Clinical Study Report — ACZ ROS 01
Aczone™ (dapsone) Gel, 5%

A Phase II, Randomized, Partial-Blind, Parallel-Group, Active- and Vehicle-Controlled, Multicenter Study of the Safety and Efficacy of Aczone™ (Dapsone) Gel, 5% in Subjects With Papulopustular Rosacea

Date of Report: 05 February 2007

This Study Report is written as an accurate record of the conduct and the results of the study by:

Study Director: 7 Feb 2007
Steve Garrett, MS, DDS, FACD — Date
QLT USA, Inc.

Study Biostatistician: 7 Feb 2007
Craig Wesselman, MS — Date
QLT USA, Inc.

Approved by: 7 FEB 2007
Sean Moriarty — Date
President, QLT USA, Inc.

The study was conducted in accordance with the ICH GCP guidelines; Division 5 of the Canadian Food and Drug Regulations; US 21 CFR Parts 50, 54, 56, and 312; and the principles enunciated in the Declaration of Helsinki.

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Study Number and Title: ACZ ROS 01. A Phase II, Randomized, Partial-Blind, Parallel-Group, Active- and Vehicle-Controlled, Multicenter Study of the Safety and Efficacy of Aczone™ (dapsone) Gel, 5% in Subjects with Papulopustular Rosacea

This Study Report is written as an accurate record of the conduct and the results of the study by:

Medical Writer: _____ 5 Feb 2007
Denise Galipeau, MSc — Date
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QUALITY ASSURANCE REVIEW STATEMENT

The content of this report has been reviewed against the data listings, summary tables, references, protocol, and amendments for accuracy and completeness by:

Reviewed by: J. Cable 5 Feb 2007
Joan Cable, RCT (A) — Date
Senior Manager, Clinical Quality
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ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
Aczone	Aczone™ (dapsone) Gel, 5%
ALA	5-aminolenulinic acid
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CRF	Case report form
ET	Early termination
G6PD	Glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Conference on Harmonization
IGA	Investigator's Global Assessment (5-point scale of disease severity)
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine Device
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MetroGel	MetroGel® (metronidazole gel), 1%
N	Number
NOS	Not otherwise specified
NSAIDS	Nonsteroidal anti-inflammatory drugs
PP	Per protocol
PUVA	Psoralen ultraviolet A
RBC	Red blood cell
ROS	Rosacea
SAE	Serious adverse event
SD	Standard deviation
USP	United States Pharmacopeia
VC	Vehicle Control
WHO DD	World Health Organization Drug Dictionary

1 INTRODUCTION

Rosacea is a multifactorial chronic skin disorder that most often affects the central face including the nose, forehead, cheeks, and chin. Rosacea usually affects fair-skinned people 30 to 50 years of age who tend to blush or flush easily. Four subtypes of rosacea are described: papulopustular, erythematotelangiectatic, phymatous, and ocular [1]. In a recent study of clinical patterns of rosacea, papules and pustules were found in 83% and 67% of a sample of 108 rosacea patients, respectively [2]. In the papulopustular subtype of rosacea, patients typically present with persistent central facial erythema with transient papules or pustules or both. Symptoms of burning, stinging, and dry skin are common [1,3]. Other symptoms include flushing, erythema, and telangiectasia. While the exact pathogenesis of rosacea is unknown, inflammatory and vascular components are believed to be important in its pathogenesis.

Dapsone has been recognized as being effective orally against a number of non-infectious inflammatory diseases, of which dermatitis herpetiformis is best known. A number of other inflammatory, as well as bullous, diseases have been reported to respond in varying degrees to dapsone [4]. Anecdotal case reports of the use of oral dapsone in treating patients with various forms of rosacea support the hypothesis that dapsone may have activity in treating papulopustular rosacea [5,6,7]. Topical administration of dapsone may be more appropriate than oral administration for the treatment of rosacea since it can be delivered directly to the skin, with lower systemic exposure and less risk of systemic toxicity.

Aczone™ (dapsone) Gel, 5% is a new topical formulation of dapsone that is approved for the treatment of acne vulgaris in the US and Canada. In previous clinical studies for acne vulgaris, Aczone significantly reduced inflammatory and non-inflammatory lesion counts. In 2 vehicle-controlled studies (Studies DAP0203 and DAP0204), inflammatory lesion counts were reduced by 46% and 48% in Aczone-treated groups compared with 42% and 40% for the vehicle-treated groups, respectively. The percentage reduction in non-inflammatory lesion counts were 31% and 30% for Aczone compared with 24% and 21% for vehicle. An important component of the Aczone effects observed in these trials was anti-inflammatory. Since inflammation is a component of papulopustular rosacea and anti-inflammatory properties are a common characteristic of systemic and topical therapies used for rosacea [8,9,10], Aczone may also have potential treatment effects on the signs and symptoms of papulopustular rosacea.

This report presents the results of a phase II study to evaluate the safety and preliminary efficacy of Aczone in the treatment of papulopostular rosacea. It was conducted as a randomized, partial-blind, parallel-group study with both an active and vehicle control. This was the first study of Aczone in this patient population and was designed to provide an estimate of safety and efficacy to guide the design of any potential future trials.

2 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

2.1 Study Investigators

The study enrolled a total of 400 subjects across 27 study centers in the United States. Following is a list of study investigators, centers, and the number of subjects enrolled at each center. A list of other essential study personnel is provided in Appendix D.3.

Center Number	Investigator	Study Center	Number of Subjects
01	Paul Yamauchi, MD	Clinical Research Specialists, Inc., Santa Monica, CA	15
02	Hector Wiltz, MD, CCTI	FXM Research, Miami FL	28
03	Pranav Sheth, MD	University Dermatology Consultants, Inc. Cincinnati, OH	25
04	Stacy R. Smith, MD	Therapeutics Clinical Research, San Diego, CA	16
05	Harry Sharata, MD	Madison Skin & Research, Inc., Madison, WI	14
06	Joel Schlessinger, MD	Skin Specialists, PC, Omaha, NE	30
07	Ronald C Savin, MD	Savin Center, PC, New Haven, CT	3
08	Janet L Roberts, MD	Northwest Dermatology and Research, Portland, OR	25
09	Lawrence C Parish, MD	Paddington Testing Clinic, Philadelphia, PA	10
10	Jeffrey Moore, MD	Welborn Clinic, Evansville, IN	14
11	Robert Matheson, MD	Oregon Medical Research Center, Portland, OR	9
12	J Michael Maloney, MD	Cherry Creek Research, Inc., Denver, CO	20[a]
13	Anne Lucky, MD[a]	Dermatology Research Associates, Inc., Cincinnati, OH	4
14	Mark R Ling, MD, PhD	MedaPhase, Inc., Newnan GA	17
15	Terry M Jones, MD	J&S Studies, Inc., Bryan, TX	7
16	Michael T Jarratt, MD	DermResearch, Inc., Austin, TX	19
17	Jolynne Herzog, MD	Radiant Research, Inc., Birmingham, AL	20
18	Lynn A Cornelius, MD	Dermatology Clinical Trials Unit, Washington University, St. Louis, MO	5
19	William B Harwell, MD	Dermatology Research Associates, Nashville, TN	14
20	Larry I Gilderman, DO	University Clinical Research, Pembroke Pines, FL	15
21	David Fried, MD	Omega Medical Research, Warwick, RI	0
22	Frank Dunlap, MD	Radient Research, Tuscon, AZ	10
23	Zoe Draelos, MD	Dermatology Consulting Services, High Point, NC	13
24	Sunil S Dhawan, MD	East Bay Dermatology Medical Group, Inc., Fremont, CA	5
25	Alicia Bucko, DO	Academic Dermatology Associates, Albuquerque, NM	20
26	Steven Bowman, MD	Tampa Bay Medical Research, Clearwater, FL	30
27	Keith Aqua, MD	Visions Clinical Research, Boynton Beach, FL	7
28	Anne Lucky, MD[b]	Dermatology Research Associates, Inc., Cincinnati, OH	5

[a] One subject was randomized in error at Center 12. Data were collected from only 19 subjects at this center.
[b] Dr. Lucky enrolled subjects at 2 different clinic locations in Cincinnati, which had separate randomization sequences and were therefore assigned separate center identification numbers.

2.2 Study Administrative Structure

The following Sponsor individuals were involved in the design, conduct, analysis, and/or reporting of the study:

Individual	Title	Responsibility
QLTUSA, Inc.		
Steve Garrett, MS, DDS, FACD	Senior Vice President, Dermatology	Overall study responsibility
Craig Wesselman, MS	Biostatistician	Statistical analyses and design
Cynthia Strock, MPH	Senior Manager, Clinical Operations	Study operations
Mary McManus, CCRA	Clinical Research Associate	Lead CRA, study monitoring
Adam James, CCRA	Senior Clinical Research Associate	Study monitoring
QLT, Inc.		
Denise Galipeau, MSc	Medical Writer	Medical writing
Jane Liu, MS	Clinical Data & Application Manager	Study database and CRF
Gina Briggs	Clinical Research Associate	Study monitoring
Sheryl Myers, RN, CCRA	Senior Clinical Research Associate	Study monitoring
Wendy Wilson, RN	Clinical Research Associate	Study monitoring
Other		
Mary Beth McClain, RN, MBA, CCRA	Contract Monitor	Study monitoring
Stephanie Costa, RT	Contract Monitor	Study monitoring

2.3 Contract Services

2.3.1 Randomization and Clinical Trial Supplies

Labeling, distribution, and tracking of study treatment supplies and randomization services were provided by:

Fisher Clinical Services
7554 Schantz Road
Allentown, PA
18106

2.3.2 Laboratory Analyses

The following was the central laboratory for the study:

Quintiles Laboratories, Ltd.
5500 Highlands Parkway
Suite 600
Smyrna, GA 30082
Tel: 770-373-3500

Quintiles was responsible for receipt and handling of all blood samples required for this study, for reporting results back to the study center, and for providing an electronic data

transfer to the Sponsor at the end of the study. Quintiles also performed the analysis of clinical chemistry and hematology. The following laboratories performed the specialized laboratory tests indicated:

Plasma dapsone and metabolites	G6PD Activity
CANTEST BioPharma Services	ARUP Laboratories
4606 Canada Way	500 Chipeta Way
Burnaby, British Columbia	Salt Lake City, Utah
Canada V5G 1K5	United States 84108-1221

3 STUDY ETHICAL CONSIDERATIONS

3.1 Ethical Conduct of Study

The study was conducted in accordance with the International Conference on Harmonization (ICH) GCP guidelines; Division 5 of the Food and Drugs Regulations of Canada; the US 21 CFR Parts 50, 54, 56, and 312; and the principles enunciated in the Declaration of Helsinki.

3.2 Institutional Review Board, Ethics Committee, or Research Ethics Board (IRB)

The protocol and informed consent form for this study were reviewed and approved by an Institutional Review Board, Ethics Committee, or Research Ethics Board (IRB) at each study center prior to implementation. No subject was treated until the IRB had provided written approval of the study and the informed consent form to the Investigator and the Sponsors. The IRB regulations in each country were followed at respective centers. Appendix D.4.1 contains a list of the names and addresses of each IRB and their corresponding approval letters.

3.3 Subject Information and Consent

The Informed Consent form used for each study center complied with the Declaration of Helsinki, federal regulations (US 21 CFR 50 and other national requirements), and ICH GCP guidelines and was approved by the Sponsor and the Investigator's IRB. The Investigator explained orally and in writing the medical aspects of the study, including the nature of the study and the treatment, in such a manner that each subject was aware of potential benefits and risks. Other elements of the informed consent process may have been delegated by the Investigator. After having been informed that participation was voluntary and that subjects may withdraw from the study at any time, without prejudice, each subject signed the IRB-approved informed consent form prior to enrollment in the study. A sample informed consent form, including information for subjects, is provided in Appendix D.4.2.

4 STUDY OBJECTIVES

The objective of this study was to evaluate the safety and preliminary efficacy of Aczone in subjects with papulopustular rosacea.

5 STUDY DESCRIPTION (METHODS AND INVESTIGATIONAL PLAN)

This section describes the design and conduct of the study, as outlined in the protocol. The protocol is provided in Appendix D.1. There were no amendments or changes to the study design described in the protocol.

