CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-142

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

MAR - 3 2000

NDA/DRUG CLASS: 21-142/3S

NAME OF DRUG: Olux (clobetasol propionate) Foam, 0.05%

APPLICANT: Connetics Corporation

INDICATION(S): [redacted]

DOCUMENTS REVIEWED: A Phase 3 Study (CPCD.C.002), Dated 29, July 1999

MEDICAL REVIEWER: Phyllis Heune, M.D./HFD-540

STATISTICAL REVIEWER: Shahla S. Farr, M.S./HFD-725

I. INTRODUCTION:

The sponsor has submitted NDA 21-142 which includes three studies:

1) A comparative vasoconstrictor study
2) A Phase 3, randomized, multicenter, double-blind, double-dummy, active-controlled clinical
3) A comparative HPAaxis suppression study

Of these, the Phase 3 trial is the only study requiring statistical review to assess efficacy of Clobetasol Propionate Foam, 0.05% (Olux) in the treatment of Pruritic & Inflammatory Manifestations of Corticosteroid Responsive Dermatioses of the Scalp. Conducting only one adequate and well-controlled, Phase 3 study is acceptable by the Division for this indication.

Table I summarizes this pivotal trial:

Table I
Summary of the Pivotal Study

Study # (# of Centers)	Study Design (Duration)	Treatment Arm (n)	N	Endpoint
CPCD.C.002 (12)	Randomized, Multicenter, Double-Blind, Double-Dummy, Parallel, Active-Controlled (14 Days)	Clobetasol Foam bid (62) Clobetasol Solution bid (63) Vehicle Foam bid (31) Placebo Solution bid (32)	188	1. Investigator's Global Assessment 2. Erythema Score 3. Plaque thickness 4. Scaling Score

II. REVIEW:

Design, Patient Population, Primary Endpoint Variables, Statistical Methods:
The sponsor has conducted a Phase 3, multicenter (12 sites), randomized, double-blind, double-dummy, active-controlled study of subjects with moderate to severe scalp psoriasis (minimum score of 2 on a 0-4 scale for each of erythema, scaling, and plaque thickness) and involvement of at least 10% of the scalp. One hundred eighty-eight subjects were enrolled and randomized to one of four parallel treatment groups in a 2:1:2:1 ratio (Clobetasol foam: Vehicle foam: Clobetasol solution: Placebo solution), using random permuted blocks of six.

As per agreement between the sponsor and the Division, since no statistically significant difference was observed between the two placebo arms (placebo foam and placebo solution), these two arms were combined and the data was analyzed based on three arms instead of four.

In response to the comments received from the Agency on October 1, 1998 and March 10, 1999, regarding the design of Study CPCD.C.002, the sponsor redefined the primary response variable of this study from "Change in Mean Score at Day 15" to "Treatment Success at Day 15".

According to the agreement between the Division and the sponsor, Treatment Success is defined as subjects who had:
1) An Investigator's Global Assessment Score of "Completely Clear" or "Almost Clear".
2) An Erythema Score of 0 or 1
3) A Plaque Thickness Score of 0
4) A Scaling Score of 0 or 1, at Day 15.

The primary efficacy variable was based on day 15, however, the subjects were followed up to 29 days. In this review, the results of the analyses are presented at all the time points (Day 8, Day 15 and Day 29).

It was agreed at the protocol stage, in order for this drug product to prove efficacy, the sponsor has to demonstrate:
a) The superiority of Olux Foam 0.05% to the placebo arm, in the intent-to-treat (ITT) population. (ITT population is defined as all patients who were randomized and received drug, regardless of their use. At day 15, if an observation was missing, it was considered "Failure".)

b) Non-inferiority of Olux Foam 0.05% to the Solution form, in the per-protocol population.

For testing efficacy between the two treatment arms, a Chi-Square test was used for superiority, and a 95% Confidence Interval (CI) for non-inferiority, at a two-sided alpha=0.05.

Comparability of the two treatment groups at baseline was assessed using Chi-Square test at a two-sided alpha=0.05.

In order to show the non-inferiority, a 95% CI around the difference (Foam – Solution) for the Treatment Success rate will be constructed. The 95% CI should include 0 and the lower bound should not be less than –0.1.

The results presented throughout this document are based on the statistical reviewer's reevaluation of the data.

Demographics:

A total of 188 subjects from twelve centers were enrolled into this study, where 62 subjects were randomized into the Olux Foam, 63 into the Active Solution and 63 into the combined Placebo arm.

