CLINICAL REVIEW

Application Type	NDA
Application Number(s)	207154
Priority or Standard	Standard
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Division / Office	DDDP/ODEIII
Reviewer Name(s)	Patricia C. Brown, MD
Review Completion Date	January 20, 2016
Established Name	Dapsone gel, 7.5%
(Proposed) Trade Name	ACZONE® Gel, 7.5%
Therapeutic Class	Acne agent
Applicant	Allergan, Inc.
Formulation(s)	Gel
Dosing Regimen	Once daily
Indication(s)	Topical treatment of acne vulgaris
Intended Population(s)	Patients 12 years of age and older

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends an approval action for the current NDA 207154, ACZONE ® (dapsone) Gel, 7.5% for the topical treatment of acne vulgaris in patients 12 years of age and older.

1.2 Risk Benefit Assessment

The applicant, Allergan, Inc., has submitted a 505(b)1 New Drug Application for ACZONE ® (dapsone) Gel, 7.5%. The drug product proposed in this application is a topical gel formulation containing 7.5% dapsone and intended for once daily application. ACZONE® (dapsone) Gel, 5% was approved July 7, 2005 (NDA 21794) and is currently marketed in the US for twice daily topical treatment of acne vulgaris.

To demonstrate efficacy, the applicant submitted data from two identically designed Phase 3 pivotal trials, trial 225678-006 and 225678-007 (Trials 006 and 007). These were multicenter, double-blind, randomized, parallel-group, vehicle-controlled, 12-week trials. Trials 006 and 007 were conducted in 96 and 93 US centers and 9 and 10 Canadian centers, respectively. To enroll in these trials, subjects must have been 12 years of age or older and had a Global Acne Assessment Score (GAAS) of 3 (moderate). They also must have had 20-50 inflammatory lesions (papules and pustules) and 30-100 non-inflammatory lesions (open comedones and closed comedones) on the face. Subjects applied study product to their entire face once daily for 12 weeks. Subjects also topically administered the study product once daily to acne-affected areas within reach on the neck, shoulders, upper back, and/or upper chest. The latter areas were not considered in the analysis of efficacy; however, they were considered in the analysis of safety for the pivotal trials.

In both pivotal trials the protocol specified co-primary efficacy endpoints included the proportion of subjects achieving a score of 0 (none) or 1 (minimal) on the GAAS at Week 12 and the absolute change in inflammatory and non-inflammatory lesion counts from baseline to Week 12. In both trials 006 and 007, ACZONE Gel, 7.5% was statistically superior (p-values ≤ 0.004) to vehicle gel on all three co-primary efficacy endpoints.

For the secondary endpoints which included, percent change in inflammatory and non-inflammatory lesion counts from baseline to Week 12, ACZONE Gel, 7.5% was statistically superior (p-values ≤ 0.001) to vehicle gel in both trials.

The principal evaluation of safety for ACZONE ® (dapsone) Gel, 7.5%, for the indication of topical treatment of acne vulgaris in patients 12 years of age and older, was based on trials that included subjects treating acne vulgaris on the face once daily for 12 weeks. The trials in the pooled safety database include trial **225678-006** (pivotal Phase 3, 2-arm vehicle controlled) and trial **225678-007** (pivotal Phase 3, 2-arm vehicle controlled). Additional safety information is available from the four trials; **225678-004** pharmacokinetic (PK, Phase 1, 4-arm, active controlled), **225678-009** dermal safety (Phase 1, RIPT sensitization), **225678-010** dermal safety (Phase 1, phototoxicity), and **225678-011** dermal safety (Phase 1, photoallergy). All of the trials were conducted with the final-to-be-marketed formulation. (Trial 225678-004, pharmacokinetic, included one arm with the final-to-be-marketed formulation.)

No deaths were reported in any of the six clinical trials. For the pooled trials, in the ACZONE Gel, 7.5% group, 7 of 2175 subjects (0.3%) had a total of 8 serious treatment emergent adverse events (TEAEs). These were application site dermatitis (33 days after treatment), appendicitis (46 days after treatment), tibia fracture 34 days after treatment), acute myeloid leukemia (42 days after treatment), helicobacter pylori infection (19 days after treatment), appendicitis, peritoneal hematoma (50 and 53 days, respectively after treatment), and alcoholism (28 days after treatment). The 8 serious TEAEs were considered not related to treatment with ACZONE Gel, 7.5%.

For the pooled trials, in the vehicle group: 9 of 2175 subjects (0.4%) had a total of 9 serious TEAEs. These were induced abortion (85 days after treatment), lumbar vertebral fracture (62 days after treatment), affective disorder (56 days after treatment), depression (75 days after treatment), anxiety (36 days after treatment), spontaneous pneumothorax (36 days after treatment), appendicitis (62 days after treatment), spontaneous abortion (16 days after treatment) and suicidal ideation (16 days after treatment). One serious TEAE, depression, was considered related to study medication (in this case vehicle).

For the pivotal trials, in the ACZONE gel, 7.5% group, 6 of 2161 subjects (0.3%) had adverse events (TEAEs) leading to discontinuation. Of the TEAEs that led to discontinuation in subjects in the ACZONE group, 7 that occurred in 3 subjects were considered to be treatment related by the investigator. These events included application site acne and application site dermatitis in 1 subject; application site vesicles, application site swelling, application site pruritus, and pruritus in 1 subject; and application site discomfort (described as mild in severity) in 1 subject.

For the pivotal trials, in the vehicle group: 7 of 2175 subjects (0.3%) had adverse events (TEAEs) leading to discontinuation. Of the TEAEs that led to discontinuation in patients in the vehicle group, 3 TEAEs that occurred in 3 subjects in the vehicle group were considered to be treatment related by the investigator. These events included application site pain (described as mild in severity) in 2 subjects and application site acne (described as severe) in 1 subject.

Treatment-related TEAEs, or adverse drug reactions, were reported in 3.5% (75/2161) of subjects in the ACZONE Gel, 7.5% group and 3.4% (73/2175) of patients in the vehicle group. The most common treatment related TEAEs (i.e., those occurring in ≥ 0.9% of subjects and at a rate greater than vehicle) were application site events: application site dryness (1.1% in the ACZONE Gel, 7.5% group versus 1.0% in the vehicle group) and application site pruritus (0.9% versus 0.5%).

Regarding pediatric use, safety was evaluated in 1066 pediatric subjects 12 to 17 years of age treated with ACZONE Gel, 7.5%. Within this age subgroup, the safety profile, in terms of TEAEs, for ACZONE Gel, 7.5 % was similar to that of the vehicle control. In addition, the frequency of TEAEs was similar among those aged 12 to 17 years of age as compared with subjects ≥ 18 years of age.

Three dermal safety trials were performed in support of this application; **225678-009** (RIPT sensitization), **225678-010** (phototoxicity), and **225678-011** (photoallergy). Under the conditions of the trials performed, ACZONE Gel, 7.5% and its vehicle did not show potential for sensitization and are unlikely to cause clinically meaningful irritation under normal use conditions. ACZONE Gel, 7.5% and its vehicle also did not show potential for phototoxicity in and did not show clinically significant potential for photoallergy in healthy subjects.

For this 505(b)(1) application, based on the data submitted from the six trials in the clinical development program, safety and efficacy of ACZONE ® (dapsone) Gel, 7.5% have been established for the topical treatment of acne vulgaris in patients 12 years of age and older.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

At this time, a postmarketing Risk Evaluation and Mitigation Strategy (REMS) is not recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

Postmarket Requirement:
For pediatric patients age 9 to 1 years and 11 months, information is needed about systemic exposure and safety after exposure to ACZONE® Gel, 7.5% applied to acne vulgaris. Deferred pediatric studies in pediatric patients age 9 to 11 years 11 months will be conducted as required by PREA.

A proposal for the PMR is as follows:

> Conduct an open-label study to assess safety, pharmacokinetics, and treatment effect of ACZONE® Gel, 7.5% in 100 pediatric subjects age 9 to 11 years 11

months with acne vulgaris. Pharmacokinetic assessments will be done in at least 16 evaluable subjects under maximal use conditions.

2 Introduction and Regulatory Background

2.1 Product Information

The applicant, Allergan, Inc., has submitted a 505(b)1 New Drug Application for ACZONE ® (dapsone) Gel, 7.5%. The objective of the current NDA is to provide data to support approval for the marketing of ACZONE® Gel for the topical treatment of acne vulgaris in patients 12 years of age and older.

The drug product proposed in this application comprises a topical gel formulation containing 7.5% dapsone. ACZONE® (dapsone) Gel, 5% has been shown to be an effective treatment for acne with twice daily dosing. Allergan is developing a 7.5% dapsone formulation for once daily dosing. All excipients used in the formulation are listed on the FDA Inactive Ingredient Database and are in FDA-approved topical products.

ACZONE® (dapsone) Gel, 7.5% is an off-white to yellow gel with suspended dapsone particles. It comprises (b) (4), diethylene glycol monoethylether (DGME) as a (b) (4), and methylparaben (MP) as a (b) (4). The drug product is packaged in an airless pump (b) (4). The airless pump (b) (4) consists of a bottle and pump actuator assembly.

The applicant has proposed that ACZONE® (dapsone) Gel, 7.5% be presented in (b) (4) packaging configurations which are described in the following table:

Table 1: ACZONE Packaging Configurations

Configuration	Fill	Packout
Professional sample pack	3 g in 3 g tube	8 tubes per (b) (4)
30 g pump container	30 g in 30 mL bottle	1 bottle per
60 g pump container	60 g in 75 mL bottle	1 bottle per
90 g pump container	90 g in 90 mL bottle	1 bottle per

(b) (4)

Source: Applicant's NDA, Module 3, 3.2.P.7, p. 2.

The applicant proposed indication is "topical treatment of acne vulgaris in patients 12 years of age and older."

Proprietary Name:
The Division of Medication Error Prevention and Analysis, Office of Medication Error Prevention and Risk, reviewed the proposed proprietary name, Aczone, and concluded that it is conditionally acceptable. This was communicated to the applicant in a letter dated July 7, 2015. The applicant's request for review of the proprietary name was dated April 28, 2015.

2.2 Tables of Currently Available Treatments for Proposed Indications

A number of topical and systemic drugs are available for the treatment of acne vulgaris. Approved therapies for acne vulgaris include oral and topical antibiotics and antimicrobials (e.g. erythromycin, clindamycin, benzoyl peroxide) systemic hormonal therapies (e.g. ethinyl estradiol/norgestimate) and topical retinoids (e.g. tretinoin, tazarotene). The oral formulation of isotretinoin is also available for severe, recalcitrant, nodulo-cystic acne.

Table 2: Topical Acne Products (Acne Vulgaris) – Single Active

Generic Name	Brand Name	Formulations	Applicant/Owner
Topical Antimicrobials			
Clindamycin phosphate	Cleocin T	Solution 1%, lotion 1%, gel 1%	Pharmacia & Upjohn
	Clindagel	Gel 1%	Precision Dermatology
	Evoclin	Foam 1%	Delcor Asset
Erythromycin	Erygel	Gel 2%	Delcor Asset Corp
Sulfacetamide sodium	Klaron	Lotion, 10%	Valeant
Retinoids			
tretinoin	Retin-A	Solution .05%, cream 0.1% & .05% & 0.025%, gel 0.025% & 0.01%,	Valeant
	Retin-A Micro	Gel 0.1%, 0.04%, 0.08%	Valeant
	Atralin	Gel 0.05%	Dow Pharm
	Avita	Gel 0.025%	Mylan
	generic	Cream 0.1%, 0.05%,0.025%;gel	Matawan Pharms

Generic Name	Brand Name	Formulations	Applicant/Owner
		0.025%, 0.01%	
		Cream 0.05%	Suneva
		Cream 0.0375%, 0.075%	Watson labs Inc
		Gel 0.1%, 0.04%, 0.05%	Spear Pharms Inc
adapaline	Differin	Gel 0.1%, 0.3%; cream 0.1%, lotion 0.1%	Galderma Labs LP
	generic	Cream 0.1%	Fougera Pharms
		Gel 0.1%	Pliva Hrvatksa Doo
		Gel 0.1%	Glenmark Generics
		Gel 0.3%	Tolmar
		Gel 0.3%	Actavis Mid Atlantic
tazarotene	Tazorac	Cream 0.1%, 0.05%	Allergan
		Gel 0.1%, 0.05%	Allergan
	Fabior	Aerosol, foam, 0.1%	Stieffel Labs, Inc

Compiled by reviewer from website "Drugs at FDA" accessed October 28, 2015

Table 3: Topical Acne Products (Acne Vulgaris) – Combination

Generic Name	Brand Name	Formula-tions	Applicant/Owner
Combination Products			
Adapalene 0.1 %; benzoyl peroxide 2.5%	Epiduo	gel	Galderma Labs LP
Adapalene 0.3 %; benzoyl peroxide 2.5%	Epiduo Forte	gel	Galderma Labs LP
Adapalene 0.1 %; benzoyl peroxide 2.5%	generic	gel	Actavis Mid Atlantic
Benzoyl peroxide 2.5%; clindamycin phosphate 1.2%	Acanya	gel	Dow Pharm
Benzoyl peroxide 3.75%; clindamycin phosphate 1.2%	Onexton	gel	Dow Pharm
Benzoyl peroxide 5%; clindamycin phosphate 1%	Benzaclin	gel	Valeant
Benzoyl peroxide 5%; clindamycin phosphate 1.2%	Duac	gel	Stiefel
Benzoyl peroxide 5%; clindamycin phosphate 1%	generic	gel	Mylan Pharms Inc
Benzoyl peroxide 5%; clindamycin phosphate 1.2%	generic	gel	Perrigo Israel
Benzoyl peroxide 5%; clindamycin phosphate 1%	generic	gel	Perrigo Israel
Benzoyl peroxide 5%; clindamycin phosphate 1%	generic	gel	Actavis Labs Ut Inc
Benzoyl peroxide 5%; erythromycin 3%	Benzamycin	gel	Valeant Intl
Benzoyl peroxide 5%; erythromycin 3%	Benzamycin	gel	Valeant Luxemborg

Generic Name	Brand Name	Formula-tions	Applicant/Owner
	Pak		
Benzoyl peroxide 5%; erythromycin 3%	generic	gel	Tolmar
Benzoyl peroxide 5%; erythromycin 3%	generic	gel	Lyne
Clindamycin phosphate 1.2%; tretinoin .025%	Veltin	Gel	Stiefel GSK
Clindamycin phosphate 1.2%; tretinoin .025%	Ziana	Gel	Medicis

Compiled by reviewer from website "Drugs at FDA" accessed October 28, 2015

Table 4: Oral Acne Products

Generic Name	Brand Name	Formulations	Applicant/ Owner	Indication
Oral Antibiotics				
Minocycline HCl	Solodyn	Extended release tablets 55mg, 65 mg, 105 mg, 115 mg	Medicis	Only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.
Doxycycline hyclate	Doryx	Delayed release tablets, 100mg, 150 mg, 200mg	Mayne pharma	Adjunctive therapy in severe acne
Doxycycline Monohydrate	Monodox	Capsule; 50 mg,75 mg, 100mg	Aqua Pharms	In severe acne may be useful adjunctive therapy
Tetracycline Hydrochloride	Achromycin V	Capsule; 250 mg, 500 mg	Heritage Pharms Inc	In severe acne may be useful adjunctive therapy
Isotretinoin	Absorica	Capsules; 10, 20, 30, 40, 25, 35 mg	Ranabxy	Severe recalcitrant nodular acne in patients 12 years of age and older
Isotretinoin	Amnesteem generic	Capsules; 10, 20, 40 mg	Mylan Pharms Inc.	Severe recalcitrant nodular acne
	Claravis Generic	Capsules; multiple strengths	Teva Pharms USA	Severe recalcitrant nodular acne
Drospirenone 3 mg/ethinyl estradiol .02 mg	Yaz	Tablets	Bayer Healthcare	Moderate acne for women at least 14 years old only if patient desires an oral contraceptive for birth control

Generic Name	Brand Name	Formulations	Applicant/ Owner	Indication
Norgestimate .025 mg/ ethinyl estradiol .35 mg	Orhto-cyclen Orhto Tri-cyclen	Tablets	Janssen Pharms	moderate acne vulgaris in females at least 15 years of age, who have no known contraindications to oral contraceptive therapy and have achieved menarche

Compiled by reviewer from website "Drugs at FDA" accessed October 28, 2015

2.3 Availability of Proposed Active Ingredient in the United States

ACZONE® (dapsone) Gel, 5% was approved July 7, 2005 (NDA 21794). It is currently marketed in the US for twice daily topical treatment of acne vulgaris.

Dapsone is also available, generically, in oral tablet form (25mg and 100mg) and is indicated for the treatment of dermatitis herpetiformis and leprosy (all forms except for cases of proven dapsone resistance).

2.4 Important Safety Issues with Consideration to Related Drugs

Dapsone is a synthetic sulfone with antimicrobial and anti-inflammatory properties. It has been available for over 60 years in oral form and used to treat leprosy and dermatitis herpetiformis. The topical form, ACZONE® (dapsone) Gel, 5% was approved July 7, 2005 (NDA 21794).

