

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-794**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## Clinical Pharmacology/Biopharmaceutics Review

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<b>Submission:</b>	NDA 21-794
<b>Product Trade Name:</b>	Aczone®
<b>Product:</b>	Dapsone 5% Gel
<b>Indication:</b>	Treatment of Acne vulgaris
<b>Submission Dates:</b>	August 31, 2004; January 14, 2005; January 19, 2005, February 9, 2005, February 24, 2005, February 25, 2005, March 1, 2005, March 4, 2005, March 7, 2005, , April 7, 2005, April 8, 2005, April 27, 2005.
<b>Type of Submission:</b>	Original NDA (1S)
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### ***I. Executive Summary:***

Dapsone (DAP) is a sulfone with anti-inflammatory and antimicrobial properties. DAP oral tablets (25 mg and 100 mg) have been approved since 1980s to control the dermatologic symptoms of dermatitis herpetiformis and for the treatment of leprosy. Atrix Laboratories, Inc. (Atrix), submitted NDA 21-794 as a 505(b) (1) application for 5% DAP Topical Gel (DTG) to be administered twice a day for the treatment of *acne vulgaris*. The gel is intended to be applied to affected areas on the face, chest, back, and shoulders twice daily. In 4 clinical pharmacokinetic studies conducted in the intended patient population, which employed a range of doses, application areas and durations, twice-daily application of 5% DTG resulted in minimal (i.e., only about 1% of that from the 100 mg oral dose) systemic exposure to DAP and its principal metabolites. A dose/formulation was selected based on demonstration of maximum skin penetration of DAP and its minimal systemic breakthrough. While selection of the bid dosing of 5% DTG based on the systemic exposure information is acceptable from a pharmacokinetic point of view, the clinical basis of the selection of the dose and dosing regimen is unknown.

DAP absorption after twice daily topical application of 5% DTG in subjects with acne vulgaris results in low systemic exposure to DAP and its metabolites, regardless of acetylator phenotype, G6PD activity, gram usage or body surface area treated. DAP exposure as measured as AUC after topical application of 5% DTG in acne patients treated under maximal usage conditions was  $415 \pm 224$  ng-h/mL. In contrast, DAP exposure after a single oral 100 mg DAP dose was  $52,641 \pm 36,224$  ng-h/mL. The short-term exposure study indicates that DAP concentrations at steady-state in plasma was about 1% of that observed following a single 100 mg oral dose of DAP. There was no apparent evidence of increased exposure or of any relationship between adverse events and DAP plasma levels. The long-term study (12-month) also demonstrated low systemic

absorption following topical application and absence of systemic accumulation following long-term use. This study also demonstrated no effects of gender, race, glucose-6-phosphate dehydrogenase (G6PD) deficiency or acetylator phenotype on the levels of DAP in plasma during 5% DTG bid treatment for up to a year.

Given the low systemic absorption of DAP following topical administration, it may take a daily application of 140 to 280 grams to achieve a DAP exposure level similar to a single oral DAP dose of 50 and 100 mg, respectively. Since 30 g would typically cover 100% of a 70 kg person, application of 140 to 280g of 5% DTG is not feasible. In the 4 clinical trials described in this document, the average daily gram use ranged from 1.3 to 2.2 grams per day, a dose considerably lower than DAP doses needed for hemolytic effects. Literature suggests that hemolytic effects are typically associated with DAP doses of >100 mg per day in normal patients and >50 mg in G6PD deficient patients. Given the low absorption profile of DAP after 5% DTG application relative to oral DAP, the likelihood of hematologic adverse events is very low, even in patients with G6PD deficiency. In fact, patients with high plasma concentrations did not have a change in hemoglobin levels and patients with a  $\geq 1$  or  $\geq 2$  g/dL decrease in hemoglobin did not have high plasma DAP levels (Of note, plasma hemoglobin is a very sensitive biomarker for DAP toxicity).

A drug-drug interaction study evaluated the effect of the use of 5%DTG in combination with double strength (160 mg/800 mg) trimethoprim/sulfamethoxazole (TMP/SMX). During co-administration, systemic levels of TMP and SMX were essentially unchanged. However, levels of DAP and its metabolites increased in presence of TMP/SMX. Systemic exposure ( $AUC_{0-12}$ ) of DAP and N-acetyl-dapsone (NAD) were increased by about 40% and 20% respectively in presence of TMP/SMX. Notably, systemic exposure ( $AUC_{0-12}$ ) of dapsone hydroxylamine (DHA) was more than doubled in presence of TMP/SMX. Given that exposure from the proposed topical dose is only about 1% of that from the 100 mg oral dose, the increases in the exposure of DAP and its metabolites are not considered to be clinically relevant.

**Overview of Efficacy:** The clinical program included 4,622 healthy subjects and patients. The 2 pivotal studies (DAP0203 and DAP0204) were identically designed with respect to objective, procedures, treatment duration, endpoints, and statistical analyses. The objective of both randomized, double-blind, parallel group, 2-arm, vehicle-controlled, multi-center studies was to evaluate the safety and efficacy of topically applied 5% DTG in patients with *acne vulgaris* compared to a vehicle control (VC). Patients applied a thin film of 5% DTG or vehicle to the face twice daily (approximately 10 to 14 hours apart for 12 weeks). Patients were also allowed to treat other acne affected areas; however, these areas were not assessed for efficacy. Patients included males and females, 12 years of age or older. The patients had a clinical diagnosis of *acne vulgaris* of the face, with 20 to 50 inflammatory lesions and 20 to 100 non-inflammatory lesions above the mandibular line at baseline.

The results of each of the pivotal studies demonstrate that 5% DTG is significantly more effective than vehicle control (VC) in each of the populations analyzed.

In Study DAP0203, for the Global Acne Assessment Score, the Week 12/early termination success rate for the 5% DTG group was significantly higher than the VC group, 44.2% versus 35.9% ( $p = 0.0003$ ), in the ITT population. The mean percent reductions from Baseline to Week 12/early termination were statistically greater in the 5% DTG group compared with the VC group. In Study DAP0204, for the Global Acne Assessment Score, the Week 12/early termination success rate for the 5% 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 3 acne lesion types, the mean percent reductions from Baseline to Week 12/early termination were statistically greater in the 5% DTG group compared with the VC group.

For all analyses of the primary and secondary efficacy variables for the 2 pivotal trials and the other large 12-week, vehicle controlled trial, there are statistically significant differences in favor of DTG.

In summary, two identically designed pivotal clinical studies demonstrated that 5% DTG is significantly more effective than VC in each of the populations analyzed (see clinical review for details).

**Overview of Safety:** The 5% DTG clinical program included over 4,000 participants and 5% DTG has been evaluated in more than 2,300 acne patients. No adverse events of potential clinical concern were identified in the dermal safety studies and the microbiology study in healthy subjects. Although hematological effects such as methemoglobinemia and decreased hemoglobin are well known side effects of oral DAP, no relationship between these events and 5% DTG treatment was observed. There were no clinically important differences between 5% DTG-treated patients and VC-treated patients. Length of exposure to 5% DTG did not affect the prevalence of non-application site adverse events. No clear trends were identified in the subpopulations. There were no deaths in the program and serious adverse events were rare and unrelated to 5% DTG use. No agranulocytosis was reported.

#### ***A. Recommendations:***

Based on this review, NDA 21-794 is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective. A review of the PK data in this submission has resulted in certain changes in the appropriate sections of the product label. The suggested changes have been incorporated in the section "Labeling Comments".

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## II. Table of Contents

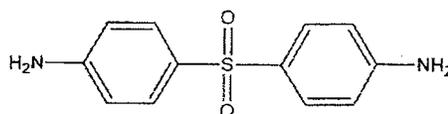
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## III. Question-Based Review

### A. General Attributes

1. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product? What is the proposed mechanism of drug action and therapeutic indications? What is the proposed dosage and route of administration?

Dapsone (Molecular formula:  $C_{12}H_{12}N_2O_2S$ ; MW: 248.30) is a white to off-white fine crystalline powder with the following structural formula:



It is very slightly soluble in water, freely soluble in acetone, sparingly soluble in alcohol, and dissolves freely in dilute mineral acids. DAP Topical Gel, 5%, is a topical formulation containing DAP, USP (diethylene glycol monoethyl ether, NF, (DGME) base as shown in the following table:

Table 3.2.P-1 5% Dapsone Topical Gel Composition

Component	Quality Standard	Function	Percent w/w	Milligrams per gram
Dapsone	USP			
Diethylene Glycol Monoethyl Ether	NF			
Carbomer 980	a			
Methylparaben	NF			
Sodium Hydroxide	NF			
Purified Water	USP			
Nominal Fill Weight	<b>Prescription:</b> 30 g provided in a multi-dose tube <b>Professional Sample:</b> 3 g provided in a multi-dose tube			

a. Carbomer 980 polymer is processed by the manufacturer \_\_\_\_\_ as used in the carbomer 940, NF. Carbomer 980 is understood to be chemically equivalent to carbomer 940, NF by FDA.

Dapsone is a sulfone with anti-inflammatory and antimicrobial properties. Its anti-inflammatory properties include inhibition of neutrophil myeloperoxidase and eosinophil peroxidase and suppression of hypochlorous acid production. DAP also scavenges reactive oxygen species and minimizes inflammation associated with the generation of these highly reactive species. It also suppresses neutrophil recruitment and local production of toxic respiratory and secretory products, and inhibits chemoattractant-induced signal transduction.

Atrix Laboratories, Inc. (Atrix), submitted NDA 21-794 as a 505(b)(1) application for 5% DAP Topical Gel (DTG) to be used twice a day for the treatment of *acne vulgaris*. The gel is intended to be applied to affected areas on the face, chest, back, and shoulders twice daily.

### **B. General Clinical Pharmacology**

DAP has been recognized since the 1950s as being effective against a number of non-infectious inflammatory diseases, of which dermatitis herpetiformis is the best known. The drug is particularly effective against dermatoses that are characterized by abnormal neutrophil accumulation. A considerable number of other inflammatory as well as bullous diseases have been reported to respond in varying degrees to DAP. DAP's antimicrobial activity is unrelated to its anti-inflammatory activity. Its antimicrobial activity is similar to that for other sulfonamides. With dual anti-inflammatory and antimicrobial mechanisms of action, topical DAP may be of significant benefit to patients with acne.

#### **1. What is the basis for selecting the dose in dapsone topical gel?**

A dose/formulation was selected based on demonstration of maximum skin penetration of DAP and minimal systemic breakthrough. The systemic bioavailability at steady-state of 2 dose formulations (1% and 5% DTG) and 2 treatment regimens (qd and bid) were evaluated. DAP exposure (AUC and  $C_{max}$ ) increased less than proportionally (i.e., 10-fold increase in dose brought about a 3-fold increase in systemic exposure) over the range of doses studied (10 to 100 mg/day). Comparison of qd and bid doses of 5% DTG also

demonstrated increase in systemic bioavailability with bid dosing compared to qd dosing. While selection of the bid dosing of 5% DTG based on these observations is acceptable from a systemic exposure perspective, the clinical basis of the selection of the dose and dosing regimen is unknown.

**2. What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?**

The primary pharmacodynamic properties that have been summarized and presented are anti-inflammatory and immunological activities. Patients were evaluated at Baseline, during treatment (Weeks 2, 4, 6, 8), and at Week 12 or end of treatment (ET).

The primary efficacy endpoints at Week 12/ET were the:

- Incidence of Success obtained from the GAAS (Global Acne Assessment Scale). Success was defined as a score of 0 (none) or 1 (minimal) on a 5-point static GAAS, and
  - Mean percent reduction in inflammatory, non-inflammatory, and total lesion counts.
- The efficacy endpoints were achieved if DTG was superior to VC based on the incidence of "Success", and the mean percent reduction in 2 of the 3 lesion count parameters.

The 2 secondary efficacy variables were as follows:

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

**3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**

Yes.

**4. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?**

The relationship between response in terms of efficacy (reduction in the number and severity of inflammatory and non-inflammatory lesions) and systemic safety, and blood (plasma) levels of DAP were not investigated in any of the clinical studies. The 5% DTG formulation was designed to deliver drug directly to areas affected by acne on the skin and to avoid systemic effects of both the drug and its metabolites; therefore, a blood level response relationship was not anticipated.

**5. What are the basic PK parameters?**

$C_{max}$ , AUC and  $t_{1/2}$  values have been used as basic PK parameters.

**6. Is there any relationship between %BSA and DAP exposure? Also, is there any relationship between amount (gm) used and DAP exposure?**

%BSA: Plasma DAP levels and their relationship to body surface area were addressed in 3 pharmacokinetic studies [Studies DAP9903, DAP0110, and 03-0-182] which had three different fixed body surface treatment areas throughout the study. Patients in these pharmacokinetic studies had similar plasma DAP levels after application of 5% DTG to body surface areas ranging from ~5% (face only) to ~22.5% (maximum treatment area to face, chest, back and shoulders). The difference in exposure between face-only treatment (4.5% BSA) at 100 mg/day DAP (DAP9903) and maximum treatment area (22.5% BSA) at 110 mg/day DAP (DAP0110) was small, suggesting there is little correlation between treatment area and DAP exposure for 5% DTG (Table 1).

Amount used: The relationship between individual plasma DAP concentrations and product use (dose) was investigated for Study DAP0110 and Study 03-0-182. The data from both studies show little, if any, correlation between the amount of product applied and DAP concentration between individuals, for product usage ranging from less than 1 to over 14 g/day (Table 1).

