CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-934

STATISTICAL REVIEW(S)

CLINICAL/STATISTICAL REVIEW AND EVALUATION

SEP 2 1998

NDA/DRUG CLASS:	20-934/3S
NAME OF DRUG:	Betamethasone Valerate Foam, 0.1%
APPLICANT:	Connetics Corporation
INDICATION(S):	Relief of Inflammatory & Pruritic Manifestations of Corticosteroid Responsive Dermatoses
TYPE OF REVIEW:	Clinical/Statistical
DOCUMENTS REVIEWED:	Studies: BMSP.C.006 (Phase III), Dated 12/17/97
MEDICAL REVIEWER:	Phyllis Huene, M.D./ HFD-540
STATISTICAL REVIEWER:	Shahla S. Farr, M.S./ HFD-725

I. INTRODUCTION

Psoriasis is a common chronic skin disorder, estimated to affect about 2% of the United States population. It usually appears initially between the ages of 15 and 30 years and may occur anywhere on the skin, including the scalp. Psoriasis typically appears as raised, sharply demarcated, red plaques with scaly surface.

Because of their anti-inflammatory and anti-pruritic actions, topical corticosteroids, including Betamethasone Valerate (BMV) have been used effectively for many years for the treatment of corticosteroid-responsive dermatoses of the skin and scalp, including psoriasis, contact dermatitis, atopic dermatitis, and seborrheic dermatitis,

The sponsor intends to demonstrate the safety and efficacy of BMV foam for the indication of "relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses".

II. REVIEW

The sponsor has submitted three studies:
1) A comparative vasoconstrictor study,
2) A Phase III, randomized, multicenter, double-blind, double-dummy, active-controlled clinical trial comparing the safety and efficacy of BMV foam, foam vehicle, BMV lotion, and lotion placebo, and
3) A comparative HPAaxis suppression study.

Of these, the Phase III trial is the only study requiring statistical review. Table I lists this pivotal study:

Table I
Summary of the Pivotal Study

Study # (# of Centers)	Study Design, Duration	Treatment Arm (n)	N	Endpoint
BMSP.C.006 (15)	Multicenter, Randomized, Active-Controlled, Double-Blind, Double Dummy (28 Days)	1) BMV Foam, 3g bid (64) 2) BMV Lotion, 1-1.5 mL bid (63) 3) Vehicle Foam, 3g bid (32) 4) Placebo Lotion, 1-1.5 mL bid (31)	190	1) Decrease in: - Scaling Score - Erythema Score - Plaque Thickness score from baseline 2) Investigators' Global

Study BMSP.C.006:

Objective & Design:
The objective of this trial was to assess the efficacy and safety of Betamethasone valerate 0.1% foam (BMV) in the treatment of psoriasis of the scalp as compared to vehicle and to a lotion dosage form of BMV.

This was a randomized, multicenter (15 centers), double-blind, double-dummy, active-controlled, parallel group, 28-day evaluation of the efficacy and safety of Betamethasone valerate foam 0.1% in ambulatory adult subjects with moderate to severe scalp psoriasis.

Subjects with moderate to severe psoriasis of the scalp were randomly assigned to one of four parallel treatment groups in a 2:1:2:1 ratio, BMV foam, vehicle foam, BMV lotion, and placebo lotion. The study consisted of a screening phase (one visit) and a four-week treatment phase (visits at baseline, Day 15 and Day 29). All treatments were administered twice daily (morning and evening) for 28 days to the entire scalp area even though some areas could be disease-free.

Primary & Secondary Efficacy Variables:
The primary efficacy variables were evaluated at endpoint:
1) Change in the scores of the signs of psoriasis (scaling, erythema and plaque thickness) at target lesion;
2) Investigators' Global Assessment of response to treatment.

The FDA's recommendation for global assessment has changed since these trials had been conducted. Therefore, in addition to investigating the mean percent change in the global assessment, this parameter was examined in a dichotomized fashion, with two outcome categories, success and failure. At the end of the treatment, if a subject's signs and symptoms are completely clear, they will be considered "Cured" (Success) and the rest will be classified as "Not Cured" (Failure).

