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RESEARCH**

*APPLICATION NUMBER:*

**75633**

**BIOEQUIVALENCY REVIEW(S)**

Clobetasol propionate  
Emollient Cream USP, 0.05%  
ANDA #75-633  
Reviewer: Sikta Pradhan  
File #75633S2.599

1-1  
Taro Pharmaceuticals Inc.  
Bramalea, Ontario  
Submission Dates:  
May 7, 1999

## Review of a pilot dose response study and a pharmacodynamic bioequivalence study

### BACKGROUND

Clobetasol propionate 0.05% emollient cream (Temovate E<sup>R</sup> 0.05%, Glaxo) is a high potency corticosteroid (potency I) indicated for the relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. The reference product is indicated for topical dermatologic use only.

This application contains two in vivo vasoconstrictor studies; a pilot dose response study and a pivotal bioequivalence study based on the June 2, 1995 guidance. This guidance was issued by the Office of Generic Drugs (OGD) for documentation of in vivo bioequivalence of topical dermatological corticosteroids, and it recommended the use of dose duration method to study pharmacodynamic effects of topical corticosteroids. The pharmacodynamic effect is manifested as blanching of treated skin. In this method, vasoconstrictor (skin blanching) responses of increasing durations of treatment with the test formulation are measured as a function of time after treatment administration. Because different dose durations represent different times for skin exposure to the test product, it has been assumed that increasing dose durations would result in correspondingly increasing amount of the drug available to penetrate the skin.

OGD guidance is based on recommendations of the September 12-13, 1994, Generic Drugs Advisory Committee meeting with representation of Dermatologic Drugs Advisory Committee. The committee recommended that bioequivalence of dermatologic corticosteroids be documented using the vasoconstrictor assay and the dose duration method. The dose duration to be used in the bioequivalence study comparing the test and the reference product should be based on the population ED<sub>50</sub> value obtained from a pilot dose response study on the reference listed drug (RLD). The pivotal bioequivalence study also requires two calibrator dose durations D<sub>1</sub> and D<sub>2</sub>, in addition

to the ED<sub>50</sub>, where D<sub>1</sub> is approximately half of the bioequivalence study dose (ED<sub>50</sub>) and D<sub>2</sub> is approximately 2 times the bioequivalence study dose.

The methodology employed to determine bioequivalence of Taro's Clobetasol Propionate Emollient Cream USP, 0.05% is based on the above pilot-pivotal study concept. Both pilot and pivotal studies are reviewed hereafter.

### PILOT DOSE RESPONSE STUDY

**OBJECTIVE:** To demonstrate dose response relationship of Clobetasol Propionate Topical Emollient Cream USP, 0.05% (Temovate E<sup>R</sup> 0.05% Cream) manufactured by Glaxo, and determine the population ED<sub>50</sub> for its vasoconstrictor response.

**STUDY SITE, PERSONNEL AND DATES:** The vasoconstrictor pilot study was performed by

Principal Investigator:

Dosing Dates: March 28, 1997

Study Protocol and Informed Consent: The protocol used for this study (#9615052D) and Informed Consent were approved by

**SUBJECT SELECTION:** Fifteen (15) healthy female volunteers in the age range of 19 to 49 years were screened for vasoconstrictor response to the RLD, Temovate E<sup>R</sup> 0.05% Cream and enrolled for this study. Subjects were selected based on acceptable medical history and negative pregnancy test. Each subject signed informed consent. The exclusion criteria used for this study were the following:

- Significant history or current evidence of chronic or infectious skin disease.
- Strenuous exercise.
- Skin defects that may interfere with evaluation of test sites.
- Clinically significant history of alcohol or drug abuse.
- Alcohol consumption within 24 hours and throughout the study.
- Greater than 300 mg caffeine intake within 24 hours of study and during study.
- History of allergy to clobetasol, corticosteroids, gels, lotions, ointments or cosmetics.
- History or concurrent evidence of hypertension or other medical conditions requiring regular treatment with prescription drugs.

- Skin coloration, which would interfere with assessment of skin blanching.
- Use of prescription medicine within 7 days, over-the-counter medication within 48 hours.
- Use of topical steroids on flexor surface of forearm within 30 days of dosing.
- Use of lubricant creams within 24 hours of dosing.
- Use of tobacco products within 7 days.
- Use of dermatologic drug therapy on ventral forearms, including prior involvement in a topical corticosteroid pharmacodynamic/pharmacokinetic study within one month of the current study.
- Pregnancy or lactating females.

