minutes following intravenous dosing. Systemic exposure in the minipig was very low following a topical dose of 8.59 ± 0.34 mg/kg (10% solution applied to 5% body surface area). A Cmax of 184 ± 110 ng/mL was observed at 2 h. At the ten-fold lower dose of 0.859 ± 0.034 mg/kg, all plasma concentrations were below the limit of quantitation. The purpose of this study was to define the extent of human systemic exposure when AN2690 solution, at 7.5%, was applied to all 10 toenails of subjects with moderate to severe onychomycosis. 15 subjects with a body mass index between 19-35, onychomycosis involving greater than 80% of both great nails, a combined thickness of the nail plate and nail bed > 3 mm, and at least 6 additional onychomycotic nails were enrolled to be treated daily for 28 days. A total dose of 0.25 ml was distributed over the subjects' 10 toenails daily for 28 days at the study site. Plasma samples for quantitation of AN2690 were collected prior to and 0.25, 0.5, 1, 2, 3, 4, 6, 8 hours after test agent application on days 0, 14, and 28. Samples were analyzed for AN2690 by a LC/MS/MS method with a lower limit of quantitation of 25 ng per ml.

PURPOSE

The purpose of this study was to define the extent of human systemic exposure when AN2690 solution, at 7.5%, was applied to all 10 toenails of subjects with moderate to severe onychomycosis.

METHODS

This open-label, multiple-dose study enrolled 15 male or female subjects of any race, 18-65 years of age, with Body Mass Index (BMI) of 19-35 and a protocol "case definition" of onychomycosis:

- Onychomycosis of both great toenails
- At least 80% involvement of both great toenails
- Combined thickness of the nail plate and nail bed of each great toenail is > 3mm
- Positive KOH wet mount from at least one great nail
- At least six additional toenails with clinical diagnosis of onychomycosis

AN2690 7.5% solution was topically applied once daily for 28 days to all 10 toenails and no more than 1 mm of surrounding skin. A total dose of 0.25 ml was distributed over the subjects' 10 toenails.

On days 0, 14 and 28, a pharmacokinetic blood sample was obtained from the subject prior to the subject receiving the scheduled dose of AN2690. Blood samples were obtained at 0.25, 0.5, 1, 2, 3, 4, 6 and 8 hours after dosing. All other doses were applied during outpatient visits on days 1-13 and 15-27; on days 1 and 15, single pharmacokinetic blood samples were taken prior to dosing.

Samples were analyzed for AN2690 by a validated LC/MS/MS method with a lower limit of quantitation of 25 ng/ml. In addition to evaluating plasma levels of AN2690 after topical dosing, descriptive statistics were collected for fungal culture results for one or both great toenails. The 15 subjects in this study yielded 25 infected toenails for evaluation.

RESULTS AND CONCLUSIONS

As shown in the following table, the fungal culture results indicate that AN2690 markedly reduced the number of positive cultures after only 2 weeks of dosing and all cultures were negative by the end of 4 weeks of treatment.

Positive Fungal Culture Results

	Number	Percentage
Positive at baseline	25	93
Positive at 2 weeks	3	10
Positive at 4 weeks	0	0
Positive at 6 weeks	Pending	

The concentration of AN2690 in the plasma samples taken at all time points were below the limits of quantitation (25 ng/mL) of the validated HPLC assay.

These results indicate a very low systemic exposure for AN2690 after topical dosing of toenails and a rapid conversion from fungal culture positive to culture negative.