The secondary endpoint variables consist of:
1) Pruritus score
2) Extent of Psoriatic Scalp Involvement;
3) Subjects' Global Assessment of response to treatment.

The investigators evaluated the target lesion for each sign of psoriasis using a five point grading scales from 0 (no plaque elevation, no scaling, no erythema) to 4 (very thick plaque with sharp edge, very thick coarse scales, and very dark red erythema).

Patient Population, Sample Size & Statistical Methods:
The study population included ambulatory male and female subjects, aged 18 years and older, with moderate to severe scalp psoriasis.

The results of this review are based on the Intent-to-Treat (ITT) population, where ITT includes all subjects who were randomized to the study and were given the study medication, regardless of their use of the dispensed drug. For subjects with no week 4 data available, their last observation data was carried forward. For subjects with no post baseline data, their baseline value was carried forward.

The study was designed to detect treatment differences with regard to change from baseline to Day 29 in the signs of scalp psoriasis (scaling, erythema, plaque thickness) and Investigators' Global Assessment of response.

The sample size was calculated based on detection of a clinical benefit of at least one unit (as measured on the severity scale for the signs of psoriasis), and also based on a 35% improvement between vehicle and BMV foam in the investigators' global assessment. A total of 190 subjects were randomized into the study which was the maximum sample size of the two estimates plus allowing 10% for dropouts and block size adjustments. The sample size calculations were attained with power of 80%, alpha level of 0.05, and were based on a two-sided test.

Baseline categorical demographic variables (race and sex) were analyzed using Chi-Square test. Continuous demographic variables (age, weight) were analyzed using one-way analysis of variance (ANOVA).

In order to demonstrate efficacy, the sponsor should establish statistical superiority of BMV foam to its vehicle and therapeutic non-inferiority of the foam formulation to the BMV lotion in all the signs and symptoms of psoriasis in addition to the investigators' global assessment at a two-sided alpha=0.05.

Demographics:
A total of 190 subjects were randomized to participate in this study. Of these, 64, 63, 32 and 31 subjects received the foam formulation, the lotion formulation, foam placebo and lotion placebo respectively.

Table II summarizes the demographics of these subjects.

Table II
Demographics of All Randomized Subjects
Study BMSP.C.006

	Whole Population (N=190)	BMV foam (n=64)	BMV Lotion (n=63)	Vehicle Foam (n=32)	Vehicle Lotion (n=31)	P-Value
Gender (n):						
Male	93 (49%)	28 (44%)	34 (54%)	15 (47%)	16 (52%)	0.7
Female	97 (51%)	36 (56%)	29 (46%)	17 (53%)	15 (48%)	
Race (n):						
White	181 (95%)	60 (94%)	58 (92%)	32 (100%)	31 (100%)	0.7
Hispanic	6 (3%)	3 (5%)	3 (5%)	0 (0%)	0 (0%)	
Black	1 (0.5%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	
Other	2 (1.5%)	1 (2%)	1 (2%)	0 (0%)	0 (0%)	
Age (Mean ± Std):	49 ± 16	47 ± 17	49 ± 14	51 ± 16	49 ± 18	0.8
Investigator (n):						
Bronsky	12 (6%)	4 (6%)	4 (6%)	2 (6%)	2 (6%)	
Dunlap	24 (13%)	8 (13%)	8 (13%)	4 (13%)	4 (13%)	
Faust	6 (3%)	2 (3%)	2 (3%)	1 (3%)	1 (3%)	
Fivenson	18 (10%)	6 (9%)	6 (10%)	3 (9%)	3 (10%)	
Guzzo	11 (6%)	4 (6%)	4 (6%)	2 (6%)	1 (3%)	
Lebwohl	12 (6%)	4 (6%)	4 (6%)	2 (6%)	2 (6%)	
Martin	12 (6%)	4 (6%)	4 (6%)	2 (6%)	2 (6%)	
Miller_B.	12 (6%)	4 (6%)	4 (6%)	2 (6%)	2 (6%)	
Miller_D.	18 (10%)	6 (9%)	6 (10%)	3 (9%)	3 (10%)	
Muglia	12 (6%)	4 (6%)	4 (6%)	2 (6%)	2 (6%)	
Parish	12 (6%)	4 (6%)	4 (6%)	2 (6%)	2 (6%)	
Rist	12 (6%)	4 (6%)	4 (6%)	2 (6%)	2 (6%)	
Savin	12 (6%)	4 (6%)	4 (6%)	2 (6%)	2 (6%)	
Washenik	11 (6%)	4 (6%)	3 (5%)	2 (6%)	2 (6%)	
Weinstein	6 (3%)	2 (3%)	2 (3%)	1 (3%)	1 (3%)	

