CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-300

BIOEQUIVALENCE REVIEW(S)

Fluticasone Propionate Ointment
0.005%
ANDA #76-300
Reviewer: Chandra S. Chaurasia

Altana Inc.
Melville, NY
Submission dates:
December 17, 2001
~~April 22, 2002~~
~~May 21, 2002~~

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Review of a Pilot Dose Response Study, a Pharmacodynamic Bioequivalence Study and Two Amendments

I. Introduction

Altana Inc. is seeking approval to market its Fluticasone Propionate Ointment, 0.005%. The firm has submitted pilot dose-response and pivotal in vivo bioequivalence studies based on the OGD guidance "*Topical Dermatologic Corticosteroids: In Vivo Bioequivalence, June 2, 1995*".

Type of Submission: Original ANDA

First Generic: Yes

Reference Listed Drug: Cutivate® Ointment 0.005% (NDA #19957, 12/14/1990; manufactured by Glaxo Wellcome)

Indications: Fluticasone Propionate, 0.005% is a medium potency corticosteroid indicated for the relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

History: As of the review of this ANDA (May 30, 2002), there were no control or protocol correspondence on this drug product in the OGD Bioequivalence Tracking Data Base.

II. Pilot Study – Dose-Response Study of Fluticasone Propionate Ointment, 0.005% (Vasoconstrictor Assay: Study No. 10128208)

A. Objective:

To determine the dose-response relationship for Cutivate® Ointment 0.005% to be used to estimate the ED_{50} of D1 and D2 parameters for use in a full bioequivalence study.

B. Study Information:

Clinical Site: [redacted]

Principal Investigator: [redacted]

Clinical Dates: August 17-19, 2001 (Vol. 1.3, pp. 985)

Subjects: Fifteen normal healthy non-tobacco-using (for 30 days prior to dosing) female subjects were enrolled in the study. Subjects' demographic data are summarized in the Table below. All the 15 subjects completed the study.

Demographic Data for Study 10128208:

No of Subj	Race /Ethnic Group						Sex		Age Group (Yr.)						Height (in)		Weight (lb.)	
Total	A[¶]	B[¶]	C[¶]	H[¶]	NA[¶]	OT[¶]	M	F	Mean	Range[§]					Mean	Range	Mean	Range
										R1	R2	R3	R4	R5				
15	0	0	4	11	0	0	0	15	29.3	0	13	2	0	0	64.1	58-69	134.7	94-165

[¶] A: Asian, B: Black, C: Caucasian, H: Hispanic, NA: Native American, OT: Other
[§] R1: <18, R2: 18-40, R3: 41-64, R4: 65-75, R5: >75

Inclusion/Exclusion Criteria: Listed in vol. 1.3, pp. 948.

Subject Selection:

Subject selection for this study was carried out according to the procedure described in the OGD guidance (*Topical Dermatologic Corticosteroids: In Vivo Bioequivalence, June 2, 1995).* Potential study participants were screened to determine blanching response to Cutivate® Ointment (fluticasone propionate ointment) 0.005%. A 10 µL of the ointment was applied to the upper arm (above the forearm), and left in place for 3 hours (± 15 minutes) under occluded conditions. The site was evaluated visually approximately 6-9 hours after application. All subjects were selected based on a demonstrated blanching response and the absence of any clinically significant findings on the medical history or clinical assessment. Selected subjects had no history of allergy or hypersensitivity to any corticosteroids or to any topical products. They had no skin condition or coloration that would interfere with the placement of test sites or the response or assessments of skin blanching. All subjects tested negative on a urine pregnancy test (Vol. 1.3, pp. 938).

Dosing Procedures:

Drug Treatment:	Cutivate® Ointment (Fluticasone Propionate Ointment) 0.005%
Manufacturer:	Glaxo Wellcome Inc.
Lot No.:	1A290
Expiration Date:	01/2003

Study Design: One Period, Randomized, Vasoconstrictor Study

Confinement/Restrictions: Described in Vol. 1.3, pp. 940. The subjects were dosed on 08/18/01 and completed the study approximately 30 hours after first application.

Application and Removal: Listed in Vol. 1.3, pp. 939.

The sponsor has followed the *staggered application and synchronized removal methodology* in this study.

Ten circular (approximately 1.6 cm diameter) application sites were designated on the flexor surface of each forearm between the wrist and the elbow. The sites were marked with numbers 1-10 on the right arm from wrist to elbow and 11-20 on the left arm from wrist to elbow for ease of identification. Care was taken that sites were not placed within 3 cm of the wrist or antecubital fossa. Of the ten sites, eight were assigned as treatment sites as determined by the randomization schedule (Vol. 1.3, pp. 956). Two untreated reference sites were also randomly assigned on each arm as reference sites.

After baseline chromameter and visual readings, an open washer was positioned over each site and taped to the forearm using hypoallergenic paper tape on the sides of the washer. The washers were not closer than 2 cm apart center-to-center. Using a 250 uL glass ——— syringe, a 10 uL application of Cutivate ointment 0.005% was applied to the 8 assigned sites on each arm at times according to the randomization schedule. Immediately after dosing, a piece of hypoallergenic paper tape was placed over the open area of the washer to occlude the site. The untreated sites were also occluded. Two sites on each arm were left untreated.

