

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-794

MEDICAL REVIEW

Clinical Team Leader Interdisciplinary Summary
NDA 21-794 ACZONE (dapson) Gel, 5%

June 29, 2005

The Clinical Team Leader concurs with the Primary Clinical Reviewer, as per her careful review, that this application for ACZONE (dapson) Gel, 5%, for the treatment of acne vulgaris should be approved. Certain specific issues regarding the nature of this product have arisen during review and discussion about ACZONE Gel, 5% with other review disciplines. The intent of this brief review is to summarize these concerns.

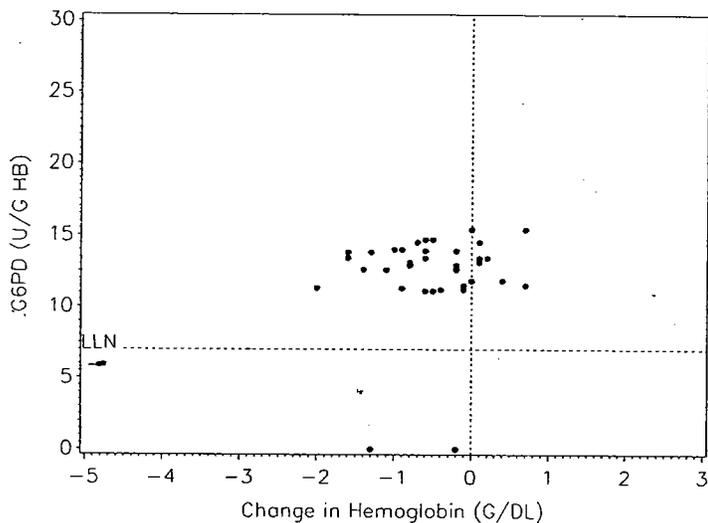
Safety of Drug Product

The main issue of discussion with the applicant for labeling was whether patients to be treated with ACZONE Gel, 5%, should have glucose 6-phosphate dehydrogenase (G6PD) and complete blood count evaluations. This evaluation of safety was approached by the clinical team from two main avenues.

The first approach was whether there was a potential for adverse events given the level of systemic exposure of dapson with this topical product. The clinical team expected a low level of exposure relative to the oral form of this drug and this was confirmed by the FDA clinical pharmacologist, Dr. Tapash Ghosh. Following this line of thought, what is the threshold level of dapson exposure that would lead to a concern (i.e., for hemolysis). Given prior clinical experience with dapson, a lower threshold of dapson exposure could be concern for sensitive individuals (e.g., G6PD deficient patients and methemoglobin reductase deficient patients according to the oral dapson label). The applicant was asked this question directly, but was unable to answer this definitively. In fact, the data provided by the sponsor regarding ACZONE Gel treated patients in their study DAP0110 suggest a drop in hematocrit (see graph below). The drop in hematocrit was attributed by the applicant to be possibly due to loss of blood from blood draws. It is not clear to this reviewer that the amount of blood drawn for this study would lead to such a drop in hematocrit. The sponsor had not provided any supportive evidence (e.g., placebo treated patients and their change in hemoglobin with the same amount of blood draws). Loss of blood due to hemolysis remains a viable explanation for these changes.

It will be important to have any further studies conducted to carefully address this by evaluating dapson levels along with documenting changes in hematocrit, reticulocyte count, and other hematologic parameters.

Change in Hemoglobin from Baseline by G6PD Activity in Study DAP0110 (Amend 15)



LLN = Lower Limit of Normal

The second approach was a data driven analysis of patients exposed to topical dapsons and a separate evaluation of G6PD deficient patients.

As was noted by the Primary Reviewer, the monitoring for dapsons related hemolysis was not the most careful or thorough (for example, reticulocyte counts were not available for all patients with complete blood counts and dapsons levels were available for very few patients).

A well known fact regarding dapsons hemolysis is that patients with glucose 6-phosphate dehydrogenase deficiency are more sensitive to the oxidative stress and dapsons related hemolysis. The applicant did not enroll adequate numbers of subjects with glucose 6-phosphate dehydrogenase (G6PD) deficiency in the clinical studies to be able to make reasonable conclusions about the safety of ACZONE Gel in this population. Only 25 G6PD deficient subjects were treated with ACZONE were enrolled in the clinical studies.

For this reason, the label should include the concerns in the PRECAUTIONS and INDICATIONS AND USAGE sections outlining this concern and informing practitioners to obtain G6PD levels and baseline CBC prior to treatment with ACZONE Gel, 5%. Additionally, a post-marketing commitment to evaluate the safety in sufficient numbers of G6PD deficient patients is recommended by the Primary Reviewer. The clinical TL is in agreement with such a required commitment.

Carcinogenicity

The current oral dapsone label states that dapsone is a carcinogen, but was based on older data than what was submitted to this NDA.

The pharmacologist/toxicologist, Dr. Norman See, states in his review that dapsone is not carcinogenic in rats, nor was there evidence of any potential to induce carcinogenicity in a 26 week dermal study conducted in Tg.AC mice. In addition, dapsone topical gel did not increase the rate of formation of UV induced skin tumors when applied topically to hairless mice in a 12-month photocarcinogenicity study.

This assessment of lack of carcinogenicity was based on review of the latest proprietary studies conducted by this applicant.

Efficacy and Risk vs. Benefit

This product appears to have limited efficacy as per the observed difference in efficacy vs. vehicle in the two pivotal studies conducted. However, this difference is statistically significant (see Dr. Kathy Fritsch's statistics review). The benefit achieved with this product may be relatively small but appear in the estimate of this reviewer to be sufficient to counter the perceived risks associated with the use of this product. The somewhat unknown risks of use in the G6PD deficient population will be mitigated by the recommended closer monitoring of the patients' hematocrit and the language in the labeling proposed.

Mechanism of Action

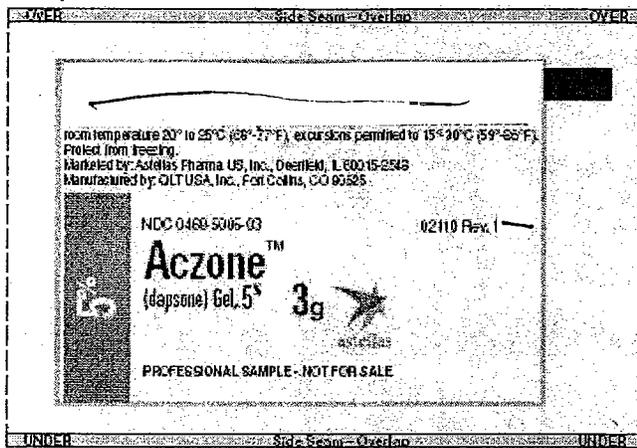
The mechanism of action of dapsone for the treatment of acne vulgaris has been postulated to be via an anti-inflammatory mechanism of some sort. However, this has not been adequately characterized nor its clinical relevance evaluated.

A non-committal attempt by the applicant at evaluating the anti-microbial effect of dapsone on acne was conducted (see Clinical Microbiology review by Mr. Harold Silver). There is not sufficient evidence submitted in the NDA to introduce any information regarding anti-microbial claims into labeling.

Chemistry, Manufacturing, and Controls Concerns

- 1) A sample of the drug product was sent to the Agency by the applicant. On evaluation, the substance was gritty with crystals or particles dispersed in the gel. According to the CMC review, these particles are drug substance (dapsone). Discussion regarding this aspect of the product was held between CMC, Biopharm, and Clinical reviewers. It was determined that this product's grittiness, while possibly a reflection of poor formulation design, did not impact safety and effectiveness so long as the marketed product met the same specifications on particle size distribution as the product that was investigated in the clinical and pharmacokinetic studies.

- 2) The product packaging (container) is translucent to light. Apparently, the drug substance is also photolabile. This apparently was not well-thought out by the applicant. Recommending that the drug product be placed into the opaque cardboard container each time after use appears to be a stop gap measure until a better product with an opaque container is used. Apparently, the professional sample tube is opaque and will not need to be placed in a light-tight box. According to the Chemistry reviewer, Mr. Ernie Pappas, having a marketed product placed in a larger tube of the same material as the professional sample tube would not require extensive regulatory evaluation.
- 3) The applicant stated they had produced at their own risk approximately _____ professional sample tubes with labeling prior to Agency evaluation and approval (see graphic below).



This is acceptable from a clinical perspective for a one time exception for this current printed batch of 3 gram physician samples only. The next printing or in 6 months, which ever comes first, should use the approved label.

Pediatric Waiver Request

The applicant requested a pediatric waiver for subjects under that age of 12. While acne does occur in patients younger than age 12, a waiver to study patients with acne younger than age 12 has been routinely granted for products intended to treat acne. No extenuating circumstances exist with regard to this product from our review so granting of a waiver appears to be reasonable.

Conclusion

Thus, in conclusion, this NDA is recommended for approval with the labeling that addresses the concerns described above (see Primary Clinical Review) and with the post-marketing commitment to address the need for additional safety data in G6PD deficient patients.

Markham C. Luke, M.D., Ph.D.
Lead Medical Officer, Dermatology

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this page is the manifestation of the electronic signature.**

/s/

Markham Luke
6/30/05 09:03:25 AM
MEDICAL OFFICER

Interdisciplinary summary for NDA

Stanka Kukich
7/5/05 10:56:16 AM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 20, 2005

TO: Frank Cross
Project Manager
DDDDP, HFD-540

FROM: George Shashaty, M.D.
Acting Medical Team Leader, Hematology
Division of Gastrointestinal and Coagulation Drug Products
HFD-180

THROUGH: Kathy Robie Suh, M.D., Ph.D.
Acting Division Deputy Director
Division of Gastrointestinal and Coagulation Drug Products
HFD-180
and
Joyce Korvick, M.D.
Acting Division Director
Division of Gastrointestinal and Coagulation Drug Products
HFD-180

SUBJECT: **Consultation Review**
NDA 21-794 5%Dapsone Topical Gel (Atrix Laboratories)

Dapsone Oral Tablet (4,4'-diaminodiphenylsulfone, DDS) is chemically classified as a sulfone. Dapsone is approved for the indications of dermatitis herpetiformis and leprosy. The sponsor is developing a topical formulation for use in patients with acne vulgaris.

The review division asks the following question: "Do you have any safety concerns with the topical application of dapsone gel for the treatment of acne vulgaris based on the data (see attached) submitted as described in this NDA application? Is the patient population adequate?"

Background

The Division of Dermatological and Dental Drug Products (HFD-540) had previously consulted the Division of Gastrointestinal and Coagulation Drug Products (HFD-180) regarding a lower

threshold for dapsone levels causing hemolytic crisis in glucose-6-phosphate dehydrogenase (G6PD)-deficient patients. The consult was completed by Kathy Robie-Suh, M.D., Ph.D. and is dated March 29, 2004. The conclusion was that there was no known absolute lower threshold for serum dapsone serum levels at which hemolysis did not occur in G6PD deficient individuals even though the degree of hemolysis may be related to dose.

Dapsone belongs to the sulfone class of drugs. The administration of dapsone is associated with a dose dependent hemolytic process that is most likely related to metabolites of dapsone (particularly the N-hydroxylamine product) rather than to the parent compound. The metabolites interfere with the pathway that includes glucose, G6PD, NADPH and reduced glutathione in a series of linked reactions that provide hydrogen ions to maintain the iron in hemoglobin in its reduced Fe^{2+} (functional) state. The inability to generate hydrogen ions converts the iron in hemoglobin to its oxidized Fe^{3+} (non-functional) state thereby producing methemoglobin.

G6PD deficiency is the most common of the inherited disorders that involve this pathway. G6PD deficiency is inherited as a sex-linked recessive characteristic, and is present in greater frequencies in populations derived from certain geographic areas (Africa, the Mediterranean, Southeast Asia) although it has been described in many ethnic groups. G6PD deficiency is not a single genetic defect, but comprises a host of variants, each with its specific structural, biological and clinical characteristics. Most variants cause few, if any, problems. Some are associated with a chronic hemolytic process. The most common variants, however, are clinically inapparent until the host is exposed to an oxidizing challenge, most often in the form of a drug, but also associated with various infections, favism and neonatal jaundice. Under these circumstances, the G6PD mediated H^+ production from the conversion of glucose-6-phosphate to 6-phosphogluconic acid is insufficient to provide adequate reducing capability to maintain hemoglobin iron in the Fe^{2+} state. This leads to methemoglobinemia, hemoglobin precipitation within the red cell (Heinz bodies), pitting of Heinz bodies in the spleen (bite cells) and hemolysis. The degree of hemolysis is quite variable, from mild to severe, and usually self-limited because young red cells, even in G6PD deficient individuals, contain more of the enzyme than do old red cells. Clinical findings are usually commensurate with the degree of hemolysis. These range from asymptomatic jaundice to severe anemia. Although uncommon, renal failure, death and the need for transfusions may occur.

For the indication of dermatitis herpetiformis, the initial recommended dose of dapsone for adults is 50 mg daily with a titration upward to 300 mg daily to control symptoms. Doses greater than 300 mg daily are permissible. Therapy has extended for up to 9 years. For the indication of leprosy, the recommended dose is 100 mg daily (in combination with rifampin) with the length of treatment potentially lasting the patient's lifetime. Hemolysis due to dapsone is a well known complication of treatment of these disorders. In one retrospective study of 138 patients diagnosed with methemoglobinemia, dapsone was the proximate cause in 42% of patients. In one series of 100 patients with leprosy treated with approximately 100 mg of dapsone daily, the average fall in hemoglobin was almost 2 gm/dl. These events occurred in both normal and G6PD deficient patients, but were more marked in the latter.

The agent in question is 5%DapsoneTopical Gel. The sponsor is developing this agent for the topical therapy of acne vulgaris because dapsone has both anti-infective and anti-inflammatory

properties. It is believed that topical delivery to the skin lesions would avoid the systemic toxicity of the orally administered preparation. Whether or not the topical preparation will cause hemolysis in the population with acne vulgaris depends on several factors:

- The total dose applied to the body.
- The transdermal absorption of the drug.
- The metabolic mechanics in the individual patient.
- The presence or absence of G6PD deficiency.
- The specific nature of the G6PD deficiency, if present.
- Additional circumstances (e.g., the use of other oxidizing agents, the presence of infection, etc).

Materials Reviewed

The following were included:

- Protocol DAP0114, entitled "A 12 Month, Multicenter, Open-Label, Non-Comparative Design Study of 5% Dapsone Topical Cream in Patients with Acne Vulgaris". Date 2/21/05.
- Report entitled "Hematological Effects of Oral and Topical Dapsone in Subjects with Normal and Reduced Glucose-6-Phosphate Dehydrogenase Activity". Date 3/4/05.
- 5% Dapsone Topical Gel. Module 2.5 Clinical Overview. Date 4/8/05 (Amended).

Review

Protocol DAP0114. Enrollment was begun on January 24, 2002 and a total of 506 patients were entered on to the protocol. Two hundred seventy five were females and 231 were males. There were 403 whites, 48 black, 36 Hispanic, 9 Asians and 10 "other". The mean age was 20.3 years (range 12-77). Concomitant medications used commonly included hormonal contraceptives, ascorbic acid, anti-inflammatory and anti-rheumatic products.

5%Dapsone Topical Gel (DTG) was applied twice daily as needed to acne involved areas for a mean of 253 days with a mean number of applications of 491 over the study period. The average daily use of DTG was 1.35 g (median, 1.07; range, 0.0-11.02). Adverse events and laboratory studies were performed at baseline and at months 1, 3, 4, 6, 9 and 12. In a subset of patients, laboratory studies were also performed at weeks 1 and 2. G6PD deficiency was not an exclusion criterion in the study, and there was no specific instruction to elicit a history of G6PD during screening. A Letter of Clarification, dated May 20, 2002, mandated a G6PD evaluation on all patients at the 6 month visit. No subjects had completed the trial prior to the issuance of the Letter of Clarification.

There were no patient deaths in the study. Five patients experienced one or more treatment – emergent serious adverse events, none of which were believed related to the drug, was considered life threatening or led to drug discontinuation. Eleven patients had an adverse event

that led to discontinuation of the drug. Ten of these were application site events. One patient developed nausea, weakness and dizziness on day 2 of treatment and discontinued treatment on day 4. No patients were discontinued from the study because of the development of anemia.

The mean plasma dapsonе concentrations ranged between 7.5 and 10.98 ng/ml (maximum, 49.26-107.01), and the mean plasma n-acetyl dapsonе concentrations ranged between 2.96 and 4.49 ng/ml (maximum, 11.65-70.11) throughout the study. There was a linear relationship between the plasma levels of dapsonе and n-acetyl dapsonе ($R^2 = 0.5639$). Plasma levels of dapsonе following topical application for acne vulgaris are approximately 100-fold lower than those seen following the oral administration of 100 mg of dapsonе.

The following table shows the hematology values for all patients over the course of the trial.

Table Q. Summary Statistics for Hematology Parameters

| Parameter | Mean (\pm SD) | | |
|--------------------------------------|--|--|--|
| | Baseline (N=481) | Month 1 (N=458) | Month 12 (N=336) |
| Hematocrit (%) | 42.53 (\pm 3.98) Range 25.10–55.20 | 41.78 (\pm 3.87) Range 27.50–55.00 | 42.31 (\pm 4.25) Range 26.60–54.50 |
| Hemoglobin (g/dL) | 14.23 (\pm 1.40) Range 7.70–18.90 | 13.97 (\pm 1.37) Range 7.60–18.80 | 14.00 (\pm 1.50) Range 7.40–17.90 |
| Red blood cells ($10^6/\mu$ L) | 4.78 (\pm 0.48) Range 2.81–6.33 | 4.70 (\pm 0.46) Range 3.18–6.00 | 4.75 (\pm 0.49) Range 3.03–6.27 |
| White blood cells ($10^3/\mu$ L) | 7.22 (\pm 1.96) Range 2.50–15.50 | 7.02 (\pm 1.88) Range 2.50–13.70 | 7.10 (\pm 2.01) Range 2.70–18.80 |

Patient base: safety-evaluable dataset

Source: Table 19

SD = standard deviation; N = number of patients

The results for the subset of patients who had evaluations at weeks 1 and 2 were similar. Most of the subjects maintained their hemoglobin/hematocrit within the strata in which they entered the study for the duration of the study. A small percent (1-3%) had a decline within the normal range or to a slightly lower than normal value while a slightly smaller percent (0-1%) had an increase within the normal range at various times over the course of the study.

Seventeen subjects experienced a fall in hemoglobin ≥ 2 g/dl at some point during the course of the study. In 11, only a single lowered hemoglobin occurred during the course of the study. In 12, despite the fall, the hemoglobin remained within the normal range. Sixteen of these subjects were white and one Hispanic. In 3 subjects, 3 or more values for hemoglobin were ≥ 2 g/dl lower than baseline. They are described as follows:

- Subject #1303. A 43 year old menstruating female whose hemoglobin fell progressively from 13.4 to 9.3 g/dl. She had a history of menorrhagia and metrorrhagia. Her MCV fell from 90.8 at baseline to 72.3 at month 12. Her bilirubin and LDH level remained normal

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throughout the study. Her G6PD assay was 14.1 (normal). It is unlikely that she had a hemolytic process.

- Subject #1403. A 14 year old female whose hemoglobin fell from 15.5 at baseline to 12.5 at month 6 with an increase to 13.5 at month 12. Her bilirubin and LDH level remained normal throughout the study. Her G6PD assay was 12.1 (normal). There was no apparent explanation for the fall in hemoglobin.
- Subject #1821. An 18 year old male whose hemoglobin fell from 17.9 g/dl at baseline to 15.5 g/dl at month 3 and remained at that level for the remainder of the study. His bilirubin and LDH levels were normal throughout the course of the study. His G6PD assay was 10.2 (normal).

Subjects who had a decline of ≥ 2 g/dl in hemoglobin are listed in the table below.

Table S. Summary of Hemoglobin Levels ≥ 2 g/dL Lower than Baseline at Any Study Time Point

| Patient No. | Gender | Laboratory Values | | | | | | |
|-------------|--------|-------------------|--------|-------------------|---------------------|---------------------|---------------------|--------------------|
| | | Analysis | BL | Month 1 | Month 3 | Month 6 | Month 9 | Month 12/ET |
| 0730 | Male | HGB (g/dL) | 17.3 | 15.9 | 15.4 | 15.6 | 15.3 ^a | 14.3 ^a |
| | | Dapsone (ng/mL) | < 0.05 | 7.56 | 0.71 | 39.03 | 23.41 | 37.79 |
| 0802 | Female | HGB (g/dL) | 15.1 | 15.4 | 15.2 | 12.7 ^a | 14.1 | 11.9 ^a |
| | | Dapsone (ng/mL) | < 0.05 | 17.09 | 21.69 | 19.12 | 12.62 | 2.96 |
| 0915 | Male | HGB (g/dL) | 15.6 | 14.5 | 13.2 ^a | 14.0 | 13.9 | 14.2 |
| | | Dapsone (ng/mL) | < 0.05 | 8.24 | 7.51 | 2.02 | 1.00 | 7.78 |
| 1015 | Female | HGB (g/dL) | 13.1 | 12.8 | 11.0 ^a L | NA | NA | NA |
| | | Dapsone (ng/mL) | < 0.05 | 0.89 | 1.30 | NA | NA | NA |
| 1303 | Female | HGB (g/dL) | 13.4 | 12.5 | 11.3 ^a L | 10.6 ^a L | 10.1 ^a L | 9.3 ^a L |
| | | Dapsone (ng/mL) | < 0.05 | 6.90 | 14.43 | 14.22 | 10.94 | 0.49 |
| 1315 | Male | HGB (g/dL) | 16.3 | 13.6 ^a | 15.9 | 15.8 | 16.9 | 16.4 |
| | | Dapsone (ng/mL) | < 0.05 | 2.49 | 22.39 | 0.17 | 4.68 | < 0.05 |
| 1318 | Male | HGB (g/dL) | 13.6 | 13.9 | 11.4 ^a L | 13.4 | 13.6 | 13.2 |

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| Patient No. | Gender | Laboratory Values | | | | | | |
|-------------|--------|-------------------|--------|-----------------------------|----------------------------|---------------------|-------------------|-------------------|
| | | Analysis | BL | Month 1 | Month 3 | Month 6 | Month 9 | Month 12/ET |
| | | Dapsone (ng/mL) | < 0.05 | 22.59 | 22.29 | 3.01 | 0.09 | 0.09 |
| 1319 | Female | HGB (g/dL) | 14.4 | 13.5 | 13.0 | 13.2 | 12.4 ^a | 13.6 |
| | | Dapsone (ng/mL) | < 0.05 | 6.57 | 6.61 | < 0.05 | 0.18 | 4.67 |
| 1409 | Female | HGB (g/dL) | 15.5 | 14.1 | 14.4 | 12.5 ^a | 13.2 ^a | 13.5 ^a |
| | | Dapsone (ng/mL) | < 0.05 | 7.54 | 7.48 | 15.73 | NA | NA |
| 1414 | Male | HGB (g/dL) | 15.6 | 13.3 ^a | 15.0 | 14.5 | 14.2 | 14.5 |
| | | Dapsone (ng/mL) | < 0.05 | 45.63 25.22 ^b | 7.91 35.72 ^b | NA | NA | NA |
| 1507 | Male | HGB (g/dL) | 14.0 | 13.5 | 13.8 | 12.0 ^a L | 13.8 | 14.4 |
| | | Dapsone (ng/mL) | < 0.05 | 4.26 | 0.37 | 0.49 | < 0.05 | < 0.05 |
| 1710 | Male | HGB (g/dL) | 16.1 | 14.6 | 15.7 | 14.8 | 15.3 | 14.0 ^a |
| | | Dapsone (ng/mL) | < 0.05 | 8.93 | 9.46 | 7.68 | 13.46 | 9.58 |
| 1718 | Female | HGB (g/dL) | 15.1 | 14.7 | 13.4 | 13.7 | 13.6 | 13.0 ^a |
| | | Dapsone (ng/mL) | < 0.05 | 4.79 | 0.57 | 7.47 | 3.55 | 2.63 |
| 1738 | Female | HGB (g/dL) | 13.8 | 13.5 | 13.7 | 11.8 ^a | 13.1 | 13.2 |
| | | Dapsone (ng/mL) | < 0.05 | 0.16 | 3.29 | < 0.05 | 2.82 | 0.49 |
| 1821 | Male | HGB (g/dL) | 17.9 H | NA | 15.5 ^a | 15.4 ^a | 15.7 ^a | 15.7 ^a |
| | | Dapsone (ng/mL) | < 0.05 | 0.11 | 0.23 | 1.33 | < 0.05 | 3.43 |
| 1848 | Female | HGB (g/dL) | 14.9 | 12.8 ^a | 13.9 | 14.2 | 12.4 ^a | 13.6 |
| | | Dapsone (ng/mL) | 0.12 | 22.87 | 13.04 | 22.96 | 16.61 | 25.26 |
| 1920 | Female | HGB (g/dL) | 14.4 | 13.1 | 12.9 | 12.8 | 13.1 | 12.4 ^a |
| | | Dapsone (ng/mL) | < 0.05 | 8.61 | 2.04 | 0.11 | 0.46 | 0.18 |

Patient base: all-patient dataset

Source: Appendices 2.4.1, 2.6.2, 2.7.8, and 7.11

BL = Baseline; ET = early termination; NA = Not available; L = below normal range;

H = above normal range

Note: Normal HGB range was 12.3–17.0 g/dL for 12 to 17-year-old males, 13.0–17.5 g/dL for 18 to 65-year-old males, and 11.6–16.2 g/dL for 12 to 65-year-old females.

^a HGB value decreased by ≥ 2 g/dL from Baseline.

^b Values from a laboratory retest which resulted in an unscheduled plasma dapsone result.

Five of 358 patients assayed were G6PD deficient. Four were females whose G6PD assay values were typical for the heterozygote state. The one male was severely deficient (G6PD assay, 1.0; normal, 7.0-20.5) as would be expected. Hematology results for G6PD deficient patients, along with plasma dapsone levels are shown in the following table.

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Table R. Hemoglobin and Plasma Dapsone Levels for G-6-PD Deficient Patients

| Patient No. | Gender | Age (years) | Dapsone Level (ng/mL) | Hemoglobin (g/dL) | | | |
|-------------|--------|-------------|-----------------------|-------------------|---------|---------|----------|
| | | | | Baseline | Month 1 | Month 6 | Month 12 |
| 0317 | Male | 12 | < 0.05–8.37 | 13.2 | 12.8 | 13.2 | 13.1 |
| 1215 | Female | 22 | < 0.05–14.99 | 12.2 | 12.6 | 11.9 | 12.4 |
| 1312 | Female | 16 | < 0.05–18.27 | 12.5 | 12.0 | 12.6 | 13.0 |
| 1314 | Female | 21 | < 0.05–63.35 | 12.9 | 13.5 | NA | 13.5 |
| 1424 | Female | 29 | < 0.05–31.92 | 13.3 | 14.0 | 13.9 | 12.1 |

Patient base: all-patient dataset

Source: Appendices 2.4.1, 2.62, and 2.7.8

NA = Not available

The changes appear to be within the range of those expected in individuals who have repeat hemoglobin testing performed over a period of months. Bilirubin and LDH levels remained normal for all five subjects throughout the course of the trial.

Hematological Effects of Oral and Topical Dapsone in Subjects with Normal and Reduced Glucose-6-Phosphate Dehydrogenase Activity. In this document, the sponsor extracts data the literature and from more than 4000 subjects who have been enrolled in trials in the clinical development program for topical dapsone. The extracted data were analyzed in response to the reviewing division's requests for information related to the systemic absorption from DTG and the hematological effects of DTG. The information can be summarized as follows:

1. There is a linear relationship between an oral dose of dapsone and its plasma levels. At doses of 50 and 100 mg, plasma levels are approximately 800 and 2,000 ng/ml. Repeat dosing results in some degree of accumulation, increasing plasma concentrations by about 50%.
2. The degree of methemoglobinemia that develops at an oral dose of 100mg of dapsone in persons with a normal G6PD level is clinically insignificant. Methemoglobinemia typically develops at a dose of approximately 200 mg of dapsone, and is seen in almost all persons at a dose of 200-300 mg per day. In persons with leprosy treated with 100 mg of dapsone plus 600 mg of rifampin daily, 83 % had a ≥ 1 g/dl fall in hemoglobin over four months.
3. In persons with very low levels of G6PD (approximately 7 % of normal), a reduced hematocrit and red cell survival occurred generally at oral doses of approximately 50 mg of dapsone. In patients with leprosy and G6PD deficiency, treatment with 100 mg of dapsone caused infrequent or mild hemolysis.
4. In a pharmacokinetic study comparing the oral administration of 100 mg of dapsone and the twice daily application of DTG to 22.5% of the body surface, the ratio of the C_{max} and the AUC for dapsone and its primary metabolite were approximately 70:1 and over 100:1, respectively. To achieve plasma levels associated with the administration of a single 100 oral dose, 280 grams of DTG would have to be applied per day. The

application of this amount of gel is not feasible. As noted above, the mean dose was 1.35 g daily with a maximum of 11 g daily.