When a range of topical DAP doses (10 to 100 mg/day) was compared (DAP9903), plasma exposure to DAP increases less than proportionally, suggesting that there may be a reasonably low upper limit to total dermal absorption. Consequently, even excessive application of the product would not lead to plasma exposures in the range of that observed during oral DAP therapy.

In Study DAP0114, the highest DAP concentration (107 ng/mL) during 5% DTG treatment occurred in a patient who used over 11 g/day of product (over 550 mg/day of DAP) for 12 months. In Study 03-0-182 one patient had a DAP concentration of 112 ng/mL on Day 35 (the final day of the DTG only treatment) and 120 ng/mL on Day 42 (final day of DTG and TMP/SMX treatment). DAP levels in these patients were also well below those associated with oral DAP use.

**Table 1: Plasma DAP Concentrations in Acne Vulgaris Patients Treated Twice Daily with 5% DAP Topical Gel**

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Treatment [route]	N	No. Doses [frequency]	Dapsone Application (mg/day) Mean±SD [Range]	Application Area (% BSA)	C <sub>max</sub> (ng/mL) Mean±SD [Range]	AUC(ng·h/mL) Mean±SD [Range]	Study No.
5% DTG [topical]	439	491 <sup>a</sup> [2x/d]	67.5 ± 54.0 [0 - 551]	Up to 22.5%	7.5 ± 10.1 <sup>b</sup> [0.05 - 107]	ND	DAP0114
5% DTG [topical]	12	55 [2x/d]	100 ± 0 <sup>c</sup>	4.5%	15.1 ± 7.5 [2.66 - 31.4]	318 ± 159 [46.0 - 657]	DAP9903
5% DTG [topical]	18	28 [2x/d]	110 ± 60 [40 - 275]	22.5%	19.7 ± 10.2 [8.8 - 48.6]	415 ± 224 [184 - 1067]	DAP0110
Dapsone [Oral]	10	1 (single dose)	100 ± 0	NA	1375 ± 517 [623 - 2353]	52,641 ± 36,224 [23156 - 137810]	DAP0110
5% DTG [topical]	20	42 [2x/d]	329 ± 197 [93 - 736]	20%	26.8 ± 23.2 [6.77 - 101.3]	584.9 ± 516.1 <sup>d</sup> [120.2 - 2260]	03-0-182

Values shown are mean ± S.D.

Abbreviations: BSA=body surface area; C<sub>max</sub>=Maximum plasma concentration after last dose; AUC=Area under plasma concentration versus time curve over 24 hours after last dose; ND=Not determined, NA=Not applicable.

<sup>a</sup> Mean number of applications per patient.

<sup>b</sup> For Study DAP0114 a single sample for each patient was taken at some time during the day. See Figure 4.

<sup>c</sup> For study DAP9903 DTG was provided in a foil pouch with 1 g of the formulation for each application.

<sup>d</sup> For study 03-0-182, the AUC = 2 x AUC<sub>0-12</sub>.

## 7. Is there any relationship between G6PD deficiency, systemic exposure and adverse events from topical 5% DTG applications?

The following sections will discuss this issue:

*What is the pharmacological implication of G6PD deficiency?*

Glucose-6-phosphate dehydrogenase (G6PD) plays an important role in preventing oxidative injury to red blood cells and preventing lysis. This enzyme catalyzes the oxidation of glucose-6-phosphate to 6-phosphogluconate, while concomitantly reducing nicotinamide adenine dinucleotide phosphate (NADP<sup>+</sup> to NADPH). NADPH is particularly important in red blood cell physiology as a necessary co-factor for glutathione reduction as reduced glutathione scavenges oxidative metabolites. Patients who are G6PD deficient are more sensitive to hemolytic changes associated with oxidative stress, which may result from DAP or other drug exposure, infection and ingestion of fava beans (favism). Individuals with G6PD deficiency may experience adverse effects at lower plasma DAP concentrations than G6PD normal subjects. Literature suggests that hemolytic effects are typically associated with DAP doses of >100 mg per day in normal patients and >50 mg in G6PD deficient patients.

*What is the possibility of hemolytic effects in normal and in G6PD deficient patients from 5% DTG exposure?*

Based on the following discussion, it appears that the DAP exposure at which normal (i.e., exposure equivalent to 100 mg oral DAP) as well as G6PD deficient patients (i.e.,

exposure equivalent to 50 mg oral DAP) may suffer from hemolytic adverse events is practically unattainable from 5% DTG.

The mean AUC<sub>0-24</sub> after topical application was 415 ng·hr/mL and the mean gram usage was 2.2 grams per day. The mean AUC<sub>0-inf</sub> after a single 100 mg oral dose was 52,641 ng·h/mL. However, we need to keep in mind that systemic exposure from topical application does not change linearly with dose (amount) applied because systemic exposure from topical application is an interplay between application area and amount used. Therefore estimation of systemic exposure from any particular topical dose is difficult simply based on systemic exposure data from another topical dose. However, an approximate estimation may be made in the following way. In order to achieve a DAP exposure level consistent with a 100 mg oral DAP dose using topical administration of 5% DTG, 280 grams [(52641 ng·h/mL / 415 ng·h/mL)\*2.2 g] of 5% DTG would have to be applied per day. A similar calculation for a 50 mg oral DAP dose would result in a topical administration of 5% DTG of 140 grams per day. Since 30 grams would typically cover 100% of a 70 kg person, application of 140 to 280 grams of 5% DTG is not feasible. To put this in perspective, the average daily gram use in the studies presented in this NDA ranged from 1.3 grams to 2.2 grams. The highest daily gram use in Study DAP0114 was 11.0 grams. Concentrations of DAP hydroxylamine, a metabolite postulated to be responsible for hematologic effects, including idiosyncratic agranulocytosis and dose-dependent hemolysis were measured in study 03-0-182. This is a pharmacokinetic drug-drug interaction study with trimethoprim/sulfamethoxazole conducted under maximal 5% DTG usage conditions in patients with acne vulgaris. DAP hydroxylamine levels were minimal, stable and approximately 12% of the parent compound, a ratio similar to oral dosing reported in the literature. Therefore, the relationship between oral and topical exposure for the DAP hydroxylamine metabolite is expected to be similar to the relationship observed for the DAP parent compound.

Plasma DAP and NAD levels were collected in two studies, DAP0110 and DAP0114, which enrolled a total of six G6PD deficient patients, 1 patient in DAP0110 and 5 patients in DAP0114 (Table I). Five patients identified as G6PD deficient were treated with 5% DTG twice daily for up to 12 months in Study DAP0114. One G6PD patient was treated for 2 weeks in Study DAP 0110. The G6PD deficient patients (2 males, 4 females) ranged in age from 12 to 32 years.

**Table I: Number of Patients with G6PD Deficiency in Clinical Studies of DAP 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%) <sup>†</sup>
<b>Total</b>	<b>25</b>	<b>25</b>

Denominator represents number of patients who had G6PD activity measured

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

NA: not applicable

Overall, plasma concentrations of DAP and NAD in these patients, determined at various times after 1 week to 12 months of treatment, were similar to those in G6PD normal patients. This was expected as G6PD deficiency is not supposed to alter systemic exposure of DAP. There were no patients (normal or G6PD deficient) with hemolysis or

hemolytic anemia reported in any studies conducted in support of the *acne vulgaris* development program. There were no patients with methemoglobinemia reported in any studies conducted in support of the topical DAP gel *acne vulgaris* development program.

*Was any relationship observed between changes in hemoglobin and plasma DAP levels following 5% DTG application?*

Fluctuations in plasma hemoglobin is the most sensitive biomarker for hemolytic adverse events attributed to DAP toxicity. Overall, hemoglobin values stayed nearly constant and did not correlate with plasma DAP levels. Plasma DAP levels were low (< 40 ng/mL) in most patients at all time points. Patients with high plasma DAP concentrations did not have a change in hemoglobin levels, and patients with a  $\geq 1$  or  $\geq 2$  g/dL decrease in hemoglobin did not have high plasma DAP levels, as described in the following section.

The change in hemoglobin versus DAP plasma levels for all patients with DAP blood levels from Study DAP0114 and the G6PD deficient patients (N=5) from this study is shown in Figure I. The negative change in hemoglobin versus DAP plasma levels is shown in Figure II.

In Study DAP0110, there was no correlation between plasma DAP concentrations and changes in hemoglobin. The G6PD deficient patient (Patient 0103) in this study, had a 1.3 g/dL reduction in hemoglobin, which was comparable to reductions observed in six non-G6PD deficient patients and his  $C_{max}$  was 21.82 ng/ml compared to the mean  $C_{max}$  of 19.66 ng/ml for all 18 patients in this study. Similarly in Study DAP0114 also, there was no correlation between plasma DAP concentrations and changes in hemoglobin. Fluctuations in hemoglobin values for the G6PD deficient patients in this study were similar compared to the non-G6PD deficient patients after long-term treatment. In all G6PD deficient patients, hemoglobin levels were generally stable over time. Of note, Patient 0317 (patient with severe G6PD deficiency) did not have a reduction in hemoglobin of  $\geq 1$  g/dL at any time during the study. Based on data from DAP0110 and DAP0114, there does not appear to be a relationship between plasma DAP levels and changes in hemoglobin, regardless of G6PD activity.

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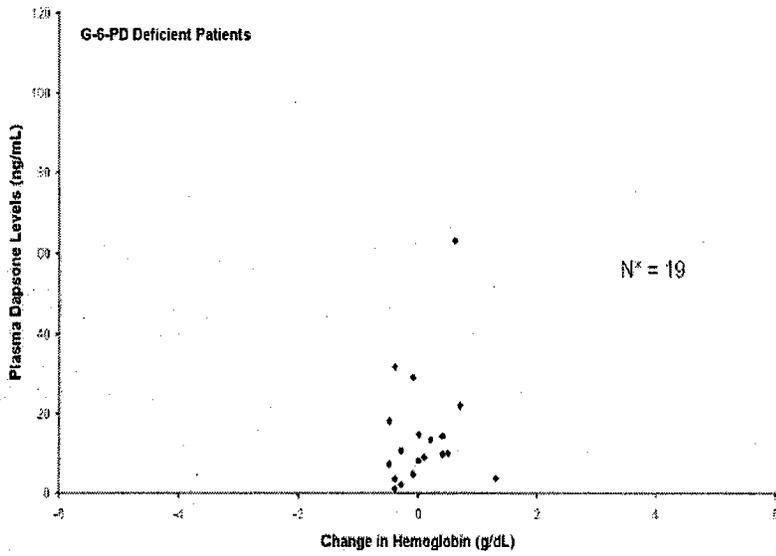
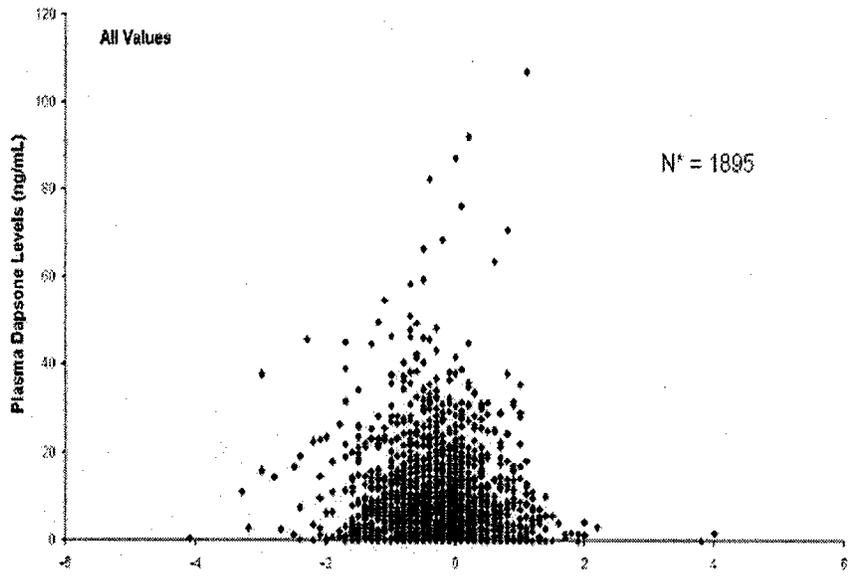
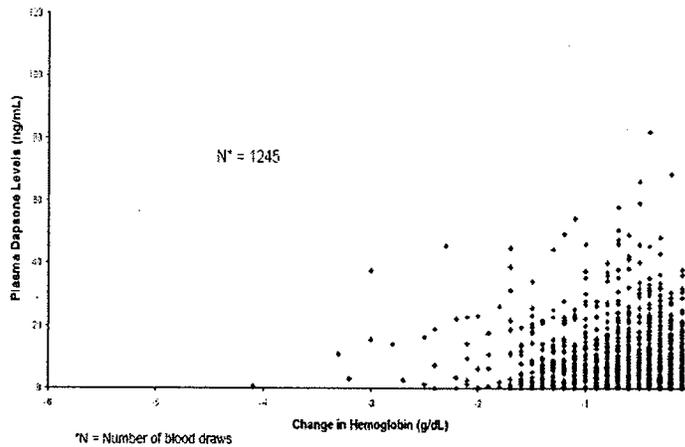


Figure I: Change in Hemoglobin vs. DAP Plasma Levels (\*N = Number of blood draws)



**Figure II: Negative Change in Hemoglobin vs. Plasma DAP Levels**

In Studies DAP0203 and DAP0204, no differences were observed in hemoglobin changes between 5% DTG treated patients and vehicle treated patients, regardless of G6PD activity. The variability of the changes in hemoglobin for the G6PD deficient patients was smaller than that of the overall population; the maximum reduction in hemoglobin in any G6PD deficient patient was 1.5 g/dL.