There were no dropouts in this study.

Tables II and III summarize the demographics and baseline characteristics of all subjects randomized.

Table II
Demographics
All Randomized Subjects

	Whole Population (N=188)	Olux Foam (n=62)	Clobetasol Solution (n=63)	Placebo (n=63)	P-Value
Gender:					0.3
Female	95 (51%)	28 (45%)	37 (59%)	30 (48%)	
Male	93 (49%)	34 (55%)	26 (41%)	33 (52%)	
Race:					0.3
White	173 (92%)	57 (92%)	60 (95%)	56 (89%)	
Other	15 (8%)	5 (8%)	3 (5%)	7 (11%)	
Age (Mean ± Std)	45 ± 15	46 ± 17	46 ± 15	44 ± 14	0.8
Investigator:					
1	16 (9%)	6 (10%)	5 (8%)	5 (8%)	
2	17 (9%)	6 (10%)	5 (8%)	6 (10%)	
3	14 (7%)	4 (6%)	5 (8%)	5 (8%)	
4	18 (10%)	6 (10%)	6 (10%)	6 (10%)	
5	9 (5%)	2 (3%)	4 (6%)	3 (5%)	
6	18 (10%)	6 (10%)	6 (10%)	6 (10%)	
7	18 (10%)	6 (10%)	6 (10%)	6 (10%)	
8	18 (10%)	6 (10%)	6 (10%)	6 (10%)	
9	18 (10%)	6 (10%)	6 (10%)	6 (10%)	
10	18 (10%)	6 (10%)	6 (10%)	6 (10%)	
11	12 (6%)	4 (6%)	4 (6%)	4 (6%)	
12	12 (6%)	4 (6%)	4 (6%)	4 (6%)	

Table III
Baseline Characteristics
All Randomized Subjects

	Olux Foam (n=62)	Clobetasol Solution (n=63)	Placebo (n=63)	P-Value
Erythema:				0.4
2	39 (63%)	34 (54%)	39 (62%)	
3	18 (29%)	25 (40%)	23 (37%)	
4	5 (8%)	4 (6%)	1 (2%)	
Plaque:				0.7
1	1 (2%)	1 (2%)	0 (0%)	
2	42 (68%)	37 (59%)	45 (71%)	
3	16 (26%)	22 (35%)	17 (27%)	
4	3 (5%)	3 (5%)	1 (2%)	
Scaling:				0.6
2	36 (58%)	38 (60%)	32 (51%)	
3	22 (35%)	22 (35%)	29 (46%)	
4	4 (6%)	3 (5%)	2 (3%)	
Pruritus:				0.9
0	1 (2%)	0 (0%)	2 (3%)	
1	6 (10%)	5 (8%)	6 (10%)	
2	17 (27%)	15 (24%)	17 (27%)	
3	26 (42%)	33 (52%)	29 (46%)	
4	12 (19%)	10 (16%)	9 (14%)	

As it is shown in Tables II and III, no statistical significant differences were found between the two treatment arms in regards to the demographics and baseline characteristics of the subjects ($p \geq 0.3$).

The entry criteria, as the sponsor had mentioned in the protocol, was subjects with moderate to severe scalp psoriasis (minimum score of 2 on a 0-4 scale for each of erythema, scaling, and plaque thickness). However, as it is seen in Table III, 2 subjects were enrolled into the study with a score of 1 for plaque.

Clinical Efficacy Analysis & Results:

The primary efficacy endpoint (Treatment Success) was analyzed based on ITT population.

Table IV summarizes the results of the analysis for subjects with Erythema score of 0 and 1 (clear and almost clear) at different time points.

Table IV
Erythema
(Clear & Almost Clear)

	Olux Foam (n=62)	Clobetasol Solution (n=63)	Placebo (n=63)	P-Value Foam vs. Plc	P-Value Foam vs. Lotn
Day 8	42 (68%)	35 (56%)	9 (14%)	0.001	0.2
Day 15	**50 (81%)**	**50 (79%)**	**16 (25%)**	**0.001**	**0.9**
Day 29	39 (63%)	37 (59%)	12 (63%)	0.001	0.6

Table V summarizes the results of the analysis for subjects with Plaque score of 0 (clear) at different time points.