5.1 Overall Study Design

This was a multicenter, randomized, partial-blind, parallel-group study in male and female adult subjects with papulopustular rosacea. Subjects were randomly assigned to 1 of the following 5 treatment groups, in an equal ratio, according to a computer-generated randomization scheme:

- Vehicle Control (VC), 2x/day.
- Aczone (dapsone) Gel, 5%, 2x/day.
- Aczone (dapsone) Gel, 5%, 1x/day.
- MetroGel® (metronidazole gel), 1%, 1x/day.
- Aczone (dapsone) Gel, 5% 1x/day + MetroGel (metronidazole gel), 1%, 1x/day.

Subjects were instructed to apply the assigned study treatment to the entire face, after cleansing, for 12 weeks. Subjects were not blinded; however, they were not specifically told which treatment group they belonged to. Study personnel who dispensed the study treatment and the Sponsor were not blinded to treatment, but the evaluators of efficacy and safety variables were blinded.

Efficacy assessments included monitoring inflammatory lesion counts, Investigator Global Assessment (IGA) scores, erythema scores, and telangiectasia scores. Plasma dapsone concentrations were measured to assess systemic exposure to the study treatment. Safety was evaluated by monitoring adverse events, hematology and serum chemistry parameters, concomitant medications, vital signs, and local symptoms (dryness, itching, stinging, and burning).

5.2 Discussion of Study Design

A partial-blind study design, in which the evaluators of efficacy and safety variables are blinded, was chosen to avoid bias in the assessment of those variables. Subjects' knowledge of their treatment assignment was not believed to affect the outcome of these assessments, therefore rigorous blinding of the subject was not considered necessary. Because the study included 2 different active treatments (Aczone and MetroGel) with different packaging and different treatment regimens (once-daily and twice-daily), a double-blind design was not considered reasonable for this phase II study.

MetroGel is an approved product for the treatment of papulopustular rosacea and recent studies used the same efficacy assessments used in this study. A VC arm was included in order to compare the effects of each treatment against an inactive treatment and to establish

the magnitude of any potential treatment effects, since some improvement was observed in subjects treated with VC alone in Aczone studies with acne vulgaris subjects.

Several measures of efficacy were included in the study. Success rates, based on a 5-point IGA, and changes from baseline in lesion counts, are direct indications of treatment response, and were used in recent studies of other rosacea therapies [11,12]. Both of these endpoints are considered important and clinically relevant in evaluating the efficacy of treatments for rosacea. Erythema and telangiectasia are signs of rosacea that were evaluated according to standardized 4-point scales, and treatment-induced changes in these signs were considered to be clinically meaningful to subjects.

The treatment period was designed to be 12 weeks, which is sufficient for any potential treatment benefits to become apparent, and is consistent with other studies of topical therapies for rosacea [12,13]. Subjects were followed for 7 days after stopping treatment to monitor any ongoing adverse events. This length of time was longer than or equivalent to 5 half-lives of dapsone after topical application ($t_{1/2}$=27.8 ± 8.31 hours [Study DAP9903]).

5.3 Study Population

5.3.1 Number of Subjects

As planned in the protocol, a total of 400 subjects were enrolled in this study. However, data were only collected from 399 subjects because there was 1 subject randomized in error who was never dispensed any study treatment (randomization number 7519 at center 12, which was not re-used).

5.3.2 Inclusion Criteria

To be eligible for the study, subjects had to fulfill all of the following criteria:

1. Men or women ≥18 years of age.
2. Had a diagnosis of papulopustular rosacea, with ≥10 inflammatory lesions (papules and/or pustules) above the mandibular line at baseline.
3. Had an IGA score ≥2.

Score	Severity	Description
0	Clear	No signs or symptoms present; at most, mild erythema
1	Almost Clear	Very mild erythema present. Very few small papules/pustules
2	Mild	Mild erythema. Several small papules/pustules
3	Moderate	Moderate erythema. Several small or large papules/pustules, and up to 2 nodules
4	Severe	Severe erythema. Numerous small and/or large papules/pustules, up to several nodules.

4. Was in good physical and mental health.

5. Signed an approved informed consent form for the study and HIPAA authorization (if applicable).
6. Was willing to comply with the protocol.

5.3.3 Exclusion Criteria

Subjects who met any of the following criteria were excluded from the study:

1. A skin examination revealed the presence of another skin disease and/or condition (excessive facial hair, excessive scarring, sunburn, or other disfigurement) located on the face that, in the study physician's opinion, would have confounded the evaluation of the rosacea condition.
2. Current or past ocular rosacea, such as conjunctivitis, iritis, and keratitis, of sufficient severity to require topical or systemic antibiotics, in the opinion of the Investigator.
3. Treatment with topical antibiotics, topical steroids and other topical rosacea treatments on the face within 14 days of Baseline and throughout the study. This included other topical rosacea treatments including, but not limited to, treatments containing metronidazole (other than the MetroGel product supplied for this study), azelaic acid, and treatments containing sodium sulfacetamide and sulfur.
4. Treatment with systemic steroids within 30 days of Baseline and throughout the study (glucocorticoids were the only steroids excluded – intranasal and inhaled corticosteroids, and eye drops containing corticosteroids did not require a washout and were acceptable for use throughout the study, if at a stable and standard dose as labeled within the Package Insert).
5. Treatment with any systemic antibiotics within 30 days of Baseline and throughout the study. Short-term treatment with antibiotics for non-rosacea related conditions during the study was acceptable provided that exposure was limited to ≤14 days per course.
6. Treatment with any systemic medication or therapy known to affect inflammatory responses within the 30 days prior to Baseline or throughout the study. These medications included but were not limited to: oral corticosteroids, cyclosporin, and methotrexate. Short-term treatment with NSAIDS before or during the study for non-rosacea related conditions was acceptable provided that exposure was limited to ≤14 days per course. Chronic low-dose aspirin use was also acceptable.
7. Treatment with topical retinoids within 30 days or systemic retinoids within 180 days of Baseline and throughout the study.
8. Treatment with physical modalities such as ultraviolet light, tanning, psoralen ultraviolet-A (PUVA), 5-aminolevulinic acid (ALA) photodynamic therapy, chemical exfoliative treatments (alpha-hydroxy acid or "fruit-wash," "lunchtime" or phenol peels), laser, "dry ice" peels, and cosmetic procedures that could benefit rosacea are prohibited within 30 days of Baseline and throughout the study.
9. Had facial surgery (dermabrasion, laser resurfacing or other facial cosmetic surgeries) within 3 months of Baseline.

10. Initiated or changed hormonal therapy, including oral contraceptives, within 3 months of Baseline. Changes in hormonal therapy were prohibited throughout the study.
11. Had a history of hypersensitivity to dapsone, sulfamethoxazole, trimethoprim, parabens, metronidazole or any component of the study products.
12. Participated in any clinical study involving an investigational product in the 30 days prior to the Baseline visit or throughout the study.
13. Had a history of alcohol and/or drug abuse within 12 months prior to the Baseline visit.
14. Females who were lactating; had a positive pregnancy test at Day 0; or, if sexually active and menstruating, were not practicing an adequate method of birth control. Acceptable methods of birth control included intrauterine device (IUD); oral, dermal ("patch"), implanted or injected contraceptives; tubal ligation or hysterectomy (medical documentation required); and barrier methods with spermicide. A surgically sterile partner was not considered an adequate method of birth control.
15. Had a serious concurrent illness(es) or disease(s) (e.g., hematological, renal, hepatic, respiratory, endocrine, psychiatric) that might have interfered with the study or put the subject at risk, in the opinion of the Investigator.

5.3.4 Withdrawal of Subjects From Treatments or Assessments

Subjects could voluntarily withdraw at any time during the study. Subjects were able to withdraw from study treatment but still continue study follow-up procedures. Also, Investigators could have withdrawn a subject from study treatment because

- a new health condition appeared that required care or medications prohibited by the protocol.
- the subject had unacceptable adverse events.
- the subject had disease progression.
- it was in the subject's best interest according to the Investigator's clinical judgment.

If a subject prematurely withdrew from study treatment, the reason(s) for withdrawal were recorded on the relevant page of the subject's case report form (CRF).

For subjects willing to continue study follow-up procedures, the Investigator reviewed the follow-up procedures with the subject, including the number of visits, the specific procedures to be done, and the total length of the follow-up period. The Investigator also ensured the subject understood that his/her medical records would continue to be available for the follow-up period as described in the approved informed consent form for the entire study period.

If a subject refused to undergo the study follow-up procedures, the reason for refusal was fully documented.

Subjects who withdrew after randomization were not replaced.

5.3.5 Special Restrictions

During the study, subjects were prohibited from taking any of the concomitant medications listed in the exclusion criteria in Section 5.3.3.

Subjects were instructed to maintain their baseline skin care regimen during the study. Subjects were allowed to continue to use moisturizers, sunscreens, and cosmetics that were in use prior to the study, as long as they were applied at least 1 hour after applying the study treatment. Any *new* cosmetics, cleansers, or moisturizers were prohibited throughout the study. In addition, alcoholic toners, astringents, and abrasive cleansers or washes were not allowed to be used on the facial area throughout the study. Sunbathing and tanning bed exposure were prohibited.

Subjects were required to use a standardized facial cleanser throughout the study (Cetaphil®).

In the study consent form, subjects were also advised to avoid anything that triggered rosacea signs and symptoms, such as bright sunlight, spicy foods, alcohol, wind, and hot liquids.

5.4 Study Treatments

5.4.1 Treatments Administered

The study contained 5 treatment groups. Treatment regimens for each group are listed in Table 1.

TABLE 1. Treatment Regimens

Treatment Group	Morning Application (AM)	Evening Application (PM)
1. Vehicle Control (VC)	Aczone vehicle	Aczone vehicle
2. Aczone 2x/day	Aczone Gel, 5%	Aczone Gel, 5%
3. Aczone 1x/day	None	Aczone Gel, 5%
4. MetroGel	None	MetroGel, 1.0%
5. Aczone + MetroGel	Aczone Gel, 5%	MetroGel, 1.0%

Note: Only the evening application was performed on Day 0.

Subjects applied study treatment to their face for up to 12 weeks, according to the regimen specified for their treatment group. The first application of study treatment was the evening of the Day 0 visit, regardless of treatment group, such that there was only 1 application on Day 0, even for twice-daily regimens.

The application procedures for vehicle, Aczone, and MetroGel were the same. Subjects were instructed to apply a thin film of the study treatment onto the entire face and rub gently until it completely disappeared, after first washing the face with a standard cleanser. For twice-daily regimens, applications occurred once in the morning (AM) and once in the evening (PM). For once-daily regimens, applications were to occur in the evening (PM). For

the combination regimen, Aczone was applied in the AM and MetroGel was applied in the PM.

Subjects were instructed to avoid swimming, bathing, and to otherwise keep their skin dry, for 2 hours following application of study treatment. The use of moisturizers, sunscreens, and/or cosmetics was permitted no sooner than 1 hour following study treatment application.

For the Weeks 2, 4, and 12 visits, subjects were instructed to apply the study treatment at least 6 hours prior to the visit (which could have included the evening before the visit). The purpose of this instruction was to provide some consistency between the last application of Aczone and the blood draw to determine plasma levels of dapsone and metabolites.

5.4.2 Rationale for Dose Selection

The strength of Aczone selected for this study (5% dapsone) is the same strength approved for the treatment of acne vulgaris in the US. It was hypothesized that the effects on inflammatory and non-inflammatory lesion counts observed in subjects with acne vulgaris may occur similarly in subjects with papulopustular rosacea. The approved dosage regimen for Aczone for acne vulgaris is twice-daily; this study included a twice-daily and a once-daily regimen in order to select an appropriate dosing regimen for further study in rosacea subjects.

MetroGel was selected to be the active comparator because, like Aczone, it is a topical product and it has been approved for the treatment of papulopustular rosacea. The 1% strength of MetroGel, using the regimen recommended on the product label (once-daily), was chosen over the 0.75% strength (twice-daily) because it is expected to become the standard of care and it provides a once-daily regimen to compare with once-daily Aczone.

In addition to single-agent treatment regimens, a combination regimen with once-daily MetroGel and once-daily Aczone was included in the study to evaluate any potential synergistic effects. Dapsone, the active ingredient in Aczone, and metronidazole, the active ingredient in MetroGel, are both classified as antibacterial agents, with potentially different mechanisms of action in altering the signs and symptoms of rosacea. Given that dapsone also has anti-inflammatory activities, it is possible that the 2 products may demonstrate greater efficacy than either product used alone. With combination treatment, Aczone was administered in the AM and MetroGel was administered in the PM to limit any potential interactions.