*Was any relationship observed between changes in hemoglobin and G6PD deficiency following 5% DTG application?*

There was no relationship between changes in hemoglobin and extent of G6PD activity, even in patients with severe G6PD deficiency, as described in the following section.

Changes in hemoglobin were assessed in the patients in the four studies (Studies DAP0110, DAP0114, DAP0203 and DAP0204) where G6PD activity was measured. A summary of reductions in hemoglobin by G6PD status is provided in the following Tables:

**Table II: Reduction in Hemoglobin by G6PD Activity in Study DAP0110**

Reduction in Hemoglobin	G6PD Deficient Patients n=1	Non-G6PD Deficient Patients n=17
≥ 1 g/dL Reduction	1	6
≥ 2 g/dL Reduction	0	1

**Table III: Reduction in Hemoglobin by G6PD Activity in Study DAP0114**

Reduction in Hemoglobin	G6PD Deficient Patients n=5	Non-G6PD Deficient Patients N=481
≥ 1 g/dL Reduction		
Overall	1	155
Month 1	0	42
≥ 2 g/dL Reduction		
Overall	0	16
Month 1	0	3

**Table IV: Reduction from Baseline to End of Treatment in Hemoglobin by G6PD Activity in Studies DAP0203/DAP0204**

Reduction in Hemoglobin	G6PD Deficient Patients		Non-G6PD Deficient Patients	
	5% DTG n=19	Vehicle n=25	5% DTG n=1487	Vehicle n=1479
≥ 1 g/dL Reduction	3	5	152	146
≥ 2 g/dL Reduction	0	0	10	8

In all studies, the reduction in Hemoglobin in G6PD deficient patients are comparable to that from nonG6PD deficient patient. Prolonged use of 5% DTG did not lead to differences in reductions in hemoglobin compared to the vehicle controlled Studies DAP0203/DAP0204.

### 8. What is the major route of elimination?

A major pathway of DAP metabolism is the formation of NAD (NAD) by N-acetyl transferase. The acetylation of DAP is reversible, resulting in a relatively constant ratio of the N-acetyl metabolite to DAP in plasma during the elimination phase. DAP is also N-oxidized by CYP2E1 and CYP 3A4 to produce DAP hydroxylamine (DHA). The major side effects of DAP (methemoglobinemia, agranulocytosis) are linked to the formation of DAP hydroxylamine.

Plasma exposure to the metabolite NAD after 5% DTG treatment was approximately 1% to that obtained after oral DAP (Study DAP0110). After administration of 5% DTG, NAD levels remained less than, and declined in parallel with the levels of DAP in plasma observed for oral DAP. Limited data obtained in this study also suggest that urinary excretion of DAP hydroxylamine was also about 1% to that that obtained following the oral formulation. These data show that 5% DTG treatment is not associated with increased DAP metabolite exposure, and that topical administration should not alter the metabolism of DAP.

### C. Intrinsic Factors

1. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

<i>What are the effects of Gender, Race and Age on 5% DTG exposure?</i>
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No significant effects of gender or race on the levels of DAP in plasma during 5% DTG treatment were apparent in these data. Similarly, DAP exposures are consistent between the two age groups (12-15 years vs ≥ 16 years) indicating no difference in DAP plasma levels related to age. Overall, gender, race and age did not demonstrate any clinically

significant effect on DAP pharmacokinetics following use of 5% DTG in these patient populations.

During the clinical development of 5% DTG, DAP pharmacokinetics were monitored in studies that enrolled male and female acne patients between the ages of 12 and 77 years, and from ethnic groups identified as white, black, Hispanic, Asian, and other. Since the greatest number of patients (Study DAP0114) had DAP concentration measured at Month 3, the following tables are based on these data. Data from other time points were consistent with Month 3 data.

**Table 2: Plasma DAP Concentrations (ng/ml) in Male and Female Acne Patients after 3 Months of Twice-Daily Application of 5% DAP Topical Gel (Study DAP0114)**

	Female	Male
N	216	192
Mean ± SD	8.7 ± 10.0	9.6 ± 11.9
Median	6.2	6.1
Range	0.0 - 68.5	0.0 - 87.1

All patients with plasma levels at Month 3 included.

**Table 3: Plasma DAP Concentrations (ng/ml) by Race/Ethnicity in Acne Patients after 3 Months of Twice-Daily Application of 5% DAP Topical Gel (Study DAP0114)**

	White	Black	Hispanic	Asian	Other
N	321	35	28	8	6
Mean ± SD	9.5 ± 11.4	7.6 ± 8.7	6.0 ± 6.3	17.0 ± 9.9	2.5 ± 3.1
Median	6.4	3.4	4.0	14.7	1.7
Range	0.0 - 87.1	0.0 - 30.4	0.0 - 24.9	7.4 - 31.9	0.0 - 8.4

Includes all patients with plasma levels at Month 3 in the ethnicity groups shown.

**Table 4: Plasma DAP Concentrations by Age in Acne Patients after 3 Months of Twice Daily Application of 5% DAP Topical Gel (Study DAP0114)**

Parameter	Plasma Dapsone Level	Plasma Dapsone Level
	12-15 years (ng/mL)	≥16 years (ng/mL)
N	155	253
Mean ± SD	8.77 ± 11.5	9.35 ± 10.6
Median	5.8	6.6
Range	0.0 - 87.1	0.0 - 82.2

Does genetic polymorphism  play any role on clinical outcome following 5% DTG application?

[ ]

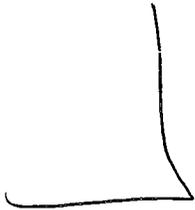
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  1   Trade Secret / Confidential

       Draft Labeling

       Deliberative Process

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#### **D. Extrinsic Factors**

- 1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?**

A drug-drug interaction study evaluated the effect of the use of 5%DTG in combination with double strength (160 mg/800 mg) trimethoprim/sulfamethoxazole (TMP/SMX). During co-administration, systemic levels of TMP and SMX were essentially unchanged. However, levels of DAP and its metabolites increased in presence of TMP/SMX. Systemic exposure ( $AUC_{0-12}$ ) of DAP and N-acetyl-dapsone (NAD) were increased by about 40% and 20% respectively in presence of TMP/SMX. Notably, systemic exposure ( $AUC_{0-12}$ ) of dapsone hydroxylamine (DHA) was more than doubled in presence of TMP/SMX. Given that exposure from the proposed topical dose is only about 1% of that from the 100 mg oral dose, the increases in the exposure of DAP and its metabolites are not considered to be clinically relevant.

#### **E. Analytical Section**

- 1) How are the active moieties identified and measured in the blood in the clinical pharmacology and biopharmaceutics studies? What bioanalytical methods are used to assess concentrations?**

All the moieties in the biological fluids were quantitated by validated analytical methods. The details of the methods are as follows:

*Performance Characteristics for Assay of Dapsone and N-Acetyl Dapsone in Plasma:* The lower LOQ for dapsone was 50.3 pg/mL and 50.2 pg/mL for N-acetyl dapsone, with a calibrated linear range of \_\_\_\_\_ for dapsone (mean  $r^2$  of standard curves = 0.9987) and a calibrated linear range of \_\_\_\_\_ for N-acetyl dapsone (mean  $r^2$  of standard curves = 0.9992). Inter-assay accuracy, as determined by deviation of mean from theoretical concentration for the quality control samples measured during sample analysis, was within \_\_\_\_\_ for the \_\_\_\_\_ concentrations, respectively, for dapsone and within \_\_\_\_\_ concentrations, respectively, for N-acetyl dapsone. The corresponding precision, indicated by the relative standard deviation, was 6.7%, 1.9%, and 1.4% for the \_\_\_\_\_ concentrations, respectively, for dapsone and 7.7%, 3.0%, and 3.4% for the \_\_\_\_\_ concentrations, respectively, for N-acetyl dapsone.

*Performance Characteristics for Assay of Dapsone, N-Acetyl Dapsone, and Dapsone Hydroxylamine in Urine:* The lower LOQ was 5.03 ng/mL for dapsone, 5.02 ng/mL for N-acetyl dapsone, and 5.02 ng/mL for dapsone hydroxylamine with a calibrated linear range of \_\_\_\_\_ for dapsone (mean  $r^2$  of standard curves = 0.9991), a calibrated linear range of \_\_\_\_\_ for N-acetyl dapsone (mean  $r^2$  of standard curves = 0.9988), and a calibrated linear range of \_\_\_\_\_ for dapsone hydroxylamine (mean  $r^2$  of standard curves = 0.9984). Inter-assay accuracy, as determined by deviation from the mean of the theoretical concentration for the quality control samples measured during sample analysis, was within \_\_\_\_\_ for the \_\_\_\_\_ concentrations, respectively, for dapsone; \_\_\_\_\_ concentrations, respectively, for N-acetyl dapsone; and within \_\_\_\_\_ concentrations, respectively, for dapsone hydroxylamine. The corresponding precision, indicated by the relative standard deviation, was 6.3%, 5.4%, and 7.0% for the \_\_\_\_\_ concentrations, respectively, for dapsone; 4.2%, 1.9%, and 4.6% for the \_\_\_\_\_ concentrations, respectively, for N-acetyl dapsone; and 6.5%, 2.8%, and 3.7% for the \_\_\_\_\_ concentrations, respectively, for dapsone hydroxylamine.

*Performance Characteristics for Assay of Trimethoprim and Sulfamethoxazole:* The LLOQ was 0.10 mcg/mL for trimethoprim and 1.00 mcg/mL for sulfamethoxazole with a calibrated linear range of \_\_\_\_\_ for trimethoprim (mean correlation coefficient of standard curves = 0.9988) and a calibrated linear range of \_\_\_\_\_ for sulfamethoxazole (mean correlation coefficient of standard curves = 0.9996). Inter-assay accuracy, as determined by percent relative error for the quality control samples measured during sample analysis, was within \_\_\_\_\_ concentrations, respectively, for trimethoprim and \_\_\_\_\_ concentrations, respectively, for sulfamethoxazole. The corresponding precision, indicated by percent correlation of variance, was 2.8%, 1.6%, and 2.1% for the 0.30, 4.00, and 9.00 mcg/mL concentrations, respectively, for trimethoprim and 2.1%, 1.0%,

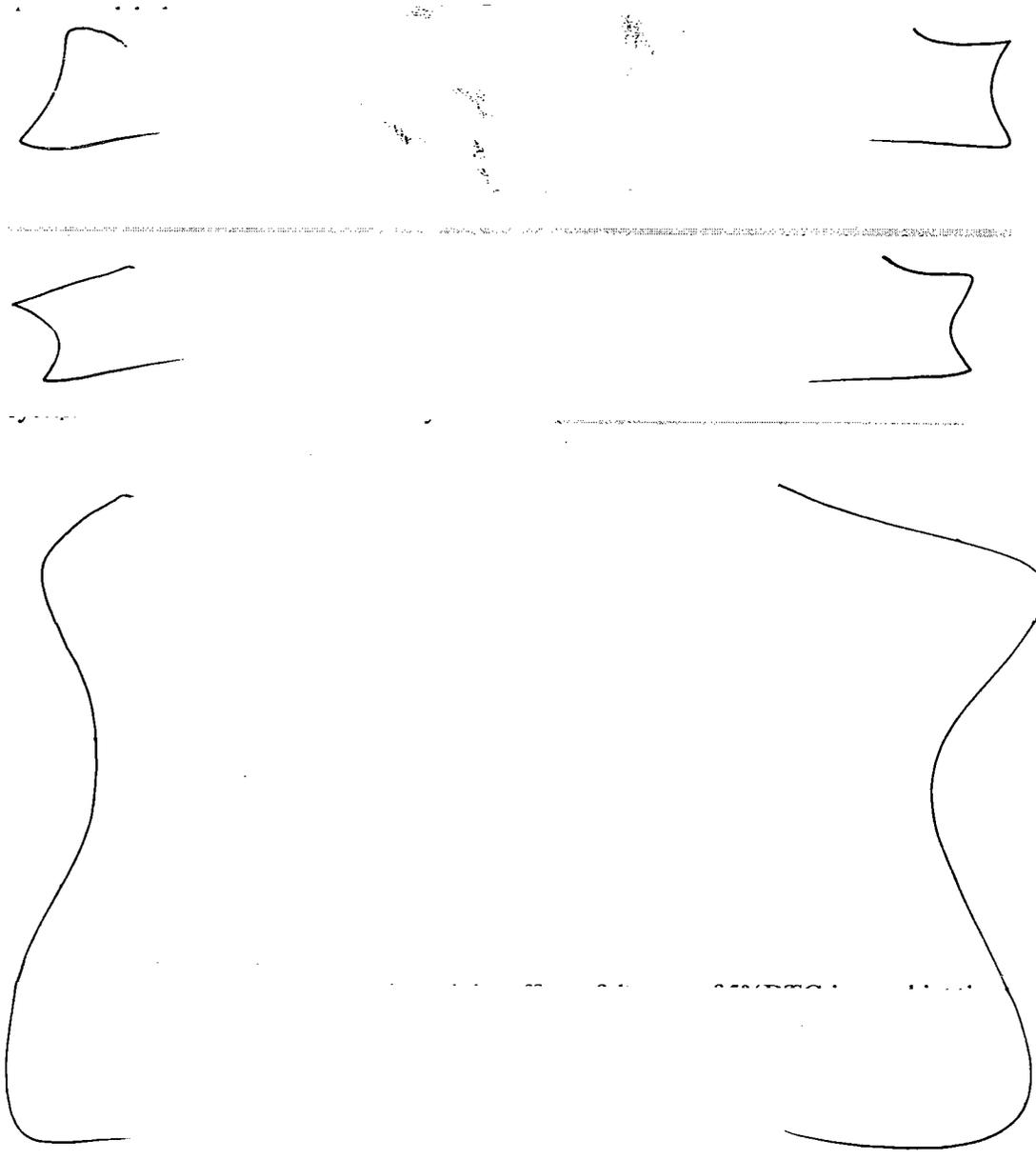
and 1.3% for the 3.0, 40.0, and 90.0 mcg/mL concentrations, respectively, for sulfamethoxazole.