**STUDY DESIGN:** The pilot study was conducted as a single period study. Clobetasol propionate topical product, Temovate E<sup>R</sup> 0.05% emollient cream (Glaxo Wellcome), lot #6J232 (expiry date: 9/98) was used for this study. One 10 µl amount of the RLD (Temovate E<sup>R</sup> 0.05% Cream) was applied to 7 sites on the flexor surface of each subject's right forearm and left in place for 3 minutes to 1 hour. Skin blanching response was determined both by visual assessment and with a ChromaMeter at 0, 2, 4, 6, 8, 10, 12, 20 and 24 hours after treatment removal.

**METHOD VALIDATION:** The sponsor has documented precision of drug application and reproducibility of chromameter readings. was used in this study to measure the reflective colors from the skin surface, and six high-sensitivity silicon photocells are used by the meter's double-beam feedback system to measure both incident and reflected light.

Prior to the study, precision of the ChromaMeter operator was evaluated from replicate evaluations (5 readings, at least 3 minutes apart) at 4 untreated skin sites on each arm of at least 4 different subjects. The between-site CV was less than 13% and the within-site CV was less than 7% for this operator (pp 361, vol 1.2).

The ChromaMeter operator and visual evaluator 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 lighting and at room temperature. All assessments were made within 5 minutes of their scheduled time with the ChromaMeter assessment always preceding the visual evaluation.

The ChromaMeter operator and visual evaluator were blinded as to the duration of application at each site.

DATA ANALYSIS: The chromaMeter data were normalized for baseline values and changes in the color of the untreated skin as recommended in the guidance. The dose-response relationship was evaluated using the ChromaMeter results for all available subjects. SAS PROC NLIN was used to fit a two-parameter, Emax model,  $E = [(E_{max} * D)/(ED_{50} + D)]$ .

AUEC's were calculated for 0-24 hours after drug application using the trapezoidal rule. The pooled AUEC data as a function of the dose duration were fitted to the simple  $E_{max}$  model using \_\_\_\_\_ at the Agency to determine the population  $ED_{50}$ .

**RESULTS**

Based on the nonlinear mixed effect modeling, values of pharmacodynamic parameters calculated by the firm and the reviewer are as follows:

**Comparison of firm and reviewer values for pilot data fits**

Method	Parameter	Firm (A)	Reviewer (B)	A/B
Chromameter	$ED_{50}$ (min)	5.10 (48.8) <sup>1</sup>	6.06 (67.4) <sup>1</sup>	0.84
	$E_{max}$ (a-scale units*min)	-27.50 (11.6) <sup>1</sup>	-29.52 (32.7) <sup>1</sup>	0.93

Data are tabulated as population mean (CV%)

For the analysis performed by the reviewer, the graphics illustrating the population fitting are given in appendix 1 (attachment). These data are indicative of an approximate population  $ED_{50}$  value of 6 minutes and that is the dose duration value used for the pivotal bioequivalence study. A lower duration for 3 minutes (D1) and a longer duration for 12 minutes (D2) would also be included to validate that a subject is a good detector.

**PIVOTAL BIOEQUIVALENCE STUDY**

OBJECTIVE: To determine in vivo bioequivalence of the test and reference Clobetasol propionate emollient creams. The test product was Taro's Clobetasol propionate 0.05%

Emollient Cream and the reference product was Temovate E<sup>R</sup> manufactured by Glaxo.

STUDY SITE & PERSONNEL: Same as that mentioned for the pilot study.

INFORMATION ON PRODUCTS TESTED: The test and the reference products used in this study are the following:

Test Drug: Clobetasol Propionate E Cream, 0.05% (Taro Pharmaceuticals, Inc.), Lot #S114-51531; Manufacture date 08/20/98

Reference Drug: Temovate E<sup>R</sup> Emollient 0.05%, Glaxo , Lot #7J384, Expiration date October, 1999.

STUDY PROTOCOL AND INFORMED CONSENT: The study protocol (#9915003) and subject's informed consent were approved by the

SUBJECT SELECTION: Potential subjects were screened for vasoconstrictor response to the reference listed drug Temovate E<sup>R</sup> 0.05% as mentioned for the pilot study. All subjects were selected based on a demonstrated skin blanching response (pp 102-107).

DOSING GROUPS AND DATES: The subjects were entered into the study as 3 dosing groups. Subjects 01-20 were dosed in the first group mon 02/13/99; Subjects 21-40 were dosed in the second group on 02/20/99 and Subjects 41-60 were dosed in the third group on 02/27/99.

BIOEQUIVALENCE STUDY: A one-period, randomized, study was performed with sixty (59 completing) pre-screened, healthy female subjects. A 10 µl amount of each emollient cream was applied in triplicate to the flexor surface of each subject's forearms and left in place for 6 minutes. This duration time is based on ED<sub>50</sub> estimates from a previous dose response (pilot) study conducted at

The Temovate E<sup>R</sup> was also applied to two additional sites on each forearm for durations of 3 minutes (D1) and 12 minutes (D2), respectively. There were two untreated control sites on each arm.

