

CLINICAL STUDY REPORT

Alclometasone Dipropionate Lotion, 0.05%

Study No. 10628201

2.0 SYNOPSIS

SPONSOR:

NAME OF TEST PRODUCT(s): Alclometasone dipropionate lotion, 0.05%

ACTIVE INGREDIENTS: Alclometasone

STUDY TITLE: A Potency Ranking Study to Determine the Relative Potency of a New Alclometasone Dipropionate 0.05% Lotion Formulation

PRINCIPAL INVESTIGATOR AND STUDY SITE:

STUDY DURATION: The time from first subject dosed to when the last subject completed was approximately 2 days.

STUDY TYPE: An open-label, one-period, randomized, vasoconstrictor assay study.

OBJECTIVE: The purpose of this study was to compare the relative potency of a test formulation of alclometasone dipropionate lotion, 0.05% with the already approved formulations of alclometasone dipropionate cream and ointment, 0.05% (Aclovate[®], GlaxoSmithKline), a placebo lotion, and four other comparator topical corticosteroids of known potency, in asymptomatic subjects.

METHODOLOGY: A one-period, randomized study was conducted to compare the relative potency of a test formulation of alclometasone dipropionate lotion, 0.05% with that of a placebo (vehicle) lotion and the following six already approved, super-high to low potency topical corticosteroids: Clobex[™] (clobetasol propionate) Topical Lotion, 0.05% (Class I); Diprolene[®] (brand of augmented betamethasone dipropionate) Lotion, 0.05% (Class II); Elocon[®] (brand of mometasone furoate) Lotion, 0.1% (Class IV); Aclovate[®] Cream, 0.05% (alclometasone dipropionate cream) (Class VI); Aclovate[®]

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Ointment, 0.05% (alclometasone dipropionate ointment), (Class VI); Hydrocortisone Lotion USP, 1% (Class VII). This study was conducted in 40 asymptomatic, healthy, non-tobacco using female subjects, who had been pre-screened to show a vasoconstrictor response to Aclovate[®] Cream, 0.05% (alclometasone dipropionate cream).

Each formulation was applied to one site on the flexor surfaces of the subjects' forearms (left and right) and kept in place for a duration of 6 hours. Two untreated control sites were also designated on each forearm as ChromaMeter reference sites. All sites remained under non-occluded conditions throughout the study.

Vasoconstriction was measured by the degree of skin blanching observed after treatment removal using a ChromaMeter (a-scale reading). Evaluations were performed at pre-dose and at 0.5, 2, 4, 6, 8, 10, 12, 20, and 24 hours after removal.

NUMBER OF SUBJECTS: A total of 40 healthy adult female subjects.

MAIN DIAGNOSIS FOR ENTRY: Diagnosis was not required for this study. All subjects were asymptomatic, healthy, adult female subjects.

TEST PRODUCT(s): Alclometasone dipropionate lotion, 0.05%;

ROUTE OF ADMINISTRATION: The formulations were applied topically to the flexor surface of each forearm.

DURATION OF TREATMENT: In the conduct of this study, 8 applications were applied to the flexor regions of each forearm and kept in place for a duration of 6 hours minutes. The study began dosing on 07/08/06 and was completed on 07/09/06.

PRIMARY EFFICACY VARIABLE: Not applicable.

SECONDARY EFFICACY VARIABLES: Not applicable.

SAFETY ANALYSIS: Adverse events were collected and tabulated. No formal statistical analyses were performed.

STATISTICAL METHODS: The post-dose ChromaMeter readings were corrected for both the average pre-dose readings and the average readings from the untreated sites.

The area under the response/time curve for each site was calculated by the linear trapezoidal method. The mean area for each formulation was calculated and the areas were ranked in order by treatment. ~~The formulation showing the greatest blanching~~

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over 24 hours was considered the most potent product. The formulation showing the least blanching over 24 hours was considered the least potent product. The statistical significance of the difference between each of the products was calculated using appropriate statistical analysis.

The relative potency of the test formulation of alclometasone dipropionate 0.05% lotion was estimated by comparing it with the comparator products and placebo.

The Statistical Analysis System (SAS, Version 9.1) was used for all statistical calculations.