***V. OCPB labeling recommendations***

The following changes are suggested. ~~ABC~~ suggests deletion of text and ~~ABC~~ suggests insertion of new text:

**CLINICAL PHARMACOLOGY:**

**Pharmacokinetics**





**VI. Appendices**

- A. Package Insert (annotated)
  - B. Clinical Pharmacology and Biopharmaceutics Individual Study Reviews
  - C. Cover Sheet and OCPB Filing/Review Form
- 

**Tapash K. Ghosh, Ph.D.**  
**Pharmacokineticist/DPE III**

**Team Leader: Raman K. Baweja, Ph.D.** \_\_\_\_\_

**CC: NDA 21-794 (DFS)**  
**HFD-540/Div File**  
**HFD-540/CSO/Cross**  
**HFD-880 (Baweja/Ghosh)**  
**HFD-880 (Lazor/Selen)**

# **Appendix A**

Package Insert (annotated)

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X Draft Labeling

       Deliberative Process

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# **Appendix B**

## **Clinical Pharmacology and Biopharmaceutics Individual Study Review**

- ◆ Study DAP 9903
- ◆ Study DAP 0110
- ◆ Study DAP 0114
- ◆ Study DAP 03-0-182

*A 28-Day, Multicenter, Open-Label, Dose-Ranging, Pharmacokinetic Study of Dapsone Topical Gel in Subjects with Facial Acne vulgaris*

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**Objective(s):** The objectives of the study were as follows: 1) To evaluate the systemic bioavailability (pharmacokinetic profile) of 2 dose formulations and treatment regimens, of 1% and 5% DTG at steady-state plasma levels for the purpose of selecting a formulation that demonstrated maximum skin penetration of DAP and minimal systemic breakthrough; 2) To obtain information on the safety of 1% and 5% DTG; 3) To obtain preliminary efficacy of 1% and 5% DTG; 4) To determine the application regimen of 1% and 5% DTG.

**Methods:** In this Phase 1, 2-center, parallel-design study, 48 subjects (male or female, between the ages of 13 to 40 years with diagnosed mild to moderate facial *acne vulgaris*) were randomized to 1 of 4 treatment groups. Treatments consisted of 1% or 5% DTG applied once or twice daily for 28 days to acne-affected facial skin (approximately 250 cm<sup>2</sup> or 4.5 % of BSA). The amount of product applied at each dose was approximately 1 g so that the daily DAP dose applied topically ranged from 10 mg (1% DTG once daily) to 100 mg (5% DTG twice daily). The application regimen (1 or 2 times daily) and dose (1% and 5%) were varied to provide an assessment of systemic exposure of DAP with these regimens and concentrations. DGME is a DAP solubilizer. Its concentration varied according to the concentration of DAP in the test product.

Plasma samples for pharmacokinetic analysis were obtained prior to the first dose, and at 1, 2, 3, 4, 6, 8, 10, 12, and 24 hours, and prior to dosing on Days 7, 14, 21, and 28. After the last dose, (Day 28), samples were obtained at 1, 2, 3, 4, 6, 8, 10, and 12 hours and on Days 29, 30, and 31.

DAP concentrations in plasma were determined by an HPLC/MS/MS assay with a LLOQ of 0.05 ng/mL. Pharmacokinetic parameters, including T<sub>max</sub>, C<sub>max</sub>, and AUC<sub>(0-24)</sub> were determined for each patient on Days 1 and 28. In addition, K<sub>el</sub> and half-life were calculated after the Day 28 dose.

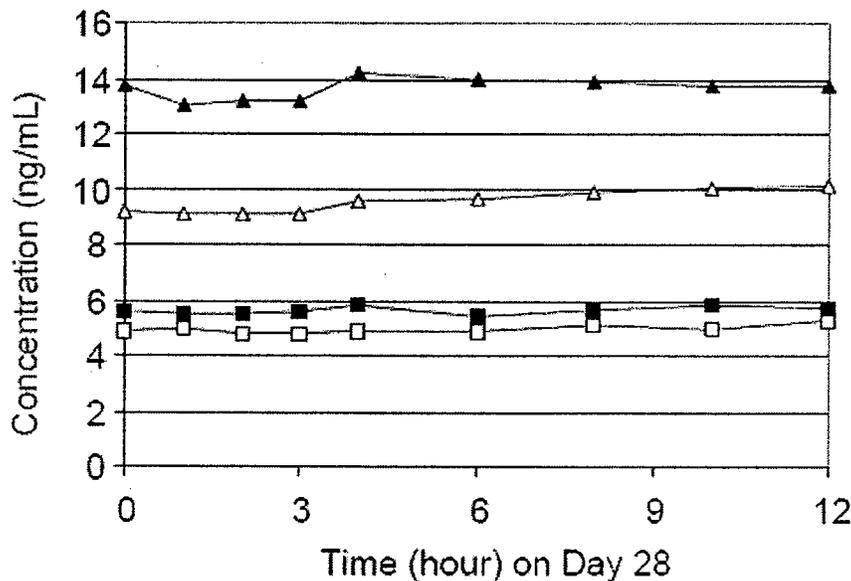
**Results:** As shown in Table 1A, systemic absorption of DAP after application of 1% and 5% DAP Topical Gels at doses up to 100 mg/day, was very low, with mean plasma C<sub>max</sub> values ranging from 2 to 15 ng/mL. After the first dose, DAP plasma levels rose slowly (T<sub>max</sub>, 20 to 24 hours) indicating the drug was neither rapidly nor extensively absorbed from the topical gel formulations. DAP concentrations reached steady-state by 1 week in all groups. After the last dose, DAP concentrations were essentially constant for the first 12 hours (Figure 1A). Concentrations then fell with a half-life of approximately 30 hours in all groups. DAP exposure (AUC and C<sub>max</sub>) increased less than proportionally (i.e., 5-fold increase in dose brought about 3-fold increase in systemic exposure) in over the range of doses studied (10 to 100 mg/day). DAP concentrations in all groups remained

far below those associated with oral DAP treatment (average plateau levels, 2300 ng/mL).

**Table 1A: Pharmacokinetics of Dapone Topical Gel, Study DAP9903**

Parameter	Formulation Regimen Dapsone dose	1% Dapone 1x Daily 10 mg/day	Topical Gel 2 x Daily 20 mg/day	5% Dapone 1x Daily 50 mg/day	Topical Gel 2 x Daily 100 mg/day
$C_{max}$ (ng/mL)	Day 1	2.11 ± 1.19	2.49 ± 1.04	5.02 ± 2.21	6.16 ± 2.82
	Day 28	5.54 ± 4.38	6.29 ± 3.41	10.8 ± 6.99	15.1 ± 7.50
$T_{max}$ (h)	Day 1	22.9 ± 3.6	23.9 ± 0.04	20.3 ± 5.73	22.6 ± 4.58
	Day 28	11.4 ± 9.15	8.52 ± 6.74	10.9 ± 7.52	7.49 ± 8.65
$AUC_{0-24h}$ (ng·h/mL)	Day 1	30.0 ± 14.8	29.7 ± 12.1	81.9 ± 34.0	84.2 ± 42.6
	Day 28	121 ± 96.6	133 ± 69.9	233 ± 145	318 ± 159
Half-life (h)	Day 28	31.9 ± 8.9	30.1 ± 9.99	30.5 ± 8.37	27.8 ± 8.31

Values shown are group means ± SD (N=11 to 13).



**Figure 1A: Dapone Plasma Concentrations on Day 28 of Dosing in Study DAP9903 (▲5% bid; △5% qd; ■ 1%bid; □ 1%qd)**

**Conclusions:** Systemic absorption of DAP after repeated administration of 1% and 5% DTG formulations was neither rapid nor extensive. The maximum mean plasma concentrations observed (15 ng/mL on Day 28 after twice daily 5% DTG) were approximately 100-fold lower than those seen after a single 100 mg oral dose in Study DAP0110.

**Comments:** DAP exposures ( $AUC$  and  $C_{max}$ ) increased over the range of doses studied (10 to 100 mg/day), however comparison of qd and bid doses at 5% DTG did not demonstrate much difference. Therefore, while selection of bid dosing based on total systemic exposure is not justified, it may be justified from the standpoint of less than expected systemic exposure which may translate into more retention by the skin layers as opposed to systemic penetration.

*An open-label, cross-over design, pharmacokinetic study to evaluate systemic Dapsone levels after topically applied 5% DAP Topical Gel and after single oral dose*

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**Objective(s):**

1. The primary objective of this study was to evaluate the pharmacokinetic (PK) profile of 5% DAP Topical Gel applied twice daily to the face, upper chest, upper back, and shoulders for 15 days for patients with acne vulgaris. A subset of 10 patients also received a single, 100 mg oral DAP dose after a 2-week washout to evaluate the relative systemic drug concentrations following oral and topical administration.
2. The secondary objectives of this study were to gain information on the safety of 5% DAP Topical Gel in patients with acne vulgaris, to determine the systemic concentrations of NAD and diethylene glycol monoethyl ether (DGME), a major component of the vehicle, and to determine the urinary excretion of DAP, NAD, and DAP hydroxylamine.

**Study Design:**

This study was a single-center, open-label, cross-over design PK and safety study. A total of 18 patients were enrolled and received at least 1 dose of 5% DAP Topical Gel (all patients dataset). Ten patients were enrolled for the oral phase of the study. There were an equal number of male (9/18; 50%) and female (9/18; 50%) patients, and 17 of the 18 patients (94.4%) were white. The mean  $\pm$  standard deviation (SD) age was  $22.2 \pm 4.5$  years, and the mean  $\pm$  SD weight was  $177.2 \pm 56.3$  pounds. The patients were instructed to rub the 5% DAP Topical Gel formulation gently into the face, upper back, shoulders, and upper chest, regardless of the extent of the disease involvement. The treatment area was approximately  $3000 \text{ cm}^2$  (estimated body surface area (BSA) of 27%). The average amount of 5% DAP Topical Gel applied per person per day was  $2.2 \pm 1.2$  g.

Patients received one application of 5% DAP Topical Gel (Batch #1328) during the first 24 hours (Day 0), after which they initiated twice daily application (once in the morning and once prior to bedtime) for 13 days and performed a single application on Day 14. A PK profile was drawn according to the serial collection schedule determined from blood samples collected at baseline (Day 0); hours 1, 2, 3, 4, 6, 8, 10, 12; Day 1 (hour 24); Day 2 (hour 48); Day 3 (hour 72); Day 5; Day 7; Day 14, hours 1, 2, 3, 4, 6, 8, 10, 12; Day 15 (hour 24 after application); Day 16 (hour 48 after application); and Day 17 (hour 72 after application). On Day 14, patients completed a dermatologic examination and discontinued application of 5% DAP Topical Gel.

A subset of 10 patients returned to the study center, following a 14-day washout period, and received a single 100 mg dose of oral DAP (DAP, 100 mg tablets: From commercial sources). Plasma samples for PK analysis were drawn for this subset of patients at Day 28, hours 1, 2, 3, 4, 6, 8, 10, 12; Day 29 (24 hours after oral dose); Day 30 (hour 48 after oral dose); and Day 31 (hour 72 after oral dose).

Urine was collected over the 8 hours following dosing on Days 0, 14, and 28. Most patients voided more than once. The volumes were measured, and a 5 mL aliquot from each void was sent to the assay laboratory for analysis of DAP, NAD, and DAP hydroxylamine. At the assay laboratory, the aliquots for each patient on each Day were inadvertently pooled before assay. Consequently, the total amounts of DAP, NAD, and DAP hydroxylamine excreted could not be quantitated for 15 of the 18 patients. Three patients voided either equal volumes or voided once on Days 14 and 28 and, therefore, concentrations could be accurately determined for these patients (patients 104, 108, and 110).

**Safety:** All safety analyses were performed using the all patients dataset. The safety evaluation included physical examination, measurement of vital signs, clinical laboratory profiles, and the incidence of adverse events. Safety, including adverse events and use of concomitant medications, was assessed at all scheduled clinical visits. In addition, at screening, Day 14, and Day 31 (for the oral DAP subset), blood samples for hematology and chemistry were drawn and urinalysis was performed.

**PK Measurements:** Plasma concentrations of DAP and NAD and urine concentrations of DAP, NAD, and DAP hydroxylamine were analyzed by validated high performance liquid chromatography/tandem mass spectrometry (HPLC/MS/MS) methods. The lower limit of quantitation (LOQ) of the HPLC/MS/MS method in plasma for DAP was 50.3 pg/mL and for NAD was 50.2 pg/mL. The LOQ of the HPLC/MS/MS method in urine for DAP was 5.03 ng/mL and for NAD and DAP hydroxylamine was 5.02 ng/mL.

