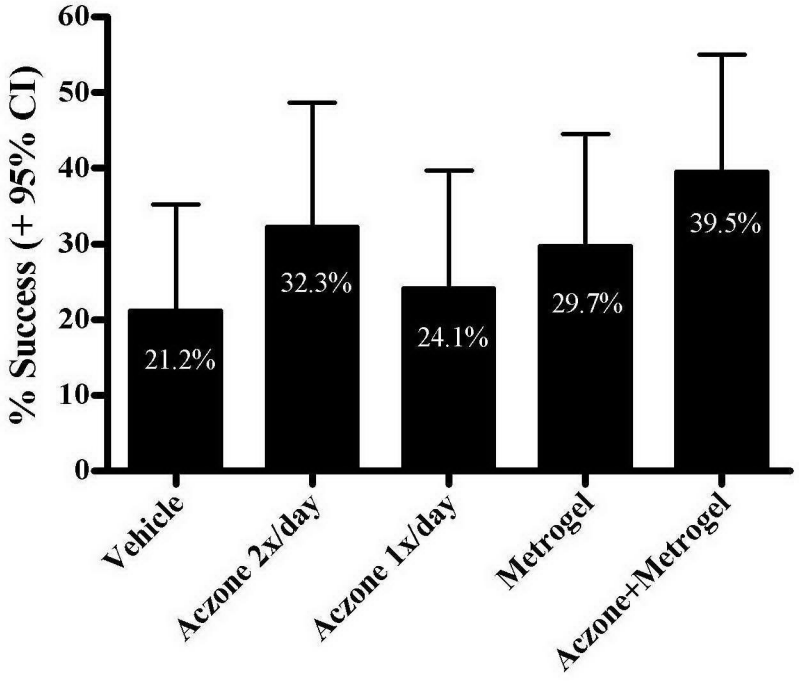
**FIGURE 5. Summary of IGA Success Rate for Subjects with ≥20 Inflammatory Lesions at Baseline**




Source: Appendix A.3.7.

The percentage of subjects with ≥20 lesions who had treatment success at Week 12 was highest in the Aczone + MetroGel group (39.5%) and lowest in the VC group (21.2%). Success rates were better in the Aczone 2x/day group (32.3%) than either the Aczone 1x/day group (24.1%) or the VC (21.2%), equivalent to an 11.1% difference favoring Aczone 2x/day treatment. Comparing the Aczone + MetroGel group to the MetroGel alone group, there was a higher success rate for the combination treatment (39.5% compared to 29.7%).

8.1.3.3 Erythema Assessment

Erythema assessment scores for the subgroups of subjects with ≥20 lesions and subjects with <20 lesions are summarized in Appendix A.3.9 and Appendix A.3.12, respectively. Table 20 presents erythema scores for the subjects with ≥20 lesions.

**TABLE 20. Summary of Erythema Assessment for Subjects with ≥20 Lesions**

| Visit | | 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 | Absent | 0 | | 0 | | 0 | | 0 | | 0 | |
| | Mild | 6 | (18.2%) | 4 | (12.9%) | 0 | | 4 | (10.8%) | 4 | (10.5%) |
| | Moderate | 20 | (60.6%) | 18 | (58.1%) | 24 | (82.8%) | 25 | (67.6%) | 26 | (68.4%) |
| | Severe | 7 | (21.2%) | 9 | (29.0%) | 5 | (17.2%) | 8 | (21.6%) | 8 | (21.1%) |
| Week 12 | Absent | 3 | (9.1%) | 1 | (3.2%) | 1 | (3.4%) | 3 | (8.1%) | 3 | (7.9%) |
| | Mild | 13 | (39.4%) | 13 | (41.9%) | 10 | (34.5%) | 19 | (51.4%) | 12 | (31.6%) |
| | Moderate | 12 | (36.4%) | 15 | (48.4%) | 14 | (48.3%) | 10 | (27.0%) | 20 | (52.6%) |
| | Severe | 5 | (15.2%) | 2 | (6.5%) | 4 | (13.8%) | 5 | (13.5%) | 3 | (7.9%) |

Source: Appendix A.3.9.

For the subgroup of subjects with ≥20 lesions at baseline, the distribution of erythema scores tended to shift towards improvement as the study progressed in all treatment groups. By Week 12, approximately half of the subjects in each group had improved to a score of absent (3.2% to 9.1%) or mild (31.6% to 51.4%) from mostly moderate at baseline (58.1% to 82.8%). There were no consistent differences between the treatment groups.

### 8.1.3.4 Telangiectasia Assessment

Telangiectasia assessment scores for the subgroups of subjects with ≥20 lesions and subjects with <20 lesions at baseline are summarized in Appendix A.3.9 and A.3.12, respectively. Table 21 presents telangiectasia assessment scores for subjects with ≥20 lesions.

**TABLE 21. Summary of Telangiectasia Assessment for Subjects with ≥20 Lesions**

| Visit | | 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 | Absent | 3 | (9.1%) | 1 | (3.2%) | 3 | (10.3%) | 6 | (16.2%) | 3 | (7.9%) |
| | Mild | 7 | (21.2%) | 16 | (51.6%) | 8 | (27.6%) | 9 | (24.3%) | 7 | (18.4%) |
| | Moderate | 21 | (63.6%) | 8 | (25.8%) | 14 | (48.3%) | 19 | (51.4%) | 20 | (52.6%) |
| | Severe | 2 | (6.1%) | 6 | (19.4%) | 4 | (13.8%) | 3 | (8.1%) | 8 | (21.1%) |
| Week 12 | Absent | 3 | (9.1%) | 4 | (12.9%) | 5 | (17.2%) | 9 | (24.3%) | 7 | (18.4%) |
| | Mild | 14 | (42.4%) | 15 | (48.4%) | 9 | (31.0%) | 12 | (32.4%) | 12 | (31.6%) |
| | Moderate | 14 | (42.4%) | 10 | (32.3%) | 12 | (41.4%) | 13 | (35.1%) | 14 | (36.8%) |
| | Severe | 2 | (6.1%) | 2 | (6.5%) | 3 | (10.3%) | 3 | (8.1%) | 5 | (13.2%) |

Source: Appendix A.3.9.

At baseline, the telangiectasia score was predominantly mild in subjects with ≥20 lesions in the Aczone 2x/day group (51.6%) and moderate (48.3% to 63.6%) for other treatments. This pattern was still evident at Week 12; however the percentages of subjects with moderate or severe telangiectasia generally decreased while the percentages of subjects with mild or absent generally increased.

## 8.2 Discussion of Efficacy Results

This study was designed to investigate the preliminary efficacy of Aczone in treating subjects with papulopustular rosacea. Two Aczone dosage regimens (1x/day and 2x/day) were included in the study order to determine the better dosing regimen to use in any potential future studies. The study was controlled with the Aczone vehicle applied 2x/day (VC) in order to determine the potential efficacy of Aczone compared to its vehicle. An active control arm (MetroGel) was also included to determine the relative efficacy of Aczone against an approved treatment. No statistical comparisons were planned and the study was not powered to detect statistical differences.

ITT Analysis (All Subjects)

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). A review of historical results for other approved therapies shows that the mean changes from baseline in lesion count for the Aczone 2x/day group was close to that of other approved products for rosacea, including Finacea® (azelaic acid) Gel, 15%, Oracea® (doxycycline) 40 mg capsules, and the active comparator in this study, MetroGel® (metronidazole), 1.0%. The changes from baseline in inflammatory lesion counts for Finacea were reported as –10.7 and –8.9 (differences of 3.6 and 2.5 lesions in favor of active treatment over vehicle) [14]. For Oracea, the changes from baseline in lesion counts were –11.8 and –9.5 (differences of 5.9 and 5.2 lesions in favor of active treatment over vehicle) [15]. Historically, subjects treated with the 1% strength of MetroGel once-daily demonstrated a reduction in lesion count from baseline of –9.4 lesions, with a difference of 5.6 lesions over vehicle [13]. The historical response for MetroGel was less than the response observed in this study (–11.3 lesion decrease from baseline), which is most likely due to differences in study conditions and the fewer numbers of subjects enrolled in this phase 2 study. In the ITT analysis, 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 the 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 proven to have an effect on either of these signs of rosacea, so this finding is not surprising.

Subgroup Analysis: Subjects With ≥20 Lesions At Baseline

In contrast to the ITT population, when the subgroup of subjects with ≥20 lesions at baseline was analyzed, the efficacy results do show a separation between Aczone 2x/day and VC. The size of this subgroup was relatively large (42% of the ITT population). The cut-off of 20 lesions was chosen as the number closely approximated the baseline mean lesion count in subjects who entered the study with a baseline IGA in the moderate or severe categories. The mean change from baseline in lesion counts for the subgroup with ≥20 lesions was –15.5 for Aczone subjects treated 2x/day, –9.3 for Aczone subjects treated 1x/day, and –11.6 for VC-treated subjects. This represents a difference over VC of 3.9 lesions in favor of Aczone 2x/day, similar to the differences between active and vehicle for other approved treatments (as described above). There was also an 11.1% difference in favor of Aczone 2x/day treatment over VC in success rate (32.3% compared with 21.2%). Consistent with the ITT analysis, the success rate for Aczone 1x/day (24.1%) was less than the success rate for Aczone 2x/day and the success rate for the group of subjects treated with the combination of Aczone + MetroGel was higher than for subjects treated with MetroGel alone (39.5% compared with 29.7%).

Possible explanations for the divergence of the response to Aczone treatment between the ITT group, which included subjects with at least 10 lesions at baseline, and the subgroup of subjects with ≥20 lesions at baseline include the cyclic nature of this disease, in which subjects may improve spontaneously without treatment. It may be more difficult to distinguish between cyclic changes and treatment effects in subjects with few lesions. Patients with milder disease may also be more likely to reach the success category in the IGA with these cyclic improvements. In addition, the vehicle also appeared to provide a modest treatment benefit, thereby making clinical improvements due to active Aczone treatment less apparent in subjects with milder disease.