Table V
Plaque
(Clear)

	Olux Foam (n=62)	Clobetasol Solution (n=63)	Placebo (n=63)	P-Value Foam vs. Plc	P-Value Foam vs. Lotn
Day 8	24 (39%)	18 (29%)	3 (5%)	0.001	0.2
Day 15	**41 (66%)**	**41 (65%)**	**4 (6%)**	**0.001**	**0.9**
Day 29	33 (53%)	23 (37%)	7 (11%)	0.001	0.06

Table VI summarizes the results of the analysis for subjects with Scaling score of 0 and 1 (clear and almost clear) at different time points.

Table VI
Scaling
(Clear & Almost Clear)

	Olux Foam (n=62)	Clobetasol Solution (n=63)	Placebo (n=63)	P-Value Foam vs. Plc	P-Value Foam vs. Lotn
Day 8	46 (74%)	41 (65%)	15 (24%)	0.001	0.3
Day 15	**55 (89%)**	**51 (81%)**	**23 (37%)**	**0.001**	**0.2**
Day 29	44 (71%)	38 (60%)	11 (17%)	0.001	0.6

Table VII summarizes the results of the analysis Investigator's Global Assessment of 1 and 2 (clear and almost clear) at different time points.

Table VII
Investigator's Global Assessment
(Clear & Almost Clear)

	Olux Foam (n=62)	Clobetasol Solution (n=63)	Placebo (n=63)	P-Value Foam vs. Plc	P-Value Foam vs. Lotn
Day 15	**46 (74%)**	**40 (63%)**	**5 (8%)**	**0.001**	**0.2**
Day 29	29 (47%)	28 (44%)	2 (3%)	0.001	0.2

As it is seen in Tables IV, V, VI and VII, highly significant results (p=0.001) were observed when Olux Foam was compared to the Placebo arm relative to Erythema, Plaque, Scaling and Global assessment at day 15, indicating the superiority of Olux to Placebo. In addition, no statistically significant results ($p \geq 0.06$) were observed when Olux Foam was compared to Clobetasol Solution. Controlling for center did not change these results.

Table VIII lists the results of the analysis for "Treatment Success" which is the basis for the approval of this NDA, which was indicated by the Division. Treatment Success included subjects who had:

An Investigator's Global Assessment Score of "Completely Clear" or "Almost Clear"
1. An Erythema Score of 0 or 1
2. A Plaque Thickness Score of 0
3. A Scaling Score of 0 or 1, at Day 15

Table VIII
Treatment Success

	Olux Foam (n=62)	Clobetasol Solution (n=63)	Placebo (n=63)	P-Value Foam vs. Plc	P-Value Foam vs. Lotn
Day 15	**39 (63%)**	**36 (57%)**	**1 (2%)**	**0.001**	**0.5**
Day 29	24 (39%)	20 (32%)	2 (3%)	0.001	0.4

As it is seen in Table VIII, highly significant results (p=0.001) were observed when Olux Foam was compared to the Placebo arm relative to the Treatment Success at day 15 and day 29, indicating the superiority of Olux to Placebo. On the other hand, no statistically significant results ($p \geq 0.4$) were observed when Olux Foam was compared to Clobetasol Solution. Controlling for center did not change these results.

In order to further look into the non-inferiority of Olux Foam to the Solution form, a 95% CI was constructed around the difference between the Foam's Treatment Success and Solution's Treatment Success (Foam – Solution), in the per-protocol population. One subject in the foam arm and one subject in the solution arm were eliminated from this analysis, since they did not meet the entry criteria (both had plaque score of less one at entry). Table IX illustrates these findings.

Table IX
95% Confidence Interval for the Difference
(Olux Foam – Clobetasol Solution)
@ Day 15

	Response Rate		95% C.I.
	Foam N=61	Solution N=62	(Foam – Solution)
Erythema	49 (80%)	49 (79%)	(-0.15, 0.17)
Plaque	40 (66%)	40 (65%)	(-0.17, 0.20)
Scaling	54 (89%)	50 (81%)	(-0.06, 0.22)
Global	45 (74%)	39 (63%)	(-0.07, 0.29)
Success	**38 (62%)**	**35 (56%)**	**(-0.11, 0.23)**

As it is seen in Table IX, the criteria for clinical non-inferiority (the 95% CI should include 0 and the lower bound should not be smaller than –0.1) of Treatment Success was not achieved. Although the 95% CI includes 0, but the lower bound was in fact smaller than –0.1.