The degree of vasoconstriction was determined by both visual assessment and with a ChromaMeter at pre-dose and at 0, 2, 4, 6, 8, 10, 12, 20 and 24 hours after treatment removal.

## DATA ANALYSIS AND RESULTS:

The average of the duplicate pre-dose ChromaMeter readings at each site and the average reading for the untreated ChromaMeter reference sites on each arm were used to normalize all the ChromaMeter readings. The firm has also reported the visual readings normalized in the same fashion. Area under the response curve (AUEC<sub>0-24</sub>) was determined for each treated site using both the visual and ChromaMeter data. The ratio of the mean area of the 12 minute Temovate<sup>R</sup> duration (D2) to that of the 3 minute Temovate<sup>R</sup> duration (D1) was determined for each subject.

The firm has stated that a subject was included in the ChromaMeter analyses if she met the qualification criteria,  $D2/D1 \geq 1.25$ . If a subject showed no vasoconstrictor response for the D1 (where, D1 is equal to or less than 0) duration, but the response ratio for the D2 duration to the ED<sub>50</sub> duration was at least 1.25, then the subject also qualified for inclusion in the data analysis. Thirty-two of 59 subjects met these qualifying criteria (29 subjects met the first criterion and 3 subjects met the second criterion) and their data were included in the statistical analysis.

The ratio of the ChromaMeter readings for the mean area of the 12 minute Temovate<sup>R</sup> duration (D2) to that of the 3 minute Temovate<sup>R</sup> duration (D1) was determined for each subject meeting  $D2/D1 \geq 1.25$  criterion (see Table 1).

Table 1

Subject #	Test (A)	Ref (B)	AUC (0-24)		
			A/B	Ax(-1)	Bx(-1)
5	22.823	11.222	2.03	-22.82	-11.22
6	4.902	8.05	0.61	-4.90	-8.05
8	7.912	13.645	0.58	-7.91	-13.65
9	23.472	16.858	1.39	-23.47	-16.86
10	14.278	21.28	0.67	-14.28	-21.28
11	11.073	9.373	1.18	-11.07	-9.37
12	17.252	21.578	0.8	-17.25	-21.58
15	3.57	14.905	0.24	-3.57	-14.91
16	13.752	17.792	0.77	-13.75	-17.79
17	21.863	12.682	1.72	-21.86	-12.68
20	9.248	0.41	22.56	-9.25	-0.41
21	20.577	14.362	1.43	-20.58	-14.36
22	7.797	17.51	0.44	-7.80	-17.51
23	25.14	21.808	1.15	-25.14	-21.81

26	8.372	9.995	0.84	-8.37	-10.00
28	12.268	7.817	1.57	-12.27	-7.82
29	15.063	14.385	1.05	-15.06	-14.39
30	22.828	26.987	0.85	-22.83	-26.99
31	33.312	33.148	1	-33.31	-33.15
34	16.183	9.242	1.75	-16.18	-9.24
35	34.467	38.223	0.9	-34.47	-38.22
36	22.833	19.668	1.16	-22.83	-19.67
39	4.758	3.3	1.44	-4.76	-3.30
41	25.24	30.97	0.81	-25.24	-30.97
42	39.063	31.737	1.23	-39.06	-31.74
45	18.667	18.838	0.99	-18.67	-18.84
47	23.917	22.702	1.05	-23.92	-22.70
48	26.242	22.268	1.18	-26.24	-22.27
52	17.488	23.025	0.76	-17.49	-23.03
55	7.368	9.522	0.77	-7.37	-9.52
56	23.515	33.895	0.69	-23.52	-33.90
58	43.075	37.038	1.16	-43.08	-37.04

↓ Locke's Method was applied for calculating confidence intervals and the results obtained by the firm were presented below:

#### CONFIDENCE INTERVALS EVALUATION

Evaluation Method	N	AUEC <sub>0-24</sub> (Mean)		Test/Ref	90% CI
		Test	Ref		
ChromaMeter	32	-18.70	-18.57	1.007	91.2-111.1
Visual Scoring	34	-16.16	-19.88	0.811	74.1-88.5

The Division of Bioequivalence has calculated the 90% confidence intervals using AUEC<sub>0-24</sub> data of all 32 subjects and also using AUEC<sub>0-24</sub> data of 29 subjects whose D<sub>2</sub>/D<sub>1</sub> ratios were ≥ 1.25. The results are presented below and in Tables 2 and 3 (attached).

(attached). These results show the 90% confidence intervals meet the acceptable limits in both cases.

Evaluation Method	N	AUEC <sub>0-24</sub> (Mean)		Test/Ref	90% CI
		Test	Ref		
ChromaMeter	32	-18.70	-18.57	1.007	91.2-111.1
ChromaMeter	29	-19.18	-19.18	1.000	90.1-110.8

Therefore, based on ChromaMeter results, Taro's test emollient cream meets the 90% CI criteria (80 - 125%) for bioequivalence.

