CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75279

BIOEQUIVALENCY REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-279 APPLICANT: Taro

DRUG PRODUCT: Clobetasol Propionate Gel 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,

/S/

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

CC: ANDA 75-279
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ M. Park

Endorsements: (Final with Dates)
HFD-658/ M. Park M.P. 4/14/98
HFD-658/ M. Makary MHM 4/14/98
HFD-650/ D. Conner DMK 4/27/98

BIOEQUIVALENCY - ACCEPTABLE submission date: 12/19/97

12-19-97 Stu pilot & Stu pivotal study

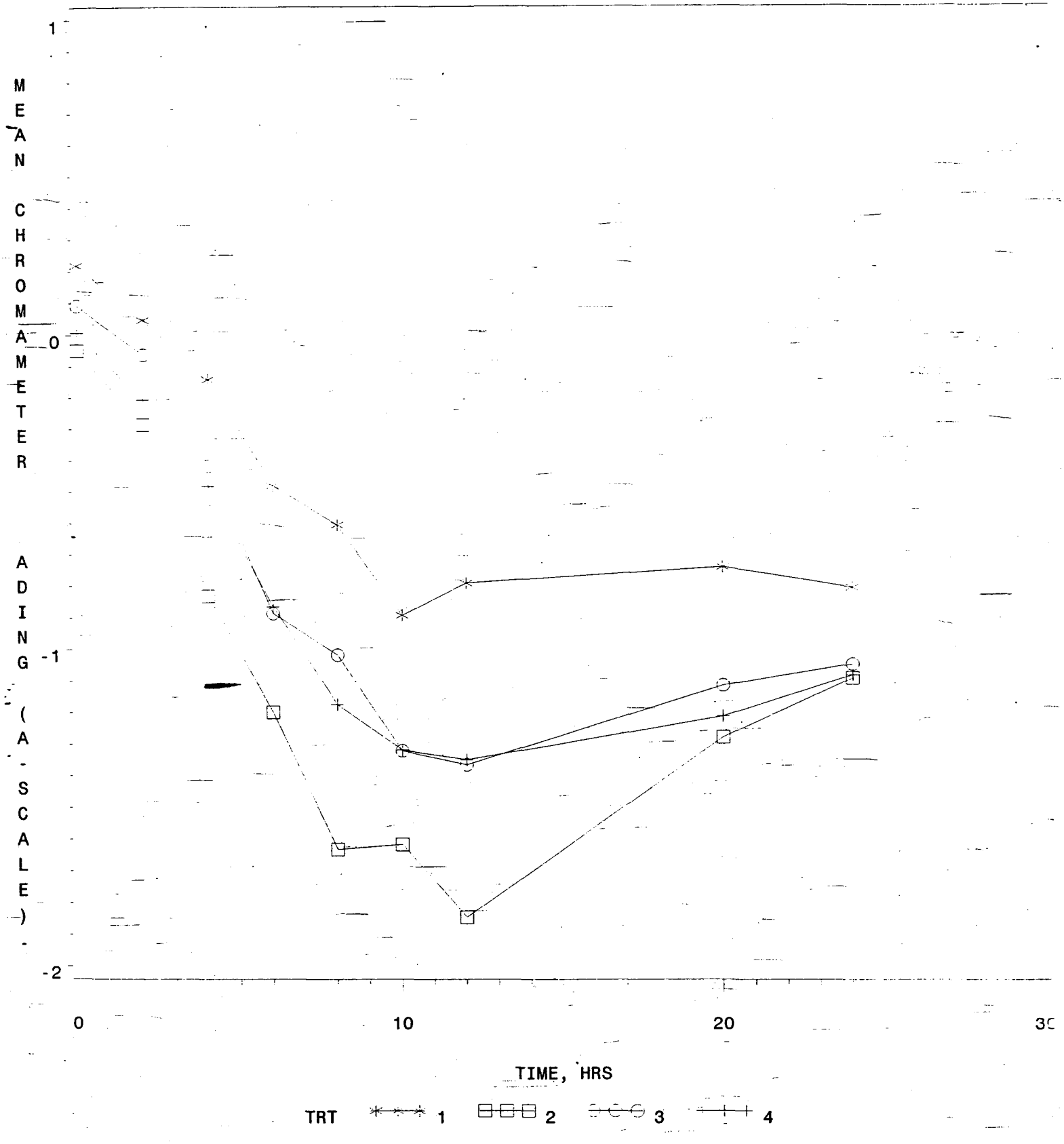
1. ~~STUDY with PD end-point (STF)~~ Strengths: 0.05%
Clinical: Novum **Outcome: AC**
Analytical: Novum

