<table>
<thead>
<tr>
<th>Name of Company:</th>
<th>Name of Finished Product:</th>
<th>Name of Active Ingredient:</th>
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</thead>
<tbody>
<tr>
<td>Allergan</td>
<td>Aczone™</td>
<td>Dapson Gel, 5%</td>
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</tbody>
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**Number and Title of Study:**
DAP0407: A Phase 3, Randomized, Double-Blind, Multi-Dose Study to Evaluate the Safety and Efficacy of 5% Dapsone Topical Gel, (DTG 5%) When Co-Administered With Vehicle Control, Adapalene Gel 0.1% or Benzoyl Peroxide Gel 4% in the Treatment of Acne Vulgaris

**Study Center(s):** 30 centers in the United States

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

**Studied Period:**
- Study Initiation Date (First Subject Screened): 02 February 2005
- Study Completion Date (Last Subject Completed): 11 July 2005

**Phase of Development:** 3

**Objectives:**
- To compare the safety and efficacy of DTG 5% twice daily in combination with once daily vehicle, adapalene gel 0.1%, or benzoyl peroxide gel 4%.
- To determine dapsone exposure after co-administration of DTG 5% with vehicle, adapalene gel 0.1%, or benzoyl peroxide gel 4%.

**Methodology:**
- **Structure:** Randomized, double-blind, multi-dose study
- **Randomization:** Randomized in a 1:1:1 ratio to receive DTG 5% twice daily + vehicle once daily, DTG 5% twice daily + adapalene gel 0.1% once daily, or DTG 5% twice daily + benzoyl peroxide gel 4% once daily
- **Visit Schedule:** Screening, Baseline (Day 0), Week 2, 4, 8, and Week 12/Early Termination (ET)

**Number of Subjects (Planned and Analyzed):**
A total of 301 subjects were enrolled in this study, with 103 subjects enrolled in the DTG 5% + vehicle group, 100 subjects enrolled in the DTG 5% + adapalene gel 0.1% group, and 98 subjects enrolled in the DTG 5% + benzoyl peroxide gel 4% group.

**Diagnosis and Main Criteria for Inclusion:**
- **Diagnosis:** Acne vulgaris of the face
- **Key Inclusion Criteria:** ≥12 years of age, a diagnosis of acne vulgaris of the face, a minimum of 20 inflammatory lesions (pustules and papules) and 20 non-inflammatory lesions (comedones) above the mandibular line at baseline
- **Key Exclusion Criteria:** Use of topical agents for acne within 14 days of baseline and throughout the study; light therapies, systemic medications, or skin treatments known to affect acne or inflammatory responses within the 28 days prior to baseline and throughout the study; received isotretinoin (Accutane®) within the 3 months prior to baseline and throughout the study; severe cystic acne or acne conglobata; and active or developing nodules above the mandibular line at baseline

**Test Product, Dose and Mode of Administration:**
DTG 5% was applied in a thin layer to a clean face twice a day, once in the morning and once in the evening.
Name of Company: Allergan
Name of Finished Product: Aczone™
Name of Active Ingredient: Dapson Gel, 5%

Duration of Treatment: 12 weeks

Reference Therapy, Dose and Mode of Administration:
The vehicle used for this study was Cetaphil® Daily Facial Moisturizer SPF 15, which was commercially supplied by Galderma Laboratories (Fort Worth, TX).

The adapalene gel used for this study was Differin® (adapalene gel) Gel, 0.1%, which was commercially supplied by Galderma Laboratories (Fort Worth, TX).

The benzoyl peroxide used in this study was Brevoxyl®-4 Gel (benzoyl peroxide 4%), which was commercially supplied by Stiefel Laboratories (Coral Gables, FL).

Criteria for Evaluation:
Efficacy: The primary efficacy evaluation was the mean percent reduction from baseline in inflammatory lesion counts at Week 12/ET. Secondary efficacy evaluations included: mean percent reduction from baseline in non-inflammatory and total lesion counts; Success rate, defined as a score of none (0) or minimal (1) based on a static 5-point Global Acne Score Assessment (GAAS) after 12 weeks of treatment; and analyses of inflammatory, non-inflammatory, and total acne lesion counts.

Safety: Safety was assessed based on reported adverse events (AEs), including local adverse reactions, concomitant medications, and results from physical examinations.

Statistical Methods:
The safety analysis set included all included all subjects who received at least one dose of study treatment or reported an AE, the ITT analysis set included all subjects who were dispensed study treatment.

The primary endpoint in this study was the percent reduction from baseline in inflammatory lesion counts (papules and pustules) at Week 12/ET for the DTG 5% + vehicle, DTG 5% + adapalene gel 0.1%, and DTG 5% + benzoyl peroxide gel 4% treatment groups. Percent reduction in inflammatory lesion counts was summarized for each treatment group at Weeks 2, 4, 8, and 12/ET.

The percent reduction in non-inflammatory (comedones) lesion counts was analyzed in the same manner as the secondary analysis of percent reduction in inflammatory lesion counts. The percent reduction in total (inflammatory and non-inflammatory) lesion counts was analyzed in the same manner as the secondary analysis of percent reduction in inflammatory lesion counts.

