### Name of Company:
Allergan  

### Name of Finished Product:
Aczone™ Gel, 5%  

### Name of Active Ingredient:
Dapsone Gel, 5%  

### Number and Title of Study:
ACZ ACN 01: A Phase 4, Double-Blind, Multicenter, Randomized, Vehicle-Controlled, Cross-Over Study to Further Evaluate the Risk of Hematological Adverse Events in Glucose-6-Phosphate Dehydrogenase (G6PD)-Deficient Subjects with Acne Vulgaris Treated with Aczone™ (dapsone) Gel, 5%  

### Study Center(s):
18 US centers  

### Publication (reference):
None at the time of the clinical study report  

### Studied Period:
- Date of First Enrollment: 10 November 2005  
- Date of Last Completed: 13 October 2006  
- Phase of Development: 4  

### Objectives:
The objectives of the study were:  
- To compare the safety profile and risk of hemolysis of Aczone to that of the vehicle, after 12 weeks each of twice-daily applications in acne vulgaris subjects with G6PD deficiency  
- To determine the systemic levels of plasma dapsone and N-acetyladapsone during treatment with Aczone  

### Methodology:
**Structure:** This was a double-blind, multicenter, randomized, cross-over study designed to evaluate the risk of hematological adverse events (AEs) in approximately 60 subjects with G6PD deficiency who applied Aczone and vehicle twice daily in random 12-week sequences.

**Randomization:** Subjects were assigned in a 1:1 ratio to the two treatment groups.

**Visit Schedule:** Visits were conducted at Screening, Baseline (Day 0), Weeks 2, 6, 12, 14, 16, and 20, Week 26 or Early Termination, and Week 28.

### Number of Subjects (Planned and Analyzed):
A total of 60 subjects were planned to be enrolled. Sixty-four subjects were enrolled in the study and were analyzed.

### Diagnosis and Main Criteria for Inclusion:
**Diagnosis:** Subjects with acne vulgaris  

**Key Inclusion Criteria:**  
- ≥12 years of age, diagnosis of acne vulgaris, and diagnosis of G6PD deficiency  
- Severe cystic acne or acne conglobata, treatment with isotretinoin (Accutane®) within 3 months of baseline, predisposition to anemia for other medical reasons, use of topical or systemic medications for acne, use of medications or eating foods that could potentially cause an event in individuals with G6PD deficiency during the study, and facial surgery within 3 months of baseline  

**Key Exclusion Criteria:** Aczone (dapsone) Gel, 5% was applied twice daily, once in the morning and once at night. Each dose of study treatment was applied to the entire face and, as required, to acne-affected areas of the neck, shoulders, upper chest, and upper back.
Name of Company: Allergan
Name of Finished Product: Aczone™ Gel, 5%
Name of Active Ingredient: Dapsone Gel, 5%

Duration of Treatment: 31 weeks

Reference Therapy, Dose and Mode of Administration:
Vehicle contained the inactive ingredients in the dapsone gel and was applied twice daily, once in the morning and once at night. Each dose of study treatment was applied to the entire face and, as required, to acne-affected areas of the neck, shoulders, upper chest, and upper back.

Criteria for Evaluation:
Efficacy:
Efficacy was assessed by lesion counts (inflammatory, non-inflammatory, and total).

Safety:
Safety was monitored by adverse events, concomitant medications, vital signs, and clinical chemistry and hematology values.

Statistical Methods:
The efficacy analysis was performed on the intent-to-treat (ITT) data set. Lesion counts (inflammatory, non-inflammatory, and total), the change from baseline in lesion counts, and the percent change from baseline lesion in counts were summarized.

The change from baseline in inflammatory lesion counts was calculated by subtracting the screening or Week 14 inflammatory lesion count from the Week 12 or Week 26 study visit lesion counts, as applicable for the treatment period, for each subject.

The percent change from baseline in inflammatory lesion counts was calculated by dividing the screening 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 major analyses of the study were performed to assess the risk of hemolysis. The analysis of variables related to the risk of hemolysis was performed on the safety evaluable data set. The following variables were summarized by treatment sequence and by treatment regardless of sequence:

- Percentage of subjects with a shift in hemoglobin of normal/high to low or low to normal/high
- Percentage of subjects with a 2:1 g/dL reduction in hemoglobin, and percentage of subjects with a 2:1 g/dL reduction in hemoglobin and at least one of the following:
  - Increase in bilirubin above the upper limit of normal
  - Increase in reticulocyte counts above the upper limit of normal
  - Reduction in haptoglobin below the lower limit of normal.