Cutivate ® ointment 0.005% was applied to 8 sites on both arms at 0.05, 0.25, and 1, 2, 3, 4 and 6 hours prior to removal. The applied ointment was spread evenly over the skin surface at each site with the conical tip of a 1.5-mL microcentrifuge tube

All applications were removed at the same time point (0.0 hour), with the shortest duration removed first. The washers were detached and the residual surface treatment was removed by gently wiping at least 3 times with separate cotton balls. The untreated sites on each arm were similarly wiped with a clean cotton ball.

Dermal Assessment:

The ——— ChromaMeter ——— was used in this study to measure the reflective colors from the skin surface.

ChromaMeter operators assessed the degree of blanching response at each site prior to treatment application and at 0, 2, 4, 6, 8, 10,12, 20, and 24 hours after removal. All sites were assessed under standard fluorescent lighting and at room temperature. The zero-hour assessments were performed within 15 minutes of their scheduled time, and the 2-hour through 24-hour assessments were made within $\pm$5 minutes of their scheduled time. Prior to the study, precision of the ChromaMeter operators were evaluated (please see below).

The chromameter operators were blinded as to the duration of application at each site. Chromameter assessments were based on a-scale measurements.

Precision of ChromaMeter (Method Validation):

The sponsor has documented precision of chromameter operators (————————) from replicate evaluations (mean of 5 a-scale readings, at least 3 minutes apart) at 4

untreated skin sites on each arm (total 8 sites for both arms) of at least four different subjects. The dates of these studies are 03/09/01 for the operators —— and ——, and 03/15/01 for—— and —— (Vol. 1.2, pp. 309-310). The between-site and within-site coefficients of variation were less than 9.2% and 6.2%, respectively for each of the three operators.

Please note the Pilot and Pivotal studies were conducted between August. 17-19, 2001 and October. 13-30, 2001, respectively.

Data Evaluation: Areas under the response curve for the ChromaMeter assessments were determined from the a-scale reading. The methodology is summarized below:

- The post-dose chromameter a-scale reading at each site and assessment time was first adjusted by subtracting the average value of the duplicate pre-dose (baseline) readings at the site. This baseline adjustment normalized the chromameter readings for variations in skin tone between the different sites on each subject's forearms.

- To compensate for skin tone changes that occur over time, the average baseline-adjusted value for the untreated sites on each arm was subtracted from the baseline-adjusted chromameter value for each site on the same arm at each assessment time. These "corrected, baseline-adjusted" chromameter values were used in all subsequent analysis.

- The sponsor has calculated chromameter areas-under-the-effect curve (AUEC) from 0-24 hours from the corrected, base line adjusted readings by the linear trapezoidal method. To conform to the usual form of the Emax model, all chromameter areas were multiplied by –1 before fitting and statistical analyses.

- The ED50 and Emax parameters were estimated using a population fitting technique.

C. Study Results:

Protocol Deviations: There were no protocol deviation reported in this study (Vol. 1.3, pp. 940).

Adverse Events: One out of 15 subjects reported headache of mild severity. The adverse event was resolved spontaneously, and was judged unrelated to the study medications.

Pharmacodynamic Data Analysis:

- The firm estimated ED_{50} and Emax parameters using a population fit of the ChromaMeter results by means of P-Pharm (Vol. 1.3, pp. 941). The firm's Emax model parameter estimates for ChromaMeter data are provided in Vol. 1.3, 942.
- The Division of Bioequivalence also analyzed the AUEC vs. dose duration data based on the non-linear mixed effect modeling method using P-Pharm. The results of population analyses performed by the Division and the firm are summarized below. The population model results using log-normalized data are given in Figures 1a and 1b.

Table 1: Estimation of Pharmacodynamic Parameters Using Nonlinear Mixed Effect Modeling (N=15)

ED50 Distribution	Data Analyst	Population Parameters	
		ED50 (%CV)	Emax (%CV)
Normal	Sponsor	149.6 (4.8)	22.5 (56.1)
Log-Normal	DBE	169.3 (56.9)	23.7 (55.0)

The firm's analyses were based on normal distribution for ED_{50}. However, based on exploratory graphic analyses of the model output, DBE determined that the ED_{50} was log-normally distributed (Figures 1a and 1b). Therefore the analyses were repeated using the homoscedastic error variance and log-normal distribution for ED_{50}. Based on this analysis the ED_{50} value was found to be 169.3 minutes.

D. Conclusion:

The Division's estimate for the ED_{50} for Cutivate® ointment is 169.3 minutes. The value reported by the firm is 149.6 minutes based on chromameter results. Based on the pilot study results, the sponsor has used dose duration of 150 minutes for the pivotal bioequivalence study. In addition, the Guidance accepts a demonstration of dose duration-response based on D1 within 0.25-0.5 times the observed ED50 and D2 within 2-4 times the observed ED50.