5.4.3 Identity of Investigational Products

Study treatments were packaged in kits that contained the study treatment tubes required for a single subject's regimen. Each kit number was the subject randomization number. There were sufficient tubes of study treatment for 12 weeks of application, as required for the regimen matching the randomization number, and tubes were dispensed individually or in batches, at the study coordinator's discretion.

5.4.3.1 Aczone™ (dapsone) Gel, 5%

Aczone was supplied in laminate 30 g tubes. Each tube of study treatment had a two-part label consisting of a part attached to the tube and a tear-off part. Both parts of the label displayed the protocol number, subject number, tube ID number, investigational use statements, and sponsor information. After dispensing, the tear-off portion was attached to the label page of the source document.

Aczone contained the active ingredient dapsone (50 mg per gram). Inactive ingredients include: carbomer 980, diethylene glycol monoethyl ether (DGME), methylparaben, propylparaben, sodium hydroxide, and purified water.

The Aczone supplied in the study came from lot 2170 and had an expiry date of August 2007.

5.4.3.2 Comparative Treatment

5.4.3.2.1 Vehicle Control

The VC was supplied in laminate 30 g tubes. Each tube of study treatment had a two-part label consisting of a part attached to the tube and a tear-off part. Both parts of the label displayed the protocol number, subject number, tube ID number, investigational use statements, and sponsor information. After dispensing, the tear-off portion was attached to the label page of the source document.

The VC contained only the inactive components in the Aczone listed above.

The VC supplied in the study came from lot 2169 and had an expiry date of August 2007.

5.4.3.2.2 MetroGel® (metronidazole), 1.0%

MetroGel was obtained commercially and supplied in aluminum 45 g tubes. Each tube was overlaid with a two-part label consisting of a part attached to the tube and a tear-off part. Both parts of the label displayed the protocol number, subject number, tube ID number, investigational use statements, and sponsor information. After dispensing, the tear-off portion was attached to the label page of the source document.

MetroGel contained the active ingredient metronidazole (10 mg per gram). Inactive ingredients include: betadex, edetate disodium, hydroxyethyl cellulose, methylparaben, niacinamide, phenoxyethanol, propylene glycol, propylparaben, and purified water.

The MetroGel supplied in the study came from lot 041062 and had an expiry date of May 2007.

5.4.4 Assignment to Treatment and Blinding

Randomization lists were generated by Fisher Clinical Services according to a computer-generated randomization scheme. Subject numbers were composed of 6 digits, including a

2-digit center number and 4-digit randomization number (which was the same as the treatment kit number). Randomization was stratified by study center.

On the day of randomization (Day 0), study center personnel accessed a central randomization system to assign a randomization number to each subject. Subjects maintained the same number throughout the study, and randomization numbers were not used more than once. Subjects were dispensed study treatment kits labeled with the subject randomization number assigned by the central randomization system.

Only study personnel who were involved in evaluating safety and efficacy variables were blinded to study treatment assignment; however subjects were not told which treatment they were assigned. The individual(s) who performed the following tasks were not allowed to be involved in evaluating any safety and efficacy variables: dispensing study treatment and application logs, provision of instructions on treatment application, and all aspects of assessing treatment compliance (weighing tubes, reviewing application logs, etc).

The following measures were taken to ensure that efficacy evaluators did not observe the identity of treatment:

- Subjects were instructed not to tell other study personnel anything about their treatment that could identify their treatment assignment (such as description, application time, etc).
- Study treatment was NOT applied at the study center.
- Subjects were instructed to bring all used, partially used, and unused study treatment to each visit, with the cap tightly closed, for study treatment accountability and weight assessments.

Breaking the treatment blind or attempting to determine the treatment allocation was expressly forbidden except in the event of a medical emergency. Such an emergency may have included, but was not limited to, a medical emergency where the health or well being of the subject was of concern.

5.4.5 Prior and Concomitant Treatment

Subjects were prohibited from or had limitations on taking any of the concomitant medications listed in the exclusion criteria for the study (described in Section 5.3.3). These included medications approved for rosacea, topical or systemic antibiotics, topical or systemic anti-inflammatory drugs, or other agents that could have potentially affected the signs and symptoms of rosacea.

5.4.6 Assessment of Treatment Compliance

Compliance with the study treatment regimens was assessed in two ways. First, the amount of study treatment used by each subject was monitored by weighing the tubes of study treatment. Tubes were weighed individually at the time of dispensing and return, and in a consistent and standardized manner (i.e., always with caps on, using calibrated scales, etc).

Second, subjects recorded all of their treatment applications in a diary; missed applications, including the date and number of missed applications, were revealed by this diary.

5.5 Study Procedures

5.5.1 Schedule of Events

Table 2 presents the schedule of events for the study.

TABLE 2. Schedule of Events

Treatment Phase Details	Visit 1 Screening/ Day 0 (baseline)	Visit 2 Week 2 (± 3 Days)	Visit 3 Week 4 (± 3 Days)	Visit 4 Week 8 (± 3 Days)	Visit 5 Week 12/ ET (± 3 Days)	Visit 6 Week 13[a] (± 3 Days)
Informed Consent	X					
Evaluate Inclusion/Exclusion Criteria	X					
Medical History/ Underlying Conditions	X					
Demographics	X					
Review skin care regimen[b]	X	X	X	X	X	
Vital Signs	X	X	X	X	X	
Physical Examination[b]	X				X	
Investigator Global Assessment (IGA)	X	X	X	X	X	
Inflammatory Lesion Count	X	X	X	X	X	
Erythema Assessment	X	X	X	X	X	
Telangiectasia Assessment	X	X	X	X	X	
Local Symptom Assessment	X	X	X	X	X	
Pregnancy Test[b]	X[c]				X[c]	
Randomization	X					
Hematology and Chemistry Blood Draw	X	X	X		X	
Dapsone Plasma Blood Draw	X	X	X		X	
G6PD Analysis Blood Draw	X					
Weigh and Dispense Study Treatment	X	X[c]	X[c]	X[c]		
Provide Instructions on Treatment and Application Logs[b]	X	X	X	X		
Dispense / Collect Application Logs	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X
Record Adverse Events		X	X	X	X	X

a Telephone contact. Had to occur within 3 days of Week 13 of the study AND no less than 5 days after the date of the Week 12/ET study visit (or last treatment application).

b If applicable. Captured in source documents only (except any changes noted during follow-up).

c Tubes were weighed at return only. New tubes were dispensed throughout the study as necessary.

Note: All visit dates were scheduled relative to the date of Day 0, and not the most recent visit.

5.5.2 Screening and Day 0 Procedures (Baseline)

After signing the informed consent form the following study procedures and tests were done to confirm subjects' eligibility and enroll them in the trial:

- All inclusion and exclusion criteria were evaluated for the subject.
- Relevant medical history (all dermatological history and within the last 5 years for other body systems) and underlying conditions were recorded.

- Demographic data including subject's initials, date of birth, race/ethnicity, height, and weight were collected.
- Subjects were interviewed regarding concomitant medication use and skin care regimen.
- A physical exam, including vital signs (temperature, heart rate, respiratory rate, and blood pressure), was performed.
- An IGA of disease severity was performed.
- An inflammatory lesion count was performed.
- Erythema was assessed, according to a standard scale.
- Telangiectasia was assessed, according to a standard scale.
- Local symptoms (dryness, itching, stinging, and burning) were assessed, using a standard scoring system.
- A urine pregnancy test was performed on all females 60 years of age or younger, unless documentation of menopause or surgical sterilization was provided. The type of birth control being used was confirmed.
- Blood samples for hematology, chemistry, G6PD levels, and plasma dapsone and metabolite levels were obtained.
- Subjects were randomized to a study treatment group, using the central randomization system.
- After randomization, the following were performed by an individual not involved in the assessment of efficacy variables:
  - Study treatment that matched the subject randomization number was weighed and dispensed, along with the cleanser and a treatment application log.
  - Instructions on the application of treatment, according to the subject's randomized treatment regimen, and completion of the application log were provided.

Subjects who required a washout before they could meet the eligibility criteria signed a consent form prior to their washout. If they returned to the study center for a Day 0 visit within 30 days, they did not sign another consent form. However, if the subject returned for a Day 0 visit >30 days from the date of signing the ICF, they had to sign a new consent form. For all subjects who returned to the study center after a washout period, all other baseline procedures listed for Day 0 were repeated, regardless of the length of the washout.

5.5.3 Procedures During Treatment (Weeks 2 to 12)

After Day 0, subjects returned for study visits at Weeks 2, 4, 8, and 12 (±3 days relative to Day 0) during the treatment period. The following tests and procedures were performed at these visits:

- Subjects were interviewed regarding concomitant medication use, occurrence of adverse events, and any changes in skin care regimen.

- Vital signs were collected (temperature, heart rate, respiratory rate, and blood pressure).
- Blood samples were collected for plasma dapsone and metabolite concentration and hematology and chemistry analysis (however, this was not scheduled at Week 8).
- The IGA, inflammatory lesion counts, erythema assessment, telangiectasia assessment, and local symptom assessments were performed.
- Subjects were interviewed to assess treatment compliance:
  - Subjects were reminded on the proper application procedures. If tube(s) of study treatment were returned at the visit, they were weighed and new tubes dispensed, as needed.
  - Treatment application logs were reviewed.

At Week 12, which was the last day of treatment, the following additional procedures were done:

- A physical exam was performed.
- A urine pregnancy test was done on all subjects who had one performed at Day 0.

5.5.4 Follow-up Procedures (Week 13)

The Week 13 visits consisted of a telephone follow-up call (at least 5 days relative to Week 12) to interview the subject regarding any concomitant medication use and to obtain information on ongoing or new adverse events. Telephone follow-ups for subjects who completed an ET visit prior to Week 12 were completed 5 days to 1 week after the date of the ET visit.

5.6 Efficacy, Pharmacokinetic, and Safety Variables

5.6.1 Efficacy Variables

The study had the following efficacy variables:

- Percent change and change from baseline in inflammatory lesion counts.
- "Success" rate, defined as the proportion of subjects with a score of 0 (clear) or 1 (almost clear) and at least a 2 point improvement from baseline on the 5-point Investigator's Global Assessment (IGA) scale of disease severity.
- Erythema assessment scores.
- Telangiectasia assessment scores.
- Lesion counts over time.

It was recommended that the same examiner perform the respective efficacy assessments at each visit for a given subject. It was also recommended that the IGA examiner and the inflammatory lesion counter be the same person for a given subject. At a minimum, it was

required that the examiner for each variable be the same for baseline and the Week 12/ET visit. For each of the study efficacy variables, the examiners were blinded (i.e., did not dispense study treatment and did not have access to study files that identified study treatment assignment).

The following sections provide more details on the assessments used to determine the study efficacy variables.

5.6.1.1 Lesion Counts

Inflammatory lesions were counted after the IGA was performed, at Day 0 (baseline) and Weeks 2, 4, 8, and 12. Subjects were not wearing any make-up for this assessment.

Inflammatory lesion counts were performed by an experienced member of the study staff. The Investigator determined which member(s) of the study staff qualified as experienced.

5.6.1.2 Investigator's Global Assessment

The IGA was performed at Day 0 (baseline) and Weeks 2, 4, 8, and 12/ET. The IGA was the first assessment conducted at the study visit and was performed standing at a distance of approximately 3 feet from the subject. Subjects were not wearing any make-up for this assessment. Table 3 presents the IGA scale of disease severity.

TABLE 3. Investigator Global Assessment of Disease Severity

Score	Severity	Description
0	Clear	No signs or symptoms present; at most, mild erythema
1	Almost Clear	Very mild erythema present. Very few small papules/pustules
2	Mild	Mild erythema. Several small papules/pustules
3	Moderate	Moderate erythema. Several small or large papules/pustules, and up to 2 nodules
4	Severe	Severe erythema. Numerous small and/or large papules/pustules, up to several nodules.

The IGA was performed by an experienced member of the study staff who was blinded to treatment. The Investigator determined which member(s) of the study staff qualified as experienced.

5.6.1.3 Erythema Assessment

Erythema was graded according to a standardized scale (Table 4), at Day 0 (baseline) and Weeks 2, 4, 8, and 12.