2-3-98 2. Study Amendment/Other Data/IC
3-31-98 3. Study Amendment -IC-

Outcome Decisions: **AC** - Acceptable

FIG P-7. MEAN CHROMAMETER READING

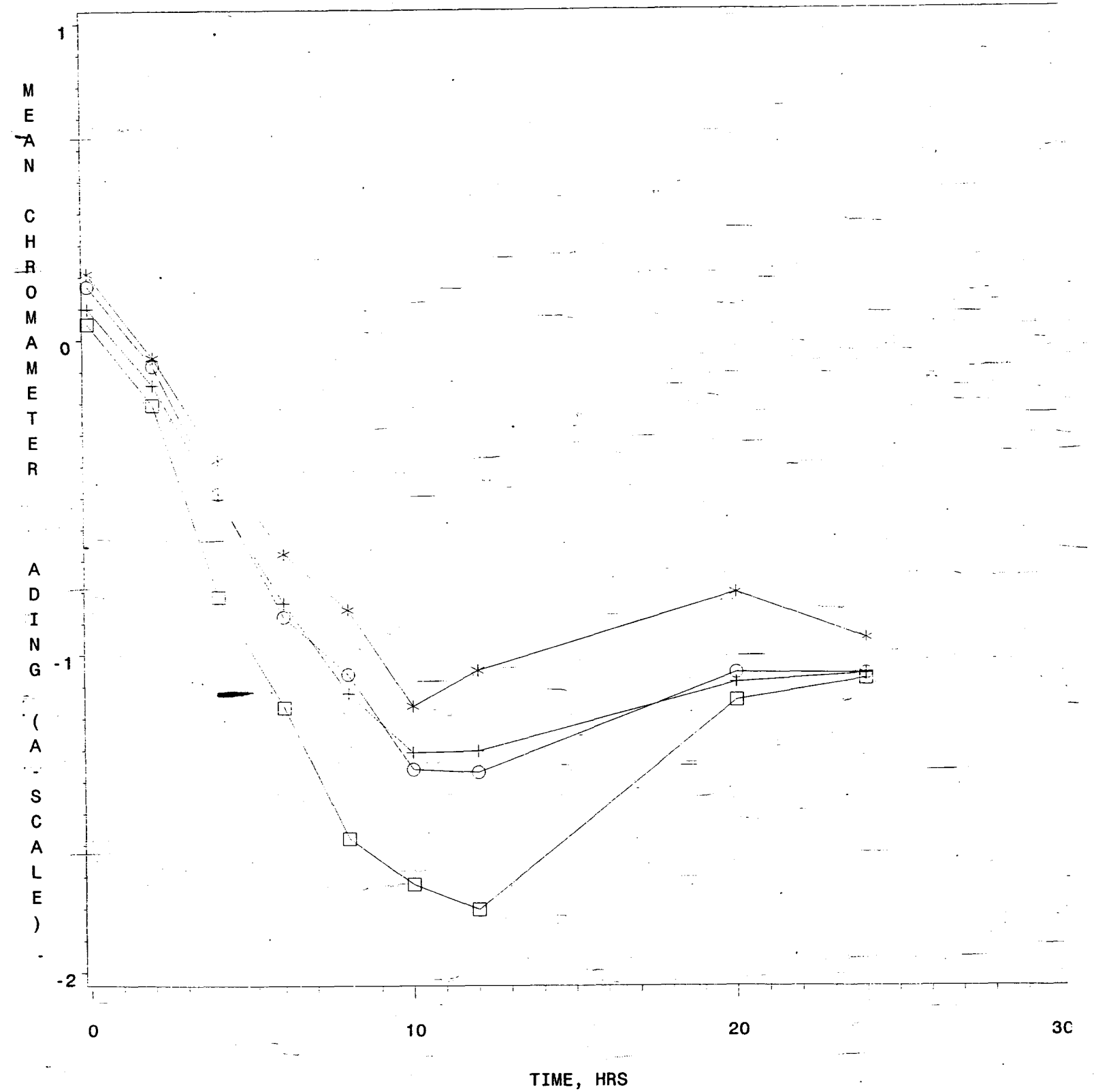
CLOBETASOL PROPIONATE GEL, 0.05%, ANDA #75-279
FOR 19 QUALIFIED SUBJECTS
DOSE=10 MICROLITER/2 SQ CM



1=D1(3 MIN) 2=D2(12 MIN) 3=TEST(TARO 6 MIN) 4=REF(GLAXO 6 MIN)

FIG P-2. MEAN CHROMAMETER READING

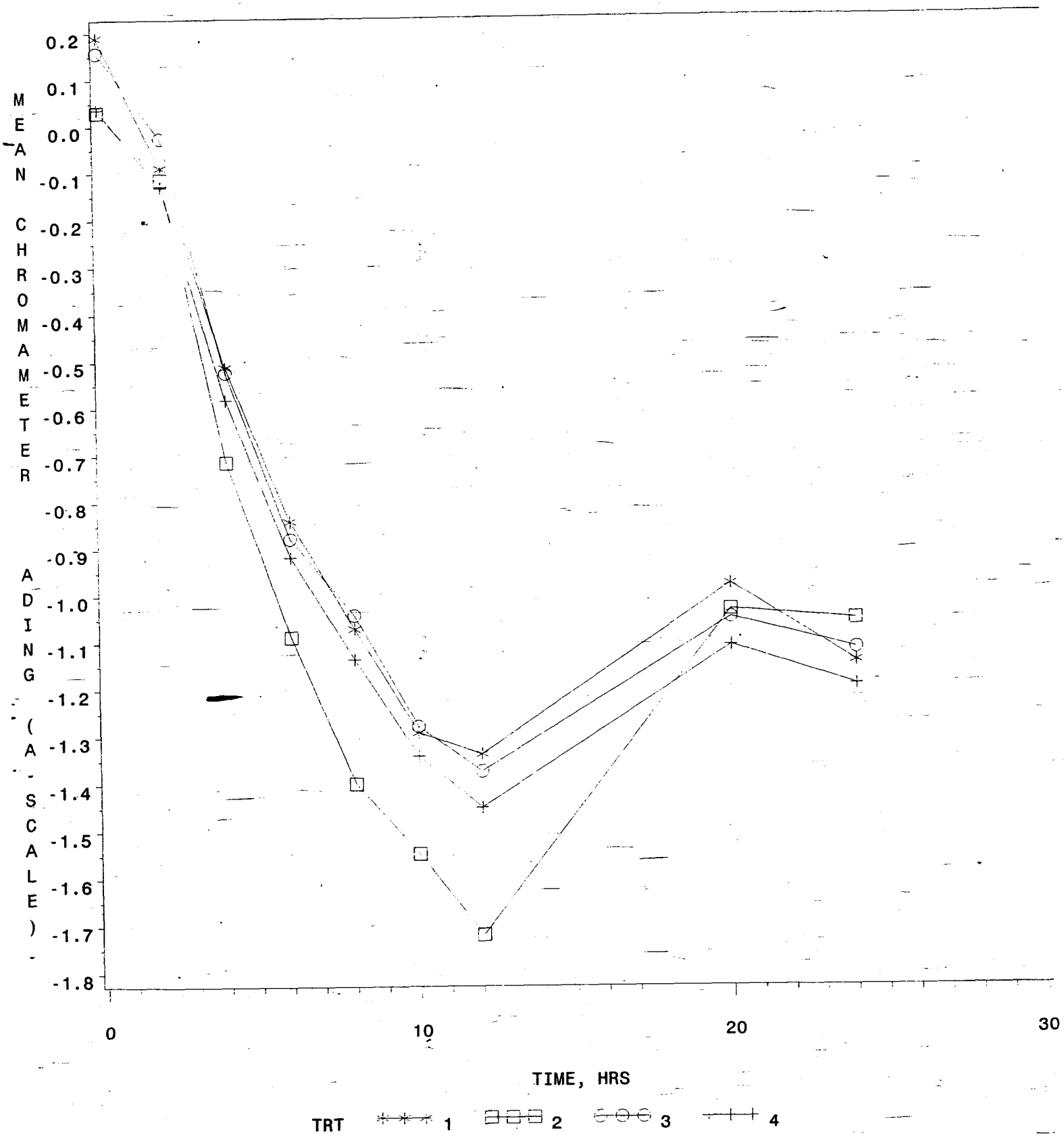
CLOBETASOL PROPIONATE GEL, 0.05%, ANDA #75-279
FOR 27 QUALIFIED SUBJECTS WITH MODIFIED CRITERIA
DOSE=10 MICROLITER/2 SQ CM