A lower duration of application (D1) at 75 minutes and a higher duration (D2) at 5 hours (300 minutes) were included to establish eligibility for BE comparisons.

E. Telephone Amendment dated April 22, 2002 on using occlusion system in drug application:

On April 19, 2002, the DBE requested the firm to clarify the following:

Why the sponsor used occlusion method for the drug- treated and untreated sites in its pilot and pivotal studies? The labeling of the reference-listed drug states "the treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive unless directed by the physician."

On April 22, 2002, the firm provided the following response:

1. *The CRO, ——— previous attempt to perform a dose response study on Fluticasone Cream, which is ten times more potent than Fluticasone Ointment, was unsuccessful in obtaining any useful data. Repeat study using light occlusion (paper tape not cellophane) gave useful reading. As per the 1995 Guidance, occlusive dressings are allowed under certain conditions, i.e., low potency corticosteroids.*
2. *Due to the ten times lower potency of Fluticasone Ointment the occlusive dressing method was used for the pilot and pivotal studies.*

Reviewer's Comment on Firm's Response to use of occlusion system:

The firm has not submitted any data on the dose response study on Fluticasone Cream conducted by ——— under occlusion conditions. The firm is, therefore, requested to provide data for further evaluation.

F. Telephone Amendment dated May 21, 2002: Additional Data from ———:

On April 30, 2002, the DBE requested the firm to provide data in support of the ——— dose response study on Fluticasone Cream under non-occlusion conditions. On May 21, 2002, the CRO ——— provided the following clarification and data on behalf of Altana Inc.:

"In 2000 ——— conducted an ED50 study for another client with fluticasone 0.05% cream (reference product Cutivate®) using un-occluded sites". Based on the data from this study presented in the Table below, the firm state*s that "the degree of blanching was extremely minimal and because of this an accurate calculation of ED50 could not be made."*

Dose Response Study No. 10016920: Summary Table: Mean results and Emax model parameter estimates for ChromaMeter areas:

Duration (Minutes)	ChromaMeter (mean)
15	-1.1
30	4.0
60	6.0
120	3.2
180	7.1
240	-0.0
300	4.4
360	2.8
Emax Standard Deviation CV%	4.3 5.6 130.0
ED50 (minutes) Standard Deviation CV%	1.8 3.5 195.0

The firm ——— further states that "*based upon experience with the cream and the fact that the ointment contains only 10% of the amount of active ingredient of the cream it was clear that a similar situation would occur with the ointment. Therefore as allowed in the Guidance: Topical Dermatological Corticosteroids: In vivo Bioequivalence Section IV.G, we conducted the ED50 study for the fluticasone ointment and the full bioequivalence study under occluded conditions."*

The firm further suggests that "*the enclosed data (referring to data in the above Table) demonstrates that fluticasone cream and ointment, while generally classified as a Group V potency product in fact demonstrates the type of vasoconstrictor response usually seen with Group VI and VII corticosteroid. Occlusion of the site is therefore essential to be able to conduct vasoconstrictor bioequivalence studies with either of these products.*"

Reviewer's Comments:

1. Based on the data submitted by the sponsor, fluticasone cream which contains 10 times greater amount of the active ingredient compared to the ointment failed to exhibit measurable dose response under un-occluded conditions. Therefore, the ointment which contains 10 times less drug is unlikely to exhibit meaningful dose response under similar conditions.

2. The Guidance Topical Dermatologic Corticosteroids: In vivo Bioequivalence, June 1995, states, "*Provided occlusion is allowed in the labeling of the specific reference listed drug, the pilot dose duration-response study and pivotal in vivo bioequivalence study may be conducted under occlusive film. ..... Evaluation of dose duration-response requires dose duration data at times less than ED50. Very short dose duration is difficult to conduct experimentally and tend to produce high variability in response. Thus occlusion may be appropriate only for the lower potency products, e.g., potency groups VI and VII.*"

3. Furthermore, from the labeling statement of the RLD Cutivate Ointment —*"the treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive unless directed by the physician" — one may interpret* that occlusion is allowed subject to physician's instructions.

4. Based on the above observations, in the reviewer's opinion the sponsor's justification of using the occlusion system for the pilot and pivotal studies is acceptable.

Overall Comments on Pilot Study:

The ED_{50} duration (150 min) and the use of D1 (75 min) and D2 (300 min) are acceptable.

III. Pivotal Study: Bioequivalence of Fluticasone Propionate Ointment, 0.005% Study No. 10128209

A. Objective:

To demonstrate *in vivo* bioequivalence between Altana's Fluticasone Propionate Ointment, 0.005% and Glaxo Wellcome's Cutivate® Ointment, 0.005%.