SUMMARY OF RESULTS:

Table 1: Mean Results for ChromaMeter Negative Areas Under the Response Curve in Order of Most to Least Potent Formulation

Formulations		N	Mean (6 Hr Duration)
Comparator 1 (Class I)	Clobex™ (clobetasol propionate) Topical Lotion, 0.05%, Manufactured by DPT Laboratories, Ltd., Marketed by Galderma Laboratories, L.P., Lot No. WIBH, Expiration Date 08/2008	40	36.1903
Comparator 2 (Class II)	Diprolene® (brand of augmented betamethasone dipropionate) Lotion, 0.05%, Schering Corporation., Lot No. 5-EAW-101, Expiration Date 06/2007	40	30.2673
Comparator 3 (Class IV)	Elocon® (brand of mometasone furoate) Lotion, 0.1%, Schering Corporation, Lot No. 5-FJF-801, Expiration Date 06/2007	40	22.2018
Comparator 5 (Class VI)	Aclovene® Ointment, 0.05% (alclometasone dipropionate ointment), GlaxoSmithKline Consumer Healthcare, L.P., Lot No. 4F001, Expiration Date 06/2007	40	17.7988
Comparator 4 (Class VI)	Aclovene® Cream, 0.05% (alclometasone dipropionate cream), GlaxoSmithKline Consumer Healthcare, L.P., Lot No. 5E002, Expiration Date 05/2008	40	9.5938
Test	Alclometasone dipropionate lotion, 0.05%, Stability Label, Lot No. U967, Manufacture Date 04/2006	40	9.5245
Placebo	Alclometasone dipropionate lotion, 0.05%, Placebo Label, Lot No. U966, Manufacture Date 04/2006	40	1.6522
Comparator 6 (Class VII)	Hydrocortisone Lotion USP, 1%, E. Fougera & Co., Lot No. T916, Expiration Date 12/2007	40	1.1313

CLINICAL STUDY REPORT**Alclometasone Dipropionate Lotion, 0.05%****Study No. 10628201****Table 2: Comparison of P-values – Scheffe's Test**

	Test	Comp. 1 (Class I)	Comp. 2 (Class II)	Comp. 3 (Class IV)	Comp. 4 (Class VI)	Comp. 5 (Class VI)	Comp. 6 (Class VII)	Placebo
Test		<0.0001	<0.0001	<0.0001	0.0066	<0.0001	0.8578	0.0071
Comp. 1	<0.0001		0.0424	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Comp. 2	<0.0001	0.0424		0.0058	<0.0001	<0.0001	<0.0001	<0.0001
Comp. 3	<0.0001	<0.0001	0.0058		<0.0001	0.1308	<0.0001	<0.0001
Comp. 4	0.0066	<0.0001	<0.0001	<0.0001		0.0051	0.0039	0.9810
Comp. 5	<0.0001	<0.0001	<0.0001	0.1308	0.0051		<0.0001	0.0047
Comp. 6	0.8578	<0.0001	<0.0001	<0.0001	0.0039	<0.0001		0.0041
Placebo	0.0071	<0.0001	<0.0001	<0.0001	0.9810	0.0047	0.0041	

Alpha level = 0.05

CONCLUSION:

alclometasone dipropionate lotion, 0.05% is considered to be a low potency steroid formulation (Class VI) relative to the Class I, II, IV, VI, and VII comparators. There was no statistically significant difference between the test product and the Class VI steroid Acloivate® Cream 0.05%.

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4.0 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ANDA	Abbreviated New Drug Application
AUC	Area Under Curve
CFR	Code of Federal Regulations
CRF	Case Report Form
CRNP	Certified Registered Nurse Practitioner
CV%	Coefficient of Variation Percent
FDA	Food and Drug Administration of the United States
GCP	Good Clinical Practices
hr	Hour
IC	Informed Consent
ICH	International Conference on Harmonisation
in.	Inches
μ l	Microliter
N/A	Not applicable
OGD	Office of Generic Drugs, Food and Drug Administration of the United States
Subj.	Subject
SAS	Statistical Analysis System
SD	Standard Deviation
USA	United States of America
VCA	Vasoconstrictor Assay