## **Results:**

### **PK of DAP:**

*DAP in Plasma After Application of 5% DAP Topical Gel:* DAP was measurable in the plasma of all patients within 2 hours of the first application on Day 0, and the concentration of DAP increased in most patients throughout the day. Figure 1 shows the mean plasma DAP concentrations for the 18 patients on Day 0 and Day 14 and Table 1 shows the PK parameters of DAP in plasma after topical gel application.

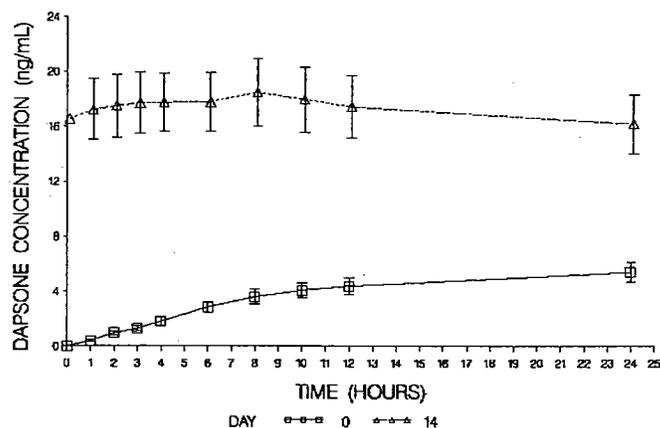


Figure 1B: Mean ( $\pm$ SE) Plasma DAP Concentrations for 18 Patients on Day 0 and Day 14

Table 1B: Pharmacokinetic Parameters of DAP in Plasma after Application of 5% DAP Topical Gel

	$C_{max}$ ng/mL	$T_{max}$ hr	$AUC_{0-12}$ ng•hr/mL	$AUC_{0-24}$ ng•hr/mL	Half-life hr
<b>Day 0</b>					
Mean	5.43	Not Determined	30.66	88.72	Not Estimatable
SD	3.220		17.801	51.003	
Median	4.79	25.2	24.91	76.50	
Minimum	1.92	12.0	11.10	32.76	
Maximum	12.86	27.6	74.40	213.82	
n	18	18	18	18	
<b>Day 14</b>					
Mean	19.66	Not Determined	212.26	415.02	Not Determined
SD	10.218		112.863	224.427	
Median	16.44	6.0	180.88	359.59	46.3
Minimum	8.84	0.9	87.09	184.47	24.7
Maximum	48.57	26.0	538.63	1067.38	68.3
n	18	18	18	18	17

The trough concentrations are summarized in Table 2. It appears that DAP plasma concentration reached steady state by approximately Day 7.

Table 2B: Trough Concentrations of DAP in Plasma after Application of 5% DAP Topical Gel

Day	1	2	3	5	7	14	15
Mean	5.4	8.5	11.8	14.7	13.8	16.6	16.2
SD	3.22	4.25	6.07	5.72	6.68	9.71	9.19
Median	4.8	7.5	10.3	12.7	13.4	13.4	14.0
Minimum	1.9	3.0	3.7	5.3	2.2	6.7	6.9
Maximum	12.9	18.3	24.6	25.1	32.0	43.9	43.9
n	18	18	18	18	18	18	18

**DAP in Plasma after a Single 100 mg Oral Dose of DAP:** After a 100 mg oral dose of DAP, plasma concentrations peaked at approximately 4 hours and declined with a median half-life of 19.3 hours. Figure 2 shows the mean concentration for the 10 patients who received the oral dose on Day 28 and Table 3 shows the PK parameters of DAP after an oral dose.

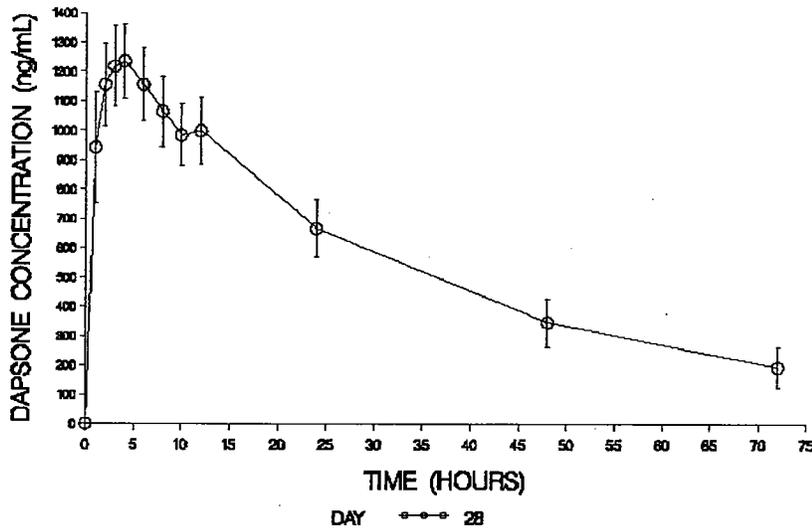


Figure 2B: Mean ( $\pm$ SE) Plasma Concentration of DAP for 10 Patients after a Single 100 mg Oral Dose on Day 28

Table 3B: Pharmacokinetic Parameters of DAP in Plasma after a Single Oral Dose of DAP

	$C_{max}$ ng/mL	$T_{max}$ hr	$AUC_{0-24}$ ng•hr/mL	$AUC_{inf}$ ng•hr/mL	Half-life hr
Mean	1375	3.8	22783	52641	24.3
SD	517.3	1.83	7734.7	36223.8	12.73
Median	1342	3.8	25024	43340	19.3
Minimum	623	1.0	12597	23156	14.9
Maximum	2352	6.2	36792	137810	54.1
n	10	10	10	10	10

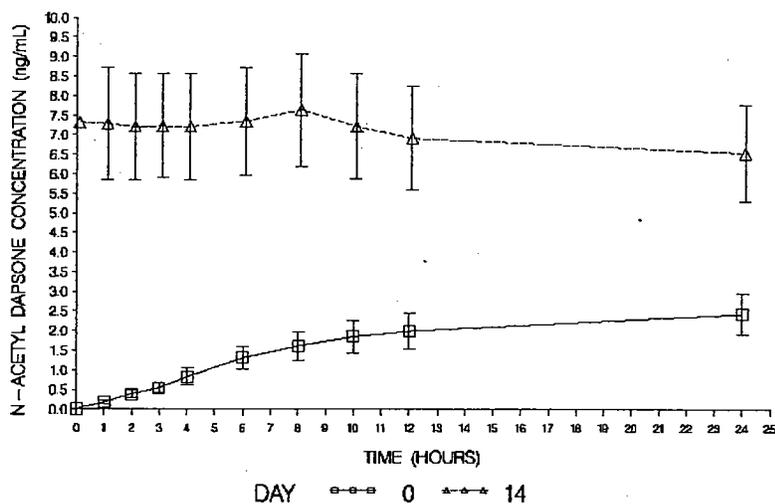
**Comparison of DAP in Plasma After Topical Application and a Single 100 mg Oral Dose of DAP:** Table 4 compares the steady-state  $AUC_{0-t}$  for topical dosing to the  $AUC_{inf}$  for oral dosing. For topical dosing, the mean AUC values are 126-fold lower than for oral dosing. The median apparent half-life for topical dosing was more than twice as long as that for oral dosing.

**Table 4B: Comparison of DAP in Plasma after Topical Application and a Single 100 mg Oral Dose of DAP**

	Topical Day 14		100 mg Single Oral Dose		Ratio (Median) (Oral/Topical)
	AUC <sub>0-24</sub> ng•hr/mL	Half-life hr	AUC <sub>inf</sub> ng•hr/mL	Half-life hr	
Mean	417.51	Not	52641	24.3	AUC 145.33
SD	292.89	Determined	36224	12.73	
Median	298.21	53.5	43340	19.3	Half-life 0.36
Minimum	184.47	24.7	23156	14.9	
Maximum	1067.38	68.3	137810	54.1	
n	10	10	10	10	

**PK of N-acetyl DAP:**

**NAD in Plasma after Application of 5% DAP Topical Gel:** NAD was measurable in the plasma of all patients by 3 hours on Day 0. On Day 0, the concentration of NAD increased in 14/18 patients throughout the day. In the remaining 4 patients, the C<sub>max</sub> was between 10 and 12 hours. Figure 3 shows the mean plasma concentrations of NAD for the 18 patients on Day 0 and Day 14 and Table 5 summarizes the pharmacokinetic parameters of NAD in Plasma after application of 5% DAP Topical Gel. The plasma concentration of NAD reached steady-state by about Day 5 after the first topical application.

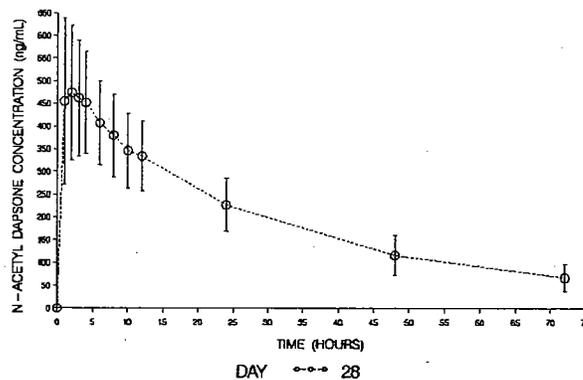


**Figure 3B: Mean Plasma Concentrations (±SE) of NAD for 18 Patients on Day 0 and Day 14**

**Table 5B: Pharmacokinetic Parameters of NAD in Plasma after Application of 5% DAP Topical Gel**

Patient	C <sub>max</sub> ng/mL	T <sub>max</sub> hr	AUC <sub>0-24</sub> ng•hr/mL	Half-life hr
<b>Day 0</b>				
Mean	2.45	Not Determined	40.13	Not Estimatable
SD	2.205		37.57	
Median	1.74	24.9	29.80	
Minimum	0.32	10.0	4.64	
Maximum	8.72	27.6	155.01	
n	18	18	18	
<b>Day 14</b>				
Mean	8.23	Not Determined	167.81	Not Determined
SD	6.297		134.48	
Median	6.45	5.0	137.07	44.90
Minimum	1.67	0.0	34.92	18.0
Maximum	27.09	26.0	594.11	75.8
n	18	18	18	17†

**NAD in Plasma after an Oral Dose of DAP:** After a 100 mg oral dose of DAP, plasma concentrations of NAD peaked at approximately 3.8 hours and declined with a median half-life of 18.8 hours. Figure 4 shows the mean concentration for the 10 patients after the oral dose on Day 28 and Table 6 shows the PK parameters of NAD after an oral dose of DAP.



**Figure 4B: Mean Concentrations ( $\pm$ SE) of NAD for 10 Patients after a Single 100 mg Oral Dose of DAP on Day 28**

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**Table 6B: Pharmacokinetic Parameters of NAD in Plasma after a Single 100 mg Oral Dose of DAP**

	C <sub>max</sub> ng/mL	T <sub>max</sub> hr	AUC <sub>0-24</sub> ng•hr/mL	AUC <sub>inf</sub> ng•hr/mL	Half-life hr
Mean	553	3.5	8095	18047	24.2
SD	568.7	1.76	6232.6	18128.3	11.16
Median	324	3.8	5230	11398	18.8
Minimum	162	1.0	2758	4682	15.9
Maximum	1986	6.2	19238	64754	46.0
n	10	10	10	10	10

**Comparison of NAD in Plasma after Topical Application and Oral Dose of DAP:** Table 7 compares the steady-state AUC<sub>0-t</sub> for topical dosing to the AUC<sub>inf</sub> for oral dosing. For topical dosing, the mean AUC values were 122-fold lower than for oral dosing. The median apparent half-life for topical dosing is about twice as long as for oral dosing.

**Table 7B: Comparison of NAD in Plasma after Topical Application and a Single 100 mg Oral Dose of DAP**

	Topical Day 14		100 mg Single Oral Dose		Ratio (Median) (Oral/Topical)
	AUC <sub>0-24</sub> ng•hr/mL	Half-life hr	AUC <sub>inf</sub> ng•hr/mL	Half-life hr	
Mean	147.97	Not	18047	24.2	AUC 111.5
SD	162.013	Determined	18128.3	11.16	
Median	102.21	46.6	11398	18.8	Half-Life 0.40
Minimum	34.92	18.0	4682	15.9	
Maximum	594.11	75.8	64754	46.0	
n	10	10	10	10	

**Excretion of DAP, NAD, and DAP Hydroxylamine in Urine:**

According to the sponsor, in three patients (104, 108, and 110), the urine DAP metabolites could be determined (Table 10). Higher amounts of DAP hydroxylamine were excreted following a single 100 mg oral DAP dose than after 14 days of topical application of 5% DAP Topical Gel.

**Table 10B: Amounts of DAP Hydroxylamine in Urine of Patients for Whom Amounts could be accurately calculated for both Days 14 (Topical) and 28 (po)**

Patient	Day	Urine Volume Total mL	Urine Conc. ng/mL	Amount mcg	Amount Ratio (po/topical)
104.	14.	100.	68.	6.79.	119.
	28.	300.	2687.	806.03.	
108.	14.	150.	84.	12.55.	32.
	28.	300.	1336.	400.82.	
110.	14.	400.	21.	8.24.	71.
	28.	400.	1468.	587.33.	

**Discussion:** Plasma concentrations of DAP and NAD were greater after a single oral dose of 100 mg DAP than after 15 days of repeated application of 5% DAP Topical Gel. Steady-state for DAP was reached by approximately Day 7 and steady state for NAD was reached by approximately Day 5. The half-life of DAP was longer for 5% DAP Topical Gel than for 100 mg oral DAP.