TABLE 4. Erythema Assessment

Score	Severity	Description
0	Absent	No perceptible erythema.
1	Mild	Slight erythema with either restricted central involvement or generalized whole face.
2	Moderate	Pronounced erythema with either restricted central involvement or generalized whole face.
3	Severe	Severe erythema or red-purple hue with either restricted central involvement or generalized whole face.

The assessment was based on the subject's condition at the time of the evaluation. Subjects were not allowed to wear any make-up at the time of the evaluation.

5.6.1.4 Telangiectasia Assessment

Telangiectasia was graded according to a standardized scale (Table 5) at Day 0 (baseline) and Weeks 2, 4, 8, and 12/ET.

TABLE 5. Telangiectasia Assessment

Score	Severity	Description
0	Absent	No perceptible telangiectasia.
1	Mild	Involvement of the nose.
2	Moderate	Involvement of the nose and infraorbital region.
3	Severe	Involvement of the nose, infraorbital region, and other areas of the face.

The assessment was based on the subject's condition at the time of the evaluation. Subjects were not allowed to wear any make-up at the time of the evaluation.

5.6.2 Safety Variables

The study included the following safety variables:

- Adverse events.
- Concomitant medications.
- Clinical chemistry and hematology values.
- Local symptom scores.
- Vital signs.
- Other: plasma dapsone, N-acetyl dapsone, and dapsone hydroxylamine concentrations.

The following sections provide more details on the assessments used to determine some of these variables.

5.6.2.1 Adverse Events (AEs)

a) Evaluating and Reporting of Adverse Events

Adverse events were collected and followed throughout the study to the final study visit until they resolved or became chronic (as judged by the Investigator).

All adverse events either observed by the Investigator or one of his/her medical collaborators, or reported by the subject spontaneously, or in response to the direct question below, were noted in the adverse events section of the subject's CRF and in the source document. Only treatment-emergent adverse events (those occurring during or after the start of study treatment) were recorded as adverse events. Events with an onset before the initial study treatment were recorded as medical history.

In an attempt to optimize consistency of adverse event reporting across centers, subjects were asked a standard question to elicit any adverse events. At each clinic or telephone contact with the subject, study personnel asked the following question: "Have you had any problems since your last visit or telephone call?"

When an adverse event was reported, the date of onset, intensity, relationship to study medication or treatment, date of resolution (or the fact that it is still continuing or has become chronic), action taken, and whether the adverse event is serious or not was recorded.

For any change in laboratory results or vital signs that arose after treatment, the Investigator was responsible for determining if the value was clinically significant and if it was necessary to repeat the evaluation. If the laboratory result was judged to be clinically significant, it had to be recorded as an adverse event.

At the final study visit, new adverse events, as well as follow-up information for continuing adverse events, were recorded in the CRF and source document. If a serious adverse event was unresolved at the final study visit, it was followed by the Investigator until it resolved or became chronic (as judged by the Investigator). Follow-up data for such serious adverse events was to be recorded in the source document and reported to the Sponsor's safety contacts. Non-serious ongoing adverse events were followed beyond the final study visit at the discretion of the Investigator and recorded in the source documents, but not the CRF.

b) Definition of Adverse Events (AEs)

Adverse Event (AE): any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the administration of a medicinal product, whether or not considered related to the investigational product or device.

Medical conditions or diseases present before a subject starts study treatment are only considered adverse events if they worsen after the subject starts study treatment.

c) Definition of Serious Adverse Drug or Device Events (SAEs)

Serious Adverse Event (SAE): defined as any AE that (at any dose):

- Resulted in death.
- Was life-threatening.
- Required inpatient hospitalization or prolonged existing hospitalization.
- Resulted in persistent or significant disability / incapacity.
- Was a congenital anomaly / birth defect.
- Jeopardized the subject or required an intervention to prevent one of the outcomes listed above.

A subject admitted to a hospital as a result of an AE, even if released on the same day, qualified for inpatient hospitalization. An emergency room visit that resulted in admission to the hospital also qualified for inpatient hospitalization. However, emergency room visits that did not result in admission to the hospital did not qualify for inpatient hospitalization and, instead, were evaluated for one of the other criteria for SAEs (e.g., life-threatening AE or medically significant event), or reported as non-serious.

Hospitalization scheduled before the subject enrolled in the study was not considered the result of a treatment-emergent AE, and therefore events that led to such hospitalization were not considered study AEs or SAEs. During the study, if a subject had elective surgery for a condition present at inclusion into the study, and the condition did not worsen during the study, the reason for elective surgery (and resulting hospitalization, if applicable) was not considered or reported as an SAE. For AEs that resulted in persistent or significant disability/incapacity, disability/incapacity referred to a substantial disruption of a subject's ability to carry out normal life functions.

d) Intensity

The intensity of systemic adverse events was characterized as mild, moderate, or severe, according to the following definitions:

Mild	Usually transient, requiring no special treatment, and did not interfere with the subject's daily activities.
Moderate	Introduced a low level of inconvenience or concern to the subject and may have interfered with daily activities, but was ameliorated by simple therapeutic measures.
Severe	Significantly interfered with a subject's usual daily activities and required systemic drug therapy or other treatment, if available.

For local application-site reaction adverse events, the intensity of events were characterized as mild, moderate, or severe according to the following definitions (which are the same as those used in the local symptom assessment scale, described in Section 5.6.2.3 below):

Mild	Barely perceptible.
Moderate	Definitely present.
Severe	Marked, intense.

e) Relationship to Study Treatment

The causal relationship to study drug or treatment was determined by the Investigator according to best medical judgment, as follows:

Suspected	There was a reasonable possibility that the adverse event was associated with use of the study treatment, such as a temporal relationship of the event to study treatment administration, or when other drugs, therapeutic interventions, or underlying conditions did not provide a sufficient explanation for the observed event. This category encompassed the causality relationships of possibly and probably. Subjects who experienced an adverse event that was suspected to be related to systemic dapsone exposure had a blood draw for plasma dapsone and N-acetyl dapsone concentrations and any other analysis considered important by the Investigator, at the time the adverse event was reported.
Not suspected	A relationship between the adverse event and the study treatment could reasonably be ruled out based on lack of any temporal relationship of the event to study treatment administration, or the subject's underlying condition, medical history, or other therapy provided sufficient explanation for the observed event.

5.6.2.2 Clinical Chemistry and Hematology

Blood samples were collected at Day 0 (baseline) and Weeks 2, 4, and 12 to measure the clinical chemistry and hematology parameters listed in Table 6.

TABLE 6. Clinical Laboratory Tests

Hematology	Serum Chemistry
- Hemoglobin	- Blood urea nitrogen (BUN)
- Hematocrit	- Creatinine
- White blood cell count	- Total protein
- Differential	- Albumin
- Red blood cell count	- Lactate dehydrogenase (LDH)
- Mean corpuscular volume (MCV)	- Glucose
- Mean corpuscular hemoglobin (MCH)	- Alanine aminotransferase (ALT)
- Reticulocyte count	- Aspartate aminotransferase (AST)
	- Alkaline phosphatase
	- Total bilirubin
	- Calcium
	- Phosphorus
	- Electrolytes (NA,K,HCO_3)
	- Haptoglobin

Clinical chemistry and hematology samples were analyzed centrally. The central laboratory provided visit-specific kits containing all of the supplies needed for drawing blood and shipping of samples. The exact time of collection for each blood sample was recorded in the CRF.

Results of clinical hematology and chemistry tests were sent to the Investigator. The laboratory reports identified if a laboratory result was significantly outside the age-adjusted reference range. A copy of all laboratory results with Investigator review and signature was maintained with the subject's source documents and another copy, identifying the clinical significance of out-of-range results, was collected for the CRF.

Clinical chemistry and hematology values were assigned a high or low flag by the laboratory if the value was determined to be out of the normal range. Values were converted from conventional units, which were used for reporting results to study Investigators, into SI units for reporting in the study database. The high or low flags were assigned based on the normal range applied in the conventional units for each parameter.

5.6.2.3 Local Symptoms

The following local symptoms were evaluated at Day 0 (baseline) and Weeks 2, 4, 8, and 12: dryness, itching, stinging, and burning, using the symptom score categories listed in Table 7.

TABLE 7. Local Symptoms Assessment (Dryness, Itching, Stinging, and Burning)

Score	Severity	Description
0	Absent	None
1	Mild	Barely perceptible
2	Moderate	Definitely present
3	Severe	Marked, intense

Subjects were interviewed by a blinded evaluator. The local symptom scores were based on the subject's perception of their symptoms at the time of the assessment. Subjects were not allowed to be wearing any make-up at the time of the evaluation. It was recommended that the local symptom assessment be conducted by the same examiner at each visit. At a minimum, was required that the local symptom examiner be the same for baseline and the Week 12/ET visit.

If the local symptom score for dryness, itching, stinging, and/or burning worsened after baseline (i.e., score at any follow-up visit was greater than the score at Day 0), then this symptom was reported as an adverse event. The adverse event intensity of these symptoms was recorded using the severity definitions listed above in Table 7, rather than those defined in Section 5.6.2.1.

5.6.2.4 Vital Signs

The following vital signs were evaluated at Day 0 (baseline) and Weeks 2, 4, 8, and 12: heart rate, blood pressure, temperature, and respiratory rate. Vital signs were collected before any blood sampling, if applicable, to avoid any effects of the blood draw on vital signs.

5.6.3 Other Variables

Concentrations of plasma dapsone, N-acetyl dapsone, and dapsone hydroxylamine were measured at Day 0 (baseline), and Weeks 2, 4, and 12. In addition, if any adverse event occurred that was suspected to be related to dapsone, Investigators were instructed to take an unscheduled blood sample for measurement of plasma dapsone and N-acetyl dapsone concentrations at the time of the adverse event.

Subjects were instructed to apply study treatment no less than 6 hours prior to the study visits at which plasma dapsone, N-acetyl dapsone, and dapsone hydroxylamine were to be assessed. The time of last application of study treatment and the time of blood collection were recorded in the CRF.

Blood samples were centrifuged by study personnel, who then transferred the plasma to cryovials that were immediately frozen. Vials were shipped to Quintiles, who was responsible for shipping samples subsequently to CANTEST Laboratories for analysis. Plasma dapsone and metabolites were measured using a LC-MS/MS method validated for human plasma (refer to Appendix D.8 for the bioanalytical report).

5.7 Data Quality Assurance

5.7.1 Standardization of Study Procedures

All study centers received center-specific initiation visits prior to starting the study. A training video on the background/etiology of rosacea and instructions on conducting lesion counts and the IGA was presented at each center's initiation visit. A study start-up binder was prepared for all study centers that included the protocol, source documents, case report forms, and regulatory binder documents, serious adverse event forms, central laboratory information and regulatory guidelines. There was no study-wide Investigator meeting.

5.7.2 Study Monitoring

All investigating centers were visited by trained clinical research monitors at intervals of 4 to 6 weeks. Protocol compliance, source data verification, and compliance with Good Clinical Practice guidelines were the focus of these center visits.

5.7.3 Study Database

All data from the case report forms (CRF) were entered into an electronic database (Clintrial™, version 4.4 and verified using interactive double-data entry before the database was closed.

The information contained in the database was validated through computerized logic and consistency checks, as well as by thorough checks for missing or invalid data (refer to Appendix D.7.1 for database conventions). Manual review of data listings was also done to detect protocol deviations and logic/inconsistency issues that could not be checked by computer. After all relevant corrections and clarifications were made in the database, the database was closed on 23 June 2006, and the statistical analyses were initiated. The database was re-opened 3 times. First, it was re-opened on 12 July 2006 to correct missed application data based on the knowledge of randomization assignments (i.e., 1x/day or 2x/day) and to add new laboratory data that was received from the central laboratory. It was re-opened again on 31 August 2006 to correct inconsistencies and add comments to clarify certain data. The third time the database was re-opened was 11 January 2007 in order to replace the plasma dapsone and metabolite concentration data with a new, final data set that had been provided by the contract laboratory. The database was closed and final on 16 January 2007. During the periods of opening the database, only the study data manager had limited access to the database.

5.7.4 Quality Assurance Audits

No study centers were audited for this study.

The study database underwent a clinical quality assurance review following close of the database. The purpose of this was to review the data listings against the CRFs to ensure a consistent, correct, and complete study database. The review included a verification of 100% of data from 10% of the total study subjects.

5.8 Statistical Methods

5.8.1 Sample Size

The planned sample size of 400 subjects (80 per treatment group) was based on clinical considerations and was believed to be sufficient to meet study objectives. No power calculation was performed.

