2. SYNOPSIS

Name of Sponsor/Company: Anacor Pharmaceuticals, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: AN2728 Ointment, 5%		
Name of Active Ingredient: AN2728 (5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole)		

Title of Study:
A Double-Blind, Randomized, Bilateral Study of the Safety and Efficacy of AN2728 Ointment, 5%, versus Ointment Vehicle in the Treatment of Subjects with Plaque Type Psoriasis

Investigator:
[redacted]

Study Centers:
One (1) investigational site in Mexico participated in the study.

Publication (reference): None

Studied Period (years):	**Phase of Development:**
Date first subject signed ICF: November 26, 2007 Date last subject exited the study: March 5, 2008	IIb

Objectives:
The objective of the study was to evaluate the safety and efficacy of AN2728 Ointment, 5%, compared to AN2728 Ointment Vehicle in the treatment of plaque type psoriasis.

Methodology:
The study was a randomized, multi-center, double-blind, bilateral design. Approximately 40 subjects were to be enrolled to complete 30 subjects. At the screening visit, the Investigator identified two psoriasis plaques representative of the severity of the disease necessary for inclusion into the study, located bilaterally on the arms or anterior/posterior trunk. Plaques located on the trunk were to be separated by at least 10 cm. Plaques were to be approximately the same size and of the same degree of disease as evidenced by the same overall severity score. The Investigator identified the plaques for the subjects and marked the targeted plaques on the instruction card for the subjects.

Two targeted plaques were treated on each subject, one plaque was randomized to treatment with AN2728 Ointment, 5%, and a separate anatomically distinct plaque was randomized to treatment with the AN2728 Ointment Vehicle. In addition to identifying the plaques for the subjects, the Investigator indicated on the subject medication application cards how much study medication to apply to each plaque, and recorded that information in the source documentation.

Total duration of subject participation in the study was to be no more than 65 days. The treatment period was 28 days. Subjects could be screened for enrollment into the study up to 28 days prior to randomization to allow for wash-out from topical psoriasis treatments and UV-B therapy. There was one follow-up visit 7 days following the end of treatment.

AN2728 Ointment, 5%, and AN2728 Ointment Vehicle were dispensed according to the

randomization schedule to subjects at the Baseline, Day 7, Day 14, and Day 21 visits, as necessary. Subjects received one tube each of AN2728 Ointment, 5%, and AN2728 Ointment Vehicle. Neither the Investigator nor the subject knew which tube contained AN2728 Ointment, 5% and which tube contained AN2728 Ointment Vehicle. Subjects applied medication from each tube, as instructed, twice daily (AM and PM prior to bedtime), waiting one hour after bathing/showering to apply medication. Subjects received verbal and written instructions on how much study medication to apply to each psoriatic plaque and how the medication was to be applied. Additionally, each subject received a study medication application card which measured how much study medication to apply and a diagram marking the targeted plaques to be treated.

Each treated plaque was evaluated using the Overall Target Plaque Severity Score at each visit (See Table 9.5.1.1-1). In addition to the Overall Target Plaque Severity Score, each treated plaque was evaluated for the individual signs of psoriasis (scaling, erythema, and plaque elevation). Subject visits occurred every 7 ± 2 days after baseline. At every visit, subjects were evaluated for adverse events and changes in concomitant medications. At Baseline and Visit 6 (Day 28), subjects also underwent laboratory evaluations that included CBC, chemistry, and urinalysis. All subjects exited from the study at Visit 7 (Day 35), which occurred one week after treatment completion.

Number of Subjects (planned, enrolled and analyzed):

Planned:	40 subjects
Enrolled:	35 subjects
Analyzed:	35 subjects

Diagnosis and Main Criteria for Inclusion:

Male and females of non-childbearing potential, over the age of 18 years, with the clinical diagnosis of stable plaque psoriasis. Subjects with two target plaques of similar severity, ≥ 5 cm^2 but ≤ 100 cm^2, bilaterally located (right/left) plaques on the arms or plaques located on the upper and lower trunk, and a target plaque severity score of 2-4 (mild to moderate).

Test product, dose and mode of administration, batch number:

AN2728 Ointment, 5%, applied topically twice daily (AM and PM prior to bedtime), waiting one hour after bathing/showering to apply medication.

Batch number: 1251

Duration of Treatment:

28 days

Reference therapy, dose and mode of administration, batch number:

AN2728 Ointment Vehicle, applied topically twice daily (AM and PM prior to bedtime), and waiting one hour after bathing/showering to apply medication.