Approved labeling for topical dapsone, ACZONE® (dapsone) Gel, 5%, includes the following, excerpted from Warnings and Precautions (July 2015):

1) Methemoglobinemia: Cases of methemoglobinemia, with resultant hospitalization, have been reported postmarketing in association with ACZONE® Gel, 5% treatment. Patients with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methemoglobinemia are more susceptible to drug-induced methemoglobinemia. (b) (4)

2) Hematologic Effects: 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. Some subjects with G6PD deficiency using ACZONE® Gel, 5% developed laboratory changes suggestive of hemolysis. There was no evidence of

clinically relevant hemolysis or anemia in patients treated with ACZONE® Gel, 5%, including patients who were G6PD deficient.
3) Peripheral Neuropathy: Peripheral neuropathy (motor loss and muscle weakness) has been reported with oral dapsone treatment. No events of peripheral neuropathy were observed in clinical trials with topical ACZONE® Gel, 5% treatment.
4) Skin: Skin reactions (toxic epidermal necrolysis, erythema multiforme, morbilliform and scarlatiniform reactions, bullous and exfoliative dermatitis, erythema nodosum, and urticaria) have been reported with oral dapsone treatment. These types of skin reactions were not observed in clinical trials with topical ACZONE® Gel, 5% treatment.

The following is excerpted from the Adverse Reactions section Approved labeling for topical dapsone, ACZONE® (dapsone) Gel, 5% (July 2105):

Clinical Studies Experience:
Serious adverse reactions reported in patients treated with ACZONE® Gel, 5%, during clinical trials included but were not limited to the following:

- Nervous system/Psychiatric – Suicide attempt, tonic clonic movements.
- Gastrointestinal – Abdominal pain, severe vomiting, pancreatitis.
- Other – Severe pharyngitis

In the clinical trials, a total of 12 out of 4032 patients were reported to have depression (3 of 1660 treated with vehicle and 9 of 2372 treated with ACZONE® Gel, 5%). Psychosis was reported in 2 of 2372 patients treated with ACZONE® Gel, 5%, and in 0 of 1660 patients treated with vehicle.

Experience with Oral Use of Dapsone:
Although not observed in the clinical trials with ACZONE® Gel, 5% (topical dapsone) serious adverse reactions have been reported with oral use of dapsone, including agranulocytosis, hemolytic anemia, peripheral neuropathy (motor loss and muscle weakness), and skin reactions (toxic epidermal necrolysis, erythema multiforme, morbilliform and scarlatiniform reactions, bullous and exfoliative dermatitis, erythema nodosum, and urticaria).

At approval Aczone® (dapsone) Gel, 5% was categorized as a pregnancy category C product.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The clinical development program for Aczone 7.5% gel was conducted under IND 054440.

An End of Phase 2 meeting was held August 28, 2013. Key discussion points included the following:

- The Division did not agree with the applicant's [redacted] (b) (4) The Division stated that [redacted] (b) (4) should be assessed because the proposed 7.5% dapsone gel product differs from the approved ACZONE Gel, 5% in both concentration of the active ingredient as well as the excipients in the formulation.
- The applicant's rationale based on low plasma concentration, historical clinical use and relative bioavailability data to (dapsone) Gel, 5% seemed reasonable to support a waiver to conduct a thorough QT/QTc study for (dapsone) Topical Gel, 7.5%.
- For assessing efficacy for acne indication, the co-primary endpoints regarding the lesion counts recommended by the division are the absolute change in inflammatory and the absolute change in non-inflammatory lesion counts from baseline. Facial counts should include lesions on the nose.
- The proposed secondary efficacy endpoints of percentage change in inflammatory and noninflammatory lesion counts from baseline to week 12 are acceptable. Patient reported outcomes may have limited utility for eventual product labeling.
- For handling missing data, the applicant proposed to impute missing value using last observation carried forward (LOCF) as the primary method. However, as the scientific rationale for LOCF method is weak, the applicant was requested to provide either a justification that the LOCF is appropriate for their application or propose a more scientifically sound methodology.

A Pre-NDA with the applicant occurred on November 19, 2014. Key points of discussion included the following:

- The applicant stated that they had conducted four phase 1 studies (three dermal tolerability studies and one PK study) and two identical, pivotal phase 3 studies to support the NDA submission for ACZONE 7.5%. The applicant planned to integrate the two pivotal phase 3 studies for the ISS and ISE. The applicant stated that the four phase 1 studies will not be part of the integrated analysis because the design, treatment exposures, and objectives of those studies were different than the phase 3 studies. The Agency stated that the proposed approach for the ISS and ISE appeared reasonable.
- In July of 2014, the applicant became aware of a site-specific issue concerning the phase 3 Clinical Study 225678-006 and Principal Investigator Dr. Ellen Marmur (Site 16078, located at Marmur Medical in New York City, New York). Allergan investigated the issue, which culminated in an on-site assessment September, 11-12, 2014, and confirmed the existence of Good Clinical Practice (GCP) compliance issues in the areas of Protocol Adherence and Clinical Study Management. Due to concerns over the overall data integrity for Dr. Marmur's site, Allergan made the decision to exclude all patients randomized at the site (51 patients) from the Intent-to-Treat (ITT) analysis.
  The Agency stated that specific recommendations from Office of Scientific Investigations (OSI) regarding this study site are pending at the current time and

will be forthcoming from the Agency. Given the potential seriousness of the violations described, data from this investigative site should not be included in the primary efficacy analysis. Line listings should be provided for any safety data collected at this site, but should not be included in analyses.

- The Agency agreed with the sponsor proposal of using the gatekeeping approach without the Hochberg's Step-up method when controlling for multiplicity after the sponsor clarified that the testing would be done sequentially for total lesion counts followed by inflammatory and noninflammatory lesion counts before testing the next secondary endpoints.

2.6 Other Relevant Background Information

The applicant's formulation of dapsone 7.5% gel is not marketed in foreign countries at this time. There is no additional foreign regulatory information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Site Specific Issue: Trial 225678-006 site16078 (Ellen Marmur, MD) New York City, NY

In July of 2014, the applicant became aware of a site-specific issue concerning the phase 3 Clinical Study 225678-006 and Principal Investigator Dr. Ellen Marmur (Site 16078). Allergan investigated the issue, which culminated in an on-site assessment September, 11-12, 2014, and confirmed the existence of Good Clinical Practice (GCP) compliance issues in the areas of Protocol Adherence and Clinical Study Management. The concerns were based upon the following instances of serious non-compliance:

- Numerous inconsistencies in documentation indicating that Dr. Marmur conducted patient assessments when it was confirmed she was not present in the office
- Consenting, screening, and enrolling patients into the study, as well as efficacy and safety assessments, conducted by a study coordinator who was not eligible to conduct the assessments, per protocol, and not listed on the Investigator's Form FDA 1572
- Lack of documentation for numerous patients who were randomized but who do not appear to have returned for any follow-up visits

According to the applicant, due to the issues identified, the site was terminated from the study and all ongoing patients at the site were discontinued from the study.

At the Pre-NDA meeting of November 19, 2014, the Agency stated that, given the potential seriousness of the violations described, data from this investigative site should not be included in the primary efficacy analysis. Line listings should be provided for any safety data collected at this site, but should not be included in analyses.

OSI conducted an inspection of Dr. Ellen Marmur's site (16078 in New York City, NY) for cause in response to a report from Allergan Inc. including the noncompliance issues listed above. According to the OSI Letter (to IND 054440) signed by Constance Cullity, MD, MPH, dated 7/10/2015, at this site, 57 subjects were screened, 53 subjects were enrolled, and 43 completed the study. Inspectional findings included the following:

> A Form FDA 483, Inspectional Observations, was issued at the close of the inspection. Key inspectional findings are:
>
> - Failure to adhere to the protocol
> - Height and weight assessments were not completed at screening visit (1 subject)
> - Inadequate recordkeeping
> - Discrepancy between Visit 7/Week 12 source record and corresponding eCRF – the Global Acne Assessment Score (GAAS) score of 2 was recorded on source document; however, eCRF showed a score of 3 (1 subject)
> - Discrepancy in subject identification number on the Subject Identification Log (1 subject)

In the Clinical Overview Module 2.5, provided with the current application, the applicant states, in reference to the pre-NDA telephone conference held with the Division on November 19, 2014, that:

> "It was also agreed that due to GCP compliance issues identified at 1 investigational center in Study 225678-006 (center 16078) and the resulting concerns over data integrity, all 51 patients at the center were to be excluded from all analysis populations…"

DSI Inspections:
Department of Scientific Investigations (DSI) inspections were requested for a total of 4 sites with rationales as described:

Trial 006:
●Site 16030: Tracy Klein, MD in Wichita Kansas
This site was selected because there was a large treatment effect for active with none of the placebo achieving GAAS (Global Acne Assessment Score) success (score 0 or 1) at Week 12. The site had a total of 53 subjects (26 active and 27 vehicle).

●Site 16062: Douglass Forsha, MD in West Jordan, Utah

This center was selected because there was a large treatment effect (59.6% active versus 24.2% vehicle) for GAAS success (score of 0 or 1) at Week 12. This site had a total of 50 subjects (24 active and 26 vehicle).

Trial 007:

●Site 27032: Francisco Flores, MD in Miramar, Florida

This center had a fairly large number of subjects and there was a large treatment effect (59.2% active versus 18.2% vehicle) for GAAS success (score of 0 or 1) at Week 12. This site had a total of 66 subjects (33 active and 33 vehicle).

●Site 27084: Jennifer Parish, MD in Philadelphia, PA

This center was selected because while there was a large treatment effect for success on GAAS (75.7% vs. 45.1%), there wasn't a treatment effect for change in lesion counts. Generally, a large treatment effect for success on GAAS translates to large treatment effect for change in lesion counts; therefore, the results in this center are not consistent. This site had a total of 88 subjects (43 active and 45 vehicle).

Inspection Results:

Trial 006:

Site 16030: Tracy Klein, MD in Wichita Kansas

OSI Letter by Susan D. Thompson, MD, dated 9/29/2015:

> A Form FDA 483 was not issued at the conclusion of the inspection. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

Site 16062: Douglass Forsha, MD in West Jordan, Utah

From OSI Clinical Inspection Summary by Roy Blay, PhD, dated 1/13/2016

> The site of Dr. Forsha was issued a Form FDA 483 noting deficiencies including a lack of adherence to the protocol, and inadequate documentation of adverse events (AEs), concomitant medications, informed consent or assent, and drug accountability. The preliminary classification of this inspection is Voluntary Action Indicated (VAI).

Trial 007:

Site 27032: Francisco Flores, MD in Miramar, Florida

OSI Letter by CDR LaKisha Williams-Patterson, USPHS. dated 12/02/2015

> A Form FDA 483 was not issued at the conclusion of the inspection. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

Site 27084: Jennifer Parish, MD in Philadelphia, PA

OSI Letter by CDR LaKisha Williams-Patterson, USPHS. dated 12/02/2015

A Form FDA 483 was not issued at the conclusion of the inspection. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

From OSI Clinical Inspection Summary by Roy Blay, PhD, dated 1/13/2016:

"The clinical sites of Drs. Flores, Forsha, Klein, and Parish were inspected in support of this NDA. The sites of Drs. Flores, Klein, and Parish were not issued Form FDA 483s. The final classification of these inspections was No Action Indicated (NAI).

The site of Dr. Forsha was issued a Form FDA 483 noting deficiencies including a lack of adherence to the protocol, and inadequate documentation of adverse events (AEs), concomitant medications, informed consent or assent, and drug accountability. Although deficiencies were noted, they would not appear to affect subject safety or data integrity. Dr. Forsha submitted a corrective action plan to prevent such deficiencies from occurring in future clinical trials. The preliminary classification of this inspection is Voluntary Action Indicated (VAI); final classification is pending receipt and review of the EIR." *(Establishment Inspection Report)**

*Added by reviewer

3.2 Compliance with Good Clinical Practices

The applicant states that all clinical studies in the development program were conducted in compliance with Good Clinical Practice (GCP). The investigator obtained approval of the study from a properly constituted institutional review board (IRB) or independent ethics committee (IEC) prior to study initiation. Written informed consent and privacy-related documentation were obtained from each patient and/or the patient's legally authorized representative prior to any study-related activities or procedures.

3.3 Financial Disclosures

The applicant submitted form FDA 3454 for covered clinical trials, 225678-006 and 225678-007. A list of clinical investigators was provided: 106 investigators for trial 006 and 106 investigators for trial 007. There were no investigators who are full or part-time sponsor employees.

For trial 225678-006, a total of 2 investigators had disclosable financial interests, as defined in 21 CFR 54.2(a), (b), (c), and (f). Attachments were provided that with details of the disclosable financial interests.

- One investigator (principal investigator – site (b) (6)) had significant payments of other sorts – grants, consultations, and honoraria that have a monetary value that can go over $25,000.

- One investigator (principal investigator – site (b) (6)) had significant equity interest in the sponsor company.

For trial 225678-007, a total of 4 investigators had disclosable financial interests, as defined in 21 CFR 54.2(a), (b), (c), and (f). Attachments were provided that with details of the disclosable financial interests.

- One investigator (principal investigator – site (b) (6)) had significant payments of other sorts – consultation, payments from previous studies, residuals from commercial for other sponsor product that have a monetary value that can go over $25,000.
- Another investigator (subinvestigator – site (b) (6)) had significant payments of other sorts – grants, consulting retainer, reimbursement for travel (per diem), and patent in last 10 years that have a monetary value that can go over $25,000.
- An additional investigator (principal investigator - site (b) (6)) had significant payments of other sorts – honoraria for advisory board and speaking that have a monetary value that can go over $25,000.00
- A fourth investigator (principal investigator – site (b) (6)):
  - Had significant payments of other sorts – payments for helping sponsor a conference (along with multiple other sponsors) that have a monetary value that can go over $25,000.
  - This investigator also had a significant equity interest in the sponsor company

The applicant did not provide a description of the steps taken to minimize potential bias. In the filing letter dated June 30, 2015, the Agency requested this information and the applicant responded that:

> "The double blind nature of studies 225678-006 and 225678-007 minimizes the possibility of this potential bias influencing study results. The sites of the 6 investigators with disclosable financial interests or arrangements only enrolled a total of (b) (6) patients (b) (6) in 006, (b) (6) in 007)."

One investigator (subinvestigator) in trial 225678-007 did not provide financial disclosure information. Information was provided by the applicant indicating that the applicant acted with due diligence to obtain the information. The investigator had resigned from the study site and multiple attempts were made to contact the investigator.

In the opinion of this reviewer, the presence of the 6 investigators having the disclosable financial interests as described above (out of a total of 212 investigators) does not raise questions about the integrity of trial data, and by extension, the approvability of the application. The design of trials studies 225678-006 and 225678-007, randomized and double-blinded, would have made data alteration difficult.

Trial 225678-006 was conducted at 106 investigational centers (105 enrolling subjects). Sites of investigators with disclosable financial interests were [redacted] with [redacted] subjects and site [redacted] with [redacted] subjects for a total of [redacted] out of 2102 [redacted] % of subjects). A total of 2153 subjects were enrolled in the trial but [redacted] from site [redacted] were excluded leaving a total of 2102. Trial 225678-007 was conducted at 106 investigational centers (103 enrolling subjects). Sites of investigators with disclosable financial interests were [redacted] with [redacted] subjects investigator and [redacted] subjects subinvestigator, [redacted] with [redacted] subjects, [redacted] with [redacted] subjects and [redacted] with no subjects for a total of [redacted] out of 2238 ([redacted] %) of subjects enrolled.

The FDA statistician performed an analysis of the co-primary efficacy results at Week 12 with and without the centers with financial interests. The results are very similar with and without these centers, and these centers did affect the overall conclusion.

Table 5: Co-Primary Efficacy Results at Week 12 for All Centers and Centers with Financial Disclosures Removed (MI, ITT)

		GAAS (none or minimal)		Absolute Change in Inflammatory Lesions		Absolute Change in Non-Inflammatory Lesions	
		ACZONE	Vehicle	ACZONE	Vehicle	ACZONE	Vehicle
Trial 006[1]	All Centers	N=1044	N=1058	N=1044	N=1058	N=1044	N=1058
	Rate/Change	30%	21%	16.1	14.3	20.7	18.0
	P-value	<0.001[2]		<0.001[3]		<0.001[3]	
	Centers with Disclosures Removed	N=1027	N=1040	N=1027	N=1040	N=1027	N=1040
	Rate/Change	30%	21%	16.1	14.3	20.8	18.1
	P-value	<0.001[2]		<0.001[3]		<0.001[3]	
Trial 007	All Centers	N=1118	N=1120	N=1118	N=1120	N=1118	N=1120
	Rate/Change	30%	21%	15.6	14.0	20.8	18.7
	P-value	<0.001[2]		<0.001[3]		0.004[3]	
	Centers with Disclosures Removed	N=1108	N=1104	N=1108	N=1104	N=1108	N=1104
	Rate/Change	30%	21%	15.6	14.1	20.9	18.8
	P-value	<0.001[2]		<0.001[3]		0.006[3]	

*The values displayed are the averages over the 20 imputed datasets (MI).
[1] Excluding subjects from center [redacted] (a total of [redacted] subjects).
[2] P-value based on a CMH test stratified by gender.
[3] P-value from an ANCOVA model with terms for treatment, gender, and baseline lesion counts.
Source: Statistician's Review, NDA 207154, Table 23, p. 25.

