CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207154Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 207154	Submission Date(s): 4/28/2015
Brand Name	Aczone Gel, 7.5%
Generic Name	Dapsone
Primary Reviewer	Doanh Tran, Ph.D.
Secondary Reviewer	Capt. E. Dennis Bashaw, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Dermatology and Dental Products
Sponsor	Allergan
Submission Type; Code	Original NDA
Formulation; Strength(s)	Gel, 7.5%
Indication	Topical treatment of acne vulgaris in patients 12 years of age and older

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1 Executive Summary

The applicant submitted an application for a new gel formulation of Aczone (dapsone) Gel, 7.5%, for topical treatment of acne vulgaris in patients 12 years of age and older. Dapsone is a synthetic sulfone with antimicrobial and anti-inflammatory properties. Dapsone is the same drug substance contained in Aczone (dapsone) Gel, 5% (NDA 21794), which is currently approved for twice daily application for the topical treatment of acne vulgaris. The recommended dosage and administration of Aczone Gel, 7.5% will be to apply a thin layer to the entire face once daily. In addition, a thin layer may be applied to other affected areas once daily.

The clinical development program comprised 2 pivotal phase 3 studies, and 4 phase 1 studies including a pharmacokinetic (PK) study in patients with moderate acne vulgaris (Study 225678-004) and 3 dermal tolerability studies in healthy subjects. The development program was based on the target population of patients 12 years of age and older. The Division of Dermatology and Dental Products recommends that for the acne indication, the target age be 9 years of age and older. Therefore, a post marketing requirement to assess PK in subjects 9 years to 11 years 11 months is included in section 1.2 of this review.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds NDA 207154 acceptable pending agreement on recommended labeling changes.

1.2 Phase IV Requirements and Commitments

The following post marketing requirement is recommended:

An open-label study to assess safety, pharmacokinetics, and treatment effect of Aczone Gel, 7.5% in 100 pediatric subjects age 9 years to 11 years 11 months with acne vulgaris. Pharmacokinetic assessments will be done in at least 16 evaluable subjects under maximal use conditions.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Bioavailability:

Study 225678-004 compared the PK of dapsone gel, 7.5% (formulation 11080X, to-be-marketed formulation) applied once-daily (QD) for 28 days with Aczone Gel, 5% applied twice-daily (BID) for 28 days in subjects (≥16 years of age) with acne vulgaris. Study medication was applied for 28 days to the skin of male and female patients with moderate acne vulgaris by the clinical site staff. For each application, study treatment (2 grams) was topically applied to the face, upper chest, upper back, and shoulders corresponding to a treatment area of approximately 1000 cm^2.

Mean Ctroughs for plasma dapsone were similar for days 7 - 28 suggesting steady state PK was achieved by Day 7 and maintained until Day 28. PK parameters for plasma dapsone following 28 days of dosing are shown in Table 1.

Relative to Aczone Gel, 5%, daily systemic exposure of dapsone, defined by the geometric mean ratio for maximum plasma concentration (Cmax) and area under the concentration-time curve from time 0 to 24 hours postdose (AUC0-24), was approximately 28.6% and 28.7% lower for formulation 11080X, respectively. Based on the 90% CIs for Cmax and AUC0-24, these differences were statistically significant; however, the upper limit of 90% CI were close to 100% (93% for Cmax and 92% for AUC0-24) and therefore the statistically significantly lower systemic exposure may not be clinically meaningful.

Table 1: Summary of plasma dapsone PK parameters

PK parameter	Dapsone Gel, 7.5% QD (TBM formulation 11080X) N=19	Aczone Gel, 5% BID N=18
Cmax (ng/mL)	13.0 ± 6.8	17.6 ± 6.7
AUC0-12 (ng*h/mL)	NA	186 ± 71
AUC0-24 (ng*h/mL)	282 ± 146	379 ± 142

Drug-drug interactions:
The sponsor proposed to omit information contained in section 7.3 of Aczone Gel, 5% label regarding potential interaction with oral dapsone and enzyme inducers such as rifampin, anticonvulsants, St. Johns' wort or folic antagonist such as pyrimethamine that may lead to increased risk of hemolysis. Compared to oral dapsone, the risk of drug interactions is anticipated to be low due to much lower systemic concentration observed following topical dosing of Aczone Gel, 5% and 7.5%. However, because risk of methemoglobinemia has been reported following treatment with Aczone gel, 5% (Aczone Gel, 5% product label), such risk cannot be ruled out for dapsone gel, 7.5%. In addition, risk of hemolysis due to dapsone or its metabolites cannot be ruled out. Therefore, this reviewer concurs with the clinical team's recommendation that the interactions potential as noted in section 7.3 of the Aczone Gel, 5% label should be included in the label for dapsone gel, 7.5%.

Pediatrics:
Pharmacokinetic trial 225678-004 included pediatrics ≥16 years of age (7 of 19 in dapsone gel, 7.5% group and 6 of 18 in Aczone Gel, 5% group). Aczone Gel, 5% label indicates that systemic exposure is pediatrics 12 – 15 years of age is similar to those 16 years and older. Therefore, additional PK trial in subjects ages 12 -15 was not requested for dapsone gel, 7.5%.

Because acne vulgaris do occur in children younger than 12 years of age, the Division of Dermatology and Dental Products recommends evaluation of subjects down to 9 years of age. As part of a post marketing requirement, the Applicant should evaluate the

pharmacokinetic properties of dapsone gel, 7.5% in subjects 9 years to 11 years 11 months of age with acne vulgaris under maximal use conditions. The plan was discussed with the pediatric review committee (PeRC) on 12/2/2015 and the PeRC agreed.

Clinical vs. to-be-marketed formulation:
The to-be-marketed dapsone gel, 7.5% formulation (11080X) was used in all clinical studies, including the 2 phase 3 trials and the 4 phase 1 studies.

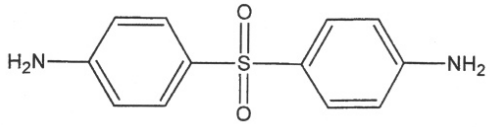
Method validation:
Human plasma concentrations of dapsone, N-formyl dapsone (NFD), N-acetyl dapsone (NAD), and dapsone hydroxylamine (DHA) were measured using validated liquid chromatography tandem mass spectrometry methods (LC-MS/MS).

2 Question-Based Review

2.1 General Attributes

2.1.1 What is dapsone?

Dapsone is a sulfone with anti-inflammatory and antimicrobial properties. 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:



Aczone Gel, 7.5% is an off-white to yellow aqueous gel with suspended drug particles for topical dermatologic use.

2.1.2 What are the proposed indication and dosing regimen for dapsone gel, 7.5%?

Aczone (dapsone) Gel, 7.5%, is indicated for the topical treatment of acne vulgaris in patients 12 years of age and older. The proposed dosing regimen is: after the skin is gently washed and patted dry, apply approximately a pea-sized amount of Aczone Gel, 7.5%, in a thin layer to the entire face once daily. In addition, a thin layer may be applied to other affected areas once daily. Rub in Aczone Gel, 7.5%, gently and completely.

2.1.3 What is acne vulgaris?

Acne vulgaris is the most common dermatological disorder in the US. Acne vulgaris is a complex skin disorder involving multiple abnormalities of the pilosebaceous unit, including 1) hyperkeratinization, 2) increased sebum production, 3) bacterial proliferation, and 4) inflammation. The face, anterior trunk, and upper back are the most commonly affected areas due to a greater concentration of sebaceous glands in these areas. Clinically, acne is graded according to the number and types of lesions present: open and closed comedones, inflammatory papules, pustules, cysts, nodules, and even scarring may be seen. Current topical and systemic therapies recommended for the treatment of acne include dapsone, retinoids, benzoyl peroxide, antibiotics, and hormonal therapy. However, most anti-acne medications do not act against all of the pathophysiological features of acne, so combination therapy is often used.