Batch number: 1254

Criteria for Evaluation:

Primary Efficacy:

The hypothesis of this trial was that the plaques treated with AN2728 Ointment, 5%, would have a lower Overall Target Plaque Severity Score than plaques treated with vehicle alone. The proportion of subjects in which the AN2728 Ointment, 5%-treated plaque achieved a lower Overall Target Plaque Severity Score than the AN2728 Ointment Vehicle-treated plaque were compared to the proportion of subjects in which the AN2728 Ointment Vehicle-

treated plaque achieved a lower Overall Target Plaque Severity Score than the AN2728 Ointment, 5%-treated plaque, at Day 28.

Secondary Endpoints

Secondary efficacy endpoints were:

- Change from baseline to Day 7 in the Overall Target Plaque Severity Score and erythema, scaling, and plaque elevation assessments;
- Change from baseline to Day 14 in the Overall Target Plaque Severity Score and erythema, scaling, and plaque elevation assessments;
- Change from baseline to Day 21 in the Overall Target Plaque Severity Score and erythema, scaling, and plaque elevation assessments;
- Change from baseline to Day 35 in the Overall Target Plaque Severity Score and erythema, scaling, and plaque elevation assessments;
- Change from baseline to Day 28 in the Overall Target Plaque Severity Score and erythema, scaling, and plaque elevation assessments;
- Proportion of subjects in which AN2728 Ointment, 5%, achieved a lower Overall Target Plaque Severity Score than AN2728 Ointment Vehicle compared descriptively to the proportion of subjects in which AN2728 Ointment Vehicle achieved a lower Overall Target Plaque Severity Score than AN2728 Ointment, 5%, at Days 7, 14, 21, and 35.

Safety:

Safety endpoints were:

- Adverse Events (AEs);
- Laboratory test results.

Statistical Methods:

All statistical processing was performed using SAS® software, Version 9.1. Statistical significance was based on two-tailed tests of the null hypothesis resulting in p-values of 0.05 or less. The primary and secondary efficacy analyses were based on the Intent-to-Treat (ITT) population.

Demographic and Baseline Characteristics:

Demographic variables (age, gender, ethnicity, and race) were recorded in the eCRF. Because all subjects were treated simultaneously with AN2728 Ointment, 5% and AN2728 Ointment Vehicle, between treatment-group comparisons of baseline demographic data was not possible. As such, all demographic variables were summarized solely using descriptive statistics.

Baseline comparisons of the target plaque severity, scaling, erythema, and plaque elevation scores were analyzed with a paired t-test.

Efficacy Analyses

Primary Analysis

At the screening visit and all subsequent study visits (baseline [Day 1], and Days 7, 14, 21, 28, and 35), the Investigator determined an Overall Target Plaque Severity Score for each of the two treated plaques on every subject. The evaluation was made using a scale that ranged

in one-unit increments from 0 (none) to 8 (very severe). The primary analysis compared the severity scores at Day 28 between treatment groups using a two-sided sign test with a null hypothesis of 50%. The null hypothesis was rejected in favor of AN2728 Ointment, 5% if the proportion of plaques in the active treatment group with lower severity scores than the AN2728 Ointment Vehicle-treated plaques exceeded 50%. The null hypothesis was rejected in favor of the AN2728 Ointment Vehicle if the reverse was true.

Secondary Analysis

At all study visits, the Investigator evaluated Overall Target Plaque Severity, scaling, erythema, and plaque elevation for each of the two treated plaques on every subject. The evaluations were made using scales that ranged in one-unit increments from 0 (none) to 8 (very severe). The secondary efficacy analyses descriptively compared the differences in the severity scores for each of the four variables by treatment group from baseline to Days 7, 14, 21, 28, and 35. A paired t-test was used to compare the treatment group differences at Day 28.

Subgroup Analysis

Primary efficacy variables were summarized for the subgroups gender, age, and race.

Safety Analyses

The safety population consisted of all subjects who used the study medication and provided a safety evaluation. All AEs that occurred after application of the study medication during the study were classified on the basis of MedDRA terminology. Descriptions of AEs included the date of onset, the date the AE ended (if it resolved), the severity and seriousness of the AE, the relationship of the AE to study medication, and the outcome.