1=D1(3 MIN) 2=D2(12 MIN) 3=TEST(TARO 6 MIN) 4=REF(GLAXO 6 MIN)

FIG P-3. MEAN CHROMAMETER READING

CLOBETASOL PROPIONATE GEL, 0.05%, ANDA #75-279
FOR ALL 49 SUBJECTS
DOSE=10 MICROLITER/2 SQ CM



1=D1(3 MIN) 2=D2(12 MIN) 3=TEST(TARO 6 MIN) 4=REF(GLAXO 6 MIN)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

Clobetasol Propionate Gel	Taro
0.05%	Bramalea, Ontario, Canada
ANDA #75-279	Submission date: 12/19/1997; 3/31/98
Reviewer: Moo Park	

REF PRODUCT	Glaxo Wellcome's Temovate® Gel, 0.05%.
BE STUDY DESIGN	Skin blanching study in one-period randomized design.
STUDY RESULTS	Acceptable.
DISSOLUTION	n/a
WAIVER	n/a

INITIAL: /S/ DATE: 4/14/98
REVIEWER: Moo Park, Ph.D.
BRANCH: III

INITIAL: /S/ DATE: 4/14/98
TEAM LEADER: Moheb Makary, Ph.D.
BRANCH: III

INITIAL: DMC DATE: 4/27/98
DIRECTOR: Dale P. Conner, Pharm.D.
DIVISION OF BIOEQUIVALENCE

INITIAL: _____ DATE: _____
DIRECTOR
OFFICE OF GENERIC DRUGS

3·13·98
Sue

Clobetasol Propionate Gel	Taro
0.05%	Bramalea, Ontario, Canada
ANDA #75-279	Submission date: 12/19/1997; 3/31/98
Reviewer: Moo Park	

Review of a Pilot Study and a Bioequivalence Study

I. Objective

Review of Taro's *in vivo* pilot and pivotal bioequivalence studies using vasoconstrictor assay comparing its Clobetasol Propionate Gel, 0.05%, to Glaxo Wellcome's Temovate^{R} Gel, 0.05%.

II. Background

Clobetasol propionate is a synthetic corticosteroid and an analog of prednisolone. It has a high degree of glucocoritcoid activity and a slight degree of mineralocorticoid activity. It is a white to cream-colored crystalline powder insoluble in water.

Clobetasol has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear.

The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Topical corticosteroids can be absorbed from normal intact skin, while inflammation and/or other disease processes in the skin may increase percutaneous absorption.

III. Study Details

The two studies were conducted following the Topical Dermatologic Corticosteroids: *In Vivo* Bioequivalence Guidance dated June 2, 1995. Details of the pilot and pivotal studies are given below.

A. Pilot study

The study was designed to determine the dose-response relationship for Temovate E[R] emollient cream and Temovate[R] gel. The results of the pilot study were used to estimate the ED_{50}, D1 and D2 parameters for use in the pivotal bioequivalence study. Only the results for the gel were discussed in the submission.

Protocol No.	9615052
Study No.	9615052D Report B (Temovate[R] gel)
Applicant	Taro, Hawthorne, NY
Study sites	
Investigators	
Study dates	3/27/97-3/29/97
Study design	One-period randomized design.
Subjects	Fifteen subjects who were chosen for participation in this study were healthy, asymptomatic, non-tobacco-users (for 30 days prior to dosing), fair-skinned women in the age range of 19 to 49 years. They were within 15 % of their ideal weight as specified in the protocol.

Screening of subjects

Fifteen potential study participants were screened to determine blanching response to Temovate E[R] emollient cream and Temovate[R] gel. A 10 microliter of the emollient cream was applied to the right upper arm and the gel was applied to the left upper arm and left in place for 15 minutes (±5 minutes). The sites were evaluated visually 7-10 hours after application. All subjects were selected based on a demonstrated blanching response to both products, and the absence of any clinically significant findings on the medical history and vital sign 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 which would interfere with the assessment of skin blanching. All subjects tested negative on the urine pregnancy test and drug screen.