B. Study Information:

Clinical Site: [redacted]

Principal Investigator: ———————

Dosing Dates: (Vol.1.2, pp. 128)

Group 1: 10/13/01 (Subject # 01-28)
Group 2: 10/20/01 (Subject # 29-57)
Group 3: 10/31/01 (Subject # 57-68)

Subjects: Sixty-eight normal healthy female subjects were enrolled in the study (Vol. 1.2, pp. 126). All 68 subjects completed the study. Subjects' demographic data are summarized in the Table below:

Demographic Data for Study 10128209:

No of Subj	Race /Ethnic Group						Sex		Age Group (Yr.)						Height (in)		Weight (lb.)	
Total	A[¶]	B[¶]	C[¶]	H[¶]	NA[¶]	OT[¶]	M	F	Mean	Range[§]					Mean	Range	Mean	Range
										R1	R2	R3	R4	R5				
68	3	2	21	41	1	0	0	68	28.2	0	56	12	0	0	63.9	58-71	135.1	82-196

[¶] A: Asian, B: Black, C: Caucasian, H: Hispanic, NA: Native American, OT: Other
[§] R1: <18, R2: 18-40, R3: 41-64, R4: 65-75, R5: >75

Inclusion/Exclusion Criteria: Listed in Vol. 1.2, pp. 137.

Subject Selection: Same as that given for the pilot study.

Product Information: The following drug products were used in this study:

Test: Fluticasone Propionate ointment 0.005%, Altana Inc., Lot #G280, Mfg. Date: 04/2001; Batch Size: Bio Batch ———, Scale-up Batch ———

Reference: Cutivate ® (Fluticasone Propionate) Ointment, 0.005%, Glaxo Wellcome, Lot #1A290, Exp. Date: 01/2003 (same as used in the Pilot Study).

Study Design: The pivotal study was conducted as one-period study involving randomized applications of the test formulations to both arms along with the replicate applications of the calibrator doses (D1 and D2) of the reference product.

Randomization: The ointments were applied to 6 sites on the flexor surface of each forearm determined by the randomization schedule listed in Vol. 1.2, pp. 144-146. Consistent with the Agency guidance, the treatment randomization provided complementary applications on left and right arms. Two untreated (control) sites were also randomized on each arm.

Application and Removal: The arms of each subject were washed with a mild soap and gently dried at least 2 hours prior to initial dosing.

The sponsor has followed the *staggered application and synchronized removal methodology* in this study.

- Eight circular (approximately 1.6 cm diameter) application sites were designated on the flexor surface of each forearm between the wrist and the elbow. The sites were marked with numbers (1-8) on the right arm and 9-16 on the left arm from wrist to elbow for ease of identification. After baseline chromameter (in duplicate) readings, an open washer was positioned over each site and taped to the forearm using hypo-allergic paper tape on the sides of the washer. All sites were evaluated prior to dosing for the presence of any skin condition (e.g., coloration, freckles, moles, scratches, etc.) that would interfere with the assessment of the response of skin blanching.

- Using a 250 uL glass ——— syringe with a ———"Repeating Dispenser", a 10 uL application of each formulation was applied to the assigned sites on each arm according to the randomization schedule. The test and reference products were each applied to 2 sites on each arm. The reference product was also applied to 2 additional sites on each arm for D1 and D2 duration. All applications were spread evenly over the skin surface at each site with the tip of a 1.5-mL polypropylene microcentrifuge tube. Immediately after dosing, a piece of hypoallergenic paper tape was placed over the open area of the washer to occlude the site. Two sites on each arm were left untreated and were also occluded. The Guidance On Topical Corticosteroids (June 2, 1995) recommends two sites per arm for untreated control treatments and one site per arm for the RLD D1 and D2 treatments.

- Baseline assessments were started approximately 2 hours prior to first application. The test and reference products were applied to 6 sites on each arm; these treatments were applied 1.25 hours (reference product only), 2.5 hours (test and reference products in duplicate) and 5 hours (reference product only) prior to removal. All sites were on, or staggered about, the midline axis of the subject's forearm and at least 3 cm form the wrist or antecubital fossa.

- All applications were removed at the same time point (0 hour). The washers were detached and the residual surface treatment was removed by gently wiping the application site at least 3 times with separate cotton balls. The untreated site on each arm was similarly wiped with a clean cotton ball.

Housing and Meals: Described in Vol. 1.2, pp. 129.
Confinement/Restrictions: Described in Vol. 1.2, pp. 129.
Dermal Assessment: Same as that provided for the pilot study.

Precision of the ChromaMeter Operators Validation: Same as described above for the pilot study.

The degree of skin blanching was determined by chromameter at each site prior to treatment application, and at 0, 2, 4, 6, 8, 10, 12, 20 and 24 hours after drug removal (Vol. 1.2, pp. 128). The 0-hour assessments were made within 15 minutes of their scheduled time and the 2- through 24-hour assessments were made within $\pm$ 5 minutes of their scheduled time. All assessments were made under standard fluorescent lighting and at room temperature. The chromameter operators were blinded as to the treatment and duration of application at each site. Chromameter assessments were based on a-scale reading.

Data Evaluation: Described on page 128, Vol. 1.2

- The post-dose chromameter a-scale reading at each site and assessment time was obtained as described in the pilot study.

- Chromameter areas under the effect curve (AUEC) from 0-24 hours were calculated from the corrected, baseline-adjusted readings by the linear trapezoidal method.