As it is shown in Table II, no statistical differences were found among the four treatment groups in regards to the demographics of the subjects ($p>0.05$).

Clinical Efficacy Analysis & Results:

Table III illustrate the baseline and Week-4 values, as well as the change from baseline at Week-4 and the percent change from baseline at Week-4 for the primary endpoint variables for each treatment arm without the center interaction.

Table III
Mean ± SD &P-Values for
Baseline, EOT, the Difference & Percent Difference
for the Primary Endpoint Variables
(Without Center Adjustment)
Study BMSP.C.006

	BMV Foam (n=64)	BMV Lotion (n=63)	Vehicle Foam (n=32)	Vehicle Lotion (n=31)	P-Value				
					Whole	Foam vs. Lotion	Foam vs. Foam_Pl	Lotion vs. Lotion_Pl	Foam_Pl vs. Lotion_Pl
Erythema:									
Baseline	2.47 ± 0.62	2.48 ± 0.56	2.72 ± 0.68	2.58 ± 0.56	0.2				
Week-4	0.94 ± 0.99	1.30 ± 1.04	2.13 ± 0.91	2.03 ± 0.98	0.001	0.04	0.001	0.001	0.7
Difference	-1.53 ± 1.01	-1.17 ± 0.99	-0.59 ± 0.95	-0.55 ± 0.85	0.001	0.04	0.001	0.004	0.9
Percent Difference	-0.62 ± 0.39	-0.48 ± 0.39	-0.20 ± 0.33	-0.22 ± 0.32	0.001	0.03	0.001	0.002	0.8
Plaque Thickness:									
Baseline	2.56 ± 0.59	2.48 ± 0.59	2.59 ± 0.76	2.68 ± 0.65	0.5				
Week-4	0.61 ± 0.99	1.14 ± 1.13	1.84 ± 1.02	2.00 ± 1.15	0.001	0.006	0.001	0.001	0.6
Difference	-1.95 ± 0.92	-1.33 ± 1.05	-0.75 ± 0.95	-0.68 ± 1.17	0.001	0.001	0.001	0.004	0.8
Percent Difference	-0.78 ± 0.34	-0.55 ± 0.43	-0.29 ± 0.40	-0.23 ± 0.44	0.001	0.002	0.001	0.001	0.6
Scaling:									
Baseline	2.70 ± 0.71	2.71 ± 0.68	2.84 ± 0.77	2.81 ± 0.70	0.8				
Week-4	0.92 ± 1.09	1.19 ± 1.11	2.16 ± 1.05	1.87 ± 1.12	0.001	0.2	0.001	0.005	0.3
Difference	-1.78 ± 1.09	-1.52 ± 1.05	-0.69 ± 0.97	-0.94 ± 0.96	0.001	0.2	0.001	0.01	0.3
Percent Difference	-0.67 ± 0.38	-0.57 ± 0.39	-0.24 ± 0.34	-0.34 ± 0.38	0.001	0.1	0.001	0.006	0.3
Investigators' Global	2.42 ± 1.75	3.29 ± 1.95	4.81 ± 1.77	4.70 ± 1.88	0.001	0.009	0.001	0.001	0.8

As it is seen in Table III, no statistical difference was found among the four arms in regards to the baseline characteristics of the subjects ($p>0.05$).