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5.0 ETHICS

5.1 Institutional Review Board (IRB)

The protocol and informed consent form were initially reviewed and approved by the Independent Institutional Review Board on 05/09/06. Comparator 2, 3, and 6 listed in the Revision 0 protocol and informed consent form were not available from their respective manufacturers. As a result, the protocol was subsequently revised to change comparator 2 from Cyclocort (amcinonide) Lotion by Galderma Labs LP to Diprolene® (betamethasone dipropionate, augmented) by Schering-Plough, to change comparator 3 from Betamethasone Valerate Lotion to Elocon® (mometasone furoate) Lotion by Schering-Plough, to change comparator 6 from Hytone® by Dermik to Hydrocortisone Lotion by Fougera, to change the exclusion criterion from "history of allergy to amcinonide" to "history of allergy to mometasone," and to update the Table of Contents accordingly. The informed consent form underwent the following revisions: changed amcinonide lotion to mometasone lotion (p. 1), changed betamethasone valerate lotion to betamethasone dipropionate lotion (p. 1), changed Comparator 2 from Cyclocort (amcinonide) Lotion to Diprolene (betamethasone dipropionate, augmented), changed Comparator 3 from Betamethasone Valerate Lotion to Elocon (mometasone furoate) (p. 2), changed Comparator 6 from Hytone lotion to Hydrocortisone Lotion (p. 3), and changed "report an allergy amcinonide" to "report an allergy to mometasone." Revision 1 of the protocol and informed consent form was reviewed and approved by the on 06/06/06, prior to study commencement. Copies of the approval forms from the , as well as the approved protocol (Revision 1) are provided in 16.1.1. Additionally, a copy of the membership roster and the approved consent form are provided in 16.1.3.

The complies with the requirements of FDA 21 CFR, Parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards). These are the principles that govern the in assuring that the rights and welfare of subjects are protected in the Belmont Report: *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, and the Declaration of Helsinki.

5.2 Ethical Conduct of the Study

The study was conducted according to the U.S. Code of Federal Regulations Guidelines for Good Clinical Practice (Code of Federal Regulations (21 CFR), Parts 50, 54, 56, 312 and 314), the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (ICH Guideline E6), the

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Declaration of Helsinki on the ethical conduct of medical research (Edinburgh, Scotland, 2002), and the Belmont Report.

5.3 Subject Information and Consent

Information as to the objective, procedures, risks, benefits, restrictions, and requirements of the study was presented to all subjects before the start of the study. The subjects were encouraged to ask questions, which were fully answered. All of the subjects signified their willingness to participate in this study by reading, signing, and dating the approved consent form (Revision 1); copies were provided to each subject. Signed, dated, and witnessed informed consent forms are on file at [redacted]. A sample copy of the subject consent form (Revision 1) is provided in 16.1.3.

6.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

[redacted] was the Principal Investigator and was responsible for the conduct of this study.

[redacted] were sub-investigators for this study. The signature of the coordinating investigator is provided in Appendix 16.1.5.

Copies of curriculum vitae, medical and professional licenses as appropriate, of the study staff listed on the FDA Form 1572, along with financial disclosure statements, a good clinical practice statement, and debarment certificates are provided in 16.1.4.

All subjects were housed and fed at the clinical facility of [redacted].

Statistical analyses were performed by [redacted] Biostatistician, [redacted], Telephone [redacted], Fax [redacted].

The clinical portion of the study was monitored and audited for compliance with GCP regulations by the Quality Assurance Department at [redacted].

The Clinical Report was written by [redacted].

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7.0 INTRODUCTION

A one-period, randomized study was conducted to compare the relative potency of a test formulation of alclometasone dipropionate lotion, 0.05% with two already approved alclometasone dipropionate 0.05% formulations (Aclovate[®] Cream and Aclovate[®] Ointment), a placebo (vehicle lotion), and four other already approved topical corticosteroids of known potency. This study was conducted in 40 asymptomatic, healthy, non-tobacco using female subjects, who had been pre-screened to show a vasoconstrictor response to Aclovate[®] Cream, 0.05% (alclometasone dipropionate cream).

Each formulation was applied to one site on the flexor surfaces of the subjects' forearms (left and right) and kept in place for a duration of 6 hours. Two untreated control sites were also designated on each forearm as ChromaMeter reference sites. All sites remained under non-occluded conditions throughout the study.

Vasoconstriction was measured by the degree of skin blanching observed after treatment removal using a ChromaMeter (a-scale reading). Evaluations were performed at pre-dose and at 0.5, 2, 4, 6, 8, 10, 12, 20, and 24 hours after removal.

Study data were collected on source documents. Completed case report forms were reviewed and signed by the Investigator and are on file at :

Copies of each subject's case report forms are included in Appendix 16.3. A sample copy of the CRF can be found in Appendix 16.1.2.

Statistical analysis was performed to compare the relative vasoconstrictive effects of the test formulation of alclometasone dipropionate lotion, 0.05% with that of placebo (vehicle lotion) and six already approved, low to super-high potency topical corticosteroids (including Aclovate[®] Cream, 0.05% and Aclovate[®] Ointment, 0.05%).