2.2 General Clinical Pharmacology

2.2.1 What were the design features of the clinical pharmacology and clinical trials used to support dapsone gel, 7.5%?

The clinical development program comprised 2 pivotal phase 3 studies (Studies 225678-006 and 225678-007), and 4 phase 1 studies including a pharmacokinetic study in patients with moderate acne vulgaris (Study 225678-004) and 3 dermal tolerability

studies in healthy subjects (Studies 225678-009, 225678-010, and 225678-011). An overview of the clinical development program is shown in Table 2.

Table 2: Clinical development program

Study No	Study Type	Treatment Regimen/ Randomization Ratio	Duration of Treatment	No. of Subjects/ Age Range (yrs)*	Primary Efficacy/Safety Measures
Phase 1 studies in male/female patients with moderate acne vulgaris					
225678-004	Investigator-blinded, active-controlled, safety, tolerability, and pharmacokinetics study	Dapsone 7.5% (formulations 11080X[a], 11078X, and 11079X) QD, and ACZONE 5% BID/ 1:1:1:1 ratio of 4 treatment groups	28 days	77/ 13 to 30	Lesion count (manual and automated), GAAS/AEs, local tolerability, physical exam, vital signs, 12-lead ECGs, lab tests, methemoglobin, serology, UPT
Phase 1 dermal safety studies in male/female healthy subjects					
225678-009	Repeated insult patch test with cumulative irritation test at induction	ACZONE 7.5%[a] versus vehicle under patch occlusion 3 times weekly for 21 days	~ 6 weeks	237/ 18 to 65	Assessment of irritation and contact sensitization, AEs, UPT
225678-010	Phototoxicity	ACZONE 7.5%[a] versus vehicle under patch occlusion	1 day	33/ 18 to 65	AEs, phototoxicity, local tolerability, physical examination, UPT
225678-011	Photoallergenicity	ACZONE 7.5%[a] versus vehicle Induction phase: two 24-hour patch applications per week x 3 weeks Challenge phase: one 24-hour patch application	~ 6 weeks	58/ 19 to 64	AEs, photoallergenicity, local tolerability, physical examination, UPT
Phase 3 studies in male/female patients with moderate acne vulgaris					
225678-006	Double-blind, vehicle-controlled, efficacy/safety (pivotal)	ACZONE 7.5%[a] versus vehicle QD/ 1:1 ratio of 2 treatment groups	12 weeks	2153/ 12 to 63	GAAS, lesion counts (entire face)/ local tolerability, AEs, physical exam, vital signs, UPT, concomitant medications
225678-007	Double-blind, vehicle-controlled, efficacy/ safety (pivotal)	ACZONE 7.5%[a] versus vehicle QD/ 1:1 ratio of 2 treatment groups	12 weeks	2238/ 12 to 61	GAAS, lesion counts (entire face)/ local tolerability, AEs, physical exam, vital signs, UPT, concomitant medications

AEs = adverse events; BID = twice-daily; CSR = clinical study report; ECGs = electrocardiograms; GAAS = Global Acne Assessment Score; No. = number; QD = once-daily; UPT = urine pregnancy test; yrs = years
* Actual number of patients enrolled in the study and age range
[a] ACZONE 7.5% (formulation 11080X) was selected for further development

2.2.2 What is the systemic bioavailability of dapsone gel, 7.5% under maximal use conditions and what is the relative bioavailability compared to Aczone (dapsone) Gel, 5%?

Study 225678-004 compared the PK of dapsone gel, 7.5% (formulation 11080X, to-be-marketed formulation) applied once-daily for 28 days with Aczone Gel, 5% applied twice-daily for 28 days in subjects (≥16 years of age) with acne vulgaris. Study medication was applied for 28 days to the skin of male and female patients with moderate acne vulgaris by the clinical site staff. For each application, study treatment (2 grams) was topically applied to the face, upper chest, upper back, and shoulders corresponding to a treatment area of approximately 1000 cm^2.

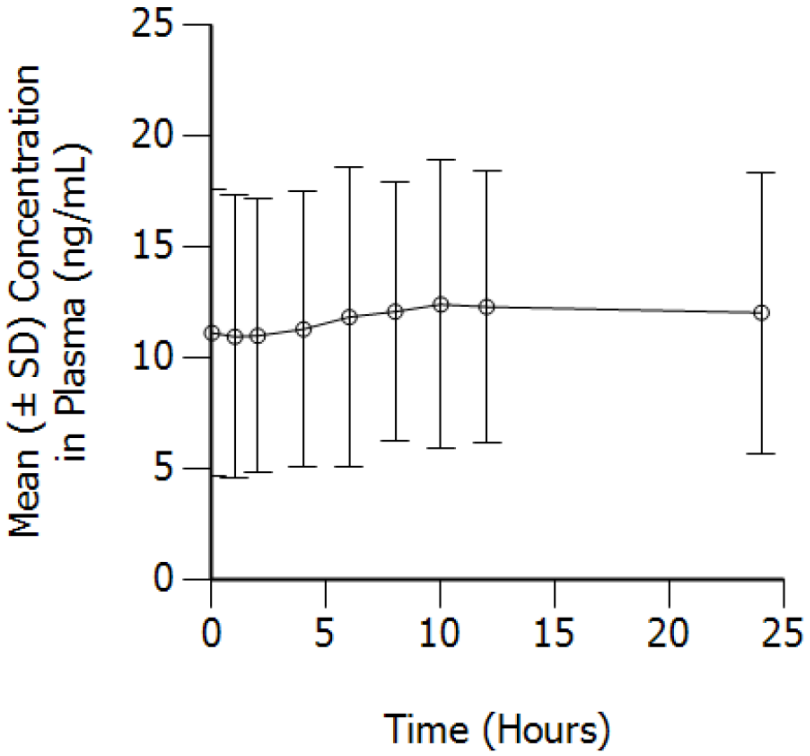
Mean Ctroughs for plasma dapsone were similar for days 7 - 28 suggesting steady state PK was achieved by Day 7 and maintained until Day 28. PK parameters for plasma dapsone following treatment with dapsone gel, 7.5% and Aczone Gel, 5% for 28 days are shown in Table 3 and the PK profile for dapsone gel, 7.5% is shown in Figure 1. PK parameters and PK profile for metabolites dapsone hydroxylamine (DHA) and N-acetyl dapsone (NAD) can be found in the Appendix. Plasma concentration of metabolite N-formyl dapsone (NFD) were measured but found to be below the lower limit of quantitation (0.100 ng/mL) for all subjects at all timepoints.

Relative to Aczone Gel, 5%, daily systemic exposure of dapsone, defined by the geometric mean ratio for maximum plasma concentration (Cmax) and area under the concentration-time curve from time 0 to 24 hours postdose (AUC0-24), was approximately 28.6% and 28.7% lower for formulation 11080X, respectively. Based on the 90% CIs for Cmax and AUC0-24, these differences were statistically significant; however, the upper limit of 90% CI were close to 100% (93% for Cmax and 92% for AUC0-24) and therefore the statistically significantly lower systemic exposure may not be clinically meaningful.