During analysis of urine for DAP, NAD, and DAP hydroxylamine, the aliquots for each patient on each Day were inadvertently pooled before assay at the assay laboratory. Consequently, the total amounts of DAP, NAD, and DAP hydroxylamine excreted could not be quantitated for 15 of the 18 patients. Three patients voided either equal volumes or voided once on Days 14 and 28 and, therefore, concentrations could be accurately determined for these patients (patients 104, 108, and 110). Based on the data from these 3 patients, lower levels of DAP hydroxylamine may be expected after topical treatment than after a single oral dose of DAP.

In summary, these data demonstrate that total systemic exposure and peak plasma concentrations of DAP and NAD following topical application of 5% DAP Topical Gel are approximately 1% to the same parameters following oral administration.

**Comments:**

- *While the sponsor has maintained a log of amount dispensed to each patient at each application, they should have maintained a log of % BSA affected especially at baseline and at some intermediate time points for each patient to draw the meaningful relationship between % BSA and systemic exposure. In absence of lesion count of each patient and an approximation of 27% BSA involvement, fulfillment of "maximal usage condition" of this pivotal PK study is questionable.*
- *The sponsor mentioned that "At the assay laboratory, the aliquots for each patient on each Day were inadvertently pooled before assay." Even in that case, the sponsor should have kept the original urine samples to perform reanalysis. Based on data from 3 patients only as presented in Table 10, no discussion and/or inference on urine DAP hydroxylamine data can be entertained in this review.*

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*A 12-Month, Multicenter, Open-Label, Non-Comparative Design Study of 5% Dapsone Topical Gel in Patients with Acne Vulgaris*

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**Objective(s):**

1. The primary objective of this study was to evaluate the long-term safety of 5% DAP Topical Gel (DTG) when used for up to 12 months in patients with acne vulgaris.
2. The secondary objective of this study was to obtain information on the efficacy of 5% DTG when used for up to 12 months in patients with acne vulgaris.

**Study Design:**

This study was a 12-month, multicenter, open-label, non-comparative study of the safety of 5% DTG when applied twice daily in patients with acne vulgaris conducted at 18 study centers located in the United States. All patients applied a thin film of DTG (Lot #s 1328, 1478 and 1543) twice daily (once in the morning and once at least 1 hour prior to bedtime) for up to 12 months into acne involved areas of the face, back, shoulders, and chest and rubbed until it completely disappeared. The average daily use of DTG was 1.35 grams (g). The mean  $\pm$  SD amount of DTG applied per day was  $1.35 \pm 1.08$  g, with a range of 0.00–11.02 g. The mean  $\pm$  SD amount of DTG applied per application was  $0.72 \pm 0.57$  g, with a range of 0.00 – 5.52 g.

Patients were male or female, 12 years of age or older. Patients had a clinical diagnosis of acne vulgaris, with at least 20 inflammatory lesions at Baseline ( $\geq 10$  of the inflammatory lesions were on the face). A total of 506 patients were enrolled in this study. 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 white (403; 79.6%). Forty-eight patients (9.5%) in the study population were black and 36 (7.1%) were Hispanic. 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. A total of 368 patients were followed for 6 months, and 340 patients were followed for 12 months.

Drug exposure was assessed by determining the grams of product used by each patient, as well as plasma DAP levels. Drug weights were recorded at each scheduled visit. In addition, plasma DAP levels were evaluated at Baseline, and Months 1, 3, 4, 6, 9, 12 and early termination (ET). A subset of patients had additional blood drawn at Weeks 1 and 2 for DAP level determinations.

Although this was predominantly a safety study, efficacy was evaluated. Acne lesion counts were assessed at Screening/Baseline, and then repeated at Months 1, 3, 4, 6, 9, 12 and ET.

Safety evaluations, including adverse events and laboratory analyses, were assessed at all scheduled visits. Blood was drawn for hematology and serum chemistry determinations at Baseline, and Months 1, 3, 6, 9, 12 and ET. A subset of patients had additional blood drawn for hematology at Weeks 1 and 2. All available patients were screened for glucose-6-phosphate dehydrogenase deficiency (G6PD) at Month 6.

The quantitation of DAP in plasma was performed at \_\_\_\_\_ using a validated high performance liquid chromatography/mass spectrometry (HPLC/MS) method. The lower limit of quantitation (LOQ) was 0.05 ng/mL. Using the most conservative estimate, concentrations that were below the LOQ were considered to be 0.049999 ng/mL for all DAP level calculations.

**Results:**

A summary of plasma DAP concentrations over time is shown in Table 1C, and plasma NAD concentrations over time are summarized in Table 2C.

**Table 1C. Plasma DAP Concentrations Over Time**

Time Point	Plasma DAP Levels (ng/mL)		
	Mean ± SD	Median	Maximum
Week 1 (N=35)	10.39 ± 9.70	7.74	49.26
Week 2 (N=35)	9.68 ± 11.17	5.89	59.34
Month 1 (N=459)	10.98 ± 11.55	7.52	91.93 <sup>a</sup>
Month 3 (N=408)	9.13 ± 10.94	6.19	87.06 <sup>a</sup>
Month 6 (N=350)	8.06 ± 9.20	5.26	76.07
Month 9 (N=312)	7.55 ± 9.61	4.61	70.71 <sup>a</sup>
Month 12 (N=308)	7.50 ± 10.12	4.81	107.01 <sup>a</sup>

<sup>a</sup> Values belong to Patient #1809.

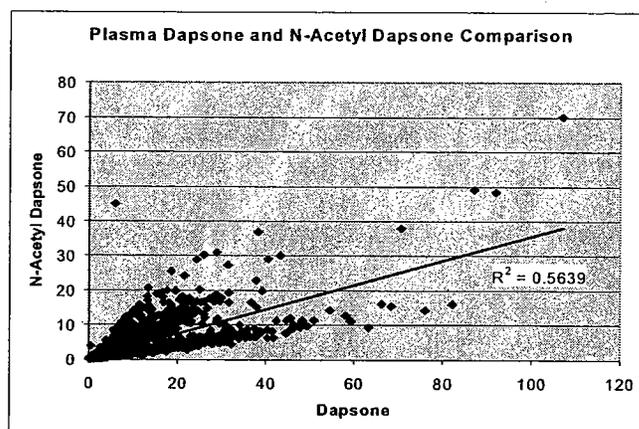
**Table 2C. Plasma NAD Concentrations Over Time**

Time Point	Plasma NAD Levels (ng/mL)		
	Mean ± SD	Median	Maximum
Week 1 (N=35)	2.96 ± 2.85	2.29	11.65
Week 2 (N=35)	2.78 ± 3.59	1.51	16.99
Month 1 (N=459)	4.49 ± 5.77	2.48	48.40 <sup>a</sup>
Month 3 (N=408)	3.69 ± 4.77	2.04	49.02 <sup>a</sup>
Month 6 (N=350)	3.26 ± 4.20	1.71	20.03
Month 9 (N=312)	3.17 ± 4.47	1.44	37.91 <sup>a</sup>
Month 12 (N=308)	3.16 ± 5.62	1.57	70.11 <sup>a</sup>

<sup>a</sup> Values belong to Patient #1809.

Median plasma DAP concentrations ranged between 4.6 and 7.7 ng/mL and mean (± SD) were nearly constant throughout the study around 9 ± 10 ng/ml. In addition, median plasma NAD concentrations ranged between 1.4 and 2.5 ng/mL and mean (± SD) were nearly constant throughout the study around 3 ± 4 ng/ml. A correlation (r = 0.75) between DAP and NAD concentrations is shown in Figure 1C. It appears that as plasma DAP levels rise, NAD levels tend to rise.

**Figure 1C. Correlation of Plasma DAP Concentrations and NAD Concentrations**



**Efficacy:**

Lesions counts were summarized using descriptive statistics for continuous data (i.e., mean, median, standard error, range, min and max). Three types of lesions were summarized: inflammatory lesions (pustules and papules), non-inflammatory lesions (comedones), and total lesions (sum of inflammatory and non-inflammatory lesions). Lesion counts were summed over the face, back, and chest to create a total count. Mean percent reduction-from-Baseline lesion counts are summarized in Table 3C.

**Table 3C. Mean Percent Reduction-from-Baseline of Three Lesion Types**

Time Point	Mean Percent Reduction (±SE)		
	Inflammatory Lesions	Non-Inflammatory Lesions	Total Lesions
Month 1 (N=464)	30.6 (±1.6)	-3.5 (±7.3)	22.8 (±1.5)
Month 3 (N=409)	49.3 (±1.8)	4.7 (±6.6)	37.8 (±1.9)
Month 6 (N=367)	56.1 (±2.0)	17.6 (±5.7)	45.9 (±2.0)
Month 9 (N=345)	57.3 (±1.9)	17.2 (±7.3)	48.2 (±2.0)
Month 12 (N=337)	58.2 (±2.5)	19.5 (±6.3)	49.0 (±2.2)

Efficacy was observed as early as Month 1, and showed further improvement throughout the 12-month study period. Patients showed an improvement in their disease status as

evidenced by a reduction in inflammatory lesions, non-inflammatory lesions, and total lesions. Total lesion count showed a 49% reduction at Month 12.

**Safety:** The safety profile of the subjects will be reviewed in detail by the medical reviewer. According to the sponsor, no trends in laboratory profile suggestive of a safety concern were observed.

**Effect of G6PD deficiency:** Five of 358 patients assayed were G6PD deficient, with one being severely deficient. The adverse event profiles, including laboratory studies, for these patients was similar to the study population.

For all five G6PD deficient patients, HGB was within the normal range at Baseline and remained within the normal range (as described in the footnote of Table 4) throughout the study. For patient # 1424, a decrease of HGB by about one unit was observed at month 12 compared to baseline. Plasma DAP levels for these patients ranged between < 0.05 and 63.35 ng/mL. No hematologic adverse events were experienced over the course of the study in these patients.

A summary of laboratory values for the G6PD deficient patients is shown in Table 4C.

**Table 4C. Hemoglobin and Plasma DAP Levels for G-6-PD Deficient Patients**

Patient No.	Gender	Age (years)	DAP 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

NA = Not available

**Discussion:** Patients applied 5% DTG for an average of 256.33 days, with an average daily use of 1.35 g. Plasma DAP levels were low and the mean levels range between 7.50 ( $\pm$  10.12) and 10.98 ( $\pm$  11.55) ng/mL over time. There was no evidence of systemic accumulation over 12 month period. However, one patient (#1809) showed persistently high level of DAP and NAD throughout 12 month period. In order to understand any possible reason for these high levels, the following information was excerpted about the patient:

Patient Description	Visit	DAP Conc (ng/ml)	NAD Conc (ng/ml)
# 1809 (15 yr white male, 152 lbs, 71 inches)	Baseline	<0.05	<0.05
	Month 1	91.93	48.40
Pustules (0/12) <sup>a</sup> : 23/2	Month 3	87.05	49.02
Papules (0/12): 113/17	Month 6	28.97	18.71
Comedones (0/12): 26/13	Month 9	70.70	37.91
Nodules (0/12): 21/0	Month 12	107.01	70.11

a: Count at baseline and at month 12.

It appears that the patient had a very high count of papules at baseline (113). That might have contributed to the high level of DAP and NAD at the beginning. However, surprisingly level at month 12 was even higher though the lesions count improved

significantly. This level, however, was not found to be associated with any unusual adverse events. This patient was not identified as one of 17 patients who experienced a drop in HGB from baseline of  $\geq 2$  g/dL or a G6PD deficient one. During the study period, a total of 17 patients experienced a drop in HGB from Baseline of  $\geq 2$  g/dL, however values for 12 patients were within the normal range throughout the study. Nine patients (52.9%) were female and 8 (47.1%) were male; 16 patients (94.1%) were white and one (6.9%) was Hispanic. A listing of patient data is shown in Table 4C.

The majority of these patients (11/17; 64.7%) presented with only one HGB value that was  $\geq 2$  g/dL lower than Baseline, and that value was within the normal range at study completion.

Three patients (#1303, #1409, and #1821) presented with three or more HGB values  $\geq 2$  g/dL lower than Baseline:

Three patients (#0730, #0802, and #1848) presented with two HGB values  $\geq 2$  g/dL lower than Baseline. All of these patients' HGB values remained within the normal range.

Improvement in disease status occurred by Month 1 and continued throughout the course of the study. By Month 12, the mean percent reduction from Baseline for inflammatory, non-inflammatory, and total lesion counts was 58.2, 19.5, and 49.0, respectively.

**Conclusion:** This study demonstrates low systemic exposure following long-term, twice-daily topical application. The test article was well tolerated. Treatment-emergent adverse events generally did not increase during the study. Improvements in acne were observed by Month 1 (the first planned visit of the study), with further improvement throughout the study.

Based upon the above data, no causal relationship between DAP level and decrease in HGB values could be established. Similarly, based on data from only 5 patients who were G6PD deficient, no causal relationship between G6PD deficiency and DAP levels could be established.