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.

## 9 SAFETY RESULTS AND DISCUSSION

Safety analyses were performed on the safety data set, which included 393 subjects who were confirmed to have applied study treatment or reported at least 1 AE. Where the study treatment regimen actually used differed from the treatment regimen assigned at randomization, subjects were analyzed for safety according to the treatment regimen they actually used.

## 9.1 Extent of Exposure

### 9.1.1 Exposure to Trial Treatment(s)

#### 9.1.1.1 Study Treatment Usage

Study treatment usage for the safety population is summarized in Appendix A.4.1 and Table 9 in Section 6.2. A listing of treatment usage by subject is provided in Appendix E.4.5. Missed applications are listed in Appendix E.4.2.

Several subjects in the study missed at least 1 application of study treatment, but in general, the missed applications were not continuous over lengthy periods during the 84-day study period. The measured tube weights and calculated parameters for usage of study treatment are consistent with the usage expected based on the application instructions that were provided to subjects (i.e., apply a thin layer of treatment to the face).

#### 9.1.1.2 Plasma Dapsone and Metabolite Concentrations

The amounts of dapsone and metabolites in plasma were measured at baseline, Week 2, Week 4, and Week 12. Plasma concentrations of dapsone, N-acetyl dapsone, and N-hydroxylamine dapsone are summarized in Appendix A.4.2 and Table 22, and listed by subject in Appendix E.4.3.

**TABLE 22. Plasma Dapsone and Metabolite Concentrations**

| Visit | | 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) |
|---|---|---|---|---|---|---|
| Dapsone (ng/mL) | | | | | | |
| Baseline | n | 76 | 82 | 80 | 76 | 73 |
| | Mean | 0.000 | 0.000 | 0.032 | 0.000 | 0.000 |
| | SD | 0.000 | 0.000 | 0.282 | 0.000 | 0.000 |
| Week 2 | n | 76 | 81 | 77 | 74 | 70 |
| | Mean | 0.005 | 10.555 | 7.006 | 0.000 | 6.078 |
| | SD | 0.045 | 12.008 | 6.962 | 0.000 | 5.822 |
| Week 4 | n | 73 | 81 | 75 | 71 | 71 |
| | Mean | 0.073 | 9.377 | 7.348 | 0.000 | 6.193 |
| | SD | 0.625 | 10.714 | 7.841 | 0.000 | 5.537 |
| Week 12 | n | 75 | 76 | 73 | 72 | 69 |
| | Mean | 0.000 | 6.732 | 5.548 | 0.000 | 4.508 |
| | SD | 0.000 | 6.997 | 6.191 | 0.000 | 4.016 |
| N-Acetyl Dapsone (ng/mL) | | | | | | |
| Baseline | n | 76 | 82 | 80 | 76 | 73 |
| | Mean | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| | SD | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| Week 2 | n | 76 | 79 | 75 | 74 | 70 |
| | Mean | 0.000 | 4.943 | 3.112 | 0.000 | 2.891 |
| | SD | 0.000 | 5.548 | 3.241 | 0.000 | 2.764 |
| Week 4 | n | 72 | 79 | 72 | 72 | 71 |
| | Mean | 0.000 | 4.260 | 3.005 | 0.000 | 2.909 |
| | SD | 0.000 | 5.099 | 3.402 | 0.000 | 2.751 |
| Week 12 | n | 75 | 75 | 73 | 72 | 69 |
| | Mean | 0.000 | 3.371 | 3.110 | 0.000 | 2.002 |
| | SD | 0.000 | 4.630 | 6.072 | 0.000 | 2.037 |
| N-Hydroxylamine Dapsone (ng/mL) | | | | | | |
| Baseline | n | 76 | 81 | 78 | 74 | 72 |
| | Mean | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| | SD | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| Week 2 | n | 74 | 79 | 76 | 74 | 70 |
| | Mean | 0.000 | 0.622 | 0.341 | 0.000 | 0.344 |
| | SD | 0.000 | 0.899 | 0.439 | 0.000 | 0.482 |
| Week 4 | n | 72 | 81 | 74 | 71 | 70 |
| | Mean | 0.000 | 0.541 | 0.329 | 0.000 | 0.311 |
| | SD | 0.000 | 0.661 | 0.484 | 0.000 | 0.469 |
| Week 12 | n | 75 | 76 | 73 | 72 | 69 |
| | Mean | 0.000 | 0.288 | 0.202 | 0.000 | 0.156 |
| | SD | 0.000 | 0.421 | 0.348 | 0.000 | 0.266 |

Source: Appendix A.4.2.

Mean plasma concentrations of dapsone and metabolites were low in study treatment groups using Aczone at all time points measured in the study. The highest mean plasma concentrations were observed at Week 2, where subjects had a mean dapsone concentration of 10.6 ng/mL, 7.0 ng/mL, and 6.1 ng/mL in the Aczone 2x/day group, Aczone 1x/day group, and Aczone + MetroGel group, respectively. The maximum plasma concentration of dapsone observed in any subject was 87.43 ng/mL, at Week 2 in Subject 035160 (Aczone 2x/day group). Plasma concentrations of N-acetyl dapsone were also highest at Week 2 (means of 4.9, 3.1, and 2.9 ng/mL in the Aczone 2x/day, Aczone 1x/day, and combination groups respectively). Plasma concentrations of the hydroxylamine metabolite, which is believed to

be the primary factor associated with dapsone hematological toxicities, were much lower than the parent (mean values <1 ng/mL in all Aczone-treated groups, maximum in any subject using Aczone 2x/day was 6.7 ng/m; Subject 035160).

In subjects treated with the combination of Aczone and MetroGel, plasma levels of dapsone and metabolites were similar to or lower than subjects treated with the same amount of Aczone only (1x/day), suggesting that there are no pharmacokinetic interactions between these 2 drugs.

Dapsone was found to be present in 1 sample apparently from a vehicle subject, but an examination of the data identified a probable switch in labeling of the Week 4 samples at the study center for Subjects 099812 (VC) and 091410 (Aczone 2x/day), as these samples were taken at the same study center, on the same day, within 30 minutes of each other.

#### 9.1.2 Exposure to Concomitant Treatment

Concomitant medications are summarized by treatment group in Appendix A.4.3 and listed by subject in Appendix E.5.1. A total of 78% of subjects used at least 1 concomitant medication during the study. The most common classes of medications were for the Alimentary Tract and Metabolism (36%) and the Cardiovascular System (31%). A small percentage of subjects took a dermatologic concomitant medication (5%), which was slightly higher in the MetroGel group (9% compared with 3% to 6% for other groups).

### 9.2 Overview of Adverse Events

Appendix A.4.4 and Table 23 present an overview of safety in the study.

**TABLE 23. Summary of Safety**

| | All Adverse Events | | | | | Associated Adverse Events | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 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) | 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) |
| Adverse events | 60 (75.9%) | 61 (73.5%) | 59 (72.8%) | 53 (68.8%) | 52 (71.2%) | 49 (62.0%) | 46 (55.4%) | 49 (60.5%) | 33 (42.9%) | 34 (46.6%) |
| Treatment discontinuation[a] due to AEs | 5 (6.3%) | 6 (7.2%) | 2 (2.5%) | 2 (2.6%) | 4 (5.5%) | 4 (5.1%) | 5 (6.0%) | 2 (2.5%) | 0 | 4 (5.5%) |
| Serious adverse events | 0 | 0 | 0 | 0 | 1 (1.4%) | 0 | 0 | 0 | 0 | 0 |
| Deaths | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Treatment discontinuation due to SAEs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Other SAEs | 0 | 0 | 0 | 0 | 1 (1.4%) | 0 | 0 | 0 | 0 | 0 |

[a] Includes subjects who temporarily or permanently discontinued applying the study treatment due to an adverse event.
Source: Appendix A.4.4.

The overall frequency of adverse events ranged from 68.8% in the MetroGel group to 75.9% in the Vehicle Control group. With respect to adverse events that were considered associated to study treatment, the frequency was also lowest in the MetroGel group (43%) and highest in the Vehicle Control group (62%). There was 1 serious adverse event during the study, which occurred in a subject treated with Aczone + MetroGel and was unrelated to study treatment (refer to Section 9.3.3 below). There were more subjects in the Vehicle Control and Aczone 2x/day groups who temporarily or permanently discontinued treatment due to an adverse event (6.3% and 7.2%, respectively) compared with Aczone 1x/day, MetroGel, or the Aczone + MetroGel groups (2.5%, 2.6%, and 5.5%). Adverse events that led to discontinuation from both treatment and the study are discussed in more detail in Section 9.3.2 below.

### 9.2.1 Common Treatment-Emergent Adverse Events

All treatment-emergent adverse events are summarized in Appendix A.4.5.1 and listed by subject in Appendix E.5.2. There were a total of 772 events in 285 subjects (72.5% of the total study subjects); however most of the events occurred in only 1 or 2 subjects. Table 24 summarizes the most frequent adverse events that occurred in the study (≥2% [4 subjects]).

