



Preclinical toxicology of AN2728, a novel oxaborole in development for the topical treatment of psoriasis

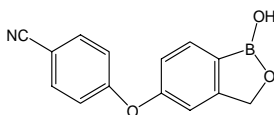
Heyman, I., Ip, E., Liu, L., Sanders, V. and Maples, K.

Anacor Pharmaceuticals, Inc., 1020 East Meadow Circle, Palo Alto, CA 94043, USA

Introduction

AN2728 is a novel oxaborole compound that decreases TNF α release through inhibition of PDE4 (See Posters 88,89,367). This new drug is currently in early stage clinical trials for psoriasis, a common skin disease that is characterized by chronic inflammation. Psoriasis is driven by a Th1 response and generally responds well to anti-inflammatory treatments, namely steroids and TIMS. Early studies suggest that AN2728 has the required *in vivo* biological activity and preclinical safety profile to be an effective topical treatment for this clinical condition.

AN2728 Structure/Nomenclature



5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole

Results

Preclinical toxicity data is available for *in vitro* studies and *in vivo* studies following systemic and topical administration to shrews, ferrets, rats, rabbits, mice and minipigs. AN2728 (1 μ M) was classified as a low potency hERG-channel blocker, minimizing concerns over cardiovascular safety. AN2728 (up to 5000 μ g per plate) demonstrated no mutagenic activity in the presence or absence of Aroclor-induced S9 liver fraction against *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 *uvrA*. AN2728 (up to 500 μ g/mL) demonstrated no clastogenic activity in the *In Vitro* Mammalian Chromosome Aberration Assay in the presence or absence of Aroclor-induced S9 using human peripheral blood lymphocytes and did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in the Rat Micronucleus Assay at oral doses up to 2000 mg/kg.

Following oral administration of 10, 30, and 100 mg/kg to shrews, (*Suncus murinus*), dose-responsive emetic effect was observed. The no-observed-effect level (NOEL) was 10 mg/kg, and was associated with significant plasma exposure. Following oral administration of 10, 30, and 100 mg/kg to ferrets, no emetic episodes were observed in any dose group although plasma levels were lower than those in shrews.

In the local lymph node assay, mice were dosed on the dorsal surface of both ears with AN2728 solutions (acetone/ethanol 50:50, v/v) containing 1%, 5% or 10% (w/v) for 3 days. Treatment with AN2728 at 1%, 5% or 10% (w/v) did not demonstrate skin sensitizing activity. In a rabbit eye irritation study, AN2728 Cream, 2%, was classified as a moderate irritant and AN2728 Cream Vehicle was classified as a non-irritant and in a rabbit skin irritation study, AN2728 Cream, 2%, was classified as a mild or slight irritant and was no more irritating than AN2728 Cream Vehicle. Abrasion did not affect irritation potential.

AN2728 was administered by oral gavage to Sprague-Dawley rats at dosages of 50, 150, 400 and 1000 mg/kg/day for 28 consecutive days with a 14-day recovery period (high dose and vehicle). Mortality and clinical signs were observed in males (only) while hematology, clinical signs and liver weight changes were observed in females dosed at 1000 mg/kg/day. Toxicokinetic parameters and plasma concentrations of AN2728 increased with increasing dose and the values in males were substantially greater than females by approximately 2-7 fold. Based on these results the NOEL in males was 150 mg/kg/day and in females was 400 mg/kg/day. Göttingen minipigs were dosed by dermal application once daily for up to 28-days with a cream formulation of AN2728 at concentrations of vehicle, 0.3%, 2% and 5% with a 14-day recovery period (high dose and vehicle). Varying degrees of erythema/edema were present primarily in the 2% and 5% concentrations but no systemic toxicity was present at any dose level. Plasma levels increased in a dose-related manner and were significantly higher on Day 28 relative to Day 1 in all dose groups. The NOAEL for the AN2728 Cream formulation was 0.3% for dermal toxicity and 5% for systemic toxicity.

Conclusions

- AN2728 is a novel oxaborole compound that is effective in both *in vitro* and *in vivo* anti-inflammatory studies.
- A comprehensive preclinical safety assessment program has been completed with AN2728 which showed that it was devoid of mutagenic, clastogenic and skin sensitizing potential, was emetogenic in shrews but not ferrets, was well tolerated orally in rats up to 150 (males) and 400 (females) mg/kg/day for 28-days, was a mild/moderate skin and eye irritant in rabbits (2%) and was locally irritating (2% and 5%) but devoid of any systemic toxicity (5%) in minipigs dosed topically for 28-days with a cream formulation.
- AN2728 has demonstrated both the *in vitro* and *in vivo* efficacy and preclinical safety profiles to enable clinical trials for the treatment of psoriasis.