The sponsor's results for the 95% CI in the Treatment Success at Day 15 for the difference is response rate between Foam and the Solution are similar to that of this reviewer's results (-11%, 23%).

Subset Analyis:
Subset analysis was done based on gender, age category (younger than 60, 60 and older).

Table X
Clear or Almost Clear @ Day 15
Females

	Olux Foam (n=28)	Clobetasol Solution (n=37)	Placebo (n=30)	P-Value Foam vs. Plc	P-Value Foam vs. Lotn
Erythema	23 (82%)	31 (84%)	9 (30%)	0.001	0.9
Plaque	18 (64%)	22 (59%)	2 (7%)	0.001	0.7
Scaling	25 (89%)	29 (78%)	11 (37%)	0.001	0.2
Global	22 (79%)	23 (62%)	3 (10%)	0.001	0.2
Success	**18 (64%)**	**20 (54%)**	**1 (3%)**	**0.001**	**0.4**

Table XI
Clear or Almost Clear @ Day 15
Males

	Olux Foam (n=34)	Clobetasol Solution (n=26)	Placebo (n=33)	P-Value Foam vs. Plc	P-Value Foam vs. Lotn
Erythema	27 (79%)	19 (73%)	7 (21%)	0.001	0.6
Plaque	23 (68%)	19 (73%)	2 (6%)	0.001	0.6
Scaling	30 (88%)	22 (85%)	12 (36%)	0.001	0.7
Global	24 (71%)	17 (65%)	2 (6%)	0.001	0.7
Success	**21 (62%)**	**16 (62%)**	**0 (0%)**	**0.001**	**0.9**

Table XII
Clear or Almost Clear @ Day 15
Less Than 60 Years of Age

	Olux Foam (n=47)	Clobetasol Solution (n=50)	Placebo (n=55)	P-Value Foam vs. Plc	P-Value Foam vs. Lotn
Erythema	42 (89%)	39 (78%)	12 (22%)	0.001	0.1
Plaque	36 (77%)	32 (64%)	4 (7%)	0.001	0.2
Scaling	42 (89%)	41 (82%)	19 (35%)	0.001	0.3
Global	39 (83%)	31 (62%)	4 (7%)	0.001	0.02
Success	**34 (72%)**	**27 (54%)**	**1 (2%)**	**0.001**	**0.06**

Table XIII
Clear or Almost Clear @ Day 15
60 Years & Older

	Olux Foam (n=15)	Clobetasol Solution (n=13)	Placebo (n=8)*	P-Value Foam vs. Plc	P-Value Foam vs. Lotn
Erythema	8 (53%)	11 (85%)	4 (50%)	0.9	0.08
Plaque	5 (33%)	9 (69%)	0 (0%)	0.07	0.06
Scaling	13 (87%)	10 (77%)	4 (50%)	0.06	0.5
Global	7 (47%)	9 (69%)	1 (13%)	0.1	0.2
Success	**5 (33%)**	**9 (69%)**	**0 (0%)**	**0.07**	**0.06**

* The results of the statistical analysis should be interpreted with caution, since the number of subjects are extremely small in this sub-category.

Highly significant results were observed when Olux Foam was compared to the Placebo arm in all the sub-categories for all the endpoints (p=0.001) (except for the older population, perhaps because the number of subjects in that sub-category was very small). However, no statistically significant results were found when Olux Foam was compared to the Solution form ($p \geq 0.06$). Only in the younger category, Global Assessment showed a statistically significant result when Foam was compared to the Solution form (p=0.02).

III. CONCLUSIONS:

The results of the analyses of efficacy of Study # CPCD.C.002 demonstrate that Olux Foam 0.05% is statistically significantly better than Placebo in the treatment of Corticosteroid Responsive Dermatioses of the Scalp at Day 15 (p=0.001).

However, Olux Foam did not meet the criteria for non-inferiority to the Clobetasol Solution form.

95% CI (Foam – Solution): (-11%, 23%)

The subset analyses relative to gender and age category (<60, ≥60) also demonstrated similar statistically significantly results favoring Olux Foam over Placebo (p=0.001) in all the sub-categories except the 60 years and older group (p≥0.06) which might be as the results of a very small sample size.