Table 3: Summary of plasma dapsone PK parameters following dosing on Day 28

PK parameter	Dapsone gel, 7.5% QD (TBM formulation 11080X) N=19	Aczone Gel, 5% BID N=18
Cmax (ng/mL)	13.0 ± 6.8	17.6 ± 6.7
AUC0-12 (ng*h/mL)	NA	186 ± 71
AUC0-24 (ng*h/mL)	282 ± 146	379 ± 142

Figure 1: Mean Plasma Concentrations of Dapsone (ng/mL) on Day 28 Following Once Daily Topical Application of dapsone gel, 7.5% (Formulation 11080X)



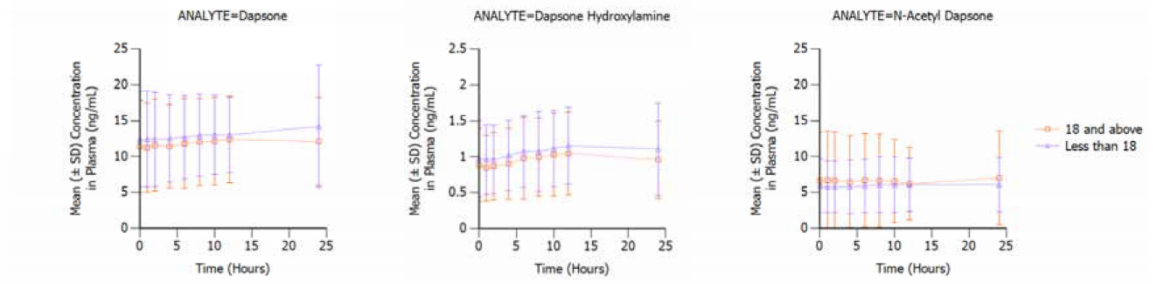
Note: This trial also include 2 additional treatment arms of other dapsone gel, 7.5% formulations, namely formulations 11078X and 11079X; however, these are pilot formulations that were not developed and they are not discussed further here. Please see Appendix for additional details.

2.3 Intrinsic Factors

2.3.1 What is the systemic exposure of dapsone gel, 7.5% in pediatrics?

Pharmacokinetic trial 225678-004 included pediatrics ≥16 years of age (7 of 19 in dapsone gel, 7.5% group and 6 of 18 in Aczone Gel, 5% group). The data showed similar systemic exposure to dapsone and its metabolites DHA and NAD between subjects 16-<18 years of age and those ≥18 years of age (Figure 2). In addition, Aczone Gel, 5% label indicates that systemic exposure is pediatrics 12 – 15 years of age is similar to those 16 years and older. Therefore, additional PK trial in subjects ages 12 -15 was not requested for dapsone gel, 7.5%.

Figure 2: Comparison of Plasma Concentrations of Dapsone, Dapsone Hydroxylamine, and N-Acetyl Dapsone (ng/mL) on Day 28 in subjects ≥18 years of age and subjects 16-17 years of age (all treatment groups combined)



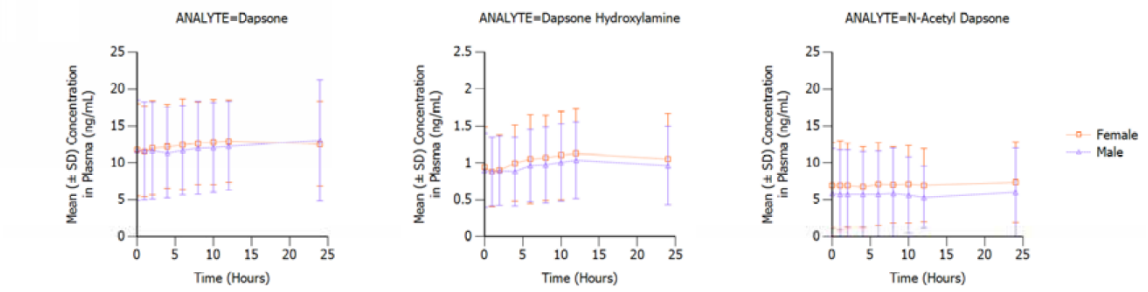
N = 47 to 48 subjects with age of 18 and above, and 24 subjects with age less than 18 per timepoint
SD = standard deviation

Because acne vulgaris do occur in children younger than 12 years of age, the Division of Dermatology and Dental Products recommends evaluation of subjects down to 9 years of age. As part of a post marketing requirement, the Applicant should evaluate the pharmacokinetic properties of dapsone gel, 7.5% in subjects 9 years to 11 years 11 months of age with acne vulgaris under maximal use conditions. The plan was discussed with the pediatric review committee (PeRC) on 12/2/2015 and the PeRC agreed.

2.3.2 What is the effect of sex on the systemic exposure of dapsone gel, 7.5%?

A comparison of the systemic exposure of dapsone and its metabolites DHA and NAD for all treatment arms combined showed that there was similar systemic exposure in male and females (Figure 3). This is consistent with the findings noted in the current label for Aczone Gel, 5%.

Figure 3: Comparison of Plasma Concentrations of Dapsone, Dapsone Hydroxylamine, and N-Acetyl Dapsone (ng/mL) on Day 28 in males and females (all treatment groups combined)



N = 35 to 36 male subjects and 36 female subjects per timepoint
SD = standard deviation

2.4 Extrinsic Factors

The applicant did not provide any information on the effect of extrinsic factors on the PK of dapsone gel, 7.5%. Because the systemic bioavailability of dapsone gel, 7.5% is similar to approved Aczone Gel, 5%, a request for additional studies is not warranted.

Drug-drug interactions:

The sponsor proposed to omit information contained in section 7.3 of Aczone Gel, 5% label regarding potential interaction with oral dapsone and enzyme inducers such as rifampin, anticonvulsants, St. Johns' wort or folic antagonist such as pyrimethamine that may lead to increased risk of hemolysis. Compared to oral dapsone, the risk of drug interactions is anticipated to be low due to much lower systemic concentration observed following topical dosing of Aczone Gel, 5% and 7.5%. However, because risk of methemoglobinemia has been reported following treatment with Aczone gel, 5% (Aczone Gel, 5% product label), such risk cannot be ruled out for dapsone gel, 7.5%. In addition, risk of hemolysis due to dapsone or its metabolites cannot be ruled out. Therefore, this reviewer concurs with the clinical team's recommendation that the interactions potential as noted in section 7.3 of the Aczone Gel, 5% label should be included in the label for dapsone gel, 7.5%.

2.5 General Biopharmaceutics

2.5.1 What is the formulation composition of dapsone gel, 7.5%?

Aczone Gel, 7.5% (11080X) is an off-white to yellow gel with suspended dapsone particles. The Aczone Gel, 7.5% formulation is packaged in an airless pump container closure system and provided in 30 g, 60 g, 90 g, (b) (4) fill sizes and 3 g professional sample tube. The composition is shown in Table 4.

Table 4: Composition of dapsone gel, 7.5%

Component	Function	Quality Standard	Concentration (% w/w)
Dapsone	Drug substance	USP	7.5
DGME	(b) (4)	NF	(b) (4)
(b) (4		Non-compendial	
MP		NF	
Purified Water		USP	

2.5.2 Was the to-be-marketed formulation used in the clinical trials?

Yes. The to-be-marketed dapsone gel 7.5% formulation (11080X) was used in all clinical studies, including the 2 phase 3 trials and the 4 phase 1 studies.

2.6 Analytical

2.6.1 What bioanalytical methods were used to assess dapsone and its metabolites N-acetyl dapsone, N-hydroxy dapsone and N-formyl dapsone and were they adequately validated?

Human plasma concentrations of dapsone, N-formyl dapsone (NFD), N-acetyl dapsone (NAD), and dapsone hydroxylamine (DHA) were measured using adequately validated liquid chromatography tandem mass spectrometry methods (LC-MS/MS). A summary of selected assay validation results are shown in Table 5.