Highly statistically significant results ($p<0.05$) were observed when BMV foam dosage was compared to its comparator, BMV lotion, and the vehicle arms in regards to Erythema, Plaque Thickness and Investigators' Global Assessment at Week-4, the change from baseline and the percent decrease from baseline, which could be interpreted as the superiority of BMV foam to the BMV lotion and the vehicle arms. However, the results of Scaling at Week-4, the difference from baseline and the percent change from baseline were not statistically significantly different between BMV foam and BMV lotion, although BMV foam showed better numerical outcomes ($p>0.05$).

Table IV represents the same analysis and results with center adjustment.

Table IV
Least Squares Means & P-Values for EOT, the Difference & Percent Difference for the Primary Endpoint Variables
(With Center Adjustment)
Study BMSP.C.006

	BMV Foam (n=64)	BMV Lotion (n=63)	Vehicle Foam (n=32)	Vehicle Lotion (n=31)	P-Value			
					Foam vs. Lotion	Foam vs. Foam_Pl	Lotion vs. Lotion_Pl	Foam_Pl vs. Lotion_Pl
Erythema:								
Week-4	0.96	1.27	2.04	2.02	0.09	0.001	0.001	0.9
Difference	-1.5	-1.19	-0.67	-0.58	0.1	0.001	0.01	0.8
Percent Difference	-0.62	-0.49	-0.23	-0.23	0.08	0.001	0.004	0.9
Plaque Thickness:								
Week-4	0.65	1.09	1.77	2.01	0.03	0.001	0.001	0.4
Difference	-1.94	-1.38	-0.82	-0.73	0.004	0.001	0.008	0.7
Percent Difference	-0.77	-0.57	-0.31	-0.24	0.009	0.001	0.001	0.6
Scaling:								
Week-4	0.93	1.12	2.05	1.87	0.3	0.001	0.004	0.5
Difference	-1.75	-1.50	-0.77	-0.97	0.2	0.001	0.03	0.3
Percent Difference	-0.67	-0.58	-0.27	-0.35	0.2	0.001	0.009	0.4
Investigators' Global	2.41	3.15	4.63	4.66	0.03	0.001	0.001	0.9

Table IV shows the results of the analysis with Center Interaction. As it is shown the results of Plaque Thickness, Scaling and Investigators' Global Assessment did not change from the previous analyses (analysis without the center interaction). However, the results of Erythema were not statistically significant after center adjustment ($p>0.05$).

Table V illustrates the results of the baseline and Week-4 values, as well as the change from baseline at Week-4 and the percent change from baseline at Week-4 for the secondary endpoint variables for each treatment arm without the center interaction.

Table V
Mean ± SD & P-Values
for Baseline, EOT, the Difference & Percent Difference
for the Secondary Endpoint Variables
(Without Center Adjustment)
Study BMSP.C.006

	BMV Foam (n=64)	BMV Lotion (n=63)	Vehicle Foam (n=32)	Vehicle Lotion (n=31)	P-Value				
					Whole	Foam vs. Lotion	Foam vs. Foam_Pl	Lotion vs. Lotion_Pl	Foam_Pl vs. Lotion_Pl
Pruritus: Baseline Week-4	2.56 ± 1.07 0.91 ± 1.29	2.68 ± 0.91 1.19 ± 1.18	2.47 ± 1.14 1.59 ± 1.16	2.52 ± 1.03 1.74 ± 1.34	0.8 0.007	0.2	0.01	0.04	0.6
Psoriatic Involvement: Baseline Week-4	3.98 ± 1.16 2.30 ± 1.49	3.83 ± 1.06 2.90 ± 1.56	3.78 ± 1.10 3.47 ± 1.44	3.87 ± 0.96 3.52 ± 1.21	0.8 0.001	0.02	0.001	0.06	0.9
Subjects' Global	2.27 ± 1.68	2.97 ± 1.67	4.25 ± 1.65	4.57 ± 1.65	0.001	0.02	0.001	0.001	0.5

foam is not in favor to lotion (RLD)

As it is shown in Table V, BMV foam showed superiority to the lotion formulation and to its vehicle in regards to Psoriatic Involvement and Subjects' Global Assessment at Week-4 ($p<0.05$). However, BMV foam was not statistically significantly different from the lotion dosage form in regards to Pruritus at Week-4 ($p=0.2$).