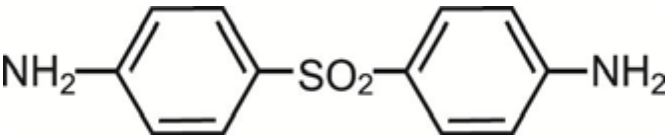
4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please see Quality Assessment by the Quality Review Team with Yichun Sun, PhD, as application technical lead, Branch V, Division of New Drug Products, II, final signature date, January 11, 2016.

The following is based on the Summary of Quality Assessments.

Drug Substance:
The drug substance/active pharmaceutical ingredient (API) used in the drug product, (dapsone gel), is dapsone which is chemically produced. The chemical name of dapsone is: 4-[(4-aminobenzene)sulfonyl]aniline and it has the following structural formula:



Dapsone is a white or slightly yellow-white, crystalline powder that has an empirical formula of C12H12N2O2S and a molecular weight of 248.30. Dapsone melts in the temperature range of 175 – 181°C. Dapsone is very slightly soluble in water, freely soluble in acetone, sparingly soluble in alcohol, and dissolves freely in dilute mineral acids. The amine groups on the aminobenzene rings have calculated pKa1 of 0.5 and calculated pKa2 of 1.2, respectively.

Drug Product:
The drug product, ACZONE (dapsone) Gel, is an off-white to yellow gel with suspended dapsone particles. The strength of dapsone gel is 7.5% (w/w). Dapsone is a sulfone indicated for the topical treatment of acne vulgaris in patients 12 years of age and older. Each gram of ACZONE contains 75 mg of dapsone in a gel of diethylene glycol monoethyl ether, methylparaben, acrylamide/sodium acryloyldimethyl taurate copolymer, isohexadecane, polysorbate 80, and purified water.

Table 6: Composition of ACZONE (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	
			(b) (4)

Source: Applicant's NDA from Module 2, 2.3.P.1, p. 1.

ACZONE (dapsone) Gel, 7.5%, is packaged in an airless pump container closure system in 3 different sizes (30 g, 60 g and 90 g). The airless pump contains a polypropylene bottle with a high density polyethylene piston. Additionally, 3 g professional samples packaged in an (b) (4) laminated tube are also available.

The identity, strength, purity including microbial limits, and quality of the drug product are deemed assured by the drug product specification. An in vitro release test (IVRT) of dapsone gel has been developed but not fully validated. The facility review team from the Office of Process and Facilities has provided an Overall Acceptable recommendation for the facilities involved in the manufacture and test of the drug substance and drug product. The expiration dating period of 24 months is recommended for the drug product when stored at controlled room temperature based on the 12-month long-term and 6- month accelerated stability data obtained from 3 registration batches of the drug product.

Recommendation and Conclusion on Approvability
The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance and drug product.

The facility review team from the Office of Process and Facility has issued an "Approval" recommendation for the facilities involved in this application.

However, the issues on labels/labeling are not completely resolved at this time. Therefore, from the OPQ perspective, this NDA is not ready for approval in its present form per 21 CFR 314.125(b)(6) until the aforementioned issues are satisfactorily resolved.

List of Deficiencies To Be Communicated

Regarding Label/labeling

Immediate container labels:
The 30 g, 60 g and 90 g pump labels should be revised to include the following information:

- Display "Lot:" and "Exp:"
- Display a barcode
- Add the following statement in the storage condition description
  "[See USP Controlled Room Temperature]"
- List ingredients as shown below:
  "Each gram of gel contains 75 mg of dapsone, diethylene glycol monoethyl ether, methyl paraben, acrylamide/sodium acryloyldimethyl taurate copolymer, isohexadecane, polysorbate 80 and purified water."

The 3 g sample tube labels should be revised to include the following information:

- Display "Lot:" and "Exp:"
- Add the following statement in the storage condition description
  "[See USP Controlled Room Temperature]"
- Include "Manufactured for: and by:" same as pump labels.

Carton labels:
The 8 x 3 g sample tubes, 30 g, 60 g and 90 g carton labels should be revised to include the following information:

- Add the following statement in the storage condition description
  "[See USP Controlled Room Temperature]"
- List ingredients as shown below:
  "Each gram of gel contains 75 mg of dapsone, diethylene glycol monoethyl ether, methyl paraben, acrylamide/sodium acryloyldimethyl taurate copolymer, isohexadecane, polysorbate 80 and purified water."

The 8 x 3 g sample tube carton labels should be revised to include the following information:

- Display "Lot:" and "Exp:"

Physician Insert
"Highlights" Section
This section should be revised as follows:

- Display the drug product title as shown below:
  ACZONE (dapsone) gel, for topical use
- Delete the following statement:

"Each gram of ACZONE Gel, 7.5% contains 75 mg of dapsone in an off-white to yellow gel"

 # 3 "Dosage Forms and Strength" Section
This section should be revised as follows:

- Revise the dosage form description as shown below:
  "Each gram of ACZONE Gel, 7.5% contains 75 mg of dapsone in an off-white to yellow gel with suspended particles."

#11 Description
This section should be revised as follows:

- Revise the drug product title as shown below:
  ACZONE (dapsone) gel, 7.5%
- Replace the chemical name with the following IUPAC name:
  4-[(4-aminobenzene)sulfonyl] aniline
- The molecular weight of dapsone should be revised to "248.30"

#16 How supplied/storage and handling
This section should be revised as follows:

- The following drug product and container closure description should be added.
  "ACZONE gel is an off-white to yellow gel with suspended particles It is supplied in airless pumps containing polypropylene bottles with high density polyethylene pistons."
- The following statement should be added to the storage condition
  "[See USP Controlled Room Temperature]"

4.2 Clinical Microbiology

No clinical microbiology studies were performed during the Aczone 7.5 % gel development program.

4.3 Preclinical Pharmacology/Toxicology

Please see Pharmacology/Toxicology Review (dated 11/12/2015) by Norman A. See, PhD.

The pharmacology/toxicology reviewer states that Dapsone has been evaluated in a battery of nonclinical studies that included evaluation of pharmacology, pharmacokinetics, general (repeated-dose) toxicology, genetic toxicology, carcinogenicity, reproductive toxicology, and special toxicity studies. The reader is referred to reviews of NDA 21794 for detailed analysis of those data.

It is noted that special toxicology studies revealed that dapsone topical gel is not an irritant of skin or eyes, is not phototoxic, and is nonsensitizing.

From the pharmacology/toxicology review, Executive Summary:

"Topical use of dapsone in the treatment of acne vulgaris, involving twice daily application of ACZONE® (dapsone topical gel), 5%, has been found to be safe under NDA 21-794 (approved 07-JUL-2005). Under NDA 207154 the sponsor has proposed to market a 7.5% dapsone topical product (ACZONE® (dapsone topical gel), 7.5%). The conditions of use of the 7.5% product, including the volume of product applied per treatment, the maximum area treated, and the patient population, will be similar to those associated with 5% dapsone gel, with the exception that the 7.5% product will be labeled for once daily application (in comparison to two daily applications of the 5% product). The approved label of NDA 21-794, and the proposed label of 207154, discuss application of a "pea-sized" amount; a typical individual dose is estimated to approximate (b) (4) per application. Therefore, clinical use of ACZONE® Gel, 7.5%, typically involves application of approximately (b) (4) of product, containing (b) (4) mg dapsone, while use of ACZONE® Gel, 5%, typically involves application of approximately (b) (4) of product, containing (b) (4) mg dapsone."

From the pharmacology/toxicology review, Integrated Summary and Safety Evaluation:

"For a given dose volume, once daily application of the 7.5% formulation will result in lower mean systemic exposures to dapsone than are associated with twice daily application of the 5% product. In a comparison trial involving acne patients treated for 28 days (clinical study No. 225678-004), once daily application of ACZONE® Gel, 7.5%, resulted in C_{max} and AUC_{0-24h} values of 13.0±6.8 ng/mL and 282±146 ng•h/mL, respectively, while twice daily application of ACZONE® Gel, 5%, resulted in C_{max} and AUC_{0-24h} values of 17.6±6.7 ng/mL and 379±142 ng•h/mL, respectively. ACZONE® Gel, 7.5%, was well tolerated in clinical and nonclinical safety studies. The proposed exposures to the API (dapsone), excipients, and impurities have been qualified under NDA 21-794 and IND 54,440."

Labeling:
The pharmacology/toxicology reviewer recommends that section 8.1 (Pregnancy), section 12.1 (Mechanism of Action), and section 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility) of the draft label be modified to the statements indicated below:

"**8.1 Pregnancy**

Teratogenic Effects: Pregnancy Category C
There are no adequate and well controlled studies in pregnant women. **ACZONE®** Gel, 7.5%, should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Dapsone has been shown to have an embryocidal effect in rats and rabbits when administered orally during the period of organogenesis in doses of 75 mg/kg/day and 150

mg/kg/day, respectively (approximately 1400 and 425 times, respectively, the systemic exposure that is associated with the maximum recommended human dose (MRHD) of **ACZONE®** Gel, 7.5%, based on AUC comparisons). These effects may have been secondary to maternal toxicity."

"**12.1 Mechanism of Action**
The mechanism of action of dapsone gel in treating acne vulgaris is not known."

"**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**
Dapsone was not carcinogenic to rats when orally administered for a lifetime at dose levels up to 15 mg/kg/day (approximately 340 times the systemic exposure that is associated with the MRHD of **ACZONE®** Gel, 7.5%, based on AUC comparisons).

No evidence of potential to induce carcinogenicity was obtained in a dermal study in which dapsone gel was topically applied to Tg.AC transgenic mice for approximately 26 weeks. Dapsone concentrations of 3%, 5%, and 10% were evaluated; 3% material was judged to be the maximum tolerated dosage.

Topical gels that contained dapsone at concentrations up to 5% did not increase the rate of formation of ultraviolet light-induced skin tumors when topically applied to hairless mice in a 12-month photocarcinogenicity study.

Dapsone was not mutagenic in a bacterial reverse mutation assay (Ames test) using *S. typhimurium* and *E. coli*, with and without metabolic activation, and was negative in a micronucleus assay conducted in mice. Dapsone increased both numerical and structural aberrations in a chromosome aberration assay conducted with Chinese hamster ovary (CHO) cells.

The effects of dapsone on fertility and general reproduction performance were assessed in male and female rats following oral (gavage) dosing. Dapsone reduced sperm motility at dosages of 3 mg/kg/day or greater (approximately 22 times the systemic exposure that is associated with the MRHD of **ACZONE®** Gel, 7.5%, based on AUC comparisons). The mean numbers of embryo implantations and viable embryos were significantly reduced in untreated females mated with males that had been dosed at 12 mg/kg/day or greater (approximately 187 times the systemic exposure that is associated with the MRHD of **ACZONE®** Gel, 7.5%, based on AUC comparisons), presumably due to reduced numbers or effectiveness of sperm, indicating impairment of fertility.

Dapsone had no effect on male fertility at dosages of 2 mg/kg/day or less (approximately 15 times the systemic exposure that is associated with the MRHD of **ACZONE®** Gel, 7.5%, based on AUC comparisons). When administered to female rats at a dosage of 75 mg/kg/day (approximately 1400 times the systemic exposure that is associated with the MRHD of **ACZONE®** Gel, 7.5%, based on AUC comparisons) for 15 days prior to mating and for 17 days thereafter, dapsone reduced the mean number of implantations, increased the mean early

resorption rate, and reduced the mean litter size. These effects may have been secondary to maternal toxicity.

Dapsone was assessed for effects on perinatal/postnatal pup development and postnatal maternal behavior and function in a study in which dapsone was orally administered to female rats daily beginning on the seventh day of gestation and continuing until the twenty-seventh day postpartum. Maternal toxicity (decreased body weight and food consumption) and developmental effects (increase in stillborn pups and decreased pup weight) were seen at a dapsone dose of 30 mg/kg/day (approximately
560 times the systemic exposure that is associated with the MRHD of **ACZONE®** Gel, 7.5%, based on AUC comparisons). No effects were observed on the viability, physical development, behavior, learning ability, or reproductive function of surviving pups."

Approvability
The pharmacology/toxicology reviewer states that the product is approvable with respect to nonclinical concerns.

4.4 Clinical Pharmacology

Please see Clinical Pharmacology Review (dated 1/11/16) by Doanh Tran, PhD, DCP-3.

4.4.1 Mechanism of Action

The mechanism of action of dapsone gel in treating acne vulgaris is unknown.

4.4.2 Pharmacodynamics

For NDA 21-794, ACZONE® Gel, 5% and vehicle were evaluated in a randomized, double-blind, cross-over design clinical study of 64 subjects with G6PD deficiency and acne vulgaris. Subjects were Black (88%), Asian (6%), Hispanic (2%) or of other racial origin (5%). Blood samples were taken at Baseline, Week 2, and Week 12 during both vehicle and ACZONE® Gel, 5% treatment periods. Some of these subjects developed laboratory changes suggestive of hemolysis, but there was no evidence of clinically significant hemolytic anemia in this study.

4.4.3 Pharmacokinetics

Trial 225678-004, pharmacokinetics
The pharmacokinetics of ACZONE Gel, 7.5 % were examined in trial 225678-004.

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; DAP- 11078, DAP-11079, DAP-11080 = to be marketed formulation (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.

Male and female subjects 16 years of age or older with acne vulgaris (N=19) received two grams of formulation DAP-11080 = ACZONE Gel, 7.5% applied topically by clinical site staff to the face, upper chest, upper back and shoulders (a treatment area of approximately 1000 cm^2) once daily for 28 days. As stated by the clinical pharmacology reviewer, 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.

The following table shows pharmacokinetic parameters for plasma dapsone following 28 days of dosing:

Table 7: Summary of Plasma Dapsone PK Parameters

PK parameter	Dapsone Gel, 7.5% QD (TBM formulation DAP-11080) 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

Source: Clinical Pharmacology Review, NDA 207154, Table 1, p. 3.

The clinical pharmacology reviewer explains that: “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.”

TEAEs were reported for 10 (50.0%), 6 (31.6%), 7 (36.8%), and 6 (31.6%) subjects in the DAP-11078, DAP-11079, DAP-11080, and ACZONE Gel, 5% groups, respectively. The most frequent TEAE was headache in the DAP-11078 (6 [30.0%]) and DAP-11079 (2 [10.5%]) groups, and cough in the DAP-11080 (2 [10.5%]) group. There were no deaths, no serious adverse events, and no discontinuations due to adverse events during the study. For the to-be-marketed formulation, DAP-11080, there were no treatment-related TEAEs and no TEAEs of severe intensity.

Drug-drug interactions:
Regarding drug-drug interactions, according to the clinical pharmacology reviewer: "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."

Pediatrics:
The clinical pharmacology reviewer notes that the pharmacokinetic trial 225678-004 included pediatric subjects ≥16 years of age (7 of 19 in the ACZONE Gel, 7.5% group and 6 of 18 in the ACZONE Gel, 5% group). The ACZONE Gel, 5% label indicates that systemic exposure is pediatric subjects 12 – 15 years of age is similar to that in subjects 16 years and older. Therefore, an additional PK trial in subjects ages 12 -15 was not requested for ACZONE Gel, 7.5%.

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 thepresence of TMP/SMX. The systemic exposure from **ACZONE®** Gel, 7.5% is expectedto be about 1% of that from the 100 mg oral dose, even when co-administered withTMP/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.

(Comment: The applicant also proposed to omit 7.4 of ACZONE Gel, 5% label regarding concomitant use with drugs that induce methemoglobinemia. Relative to ACZONE Gel, 5%, daily systemic exposure of dapsone, defined by the Cmax and AUC0-24, was approximately 28.6% and 28.7% lower for formulation DAP-11080, respectively. Although, 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). The statistically significantly lower systemic exposure may therefore not be clinically meaningful and a caution regarding concomitant use of drugs that induce methemoglobinemia that is pertinent for ACZONE Gel, 5% is also understood to be pertinent for ACZONE Gel, 7.5%.)