Table 5: Summary of assay performance

Parameter	Dapsone	N-acetyl dapsone	N-hydroxy dapsone	N-formyl dapsone
Assay range	50 – 25,000 pg/mL	50 – 25,000 pg/mL	100 – 25,000 pg/mL	100 – 20,000 pg/mL
Intra-run precision	0.907 to 4.01%	0.602 to 7.32%	0.534 to 7.24%	1.47 to 8.38%
Intra-run accuracy	0.733 to 4.89%	-7.67 to -0.111	-7.78 to -1.68%	-3.68 to -2.06%
Inter-run precision	3.38 to 4.83%	1.68 to 5.45%	0.939 to 6.07%	2.15 to 7.04%
Inter-run accuracy	-3.36 to 2.96%	-4.81 to 0.500%	-5.76 to -2.92%	-2.07 to -3.38%
Long term storage stability	563 days at -80°C	563 days at -80ºC and 475 days at -20°C	563 days at -80°C (required wider 75% -125% threshold to pass stability)	97 days at -80ºC and -20°C

Note: assay for N-hydroxy dapsone (aka dapsone hydroxylamine) used more relaxed criteria of accuracy within ±25% at each QC and ±30% at LLOQ due to the unstable nature of the analyte.

Storage stability:
Study samples from Study 225678-004 were analyzed within the demonstrated long-term sample stability duration for each analyte. Samples were stored at -70ºC for up to 80 days before analysis for dapsone, NAD, and DHA concentrations. Long-term stability has been established for dapsone, NAD, and DHA in human plasma for 563 days at -70ºC. In addition, samples from Study 225678-004 were stored at -70ºC for up to 97 days before analysis for NFD concentrations, and long-term stability has been established for NFD in human plasma for 97 days at -70ºC.

3 Detailed Labeling Recommendations

The following changes are recommended for sections 5, 7 and 12 of the label. Deletions are noted as ~~strikethrough~~ and additions are noted as double underline.

5 WARNINGS AND PRECAUTIONS

5.1 Hema (b) (4)

Oral dapsone treatment has produced dose-related hemolysis and hemolytic anemia. Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more prone to hemolysis with the use of certain drugs. G6PD deficiency is most prevalent in populations of African, South Asian, Middle Eastern, and Mediterranean ancestry.

In clinical studies, there was no evidence of clinically relevant hemolysis or hemolytic anemia in patients treated with topical dapsone. Some patients with G6PD deficiency using twice daily dapsone gel, 5%, developed laboratory changes suggestive of mild hemolysis (b) (4)
(b) (4)

Combination of topical dapsone with trimethoprim/sulfamethoxazole (TMP/SMX) may increase the likelihood of hemolysis in patients with G6PD deficiency.

(b) (4)

If signs and symptoms suggestive of hemolytic anemia (b) (4) occur,
(b) (4)

ACZONE® Gel, 7.5% (b) (4) in patients who are taking oral dapsone or antimalarial medications because of the potential for (b) (4) hemolytic reactions.

7 DRUG INTERACTIONS

(b) (4)

No formal drug-drug interaction studies were conducted with **ACZONE®** Gel, 7.5%.

7.1 Trimethoprim-Sulfamethoxazole

A drug-drug interaction study evaluated the effect of the use of dapsone gel, 5% 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 dapsone and its metabolites increased in the presence of TMP/SMX. The systemic exposure from **ACZONE®** Gel, 7.5% is expected to be about 1% of that from the 100 mg oral dose, even when co-administered with TMP/SMX.

7.2 Topical Benzoyl Peroxide

Topical application of dapsone gel followed by benzoyl peroxide in patients with acne vulgaris may result in a temporary local yellow or orange discoloration of the skin and facial hair.

7.3 Drug Interactions with Oral Dapsone

Certain concomitant medications (such as rifampin, anticonvulsants, St. John's wort) may increase the formation of dapsone hydroxylamine, a metabolite of dapsone associated with hemolysis. With oral dapsone treatment, folic acid antagonists such as pyrimethamine have been noted to possibly increase the likelihood of hematologic reactions.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

(b) (4)

(b) (4) The mechanism of action of dapsone gel in treating acne vulgaris is not known.

12.3 Pharmacokinetics

In a pharmacokinetic study, male and female subjects 16 years of age or older with acne vulgaris (N=19) (b) (4) received 2 grams of **ACZONE** Gel, 7.5%, topically to the (b) (4) face, upper chest, upper back and shoulders once daily for 28 days (b) (4) (b) (4). Steady state for dapsone was reached within 7 days of dosing. On Day 28, the mean dapsone maximum plasma concentration (Cmax) and area under the concentration-time curve from 0-24 hours post dose (AUC_{0-24h}) were 13.0 ± 6.8 ng/mL and (b) (4) 282 ± 146 ng·h/mL, respectively (b) (4)

(b) (4)

[redacted] The systemic exposure from **ACZONE®** Gel, 7.5% is expected to be about 1% of that from a 100 mg oral dose.

Long-term safety studies were not conducted with **ACZONE®** Gel, 7.5%, however, in a long-term clinical study of [redacted] dapsone gel, 5%, periodic blood samples were collected up to 12 months to determine systemic exposure of dapsone and its metabolites in approximately 500 [redacted]. Based on the measurable dapsone concentrations from 408 patients (M=192, F=216), obtained at month 3, neither gender nor race appeared to affect the pharmacokinetics of dapsone. Similarly, dapsone exposures were approximately the same between the age groups of 12-15 years (N=155) and those greater than or equal to 16 years (N=253). There was no evidence of increasing systemic exposure to dapsone over the study year in these [redacted].

4 Appendix

4.1 Individual Study Reviews

Maximal use PK Trial 225678-004

Title:
Safety, Tolerability, and Pharmacokinetics of Dapsone Dermal Formulations in Subjects with Acne Vulgaris

Study Centers:
There were a total of 2 study sites in the United States (US).

Study period:
Study Initiation Date (First Subject Enrolled): 21 January 2013
Study Completion Date (Last Subject Completed): 13 May 2013

Objectives:
To evaluate the safety and tolerability of 3 dapsone 7.5% gel formulations dosed once daily, and dapsone 5% gel (ACZONE® 5% Gel) dosed twice daily following 28 days repeat topical administration in male and female subjects with moderate acne vulgaris.

To evaluate the pharmacokinetics of dapsone and dapsone metabolites following 28 days repeat topical administration of 3 dapsone 7.5% gel formulations dosed once daily, and ACZONE 5% Gel dosed twice daily in male and female subjects with moderate acne vulgaris.

To explore efficacy measures.

Design:
This study was a multicenter, randomized, investigator-blinded, active-controlled, multiple-dose, parallel-group study that evaluated the safety, tolerability, and pharmacokinetics of 3 dapsone 7.5% gel formulations (dosed once daily) and ACZONE 5% gel (dosed twice daily) in male and female subjects with moderate acne vulgaris. Eligible subjects were randomized to 1 of the 4 treatment groups (in a 1:1:1:1 allocation ratio) to receive 1 of 3 dapsone 7.5% formulations, or ACZONE 5% gel; subjects were stratified by gender and age group. Study medication was applied to the subject's entire face, upper chest, upper back, and shoulders. The total surface area covered by the study medication was approximately 1000 cm^2 for each study medication application administered by the drug administrator (or designee). Subjects were to be administered study medication on days 1 to 28, were scheduled for daily clinic visits for study procedures on days 29 to 34 (during which they received no study medication), and exited the study on day 35.

Number of subjects:
Approximately 72 subjects were planned for this study. A total of 77 subjects (41 males and 36 females) were enrolled.