/S/ 3/8/00

Shahla S. Farr, M.S.
Mathematical Statistician, Biometrics III

/S/ 3/8/2000

Concur: Mohamed Al-Osh, Ph.D.
Acting Team Leader, Biometrics III

cc:
Archival NDA 21-142
HFD-540
HFD-540/Dr. Huene
HFD-540/Dr. Okun
HFD-540/Dr. Wilkin
HFD-540/Ms. Cintron
HFD-725/Ms. Farr
HFD-725/Dr. Al-Osh
HFD-725/Dr. Huque
Chron.

This review contains 9 pages.
Farr\X7-2076\c:\Data\wordfiles\Olux\NDA21142, Dated 2/10/2000

APPEARS THIS WAY
ON ORIGINAL

Statistical Review and Evaluation
Addendum

Date:

NDA/ Drug Class: 21-142/3S
Name of Drug: Olux (Clobetasol Propionate) Foam, 0.05%
Applicant: Connetics Corporation
Indication: [redacted]

Medical Reviewer: Phyllis Heune, M.D., HFD-540
Statistical Reviewer: Mohamed Alosh,HFD-725

1. Background:

The Statistical Review, dated March 8, 2000, compared the efficacy of Clobetasol Propionate Foam, 0.05% (Olux) with that of Clobetasol solution, in the treatment of pruritic and inflammatory manifestations of corticosteriod responsive dermatioses of the scalp based on the results of sponsor's Study CPCD.C.002. The Statistical reviewer concluded, based on success rates for the two treatments arms, and for equivalence margin of 0.10, that Olux foam did not meet the criteria for non-inferiority to the clobetasol lotion.

The purpose of this addendum is to present some additional information, which might be of help in making a regulatory decision, concerning the non-inferiority claim. The primary endpoint used for efficacy evaluation is treatment success, at Day 15, defined to meet the following criteria:

1) An investigator's Global Assessment Score of 'Completely Clear' or ' Almost clear'
2) An Erythema Score of 0 or 1
3) A Plaque Thickness Score of 0
4) A Scaling Score of 0 or 1

2. Efficacy Results:

Table 1 below presents the success rates for the treatment arms along with 95% C.I . intervals on the difference on the response rates for the two treatment arms, per-protocol population;

Table 1: Comparison of Response Rates for Foam Against Lotion, Study CPCD.C.002
Per-Protocol Population Analysis

Marker	Treatment Response		Difference	95% C.I .(Foam – Lotion)	
	Foam	Lotion	Foam –	Asymptotic	Exact
	n/N (%)	n/N (%)	Lotion		
Erythema	49/61 (80%)	49/62 (79%)	0.01	(-0.13, 0.16)	(-0.15, 0.20)
Plaque	40/61 (66%)	40/62 (65%)	0.01	(-0.16, 0.18)	(-0.16, 0.21)
Scaling	54/61 (89%)	50/62 (81%)	0.08	(-0.05, 0.21)	(-0.07, 0.25)
Global	45/61 (74%)	39/62 (63%)	0.11	(-0.05, 0.27)	(-0.06, 0.30)
Success	38/61 (62%)	35/62 (56%)	0.06	(-0.11, 0.23)	(-0.12, 0.26)

Data source: Sponsor's submission

It can be seen from the above table that the lower limit of the 95% C.I. for the success rate (-0.11) is slightly lower than the equivalence limit (-0.10). For non-inferiority it is required that the lower limit of the 95% C.I .for the success rate (-0.11) to be greater than the negative of the equivalence limit (-0.10). However, from the above table it can be seen that the lower limit of the 95% C.I is slightly lower than the equivalence limit (-0.10). It should be noted that the Foam response rate for each of the above endpoints as well as success rates is significantly more effective than vehicle ($p < 0.001$) and the confidence interval contains zero.
Table 1 shows that at least for 2 of the 4 markers, which define the success rate meet the non-inferiority criteria as outlined above.

3. Conclusion:

As the lower limit for the 95% (-0.11) is slightly lower than the negative of the equivalence limit (-0.10); one might consider other supporting information, such as those of the individual markers. For 2 out of the 4 markers, which define the success rate, the condition for inferiority of the foam relative to the solution is satisfied.