5. A total of 25/1834 (1.36%) patients treated with DTG were determined to have quantitative G6PD deficiency in 4 studies conducted by the sponsor (Studies DAP0110, 0114, 0203 and 0204). In 2 of these 25 patients, the G6PD deficiency was severe (less than 15% normal). These are further described:
 - PT# DAP0110-0103, a 32 year old white male with a G6PD level of <1.0 U, was treated with DTG for 14 days in a pharmacokinetic study. Maximum plasma dapsone level was 25.1 ng/ml. His hemoglobin fell from 14.3 to 13 over the two week period of treatment and his reticulocyte count increased from 103,000 to 146,000 x 10⁹/L (nl, 40,000-100,000 x 10⁹/L). His bilirubin was 0.5 mg/dl prior to treatment and 0.9mg/dl on day 14. His LDH level was 282 and 253 U/L on day 1 and 14, respectively. During this time, multiple phlebotomies for research testing were performed.
 - PT# DAP0114-0317, a 12 year old black male, with a G6PD level of 1.0 U, was treated with DTG for 12 months. Maximum plasma dapsone level was 8.4 ng/ml. His hemoglobin, total bilirubin and LDH remained within normal limits throughout the entire course of the trial.
- Two other patients treated with DTG (#DAP0114-1424 and DAP0204-375422) had moderate G6PD deficiency. In both individuals, the hemoglobin, bilirubin and LDH remained reasonably stable. In the first person, there was a single raised LDH (423 u/L) at month 12 that occurred in association with an episode of influenza and pancreatitis. In the second person, the bilirubin was raised on entry into the study and he was subsequently diagnosed as having Gilbert's disease. No evidence of hemolysis was observed in the remaining 21 persons with G6PD deficiency. Based on limited data, mean plasma levels of dapsone were somewhat higher during the 1st and 3rd month of topical therapy in G6PD deficient persons compared to normals, but were similar at 6, 9 and 12 months.
6. There is a slight, clinically insignificant decrease in hemoglobin in persons treated with DTG which is not correlated with plasma dapsone concentrations. Limited data suggest that persons with G6PD deficiency do not react differently from normal individuals.
 7. Persons with and without G6PD deficiency have similar changes in hemoglobin levels independent of the total quantity of DTG used.
 8. Methemoglobin measured in a phase II study (DAP9903) of DTG was undetectable although the G6PD status of the subjects was not known.

Clinical Overview. This is a summary of the all of the studies performed during the clinical program development. There is no additional information provided that adds to the two studies reviewed above.

Conclusions and Recommendations

The sponsor has provided both data generated from its own studies and information from the literature that supports the contention that the topical application of DTG for the treatment of acne vulgaris is unlikely to produce hemolysis in persons with G6PD deficiency. There is no information available to determine the effects of the topical application of DTG in persons with rarer genetic abnormalities, such as methemoglobin reductase or the congenital methemoglobinemias, in which the oxidant stress of dapsonone and its metabolite may also induce methemoglobinemia.

Despite this documentation, there are several caveats that should be taken into account before completely absolving this drug from any hematological adverse events. These include:

1. The sponsor's studies indicate that individuals treated with DTG have a small fall in hemoglobin that is not related to the person's G6PD activity level. This is a well known adverse event associated with the oral administration of dapsonone. The clinical significance of this fall in hemoglobin appears to be minimal.
2. G6PD deficiency is not a single genetic abnormality. Although the most common type in the United States (Type A) has been extensively studied, other variants are uncommon or rare. These latter may respond differently to the challenge of the topical administration of DTG.
3. It is theoretically possible that additive oxidant stresses (medications, infections, foodstuffs, etc) may combine with that of DTG to induce hemolysis even when the gel alone does not cause hemolysis.
4. Based on previous experience, after this drug has entered widespread use, someone somewhere will be describing that rare patient who develops hemolysis in association with the use of DTG. The reviewing division should weigh the benefit of the drug in comparison to this very small risk.
5. Labeling should include information about the possibility of the development of hemolysis in persons with G6PD deficiency treated with DTG as it is with oral dapsonone.

Responses to the Consult Questions

1. The safety concerns regarding hemolysis in persons with G6PD deficiency treated with 5%Dapsonone Topical Gel appear to be small and are reasonably well addressed by the sponsor.
2. The patient population enrolled in the study is adequate. However, it would be useful to closely monitor adverse events after exposure in a more widespread population.

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/s/

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4/27/05 04:02:38 PM
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Kathy Robie-Suh
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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: March 29, 2004

From: Kathy M. Robie-Suh, M.D., Ph.D.
Medical Team Leader, Hematology, HFD-180

Subject: Consultation Review
IND 54,440 Dapsone Topical Gel (Atrix)

To: Division of Dermatologic and Dental Drug Products (HFD-540)

Dapsone, 4,4'-diaminodiphenylsulfone, is approved as an oral tablet formulation for treatment of dermatitis herpetiformis (dose range of 50-300 mg daily) and leprosy (dose of 100 mg daily [usually in conjunction with rifampin]). Atrix is developing a topical gel formulation of dapsone for use in treating acne vulgaris.

The reviewing division has sent this consultation request asking: What is the lower threshold for dapsone levels for hemolytic crisis in glucose-6-phosphate dehydrogenase (G6PD)-deficient patients?

Review comments:

G6PD is a sex-linked red cell abnormality occurring primarily in populations where there is a high incidence of falciparum malaria, and is seen particularly in men of African or Mediterranean descent. Individuals deficient in G6PD show about 2-fold increased sensitivity to dapsone-induced hemolytic anemia as compared to normal individuals. The underlying mechanism is not completely explained but is thought to be related to impaired ability of G6PD-deficient cells to generate NADPH. G6PD is the first enzyme in the hexose monophosphate (HMP) shunt which is the only source of NADPH in the red blood cell. NADPH provides the reducing equivalents for glutathione reductase to recycle glutathione disulfide back to reduced glutathione. NADPH deficiency results in a functional deficiency of glutathione peroxidase and consequent impairment of the ability of the cell to detoxify peroxides. Normal human red blood cells appear to be able to increase HMP shunt activity by 8- 10-fold in response to an oxidative challenge. However, in genetically G6PD-deficient red blood cells, this response is markedly diminished. The hematologic toxicity of dapsone appears to be due to its N-hydroxylamine metabolite. Arylhydroxyamines (like N-hydroxy-dapsone) react with oxyhemoglobin generating methemoglobin and the aryl nitroso compound, generating oxygen radicals and hydrogen peroxide in the process. Detoxification of these active oxygen species oxidizes glutathione to glutathione peroxide and converts the aryl nitroso compound back to an arylhydroxyamine which can then react with more hemoglobin and thus generate additional active oxygen. Thus, NADPH plays a role in redox cycling and

acts to enhance production of active oxygen species as well as enabling protective effects of catalase and/or glutathione-dependent glutathione peroxidase detoxification of the active oxygen species.

The situation is further complicated by the fact that there is genetic polymorphism in the ability to metabolize foreign compounds. Cytochromes P-450 CYP3A3, CYP3A4, CYP3A5, CYP2E1 and CYP2C9 appear to be involved in the metabolism of dapsone, with the CYP3A family being mainly responsible for the N-hydroxylation of dapsone and its acetylated derivative. (Coleman, MD. Gen. Pharmacol. 26:1461-1467 (1995)).

The literature does not provide any threshold blood level for hemolysis in G6PD deficient patients. Degowin, RL et al (Bull. WHO, 35:165-179 (1966)) studied hemolytic effects of dapsone in 15 volunteers at the Illinois State Penitentiary (10 normal men [negative G6PD screening test; 4 white, 9 black] and 5 black men who were G-6-PD deficient). He found that in 3 of 4 normal subjects who received 300 mg dapsone PO daily for up to 21 days hematocrit levels decreased by about 25% and erythrocyte survival was markedly diminished. In 3 G6PD-deficient subjects who received dapsone 100 mg (2 subjects) or 200 mg (1 subject) daily for 21 days, shortening of erythrocyte survival was more marked than in normal subjects receiving the same daily dose of dapsone. G6PD-deficient subjects who received 25 mg (1) or 50 mg (1) dapsone daily and one who received 100 mg daily showed decreases in hematocrit similar to that seen in the one G6PD control patient who received no dapsone (about 10-15%). The percentage of erythrocytes lysed during administration of dapsone was fairly linear with increasing dose on a mg/kg/day basis for both the G6PD-deficient subjects and the normal subjects; however, the G6PD-deficient subjects were more sensitive to the effect. Also of note is that one G6PD-deficient subject who received the 100 mg dose and who had an intercurrent streptococcal infection showed hemolysis, decreased erythrocyte survival time and decreased erythrocyte glutathione levels comparable to the G6PD-deficient patient who received the 200 mg dose. In most of the normal subjects who received 200 or 300 mg of dapsone daily, the erythrocyte glutathione levels rose during the first weeks of treatment, while erythrocyte glutathione levels in G6PD-deficient patients decreased during this time. Mean blood levels of dapsone during the second week of treatment for the 18 subjects who received dapsone are summarized in the following table:

Mean blood levels of dapsone during the second week of treatment

| Dapsone dose (mg/day) | Normal subjects | | G6PD-deficient subjects | |
|-----------------------|-----------------|--|-------------------------|--|
| | N | Mean blood level of dapsone, range (mg/dL) | N | Mean blood level of dapsone, range (mg/dL) |
| 0 | 3 | 0 | 1 | 0 |
| 25 | 0 | N/A | 1 | 0.04 |
| 50 | 1 | 0.04 | 1 | 0.07 |
| 100 | 2 | 0.13-0.15 | 2 | 0.10-0.19 |
| 200 | 3 | 0.24-0.60 | 1 | 0.45 |
| 300 | 4 | 0.42-0.98 | 0 | N/A |

The authors concluded that both in normal subjects and in G-6-PD-deficient American Negro men, daily administration of relatively low doses [25 mg or 50 mg] of dapsone does not cause marked hemolysis. The paper cautions that additional information is needed regarding dapsone induced hemolysis in persons receiving long-term treatment and in individuals with other genetic variants of G-6-PD deficiency. Todd, P et al (Clin. Exp. Dermatol. 19:217-8 (1994)) reported a case of an 18 year old Greek girl who had a negative G6PD screening test but developed acute hemolytic anemia after two days on 50 mg daily of dapsone for pityriasis lichenoides chronica. Therefore, the author recommends that "quantitative assays, rather than screening tests, are mandatory in any female patients from susceptible racial groups, particularly Mediterraneans, for whom dapsone therapy is contemplated".

Conclusions:

There is no known threshold for hemolytic effect of dapsone. Significant hemolysis can occur in apparently normal individuals as well as in G6PD-deficient individuals, though G6PD-deficient patients are more sensitive to the dapsone-induced effect. Other factors, such as infection, appear to worsen the degree of hemolysis in susceptible individuals. Hemolysis appears to be dose related with dapsone oral doses of 25 mg or 50 mg daily being less likely to cause hemolytic crisis. However, sensitivity to dapsone-induced hemolysis may vary with racial, ethnic groups, specific lesion responsible for G6PD deficiency and may be enhanced with intercurrent stresses such as infection. Blood levels after a week of dosing with dapsone 25 mg daily have been reported as 0.04 mg/dL and with 50 mg daily as 0.04-0.07 mg/dL, however, numbers of patients were very small. It is advisable to screen patients for glucose-6-phosphate dehydrogenase deficiency using quantitative rather than qualitative assays, especially in any female patients from susceptible racial groups, particularly Mediterraneans, when dapsone therapy is being considered. There is a potential role for evaluation of cytochrome P-450 polymorphism in further fine tuning the estimate of risk of dapsone-induced hemolysis in individual patients.

cc:

IND 54,440

HFD-180/RJustice

HFD-180/JKorvick

HFD-180/KRobie-Suh

HFD-180/JDuBeau

HFD-540/FCross

HFD-540/MLuke

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/s/

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CLINICAL REVIEW

Application Type 505 (b)(1)
Submission Number NDA 21-794
Submission Code 000

Letter Date 08-31-04
Stamp Date 09/07/04
PDUFA Goal Date 07/07/05

Reviewer Name Brenda E. Vaughan, M. D.
Review Completion Date 06-20-05

Established Name Dapsone
(Proposed) Trade Name ACZONE
Therapeutic Class Sulfone
Applicant Atrix Laboratories

Priority Designation 3S

Formulation Topical Gel, 5%
Dosing Regimen Twice daily applications
Indication Treatment of Acne Vulgaris
Intended Population ≥ 12 years of age

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Clinical Review
{Brenda Vaughan, M.D.}
{NDA 21-794/N-000
{ACZONE™ (dapson) Gel 5%}

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical perspective, an *Approval* recommendation is being made for use of Aczone™ (dapson) topical gel, 5% in treatment of acne vulgaris for up to 12 weeks. In patients with a history of anemia and predisposition to increased hemolytic effect with dapson (e.g., glucose-6-phosphate dehydrogenase deficiency), closer follow-up for blood hemoglobin levels and reticulocyte counts should be implemented. Alternatively, other therapies for acne than ACZONE Gel, 5% may be considered. CMC deficiencies are outstanding at the date of this review.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Post approval safety monitoring for hemolysis is needed with use of ACZONE (dapson) topical gel, 5% in the glucose-6-phosphate dehydrogenase (G6PD) deficient patients because the number of evaluable G6PD patients exposed to ACZONE Gel, 5% during clinical development is small. Additionally, there is no information available to determine the effects of the topical application of ACZONE Gel, 5% in persons with rarer genetic abnormalities, such as methemoglobin reductase or the congenital methemoglobinemias, in which the oxidant stress of dapson and its metabolite may also induce methemoglobinemia. The applicant should investigate, compile, and report all instances of hematological abnormalities associated with use of ACZONE Gel, 5%.

1.2.2 Required Phase 4 Commitments

Agree to conduct a randomized, blinded, cross-over safety study with each acne patient treated with ACZONE Gel, 5% for 12 weeks and vehicle for 12 weeks with at least a two week washout period in at least 50 evaluable G6PD deficient patients with acne vulgaris to further evaluate the risk of hematological adverse events with use of ACZONE Gel, 5% in this population. Patients with rarer genetic abnormalities such as methemoglobin reductase or the congenital methemoglobinemias may also be studied. Obtain baseline, week 2, and end of each 12 week treatment period laboratory testing including complete blood count, reticulocyte counts, haptoglobin, and LDH levels. Plasma dapson levels and N-acetyl dapson levels should be obtained at baseline, week 2, and at the end of each 12 week treatment period. Additionally, plasma dapson and its metabolite levels should be obtained in relation to adverse events which may be considered dapson related.

Study Protocol Submission: November 1, 2005
Study Initiation: March 1, 2006
Final Study Report Submission: January 1, 2008

1.2.3 Other Phase 4 Requests

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The applicant's clinical program enrolled 4,622 subjects/patients that included a total of 412 healthy subjects, 4,196 patients with *acne vulgaris*, and 15 burn patients in the dapsone topical gel (DTG) development program. There were only 50 G6PD deficient patients studied in the clinical development program. In patients with acne, the Applicant conducted three pharmacokinetic studies, one double-blind dose ranging study, three 12-week, double-blind, vehicle-control studies (of which two were considered pivotal studies), and a 1-year open-label safety study. One study provided dose-finding information and evaluated the pharmacokinetics of oral dapsone and DTG. In support of the application data were submitted from five dermal safety studies.

1.3.2 Efficacy

Statistical superiority of dapsone gel over vehicle was demonstrated for all primary endpoints (percent change in inflammatory, non-inflammatory, and total lesions, and success on the Global Acne Assessment Scale (GAAS) in two Phase 3 multicenter, randomized, blinded, vehicle controlled studies by enrolling 3,010 subjects at 105 study sites to adequately power the studies in order to facilitate detecting a small treatment effect (See Statistical Review). According to the statistical review, efficacy of dapsone gel is only about 4 to 9% better than vehicle.

A post hoc modified intent-to-treat (MITT) analysis was conducted that required at least two grades reduction in addition to achieving none or minimal on the GAAS. The MITT population analysis was needed to exclude subjects enrolled with a GAAS Baseline score of 1 (minimal). Although no baseline GAAS was mandated, enrollment of patients with a GAAS score of 1 appears inconsistent with the entry criteria. GAAS score of 1 is defined as having a few non-inflammatory and a few inflammatory lesions present; however, entry criterion specified 20-50 inflammatory acne lesions (pustules and papules) and 20-100 comedones above the mandibular line at Baseline. Nonetheless, the ITT, MITT, and the requirement of at least 2 grade-reduction in addition to achieving none or minimal were all statistically significant.

Pivotal studies DAP0203 and DAP0204 were identically designed multi-center, randomized, double-blind, parallel group, 2-arm, vehicle-controlled, 12-week studies to evaluate the safety and efficacy of topically applied 5% DTG in patients with *acne vulgaris* compared to vehicle control (VC). These studies were conducted in the United States and Canada. At baseline, determinations of the number of inflammatory and non-inflammatory acne lesions were made. Blood samples were drawn for hematology and chemistry analyses. Glucose-6-phosphate dehydrogenase (G6PD) enzyme activity was screened; however, G6PD deficient patients were not excluded from study participation. Patients who met all of the eligibility criteria were randomly assigned to Dapsone Topical Gel (DTG) or the Vehicle Control (VC) in a 1:1 ratio.

Blinding may have been problematic in that the active study drug has a gritty feel and contains visible particles. Physical characteristics of the vehicle used in the studies are unknown. Blinding may have also been compromised at 13 pivotal study sites. Study DAP0114, an unblinded 12-month safety study, was started prior to initiation of the blinded 12 week pivotal studies and 13 investigators participated in both the unblinded safety study and blinded pivotal studies (DAP0203 and DAP0204).

According to the protocol, study site personnel who were responsible for conducting safety and efficacy assessments were not to handle the study medication and patients were instructed not to discuss appearance of study medication with study site personnel. Adequacy of blinding was not referred to the Division of Scientific Investigation (DSI) because the presence of visible particles and gritty texture of the active drug was not known until late in the review cycle and study results for the pivotal studies indicate that at some centers the vehicle study arm did better than the active study drug. In the overlapping centers no type of trend was noted that indicated that those participating in the open label study had better efficacy results than those who did not. In terms of the efficacy results for the pivotal studies, the overlapping 13 centers appeared evenly balanced as to how many sites favored dapson or vehicle except for Center 40 that had the most favorable results for DTG (Study DAP0204) according to the FDA Statistical Reviewer.

1.3.3 Safety

ACZONE™ Gel 5% contains dapson, a sulfone, in an aqueous gel base for topical dermatologic use in treatment of acne vulgaris. The gel is unusual in that it contains visible particles and has a gritty feel. Dapson, 4,4'-diaminodiphenylsulfone, is a sulfone with antimicrobial properties that is approved in an oral tablet formulation for treatment of dermatitis herpetiformis and all forms of leprosy except for cases of proven dapson resistance. Oral dapson has been commercially available for over 60 years.

Patients on oral dapson may experience hematologic adverse effects; including drug induced hemolysis and elevated methemoglobin levels. Hemolytic effects associated with the use of oral dapson occur early, are dose-dependent (increasing with higher dosing) and are typically associated with doses greater than 100 mg per day. Nearly all patients who receive oral dapson at doses of 200 or 300 mg per day will develop hemolysis. G6PD deficient patients are the most sensitive to the hematological effects of dapson. Methemoglobinemia associated with oral dapson exposure typically occurs at doses above 200 mg/day and is not clinically significant at doses below 100 mg/day.

Safety Population

The "Safety Evaluable" population was used to summarize the safety parameters. Subjects without evidence of study drug application and no adverse events reported in the database were excluded from the safety evaluable population. According to the Applicant, this is a more conservative approach relative to presenting adverse event rates, as the inclusion of these patients would lower the incidence rates of adverse events.

A total of 4,506 patients are included in the applicant's safety database and 4,086 of these were acne vulgaris patients (VC, 1660; 1% DTG, 23; 3% DTG, 31; 5% DTG, 2372) and 15 were burn patients with at least 1 dose of study drug or reporting an adverse event during the study. Overall, safety assessment appears adequate in the study population with normal G6PD levels; however, safety population database is insufficient for the most sensitive population to the hemolytic effects of dapsone (e.g., patients with deficient G6PD activity levels, etc.).

Of the 4,086 acne patients only 50 (1%) patients with G6PD deficiency were studied in the clinical development program. A total of 25 G6PD deficient patients were exposed to active drug and 25 to vehicle. Of the 50 G6PD deficient patients, 44 participated in the Phase 3 pivotal vehicle controlled Studies DAP0203 and DAP0204, 5 are known to have participated in the 12 month safety Study DAP0114, and one G6PD deficient patient was enrolled in PK Study DAP0110. G6PD level determinations were not obtained until Month 6 in Study DAP0114 and the G6PD activity level of patients who dropped out prior to Month 6 is unknown. There is a lack of confidence in quality of the safety database for the 5 G6PD deficient patients in Study DAP0114. The database is incomplete as laboratory samples were lost and line listings may be incorrect for at least one G6PD patient.

Safety Monitoring Program

Clinical laboratory data (including hematology and serum chemistry panels, plasma dapsone concentrations), electrocardiograms, and physical examinations were conducted. Glucose-6-phosphate dehydrogenase (G-6-PD) enzyme activity was screened at baseline in the pivotal studies but not assessed until Month 6 in the long term safety study (rationale not provided). Dapsone and N-acetyl dapsone (NAD) levels were to be obtained on a scheduled basis in the long term safety Study DAP0114. Dapsone and NAD levels were to be obtained in the Phase 3 studies for any patient with an adverse event believed to correlate with systemic exposure (February 14, 2003 Letter of Clarification No. 3) and no plasma levels were obtained. Changes in clinical laboratory parameters, vital signs, electrocardiogram, and physical examination were identified. Adverse events were collected.

Reticulocyte counts were performed in PK Study DAP0110; however, not performed in the Phase 3 or in the long term safety studies. According to Burns *et al* (Am J Hematol. 2000 Jul;64(3):180-3), red blood hemolysis is classically diagnosed by a combination of nonspecific laboratory tests, including serum bilirubin, LDH, and reticulocyte count. A more robust hematological assessment in the clinical studies (e.g., reticulocyte counts, haptoglobin levels, erythrocyte adenylate kinase levels, etc.) would have been useful for establishing a diagnosis of hemolysis.

Safety Population

Safety population was defined by the Applicant as those subjects without evidence of study drug application and no adverse events (AEs) reported in the database were excluded from the safety evaluable population. One hundred nine patients did not return for a study visit after being dispensed study drug, did not have any adverse event reported, and are not contained in the safety evaluable set.

Discontinuations

Discontinuations were similarly distributed between active and vehicle groups and also between the G6PD deficient population on active and vehicle, 19 and 15, respectively. Five hundred sixty-three patients (15.6%) discontinued during the 12-week, vehicle-controlled studies. The most common reason for discontinuation was lost to follow-up (287, 8.0%). Eight patients (6, VC; 2, DTG) discontinued the study due to a treatment-related adverse event.

Deaths and Serious AEs

No deaths were reported in any of the studies in the clinical program. Serious adverse events were reported for 18 patients (DTG 11, VC 7) and none were considered by the Investigators as being related to study treatment.

Duration of Exposure

Duration of exposure for the pivotal studies was adequate; in fact patients were exposed beyond the scheduled 12 week study duration. Patients in Study DAP0114 were exposed to active study drug up to 12 months with mean number of days of study drug exposure of 252.63 days.

Dapsone (DAP) and N-acetyl Dapsone (NAD) Plasma Concentrations

Based on the available data, systemic exposure under maximal use conditions with 5% DTG is 127-fold lower than with a single 100 mg oral dapsone dose and 63-fold lower than with a single 50 mg oral dapsone dose. No differences in absorption were observed in G6PD deficient patients. Plasma levels were not obtained in the Phase 3 studies.

Based on the data, after topical application of 5% DTG there is no correlation or trend in systemic exposure to dapsone or its metabolite based on gram usage or % body surface (BSA) of application. In PK Studies DAP9903, DAP0110, and 03-0-18, similar plasma dapsone levels were demonstrated after application of 5% DTG to fixed body surface areas ranging from ~5% (face only) to ~22.5% (maximum treatment area to face, chest, back and shoulders). According to the FDA Chemistry Reviewer all DTG batches should be consistent in regards to distribution of particles _____; therefore, particle size distribution should not be a confounding factor in none linearity or lack of trend in % BSA application and systemic availability observed in Applicant's database.

Reviewer comment:

There is lack of confidence with the DAP and NAD plasma dataset. Under pretext of the 120-Day Safety Update, 333 additional samples from Study DAP0114 (the 12 month safety) were submitted to the NDA. According to the Amended Report dated April 8, 2005, the module originally submitted with NDA 21-794 contained figures that were based on available plasma dapsone information. After reviewing the original data, Atrix Laboratories discovered that some laboratory data were missing from the dataset. When contacted about this error, _____ located the remaining samples, which were stored frozen, and sent them to the laboratory _____ for analysis. These results were pending at the time of the 5% Dapsone Topical Gel submission although data were characterized as "final" study reports.

Although some PK samples were found in a freezer, others were apparently lost during shipping. Plasma dapson levels, for Months 6, 9, and 12 are not available for the patient of special interest, Patient 1424 in Study DAP0114. According to Amendment 030 (in response to FDA clinical information request dated April 21, 2005), there is documentation from the clinical site _____ that Months 6, 9, and 12 plasma dapson samples were drawn and shipped to the central laboratory; however, the Applicant has no explanation for the samples not arriving at _____ other than they were somehow lost during the shipping period.

Hematologic Profiles

According to the FDA Hematology Consultant (dated April 20, 2005) the Applicant's studies indicate that individuals treated with DTG have a small fall in hemoglobin that is not related to the person's G6PD activity level. The clinical significance of this fall in hemoglobin level appears to be minimal (See Hematology Consult). In patients with normal G6PD enzyme activity levels there is a similar distribution in ≥ 1 g/dL decrease in hemoglobin level, 10% (152 of 1487) and 10% (146 of 1479), active and vehicle; respectively, for the pivotal studies. Ten patients on active and 8 patients on vehicle had a ≥ 2 g/dL decrease hemoglobin level in these studies. None were considered related to use of study drug. No documented evidence of hemolytic anemia was reported under conditions of this study.

The applicant states that fluctuations in hemoglobin values did not correlate with plasma dapson levels. Plasma dapson levels were low (< 40 ng/mL) in most patients at all time points. According to the Applicant, plasma hemoglobin is a very sensitive biomarker for dapson toxicity. Patients with high plasma concentrations did not have a change in hemoglobin levels, and patients with a ≥ 1 or ≥ 2 g/dL decrease in hemoglobin did not have high plasma dapson levels. Although hematological effects such as methemoglobinemia and decreased hemoglobin are well known side effects of oral dapson, no relationship between these events and 5% DTG treatment was observed.

The applicant concludes that hematologic profiles after topical application of 5% DTG were consistent between patients who were G6PD deficient (regardless of severity) versus non-G6PD deficient patients, regardless of dapson plasma levels, gram use or treatment group (i.e., 5% DTG or vehicle control); however, this conclusion is based on a limited and incomplete dataset consisting of 25 G6PD deficient patients on dapson gel. Three of the 25 G6PD deficient patients are of interest in that in addition to the ≥ 1 g/dL decrease in hemoglobin, other indices associated with possible hemolysis were noted: an elevated total bilirubin (Study DAP0204, Patient 375422), elevated reticulocyte count (Study DAP0110, Patient 0103), and an elevated LDH (Study DAP0114, Patient 1424). Reticulocyte counts were only provided for PK Study DAP0110.