**PRODUCT COMPOSITION:**

Composition of Taro's Clobetasol propionate 0.05% Emollient Cream is presented in Table 4 below:

Table 4

Ingredient	TEST % (w/w)
Isopropyl Myristate	
Cetostearyl Alcohol	
Dimethicone (350 cst)	
Cetomacrogol 1000	
Purified Water	
Propylene Glycol	
Imidurea	
Citric Acid	
Sodium Citrate	

COMMENTS:

1. The sponsor performed a pilot dose response study on RLD (Temovate E<sup>R</sup> 0.05% Cream) based on the OGD guidance. Based on the nonlinear mixed effect modeling of the chromameter dose response data, an ED<sub>50</sub> of approximately 5.1 minutes was calculated. ED<sub>50</sub> value based on visual scoring was 3.67 minutes. For the pivotal bioequivalence study the sponsor used D<sub>1</sub>, ED<sub>50</sub> and D<sub>2</sub> values of 3, 6 and 12 minutes, respectively. Based on reviewer's analyses the selection of these values is appropriate.
2. Sixty (60) subjects were dosed for pivotal bioequivalence study. Fifty-nine (59) subjects completed the study. For bioequivalence evaluation there were 32 "evaluable subjects".
3. Based on the chromameter evaluation of skin blanching, test product's AUEC<sub>0-24</sub> was 0.7% higher than that of the reference product. The 90% confidence intervals comparing these products were within the acceptable limit of 80-125%.

RECOMMENDATIONS

1. The *in vivo* bioequivalence study conducted by Taro comparing its Clobetasol propionate 0.05% Emollient Cream (lot #S114-51531) to the reference product, Temovate E<sup>R</sup> 0.05% Cream (lot #7J384) has been found to be acceptable to the Division of Bioequivalence. The results of this vasoconstrictor study demonstrate that Taro's Clobetasol propionate 0.05% Emollient Cream is bioequivalent to the reference product, Temovate E<sup>R</sup> 0.05% Cream, manufactured by Glaxo.
2. From the bioequivalence stand point the sponsor has met the requirements of *in vivo* bioequivalence on its Clobetasol propionate 0.05% Emollient Cream.

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Sikta Pradhan, Ph. D.  
Division of Bioequivalence  
Review Branch I

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8/5/99

Concur:           / S /          

Date: 8/11/99

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

cc: ANDA # 75-633S2.599 (original, duplicate), HFD-652 (Huang, Pradhan),  
HFD-650 (Director), Drug File, Division File  
Attachment - 8 pages

Appendix I (P.1-6)  
(Pilot Study)

ate : 07-01-1999

Individual parameters

Subject	C50	EMAX
Sbj 1		
Sbj 2		
Sbj 3		
Sbj 4		
Sbj 5		
Sbj 6		
Sbj 7		
Sbj 8		
Sbj 9		
Sbj 10		
Sbj 11		
Sbj 12		
Sbj 13		
Sbj 14		
Sbj 15		
N	15.	15.
Mean	8.45025	-29.52575
Min		
Max		
S.D.	6.97692	7.37121
Var.	48.67746	54.3347
C.V.	82.56474	-24.96535

ate : 07-01-1999

EM Algorithm: NO COVARIABLES (07-01-1999 - 10:24:26)

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	1.79176E+0 (6.000003E+0 )	7.728195E-1	4.313187E+1 (9.03944E+1 )	Log.Normal
EMAX	-2.596664E+1	8.829488E+0	3.40032E+1	Normal

Sigma = 1

Nb of EM iterations : 5

Final population parameter estimates :