Inclusion criteria:
Adolescent and adult male and female subjects who were 16 to 35 years of age; subjects with a minimum weight of 35 kg, and a body mass index (BMI) of ≥ 15 and ≤ 30 kg/m^2 (if BMI was > 30 to ≤ 35 kg/m^2, waist circumference must have been below 40 inches for male and 35 inches for female); subjects with a minimum of 20 but not more than 50 inflammatory lesions (papules and pustules) on the face (excluding the nose); subjects with a minimum of 30 but not more than 100 noninflammatory lesions (open comedones and closed comedones) on the face (excluding the nose); and subjects with a score of 3 (moderate) on the Global Acne Assessment Scale (GAAS).

Test Product, Dose and Mode of Administration, Batch Number:
Dapsone 7.5% gel, 2 g applied topically; formulation number 11078X, batch ENB-C (herein referred to as DAP-11078)

Dapsone 7.5% gel, 2 g applied topically; formulation number 11079X, batch ENC-1C (herein referred to as DAP-11079)

Dapsone 7.5% gel, 2 g applied topically; formulation number 11080X, batch ENA-1C (herein referred to as DAP-11080)

Reference Therapy, Dose and Mode of Administration, Batch Number:
ACZONE (dapsone 5% gel), 2 g applied topically; batch END-C

Duration of Treatment: 28 days

Pharmacokinetic assessment:
Plasma concentrations of dapsone, its metabolites (NAD and DHA), and NFD were collected prior to administration of the morning dose on days 1, 7, 14, 18, 21, 26, 27, on day 28 (predose, 1, 2, 4, 6, 8, 10, and 12 hours postdose), on days 29 to 32 (24, 30, 36, 48, 72, and 96 hours after the last dose), on day 35 (168 hours after the last dose), and early exit (if applicable), and were determined using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods.

Assay method validation: See section 2.6 of this review.

Results:

Subject disposition:
A total of 77 subjects were enrolled and randomized into 1 of 4 treatment groups: DAP-11078 (20 subjects), DAP-11079 (19 subjects), DAP-11080 (19 subjects), and ACZONE (19 subjects), and had at least 1 study medication administration. All 77 subjects had at least 1 application of study medication; therefore all subjects were included in the safety population. Five subjects aged between 12 and 15 years old were discontinued from the study following Protocol Amendment 2 which excluded subjects 12 to 15 years old. The remaining 72 subjects completed the study as scheduled.

Two subjects were excluded from the PP population; 1 subject missed more than 20% of the study visits (Subject 1002-1597, DAP-11078 treatment arm) and the second subject had taken prohibited medication for 15 days during the treatment period (subject 1002-1552, Dapsone 5% gel treatment arm). Therefore, 70 subjects were included in the PP population. However, both subjects were included in the PK population. Subject 1002-1552 had AUC0-24 of 394 ng*hr/mL and Cmax of 18 ng/mL, which were similar to the means for Dapsone 5% gel arm, suggesting that its inclusion would not alter the results. Subject 1002-1597 had AUC0-24 of 164 ng*hr/mL, which was lower than the mean of 235 ng*hr/mL for the DAP-1078 treatment arm and may lower the group mean by several units; this was not followed up further because DAP-1078 is not the proposed to-be-marketed formulation.

The mean percentage BSA treated was similar among all four treatment groups: 5.5% in the DAP-11079 treatment group, 5.7% in the DAP-11078 and ACZONE treatment groups, and 5.8% in the DAP-11080 treatment group.

Subject disposition and demographic information are shown in Tables 6 and 7, respectively. Note that data in Table 7 includes the 5 pediatric subjects 12 – 15 years of age that were discontinued due to a change in protocol. Of relevant to the current NDA, the Aczone 5% gel arm had 1 subject discontinued; therefore the number of pediatric subjects in the PK population was 6 instead of the 7 listed in that table. No subjects were discontinued in the to-be-marketed formulation DAP-11080 treatment arm.

Table 6: Subject disposition (Safety population)

Disposition	Treatment Group				Total
	DAP-11078 (N = 20)	DAP-11079 (N = 19)	DAP-11080 (N = 19)	ACZONE (N = 19)	(N = 77)
Enrolled	20	19	19	19	77
Completed	17 (85.0%)	18 (94.7%)	19 (100%)	18 (94.7%)	72 (93.5%)
Discontinued[a]	3 (15.0%)	1 (5.3%)	0	1 (5.3%)	5 (6.5%)

[a] 5 subjects between 12 and 15 years of age were discontinued due to a protocol amendment.

Table 7: Demographic and baseline characteristics (Safety population)

Characteristics	Attributes	Treatment Group DAP-11078 (N = 20)	DAP-11079 (N = 19)	DAP-11080 (N = 19)	ACZONE (N = 19)	Total (N = 77)
Age (years)	Mean	19.2	18.8	20.7	19.4	19.5
	SD	4.15	3.35	4.43	3.74	3.93
	Median	19.0	18.0	20.0	19.0	19.0
	Min	13	14	16	14	13
	Max	30	30	29	27	30
	12 to 17 years	8 (40.0%)	7 (36.8%)	7 (36.8%)	7 (36.8%)	29 (37.7%)
	18 to 35 years	12 (60.0%)	12 (63.2%)	12 (63.2%)	12 (63.2%)	48 (62.3%)
Sex	Male	12 (60.0%)	10 (52.6%)	9 (47.4%)	10 (52.6%)	41 (53.2%)
	Female	8 (40.0%)	9 (47.4%)	10 (52.6%)	9 (47.4%)	36 (46.8%)
Race	Caucasian	11 (55.0%)	16 (84.2%)	12 (63.2%)	10 (52.6%)	49 (63.6%)
	Non-Caucasian	9 (45.0%)	3 (15.8%)	7 (36.8%)	9 (47.4%)	28 (36.4%)
	Black	2 (10.0%)	0 (0.0%)	1 (5.3%)	1 (5.3%)	4 (5.2%)
	Asian	0 (0.0%)	0 (0.0%)	2 (10.5%)	1 (5.3%)	3 (3.9%)
	Hispanic	3 (15.0%)	0 (0.0%)	1 (5.3%)	4 (21.1%)	8 (10.4%)
	Other[a]	4 (20.0%)	3 (15.8%)	3 (15.8%)	3 (15.8%)	13 (16.9%)
Height (cm)	Mean	170.1	172.7	168.4	167.7	169.7
	SD	10.25	9.52	9.84	8.86	9.64
	Median	171.0	172.0	167.0	165.0	170.0
	Min	153	149	154	154	149
	Max	188	188	188	182	188
Weight (kg)	Mean	69.0	70.4	66.6	66.6	68.1
	SD	10.96	12.65	16.69	14.19	13.57
	Median	69.0	68.0	64.0	63.0	67.0
	Min	50	53	44	44	44
	Max	85	105	107	111	111
BMI (kg/m^2)	Mean	23.86	23.68	23.25	23.65	23.61
	SD	2.984	4.142	3.767	4.029	3.681
	Median	23.80	22.00	23.00	22.90	23.00
	Min	17.4	18.5	18.3	17.6	17.4
	Max	29.9	33.1	31.3	33.2	33.2

Pharmacokinetics:

Plasma concentration of dapsone and its metabolites NAD and DHA were measurable and their PK properties are described below. PK parameters estimates are shown in Table 9 and mean concentration versus time profiles are shown in Figures 4 – 6. Plasma concentrations of metabolite NFD were found to be below the lower limit of quantitation (0.100 ng/mL) for all subjects at all timepoints.

Relative to ACZONE 5% gel, the mean systemic exposures of dapsone was approximately 25% to 40% lower for the 3 dapsone 7.5% gel formulations. Among the dapsone 7.5% gel formulations, the highest exposure of dapsone in terms of AUC was

observed with the to-be-marketed formulation (DAP-11080), with respective mean Cmax and AUC0-24 being approximately 28.6% and 28.7% lower relative to ACZONE 5% gel (Table 9).