5.8.2 Statistical Analysis

This section describes the statistical methods used to analyze the study variables. When these methods differ from the methods described in the statistical analysis plan (Appendix D.6), the differences are clearly described. The differences between the planned and actual analyses are also listed in Section 5.9.2.

5.8.2.1 Analysis of Baseline and Demographic Variables

Subject disposition including the reasons for early termination and reasons for exclusion from the per protocol (PP) data set were summarized by treatment group using frequencies and percentages according to the study visit and termination CRF pages.

Subject demographics and other baseline characteristics (e.g., age, gender, inflammatory lesions, G6PD values and status) in each treatment group were summarized using descriptive statistics. Mean, standard deviation, minimum, median, and maximum were used for describing the quantitative variables and frequencies and percentages were used to summarize categorical variables. G6PD status was categorized as either G6PD-deficient or not deficient. G6PD-deficient was defined as G6PD level below the lower limit of normal.

Medical history and underlying medical conditions were summarized separately by body system for all subjects and each treatment group using frequencies and percentages. If a subject had more than one condition in a body system, the body system was only counted once.

5.8.2.2 Analysis of Study Treatment Use

The extent of treatment was summarized using the following variables:

- Total amount of study treatment (g) used in the study.
- Amount of study treatment used per day (g/day).
- Number of study treatment applications during the study.
- Amount of study treatment used per application (g/application).

For all variables, the amounts of Aczone and MetroGel were calculated separately in subjects randomized to the combination treatment. These variables were summarized using mean, standard deviation, minimum, median, and maximum.

The total amount of study treatment used in the study for each subject was calculated by subtracting the weight of each tube when returned from the respective weight of each tube when dispensed. The resulting individual drug used per tube for each subject was summed for the total amount of study treatment used. If a tube did not have a return weight, then the total amount of study treatment used was not calculated and was considered missing for that subject. If a tube did not have a dispense weight, it was estimated by using the average dispense weight of all tubes containing the same treatment in the study.

The amount of study drug used per day was calculated by dividing the number of days a subject applied drug into the total amount of drug used by that subject. The number of days a subject applied drug was calculated by subtracting the date of first application from the date of last application and adding one day for the first day. Then the number of days where no drug was applied was subtracted from the result. The number of days where no drug was applied was calculated by adding the number of days where both applications were missed for each subject.

The number of study treatment applications was calculated by subtracting the date of first application from the date of last application, adding 1 to include the first day, multiplying the result by the number of expected daily treatment applications, and subtracting 1 from the result for the groups of subjects applying drug twice daily to account for the fact that only the evening application of study treatment was to be applied on the first day for each subject in those groups. Then the total number of missed applications for each subject was subtracted from this result.

The amount of study drug used per application was calculated by dividing the total amount of study treatment used by the number of study treatment applications.

5.8.2.3 Efficacy Analysis

No statistical tests of any efficacy variables were planned. Only descriptive statistics and 95% confidence intervals were summarized. The analysis was performed on both the ITT and PP data sets. The ITT analysis was considered primary.

The study had the following efficacy variables:

- Change and percent change from baseline in inflammatory lesion counts.
- Lesion counts over time.
- "Success" rate, defined as the proportion of subjects with a score of 0 (clear) or 1 (almost clear) and at least a 2 point improvement from baseline on the 5-point Investigator's Global Assessment (IGA) scale of disease severity.
- Erythema assessment scores.
- Telangiectasia assessment scores.

The change from baseline in inflammatory lesion counts, percent change from baseline in inflammatory lesion counts, and lesion counts over time were summarized by N, mean,

standard deviation, median, minimum, and maximum. Summaries were provided separately for each treatment group and study visit. In addition, 95% confidence intervals were provided for each treatment group and for the difference between VC and each active treatment group.

The change from baseline in inflammatory lesion counts for each study visit was calculated by subtracting the baseline inflammatory lesion count from the post baseline study visit lesion counts for each subject.

The percent change from baseline in inflammatory lesion counts was calculated by dividing the baseline inflammatory lesion count into the change from baseline in inflammatory lesion counts and then multiplying by 100 for each subject at each study visit.

The IGA score, success rate from the IGA, erythema assessment scores, and telangiectasia assessment scores were summarized by frequencies and percents. Summaries were provided separately for each treatment group and study visit. In addition, 95% confidence intervals were calculated for the success rate from the IGA for each treatment group and for the difference between VC and each active treatment group.

5.8.2.4 Safety Analysis

The safety analysis was performed on the safety data set.

5.8.2.4.1 Concomitant Medications.

Concomitant medications were coded using the World Health Organization Drug Dictionary (WHO-DD) and classified using the Anatomical Therapeutic Chemical (ATC) Index. The number and percentage of subjects taking concomitant medications were summarized by each drug class for each treatment group.

5.8.2.4.2 Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and system organ class.

An overall safety summary table listing the number and percentage of subjects who experienced any adverse event (AE), death, a serious adverse event, or who withdrew from treatment was prepared by treatment group.

The number and percentage of subjects with at least one event and the total number of events were tabulated by treatment group. Summary tables were also provided by intensity. Similar tables were generated for associated adverse events, serious adverse events, and serious associated adverse events. Associated adverse events were defined as those that the Investigator considered suspected to be related to treatment.

5.8.2.4.3 Clinical Chemistry and Hematology

Clinical chemistry and hematology values were summarized for each time point using mean, standard deviation, median, minimum, and maximum. The change from baseline was also summarized at each follow-up visit using N, mean, standard deviation, median, minimum, and maximum. Shift tables were constructed for each time point by treatment group as an additional method of indicating changes from baseline, based on normal/abnormal classification defined by the central laboratory. The number and percent of subjects with a laboratory value judged by the Investigator to be clinically significant was also summarized by time point and treatment group.

5.8.2.4.4 Vital Signs

Vital signs (blood pressure, body temperature, heart rate, and respiratory rate) were summarized using mean, standard deviation, median, minimum, and maximum by treatment group at every time point.

5.8.2.4.5 Local Symptom Scores

Local symptom scores for each of dryness, itching, stinging, and burning were summarized using frequencies and percentages by treatment group at each visit.

5.8.2.5 Other Analyses

Plasma dapsone and metabolite concentrations were summarized with N, mean, standard deviation, median, minimum, and maximum at each time point by treatment group.

5.8.2.6 Subgroup Analyses

After the study database was closed, ad hoc exploratory subgroup analyses of the subjects from the ITT data set who had ≥20 lesions at baseline and <20 lesions at baseline were performed. In these analyses, demographic and efficacy variables were summarized in the same manner as for the complete ITT and PP data sets. The cut-off of 20 lesions was approximately the median lesion count for subjects who entered the study with moderate or severe rosacea according to the IGA.

5.9 Study Modifications

5.9.1 Protocol Amendments

There were no amendments to the original protocol (dated 7 October 2005).

5.9.2 Other Changes in the Conduct of the Study or Planned Analyses

There were no changes in the conduct of the study other than those described in the amendments. There were also no changes to the planned analyses described in the statistical analysis plan; however subgroup analyses based on baseline lesion count were added to the study analyses after those that were specified in the statistical analysis plan were completed

and reviewed. Summaries of demographic variables and all efficacy variables were prepared for the subgroups of subjects who entered the study with ≥20 lesions and <20 lesions.

In addition, the per protocol data set was changed to exclude 2 subjects who did not receive the regimen they were randomized to (i.e., 2 subjects were randomized to Aczone + MetroGel but only received Aczone 1x/day). This additional exclusion was added after the database was closed and knowledge of the treatment assignment was revealed.

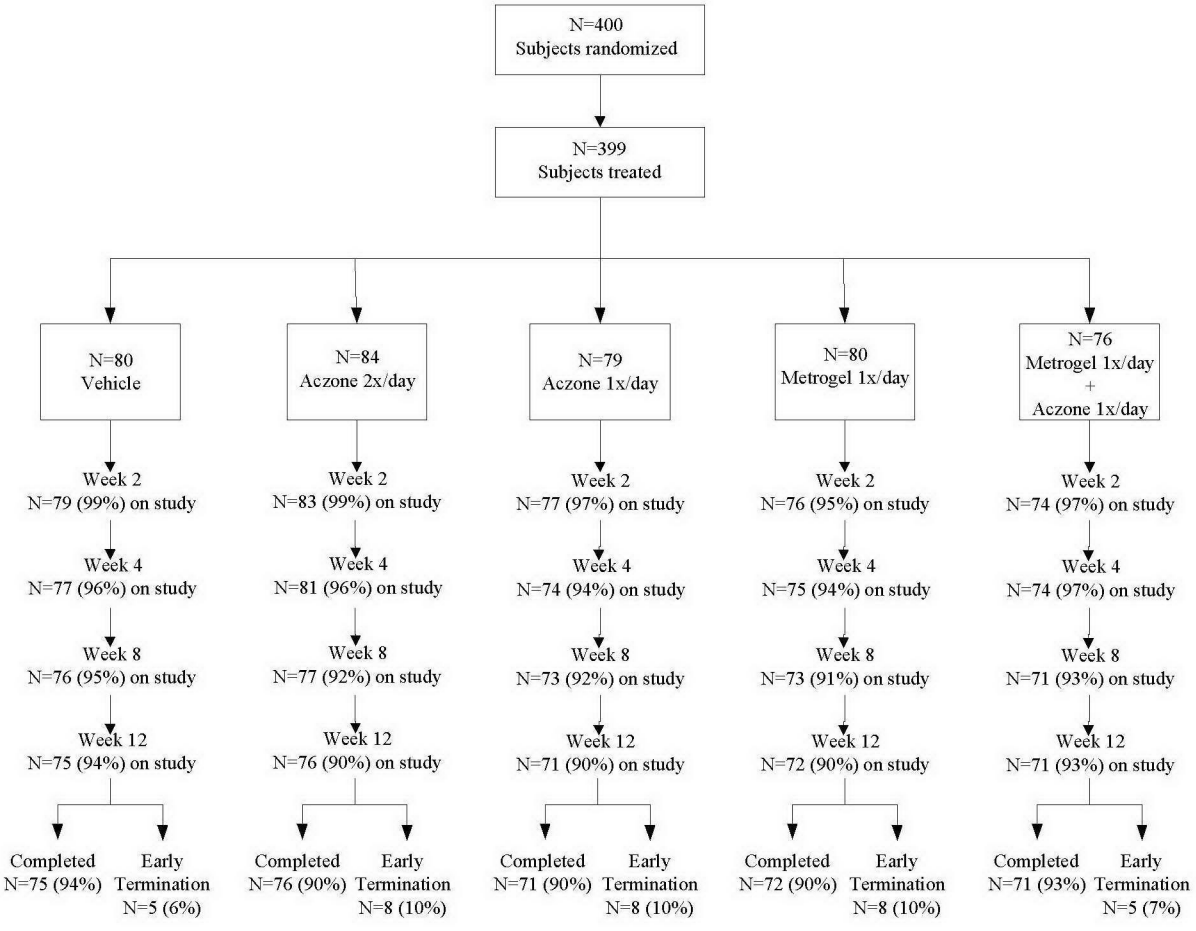
6 STUDY SUBJECTS: DISPOSITION AND DEMOGRAPHY

6.1 Disposition of Subjects

The study enrolled 400 subjects, but 1 subject was randomized in error and was not dispensed any study treatment, therefore data was only collected on 399 subjects.

Subject disposition is summarized in Appendix A.1.1 and cumulatively in Appendix A.1.2. Subject visit dates are listed in Appendix E.1.3. The reasons for study discontinuation are summarized in Appendix A.1.1 and listed by subject in Appendix E.1.4. Figure 1 illustrates subject disposition.

FIGURE 1. Subject Disposition



Within each study treatment group, 90%-94% of subjects completed the study. In total, 34 subjects (9%) did not complete the study, who were approximately equally distributed among the study treatment groups.

Table 8 presents the reasons for withdrawal from the study.