8.0 STUDY OBJECTIVES

The purpose of this study was to compare the relative potency of a test formulation of alclometasone dipropionate lotion, 0.05% with the already approved formulations of alclometasone dipropionate cream and ointment, 0.05% (Aclovate[®], GlaxoSmithKline), a placebo lotion, and four other comparator topical corticosteroids of known potency, in asymptomatic subjects.

9.0 INVESTIGATIONAL PLAN

9.1 Study Design and Plan Description

A one-period, randomized, vasoconstrictor study was performed with 40 pre-screened, asymptomatic, healthy, non-tobacco using, female subjects to compare the relative potency of a test formulation of alclometasone dipropionate lotion, 0.05% with two already approved

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alclometasone dipropionate 0.05% formulations (Aclovate[®] Cream and Aclovate[®] Ointment), a placebo (vehicle lotion), and four other approved topical corticosteroids of known potency.

Vasoconstriction was measured by the degree of skin blanching observed after treatment removal using a ChromaMeter (a-scale reading). Evaluations were performed at pre-dose and at 0.5, 2, 4, 6, 8, 10, 12, 20, and 24 hours after removal.

9.2 Selection of Study Design

The study was designed based on the FDA guidance "Topical Dermatologic Corticosteroids: *in vivo* Bioequivalence, Issue Date: 2 June 1995". This guidance provides recommendations to pharmaceutical sponsors on methods to document *in vivo* bioequivalence of topical dermatologic corticosteroids. The guidance utilizes a pharmacodynamic approach, based on an update of the Stoughton-McKenzie vasoconstrictor bioassay, to assess bioequivalence of topical corticosteroids. The method utilizes a duration of exposure (dose-duration) approach to control the dose of topical corticosteroid that is delivered.

Use of the ChromaMeter in bioanalytical studies addresses the problem of quantitatively measuring the action of topical corticosteroids that are generally not absorbed into the subject's blood stream. Many of these products cause vasoconstriction in the area of application which causes the skin to blanch, or become very pale, as less blood is able to travel through that area. The ChromaMeter measures the extent to which the site blanches by detecting the accompanying skin-tone changes.

The Minolta ChromaMeter CR-300 was used in this study to measure the reflective colors from the skin surface. A pulsed xenon arc lamp in a mixing chamber provides illumination on 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.

The protocol was reviewed and approved by the Sponsor prior to commencement of the study.

9.3 Selection of Study Population

The study population included 40 healthy, adult female subjects who satisfied all entry criteria.

9.3.1 Inclusion Criteria

1. Non-tobacco-using subjects, 18 to 65 years of age, inclusive.

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2. A demonstrated blanching response to Aclovate® (alclometasone dipropionate) Cream, 0.05%.
3. A body mass index (BMI) of 18-30 inclusive as calculated according to Standard Operating Procedures.
4. Good health as determined by lack of clinically significant abnormalities in medical history and clinical assessment, as judged by the Investigator.
5. Signed and dated informed consent form which meets all criteria of current FDA regulations.

9.3.2 Exclusion Criteria

1. History of allergy to systemic or topical corticosteroids (including alclometasone, clobetasol, betamethasone, mometasone, or hydrocortisone) or to any ointment, lotion, cream, gel, cotton, soap, cosmetic, rubber or tape, which in the opinion of the Investigator would compromise the safety of the subject or the study.
2. Presence of any skin condition or coloration that would interfere with the placement of test sites or the response or assessment of skin blanching.
3. Significant history or current evidence of chronic infectious disease, system disorder (especially hypertension or circulatory disease) or organ dysfunction.
4. Presence of a medical condition requiring regular treatment with prescription drugs.
5. Drug or alcohol addiction requiring treatment (in-patient or out-patient) in the past 12 months prior to dosing.
6. Use of any dermatological drug therapy (including topical corticosteroids) on the flexor surface of the forearms within 30 days of dosing.
7. Use of any tobacco products in the 30 days prior to study dosing.
8. Receipt of any drug as part of a research study within 30 days prior to study dosing.
9. Pregnant or lactating.
10. Consumption on average of more than 500 mg/day of caffeine containing beverages.

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9.3.3 Removal of Subjects from the Study

Subjects were advised that they were free to withdraw from the study at any time for any reason or, if necessary, the Investigator or Sponsor could withdraw a subject from the study to protect the health of a subject. A subject could also be withdrawn for not complying with study procedures.

9.4 Treatments

9.4.1 Treatments Administered

See Appendix 16.1.6 for a schedule of treatment and actual application and removal times listed by subject.

