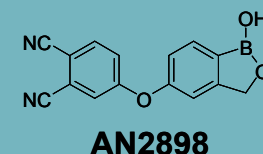




## Dermal Tolerability and Preliminary Efficacy of AN2728 and AN2898, Novel Boron-Based Small Molecules, in the Treatment of Psoriasis

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## Introduction

AN2728 and AN2898 are novel boron-based phosphodiesterase-4 inhibitors, which reduce the production of TNF-alpha, IL-12, IL-23, and other pro-inflammatory cytokines. AN2898 has a similar structure and mechanism of action to that of AN2728, but with greater in vitro potency and anti-inflammatory activity in a larger set of animal models. Both compounds have been formulated as ointments and are in development for the treatment of inflammatory skin disorders including psoriasis and atopic dermatitis. These studies sought to characterize the early dermal tolerability on healthy skin and preliminary efficacy on psoriatic skin for both molecules.

## Methods

The tolerability and efficacy of these two compounds were evaluated in two randomized, controlled phase 1 trials: a Dermal Irritation Test and a Psoriasis Plaque Test.

### Dermal Irritation Test

Twenty healthy male subjects each had 5 test fields on the back treated once daily under occlusion for 4 days. Test fields were randomly assigned and included AN2728 Ointment, 5%; AN2898 Ointment, 5%; vehicle ointment; water (aqua ad injectabilia, negative control); and sodium dodecyl sulfate (SDS), 0.2% (positive control). Clinical assessment of the test fields was performed by a blinded observer on days 2 to 5. Cumulative dermal irritation scores were calculated as the sum of all previous assessments scores.

### Psoriasis Plaque Test

Twelve adult males with chronic stable psoriasis each had 6 test fields on  $\geq 1$  plaque treated once daily under occlusion for 12 days. Test fields were randomly assigned and included AN2728 Ointment, 5%, in 2 fields; AN2898 Ointment, 5%, in 2 fields; vehicle ointment in 1 field; and betamethasone valerate cream, 0.1% (positive control) in 1 field. The primary endpoint was the change in inflammatory infiltrate thickness of the plaque as measured by ultrasound in micrometers ( $\mu\text{m}$ ). The secondary endpoint was the sum of clinical assessment scores (each treatment area was graded on a 5-point scale: -1, worsened; 0, no change; 1, slight improvement; 2, clear improvement but not completely healed; 3, completely healed). For 12 subjects per group the maximum sum score was 36, with higher scores indicating greater clinical improvement.

## Conclusions

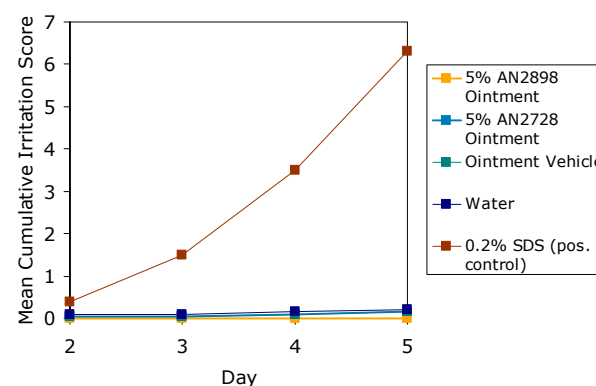
- **Dermal Irritation Test:** No irritation potential seen with either ointment
- **Psoriasis Plaque Test:** A significant antipsoriatic effect was found for AN2728 Ointment, 5% and AN2898 Ointment, 5% after 12 days of occlusive treatment on the basis of ultrasonic measurements of inflammatory infiltrate thickness
- AN2728 and AN2898 both demonstrated improvement in the clinical assessment of psoriatic plaque severity

## Results

### Dermal Irritation Test

AN2728, AN2898, and vehicle were well tolerated with only isolated slight erythematous reactions observed for AN2728 in 1 subject and for vehicle in 3 subjects. No irritation reactions were observed for AN2898 (Figure 1).

Figure 1. Cumulative Dermal Irritation Scores by Study Day



### Psoriasis Plaque Test

AN2728 and AN2898 both demonstrated significant reductions in mean inflammatory infiltrate thickness as measured by ultrasound (Figure 2) and clinical improvement in the psoriatic plaque as measured by sums of clinical assessment scores at Days 8 and 12 (Figure 3). Both AN2728 and AN2898 demonstrated statistically greater reduction (44% and 39%, respectively) in infiltrate thickness than vehicle (8%) and were well tolerated.

Figure 2. Plaque Infiltrate Thickness by Treatment and Study Day

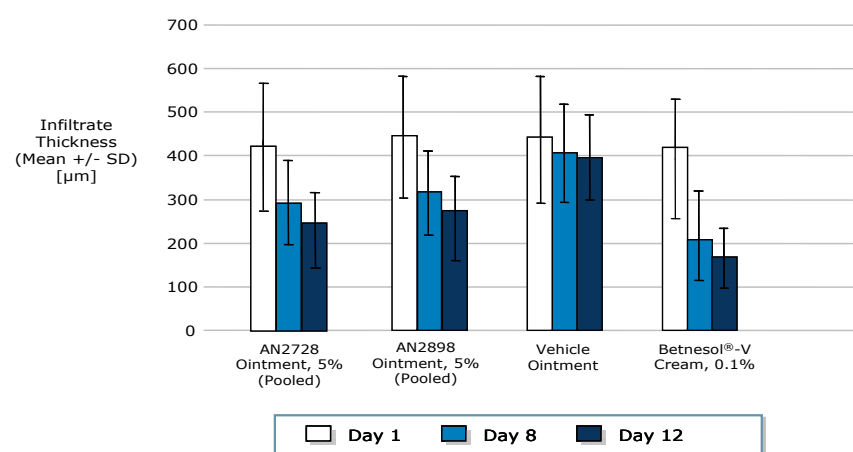


Figure 3. Score Sums of Clinical Assessment by Treatment and Study Day