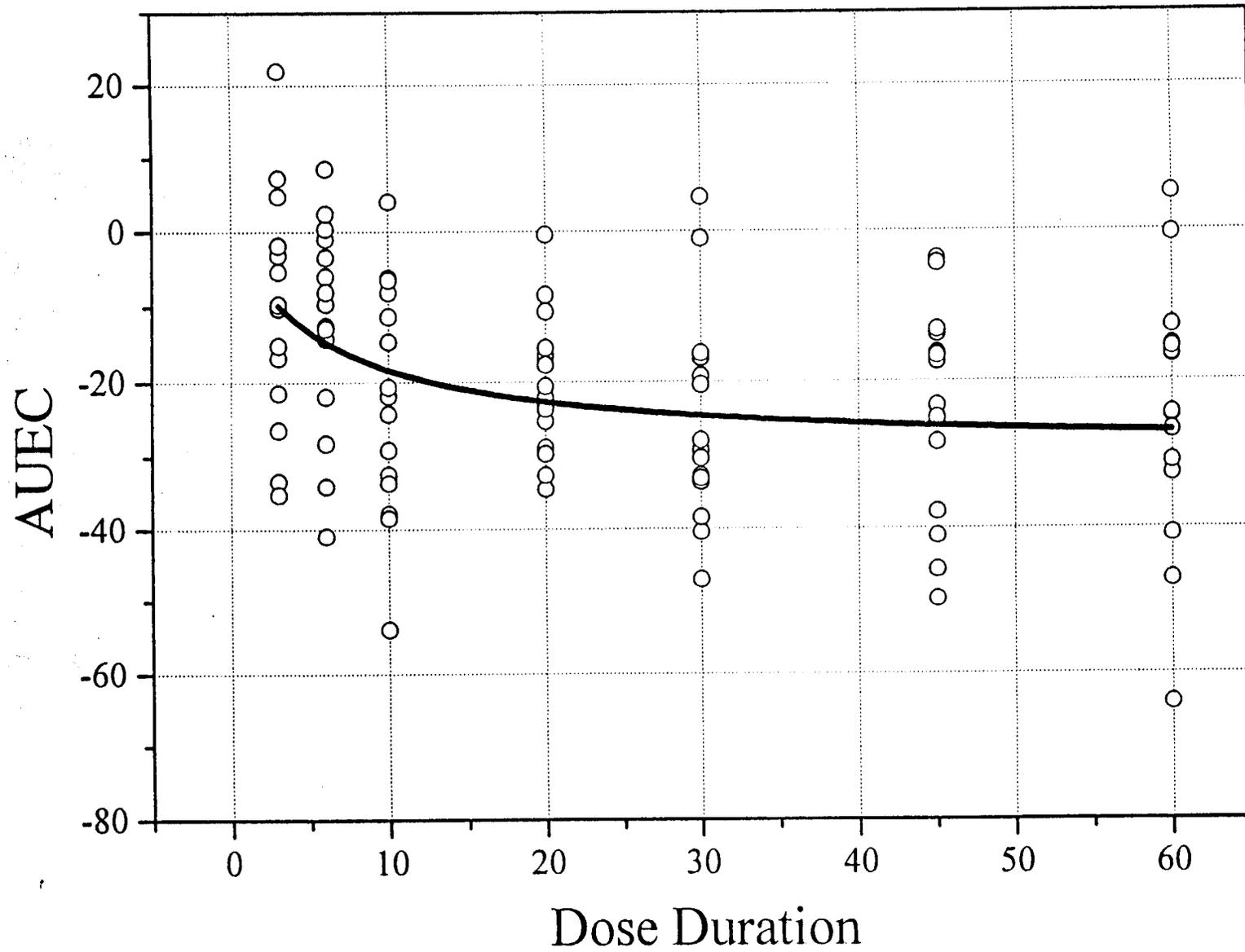
	Mean	Std. Dev.	C.V.%	Distrib.
C50	1.801738E+0 (6.060173E+0 )	1.213593E+0	6.735677E+1 (1.833429E+2 )	Log.Normal
EMAX	-2.952575E+1	9.656117E+0	3.270405E+1	Normal