7.4 Concomitant Use with Drugs that Induce Methemoglobinemia
Concomitant use of ACZONE® Gel, 7.5% with drugs that induce methemoglobinemia such as sulfonamides, acetaminophen, acetanilide, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine, and quinine may increase the risk for developing methemoglobinemia *[see Warnings and Precautions (5.1)]*.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
(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) Steady state for dapsone was reached within 7 days of dosing (b) (4) . On Day 28, the mean dapsone maximum plasmaconcentration (Cmax) and area under the concentration-time curve from 0-24 hours post dose (AUC0-24h) were 13.0 ± 6.8 ng/mL and (b) (4) 282 ± 146 ng·h/mL, (b) (4) (b) (4) . 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 (b) (4) dapsone gel, 5%, treatment (twice daily) periodic blood samples were collected up to 12 months to determine systemic exposure of dapsone and its metabolites in approximately 500 subjects (b) (4) . Based on the measurable dapsone concentrations from 408 subjects (b) (4) (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 subjects (b) (4)

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

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Protocol #	Type of trial	Trial Design	Subject Population/ # of sites	Test products/dosage regimen	Subjects in group: randomized/ completed	Diagnosis/ treatment duration
225678-0009	RIPT Sensiti-zation	Phase 1 single-center, evaluator-blinded, within subject comparison	between 18 and 65 1 US	1. Aczone gel, 7.5% 2. vehicle 3 x weekly, for 21 days	Subset I 40/32 Subset 2 197/170 Total: 237/202	Healthy subjects ~ 6 weeks
225678-10	Phototo xicity	Phase 1 single-center, double-blinded, within subject comparison	between 18 and 65 1 US	1. Aczone gel, 7.5% 2. vehicle One day	Total: 33/30	Healthy subjects One day
225678-11	Photo-allergy	Phase 1 single-center, double-blinded, controlled , randomized, within subject comparison	between 18 and 65 1 US	1. Aczone gel, 7.5% 2. vehicle 2 x weekly, for 21 days	Total:58/49	Healthy subjects ~ 6 weeks
225678-004	PK	Phase 1, multicenter, randomized, investigator-blinded, active-controlled, multiple-dose, parallel-group study	Age 16 to 35 2 US	1. dapsone 7.5% gel (DAP-11080)* *ACZONE 2.dapsone 7.5% gel (DAP-11078) 3. dapsone 7.5% gel (DAP-11079) Once daily 4. ACZONE Gel, 5%l Twice daily	Total: 77/72	Moderate acne vulgaris, 3 on GAAS 28 days

Protocol #	Type of trial	Trial Design	Subject Population/ # of sites	Test products/dosage regimen	Subjects in group: randomized/ completed	Diagnosis/ treatment duration
225678-006	Safety and efficacy	Phase 3 multicenter, randomized, double-blind, vehicle controlled, parallel group study	Age 12 and older 105: 96 US, 9 Canada	1. Aczone gel, 7.5 % 2. Vehicle Once daily	1044/948 1058/976 Total: 2102/1924	moderate facial acne vulgaris (a score of 3 [moderate] on the GAAS) 12 weeks
225678-007	Safety and efficacy	Phase 3 multicenter, randomized, double-blind, vehicle controlled, parallel group study	Age 12 and older 103: 93 US, 10 Canada	1. Aczone gel, 7.5% 2. Vehicle Once daily	1118/1026 1120/1027 Total: 2238/2053	moderate facial acne vulgaris (a score of 3 [moderate] on the GAAS) 12 weeks

Source: Applicant's NDA, from Module 5, adapted from 5.2 Tabular Listing of all Clinical Studies and from 5.3.5.4 Clinical Study Reports 225678-009, 225678-10, 225678-11; 5.3.3.2 225678-004; and 5.3.5.1 225678-006, 225678-007.

5.2 Review Strategy

The pivotal Phase 3 trials, 225678-006 and 225678-007 are reviewed in detail for safety and efficacy. These trials had a two arm design with vehicle control.

The safety database consists primarily of the pooled data from the two pivotal trials and safety data from these trials is pooled because study population, trial design, and safety assessment are the same. Both trials are vehicle controlled.

Other trials performed in support of the current application include:

- 225678-004 PK (Phase 1, 4-arm, active controlled): "Safety, Tolerability, and Pharmacokinetics of Dapsone Dermal Formulations in Subjects with Acne Vulgaris" Safety data from this trial is examined but not included in pooled safety data due to differing study population and trial design.

Special safety studies:

- 225678-009 dermal safety (Phase 1, RIPT sensitization): "Combined Cumulative Irritation Potential and Repeat InsultPatch Test of Dapsone 7.5% Gel in Healthy Volunteers"

- 225678-010 dermal safety (Phase 1, phototoxicity): "Phototoxicity Test of Dapsone 7.5% Gel in Healthy Volunteers"
- 225678-011 dermal safety (Phase 1, photoallergy): "Evaluation of Photoallergy Potential of Dapsone 7.5% Gel in Healthy Volunteers"

Safety data from the special safety studies is examined in support of the application but is not included in pooled safety data due to differing study populations and trial designs.

5.3 Discussion of Individual Studies/Clinical Trials

Pivotal Phase 3 Trials:
The applicant submitted data from two identically designed two arm, vehicle controlled pivotal trials.

Title: "A Safety and Efficacy Study to Compare Dapsone Dermal Gel with Vehicle Control in Patients with Acne Vulgaris"

Objective: To assess the safety and efficacy of dapsone 7.5% gel versus vehicle control administered topically once daily for 12 weeks in patients with acne vulgaris

Protocol Numbers: 225678-006 & 225678-007

For both trials the original protocols were approved on September 30, 2013. The protocols were subsequently amended once in August 2014. For trials 225678-006 & 007, by the time Amendment 1 was approved and implemented at the centers all 2156 and 2238 subjects, respectively, included in the trial had already been enrolled.

For the purposes of the submitted NDA, the key changes included in Amendment 1 were:

1. For the primary and secondary efficacy analyses: the CMH test, the Breslow-Day homogeneity test, and the ANCOVA model were altered to remove analyses by investigator center. This was performed as some investigational centers enrolled a relatively small number of patients, leading to a small cell issue, potentially making estimates unstable. Further testing of the model using the Shapiro Wilks test and the analysis using rank transformation was deleted from the protocol.
2. To allow for an assessment of treatment-by-center interaction, an additional sensitivity analysis using the pre-specified ANCOVA model was added for the primary efficacy analysis of inflammatory and noninflammatory lesion count data. This sensitivity analysis included the interaction term of treatment-by-center. In addition, a supportive analysis of change from baseline in inflammatory and noninflammatory lesion counts at week 12 between treatment groups using a t-test was added.

3. As a correction, the additional timepoints listed for the secondary endpoint of total lesion count (weeks 2, 4 and 8) were removed from Section 3 Study Design

Study Sites:
Trial 225678-006 was conducted at 96 investigational sites in the United States and 9 in Canada. The first subject enrolled November 27, 2013 and the last subject completed October 28, 2014.

Table 8: Top 25 Sites - Trial 006 by Sample Size

Site ID	Investigator	Site Location	Subjects		
			Total	Aczone	Vehicle
16090	Hector Wilitz, MD	Miami, FL	83	42	41
16061	Joel Neutel, MD	Tustin, CA	69	34	35
16012	Tooraj Raoof, MD	Encino, CA	57	28	29
16098	Jeanine Downie, MD	Montclair, NJ	56	28	28
16015	Joshua Berlin, MD	Boynton Beach, FL	53	26	27
*16030**	Tracy Klein, MD	Wichita, KS	53	26	27
16035	Neil Sadick, MD	New York, NY	52	27	25
*16062**	Douglas Forsha, MD	West Jordan, UT	50	24	26
16045	Adnan Nasir, MD	Raleigh, NC	47	23	24
16004	Marina Peredo, MD	Smithtown, NY	45	22	23
16006	Craig Teller, MD	Bellaire, TX	40	19	21
16029	Michael Jarratt, MD	Austin, TX	40	20	20
16099	Holly Harris, MD	South Bend, IN	40	20	20
16036	Michael Bukhalo, MD	Arlington Heights, IL	35	17	18
16019	William Werschler, MD	Spokane, WA	34	18	16
16026	Aldo Trovato, MD	Mobile, AL	34	17	17
16103	Cheryl Hull, MD	Rogers, AR	34	17	17
16009	Steven Bowman, MD	Clearwater, FL	33	17	16
16049	Walter Nahm, MD, PhD	San Diego, CA	33	17	16
16018	Steven Grekin, DO	Warren, MI	32	16	16
16086	William Coleman IV, MD	Metairie, LA	32	17	15
16093	David Bank, MD	Mount Kisco, NY	30	15	15
16084	David Kerr, MD	Denver, CO	29	15	14
16033	Charles Debusk, MD	New Tazewell, TN	28	14	14
16044	Melanie Appell, MD	Birmingham, AL	28	14	14

* Trial centers recommended for inspection
Source: Applicant's NDA, Clinical Study Report Trial 2256-006, Listing 16.1.4 List and Description of Investigators, and FDA Statistician.

Trial 225678-007 was conducted at 93 investigational sites in the United States and 10 in Canada. The first subject enrolled November 27, 2013 and the last subject completed October 21, 2014.

Table 9: Top 25 Sites - Trial 007 by Sample Size

Site ID	Investigator	Site Location	Subjects		
			Total	Aczone	Vehicle
27016	Anna Damian, MD	Bryan, TX	94	47	47
27047	Sinikka Green, MD	La Mesa, CA	92	46	46
*27084**	Jennifer Parish, MD	Philadelphia, PA	88	43	45
27055	Ellen Frankel, MD	Johnson, RI	86	42	44
27024	David Fried, MD	Warwick, RI	66	33	33
*27032**	Francisco Flores, MD	Miramar, FL	66	33	33
27036	Mark Nestor, MD	Aventura, FL	60	30	30
27005	Edward Lain, MD	Pflugerville, TX	58	30	28
27059	Rion, Forconi, MD	Sanford, FL	51	26	25
27078	Lucius Blanchard, MD	Las Vegas, NV	47	25	22
27065	James Campbell, MD	Newington, NH	46	22	24
27042	Heidi Kabler, MD	San Diego, CA	43	22	21
27013	Jennifer Soung, MD	Irvine, CA	42	21	21
27040	Susan Barker, MD	Brandon, FL	42	22	20
27053	Jeffrey Overcash, MD	San Diego, CA	40	21	19
27051	Mark Lomaga, MD, FRCPC	Mississauga, Ontario	38	18	20
27008	Robert Haber, MD	Beachwood, OH	37	18	19
27026	Javier Alonso-Llamazares, MD	Miami, FL	37	18	19
27025	James Borders, MD	Lexington, KY	36	18	18
27034	Terry Jones, MD	College Station, TX	36	17	19
27067	Jennifer Cather, MD	Dallas, TX	36	19	17
27048	Stephen Tyring, MD	Houston, TX	34	17	17
27105	Angela Moore, MD	Arlington, TX	33	17	16
27099	Raymond Garcia, MD	Irving, TX	30	15	15
27023	Suzanne Bruce, MD	Houston, TX	28	15	13

* Trial centers recommended for inspection

Source: Applicant's NDA, Clinical Study Report, Trial 2256-007, Listing 16.1.4 List and Description of Investigators, and FDA Statistician.

Principal Inclusion Criteria:

1. Male or female, 12 years of age or older
2. Patients with acne vulgaris and a minimum of 20 but not more than 50 inflammatory lesions (papules and pustules) on the face; a minimum of 30 but not more than 100 noninflammatory lesions (open comedones and closed comedones) on the face
3. Patients with a score of 3 (moderate) on the Global Acne Assessment Score (GAAS) as assessed by the investigator at screening and baseline
4. A negative urine pregnancy test result for females of childbearing potential at the screening and day 1 visits. A female was considered NOT to be of childbearing potential if she was premenarchal, postmenopausal with at least 12 consecutive months of amenorrhea, or had had a hysterectomy or bilateral oophorectomy.

Principal Exclusion Criteria:

1. Uncontrolled systemic disease(s)
2. Patients with severe cystic acne, acne conglobata, acne fulminans, or secondary acne (chloracne, drug-induced acne, etc)
3. Patients with one or more nodule(s) or cyst(s) above the mandibular line
4. Patients had used systemic immunosuppressive drugs within 4 weeks prior to screening or were anticipated to use any systemic therapy with the potential to affect acne during the study
5. Skin abnormalities (other than acne vulgaris), excessive hair, or other physical characteristics in or around the test sites that could confound the study results based on the investigator's judgment
6. Patients were using oral contraceptives solely for the control of acne
7. Females who are pregnant, nursing, or planning a pregnancy during the study or think they may be pregnant at the start of the study

Trial **Design and Plan:**
This was a multicenter, double-blind, randomized, parallel-group, vehicle-controlled, 12-week trial. Subjects were randomly assigned in a 1:1 ratio to receive dapsone 7.5% or vehicle. Randomization was stratified by sex (male versus female) and carried out using an IVRS or IWRS. Patients topically administered study product to their entire face once daily for 12 weeks. Subjects also topically administered the study product once daily to acne-affected areas within reach on the neck, shoulders, upper back, and/or upper chest, although these nonfacial areas were not considered in the analysis of efficacy for this study. Subjects were at least 12 years of age with moderate acne vulgaris according to the Global Acne Assessment Score (GAAS), score of 3, as determined by the investigator at screening and baseline. The screening period lasted for up to 30 days prior to baseline. Following the baseline visit, subjects returned for visits at weeks 1 and 2, then at weeks 4, 8, and 12. The first application of study product was carried out by the subject at the investigational center under the supervision of qualified study staff.

Product Application:
All study treatments were provided in identical 75-mL (b) (4) containers.

Subject treatment instructions included the following (among others):

- Wash your hands before and after each application.
- Wash your face using non-medicated soap or cleanser and gently pat dry using a cotton towel.
- Squeeze out approximately a pea-size amount of gel on your index fingertip.
- Using your fingertip, dot the study drug on to the forehead, cheeks, nose, and chin (*subject referred to a Figure 1*).
- Gently spread a thin layer of gel to cover your entire face, from your hairline (or where your forehead ends) to your jawline and from ear to ear, and massage until you can't see the gel (*subject referred to a Figure 2*). Apply to your entire

face, even if there are areas on your face that do not have acne. Do Not Spot Treat

- Avoid applying the gel to the eyes, eyelids, scalp, ears, inner nose, mouth, lips, or open wounds. In the event of accidental contact with sensitive surfaces such as mouth or eye, rinse with cool tap water.
- Acne affected areas on your neck, upper chest, upper back, and shoulders (where you can reach) should also be treated. Apply enough study drug to cover the affected areas, then rub in gently and completely until you can't see the gel.

Product Used/Treatment Compliance:
Study product had to be stored in a secure area at room temperature and dispensed only to patients enrolled in the clinical study. Dapsone 7.5% and vehicle control were supplied to investigators in identical 75-mL (b) (4) containers. One 75-mL (b) (4) container was dispensed to each patient upon randomization. Patients were instructed to bring their study product to the week 4, 8, and 12/early exit visits. Study product containers were weighed at the week 4, 8, and 12/early exit visits. At the week 4 and 8 visits, new containers were dispensed.

Blinding:
All study treatments were provided in identical 75-mL (b) (4) containers to maintain blinding in study. There was a small variation in color between the study treatment formulations from white to slightly off white, but the unblinding of the patient to the treatment allocation due to this variation was considered unlikely by the applicant. According to the applicant, additional precautions were taken to further ensure the blinding of the investigator and/or other evaluators. The study product was to be dispensed by and returned to study personnel other than the investigator or other evaluators. The study personnel dispensing the study product instructed the patient not to discuss the appearance of the study product with other study participants, the investigator, and/or other evaluators. The study personnel dispensing the study product did not have study responsibilities that required interaction with patients or with safety and efficacy evaluations/data. Patients, investigators, center staff, and Allergan personnel directly involved with the operational activities of the clinical study were to remain blinded to treatment assignment.

Table 10: Flow Chart – Trials 225678-006 & 007

Study Period	Screening[a]	Baseline / Day 1[a]	Weeks 1 and 2	Weeks 4 and 8	Week 12/ Early Exit
Visit Windows	-30 days	0 days	+/- 3 days	+/- 7 days	+/- 7 days
Informed consent/authorization and (for patients < 18 years of age) minor assent[b]	X				
Patient registered in IVRS/IWRS	X				
Inclusion/exclusion criteria	X	X			
Medical history	X	X			
Demographics	X				
Skin phototype assessment	X				
Physical examination including vital signs[c]	X				X
Pregnancy test (urine)[d]	X	X			X
Lesion count	X	X	X	X	X
GAAS	X	X	X	X	X
Randomization		X			
Dispense study product, training on application/return[e]		D		R/D	R
Standardized photographs[f]		X			X
Local tolerability[g]		X	X	X	X
ASIS[h]		X		X	X
Concomitant medications	X	X	X	X	X
Concomitant procedures	X	X	X	X	X
Adverse events	X	X	X	X	X

ASIS = Acne Symptom and Impact Scale; D = dispense; GAAS = Global Acne Assessment Score; IVRS/IWRS = interactive voice response system/interactive web response system; R = return

[a] If a washout period was not required, then screening and baseline visits could occur on the same day.

[b] Consent for photography was included in the informed consent process at select centers.

[c] Physical examination and vital signs were to be performed if inclusion/exclusion criteria were met at screening; not required for screen failures. Vital signs included blood pressure, heart rate, and body temperature.

[d] Female patients of childbearing potential only. The urine pregnancy test could also be performed at any timepoint during the course of the study at the investigator's discretion.

[e] Returned study product was weighed at the study center.

[f] At select centers, patients had photographs taken of their face for illustration or presentation purposes. Selected centers were notified by Allergan prior to enrollment of the first patient. Patients were required remove all make-up at least 20 minutes prior to having photographs taken.

[g] Local tolerability was assessed prior to drug administration on day 1.

[h] ASIS was completed by the patient prior to any other visit procedures.

Source: Applicant's NDA, Clinical Study Reports, Trials 225678-006 & 007, Table 9-2, pp 53 & 52, respectively.

Efficacy Analysis:
The protocol specified co-primary endpoints were:

- The proportion of patients with a score of 0 (none) or 1(minimal) on the GAAS at Week 12;
- Absolute change from baseline at Week 12 in inflammatory and non-inflammatory lesion counts.

Table 11: Global Acne Assessment Score

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

Source: Applicant's NDA, Clinical Study Reports, Trials 225678-006 & 007, Table 9-1, pp 46 & 45, respectively.

Lesion Counts:
The lesion counts including inflammatory lesions and noninflammatory lesions were performed at screening, day 1, and weeks 1, 2, 4, 8, and 12/early exit visits. The lesion counts were performed on the entire face and were evaluated by the investigator or an appropriately trained designee.