9.4.2 Identity of Investigational Products

The test and comparator products were supplied by the sponsor of the study, All of the products were logged in upon receipt. The same lot of each of the products was used during the entire study. All drug receipt, inventory, dispensing, dosing, and reconciliation records are maintained in compliance with Standard Operating Procedures. The study drug was dispensed by the Investigator or by a qualified individual under the Investigator's direct supervision according to established procedures. Upon completion or termination of the study, unused drug was reconciled with administered drug, and all remaining study drug has been retained by under current FDA regulations (21 CFR, Sections 320.38 and 320.63). A copy of the drug receipt records and a copy of the drug accountability records are included in Appendix 16.1.6. The following study drugs were used in this study:

Test	Alclometasone dipropionate lotion, 0.05%, Stability Label; Lot No. U967; Manufacture Date 04/2006
Comparator 1	Clobex™ (clobetasol propionate) Topical Lotion, 0.05%; Manufactured by DPT Laboratories, Ltd., Marketed by Galderma Laboratories, L.P.; Lot No. WIBH; Expiration Date 08/2008
Comparator 2	Diprolene® (brand of augmented betamethasone dipropionate) Lotion, 0.05%; Schering Corporation; Lot No. 5-EAW-101; Expiration Date 06/2007

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Comparator 3	Elocon [®] (brand of mometasone furoate) Lotion, 0.1%, Schering Corporation; Lot No. 5-FJF-801; Expiration Date 06/2007
Comparator 4	Aclovate [®] Cream, 0.05% (alclometasone dipropionate cream); GlaxoSmithKline Consumer Healthcare, L.P.; Lot No. 5E002; Expiration Date 05/2008
Comparator 5	Aclovate [®] Ointment, 0.05% (alclometasone dipropionate ointment); GlaxoSmithKline Consumer Healthcare, L.P.; Lot No. 4F001; Expiration Date 06/2007
Comparator 6	Hydrocortisone Lotion USP, 1%; E. Fougera & Co.; Lot No. T916; Expiration Date 12/2007
Placebo	Alclometasone dipropionate lotion, 0.05%, Placebo Label; Lot No. U966; Manufacture Date 04/2006

9.4.3 Method of Assigning Subjects to Treatment Groups

The formulations were applied to the designated sites according to a randomization schedule prepared prior to dosing by

using SAS

Version 9.1. The schedule selected the location of the sites. A copy of the randomization is presented in Appendix 16.1.7.

9.4.4 Selection of Doses in the study

See Section 9.2.

9.4.5 Selection and Timing of Dose for Each Subject

The arms of each subject were washed with a mild soap (Liquid Neutrogena Facial Cleansing Formula[®]) and gently dried at least 2 hours prior to initial dosing.

Ten (10) circular (approximately 1.6 cm inside 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 to ensure that the sites were no closer than 2 cm apart center-to-center. All sites were evaluated prior to dosing for the presence of any skin condition (e.g.

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coloration, freckles, moles, scratches) that would interfere with the assessment or response of skin blanching.

After baseline ChromaMeter 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 area to be treated was not occluded. Using a 250 µl glass Hamilton syringe with a Hamilton "Repeating Dispenser", a 20 µl application of each formulation was applied to 8 sites. Two (2) sites on each arm were left untreated. 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 ChromaMeter assessments were started approximately 3 hours prior to first application. All sites were on, or staggered about, the midline axis of the subject's forearm and at least 3 cm from the wrist or antecubital fossa.

All applications were removed at the same time point (0.0 hour) in the order that they were applied. The washers were detached and residual surface treatment was removed by gently wiping with at least three separate clean dry cotton balls. The untreated sites on each arm were similarly wiped at the same time as the treated sites.

The subjects were dosed on 07/08/06 and completed the study approximately 30 hours after their first application of study drug. A schedule of the actual dosing times and dates is included in Appendix 16.1.6.

9.4.6 Blinding

The ChromaMeter operators were blinded as to the treatment at each site. The subjects and all other clinic staff were not blinded.

9.4.7 Prior and Concomitant Therapy

Prior to check-in for the study, the subjects were instructed to avoid prescribed medications (other than contraceptives) for at least 7 days prior to dosing or any over-the-counter medications for 72 hours prior to dosing. The subjects were not allowed to use any topical dermatological drug therapy (including topical corticosteroids) on the flexor surface of the ventral forearms within 30 days of dosing, other than that used for screening, or any other creams, gels, lotions, emollients, ointments or similar products for 24 hours prior to dosing. None of the subjects reported using any of the restricted items during

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the timeframes indicated. A listing of concomitant medications is provided in Appendix 16.2.3.