Drug products

Temovate E[R] emollient cream (clobetasol propionate 0.05%), Glaxo Wellcome (Lot #6J232 exp. date 9/98).
Tevomate[R] Gel (clobetasol propionate 0.05 %, Glaxo Wellcome, Inc. (Lot #6J231, exp. date 9/98).

Dosing

Randomization: Temovate E[R] emollient cream was applied to the right arm and Temovate[R] gel was applied to the left arm at sites determined by the randomization schedule. The untreated reference sites were not randomized (sites 4 and 12).

Preparation: The arms of each subject were washed with a mild soap (Liquid Neutragena Facial Cleansing Formula) and gently dried within approximately 2 hours prior to dosing.

Staggered Application: Eight (8) 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 from wrist to elbow and 9-16 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. The washers were no closer than 2 cm apart center-to-center.

After baseline ChromaMeter (in duplicate) 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 so that the treated area was not occluded. Using a 250 microliter glass Hamilton syringe, a 10 microliter application of each active product was applied to the assigned sites on each arm at times according to the randomization schedule.

Baseline assessments were started approximately 1.5 hours prior to first application. Temovate E[R] emollient cream and Temovate[R] gel were applied to both arms 3, 6, 10, 20, 30, 45 minutes and 1 hour prior to removal. The applications were spread evenly over the skin surface at each site with the conical tip of a 1.5 mL polypropylene microcentrifuge tube.

Assessment of blanching

Synchronized Removal: The taped washers were removed immediately prior to each participants' scheduled application removal time. All applications on each participant's arm were removed at the same time point (0.0 hour), with the shortest durations removed first.
Residual surface treatment was removed by gently wiping several times with a cotton ball. The untreated site on each arm was similarly wiped with a clean cotton ball.

Assessments: The ChromaMeter 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.
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. ChromaMeter assessments were based on the a-scale response. Visual scoring used 0-3 rating scale.

Food and fluid	A meal was provided on check-in day. Meals were served at traditional times thereafter; caffeine and alcohol were restricted during the study. Water was permitted ad lib throughout the study.
Housing	During this study, the subjects were housed and fed at the clinical facility. All subjects reported for check-in (Day -1) at least 12 hours before dosing. The subjects were dosed on 3/28/97 and completed the study approximately 24 hours after first application.
Restrictions	Prior to check-in for the study, the subjects were instructed to take no prescribed medications (other than contraceptives) for at least 7 days nor any over-the-counter medications for 72 hours prior to dosing. Alcohol and caffeine were restricted for 48 hours prior to dosing and throughout the study. The subjects were not allowed to use any dermatological drug therapy (including topical corticosteroids) within 30 days of dosing other than that used for screening. The subjects were instructed to avoid contact with water on their arms, extremes of temperature and strenuous physical exercise during the study. Tight clothing on the forearms was not permitted. The subjects were not allowed to rest their heads on their arms during the hour before any assessment time.
IRB	Novum Independent Institutional Review Board
Informed consent	All subjects signed and dated the form.

Data analysis The area under the response-time curve for each site were calculated by the linear trapezoidal method. A naive pooling of the areas from all subjects were used to estimate the population dose-response relationship. Nonlinear estimation of the Emax model were used to determine the population ED_{50} and Emax values. The ED_{50} was used to calculate D1 and D2 values, which correspond to approximately one-half and two-times the ED_{50}, respectively. Analyses were performed separately for the visual and ChromaMeter assessments.

B. Pivotal study

The purpose of this study was to compare the relative vasoconstrictive effects of test and reference topical clobetasol propionate gels in asymptomatic subjects.

Protocol No.	9715098
Study No.	9715098 (Temovate^{R} gel)
Applicant	Taro, Hawthorne, NY
Study sites	
Investigators	
Study dates	Group 1 (Subjects #1-15): 10/31/97-11/2/97 Group 2 (Subjects #16-40): 11/7/97-11/9/97 Group 3 (Subjects #41-50): 11/21/97-11/23/97
Study design	One-period randomized design.
Subjects	Fifty subjects who were chosen for participation in this study were healthy, asymptomatic, non-tobacco-users (for 30 days prior to dosing), fair-skinned women in the age range of 18 to 44 years. They were within 15 % of their ideal weight as specified in the protocol.

Screening of subjects

Fifty potential study participants were screened to determine blanching response to Temovate[R] gel. A 10 microliter of the gel was applied to the upper arm and left in place for 15 minutes. The sites were evaluated visually 7-10 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 and vital sign 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 which would interfere with the assessment of skin blanching. All subjects tested negative on the urine pregnancy test and drug screen.

Drug products

Test: Clobetasol propionate topical gel 0.05%, Taro Pharmaceuticals, Inc. (Lot #S118-5994)

Reference: Temovate[R] 0.05% gel (clobetasol propionate), Glaxo Dermatology (Lot #6J231, expiration date 9/98)

Dosing

Randomization: The gels were applied to 16 of the 20 forearm sites determined by the randomization schedule. Two sites on each arm were randomized as untreated ChromaMeter reference sites.

Application and Removal: Ten (10) circular (approximately 1.6 cm diameter) application sites were designated on the flexor surface of each forearm between the wrist and the elbow. After baseline ChromaMeter (in duplicate) and visual readings, an open washer was positioned over each site and taped to the forearm using hypo-allergenic Scanpor paper tape on the sides of the washer so that the treated area was not occluded. Using a 250 microliter glass Hamilton syringe, a 10 microliter application of each active formulation was applied to the assigned sites on each arm according to the randomization schedule. All applications were spread evenly over the skin surface at each site with the conical tip of a 1.5 mL polypropylene microcentrifuge tube.