**Comments:**

*While the sponsor has maintained a log of amount dispensed to each patient at each application, they should have maintained a log of % BSA affected especially at baseline and at some intermediate time points for each patient to draw the meaningful relationship between % BSA and systemic exposure.*

**Table 4C. Summary of Hemoglobin Levels  $\geq 2$  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 <sup>a</sup>	14.3 <sup>a</sup>
		DAP (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 <sup>a</sup>	14.1	11.9 <sup>a</sup>
		DAP (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 <sup>a</sup>	14.0	13.9	14.2

Patient No.	Gender	Laboratory Values						
		Analysis	BL	Month 1	Month 3	Month 6	Month 9	Month 12/ET
1015	Female	DAP (ng/mL)	< 0.05	8.24	7.51	2.02	1.00	7.78
		HGB (g/dL)	13.1	12.8	11.0 <sup>a</sup> L	NA	NA	NA
1303	Female	DAP (ng/mL)	< 0.05	0.89	1.30	NA	NA	NA
		HGB (g/dL)	13.4	12.5	11.3 <sup>a</sup> L	10.6 <sup>a</sup> L	10.1 <sup>a</sup> L	9.3 <sup>a</sup> L
1315	Male	DAP (ng/mL)	< 0.05	6.90	14.43	14.22	10.94	0.49
		HGB (g/dL)	16.3	13.6 <sup>a</sup>	15.9	15.8	16.9	16.4
1318	Male	DAP (ng/mL)	< 0.05	2.49	22.39	0.17	4.68	< 0.05
		HGB (g/dL)	13.6	13.9	11.4 <sup>a</sup> L	13.4	13.6	13.2
1319	Female	DAP (ng/mL)	< 0.05	22.59	22.29	3.01	0.09	0.09
		HGB (g/dL)	14.4	13.5	13.0	13.2	12.4 <sup>a</sup>	13.6
1409	Female	DAP (ng/mL)	< 0.05	6.57	6.61	< 0.05	0.18	4.67
		HGB (g/dL)	15.5	14.1	14.4	12.5 <sup>a</sup>	13.2 <sup>a</sup>	13.5 <sup>a</sup>
1414	Male	DAP (ng/mL)	< 0.05	7.54	7.48	15.73	NA	NA
		HGB (g/dL)	15.6	13.3 <sup>a</sup>	15.0	14.5	14.2	14.5
1507	Male	DAP (ng/mL)	< 0.05	45.63	7.91	NA	NA	NA
		HGB (g/dL)	14.0	13.5	13.8	12.0 <sup>a</sup> L	13.8	14.4
1710	Male	DAP (ng/mL)	< 0.05	25.22 <sup>b</sup>	35.72 <sup>b</sup>			
		HGB (g/dL)	16.1	14.6	15.7	14.8	15.3	14.0 <sup>a</sup>
1718	Female	DAP (ng/mL)	< 0.05	8.93	9.46	7.68	13.46	9.58
		HGB (g/dL)	15.1	14.7	13.4	13.7	13.6	13.0 <sup>a</sup>
1738	Female	DAP (ng/mL)	< 0.05	4.79	0.57	7.47	3.55	2.63
		HGB (g/dL)	13.8	13.5	13.7	11.8 <sup>a</sup>	13.1	13.2
1821	Male	DAP (ng/mL)	< 0.05	0.16	3.29	< 0.05	2.82	0.49
		HGB (g/dL)	17.9 H	NA	15.5 <sup>a</sup>	15.4 <sup>a</sup>	15.7 <sup>a</sup>	15.7 <sup>a</sup>
1848	Female	DAP (ng/mL)	< 0.05	0.11	0.23	1.33	< 0.05	3.43
		HGB (g/dL)	14.9	12.8 <sup>a</sup>	13.9	14.2	12.4 <sup>a</sup>	13.6
1920	Female	DAP (ng/mL)	0.12	22.87	13.04	22.96	16.61	25.26
		HGB (g/dL)	14.4	13.1	12.9	12.8	13.1	12.4 <sup>a</sup>
		DAP (ng/mL)	< 0.05	8.61	2.04	0.11	0.46	0.18

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.

<sup>a</sup> HGB value decreased by  $\geq 2$  g/dL from Baseline.

<sup>b</sup> Values from a laboratory retest which resulted in an unscheduled plasma DAP result.

NDA: 21-794/Study 03-0-182

Study Dates: Feb '04 – May '04

*A Phase I Repeat Dose Drug Interaction Study of 5% Dapsone Topical Gel and Oral TMP/SMX in Subjects with Acne*

Objectives :

The objectives of this study were:

To characterize the effect of 5% DAP topical gel (5%DTG), administered twice daily, on the repeated-dose pharmacokinetics of twice daily oral trimethoprim (TMP)/sulfamethoxazole (SMX) in female and male acne patients;

To characterize the effect of twice daily dosing of oral TMP/SMX on the steady-state pharmacokinetics of twice daily topical 5%DTG in female and male acne patients.

**Study Design:**

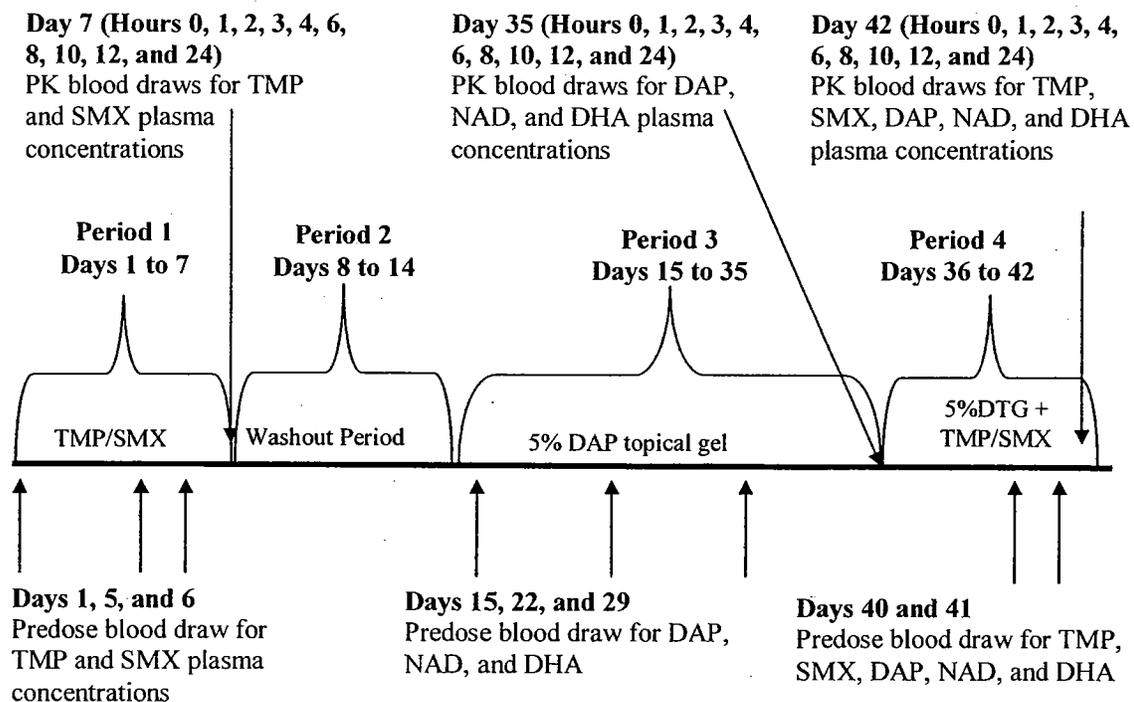
This was a Phase 1, prospective, open-label, repeat-dose, fixed-treatment, drug interaction study conducted in male and female patients with acne. This study was designed to evaluate possible drug interactions when oral TMP/SMX and topical 5%DTG are dosed concomitantly. The study design is presented in Figure 1D.

The effects of 5%DTG at steady-state on TMP and SMX were determined by comparing TMP and SMX pharmacokinetic parameters on Day 42 (TMP/SMX with 5%DTG at steady state) with Day 7 (TMP/SMX alone at steady state). The effects of TMP/SMX on repeat-dose DAP were determined by comparing DAP pharmacokinetic parameters on Day 42 (5%DTG with TMP/SMX) with Day 35 (5%DTG alone). The pharmacokinetic parameters of the two DAP metabolites found in the plasma (NAD and DHA) were also studied.

The patients were instructed to rub a thin layer of the medication gently into the face, neck, shoulders, upper back and upper chest, regardless of the extent of disease involvement. The treatment area was approximately 3000 cm<sup>2</sup> (estimated body surface area (BSA) of ~20%). This treatment area was the same throughout the study.

TMP/SMX double strength (160 mg/800 mg) was taken twice a day from study Days 1 to 7 and study Days 36 to 42. Oral TMP/SMX was administered with a full glass of water, one hour before meals or 2 hours after meals.

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**Figure 1D: Study Design: Pharmacokinetic Blood Draws**

Quantitation of DAP, DHA, and NAD in heparinized plasma was performed using a high performance liquid chromatography/tandem mass spectrometry (LC/MS/MS). DAP, NAD, DHA and the internal standard, \_\_\_\_\_ were extracted from 1.00 mL plasma by liquid/liquid extraction. The lower limit of quantification (LLOQ) was 0.30 ng/mL for DAP, DHA, and NAD.

Quantitation of TMP and SMX in plasma was performed using a high performance mass spectrometry method (Report Number 03-334-VRPT-01) validated at \_\_\_\_\_ TMP, SMX, and the internal standard, SMX were extracted from 0.1 mL plasma by liquid/liquid extraction. The LLOQ for TMP was 0.10 mcg/mL and the LLOQ for SMX was 1.00 mcg/mL.

A total of 33 individuals were screened for this study. Of these, 24 patients (12 M and 12 F; Age:  $27.7 \pm 7.5$  yrs) were enrolled into the study. Data from 17 patients who completed the study has been included in the data analysis.

G6PD deficiency is a relative contraindication for administration of TMP/SMX. Patients were screened for G6PD deficiency at screening. No patients were G6PD deficient.

**Results:**

**TMP Plasma Pharmacokinetics Alone as TMP/SMX and Administered With 5%DTG**

The pharmacokinetic parameters for TMP and 90% confidence interval around the ratio of the means (Day 42/Day 7) are presented in Table 1D. TMP plasma concentrations reached steady state by dosing Day 5, both when given alone and when given with 5%DTG.

**SMX Plasma Pharmacokinetics Alone as TMP/SMX and Administered With 5%DTG**

SMX plasma concentrations reached steady state by dosing Day 5, both when given alone and when given with 5%DTG. The pharmacokinetic parameters and 90% confidence interval around the ratio of the means (Day 42/Day 7) for SMX are presented in Table 2D.

**Table 1D: The Effect of Steady-State DAP on the Pharmacokinetics of TMP**

		TMP at Steady State (Day 7) (n=17)	TMP With 5%DTG at Steady State (Day 42) (n=17)	Ratio Combination/Drug Alone (90% CI) (n=17)
<b>C<sub>max</sub></b> (mcg/mL)	Mean ± SD	2.91 ± 1.105	3.06 ± 1.115	104.0% (89.6 to 120.6)
	Median	2.84	3.07	
	Range	1.14 to 5.79	0.84 to 5.90	
	Geo. Mean	2.74	2.85	
<b>AUC<sub>0-12</sub></b> (mcg•hr/mL)	Mean ± SD	25.34 ± 10.110	26.78 ± 10.289	105.9% (92.1 to 121.8)
	Median	24.35	26.04	
	Range	8.93 to 55.72	7.99 to 56.39	
	Geo. Mean	23.51	24.91	
<b>T<sub>max</sub></b> (hr)	Mean ± SD	1.30 ± 0.471	1.30 ± 0.472	NA
	Median	1.00	1.00	
	Range	0.98 to 2.02	0.97 to 2.02	

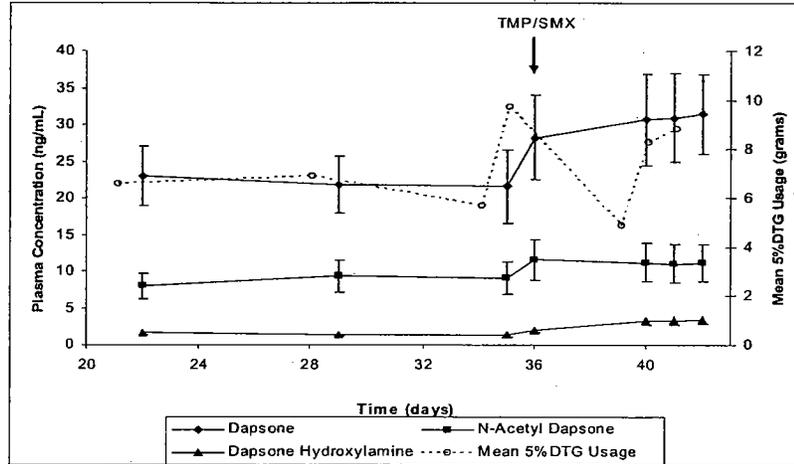
**Table 2D: The Effect of Steady-State DAP on the Pharmacokinetics of SMX**

		SMX at Steady State (Day 7) (n=17)	SMX With 5%DTG at Steady State (Day 42) (n=17)	Ratio Combination/Drug Alone (90% CI) (n=17)
<b>C<sub>max</sub></b> (mcg/mL)	Mean ± SD	80.04 ± 18.183	81.59 ± 28.751	96.5% (82.2 to 113.2)
	Median	81.45	81.18	
	Range	52.16 to 119.62	15.09 to 144.17	
	Geo. Mean	78.04	75.27	
<b>AUC<sub>0-12</sub></b> (mcg•hr/mL)	Mean ± SD	709.96 ± 162.244	721.80 ± 232.551	96.3% (81.6 to 113.7)
	Median	714.78	731.90	
	Range	422.10 to 931.67	118.29 to 1225.24	
	Geo. Mean	691.41	665.96	
<b>T<sub>max</sub></b> (hr)	Mean ± SD	2.06 ± 0.747	2.18 ± 0.634	NA
	Median	2.00	2.02	
	Range	1.00 to 3.03	1.00 to 4.00	