Basically, the results remained the same when the analysis were adjusted for the center interaction. However, BMV foam was statistically significantly different from the lotion formulation at Week-4 in regards to Psoriatic Involvement after center adjustment ($p=0.02$). In addition, BMV foam was not statistically significantly different from the lotion after center adjustment in regards to Subjects' Global Assessment ($p=0.09$).

In addition to the analysis of mean change and mean percent change from baseline in the primary endpoint variables, these parameters were examined in a dichotomized fashion, with two outcome categories, success and failure. At the end of the treatment, if a subject's signs and symptoms are completely clear, they are considered "Cured" (Success) and the rest are classified as "Not Cured" (Failure).

Table VI represents the actual counts, the proportions and the results of the analysis for the primary endpoint variables as well as the Subjects' Global Assessment.

Table VI
Number and Proportion of the Cured Subjects @ EOT & P-Values for the Primary Endpoint Variables, & Subjects' Global Assessment
(Without Center Adjustment)
Study BMSP.C.006

	BMV Foam (n=64)	BMV Lotion (n=63)	Vehicle Foam (n=32)	Vehicle Lotion (n=31)	P-Value	
					Whole	Foam vs. Lotion
Erythema	26 (41%)	16 (25%)	2 (6%)	1 (3%)	0.001	0.07
Plaque Thickness	42 (66%)	25 (40%)	5 (16%)	5 (16%)	0.001	0.003
Scaling	30 (47%)	22 (35%)	2 (6%)	4 (13%)	0.001	0.2
Investigators' Global	26 (41%)	16 (25%)	2 (6%)	2 (6%)	0.001	0.07
Subjects' Global	26 (41%)	15 (24%)	2 (6%)	1 (3%)	0.001	0.04

The above results did not change after controlling for the Investigator.

Since the two placebo arms were not statistically different from each other, they were combined and the same analyses were repeated. The results of these analyses were similar to that of previous analysis of the four arms.

In order to further look into the non-inferiority of BMV Foam to BMV Lotion, 95% confidence intervals were constructed around the difference (Foam - Lotion) in the success rates of all the signs and symptoms and the Investigators' Global Assessment at Week-4. Table VII illustrates these findings.

Table VII
95% Confidence Interval for the Difference in Success Rates (BMV Foam - BMV Lotion)
All Primary Endpoint Variables
Study BMSP.C.006

Primary Endpoint Variables	95% CI
Erythema	64, 63 (-0.02, 0.33) 41%, 25%
Plaque Thickness	64, 63 (0.08, 0.44) 66%, 40%
Scaling	64, 63 (-0.07, 0.31) 47%, 35%
Investigators' Global	64, 63 (-0.02, 0.33) 41%, 25%

As it can be seen in Table VII, the criteria for clinical equivalence (the 95% CI includes 0 and the lower bound is not smaller than -0.10) is evident in Erythema, Scaling and the Investigators' Global Assessment. However, for Plaque Thickness, the confidence interval does not include 0 and is on the positive side. Therefore, it can be inferred that the BMV foam formulation is superior to that of lotion.

Subset Analysis:

One hundred and fifty one (79%) of the subjects were younger than 65 years old. Table VIII summarizes the results of the analysis of the primary endpoint variables for the age categories of younger than 65, and 65 years and older separately.