Baseline assessments were started approximately 2 hours prior to first application. The test and reference gels were applied to 16 sites on each arm; these treatments were applied 3, 6 or 12 minutes prior to removal. All sites were on, or staggered about, the midline axis of the subject's forearm. All applications were removed at the same time point (0.0 hour). The washers were detached and residual surface treatment was removed by gently wiping several times with cotton balls. The untreated sites were similarly wiped with clean cotton balls.

Assessment of blanching

Prior to the study, precision of three ChromaMeter operators 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% for all operators and the within-site %CV was less than 7%.

ChromaMeter operators and visual evaluators 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 assessments were made under standard lighting and at room temperature within 5 minutes of their scheduled time.

The ChromaMeter operators and visual evaluators were blinded as to the treatment and duration of application at each site. ChromaMeter assessments were based on the a-scale response.

Visual scoring used the following rating scale:

0 = No pallor; no change from surrounding area.

1 = Mild pallor; slight or indistinct outline of application site.

2 = Moderate pallor; discernible outline of application site.

3 = Intense pallor; clean, distinct outline of application site.

Food and fluid

A meal was provided on check-in day. Meals were served at traditional times thereafter; caffeine and alcohol were restricted during the study. Water was permitted ad lib throughout the study.

Housing

During this study, the subjects were housed and fed at the clinical facility. All subjects reported for check-in (Day -1) at least 12 hours before dosing. The subjects were dosed on Day 1 and completed the study approximately 25 hours after first application.

Restrictions	Prior to check-in for the study, the subjects were instructed to take no prescribed medications (other than contraceptives) for at least 7 days nor any over-the-counter medications for 72 hours prior to dosing. Alcohol and caffeine were restricted for 48 hours prior to dosing and throughout the study. The subjects were not allowed to use any dermatological drug therapy (including topical corticosteroids) within 30 days of dosing other than that used for screening. The subjects were instructed to avoid contact with water on their arms, extremes of temperature and strenuous physical exercise during the study. Tight clothing on the forearms was not permitted. The subjects were not allowed to rest their heads on their arms during the hour before any assessment time.
IRB	Novum Independent Institutional Review Board
Informed consent	All subjects signed and dated the form.
Data analysis	Negative areas under the response curve for the ChromaMeter assessments were determined from the a-scale reading using a Minolta CR-300 ChromaMeter. The areas under the response curves for the visual assessments were determined directly from the raw blanching scores of the evaluator. The ratio of the mean area for the 12 minute Temovate^{R} duration (D2) to that of the 3 minute Temovate^{R} duration (D1) was determined for each subject. A subject was included in the analyses if she met the qualification criteria ($D2/D1 \geq 1.25$). Locke's Method for calculating confidence intervals was applied to the ChromaMeter and visual area results from those subjects included in the analyses.

IV. Validation of Assay Method (ChromaMeter)

The blanching response of the corticoid was measured by ChromaMeter and visual evaluation. No validation data were submitted for the visual method.

Precision of the ChromaMeter operators was evaluated from replicate evaluations (five readings at least three minutes apart) at four untreated skin sites on each arm of four subjects.

Two ChromaMeter operators measured five replicate ChromaMeter readings from a total of 8 sites for each of the four subjects. This experiment was repeated using partial replacement of the operators and subjects. The second experiment had a total of 10 sites for each subject. Results of PROC VARCOMP (SAS) are shown in Table IV-1. The within-site %CVs range from 5.4% to 6.3% and the method using ChromaMeter reading is acceptable. The %CVs for the between-subject and between-site may be irrelevant to the precision of the method even though they estimate the subject variability.

Table IV-1. Variations of ChromaMeter Reading

Operator	%CV, between-subject	%CV, between-site	%CV, within-site
1	13.0	12.1	5.4
2	12.9	12.9	6.2
1	9.3	8.9	5.4
3	11.1	8.3	6.3

V. Results of the Studies

A. Pilot study

Fifteen potential study participants were screened to determine blanching response to Temovate^{R} gel. All subjects were selected based on a demonstrated blanching response.

Adverse Events: None of the subjects reported any adverse events

during this study.

The areas under the response curves for the visual assessments were determined directly from the raw blanching scores. The visual results from all 15 subjects were used in the evaluation of the dose-response relationship.
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 forearm. To compensate for skin tone changes that occur over time, the baseline-adjusted value for the untreated site was subtracted from the baseline-adjusted ChromaMeter value for treated sites at each assessment time. These "corrected" baseline-adjusted ChromaMeter values were used in all subsequent analyses.

The ChromaMeter a-scale reading lowers with increased blanching. ChromaMeter areas under the response curve over 24 hours were calculated from the corrected, baseline-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 to the model.

The dose-response relationship was evaluated using the ChromaMeter results for all available subjects. SAS version 6.12 PROC NLIN was used to fit a two-parameter, Emax model, $E=(Emax*D)/(ED_{50}+D)$. In this model, E is the response (area) at D, the duration of application, and ED_{50} is the duration at which half-maximal response occurs.

Plots of the mean area and the predicted area from the fitted Emax model for each duration of application were prepared for both the visual and ChromaMeter to graphically assess the dose-response relationship. These plots appeared to follow a simple Emax dose-response relationship.

The ED_{50} for Temovate^{R} Gel appears to be approximately 3.81 minutes based on visual results and 3.66 minutes based on ChromaMeter results. Therefore, in a pivotal bioequivalence study a testing duration of 4 minutes for the test and reference products would be chosen according to the Agency guidance along

with a lower duration for 2 minutes (D1) and a longer duration of 8 minutes (D2). Instead, the firm chose 3 minutes for D1, 6 minutes for the test and reference products, and 12 minutes for D2. The reasoning behind this decision was that based on the potency of the product and the speed with which subjects reach maximal blanching effect a 4 minute ED_{50} would cause operational difficulties (i.e. dosing procedures, visual assessments, ChromaMeter assessments) and in a pivotal bioequivalence study an ED_{50} of at least 6 minutes would be necessary to properly conduct a vasoconstrictor study.