Reported AEs were summarized by the number of subjects reporting the events, as well as by System Organ Class (SOC), Preferred Term (PT), severity, seriousness, and relationship to study medication. For the summary of AEs by severity, each subject was counted only once within a SOC or a PT by using the AEs with the highest intensity within each category for each analysis. For the summary of AEs by relationship to study medication, each subject was counted only once within a SOC or a PT by using the AEs with the greatest reported relationship within each category. There were no treatment related, topical, or serious adverse events reported, therefore the planned summarizations were not performed.

Results from laboratory analyses (CBC, chemistry, and urinalysis) were tabulated using descriptive statistics. A tabulation of by-subject abnormal/out-of-range findings was provided and changes from baseline to Day 28 in all laboratory variables were tabulated.

Summary:

Demographic and Baseline Characteristics:

For the intent-to-treat population:

- The mean age of the subjects was 45.0 years (25 to 61 years);
- 100% (35) of the subjects were male;
- 97.1% (34) of the subjects were Hispanic; 2.9% (1) were White

The baseline characteristics of the targeted plaques are summarized in Tables 14.1.4.1 and 14.1.4.2 for the intent-to-treat and safety populations, respectively. For the intent-to-treat population:

Targeted Plaques Treated with AN2728 Ointment, 5%

- The average Overall Target Plaque Severity Score was 2.8: 25.7% (9) were grade 2, 68.6% (24) were grade 3, and 5.7% (2) were grade 4;
- The average severity score for scaling was 3.2: 17.1% (6) were grade 2, 42.9% (15) were grade 3, and 40.0% (14) were grade 4;
- The average severity score for erythema was 2.8: 28.6% (10) were grade 2, 60.0% (21) were grade 3, and 11.4% (4) were grade 4;
- The average severity score for plaque elevation was 2.7: 34.3% (12) were grade 2; 57.1% (20) were grade 3, 8.6% (3) were grade 4.

Targeted Plaques Treated with AN2728 Ointment Vehicle

- The average Overall Target Plaque Severity Score was 2.8: 25.7% (9) were grade 2; 68.6% (24) were grade 3, and 5.7% (2) were grade 4;
- The average severity score for scaling was 3.1: 14.3% (5) were grade 2, 60.0% (21) were grade 3, and 25.7% (9) were grade 4;
- The average severity score for erythema was 2.8: 25.7% (9) were grade 2, 65.7% (23) were grade 3, and 8.6% (3) were grade 4;
- The average severity score for plaque elevation was 2.7: 37.1% (13) were grade 2; 57.1% (20) were grade 3, and 5.7% (2) were grade 4.

No statistically significant differences were found among the treatment groups ($p \geq 0.254$).

Efficacy Results:

The hypothesis of this trial was that the plaques treated with AN2728 Ointment, 5%, would have a lower Overall Target Plaque Severity Score than plaques treated with vehicle alone. More subjects (68.6%) had a lower Overall Target Plaque Severity Score for the AN2728 Ointment, 5% treated plaque compared to the AN2728 Ointment Vehicle treated plaque.

- The magnitude of the mean reduction in Overall Target Plaque Severity, scaling, erythema, and plaque elevation evaluation scores from baseline to every time point was greater for the AN2728 Ointment, 5% treatment group than for the AN2728 Ointment Vehicle and statistically significant at the Day 28 assessment.
- More plaques treated with AN2728 Ointment, 5% had lower Overall Target Plaque Severity Score at Day 14, 21, 35 than those treated with AN2728 Ointment Vehicle.

Safety Results:

In this study, AN2728 Ointment, 5% was well tolerated. One subject (2.9%) reported two adverse events. The two adverse events (diarrhea and gingivitis) were mild in severity and considered unrelated to study medication; no topical adverse events were reported. No deaths or other serious adverse events were reported, and no subjects discontinued the study due to adverse events.

Conclusions:

The study statistically favored AN2728 Ointment, 5% over AN2728 Ointment Vehicle in the treatment of plaque type psoriasis. The change from baseline characteristics (Overall Target Plaque Severity, erythema, scaling, and plaque elevation) at Day 28 was statistically greater for plaques treated with AN2728 Ointment, 5% than those treated with AN2728 Ointment

Vehicle. Within 14 days, a greater percentage of subjects had lower Overall Target Plaque Severity Scores for the AN2728 Ointment, 5% treated plaque than AN2728 Ointment Vehicle treated plaque and this continued to the final Day 35 assessment.

AN2728 Ointment, 5% was well tolerated and no safety concerns were identified that would prevent conducting additional clinical trials.