Sigma = 121.4684

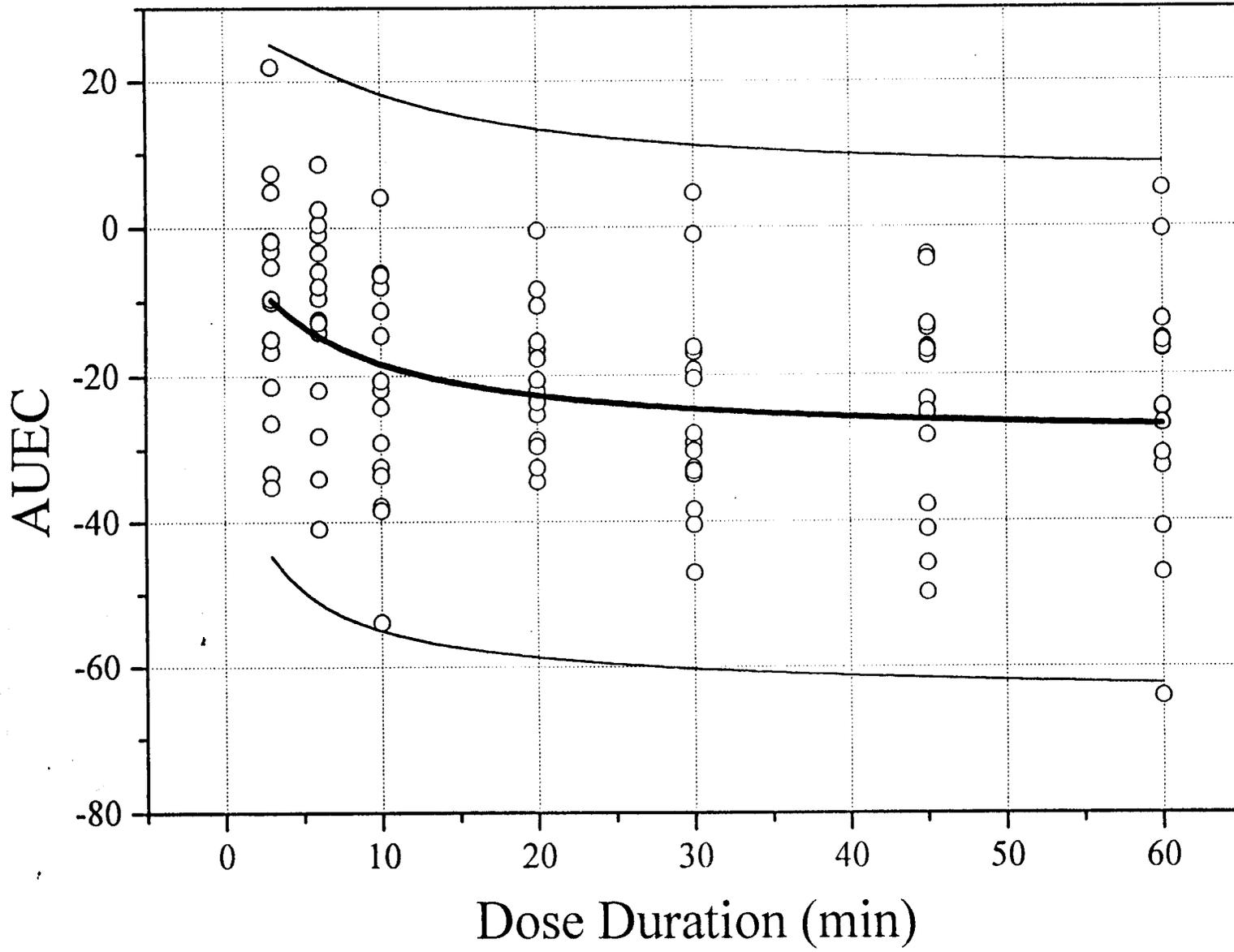
Maximum Likelihood = -415.7412

AIC = 3.997535

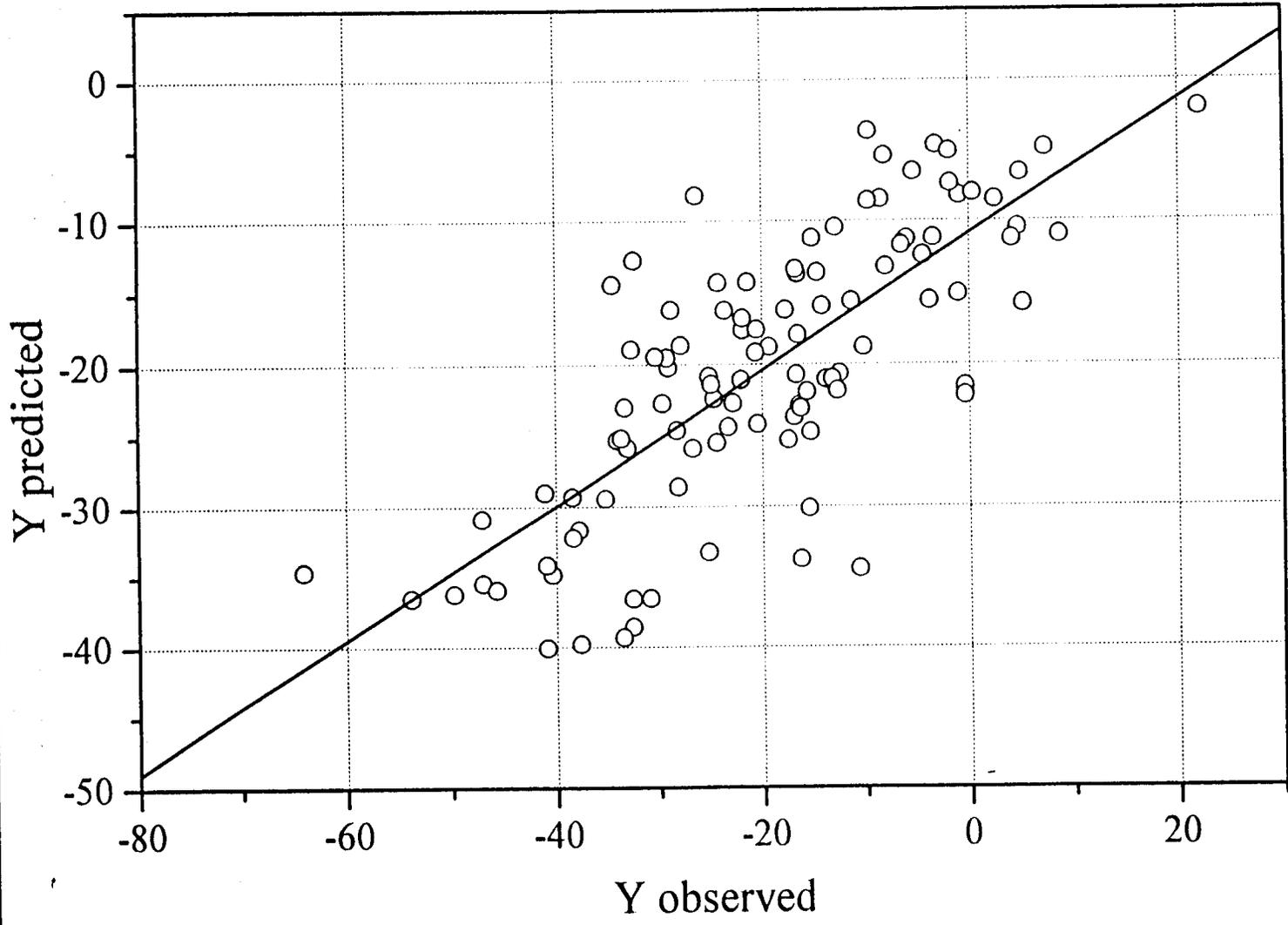