9.4.8 Dosing Compliance

All subjects were dosed and monitored at the clinical facility. During this study, the subjects were housed and fed at the clinical facility. All subjects reported for check-in on the evening of Day -1. A meal was provided on check-in day. Caffeine-free meals/snacks, which did not contain excessive amounts of sodium, were served at traditional times; thereafter. Meals/snacks were consumed at least one hour prior to ChromaMeter assessments. Water was permitted *ad lib* throughout the study.

Alcohol and caffeine consumption was not permitted for 48 hours prior to dosing and throughout the study. None of the subjects reported using products containing alcohol or caffeine within the time frames indicated.

The subjects were instructed to avoid contact with water on their arms, extremes of temperature and 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. All subjects followed the above restrictions during the time frames indicated.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

The study was designed to compare the relative potency of eight topical corticosteroid formulations (including one placebo formulation); therefore, efficacy was not measured.

Safety was evaluated by collection of adverse events. Adverse events were collected through both solicited and unsolicited means.

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Procedure	Screen ¹			
	Day -28 to -1	Day -1	Day 1	Day 2
Informed Consent	X			
Medical History	X			
Clinical Assessment	X			
Vital Signs ²	X	X		
Alcohol and Drug Screen		X		
Urine Pregnancy Test ³	X	X		
Admission to Clinical Site		X		
Drug Administration ⁴			X	
ChromaMeter Assessments ⁵			X	X
Release from Clinical Site				X
Monitor and/or Record Adverse Events			X	X

¹Within 28 days of the first dose (Day 1).

²Vital signs were measured at check-in.

³For all subjects, results must be negative before the drug is applied.

⁴All formulations applied 6 hours prior to synchronized removal at Time 0 (0 hour).

⁵ChromaMeter assessments were performed prior to application, and at 0.5, 2, 4, 6, 8, 10, 12, 20, and 24 hours after product removal.

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9.5.2 Appropriateness of Measurements

This was a vasoconstrictor assay study; therefore, no blood was collected during the study.

9.5.3 Primary Efficacy Variables

Not applicable

9.5.4 Pharmacodynamic Measurements

The Minolta ChromaMeter CR-300 was used in this study to measure the reflective colors from the skin surface, and six high-sensitivity silicon photocells were used by the meter's double-beam feedback system to measure both incident and reflected light.

Two ChromaMeter instruments (Serial No. 660-H and 661-H) were used for all assessments. Both instruments were calibrated against the manufacturer's standard calibration plate prior to each interval reading.

The intra-meter coefficient of variation (CV%) for ChromaMeter 660-H and 661-H was 5.69% and 5.35%, respectively. Inter-meter CV% was 5.48%. ChromaMeter instrument cross-validation analyses are provided in Appendix 16.1.10.

Prior to the study, the precision of the ChromaMeter operators (RWF and RWM) was evaluated. The supporting operator validation reports are on file at Novum and are provided in Appendix 16.1.10.

The ChromaMeter operators measured the degree of blanching at each site prior to treatment application (in duplicate) and at 0.5, 2, 4, 6, 8, 10, 12, 20, and 24 hours after removal using the ChromaMeter a-scale reading. All sites were assessed under standard fluorescent lighting and at room temperature. The 0.5-hour through 24-hour assessments were performed within 5 minutes of their scheduled time. The ChromaMeter operators were blinded as to the treatment at each site.

9.6 Data Quality Assurance

To ensure the quality of the data, all source data records went through a 100% monitoring process to confirm accuracy of the transcription to the CRFs.

Study procedures, study drug, regulatory aspects of study conduct, source documentation, and CRF transcription were monitored for accuracy and

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compliance with GCP regulations by the Quality Assurance Department at A Quality Assurance Statement can be found in 16.1.8.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

The post-dose ChromaMeter readings are to be corrected for both the average pre-dose readings and the average readings from the untreated sites.

The area under the response/time curve for each site is to be calculated by the linear trapezoidal method.

The mean area for each formulation is to be calculated, and the areas are to be ranked in order by treatment. The formulation that shows the greatest blanching over 24 hours is to be considered the most potent product. The formulation that shows the least blanching over 24 hours is to be considered the least potent product. The statistical significance of the difference between each of the products is to be calculated using appropriate statistical analysis.

The relative potency of the test formulation of alclometasone dipropionate 0.05% lotion is to be estimated by comparing it with the comparator products and placebo.

The Statistical Analysis System (SAS) is to be used for all statistical calculations.