Table V-A-1. Mean AUEC (n= 15)
(%CV in Parentheses)

Duration	AUEC by Visual	AUEC by ChromaMeter
3 min.	16.1(102)	17.0(80)
6 min.	27.5(50)	19.2(71)
10 min.	25.5(74)	20.6(63)
20 min.	26.5(70)	18.2(108)
30 min.	28.6(71)	25.0(79)
45 min.	34.9(56)	27.4(75)
1 hr.	41.8(34)	35.8(44)

Table V-A-2. Emax Model Parameters Estimated by SAS PROC NLIN using Pooled AUEC Data for 15 Subjects

Parameter	Method	Estimate	Std. Error
Emax	Visual	37.4	3.54
ED_{50}	Visual	3.81	1.70
Emax	ChromaMeter	30.0	3.38
ED_{50}	ChromaMeter	3.66	1.98

B. Pivotal study

The firm collected and evaluated skin blanching data by visual and ChromaMeter methods. The firm claimed that the visual method

rendered similar results to the ChromaMeter method showing the bioequivalence of the test and reference products. In this review, however, only ChromaMeter data were used to show the bioequivalency. According to Dr. Gur Singh of the Division of Bioequivalence, there are enough historical data showing that the ChromaMeter method outperforms the visual method in detecting the skin blanching and ChromaMeter data alone will be enough to prove bioequivalency.

In this review, this reviewer made all the calculations. The results from the calculations were found to be in agreement with the results the firm submitted.

A total of 50 subjects were entered into the study and 49 subjects completed the study. Subject #29 withdrew from the study on 11/8/97 after dosing due to menstrual cramps.

Due to an anomalous reading for subject #47, site 1, hour 0 (zero), this value was replaced by the average of the pre-dose and 2 hour readings.

Adverse Events: None of the adverse events experienced by the subjects during this study was judged as serious.

Application of treatments: The 20 sites for each subject (10 sites for each arm) were treated following the schedule as shown in Table V-B-1.

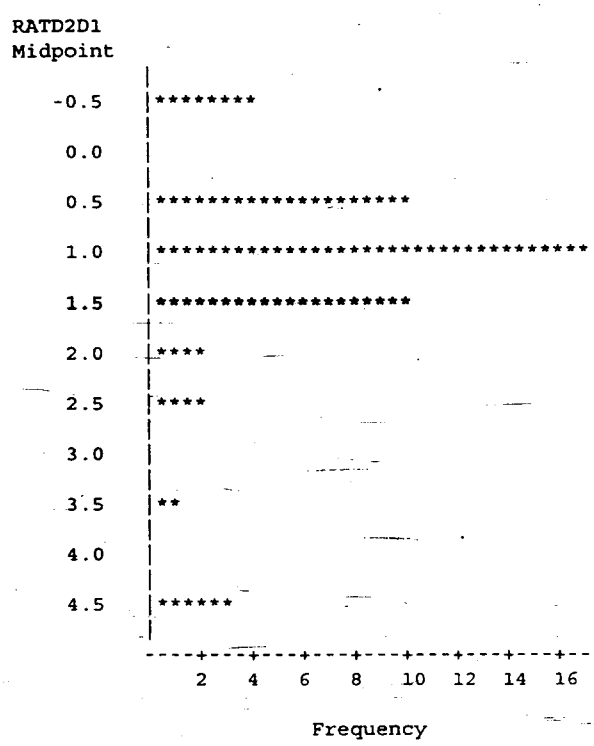
Table V-B-1. Application of Treatments

Treatment	Duration of treatment	Arm	Number of sites
No treatment	0	Right	2
No treatment	0	Left	2
Reference (D1)	3 minutes	Right	1
Reference (D1)	3 minutes	Left	1
Test	6 minutes	Right	3
Test	6 minutes	Left	3
Reference	6 minutes	Right	3
Reference	6 minutes	Left	3
Reference (D2)	12 minutes	Right	1
Reference (D2)	12 minutes	Left	1

Mean vasoconstrictive response-time profiles and 90% confidence intervals: Even though 49 subjects completed the study, only 19 subjects (39%) qualified for the further analysis based on the criterion for qualification described in the guidance. The qualification criterion is that the ratio of (AUEC for D2)/(AUEC for D1) should be greater than or equal to 1.25. The guidance indicates that Locke's 90% confidence intervals for the AUEC for the test product are to be calculated using the 19 qualified subjects.

Frequency distribution of (AUEC for D2)/(AUEC for D1) ratios was charted in Fig 1. The 19 subjects qualified are shown in the frequency chart as the sum of the frequencies between 1.5(1.25-1.75) and 4.5. The highest frequency was found at 1.0 (0.85-1.25). The overall frequency distribution shows that approximately 60% all subjects participated in the study could not differentiate D1 (3-minute application) from D2 (12-minute application). This phenomenon may be related to the potency of clobetasol itself, the formulation containing propylene glycol and carbopol (film former), or experimental procedures involving the removal of the gel (or dried film) from the skin.

FIG 1. FREQUENCY DISTRIBUTION OF AUEC(D2)/AUEC(D1) RATIOS FOR 49 SUBJECTS



The mean ChromaMeter reading-time data for the 19 qualified subjects were listed in Table V-B-2 and plotted in Fig P-1. The ChromaMeter readings for D1, D2, the test product and the reference product are shown in the table. The mean readings for the test and reference products for 4-24 hours are similar as shown in Table V-B-2 and Fig P-1. Locke's 90% confidence interval for the AUEC was calculated and shown in Table V-B-5. The confidence interval was 83.6%-105.9%, which met the Agency requirement for the bioequivalency. The test mean/reference mean ratio was 0.942. (D2/D1$\geq$1.25 is equivalent to D1/D2$\leq$0.8. D1/D2 values are listed in tables below.)