Adverse Events Profile

No systemic AE trend was noted in the 12-Week vehicle controlled studies and no difference was noted between the 5 DTG and 7 vehicle G-6-PD deficient patients (Study DAP0203) and the 14 DTG and 18 vehicle G-6-PD deficient patients in Study DAP0204.

Laboratory Abnormalities

The majority of patients had hematology (hematocrit, hemoglobin, red blood cells, and white blood cells) and serum chemistry values that were within the normal range at Baseline and Week 12. Changes in laboratory values were similarly distributed between the 2 treatment groups. No apparent differences in laboratory values between Baseline and the end of the study were observed in VC-treated and 5% DTG-treated patients.

The most common marked abnormality in the 2 pivotal studies was elevated creatine kinase (CK). This laboratory abnormality was observed in 40 patients at Week 12 and occurred at a similar incidence in VC-treated and 5% DTG-treated patients (VC: 21 patients; 5% DTG: 19 patients).

A total of 42 patients (VC: 22 patients; 5% DTG: 20 patients) had a laboratory abnormality reported as an adverse event during the study. These events were generally mild or moderate in severity. The laboratory abnormality most frequently reported as an adverse event was elevated CK (VC: 11 patients; 5% DTG: 12 patients). The majority (14/23; 60.9%) of elevated CK events were reported by the Investigator to be related to physical activity.

In the 12 month safety study, a total of 15 patients had values that were considered markedly abnormal at some point during the long-term safety study. The most common marked abnormality was elevated potassium, which was observed in 6 patients during the treatment period.

Four of 6 patients (66.7%) with a markedly abnormal potassium level had normal potassium levels measured at the next scheduled visit or retest. The abnormal potassium level of 7.1 MMOL/L (normal 3.3-5 MMOL/L) for 1 of these patients (Patient #0410; Study DAP0114) was attributed to hemolysis. According to the line listings, no AEs were reported for this patient and the patient voluntarily withdrew on study Day 162. The G6PD status of this patient is unknown because levels were not determined until Month 6 in Study DAP0114. Two patients had markedly abnormal potassium at the end of the study and the investigators did not feel a retest was necessary.

Application Site AEs

The most common application site adverse events in the 12-Week VC studies (N =1819) were application site reaction (NOS = facial oiliness and peeling) 18% (n=323), 16% (n=294) reported application site dryness, 13% (n=241) reported application site erythema, burning was reported in 1% (n=23), pruritus in 1% (n=19) patients. These AE rates were similar for DTG and VC study arms in Studies PAP0203 and DAP0204. Similar application site AEs were also reported (n=486); however, the percentage of reported AEs were fewer: (NOS = facial oiliness and peeling) 1% (n=5), 3% (n=13) reported application site dryness, 2% (n=8) reported application site erythema, burning was reported in 21% (n=8), pruritus in 1% (n=7) patients.

Dermal Safety Studies

There is a contact sensitization signal with use of DTG. Under conditions of the Study DAP9902, 1.4% (3) subjects exhibited sensitization reactions to the final-to-be marketed formulation. There is a trend to suggesting that DGME (a vehicle component) is a mild to moderate sensitizer under occlusion; however according to the applicant, up to 40% DGME is currently used non-occluded in a number of marketed cosmetic products without significant reported sensitization.

Conclusion

Treatment Site Safety

Local cutaneous adverse events were primarily of mild intensity. Dryness, erythema, oiliness and peeling (events specifically elicited at each visit in the pivotal studies) were all more common at Baseline than during the study. There were no differences in the application site adverse event rates between treatment groups and no trends were identified in the subpopulations.

Systemic Safety

Overall, the safety populations for patients with normal G6PD levels appear adequate and the small fall in hemoglobin noted in the applicant's studies in individuals treated with DTG is minimal and not clinically significant according to the FDA Hematology Consultant. The 5% DTG clinical program included over 4,000 participants and 5% DTG has been evaluated in more than 2,300 acne patients. No deaths were reported in the clinical development program. Overall, short-term and long-term treatment with 5% DTG did not appear to have any adverse effects on laboratory parameters. There were no vital sign or physical examination findings identified of potential clinical concern in the DTG clinical program.

G6PD Deficient Patient Population

Systemic exposure after topical application of DTG is considered low; however, there is no known threshold for hemolytic effect of dapson according to an FDA hematology consult dated March 29, 2004. Insufficient numbers of G6PD deficient patients were studied in the applicant's clinical development and the dataset is incomplete. Of the 4,196 subjects with acne vulgaris a total of 50 patients were G6PD deficient with only 25 subjects exposed to active study drug. In the 12-Week vehicle control groups for studies 203 and 204, no trend in AEs were noted between the 5 dapson and 7 vehicle G-6-PD deficient subjects (Study 0203) and the 14 dapson and 18 vehicle G-6-PD deficient patients in Study 0204.

The applicant was advised early on (End-of-Phase 2 Meeting, December 18, 2000) that the submission should very clearly delineate the risk/benefit assessment for treatment of acne with dapson, by providing adequate data to demonstrate that the inherent risk for serious side effect is vanishingly small. -

1.3.4 Dosing Regimen and Administration

Apply a thin layer of ACZONE™ Gel 5% to the acne affected areas of skin twice daily up to 12 weeks. Skin should be gently washed prior to applying ACZONE™ Gel and the gel should be rubbed in gently and completely. Hands should be washed after application of ACZONE™ Gel. Patients with a history of anemia and predisposition to increased hemolytic effect with dapson (e.g. low glucose-6-phosphate dehydrogenase plasma levels) should be closely monitored for hematological adverse events especially during periods of additive oxidative stresses (e.g., medication, infections, etc.).

1.3.5 Drug-Drug Interactions

Co-administration of TMP/SMX and Aczone™ Gel 5% resulted in higher exposure to dapson and its metabolites. One drug-drug interaction was studied in Study 03-0-182, a multiple-dose study conducted to evaluate the possibility of a drug-drug interaction between Aczone™ Gel 5% and trimethoprim/sulfamethoxazole (TMP/SMX) at steady-state. Neither TMP nor SMX levels were affected by co-administration with Aczone™ Gel 5%.

For oral dapson the following drug-drug interactions are listed: rifampin lowers dapson levels 7 to 10-fold by accelerating plasma clearance; in leprosy this reduction has not required a change in dosage, folic acid antagonists such as pyrimethamine may increase the likelihood of hematologic reactions, and that there is a mutual interaction between Dapson and trimethoprim in which each raises the level of the other about 1.5 times.

Drug-Drug Interactions

There were no documented interactions observed in any of the clinical studies when patients were treated with 5% DTG and took systemic medication known to result in interactions with systemically administered dapson; however, coinciding dapson plasma levels were not drawn.

1.3.6 Special Populations

As previously stated, dose related hematological adverse reactions (e.g., hemolysis, methemoglobinemia, and anemia) are most common adverse effect associated with use of oral dapson. The hemolytic process is most likely related to metabolites of dapson (particularly the N-hydroxylamine product) rather than to the parent compound. The metabolites interfere with the pathway that includes glucose, G6PD, NADPH and reduced glutathione in a series of linked reactions that provide hydrogen ions to maintain the iron in hemoglobin in its reduced Fe²⁺ (functional) state. Patients who are G6PD deficient are more sensitive to hemolytic changes associated with oxidative stress, which may result from oral dapson or other drug exposure, infection and ingestion of fava beans (favism). G6PD deficient patients are less susceptible to methemoglobinemia according to Zhu and Stiller, 2001 and Beutler, 1994.

G6PD deficiency is the most common enzymopathy in the world and affects up to 400 million people. G6PD deficiency is not a single genetic abnormality. Over 400 different enzyme defects have been described; however, common mutations are often shared within populations. The prevalence of G6PD deficiency is highest in Africa, Southeast Asia and the Middle East with the highest rates observed in African-Americans, and tribes from parts of Africa, and Southeast Asia. G6PD is encoded on the X chromosome and G6PD deficiency is generally more severe in males (homozygous). Females are affected by the phenomenon of X-inactivation where random X-chromosome inactivation can lead to mosaics that are functionally deficient in G6PD (heterozygous). In some populations, true homozygous females are described.

The Mediterranean variant is most common in patients from countries bordering the Mediterranean, while the A- variant is most common in African-Americans and Africans. The most common type in the United States is Type A and other variants are uncommon or rare. These latter variants may respond differently to the challenge of the topical administration of DTG.

According to the Hematology Consultant dated April 20, 2005, there is no information available to determine the effects of the topical application of DTG in persons with rarer genetic abnormalities, such as methemoglobin reductase or the congenital methemoglobinemias, in which the oxidant stress of dapson and its metabolite may also induce methemoglobinemia. The Consultant goes on to say that based on previous experience, after this drug has entered widespread use, someone somewhere will be describing that rare patient who develops hemolysis in association with the use of DTG and the reviewing division should weigh the benefit of the drug in comparison to this very small risk.

According to an FDA hematology consult dated March 29, 2004, there is no known threshold for hemolytic effect of dapson. According to the FDA Hematology Consultant, while the topical gel alone may not be able to induce hemolysis, it is theoretically possible that use of the gel could be contributory under conditions of oxidative stress. Although the risk associated with use of DTG might be perceived as small, efficacy is marginal at 4 to 9% better than vehicle and there are numerous alternative therapies for treatment of acne.

The number of G6PD deficient patients studied in the applicant's clinical development program is small and the adverse effect of dapson in this patient population is not clear. While overt anemia did not occur, a decrease in hemoglobin of ≥ 1 g/dL did occur in 3 of 25 (12%) G6PD patients exposed to active drug. A discussion of the 3 G6PD deficient patients follows:

- Of interest is Patient #1424, a 29-year-old G6PD deficient Asian female, admitted to the hospital for acute pancreatitis and influenza on Day 310 (Study DAP0114). Laboratory values for Patient 1424 are not available at the time of the AE; however at Visit 12 (Day 339) the following lab values were recorded approximately one month after hospitalization (Month 12 Visit): 1.2 g/dL decrease in hemoglobin level over baseline, 1+ poikilocytosis and an elevated LDH of 423 IU/L (normal range 94-250 IU/L). Bilirubin levels remained constant. Plasma dapson levels for Months 6, 9, and 12 are not available for this patient as they were lost in shipping. Prior plasma dapson levels ranged from <0.05 ng/mL at Baseline to 31.92 ng/mL at Month 3.

The applicant's assessment is that both the change in hemoglobin and elevated LDH were attributed to the pancreatitis and influenza occurring the month prior to the 12 month visit. Topical dapson use may have been a contributory factor in the decrease in hemoglobin level in this patient.

- Patient 375422, a 16 year old Caucasian male with G6PD deficiency, had a 1.2 g/dL reduction in hemoglobin over baseline. The Baseline total bilirubin was 2 mg/dL (normal range 0.2 -1.2) and total bilirubin was 3.6 mg/dL at the end of the study. The elevated bilirubin level was deemed as possibly related to study drug by the Investigator (Mod 5, Vol. 54, pg. 167 of 266); however, dapson and N-acetyl metabolite levels were not determined as required by Study Protocol DAP0204.

According to the applicant, the patient was diagnosed with Gilbert disease; however, Gilbert disease is not known to be associated with a decrease in hemoglobin. The patient's baseline medical history did not include this diagnosis. Indirect bilirubin levels would have been useful in confirming a diagnosis of Gilbert disease.

- Patient 0103, a severely deficient G6PD Caucasian male, had a 1.3 g/dL reduction in hemoglobin (Hgb), slight elevation of total bilirubin, and increased reticulocyte count over the course of the 14 day PK study. In PK Study DAP0110, DTG was applied to a fixed % BSA for 14 days.

According to the Submission dated March 4, 2005 (Hematolytic Effects of Dapson in G6PD Subjects), 7 of 18 patients in the study had a hemoglobin of 1 g/dL. The Applicant stated that the decreases in hemoglobin may have been related to the number of blood draws; however the G6PD subject was the only one of 7 with a decrease in hemoglobin and an associated increased reticulocyte count.

Of the 4,196 acne vulgaris patients studied, a total of 50 G6PD deficient patients were enrolled and only 25 of these patients were exposed to active study drug. The applicant concludes that no differences were noted between G6PD deficient patients and patients with normal G6PD activity levels; however, the number of G6PD deficient patients studied is too small to adequately assess the risk/benefit with use of a marginally effective drug containing dapson in this subset of acne patients.

The applicant was advised early on (End-of-Phase 2 Meeting, December 18, 2000) that the submission should very clearly delineate the risk/benefit assessment for treatment of acne with dapson, by providing adequate data to demonstrate that the inherent risk for serious side effect is vanishingly small.

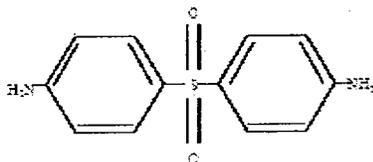
Geriatric Use Clinical studies of DTG 5% did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. There were two patients 65 years or older [Archival Vol. 1.112, Mod 5, Vol. 104E, ISS (Vol. 22, Appendix 17,

pg. 1 of 1) pg. 89]; one patient was 77 years old and the other 81 years old.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

ACZONE™ Gel 5% contains dapsonsone, a sulfone, in an aqueous gel base for topical dermatologic use. Chemically, dapsonsone has an empirical formula of $C_{12}H_{12}N_2O_2S$. It is a white, odorless crystalline powder that has a molecular weight of 248. Dapsonsone's chemical name is 4,4'-diaminodiphenylsulfone and its structural formula is:



Each gram of Aczone™ Gel 5% contains (w/w) 5% dapsonsone, USP, in a gel of carbomer 980; diethylene glycol monoethyl ether, NF; methylparaben, NF; sodium hydroxide, USP; and purified water, USP.

- The proposed name is Aczone™ Gel, 5%
- Dapsonsone, 4,4'-diaminodiphenylsulfone, is a sulfone with anti-inflammatory and antimicrobial properties that is approved as an oral tablet formulation for treatment of dermatitis herpetiformis and all forms of leprosy except for cases of proven dapsonsone resistance.
- The applicant proposes use of Aczone™ Gel, 5% for the topical treatment of acne vulgaris
- The glossy gel has a gritty consistency and contains visible particles up to --- in diameter

2.2 Currently Available Treatment for Indications

Acne is a common skin disease with onset in adolescence and characterized by papules, pustules, and comedones. Acne vulgaris is multi-factorial in etiology, but is known to develop in the sebaceous follicles with the face as the primary site of involvement face; however, the trunk, buttocks, and extremities can also be affected. Acne vulgaris can present with varying lesion types, sizes and numbers and varying degrees of severity. The prevalence of acne is close to 100% of the population, with individuals differing only in severity of expression. A plethora of topical and systemic drug products are currently available for treatment of acne.

2.3 Availability of Proposed Active Ingredient in the United States

Oral dapson is marketed in the US; however, topical dapson is not available. The major safety concerns with the oral product are associated with frequent hematologic side effects, such as methemoglobinemia, hemolysis, and anemia.

2.4 Important Issues With Pharmacologically Related Products

The following information is from the orally administered dapson label. Hemolysis and Heinz body formation may be exaggerated in individuals with a glucose-6-phosphate dehydrogenase (G6PD) deficiency, or methemoglobin reductase deficiency, or hemoglobin M. This reaction is frequently dose-related. Dapson should be given with caution to these patients or if the patient is exposed to other agents or conditions such as infection or diabetic ketosis capable of producing hemolysis. Deaths associated with the administration of Dapson have been reported from agranulocytosis, aplastic anemia and other blood dyscrasias. Cutaneous reactions, especially bullous, include exfoliative dermatitis and are probably one of the most serious, though rare, complications of sulfone therapy. They are directly due to drug sensitization. Such reactions include toxic erythema, erythema multiforme, toxic epidermal necrolysis, morbilliform and scarlatiniform reactions, urticaria and erythema nodosum. If new or toxic dermatologic reactions occur, sulfone therapy must be promptly discontinued and appropriate therapy instituted.

Toxic hepatitis and cholestatic jaundice have been reported early in therapy. Hyperbilirubinemia may occur more often in G6PD deficient patients. When feasible, baseline and subsequent monitoring of liver function is recommended. If abnormal, Dapson should be discontinued until the source of the abnormality is established.

Nervous system effects include peripheral neuropathy, a definite but unusual complication of Dapson therapy in non-leprosy patients. Motor loss is predominant. If muscle weakness appears, Dapson should be withdrawn. Recovery on withdrawal is usually substantially complete. The mechanism of recovery is reportedly by axonal regeneration. Some recovered patients have tolerated retreatment at reduced dosage. In leprosy this complication may be difficult to distinguish from a leprosy reactional state.

Body as a whole effects include the following additional adverse reactions: nausea, vomiting, abdominal pains, pancreatitis, vertigo, blurred vision, tinnitus, insomnia, fever, headache, psychosis, phototoxicity, pulmonary eosinophilia, tachycardia, albuminuria, the nephrotic syndrome, hypoalbuminemia without proteinuria, renal papillary necrosis, male infertility, drug-induced Lupus erythematosus and an infectious mononucleosis-like syndrome. In general, with the exception of the complications of severe anoxia from overdosage (retinal and optic nerve damage, etc.) these adverse reactions have regressed off drug.

2.5 Presubmission Regulatory Activity

- End-of-Phase 2 Meeting was held on December 18, 2000. Study design, efficacy endpoints for acne vulgaris, protocol design, and adequate numbers of patients to assess safe use of dapson were discussed. The Applicant was advised (Meeting Minutes, pg. 7) that the submission should very clearly delineate the risk/benefit assessment for treatment of facial acne with dapson, by providing adequate data to demonstrate that the inherent risk for serious side effects is vanishingly small.
- Special protocol assessment (SPA), letter date June-10, 2002
- Pre-NDA Meeting held on April 7, 2004.
- NDA submission (Letter date 08-31-04)

2.6 Other Relevant Background Information

Topical dapson gel is not approved in any country.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

As of 05-23-05, the following CMC deficiencies are outstanding:

1. Under section 3.2.P.3.4 (Module 3 Volume 3) titled "Controls of Critical Steps and Intermediates [5% Dapson Topical Gel]":

The critical processing steps _____ should have a _____

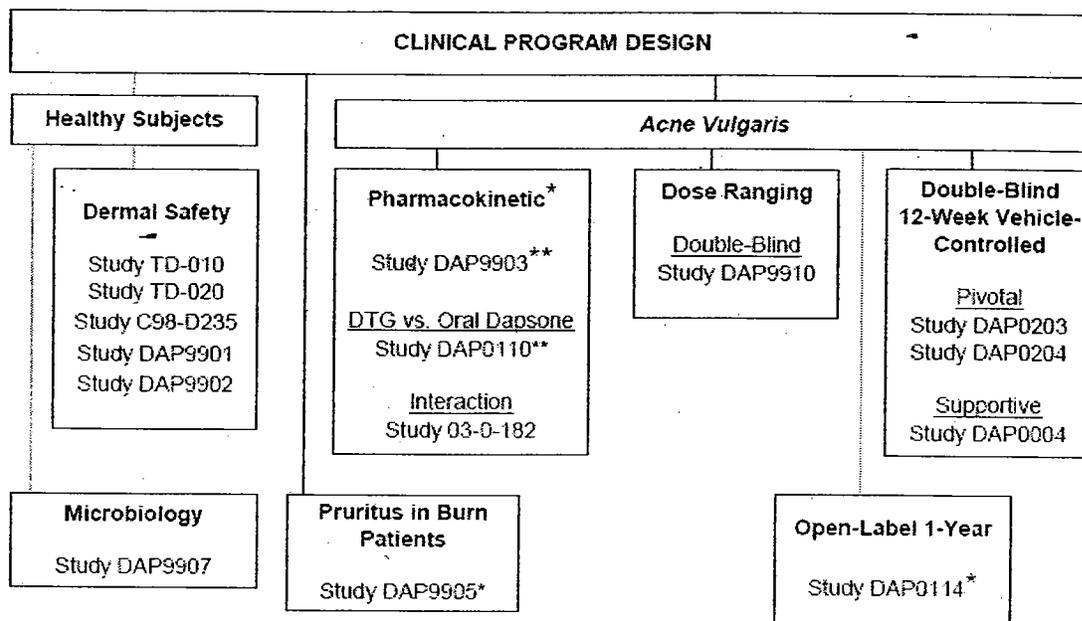
2. Under section 3.2.P.5.1 titled "Specification [Dapson Topical Gel]", the regulatory release specification 26005C.005 and the regulatory shelf-life specification 26005B.005 for the 5% Dapson Topical Gel product should be revised as follows:

a) The appearance attribute should be describe as being a ' _____

b) The specification for particle size should be revised to accurately reflect the particle size distribution found from data derived for Particle Size of 5% Dapson Topical Gel (Document # 50916.001 R). Therefore, it is recommended that acceptance criteria in the specification for the following particle sizes be proposed as:

- Mean % particles \leq μm and less
- Mean % particles \leq μm and less
- Mean % particles \leq μm and less
- Maximum particle size (μm) equal to NMT μm

Figure 1 Clinical Program Design



* Blood levels collected.

** Dose-finding study.

4.3 Review Strategy

Data submitted from two clinical trials (DAP0203 and DAP0204) are considered pivotal and were reviewed in support of efficacy. All studies submitted were included in the safety assessment. A hematology consult was obtained to assist with safety assessment due to the known effect of oral dapsone on hematological parameters.

4.4 Data Quality and Integrity

Division of Scientific Investigation (DSI) findings are pending. The following clinical sites are approved for DSI audit and are listed in order of priority.

Table 1: Clinical Sites for DSI Inspection

Clinical Review
 {Brenda Vaughan, M.D.}
 {NDA 21-794/N-000
 {ACZONE™ (dapson) Gel 5%}

| Indication | Protocol # | Site (name and address) | # of Subjects |
|---------------|------------|-----------------------------|---------------|
| Acne vulgaris | DAP0203 | [Redacted Site Information] | 31 |
| Acne vulgaris | DAP0203 | | 12 |
| Acne vulgaris | DAP0204 | | 59 |

The rationale for evaluating these sites follows:

1. These sites had a high rate of efficacy relative to other centers on all of the primary efficacy endpoints.
2. There appears to be an undue lack of correlation between numbers of lesions and disease severity. Evaluation of Investigator's Global assessment was performed in a proper manner was requested.
3. Assessment for correlation between patient's historical record and the recorded disease severity was requested.

Reviewer comments:

Requests for DSI inspections are made early on prior to in depth review of the application. This application was found to have additional irregularities that might warrant DSI assessment.

Adequacy of Blinding

- *Dapsone gel contains visible particles and it is uncertain whether the vehicle was identical in appearance. The protocol states that patients were not to discuss the appearance of the study drug with study site personnel.*
- *Study DAP0114 is a 12-month open label study that started prior to the pivotal studies. Of the 18 investigators in Study 0114, 6 also participated in DAP0203 and 7 participated in DAP0204. According to the FDA Statistical Reviewer, in terms of the efficacy results for these 13 centers, they seemed pretty evenly balanced as to how many sites favored dapsone or vehicle. Probably the site that had the most favorable results for dapsone was _____ center (Site 40, Study DAP0204). According to the Statistical Reviewer, overall there was no type of trend indicating that those who participated in the open label study had better efficacy results than those who didn't.*

The open-label study commenced prior to the blinded pivotal studies. The following investigator's participated in the open label study and in one of the Phase 3 pivotal studies as follows:

| <u>Study 0203 #</u> | <u>Name</u> | <u>Study 0114 #</u> |
|---------------------|-------------|---------------------|
|---------------------|-------------|---------------------|

| | | |
|----|--|----|
| 3 | | 17 |
| 20 | | 7 |
| 26 | | 8 |
| 28 | | 9 |
| 41 | | 13 |
| 44 | | 19 |

| <u>Study 0204 #</u> | <u>Name</u> | <u>Study 0114 #</u> |
|---------------------|-------------|---------------------|
| 11 | | 3 |
| 12 | | 4 |
| 18 | | 10 |
| 26 | | 18 |
| 39 | | 11 |
| 40 | | 12 |
| 51 | | 16 |

Quality Control (Study DAP0114)

- There were 333 samples located after the study reported had been finalized and submitted to the Agency under the NDA under pretext of the 120-Day Safety Update. According to the Amended Report dated April 8, 2005, the module originally submitted with NDA 21-794 contained figures that were based on available plasma dapsone information. After reviewing the original data, Atrix Laboratories discovered that some laboratory data were missing from the dataset. When contacted about this error, _____ located the remaining samples, which were stored frozen, and sent them to the laboratory _____ for analysis. These results were pending at the time of the 5% Dapsone Topical Gel submission.
- Although some PK samples were found in a freezer, others were apparently lost during shipping. Plasma dapsone levels for Months 6, 9, and 12 are not available for Patient 1424. According to Amendment 030 (which was a response to FDA clinical information request dated April 21, 2005), there is documentation from the clinical site _____ that Months 6, 9, and 12 plasma dapsone samples were drawn and shipped to the central laboratory; however, the Applicant has no explanation for the samples not arriving at _____ other than they were somehow lost during the shipping period.

Inaccurate Data Listing (Study DAP0114)

- Response to request for information dated March 4, 2005 (Appendix 18, pg. 4 of 8) provided an additional abnormal lab value at Visit 12 of an elevated LDH of 423 IU/L (normal range 94-250 IU/L) for Patient 1424. It appears that some data from _____ or a post treatment follow-up (LDH of 165 IU/L rather than 423 IU/L) were conveyed as 12-Month Visit data (Mod 5, Vol. 80, pg. 333 of 588 vs. Submission dated 03-04-05, Appendix 18, pg. 4 of 8).

Study Duration

- *Pivotal studies were 12 weeks in duration; however, there were patients treated for >3-4 Months 759 (51.7%) 782 (53.3%) >4-6 Months 5 (0.3%) 8 (0.5%) in the vehicle and active controlled groups, respectively for Studies DAP0203 and DAP0204 (Source: Revised ISS, Table 13A.). It is not clear why patients should have sufficient study drug to continue therapy for prolong periods in a controlled environment with a potentially hazardous study drug.*
- *There were numerous protocol violations in regards to end of study at Week 12 in Studies DAP0203 and DAP0204 (ISS, Mod 5, Vol., 87, Table 24, pg. 38); however, the Applicant did not consider these protocol violations. According to the protocol, visit window was to be ± 3 days; however, 759 (51.7%) VC and 782 (53.3%) DTG patients who were treated > 3-4 months and 5 (0.3%) VC and 8 (0.5%) DTG patients treated >4 -6 months. According to the FDA statistical reviewer, visits outside the visit window did not impact efficacy results.*

4.5 Compliance with Good Clinical Practices

According to the applicant, all studies were conducted in accordance with FDA Good Clinical Practice guidelines and Health Canada regulations.

4.6 Financial Disclosures

The applicant certifies that investigators have not entered into any financial arrangement whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Four pharmacokinetic studies (DAP9903, DAP0110, 03-0-182; and DAP0114) demonstrated that dapsonsone is slowly absorbed after topical administration of 5% DTG. Systemic exposure to dapsonsone and its metabolites after 5% DTG are approximately 100-fold lower than those observed after oral dapsonsone treatment and that accumulation does not occur after repeated dosing with 5% DTG for up to 12 months. Mean peak plasma concentrations (C_{max}) of dapsonsone achieved after repeated dosing with 5% DTG ranged from 7.5 to 26.8 ng/mL, about 50- to 100-fold lower than those observed after a single, oral 100-mg dose of dapsonsone (mean C_{max} 1375 ng/mL). Plasma AUCs after 5% DTG were about 100-fold lower than those after oral dapsonsone.

Drug-drug interaction was studied in Study 03-0-182, a multiple-dose study conducted to evaluate the possibility of a drug-drug interaction between Aczone™ Gel 5% and trimethoprim/sulfamethoxazole (TMP/SMX) at steady-state. Neither TMP nor SMX levels were affected by co-administration with Aczone™ Gel 5%. However, co-administration of TMP/SMX

and Aczone™ Gel 5% resulted in higher exposure to dapson and its metabolites. No other drug-drug interaction studies were performed.