- The ratio of the mean area under the response curve for the reference 300-minute duration (D2) to that of the 75-minute duration (D1) was calculated for each subject. Subjects whose D2/D1 ratio was at least 1.25 were considered qualified for inclusion in the statistical analysis. The firm states that the data from 30 subjects qualified for inclusion within these criteria using ChromaMeter results.

- Locke's method for calculating confidence intervals was applied to the chromameter area results from qualifying subjects.

C. Study Results:

Sixty-eight subjects entered and all of them completed the study.

Protocol Deviations: Subject 28, chromameter readings for 15 of 16 sites (site 8 missing) were obtained at the 6-hour assessment interval. An AUC 0-24 hr was calculated for this subject with the data available. The subject did non meet the D2/D1 $\geq$ 1.25 criteria and was not included in the BE comparison (Vol. 1.2, pp. 129).

Adverse Events: The firm reported a total of 5 mild adverse events. Two of these 5 events, one each of nasal congestion and headache were judged remotely related to study medications. These adverse events were resolved with medication (fluticasone nasal spray as needed during10/21/01 to 10/24/01, and Aleve, 2 tablets twice daily on 10/21/01, respectively). Three other events (one each of intermittent nausea, intermittent photophobia and vomiting) were judged remotely related to study medications, and were resolved spontaneously (Vol. 1.2, pp. 178).

Pharmacodynamic Data Analysis:

1. Based on the D2/D1 ratio criterion of 1.25, 30 subjects qualified for the chromameter results. ***Reviewer's Note:*** *Although the D2/D1 ratio for subject 67 was more than 1.25, the firm did not use this subject in data analysis, presumably due to no observed blanching in this subject (see Table 2 below).*

2. Mean $AUEC_{(0\text{-}24)}$ for the subjects for the test and reference products are shown in Table 2 below.

3. Locke's method for calculating confidence intervals was applied to the chromameter data from the qualifying subjects. The results are given in Table 3A below. The reviewer's calculated data analyses using 30 (excluding subject 67) and 31 (including subject 67)

subjects. Results based on Locke's method calculations performed by the sponsor are represented in Table 3B.

Table 2. Mean AUEC Test and Ref and Ratios of Mean AUEC D2/Mean AUEC D1

Sub#	Test Mean	Ref Mean	Mean D1	Mean D2	D2/D1
1	3.16	8.63	-0.49	18.33	-37.40
2	42.72	47.16	20.49	22.00	1.07
3	**10.95**	**11.24**	**3.49**	**17.58**	**5.04**
4	3.36	5.43	-17.40	29.68	-1.71
5	20.37	33.19	12.75	15.41	1.21
6	**47.41**	**44.02**	**19.80**	**54.74**	**2.76**
7	**13.57**	**7.38**	**6.61**	**19.81**	**3.00**
8	**7.50**	**1.32**	**3.24**	**7.47**	**2.31**
9	-2.26	-14.02	-2.97	3.17	-1.07
10	6.41	14.60	-4.51	35.06	-7.78
11	9.57	8.78	-0.19	34.64	-187.24
12	19.00	19.34	19.89	21.80	1.10
13	**15.17**	**17.62**	**1.08**	**29.18**	**27.14**
14	**38.78**	**30.33**	**13.41**	**44.91**	**3.35**
15	-0.08	-8.49	-0.30	9.80	-33.22
16	**28.39**	**23.80**	**11.86**	**33.58**	**2.83**
17	**10.58**	**4.45**	**0.61**	**7.30**	**12.07**
18	12.92	-6.13	-9.34	11.04	-1.18
19	**11.84**	**14.33**	**14.24**	**39.17**	**2.75**
20	**19.27**	**13.91**	**5.65**	**24.73**	**4.38**
21	-1.85	-3.91	-13.71	-4.17	0.30
22	28.89	46.02	32.57	29.73	0.91
23	**20.12**	**17.21**	**11.09**	**26.00**	**2.34**
24	6.63	14.23	-5.97	15.54	-2.61
25	**11.41**	**18.67**	**0.24**	**18.25**	**76.04**
26	**-7.45**	**1.07**	**3.99**	**9.91**	**2.48**
27	25.04	19.14	27.48	29.74	1.08
28	17.01	20.93	-10.40	32.02	-3.08
29	4.41	-0.32	-4.69	-1.61	0.34
30	32.77	26.46	18.43	21.30	1.16
31	**10.44**	**-1.06**	**8.39**	**11.16**	**1.33**
32	-1.74	0.47	-4.61	-5.29	1.15
33	**30.78**	**30.21**	**11.03**	**39.19**	**3.55**
34	17.49	14.80	-0.88	22.61	-25.69
35	-1.49	-3.56	16.59	15.05	0.91
36	4.63	15.38	-1.44	38.37	-26.74
37	**15.06**	**12.84**	**8.21**	**19.04**	**2.32**
38	**41.45**	**35.59**	**8.29**	**48.43**	**5.84**
39	-6.91	8.13	-0.88	8.59	-9.81
40	**27.75**	**35.34**	**2.98**	**22.61**	**7.59**
41	17.26	11.95	-8.87	15.73	-1.77
42	8.98	15.31	-4.19	6.91	-1.65
43	-7.27	1.21	-7.77	-4.96	0.64
44	**51.32**	**47.99**	**38.06**	**57.50**	**1.51**