In a separate calculation, the firm included 8 more subjects to a total of 27 subjects by loosening the qualification criteria for (AUEC for D2)/(AUEC for D1) (D2/D1 will be used to denote the AUEC ratios.). The loosened criteria used were that the subject is qualified if D2/D1$\geq$1.25 or D2/reference$\geq$1.25 or reference/D1$\geq$1.25. The mean ChromaMeter reading-time data and profiles are shown in Table V-B-3 and Fig P-2, respectively.

The mean ChromaMeter reading-time data and profiles for all 49 subjects are shown in Table V-B-4 and Fig P-3, respectively.

Table V-B-5 summarizes the mean ChromaMeter readings, standard deviations, and 90% confidence intervals for the three occasions involving 19, 27 and 49 subjects. The mean ChromaMeter readings and standard deviations are similar in all three occasions. The 90% confidence intervals calculated for the three occasions are all within the 80-125% range. However, the regulatory decision will be made based on the confidence intervals calculated from the 19 qualified subjects.

Table V-B-2. MEAN ChromaMeter READING FOR D1, D2, TEST AND REFERENCE PRODUCTS
For 19 Qualified Subjects
MEAN1=D1; MEAN2=D2; MEAN3=Test; MEAN4=Reference; SD=Std Dev
RMEAN12= D1/D2 Ratio; RMEAN34=Test/Reference Ratio

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	MEAN4
TIME HR							
0	0.22	0.77	-0.05	0.93	0.09	0.73	0.01
2	0.05	0.80	-0.29	0.48	-0.06	0.67	-0.21
4	-0.14	0.93	-0.83	0.77	-0.42	0.90	-0.48
6	-0.48	0.91	-1.20	0.93	-0.89	0.91	-0.86
8	-0.60	0.94	-1.63	0.88	-1.02	0.97	-1.17
10	-0.89	0.80	-1.62	1.05	-1.32	1.08	-1.32
12	-0.79	0.86	-1.84	0.92	-1.37	0.99	-1.35
20	-0.74	0.94	-1.28	0.79	-1.11	0.88	-1.21
24	-0.80	0.98	-1.09	0.84	-1.05	0.90	-1.08

(CONTINUED)

	SD4	RMEAN12	RMEAN13	RMEAN14	RMEAN23	RMEAN24	RMEAN34
TIME HR							
0	0.76	-4.50	2.39	29.36	-0.53	-6.53	12.31
2	0.68	-0.16	-0.74	-0.23	4.56	1.39	0.30
4	0.87	0.17	0.34	0.29	1.99	1.72	0.87
6	0.99	0.40	0.54	0.55	1.35	1.39	1.02
8	0.93	0.37	0.59	0.51	1.60	1.39	0.87
10	1.03	0.55	0.67	0.68	1.22	1.23	1.00
12	1.05	0.43	0.58	0.59	1.35	1.37	1.01
20	0.83	0.58	0.66	0.61	1.15	1.06	0.92
24	0.82	0.74	0.77	0.74	1.04	1.01	0.97

Table V-B-3. MEAN ChromaMeter READING FOR D1, D2, TEST AND REFERENCE PRODUCTS
For 27 Subjects
MEAN1=D1; MEAN2=D2; MEAN3=Test; MEAN4=Reference; SD=Std Dev
RMEAN12= D1/D2 Ratio; RMEAN34=Test/Reference Ratio

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	MEAN4
TIME HR							
0	0.21	0.77	0.05	0.95	0.17	0.85	0.10
2	-0.06	0.78	-0.21	0.54	-0.08	0.61	-0.14
4	-0.38	0.97	-0.82	0.82	-0.49	0.85	-0.51
6	-0.68	0.99	-1.17	0.93	-0.88	0.90	-0.84
8	-0.86	0.98	-1.58	0.80	-1.06	0.93	-1.12
10	-1.16	1.01	-1.72	1.00	-1.36	1.09	-1.31
12	-1.05	0.94	-1.80	0.93	-1.37	0.99	-1.30
20	-0.80	0.87	-1.14	0.78	-1.06	0.88	-1.09
24	-0.95	0.94	-1.08	0.77	-1.06	0.91	-1.06

(CONTINUED)

	SD4	RMEAN12	RMEAN13	RMEAN14	RMEAN23	RMEAN24	RMEAN34
TIME HR							
0	0.86	4.10	1.24	2.11	0.30	0.51	1.70
2	0.64	0.27	0.68	0.39	2.49	1.43	0.57
4	0.85	0.47	0.78	0.75	1.67	1.62	0.97
6	0.97	0.58	0.77	0.81	1.32	1.39	1.05
8	0.87	0.54	0.81	0.76	1.49	1.41	0.95
10	1.01	0.67	0.85	0.89	1.27	1.32	1.04
12	1.00	0.58	0.77	0.81	1.32	1.38	1.05
20	0.82	0.70	0.76	0.74	1.08	1.05	0.97
24	0.80	0.88	0.89	0.89	1.02	1.01	1.00

Table V-B-4. MEAN ChromaMeter READING FOR D1, D2, TEST AND REFERENCE PRODUCTS
For All 49 Subjects
MEAN1=D1; MEAN2=D2; MEAN3=Test; MEAN4=Reference; SD=Std Dev
RMEAN12= D1/D2 Ratio; RMEAN34=Test/Reference Ratio