**TABLE 24. Summary of Common Treatment-Emergent Adverse Events (Occurring in ≥2% of Subjects)**

| | 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) | |
|---|---|---|---|---|---|---|---|---|---|---|
| **SYSTEM ORGAN CLASS : - Preferred Term** | **Subjects n %** | **Events n** | **Subjects n %** | **Events n** | **Subjects n %** | **Events n** | **Subjects n %** | **Events n** | **Subjects n %** | **Events n** |
| ANY EVENT | 60 (75.9%) | 187 | 61 (73.5%) | 155 | 59 (72.8%) | 181 | 53 (68.8%) | 124 | 52 (71.2%) | 125 |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: | | | | | | | | | | |
| - Any Event | 49 (62.0%) | 117 | 47 (56.6%) | 91 | 50 (61.7%) | 113 | 33 (42.9%) | 68 | 37 (50.7%) | 68 |
| - APPLICATION SITE DRYNESS | 29 (36.7%) | 32 | 27 (32.5%) | 30 | 29 (35.8%) | 34 | 26 (33.8%) | 29 | 24 (32.9%) | 27 |
| - APPLICATION SITE PAIN | 23 (29.1%) | 28 | 14 (16.9%) | 14 | 19 (23.5%) | 20 | 11 (14.3%) | 12 | 6 (8.2%) | 8 |
| - APPLICATION SITE BURNING | 15 (19.0%) | 21 | 16 (19.3%) | 17 | 22 (27.2%) | 23 | 10 (13.0%) | 11 | 8 (11.0%) | 9 |
| - APPLICATION SITE PRURITUS | 16 (20.3%) | 19 | 17 (20.5%) | 17 | 18 (22.2%) | 20 | 6 (7.8%) | 7 | 6 (8.2%) | 7 |
| - APPLICATION SITE ERYTHEMA | 11 (13.9%) | 15 | 11 (13.3%) | 11 | 12 (14.8%) | 12 | 7 (9.1%) | 8 | 11 (15.1%) | 11 |
| INFECTIONS AND INFESTATIONS: | | | | | | | | | | |
| - Any Event | 18 (22.8%) | 21 | 14 (16.9%) | 17 | 16 (19.8%) | 20 | 18 (23.4%) | 19 | 16 (21.9%) | 21 |
| - NASOPHARYNGITIS | 6 (7.6%) | 6 | 3 (3.6%) | 3 | 5 (6.2%) | 7 | 7 (9.1%) | 7 | 4 (5.5%) | 5 |
| - UPPER RESPIRATORY TRACT INFECTION NOS | 4 (5.1%) | 4 | 4 (4.8%) | 4 | 6 (7.4%) | 6 | 5 (6.5%) | 5 | 5 (6.8%) | 6 |
| - SINUSITIS NOS | 4 (5.1%) | 4 | 5 (6.0%) | 6 | 1 (1.2%) | 1 | 0 | 0 | 4 (5.5%) | 5 |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS: | | | | | | | | | | |
| - Any Event | 10 (12.7%) | 10 | 10 (12.0%) | 10 | 14 (17.3%) | 16 | 16 (20.8%) | 19 | 10 (13.7%) | 10 |
| - TELANGIECTASIA | 9 (11.4%) | 9 | 9 (10.8%) | 9 | 11 (13.6%) | 12 | 11 (14.3%) | 11 | 9 (12.3%) | 9 |

Source: Appendix: A.4.5.1, A.4.5.2.

Application site adverse events were the most common type of adverse event reported during the study (General Disorders and Administration Site Conditions System Organ Class). The majority of application site adverse events that were reported are signs and symptoms of rosacea that were solicited and scored using a standardized grading system throughout the study (dryness, itching, burning, and stinging; refer to Section 9.6 below for a discussion of local symptom scores). An increase from baseline in the score for any sign or symptom was recorded as an adverse event. The most frequent application site adverse event was dryness, which occurred at a similar frequency among study treatment groups (32.5% to 36.7%) and was typically mild to moderate in intensity. Other frequent application site adverse events were pain (8.0% to 29.1%), burning (10.7% to 27.8%), pruritis (8.0% to 22.8%), and erythema (9.1% to 13.9%). The frequency of these application site adverse events was numerically lower in groups treated with MetroGel alone or MetroGel + Aczone compared with the vehicle control or Aczone-only treated groups. For all groups, the intensity of application site pain, burning, and pruritus was mostly mild while the intensity of application site erythema was mostly moderate to severe. The higher severity of application site erythema compared with other signs/symptoms of rosacea may be explained by the presence of erythema at baseline (which was mostly moderate) as part of the underlying rosacea characteristics whereas other local signs and symptoms were mostly absent or mild (refer to Appendix A.2.1.1).

Skin and Subcutaneous Disorders occurred at a frequency ranging from 12.0% to 20.8%. The frequency was higher in the MetroGel group (20.8%) compared with other groups (12.0% to 17.7%). Telangectasia, reported as a worsening of baseline telangiectasia that was part of the subject's underlying rosacea, was the only adverse event in this System Organ Class to occur with a frequency higher than 1% (10.8% to 14.3%). The incidence of telangiectasia was slightly higher in groups treated with MetroGel or MetroGel + Aczone than the vehicle or Aczone-only treated group.

Adverse events that are related to the common cold or flu were the most frequent types of systemic adverse events, affecting System Organ Classes that are related to infections, musculoskeletal, and respiratory systems. Nasopharyngitis, upper respiratory tract infections, bronchitis, influenza, arthralgia, headaches, sinusitis, nasal congestion, pharyngitis, and cough each occurred in 1%-8% of subjects. There was no trend among treatment groups and this incidence is consistent with the timing of conducting this study through the winter months.

### 9.2.2 All Associated Adverse Events

Associated adverse events, defined as those judged to have a suspected relationship to the study treatment by the study Investigator, are summarized in Appendix A.4.5.3 and Table 25.

**TABLE 25. Summary of All Associated Adverse Events**

| SYSTEM ORGAN CLASS: - Preferred Term | 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) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Subjects n % | Events n | Subjects n % | Events n | Subjects n % | Events n | Subjects n % | Events n | Subjects n % | Events n |
| ANY ASSOCIATED EVENT | 49 (62.0%) | 123 | 46 (55.4%) | 92 | 49(60.5%) | 119 | 33 (42.9%) | 71 | 34(46.6%) | 67 |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS: | | | | | | | | | | |
| - Any Event | 1 (1.3%) | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| - ANISOCYTOSIS | 1 (1.3%) | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| EYE DISORDERS: | | | | | | | | | | |
| - Any Event | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.3%) | 1 | 0 | 0 |
| - CONJUNCTIVITIS | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.3%) | 1 | 0 | 0 |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: | | | | | | | | | | |
| - Any Event | 46(58.2%) | 113 | 45(54.2%) | 85 | 47(58.0%) | 105 | 31(40.3%) | 60 | 34(46.6%) | 62 |
| - APPLICATION SITE DRYNESS | 28(35.4%) | 31 | 26(31.3%) | 29 | 27(33.3%) | 32 | 23(29.9%) | 26 | 23(31.5%) | 26 |
| - APPLICATION SITE PAIN | 23(29.1%) | 28 | 14(16.9%) | 14 | 19(23.5%) | 20 | 10(13.0%) | 11 | 6 (8.2%) | 8 |
| - APPLICATION SITE BURNING | 15(19.0%) | 21 | 15(18.1%) | 16 | 22(27.2%) | 23 | 9(11.7%) | 10 | 8(11.0%) | 9 |
| - APPLICATION SITE PRURITUS | 16(20.3%) | 19 | 17(20.5%) | 17 | 17(21.0%) | 19 | 6 (7.8%) | 7 | 6 (8.2%) | 7 |
| - APPLICATION SITE ERYTHEMA | 9(11.4%) | 13 | 8 (9.6%) | 8 | 9(11.1%) | 9 | 5 (6.5%) | 5 | 10(13.7%) | 10 |
| - APPLICATION SITE PAPULES | 0 | 0 | 0 | 0 | 1 (1.2%) | 1 | 0 | 0 | 1 (1.4%) | 1 |
| - APPLICATION SITE REACTION NOS | 0 | 0 | 1 (1.2%) | 1 | 1 (1.2%) | 1 | 0 | 0 | 0 | 0 |
| - APPLICATION SITE RASH | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.3%) | 1 | 0 | 0 |
| - NODULE | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.4%) | 1 |
| - PAIN NOS | 1 (1.3%) | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS: | | | | | | | | | | |
| - Any Event | 1 (1.3%) | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| - SUNBURN | 1 (1.3%) | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| INVESTIGATIONS: | | | | | | | | | | |
| - Any Event | 2 (2.5%) | 2 | 0 | 0 | 1(1.2%) | 3 | 0 | 0 | 0 | 0 |
| - BLOOD GLUCOSE INCREASED | 0 | 0 | 0 | 0 | 1(1.2%) | 1 | 0 | 0 | 0 | 0 |
| - HAEMATOCRIT DECREASED | 0 | 0 | 0 | 0 | 1(1.2%) | 1 | 0 | 0 | 0 | 0 |
| - HAEMOGLOBIN DECREASED | 0 | 0 | 0 | 0 | 1(1.2%) | 1 | 0 | 0 | 0 | 0 |
| - HAPTOGLOBIN INCREASED | 1 (1.3%) | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| - WHITE BLOOD CELL COUNT DECREASED | 1 (1.3%) | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| NERVOUS SYSTEM DISORDERS: | | | | | | | | | | |
| - Any Event | 1 (1.3%) | 1 | 1 (1.2%) | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| - DYSGEUSIA | 1 (1.3%) | 1 | 1 (1.2%) | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS: | | | | | | | | | | |
| - Any Event | 5 (6.3%) | 5 | 6 (7.2%) | 6 | 10(12.3%) | 11 | 8 (10.4%) | 9 | 5 (6.8%) | 5 |
| - TELANGIECTASIA | 5 (6.3%) | 5 | 6 (7.2%) | 6 | 8 (9.9%) | 9 | 7 (9.1%) | 7 | 5 (6.8%) | 5 |
| - ROSACEA | 0 | 0 | 0 | 0 | 2 (2.5%) | 2 | 0 | 0 | 0 | 0 |
| - DRY SKIN | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.3%) | 1 | 0 | 0 |
| - RASH NOS | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.3%) | 1 | 0 | 0 |
| VASCULAR DISORDERS: | | | | | | | | | | |
| - Any Event | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.3%) | 1 | 0 | 0 |
| - HOT FLUSHES NOS | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.3%) | 1 | 0 | 0 |

Source: Appendix A.4.5.3.

The frequency of any associated adverse event was highest in the Vehicle Control group (62%) and lowest in the MetroGel group (42.9%).