5.2 Pharmacodynamics

For oral dapson, there is a linear relationship between oral dose and plasma concentration of dapson within the dose range of 50 to 300 mg. Following daily dosing, the mean maximum plasma levels are approximately 1.5-fold higher (for example, range of 2580 to 3260 ng/mL for a 100 mg oral dose) than after a single dose [Balakrishna et al, 1989; Zuidema et al, 1986]. DeGowin et al (1966), reported that the pharmacokinetic profile is not different in G6PD deficient patients.

Patients on oral dapson may experience hematologic adverse effects, including drug induced hemolysis and elevated methemoglobin levels. Hemolytic effects associated with the use of oral dapson occur early, are dose-dependent (increase with increase in dose) and are typically associated with doses greater than 100 mg per day. Nearly all patients who receive oral dapson at doses of 200 or 300 mg per day will develop hemolysis. Methemoglobinemia associated with oral dapson exposure typically occurs at doses above 200 mg/day and is not clinically significant at doses below 100 mg/day. [Zhu and Stiller, 2001; Jollow et al, 1995; Cream and Scott, 1970; DeGowin et al, 1967]

According to the applicant (Letter Date March 4, 2005) 140 to 280 grams of 5% DTG would need to be applied per day in order to achieve an exposure level similar to an oral dapson dose of 50 or 100 mg, respectively. The average daily gram use ranged from 1.3 to 2.2 grams in the 4 studies for which G6PD status was assessed (maximum daily gram use for any patient in these studies was 11.0 grams). Systemic exposure under maximal use conditions with 5% DTG is 127-fold lower than with a single 100 mg oral dapson dose and 63-fold lower than with a single 50 mg oral dapson dose.

The anti-inflammatory effects of dapson that are described in the literature have been reported to provide a beneficial effect in diseases with an inflammatory component to their pathophysiology.

5.3 Exposure-Response Relationships

Study DAP9903 is a 28-Day, multicenter, dose-ranging, pharmacokinetic of study topical dapson gel in patients with facial acne where systemic bioavailability of the dose formulations and regimens of 1% and 5% DTG were evaluated in a dose-escalating manner until steady-state plasma levels were achieved. According to the Applicant, the PK profile for all four Dapson Gel treatment groups was far below the 10µg/mL considered to the threshold level for precipitating dose-related adverse events associated with chronic oral dapson therapy (Mod 5, Vol. 3, DAP9903, Synopsis, pg. v). The study was not powered for efficacy; however overall, the 5% formulation applied twice daily appeared to be the most effective formulation.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Topical treatment of acne vulgaris

6.1.1 Methods

The applicant conducted eight studies in patients with acne vulgaris. Data from two identical 12-week, multicenter, double blind, randomized, parallel-design Phase 3 studies of 5% dapsone topical gel and vehicle gel in patients with acne vulgaris (DAP0203 and DAP0204) were submitted for review and are considered pivotal studies in support of efficacy. Study DAP0004 is a 12-week, multicenter, double blind, randomized parallel-design study of dapsone topical gel and vehicle control, in patients with acne vulgaris that is considered supportive. According to the applicant, all of the studies used the "to-be-marketed" formulation of DTG except for Study TD-010 which was a contact allergenicity and skin sensitization potential by means of the maximization assay conducted in 38 subjects.

Study objectives were to determine the safety and efficacy of twice daily applications of 5% dapsone topical gel applied for 12 weeks in patients with acne vulgaris. At baseline, a determination of the number of inflammatory and non-inflammatory acne lesions was made. Blood samples were drawn for hematology and chemistry analyses. Glucose-6-phosphate dehydrogenase (G6PD) enzyme activity was also screened; however, these patients were not excluded from study participation. Patients who met all of the eligibility criteria were randomly assigned to Dapsone Topical Gel (DTG) or the Vehicle Control (VC) in a 1:1 ratio.

Admission Criteria

Inclusion Criteria (Inclusion criteria are as listed in the protocols. Only those criteria that might have an impact on labeling are listed.)

1. Male and female patients, 12 years of age and older.
2. Female patients of childbearing potential must not be pregnant or nursing. All female patients were to practice an effective method of birth control as determined by the Investigator. Any female who is not sexually active must agree to begin using an effective method of birth control, excluding birth control pills, if she becomes sexually active during the study.
3. Patients must have a clear diagnosis of acne vulgaris of the face, as defined by having 20-50 inflammatory acne lesions (pustules and papules) and 20-100 comedones above the mandibular line at Baseline.
4. Patient was willing to avoid swimming and bathing for 2 hours following test article application.
5. Patient was willing to avoid moisturizers, sunscreens, and cosmetics for 1 hour following test article application.

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6. Patients must be willing to undergo hematology and chemistry blood draws at study initiation and at study completion.

Exclusion Criteria

Reviewer comments:

G6PD deficient patients were not excluded from the pivotal Phase 3 clinical trials DAP0203 and DAP0204. Exclusion criteria are acceptable for the indication and with use of this drug.

Materials and Supplies

Dapsone Topical Gel and Vehicle Control

Atrix Labs prepared and supplied the Dapsone Topical Gel and Vehicle Control in 30 gram tubes.

Ingredient

Dapsone USP* (DAP)

Diethylene glycol monoethyl ether (DGME)

Methylparaben USP

Carbomer _____

Sodium hydroxide USP 1 _____

Purified water USP

* Dapsone Topical Gel only – not Vehicle Control

Test Article/Blinding

Patients, investigators, and Atrix clinical personnel were to be blinded to the study treatment. Study site personnel who were responsible for conducting the safety and efficacy assessments were not to handle the study medication. Patients were instructed not to discuss the appearance of the study medication with the study site personnel. The drug accountability and study drug weight assessments were to be conducted by a person not involved with the safety and efficacy assessments.

Reviewer comments:

It is not known whether active and vehicle study drugs were identical in appearance. The active gel contains visible particles ranging in size from _____ μm in diameter.

Test Article Accountability

Test article was to be weighed at each visit to assess patient compliance.

Treatment

A thin film of 5% Dapsone Topical Gel, or Vehicle Control was to be rubbed gently onto the entire facial skin twice daily (once in the morning and once prior to bedtime) for 12 weeks. Test article could also be applied to acne involved areas other than the face. However, efficacy assessments, local adverse reaction assessment, and photographs (if applicable) were of facial skin only. All adverse events regardless of treatment area were collected. Patients returned to the study site every 2 weeks. Study drug was dispensed and collect at each visit.

Reviewer comments:

Percent body surface area (BSA) of application was not provided.

6.1.2 General Discussion of Endpoints

The primary efficacy variables were success on 1) the static Investigator's Global Assessment called Global Acne Assessment Score (GAAS) and 2) mean percent reduction in inflammatory, non-inflammatory, and total lesion counts at Week 12 or early termination (ET) in the ITT population.

Efficacy Evaluation

The static Global Acne Assessment is based on the following 5-point scale:

The Global Acne Assessment

- 0 None: no evidence of facial acne vulgaris
- 1 Minimal: a few non-inflammatory lesions (comedones) are present; a few inflammatory lesions (papules/pustules) may be present
- 2 Mild: several to many non-inflammatory lesions (comedones) are present; a few inflammatory lesions (papules/pustules) are present
- 3 Moderate: many non-inflammatory (comedones) and inflammatory lesions (papules/pustules) are present; no nodulo-cystic lesions are allowed
- 4 Severe: significant degree of inflammatory disease; papules/pustules are a predominant feature; a few nodulo-cystic lesions may be present; comedones may be present

The intent-to-treat (ITT) population was used to analyze the primary efficacy measures. ITT population is defined as all patients randomized into the trial that are dispensed study medication.

Variation from Scheduled Visit Days

To allow for scheduling flexibility, reasonable ± 3 days variation will be permitted from the specified time of each visit.

Departure from Protocol for an Individual

Only very unusual circumstances may justify a departure from the protocol for an individual patient. Except in an emergency, the Investigator or designated study staff member must contact, request, and receive permission from the Atrix Laboratories Study Director (or Atrix Laboratories monitor if the Study Director is not available) to allow such a departure.

Reviewer comment:

There were numerous protocol violations in regards to end of study at Week 12 Studies DAP0203 and DAP0204 (ISS, Mod 5, Vol., 87, Table 24, pg. 38); however, the Applicant did not consider these protocol violations. There were 759 (51.7%) VC and 782 (53.3%) DTG patients who were treated > 3 -4 months and 5 (0.3%) VC and 8 (0.5%) DTG patients treated >4 -6 months; however, according to the Statistical reviewer, they did not have much impact on efficacy outcomes. According to the FDA Statistical Reviewer, the subjects with longer durations had very similar success rates to those with 12 weeks duration. An analysis was run where if a subject had duration of greater than 90 days (12 weeks + 6 days) results at Week 8 rather than the final visit results were used. The success rates did not change substantially. Both the active and vehicle success rates dropped by about 1% (so the difference remained about the same) and the p-values were virtually identical.

Efficacy Endpoints

Primary

The primary efficacy endpoints at Week 12 or early termination were:

- Incidence of Success based on GAAS. Success was defined as a score of 0 (none) or 1 (minimal) on a 5-point static GAAS.
- Mean percent reduction in inflammatory, non-inflammatory, and total acne lesion counts.

The same efficacy parameters were analyzed for the modified intent-to-treat (MITT) and per-protocol (PP) populations at Week 12/ET and Week 12, respectively. The MITT analyses were added post hoc; this population was defined as patients enrolled in the study with a Baseline GAAS ≥ 2 . The PP population was defined as all ITT patients without major protocol deviations.

Secondary

The secondary efficacy endpoints for the ITT population included:

- Mean lesion count at Week 12/ET for inflammatory, non-inflammatory, and total acne lesions.
- Mean reduction-from-Baseline for inflammatory, non-inflammatory, and total acne lesions.

6.1.3 Study Design

Both pivotal studies (DAP0203 and DAP0204) were randomized, double-blind, parallel-design, multicenter studies of the efficacy and safety of 5% Dapsone Topical Gel (DTG) and Vehicle Control (VC) when applied twice daily for 12 weeks in patients with acne vulgaris.

Statistical Methods (See Statistical Review for full details):

Success based on the GAAS was determined using the Cochran-Mantel-Haenszel procedure. The mean percent reduction-from-Baseline acne lesion count parameters (inflammatory, non-inflammatory, and total) were analyzed using an analysis of covariance (ANCOVA) with the Baseline value as a covariate. Efficacy was demonstrated if statistical significance was achieved for: (1) "Success" based on GAAS; and (2) mean percent reduction-from-Baseline in acne lesion counts for two of three parameters (i.e., inflammatory, non-inflammatory, and total). Similar analyses were performed for the secondary efficacy endpoints.

Letters of Clarification

There were four Letters of Clarification during the course of the study, dated November 6, 2002, December 20, 2002, and February 14, 2003 (two separate letters).

Other Changes in Study Conduct or Planned Analyses

There were three changes in the planned analyses:

- An ad-hoc MITT population was defined as patients who enrolled in the study with a Baseline GAAS ≥ 2 . This population excluded the 99 patients who had a Baseline GAAS of 1. The MITT population was analyzed for the primary and secondary efficacy endpoints.

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- DTG and VC adverse event data were compared using the Fisher's Exact Test for adverse events with an incidence rate of $\geq 2\%$.
- Additional evaluations of application site and non-application site adverse events were performed.

Study DAP0203 Results

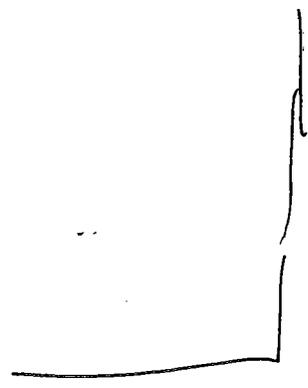
Number of Patients:

A total of 1,485 patients were randomized to active or vehicle at 52 study sites located in the US and Canada. There were 745 patients randomized to DTG and 740 patients randomized to vehicle control (VC). Of those, 1,255 patients (84.5%) completed the study and 230 (15.5%) withdrew or were lost to follow-up.

Study dates: Study initiation date: November 18, 2002
Study completion date: August 15, 2003

Investigators

Study Centers:



Demographics:

The treatment groups were balanced with respect to gender, age, race/ethnicity, and Baseline GAAS and acne lesion counts. There was a similar distribution of female (788; 53.1%) and male patients (697; 46.9%) enrolled in the study. The majority (1090/1485; 73.4%) of patients were Caucasian. One hundred seventy-seven patients (11.9%) in the study population were Black, and 154 (10.4%) were Hispanic. The mean patient age was 19 years in each treatment group. Twelve patients were identified as G-6-PD deficient (5 DTG; 7 VC) patients.

The majority (872/1485; 58.7%) of patients had moderate acne, as defined by a Baseline GAAS of 3; 479 patients (32%) had mild acne with a Baseline GAAS of 2. The mean number of total acne lesions determined at Baseline for patients in the DTG group was 79.7, and the mean numbers of inflammatory and non-inflammatory lesions were 30.8 and 48.9, respectively. The mean number of total acne lesions at Baseline for patients in the VC group was 80.0, and the mean number of inflammatory and non-inflammatory lesions was 30.2 and 49.8, respectively.

Table 2 (Applicant's Table A)

Table A. Patient Populations

| Classification | Treatment Group | | Total Patients |
|--------------------------|-----------------|---------------|----------------|
| | DTG (N=745) | VC (N=740) | |
| All-patient dataset | 745 (100.0%) | 740 (100.0%) | 1485 (100.0%) |
| ITT dataset | 745 (100.0%) | 740 (100.0%) | 1485 (100.0%) |
| MITT dataset | 699 (93.8%) | 687 (92.8%) | 1386 (93.3%) |
| PP dataset- | 573 (76.9%) | 555 (75.0%) | 1128 (76.0%) |
| Safety-evaluable dataset | 730 (98.0%) | 726 (98.1%) | 1456 (98.0%) |

ITT dataset: Contains all data for all patients who were dispensed test article. For patients who did not complete the study, the last available observation was carried forward to the Week 12 time point.

MITT dataset: Ad-hoc dataset that contains efficacy data for patients enrolled in the study with a Baseline GAAS \geq 2.

PP dataset: Contains all data for patients without major protocol deviations in the ITT dataset.

Safety-evaluable dataset: Contains all data for patients who applied at least one dose of test article or reported an adverse event in the ITT dataset. Note: There were 29 patients who did not return for a study visit after being dispensed study drug, and did not report an adverse event in a telephone interview.

Source: Table 1A

N = number of patients; ITT = intent to treat; MITT = modified intent to treat; PP = per protocol

Table 3 (Applicant's Table B)

Table B. Summary of Patient Disposition

| Disposition | Treatment Group | | Total Patients |
|-----------------------------|-----------------|-------------|----------------|
| | DTG | VC | |
| Enrolled ^a | 745 (100%) | 740 (100%) | 1485 (100%) |
| Completed study | 638 (85.6%) | 617 (83.4%) | 1255 (84.5%) |
| Discontinued study | 107 (14.4%) | 123 (16.6%) | 230 (15.5%) |
| Adverse event | 3 (0.4%) | 5 (0.7%) | 8 (0.5%) |
| Lack of Efficacy | 3 (0.4%) | 7 (0.9%) | 10 (0.7%) |
| Administrative ^b | 101 (13.6%) | 111 (15.0%) | 212 (14.3%) |

Patient base: all-patient dataset

Source: Tables 1B, 2, and 4

^a Enrolled = All randomized patients dispensed test article (i.e., ITT population).

^b Administrative reasons for withdrawal include: lost to follow up, patient voluntarily withdrew, and patient non-compliance.

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Four (0.3%) withdrawals (1 DTG; 3 VC) were due to treatment-related adverse events. Application site pruritus, erythema, and oiliness (active). Erythema, dryness, stinging, and peeling were reported in the vehicle as reasons for study discontinuation.

Sixteen hundred seventy-eight (1678) protocol deviations were attributable to 762 patients (out of 1485 patients) during the study. Patient visits outside the visit window accounted for the majority of protocol deviations (911; 499 patients). The remaining deviations included acne lesions not counted by the same clinician as at Baseline (273; 147 patients), missed patient visits (132; 116 patients), and prohibited medication (74; 69 patients). Six patients became pregnant during the study. One patient was 11 years old when enrolled in the study. The distribution of protocol violations was similar across treatment groups. Protocol deviations were not considered to affect the results of the study.

Reviewer comments:

According to the FDA Statistical Reviewer, visits outside the visit window did not impact efficacy results.

Baseline demographics for the ITT population are summarized in Table C.

Table 4 (Applicant's Table C.) Distribution of Patients by Treatment Group

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| Demographic | Treatment Group | | Total Patients (N=1485) |
|--------------------------|-----------------|---------------|----------------------------|
| | DTG (N=745) | VC (N=740) | |
| Gender | | | |
| Male | 358 (48.1%) | 339 (45.8%) | 697 (46.9%) |
| Female | 387 (51.9%) | 401 (54.2%) | 788 (53.1%) |
| Age, years | | | |
| Mean | 19.01 | 19.46 | 19.24 |
| SD | 7.27 | 7.54 | 7.41 |
| Range | 12-53 | 11-59 | 11-59 |
| Race/Ethnicity | | | |
| White | 548 (73.6%) | 542 (73.2%) | 1,090 (73.4%) |
| Black | 94 (12.6%) | 83 (11.2%) | 177 (11.9%) |
| Hispanic | 73 (9.8%) | 81 (10.9%) | 154 (10.4%) |
| Asian | 19 (2.6%) | 19 (2.6%) | 38 (2.6%) |
| Other | 11 (1.5%) | 15 (2.0%) | 26 (1.8%) |
| Baseline GAAS | | | |
| 0 = None | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| 1 = Minimal | 46 (6.2%) | 53 (7.2%) | 99 (6.7%) |
| 2 = Mild | 236 (31.7%) | 243 (32.8%) | 479 (32.3%) |
| 3 = Moderate | 447 (60.0%) | 425 (57.4%) | 872 (58.7%) |
| 4 = Severe | 16 (2.1%) | 19 (2.6%) | 35 (2.4%) |
| Inflammatory Lesions | | | |
| Mean | 30.82 | 30.21 | 30.51 |
| SD | 10.35 | 9.86 | 10.11 |
| Range | 14-84 | 18-114 | 14-114 |
| Non-inflammatory Lesions | | | |
| Mean | 48.86 | 49.82 | 49.34 |
| SD | 25.55 | 24.77 | 25.16 |
| Range | 13-240 | 8-172 | 8-240 |
| Total Lesions | | | |
| Mean | 79.68 | 80.03 | 79.85 |
| SD | 29.60 | 28.82 | 29.20 |
| Range | 39-288 | 37-261 | 37-288 |

Patient base: ITT dataset

Source: Table 6A

N = Number of patients; SD = standard deviation; GAAS = Global Acne Assessment Score

There was a similar distribution of female (788; 53.1%) and male patients (697; 46.9%) between treatment groups in the ITT population. The majority (1090/1485; 73.4%) of patients were

Caucasian. One hundred seventy-seven patients (11.9%) in the study population were Black and 154 patients (10.4%) were Hispanic. The mean \pm SD age of patients was 19.24 ± 7.41 years, and the age range of all patients in the study was 11–59 years. The treatment groups were balanced with respect to gender, age, race/ethnicity, weight, height, and Baseline GAAS and acne lesion counts for all populations.

Three populations were analyzed ITT, MITT, and per protocol populations. The ITT population is defined as all subjects randomized and dispensed test article. The MITT population is defined as all ITT subjects with a baseline GAAS ≥ 2 . The per protocol population is defined in the protocol as those subjects without major protocol violations.

The ITT and MITT populations are presented for the GAAS Success rate and lesion counts.

The GAAS Success rate for the ITT population is summarized in Table E.

Table 5 (Applicant's Table E. GAAS) Success Rate at Week 12/ET (ITT Population)

| Efficacy Measure | Mean Percent Reduction | | p-value ^b |
|---|------------------------|--------------------|----------------------|
| | DTG (N=745) | VC (N=740) | |
| Success Rate Based Upon the GAAS ^a | 329/745 (44.2%) | 266/740 (35.9%) | 0.0003 |

Patient base: ITT dataset

Source: Table 10A

N = number of patients; GAAS = Global Acne Assessment Score

^a Score was 0 or 1 at Week 12/ET.

^b Cochran-Mantel-Haenszel procedure adjusting for center.

For success rate based upon the GAAS endpoint for the ITT population, the FDA assessment concurs with the Applicant's conclusion that statistical significance is demonstrated for DTG over VC.

Mean percent reduction-from-Baseline of acne lesion counts for the ITT is presented in Table F that follows.

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Table 6 (Applicant's Table F.) Mean Percent Reduction-from-Baseline of Acne Lesion Counts at Week 12/ET (ITT Population)

| Efficacy Measure | Treatment Group | | | | p-value Mean Percent Reduction |
|--------------------------|------------------------------------|---------------------------------------|------------------------------------|---------------------------------------|---|
| | DTG (N=745) | | VC (N=740) | | |
| | Mean Baseline Count (±SE) | Mean Percent Reduction (±SE) | Mean Baseline Count (±SE) | Mean Percent Reduction (±SE) | |
| Inflammatory Lesions | 30.8 (±0.4) | 45.9% (±1.8) | 30.2 (±0.4) | 41.7% (±1.8) | 0.0302 |
| Non-Inflammatory Lesions | 48.9 (±0.9) | 31.1% (±2.1) | 49.8 (±0.9) | 23.9% (±2.2) | 0.0022 |
| Total Lesions | 79.7 (±1.1) | 38.3% (±1.6) | 80.0 (±1.1) | 32.0% (±1.7) | 0.0004 |

Note: For the mean percent reduction in acne lesion counts, least squares means (±SE) are displayed. P-values are based upon ANCOVA adjusting for Baseline count.

Patient base: ITT dataset

Source: Tables 9A and 17

N = number of patients; SE = standard error

For success based upon the percent reduction in lesion count endpoints for the ITT population in Study 0203, the FDA assessment concurs with the Applicant's conclusion that statistical significance is demonstrated for DTG over VC for three lesion count endpoints.

According to the applicant, statistically significant differences were observed between the treatment groups for all six secondary endpoints. Significantly greater responses were observed for the DTG group compared with the VC group. The mean acne lesion counts (inflammatory, non-inflammatory, and total) were significantly lower for DTG-treated patients versus VC treated patients. Additionally, the mean reduction in acne lesion counts was significantly greater for DTG-treated patients versus VC-treated patients.

The secondary efficacy analyses in this study support the conclusions of the primary efficacy analyses, which showed that 5% DTG is effective for the treatment of acne vulgaris.

MITT Population

Ninety-nine (46 DTG; 53 VC) patients were entered into the study with a Baseline GAAS of 1. An ad-hoc MITT population excluding these patients was also evaluated.

Efficacy results for the MITT population are presented in Tables 9C and 10C. Additionally, the GAAS Success rate for the MITT population is summarized in Table I, and the mean percent reduction-from-Baseline of acne lesion counts are summarized in Table J.

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Table 7 (Applicant's Table I.) GAAS Success Rate at Week 12/ET (MITT Population)

| Efficacy Measure | Treatment Group | | p-value ^b |
|---|-----------------|-----------------|----------------------|
| | DTG (N=699) | VC (N=687) | |
| Success Rate Based Upon the GAAS ^a | 291/699 (41.6%) | 223/687 (32.5%) | 0.0001 |

Patient base: MITT dataset (Baseline GAAS ≥ 2)

Source: Table 10C

N = number of patients; GAAS = Global Acne Assessment Score

^a Score was 0 or 1 at Week 12/ET.

^b Cochran-Mantel-Haenszel procedure adjusting for center.

For success rate based upon the GAAS endpoint for the MITT population, the FDA assessment concurs with the Applicant's conclusion that statistical significance is demonstrated for DTG over VC.

Table 8 (Table J.) Mean Percent Reduction-from-Baseline of Acne Lesion Counts at Week 12/ET (MITT Population)

| Efficacy Measure | Treatment Group | | | | p-value Mean Percent Reduction |
|--------------------------|------------------------------------|---------------------------------------|------------------------------------|---------------------------------------|---|
| | DTG (N=699) | | VC (N=687) | | |
| | Mean Baseline Count (±SE) | Mean Percent Reduction (±SE) | Mean Baseline Count (±SE) | Mean Percent Reduction (±SE) | |
| Inflammatory Lesions | 31.2 (±0.4) | 45.8% (±1.8) | 30.7 (±0.4) | 40.8% (±1.9) | 0.0158 |
| Non-Inflammatory Lesions | 49.8 (±1.0) | 30.6% (±2.2) | 50.7 (±1.0) | 22.5% (±2.2) | 0.0009 |
| Total Lesions | 80.9 (±1.1) | 37.9% (±1.7) | 81.4 (±1.1) | 30.8% (±1.7) | 0.0001 |

Note: For mean percent reduction in acne counts, least square means (±SE) are displayed.

P-values are based upon ANCOVA adjusting for Baseline count.

Patient base: MITT dataset (Baseline GAAS ≥ 1)

Source: Tables 6C and 9C

N = number of patients; SE = standard error

For Study DAP0203, success based upon the percent reduction in lesion count endpoints for the MITT population, the FDA assessment concurs with the Applicant's conclusion that statistical significance is demonstrated for DTG over VC for three lesion count (inflammatory, non-inflammatory, and total lesions) endpoints.

Efficacy Conclusion

The statistical review is consistent with the applicant results that demonstrates a statistically higher response for DTG group than VC group at Week 12/ET for all four primary efficacy endpoints (percent change in inflammatory, non-inflammatory, and total lesions and success on the GAAS). The results of this study demonstrate that 5% DTG was effective when administered twice daily for 12 weeks for the treatment of acne vulgaris. Efficacy was demonstrated on all four primary efficacy parameters: Success (none or minimal disease at the end-of-treatment) based on the static GAAS and significant improvement in all three acne lesion count parameters (mean percent reduction in inflammatory, non-inflammatory, and total lesion counts).

Results for the MITT and per protocol populations were consistent with those of the ITT population in Study 0203. Although statistical significance is achieved, the numerical difference between active and vehicle are not that great. The benefit should greatly outweigh the risk with use of a product with marginal efficacy in treatment of acne vulgaris for which a plethora of safe and effective products are available.

Study DAP0204 Results

Protocol Title: "A 12-Week, Multicenter, Double-Blind, Randomized, Parallel-Design Study of 5% Dapsone Topical Gel and Vehicle Control in Patients with Acne Vulgaris"

Study dates: November 20, 2002 to September 12, 2003

Study Initiation Date: November 20, 2002

Study Completion Date: September 12, 2003

Number of Patients:

A total of 1,525 patients were enrolled in this study; 761 to the DTG group and 764 to the VC group. A total of 1525 patients were enrolled in this study; 761 to the DTG group and 764 to the VC group. The following 53 study sites and investigators were located in the US and Canada.

Investigators/Study Centers:

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 X § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 1

Demographics:

The treatment groups were balanced with respect to gender, age, race/ethnicity, and Baseline GAAS and acne lesion counts. There was a similar distribution of female (799; 52.4%) and male patients (726; 47.6%) enrolled in the study. The majority (1105/1525; 72.5%) of patients were Caucasian. Two hundred forty-three patients (15.9%) in the study population were Black, and 129 (8.5%) were Hispanic. The mean patient age was 19 years in each treatment group.

Reviewer comments:

Thirty-two patients were G-6-PD deficient (14 DTG; 18 VC).