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	MEAN4
TIME HR							
0	0.19	0.93	0.03	0.92	0.16	0.85	0.04
2	-0.09	0.74	-0.11	0.63	-0.03	0.66	-0.13
4	-0.51	0.96	-0.71	0.91	-0.52	0.95	-0.58
6	-0.84	1.10	-1.09	1.05	-0.88	1.01	-0.92
8	-1.07	1.03	-1.40	0.96	-1.04	1.02	-1.14
10	-1.29	1.13	-1.55	1.14	-1.28	1.19	-1.34
12	-1.34	1.20	-1.72	1.15	-1.37	1.15	-1.45
20	-0.98	0.95	-1.03	0.81	-1.05	0.89	-1.11
24	-1.14	1.09	-1.05	0.96	-1.12	1.01	-1.19

(CONTINUED)

	SD4	RMEAN12	RMEAN13	RMEAN14	RMEAN23	RMEAN24	RMEAN34
TIME HR							
0	0.88	6.20	1.21	5.13	0.19	0.83	4.25
2	0.72	0.78	3.40	0.68	4.37	0.87	0.20
4	0.94	0.72	0.98	0.88	1.36	1.23	0.90
6	1.04	0.77	0.96	0.92	1.24	1.19	0.96
8	1.00	0.77	1.03	0.94	1.34	1.23	0.92
10	1.13	0.84	1.01	0.96	1.21	1.15	0.95
12	1.14	0.78	0.97	0.92	1.25	1.19	0.95
20	0.84	0.95	0.93	0.88	0.98	0.93	0.95
24	0.97	1.09	1.02	0.96	0.94	0.88	0.94

Table V-B-5. Locke's 90% Confidence Intervals

Subjects (N)	Mean AUEC test product	std	Mean AUEC ref product	std	Test Mean /Ref Mean Raio	Locke's 90% CI
19	-22.9197	12.3559	-24.2625	11.9319	0.942	83.6-106
27	-22.8959	11.3673	-22.8989	11.0162	1.00	90.9-110
49	-22.7500	13.8242	-24.4828	12.6572	0.931	86.7-99.0

VI. Formulation

1. Formulation Comparison

The test and reference formulations are almost identical except the amount of Carbomer 934P as shown in Table VI-1.

Table VI-1. Formulation Comparison
DO NOT RELEASE THE FOLLOWING INFORMATION UNDER FOI.

Ingredient	Test w/w%	Reference (Temovate Gel), w/w%
Clobetasol Propionate, USP		
Carbomer 934P		
Propylene Glycol		
Sodium Hydroxide		
Purified Water		
Total		

2. Assay and content uniformity

According to the batch record of the test product, clobetasol propionate is in dissolved state in the formulation. The content uniformity of the test product was shown by assaying three samples from a tube, i.e., top, middle, and bottom.

Product	Assay	Content uniformity
Taro's test product, Lot #S118-5994, Mfg date: 7/14/97, Lot size: kg	%	%
Glaxo Wellcome's Temovate Gel, Lot #6J231, Exp. Date: 9/98	%	-

3. In vitro drug release

The firm did not perform the *in vitro* drug release test. The *in vitro* drug release test is not required for the demonstration of bioequivalency.

VII. Comments

1. The firm used both visual evaluation and ChromaMeter readings. In this review only ChromaMeter data were used for the calculation of mean ChromaMeter readings and 90% confidence intervals.

2. **Pilot study**: The ED_{50} for Temovate^{R} Gel was 3.66 minutes based on ChromaMeter results. However, the firm chose to adopt 3 minutes for D1, 6 minutes for the ED_{50} (for the test and reference products), and 12 minutes for D2. The reasoning behind this decision was that based on the potency of the product and the speed with which subjects reach maximal blanching effect a 4 minute ED_{50} would cause operational difficulties (i.e. dosing procedures, visual assessments, ChromaMeter assessments) and in a pivotal bioequivalence study an ED_{50} of at least 6 minutes would be necessary to properly conduct a vasoconstrictor study. This decision by the firm is acceptable.

3. **Pivotal study**: A total of 50 subjects were entered into the study and 49 subjects completed the study. The four treatments, D1, D2, the test product, and the reference product, were applied to 20 sites for each subject (10 sites for each arm) following the schedule as shown in Table V-B-1. It was found that only 19 subjects (39%) qualified for further analysis based on the criterion for qualification described in the guidance. The qualification criterion is that the ratio of (AUEC for D2)/(AUEC for D1) should be greater than or equal to 1.25. The mean readings for the test and reference products at all time points were similar. The ratio of test AUEC/reference AUEC was 0.942. Locke's 90% confidence interval for the AUEC for the 19 subjects was 83.6-105.9, which met the Agency requirement for the bioequivalency.

4. The pivotal study results show that approximately 60% all subjects participated in the study could not differentiate

D1 (3-minute application) from D2 (12-minute application). This phenomenon may be related to the potency of clobetasol itself, the formulation containing propylene glycol and carbopol (film former), or experimental procedures involving the removal of the gel (or dried film) from the skin.

5. **Validation of Assay Method (ChromaMeter)**: The within-site %CVs range from 5.4% to 6.3% and the precision of the method using ChromaMeter reading is acceptable.

6. **Formulation**: The test and reference products contain the same active and inactive ingredients. The test formulation is acceptable.

7. **Assay and content uniformity**: The assay and content uniformity for the test product are acceptable.

8. **In vitro drug release**: The firm did not perform the *in vitro* drug release test. The *in vitro* drug release test is not required for the demonstration of bioequivalency.

VIII. Deficiency

None.

IX. Recommendation

The *in ~~vivo~~ vivo* bioequivalence study using pharmacodynamic end points conducted by Taro comparing its Clobetasol Propionate Gel, 0.05%, Lot #S118-5994, to Glaxo Wellcome's Temovate^{R} Gel, 0.05%, Lot #6J231, has been found acceptable. The results of the vasoconstrictor study demonstrate that Taro's Clobetasol Propionate Gel, 0.05%, is bioequivalent to Glaxo Wellcome's Temovate^{R} Gel, 0.05%.

/S/

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