Similar to the pattern for all adverse events, application site adverse events were the most frequent associated adverse event, including dryness (32.3%), pain (18.3%), burning (17.6%), pruritus (15.8%), and erythema (10.4%). The frequency of these adverse events was generally lowest in groups treated with MetroGel or MetroGel + Aczone compared with the Vehicle Control or Aczone only. Other types of events at the application site were rare (<1%), including application site reaction in the Aczone 1x/day and 2x/day groups (reported as scaling), papules in the MetroGel group, and rash in the MetroGel + Aczone group. Application site reactions were mostly mild to moderate and transient.

There was a low incidence of associated adverse events of rosacea (0.5%) and telangiectasia (7.9%), indicating that few subjects experienced treatment-related worsening of baseline disease. There appears to be no difference among the treatment groups in the frequency of these types of events.

Dapsone, the active ingredient of Aczone, is known to be associated with hematological toxicities when taken orally. There were some associated adverse events related to the Blood and Lymphatic System and Investigations that indicate treatment-emergent changes in hematology parameters, however these occurred in only 1 subject each and were observed in subjects treated with Vehicle as well as Aczone or MetroGel. Furthermore, there were no clinical signs or symptoms reported as adverse events to correlate with these laboratory findings. This suggests that these hematology adverse events may be a chance finding. Please refer to Section 9.4 below for a more detailed discussion of the laboratory data.

### 9.2.3 Special Safety Issues: Glucose-6-Phosphate Dehydrogenase Deficiency

Subjects with G6PD-deficiency are known to be at higher risk of developing dapsone-related hematological toxicities following oral dapsone use. However, a topical mode of administration is not expected to result in systemic absorption of dapsone in sufficient amounts to result in any hematological toxicity, regardless of G6PD status. In this study, 1 subject with G6PD-deficiency was enrolled and treated with Aczone (1x/day). Subject 260080 was a 63 year old Caucasian woman with G6PD-deficiency (6.2 U/g Hgb). She used approximately 0.43 g of study treatment per application and did not report missing any applications throughout the study to completion at Week 12. When measured at Weeks 2, 4, and 12, her plasma dapsone levels were approximately 11 to 12 ng/mL and hydroxylamine levels <1 ng/mL. An examination of her laboratory data does not reveal any changes from baseline, except for slightly elevated non-fasting blood glucose at Week 4 and slightly low monocyte counts at Weeks 2 and 4 that were not deemed to be clinically significant. There were no changes in any hematological parameters. Furthermore, there were no adverse events reported indicative of systemic dapsone toxicity; only mild, transient application site adverse events were reported by this subject. Overall, there is no evidence to indicate that application of Aczone once daily to this G6PD-deficient subject resulted in any hematological toxicity.

## 9.3 Deaths, Withdrawals, and Serious or Clinically Significant Adverse Events

### 9.3.1 Deaths

No deaths occurred during the study.

### 9.3.2 Withdrawal Due to Adverse Events

Appendix E.5.4 list subjects who discontinued treatment because of adverse events. There are 6 subjects listed who only temporarily stopped the study treatment, generally due to a transient application site adverse event. This includes 3 subjects who belonged to the Vehicle Control group (065188, 083011, and 099812), 1 subject in the Aczone 2x/day group (200320), 1 subject in the Aczone 1x/day group (266191), and 1 subject in the Aczone + MetroGel group (067819). In each of these cases, subjects missed some or all applications of study treatment during the course of each adverse event, but all subjects began to re-apply the study treatment and did not permanently discontinue the study treatment or the study as a result of the adverse event. The adverse events generally resolved. There was 1 subject who experienced a systemic adverse event of muscle cramps (105308, Vehicle group) and she permanently stopped taking the study treatment as a result of this adverse event, but continued to be followed in the study. The study Investigator did not consider the muscle cramps to be related to the study treatment.

Table 26 lists the subjects who permanently discontinued treatment and the study due to an adverse event (10 subjects [2.5%]).

**TABLE 26. Subjects Who Permanently Discontinued Study Treatment and Study Follow-Up Due to Adverse Events**

| Subject Number | Age[a]/ Sex | Day of Study Discontin. | Day at Start of Event | Reported Term of Adverse Event | Intensity | Association to Treatment |
|---|---|---|---|---|---|---|
| **Vehicle Control** | | | | | | |
| 045915 | 56 / F | Day 64 | Day 14 | Increased dryness (facial) | Moderate | Suspected |
| | | | Day 14 | Increased erythema | Moderate | Suspected |
| **Aczone 2x/Day** | | | | | | |
| 080753 | 33 / F | Day 35 | Day 21 | Facial dryness | Severe | Suspected |
| | | | Day 21 | Facial itching | Severe | Suspected |
| | | | Day 21 | Facial burning | Severe | Suspected |
| | | | Day 21 | Facial stinging | Severe | Suspected |
| 091142 | 34 / F | Day 23 | Day 4 | Scaling | Moderate | Suspected |
| 261777 | 67 / F | Day 21 | Day 8 | Intense facial pruritis | Severe | Suspected |
| | | | Day 14 | Burning | Mild | Suspected |
| | | | Day 14 | Stinging | Mild | Suspected |
| 264167 | 58 / F | Day 62 | Day 3 | Shortness of breath | Mild | Not suspected |
| 277570 | 80 / M | Day 63 | Day 56 | Facial burning | Mild | Suspected |
| **Aczone 1x/Day** | | | | | | |
| 278352 | 72 / F | Day 63 | Day 14 | Facial stinging | Moderate | Suspected |
| | | | Day 56 | Facial itching | Mild | Suspected |
| | | | Day 56 | Facial burning | Moderate | Suspected |
| **Aczone + MetroGel** | | | | | | |
| 051591 | 43 / M | Day 34 | Day 14 | Itching | Mild | Suspected |
| | | | Day 14 | Increase erythema | Severe | Suspected |
| | | | Day 27 | Dryness | Mild | Suspected |
| 092225 | 77 / M | Day 23 | Day 12 | Burning | Moderate | Suspected |
| 270244 | 45 / F | Day 29 | Day 16 | Painful nodules on chin | Severe | Suspected |

[a] Age at study entry.
Source: Appendix E.1.3, E.2.1, E.5.4.

The overall rate of study discontinuation due to an adverse event was low (2.5%). There were more subjects in the Aczone 2x/day group who discontinued the study due to an adverse event than other study groups (5 subjects compared with 1 to 3 subjects for the Vehicle, Aczone 1x/day, and Aczone + MetroGel groups, respectively, and 0 subjects for the MetroGel group). Except for 1 subject, the reasons for discontinuation were application site adverse events of mostly moderate to severe intensity. Many discontinued subjects experienced multiple application site adverse events that led to discontinuation from treatment and the study. Brief descriptions of the subjects who discontinued treatment and the study due to an adverse event are provided below, and complete subject narratives are provided in Appendix C.

**Subject 045915, Vehicle;** **Application site dryness (suspected)**
**Application site erythema (suspected)**

Subject 045915 was a 56-year-old Hispanic woman who was diagnosed with papulopustular rosacea in 1998. At baseline (03 JAN 2006, Day 0), she had an IGA score of 3 (moderate) and 21 papules and pustules. Erythema was graded 1 (mild) and telangiectasia was graded 0

(absent). Local symptoms of dryness, stinging, and burning were absent and itching was moderate. At the Week 2 study visit on 17 JAN 2006 (Day 14), the subject had the following non-serious adverse events: application site dryness and application site erythema. At this visit, the local symptom score for dryness increased from baseline to moderate and the erythema score increased to moderate. The worst reported intensity of the events was moderate and they were suspected to be related to the study treatment by the Investigator. The subject stopped applying the study treatment on 19 FEB 2006 (Day 47) as a result of these adverse events, and her primary care physician prescribed oral minocycline to treat rosacea flare-up. The application site adverse events resolved on 23 FEB 2006 (Day 51), 4 days after discontinuing the study treatment. The subject discontinued the study as a result of these adverse events. Her last study contact was a telephone follow-up call on 08 MAR 2006 (Day 64).

**Subject 080753, Aczone 2x/day;** **Application site dryness (suspected)**
**Application site pruritis (suspected)**
**Application site burning (suspected)**
**Application site stinging (suspected)**

Subject 080753 was a 33-year-old Caucasian woman diagnosed with papulopustular rosacea in 2005. At baseline (31 JAN 2006, Day 0), she had an IGA score of 4 (severe) and 64 papules and pustules. Erythema was graded 2 (moderate) and telangiectasia was graded 1 (mild). Local symptoms of itching, stinging, and burning were mild and dryness was moderate. On 21 FEB 2006 (Day 21), the subject experienced severe application site dryness, pruritis, burning, and stinging. No local symptom scores are available at the time of the events. All of these non-serious adverse events were suspected to be related to the study treatment by the Investigator. The subject stopped applying the study treatment on 25 FEB 2006 (Day 25) as a result of these adverse events. The application site adverse events resolved on 06 MAR 2006 (Day 34), 9 days after discontinuing the study treatment. The subject discontinued the study as a result of these adverse events. Her last study contact was a telephone follow-up call on 07 MAR 2006 (Day 35).

**Subject 091142, Aczone 2x/day;** **Application site reaction NOS (suspected)**

Subject 091142 was a 34-year-old Hispanic woman diagnosed with papulopustular rosacea in 2003. At baseline (06 DEC 2005, Day 0), she had an IGA score of 3 (moderate) and 35 papules and pustules. Erythema was graded 3 (severe) and telangiectasia was graded 1 (mild). Local symptoms of dryness, itching, and burning were moderate and stinging was mild. On 10 DEC 2005 (Day 4), the subject began to experience scaling (MedDRA term: application site reaction NOS). The event was moderate and suspected to be related to the study treatment by the Investigator. The subject discontinued applying the study treatment on 19 DEC 2005 (Day 16). The event resolved on 19 DEC 2005 (Day 16) after discontinuing the study treatment. The subject discontinued the study as a result of this application site adverse event after her early termination study visit on 29 DEC 2005 (Day 23).