The following lesion types were evaluated:

- Inflammatory lesions
  - Papule – a small, red, solid elevation less than 1.0 cm in diameter
  - Pustule – a small, circumscribed elevation of the skin that contains yellow-white exudate
  - Nodule / cyst – a circumscribed, elevated, solid lesion generally more than 1.0 cm in diameter with palpable depth

- Noninflammatory lesions
  - Open comedo – a pigmented dilated pilosebaceous orifice (blackhead)
  - Closed comedo – a tiny white papule (whitehead)

Secondary endpoints specified in the protocol included the following:

- Absolute change from baseline in total lesion counts (sum of inflammatory lesion counts and noninflammatory lesion counts) at Week 12
- Percentage change from baseline in lesion counts (total, inflammatory, and noninflammatory lesion counts) to Week 12:
- The proportion of patients who reported "Very good" or "Excellent" in Acne Symptom and Impact Scale (ASIS) Item 10 (facial appearance) at Week 12
- The change from baseline to Week 12 in ASIS Sign Domain Score (facial acne signs)
- The proportion of patients with at least a 1-grade improvement from baseline at week 12 in ASIS Item 1 (subject's assessment of facial oiliness)
- The proportion of patients with at least a 1-grade improvement from baseline at week 12 in ASIS Item 8 (subject's assessment of facial redness)

Comment: At the End-of-Phase 2 meeting (August 28, 2013) the Agency stated that several of the secondary endpoints are closely related and some of the endpoints may not be clinically relevant for labeling. The Agency also stated that the proposed patient reported outcomes may have limited utility for eventual product labeling.

Analysis Populations:
Three analysis populations were utilized:

1. The intent-to-treat (ITT) population included all randomized subjects. (For trial 225678-006: this population excluded subjects from one investigational center, 16078)
2. The per-protocol (PP) population included randomized subjects with no protocol deviation during the study that might potentially affect the primary efficacy analyses. This population was to be determined prior to database lock.
3. The safety population included all subjects who were treated with at least one application of study treatment. (For trial 225678-006: this population excluded subjects from one investigational center, 16078)

Safety Assessments:
The following safety assessments were performed:

- adverse events
- local dermal tolerability assessments (stinging/burning rated by the patient; dryness, scaling, and erythema rated by the investigator or appropriately trained designee) – for the face only
- physical examination
- vital signs (heart rate, blood pressure, and body temperature)
- urine pregnancy tests for females of childbearing potential

Local Tolerability:
Local dermal tolerability (face only) was assessed based on patient-rated stinging/burning, and investigator or trained evaluator assessments of dryness, scaling, and erythema. Dryness, scaling, and erythema were to be assessed by the same person throughout the study whenever possible.

Stinging and burning on the face was defined as a prickling pain sensation within 5 minutes after dosing for postbaseline visits and was rated by the patient as follows:

None (0) = No stinging/burning
Mild (1) = Slight warm, tingling/stinging sensation; not really bothersome
Moderate (2) = Definite warm, tingling/stinging sensation that was somewhat bothersome
Severe (3) = Hot, tingling/stinging sensation that had caused definite discomfort

Dryness was defined as brittle or tight sensation and rated by the investigator/trained designee as follows:

None (0) = No dryness
Mild (1) = Slight but definite roughness
Moderate (2) = Moderate roughness
Severe (3) = Marked roughness

Scaling was defined as abnormal shedding of the stratum corneum and rated by the investigator/trained designee as follows:

None (0) = No scaling
Mild (1) = Barely perceptible shedding, noticeable only on light scratching or rubbing
Moderate (2) = Obvious but not profuse shedding
Severe (3) = Heavy scale production

Erythema was defined as abnormal redness of the skin and rated by the investigator/trained designee as follows:

None (0) = No erythema
Mild (1) = Slight pinkness present
Moderate (2) = Definite redness, easily recognized
Severe (3) = Intense redness

Comment: In an advice letter dated January 15, 2014, the Agency noted that the applicant's Phase 3 trials did not include an assessment of systemic safety (e.g. laboratory analysis or ECG monitoring). The Agency stated further that if both peak and trough systemic levels are lower than that of the twice daily 5% approved strength, then relying on the systemic safety of Aczone 5 % appears reasonable.

6 Review of Efficacy

Efficacy Summary

To demonstrate efficacy, the applicant submitted data from two identically designed Phase 3 pivotal trials, trial 225678-006 and 225678-007 (Trials 006 and 007). These were multicenter, double-blind, randomized, parallel-group, vehicle-controlled, 12-week trials. Trials 006 and 007 were conducted in 96 and 93 US centers and 9 and 10 Canadian centers, respectively. To enroll in these trials subjects must have been 12 years of age or older and had a Global Acne Assessment Score (GAAS) of 3 (moderate). They also must have had 20-50 inflammatory lesions (papules and pustules) and 30-100 non-inflammatory lesions (open comedones and closed comedones) on the face.

For trials 006 and 007, baseline demographics including age, gender, race, and country where studied were generally balanced across treatment arms within the two trials and between each trial. The mean age was 20 in all treatment groups. Slightly more females (55 to 57%) were studied than males (43 to 45%). The predominant race studied was White (54 to 62% across treatment groups). Baseline disease characteristics were generally balanced across treatment arms within the two trials and between each trial. For inflammatory lesion counts, mean (28.8 to 30.0) and median (26.0 to 28.0) were similar across treatment arms within trials and between trials. For non-inflammatory lesion counts mean (46.7 to 48.6) and median (41.0 to 43.0) were similar across treatment arms within trials and between trials.

The protocols specified the following co-primary efficacy endpoints; the proportion of subjects achieving a score of 0 (none) or 1 (minimal) on the GAAS at Week 12 and the absolute change in inflammatory and non-inflammatory lesion counts from baseline to Week 12. In both trials 006 and 007, ACZONE Gel, 7.5% was statistically superior (p-values ≤ 0.004) to vehicle gel on all three co-primary efficacy endpoints for the Intent-To-Treat (ITT) population.

For the secondary endpoints which included, percent change in inflammatory and non-inflammatory lesion counts from baseline to Week 12, ACZONE Gel, 7.5% was statistically superior (p-values ≤ 0.001) to vehicle gel in both trials.

Results for the co-primary endpoints were examined in subpopulations for both trials 006 and 007. For gender, the treatment effect was greater in females for all three co-primary endpoints in both trials. Results in the race subgroups were mixed. For age, adult subjects had better results than adolescent subjects for ACZONE Gel, 7.5% and vehicle gel in all three co-primary efficacy endpoints.

With regard to data integrity, the applicant notified the Agency that a clinical center (16078 – Dr. Ellen Marmur) did not follow Good Clinical Practice (GCP) procedures

regarding areas of protocol adherence and clinical study management. In the Clinical Overview Module 2.5, provided with the current application, the applicant states, in reference to the pre-NDA telephone conference held with the Division on November 19, 2014, that due to GCP compliance issues identified at center 16078 in trial 006 and the resulting concerns over data integrity, all 51 patients at the center were to be excluded from all analysis populations.

6.1 Indication

The applicant has proposed that the indication be; "…the topical treatment of acne vulgaris in patients 12 years of age and older."

6.1.1 Methods

To demonstrate efficacy, the applicant submitted data from two identically designed Phase 3 pivotal trials, trial 225678-006 and 225678-007. These were multicenter, double-blind, randomized, parallel-group, vehicle-controlled, 12-week trials. These are further described in the table below:

Table 12: Trials Used to Evaluate Efficacy

Protocol #	Type of trial	Trial Design	Subject Population/ # of sites	Test products/dosage regimen	Subjects in group: randomized/ completed	Diagnosis/ treatment duration
225678-006	Safety and efficacy	Phase 3 multicenter, randomized, double-blind, vehicle controlled, parallel group study	Age 12 and older 105: 96 US, 9 Canada	1. Aczone gel, 7.5 % 2. Vehicle Once daily	1044*/948 1058*/976 Total: 2102/1924	moderate facial acne vulgaris (a score of 3 [moderate] on the GAAS) 12 weeks
225678-007	Safety and efficacy	Phase 3 multicenter, randomized, double-blind, vehicle controlled, parallel group study	Age 12 and older 103: 93 US, 10 Canada	1. Aczone gel, 7.5 % 2. Vehicle Once daily	1118/1026 1120/1027 Total: 2238/2053	moderate facial acne vulgaris (a score of 3 [moderate] on the GAAS) 12 weeks

*Excludes subjects from center 16078 (25 on Aczone 7.5% gel and 26 on vehicle gel.)
Source: Applicant's NDA, from Module 5, adapted from 5.2 Tabular Listing of all Clinical Studies and from 5.3.5.1 Clinical Study Reports for trials 225678-006 and 225678-007.

6.1.2 Demographics

Baseline demographics including age, gender, race, and country where studied were generally balanced across treatment arms within the two trials and between each trial. The mean age was 20 in all treatment groups. Slightly more females (55 to 57%) were studied than males (43 to 45%). The predominant race studied was White (54 to 62% across treatment groups).

Table 13: Demographics ITT Population

	Trial 006[1]		Trial 007	
	ACZONE (N=1044)	**Vehicle (N=1058)**	**ACZONE (N=1118)**	**Vehicle (N=1120)**
Age				
Mean (SD)	20.0 (7.4)	20.0 (7.5)	20.5 (8.2)	20.4 (7.4)
Median	17.0	17.0	18.0	18.0
Range	12 – 63	12 – 53	12 – 61	12 – 54
12-17	525 (50%)	554 (52%)	541 (48%)	530 (47%)
18+	519 (50%)	504 (48%)	577 (52%)	590 (53%)
Gender				
Male	453 (43%)	476 (45%)	500 (45%)	489 (44%)
Female	591 (57%)	582 (55%)	618 (55%)	631 (56%)
Race				
White	647 (62%)	623 (59%)	601 (54%)	619 (55%)
Black	173 (17%)	189 (18%)	230 (21%)	220 (20%)
Hispanic[2]	135 (13%)	156 (15%)	212 (19%)	191 (17%)
Asian	44 (4%)	43 (4%)	37 (3%)	44 (4%)
Other	45 (4%)	47 (4%)	38 (3%)	46 (4%)
Country				
U.S.	984 (94%)	997 (94%)	1057 (95%)	1058 (94%)
Canada	60 (6%)	61 (6%)	61 (5%)	62 (6%)

SD: Standard Deviation

[1] Excludes subjects from center 16078 (a total of 51 subjects)

[2] The applicant uses Hispanic as a racial category rather than as an ethnic category as used by the U.S. Census Bureau.

Source: Statistical Review NDA 207154, Table 5, p. 9.

Baseline disease characteristics were generally balanced across treatment arms within the two trials and between each trial.

Table 14: Baseline Disease Characteristics ITT Population

	Trial 006[1]		Trial 007	
	ACZONE (N=1044)	Vehicle (N=1058)	ACZONE (N=1118)	Vehicle (N=1120)
GAAS				
3 – Moderate	1043	1058	1118	1119
4 - Severe	1	0	0	0
Inflammatory Lesion Counts				
Mean (SD)	28.8 (8.0)	29.3 (8.1)	29.6 (7.7)	30.0 (7.9)
Median	26.0	27.0	28.0	28.0
Range	11 – 50	20 – 50	20 – 62	20 – 57
Non-Inflammatory Lesion Counts				
Mean (SD)	46.9 (16.6)	48.6 (17.5)	46.7 (15.3)	46.7 (15.0)
Median	41.0	43.0	42.0	42.0
Range	4 – 100	30 – 106	21 – 112	30 – 100

SD: Standard Deviation

[1] Excludes subjects from center 16078 (a total of 51 subjects)

Source: Statistical Review NDA 207154, Table 5, p. 9.

For inflammatory lesion counts, mean (28.8 to 30.0) and median (26.0 to 28.0) were similar across treatment arms within trials and between trials. For non-inflammatory lesion counts mean (46.7 to 48.6) and median (41.0 to 43.0) were similar across treatment arms within trials and between trials.

6.1.3 Subject Disposition

In general, subject discontinuation was balanced across treatment arms within the two trials and between each trial. (It is noted that the rate of discontinuation in trial 006 was slightly higher in the Aczone 7.5% gel arm comparted to the vehicle arm.)

Table 15: Disposition of Subjects ITT Population

	Trial 006[1]		Trial 007	
	ACZONE (N=1044)	Vehicle (N=1058)	ACZONE (N=1118)	Vehicle (N=1120)
Discontinued	96 (9.2%)	82 (7.8%)	92 (8.2%)	93 (8.3%)
Adverse Event	4 (0.4%)	5 (0.5%)	2 (0.2%)	2 (0.2%)
Lack of Efficacy	0	1 (0.1%)	1 (0.1%)	1 (0.1%)
Lost to Follow-Up	38 (3.6%)	29 (2.7%)	45 (4.0%)	40 (3.6%)
Other	28 (2.7%)	18 (1.7%)	25 (2.2%)	28 (2.5%)
Personal Reasons	21 (2.0%)	20 (1.9%)	15 (1.3%)	19 (1.7%)
Pregnancy	3 (0.3%)	3 (0.3%)	2 (0.2%)	1 (0.1%)
Protocol Violations	2 (0.2%)	6 (0.6%)	2 (0.2%)	2 (0.2%)

[1] Excludes subjects from center 16078 (a total of 51 subjects)

Source: Statistical Review NDA 207154, Table 4, p. 8.

6.1.4 Analysis of Primary Endpoint(s)

The primary analysis population specified in the protocol was the intent-to-treat (ITT) population, defined as all randomized subjects. The protocol also specified supportive analyses using the per-protocol (PP) population which was defined as all randomized subjects with no protocol deviations during the trial that might potentially affect the primary efficacy analyses.

The protocol specified the following co-primary efficacy endpoints:

- Proportion of subjects with a 0 (none) or 1 (minimal) on the GAAS at Week 12
- Absolute change in inflammatory lesion counts from baseline to Week 12
- Absolute change in non-inflammatory lesion counts from baseline to Week 12

Aczone gel, 7.5% was statistically superior (p-values ≤ 0.004) to vehicle gel on all three co-primary efficacy endpoints in both trials for the ITT population.

Table 16: Results for the Co-Primary Efficacy Endpoints at Week 12 (MI, ITT)

Endpoint	**Trial 006(1)**			**Trial 007**		
	ACZONE (N=1044)	**Vehicle (N=1058)**	**P-value**	**ACZONE (N=1118)**	**Vehicle (N=1120)**	**P-value**
GAAS:						
None or Minimal*	311.9 (30%)	224.2 (21%)	<0.001(2)	333.3 (30%)	234.1 (21%)	<0.001(2)
Absolute Change in Inflammatory Lesion Counts:						
Mean*	16.1	14.3		15.6	14.0	
LS Mean(3)	16.1	14.1	<0.001(3)	15.6	13.8	<0.001(3)
Absolute Change in Non-Inflam. Lesion Counts:						
Mean*	20.7	18.0		20.8	18.7	
LS Mean(3)	20.8	17.6	<0.001(3)	20.7	18.5	0.004(3)

*The values displayed are the averages over the 20 imputed datasets (MI).
(1) Excluding subjects from center 16078 (a total of 51 subjects).
(2) P-value from a CMH test stratified by gender.
(3) LS means and p-values from an ANCOVA model with terms for treatment, gender, and baseline lesion counts.

Source: Statistical Review NDA 207154, Table 6, p. 10. (Results are noted to be the same as applicant's analysis.)

Results for the PP analysis were similar and were statistically significant. Please see statistician's review.

6.1.5 Analysis of Secondary Endpoints(s)

For the secondary efficacy endpoints based on lesion counts [i.e., absolute change from baseline in total lesion counts and percent change in lesions counts (inflammatory, non-inflammatory, and total)], Aczone gel, 7.5% was statistically superior (p-values ≤ 0.001) to vehicle gel in both trials.

Table 17: Results for the Secondary Efficacy Endpoints (Based on Lesion Counts) at Week 12 (MI(1), ITT)

Endpoint	Trial 006(2)			Trial 007		
	ACZONE (N=1044)	**Vehicle (N=1058)**	**P-value**	**ACZONE (N=1118)**	**Vehicle (N=1120)**	**P-value**
Absolute Change in Total Lesion Counts:						
Mean*	36.9	32.3		36.5	32.7	
LS Mean(3)	36.9	31.7	<0.001(4)	36.2	32.3	<0.001(4)
Percent Change in Total Lesion Counts:						
Mean*	49.4%	42.7%		49.2%	43.6%	
LS Mean(3)	48.7%	42.4%	<0.001(4)	48.9%	43.2%	<0.001(4)
Percent Change in Inflammatory Lesion Counts:						
Mean*	56.2%	49.5%		54.2%	47.6%	
LS Mean(3)	55.5%	49.0%	<0.001(4)	53.8%	47.3%	<0.001(4)
Percent Change in Non-Inflammatory Lesion Counts:						
Mean*	45.0%	38.9%		46.2%	40.8%	
LS Mean(3)	44.4%	38.4%	<0.001(4)	45.9%	40.4%	0.001(4)

*The values displayed are the averages over the 20 imputed datasets (MI).
(1) Missing data for lesion count endpoints were imputed using multiple imputation (MI).
(2) Excluding subjects from center 16078 (a total of 51 subjects).
(3) LS means and p-values from an ANCOVA model with terms for treatment, gender, and baseline lesion counts. LS = least squares

Source: Statistical Review NDA 207154, Table 6, p.10. (Results are noted to be the same as applicant's analysis.)