/S/ 4/24/00
Mohamed Alosh, Ph.D.
Mathematical Statistician

/S/ 4/25/00
Mo Huque, Ph.D.
Director, Division Biometrics III

Cc:
Arcival NDA 21-142
HFD-540/ Dr. Huene, Dr. Okun, Dr. Wlkin, Ms Cintron
HFD-725/ Ms. Farr, Dr. Alosh, Dr. Huque
Chronical

APPEARS THIS WAY
ON ORIGINAL

STATISTICAL REVIEW AND EVALUATION: 45 DAY MEETING REVIEW
(COMPLETED REVIEW FOR INTERNAL DISTRIBUTION ONLY)

NDA:	21-142
DRUG CLASS:	3S
NAME OF DRUG:	Olux (Clobetasol Propionate, USP) Foam, 0.05%
APPLICANT:	Connetics Corporation
SUBMISSION DATE:	July 29, 1999
INDICATION(S):	[redacted]
CONTROLLED CLINICAL TRIALS:	One Phase 3 Study (CPCD.C.002)
STATISTICAL REVIEWER:	Shahla S. Farr, M.S./ HFD-725
CLINICAL REVIEWER:	Phyllis Huene, M.D./ HFD-540
PROJECT MANAGER:	Kalyani Bhatt
45 DAY MEETING DATE:	September 27, 1999
WAS THE NDA FILED:	Yes
IF YES, DUE DATE:	May 29, 2000
USER FEE DATE:	May 29, 2000

SEP - 7

1. ORGANIZATION AND DATA PRESENTATION	YES	NO	N/A
A. Is there a comprehensive table of contents with adequate indexing and pagination?	√		
B. Are the original protocols, protocol amendments and proposed label provided?	√		
C. Are the following tables/listings provided in each study report?			
- Patient profile listings by center (includes all enrolled patients).		√	
■ No need for this, since the data will be submitted electronically.			
- Lost subject tables by center which includes reason and time of loss.	√		
- Intermediate analysis summary tables (gender, age, race/ethnic, etc.).	√		
D. Adverse event listings by center and time of occurrence relative to enrollment date.	√		

- Are adverse events from cited sources (foreign and domestic) provided? ____ ____ _√_

E. Is a CANDAR or an electronic submission of the data necessary? _√_ ____ ____

F. If the data have been submitted electronically, has adequate documentation of the data sets been provided? ____ ____ _√_
■ At this point in time, the data have not been submitted.

G. Are inclusion/exclusion (evaluability) criteria adequately coded and described? ____ ____ _√_

H. Are there discrepancies between CRF information and CANDAR/ jacket data? ____ ____ _√_
■ This reviewer has no access to the CRF information.

I. If the data have been submitted electronically, can laboratory data be easily merged across studies and Indications? ____ ____ _√_

II. STATISTICAL METHODOLOGY

A. Are all primary efficacy studies of appropriate design to meet basic approvability requirements, within current Divisional policy statements or to the extent agreed upon previously with the sponsor by the Division? _√_ ____ ____

B. For each study, is there a comprehensive statistical summary of the efficacy analyses which covers the intent-to-treat population, evaluable subject population and other applicable sub populations (age, gender, race/ethnicity, etc.)? _√_ ____ ____

C. Based on the summary analyses of each study, do you believe:

- The analyses are appropriate for the type data collected, the study design, and the study objectives (based on protocol and proposed label claims)? _√_ ____ ____

- Intent-to-treat (ITT and MITT) analyses are properly performed? _√_ ____ ____
• At this point, they seem to be.

- Sufficient and appropriate references were included for novel statistical approaches? ____ ____ _√_

D. If interim analyses were performed, were they planned in the

protocol and were appropriate significance level adjustments made?	____	____	__√__
E. Are there studies which are incomplete or ongoing?	____	__√__	____
F. Is there a comprehensive, adequate analysis of safety data as recommended in the clinical/statistical guideline?	__√__	____	____

III. FILEABILITY CONCLUSIONS

From a statistical perspective, is this submission or indications therein, reviewable with only minor further input fro sponsor?

- As long as the statistical and medical reviewers agree on the primary endpoint parameter, from a statistical Perspective this submission seems to be fileable.

/S/ Sept 7, 79

/S/
Shahla S. Farr, M.S.
Mathematical Statistician, Biometrics III

Concur: R. Srinivasan, Ph.D.
Team Leader, Biometrics III

cc:
Archival: NDA 21-142
HFD-540
HFD-540/Dr. Wilkin
HFD-540/Dr. Walker
HFD-540/Dr. Huene
HFD-540/Ms. Bhatt
HFD-725/Dr. Huque
HFD-725/Dr. Srinivasan
HFD-725/Ms. Farr
HFD-344/Dr. Pierro
Chron.

APPEARS THIS WAY
ON ORIGINAL