**Subject 261777, Aczone 2x/day;** **Application site pruritis (suspected)**
**Application site burning (suspected)**
**Application site stinging (suspected)**

Subject 261777 was a 67-year-old Caucasian woman diagnosed with papulopustular rosacea in 1996. At baseline (Day 0), she had an IGA score of 2 (mild) and 11 papules and pustules. Erythema was graded 2 (moderate) and telangiectasia was graded 2 (moderate). Local symptoms of itching, stinging, and burning were absent and dryness was moderate. On 14 FEB 2006 (Day 8) the subject had the non-serious event of application site pruritus. The event was severe in intensity and suspected to be related to study treatment by the investigator. On 20 FEB 2006 (Day 14), the subject had the following non-serious adverse events: application site burning and application site pain (reported as stinging). The events were mild in intensity and suspected to be related to treatment by the investigator. The subject did not apply study treatment after her last application on 19 FEB 2006 (Day 13) as a result of these adverse events. The application site adverse event of pruritus resolved on 23 FEB 2006 (Day 17), 4 days after discontinuing the study treatment. The application site adverse events of burning and stinging both resolved on 27 FEB 2006 (Day 21), 8 days after discontinuing study treatment. The subject had an early termination visit and discontinued the study as a result of these adverse events on 20 FEB 2006 (Day 14). Her last study contact was a telephone follow-up call on 27 FEB 2006 (Day 21).

**Subject 264167, Aczone 2x/day;** **Dyspnea NOS (not suspected)**

Subject 264167 was a 58-year-old Caucasian woman diagnosed with papulopustular rosacea in 1995. At baseline (Day 0), she had an IGA score of 2 (mild) and 25 papules and pustules. Erythema was graded 2 (moderate) and telangiectasia was graded 1 (mild). On 07 JAN 2006 (Day 3) the subject began to experience shortness of breath. The subject had reported no history or underlying cardiovascular or respiratory condition. The Investigator assessed this event as mild in intensity and not suspected to be related to study treatment. The subject attended Week 2 and Week 4 study visits on 18 JAN 2006 (Day 14) and 01 FEB 2006 (Day 28). The subject discontinued applying the study treatment on 16 FEB 2006 (Day 43) based on a recommendation from her primary care physician that she discontinue the study to be tested for the etiology of her dyspnea. The subject therefore had an early termination visit on 20 FEB 2006 (Day 47) and discontinued the study as a result of the non-serious adverse event of dyspnea. Clinical chemistry and hematology tests performed for the study at Week 2 (18 JAN 2006) and ET (20 FEB 2006) were within normal ranges. The last study contact with this subject was a telephone follow-up call on 07 MAR 2006 (Day 62). The event of dyspnea was still ongoing.

**Subject 277570, Aczone 2x/day;** **Application site burning (suspected)**

Subject 277570 was an 80-year-old Caucasian man diagnosed with papulopustular rosacea in 1995. At baseline (30 NOV 2005, Day 0), he had an IGA score of 2 (moderate) and 11 papules and pustules. Erythema was graded 1 (mild) and telangiectasia was graded 2 (moderate). Local symptoms of dryness and itching were mild while stinging and burning were absent. At the Week 2 study visit on 14 DEC 05 (Day 14) the subject had worsening

application site erythema and telangiectasia. Both events were severe in intensity and suspected to be related to the treatment by the study Investigator. The subject continued in the study to Week 4. At the Week 4 study visit on 28 DEC 05 (Day 29), the adverse event of telangiectasia had resolved and the subject had a new onset adverse event of application site dryness. Dryness was moderate in intensity and suspected to be related to the treatment by the study investigator. The subject continued in the study. On 25 JAN 2006 (Day 56), the subject experienced application site burning that was mild in intensity and suspected to be related to the study treatment. The subject discontinued applying the study treatment as a result of the application site adverse event of burning on 25 JAN 2006 (Day 56). The subject discontinued the study on 01 FEB 2006 (Day 63). The application site adverse events of erythema, dryness, and burning were ongoing.

**Subject 278352, Aczone 1x/day;** **Application site stinging (suspected)**
**Application site pruritis (suspected)**
**Application site burning (suspected)**

Subject 278352 was a 72-year-old Caucasian woman diagnosed with papulopustular rosacea in 1995. At baseline (30 NOV 2005, Day 0), she had an IGA score of 2 (mild) and 11 papules and pustules. Erythema was graded 2 (moderate) and telangiectasia was graded 3 (severe). Local symptoms itching, stinging, and burning were absent and dryness was mild. At the Week 2 study visit on 14 DEC 2005 (Day 14), the subject had application site stinging. The local symptom score for stinging increased to mild while other local symptoms remained the same as baseline. The adverse event of stinging was mild in intensity and suspected to be related to the study treatment by the Investigator. On 25 JAN 2006 (Day 56), the subject had application site pruritis and application site burning. Local symptom scores for dryness and itching were mild and for stinging and burning were moderate. The events of stinging and burning were moderate while pruritus was mild, and all events were suspected to be related to the study treatment by the Investigator. The subject discontinued applying the study treatment as a result of all 3 of these application site adverse events. The last study treatment was applied on 24 JAN 2006 (Day 55) in the PM. The application site adverse events resolved on 31 JAN 2006 (Day 62), 7 days after discontinuing the study treatment. The subject discontinued the study as a result of all of these application site adverse events. The last study contact with this subject was a telephone follow-up call on 01 FEB 2006 (Day 63).

**Subject 051591, Aczone + MetroGel;** **Application site pruritis (suspected)**
**Application site erythema (suspected)**
**Application site dryness (suspected)**

Subject 051591 was a 43-year-old Hispanic man diagnosed with papulopustular rosacea in 1996. At baseline (Day 0), he had an IGA score of 3 (moderate) and 36 papules and pustules. Erythema was graded 2 (moderate) and telangiectasia was graded 2 (moderate). Local symptoms of dryness, itching, stinging, and burning were absent. At the Week 2 study visit on 22 FEB 2006 (Day 14), the subject had the following non-serious adverse events: application site pruritis and application site erythema. The local symptom score for itching at this visit was increased to mild and the erythema score was increased to severe. The intensity of application site pruritis was mild and of application site erythema was severe. The adverse

events were suspected to be related to the study treatment by the Investigator. The subject stopped applying the study treatment on 02 MAR 2006 (Day 22) as a result of these adverse events. At the ET visit on 07 MAR 2006, the subject's local symptom score for dryness increased to mild from absent at baseline. An adverse event of application site dryness, with mild intensity and suspected relationship to treatment was reported. The application site adverse event of erythema resolved on 07 MAR 2006 (Day 27), 5 days after discontinuing the study treatment. The subject's primary care physician prescribed MetroGel®, 1.0% on 10 MAR 2006 (Day 30). The subject discontinued the study as a result of the application site adverse events. His last study contact was a telephone follow-up call on 14 MAR 2006 (Day 34). The adverse events of application site reaction NOS and application site pruritis were ongoing.

**Subject 092225, Aczone + MetroGel; Application site burning (suspected)**

Subject 092225 was a 77-year-old Caucasian man diagnosed with papulopustular rosacea in 2004. At baseline (Day 0), he had an IGA score of 3 (moderate) and 21 papules and pustules. Erythema was graded 3 (severe) and telangiectasia was graded 2 (moderate). Local symptoms of dryness and itching were moderate, stinging was mild, and burning was absent. On 19 DEC 2005 (Day 12), the subject began to experience application site burning. Local symptom scores at the time of the event are not available. The adverse event was moderate and suspected to be related to the study treatment by the Investigator. The subject discontinued applying the study treatment as a result of this application site adverse event on 20 DEC 2005 (Day 13). The subject discontinued the study as a result of this application site adverse event after his ET study visit on 30 DEC 2005 (Day 23). The adverse event had resolved on 30 DEC 2005 (Day 23).

**Subject 270244, Aczone + MetroGel; Nodule (suspected)**

Subject 270244 was a 45-year-old Hispanic woman diagnosed with papulopustular rosacea in 2000. At baseline (Day 0), she had an IGA score of 2 (mild) and 17 papules and pustules. Erythema was graded 2 (moderate) and telangiectasia was graded 2 (moderate). Local symptom scores of stinging and burning were mild, itching was moderate, and dryness was absent. At the Week 2 study visit on 14 DEC 2005 (Day 15), the subject had an adverse event of application site dryness, reported as moderate in intensity and suspected to be related to the study treatment by the Investigator. The local symptom score for dryness at this visit increased to moderate from absent at baseline, whereas the local symptom score for itching decreased to mild from moderate at baseline. The subject continued to apply the study treatment. On DEC 15 2005 (Day 16), the subject began to experience painful nodules on her chin. The event was severe and suspected to be related to the study treatment by the Investigator. The subject discontinued applying the study treatment on 15 DEC 2005 (Day 16) as a result of the adverse event of nodule and discontinued the study after her telephone follow-up call on 28 DEC 2005 (Day 29).

### 9.3.3 Serious Adverse Events

One subject, who was enrolled in the Aczone + MetroGel treatment group, reported a serious adverse event of appendicitis, which was not suspected to be related to study treatment; a brief summary of this event is provided below. Refer to Appendix C.2 for a full narrative of this subject.

**Subject 236353, Aczone + MetroGel; Appendicitis (not suspected)**

Subject 236353 was a 53-year-old Caucasian woman with a medical history of hypercholesterolemia (since 1997), hypertension (since 1998), and heel pain (since 2005). She was taking Atenolol, Atorvastatin, Estrogen, Celebrex, and Ranitidine at baseline. On 23 MAR 2006 (D78), the patient was admitted to hospital for appendicitis. She underwent an appendectomy. On 25 MAR 2006 (D80), the event was considered resolved. The Investigator assessed this event as severe in intensity and not suspected to be related to study treatment. This was the only adverse event she reported during the study. The subject applied her last study treatment on 27 MAR 2006 (Day 82) and completed the study to the Week 13 telephone follow-up on 03 APR 2006 (Day 89).

