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Safety and Efficacy of AN2728 Ointment in a Phase 2b Dose-Ranging, Bilateral Study of Mild-to-Moderate Plaque Psoriasis

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Introduction

AN2728 (5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole) is a novel oxaborole compound being developed as a topical treatment for inflammatory skin diseases including plaque-type psoriasis. AN2728 demonstrates *in vitro* activity against a range of pro-inflammatory cytokines implicated in the pathogenesis of psoriasis including TNF- α , IL-12, and IL-23.¹

AN2728 has demonstrated efficacy in 7 psoriasis clinical trials, including 4 Phase 1 microplaque studies and 3 Phase 2 randomized, double-blind, vehicle-controlled, bilateral comparison trials. This poster presents the results from a recently completed dose-ranging Phase 2b trial, AN2728-PSR-203.²

Purpose

To determine the safety and efficacy of AN2728 Ointment, 2% and 0.5%, administered once daily (QD) or twice daily (BID), compared to Ointment vehicle in the treatment of mild-to-moderate plaque-type psoriasis.

Methods

Protocol Design

This multicenter, Phase 2b, randomized, double-blind, vehicle-controlled, 12-week, bilateral comparison study enrolled a total of 145 adult patients with mild-to-moderate plaque-type psoriasis. Patients were randomized (1:1:1:1) to 1 of 4 treatment regimens to 2 similar but anatomically distinct target plaques on the trunk or upper extremities for 12 weeks. The treatment groups included:

- 1) AN2728 Ointment, 2% to one target plaque and Ointment vehicle to second target plaque; applied BID (AM & PM)
- 2) AN2728 Ointment, 2% to one target plaque and Ointment vehicle to second target plaque; applied QD (AM)
- 3) AN2728 Ointment, 0.5% to one target plaque and Ointment vehicle to second target plaque; applied BID (AM & PM)
- 4) AN2728 Ointment, 0.5% to one target plaque and Ointment vehicle to second target plaque; applied QD (AM)

End Points

Plaque severity was measured using 9-point static scales for Overall Target Plaque Severity Score (OTPSS), which ranged from 0 (no evidence of disease) to 8 (very severe). Individual components of psoriasis plaque severity (erythema, scaling, and plaque elevation) were graded on similar 9-point scales.

In the primary endpoint analysis, the proportion of patients in whom the AN2728 Ointment, 2% BID-treated plaque achieved a greater decrease in OTPSS from baseline to Day 42 relative to the vehicle-treated plaque was compared to the proportion of patients in whom the reverse was true.

The secondary efficacy analysis compared the proportion of patients across treatment groups who had a greater decrease from baseline to Day 42 in OTPSS for the active-treated plaques relative to the vehicle-treated plaques. Exploratory efficacy analyses included a description of the proportion of patients in each treatment group whose plaques achieved an OTPSS of 0 or 1 and showed at least a 2-grade improvement from baseline across time points.

Results

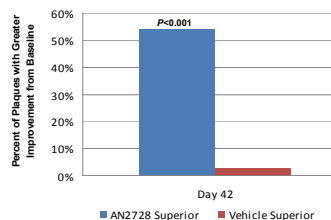
Baseline Characteristics

In this study, 36, 37, 35, and 37 patients were randomized (ITT), respectively, to apply AN2728 Ointment, 0.5% QD, 0.5% BID, 2% QD, and 2% BID to a target plaque; all 145 patients also applied Ointment vehicle to a second target plaque. Across treatment groups, the patients ranged in age (mean) from 46.8 to 48.3 years and were primarily male (83.3%-89.2%). The patients also presented at baseline with a mean OTPSS that ranged across treatment groups from 3.1 to 3.2, and had similar baseline mean erythema, scaling, and plaque elevation scores. There were no significant differences between treatment groups in any of the demographic or baseline characteristics.

Primary Efficacy Results (ITT)

At Day 42, 54.1% of the patients who applied AN2728 Ointment, 2% BID and Ointment vehicle had a greater decrease in OTPSS from baseline in the active-treated plaque than in the vehicle-treated plaque, compared to just 2.7% of the patients where the reverse was true ($P < 0.001$; **Figure 1**).