Mean Tmax for dapsone and its metabolites (NAD and DHA) was similar between each treatment group, with values ranging from 10.3 to 16.1 hours. Plasma concentrations of dapsone and its metabolites declined slowly after the last administration on day 28 for each treatment group, with mean terminal $T_{1/2}$ values ranging from 39.2 to 54.7 hours (Table 9). Base on assessment of Ctroughs, steady-state for all 3 analytes appeared to be reached within 7 days of dosing in all 4 treatment groups (data not shown). Ctrough values for dapsone were similar across Days 7 – 28 suggesting that the PK parameter estimates on Day 28 is representative of steady state (Table 8).

Mean plasma concentrations of dapsone, NAD, and DHA following once daily administration of the 3 dapsone 7.5% gel formulations (DAP-11078, DAP-11079, and DAP-11080) were lower than those following twice daily administration of ACZONE 5% gel. Relative to ACZONE 5% gel given twice daily, daily systemic exposure of dapsone, as defined by the geometric mean ratio for Cmax and AUC0-24, was approximately 36.1% and 40.4% lower for DAP-11078, 25.4% and 31.9% lower for DAP-11079, and 28.6% and 28.7% lower for DAP-11080, respectively. Based on the 90% CIs for Cmax and AUC0-24, these differences were statistically significant; however, the upper limit of 90% CI were close to 100% (93% for Cmax and 92% for AUC0-24 of to-be-marketed formulation DAP-11080, Table 9) and therefore the statistically significantly lower systemic exposure may not be clinically meaningful.

Table 8: Mean Plasma Concentrations of Dapsone (ng/mL) Following Once Daily Topical Dermal Administration of Three Different Dapsone 7.5% Gel Formulations (DAP-11078, DAP-11079 and DAP-11080) and Twice Daily Topical Dermal Administration of Dapsone 5% Gel (ACZONE) for 28 Days in Subjects with Acne Vulgaris

Day	Time (hr)	Plasma Concentrations of Dapsone (ng/mL)							
		Dapsone 5% Gel BID (ACZONE) N=19		Dapsone 7.5% Gel QD (DAP-11078) N=20		Dapsone 7.5% Gel QD (DAP-11079) N=19		Dapsone 7.5% Gel QD (DAP-11080) N=19	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
1	0	BLQ	NC	BLQ	NC	BLQ	NC	BLQ	NC
7	0	17.3	6.6	10.4	4.6	10.1	3.7	10.7	5.7
14	0	17.6	7.9	10.5	6.3	11.0	4.9	11.7	5.6
18	0	22.2	18.2	9.38	4.85	11.3	6.2	10.5	5.4
21	0	17.6	7.9	9.83	4.59	10.5	5.4	11.1	5.5
26	0	17.2	7.8	8.41	4.36	10.3	5.0	10.4	5.8
27	0	16.6	7.8	9.17	4.44	11.4	6.6	10.5	5.9
28	0	16.7	6.9	9.04	4.54	9.94	4.92	11.1	6.5
	1	16.5	6.8	8.88	4.29	9.90	4.78	11.0	6.4
	2	16.3	6.7	9.38	5.20	10.7	5.5	11.0	6.1
	4	16.0	6.2	10.1	4.8	9.60	3.96	11.3	6.2
	6	16.0	6.1	9.51	4.65	10.9	4.7	11.9	6.8
	8	16.3	6.4	9.93	4.74	10.9	4.7	12.1	5.8
	10	16.0	5.8	10.1	4.9	11.1	4.8	12.4	6.5
	12	15.9	5.7	10.4	5.0	11.7	4.8	12.3	6.1
29	24	16.4	6.2	10.0	5.2	12.6	8.8	12.1	6.3
	30	15.2	5.8	9.13	4.71	9.89	4.11	11.3	6.5
	36	14.2	5.7	8.13	4.23	8.58	3.81	9.97	5.70
30	48	12.2	4.9	6.92	3.71	7.48	3.49	8.62	5.15
31	72	8.54	3.93	4.54	2.96	4.94	2.29	5.87	3.80
32	96	6.41	2.87	2.96	1.91	3.06	1.66	4.51	3.25
35	168	2.42	1.18	1.08	0.82	1.04	0.55	1.78	1.43

BLQ = Below Limit of Quantitation; NC = Not Calculable. N = 15-20 subjects/timepoint/group

Table 9: Plasma Pharmacokinetic Parameters of Dapsone, N-Acetyl Dapsone, and Dapsone Hydroxylamine