9.7.2 Determination of Sample Size

A sample size of 40 subjects was considered large enough to compare and evaluate the relative potency of a test formulation of alclometasone dipropionate lotion, 0.05% with that of placebo (vehicle lotion) and six already approved, low to super-high potency topical corticosteroids (including Aclovate[®] Cream, 0.05% and Aclovate[®] Ointment, 0.05%).

9.8 Changes to Study Conduct or Planned Analysis

No changes to the study conduct or measurements were implemented after the start of the study.

10.0 STUDY SUBJECTS

10.1 Disposition of Study Subjects

Forty (40) subjects were enrolled in this study, and 40 subjects completed the study.

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10.2 Protocol Deviations

No protocol deviations were noted during the study.

11.0 EFFICACY EVALUATION

11.1 Data Sets Analyzed

Not applicable

11.2 Demographic and Other Baseline Characteristics

The 40 female subjects who participated and completed this study were healthy, in the age range of 18 to 51 (mean age 32.4) years, a weight range of 90 to 182 (mean weight 136.3 lbs) and a BMI (Body Mass Index) in the range of 18.0 to 30.0 kg / m², (mean BMI 23.6). The subject population consisted of 27 Hispanics, 7 Caucasian, 4 Asian, 1 Biracial, and 1 Black subject. All of the subjects were non-tobacco users for at least 30 days before the study. A table of summary demographics is provided in Appendix 16.2.4.

All study participants were screened to determine blanching response to Aclovate[®] Cream, 0.05% (alclometasone dipropionate cream). Twenty microliters (20 µl) of Aclovate[®] Cream, 0.05% (alclometasone dipropionate cream) was applied to the upper arm above the forearm and was left in place for 3 hours (± 30 minutes), and the site was visually evaluated approximately 6-9 hours after application. All subjects were selected based on a demonstrated blanching response (at least a 1 on 0-3 rating scale) and the absence of any clinically significant findings on the medical history and 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 assessment of skin blanching. A urine pregnancy test was performed on all subjects at screening, and all subjects tested negative. The subjects' characteristics and a table of summary demographics are summarized and presented in Appendix 16.2.4.

11.3 Measurements of Treatment Compliance

Not applicable

11.4 Efficacy Results and Tabulations of Individual Subject Data

11.4.1 Analysis of Efficacy

Not applicable

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11.4.2 Statistical/Analytical Issues

11.4.2.1 Adjustments for Covariants

Not applicable

11.4.2.2 Handling of Dropouts or Missing Data

Not applicable

11.4.2.3 Interim Analyses and Data Monitoring

Not applicable

11.4.2.4 Multicenter Studies

Not applicable

11.4.2.5 Multiple Comparisons/Multiplicity

Not applicable

11.4.2.6 Use of an Efficacy Subset of Subjects

Not applicable

**11.4.2.7 Active-Control Studies Intended to Show
Equivalence**

Not applicable

11.4.2.8 Examination of Subgroups

Not applicable

11.4.3 Tabulation of Individual Response Data

Not applicable

**11.4.4 Drug Dose, Drug Concentration, and Relationships to
Response**

Not applicable

11.4.5 Drug-Drug and Drug-Disease Interactions

Not applicable

11.4.6 By-Subject Listings

Not applicable

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11.4.7 Efficacy Conclusions

Not applicable

12.0 SAFETY EVALUATION

12.1 Extent of Exposure

Not applicable

12.2 Adverse Events (AEs)

12.2.1 Brief Summary of Adverse Events

The subjects were monitored throughout the study for any adverse experiences. Adverse events were collected through both solicited and unsolicited means. The subjects were encouraged to report signs, symptoms, and any changes in health to the clinic staff. Severity of each adverse event was determined by the clinic staff based on observation and questioning of the subject. The Investigator judged the relationship of the event to the study treatments. The adverse event experienced during this study was not judged as serious (21 CFR, Section 312.32).

Only one adverse event (skin irritation) was reported during this study. This event was considered mild and resolved spontaneously. A tabulation of the adverse event can be found in 16.2.7.

12.2.2 Display of Adverse Events

See Appendix 16.2.7.

12.2.3 Analysis of Adverse Events

See Section 12.2.1.

12.2.4 Listing of Adverse Events by Subject

See Appendix 16.2.7.

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1 Listing of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

12.3.1.1 Deaths

None

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12.3.1.2 Other Serious Adverse Events

None

12.3.1.3 Other Significant Adverse Events

None

12.3.2 Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events

Not applicable

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

Not applicable

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of Individual Laboratory Measurements by Subject

Urine pregnancy tests were performed on all of the subjects irrelevant of their childbearing potential at check-in. All of the subjects tested negative.