TABLE 8. Reasons For Withdrawal

Disposition	Vehicle Control (N=80)	Aczone 2x/day (N=84)	Aczone 1x/day (N=79)	MetroGel 1x/day (N=80)	Aczone + MetroGel 1x/day (N=76)	Total (N=399)
Completed study	75 (94%)	76 (90%)	71 (90%)	72 (90%)	71 (93%)	365 (91%)
Terminated study early	5 (6%)	8 (10%)	8 (10%)	8 (10%)	5 (7%)	34 (9%)
Adverse event	1 (1%)	5 (6%)	1 (1%)	0	3 (4%)	10 (3%)
Lost to follow-up	2 (3%)	1 (1%)	3 (4%)	6 (8%)	0	12 (3%)
Request to withdrawal	1 (1%)	1 (1%)	2 (3%)	0	2 (3%)	6 (2%)
Gross protocol violation	1 (1%)	1 (1%)	1 (1%)	1 (1%)	0	4 (1%)
Death	0	0	0	0	0	0
Other	0	0	1 (1%)	1 (1%)	0	2 (<1%)

Source: Appendix A.1.1.

The most common reasons for withdrawal from the study were lost to follow-up (12 subjects, 3%) and development of an adverse event (10 subjects, 3%). Subjects who discontinued the study due to an adverse event are described further in Section 9.3.2. Other reasons for withdrawal included request to withdraw (6 subjects, 2%), gross protocol violation (4 subjects, 1%), or other (2 subjects, <1%). Subjects who withdrew due to a protocol violation include 3 subjects who required a medical therapy prohibited by the protocol (for non-rosacea related conditions: Subjects 105308, 103133, 060273) and 1 subject with a sulfa allergy (Subject 177449). Other reasons for discontinuation include Sponsor request due to elevated liver enzymes at baseline (Subject 160993, Aczone 2x/day group) and lack of efficacy (Subject 146829, randomized to the MetroGel group).

6.2 Extent of Treatment

Study treatment usage for the safety population is summarized in Appendix A.4.1 and listed by subject in Appendix E.4.1. Table 9 presents study treatment usage.

TABLE 9. Study Treatment Usage (Safety Data Set)

	Vehicle Control (N=79)	Aczone 2x/day (N=83)	Aczone 1x/day (N=81)	MetroGel 1x/day (N=77)	Aczone + MetroGel 1x/day (N=73)	
					Aczone	MetroGel
Study treatment per Day (g)	71	77	72	68	68	72
Mean	0.725	0.837	1.124	0.564	0.498	0.538
SD	0.364	0.455	4.382	0.359	0.238	0.318
Median	0.700	0.797	0.586	0.510	0.445	0.477
Min.	0.13	0.11	0.09	0.08	0.08	0.08
Max.	1.70	2.10	37.70	1.54	1.29	1.63
Number of Applications	79	83	81	77	72	72
Mean	158.0	154.2	77.1	78.8	78.9	79.5
SD	26.9	34.5	19.4	16.3	13.4	13.5
Median	165.0	166.0	84.0	83.0	82.0	83.0
Min.	27	13	1	1	13	14
Max.	187	185	91	91	87	89
Study Treatment per Application (g)	71	77	72	68	68	72
Mean	0.372	0.430	1.124	0.564	0.505	0.538
SD	0.184	0.234	4.382	0.359	0.241	0.318
Median	0.363	0.404	0.586	0.510	0.450	0.477
Min.	0.06	0.05	0.09	0.08	0.08	0.08
Max.	0.86	1.06	37.70	1.54	1.31	1.63

Source: Appendix A.4.1.

The mean number of study treatment applications in each treatment group was close to that prescribed by the protocol (169 applications for twice-daily regimens and 85 for once-daily regimens over 84 days), indicating a high degree of compliance with the study treatment regimens. Mean daily use and use per application for Aczone was higher in the Aczone 1x/day group than the Aczone 2x/day group; however this is highly skewed due to the calculated use for Subject 205436 in the Aczone 1x/day group (only 1 day of application could be confirmed, but based on tube weights, 37.7 g of treatment had been used). In the combination Aczone + MetroGel group, mean usage of Aczone was similar to MetroGel.

Two subjects did not apply the study treatment regimen they were randomized to. Subjects 222803 and 228126 were both randomized to the Aczone + MetroGel group; however, they were only dispensed Aczone study treatment and instructed to apply it once daily.

6.3 Data Sets Analyzed

6.3.1 Efficacy: Intent to Treat

The intent-to-treat (ITT) data set included 399 subjects who were randomized and dispensed study treatment. Missing data was imputed using a last observation carried forward (LOCF) method.

6.3.2 Efficacy: Per Protocol

The PP data set included 347 subjects. Subjects were included in the PP data set if they completed the Week 12 efficacy evaluations without the following noteworthy study protocol violations:

- Baseline IGA score <2.
- Baseline inflammatory lesion count <8.
- Prohibited concomitant medications (pending review).
- Unblinding of any examiners of efficacy variables (e.g. IGA and lesion counts).
- Age <18.
- An adverse event such as severe sunburn, which made counting lesions difficult (pending review).
- Changes in cleansers, cosmetics, and medicated makeup (pending review).
- Week 12 visit outside +/- 7 days.
- Received an incorrect treatment regimen for their randomization assignment.

6.3.3 Safety

The safety data set included data from 393 subjects, which includes all subjects who applied study treatment or reported at least one AE. No data were excluded because of protocol violations. For the safety analysis, subjects were grouped according to the study treatment regimen that they actually applied. As such, there were 2 subjects randomized to the combination Aczone + MetroGel treatment group who were analyzed for safety in the Aczone 1x/day group because they were only dispensed the Aczone study treatment at the study center and did not receive any MetroGel in error (Subjects 222803 and 228126).

6.4 Demographics and Baseline Characteristics

6.4.1 Subject Demographic and Baseline Disease Characteristics

6.4.1.1 Intent-to-Treat Data Set

Demographics and baseline characteristics of the intent-to treat (ITT) study group are summarized in Appendix A.2.1.1 and listed by subject in Appendix E.2.1. Table 10 presents the main demographic characteristics of the ITT data set.

TABLE 10. Subject Demographic Characteristics (ITT Data Set)

Characteristics	Vehicle Control (N=80)		Aczone 2x/day (N=84)		Aczone 1x/day (N=79)		MetroGel 1x/day (N=80)		Aczone + MetroGel 1x/day (N=76)		Total (N=399)	
Age (y)												
n	80		84		79		80		76		399	
Mean	51.68		52.88		51.59		50.71		51.72		51.73	
SD	13.45		11.37		13.67		12.81		13.66		12.95	
Median	49.36		51.27		51.31		49.99		50.93		50.61	
Min.	23.9		33.1		22.4		23.1		23.6		22.4	
Max.	81.8		80.7		81.7		87.7		83.3		87.7	
Gender												
Male	27	(34%)	30	(36%)	30	(38%)	29	(36%)	26	(34%)	142	(36%)
Female	53	(66%)	54	(64%)	49	(62%)	51	(64%)	50	(66%)	257	(64%)
Race												
White	69	(86%)	75	(89%)	74	(94%)	66	(83%)	59	(78%)	343	(86%)
Black	0		0		0		1	(1%)	0		1	(<1%)
Asian	0		1	(1%)	0		1	(1%)	0		2	(<1%)
Hispanic	11	(14%)	8	(10%)	5	(6%)	10	(13%)	16	(21%)	50	(13%)
Other	0		0		0		2	(3%)	1	(1%)	3	(<1%)
G6PD status												
Not Deficient	78	(98%)	84	(100%)	78	(99%)	80	(100%)	76	(100%)	396	(>99%)
Deficient	2	(3%)	0		1	(1%)	0		0		3	(<1%)

Source: Appendix A.2.1.1.

Demographic and baseline characteristics were balanced across study treatment groups. The age of subjects ranged from 22 to 87 years, with a mean of 51 years. The majority of subjects were Caucasian (86%) and female (64%). There were 3 subjects with glucose-6-phosphate dehydrogenase (G6PD) deficiency enrolled in the study; however only 1 received any active treatment (Aczone 1x/day).

Baseline disease characteristics of the ITT study group are presented in Table 11.

TABLE 11. Baseline Disease Characteristics (ITT Data Set)

Characteristics	Vehicle Control (N=80)		Aczone 2x/day (N=84)		Aczone 1x/day (N=79)		MetroGel 1x/day (N=80)		Aczone + MetroGel 1x/day (N=76)		Total (N=399)	
Inflammatory Lesion Count												
n	80		84		79		80		76		399	
Mean	21.1		19.3		21.5		22.7		23.6		21.6	
SD	14.9		9.5		13.8		15.1		15.5		13.9	
Median	17.0		17.0		17.0		18.0		19.5		17.0	
Min.	10		10		10		10		10		10	
Max.	105		64		82		107		115		115	
Investigator's Global Assessment												
Clear	0		0		0		0		0		0	
Almost clear	0		0		0		0		0		0	
Mild	24	(30%)	27	(32%)	24	(30%)	21	(26%)	20	(26%)	116	(29%)
Moderate	49	(61%)	50	(60%)	50	(63%)	51	(64%)	48	(63%)	248	(62%)
Severe	7	(9%)	7	(8%)	5	(6%)	8	(10%)	8	(11%)	35	(9%)
Erythema												
Absent	0		0		0		0		0		0	
Mild	19	(24%)	15	(18%)	13	(16%)	17	(21%)	14	(18%)	78	(20%)
Moderate	48	(60%)	55	(65%)	56	(71%)	53	(66%)	48	(63%)	260	(65%)
Severe	13	(16%)	14	(17%)	10	(13%)	10	(13%)	14	(18%)	61	(15%)
Telangiectasia												
Absent	8	(10%)	3	(4%)	7	(9%)	9	(11%)	5	(7%)	32	(8%)
Mild	21	(26%)	29	(35%)	24	(30%)	23	(29%)	19	(25%)	116	(29%)
Moderate	46	(58%)	35	(42%)	36	(46%)	43	(54%)	39	(51%)	199	(50%)
Severe	5	(6%)	17	(20%)	12	(15%)	5	(6%)	13	(17%)	52	(13%)

Source: Appendix A.2.1.1.

At baseline, the mean inflammatory lesion count was 21.6 and most subjects had a score of moderate on the IGA (62%). Erythema and telangiectasia were typically moderate (65% and 50% of subjects, respectively). Baseline characteristics were generally similar across study treatment groups, except the percentage of patients who had severe telangiectasia at baseline was more variable (6% in the Vehicle and MetroGel groups, 20% and 15% in the Aczone 2x/day and 1x/day respectively, and 17% in the Aczone + MetroGel group).

6.4.1.2 Per Protocol Data Set

Demographics and baseline characteristics of the PP study group are summarized in Appendix A.2.1.2. The demographics and baseline characteristics of the PP study population, which included 347 subjects (87%), were similar to those of the ITT population.

6.4.1.3 Subjects With ≥20 Lesions at Baseline

Appendices A.2.1.3 and A.2.1.4 summarize the demographic and baseline characteristics of subjects who had ≥20 lesions and subjects who had <20 lesions at baseline, respectively.

There were 168 subjects who entered the study with ≥20 lesions, equivalent to 42% of the total number of subjects in the study. Table 12 presents the demographic characteristics of the subjects who had ≥20 lesions.

TABLE 12. Demographic Characteristics of Subjects With ≥20 Lesions At Baseline

Characteristics	Vehicle Control (N=33)		Aczone 2x/day (N=31)		Aczone 1x/day (N=29)		MetroGel 1x/day (N=37)		Aczone + MetroGel 1x/day (N=38)		Total (N=168)	
Age (y)												
n	33		31		29		37		38		168	
Mean	50.13		50.44		54.03		48.09		52.41		50.93	
SD	13.09		11.43		12.74		13.33		15.35		13.35	
Median	49.33		49.77		51.39		45.56		51.26		49.59	
Min.	26.9		33.1		26.2		26.5		23.6		23.6	
Max.	79.2		77.9		81.7		87.7		83.3		87.7	
Gender												
Male	11	(33%)	9	(29%)	12	(41%)	13	(35%)	17	(45%)	62	(37%)
Female	22	(67%)	22	(71%)	17	(59%)	24	(65%)	21	(55%)	106	(63%)
Race												
White	27	(82%)	27	(87%)	26	(90%)	27	(73%)	29	(76%)	136	(81%)
Black	0		0		0		0		0		0	
Asian	0		0		0		1	(3%)	0		1	(<1%)
Hispanic	6	(18%)	4	(13%)	3	(10%)	7	(19%)	8	(21%)	28	(17%)
Other	0		0		0		2	(5%)	1	(3%)	3	(2%)
G6PD status												
Not Deficient	32	(97%)	31	(100%)	29	(100%)	37	(100%)	38	(100%)	167	(>99%)
Deficient	1	(3%)	0		0		0		0		1	(<1%)

Source: Appendix A.2.1.3.