## 9.4 Laboratory Data

### 9.4.1 Laboratory Values Over Time

Clinical chemistry and hematology parameters were measured at baseline, Week 2, Week 4, and Week 12. They are summarized in Appendix A.4.6.1 and Appendix A.4.6.2 and listed by subject in Appendix E.5.7 and Appendix E.5.8. The hematology and chemistry parameters that are important indicators of potential hematological toxicity are presented in Table 27.

**TABLE 27. Selected Hematology and Chemistry Parameters**

| Laboratory Test | | 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) |
|---|---|---|---|---|---|---|
| **Hemoglobin (g/L)** | | | | | | |
| Baseline | Mean | 141.0 | 143.2 | 141.9 | 142.1 | 142.7 |
| | SD | 15.1 | 14.5 | 14.0 | 13.1 | 11.9 |
| Week 2 | Mean | 140.5 | 142.4 | 140.1 | 140.5 | 140.5 |
| | SD | 14.9 | 14.8 | 14.1 | 14.0 | 12.1 |
| Week 12 | Mean | 139.0 | 142.6 | 140.0 | 140.9 | 140.4 |
| | SD | 14.2 | 13.6 | 13.6 | 12.2 | 11.1 |
| **Hematocrit (V/V)** | | | | | | |
| Baseline | Mean | 0.412 | 0.419 | 0.414 | 0.417 | 0.415 |
| | SD | 0.040 | 0.041 | 0.038 | 0.037 | 0.032 |
| Week 2 | Mean | 0.411 | 0.417 | 0.410 | 0.412 | 0.411 |
| | SD | 0.041 | 0.041 | 0.039 | 0.039 | 0.033 |
| Week 12 | Mean | 0.411 | 0.422 | 0.414 | 0.417 | 0.414 |
| | SD | 0.039 | 0.038 | 0.039 | 0.034 | 0.033 |
| **Reticulocytes (%)** | | | | | | |
| Baseline | Mean | 0.96 | 1.06 | 1.01 | 1.03 | 1.06 |
| | SD | 0.49 | 0.44 | 0.43 | 0.61 | 0.47 |
| Week 2 | Mean | 0.96 | 1.08 | 1.05 | 1.08 | 1.09 |
| | SD | 0.47 | 0.42 | 0.49 | 0.59 | 0.48 |
| Week 12 | Mean | 1.10 | 1.27 | 1.16 | 1.16 | 1.28 |
| | SD | 0.49 | 0.50 | 0.55 | 0.62 | 0.55 |
| **Total Bilirubin (umol/L)** | | | | | | |
| Baseline | Mean | 8.9 | 9.2 | 9.0 | 9.1 | 8.7 |
| | SD | 4.7 | 6.2 | 5.9 | 6.5 | 3.9 |
| Week 2 | Mean | 8.9 | 9.4 | 8.4 | 8.6 | 8.6 |
| | SD | 4.1 | 5.6 | 5.0 | 6.4 | 3.9 |
| Week 12 | Mean | 8.7 | 8.6 | 9.8 | 9.7 | 8.8 |
| | SD | 4.6 | 5.1 | 5.6 | 5.5 | 3.8 |
| **Haptoglobin (g/L)** | | | | | | |
| Baseline | Mean | 1.29 | 1.38 | 1.40 | 1.45 | 1.50 |
| | SD | 0.58 | 0.52 | 0.63 | 0.60 | 0.63 |
| Week 2 | Mean | 1.37 | 1.43 | 1.37 | 1.35 | 1.46 |
| | SD | 0.73 | 0.55 | 0.60 | 0.53 | 0.56 |
| Week 12 | Mean | 1.30 | 1.42 | 1.35 | 1.35 | 1.53 |
| | SD | 0.63 | 0.54 | 0.63 | 0.59 | 0.62 |
| **LDH (IU/L)** | | | | | | |
| Baseline | Mean | 173.5 | 174.7 | 174.0 | 173.8 | 177.0 |
| | SD | 28.4 | 39.1 | 32.4 | 32.9 | 34.4 |
| Week 2 | Mean | 180.0 | 178.4 | 171.6 | 167.7 | 171.0 |
| | SD | 37.8 | 47.5 | 29.9 | 36.5 | 31.5 |
| Week 12 | Mean | 173.4 | 173.5 | 171.9 | 177.1 | 176.9 |
| | SD | 39.9 | 39.7 | 34.6 | 32.0 | 32.6 |

Source: Appendix A.4.6.1, A.4.6.2.

The study treatment groups had similar mean values for hemoglobin, hematocrit, red blood cells, mean corpuscular volume, mean corpuscular hemoglobin, reticulocyte count, total bilirubin, haptoglobin, or LDH between baseline and Week 12. There were no overall changes in any chemistry or hematology parameter observed during the study.

### 9.4.2 Individual Subject Changes

Overall shifts in laboratory parameters are summarized in Appendices A.4.6.3 and A.4.6.4. In general, there were few shifts from normal in laboratory parameters. Where shifts from normal were observed, they were noted in a small number of subjects (1 to 3 per group) and did not display any dependence on time point in the study or treatment group assignment. There were no trends in laboratory parameter shifts.

Subjects who experienced a clinically significant change in a laboratory parameter had the change reported as an adverse event, therefore clinically significant changes are summarized under the Investigations System Organ Class in Appendix A.4.5.1. Appendix E.5.7 and E.5.8 lists the laboratory values for all subjects and Table 28 lists those individual subjects who had a clinically significant laboratory value reported as an adverse event during the study. Laboratory normal ranges are provided in Appendix D.8.

**TABLE 28. Subjects With A Clinically Significant Change in a Laboratory Parameter**

(Page 1 of 2)

| Subject | Parameter | Baseline Value | Clin. Signif. Value (Study Day) | Follow-up Value (Study Day) | AE Relationship to Study Treatment |
|---|---|---|---|---|---|
| **Vehicle Control** | | | | | |
| 105308 | LDH IU/L (high) | 202 | 466 (Day 41/ET) | Unknown | Not suspected |
| | Haptoglobin g/L (high) | 2.2 | 3.1 (Day 16) | 3.5 (Day 41/ET) | Not suspected |
| | Neutrophil $x10^9$/L (high) | 5.30 | 19.59 (Day 41/ET) | Unknown | Not suspected |
| | WBC count $x10^9$/L (high) | 7.6 | 23.6 (Day 41/ET) | Unknown | Not suspected |
| | Morphology | Normal | Anisocytosis 1+, Burr cells, Poikilocytosis 1+ (Day 41/ET) | Unknown | Not suspected |
| 108279 | Haptoglobin g/L (high) | 2.2 | 3.5 (Day 19) | 2.7 (Day 25)<br>4.0 (Day 81) | Suspected |
| 177713 | WBC count $x10^9$/L (low) | 5.4 | 2.6 (Day 14/ET) | Unknown | Suspected |
| | Morphology | Normal | Anisocytosis +1 (Day 14/ET) | Unknown | Suspected |
| 191301 | Non-fasting glucose mmol/L (low) | 5.6 | 3.3 (Day 15) | 7.1 (Day 29)<br>3.6 (Day 85) | Not suspected |
| **Aczone 2x/Day** | | | | | |
| 068772 | ALT IU/L (high) | 27 | 215 (Day 28) | 30 (Day 84) | Not suspected |
| | Alkaline phosphatase IU/L (high) | 59 | 114 (Day 28) | 74 (Day 84) | Not suspected |
| | AST IU/L (high) | 25 | 149 (Day 28) | 24 (Day 84) | Not suspected |
| 086598 | Non-fasting glucose mmol/L (high) | 8.8 | 10.3 (Day 14) | 4.3 (Day 27)<br>7.4 (Day 33)<br>7.6 (Day 84) | Not suspected |
| | Potassium mmol/L (high) | 4.3 | 6.7 (Day 27) | 4.3 (Day 33)<br>4.5 (Day 84) | Not suspected |
| 101440 | ALT IU/L (high) | 55 | 61 (Day 83) | Unknown | Not suspected |
| 151806 | Non-fasting glucose mmol/L (high) | Missing[a] | 14.5 (Day 28) | 8.7 (Day 91) | Not suspected |
| | Hematocrit V/V (high) | 0.52 | 0.56 (Day 28) | 0.46 (Day 91) | Not suspected |
| | Hemoglobin g/L (high) | 176 | 186 (Day 28) | 157 (Day 91) | Not suspected |
| | Haptoglobin g/L (high) | Missing[a] | 3.0 (Day 28) | 2.0 (Day 91) | Not suspected |
| | RBC count $x10^{12}$/L (high) | 5.5 | 5.9 (Day 28) | 4.9 (Day 91) | Not suspected |
| 205413 | Non-fasting glucose mmol/L(high) | 15.3 | 21.2 (Day 15) | 15.9 (Day 29)<br>22.0 (Day 85) | Not suspected |
| 257947 | Bilirubin µmol/L(high) | 31 | 38 (Day 14) | 36 (Day 17)<br>43 (Day 28)<br>36 (Day 84) | Not suspected |

[a] Sample could not be analyzed by laboratory.
ET: Early termination.
Source: Appendix E.5.2, E.5.7, E.5.8.