Saliva tests for alcohol and urine tests for drugs of abuse were performed on all subjects at each check-in. All of the subjects tested negative.

12.4.2 Evaluation of Each Laboratory Parameter

12.4.2.1 Laboratory Values Over Time

Not applicable

12.4.2.2 Individual Subject Changes

Not applicable

12.4.2.3 Individual Clinically Significant Abnormalities

Not applicable

12.5 Vital Signs, Physical Findings and Other Observations Related to Safety

Temperature, pulse rate, respiration rate, and blood pressure, (sitting) were measured at check-in. The pre-dose vital sign measurements

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were found to be clinically acceptable for dosing. Each subject's vital sign measurements are provided in her Case Report Form in Appendix 16.3.

12.6 Safety Conclusions

There was only one adverse event reported during this study. This event was considered mild and resolved spontaneously.

13.0 DISCUSSION AND OVERALL CONCLUSIONS

The clinical and statistical study objectives as described in the protocol were met.

The final potency ranking, from most to least potent product, is as follows:

- Comparator 1/ Class I (Mean AUC = 36.1903)
- Comparator 2/ Class II (Mean AUC = 30.2673)
- Comparator 3/ Class IV (Mean AUC = 22.2018)
- Comparator 5/ Class VI (Mean AUC = 17.7988)
- Comparator 4/ Class VI (Mean AUC = 9.5938)
- Test (Mean AUC = 9.5245)
- Placebo (Mean AUC = 1.6522)
- Comparator 6/ Class VII (Mean AUC = 1.1313).

Based on the ChromaMeter area results, the test formulation of alclometasone dipropionate lotion, 0.05% is significantly more potent than placebo lotion ($P = 0.0071$) and significantly less potent than its class I ($P < 0.0001$), II ($P < 0.0001$), IV ($P < 0.0001$), and VI comparators ($P = 0.0066$ and $P < 0.0001$ vs. Comparator 4 and 5, respectively). No statistical difference was observed between the test formulation and its Class VII (low potency) comparator.

Therefore, relative to the Class I, II, IV, VI, and VII comparators, alclometasone dipropionate lotion, 0.05% is considered to be a low potency steroid formulation (Class VI) and was not statistically different than Aclovate® Cream 0.05%.

14.0 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic Data

See Appendix 16.2.4.

14.2 Efficacy Data

Not applicable

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14.3 Safety Data

14.3.1 Displays of Adverse Events

See Appendix 16.2.7.

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

None

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

Not applicable

14.3.4 Abnormal Laboratory Value Listing (each subject)

Not applicable

15.0 REFERENCE LIST

1. Physicians' Desk Reference. 60th Edition, 2006.
2. The United States Food & Drug Administration. *Guidance Topical Dermatologic Corticosteroids: In Vivo Bioequivalence*; 06/02/95.

16.0 APPENDICES

16.1 Study Information

- 16.1.1 Protocol, approval forms
- 16.1.2 Sample case report form
- 16.1.3 List of IECs or IRBs, sample subject consent form
- 16.1.4 List and description of investigators and other important participants in the study, including FDA Form 1572, CVs, licenses, financial disclosures, debarment certifications and GCP certification.
- 16.1.5 Signature of principal or coordinating investigator
- 16.1.6 Table of dosing dates and time and drug receipt and accountability records
- 16.1.7 Randomization scheme and codes
- 16.1.8 Quality assurance statement
- 16.1.9 Statistical report
- 16.1.10 ChromaMeter operator validations and instrument cross validation

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- 16.1.11 Publications based on the study – Not applicable
- 16.1.12 Important publications referenced in the report – N/A

16.2 Subject Data Listings

- 16.2.1 Discontinued subjects – None
- 16.2.2 Protocol deviations – None
- 16.2.3 Concomitant medications
- 16.2.4 Table of subject characteristics and table of summary demographics
- 16.2.5 ChromaMeter assessment time deviation table – None
- 16.2.6 Individual efficacy response data – Not applicable
- 16.2.7 Listing of adverse events (each subject) and frequency of adverse events by body system
- 16.2.8 Listing of individual laboratory measurements by subject – Not applicable

16.3 Case Report Forms

Case Report Forms (01 – 40)

- 16.3.1 CRFs for deaths, other serious adverse events and withdrawals for Adverse Events – Not applicable
- 16.3.2 Other CRFs submitted – Not applicable

16.4 Individual Subject Data Listings

Not applicable