

P3357

**AN2728 preclinical studies demonstrate
an acceptable safety profile for the topical
treatment of psoriasis and atopic
dermatitis**

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AN2728, A Broad Spectrum Anti-inflammatory, Currently in Clinical Development

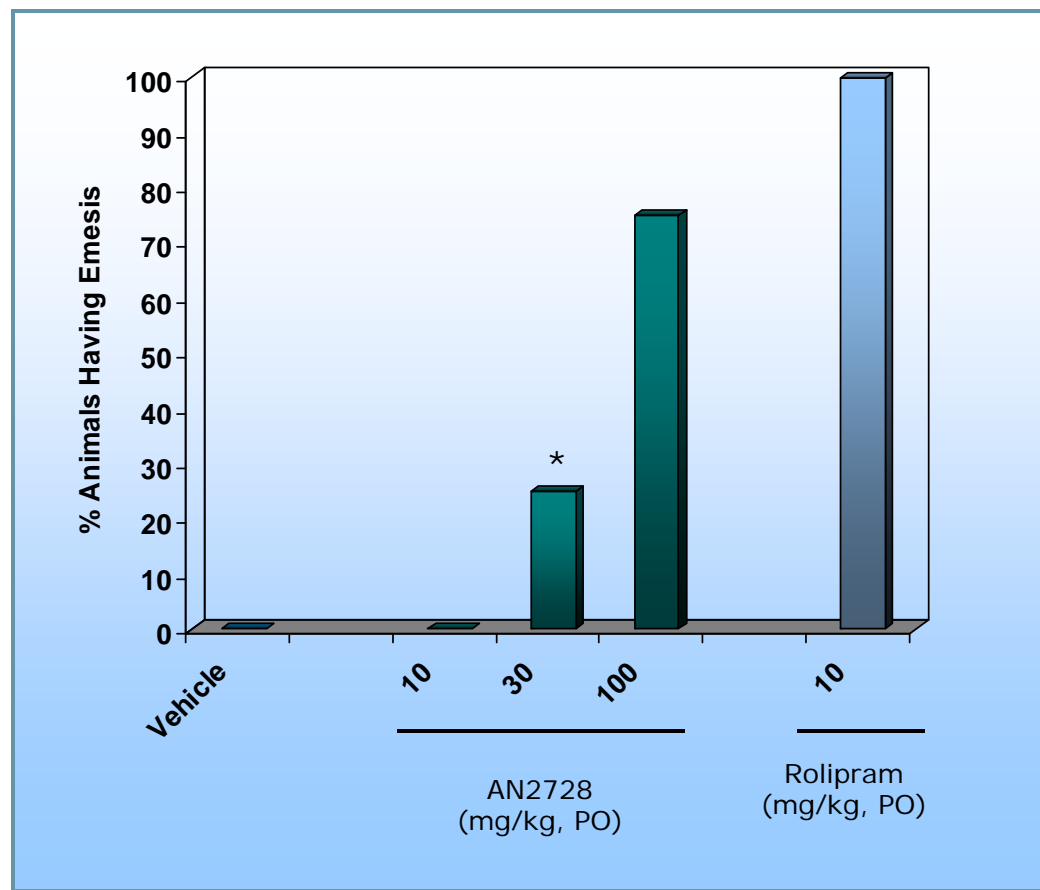
- AN2728 (5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole) is a broad spectrum anti-inflammatory compound
- AN2728 is currently in development for the topical treatment of plaque psoriasis and atopic dermatitis
- AN2728 is a novel boron-containing compound which inhibits the release of TNF- α , IL-12, IL-23, and other cytokines

AN2728 has No Safety Pharmacology and Genotoxicity Findings

Study	Treatment Duration	Species	Doses Tested	Results
Safety Pharmacology				
Emesis	Single dose	Shrew (4 ♂/dose)	0, 10, 30, & 100 mg/kg	Vomiting observed at 30 and 100 mg/kg; NOAEL = 10 mg/kg
Emesis	Single dose	Ferret (4 ♂/dose)	0, 10, 30, & 100 mg/kg	No treatment-related findings NOAEL = 100 mg/kg
hERG	NA	<i>in vitro</i>	1 uM	No block
Genotoxicity				
Ames	NA	<i>in vitro</i>	15-5000 µg/plate	Not mutagenic +/- S9
Chromosome aberration	NA	<i>in vitro</i>	12-500 µg/mL	Not clastogenic +/- S9
Rat micronucleus	Single dose	Rat (5 animals/sex/dose)	500, 1000, 2000 mg/kg	Not clastogenic