Demographic characteristics were similar across study treatments for the subgroup of subjects with ≥20 lesions at baseline. The age of subjects ranged from 23 to 87 years, with a mean of 50 years. The majority of subjects were Caucasian (81%) and female (63%). Of the 3 subjects with glucose-6-phosphate dehydrogenase (G6PD) deficiency that were enrolled in the study, one belonged to the subgroup of subjects with ≥20 lesions, but the subject did not receive any active Aczone treatment.

Baseline disease characteristics of subjects with ≥20 lesions at baseline are presented in Table 13.

TABLE 13. Baseline Disease Characteristics of Subjects With ≥20 Lesions at Baseline

Characteristics	Vehicle Control (N=33)		Aczone 2x/day (N=31)		Aczone 1x/day (N=29)		MetroGel 1x/day (N=37)		Aczone + MetroGel 1x/day (N=38)		Total (N=168)	
Inflammatory Lesion Count												
n	33		31		29		37		38		168	
Mean	31.7		28.4		33.8		33.0		33.0		32.1	
SD	18.4		10.2		16.3		16.9		17.2		16.1	
Median	25.0		24.0		29.0		26.0		27.5		26.0	
Min.	20		20		20		20		20		20	
Max.	105		64		82		107		115		115	
Investigator's Global Assessment												
Clear	0		0		0		0		0		0	
Almost clear	0		0		0		0		0		0	
Mild	6	(18%)	5	(16%)	2	(7%)	6	(16%)	2	(5%)	21	(13%)
Moderate	22	(67%)	21	(68%)	23	(79%)	23	(62%)	29	(76%)	118	(70%)
Severe	5	(15%)	5	(16%)	4	(14%)	8	(22%)	7	(18%)	29	(17%)
Erythema												
Absent	0		0		0		0		0		0	
Mild	6	(18%)	4	(13%)	0		4	(11%)	4	(11%)	18	(11%)
Moderate	20	(61%)	18	(58%)	24	(83%)	25	(68%)	26	(68%)	113	(67%)
Severe	7	(21%)	9	(29%)	5	(17%)	8	(22%)	8	(21%)	37	(22%)
Telangiectasia												
Absent	3	(9%)	1	(3%)	3	(10%)	6	(16%)	3	(8%)	16	(10%)
Mild	7	(21%)	16	(52%)	8	(28%)	9	(24%)	7	(18%)	47	(28%)
Moderate	21	(64%)	8	(26%)	14	(48%)	19	(51%)	20	(53%)	82	(49%)
Severe	2	(6%)	6	(19%)	4	(14%)	3	(8%)	8	(21%)	23	(14%)

Source: Appendix A.2.1.3.

For the subgroup of subjects with ≥20 lesions at baseline, the mean inflammatory lesion count ranged from 28.4 lesions to 33.8 lesions across groups, with an overall mean of 32.1 lesions. Most subjects had a moderate score on the IGA (70%). Erythema and telangiectasia were predominantly moderate; however in the Aczone 2x/day group the telangiectasia scores were distributed largely in the mild category compared with other groups.

6.4.2 Subject Medical History and Underlying Conditions

Subject medical history and underlying conditions are summarized in Appendix A.2.2 and listed by subject in Appendix E.2.2. In general, the types of conditions and incidence observed are not unusual given the demographic characteristics of the study population.

7 PROTOCOL DEVIATIONS

7.1 Protocol Deviations That Led to Exclusion From the Analysis

The number of subjects excluded from the PP analysis are summarized by reason in Appendix A.1.3 and Table 14. Individual subjects who were excluded and the reason for exclusion are listed in Appendix E.1.2.

TABLE 14. Reasons for Exclusion (Inevaluable Subjects)

Reason[a]	Vehicle Control (N=80)	Aczone 2x/day (N=84)	Aczone 1x/day (N=79)	MetroGel 1x/day (N=80)	Aczone + MetroGel 1x/day (N=76)	Total (N=399)
Excluded for any reason	11 (14%)	10 (12%)	12 (15%)	10 (13%)	9 (12%)	52 (13%)
Terminated early from study	5 (6%)	8 (10%)	8 (10%)	8 (10%)	5 (7%)	34 (9%)
Prohibited concomitant medication	1 (1%)	0	3 (4%)	2 (3%)	1 (1%)	7 (2%)
Week 12 visit out of window	3 (4%)	1 (1%)	1 (1%)	0	1 (1%)	6 (2%)
Adverse event	2 (3%)	0	0	0	0	2 (<1%)
Treatment regimen error	0	0	0	0	2 (3%)	2 (<1%)
No Week 12 efficacy evaluations	0	1 (1%)	0	0	0	1 (<1%)

[a] Subjects may have more than one reason for being excluded and counted multiple times.
Source: Appendix A.1.3.

There were 52 subjects excluded from the PP data set. The majority of subjects were excluded because of deviations related to the Week 12 visit; they either did not have a Week 12 visit (terminated early: 34 subjects, 9%), had a Week 12 visit that was more than 7 days before/after the expected date (6 subjects, 2%), or did not have efficacy evaluations performed at the Week 12 visit (1 subject, <1%). Other reasons for exclusion were use of prohibited medications or changes to medications (as described in the exclusion criteria: 7 subjects, 2%), and an adverse event that interfered with lesion counts at Week 12 (sunburn: 2 subjects, <1%). Two subjects (<1%) were excluded because they did not receive the treatment regimen they were randomized to.

7.2 Other Protocol Deviations

Table 15 summarizes other types of deviations that occurred in the study, but were not cause for exclusion from any analyses.

TABLE 15. Deviations That Did Not Lead to Exclusion

Deviation[a]	Vehicle Control (N=80)		Aczone 2x/day (N=84)		Aczone 1x/day (N=79)		MetroGel 1x/day (N=80)		Aczone + MetroGel 1x/day (N=76)		Total (N=399)	
BASELINE DEVIATIONS												
Allergic to sulfa drugs	2	(3%)	3	(4%)	6	(8%)	2	(3%)	1	(1%)	14	(4%)
Baseline prohibited medication	0		1	(1%)	0		1	(1%)	0		2	(<1%)
G6PD test missed	0		2	(2%)	0		0		0		2	(<1%)
POSTRANDOMIZATION DEVIATIONS												
Missed >1 application	48	(60%)	40	(48%)	15	(19%)	17	(21%)	39	(51%)	159	(40%)
Tubes not returned	9	(11%)	6	(7%)	9	(11%)	11	(14%)	5	(7%)	40	(10%)
BL & Wk12 efficacy evaluator different	1	(1%)	0		0		2	(3%)	2	(3%)	5	(1%)
PK blood draw <6 hr	10	(13%)	25	(30%)	2	(3%)	0		19	(25%)	56	(14%)
Any visit out of window	23	(29%)	18	(21%)	21	(27%)	18	(23%)	20	(26%)	100	(25%)
Missed visit	2	(3%)	2	(2%)	2	(3%)	1	(1%)	0		7	(2%)

[a] Not mutually exclusive, as subjects may have more than one deviation.
Source: Appendix E.1.1, E.1.3, E.1.8, E.2.2, E.4.1, E.4.2, E.5.9.

Baseline deviations were infrequent and include enrollment of subjects who were allergic to sulfa drugs (14 subjects, 4%), enrollment of subjects who were taking a prohibited medication at baseline (2 subjects, <1%), and missing G6PD test (2 subjects, <1%). None of these baseline deviations are believed to impact the collection and interpretation of data for this study.

The most frequent post-randomization deviation was missing more than 1 application of study treatment. This occurred in 40% of subjects overall, but was as high as 60% in the VC group and as low as 19% in the Aczone 1x/day group. Missing more than 1 application was less common in the once-daily treatment groups (Aczone 1x/day and MetroGel). There were 39 subjects (10%) who did not return their tubes of study treatment, either due to loss, forgetfulness, or lost-to-follow-up. Without the tubes, it was not possible to calculate the amounts of study treatment used for these subjects.

Protocol deviations related to the collection of data include using a different efficacy evaluator for the baseline and Week 12 visit (5 subjects, 1%), and the timing of a PK blood draw <6 hours from the most recent application of study treatment (56 subjects, 14%). Because these were infrequent, they are not considered to have an impact on the overall interpretation of the study data.

Protocol deviations related to the visits include any visit out of window (100 subjects, 25%) and missing a visit (7 subjects, 2%). As listed in the deviations that led to exclusion from the analysis, although many subjects missed one or more visits, very few of the visits that were out of window were at Week 12 (Section 7.1, 6 subjects, 2%).

8 EFFICACY RESULTS AND DISCUSSION

8.1 Efficacy Results

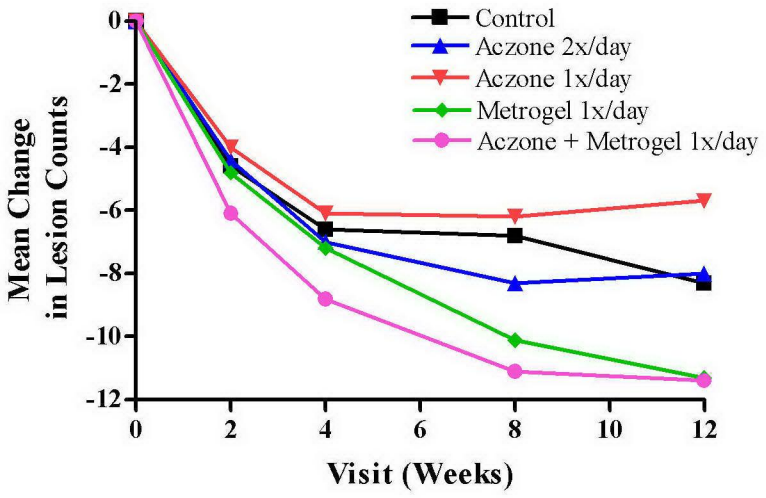
Efficacy analyses were performed on the ITT and PP data sets. The ITT analysis was considered primary.

8.1.1 Intent-to-Treat Analysis

8.1.1.1 Inflammatory Lesion Counts

Inflammatory lesion counts over time, changes from baseline, and percent changes from baseline for the ITT data set are summarized in Appendix A.3.2. Inflammatory lesion counts are listed by subject in Appendix E.3.2. Figure 2 presents the mean change from baseline in inflammatory lesion counts.

FIGURE 2. Mean Change From Baseline in Inflammatory Lesion Counts (ITT)



Source: Appendix A.3.2.

All study treatment groups experienced a mean decrease from baseline in lesion counts. At Week 12, subjects treated with MetroGel alone or Aczone + MetroGel experienced the largest mean decreases from baseline (–11.3 and –11.4 lesions, respectively) while subjects in the Aczone 1x/day group experienced the least mean decrease from baseline (–5.7 lesions from baseline). The mean change from baseline in the Aczone 2x/day group (–8.0 lesions) was higher than the Aczone 1x/day group, but similar to the VC group (–8.3 lesions).

8.1.1.2 Investigator Global Assessment

The IGA scores and success rates from the IGA for the ITT data set are summarized in Appendix A.3.1 and listed by subject in Appendix E.3.1. Table 16 presents the IGA scores at baseline and Week 12.