6.1.6 Other Endpoints

Other endpoints were analyzed based on an Acne Symptom and Impact Scale (ASIS). Please see statistician's review. At the End-of-Phase 2 meeting (August 28, 2013) the Agency had stated that the proposed patient reported outcomes may have limited utility for eventual product labeling.

6.1.7 Subpopulations

For gender, the treatment effect was greater in females for all three co-primary endpoints in both trials. Results in the race subgroups are mixed in Trials 006 and 007.

For age, adult subjects had better results than adolescent subjects for Aczone gel, 7.5% and vehicle gel in all three co-primary efficacy endpoints. In both trials, the treatment effect on GAAS success was greater in adult subjects than adolescent subjects; however, for change in inflammatory and non-inflammatory lesion counts, the treatment effect was equal or greater in adolescent subjects than adult subjects.

The majority of the subjects enrolled in the trials were from the U.S. (approximately 96%); therefore, it would be difficult to detect any differences in efficacy for subjects from Canada.

Table 18: Co-Primary Efficacy Results at Week 12 by Gender, Race, Age, and Country for Trial 006 (MI, ITT)

	GAAS (none or minimal)		Absolute Change in Inflammatory Lesions		Absolute Change in Non-Inflammatory Lesions	
Subgroup (N_A, N_V)	ACZONE (N=1044)	Vehicle (N=1058)	ACZONE (N=1044)	Vehicle (N=1058)	ACZONE (N=1044)	Vehicle (N=1058)
Gender						
Male (453, 476)	24%	18%	15.0	13.4	18.7	16.5
Female (591, 582)	34%	24%	17.0	15.0	22.3	19.3
Race						
White (647, 623)	28%	19%	15.6	13.2	19.4	16.7
Black (173, 189)	31%	22%	16.5	15.8	21.3	18.4
Other(1) (224, 246)	33%	27%	17.6	16.0	24.4	21.1
Age						
12-17 (525, 554)	24%	17%	15.2	12.9	19.5	15.3
18+ (519, 504)	36%	26%	17.1	15.8	22.0	21.0
Country						
U.S. (984, 997)	30%	22%	16.2	14.3	20.9	18.2
Canada (60, 61)	26%	9%	15.2	15.0	18.4	15.6

*The values displayed are the averages over the 20 imputed datasets (MI).
(1) Other: Hispanic, Asian and Other.
A = active
V = vehicle
Source: Statistical Review NDA 207154, Table 21, p. 20

Table 19: Co-Primary Efficacy Results at Week 12 by Gender, Race, Age, and Country for Trial 007 (MI, ITT)

Subgroup (N_A, N_V)	GAAS (none or minimal)		Absolute Change in Inflammatory Lesions		Absolute Change in Non-Inflammatory Lesions	
	ACZONE (N=1118)	Vehicle (N=1120)	ACZONE (N=1118)	Vehicle (N=1120)	ACZONE (N=1118)	Vehicle (N=1120)
Gender						
Male (500, 489)	25%	19%	14.6	13.3	18.2	18.1
Female (618, 631)	33%	22%	16.5	14.6	23.0	19.1
Race						
White (601, 619)	29%	19%	15.3	13.1	19.1	16.4
Black (230, 220)	34%	28%	16.9	17.0	23.4	22.4
Other(1) (287, 281)	30%	19%	15.3	13.8	22.4	20.7
Age						
12-17 (541, 530)	21%	16%	14.6	13.0	17.9	15.3
18+ (577, 590)	38%	26%	16.5	14.9	23.6	21.7
Country						
U.S. (1057, 1058)	30%	21%	15.8	14.5	21.5	19.0
Canada (61, 62)	25%	15%	12.2	7.0	10.1	13.1

*The values displayed are the averages over the 20 imputed datasets (MI).
(1) Other: Hispanic, Asian and Other.
A = active
V = vehicle
Source: Statistical Review NDA 207154, Table 22, p. 21

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Clinical data regarding dosing was not provided in the current submission. Some information regarding exposure-response relationships was submitted and reviewed in NDA 21794, ACZONE® (dapsone) Gel, 7.5%.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Analyses of persistence of efficacy and/or tolerance were not performed.

6.1.10 Additional Efficacy Issues/Analyses

As stated by the statistical reviewer, for the assessment of GAAS, the interpretation of a "few" or "no" lesions seemed to vary from investigator to investigator. Some subjects counted as successes under the GAAS seemed to have relatively high lesion counts for the definition of "none" (no evidence of facial acne vulgaris) or "minimal" [a few non-inflammatory lesions (comedones) are present; a few inflammatory lesions (papules/pustules) may be present]. Subjects scored as 0 (none) had as many as 10 inflammatory lesions or 45 non-inflammatory lesions. Subjects scored as 1 (minimal) had as many as 57 inflammatory lesions or 102 non-inflammatory lesions. The

statistical reviewer does not that lesion counts generally do increase with increasing Global Acne Assessment Score (GAAS).

To see the effects of the variable interpretation of the categories in the GAAS, the statistical reviewer conducted a sensitivity analysis where subjects with a GAAS score of 0 or 1 at Week 12 were imputed as failures if they had more than a certain number of inflammatory or non-inflammatory lesions. The reviewer considered three sets of values:

- Based on inclusion criteria for inflammatory and non-inflammatory lesion counts (i.e., considered failures if they had the following lesion counts - Inflammatory ≥ 20 or Non-Inflammatory ≥ 30)
- Based on overall means for inflammatory and non-inflammatory lesion counts at Week 12 for subjects with a GAAS score of 2 (mild) at Week 12 (i.e., considered failures if they had the following lesion counts - Inflammatory ≥ 12 or Non-Inflammatory ≥ 27)
- Based on overall means for inflammatory and non-inflammatory lesion counts at Week 12 for subjects with a GAAS score of 1 (minimal) at Week 12 (i.e., considered failures if they had the following lesion counts - Inflammatory ≥ 6 or Non-Inflammatory ≥ 14)

The results of the sensitivity analysis showed that while the response rates and treatment effect decreased with the stricter requirement for success, the treatment effect remained statistically significant (p-values ≤ 0.002) in both trials. Please also see statistical review.

7 Review of Safety

Safety Summary

The principal evaluation of safety for ACZONE ® (dapsone) Gel, 7.5%, for the indication of topical treatment of acne vulgaris in patients 12 years of age and older, was based on trials that included subjects treating acne vulgaris on the face once daily for 12 weeks. The trials included in the pooled safety database include trial **225678-006** (pivotal Phase 3, 2-arm vehicle controlled) and trial **225678-007** (pivotal Phase 3, 2-arm vehicle controlled). Additional safety information is available from the four trials; **225678-004** pharmacokinetic (Phase 1, 4-arm, active controlled), **225678-009** dermal safety (Phase 1, RIPT sensitization), **225678-010** dermal safety (Phase 1, phototoxicity), and **225678-011** dermal safety (Phase 1, photoallergy). All of the trials were conducted with the final-to-be-marketed formulation. (Trial 225678-004 pharmacokinetic (PK) included an arm with the final-to-be-marketed formulation.)

Pooled Safety Database (2 Vehicle Controlled Trials):
The trials in the pooled safety database were multicenter, randomized, prospective, vehicle-controlled, and parallel group trials in subjects with acne vulgaris on the face. Acne affected areas of the neck, upper chest, upper back, and shoulders could also be treated. Subjects applied study product once daily for 12 weeks. The median total dose used was 41.43 grams in the Aczone 7.5% gel group and 42.27 grams in the vehicle group. The pooled safety database includes 4336 subjects exposed to study drugs; 2161 to Aczone 7.5% gel and 2175 to vehicle. Subjects ranged in age from 12 to 63 years. The mean age for the Aczone group was 20.3 years and 20.2 years for the vehicle group. Adolescents (ages 12 to 17) comprised 49.3 % of those in the Aczone group and 49.8 % of those in the vehicle group.

Adverse Events/ Adverse Reactions:
No deaths were reported in any of the six clinical trials. For the pooled trials, in the ACZONE group, 7 of 2175 subjects (0.3%) had a total of 8 serious treatment emergent adverse events (TEAEs). These were application site dermatitis (33 days after treatment), appendicitis (46 days after treatment), tibia fracture 34 days after treatment), acute myeloid leukemia (42 days after treatment), helicobacter pylori infection (19 days after treatment), appendicitis, peritoneal hematoma (50 and 53 days, respectively after treatment), and alcoholism (28 days after treatment). The 8 serious TEAEs were considered not related to treatment with Aczone.

For the pooled trials, in the vehicle group: 9 of 2175 subjects (0.4%) had a total of 9 serious TEAEs. These were induced abortion (85 days after treatment), lumbar vertebral fracture (62 days after treatment), affective disorder (56 days after treatment), depression (75 days after treatment), anxiety (36 days after treatment), spontaneous pneumothorax (36 days after treatment), appendicitis (62 days after treatment), spontaneous abortion (16 days after treatment) and suicidal ideation (16 days after treatment). One serious TEAE, depression, was considered related to study medication (in this case vehicle).

For the pivotal trials, in the ACZONE group, 6 of 2161 subjects (0.3%) had adverse events (TEAEs) leading to discontinuation. The events were; acute myeloid leukemia (42 days after treatment), application site papules and application site discoloration (both 8 days after treatment), (application site acne and application site dermatitis (both 8 days after treatment), erythematous rash and pruritic rash (both 26 days after treatment); application site vesicles, application site swelling, application site pruritus, and pruritus (2, 1, 2, and 2 days after treatment, respectively), and application site discomfort (1 day after treatment).

Of the TEAEs that led to discontinuation in subjects in the ACZONE group, 7 that occurred in 3 subjects were considered to be treatment related by the investigator. These events included application site acne and application site dermatitis in 1 subject;

application site vesicles, application site swelling, application site pruritus, and pruritus in 1 subject; and application site discomfort (described as mild in severity) in 1 subject. For the pivotal trials, in the vehicle group: 7 of 2175 subjects (0.3%) had adverse events (TEAEs) leading to discontinuation. The events were: application site acne (2 days after treatment); application site pain in two subjects (both 1 day after treatment); urinary tract infection (59 days after treatment); contact dermatitis (38 days after treatment); anxiety (36 days after treatment); and headache (2 days after treatment). All events resolved without sequelae, with the exception of urinary tract infection in subject 16015-1396 that was ongoing at study exit.

Of the TEAEs that led to discontinuation in patients in the vehicle group, 3 TEAEs that occurred in 3 subjects in the vehicle group were considered to be treatment related by the investigator. These events included application site pain (described as mild in severity) in 2 subjects and application site acne (described as severe) in 1 subject.

In the pooled safety trials, severe TEAEs in those exposed to ACZONE Gel, 7.5% included; viral gastroenteritis and headache in 2 patients each, and, in 1 patient each, food poisoning, peritoneal hematoma, urinary tract infection, tooth abscess, appendicitis, otitis externa, helicobacter infection, sunburn, alcoholism, application site dermatitis, axillary pain, pain in jaw, and migraine.The application site dermatitis was not considered related to study medication.

In the vehicle group, severe TEAEs included; in 1 patient each, upper abdominal pain, pyrexia, application site acne, gastroenteritis viral, appendicitis, tooth infection, headache, abortion spontaneous, ovarian cyst, pneumothorax spontaneous, lumbar vertebral fracture, dehydration, depression, anxiety, and affective disorder.

Frequencies of TEAEs were similar between ACZONE Gel, 7.5%-treated and vehicle-treated subjects. TEAEs were reported in 18.3% (396/2161) of subjects in the ACZONE Gel, 7.5% group and 18.8% (409/2175) of patients in the vehicle group. The frequency of application site TEAEs was similar between ACZONE Gel, 7.5%-treated and vehicle-treated subjects. The most common application site TEAEs (i.e., those occurring in ≥ 1% of subjects in any treatment group) were: application site dryness (1.2% in the ACZONE Gel, 7.5% group versus 1.0% in the vehicle group), application site pruritus (1.1% versus 0.6%), and application site pain (0.5% versus 1.5%).

Treatment-related TEAEs, or adverse drug reactions, were reported in 3.5% (75/2161) of subjects in the ACZONE Gel, 7.5% group and 3.4% (73/2175) of patients in the vehicle group. The most common treatment related TEAEs (i.e., those occurring in ≥ 0.9% of subjects and at a rate greater than vehicle) were application site events: application site dryness (1.1% in the ACZONE Gel, 7.5% group versus 1.0% in the vehicle group) and application site pruritus (0.9% versus 0.5%).

In the pooled vehicle-controlled trials, subjects studied ranged in age from 12 to 63 years. Thus, regarding geriatric use, data is not available to determine whether geriatric subjects respond differently from younger subjects.
Regarding pediatric use, safety was evaluated in 1066 pediatric subjects 12 to 17 years of age treated with ACZONE Gel, 7.5%. Within this age subgroup, the safety profile, in terms of TEAEs, for ACZONE Gel, 7.5 % was similar to that of the vehicle control. In addition, the frequency of TEAEs was similar among those aged 12 to 17 years of age as compared with subjects ≥ 18 years of age.

Three dermal safety trials were performed in support of this application; **225678-009** (RIPT sensitization), **225678-010** (phototoxicity), and **225678-011** (photoallergy).

For trial **225678-009**, one SAE was reported, an elective abortion, that was not considered to be related to study medication. A total of 6 subjects in subset 2 (RIPT 197 randomized) had study drug withdrawn and were discontinued because of non-serious TEAEs. Two subjects discontinued due to skin discoloration and tremor, both moderate in intensity, that were considered related to study treatment. One subject discontinued due to events of application site pruritus and paraesthesia that were moderate in intensity and considered related to study treatment. One subject discontinued due to application site dermatitis that was considered moderate and probably related to study treatment. One subject discontinued due to myalgia and dyspnea that were considered mild and unlikely related to study treatment and one subject discontinued due to contact dermatitis (a “tape reaction”) that was considered moderate in intensity and not related to study treatment.

Under the conditions of this study, ACZONE Gel, 7.5% and its vehicle did not show potential for sensitization and are unlikely to cause clinically meaningful irritation under normal use conditions.

For trial **225678-010**, no adverse events were reported, and under the conditions of the trial, the investigational products ACZONE Gel, 7.5% and its vehicle did not show potential for phototoxicity in healthy human subjects.

For trial **225678-011**, one serious TEAE was reported, stress cardiomyopathy and was considered not to be related to study treatment. A total of 5 subjects (58 randomized) discontinued the trial due to TEAEs. One subject withdrew because of the serious TEAE, stress cardiomyopathy. Three subjects discontinued due to application site reactions of moderate severity that were considered related to study treatment. Two out of the 3 subjects (Nos. 001 and 008) developed application site irritation in the Induction Phase and patches were relocated twice. Per protocol, the subjects were discontinued. Subject 008 was also discontinued because of a moderate laceration on her index finger that was unrelated to study treatment. One subject (No. 016) developed application site reaction at all sites, 24 hours after patch application, in the Challenge Phase. The subject was not irradiated and was discontinued. One subject withdrew as

a result of urticaria of moderate severity that occurred bilaterally on the upper cheeks and also on the upper neck (distant from the patch sites). The urticaria was considered to be possibly related to study treatment.
Under the conditions of this study, ACZONE Gel, 7.5% and its vehicle did not show clinically significant potential for photoallergy in healthy subjects.

Long Term Safety Assessment:
The applicant did not conduct any long term trials with ACZONE Gel, 7.5 % for the indication of topical treatment of acne vulgaris in patients 12 years of age and older. The reader is referred to section 7.7 (Additional Submissions / Safety Issues) of this review for further discussion of long term safety.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Protocol #	Type of trial	Trial Design	Subject Population/ # of sites	Test products/dosage regimen	Subjects in group: randomized/ completed	Diagnosis/ treatment duration
225678-0009	RIPT Sensiti-zation	Phase 1 single-center, evaluator-blinded, within subject comparison	between 18 and 65 1 US	1. Aczone gel, 7.5% 2. vehicle 3 x weekly, for 21 days	Subset I 40/32 Subset 2 197/170 Total: 237/202	Healthy subjects ~ 6 weeks
225678-10	Phototo xicity	Phase 1 single-center, double-blinded, within subject comparison	between 18 and 65 1 US	1. Aczone gel, 7.5% 2. vehicle One day	Total: 33/30	Healthy subjects One day
225678-11	Photo-allergy	Phase 1 single-center, double-blinded, controlled , randomized, within subject comparison	between 18 and 65 1 US	1. Aczone gel, 7.5% 2. vehicle 2 x weekly, for 21 days	Total:58/49	Healthy subjects ~ 6 weeks

Protocol #	Type of trial	Trial Design	Subject Population/ # of sites	Test products/dosage regimen	Subjects in group: randomized/ completed	Diagnosis/ treatment duration
225678-004	PK	Phase 1, multicenter, randomized, investigator-blinded, active-controlled, multiple-dose, parallel-group study	Age 16 to 35 2 US	1. dapsone 7.5% gel (DAP-11080*) *ACZONE 2.dapsone 7.5% gel (DAP-11078) 3. dapsone 7.5% gel (DAP-11079) Once daily 4. ACZONE Gel, 5% Twice daily	Total: 77/72	Moderate acne vulgaris, 3 on GAAS 28 days
225678-006	Safety and efficacy	Phase 3 multicenter, randomized, double-blind, vehicle controlled, parallel group study	Age 12 and older 105: 96 US, 9 Canada	1. Aczone gel, 7.5 % 2. Vehicle Once daily	1044/948 1058/976 Total: 2102/1924	moderate facial acne vulgaris (a score of 3 [moderate] on the GAAS) 12 weeks
225678-007	Safety and efficacy	Phase 3 multicenter, randomized, double-blind, vehicle controlled, parallel group study	Age 12 and older 103: 93 US, 10 Canada	1. Aczone gel, 7.5 % 2. Vehicle Once daily	1118/1026 1120/1027 Total: 2238/2053	moderate facial acne vulgaris (a score of 3 [moderate] on the GAAS) 12 weeks

Source: Applicant's NDA, from Module 5, adapted from 5.2 Tabular Listing of all Clinical Studies and from 5.3.5.4 Clinical Study Reports 225678-009, 225678-10, 225678-11; 5.3.3.2 225678-004; and 5.3.5.1 225678-006, 225678-007.