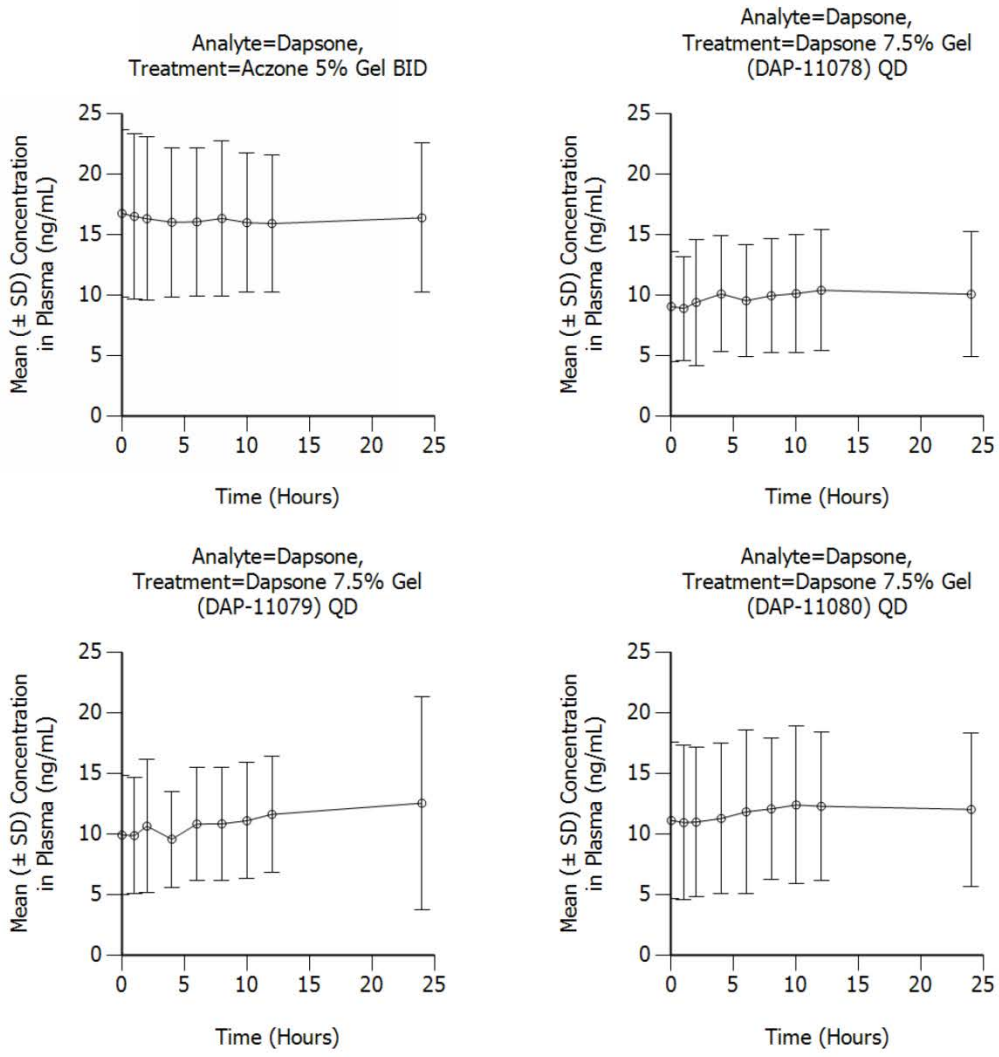
Analyte	Pharmacokinetic Parameters on Day 28	Dapsone 5% Gel Twice Daily (ACZONE) (N = 18)		Dapsone 7.5% Gel Once Daily (DAP-11078) (N = 17)		Dapsone 7.5% Gel Once Daily (DAP-11079) (N = 18)		Dapsone 7.5% Gel Once Daily (DAP-11080) (N = 19)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Dapsone	T_{max} (hr)	12.7	12.0	10.8	7.3	10.7	8.2	10.6	7.5
	C_{max} (ng/mL)	17.6	6.7	11.7	5.5	14.1	8.8	13.0	6.8
	AUC_{0-12} (ng·hr/mL)	186	71	NA		NA		NA	
	AUC_{0-24} (ng·hr/mL)	379	142	235	112	266	114	282	146
	$T_{1/2}$ (hr)	51.3	17.1	45.2	11.4	42.2	9.2	51.4	12.4
	GMR for C_{max}	NA		63.9 (48.7, 84.0)*		74.6 (57.0, 97.6)*		71.4 (54.8, 93.1)*	
	GMR for AUC_{0-24}	NA		59.6 (46.0, 77.2)*		68.1 (52.8, 87.9)*		71.3 (55.5, 91.7)*	
N-Acetyl Dapsone	T_{max} (hr)	13.0	12.5	14.4	8.7	11.8	9.4	14.0	10.2
	C_{max} (ng/mL)	11.7	8.8	5.44	4.25	6.00	3.85	6.47	5.43
	AUC_{0-12} (ng·hr/mL)	118	88	NA		NA		NA	
	AUC_{0-24} (ng·hr/mL)	236	168	111	84	120	74	135	111
	$T_{1/2}$ (hr)	52.2	20.3	44.2	11.2	43.6	11.0	49.6	11.2
	GMR for C_{max}	NA		42.4 (26.9, 66.8)*		53.7 (34.3, 84.1)*		50.6 (32.5, 78.8)*	
	GMR for AUC_{0-24}	NA		42.6 (27.3, 66.5)*		52.9 (34.1, 81.9)*		51.5 (33.4, 79.3)*	
Dapsone Hydroxylamine	T_{max} (hr)	16.1	8.2	11.9	8.7	10.3	7.3	12.1	8.0
	C_{max} (ng/mL)	1.47	0.56	0.908	0.433	1.11	0.46	1.19	0.76
	AUC_{0-12} (ng·hr/mL)	15.0	5.7	NA		NA		NA	
	AUC_{0-24} (ng·hr/mL)	31.1	11.6	17.4	7.9	22.0	9.3	24.5	15.6
	$T_{1/2}$ (hr)	54.7	21.4	39.2[a]	14.0	42.5	17.8	53.9	25.6
	GMR for C_{max}	NA		60.4 (44.7, 81.8)*		77.6 (57.6, 105)		77.2 (57.5, 104)	
	GMR for AUC_{0-24}	NA		55.0 (40.7, 74.3)*		72.6 (54.0, 97.7)*		75.0 (56.0, 100)	

AUC_{0-24} = area under the plasma concentration-time curve from time 0 to 24 hours postdose; C_{max} = maximum plasma concentration; GMR = geometric mean ratio (relative to ACZONE 5% twice daily); hr = hours; NA = not applicable; SD = standard deviation; $T_{1/2}$ = mean terminal half-life; T_{max} = mean time to maximum plasma concentration