TABLE 16. Summary of Investigator's Global Assessment Scores (ITT)

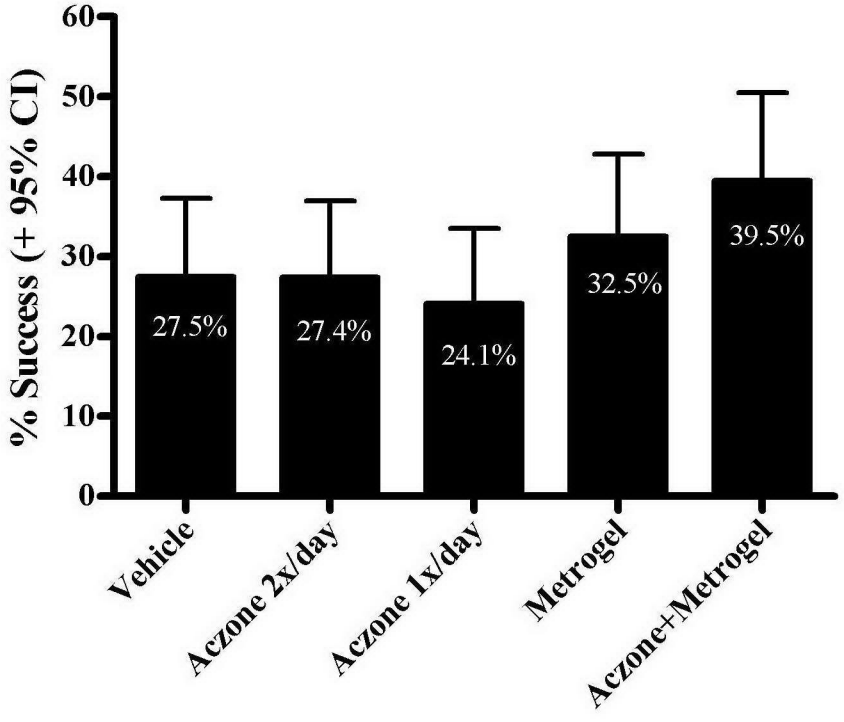
	Vehicle Control (N=80)		Aczone 2x/day (N=84)		Aczone 1x/day (N=79)		MetroGel 1x/day (N=80)		Aczone + MetroGel 1x/day (N=76)	
Baseline										
Clear	0		0		0		0		0	
Almost clear	0		0		0		0		0	
Mild	24	(30.0%)	27	(32.1%)	24	(30.4%)	21	(26.3%)	20	(26.3%)
Moderate	49	(61.3%)	50	(59.5%)	50	(63.3%)	51	(63.8%)	48	(63.2%)
Severe	7	(8.8%)	7	(8.3%)	5	(6.3%)	8	(10.0%)	8	(10.5%)
Week 12										
Clear	15	(18.8%)	7	(8.3%)	4	(5.1%)	9	(11.3%)	15	(19.7%)
Almost clear	20	(25.0%)	25	(29.8%)	26	(32.9%)	27	(33.8%)	25	(32.9%)
Mild	20	(25.0%)	26	(31.0%)	19	(24.1%)	25	(31.3%)	9	(11.8%)
Moderate	20	(25.0%)	22	(26.2%)	23	(29.1%)	13	(16.3%)	21	(27.6%)
Severe	5	(6.3%)	4	(4.8%)	7	(8.9%)	6	(7.5%)	6	(7.9%)

Source: Appendix A.3.1.

According to the inclusion criteria for the study, subjects had to have an IGA score of at least mild to enter the study. At baseline, most subjects had an IGA score of moderate (62% for all subjects combined; refer to Section 6.4.1.1). The distribution of IGA scores shifted towards improvement as early as Week 2 for all study treatments, where the percentages of subjects with scores of moderate or severe decreased and percentages of subjects with scores of mild or almost clear increased. At Week 12, approximately one third to one half of the subjects enrolled in each group had an IGA score of clear (5.1% to 19.7%) or almost clear (25.0% to 33.8%).

The IGA scores were used to determine treatment success, defined as an improvement in the IGA to a score of clear or almost clear with at least 2 points of improvement. Figure 3 depicts the success rates for each treatment group.

FIGURE 3. Summary of IGA Success Rate at Week 12 (ITT)



Source: Appendix A.3.1.

The success rate was highest in the Aczone + MetroGel group (39.5%) and lowest in the Aczone 1x/day group (24.1%). The success rate in the Aczone 2x/day group was higher than the Aczone 1x/day group but the rate was very similar to VC (27.4% and 27.5%, respectively). The combination treatment group experienced higher success than either the MetroGel alone (32.5%) or the Aczone 1x/day (24.1%).

8.1.1.3 Erythema Assessment

Erythema assessment scores for the ITT data set are summarized in Appendix A.3.3 and listed by subject in Appendix E.3.3.

TABLE 17. Summary of Erythema Assessment

Visit		Vehicle Control (N=80)		Aczone 2x/day (N=84)		Aczone 1x/day (N=79)		MetroGel 1x/day (N=80)		Aczone + MetroGel 1x/day (N=76)	
Baseline	Absent	0		0		0		0		0	
	Mild	19	(23.8%)	15	(17.9%)	13	(16.5%)	17	(21.3%)	14	(18.4%)
	Moderate	48	(60.0%)	55	(65.5%)	56	(70.9%)	53	(66.3%)	48	(63.2%)
	Severe	13	(16.3%)	14	(16.7%)	10	(12.7%)	10	(12.5%)	14	(18.4%)
Week 12	Absent	6	(7.5%)	4	(4.8%)	4	(5.1%)	7	(8.8%)	7	(9.2%)
	Mild	41	(51.3%)	36	(42.9%)	36	(45.6%)	44	(55.0%)	35	(46.1%)
	Moderate	25	(31.3%)	40	(47.6%)	27	(34.2%)	23	(28.8%)	30	(39.5%)
	Severe	8	(10.0%)	4	(4.8%)	12	(15.2%)	6	(7.5%)	4	(5.3%)

Source: Appendix A.3.3.

At baseline, all subjects had at least mild erythema present (16.5% to 23.8%) with the majority displaying moderate erythema (60.0% to 70.9%). In general, erythema scores improved throughout the study, with 4.8% to 9.2% of subjects exhibiting no erythema at Week 12. There were no consistent differences in the distribution of erythema scores across study treatment groups.

8.1.1.4 Telangiectasia Assessment

Telangiectasia assessment scores for the ITT data set are summarized in Appendix A.3.3 and listed by subject in Appendix E.3.3.

TABLE 18. Summary of Telangiectasia Assessment

Visit		Vehicle Control (N=80)		Aczone 2x/day (N=84)		Aczone 1x/day (N=79)		MetroGel 1x/day (N=80)		Aczone + MetroGel 1x/day (N=76)	
Baseline											
	Absent	8	(10.0%)	3	(3.6%)	7	(8.9%)	9	(11.3%)	5	(6.6%)
	Mild	21	(26.3%)	29	(34.5%)	24	(30.4%)	23	(28.8%)	19	(25.0%)
	Moderate	46	(57.5%)	35	(41.7%)	36	(45.6%)	43	(53.8%)	39	(51.3%)
	Severe	5	(6.3%)	17	(20.2%)	12	(15.2%)	5	(6.3%)	13	(17.1%)
Week 12											
	Absent	12	(15.0%)	11	(13.1%)	13	(16.5%)	15	(18.8%)	15	(19.7%)
	Mild	35	(43.8%)	33	(39.3%)	27	(34.2%)	31	(38.8%)	27	(35.5%)
	Moderate	28	(35.0%)	33	(39.3%)	31	(39.2%)	27	(33.8%)	27	(35.5%)
	Severe	5	(6.3%)	7	(8.3%)	8	(10.1%)	7	(8.8%)	7	(9.2%)

Source: Appendix A.3.3.

At baseline, telangiectasia was predominantly moderate (41.7% to 57.5% of subjects). Throughout the study, there was a small shift towards improvement of telangiectasia, demonstrated by an increase in the percentages of subjects with absent or mild telangiectasia and decreases in the percentages of subjects with moderate or severe telangiectasia. At Week 12, approximately half of the subjects in each group had either absent (13.1% to 19.7%) or

mild telangiectasia (34.2% to 43.8%). There were no consistent differences in the distribution of telangiectasia scores across study treatment groups.

8.1.2 Per Protocol Analysis

Inflammatory lesion counts, changes from baseline, and percent changes from baseline for the PP data set are summarized in Appendix A.3.2. The IGA scores and success rates from the IGA for the PP data set are summarized in Appendix A.3.1. Erythema and Telangiectasia assessment scores for the PP data set are summarized in Appendix A.3.3.

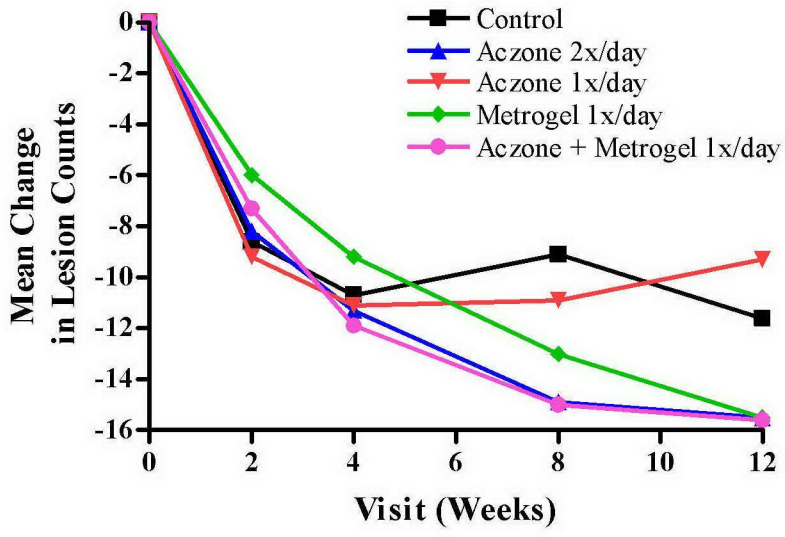
In summary, the efficacy results for the PP data set were similar to the results observed with the ITT data set, described in Sections 8.1.1 above.

8.1.3 Subgroup Analysis: Subjects With ≥20 Lesions

8.1.3.1 Inflammatory Lesion Counts

Inflammatory lesion counts, changes from baseline, and percentage changes from baseline for the subgroups of subjects with ≥20 lesions and subjects with <20 lesions are summarized in Appendix A.3.8 and A.3.11, respectively. Figure 4 depicts the mean change from baseline in lesion counts for the subgroup of subjects with ≥20 lesions at baseline.

FIGURE 4. Inflammatory Lesion Counts for Subjects With ≥20 Lesions



Source: Appendix A.3.8.

Subjects with ≥20 lesions in all treatment groups experienced a mean decrease from baseline in inflammatory lesion count that was higher than the overall mean decrease for the ITT population. In this subgroup, the Aczone 2x/day, MetroGel, and Aczone + MetroGel groups experienced the highest mean decreases by Week 12 (–15.5, –15.5, and –15.6 lesions

respectively). The Aczone 1x/day and VC groups, respectively, experienced mean decreases of –9.3 and –11.6 lesions. Comparing the Aczone 2x/day and Vehicle Control groups, there was a 3.9 lesion difference in the mean decrease from baseline in favor of Aczone.

8.1.3.2 Investigator Global Assessment

The IGA scores and success rates from the IGA for the subgroups of subjects with ≥20 lesions and <20 lesions are summarized in Appendix A.3.7 and A.3.10.

TABLE 19. Summary of Investigator's Global Assessment for Subjects with ≥20 Lesions

	Vehicle Control (N=33)	Aczone 2x/day (N=31)	Aczone 1x/day (N=29)	MetroGel 1x/day (N=37)	Aczone + MetroGel 1x/day (N=38)
Baseline					
Clear	0	0	0	0	0
Almost clear	0	0	0	0	0
Mild	6 (18.2%)	5 (16.1%)	2 (6.9%)	6 (16.2%)	2 (5.3%)
Moderate	22 (66.7%)	21 (67.7%)	23 (79.3%)	23 (62.2%)	29 (76.3%)
Severe	5 (15.2%)	5 (16.1%)	4 (13.8%)	8 (21.6%)	7 (18.4%)
Week 12					
Clear	4 (12.1%)	2 (6.5%)	2 (6.9%)	3 (8.1%)	5 (13.2%)
Almost clear	6 (18.2%)	9 (29.0%)	5 (17.2%)	11 (29.7%)	11 (28.9%)
Mild	8 (24.2%)	9 (29.0%)	6 (20.7%)	11 (29.7%)	4 (10.5%)
Moderate	11 (33.3%)	9 (29.0%)	12 (41.4%)	6 (16.2%)	14 (36.8%)
Severe	4 (12.1%)	2 (6.5%)	4 (13.8%)	6 (16.2%)	4 (10.5%)

Source: Appendix A.3.7.

Similar to the ITT analysis, the distribution of IGA scores in subjects with ≥20 lesions at baseline shifted towards improvement as early as Week 2 for all study treatments, where the percentages of subjects with scores of moderate or severe decreased and percentages of subjects with scores of mild or almost clear increased. At Week 12, approximately one third to one half of the subjects enrolled in each group had an IGA score of clear (6.5% to 13.2%) or almost clear (17.2% to 29.7%).

The IGA scores were used to determine treatment success, defined as an improvement in the IGA to a score of clear or almost clear with at least 2 points of improvement. Figure 5 depicts the success rates for subjects with ≥20 lesions at baseline in each treatment group.