The integrated analysis of safety includes trials wherein subjects with acne vulgaris applied study medicine once daily for 12 weeks. The trials included in the integrated analysis of safety include:

- 225678-006 pivotal (Phase 3, 2-arm vehicle controlled)
- 225678-007 pivotal (Phase 3, 2-arm vehicle controlled)

Deaths, serious adverse events, discontinuation due to adverse events and clinically important adverse events were considered from all clinical studies.

7.1.2 Categorization of Adverse Events

For the two pivotal Phase 3 trials, all adverse events from both studies were coded from the verbatim text to the lower level term and mapped to the PT (preferred term) and primary SOC (system organ class) using MedDRA version 17.0. MedDRA version 17.0 was also used for the 3 Phase 1 studies; 225678-0009 (RIPT sensitization), 225678-10 (phototoxicity), and 225678-11 (photoalllergy).

For the PK study, 225678-004, all adverse events were coded from the verbatim text to the lower level term and mapped to PT and primary SOC using MedDRA; version 16.0

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

For all six trials in the clinical development program, all adverse events were coded from the verbatim text to the lower level term and mapped to PT and primary SOC using MedDRA.

Pretreatment adverse events (PTAEs) were defined as adverse events that occurred after informed consent had been signed and prior to the first dose of study product.

A TEAE (treatment-emergent adverse event) was defined as a postbaseline adverse event where there was no PTAE of the same MedDRA PT, or the maximum severity during the postbaseline period was more severe than the maximal severity of any PTAE of the same MedDRA PT, or within the current period there was a PT/primary SOC within the same MedDRA PT from the previous period with a maximum severity lower than the current record or the adverse event was reported as a serious event during the postbaseline period.

For the Phase 3 trials, TEAEs were summarized by the applicant as follows:

- overall incidence of TEAEs, including the incidence of treatment-related TEAEs, treatment unrelated TEAEs, serious TEAEs, and TEAEs leading to study discontinuation
- all TEAEs, treatment-related TEAEs, and serious TEAEs by SOC and PT
- all TEAEs, treatment-related TEAEs, and serious TEAEs by SOC, PT, and maximum severity level
- all TEAEs and treatment-related TEAEs leading to patients' study discontinuation by SOC and PT

For the PK trial, 225678-004, incidences of TEAEs and treatment-related TEAEs were summarized by treatment group as well as by the total of the 3 dapsone 7.5% groups combined. TEAEs, treatment related TEAEs leading to study discontinuation, and serious TEAEs were summarized by PT within primary SOC.

For the other 3 Phase 1 trials, the number and percent of subjects reporting PTAEs, TEAEs regardless of causality, and treatment-related TEAEs at least once were tabulated by descending order of incidence, by primary SOC, PT, and by severity if warranted. Adverse events were summarized using frequency tables.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the pooled safety trials, 4336 subjects were exposed to study drugs; 2161 in the ACZONE Gel, 7.5% group and 2175 in the vehicle group.

Table 20: Subjects Exposed in Pooled Safety Trials

Treatment	Safety Population		
	Total	Trial 006	Trial 007
	Subjects (%)	Subjects (%)	Subjects (%)
ACZONE Gel, 7.5%	2161 (100)	1044 (48)	1117 (52)
Vehic e	2175 (100)	1057 (49)	1118 (51)

Source: Applicant's NDA from module 2.7.4, Summary of Clinical Safety

Duration of exposure:
In the pooled safety studies, mean duration of exposure for Aczone 7.5% gel and for vehicle was similar, 79.4 and 79.7 days respectively.

Table 21: Treatment Duration (days) Pooled Safety Trials

Exposure	Aczone Gel, 7.5%	vehicle
	N = 2161	N = 2175
Mean	79.4	79.7
SD	(17.05)	(16.54)
Median	84.0	84.0
Minimum	1	1
Maximum	147	124

Source: Applicant's NDA from Module 2.7.4, Summary of Clinical Safety, adapted from Table 8, p 29.

Amount of study medication used
In the pooled safety trials, used study drug was returned and weighed as specified in the protocol. (Study drug containers were weighed at the week 4, 8, and 12/early exist visits.)

The mean total amount of study medication used was 50.34 grams in the ACZONE Gel, 7.5% group and 51.57 grams in the vehicle group.

Table 22: Total Amount of Study Drug Used (Pooled Safety Trials)

Exposure	ACZONE Gel, 7.5%[a]	Vehicle[a]
	N = 2107	N = 2134
Mean	50.34	51.57
SD	39.359	38.682
Median	41.43	42.27
Minimum	0	0
Maximum	262.10	258.10

[a] Includes subjects who applied the medication to face only and subjects who applied medication to both face and other areas. Subjects with missing drug returns are not included in the summary.
Source: Applicant's NDA from Module 5.3.5.3, ISS adapted from Table 2-2.3, p. 198.

The mean daily amount of study medication used was .64 grams in the ACZONE Gel, 7.5% group and .65 grams in the vehicle group.

Table 23: Average Daily Use of Study Drug (Pooled Safety Trials)

Exposure	ACZONE Gel, 7.5%[a]	Vehicle[a]
	N = 2107	N = 2132
Mean	0.64 grams	0.65 grams
SD	0.770	0.513
Median	0.52	0.53
Minimum	0	0
Maximum	21.20	8.00

[a]Average daily use is equal to the weight of the medication divided by the number of days with applied doses for patients who applied the medication to face only and patients who applied medication to both face and other areas of the body.
Source: Applicant's NDA from Module 5.3.5.3, ISS adapted from Table 2-2.3, p. 198.

Demographic Characteristics
Subjects ranged in age from 12 to 63 years. The mean age for the ACZONE group was 20.3 years and 20.2 years for the vehicle group. Adolescents (ages 12 to 17) comprised 49.3 % of those in the ACZONE group and 49.8 % of those in the vehicle group.

Treatment groups exhibited a mildly higher proportion of female subjects (ACZONE 55.9 % and vehicle 55.6 %) as compared with male subjects (ACZONE 44.1 % and vehicle 44.4%). The distribution of subjects across races was similar for both the ACZONE group (Caucasian 57.7%, Black 18.6%, Hispanic 16.1%, Asian 3.7%) and the vehicle group (Caucasian 57.1%, black 18.8%, Hispanic 15.9%, 4.0%).

Table 24: Demographic Characteristics (Pooled Safety Trials)

	ACZONE Gel, 7.5%	**vehicle**
	N = 2161	N = 2175
Demographic		
Age (years)		
Mean (SD)	20.3 (7.80)	20.2 (7.44)
Median	18.0	18.0
Min to max	12 to 63	12 to 54
Age (years) (n [%]		
12 to 17	1066 (49.3)	1084 (49.8)
≥ 18	1095 (50.7)	1091 (50.2)
Sex (n [%]		
Male	953 (44.1)	965 (44.4)
Female	1208 (55.9)	1210 (55.6)
Race		
Caucasian	1247 (57.7)	1241 (57.1)
Black	403 (18.6)	409 (18.8)
Asian	81 (3.7)	87 (4.0)
Hispanic*	347 (16.1)	345 (15.9)
Other	83 (3.8)	93 (4.3)
Caucasian	1247 (57.7)	1241 (57.1)
Non-Caucasian	914 (42.3)	934 (42.9)

SD = standard deviation
* The applicant uses Hispanic as a racial category rather than as an ethnic category as used by the U.S. Census Bureau.
Source: Applicant's NDA from Module 2.7.4, Summary of Clinical Safety, Table 9, p 31.

By comparison the US population (as of 2013, 1 year estimate) was 76.2% White, 13.8% Black or African American, 6% Asian, 1.7% American Indian and Alaska Native, 0.4% Native Hawaiian and Other Pacific Islander, 5.2% other race. A total of 17.1% of the population was Hispanic (of any race) and 82.9% were not Hispanic or Latino.[1]

7.2.2 Explorations for Dose Response

Explorations for Dose response were not performed in the current submission

7.2.3 Special Animal and/or In Vitro Testing

Special animal and/or In Vitro testing was not performed in the current submission.

7.2.4 Routine Clinical Testing

The routine clinical testing was designed to assess the safety and efficacy of use of daily application for up to 12 weeks.

7.2.5 Metabolic, Clearance, and Interaction Workup

Assessment of drug-drug interactions was not performed in the current submission.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The applicant's efforts to detect adverse events that are associated with the drug class of the active ingredient (dapsone) were adequate in the development program, in regard to local safety, collection of adverse event data, and the potential for systemic effects.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in any of the six clinical trials; 225678-006 pivotal (Phase 3, 2-arm vehicle controlled), 225678-007 pivotal (Phase 3, 2-arm, vehicle controlled), 225678-004 PK (Phase 1, 4-arm, active controlled), 225678-009 dermal safety (Phase 1, RIPT sensitization), 225678-010 dermal safety (Phase 1, phototoxicity), and 225678-011 dermal safety (Phase 1, photoallergy).

[1] U. S. Census Bureau, 2013 American Community Survey, Table DP05 - ACS Demographic and Housing Estimates, 2013 American Community Survey 1-Year Estimates.

7.3.2 Nonfatal Serious Adverse Events

In the pooled safety trials:

- In the ACZONE group: 7 of 2175 subjects (0.3%) had a total of 8 serious TEAEs. These were application site dermatitis (33 days after treatment), appendicitis (46 days after treatment), tibia fracture (34 days after treatment), acute myeloid leukemia (42 days after treatment), helicobacter pylori infection (19 days after treatment), appendicitis, peritoneal hematoma (50 and 53 days, respectively after treatment), and alcoholism (28 days after treatment). The 8 serious TEAEs were considered not related to treatment with Aczone. One serious TEAE, acute myeloid leukemia, led to treatment and trial discontinuation.
- In the vehicle group: 9 of 2175 subjects (0.4%) had a total of 9 serious TEAEs. These were induced abortion (85 days after treatment), lumbar vertebral fracture (62 days after treatment), affective disorder (56 days after treatment), depression (75 days after treatment), anxiety (36 days after treatment), spontaneous pneumothorax (36 days after treatment), appendicitis (62 days after treatment), spontaneous abortion (16 days after treatment) and suicidal ideation (16 days after treatment). One serious TEAE, depression, was considered related to study medication. The remaining 8 were not considered related to study medication. One serious TEAE, anxiety, led to treatment and trial discontinuation.

Details of Cases of Interest:
Event of application site dermatitis: Trial 225678-006, subject 16018-1953:
The subject was a 33 year old black female randomized to ACZONE Gel, 7.5% on (b) (6) The subject had no relevant medical history and no concomitant medications were reported. The adverse event of moderate to severe application site dermatitis (verbatim term “contact dermatitis to application site of face”) was reported to have started on day 33 of treatment (b) (6) The AE is reported to have been caused by gardening materials – the subject had an adverse reaction to a landscaping item that caused swelling and erythema on her face for 5 to 7 days. The subject had stopped applying study product for 5 days due to the event, without abatement of the swelling and erythema. She resumed study treatment with ACZONE Gel, 7.5% after 5 days, while the event of contact dermatitis was still ongoing. On (b) (6), the event of application site dermatitis was reported as a serious TEAE. The patient then presented to the emergency room, was admitted to the hospital overnight, and treated with oral diphenhydramine hydrochloride, intramuscular corticosteroids, and oral corticosteroids taper unti (b) (6). The application site dermatitis resolved without sequelae 21 days after the start of the event, while she was still receiving treatment with ACZONE Gel, 7.5%. The patient completed the study as scheduled on June, 25 2014. This

reviewer agrees with the assessment that the "contact dermatitis to application site of face" was not related to study medication.

Event of acute myeloid leukemia: Trial 22678-007, subject 27017-6675:
The subject was a 15 year old Caucasian male randomized to ACZONE Gel 7.5% on June 23, 2014. The subject had no relevant medical history and no relevant concomitant medications were reported. According to the patient's mother, he had body aches from July 26, 2014, and a fever and headache from July 28, 2014. On (b) (6), a serious adverse event of acute myeloid leukemia of severe intensity was reported. The patient presented to the emergency room on (b) (6) as he had not been feeling well. A laboratory test revealed that the white blood cell and platelet counts were out of range. The patient began treatment with intravenous cefepime and oral sulfamethoxazole+trimethoprim for an infected pustule in the sacral area and for chemotherapy prophylaxis, with paracetamol for pain, and intravenous lorazepam and diphenhydramine hydrochloride, ondansetron and ranitidine for nausea prophylaxis on (b) (6). The patient was then directed to a children's hospital for further work-up. Treatment with study medication was stopped after application on (b) (6) and the subject was withdrawn from the trial on August 4, 2016. The investigator considered the acute myeloid leukemia not to be related to study treatment. This reviewer agrees with this assessment.

It is noted that in the safety analysis for the NDA 21-794, for ACZONE Gel, 5%, in the clinical program, SAEs were reported for 11 subjects for the ACZONE 5% group and for 7 subjects in the vehicle control group. The safety database included 2372 subjects with acne vulgaris exposed to ACZONE Gel, 5% and 1660 subjects with acne vulgaris exposed to vehicle control.

Table 25: Serious Treatment-Emergent Adverse Events (Pooled Safety Trials)

System Organ Class (SOC)	ACZONE Gel, 7.5%	vehicle
	N = 2161	N = 2175
Preferred Term[1]	n (%)	n (%)
Gastrointestinal disorders		
Peritoneal hematoma	1 (<0.1)	0 (0)
SOC total	1 (<0.1)	0 (0)
General disorders and administration site conditions		
Application site dermatitis	1 (<0.1)	0 (0)
SOC total	1 (<0.1)	0 (0)
Infections & Infestations		
Appendicitis	2 (0.1)	1 (<0.1)
Helicobacter infection	1 (<0.1)	0 (0)
SOC total	3 (0.1)	1 (<0.1)
Injury, poisoning, & procedural complications		
Tibia fracture	1 (<0.1)	0 (0)

System Organ Class (SOC)	ACZONE Gel, 7.5%	vehicle
	N = 2161	N = 2175
Preferred Term[1]	n (%)	n (%)
Lumbar vertebral fracture	0 (0)	1 (<0.1)
SOC total	1 (<0.1)	1 (<0.1)
Neoplasms benign, malignant, and unspecified		
Acute myeloid leukemia	1 (<0.1)	0 (0)
SOC total	1 (<0.1)	0 (0)
Pregnancy, puerperium, & perinatal conditions		
Abortion spontaneous[2]	0 (0)	1 (0.1)
SOC total	0 (0)	1 (<0.1)
Psychiatric disorders		
Alcoholism	1 (<0.1)	0 (0)
Affective disorder	0 (0)	1 (<0.1)
Anxiety	0 (0)	1 (<0.1)
Depression	0 (0)	1 (<0.1)
Suicidal ideation	0 (0)	1 (<0.1)
SOC total	1 (<0.1)	4 (0.2)
Respiratory, thoracic, & mediastinal disorders		
Pneumothorax spontaneous	0 (0)	1 (<0.1)
SOC total	0 (0)	1 (<0.1)
Surgical & medical procedures		
Abortion induced[2]	0 (0)	1 (0.1)
SOC total	0 (0)	1 (<0.1)
Total number of SAEs[3]	8	9
Total number of subjects	7 (0.3)	9 (0.4)

[1] Classification according to MedDRA version 17.0

[2] Percentages are based on the female population.

[3] All serious treatment-emergent adverse events are represented, regardless of relationship to treatment. Within each preferred term, a patient is counted at most once.

Source: Applicant's NDA from Module 2.7.4, Summary of Clinical Safety, Table 14, p 43.

Serious TEAEs in Phase 1 Trials:

●Trial 225678-004 PK (Phase 1, 4-arm, active controlled): no serious TEAEs

●Trial 225678-009 dermal safety (Phase 1, RIPT sensitization): One serious TEAE reported of elective abortion:

The subject was a 22 year old Black/African American female. The subject had no relevant medical history and no concomitant medications were reported. The subject underwent screening and day 1 procedures on May 21, 2014 (day 1), including a UPT that had a negative result. She was enrolled into subset 2, and underwent the RIPT procedures. She received 9 applications of study treatment (dapsone 7.5% gel, vehicle,

and saline [negative control]) over a 21-day induction period. On June 23, 2014 (day 34) she had a negative UPT and underwent the study challenge procedure, which included application of dapsone 7.5% gel and its corresponding vehicle. On June 28, 2014 (day 28), 5 days after the challenge procedure, the subject had a positive UPT. Subsequently, she informed the site that she had undergone an abortion to terminate the pregnancy on July 2, 2014 (day 43).