These outcomes were summarized using the baseline (Day 0 or Week 14) and the second week of each treatment period (Week 2 or Week 16) and the baseline and the end of each treatment period (Week 12 or Week 26) time points.

An overall safety summary table listing the number and percentage of subjects who experienced any AE, death, a serious AE, or who withdrew from treatment was prepared. The number and percentage of subjects with at least one event and the total number of events were tabulated by treatment sequence, by treatment regardless of sequence, and for all subjects combined. Summary tables were also provided by intensity. Similar tables were generated for associated AEs, which were defined as those that the Investigator assessed as suspected to be related to treatment.
Summary – Conclusions:

Efficacy:
The primary purpose of this study was to evaluate safety, and therefore no statistical tests were planned for comparisons of the efficacy variables. The lesion counts were lower at the baseline of the second treatment period compared with the first, which indicates that the clinical effects of treatment last longer than the 2-week washout period and therefore, the evaluation of changes in lesion counts in treatment period 2 is confounded by the use of treatment during treatment period 1. Because of this, it is most relevant to evaluate changes in lesion counts over the first treatment period only.

After the first 12 weeks of the study, subjects treated with Aczone experienced a 44% drop in inflammatory lesion counts and 5% drop in non-inflammatory lesion counts. This pattern is consistent with the results from the pivotal phase 3 studies, in which Aczone demonstrated a larger effect on inflammatory lesions than non-inflammatory lesions. Comparing Aczone and vehicle treatments in other lesion categories, it was observed that vehicle treatment in this study resulted in a better reduction in non-inflammatory lesion counts while the percentage reduction in total lesion counts was similar between Aczone and vehicle. However, the absolute reduction in lesion counts was numerically better with Aczone treatment for all lesion categories. This variability in lesion counts is not unexpected given the small sample size of the study.

Safety:
This study was designed specifically to evaluate the risk of hemolytic anemia with Aczone treatment in subjects with G6PD deficiency. The study employed a cross-over design in order to evaluate both Aczone and vehicle treatment within the same subject. There were 57 subjects exposed to vehicle treatment and 60 subjects exposed to Aczone in the study, with a total of 56 safety-evaluable subjects. To evaluate hemolysis, subjects were monitored for changes in hemolysis-related laboratory parameters at 2 and 12 weeks of each treatment. AEs were also evaluated to determine if there were any clinical signs of hemolytic anemia.

Plasma dapsone and N-acetyl dapsone levels were measured pre-treatment and at the 2-week and 12-week time points of each treatment period to assess systemic exposure. As expected, exposure to dapsone after topical Aczone treatment was low, considering both the mean (approximately 5 ng/mL) and the maximum exposure in the study (approximately 37 ng/mL). Within the range of daily treatment use in this study (0-3 g/day), there was no relationship between plasma dapsone concentration and daily treatment use. The N-acetyl dapsone metabolite was present at levels equivalent to approximately 40% to 50% of the levels of the parent.

An evaluation of the laboratory data shows a mean decrease from baseline in hemoglobin of approximately 0.3 g/dL after 2 weeks of Aczone treatment, which normalized by 12 weeks as treatment continued. Most importantly, there were no changes from baseline in other laboratory markers of hemolysis at either the 2-week or 12-week time point including bilirubin, haptoglobin, and lactase dehydrogenase (LDH), which argues against the presence of significant hemolysis. Reticulocyte counts appeared to be slightly elevated during Aczone treatment, but there were no values reported outside of the normal range and there was no correlation between changes in hemoglobin ≥1 g/dL and/or a decrease to below the lower limit of normal remained close to the normal range and no subjects were diagnosed clinically with hemolytic anemia.
Summary – Conclusions (continued):
Safety (continued):
For several reasons, the nominal decrease in hemoglobin at Week 2 is considered to be clinically insignificant. The relationship between changes in hemoglobin and Aczone treatment is not clear. The percentage of subjects who had a \( \geq 1 \text{ g/dL} \) decrease was similar between Aczone and vehicle treatment, including the Week 2 time point (11% of subjects on Aczone treatment compared with 7% of subjects on vehicle treatment had \( \geq 1 \text{ g/dL} \) decrease). Some of the subjects who had decreases in hemoglobin during Aczone treatment also had decreases during vehicle treatment. Furthermore, some subjects had very low or undetectable plasma levels of dapsone at the time of the decreases, providing additional support that changes in hemoglobin may not be related to Aczone treatment in all cases. On an individual basis, many of the changes in hemoglobin observed were confounded by the use of medications, laboratory evidence of a potential infection, or heavy menses as a possible alternative explanation for the event.