**TABLE 28. Subjects With A Clinically Significant Change in a Laboratory Parameter**

(Page 2 of 2)

| Subject | Parameter | Baseline Value | Clin. Signif. Value (Study Day) | Follow-up Value (Study Day) | Relationship to Study Treatment |
|---|---|---|---|---|---|
| **Aczone 1x/Day** | | | | | |
| 171324 | Neutrophil x$10^9$/L (low) | 1.61 | 0.98 (Day 33) | 2.39 (Day 36)<br>2.63 (Day 82) | Not suspected |
| 175392 | Lymphocytes x$10^9$/L (low) | 1.57 | 1.43 (Day 28) | 1.52 (Day 38)<br>1.42 (Day 87) | Not suspected |
| | Neutrophil x$10^9$/L (low) | 3.35 | 0.26 (Day 28) | 3.2 (Day 38)<br>4.26 (Day 87) | Not suspected |
| | Monocytes x$10^9$/L (high) | 0.33 | 0.40 (Day 28) | 0.38 (Day 38)<br>0.34 (Day 87) | Not suspected |
| | WBC count x$10^9$/L (low) | 5.4 | 2.2 (Day 28) | 5.2 (Day 38)<br>6.1 (Day 87) | Not suspected |
| | Morphology | Normal | Burr cells, Poikilocytosis 1+ (Day 28) | Normal (Day 38)<br>Normal (Day 87) | Not suspected |
| 287710 | Non-fasting glucose mmol/L (high) | Missing[a] | 9.2 (Day 84) | 6.2 (Day 119) | Suspected |
| | Hematocrit V/V (low) | 0.37 | 0.34 (Day 84) | 0.35 (Day 119) | Suspected |
| | Hemoglobin g/L (low) | 124 | 114 (Day 84) | 117 (Day 119) | Suspected |
| **MetroGel** | | | | | |
| 011900 | Non-fasting glucose mmol/L (high) | 13.2 | 21.6 (Day 28) | 6.1 (Day 84) | Not suspected |
| 061018 | Morphology | Normal | Burr cells (Day 28) | Normal (Day 36)<br>Normal (Day 91) | Not suspected |
| 102187 | Platelets x$10^9$/L (low) | 167 | 133 (Day 14) | 115 (Day 28)<br>143 (Day 84) | Not suspected |
| 258623 | ALT IU/L (high) | 20 | 103 (Day 29) | 66 (Day 85) | Not suspected |
| | AST IU/L (high) | 17 | 113 (Day 29) | 46 (Day 85) | Not suspected |
| **Aczone + MetroGel** | | | | | |
| 059850 | Eosinophil x$10^9$/L (high) | 0.58 | 0.99 (Day 28) | 0.83 (Day 84) | Not suspected |
| 084267 | Non-fasting glucose mmol/L (high) | 9.1 | 9.8 (Day 14) | 9.2 (Day 28)<br>9.2 (Day 83) | Not suspected |
| 089647 | WBC count x$10^9$/L (low) | 6.4 | 2.5 (Day 15) | 6.2 (Day 28)<br>6.9 (Day 84) | Not suspected |
| 176525 | Eosinophil x$10^9$/L (high) | 0.38 | 2.70 (Day 26) | 0.28 (Day 89) | Not suspected |
| 256887 | Alkaline phosphatase IU/L (high) | 131 | 133 (Day 28) | 129 (Day 35)<br>132 (Day 84) | Not suspected |
| | ALT IU/L (high) | 31 | 39 (Day 28) | 30 (Day 35)<br>22 (Day 84) | Not suspected |
| | AST IU/L (high) | 22 | 32 Day 28) | 20 (Day 35)<br>17 (Day 84) | Not suspected |

[a] Sample could not be analyzed by laboratory.
Source: Appendix E.5.2, E.5.7, E.5.8.

Most of the individual clinically significant changes in laboratory parameters were considered not suspected to be related to the study treatment; only 3 subjects had clinically significant changes in laboratory values that were suspected to be related the study treatment, including 2 subjects who were treated with vehicle. The third subject was treated with Aczone 1x/day (287710) and experienced high non-fasting glucose, low hematocrit, and low

hemoglobin at Day 84 of the study. These parameters were only slightly outside of the normal ranges (3.6-7.7 for glucose, 116-162 for hemoglobin, 0.35-0.47 for hematocrit) and resolved upon retest on Day 119. There were no abnormal clinical signs accompanying these mildly abnormal laboratory values.

### 9.4.3 Clinically Significant Abnormalities

Table 28 above lists subjects that had a clinically significant change in a chemistry or hematology parameter during the study. There were no trends in the types of parameters that were found to be clinically significant; the same parameter was high in some subjects but low in others and clinically significant abnormalities were found to be present in vehicle-treated and MetroGel-treated subjects as well as Aczone-treated subjects. The majority of clinically significant abnormalities were not considered to be related to the study treatment by the respective study investigators.

## 9.5 Vital Signs and Other Physical Findings

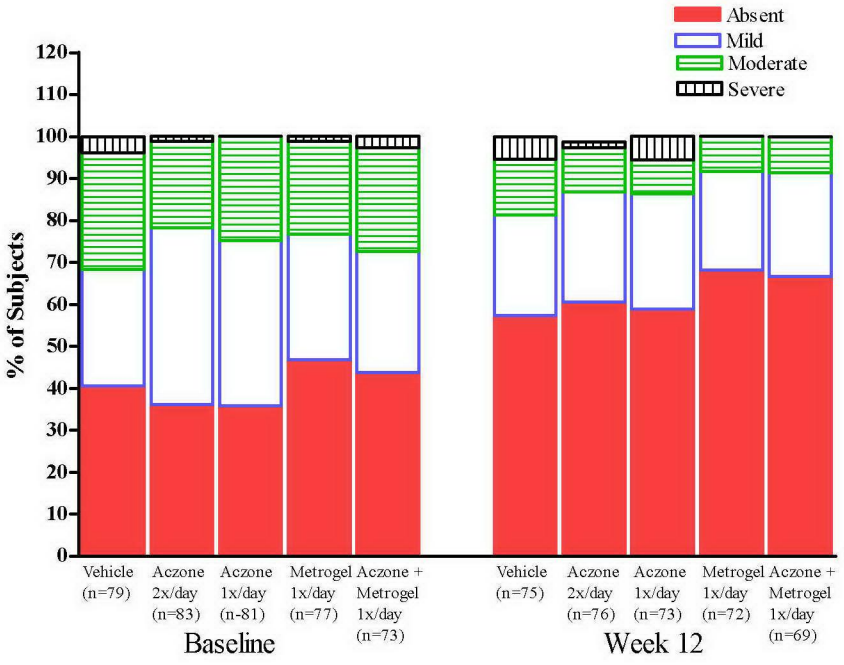
Vital signs (blood pressure, body temperature, heart rate, and respiratory rate) are summarized in Appendix A.4.7 and listed by subject in Appendix E.5.10. Mean vital signs were within normal ranges at all time points in the study and did not vary notably from baseline.

With respect to adverse events related to abnormal vital signs, 4 subjects were diagnosed with pyrexia (1.0%: Subjects 145833, 155904, 255560, and 188986) and 2 subjects (0.5%: Subjects 147030 and 160326) were diagnosed with hypertension after enrolling in the study. None of these events were considered related to study treatment. Adverse events are listed by subject in Appendix E.5.2.

## 9.6 Local Symptom Scores

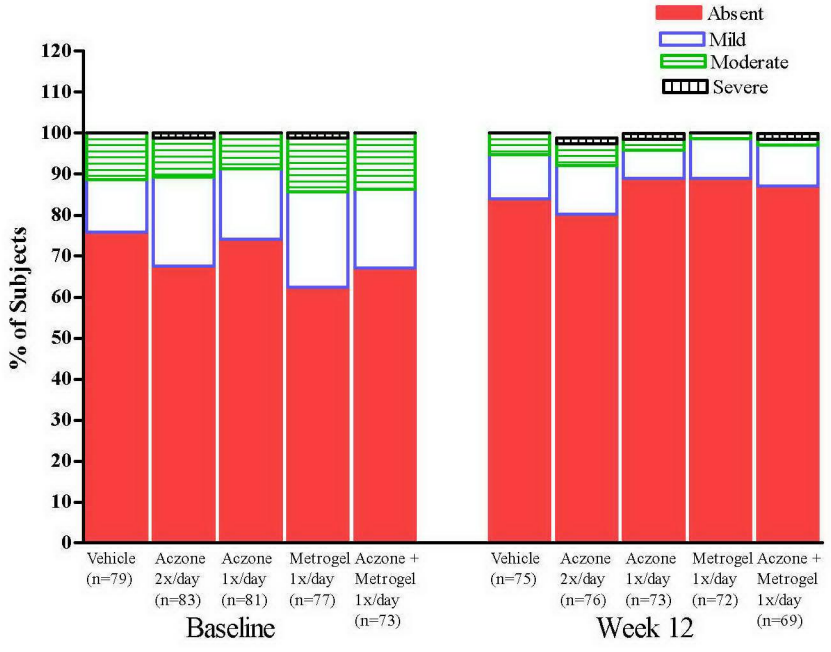
Local symptom scores for each of dryness, itching, stinging, and burning are summarized in Appendix A.4.8 and listed by subject in Appendix E.5.11. Figures 6, 7, 8, and 9 depict the distribution of local symptom scores at baseline and Week 12.

**FIGURE 6. Symptom Scores for Dryness at Baseline and Week 12**



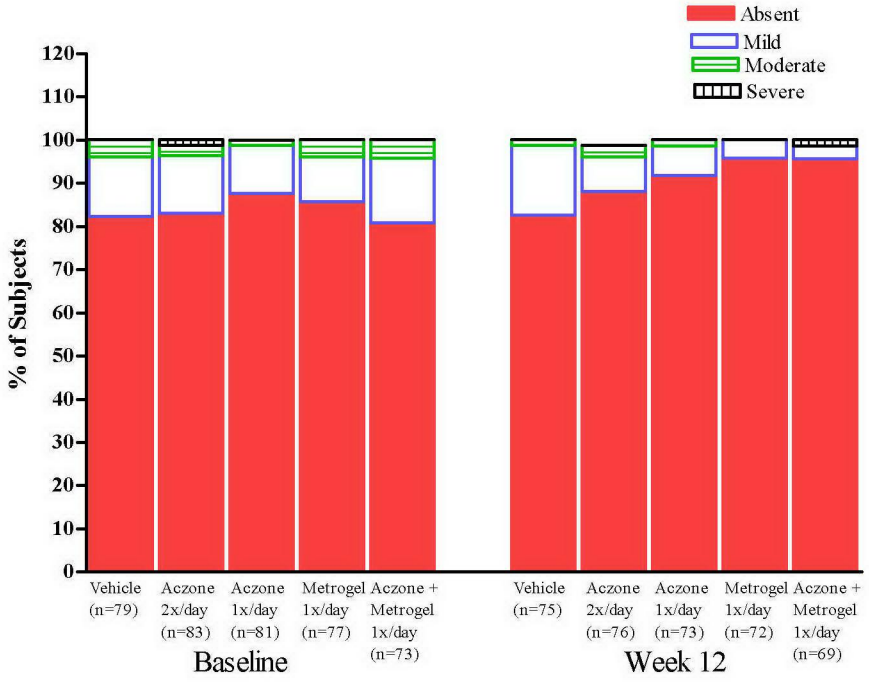

Source: Appendix A.4.8.