Baseline demographics for the ITT population are summarized in Table C.
Table 9 (Applicant's Table C.) Distribution of Patients by Treatment Group

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| Demographic | Treatment Group | | Total Patients (N=1525) |
|--------------------------|-----------------|---------------|----------------------------|
| | DTG (N=761) | VC (N=764) | |
| Gender | | | |
| Male | 367 (48.2%) | 359 (47.0%) | 726 (47.6%) |
| Female | 394 (51.8%) | 405 (53.0%) | 799 (52.4%) |
| Age, years | | | |
| Mean | 19.52 | 19.64 | 19.58 |
| SD | 7.70 | 7.57 | 7.63 |
| Range | 12-81 | 12-57 | 12-81 |
| Race/Ethnicity | | | |
| White | 559 (73.5%) | 546 (71.5%) | 1105 (72.5%) |
| Black | 115 (15.1%) | 128 (16.8%) | 243 (15.9%) |
| Hispanic | 65 (8.5%) | 64 (8.4%) | 129 (8.5%) |
| Asian | 12 (1.6%) | 16 (2.1%) | 28 (1.8%) |
| Other | 10 (1.3%) | 10 (1.3%) | 20 (1.3%) |
| Baseline GAAS | | | |
| 0 = None | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| 1 = Minimal | 32 (4.2%) | 26 (3.4%) | 58 (3.8%) |
| 2 = Mild | 264 (34.7%) | 273 (35.7%) | 537 (35.2%) |
| 3 = Moderate | 447 (58.7%) | 440 (57.6%) | 887 (58.2%) |
| 4 = Severe | 18 (2.4%) | 25 (3.3%) | 43 (2.8%) |
| Inflammatory Lesions | | | |
| Mean | 30.82 | 30.38 | 30.60 |
| SD | 10.01 | 9.93 | 9.97 |
| Range | 11-114 | 11-88 | 11-114 |
| Non-inflammatory Lesions | | | |
| Mean | 47.47 | 45.85 | 46.66 |
| SD | 22.96 | 21.76 | 22.37 |
| Range | 20-190 | 9-100 | 9-190 |
| Total Lesions | | | |
| Mean | 78.29 | 76.23 | 77.26 |
| SD | 27.01 | 25.69 | 26.37 |
| Range | 40-220 | 40-177 | 40-220 |

Patient base: ITT dataset

Source: Tables 6A and 17

N = Number of patients; SD = standard deviation; GAAS = Global Acne Assessment Score

The majority (887/1525; 58.2%) of patients had moderate acne, as defined by a Baseline

GAAS of 3; 537 patients (35.2%) had mild acne with a Baseline GAAS of 2. The mean number of total acne lesions determined at Baseline for patients in the DTG group was 78.3, and the mean numbers of inflammatory and non-inflammatory lesions were 30.8 and 47.5, respectively. The mean number of total acne lesions at Baseline for patients in the VC group was 76.2, and the mean number of inflammatory and non-inflammatory lesions was 30.4 and 45.8, respectively.

Table 10 (Applicant's Table A.): Patient Populations

| Classification | Treatment Group | | Total Patients |
|--------------------------|-----------------|---------------|----------------|
| | DTG (N=761) | VC (N=764) | |
| All-patient dataset | 761 (100.0%) | 764 (100.0%) | 1525 (100.0%) |
| ITT dataset | 761 (100.0%) | 764 (100.0%) | 1525 (100.0%) |
| MITT dataset | 729 (95.8%) | 738 (96.6%) | 1467 (96.2%) |
| PP dataset | 586 (77.0%) | 592 (77.5%) | 1178 (77.2%) |
| Safety-evaluable dataset | 736 (96.7%) | 741 (97.0%) | 1477 (96.9%) |

All-patients dataset: Contains all data for all patients who were dispensed test article.

ITT dataset: Contains all data for all patients who were dispensed test article. For patients who did not complete the study, the last available observation was carried forward to the Week 12 time point.

MITT dataset: Ad-hoc dataset that contains efficacy data for patients enrolled in the study with a Baseline GAAS \geq 2.

PP dataset: Contains all data for patients without major protocol deviations in the ITT dataset.

Safety-evaluable dataset: Contains all data for patients who applied at least one dose of test article or reported an adverse event in the ITT dataset. Note: There were 48 patients who did not return for a study visit after being dispensed study drug, and did not report an adverse event in a telephone interview.

Source: Table 1A

N = number of patients; ITT = intent to treat; MITT = modified intent to treat;

PP = per protocol

The majority of patients in both treatment groups completed the study. The distribution of patients who withdrew was similar across treatment groups (133 DTG; 139 VC). The most common reason for discontinuation was lost to follow-up (148; 9.7%).

A summary of patient disposition is shown in Table B.

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Table 11 (Applicant's Table B.) Summary of Patient Disposition

| Disposition | Treatment Group | | Total Patients |
|-----------------------------|-----------------|-------------|----------------|
| | DTG | VC | |
| Enrolled ^a | 761 (100%) | 764 (100%) | 1525 (100%) |
| Completed study | 628 (82.5%) | 624 (81.7%) | 1252 (82.1%) |
| Discontinued study | 133 (17.5%) | 140 (18.3%) | 273 (17.9%) |
| Adverse event | 3 (0.4%) | 4 (0.5%) | 7 (0.5%) |
| Lack of Efficacy | 6 (0.8%) | 8 (1.0%) | 14 (0.9%) |
| Administrative ^b | 124 (16.3%) | 128 (16.8%) | 252 (16.5%) |

Patient base: all-patient dataset

Source: Tables 1B, 2, and 4

^a Enrolled = All randomized patients dispensed test article (i.e., ITT population).

^b Administrative reasons for withdrawal include: lost to follow up, patient voluntarily withdrew, and patient non-compliance.

Seven (0.5%) withdrawals (3 DTG; 4 VC) were due to treatment-related adverse events. Fifteen hundred eighty-seven (1587) protocol deviations were attributable to 788 patients (out of 1525 patients) during the study. Patient visits outside the visit window accounted for the majority of protocol deviations (1045; 551 patients). The remaining deviations included acne lesions not counted by the same clinician as at Baseline (200; 143 patients), missed patient visits (144; 129 patients), and prohibited medication (59; 54 patients). Two patients became pregnant during the course of the study. The distribution of protocol violations was similar across treatment groups. Protocol deviations were not considered to affect the results of the study.

Reviewer comments:

As in Study DAP0203, patient visits outside the visit window accounted for the majority of protocol deviations (1045; 551 patients).

6.1.4 Efficacy Findings

Efficacy Results:

For the GAAS, the Week 12/ET Success rate for the DTG group was significantly higher than the VC group, 36.9% versus 29.8% (p=0.0017), in the ITT population. For each of the three acne lesion types, mean percent reductions from Baseline to Week 12/ET were statistically greater in the DTG group compared with the VC group.

The GAAS Success rate for the ITT population is summarized in Table E.

Table 12 (Applicant's Table E.) GAAS Success Rate at Week 12/ET (ITT Population)

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| Efficacy Measure | Mean Percent Reduction | | p-value ^b |
|---|------------------------|--------------------|----------------------|
| | DTG (N=761) | VC (N=764) | |
| Success Rate Based Upon the GAAS ^a | 281/761 (36.9%) | 228/764 (29.8%) | 0.0017 |

Patient base: ITT dataset

Source: Table 10A

N = number of patients; GAAS = Global Acne Assessment Score

^a Score was 0 or 1 at Week 12/ET.

^b Cochran-Mantel-Haenszel procedure adjusting for center.

For success rate based upon the GAAS endpoint for the ITT population in Study 0204, the FDA assessment concurs with the Applicant's conclusion that statistical significance is demonstrated for DTG over VC.

Mean percent reduction-from-Baseline of acne lesion counts for the ITT population are summarized in Table I.

Table 13 (Applicant's Table I.) Mean Percent Reduction-from-Baseline of Acne Lesion Counts at Week 12/ET (ITT Population)

| Efficacy Measure | Treatment Group | | | | p-value Mean Percent Reduction |
|--------------------------|------------------------------------|---------------------------------------|------------------------------------|---------------------------------------|---|
| | DTG (N=761) | | VC (N=764) | | |
| | Mean Baseline Count (±SE) | Mean Percent Reduction (±SE) | Mean Baseline Count (±SE) | Mean Percent Reduction (±SE) | |
| Inflammatory Lesions | 30.8 (±0.4) | 47.6% (±1.7) | 30.4 (±0.4) | 40.3% (±1.7) | < 0.0001 |
| Non-Inflammatory Lesions | 47.5 (±0.8) | 29.6% (±1.9) | 45.8 (±0.8) | 21.1% (±1.9) | < 0.0001 |
| Total Lesions | 78.3 (±1.0) | 37.4% (±1.5) | 76.2 (±0.9) | 29.3% (±1.5) | < 0.0001 |

Note: For the mean percent reduction in acne lesion counts, least squares means (±SE) are displayed. P-values are based upon ANCOVA adjusting for Baseline count.

Patient base: ITT dataset

Source: Tables 9A and 17

N = number of patients; SE = standard error

For success based upon the percent reduction in lesion count endpoints for the ITT population in Study 0204, the FDA assessment concurs with the Applicant's conclusion that statistical significance is demonstrated for DTG over VC for three lesion count endpoints. Results show that the DTG group had a statistically higher response than the VC group at Week 12/ET for all primary efficacy endpoints in the ITT population. No treatment-by-center interactions were observed. These results demonstrate that 5% DTG applied twice daily is effective for the treatment of acne vulgaris.

MITT Population

As in Study 0203, an ad-hoc MITT population excluding these patients was also evaluated for Study 0204. Fifty-eight patients (32 DTG; 26 VC) were entered into the study with a GAAS of 1. An ad-hoc MITT population excluding these patients was also evaluated. Efficacy results for the MITT population are presented in Tables 9C and 10C. Additionally, the GAAS Success rate for the MITT population is summarized in Table I, and the mean percent reduction-from-Baseline of acne lesion counts are summarized in Table J.

Efficacy results for the MITT population are presented in Tables 9C and 10C. Additionally, the GAAS Success rate for the MITT population is summarized in Table I, and the mean percent reduction-from-Baseline of acne lesion counts are summarized in Table J.

Table 14 (Applicant's Table I.) GAAS Success Rate at Week 12/ET (MITT Population)

| Efficacy Measure | Treatment Group | | p-value ³ |
|---|-----------------|-----------------|----------------------|
| | DTG (N=729) | VC (N=738) | |
| Success Rate Based Upon the GAAS ² | 253/729 (34.7%) | 206/738 (27.9%) | 0.0032 |

Patient base: MITT dataset (Baseline GAAS ≥ 2)

Source: Table 10C

N = number of patients; GAAS = Global Acne Assessment Score

² Score was 0 or 1 at Week 12/ET.

³ Cochran-Mantel-Haenszel procedure adjusting for center.

For Study 0204, success rate based upon the GAAS endpoint for the MITT population, the FDA assessment concurs with the Applicant's conclusion that statistical significance is demonstrated for DTG over VC.

Table 15 (Applicant's Table J.) Mean Percent Reduction-from-Baseline of Acne Lesion Counts at Week 12/ET (MITT Population)

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| Efficacy Measure | Treatment Group | | | | p-value Mean Percent Reduction |
|--------------------------|------------------------------------|---------------------------------------|------------------------------------|---------------------------------------|---|
| | DTG (N=729) | | VC (N=738) | | |
| | Mean Baseline Count (±SE) | Mean Percent Reduction (±SE) | Mean Baseline Count (±SE) | Mean Percent Reduction (±SE) | |
| Inflammatory Lesions | 31.0 (±0.4) | 47.2% (±1.7) | 30.5 (±0.4) | 39.8% (±1.7) | < 0.0001 |
| Non-Inflammatory Lesions | 47.6 (±0.9) | 29.4% (±1.9) | 46.1 (±0.8) | 20.6% (±1.9) | < 0.0001 |
| Total Lesions | 78.6 (±1.0) | 37.1% (±1.5) | 76.6 (±1.0) | 28.8% (±1.5) | < 0.0001 |

Note: For mean percent reduction in acne counts, least square means (±SE) are displayed. P-values are based upon ANCOVA adjusting for Baseline count.

Patient base: MITT dataset (Baseline GAAS ≥ 2)

Source: Tables 6C and 9C

N = number of patients; SE = standard error

For Study DAP0204, success based upon the percent reduction in lesion count endpoints for the MITT population, the FDA assessment concurs with the Applicant's conclusion that statistical significance is demonstrated for DTG over VC for three. The results for the MITT population were consistent with those of the ITT population.

Results show that the DTG group had a statistically greater response than the VC group at Week 12/ET for all primary efficacy endpoints. These results demonstrate that 5% DTG applied twice daily is effective for the treatment of acne vulgaris. Results for the MITT population were consistent with those of the ITT population.

Results show that the DTG group had a significantly better response than the VC group at Week 12 for all efficacy endpoints using the PP population. These PP results are consistent with the ITT and MITT analyses, which showed that 5% DTG is effective for the treatment of acne vulgaris.

There were no significant treatment-by-center interactions for non-inflammatory and total lesions. However, a treatment-by-center interaction was observed in the PP population for inflammatory lesions (p=0.0104). A treatment-by-center interaction was observed in the PP population for the mean percent reduction in inflammatory lesions.

6.1.5 Clinical Microbiology

Review is pending.

6.1.6 Efficacy Conclusions

Statistical superiority of 5% dapsone topical gel over vehicle was demonstrated for all primary endpoints (percent change in inflammatory, non-inflammatory, and total lesions, and success on the Global Acne Assessment Scale or GAAS) in two Phase 3 multicenter, randomized, blinded, vehicle controlled studies by enrolling 3,010 subjects at 105 study sites to adequately power the studies to facilitate detecting a small treatment effect. According to the statistical review, efficacy of dapsone gel is only about 4 to 9% better than vehicle.

A post hoc analysis (MITT) was conducted that required at least two grades reduction in addition to achieving none or minimal. The MITT population analysis was performed to exclude subjects enrolled with a GAAS score of 1 (minimal) at baseline. Although no baseline GAAS was mandated, enrollment of patients with a GAAS score of 1 (defined as a few non-inflammatory lesions are present; a few inflammatory lesions may be present) appears inconsistent with the entry criterion to have 20-50 inflammatory acne lesions (pustules and papules) and 20-100 comedones above the mandibular line at Baseline. Nonetheless, the ITT, MITT, and the requirement of at least 2 grade reduction in addition to achieving none or minimal were all statistically significant.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Oral dapsone is approved for treatment of leprosy and dermatitis herpetiformis and has been commercially available for over 60 years and dose related hematological adverse reactions (e.g., hemolysis, methemoglobinemia, and anemia) are most common adverse effect associated with use of oral dapsone.

Patients on oral dapsone may experience hematologic adverse effects; including drug induced hemolysis and elevated methemoglobin levels. Hemolytic effects associated with the use of oral dapsone occur early, are dose-dependent (increase with increase in dose) and are typically associated with doses greater than 100 mg per day. Nearly all patients who receive oral dapsone at doses of 200 or 300 mg per day will develop hemolysis. G6PD deficient patients are the most sensitive to the hematological effects of dapsone. Methemoglobinemia associated with oral dapsone exposure typically occurs at doses above 200 mg/day and is not clinically significant at doses below 100 mg/day.

Safety Population and Safety Monitoring Program

The "Safety Evaluable" population was used to summarize the safety parameters. Subjects without evidence of study drug application and no adverse events reported in the database were excluded from the safety evaluable population. According to the applicant, this is a more conservative approach relative to presenting adverse event rates, as the inclusion of these patients would lower the incidence rates of adverse events.

Clinical Laboratory Data, Electrocardiograms, and Physical Examinations Changes in clinical laboratory parameters, vital signs, electrocardiogram, and physical examination were identified.

A total of 4,506 patients are included in the Applicant's safety database and 4,086 of these were acne vulgaris patients (VC, 1660; 1% DTG, 23; 3% DTG, 31; 5% DTG, 2372), and 15 burn patients with at least 1 dose of study drug or reporting an adverse event during the study. Four hundred five (405) healthy volunteers and 4,086 patients with *acne vulgaris* (VC, 1660; 1% DTG, 23; 3% DTG, 31; 5% DTG, 2372), and 15 burn patients had at least 1 dose of study drug or had an adverse event reported during the study. One hundred nine patients did not return for a study visit after being dispensed study drug, did not have any adverse event reported, and are not contained in the safety evaluable set.

Table 16 (Applicant's Table 28) Overview of All Adverse Events (Application Site and Non-Application Site) in Patients With Acne: All Studies, the Four 12-Week, Vehicle-Controlled Studies, and Long-Term Safety Study

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| Adverse Events | Treatment Group | | | |
|---|-----------------|-----------------|-----------------|-----------------|
| | VC n (%) | 1% DTG n (%) | 3% DTG n (%) | 5% DTG n (%) |
| All Studies | | | | |
| N | 1660 | 23 | 31 | 2372 |
| All Adverse Events | 938 (56.5%) | 17 (73.9%) | 17 (54.8%) | 1337 (56.4%) |
| Serious Adverse Events | 7 (0.4%) | 0 | 0 | 11 (0.5%) |
| Adverse Events Resulting in Discontinuation | 9 (0.5%) | 1 (4.3%) | 0 | 20 (0.8%) |
| Severe Adverse Events | 56 (3.4%) | 1 (4.3%) | 1 (3.2%) | 119 (5.0%) |
| Four 12-Week, Vehicle-Controlled Studies | | | | |
| N | 1660 | - | 31 | 1819 |
| All Adverse Events | 938 (56.5%) | - | 17 (54.8%) | 974 (53.5%) |
| Serious Adverse Events | 7 (0.4%) | - | 0 | 6 (0.3%) |
| Adverse Events Resulting in Discontinuation | 9 (0.5%) | - | 0 | 9 (0.5%) |
| Severe Adverse Events | 56 (3.4%) | - | 1 (3.2%) | 48 (2.6%) |
| Long-Term Safety Study | | | | |
| N | - | - | - | 466 |
| All Adverse Events | - | - | - | 324 (66.7%) |
| Serious Adverse Events | - | - | - | 9 (1.0%) |
| Adverse Events Resulting in Discontinuation | - | - | - | 11 (2.3%) |
| Severe Adverse Events | - | - | - | 66 (13.6%) |

Studies DAP9903, DAP9910, DAP0004, DAP0110, DAP0114, DAP0203, DAP0204, and 03-0-182

Source: End-of-Text Tables 25A, 25B, 25C, and 25D of Amended ISS dated March 31, 2005

7.1.1 Deaths

No patient deaths were reported in any of the studies in the clinical program for DTG.

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7.1.2 Other Serious Adverse Events

Malignant neoplasms were recorded for 2 patients. As the malignant melanoma for Patient 405204 in Study DAP0204 was diagnosed at Baseline, it was not reported as an SAE. At the end of the study, Patient 026153 in Study DAP0204 was referred for a procedure for the malignant melanoma *in situ*, and no additional information is available.

7.1.3 Dropouts and Other Significant Adverse Events

Serious adverse events were reported for 18 patients (VC, 7; 5% DTG, 11). Serious adverse events are presented by patient in Table 55 for nervous system and psychiatric disorders.

Table 17 (Applicant's Table 55) Summary of Serious Adverse Events: Nervous System/Psychiatric Disorders

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| MedDRA Term/ Study Drug | Study/ Patient No. | Age | Severity | Outcome | Adverse Event Start/Stop Days | SAE Number |
|--|-----------------------|-----|----------|----------|-------------------------------------|---------------|
| Depression aggravated Vehicle Control | DAP0203/ 440321 | 14 | Severe | Ongoing | Unknown | 0203-001 |
| Mental disorder NOS Vehicle Control | DAP0204/ 448241 | 27 | Moderate | Resolved | 54/86 | 0204-003 |
| Suicide attempt 5% DTG Topical Gel | DAP0204/ 215504 | 15 | Severe | Resolved | 69/86 | 0204-002 |
| Tonic clonic movements 5% DTG Topical Gel | DAP0204/ 1604 | 14 | Severe | Resolved | 72/72 | 0204-002 |

Studies: DAP0210, DAP0204, DAP0203, DAP0204, and DAP0114.
 Source: Table 47

Table 18 (Applicant's Table 58) Summary of Serious Adverse Events: Other Adverse Events

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| MedDRA Preferred Term/ Study Drug | Study/ Patient No. | Age | Severity | Outcome | Adverse Event Start/Stop Days | SAE Number |
|---|---------------------------------|-----|----------|----------|-------------------------------------|---------------|
| Appendicitis Vehicle Control | DAP0004/ 0108 | 15 | Severe | Resolved | 63/54 | 0004-003 |
| Abdominal pain NOS 5% DTG | DAP0203/ 320537 ^a | 17 | Moderate | Ongoing | 32/- | 0203-005 |
| Abdominal pain NOS 5% DTG | DAP0114/ 1738 ^b | 37 | Moderate | Resolved | 128/128 | 0114-001 |
| Vomiting NOS 5% DTG | DAP0204/ 515534 | 29 | Severe | Resolved | 80/86 | 0204-004 |
| Pharyngitis 5% DTG | DAP0004/ 1105 | 15 | Severe | Resolved | 5/21 | 0004-001 |
| Tonsillitis 5% DTG | DAP0004/ 1105 | 15 | Severe | Resolved | 5/21 | 0004-001 |
| Appendicitis 5% DTG | DAP0114/ 1417 | 30 | Severe | Resolved | 151/152 | 0114-003 |
| Pancreatitis acute 5% DTG | DAP0114/ 1424 | 29 | Severe | Resolved | 310/312 | 0114-004 |
| Pancreatitis NOS 5% DTG | DAP0114/ 1525 | 38 | Severe | Resolved | 228/230 | 0114-002 |
| Temporo-mandibular joint surgery 5% DTG | DAP0114/ 1547 | 15 | Severe | Resolved | 227/227 | 0114-005 |

^a Patient #320537 prematurely discontinued from their study due to the serious adverse event.

^b Patient also had menorrhagia reported as a serious adverse event.

Studies: DAP9910, DAP0004, DAP0203, DAP0204, and DAP0114

Source: Table 47

Patient #1424 is of interest in that this 29-year-old G6PD deficient Asian female was admitted to the hospital for acute pancreatitis and influenza on Day 310 of Study DAP0114. Laboratory values are not available at the time of the AE; however at Visit 12/ ET (Day 337), Patient #1424 also demonstrated a 1.2 g/dL decrease in hemoglobin level over baseline from 13.3 to 12.1; at BL and Month 12, respectively (normal range of 11.6 – 16.2 g/dL). Additional abnormal lab values at Visit 12/ET include 1+ poikilocytosis, LDH, elevated creatine kinase, and glucose. Bilirubin levels were normal. Reticulocyte counts were not performed in this study.

Dapsone plasma and metabolite levels at Visit 12/ET are not available for Patient 1424 (study DAP0114). According to the applicant, samples measuring dapsone and metabolite plasma levels for Visits 6, 9, and 12 were drawn but somehow lost during the shipping period. Plasma dapsone levels available for this patient ranged from <0.05 ng/mL at Baseline to 31.92 ng/mL at

Month 3 which is above the median plasma dapson concentrations range of 4.6 and 7.7 ng/mL throughout the 12-month safety study.

7.1.3.1 Overall profile of dropouts

7.1.3.2 Adverse events associated with dropouts

Table 19 (Applicant's Table 7) Patient Disposition Including Discontinuations by Cause and Treatment Group: Four 12-Week, Vehicle-Controlled Studies

| Classification | Treatment Group | | | Total Patients n (%) |
|------------------------------|-----------------|-----------------|-----------------|-------------------------|
| | VC n (%) | 3% DTG n (%) | 5% DTG n (%) | |
| Patients enrolled | 1701 | 31 | 1867 | 3599 |
| Safety-evaluable population | 1660 (97.6%) | 31 (100%) | 1819 (97.4%) | 3510 (97.5%) |
| Patients completed | 1421 (83.5%) | 29 (93.5%) | 1586 (84.9%) | 3036 (84.4%) |
| Discontinued study | 280 (16.5%) | 2 (6.5%) | 261 (15.1%) | 563 (15.6%) |
| Adverse event | 10 (0.6%) | 0 | 9 (0.5%) | 19 (0.5%) |
| Lack of efficacy | 15 (0.9%) | 0 | 9 (0.5%) | 24 (0.7%) |
| Patient noncompliance | 8 (0.5%) | 0 | 15 (0.8%) | 23 (0.6%) |
| Protocol violation | 8 (0.5%) | 0 | 3 (0.2%) | 11 (0.3%) |
| Lost to follow-up | 138 (8.2%) | 1 (3.2%) | 147 (7.9%) | 287 (8.0%) |
| Patient voluntarily withdrew | 92 (5.4%) | 1 (3.2%) | 67 (4.7%) | 160 (5.0%) |
| Other | 8 (0.5%) | 0 | 11 (0.6%) | 19 (0.5%) |

Studies DAP9910, DAP0004, DAP0203, and DAP0204

Source: End-of-Text Tables 1 and 2C of Amended ISS dated March 31, 2005

A total of 3,599 patients were randomized and dispensed study drug in the four 12-week, vehicle-controlled studies combined: 1,701 to VC, 31 to 3% DTG, and 1,867 to 5% DTG (1898, total DTG). The safety evaluable population in the 12-week, vehicle-controlled studies consisted of 3,510 patients (1,660, VC; 31, 3% DTG; 1,819, 5% DTG).

Eighty-nine patients did not return for a study visit after being dispensed study drug, and did not have any adverse events reported. The number of patients excluded from the safety-evaluable population was similar between the VC group and the 5% DTG group (41, VC; 48, 5% DTG).

The majority (84.4%) of the patients in the 12-week, vehicle-controlled studies completed the study. The distribution of patients who withdrew was similar between the VC and 5% DTG groups (16.5%, VC; 15.1%, 5% DTG).

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Five hundred sixty-three patients (15.6%) discontinued during the 12-week, vehicle-controlled studies. The most common reason for discontinuation was lost to follow-up (287, 8.0%). Eight patients (6, VC; 2, 5% DTG) discontinued the study due to a treatment-related adverse event.

Table 20 (Table 60) Adverse Events Leading to Discontinuation: Four 12-Week, Vehicle-Controlled Studies Treatment Group

Table 60 Adverse Events Leading to Discontinuation: Four 12-Week, Vehicle-Controlled Studies

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| MedDRA Preferred Term | Treatment Group | | |
|--|-------------------------|---------------------------|-----------------------------|
| | VC (N=1660) n (%) | 3% DTG (N=31) n (%) | 5% DTG (N=1819) n (%) |
| Discontinuations due to adverse events | 10 (0.6%) | 1 (3.2%) | 8 (0.4%) |
| Application site pruritus | 2 (0.12%) | 0 | 1 (<0.1%) |
| Application site dryness | 2 (0.12%) | 0 | 1 (<0.1%) |
| Application site erythema | 2 (0.12%) | 0 | 1 (<0.1%) |
| Application site burning | 1 (0.06%) | 0 | 1 (<0.1%) |
| Application site reaction NOS ^a | 1 (0.06%) | 0 | 1 (<0.1%) |
| Application site rash | 1 (0.06%) | 0 | 0 |
| Blood creatine phosphokinase increased | 0 | 0 | 1 (<0.1%) |
| Psychosis aggravated | 0 | 0 | 1 (<0.1%) |
| Acne NOS | 1 (0.06%) | 0 | 0 |
| Rash impetiginous | 1 (0.06%) | 0 | 0 |
| Acne aggravated | 2 (0.12%) | 0 | 1 (<0.1%) |

| MedDRA Preferred Term | Treatment Group | | |
|---------------------------------|-------------------------|---------------------------|-----------------------------|
| | VC (N=1660) n (%) | 3% DTG (N=31) n (%) | 5% DTG (N=1819) n (%) |
| Dermatitis contact (poison ivy) | 0 | 0 | 1 (<0.1%) |
| Acne pustular | 1 (0.06%) | 0 | 0 |
| Swelling face | 0 | 1 (3.2%) | 0 |

Application site reaction NOS=Facial oiliness and peeling, etc. (See Appendix 11)

Studies DAP9910, DAP0004, DAP0203, and DAP0204

Source: Tables 2A and 47

A total of 3,010 patients with *acne vulgaris* were randomized in the 2 pivotal studies (1:1 ratio) and dispensed study drug. The safety evaluable population in these 2 studies consisted of 2,933 patients (1,467 VC; 1,466 5% DTG).