NOAEL: No Observable Adverse Effect Level

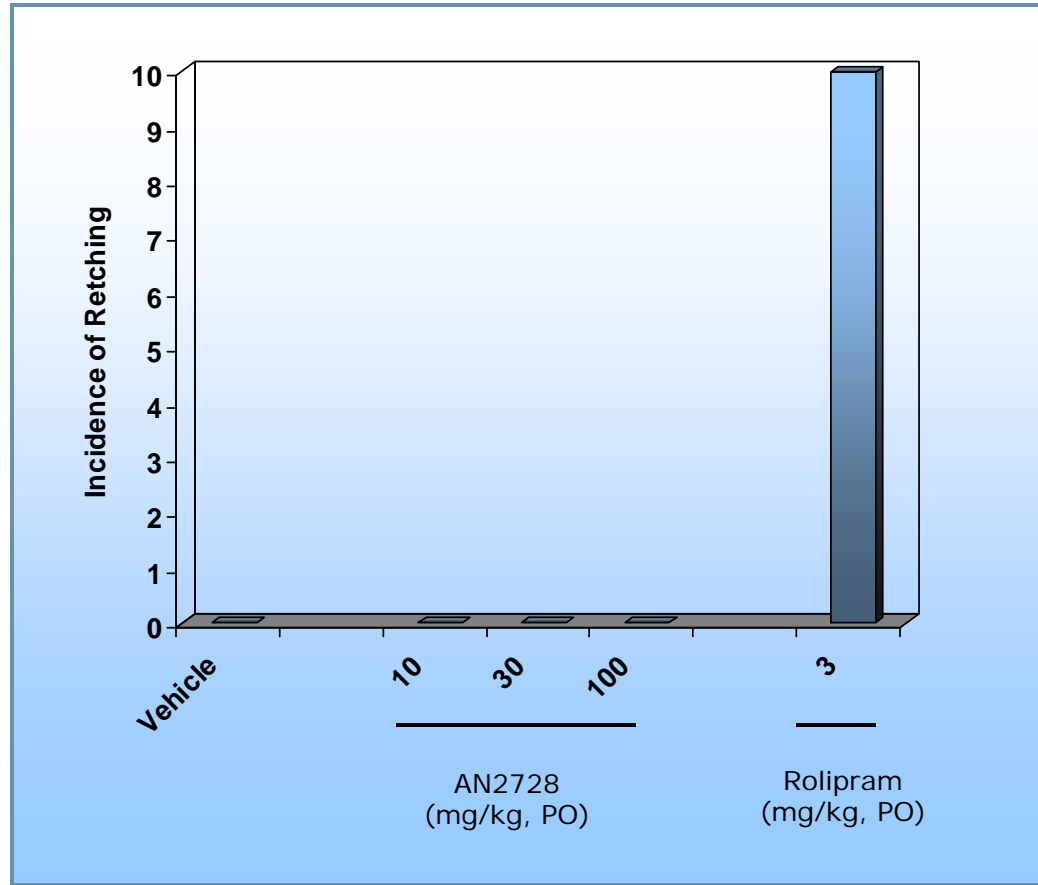
At Plasma Levels Above 10 µg/mL, Emesis was Observed for AN2728 in the Shrew



* Probably unrelated to test substance

- Only 1 episode from 1 animal 90 min after AN2728 administration out of 4 animals

AN2728, after Oral Administration, Caused No Emesis in a Ferret Model



AN2728 has a Good Systemic Safety Profile in Rats

Study	Treatment Duration	Species	Doses Tested	Results							
Systemic Toxicity											
Systemic toxicity + TK	1 Month (once daily dosing); 14 Day recovery	Rat (10-15 animals/sex/dose)	0, 50, 150, 400, & 1000 mg/kg/d; oral gavage;	Tox: Male mortality (87%, 1000 mg/kg/d, day 10), reduced erythrocyte count, increased liver weight (♂: 400 & 1000 mg/kg/d; ♀: 1000 mg/kg/d) NOAEL = 150 mg/kg/d (male) and 400 mg/kg/d (female)							
				<i>TK Parameters for 1000 mg/kg/d</i>							
				Day 1	Cmax (ng/mL)	Tmax (h)	AUC(0-24) (ng-h/mL)	Day 28	Cmax (ng/mL)	Tmax (h)	AUC(0-24) (ng-h/mL)
				♂	12200	2	142000	♂	7090	1	58100
♀	4620	2	21500	♀	5150	2	40500				
				TK: Plasma concentrations increased with dose							

NOAEL: No Observable Adverse Effect Level

AN2728 has a Good Safety Profile when Applied Topically

Study	Treatment Duration	Species	Doses Tested	Results							
<i>Dermal Toxicity & Skin Sensitization</i>											
Dermal Toxicity + TK	28 Days (once daily dosing); 14 Day Recovery	Göttingen Minipig(4 -6 animals/ sex/ dose)	Vehicle, 0.3, 2, and 5 % Cream B	TK: Erythema, edema (Day 8; 2 & 5% doses) NOAEL (Cream B) = 0.3% (dermal tox) and 5% (systemic tox)							
				<i>TK Parameters for 5% Cream B</i>							
				Day 1	C _{max} (ng/mL)	T _{max} (h)	AUC(0-24) (ng·h/mL)	Day 28	C _{max} (ng/mL)	T _{max} (h)	AUC(0-24) (ng·h/mL)
				♂	9.4	24	180	♂	196	0.75	3360
♀	7.18	8	141	♀	198	1.5	3140				
				TK: Plasma concentrations increased with dose; no gender difference; increase in overall exposure by Day 28.							
Local Lymph Node Assay	3 days (once daily dosing)	Mouse (5 ♀/dose)	1, 5, 10% solution (50:50; Acetone: Ethanol);	No findings							

NOAEL: No Observable Adverse Effect Level

AN2728 has a Good Safety Profile for the Topical Treatment of Skin Inflammatory Diseases

- AN2728 exhibits a good safety pharmacology profile
- AN2728 does not display genotoxic liabilities
- AN2728 is not a skin sensitizer
- *In vivo* toxicology profile for AN2728 establishes toxicity endpoints that can either be monitored or are at high systemic doses