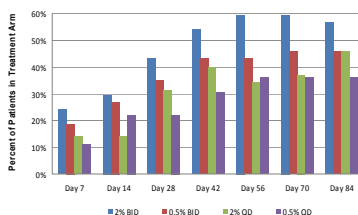
Figure 1. Primary Endpoint: AN2728 2% BID Treated Plaques Superior at Day 42 in OTPSS in Greater Proportion of Plaques than Vehicle-Treated Plaques



Secondary and Exploratory Efficacy Results (ITT)

Across treatment groups at Day 42, between 30.6% and 54.1% of patients had greater decreases in OTPSS for the active-treated plaques in a dose-responsive manner than for the vehicle-treated plaques, and the difference in proportions was significant within all but the AN2728 Ointment, 0.5% QD group ($P \leq 0.004$ for each significant comparison; **Figure 2, Day 42**).

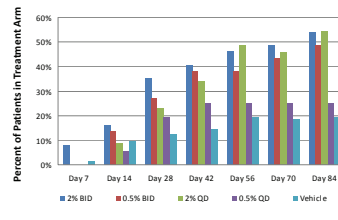
Figure 2. Proportion of Patients with Greater Improvement in OTPSS for AN2728-Treated Plaques than Vehicle-Treated Plaques by Study Day



Within treatment groups, the proportion of patients who had greater decreases in OTPSS from baseline to Day 42 for the active-treated plaque relative to the vehicle-treated plaque was larger than the proportion of patients in whom the reverse was true. The treatment response generally improved with increasing concentration and application frequency (**Figure 2**).

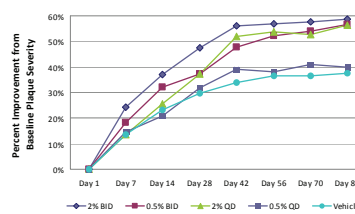
In an exploratory analysis describing the proportion of patients whose plaques achieved an OTPSS of 0 or 1 and at least a 2-grade improvement from baseline, treatment with AN2728 Ointment, 2% BID demonstrated an early and consistent benefit relative to the other treatment groups and vehicle across the treatment period. At Day 84, 54% of patients who received AN2728 Ointment, 2% BID had an OTPSS of 0 or 1 and at least a 2-grade improvement from baseline in the active-treated plaque (**Figure 3**).

Figure 3. Proportion of Patients Whose Plaques Achieved OTPSS of 0 or 1 with At Least a 2-Grade Improvement from Baseline



An examination of mean improvement in OTPSS scores by treatment group indicated a dose-responsive relationship with respect to concentration and frequency of application (**Figure 4**).

Figure 4. Mean Improvement from Baseline Plaque Severity by Study Day: All Treatment Groups



Improvements were also seen in all individual component signs of plaque severity (erythema, scaling, and plaque elevation).

Safety Results

No serious adverse events were reported. Overall, 51 patients (35.4%) experienced at least one AE during the study. The majority (86%) of AEs were considered unrelated or unlikely to be treatment-related and most (82%) were mild in severity. None of the treatment-related events was severe.

The most common AEs are listed in **Table 1**:

Table 1. Most Common AEs by Frequency

Preferred Term	n (%)
Pruritus	10 (6.9%)
Influenza	7 (4.9%)
Dermatitis contact	5 (3.5%)
Pharyngitis	5 (3.5%)

Local application site reactions requiring a dose modification were observed in 4 (2.8%) patients.

Treatment-related AEs included pruritus (reported by 6 [4%] patients, including at least 1 in each treatment group), "dermatitis contact" (reported by 3 [2%] patients, including at least 1 in the AN2728 Ointment, 2% BID and QD groups), and "transaminases increased" (reported by 1 [0.7%] patient in the AN2728 Ointment, 2% BID group).

Only 2 events led to discontinuation of treatment: "dermatitis contact" (related to treatment, mild in severity, in a patient assigned to the AN2728 Ointment, 2% BID group), and worsening of psoriasis (unrelated to treatment, moderate in severity, in a patient assigned to the AN2728 Ointment, 2% QD group).

Overall, AN2728 was generally well tolerated and no significant safety concerns were identified in this study.

Conclusions

- These Phase 2b efficacy results show that AN2728 Ointment is effective in reducing the severity and signs of plaque-type psoriasis
- Increasing treatment effects are generally correlated with increasing concentration and frequency of application
- Of the 4 treatment regimens, AN2728 Ointment, 2% BID may provide the greatest therapeutic benefit
- In general, AN2728 Ointment appears safe and well-tolerated in adult patients with mild-to-moderate plaque-type psoriasis

References

1. Nazarian R, Weinberg JM. AN-2728, a PDE4 inhibitor for the potential topical treatment of psoriasis and atopic dermatitis. *Curr Opin Investig Drugs*. 2009;10:1236-42.
2. Anacor Pharmaceuticals. Data on File (2011).