Table VIII
Mean ± SD & P-Values
Percent Difference for the Signs/Symptoms
& Investigators' Global @ EOT
Age Subset Analysis
Study BMSP.C.006

Primary Endpoint Variables	Less than 65 (n=151)					65 & Older (n=39)				
	BMV Foam	BMV Lotion	Vehicle	P-Value		BMV Foam	BMV Lotion	Vehicle	P-Value	
				Whole	Foam vs. Lotion				Whole	Foam vs. Lotion
Erythema	-0.66 ± 0.36	-0.50 ± 0.39	-0.18 ± 0.27	0.001	0.02	-0.52 ± 0.46	-0.35 ± 0.36	-0.32 ± 0.44	0.4	0.4
Plaque Thickness	-0.84 ± 0.31	-0.60 ±0.41	-0.23 ±0.34	0.001	0.001	-0.63 ± 0.40	-0.27 ±0.44	-0.34 ± 0.61	0.2	0.1
Scaling	-0.72 ± 0.36	-0.59 ±0.40	-0.25 ± 0.34	0.001	0.07	-0.52 ± 0.44	-0.46 ±0.29	-0.43 ± 0.42	0.8	0.7
Investigators' Global	2.19 ± 1.57	3.13 ± 1.93	5.15 ± 1.29	0.001	0.006	3.13 ± 2.13	4.38 ± 1.77	3.53 ± 2.20	0.4	0.2

The 65 and younger group showed similar results to that of population as a whole. However, these results were not apparent for the older subjects. This might be because of the small sample size in that age category.

Foam is not superior to lotion (RLD)

Table IX gives the results of the analysis for each gender.

Table IX
Mean ± SD & P-Values
Percent Difference for the Signs/Symptoms
& Investigators' Global @ EOT
Gender Subset Analysis
Study BMSP.C.006

Primary Endpoint Variables	Male (n=93)					Female (n=97)				
	BMV Foam	BMV Lotion	Vehicle	P-Value		BMV Foam	BMV Lotion	Vehicle	P-Value	
				Whole	Foam vs. Lotion				Whole	Foam vs. Lotion
Erythema	-0.65 ± 0.32	-0.53 ± 0.34	-0.23 ± 0.35	0.001	0.2	-0.60 ± 0.43	-0.43 ± 0.44	-0.20 ± 0.30	0.001	0.07
Plaque Thickness	-0.84 ± 0.33	-0.66 ±0.43	-0.28 ±0.43	0.001	0.08	-0.74 ± 0.35	-0.43 ±0.40	-0.23 ± 0.41	0.001	0.002
Scaling	-0.79 ± 0.34	-0.61 ±0.38	-0.28 ± 0.38	0.001	0.06	-0.58 ± 0.39	-0.53 ±0.40	-0.30 ± 0.35	0.009	0.6
Investigators' Global	1.69 ± 1.01	2.79 ± 1.63	4.6 ± 2.03	0.001	0.01	2.94 ± 1.99	3.86 ± 2.15	4.91 ± 1.59	0.001	0.06

As it can be seen in Table IX, the results of the analysis for each of the gender groups follow the same trend as the whole population.

III. CONCLUSION:

The results of the study BMSP.C.006 indicate the superiority of the Betamethasone Valerate Foam, 0.1% over the vehicle ($p \leq 0.001$), and statistical equivalence of the foam formulation to the lotion dosage form for signs and symptoms (erythema, plaque thickness, scaling) of corticosteroid responsive dermatoses as well as the investigators' global assessment at Week-4.

In some cases, when comparing the foam to the lotion, statistically significant results were observed, which indicated the superiority of BMV foam to BMV lotion group.

The secondary variable (pruritus, psoriatic involvement and subjects' global assessment) also showed statistically significant results, indicating the superiority of the BMV foam to vehicle ($p=0.001$) and equivalence or superiority of foam to the lotion ($p \geq 0.05$).

The analysis of subgroups revealed the same trend as the whole population. However, this pattern was not observed for subjects 65 years and older. This might be due to small sample size in the older group.

According to the reviewing medical officer, the data presented by the sponsor did not raise any safety issues to be analyzed and addressed by the statistical reviewer. Further, this review has been discussed with the medical officer who is in full concurrence with the findings of the review.

Thus, the results of this Phase III trial provides statistical evidence to show that Betamethasone Valerate Foam, 0.1% is safe and effective in the treatment of signs and symptoms of corticosteroid responsive dermatoses.

/S/ 9/2/98

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Chron.
This review contains 11 pages.
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