Table 21 (Applicant's Table 9) Patient Disposition Including Discontinuations by Cause and Treatment Group: Two Pivotal Studies

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Table 9 Patient Disposition Including Discontinuations by Cause and Treatment Group: Two Pivotal Studies

| Classification | Treatment Group | | Total Patients n (%) |
|------------------------------|-----------------|-----------------|-------------------------|
| | VC n (%) | 5% DTG n (%) | |
| Patients enrolled | 1504 | 1506 | 3010 |
| Safety-evaluable population | 1467 (97.5%) | 1466 (97.3%) | 2933 (97.4%) |
| Patients completed | 1241 (82.5%) | 1266 (84.1%) | 2507 (83.3%) |
| Discontinued study | 263 (17.5%) | 240 (15.9%) | 503 (16.7%) |
| Adverse event | 9 (0.6%) | 6 (0.4%) | 15 (0.5%) |
| Lack of efficacy | 15 (1.0%) | 9 (0.6%) | 24 (0.8%) |
| Patient noncompliance | 6 (0.4%) | 10 (0.7%) | 16 (0.5%) |
| Protocol violation | 7 (0.5%) | 3 (0.2%) | 10 (0.3%) |
| Lost to follow-up | 124 (8.9%) | 132 (8.8%) | 266 (8.8%) |
| Patient voluntarily withdrew | 84 (5.6%) | 71 (4.7%) | 155 (5.1%) |
| Other | 8 (0.5%) | 9 (0.6%) | 17 (0.6%) |

Studies DAP0203 and DAP0204
 Source: Tables 1 and 2A

Seventy-seven patients did not return for a study visit after being dispensed study drug and did not have any adverse events reported. These patients are not included in the safety evaluable population. The number of patients excluded from the safety-evaluable population was similar between the treatment groups (VC, 37; 5% DTG, 40). The majority (83.3%) of patients in the 2 pivotal studies completed the study.

Five hundred three patients (16.7%) discontinued during the 2 pivotal studies. The distribution of patients who withdrew was similar across treatment groups (17.4%, VC; 15.9%, 5% DTG). The most common reason for discontinuation was lost to follow-up (8.8%). Eight patients (0.4%, VC; 0.1%, 5% DTG) discontinued the study due to a treatment-related adverse event.

The majority (83.3%) of patients in the 2 pivotal studies completed the study.

Long-Term Safety Study

A summary of patient disposition including the enrolled and safety evaluable populations by treatment group for the long-term safety study is shown in Table 11.

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**Table 22 (Applicant's Table 11) Patient Discontinuations by Cause and Treatment Group:
Long-Term Safety Study**

| Classification | Treatment Group |
|------------------------------|-----------------|
| | 5% DTG n (%) |
| Patients enrolled | 506 |
| Safety-evaluable population | 486 (96.0%) |
| Patients completed | 340 (67.2%) |
| Discontinued study | 166 (32.8%) |
| Adverse event | 11 (2.2%) |
| Lack of efficacy | 4 (0.8%) |
| Patient noncompliance | 6 (1.2%) |
| Protocol violation | 1 (0.2%) |
| Lost to follow-up | 79 (15.6%) |
| Patient voluntarily withdrew | 59 (11.7%) |
| Other | 6 (1.2%) |

Study: DAP0114
Source: Tables 1 and 2B

A total of 506 patients were enrolled and dispensed 5% DTG in this 12-month study. Twenty patients did not return for a study visit after being dispensed study drug, and did not have any adverse events reported. Thus, the safety evaluable populations in the long-term safety study consisted of 486 patients. The majority (67.2%) of patients in the long-term safety study completed the study.

One hundred sixty-six patients (32.8%) discontinued during the 12-month safety study. The most common reason for discontinuation was lost to follow-up (15.6%). Eleven patients (2.2%) discontinued the study due to a 24 treatment-related adverse event. The VC and 5% DTG groups were balanced with respect to age, gender, and race.

G6PD deficient Patient Drop-outs

There was one drop-out among the known G-6-PD deficient patients (Patient 1314 withdrew with no AEs recorded). G-6-PD level determination was not obtained in the long term safety study until Month 6; therefore, the G-6-PD status of dropouts prior to this time point is unknown.

Drop Outs Among G-6-PD Deficient Patients in Phase 3 VC Controlled Studies

Study DAP0203

There were 12 G-6-PD deficient subjects (5 dapsons and 7 vehicle). There was 1 dropout among the G6PD deficient patients, Subject 09-1771 (dapsons) dropped out for Application Site AE at the Week 2 visit.

Study DAP0204

There were 32 G-6-PD deficient subjects (14 dapson) and 18 vehicle). There were 4 dropouts among these 32 patients:

Subject 01-6102 (dapson) lost to follow-up after the Week 4 visit.

Subject 14-6247 (dapson) lost to follow-up after the Week 2 visit.

Subject 13-5972 (vehicle) voluntarily withdrew at the Week 6 visit.

Subject 17-6655 (vehicle) was lost to follow-up after the baseline visit.

According to the Applicant, loss to follow-up rate in this study among the G-6-PD deficient subjects ($3/32 = 9.4\%$) is comparable to that for the study as a whole (9.7%); however, the number of G-6-PD deficient subjects (32) is too small to draw valid conclusions.

Seven patients (7/1525, 0.5%) had an adverse event that led to discontinuation (3 DTG; 4 VC). Four of the seven patients with an adverse event that led to discontinuation had events that were reported to be treatment related by the Investigator.

Adverse events leading to discontinuation are summarized in Table 60 for the four 12-week, vehicle-controlled studies.

Information on the patients who prematurely terminated from the four 12-week, vehicle-controlled studies due to a systemic adverse events is provided in Table 61.

Information on the patients who prematurely terminated from the four 12-week, vehicle-controlled studies due to a systemic adverse events is provided in Table 62. The Applicant also included data from Study DAP0114 which was 12 Months in duration and not vehicle controlled.

Long-Term Safety Study

In the long-term safety study, a total of 11 patients (2.3%) had adverse events that led to discontinuation from the study. Of these patients, 8 patients had application site events, and 3 patients had systemic events.

Narratives for patients who discontinued the long-term safety study due to an adverse event are presented in Appendix 31 of the Amended ISS dated March 31, 2005.

The most common adverse events leading to discontinuation were application site rash, aggravated acne, application site burning, and application site pruritus.

Table 23 (Applicant's Table 63) Adverse Events Leading to Discontinuation and Reported For More Than One Patient: Long-Term Safety Study

| | Treatment Group |
|--|----------------------------|
| | 5% DTG (N=486) n (%) |
| MedDRA Preferred Term | |
| Discontinuations Due to Adverse Event | 11 (2.3%) |
| Application site rash | 5 (1.0%) |
| Application site burning | 2 (0.4%) |
| Application site pruritus | 2 (0.4%) |
| Application site dryness | 1 (0.2%) |
| Application site reaction NOS ^a | 1 (0.2%) |

^a Application site reaction NOS=Facial peeling and sensitivity

Study DAP0114

Source: End-of-Text Tables 25B and 47 of Amended ISS dated March 31, 2005

The most common application site adverse events leading to discontinuation were application site rash, application site burning, and application site pruritus.

Information on the 3 patients who discontinued due to a systemic adverse event is presented in Table 89.

Table 24 (Applicant's Table 64) Patients Who Discontinued Due to Systemic Adverse Events

| Study Drug/ Patient | MedDRA Preferred Term | Severity | Outcome | Adverse Events Start/Stop Days |
|------------------------|--------------------------|----------|----------|-----------------------------------|
| 5% DTG | | | | |
| 0412 | Acne aggravated | Mild | Resolved | 42/49 |
| 1204 | Acne aggravated | Mild | Ongoing | 7- |
| 1302 | Nausea | Mild | Resolved | 2/2 |
| | Weakness | Mild | Resolved | 2/2 |
| | Dizziness | Mild | Resolved | 2/2 |

Study DAP0114

Source: Module 5.3.5.3 End-of-Text DAP0114 individual study report (Module 5.3.5.1).

Acne aggravated was the most frequently reported systemic adverse event leading to premature termination. Patient 1302 (Study DAP0114, 5% DTG) discontinued the study due to nausea secondary to odor.

Conclusion:

Overall, for the vehicle controlled studies, there did not appear to be differences between 5% DTG-treated patients and VC-treated patients. In a response from the Applicant to a faxed informational request Dated April 12, 2005 the Applicant provided tabular summary and discussion of AEs and laboratory abnormalities for Studies 0203 and 0204 in relationship to treatment beyond 12 weeks. According to the summary, the AE incidence of AEs did not increase with increased duration of therapy and the incidence of AEs was similar between G6PD

deficient and normal G6PD patients. The incidence of AEs also appeared similar between VC G6PD deficient patients and those G6PD deficient patients on active study drug; however, only a trend is noted since the number studied was small.

Burn Patients Study DAP9905

Study DAP9905, a Phase 1, single-center, open-label, pilot study, evaluated the safety, tolerance, and efficacy of 5% DTG in recovering burn patients to reduce burn itch. A total of 15 patients were enrolled in the study. Thirteen patients completed the study, and 2 discontinued due to non-compliance. No patient was withdrawn due to an adverse event.

Seven of the 15 patients (47%) had 1 or more adverse event during the course of the study. Three patients (20%) had a total of 5 events that were determined by the investigator to be possibly or probably related to treatment. Three of these events were mild application site dryness in 3 patients (Patients #0104, #0108, and #0109).

Other possibly treatment-related events were moderate abdominal pain, moderate back pain, and low methemoglobin, which were reported for Patient #0109. Methemoglobinemia values were evaluated in all patients, and no patients presented with values above the normal range.

7.1.3.3 Other significant adverse events

7.1.4 Other Search Strategies

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Phase 3 Studies

Adverse events, including local adverse reactions, were collected by interviewing and examining the patient. Adverse events and use of concomitant medications were assessed at all scheduled visits. A local reaction assessment (oiliness, peeling, dryness, and erythema) was performed at Baseline and Weeks 2, 4, 6, 8, 12, and early termination (ET).

12-Month safety Study

Safety was assessed based on the frequency and severity of adverse events, in addition to observed changes in clinical laboratory data and physical examination at Baseline and Months 1, 3, 4, 6, 9, 12 and ET. Adverse events were collected by examining and interviewing the patient. The Investigator determined the relationship of the adverse event to the test article.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 5.

7.1.5.3 Incidence of common adverse events

For all studies in acne patients, nasopharyngitis was the most frequently reported adverse event in both the 5% DTG group and the vehicle-controlled group. However, the incidence of adverse events was similar between these 2 groups for all of the adverse events reported.

7.1.5.4 Common adverse event tables

Adverse Events Reported in > 5% of Patients

The most frequently reported systemic adverse events (those occurring in at least 5% of patients in any treatment group) are presented in Table 42 for all studies combined, the 3 pharmacokinetic studies, the four 12-week vehicle-controlled studies, and the long-term safety study.

Table 25 (Applicant's Table 42) Treatment-Emergent, Systemic Adverse Events Reported For at Least 5% of Patients in Any Treatment Group: All Studies Combined, Pharmacokinetic Studies, 12-Week, Vehicle-Controlled Studies, and Long-Term Safety Study

Table 42 Treatment-Emergent, Systemic Adverse Events Reported For at Least 5% of Patients in Any Treatment Group: All Studies Combined, Pharmacokinetic Studies, 12-Week, Vehicle-Controlled Studies, and Long-Term Safety Study

| MedDRA System Organ Class MedDRA Preferred Term | Treatment Group | | | |
|--|-----------------|-----------------|-----------------|-----------------|
| | VC n (%) | 1% DTG n (%) | 3% DTG n (%) | 5% DTG n (%) |
| All Studies | (N=1660) | (N=23) | (N=31) | (N=2372) |
| Headache NOS | 81 (3.7%) | 8 (34.8%) | 6 (19.4%) | 182 (7.7%) |
| Nasopharyngitis | 102 (6.1%) | 0 | 5 (16.1%) | 185 (7.8%) |
| Pharyngitis | 40 (2.4%) | 3 (13.0%) | 0 | 21 (3.4%) |
| Dysmenorrhoea | 6 (0.5%) | 3 (13.0%) | 2 (6.5%) | 46 (2.0%) |
| Abdominal pain upper | 13 (0.8%) | 2 (8.7%) | 1 (3.2%) | 39 (1.6%) |
| Back pain | 7 (0.4%) | 2 (8.7%) | 0 | 24 (1.0%) |
| Sinus congestion | 6 (0.5%) | 2 (8.7%) | 0 | 22 (0.9%) |
| Urinary tract infection NOS | 4 (0.2%) | 0 | 2 (6.5%) | 14 (0.6%) |
| Pharmacokinetic Studies | | (N=23) | | (N=67) |
| Headache NOS | - | 8 (34.8%) | - | 17 (25.4%) |
| Nausea | - | 0 | - | 5 (7.5%) |
| Abdominal pain upper | - | 2 (8.7%) | - | 4 (6.0%) |

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| MedDRA System Organ Class MedDRA Preferred Term | Treatment Group | | | |
|--|-----------------|-----------------|-----------------|-----------------|
| | VC n (%) | 1% DTG n (%) | 3% DTG n (%) | 5% DTG n (%) |
| Dysmenorrhoea | - | 3 (13.0%) | - | 4 (6.0%) |
| Sinus congestion | - | 2 (8.7%) | - | 2 (3.0%) |
| Back pain | - | 2 (8.7%) | - | 1 (1.5%) |
| Pharyngitis | - | 3 (13.0%) | - | 1 (1.5%) |
| Four 12-Week, Vehicle-Controlled Studies | (N=1660) | | (N=31) | (N=1819) |
| Nasopharyngitis | 102 (6.1%) | - | 3 (9.7%) | 90 (4.9%) |
| Headache NOS | 81 (3.7%) | - | 6 (19.4%) | 68 (3.7%) |
| Dysmenorrhoea | 9 (0.5%) | - | 2 (6.5%) | 14 (0.8%) |
| Urinary tract infection NOS | 4 (0.2%) | - | 2 (6.5%) | 6 (0.3%) |
| Long-Term Safety Study | | | | (N=486) |
| Headache NOS | - | - | - | 67 (20.0%) |
| Nasopharyngitis | - | - | - | 74 (15.2%) |
| Pharyngitis | - | - | - | 42 (8.6%) |
| Dysmenorrhoea | - | - | - | 30 (6.2%) |
| Sinusitis NOS | - | - | - | 27 (5.6%) |

Studies DAP9903, DAP9901, DAP0004, DAP0110, DAP0114, DAP0203, DAP0204, and 02-C-182

Source: Tables 27A, 27B, 27C, 27D, and 27E

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Due to the relatively small sample size for the 1% DTG (n = 23) and the 3% DTG (N = 31) compared to the 5% DTG group (N = 2,372) and the vehicle-controlled group (N = 1,660), no conclusions can be drawn for these comparisons.

According to the Applicant, the high incidence of headache in the pharmacokinetic studies is not unexpected in these types of studies; however, no data or literature reference was provided to substantiate the association.

In the four 12-week, vehicle-controlled studies, the frequencies of treatment-emergent adverse events were distributed similarly across the VC and 5% DTG treatment groups. The majority of these adverse events were considered mild in severity. The most frequently reported treatment-emergent adverse events in the long-term safety study were headache and nasopharyngitis (common cold). These events were generally mild or moderate in severity and were more commonly reported during the first 3 months of the study.

7.1.5.5 Identifying common and drug-related adverse events

Table 26 (Applicant's Table 37) Application Site Adverse Events: Two Pivotal Studies

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Table 37 Application Site Adverse Events: Two Pivotal Studies

| MedDRA System Organ Class MedDRA Preferred Term | Treatment Group | |
|--|-------------------------|-----------------------------|
| | VC (N=1467) n (%) | 5% DTG (N=1466) n (%) |
| General disorders and administration site conditions | 616 (42.0%) | 620 (42.3%) |
| Application site reaction NOS ^a | 331 (22.6%) | 320 (21.8%) |
| Application site dryness | 277 (18.9%) | 293 (20.0%) |
| Application site erythema | 236 (16.1%) | 239 (16.3%) |
| Application site burning | 23 (1.6%) | 20 (1.4%) |
| Application site pruritus | 19 (1.3%) | 14 (1.0%) |
| Application site rash | 6 (0.4%) | 0 |
| Application site irritation | 2 (0.1%) | 2 (0.1%) |
| Application site papules | 1 (<0.1%) | 1 (<0.1%) |
| Application site pigmentation changes | 0 | 1 (<0.1%) |
| Application site pain | 1 (<0.1%) | 0 |
| Skin and subcutaneous tissue disorders | | |
| Photosensitivity reaction NOS | 0 | 1 (<0.1%) |

^a Application site reaction NOS=Facial oiliness and peeling, etc. (See Appendix 11)

Studies DAP0203 and DAP0204

Source: Table 27A

The local signs and symptoms (dryness, erythema, oiliness and peeling) were evaluated at Baseline and at every visit in the pivotal studies. These data are presented in Table 38 and are shown for Baseline and during treatment. During treatment includes the maximum reported severity at any time after Baseline.

Table 27 (Applicant's Table 40) Spontaneously Reported Application Site Adverse Events by Severity: Long-Term Safety Study

| Application Site Event | Percentage of Patients by Severity (N=465) | | | |
|------------------------|---|------|----------|--------|
| | None | Mild | Moderate | Severe |
| Oiliness/peeling | 99.9 | 0 | 0.0 | 0.2 |
| Dryness | 98.0 | 1.1 | 1.3 | 0.7 |
| Erythema | 98.2 | 0.9 | 0.9 | 0 |
| Rash | 97.4 | 1.5 | 1.1 | 0 |
| Burning | 98.2 | 0.7 | 1.1 | 0 |
| Pruritus | 98.4 | 0.7 | 0.7 | 0.2 |

Studies DAP0114
 Source: Table 32B

No application site adverse events were reported in over 90% of the patients in the 1-year study. The reports of application site adverse events were usually considered to be mild or moderate.

Table 28 (Applicant's Table 29) Application Site Adverse Events: PK Studies, 12-Week, Vehicle-Controlled Studies and Long-Term Safety Study

| Application Site Events | PK Studies | | 12-Week VC Studies | | | Long-Term Safety | All Patients |
|---------------------------|---------------------------|---------------------------|-------------------------|---------------------------|-----------------------------|----------------------------|-------------------|
| | 1% DTG (N=23) n (%) | 5% DTG (N=67) n (%) | VC (N=1660) n (%) | 3% DTG (N=31) n (%) | 5% DTG (N=1819) n (%) | 5% DTG (N=486) n (%) | (N=4086) n (%) |
| Reaction NOS ^a | 1 (4.3) | 1 (1.5) | 331 (19.9) | 0 | 323 (17.8) | 5 (1.0) | 661 (16.2) |
| Dryness | 3 (13.0) | 3 (4.5) | 278 (16.7) | 0 | 294 (16.2) | 13 (2.7) | 591 (14.5) |
| Erythema | 0 (0.0) | 1 (1.5) | 237 (14.3) | 0 | 241 (13.2) | 8 (1.6) | 467 (11.9) |
| Burning | 0 (0.0) | 0 (0.0) | 26 (1.6) | 0 | 23 (1.3) | 8 (1.6) | 57 (1.4) |
| Pruritus | 1 (4.3) | 4 (6.0) | 20 (1.2) | 0 | 19 (1.0) | 7 (1.4) | 51 (1.2) |
| Edema | 0 | 0 | 0 | 0 | 2 (0.1) | 0 | 2 (<0.1) |
| Pigmentation changes | 0 | 0 | 0 | 0 | 1 (<0.1) | 0 | 1 (<0.1) |
| Pain | 0 | 0 | 1 (<0.1) | 0 | 0 | 0 | 1 (<0.1) |
| Rash | 0 | 0 | 6 (0.4) | 0 | 1 (<0.1) | 12 (2.5) | 19 (0.5) |
| Irritation | 0 | 0 | 3 (0.2) | 0 | 3 (0.2) | 2 (0.4) | 8 (0.2) |
| Urticaria | 0 | 2 (3.0%) | 0 | 0 | 0 | 0 | 2 (0-0.1) |

^a Application site reaction NOS=Facial oiliness and peeling, etc. (See Appendix 11)

Studies DAP9903, DAP9910, DAP0004, DAP0203, DAP0204, DAP0114, and 030182

Source: End-of-Text Tables 27B, 27C, 27D, and 27E of Amended ISS dated March 31, 2005

Aside from reaction not specified, dryness and erythema were the most frequently reported adverse events in the four 12-week vehicle controlled studies, while dryness was the most frequently reported adverse event in the 3 pharmacokinetic studies. In the four 12-week vehicle controlled, the incidence of application site adverse events was similar between the vehicle control and the 5% DTG groups.

In the four 12-week, vehicle-controlled studies, the percentage of patients reporting application site adverse events was similar between the VC and 5% DTG study drug groups. No application site adverse events were reported for the 3% DTG group.

Sixty-seven patients (13.8%) in the 12-month safety study had 1 or more application site adverse events. Application site reactions were rarely reported in the safety study, which reflects the potential clinical use of DTG.

In the long-term safety study, the most common application site adverse events were application site dryness, application site rash, and sunburn. Application site adverse events were generally mild or moderate in severity. The majority (92.1%) of application site adverse events resolved during the study and rarely led to treatment discontinuation.

Other dermal-related adverse events reported for the four 12-week, vehicle-controlled studies, the long-term safety study, and all patients combined are shown in Table 30.

Table 29 (Applicant's Table 30) Other Dermal Adverse Events: 12-Week, Vehicle-Controlled Studies and Long-Term Safety Study

| MedDRA System Organ Class MedDRA Preferred Term | Pivotal and 12-Week VC Studies | | | Long-Term Safety | All Patients (N=4086) n (%) |
|--|--------------------------------|---------------------------|-----------------------------|----------------------------|-----------------------------------|
| | VC (N=1660) n (%) | 3% DTG (N=31) n (%) | 5% DTG (N=1819) n (%) | 5% DTG (N=486) n (%) | |
| Skin and subcutaneous tissue disorders | | | | | |
| Photosensitivity reaction NOS | 0 | 0 | 1 (<0.1%) | 0 | 1 (<0.1%) |
| Injury, poisoning, and procedural complications | | | | | |
| Sunburn | 13 (0.8%) | 0 | 12 (0.7%) | 14 (2.9%) | 39 (1.0%) |

Studies DAP9903, DAP9910, DAP0004, DAP0203, DAP0204, DAP0114, and 030162

Source: End-of-Text Tables 27B, 27C, and 27D of Amended ISS dated March 31, 2005

Four 12-Week, Vehicle-Controlled Studies

The most frequently reported application site adverse events (those occurring in at least 5% of patients in any treatment group regardless of gender) for the four 12-week, vehicle-controlled studies are presented by gender in Table 44.

Table 30 (Applicant's Table 44) Application Site Adverse Events Reported For at Least 5% of Patients in Any Treatment Group Regardless of Gender by Gender: Four 12-Week, Vehicle-Controlled Studies

| MedDRA Organ Class/ Preferred Term | Male | | | Female | | |
|---|------------------------|---------------------------|----------------------------|------------------------|---------------------------|----------------------------|
| | VC (N=733) n (%) | 3% DTG (N=13) n (%) | 5% DTG (N=877) n (%) | VC (N=887) n (%) | 3% DTG (N=18) n (%) | 5% DTG (N=942) n (%) |
| General disorders and administration site conditions | | | | | | |
| Application site reaction NOS ^a | 144 (18.6%) | 0 | 151 (17.2%) | 196 (22.1%) | 0 | 175 (18.6%) |
| Application site dryness | 131 (16.9%) | 0 | 148 (16.9%) | 149 (16.6%) | 0 | 154 (16.3%) |
| Application site erythema | 114 (14.7%) | 0 | 133 (15.2%) | 127 (14.3%) | 0 | 114 (12.1%) |

^a Application site reaction NOS=Facial oiliness and peeling, etc. (See Appendix 11)

Studies DAP9910, DAP0004, DAP0203, and DAP0204

Source: End-of-Text Table 33C of Amended ISS dated March 31, 2005.

Long-Term Safety Study

The most frequently reported application site adverse events (the 5 most frequently reported application site and non-application site events) for the long-term safety study are shown by gender in Table 45.

Table 31 (Applicant's Table 45) Most Frequently Reported Application Site Adverse Events by Gender: Long-Term Safety Study

| MedDRA Organ Class/Preferred Term | Male | Female |
|---|----------------------------|----------------------------|
| | 5% DTG (N=223) n (%) | 5% DTG (N=263) n (%) |
| General disorders and administration site conditions | | |
| Application site dryness | 28 (12.6%) | 48 (18.3%) |
| Application site rash | 4 (1.8%) | 10 (3.8%) |
| Application site burning | 1 (0.4%) | 11 (4.2%) |
| Application site erythema | 4 (1.8%) | 4 (1.5%) |
| | 3 (1.3%) | 5 (1.9%) |

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Study DAP0114

Source: End-of-Trial Table 33B of Amended ISS dated March 31, 2005

In the long-term safety study, there was a higher incidence of adverse events reported for female patients than for male patients.

Conclusion

Local cutaneous AEs were primarily of mild intensity. Dryness, erythema, oiliness and peeling (events specifically elicited at each visit in the pivotal studies) were all more common at Baseline than during the study. There were no differences in the application site adverse event rates between treatment groups.

7.1.5.6 Additional analyses and explorations

7.1.6 Less Common Adverse Events

7.1.7 Laboratory Findings

Standard hematology and serum chemistry analyses will be performed at Baseline and Week 12.

Clinical Laboratory Procedures

Standard hematology and serum chemistry analyses were performed at Baseline and Week 12 in the Phase 2/3 and Phase 3 pivotal studies. These lab values were obtained at Baseline and at Month 12 or ET in the long-term safety study. A central laboratory was to be used for the analysis of all clinical laboratory tests.

7.1.7.1 Overview of laboratory testing in the development program

Clinical Laboratory Tests

Hematology

Total leukocyte count (WBC) with differential, erythrocyte count (RBC), red blood cell morphology/blood film, hemoglobin concentration (HGB), hematocrit value (HCT), mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH).

Serum Chemistry

Glucose, urea nitrogen (BUN), creatinine, total protein, albumin, calcium, phosphorus, electrolytes (Na, K, Cl, bicarbonate [HCO₃]), total cholesterol, triglycerides, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, creatinine kinase (CK), and lactate dehydrogenase (LDH).

Reviewer comment:

A more robust hematological assessment (e.g., reticulocyte counts, erythrocyte adenylate kinase levels, etc.) would have been useful since evidence of hemolysis is classically diagnosed by a combination of nonspecific laboratory tests including serum bilirubin, LDH, and reticulocyte count.

Table 32 (Applicant's Table 107) Incidence of Systemic Adverse Events Reported by ≥5% of Patients by Maximum Plasma Dapsone Level Quartile: Long-Term Safety Study Maximum Plasma Dapsone Concentration (dL/ng) Quartile

Table 107 Incidence of Systemic Adverse Events Reported by ≥5% of Patients by Maximum Plasma Dapsone Level Quartile: Long-Term Safety Study

| Quartile: | Maximum Plasma Dapsone Concentration (dL/ng) Quartile (N=486) | | | |
|-----------------|--|--|---|--|
| | First (<3.056) (N=121) n (%) | Second (≥3.056 <9.4463) (N=122) n (%) | Third (≥9.4463 <17.1067) (N=122) n (%) | Fourth (≥17.1067) (N=122) n (%) |
| Nasopharyngitis | 7 (5.8%) | 20 (16.4%) | 25 (20.5%) | 23 (18.9%) |
| Sinusitis NOS | 2 (1.7%) | 10 (8.2%) | 10 (8.2%) | 6 (4.9%) |
| Headache NOS | 13 (10.7%) | 24 (19.7%) | 30 (24.6%) | 30 (24.6%) |
| Pharyngitis | 6 (5.0%) | 6 (4.9%) | 14 (11.5%) | 17 (13.9%) |
| Dysmenorrhea | 5 (6.6%) | 6 (4.9%) | 10 (8.2%) | 6 (4.9%) |

Study DAP0114

Source: Source: DAP0114 Individual study report (Module 5.3.5.1)

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According to the Applicant, no relationship between the plasma dapsone concentration quartiles and the incidence of an adverse event was identified. Incidence of headache and pharyngitis are numerically; however, are rather common. An AE comparison to that of a vehicle control study arm would have been useful; however, not available.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Chemical and hematological laboratory monitoring was conducted in the Phase 2 VC studies; however, dapsone and metabolite plasma levels are not available for any possible correlation. Study DAP0114 is a long term safety study in dapsone and metabolite plasma levels were to be obtained.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 *Analyses focused on measures of central tendency*

7.1.7.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

A total of 15 patients had values that were considered markedly abnormal at some point during the long-term safety study. The most common marked abnormality was elevated potassium, which was observed in 6 patients during the treatment period. The normal range for potassium is 3.3 to 5.1 meq/L. Four of 6 patients (66.7%) with a markedly abnormal potassium level had normal potassium levels measured at the next scheduled visit or retest. The abnormal potassium for 1 of these patients (Patient #0410; Study DAP0114) was attributed to hemolysis. Two patients had markedly abnormal potassium at the end of the study and the investigators did not feel a retest was necessary. Except for Patient #0410 (G6PD level unknown), all patients reporting markedly abnormal potassium levels had normal G6PD levels.