45	19.76	31.94	-4.90	26.57	-5.43
46	3.52	1.33	-12.37	3.48	-0.28
47	**14.71**	**27.95**	**4.10**	**7.62**	**1.86**
48	16.79	12.22	9.98	-18.63	-1.87
49	**35.46**	**39.41**	**26.45**	**40.58**	**1.53**
50	**21.78**	**24.20**	**9.75**	**21.63**	**2.22**
51	**32.28**	**25.97**	**12.47**	**32.61**	**2.61**
52	**21.78**	**28.92**	**10.59**	**34.04**	**3.22**
53	**10.10**	**23.80**	**1.92**	**10.55**	**5.51**
54	5.36	23.34	-0.31	14.15	-45.63
55	-0.15	-2.16	1.13	-1.08	-0.95
56	**40.25**	**41.67**	**9.71**	**32.65**	**3.36**
57	7.90	27.12	-2.69	39.08	-14.53
58	**14.37**	**15.90**	**4.54**	**24.27**	**5.35**
59	**22.55**	**20.96**	**5.93**	**38.14**	**6.43**
60	7.48	0.97	-2.06	1.17	-0.57
61	16.59	25.98	-1.07	35.06	-32.92
62	**19.55**	**24.89**	**19.96**	**30.65**	**1.54**
63	39.91	35.62	52.46	53.34	1.02
64	**32.05**	**30.17**	**11.16**	**22.60**	**2.02**
65	14.97	11.65	-0.11	33.74	-306.68
66	29.02	29.71	-6.57	20.99	-3.19
67	**1.66**	**2.54**	**-0.27**	**-4.44**	**16.44**
68	15.34	1.56	20.16	20.01	0.99

Table 3A. Mean results for chromameter evaluation of Altana's test ointment vs. Cutivate® Ointment using Locke's Method (**as calculated by the Division**).

Assessment Method	N	Mean Area Under the Curve		T/R (%)	Confidence Intervals	
		Test	Reference		Low	High
Chromameter	31*	21.64	21.70	99.7	97.9	102.1
	30**	22.31	22.34	99.9	97.1	103.2

**Analysis includes data from subject 67.*
***Analysis excludes data from subject 67.*

Table 3B. Mean results for chromameter evaluation of Altana's test ointment vs. Cutivate® Ointment using Locke's Method (***as reported by the sponsor***: Vol. 1.2, pp. 131).

Assessment Method	N	Mean Area Under the Curve		T/R (%)	Confidence Intervals	
		Test	Reference		Low	High
Chromameter	30	22.3	22.3	99.9	91.3	109.1

IV. Formulation. Components and composition of the test and the reference products are given in the Table below:

Table 4. Comparative Formulations (Not to be released under FOI):

Ingredients	Test, %w/w	RLD, %w/w*	RLD, %w/w **
Fluticasone Propionate	0.005	0.005	0.005
Propylene Glycol, USP	[redacted]	[redacted]	[redacted]
Sorbitan Sesquioleate, NF	[redacted]	[redacted]	[redacted]

Microcrystalline Wax, NF	[redacted]	[redacted]	[redacted]
Liquid Paraffin[¶]	[redacted]	[redacted]	[redacted]

**%w/w based on values as reported in COMIS for NDA 19957*
***As reported by the firm based on values obtained from testing of the innovator drug product (Vol. 1.1, pp. 52).*
****Determined by difference of 100%*
[¶]The NDA formulation indicates Mineral Oil, which is the same as Liquid Paraffin (Remington: The Science and Practice of Pharmacy, 20th ed., 2000, pp. 1045 and 1233).

All inactive ingredients used in the test products are within the IIG range for topical dermatologic route of administration.

V. Comments:

1. The firm has conducted pilot and pivotal dose response studies according to OGD Guidance *Topical Dermatologic Corticosteroids: In Vivo Bioequivalence, June 2, 1995* on topical corticosteroids.

2. Based on the chromameter evaluation of skin blanching, the ratio of $AUEC_{(0-24)}$ between the test and reference product is 1. The 90% confidence intervals for chromameter results are within the 80-125% range. The study is acceptable.

3. There was no severe medical event reported during pilot and pivotal studies.

VI. Recommendations

The in vivo bioequivalence study conducted by Altana Inc., on its Fluticasone Propionate Ointment, 0.005%, Lot #G280 comparing it to the reference product, Cutivate® (fluticasone propionate) Ointment 0.005%, Lot #1A290 has been found acceptable by the Division of Bioequivalence. The results of this vasoconstriction study demonstrate that Altana's Fluticasone Propionate Ointment, 0.005% is bioequivalent to the reference product, Cutivate® 0.005% ointment manufactured by Glaxo Wellcome.