Success on the GAAS was defined as a score of 0 (none) or 1 (minimal) on the GAAS at Week 12/ET. Because most study centers randomized fewer than 15 total subjects, the effect of centers was considered negligible. Therefore, the percentage of subjects categorized as "Successful" for each treatment group was compared using pair-wise chi-square tests. This analysis was performed on the ITT data set. GAAS was summarized for each treatment group at Weeks 2, 4, 8, and 12/ET.

The counts for inflammatory, non-inflammatory, and total acne lesions were analyzed in the same manner as the secondary analysis of percent reduction in acne lesion counts. This analysis was performed on the ITT data set. The reduction from baseline for inflammatory, non-inflammatory, and total acne lesion counts was analyzed in the same manner as the secondary analysis of the percent reduction in acne lesion counts. This analysis was performed on the ITT data set.

An overall safety summary of the number and percentage of subjects who experienced any AE, any local adverse reaction, death, a SAE, or discontinued due to an AE was provided by treatment group.
Summary – Conclusions:

Efficacy:
The results of this study demonstrated that DTG 5% in combination with adapalene gel 0.1% or benzoyl peroxide gel 4% was effective for the treatment of acne vulgaris when applied according to the product labeling. Efficacy was shown to be somewhat better for the DTG 5% + adapalene gel group compared to the DTG 5% + vehicle group.

For the primary efficacy evaluation, DTG 5% in combination with either adapalene gel or benzoyl peroxide gel had a numerically better response than DTG 5% + vehicle, but the differences were not significant ($P=0.0519$ and $P=0.0523$, respectively). The mean percent reductions of inflammatory lesions for subjects in the adapalene gel, benzoyl peroxide gel, and vehicle groups were 57.3%, 57.5%, and 49.2%, respectively.

For the secondary efficacy evaluations, DTG 5% + adapalene gel had a significantly better response than DTG 5% + vehicle for both non-inflammatory (46.6% vs. 30.3%, $P=0.0005$) and total acne lesion counts (50.6% vs. 39.3%, $P=0.0041$). Though not significant, DTG 5% in combination with benzoyl peroxide gel was numerically better than DTG 5% + vehicle for both these lesion count parameters.

Subjects treated with DTG 5% + adapalene gel had a significantly higher incidence of Success (none or minimal disease at the end of treatment) based on the static GAAS than subjects treated with DTG 5% + vehicle (43.0% vs. 29.1%, $P=0.0395$).

Overall, efficacy was observed as early as Week 2 and showed further improvement throughout the 12-week study period.

The results from this study show that DTG 5% in combination with a retinoid therapy such as adapalene gel provides a better outcome than DTG 5% alone in the treatment of acne vulgaris.

Safety:
A total of 301 subjects participated in this study and received treatment with 1 of 3 combination therapies. The safety results indicate that acne treatment with DTG 5% + adapalene gel 0.1% and DTG 5% + benzoyl peroxide gel 4% was safe and very well tolerated.

The incidence of treatment-emergent AEs overall, irrespective of the relationship to study treatment, was 34.6%. The most common AEs reported were nasopharyngitis (4.5%), application site burning (4.1%), and upper respiratory tract infection (3.1%). These events were generally mild in severity and rarely led to treatment discontinuation. There were no SAEs or subject deaths in this study.

The majority of AEs were considered by the Investigator to be unrelated to study treatment. Of the 101 AEs reported in the study, only 30 (10.3%) were considered associated to study treatment. The most common AEs included application site burning (4.1%), drug interaction NOS (2.4%), and application site pruritus (2.1%).

Seven subjects (7.4%) who were treated with DTG 5% + benzoyl peroxide gel experienced a drug interaction during the study. These drug interactions were reported to be application site events and involved a temporary orange or yellow discoloration of the skin or facial hair. These events were generally mild in severity and most resolved after 4 to 57 days.

Local adverse reactions were minimal and were generally mild in severity. Dryness, erythema, oiliness, and peeling (events specifically elicited at each visit) were all more common at baseline than during the study. There were no differences in the local adverse reactions rates between the treatment groups.
## Conclusion:
The results of this study support the following conclusions:

- A trend in mean percent reduction of inflammatory lesions from baseline was observed for DTG 5% in combination with either adapalene gel or benzoyl peroxide gel, but the differences between these study treatments and DTG 5% + vehicle were not significant.

- DTG 5% + adapalene gel had significantly better responses compared to DTG 5% + vehicle for the mean percent reduction in both non-inflammatory and total acne lesion counts.

- DTG 5% in combination with adapalene gel had a significantly higher incidence of Success (none or minimal disease at the end of treatment) based on the static GAAS compared to DTG 5% combined with vehicle.

- Improvements in acne were observed as early as Week 2, with further improvement throughout the study.

- Few subjects discontinued the study because of treatment-related AEs.

- Seven benzoyl peroxide gel-treated subjects experienced a drug interaction during the study. The interactions involved a temporary orange or yellow discoloration of the skin or facial hair, which was likely related to the bleaching properties associated with benzoyl peroxide.

- The combination treatments with adapalene gel and vehicle were well tolerated and did not demonstrate any safety concerns. No apparent differences were observed between DTG 5% alone or in combination with benzoyl peroxide gel.

- This study shows low systemic exposure without accumulation following twice-daily application of DTG 5%.

In conclusion, the results of this study demonstrate that DTG 5% in combination with adapalene gel 0.1% or benzoyl peroxide gel 4% is safe and well tolerated for the treatment of acne vulgaris when applied according to the product labels.