* statistically significant

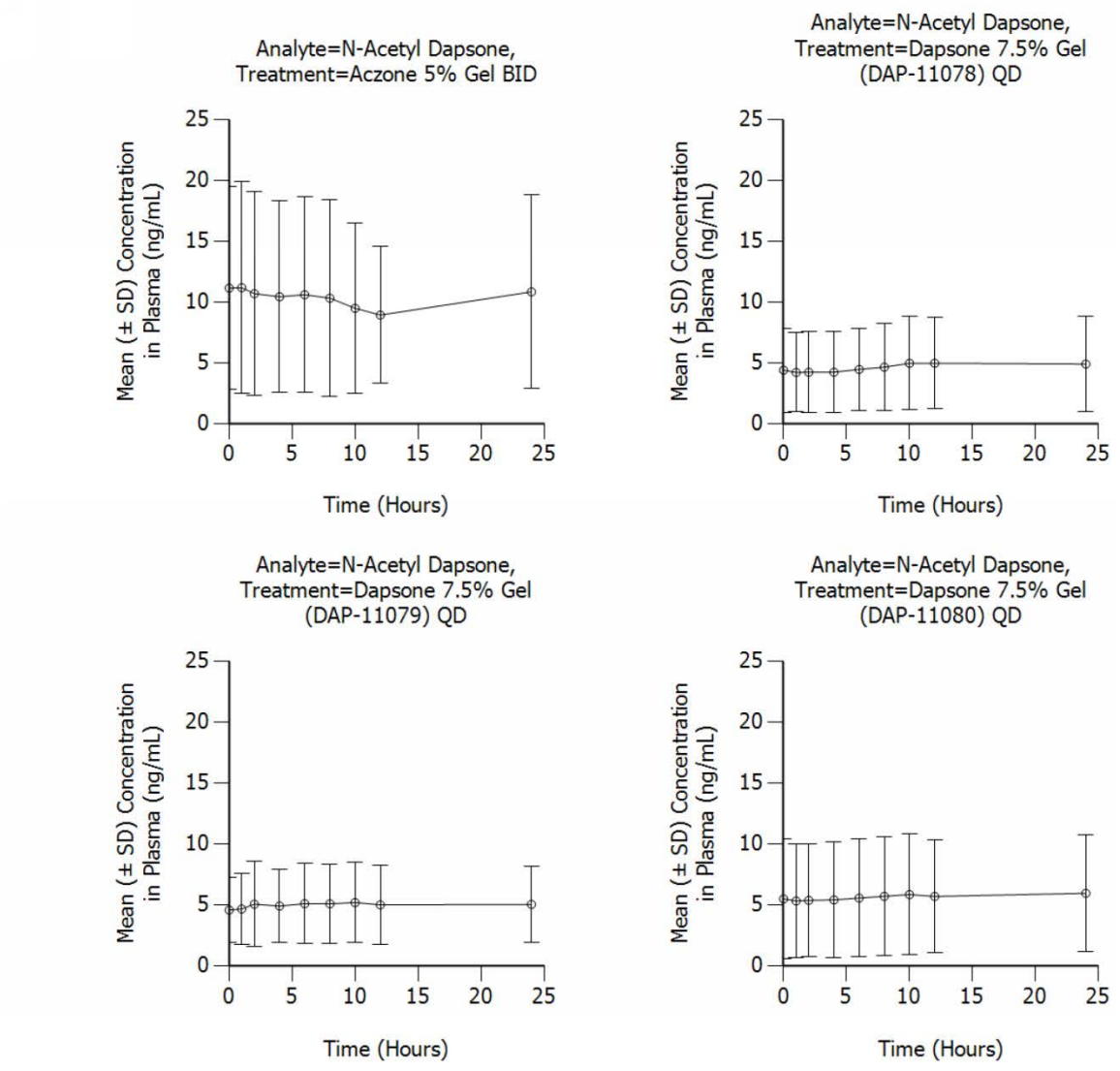
[a] N = 16

Figure 4: Plasma Concentrations of Dapsone (ng/mL) on Day 28



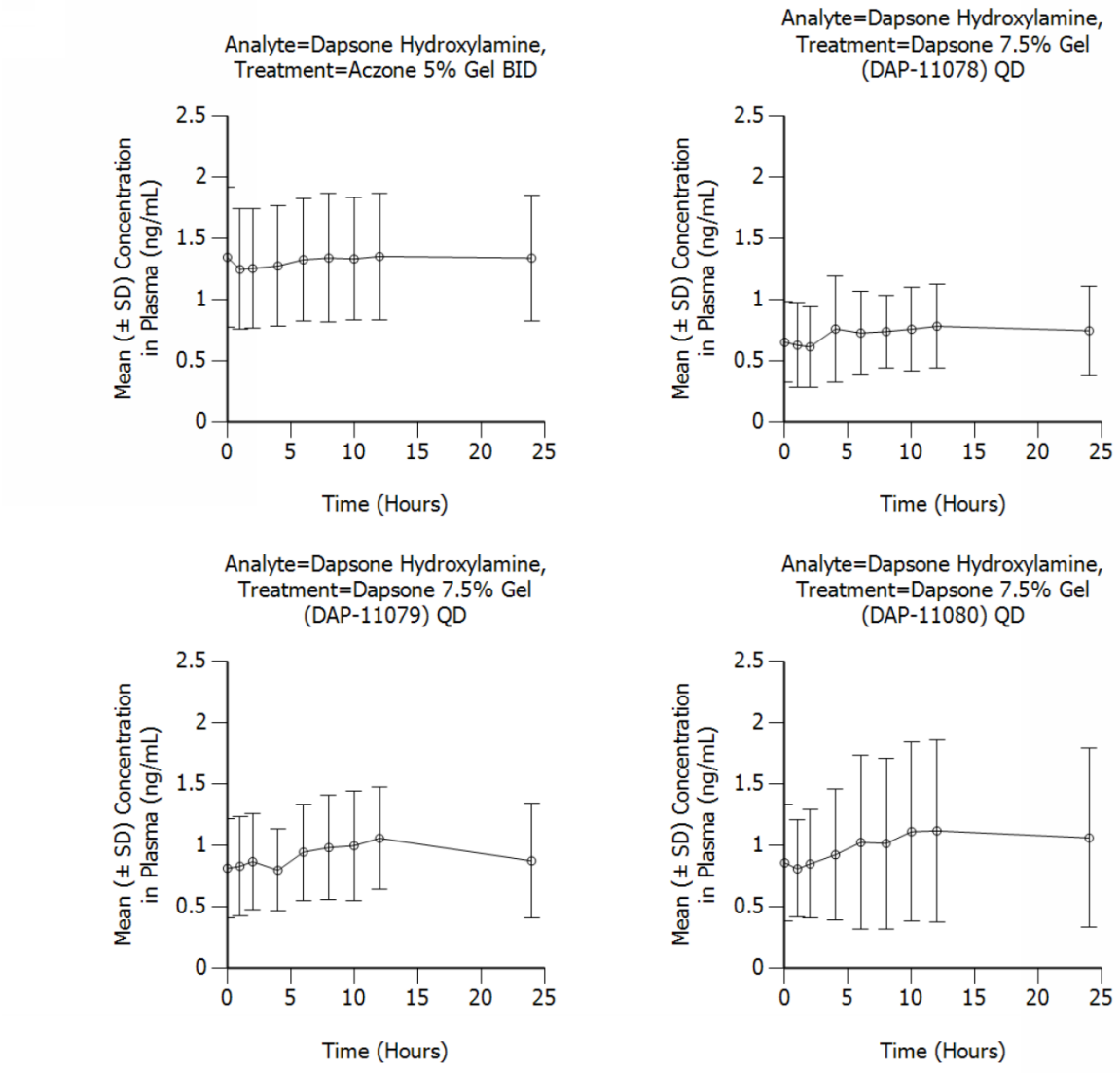
N = 17 to 19 subjects/timepoint/treatment group
BID = twice daily; QD = once daily; SD = standard deviation

Figure 5: Plasma Concentrations of N-Acetyl Dapsone (ng/mL) on Day 28



N = 17 to 19 subjects/timepoint/treatment group
BID = twice daily; QD = once daily; SD = standard deviation

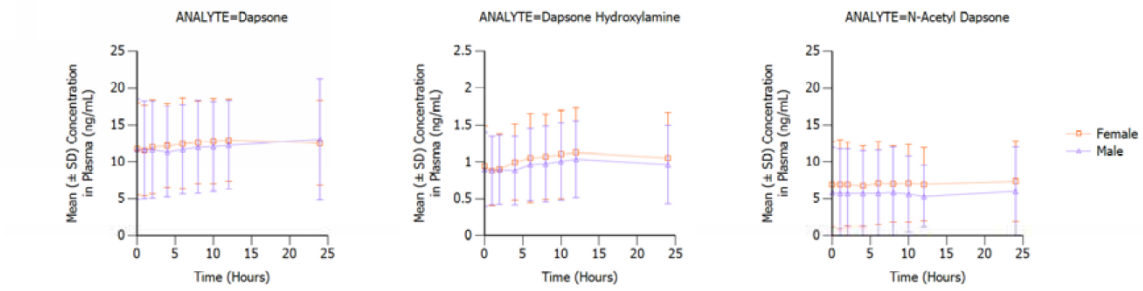
Figure 6: Plasma Concentrations of Dapsone Hydroxylamine (ng/mL) on Day 28



N = 17 to 19 subjects/timepoint/treatment group
BID = twice daily; QD = once daily; SD = standard deviation

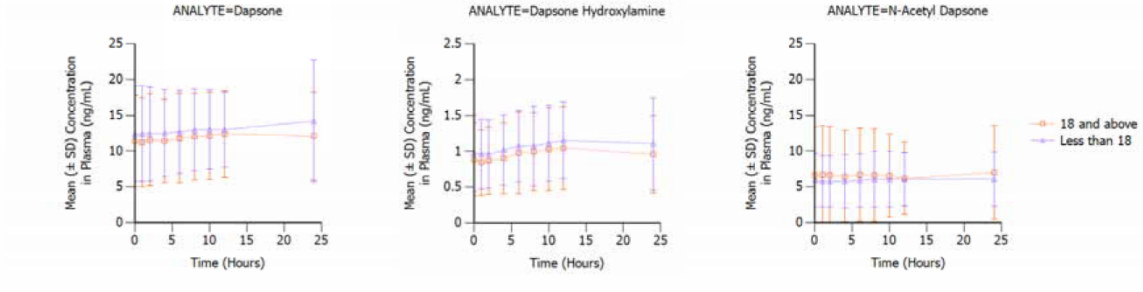
Effects of sex and age on PK:
Consistent with ACZONE 5% gel label, it did not appear that there were clinically significant effects of sex or age (age < 18 compared to age ≥ 18) on the plasma concentrations of dapsone following once daily topical dermal administration of the dapsone 7.5% gel formulations (Figures 7 and 8, respectively).

Figure 7: Comparison of Plasma Concentrations of Dapsone, Dapsone Hydroxylamine, and N-Acetyl Dapsone (ng/mL) on Day 28 in males and females (all treatment groups combined)



N = 35 to 36 male subjects and 36 female subjects per timepoint
SD = standard deviation

Figure 8: Comparison of Plasma Concentrations of Dapsone, Dapsone Hydroxylamine, and N-Acetyl Dapsone (ng/mL) on Day 28 in subjects ≥18 years of age and subjects 16-17 years of age (all treatment groups combined)



N = 47 to 48 subjects with age of 18 and above, and 24 subjects with age less than 18 per timepoint
SD = standard deviation

Safety and Efficacy:
Please see Clinical review.

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/s/

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