**FIGURE 7. Symptom Scores for Itching at Baseline and Week 12**



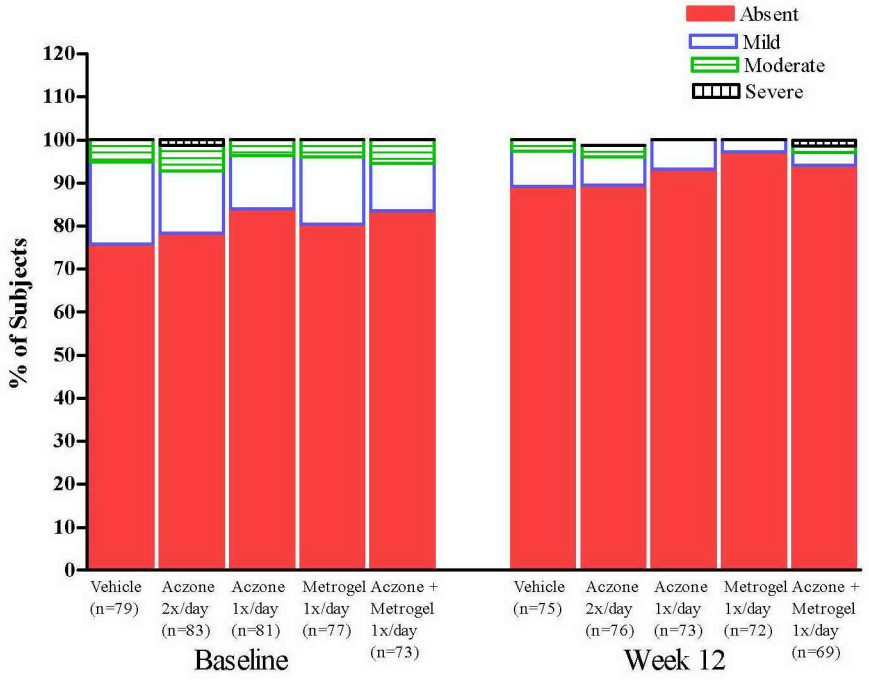

Source: Appendix A.4.8.

**FIGURE 8. Symptom Scores for Stinging at Baseline and Week 12**




Source: Appendix A.4.8.

**FIGURE 9. Symptom Scores for Burning at Baseline and Week 12**




Source: Appendix A.4.8.

Dryness was the most prevalent symptom at baseline, with approximately 60% of subjects having at least mild dryness present. There were 36.1% to 46.8% of subjects with dryness absent at baseline, 62.3% to 75.9% of subjects with absent itching, 80.8% to 87.7% of subjects with absent stinging, and 75.9% to 84% with absent burning. For all local symptoms, the number of subjects with scores of "absent" generally increased for all study groups as the study progressed, suggesting an overall improvement in rosacea local symptoms with time in all study treatment groups.

Conversely, the proportion of subjects with a severe local symptom score was low (≤5%) for all symptoms at both baseline and throughout the study. There did not appear to be any increase in the proportion of subjects with severe local symptoms as the study progressed, nor was there any difference among treatment groups.

## 9.7 Discussion of Safety Results

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 the study treatment (Aczone + MetroGel) and does not indicate a safety concern for the use of Aczone in subjects with papulopustular rosacea.

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 improvement 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.

Systemic exposure to dapsone and its metabolites was low at all time points in the study. These observations were consistent with the observations made in previous studies of subjects with acne vulgaris. This finding corroborates the low incidence of systemic adverse

events with Aczone use and supports the safety of using Aczone in subjects with papulopustular rosacea

## 10 DISCUSSION AND OVERALL CONCLUSIONS

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. Efficacy results in subjects who entered the study with ≥ 20 inflammatory lesions demonstrated a potential benefit of Aczone 2x/day treatment over VC. These data coupled with the benign safety profile indicate a favorable benefit risk ratio in this population with larger numbers of lesions at baseline. Further studies evaluating subjects with papulopustular rosacea with ≥20 inflammatory lesions appear to be warranted.

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. However, subjects who entered the study with worse disease (i.e., ≥20 inflammatory lesions) did demonstrate a potential benefit from Aczone treatment 2x/day over vehicle, which was consistent with the use of MetroGel in this study as well as historical data for other active rosacea treatments.
- The local tolerability and efficacy profile of Aczone used twice-daily was better than Aczone used once-daily. Both dosage regimens demonstrated low systemic exposure to dapsone and few systemic adverse events.

## 11 REFERENCES

1. Wilkin J, Dahl M, Detmar M, et al. Standard classification of rosacea: report of the national rosacea society expert committee on the classification and staging of rosacea. J Am Acad Dermatol. 2002;46(4):584-7.

2 . Sibenge S and Gawkrodger DJ. Rosacea: a study of clinical patterns, blood flow, and the role of *Demodex follicularum*. J Am Acad Dermatol. 1992;26:590-593.

3 . Dahl, MV. Rosacea subtypes: a treatment algorithm. Cutis. 2004;74 (suppl 3):21-27.

4 Zhu YI, Stiller MJ. Dapsone and sulfones in dermatology: overview and update. J Am Acad Dermatol. 2001; 45:420-34.

5 Bormann G, Gaber M, Fischer M, and Marsch WC. Dapsone in Rosacea Fulminans. J Eur Acad Derm. 2001;15:465-467

6 Bose SK. Association of Melkersson-Rosenthal Syndrome with Rosacea. J Derm. 1996;23:902-904.

7. Krause MH, Torricelli R, Kundig T, Trueb RM, Hafner J. Dapsone in granulomatous rosacea [in German]. Der Hautarzt. 1997;48(4):246-248.

8. Del Rosso JQ, Wolf JE, Jr., Leyden J, Millikan LE, Odom RB, Shalita A. The treatment of rosacea. Cutis. 2004;73(1 Suppl):34-6.

9. Shalita A, Leyden J. Mechanism-based selection of pharmacologic agents for rosacea. Cutis. 2004;73(1 Suppl):15-18.

10. Pelle MT. Rosacea therapy update. Adv Dermatol. 2003;19:139-170.

11. Wilkin J, Dahl M, Detmar M, et al. Standard grading system for rosacea: report of the national rosacea society expert committee on the classification and staging of rosacea. J Am Acad Dermatol. 2004;50(6):907-912.

12 Thiboutot D, Thieroff-Ekerdt R, Graupe K. Efficacy and safety of azelaic acid (15%) gel as a new treatment for papulopustular rosacea: results from two vehicle-controlled, randomized phase III studies. J Am Acad Dermatol. 2003;48(6):836-45.

13. MetroGel® (metronidazole gel), 1.0%. Package Insert. Galderma Laboratories, June 2005.

14. Finacea® (azelaic acid gel), 15%. Package Insert. Intendix, May 2005.

15. Oracea™ (doxycycline, USP capsules), 40 mg. Package Insert. CollaGenex. May 2006.

# APPENDICES

## APPENDIX A — SUMMARY TABLES AND GRAPHS

## APPENDIX E — INDIVIDUAL DATA LISTINGS

**E.1 Disposition and Baseline Data Listings**
E.1.1 Compliance with Inclusion/Exclusion Criteria
E.1.2 Listing Per Protocol Exclusions
E.1.3 Listing of Subject Visit Dates
E.1.4 Listing of Early Termination/Study Completion
E.1.5 Listing of Study Blind Information
E.1.6 Listing of Principal Investigator's Statement
E.1.7 Listing of Changes to Cosmetics, Cleansers, and Moisturizers
E.1.8 Listing of General Comments

**E.2 Demographics and Baseline Data Listings**
E.2.1 Listing of Demographics
E.2.2 Listing of Medical History and Underlying Medical Conditions

**E.3 Efficacy Data Listings**
E.3.1 Listing of Investigator's Global Assessment
E.3.2 Listing of Inflammatory Lesion Counts
E.3.3 Listing of Erythema and Telangiectasia Assessments

**E.4 Treatment Exposure**
E.4.1 Listing of Study Treatment Dispensed/Returned
E.4.2 Listing of First Treatment Date and Missed Applications
E.4.3 Listing of Plasma Dapsone, N-acetyl Dapsone, and N-hydroxlamine Dapsone Concentration Levels
E.4.4 Listing of Most Recent Application and Blood Draw Dates and Times
E.4.5 Listing of Study Treatment Use

**E.5 Safety Data Listings**
E.5.1 Listing of Concomitant Medications
E.5.2 Listing of All Adverse Events
E.5.3 Listing of Adverse Events Leading to Death
E.5.4 Listing of Adverse Events Leading to Discontinuation from Study Treatment
E.5.5 Listing of Serious Adverse Events
E.5.6 Glossary of All Reported Adverse Events Grouped by MedDRA System Organ Class, Preferred Term, and Lower Level Term
E.5.7 Listing of Laboratory Values – Hematology
E.5.8 Listing of Laboratory Values – Chemistry
E.5.9 Listing of Laboratory Values – G6PD Test
E.5.10 Listing of Vital Signs
E.5.11 Listing of Local Symptoms Assessment