Name of Company: Allergan	Name of Finished Product: Aczone™ Gel, 5%	Name of Active Ingredient: Dapsone Gel, 5%
Number and Title of Study: 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		
Study Center(s): 27 US centers		
Publication (reference): None at the time of the clinical study report		
Studied Period: Date of First Enrollment: November 2005 Date of Last Completed: May 2006		**Phase of Development:** 2
Objectives: To evaluate the safety and preliminary efficacy of Aczone in subjects with papulopustular rosacea		
Methodology: Structure: This was a multicenter, randomized, partial-blind, parallel-group study in male and female adult subjects with papulopustular rosacea. Randomization: Subjects were assigned in a 1:1:1:1:1 ratio to the five treatment groups. Visit Schedule: Visits were conducted at Screening/Day 0 (baseline), and Week 2, Week 4, Week 8, Week 12 or Early Termination, and Week 13.		
Number of Subjects (Planned and Analyzed): A total of 400 subjects were planned to be enrolled. Four hundred subjects were enrolled in the study; however, one subject was randomized in error and was not dispensed treatment. Therefore, data were only collected and analyzed on 399 subjects.		
Diagnosis and Main Criteria for Inclusion: Diagnosis: Subjects with papulopustular rosacea Key Inclusion Criteria: ≥18 years of age, diagnosis of papulopustular rosacea with ≥10 inflammatory lesions above the mandibular line at baseline, and an Investigator's Global Assessment (IGA) score ≥2 Key Exclusion Criteria: Presence of another skin disease and/or condition located on the face that would have confounded evaluation of the rosacea condition, current or past ocular rosacea of sufficient severity to require topical or systemic antibiotics, treatment with topical antibiotics, steroids, or other rosacea treatments on the face within 14 days of baseline, treatment with systemic corticosteroids within 30 days of baseline, treatment with systemic antibiotics within 30 days of baseline, treatment with systemic medication or therapy known to affect inflammatory responses within 30 days of baseline, treatment with topical retinoids within 30 days of baseline, treatment with systemic retinoids within 180 days of baseline, treatment with physical modalities within 30 days of baseline, facial surgery within 3 months of baseline, and any initiation or changes in hormonal therapy		
Test Product, Dose and Mode of Administration: Aczone (dapsone) Gel, 5% was applied once or twice daily depending on randomization assignment.		

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Duration of Treatment: 12 weeks		
Reference Therapy, Dose and Mode of Administration: Vehicle control (VC) contained the inactive ingredients in the dapsone gel. VC was applied twice daily for subjects randomized to the VC treatment group. MetroGel® (metronidazole), 1% was applied once a day for subjects randomized to the MetroGel treatment group and Aczone + MetroGel treatment group.		
Criteria for Evaluation: Efficacy: Efficacy assessments included monitoring inflammatory lesion counts, IGA scores, erythema scores, and telangiectasia scores. Plasma dapsone concentrations were also measured to assess systemic exposure to study treatment. Safety: Safety was measured by monitoring adverse events, hematology and serum chemistry parameters, concomitant medications, vital signs, and local symptoms (dryness, itching, stinging, and burning).		
Statistical Methods: No statistical tests of any efficacy variable were planned. Only descriptive statistics and 95% confidence intervals were planned. The intent-to-treat (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 a 5-point 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 The change from baseline in inflammatory lesion counts for each 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. An overall summary of the number and percentage of subjects who experienced any adverse event, 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. Local symptom scores for each of dryness, itching, stinging, and burning were summarized by treatment group at each visit.		

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Summary – Conclusions:

Demographics 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 a glucose-6-phosphate dehydrogenase (D6PD) deficiency enrolled in the study; however, only 1 received active treatment (Aczone 1x/ day).

Efficacy:

In the ITT analysis, the mean change from baseline in lesion count at Week 12 for the Aczone 2x/day group (-8.0) was better than Aczone 1x/day (-5.7), but there was no separation between Aczone 2x/day and VC (-8.3; also applied 2x/day). Treatment with the combination of MetroGel and Aczone was not different from treatment with MetroGel alone by Week 12 in terms of lesion count reduction.