The firm should be informed of the above recommendations.

Chandra S. Chaurasia, Ph. D.
Review Branch I
Division of Bioequivalence

Date: 6/19/2002

RD INITIALED YHUANG
FT INITIALED YHUANG Date: 6/20/2002

Concur:
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

Date: 6/26/02

Fluticasone Propionate Ointment, 0.005% Altana, Inc.

ANDA #76-300

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BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA: 76-300 APPLICANT: Altana, Inc.

DRUG PRODUCT: Fluticasone Propionate Ointment, 0.005%

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these regulatory reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 76-300
ANDA DUPLICATE
DIVISION FILE
HFD-652/Bio Secretary-Bio Drug File
HFD-650/C.Chaurasia

Endorsements: (Draft and Final with Dates)
HFD-652/CS Chaurasia 6/19/2002
HFD-655/Gur J.P. Singh 6/19/2002
HFD-652/YC Huang 6/20/2002
HFD-617/KScardina 6/27/02
HFD-650/Dale Conner 6/26/02

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Printed in Final on 06/19/2002

BIOEQUIVALENCY – **Acceptable**

Submission Dates:
12/17/2001

1. **Other Options** **Strength: 0.005%**
Bio study Pilot Study (STU)
Outcome: **AC**

2. **Other Options** **Strength: 0.005%**
Bio study : Pivotal Study (STU)
Outcome: **AC**

~~3. **Amendment (4/22/2002)** **Strength: 0.005%**~~
~~**(Additional Data)**~~ Outcome: ~~**AC**~~

~~4. **Amendment (5/21/2002)** **Strength: 0.005%**~~
~~**(Additional Data)**~~ ~~Outcome: **AC**~~

APPEARS THIS WAY ON ORIGINAL

Outcome Decisions:
AC - Acceptable

WinBio Comments:

- Pilot and pivotal studies on fluticasone propionate ointment 0.005% are acceptable.

Fig. 1A: Graph representing population modeling (Homoscedastic error variance with ED50 arising from log-normal distribution)

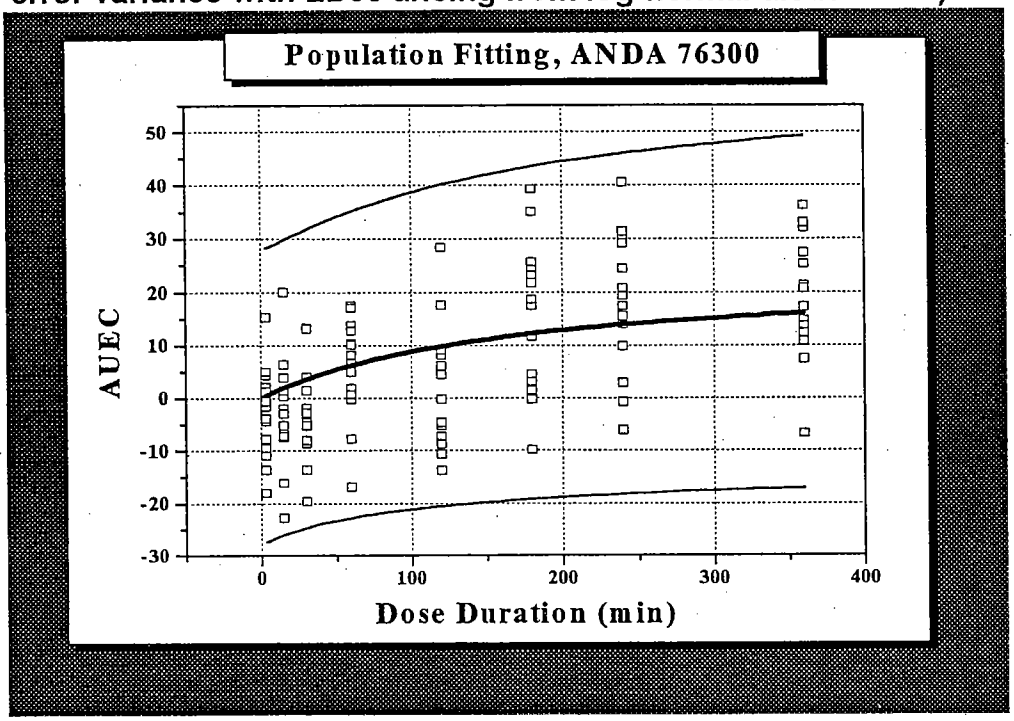
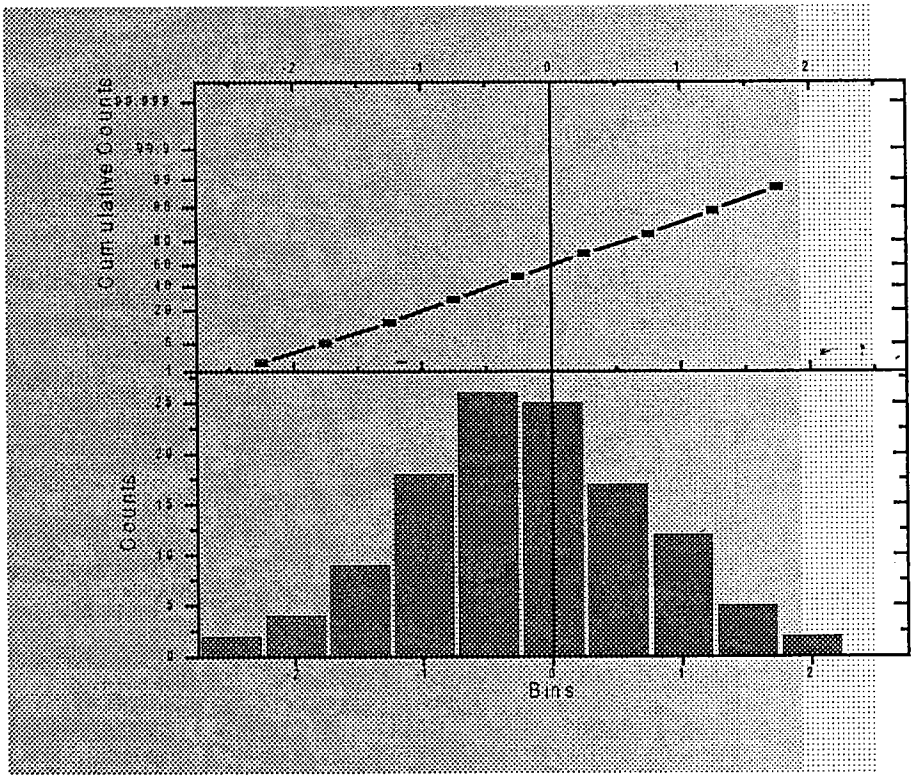


