



AN2898, a novel oxaborole compound with anti-inflammatory activity: results of *in vivo* efficacy and preclinical safety studies

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Introduction

AN2898 is the second in a series of novel oxaborole compounds that decrease TNF α release through inhibition of PDE4 (See Posters 84,86,88,89,367). This new drug is currently in preclinical development for psoriasis and atopic dermatitis, common skin diseases that are characterized by chronic inflammation. Psoriasis is driven by a Th1 response, while AD is primarily a Th2 disease. Both indications respond well to anti-inflammatory treatments, namely steroids and TIMS. Early studies suggest that AN2898 has the required *in vivo* biological activity and preclinical safety profile to enable clinical trials.

Figure 1. AN2898 (5-(3,4-dicyanophenoxy)-1-hydroxy-1,3-dihydro-2,1-benzoxaborole)

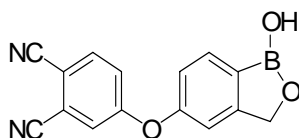


Figure 2. *In Vivo* Anti-Inflammatory Activity – Effect of AN2898 formulated in acetone/ethanol in Mouse Ear Edema Models dosed topically.

A) Acute Inflammation: AN2898 inhibits phorbol ester (PMA) induced ear edema. Dexamethasone is positive control

B) Delayed Type Hypersensitivity: AN2898 inhibits oxazolone induced ear edema. Indomethacin is positive control

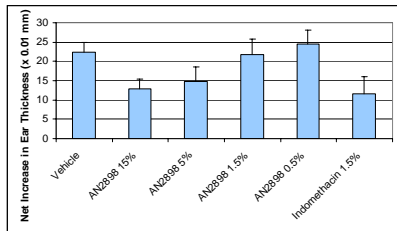
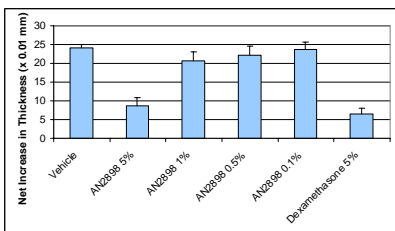


Table 1. Summary of Rat Pharmacokinetics

Study	Duration of Treatment	Species	AN2898 Doses Tested	Results
Pharmacokinetics				
IV PK	varied	Rat	20 mg/kg	Mean Residence Time = 0.64 hr
Oral PK	varied	Rat	100 mg/kg	Bioavailability = 6.92%
Skin Penetration				
Skin penetration	24 h	Human	Cream 2%, Ointment 2%	Flux demonstrated

Table 2. Summary of Safety Pharmacology and Toxicology Studies

Study	Duration of Treatment	Species	AN2898 Doses Tested	Results
Safety Pharmacology				
HERG Channel	NA	<i>In Vitro</i>	1 μ M	9.2% HERG inhibition
Receptor Binding Panel	varied	<i>In Vitro</i>	10 μ M	One significant (>50%) inhibition out of 54 assays: Cl ⁻ channel- 66% inhibition
P450 Inhibition	30 min	<i>In Vitro</i>	10 μ M	No significant (>50%) inhibition out of 5 assays.
Microsomal stability	60 min	Human, Rat, Minipig, Mouse	1, 10 μ M	No significant loss of compound
Plasma stability	8 h	Human, Mouse	10 μ M	No significant loss of compound
Systemic Safety				
Systemic Safety	14 day	Rat	10, 100, 300 mg/kg/day	NOAEL at 300 mg/kg, Plasma levels were 60 times > levels after topical application
Emesis	single dose	Suncus	10, 30, 100 mg/kg	Plasma levels required to cause emesis 1000X > levels after topical application
Dermal Toxicity				
Dermal Toxicity/ PK	single dose, occlusive	Minipig	5% cream and 5% ointment	No skin irritation; undetectable plasma levels

Conclusions

- AN2898 is a novel compound that is effective in both *in vitro* (Poster 86) and *in vivo* anti-inflammatory studies.
- Preclinical studies suggest AN2898 is safe after topical and systemic dosing.
- AN2898 has both the efficacy and safety profile to enable clinical trials in psoriasis and atopic dermatitis.