Conclusions

Short-term and long-term treatment with 5% DTG did not appear to have any adverse effects on laboratory parameters.

7.1.7.3.3 *Marked outliers and dropouts for laboratory abnormalities*

7.1.7.4 Additional analyses and explorations

7.1.7.5 Special assessments

G-6-PD level determination

G-6-PD level determination was performed at Baseline for the pivotal Phase 3 studies and was performed at Month 6 in the long-term safety study (Letter of Clarification to the file of DAP0114 dated May 20, 2002). G-6-PD level determination was not performed in the vehicle controlled Phase 2/3 Study DAP0004.

Methods for Measuring G6PD Activity

Two laboratories were utilized to determine G6PD activity in patients enrolled in the clinical studies. _____ measured G6PD activity for patients in Studies DAP0110 and DAP0114 and _____ measured G6PD activity for patients in Studies DAP0203 and DAP0204. Both laboratories used a spectrophotometric assay for the formation of NADPH in plasma (absorption at 340 nm) in conjunction with the conversion of glucose-6-phosphate to 6-phosphogluconate by G6PD. The formation of NADPH is proportional to G6PD activity. Patients were considered to be G6PD deficient if their G6PD level was below the lower limit of normal for the specific assay utilized. These assays did not include an assessment of morphology of red blood cells.

G6PD activity was measured in four studies; patients whose G6PD level was below the lower limit of normal (n=50) for the assay used were considered G6PD deficient [see Section 4]. Two patients were considered to have severe G6PD deficiency defined as a value <15% of the lower limit of normal.

Table 33 (Applicant's Table 3): Number of Patients with G6PD Deficiency in Clinical Studies of Dapsone Topical Gel

Table 3: Number of Patients with G6PD Deficiency in Clinical Studies of Dapsone Topical Gel

| Study Number | 5% Dapsone Topical Gel | Gel Vehicle |
|---------------|------------------------|----------------|
| Study DAP0110 | 1/18 (5.5%) | NA |
| Study DAP0114 | 5/360 (1.4%) | NA |
| Study DAP0203 | 5/722 (0.7%) | 7/722 (1.0%) |
| Study DAP0204 | 14/734 (1.9%) | 18/745 (2.4%)† |
| Total | 25 | 25 |

Denominator represents number of patients who had G6PD activity measured

† One G6PD deficient patient (vehicle group) did not have post-baseline data

NA: not applicable

Body surface area was fixed at 22.5% in Study DAP0110 and not specifically recorded in the other studies.

Dapsone and N-Acetyl Plasma Blood Levels

PK sampling for dapsone and metabolites were obtained in the long-term safety study in addition to the PK studies. (See Biopharm review)

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Physical examination (PE) including vital signs (heart rate and blood pressure) was performed in Phase 2 and 3 studies at baseline and Week 12 or ET. Vital signs were also measured at Baseline, Months 1, 3, 4, 6, 9, and 12 or ET in Study DAP0114.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Studies DAP2004, DAO0203, and DAP0204 were vehicle controlled studies. Study DAP0114 was an open level 12 month safety study.

7.1.8.3 Standard analyses and explorations of vital signs data

Vital signs were similar between patients in the active and vehicle controlled groups and between patients with ≥ 2 g/dL reduction in hemoglobin. There were no vital sign or physical examination findings identified of potential clinical concern in the DTG clinical program.

7.1.8.3.1 *Analyses focused on measures of central tendencies*

7.1.8.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

7.1.8.3.3 *Marked outliers and dropouts for vital sign abnormalities*

7.1.8.4 Additional analyses and explorations

7.1.9 Electrocardiograms (ECGs)

According to the ISS (Vol. 1, pg. 7), changes in electrocardiogram as well as changes in clinical laboratory parameters, vital signs, and physical examination were identified. However, ECG data was only collected in Study DAP9903, a 28 day multicenter, dose-ranging PK study of topical dapsone gel in 48 subjects with acne vulgaris.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

7.1.9.2 A 12 lead ECG was performed on all subjects at Baseline and Day 28. Ventricular rate and PR, QRSD, QT, and QTc intervals were measured for both time periods. Selection of studies and analyses for overall drug-control comparisons

7.1.9.3 Standard analyses and explorations of ECG data

According to the Applicant, ECG measurements were similar were similar across treatment groups and centers. Forty-seven of the 48 subjects (98%) had a normal ECG at screening with one exception subject (#213). The one exception (#213) had an intravascular conduction delay at Baseline that was not apparent on Day 28. At Day 28, 4/46 (9%) subjects who completed the study had an abnormal ECG tracing; however, according to the Applicant Mod 5, Vol. 3, Synopsis, pg. 45), none of the changes (e.g., bradycardia) were considered to be of clinical significance.

Table 34 Abnormal ECG Measurements

| Study Period | ECG Result | Subject | Dapsone level (ng/mL)* | Cohort | |
|--------------|------------|--|------------------------|--------|--------|
| Screen | Day 28 | | | | |
| X | - | Intraventricular conduction delay | 213 | 12.500 | 5% BID |
| - | Day 28 | Bradycardia; intraventricular conduction delay | 205 | 2.590 | 1% QD |
| - | Day 28 | Left ventricular hypertrophy | 217 | 7.590 | 1% BID |
| - | Day 28 | Bradycardia; intraventricular conduction delay | 223 | 9.920 | 5% BID |
| - | Day 28 | Bradycardia; intraventricular conduction delay | 224 | 5.460 | 1% BID |

*(Study DAP 9903, Table 27, Plasma Dapsone Concentrations, Mod 5, Vol. 4)

Reviewer comments:

There does not appear to be any correlation between the observed ECG abnormalities and dapsone levels. On Day 28 of the study, the mean C_{MAX} was 15.1 ng/mL. According to the applicant's response (Amendment 029), the variability in QRS for patients in this study ranged from a decrease of 10 msec to an increase of 16 msec between the screening day and day 28 and this variability probably represent normal variability in QRS. There were random changes in QRS amplitude in isolated leads of no clinical significance.

7.1.9.4 Additional analyses and explorations

7.1.10 Immunogenicity

No immunogenicity data provided.

7.1.11 Human Carcinogenicity

Malignant neoplasms were recorded for 2 patients; however, neither was related to study drug use. The malignant melanoma for Patient 405204 in Study DAP0204 was diagnosed at Baseline, it was not reported as an SAE. At the end of the study, Patient 026153 in Study DAP0204 was referred for a procedure for the malignant melanoma *in situ*, no additional information is available.

7.1.12 Special Safety Studies

In addition to dermal safety studies conducted for topical drug products, the Applicant conducted a 12-month open-label safety study (Study DAP0114) with use of DTG in treatment of acne. Study DAP0114 will be presented first followed by review of Study DAP9902,

Study DAP0114

Note: Efficacy is not being reviewed since this is an open-labeled, non-randomized study.

Study initiation date: January 24, 2002

Study completion date: May 20, 2003

Date of original report: June 2, 2004

Date of amendment: January 14, 2005

Date of amended report: February 21, 2005

Study DAP0114 was a 12-month, multicenter, open-label, non-comparative study of the long-term safety of 5% DTG in patients with acne vulgaris. In this open labeled study where no blinding or randomization procedures were performed, inclusion/exclusion criteria and study procedures (except for study duration) were similar to the Phase 3 pivotal studies. Although this was predominantly a safety study, efficacy was evaluated by the applicant; however, this study is only being reviewed in support of safety. Patients were instructed to apply DTG twice daily to acne areas, as needed, for up to 12 months. Blood was drawn for hematology, serum chemistry, dapsone levels, and metabolite level determinations at Baseline and Months 1, 3, 6, 9, 12 and ET. In addition, blood samples were assessed for hematology and dapsone level in a subset of patients at Weeks 1 and 2. All available patients were screened for G-6-PD at Month 6.

Reviewer comments:

It is not clear why patients were not screened for G-6-PD until Month 6.

Study drug was applied in the same manner as the Phase 3 studies into acne involved areas of the face, back, shoulders, and chest, as needed, twice daily (once in the morning and once at least 1 hour prior to bedtime) for up to 12 months. If acne cleared in a particular area, DTG use in that area may have been discontinued. However, it was required to be re-applied to those areas if acne returned. Application dates were recorded on the appropriate CRF.

Adverse events and use of concomitant medications were assessed at all scheduled visits. Application of DTG was recorded based on application logs and patient interviews. Drug weights were recorded at each scheduled visit to determine patient exposure and to confirm patient compliance. The Applicant defined the safety population as patients dispensed test article with at least one verifiable application or a reported adverse event.

Statistical Methods:

Descriptive statistics, (i.e., mean, median, standard deviation or standard error, min and max, or frequency counts and percentages) were used to summarize all efficacy and safety measures.

Changes in the Conduct of the Study or Planned Analyses

Protocol Amendments

There was one protocol amendment during the course of the study, dated January 18, 2002. The amendment specified that additional hematology profiles and plasma dapsone levels would be evaluated, and adverse events would be recorded, during Weeks 1 and 2 for a subset of patients (all patients from two predefined study centers; minimum of 35 patients planned).

Date of Amended Report: February 21, 2004

The study report dated June 2, 2004 included available plasma dapsone and n-acetyl dapsone information. After reviewing the original data, QLT USA, Inc. (formerly Atrix Laboratories, Inc.) discovered that some laboratory data were missing from the dataset. Dapsone and N-acetyl dapsone plasma levels were missing for 49 patients at Baseline; 2 patients at Week 2, 172 patients at Month 1; 10 patients at Month 3; 27 patients at Month 6; 17 patients at Month 9; 2 patients at Month 12; 45 patients at early termination (ET); and 9 patients with a repeated analysis.

When contacted about this error, _____ located the remaining samples, which were stored frozen, and sent them to the laboratory _____) for analysis. These results were pending at the time of the 5% Dapsone Topical Gel submission. The original study report (dated June 2, 2004) also indicated that a total of four patients in the study were found to be G-6-PD deficient.

The Agency requested that QLT USA, Inc. provide this amended study report, which adds these additional plasma dapsone and n-acetyl dapsone results to the original report.

Missing Samples:

The total number of missing samples was 333.

Study Results

Study DAP0114 was conducted at 18 centers in the United States.

Disposition of Patients

A total of 368 patients were followed for 6 months, and 340 patients were followed for 12 months. Five hundred eighty-six patients were screened for the study; 80 of these patients were not enrolled. According to the applicant, the most common reasons for screen failures were not enough acne (51; 63.75%) and sulfa allergies (6; 7.5%).

Of the 506 enrolled patients, 340 (67.2%) patients completed the study and 166 patients withdrew. Study withdrawal is listed as follows:

- 79 (15.6%) lost to follow-up,
- 59 (11.7%) voluntarily withdrawal
- 11 (2.2%) experienced adverse events
- 6 (1.2%) noncompliant
- 4 (0.8%) lack of efficacy
- 1 (0.2%) protocol violation and
- 6 (1.2%) withdrew for other reasons.

Safety Database

There are 486 (96.0%) patients listed in the safety database. The safety database includes only five patients G-6-PD deficient (Pts # 0317, 1215, 1312, 1314, and 1424) patients.

Demographics:

There was a similar distribution of female (275; 54.3%) and male patients (231; 45.7%) enrolled in the study. The majority of patients were Caucasian (403; 79.6%). Forty-eight patients (9.5%) in the study population were Black and 36 (7.1%) were Hispanic. Only five (1%) patients were G-6-PD deficient (Pts # 0317, 1215, 1312, 1314, and 1424). The mean number of total acne lesions determined for all patients at Baseline was 86.6. Of the total, the mean number of inflammatory lesions was 48.1 and the mean number of non-inflammatory lesions was 38.5.

Reviewer comments:

The number of G-6-PD deficient patients is small and racial distribution is not as expected. Of the five affected patients there is one Black male, two Asian females, and two Caucasian females. According to Charles A. Linder, MD (Blood, Chapter 13; Current Medical Diagnosis & Treatment – 44th Ed. 2004), G-6-PD deficiency is an X-linked recessive disorder affecting 10-15% of American Black men. Females carriers are rarely affected – only when an unusually high percentage of cells producing the normal enzyme are inactivated.

Protocol Deviations

Seven hundred fifty-two (752) protocol deviations were attributable to 300 patients (out of 506 total patients) during the study. Patient visits outside of the visit window accounted for the majority of protocol deviations (422; 231 patients). Ninety-one patients (18.0%) used 118 prohibited concomitant medications outside of protocol-specified parameters during the study period.

The remaining protocol deviations included missing blood draws (37; 26 patients) and missed visits (27; 24 patients). Three females became pregnant during the treatment period. No patients were excluded from the analyses due to protocol deviations.

Lot Numbers:

The lot numbers 1328, 1478, and 1543 of DTG were used in this study.

Study Drug Exposure:

The mean number of days in the study was 265.51 days (median = 366). The mean number of days that patients applied DTG was 252.63 days (median=326). Patients were treated for an average of 97% of study days.

Overall, patients were compliant during the study. The mean number of applications per patient throughout the 12-month study period was 490.91. The average daily use of DTG was 1.35 grams (g).

A summary of study drug exposure is shown in Table 35 (Applicant's Table C.)

Table C. 5% Dapsone Topical Gel Exposure

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| Description | Exposure |
|-----------------------------------|------------------|
| Total Number of Patients | 506 |
| Total Number of Days of Treatment | - |
| N | 506 |
| Mean ± SD | 252.63 ± 120.36 |
| Median | 326 |
| Range | 1.00–380.00 |
| Daily DTG Use During Treatment | |
| N | 349 ^a |
| Mean ± SD (g) | 1.35 ± 1.08 |
| Median (g) | 1.07 |
| Range (g) | 0.00–11.02 |

Patient base: all-patient dataset

Source: Table 10 and Appendix 7.1

N = number of patients; SD = standard deviation; DTG = Dapsone Topical Gel;

g = gram

^a Based on reconcilable study drug weights.

Plasma Dapsone Concentration (See Biopharm Review)

Median plasma dapsone concentrations ranged between 4.6 and 7.7 ng/mL throughout the study. In addition, median plasma N-acetyl dapsone concentrations ranged between 1.4 and 2.5 ng/mL throughout the study.

Adverse Events

Overall, 327 patients (67.3%) experienced one or more treatment-emergent adverse events during the course of the study; 46 patients (9.5%) experienced at least one treatment-related event. The incidence and prevalence of treatment-emergent adverse events generally did not increase over the course of the study.

Sixty-seven patients (13.8%) reported one or more treatment-emergent application site adverse events; 40 (8.2%) experienced application site adverse events that were reported to be treatment related. The most common (≥ 2%) treatment-emergent application site adverse events were dryness (14; 2.9%), rash (12; 2.5%), and sunburn (11; 2.3%). Most application site adverse events were mild or moderate in severity.

The most common (≥ 5%) treatment-emergent non-application site adverse events were: headache (98; 20.2%), common cold (nasopharyngitis; 75; 15.4%), sore throat (pharyngitis; 43; 8.8%), menstrual cramps (dysmenorrhoea; 31; 6.4%), sinusitis NOS (28; 5.8%), and upper respiratory tract infection NOS (24; 4.9%). Non-application site adverse events were generally mild or moderate in severity.

The most commonly reported adverse events experienced by at least 5% of patients) regardless of causality are summarized in Table H.

Table 36 (Applicant's Table H). Most Frequently Reported Treatment-Emerge

| MedDRA Term | Total Overall (N=486) |
|---------------------------------------|--------------------------|
| Headache NOS | 98 (20.2%) |
| Nasopharyngitis | 75 (15.4%) |
| Pharyngitis | 43 (8.8%) |
| Dysmenorrhoea | 31 (6.4%) |
| Sinusitis NOS | 28 (5.8%) |
| Upper respiratory tract infection NOS | 24 (4.9%) |

Patient base: safety-evaluable dataset

Source: Table 13

Common: experienced by at least 5% of patients

NOS = not otherwise specified; N = number of patients

There were no patient deaths in this study. Five patients (1.0%) experienced one or more treatment-emergent serious adverse events. All serious adverse events were designated as such because the patient required hospitalization for events not considered related to DTG by the Investigator. No serious adverse event was considered life threatening or led to discontinuation of the patient.

Eleven patients (2.3%) had an adverse event that led to discontinuation. Each of these adverse events was reported to be treatment related. Ten of the 11 patients had application site events, and one patient experienced nausea, weakness, and dizziness for a few hours on Day 2 and discontinued the study on Day 4.

Laboratory Profile

Although oral dapson can produce hemolysis in non-G-6-PD deficient patients, G-6-PD deficient patients are of interest since they are more sensitive to hemolytic effects. The following patients were identified at Month 6 in this long term study as G-6-PD deficient:

| Sub # | Visit | Test | Value |
|-------|------------|------------------------------------|-------|
| 0317 | Month 6 | Glucose -6-Phosphate Dehydrogenase | 1.0 |
| 1215 | Month 6 | Glucose -6-Phosphate Dehydrogenase | 6.6 |
| 1312 | Month 6 | Glucose -6-Phosphate Dehydrogenase | 6.7 |
| 1314 | Early Term | Glucose -6-Phosphate Dehydrogenase | 5.7 |
| 1424 | Month 6 | Glucose -6-Phosphate Dehydrogenase | 6.5 |

Patient 0317 (Black Male) has the lowest G-6-PD level and also had the lowest dapson levels among this subset of patients. Completed the study, one AE reported (sprained ankle), no commitment medication.

Hematology Profile

Table 37 (Applicant's Table 7): Plasma Dapsone Levels and Hemoglobin over time for G6PD Deficient Patients and All Patients in Study DAP0114

Table 7: Plasma Dapsone Levels (ng/mL) and Hemoglobin over time for G6PD Deficient Patients and All Patients in Study DAP0114

| Patient Number | Grams Used per Day/Total | Hemoglobin (g/dL) and Plasma Concentration (ng/mL) | | | | | |
|----------------------------------|--------------------------|--|-----------|-----------|-----------|-----------|------------|
| | | Baseline | Month 1 | Month 3 | Month 6 | Month 9 | Month 12 |
| 0317 (12yo male) | 0.9/305 | 13.2 | 12.8 | 12.9 | 13.2 | 12.8 | 13.1 |
| | | -- | 1.2 | 2.5 | 8.4 | 3.8 | 5.0 |
| 1215 (22yo female) | 1.1/366 | 12.2 | 12.6 | 12.2 | 11.9 | 12.6 | 12.4 |
| | | -- | 14.6 | 15.0 | 10.9 | 9.9 | 13.7 |
| 1312 (16yo female) | 1.0/323 | 12.5 | 12.0 | 12.0 | 12.6 | 13.8 | 13.0 |
| | | -- | 18.3 | 7.4 | 9.2 | 4.0 | 10.1 |
| 1314 (21yo female) | NA | 12.9 | 13.5 | 12.8 | 13.5 | NA | NA |
| | | -- | 63.4 | 29.3 | NA | NA | NA |
| 1424 (29yo female) | 2.0/756 | 13.3 | 14.0 | 12.9 | 13.9 | 13.1 | 12.1 |
| | | -- | 22.2 | 31.9 | NA | NA | NA |
| All Patients (mean and range) | 1.4 0-11.0 | 14.2 | 14.0 | 13.9 | 14.0 | 14.0 | 14.0 |
| | | -- | 7.6-18.8 | 7.8-17.6 | 7.7-17.2 | 7.7-17.1 | 7.4-17.9 |
| | | 0.64 | 11.0 | 9.1 | 8.1 | 7.6 | 7.5 |
| | | 0.05-4.3 | 0.05-91.9 | 0.05-87.1 | 0.05-76.1 | 0.05-70.7 | 0.05-107.0 |

NA: not available

Source: Appendices 1 and 6

According to the Applicant, no trends in laboratory profile suggestive of a safety concern were observed. According to the Applicant, the adverse event profile, including laboratory studies for the five G-6-PD deficient patients was similar to the study population; however, this number of patients is too small to draw a valid conclusion. Laboratory values and dapsone plasma levels do not coincide with the occurrence of an AE.

Patient #1424 is of interest due to episodic decreases of ≥ 1 g/dL in hemoglobin over the course of the study. Patient 1424, a 29-year-old G6PD deficient Asian female, used Septra (6-6-02) for a URI after the one month visit but prior to the Month 3 visit. A 1.1 g/dL reduction in hemoglobin is noted between Month 1 and 3. The patient was admitted to the hospital for acute pancreatitis and influenza on Day 310. Laboratory values are not available at the time of the AE; however at Visit 12 (Day 339), a 1.2 g/dL decrease in hemoglobin level over baseline, 1+ poikilocytosis, and an elevated LDH of 423 IU/L (normal range 94-250 IU/L) were recorded approximately one month after hospitalization (Month 12 Visit). Bilirubin levels remained constant. Dapsone and metabolite plasma levels for Months 6, 9, and 12 are not available as they were lost in shipping. Plasma dapsone levels available for Patient 1424 ranged from <0.05 ng/mL at Baseline to 31.92 ng/mL up to Month 3.

The Applicant's assessment is that both the change in hemoglobin and elevated LDH were attributed to the pancreatitis and influenza occurring the month prior to the 12 month visit. It needs to be ruled out with some reasonable degree of certainty that topical dapsone was not a contributory factor in the decrease in hemoglobin level in this patient.

Conclusion

This 12-month safety study included 5 additional G6PD deficient patients and this number is too small to draw valid conclusions. Safety assessment in G6PD, the most sensitive population to the hemolytic effects of dapson, is inadequate due to small numbers. According to the FDA Hematology Consultant, while the topical gel alone may not be able to induce hemolysis, it is theoretically possible that use of the gel could be contributory under conditions of oxidative stress.

Dermal Safety Studies

The Applicant conducted five dermal safety studies. According to the Applicant, all dermal safety studies included the final to be marketed 5% formulation. The dermal safety studies are as follows:

- 1) Cumulative Irritation: Study TD-020, a 14-day, cumulative irritation study of DTG in 38 healthy subjects,
- 2) Contact Sensitization Study TD-010 by means of the maximization assay in 33 healthy volunteers with 1% DTG,
- 3) Studies C98-D235 (35 subjects) and DAP9901 (33 subjects) were designed to assess the potential of topical dapson to induce allergic dermatitis, phototoxicity, and photoallergic contact dermatitis. Study C98-D235 was repeated as Study DAP9901 due to a protocol deviation (post-study blood analysis and post-study urine analysis were conducted after the study was complete rather than during the study as indicated by the protocol) and
- 4) Study DAP9902 assessed the safety and potential of 3 formulations of DTG to induce contact sensitization by repetitive applications to the skin.

Study DAP9902

Title: A Placebo-Controlled, Human Repeat Insult Patch test Comparing 1% Dapsone/10% DGME, 1% Dapsone/25% DGME, and 5% Dapsone/25% DGME in Healthy Subjects"

Study Dates

Date of First Enrollment: March 17, 1999

Date of Last Completed: June 11, 1999

Contact Sensitization Study DAP9902 to Determination of the Contact Allergenicity and Skin Sensitization Potential by Means of the Maximization Assay (Vol. 110) was a 7-week, single-center, vehicle-controlled, double-blinded, repeat insult patch test to assess the safety and potential of 3 formulations of DTG to induce contact sensitization by repetitive applications to the skin.

The study consisted 1) three week induction phase that involved 48-hour applications (under occlusion) of all treatments for ten applications; 2) 12-24 rest period, and 3) 48 and 96-hour challenge and re-challenge phase. In the re-challenge phase the following test articles were used: 5% dapson in petrolatum, 0.2 % methylparaben in petrolatum, and 25% DGME in water. In the Reactions to the 5 different study drugs were scored for erythema using a 5-point scale. Adverse

events were collected throughout the treatment period by examining and interviewing the subjects.

Reactions were scored using a 4-point erythema scale in addition to responses such as edema, papules, vesicle, bullae, spreading and weeping were recorded. PE and vital signs were performed and hematologic parameters were obtained. Adverse events were recorded.

Study Results

Two hundred fifty-three healthy volunteers were enrolled and received the 5 test materials: 1% dapson/10% DGME, 1% dapson/25% DGME, and 5% dapson/25% DGME, 10% DGME, and 25% DGME. Of the 253 enrolled where 189 (75%) were female and 64 (25%) were males with mean age of 37.6 years (range 18 to 65). There were 212 (84%) subjects who completed the study. Of the 41 subjects who did not complete the study, the most common reason for premature discontinuation was voluntary withdrawal in 29 subjects, adverse events in 7 subjects, 2 subjects were lost to follow-up, and 3 subjects listed as other.

During Induction, 98% of subjects displayed at each treatment site had mild or no erythema and 2 % experienced moderate erythema. From Day 12 through day 29, there were slightly higher percentage of subjects with mild erythema rather than no erythema in the 25% DGME vehicle and the 1% dapson/25% DGME groups.

During the Challenge Phase, 84% of subjects had no erythema at the original or alternative sites. There were 2 subjects (<1) who experienced severe erythema at the 25% DGME vehicle sites and at the 1% dapson/25% DGME sites.

Three subjects (1020, 1052, and 1172) were rechallenged. All 3 subjects had response to test articles except 5% dapson in petrolatum. Subject 1172 experienced weeping on Day 2 of the re-challenge. No skin reactions were recorded for dapson in petrolatum or .2% methylparaben. At Challenge (Day 5), for the to-be-marketed 5% dapson/25% DGME formulation, there were 201 (94.8%) with no visible erythema, 9 (4.2%) with mild erythema, and 2 (0.9%) with moderate erythema. Alternative site is 202 (95.3%) no visible erythema, 7 (3.3%), 3 (1.4%) moderate erythema.

Elevated Responses

Elevated responses were also assessed. All of three of the rechallenged subjects (1020, 1052, and 1172) exhibited some degree of elevated response (edema and papules) Weeping was recorded at one 25% DGME in water treated site.

Adverse events/Laboratory Assessments

There were no deaths, life-threatening, or serious test-related AEs during the study two subjects experienced serious AE (psychiatric and one hospitalized for left arm and neck pain). Subject 1031 experienced 2 severe treatment related AEs (itching patches and burning patches). Mild fluctuations and variability were observed in lab values over time.

Conclusion

Under conditions of the study, 1.4% (3) subjects exhibited sensitization reactions to the "final-to-be-marketed" formulation. Overall, no subject was sensitized to dapsone in petrolatum. There is a trend to suggesting that DGME (a vehicle component) is a mild to moderate sensitizer under occlusion; however according to the Applicant, up to 40% DGME is currently used non-occluded in a number of marketed cosmetic products without significant reported sensitization.

Study DAP9901

Title: "Combination Study Designed to Assess the Potential of Topical Dapsone to Induce Allergic Contact Dermatitis, Phototoxicity, and PhotoAllergic Dermatitis"

Study Dates:

Start Date: February 16, 1999

Completion Date: April 1, 1999

Objectives:

To assess the safety and the potential of the Sponsor's test materials (1% Dapsone with 25% DGME, 5% Dapsone with 25% DGME, 1% Dapsone with 10% DGME, placebo with 15% DGME, and placebo with 25% DGME to induce irritation (IRR), allergic contact dermatitis (ACD), phototoxicity, and photoallergic contact dermatitis (PACD) of the skin.

Each subject's Minimal Erythema Dose (MED) was determined using 7 irradiation exposures. Occlusive patches were applied on Visit 3.

For the phototoxicity (PHO) portion of the study, subjects were patched once, and sites were graded 24 hours after patch application. The sites were irradiated with UVA following 24-hour grading and again graded 72 and 96 hours after patch application.

For the irritation (IRR) portion of the study, subjects were patched once, and sites were graded 24 hours after patch application.

For the photoallergic (PACD) portion of the study, subjects were patched 6 times and graded 5 times for the induction phase. Sites were irradiated with one MED of UVA+UVB 24 hours after each application and graded 72-96 hours after each application. For the challenge phase, patches were applied to original and alternate sites, and 24 hours after patch application the sites were irradiated with 25 mW/cm² of UVA. The sites were graded twice, once at 48 hours and once at 72 hours after patch application.

For the allergic contact dermatitis (ACD) portion of the study, subjects were patched were patched 6 times and graded 5 times for the induction phase. Sites were graded 72-96 hours after each application. For challenge, patches were applied to original and alternate sites, and the sites were graded twice, once 48 hours and 72 hours after each patch application.