Fig. 1B. ED50 Frequency Plot



Data description (04-10-2002 - 09:28:19)

Input file : A:\76300.XPD
Number of subjects : 15
Route(s) of drug administration : Extravasc.
Dosage regimen : Single dose
Dose administered : 0
Number of observation(s) per subject : 8
Total number of observations : 120
Sample(s) type : AUEC

EM Algorithm: NO COVARIABLES (04-10-2002 - 09:34:27)

Model : Emax model
Measurement error variance : Homoscedastic
EM termination criteria (Relative parameter change) : .1
Marquardt precision on parameters : .001
Relative parameter change for gradient calculation : .001

Initial population parameter estimates :

	Mean	Std. Dev.	C.V.%	Distrib.
C50	5.12002E+0	5.544457E-1	1.082897E+1	Log.Normal
	(1.673387E+2)		**(5.999154E+1)**	
EMAX	2.34849E+1	1.283027E+1	5.463199E+1	Normal

Sigma = 100.8088

Nb of EM iterations : 1

Final population parameter estimates :

	Mean	Std. Dev.	C.V.%	Distrib.
C50	5.131574E+0	5.295888E-1	1.03202E+1	Log.Normal
	(1.692834E+2)		(5.689853E+1)	
EMAX	2.367213E+1	1.30171E+1	5.498915E+1	Normal

Sigma = 100.6468
Maximum Likelihood = -456.5155
AIC = 3.83763

Individual parameters

Subject	C50	EMAX
Sbj 1	179.5209	24.00486
Sbj 2	156.289	26.84495
Sbj 3	187.7305	6.93047
Sbj 4	203.9607	26.6917
Sbj 5	152.5791	29.76765
Sbj 6	167.3941	0.00499
Sbj 7	149.18	33.93959
Sbj 8	196.7957	13.51799
Sbj 9	118.621	39.33303
Sbj 10	201.1252	20.70346
Sbj 11	132.4886	35.75421
Sbj 12	201.5279	18.90022
Sbj 13	171.1797	24.23995
Sbj 14	171.7062	27.81214
Sbj 15	178.1354	26.63668
N	15.	15.
Mean	171.21559	23.67213
Min	118.621	0.00499
Max	203.9607	39.33303
S.D.	25.72673	10.53725
Var.	661.86475	111.03357
C.V.	15.02593	44.51331

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 76-300 SPONSOR: Altana, Inc.

DRUG AND DOSAGE FORM: **Fluticasone Propionate Ointment**

STRENGTH (S): **0.005%**

TYPES OF STUDIES: Pilot (Vasoconstrictor) and Pivotal (Bioequivalence) Studies.

CLINICAL STUDY SITE (S): ———————

ANALYTICAL SITE (S): N/A

STUDY SUMMARY: Pilot and pivotal studies are acceptable.

DISSOLUTION: N/A

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic No New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : CHANDRA S. CHAURASIA, Ph. D. BRANCH : I

INITIAL : CSChaurasia DATE : 6/19/2002

TEAM LEADER : YIH-CHAIN HUANG, Ph. D. BRANCH : I

INITIAL : YCH DATE : 6/20/2002

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC DATE : 6/26/02

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA: 76-300 APPLICANT: Altana, Inc.

DRUG PRODUCT: Fluticasone Propionate Ointment, 0.005%

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these regulatory reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research