**DAP Plasma Pharmacokinetics After 5%DTG Alone and Administered With TMP/SMX**

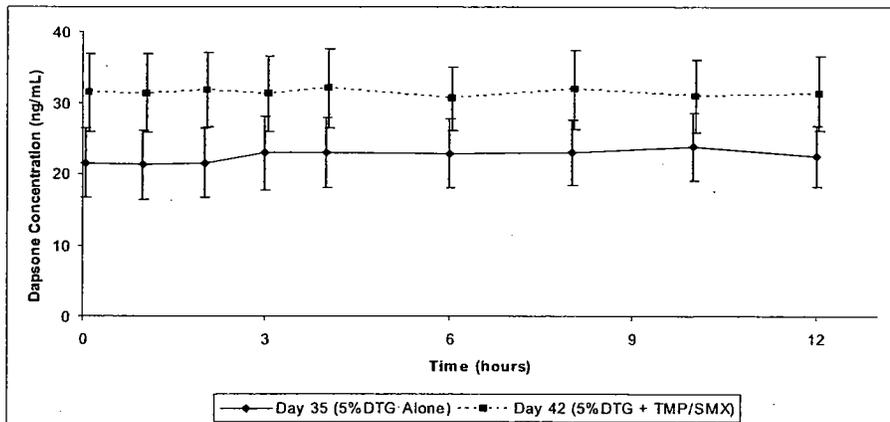
The mean trough concentrations of DAP on Days 22, 29, 35, 36, 40, 41, and 42 are presented in Figure 2D. The mean DAP plasma concentrations over time on Day 35 and Day 42 are presented in Figure 3D, and the pharmacokinetic parameters and 90% confidence interval around the ratio of the means (Day 42 to Day 7) for DAP are presented in Table 3D.

**Figure 2D: Mean ( $\pm$ SE) Trough Plasma Concentrations for DAP and DAP Metabolites and Mean Daily 5%DTG Usage**



Note: Day 36 is trough value following 5%DTG application alone.

**Figure 3D: Mean ( $\pm$ SE) Plasma DAP Concentrations on Day 35 and Day 42 in the Pharmacokinetic Evaluable Set**



**Table 3D: The Effect of TMP/SMX on the Pharmacokinetics of DAP**

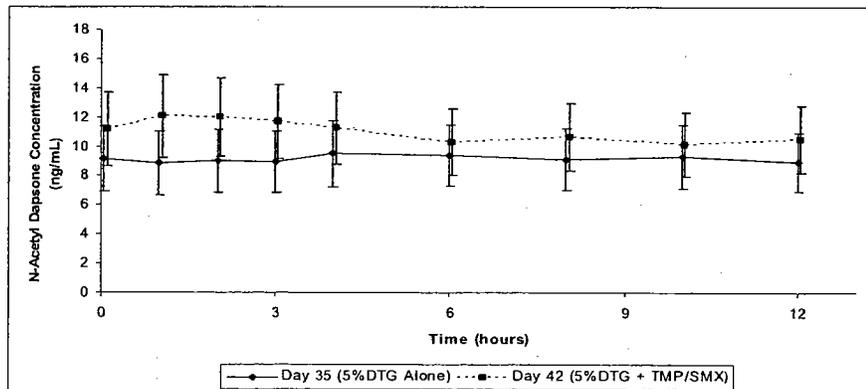
		5%DTG at Steady State (Day 35) (n=17)	5%DTG with Multiple-Dose TMP/SMX at Steady State (Day 42) (n=17)	Ratio† Combination/Drug Alone (90% CI) (n=17)
$C_{max}$ (ng/mL)	Mean ± SD	26.83 ± 23.230	35.98 ± 24.793	138.8% (112.3 to 171.5)
	Median	17.37	27.24	
	Range	6.77 to 101.27	6.18 to 103.61	
	Geo. Mean	20.71	28.74	
AUC <sub>0-12</sub> (ng•hr/mL)	Mean ± SD	292.46 ± 258.055	402.12 ± 274.746	144.6% (114.9 to 181.9)
	Median	197.67	299.82	
	Range	60.11 to 1129.77	67.15 to 1124.41	
	Geo. Mean	221.52	320.30	
$T_{max}$ (hr)	Mean ± SD	7.06 ± 3.881	5.60 ± 4.088	NA
	Median	8.00	4.02	
	Range	0.00 to 12.00	0.00 to 12.00	

Steady state for DAP plasma concentrations was reached by study Day 22 (dosing Day 7), and the new steady state for DAP, following TMP/SMX administration, was reached by Day 40 (dosing Day 5). As shown in Figure 2D, coadministration of TMP/SMX with 5%DTG resulted in higher plasma concentrations of DAP.

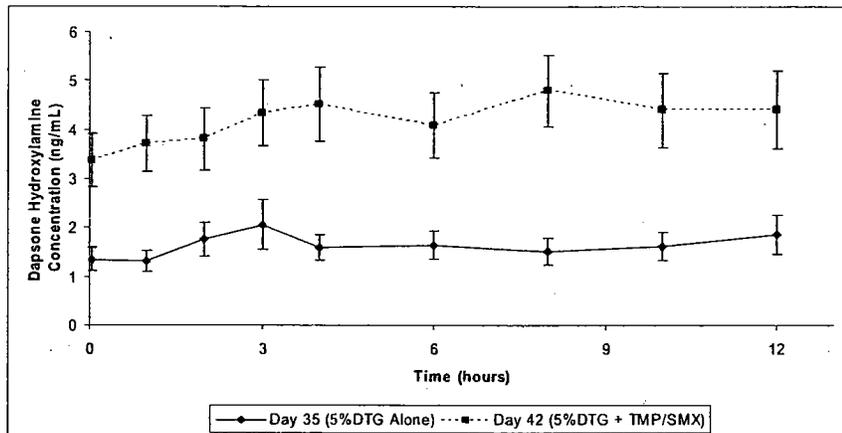
**DAP Metabolite Plasma Pharmacokinetics After 5%DTG Alone and Administered With TMP/SMX**

The mean trough concentrations of NAD (NAD) and DAP hydroxylamine (DHA) on Days 22, 29, 35, 36, 40, 41, and 42 are presented in Figure 2D. The mean NAD and DHA plasma concentrations over time on Day 35 and Day 42 are presented in Figure 4D and Figure 5D, respectively. The pharmacokinetic parameters and 90% confidence intervals for the DAP metabolites NAD and DHA are presented in Table 4D.

**Figure 4D: Mean (±SE) Plasma NAD Concentrations on Day 35 and Day 42 in the Pharmacokinetic Evaluable Set**



**Figure 5D: Mean ( $\pm$ SE) Plasma DHA Concentrations on Day 35 and Day 42 in the Pharmacokinetic Evaluable Set**



It appears from the above Table 4D and Figure 2D that co-administration of TMP/SMX with 5%DTG resulted in about 40% higher plasma exposure of DAP and 20% higher plasma exposure of NAD whereas plasma exposure of DHA was more than doubled.

#### Discussion:

5% DTG did not affect the pharmacokinetics of either TMP or SMX when administered concomitantly. Co-administration of TMP/SMX with 5%DTG, however, resulted in about 40% higher plasma exposure of DAP and 20% higher plasma exposure of NAD; plasma exposure of DHA was more than doubled. In spite of that, the values for dapsone  $C_{max}$ , with or without TMP/SMX administration, are low throughout the study and within the ranges found in previous studies with 5%DTG (Studies DAP0110 and DAP0114). The  $C_{max}$  of dapsone following a single oral dose of 100 mg dapsone (Study DAP0110) was approximately 38 times the  $C_{max}$  observed in the current study after concomitant administration of 5%DTG and TMP/SMX. Taking into account this accumulation of dapsone and its metabolite concentrations with repeated oral dosing, the AUC and  $C_{max}$  are approximately 100-fold higher than the AUC and  $C_{max}$  seen with 5%DTG in the current study.

During concomitant administration of TMP/SMX and 5%DTG, the plasma exposure for NAD was increased by about 20%. Notably, the plasma exposure for DHA more than doubled with concomitant administration. But still the  $C_{max}$  values observed in the current study were much lower than concentrations of DHA found in subjects following a single 100 mg oral dose of dapsone; the highest  $C_{max}$  observed for any patient in the current study is 43-fold lower than the  $C_{max}$  for the representative subject.

Despite increased exposure to dapsone and dapsone metabolites, following concomitant administration with TMP/SMX, there was no difference in the safety profile associated with increased dapsone exposure. Even in combination with TMP/SMX dapsone, NAD, and DHA exposure were approximately 100-fold less than the exposure observed

following oral dosing of dapsone at 100 mg/day (DAP0110). Adverse events were not increased by concomitant administration of 5%DTG and oral TMP/SMX.

**Table 4D: DAP Metabolite Pharmacokinetic Parameters on Day 35 and Day 42**

			5%DTG at Steady-State (Day 35) (n=17)	5%DTG with Multiple Dose TMP/SMX (Day 42) (n=17)	Ratio† Combination/Drug Alone (90% CI) (n=17)
NAD	$C_{max}$ (ng/mL)	Mean ± SD Median Range Geo. Mean	11.63 ± 10.589 6.22 1.23 to 31.49 7.40	14.33 ± 12.472 8.81 0.77 to 34.52 8.84	119.5% (94.7% to 150.7%)
	$AUC_{0-12}$ (ng·hr/mL)	Mean ± SD Median Range Geo. Mean	120.27 ± 112.880 62.73 12.61 to 327.03 73.28	142.81 ± 127.049 75.91 8.20 to 375.99 88.17	120.3% (96.4% to 150.2%)
	$T_{max}$ (hr)	Mean ± SD Median Range	5.70 ± 4.432 6.00 0.00 to 12.00	3.89 ± 3.658 2.97 0.00 to 12.00	NA
DHA	$C_{max}$ (ng/mL)	Mean ± SD Median Range Geo. Mean	3.18 ± 2.465 2.44 0.69 to 10.15 2.48	6.36 ± 3.614 6.08 1.17 to 13.46 5.30	213.3% (145.5% to 312.6%)
	$AUC_{0-12}$ (ng·hr/mL)	Mean ± SD Median Range Geo. Mean	21.19 ± 12.910 18.01 6.08 to 49.86 17.79	53.79 ± 33.808 44.60 9.67 to 117.52 43.50	244.5% (182.5% to 327.5%)
	$T_{max}$ (hr)	Mean ± SD Median Range	6.52 ± 4.630 6.00 0.00 to 12.00	5.47 ± 3.476 4.00 0.97 to 12.00	NA

**Comments:**

*The predose DAP concentrations at Day 36 increased significantly ( $P < 0.05$ ) by about 40%. According to the sponsor, it is most likely because the 5%DTG was applied more diligently in the in-house days than in the outpatient days. However, exposure from topical applications are dependent more on the BSA than the amount applied. As the area of application remained fixed throughout the study, the sponsor's explanation is not plausible.*

# Appendix C

OCPB Filing Form

Office of Clinical Pharmacology and Biopharmaceutics  
**New Drug Application Filing and Review Form**

General Information About the Submission

	Information		Information
NDA Number	21-794	Brand Name	Aczone Gel
OCPB Division (I, II, III)	III	Generic Name	5% Dapsone Gel
Medical Division	HFD-540	Drug Class	Antibacterial
OCPB Reviewer	Tapash K. Ghosh, Ph.D.	Indication(s)	Acne vulgaris
OCPB Team Leader	Raman Baweja, Ph.D.	Dosage Form	Topical Gel
		Dosing Regimen	BID
Date of Submission	8/31/04	Route of Administration	Topical
Estimated Due Date of OCPB Review	4/15/05	Sponsor	Atrix Lab. Inc.
PDUFA Due Date	7/7/05	Priority Classification	3S
Division Due Date	6/7/05		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<b>Healthy Volunteers-</b>				
single dose:				
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:	X	4		
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:	X			
In-vivo effects of primary drug:	X			
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:	X			
gender:	X			
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD:</b>				
Phase 2:				

Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>	X	1		
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>	6			
<b>Filability and QBR comments</b>				
	"X" if yes	<b>Comments</b>		
<b>Application fileable ?</b>	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
<b>Comments sent to firm ?</b>		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
<b>QBR questions (key issues to be considered)</b>		<ul style="list-style-type: none"> <li>• Systemic exposure of dapsone from topical gel compared to oral administration</li> <li>• Effect of G-6-PD deficiency on dapsone exposure</li> <li>• Effect of genetic polymorphism (slow and fast acetylators) on dapsone exposure</li> </ul>		
<b>Other comments or information not included above</b>				
<b>Primary reviewer Signature and Date</b>	<i>Jayash K. Ghosh 10-25-04</i>			
<b>Secondary reviewer Signature and Date</b>	<i>Raman Ravaja 10-25-04</i>			

CC: NDA 21-794, HFD-850 (Electronic Entry or Lee), HFD-540(F. Cross), HFD-880 (TL, DD, DDD), CDR (B. Murphy)

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

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Tapash Ghosh  
6/3/05 12:17:25 PM  
BIOPHARMACEUTICS

Raman Baweja  
6/3/05 12:48:39 PM  
BIOPHARMACEUTICS