Study Results

Thirty-six subjects were recruited to participate in the study. Three were disqualified prior to enrollment in the study. Thirty-three subjects were screened for participation and 26 subjects

completed the study. Seven subjects discontinued or were dropped from the study for reasons unrelated to the test material.

Study population consisted of 23 females and 3 male subjects, ages 18 – 63 years (median age 34 years). All subjects were Caucasian.

Safety

No abnormal CBC lab results were reported and no positive pregnancy tests were obtained. No serious or unanticipated AEs were noted during the study.

Conclusion

Under conditions of the study, none of the subjects exhibited evidence of phototoxicity, irritation, photoallergic contact dermatitis, or allergic contact dermatitis.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No withdrawal or abuse potential is expected.

7.1.14 Human Reproduction and Pregnancy Data

Eleven patients (VC, 4; 5% DTG, 7) were reported to have become pregnant while on study drug.

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Table 38 (Applicant's Table 53) Patients Who Became Pregnant

| Study Drug/ Protocol-Patient number | Day of Study When Pregnancy Was Determined | Outcome | Withdrawal |
|--|---|-------------------------------------|------------|
| Pivotal studies | | | |
| 5% DTG | | | |
| DAP0203-030721 | Day 36 | Termination of pregnancy (elective) | Yes |
| DAP0203-060146 | Day 34 | Unknown | No |
| DAP0203-260179 | Day 34 | Delivered a healthy male | Yes |
| DAP0204-195301 | Day 87 | Unknown | Yes |
| Test Vehicle | | | |
| DAP0203-270992 | Day 95 | Unknown | No |
| DAP0203-410400 | Day 50 | Termination of pregnancy (elective) | Yes |
| DAP0203-530032 | Day 78 | Delivered a healthy male | Yes |
| DAP0204-185850 | Day 25 | Unknown | Yes |
| Long-Term Study | | | |
| 5% DTG | | | |
| DAP0114-1220 | Day 338 | Delivered a female | No |
| DAP0114-1417 | Day 249 | Delivered Twins | Yes |
| DAP0114-1741 | Day 343 | Unknown | No |
| <small>Studies DAP0203, DAP0204, and DAP0114 Source: DAP0203 Individual study report (Module 5.3.E.1); DAP0204 Individual study report (Module 5.3.E.1); DAP0114 Individual study report (Module 5.3.E.1).</small> | | | |

Insufficient numbers of pregnancies outcome data are too small to draw valid conclusions regarding safe use in pregnancy.

7.1.15 Assessment of Effect on Growth

Growth assessment was not performed.

7.1.16 Overdose Experience

Topical dapson gel 5% is not for oral use.

7.1.17 Postmarketing Experience

Topical dapson has not been marketed.

7.2 Adequacy of Patient Exposure and Safety Assessments

Overall, patient exposure in patients with normal G6PD activity levels is adequate. According to the Consultant, the safety concerns regarding hemolysis in persons with G6PD deficiency treated with 5% Dapsone Topical Gel appear to be small and are reasonably well addressed by the sponsor. Based on previous experience, after this drug has entered widespread use, someone somewhere will be describing that rare patient who develops hemolysis in association with the use of DTG. The reviewing division should weigh the benefit of the drug in comparison to this very small risk.

Limited data indicates no differences between the 25 G6PD deficient patients that were attributable to use of 5% DTG; however, the dataset was small and incomplete. Insufficient numbers of G6PD deficient patients were studied to be able to draw valid conclusions regarding safe use this population.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

7.2.1.2 Demographics

Table 39 (Applicant's Table 13) Demographics by Treatment Group: All Studies, Excluding Studies in Healthy Volunteers

| Characteristic | Treatment Group | | | | All Treatments |
|----------------|------------------------|------------|------------|--------------|------------------------|
| | VC | 1% DTG | 3% DTG | 5% DTG | |
| Age | | | | | |
| N | 1880 | 23 | 31 | 2372 | 4086 |
| Mean ± SD | 19.3 ± 7.6 | 24.8 ± 6.3 | 19.9 ± 6.3 | 19.5 ± 7.7 | 19.4 ± 7.6 |
| Range | 11.0–59.0 ^a | 18.0–39.0 | 13.0–46.0 | 12.0–91.0 | 11.0–91.0 ^a |
| 12 to 16 | 830 (38.0%) | 0 | 14 (45.2%) | 912 (38.4%) | 1556 (38.1%) |
| ≥ 18 | 1030 (62.0%) | 23 (100%) | 17 (54.8%) | 1480 (61.6%) | 2530 (61.9%) |
| Gender | | | | | |
| N | 1880 | 23 | 31 | 2372 | 4086 |
| Male | 773 (48.8%) | 9 (39.1%) | 13 (41.9%) | 1132 (47.7%) | 1927 (47.2%) |
| Female | 887 (53.4%) | 14 (60.9%) | 18 (58.1%) | 1240 (52.4%) | 2159 (52.8%) |
| Race | | | | | |
| N | 1880 | 23 | 31 | 2372 | 4086 |
| White | 1211 (73.9%) | 20 (87.0%) | 27 (87.1%) | 1735 (74.4%) | 3023 (74.0%) |
| Black | 229 (13.8%) | 2 (8.7%) | 1 (3.2%) | 301 (12.7%) | 533 (13.0%) |
| Hispanic | 155 (9.3%) | 1 (4.3%) | 3 (9.7%) | 218 (9.2%) | 377 (9.2%) |
| Asian | 39 (2.3%) | 0 | 0 | 52 (2.2%) | 91 (2.2%) |
| Other | 26 (1.8%) | 0 | 0 | 36 (1.5%) | 62 (1.5%) |

^a Patient No. 521740 was enrolled in Study DAP0203 despite being 11 years of age.

Studies DAP0203, DAP0310, DAP0004, DAP0110, DAP0114, DAP0203, DAP0204, and 03-0-182

Source: Table 12D

The VC and 5% DTG groups were balanced with respect to age, gender, and race.

Long-Term Safety Study

A summary of the demographics for the long-term safety study is presented in Table 16.

There was a similar distribution of female (54.1%) and male patients (45.9%) in the safety evaluable population of the long-term safety study. The mean age was 20 years (range: 12 to 77 years of age). The majority of patients were Caucasian (79.6%), 9.5% Black, and 7.2% were Hispanic.

7.2.1.3 Extent of exposure (dose/duration)

The mean number of days on study was 79.4 for the VC group, 30.3 for the 1% DTG group, 79.4 for the 3% DTG group, and 117.6 for the 5% DTG group. The mean number of days of study drug use was 78.1 for VC-treated patients and 122.7 for 5% DTG-treated patients. The difference between the 2 treatment groups reflects the number of 5% DTG-treated patients in the uncontrolled, long-term safety study (Study DAP0114). Patients in the VC and 5% DTG groups applied study drug on most days of study participation (median 100%).

Table 40 (Applicant's Table 23) Daily Study Drug Use (Grams): All Studies, Excluding Studies in Healthy Subjects and Burn Patients

| Description | Treatment Group | |
|--|-----------------|-------------------------|
| | VC | 5% DTG |
| Total Amount of Study Drug Used^a | | |
| N | 1467 | 1951 |
| Mean ± SD | 101.6 ± 71.1 | 153.3 ± 105.3 |
| Median | 87.7 | 101.2 |
| Range | 0.0-492.0 | 0.0-3701.1 ^b |
| Study Drug Used Per Day^a | | |
| N | 1467 | 1950 |
| Mean ± SD | 1.3 ± 1.5 | 1.4 ± 1.1 |
| Median | 1.1 | 1.1 |
| Range | 0.0-45.3 | 0.0-14.7 |

^a Studies DAP9903, DAP9910, and DAP0004 are not included in these summaries due to insufficient data.

^b A minimum value of 0.0 represents a 1-time application of study drug that was not measurable.

Studies DAP9903, DAP9910, DAP0004, DAP0110, DAP0114, DAP0203, DAP0204, and 03-0-182.

Source: Table 15D.

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The mean total amount of study drug used during all studies, excluding studies in healthy subjects, was 101.6 grams for the VC group and 153.3 grams for the 5% DTG group. For 5% DTG-treated patients, this represents a mean total amount of dapsone applied of 7.7 grams (range 0.0 to 185.1 grams). Patients in the 5% DTG group used more study drug during the entire study period because the 12-month safety study was included in this average.

Study duration for patients in the 2 pivotal studies is summarized in Table 24.

Table 41 (Applicant's Table 24) Study Duration by Treatment Group: Two Pivotal Studies

| Duration of Exposure | Treatment Group | |
|----------------------|-------------------------|-----------------------------|
| | VC (N=1467) n (%) | 5% DTG (N=1466) n (%) |
| 0-4 Weeks | 81 (5.5%) | 67 (4.6%) |
| >4-8 Weeks | 80 (5.5%) | 60 (4.1%) |
| >8-12 Weeks | 542 (36.9%) | 525 (35.8%) |
| >3-4 Months | 759 (51.7%) | 762 (52.3%) |
| >4-8 Months | 5 (0.3%) | 8 (0.5%) |

Studies DAP0203 and DAP0204.
 Source: Table 13A.

No differences were observed between the 2 treatment groups in terms of duration of study drug exposure.

Reviewer comments:

It is not clear why the study duration was extended past 12 weeks for 764 patients.

Study drug use for the VC group was similar to that for the 5% DTG group. The mean amount of study drug applied per day was 1.4 grams.

Table 42 (Applicant's Table 31) Daily Study Drug Use (Grams): Long-Term Safety Study

| Description | | Treatment Group |
|---------------------------------|-----------|-------------------------|
| | | 5% DTG |
| Total Amount of Study Drug Used | N | 349 ^a |
| | Mean ± SD | 360.2 ± 358.7 |
| | Median | 271.0 |
| | Range | 0.0-3701.1 ^b |
| Study Drug Used Per Day | N | 349 ^a |
| | Mean ± SD | 1.3 ± 1.1 |
| | Median | 1.0 |
| | Range | 0.0-11.0 ^b |

^a Based on reconcilable study drug weights.

^b A minimum value of 0.0 represents a 1-time application of study drug that was not measurable.

Study DAP0114

Source: Table 15B

The mean total amount of study drug (5% DTG) used during the 12-month study was 360.2 grams (range 0.0 to 3701.1 grams). This represents a mean total amount of dapson applied of 18.0 grams (range 0.0 to 185.1 grams). The mean amount of study drug (5% DTG) applied per day was 1.3 grams (range 0.0 to 11.0 grams). The amount of study drug (5% DTG) used per day by adults (≥ 16 years of age) was slightly higher than the amount used by pediatrics (12 to 15 years of age).

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The mean total amount of study drug used during all studies, excluding studies in healthy subjects, was 101.6 grams for the VC group and 153.3 grams for the 5% DTG group. For 5% DTG-treated patients, this represents a mean total amount of dapson applied of 7.7 grams (range 0.0 to 185.1 grams). Patients in the 5% DTG group used more study drug during the entire study period because the 12-month safety study was included in this average. Study drug use for the VC group was similar to that for the 5% DTG group. The mean amount of study drug applied per day was 1.4 grams.

The mean total amount of study drug (5% DTG) used during the 12-month study was 360.2 grams (range 0.0 to 3701.1 grams). This represents a mean total amount of dapson applied of 18.0 grams (range 0.0 to 185.1 grams).

The mean amount of study drug (5% DTG) applied per day was 1.3 grams (range 0.0 to 11.0 grams). The amount of study drug (5% DTG) used per day by adults (≥ 16 years of age) was slightly higher than the amount used by pediatrics (12 to 15 years of age).

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

7.2.2.2 Postmarketing experience

7.2.2.3 Literature

2.7.4.2.1.5.1.1 Literature: Oral Dapson

Information from the literature that addressed these side effects is summarized.

2.7.4.2.1.5.1.1.1 Hemolysis

Key points reported in the literature include the following:

- Almost every individual treated with 200 to 300 mg/day oral dapson will develop hemolysis. Doses of 100 mg or less in normal subjects do not cause hemolysis (DeGowin, 1967).
- Reticulocytosis was noted in most patients with dermatitis herpetiformis receiving 50 mg or more a day of oral dapson. There was a dose-related effect (Cream and Scott, 1970).
- Excluding one result, the red cell life span decreased as the dosage increased. The $51Cr$ half-life for patients receiving 50 mg dapson daily was 23 days, for those receiving 100 mg PO daily, 17.5 days, and for those receiving more than 100 mg, 17.0 days. Patients who received 100 mg or more of oral dapson daily showed red cell morphology abnormalities of which red cell fragmentation and macrocytosis were the most frequent. Macrocytosis was unrelated to B_{12} or folate deficiency. Red cell fragmentation was very apparent in the first few weeks of oral treatment, and the severity tended to be dose dependent. Spherocytosis was seen in only the most severely affected patients (Cream and Scott, 1970).

2.7.4.2.1.5.1.1.2 Methemoglobinemia

Key points reported in the literature on methemoglobinemia included the following:

- Methemoglobinemia is a common side effect of orally administered dapson. The means of the hemoglobin levels of patients with dermatitis herpetiformis treated with dapson were significantly lower than those of the normal controls. There was a dose-related effect (Cream and Scott, 1970).
- Longitudinal analysis of patients with acute dapson intoxication showed a significant association between methemoglobinemia and the time elapsed after the intake (t), according to the equation: $\text{Dapsonemia} = 12.9256 - 0.0682t + 0.234 \text{ methemoglobinemia}$ (Carrazza, et al., 2000).
- Side effects associated with methemoglobin, such as cyanosis, headache, vertigo, and general weakness and rarely dyspnea, were observed in patients with dermatitis herpetiformis. The severity of these symptoms was not directly proportional to the methemoglobin level (Pawlik, et al., 1980).

7.2.3 Adequacy of Overall Clinical Experience

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

See Pharm/Tox review.

7.2.5 Adequacy of Routine Clinical Testing

Although routine clinical testing was adequate, a more robust hematological assessment (e.g., reticulocyte counts, erythrocyte adenylate kinase levels, etc.) would have been useful since evidence of hemolysis is classically diagnosed by a combination of nonspecific laboratory tests including serum bilirubin, LDH, and reticulocyte count.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

7.2.8 Assessment of Quality and Completeness of Data

As mentioned above, quality control (e.g., handling of the laboratory specimen and data monitoring) is problematic in that:

- Samples were found in a freezer and subsequently analyzed after supposedly final study reports had been submitted to the Agency for review in support of the NDA application.
- Three separate samples for the same patient (#1424, Study DAP0114) were lost in shipping on apparently 3 separate occasions.

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{NDA 21-794/N-000
{ACZONE™ (dapsonsone) Gel 5%}

- Inaccurate data listing for Patient #1424 (Study DAP0114). Response to request for information dated March 4, 2005 (Appendix 18, pg. 4 of 8) provided an additional abnormal lab value at Visit 12 of an elevated LDH of 423 IU/L (normal range 94-250 IU/L) for Patient 1424. It appears that some data from a post treatment follow-up (LDH of 165 IU/L rather than 423 IU/L) were conveyed as 12-Month Visit-data (Mod 5, Vol. 80, pg. 333 of 588 vs. Submission dated 03-04-05, Appendix 18, pg. 4 of 8).

7.2.9 Additional Submissions, Including Safety Update

The 120-day Safety Update (Letter date 02-22-05) certifies that a review of new animal and clinical data reveals no new information about 5% Dapsone Topical Gel product that may affect the statement of contraindications ; warnings, precautions, and adverse events in the draft labeling.

**APPEARS THIS WAY
ON ORIGINAL**

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

7.4.1.2 Combining data

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

7.4.2.2 Explorations for time dependency for adverse findings

7.4.2.3 Explorations for drug-demographic interactions

7.4.2.4 Explorations for drug-disease interactions

7.4.2.5 Explorations for drug-drug interactions

7.4.3 Causality Determination

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

8.2 Drug-Drug Interactions

The trimethoprim (TMP)/sulphamethoxazole (SMX) interaction study (Study 03-0-182) was performed. The pharmacokinetic parameters for TMP and SMX (C_{max} , T_{max} , and AUC_{0-12}) were unaffected by concomitant administration of 5% DTG. Concomitant administration of 5% DTG and oral TMP/SMX increased the C_{max} and AUC_{0-12} of dapson and its metabolites, N-acetyl dapson and hydroxylamine dapson. Overall, dapson and metabolite concentrations were 100-fold lower relative to oral administration and 5% DTG was well tolerated, given alone or in combination with TMP/SMX.

Oral Dapson Literature

The key findings from the literature are as follows:

- Rifampicin 600 mg has been reported to modestly decrease the plasma half-life of dapsone and to significantly increase its urinary excretion. The mechanism is probably related to liver enzyme induction by rifampicin (Balakrishnan and Sheshadri, 1979).
- Concomitant oral administration of pyrimethamine 25 mg and oral dapsone does not alter the plasma half-life values of dapsone or its N-acetyl metabolite. However, pyrimethamine increases the volume of distribution of dapsone and lowers the peak serum concentrations. This has been demonstrated to be correlated with higher salivary concentrations, suggesting an increase in the free levels of the drug (Ahmad and Rogers, 1980).
- Probenecid 500 mg administered orally with dapsone causes a significant reduction in the urinary excretion of free and conjugated dapsone together with an increase in dapsone concentrations in blood (Goodwin and Sparell, 1969).
- Oral administration of disulfiram 500 mg at 18 hours before oral dosing with dapsone decreased plasma concentrations of dapsone and attenuated the formation of methemoglobin (Mitra, et al., 1995).
- Intravenous injection of ascorbic acid 500 mg did not affect the absorption of dapsone but decreased its plasma concentrations in leprosy and borderline leprosy patients (Venkenesan, et al., 1979).
- Concomitant oral administration of cimetidine 400 mg TID inhibits the N-hydroxylation of dapsone, resulting in elevated plasma concentrations of the parent drug (Coleman, et al., 1990).

2.7.4.2.1.1.7.4 Conclusions

There were no interactions observed in any of the clinical studies when patients were treated with 5% DTG and took systemic medication known to result in interactions with systemically administered dapsone. Due to low systemic absorption following topically applied dapsone gel, no clinically relevant interactions would be anticipated.

8.3 Special Populations

As previously stated, dose related hematological adverse reactions (e.g., hemolysis, methemoglobinemia, and anemia) are most common adverse effect associated with use of oral dapsone. The hemolytic process is most likely related to metabolites of dapsone (particularly the N-hydroxylamine product) rather than to the parent compound. The metabolites interfere with the pathway that includes glucose, G6PD, NADPH and reduced glutathione in a series of linked reactions that provide hydrogen ions to maintain the iron in hemoglobin in its reduced Fe^{2+} (functional) state. Patients who are G6PD deficient are more sensitive to hemolytic changes associated with oxidative stress, which may result from oral dapsone or other drug exposure, infection and ingestion of fava beans (favism). G6PD deficient patients are less susceptible to methemoglobinemia according to Zhu and Stiller, 2001 and Beutler, 1994.

G6PD deficiency is the most common enzymopathy in the world and affects up to 400 million people. G6PD deficiency is not a single genetic abnormality. Over 400 different enzyme defects have been described; however, common mutations are often shared within populations. The prevalence of G6PD deficiency is highest in Africa, Southeast Asia and the Middle East with the highest rates observed in African-Americans, and tribes from parts of Africa, and Southeast Asia.

G6PD is encoded on the X chromosome and G6PD deficiency is generally more severe in males (homozygous). Females are affected by the phenomenon of X-inactivation where random X-chromosome inactivation can lead to mosaics that are functionally deficient in G6PD (heterozygous). In some populations, true homozygous females are described.

The Mediterranean variant is most common in patients from countries bordering the Mediterranean, while the A- variant is most common in African-Americans and Africans. The most common type in the United States is Type A and other variants are uncommon or rare. These latter variants may respond differently to the challenge of the topical administration of DTG.

According to the Hematology Consultant dated April 20, 2005, there is no information available to determine the effects of the topical application of DTG in persons with rarer genetic abnormalities, such as methemoglobin reductase or the congenital methemoglobinemias, in which the oxidant stress of dapson and its metabolite may also induce methemoglobinemia. The Consultant goes on to say that based on previous experience, after this drug has entered widespread use, someone somewhere will be describing that rare patient who develops hemolysis in association with the use of DTG and the reviewing division should weigh the benefit of the drug in comparison to this very small risk.

According to an FDA hematology consult dated March 29, 2004, there is no known threshold for hemolytic effect of dapson. According to the FDA Hematology Consultant, while the topical gel alone may not be able to induce hemolysis, it is theoretically possible that use of the gel could be contributory under conditions of oxidative stress. Although the risk associated with use of DTG might be perceived as small, efficacy is marginal at 4 to 9% better than vehicle and there are numerous alternative therapies for treatment of acne.

The number of G6PD deficient patients studied in the applicant's clinical development program is small and the adverse effect of dapson in this patient population is not clear. While overt anemia did not occur, a decrease in hemoglobin of ≥ 1 g/dL did occur in 3 of 25 (12%) G6PD patients exposed to active drug. A discussion of the 3 G6PD deficient patients follows:

- Of interest is Patient #1424, a 29-year-old G6PD deficient Asian female, admitted to the hospital for acute pancreatitis and influenza on Day 310 (Study DAP0114). Laboratory values for Patient 1424 are not available at the time of the AE; however at Visit 12 (Day 339) the following lab values were recorded approximately one month after hospitalization (Month 12 Visit): 1.2 g/dL decrease in hemoglobin level over baseline, 1+ poikilocytosis and an elevated LDH of 423 IU/L (normal range 94-250 IU/L). Bilirubin levels remained constant. Plasma dapson levels for Months 6, 9, and 12 are not available for this patient as they were lost in shipping. Prior plasma dapson levels ranged from <0.05 ng/mL at Baseline to 31.92 ng/mL at Month 3.

The applicant's assessment is that both the change in hemoglobin and elevated LDH were attributed to the pancreatitis and influenza occurring the month prior to the 12 month visit. Topical dapson use may have been a contributory factor in the decrease in hemoglobin level in this patient.

- Patient 375422, a 16 year old Caucasian male with G6PD deficiency, had a 1.2 g/dL reduction in hemoglobin over baseline. The Baseline total bilirubin was 2 mg/dL (normal range 0.2 -1.2) and total bilirubin was 3.6 mg/dL at the end of the study. The elevated bilirubin level was deemed as possibly related to study drug by the Investigator (Mod 5, Vol. 54, pg. 167 of 266); however, dapsone and N-acetyl metabolite levels were not determined as required by Study Protocol DAP0204.

According to the applicant, the patient was diagnosed with Gilbert disease; however, Gilbert disease is not known to be associated with a decrease in hemoglobin. The patient's baseline medical history did not include this diagnosis. Indirect bilirubin levels would have been useful in confirming a diagnosis of Gilbert disease.

- Patient 0103, a severely deficient G6PD Caucasian male, had a 1.3 g/dL reduction in hemoglobin (Hgb), slight elevation of total bilirubin, and increased reticulocyte count over the course of the 14 day PK study. In PK Study DAP0110, DTG was applied to a fixed % BSA for 14 days.

According to the Submission dated March 4, 2005 (Hematolytic Effects of Dapsone in G6PD Subjects), 7 of 18 patients in the study had a hemoglobin of 1 g/dL. The Applicant stated that the decreases in hemoglobin may have been related to the number of blood draws; however the G6PD subject was the only one of 7 with a decrease in hemoglobin and an associated increased reticulocyte count.

Of the 4,196 acne vulgaris patients studied, a total of 50 G6PD deficient patients were enrolled and only 25 of these patients were exposed to active study drug. The applicant concludes that no differences were noted between G6PD deficient patients and patients with normal G6PD activity levels; however, the number of G6PD deficient patients studied is too small to adequately assess the risk/benefit with use of a marginally effective drug containing dapsone in this subset of acne patients.

The applicant was advised early on (End-of-Phase 2 Meeting, December 18, 2000) that the submission should very clearly delineate the risk/benefit assessment for treatment of acne with dapsone, by providing adequate data to demonstrate that the inherent risk for serious side effect is vanishingly small.

8.4 Pediatrics

Safety and efficacy was evaluated in 1,169 ACZONE™ Gel 5%-treated children aged 12-17 years old in the clinical studies. The adverse event rate for ACZONE™ Gel 5% was similar to the vehicle control group and the adverse event profile was no different from the overall study population in a 12 month safety study. Safety and efficacy was not studied in pediatric patients less than 12 years of age, therefore ACZONE™ Gel 5% is not recommended for use in this age group

8.5 Advisory Committee Meeting

NA

8.6 Literature Review

The literature presented related to use of oral dapson.

8.7 Postmarketing Risk Management Plan

Education and monitoring are needed with use of Aczone™ (dapson topical gel) Gel, 5% in G6PD deficient patient population-as it is not a homogeneous group and the number exposed to active drug during clinical development is too small to adequately assess the risk/benefit ratio for this study population. The Applicant should investigate, compile, and report all instances of hematological abnormalities associated with use of DTG.

8.8 Other Relevant Materials

9 OVERALL ASSESSMENT

9.1 Conclusions

Overall, safety assessment appears adequate in the study population with normal G6PD levels, although a more robust hematological assessment (e.g., reticulocyte counts, haptoglobin, erythrocyte adenylate kinase levels, etc.) would have been useful in some cases; however, safety population is insufficient for patients with deficient G6PD levels, the most sensitive population to the hemolytic effects of dapson most sensitive.

Of the 4,196 subjects with acne vulgaris a total of 50 patients were G6PD deficient with only 25 G6PD deficient patients exposed to active study drug. The applicant concludes that no differences were noted for G6PD deficient patients; however, the number of G6PD deficient patients studied is too small to draw valid risk/benefit conclusions for use of with a marginally effective drug containing dapson in this subset of acne patients.

The applicant was advised early on (End-of-Phase 2 Meeting, December 18, 2000) that the submission should very clearly delineate the risk/benefit assessment for treatment of acne with dapson, by providing adequate data to demonstrate that the inherent risk for serious side effect is vanishingly small.

9.2 Recommendation on Regulatory Action

From a clinical perspective, an *Approval* recommendation is being made for use of Aczone™ (dapson topical gel) Gel, 5% in treatment of acne vulgaris for up to 12 weeks of therapy. In patients with a history of anemia and predisposition to increased hemolytic effect with dapson

(e.g., glucose-6-phosphate dehydrogenase deficiency), closer follow-up for blood hemoglobin levels and reticulocyte counts should be implemented. Alternatively, other therapies for acne than ACZONE Gel, 5% may be considered.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Post approval safety monitoring for hemolysis is needed with use of ACZONE (dapsone topical gel) Gel, 5% in the glucose-6-phosphate dehydrogenase (G6PD) deficient patients because the number of evaluable G6PD patients exposed to ACZONE Gel, 5% during clinical development is small. Additionally, there is no information available to determine the effects of the topical application of ACZONE Gel, 5% in persons with rarer genetic abnormalities, such as methemoglobin reductase or the congenital methemoglobinemias, in which the oxidant stress of dapsone and its metabolite may also induce methemoglobinemia. The applicant should investigate, compile, and report all instances of hematological abnormalities associated with use of ACZONE Gel, 5%.

9.3.2 Required Phase 4 Commitments

Agree to conduct a randomized, blinded, cross-over safety study with each acne patient treated with ACZONE Gel, 5% for 12 weeks and vehicle for 12 weeks with at least a two week washout period in at least 50 evaluable G6PD deficient patients with acne vulgaris to further evaluate the risk of hematological adverse events with use of ACZONE Gel, 5% in this population. Patients with rarer genetic abnormalities such as methemoglobin reductase or the congenital methemoglobinemias may also be studied. Obtain baseline, week 2, and end of each 12 week treatment period laboratory testing including complete blood count, reticulocyte counts, haptoglobin, and LDH levels. Plasma dapsone levels and N-acetyl dapsone levels should be obtained at baseline, week 2, and at the end of each 12 week treatment period. Additionally, plasma dapsone and its metabolite levels should be obtained in relation to adverse events which may be considered dapsone related.

| | |
|--------------------------------|------------------|
| Study Protocol Submission: | November 1, 2005 |
| Study Initiation: | March 1, 2006 |
| Final Study Report Submission: | January 1, 2008 |

12 Page(s) Withheld

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