There were no therapeutic interventions or modifications to study treatment initiated as a consequence of a laboratory finding, even for subjects who experienced the largest decreases of hemoglobin (1.7 g/dL and 1.5 g/dL for vehicle and Aczone treatment, respectively). Although hemoglobin levels shifted to below normal in a few subjects, they remained close to the normal range and no hemoglobin value less than 10.5 g/dL was observed during Aczone treatment (with the exception of 1 subject who was enrolled with pre-existing anemia).

Laboratory data were evaluated for the individual subjects who had the highest exposure to treatment in terms of both the highest plasma dapsone concentrations and the highest body area use. Two subjects with the highest systemic dapsone exposure had plasma dapsone levels that were greater than 30 ng/mL at either 2 weeks or 12 weeks of Aczone treatment. There were no changes in hematology or chemistry parameters in either subject. These data support that the systemic levels of dapsone after topical application of Aczone are insufficient to induce hemolytic anemia. Six subjects in the study consistently applied treatment to the face, neck, shoulders, upper chest, and upper back throughout their period of Aczone treatment. Applying treatment to all of these areas completely represents exposure of up to approximately 22% of the body surface. There was also no laboratory or clinical evidence of hemolysis or hemolytic anemia related to Aczone treatment in any of these subjects with larger body surface exposure.

The risk of hemolytic anemia was also evaluated in various subgroups, including a subgroup based on degree of G6PD enzyme deficiency (which was defined a priori). Subjects who had very low G6PD enzyme activity (\( \leq 2 \text{ U/g Hb} \)) had similar hemoglobin bilirubin, reticulocyte and haptoglobin values and changes from baseline as the subjects with \( > 2 \text{ U/g Hb} \) activity during Aczone and vehicle treatment. There were both positive and negative changes from baseline in hemoglobin in subjects with \( \leq 2 \text{ U/g Hb} \) and the distribution of changes was similar to that for subjects with \( > 2 \text{ U/g Hb} \) activity. The subject with the lowest G6PD activity measured in the study (0.7 U/g Hb) had a bilirubin increase to slightly above the normal limit after 2 and 12 weeks of Aczone treatment and a 1.3 g/dL hemoglobin decrease from baseline at 12 weeks of Aczone treatment, but other hemolysis indicators were normal and he had no clinical symptoms, which argues against hemolysis as an explanation for the laboratory observations in this subject. The findings from the subgroups by G6PD enzyme activity support that, in G6PD-deficient subjects, the lowest levels of G6PD enzyme activity do not carry a greater risk of hemolytic anemia.

Application site AEs are the most common expected AE with Aczone treatment. The incidence of application site AEs was low in this study, which was consistent with similar previous studies in which these types of events were not solicited. One subject discontinued the study due to an application site AE of contact dermatitis during Aczone treatment (MedDRA term: application site rash). The event was mild, resolved upon discontinuing treatment, and did not require any intervention.
Summary - Conclusions (continued):

Safety (continued):

In summary, the results of this study show that there was no evidence of hemolytic anemia after Aczone treatment in subjects with G6PD deficiency. The minor changes in hemoglobin observed at 2 weeks of Aczone treatment were transient, did not require intervention, and were not associated with any other laboratory or clinical evidence of hemolytic anemia and are therefore not clinically relevant. The G6PD-deficient patient population represents a sensitive indicator group to detect the possibility of hemolytic reactions with drug treatment. Based on the results of this study, the risk of hemolytic anemia with topical Aczone treatment in subjects with G6PD deficiency is expected to be remote. There were no new safety findings and the AE profile observed in the study was consistent with the product label.

Conclusion:
The results of this study support the following conclusions:

- There was no evidence of hemolytic anemia in acne subjects with G6PD deficiency. Any minor changes in hemoglobin observed were transient, not clinically relevant, did not require intervention, and were not associated with any other laboratory or clinical evidence of hemolysis. In addition, there were no new findings in the safety profile for Aczone observed in this study.

- Systemic exposure to dapsone was low, similar to previous studies of Aczone in acne subjects with or without G6PD deficiency. The amount of treatment use in this study reflects the expected usage in clinical practice.

- Monitoring complete blood counts and reticulocyte levels during Aczone treatment in G6PD-deficient subjects did not reveal any clinically significant findings and did not alter treatment decisions. Therefore identifying and monitoring subjects with G6PD deficiency as a part of Aczone treatment is not justified.