Success rates, defined in this study as a score of clear or almost clear with at least 2 points of improvement on a 5-point IGA, showed that more subjects treated with Aczone 2x/day had success (27.4%) than subjects treated with Aczone 1x/day (24.1%), but there was no difference from VC (27.5%). The success rate for the combination treatment of Aczone + MetroGel was higher than MetroGel alone (39.5% success rate compared with 32.5%), but since there was no difference in the reduction in lesion counts between these regimens, this result probably does not reflect a real additive effect of using these 2 treatments in combination.

Erythema and telangiectasia were also evaluated, using a standardized 4-point grading system. Both erythema and telangiectasia were noted to improve, though not substantially, in all study treatment groups by Week 12. There were no differences apparent between treatment groups. No medical therapies have yet been proved to have an effect on either of these signs of rosacea, so this finding is not surprising.

In summary, subjects in all treatment groups experienced an improvement in the signs and symptoms of rosacea; however, there was no separation between Aczone 2x/day or 1x/day treatment and the VC group in the ITT population. However, there may have been an improved treatment effect with Aczone 2x/day treatment compared with VC in subjects with more moderate disease (i.e., ≥20 inflammatory lesions at baseline). In all analyses, subjects treated with Aczone 2x/day demonstrated better responses than subjects treated with Aczone 1x/day. These results suggest that any future studies of Aczone in this disease should include a twice-daily dosage regimen and a subject population with a higher number of baseline lesions.

Safety:

This study demonstrated that treatment with Aczone, either 1x/day or 2x/day, was safe and well tolerated in subjects with papulopustular rosacea. Most adverse events were at the application site, were mild, and transient. Systemic adverse events were infrequent and were generally indicative of the common cold or flu. There was 1 serious adverse event in the study (appendicitis), but it was not related to study treatment (Aczone + MetroGel) and does not indicate a safety concern for the use of Aczone in subjects with papulopustular rosacea.

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Summary – Conclusions (continued):

Safety (continued):

As expected, the most frequent adverse events were application site events including dryness, pain, burning, pruritis, and erythema, which are also known signs and symptoms of rosacea. Although the majority of application site adverse events were considered related to the study treatment by the study Investigators, rosacea is a cyclic disease and it is also possible that these events were related to flare-ups of the underlying condition. In general, the frequency of application site adverse events exhibited a dose-response relationship, being lowest in the Aczone 2x/day group and highest in the VC group. This finding suggests the possibility that active treatment with Aczone may have reduced the incidence of rosacea signs and symptoms compared with vehicle treatment. The frequency of application site adverse events was generally lowest in the MetroGel group, however the tolerability of both active treatments was considered reasonable and clinically acceptable. This is supported by the improvements of local symptom scores in all treatment groups over the course of the study. Most application site adverse events were mild and transient, and did not usually lead to discontinuation or interruption of treatment. The use of Aczone once-daily (AM) with MetroGel once-daily (PM) did not appear to result in any increase in the frequency of application site adverse events, nor was there any increase in the systemic exposure to dapsone, indicating that the use of these 2 products in combination is also safe and well-tolerated.

Conclusion:

Aczone appears safe and well-tolerated when used to treat subjects with papulopustular rosacea. Systemic levels of dapsone and its metabolites were low during the study with no evidence of increasing exposure over time. No subjects in the study demonstrated evidence of hemolysis or treatment related hematological adverse events. There was an overall improvement from baseline in local symptom scores with treatment.

The results of this study support the following conclusions:

- Treatment with Aczone 1x/day or 2x/day was safe and well-tolerated in subjects with papulopustular rosacea.
- In the overall study population, Aczone was no better than the vehicle in reducing the signs and symptoms of papulopustular rosacea whether applied twice or once daily.
- The local tolerability and efficacy profile of Aczone used twice-daily was better than Aczone used once-daily. Both dosage regimes demonstrated low systemic exposure to dapsone and few systemic adverse events.