# Population Fitting

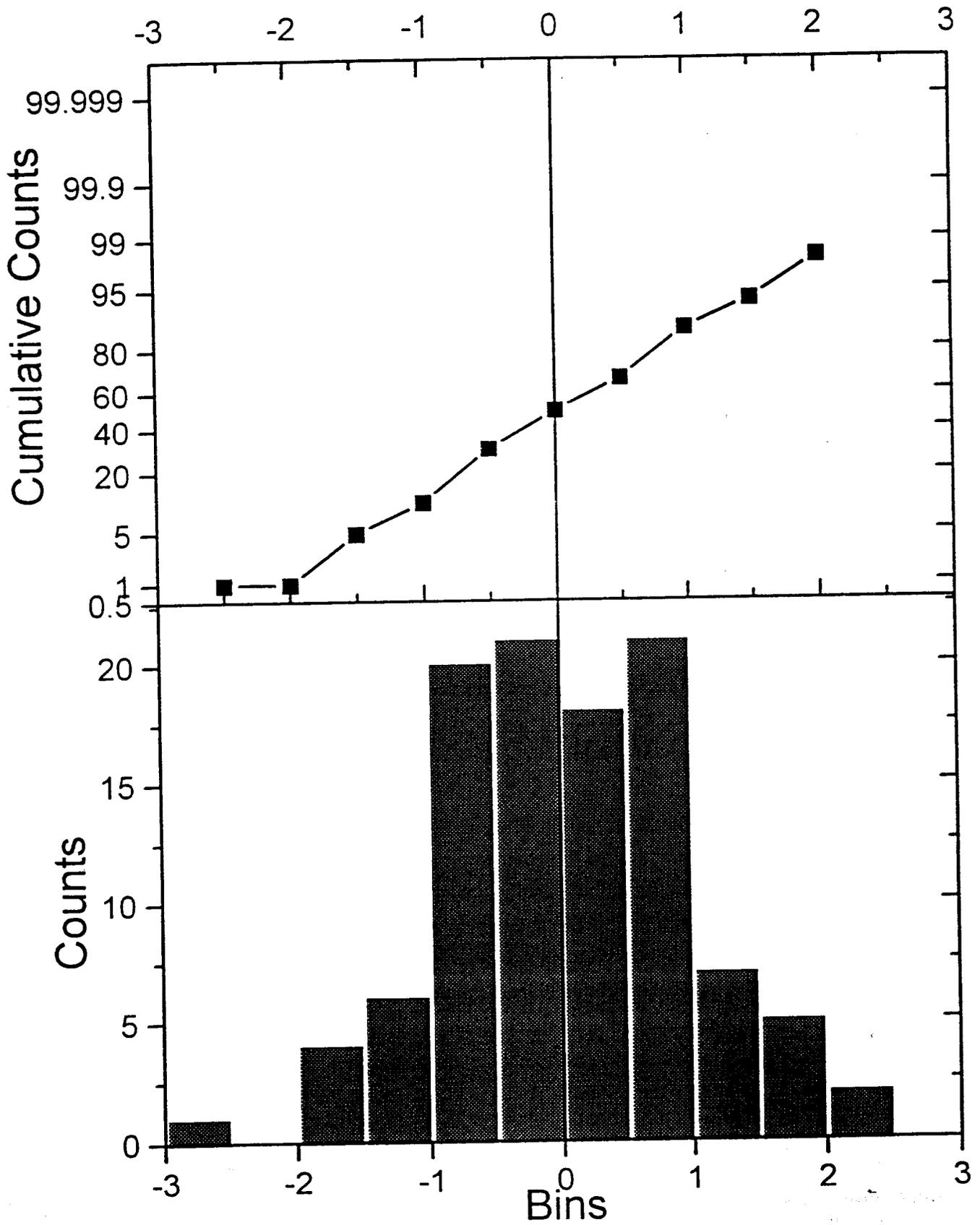


# Population Fitting



P.5





Residuals' Histogram  
P. 6

Table 3:

Locke, CS (1984) An exact confidence interval from untransformed data for the ratio of two formulation means. *J. Pharmaco. Biopharm.* 12: 649-655 (N: 9)

AVETest	-19.18		
AVEREF	-19.18		
DTR	79.45		
DRR	95.94		
DTT	101.48		
Inta Sub Var (%)	23		
K	0.39		
SQRT(K)	0.63		
W	0.03		
n	29		
t	1.7011		
t^2	2.89		
Gr	0.03		
DRR*W	3.31		
SQRT(DRR*W)	1.82		
+CINT	0.9010		
-CINT	1.1084		
<b>90% CI:</b>	<b>90.10</b>	<b>110.84</b>	

SUB	TEST	REF	(TEST)^2	(REF)^2	(TEST)*(REF)
5	-22.82	-11.22	520.89	125.93	256.12
6	-4.90	-8.05	24.03	64.80	39.46
8	-7.91	-13.65	62.60	186.19	107.96
10	-14.28	-21.28	203.86	452.84	303.84
11	-11.07	-9.37	122.61	87.85	103.79
12	-17.25	-21.58	297.63	465.61	372.26
15	-3.57	-14.91	12.74	222.16	53.21
17	-21.86	-12.68	477.99	160.83	277.27
20	-9.25	-0.41	85.53	0.17	3.79
21	-20.58	-14.36	423.41	206.27	295.53
22	-7.80	-17.51	60.79	306.60	136.53
23	-25.14	-21.81	632.02	475.59	548.25
26	-8.37	-10.00	70.09	99.90	83.68
28	-12.27	-7.82	150.50	61.11	95.90
29	-15.06	-14.39	226.89	206.93	216.68
30	-22.83	-26.99	521.12	728.30	616.06
31	-33.31	-33.15	1109.69	1098.79	1104.23
34	-16.18	-9.24	261.89	85.41	149.56
35	-34.47	-38.22	1187.97	1461.00	1317.43
36	-22.83	-19.67	521.35	386.83	449.08
41	-25.24	-30.97	637.06	959.14	781.68
42	-39.06	-31.74	1525.92	1007.24	1239.74

Table 2.

Locke, CS (1984) An exact confidence interval from untransformed data for the ratio of two formulation means. *J. Pharmaco. Biopharm.* 12: 649-655 (N:9)

AVETest	-18.70	
AVEREF	-18.57	
DTR	78.76	
DRR	94.64	
DTT	99.67	
Intra Sub Var (%)	23	
K	0.38	
SQRT(K)	0.62	
W	0.03	
n	32	
t	1.6950	
t <sup>2</sup>	2.87	
Gr	0.02	
DRR*W	2.96	
SQRT(DRR*W)	1.72	
+CINT	0.9118	
-CINT	1.1108	
<b>90% CI:</b>	<b>91.18</b>	<b>111.08</b>

SUB	TEST	REF	(TEST) <sup>2</sup>	(REF) <sup>2</sup>
5	-22.82	-11.22	520.89	125.93
6	-4.90	-8.05	24.03	64.80
8	-7.91	-13.65	62.60	186.19
9	-23.47	-16.86	550.93	284.19
10	-14.28	-21.28	203.86	452.84
11	-11.07	-9.37	122.61	87.85
12	-17.25	-21.58	297.63	465.61
15	-3.57	-14.91	12.74	222.16
16	-13.75	-17.79	189.12	316.56
17	-21.86	-12.68	477.99	160.83
20	-9.25	-0.41	85.53	0.17
21	-20.58	-14.36	423.41	206.27
22	-7.80	-17.51	60.79	306.60
23	-25.14	-21.81	632.02	475.59
26	-8.37	-10.00	70.09	99.90
28	-12.27	-7.82	150.50	61.11
29	-15.06	-14.39	226.89	206.93
30	-22.83	-26.99	521.12	728.30
31	-33.31	-33.15	1109.69	1098.79
34	-16.18	-9.24	261.89	85.41
35	-34.47	-38.22	1187.97	1461.00
36	-22.83	-19.67	521.35	386.83

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-633

APPLICANT: Taro Pharmaceuticals Inc.

DRUG PRODUCT: Clobetasol Propionate Emollient Cream 0.05%

The Division of Bioequivalence has completed its review 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 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