Study treatment had been completed prior to this event, so no action was taken regarding the study drug. The adverse event did not result in discontinuation from the trial. The investigator assessed the treatment emergent adverse event (TEAE) of abortion to be moderate in severity and not related to the study treatment. It was classified as "serious" in accord with the sponsor's definition of a serious TEAE (i.e., that includes any "medically important event or reaction," including "all cancers and abortions").

●Trial 225678-010 dermal safety (Phase 1, phototoxicity): no serious TEAEs

αTrial 225678-011 dermal safety (Phase 1, photoallergy): One serious TEAE reported of stress (takotsubo) cardiomyopathy:
The subject was a 52 year old white female. The subject's medical history included hypothyroidism (ongoing since 1981), depression (ongoing since 2012), herniated discs (ongoing since 2012), a benign tumor in her left ovary (2009), and hysterectomy (2009). The subject's hospital records note that she was a current smoker (1.5 packs/day) for 23 years. The subject's relevant concomitant medications included levothyroxine (125 mcg qd orally, ongoing since 1981) for hypothyroidism and bupropion SR for depression (150 mg bid orally, ongoing since 2012).

The subject received patch applications of dapsone 7.5% topical gel and vehicle gel, applied topically to the back on (b) (6), and (b) (6) during the Induction Phase of this photoallergy study. On the evening of (b) (6), approximately 2 days after the most recent patch application, the subject experienced severe chest pain and reported to the hospital emergency department. The hospital records report that she complained of chest pain and shortness of breath; she also reported back and left arm pain which she attributed to back pain from herniated discs. The subject reportedly had an "erratic pulse" upon her arrival at the hospital and underwent the first of 3 blood draws for assessment of cardiac enzymes. She was admitted to the hospital. While hospitalized, the subject had the following concomitant medical procedures: cardiac enzyme blood work-up (troponin), left heart catheterization, coronary arteriography, left ventriculogram, electrocardiogram, hematology work-up, and chemistry work-up. Hospital records show a peak troponin level of 0.180. The catheterization results showed that her coronary arteries were normal. The left ventriculogram results showed an estimated ejection fraction of 60% with abnormal left ventricular wall motion analysis showing apical akinesis.

The subject's initial diagnosis was "non-ST elevation myocardial infarction (>12 to <24 hours)." The diagnosis was revised to "cardiomyopathy (Takotsubo type)" or "stress cardiomyopathy." She continued to receive levothyroxine and was given the following medications for the cardiomyopathy:

- Atorvastatin: 80 mg once orally on (b) (6)
- Clopidogrel:
  - 75 mg qd orally on (b) (6)
  - 300 mg qd orally (b) (6)
- Enoxaparin: 60 mg bid subcutaneously from (b) (6)
- Lopressor: 25 mg once orally on (b) (6)
- Glyceryl trinitrate:
  - 0.4 mg prn sublingually from (b) (6)
  - 2% prn topically from (b) (6)
- Oxycocet: 5 to 325 mg prn orally from (b) (6)
- Aspirin: 81 mg qd orally from (b) (6) – ongoing

The site learned of the serious TEAE when the subject called the site on (b) (6) to inform the investigative staff that she would miss that day's site visit as she was still undergoing tests at the hospital. The subject received no additional study treatment after the third patch application on (b) (6) followed by patch removal and skin site irradiation on (b) (6) Treatment exposure at exit was approximately 1200 µL of dapsone 7.5% gel topical gel (approximately 600 µL with irradiation and 600 µL without irradiation) and approximately 1200 µL of vehicle gel (approximately 600 µL with irradiation and 600 µL without irradiation). The investigator assessed the diagnosis of stress (takotsubo) cardiomyopathy to be severe; the event to be serious (because it resulted in persistent or significant disability/incapacity and because it required inpatient hospitalization); and not related to study treatment. The event was recorded as ongoing.

Comment: A paper reporting findings from The International Takotsubo Registry noted that of 1750 patients with takotsubo cardiomayopathy, 89.8% were women, they had a higher prevalence of neurologic or psychiatric disorders than did those with an acute coronary syndrome, and the mean age was 66.8±13.0 years. The predominant symptom on admission was chest pain (75.9%), followed by dyspnea (46.9%) and syncope (7.7%).[1]

7.3.3 Dropouts and/or Discontinuations

In the pooled safety trials:

- In the ACZONE group: 6 of 2161 subjects (0.3%) had adverse events (TEAEs) leading to discontinuation. The events were: acute myeloid leukemia (42 days

[1] Templin C, Ghadri JR, Diekmann J, et al. 2015. Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy. The New England Journal of Medicine. 373 (10):929-938.

after treatment), application site papules and application site discoloration (both 8 days after treatment), (application site acne and application site dermatitis (both 8 days after treatment), erythematous rash and pruritic rash (both 26 days after treatment); application site vesicles, application site swelling, application site pruritus, and pruritus (2, 1, 2, and 2 days after treatment, respectively), and application site discomfort (1 day after treatment). All events resolved without sequelae, with the exception of application site dermatitis in Subject 16021-2858 and acute myeloid leukemia in Subject 27017-6675 that were ongoing at study exit.

Of the TEAEs that led to discontinuation in subjects in the ACZONE group, 7 that occurred in 3 subjects were considered to be treatment related by the investigator. These events included application site acne and application site dermatitis in 1 subject (subject 16021-2858); application site vesicles, application site swelling, application site pruritus, and pruritus in 1 subject (subject 16059-1901); and application site discomfort (described as mild in severity) in 1 subject (subject 16061-2915).

- In the vehicle group: 7 of 2175 subjects (0.3%) had adverse events leading to discontinuation. The events were: application site acne (2 days after treatment); application site pain in two subjects (both 1 day after treatment); urinary tract infection (59 days after treatment); contact dermatitis (38 days after treatment); anxiety (36 days after treatment); and headache (2 days after treatment). All events resolved without sequelae, with the exception of urinary tract infection in subject 16015-1396 that was ongoing at study exit.

Of the TEAEs that led to discontinuation in patients in the vehicle group, 3 TEAEs that occurred in 3 subjects in the vehicle group were considered to be treatment related by the investigator. These events included application site pain (described as mild in severity) in 2 subjects (subjects 16015-2396 and 27501-7260) and application site acne (described as severe) in 1 subject (subject 27005-5027).

Table 26: Treatment Emergent Adverse Events Leading to Study Discontinuation (Pooled Safety Trials)

	ACZONE Gel, 7.5%	**vehicle**
System Organ Class (SOC)	N = 2161	N = 2175
Preferred Term[1]	n (%)	n (%)
General disorders and administration site conditions		
Application site acne	1 (<0.1)	1 (<0.1)
Application site dermatitis	1 (<0.1)	0 (0)
Application site discoloration	1 (<0.1)	0 (0)
Application site discomfort	1 (<0.1)	0 (0)
Application site papules	1 (<0.1)	0 (0)

System Organ Class (SOC)	ACZONE Gel, 7.5% N = 2161	vehicle N = 2175
Preferred Term[1]	n (%)	n (%)
Application site pruritus	1 (<0.1)	0 (0)
Application site swelling	1 (<0.1)	0 (0)
Application site vesicles	1 (<0.1)	0 (0)
Application site pain	0 (0)	2 (0.1)
SOC total	4 (0.2)	3 (0.1)
Infections & Infestations		
Urinary tract infection	0 (0)	1 (<0.1)
SOC total	0 (0)	1 (<0.1)
Neoplasms benign, malignant, and unspecified		
Acute myeloid leukemia	1 (<0.1)	0 (0)
SOC total	1 (<0.1)	0 (0)
Nervous system disorders		
Headache	0 (0)	1 (<0.1)
SOC overall	0 (0)	1 (<0.1)
Psychiatric disorders		
Anxiety	0 (0)	1 (<0.1)
SOC total	0 (0)	1 (<0.1)
Skin and subcutaneous tissue disorders		
Pruritus	1 (<0.1)	0 (0)
Rash erythematous	1 (<0.1)	0 (0)
Rash pruritic	1 (<0.1)	0 (0)
SOC total	2 (0.1)	1 (<0.1)
Total number of Events	12	7
Total number of subjects	6 (0.3)	7 (0.3)

All treatment-emergent adverse events leading to study discontinuation are represented, regardless of relationship to treatment. Within each preferred term, a patient is counted at most once.
Source: Applicant's NDA from Module 2.7.4, Summary of Clinical Safety, Table 16, p 48.

- Details of cases of interest, subjects exposed to Aczone Gel, 7.5%:

Event of application site vesicles, swelling, pruritus and pruritus of body: Trial 225678-006, subject 16059-1901:

The subject was a 29 year old Asian female randomized to ACZONE Gel, 7.5% on March 27, 2014. Relevant medical history included seasonal allergies. No concomitant medications were reported. On March 27, 2014, the first day of treatment, the subject experienced an adverse event of application site swelling of the upper and lower lips that was assessed as mild in intensity. Study medication was discontinued after March 27, 2014. On March 28 adverse events were reported consisting application site vesicles (blisters on lips) of moderate intensity, application site pruritus of the face, and pruritus (itching not on application site due to possible allergic reaction to study drug) all

assessed as mild intensity. Treatment with oral diphenhydramine hydrochloride was initiated on March 29, 2014 and cetirizine hydrochloride was administered on April 1, 2014. The diphenhydramine hydrochloride was stopped on April 2, 2014. The application site vesicles, swelling, and pruritus as well as the pruritus of the body resolved without sequelae on April 7, 2014. Study medication was discontinued due to the adverse events, which the Investigator considered related to study treatment. The subject was withdrawn from the trial on May 5, 2014 because of the adverse events of body pruritus and application site vesicles, swelling, and pruritus.

Events of application site acne and application site dermatitis: Trial 225678-006, subject 16021-2858

The subject was a 14-year-old black female, who was randomized on July 9, 2014 to receive ACZONE Gel, 7.5%. The patient's medical history included acne, obesity, and athletic-induced asthma. Relevant medication at the time of the event included salbutamol sulfate for asthma. On July 16, 2014 (Day 8), the patient experienced nonserious adverse events of application site acne (verbatim term was "exacerbation of acne at application site") and application site dermatitis of moderate intensity. No treatment was reported. The application site acne resolved without sequelae on July 16, 2014 and the application site dermatitis was ongoing. Study medication was discontinued after the last dose on August 7, 2014, as a result of the application site acne and application site dermatitis, which the investigator considered related to study treatment. The patient was withdrawn from the study on August 13, 2014 due to the adverse events of application site acne and application site dermatitis.

- Details of case of interest, subject exposed to vehicle gel:

Event of application site acne: Trial 225678-007, subject 27005-5027

The subject was a 15 year old Caucasian male randomized to vehicle on January 2, 2014. The patient's relevant past medical history included acne (2009) and no relevant concomitant medications were reported. On January 3, 2014 (Day 2), a nonserious adverse event of application site acne of severe intensity was reported. Study medication was withdrawn as a result of the application site acne. The patient last used the study medication on January 13, 2014 and the application site acne resolved on January 16, 2014. The investigator considered the application site acne to be related to study treatment. The patient was discontinued from the study on January 16, 2014 (Day 17) as a result of the adverse event.

Phase 1 Trials:

Trials 225678-004 (PK) and 225678-10 (phototoxicity): No serious TEAEs or discontinuations due to TEAEs were reported.

Trial 225678-009 (RIPT sensitization): A total of 6 subjects in subset 2 (RIPT with 197 randomized) had study drug withdrawn and were discontinued because of non-serious TEAEs.

- Two subjects (Nos. 109 and 111) discontinued due to skin discoloration and tremor, both moderate in intensity, that were considered related to study treatment.
- One subject (No. 224) discontinued due to events of application site pruritus and paraesthesia that were moderate in intensity and considered related to study treatment.
- One subject (No. 139) discontinued due to application site dermatitis that was considered moderate and probably related to study treatment.
- One subject (No. 100) discontinued due to myalgia and dyspnea that were considered mild and unlikely related to study treatment.
- One subject (No. 014) discontinued due to contact dermatitis (a "tape reaction") that was considered moderate in intensity and not related to study treatment.

Details of cases of interest for subjects discontinued from trial 225678-009:
Subject 109:
The subject was a 36-year-old White, non-Hispanic female who had a history of tonsillectomy, shoulder pain, right torn rotator cuff, and right shoulder surgery. She had patches of test product applied to her back on April 28, 2014 (day 1) at 3:30 pm. At 8:30 pm on April 28, 2014 (day 1), the subject noted that her palms and palmer fingers had turned blue (skin discoloration) and her hands were shaking (tremor). The subject stated that she removed the patches at home and the symptoms resolved in approximately 30 minutes on April 28 (day 1). She returned to the site on April 30; on examination, no significant findings were noted and the subject was discontinued from the study. The TEAEs were reported as resolved on April 28, 2014 (day 1). The TEAEs were considered moderate and related to study treatment. The subject was asked to return to the site for follow-up tests to investigate these AEs. The subject returned for a follow-up blood draw and methemoglobin measurement via pulse co-oximetry on July 11, 2014. Methemoglobin levels measured were normal (0.90%). Results of laboratory testing revealed the following: low serum creatinine (0.54 mg/dL), high total cholesterol (206 mg/dL), high triglycerides (162 mg/dL), high neutrophils (78%) and high absolute neutrophils (7.2 x 10E3/µL). The results of hemoglobin electrophoresis revealed a high percentage (1.1%) of a hemoglobin variant, with the hemoglobin pattern and concentration suggestive of delta variant, which was considered by the hematologist as not clinically significant.

Subject 111:
The subject was a 61-year old, White, non-Hispanic male who had a history of surgery for broken left tibia and fibula. He had patches of test product applied to his back on April 28, 2014 (day 1) at 3:36 pm. At 7:30 pm on 28 April 28, 2014 (day 1), the subject noted that the palms of his hands turned blue (skin discoloration) and his hands were shaking (tremor). The subject stated that he removed the patches at home and the symptoms resolved by 8:00 pm on April 28, (day 1). He returned to the site on 30 April; on examination, no significant findings were noted and the subject was discontinued from the study. The TEAEs were reported as resolved on 28 April 28, 2014 (day 1). The

TEAEs were considered moderate and related to study treatment. The subject was asked to return to the site for follow-up tests to investigate these AEs. The subject returned for a follow-up blood draw and methemoglobin measurement via pulse co-oximetry on July 9, 2014. Methemoglobin levels measured were normal (0.60%). Results of laboratory testing revealed the following: high serum glucose (105 mg/dL), high total carbon dioxide (30 mmol/L) and high total cholesterol (217 mg/dL). The results of hemoglobin electrophoresis revealed a high percentage (1.0%) of a hemoglobin variant, with the hemoglobin pattern and concentration suggestive of delta variant, which was considered by the hematologist as not clinically significant.

It is noted by the applicant that the subjects are direct blood relations (ie, No. 109 is the daughter of No. 111).

Discussion: In the Clinical Study Report for trial 225678-009, the applicant considered these AEs unlikely to be caused by methemoglobinemia arguing that methemoglobinemia is not associated with tremor and that the time course of these AEs is inconsistent with the known pharmacokinetic profile of topically applied dapsone. Citing studies DAP9903 and DAP0110 (submitted to NDA 2-794 ACZONE® (dapsone) Gel, 5%), the applicant states that dapsone concentration is expected to be still rising in the systemic circulation with T_{max} occurring at least 24 hours post dose following a single topical application. The applicant states also that the mean apparent half-life for topical application of dapsone is approximately 51 hours in plasma (Study 225678-004 PK), which makes spontaneous methemoglobinemia resolution 30 minutes after patch removal unlikely.

Acquired methemoglobinemia can be caused by exposure to oxidizing agents such as nitrites and nitrates, nitric oxide, sulfones (e.g. dapsone), local anesthetics (e.g. benzocaine), aniline dyes, chlorates, pyridium, phenacetin, and sulfonamides. The blood level of methemoglobin determines the clinical severity of the signs and symptoms. Levels of greater than 10% may be associated with cyanosis. Headache, lethargy, tachycardia, and dizziness may be seen at levels between 30 to 40%. Dyspnea, acidosis, seizures, cardiac dysrhythmias, heart failure and coma may occur at levels above 45%.[1,2] Thus, noticeable cyanosis is usually the first presenting symptom for methemoglobinemia. There is little information regarding time-to-onset of methemoglobinemia associated with topical dapsone. In one case the a patient had been applying a pea-sized amount of topical dapsone (5%) twice daily as prescribed for 7 days before presenting with blue lips and nail beds, mild headache and mild dyspnea.[3] The onset of methemoglobinemia is usually within 20 to 60 minutes after administration

[1] Barclay JA, Ziemba SE, and Ibrahim RB. 2011. Dapsone-Induced Methemoglobinemia: a Primer for Clinicians. The Annals of Pharmacotherapy. 45:1103-15
[2] Sunilkumar MN, Ajith TA, and Parvathy VK. 2015.Acute dapsone poisoning in a 3-year-old child: Case report with review of literature. World J Clinical Cases3(10);911-914.
[3] Swartzentruber GS, Yanta JH, and Pizon AF. 2015. Mehtemoglobinemia as a Complication of Topical Dapsone. Letter to the Editor. The New England Journal of Medicine. 372(5):491-492.

of topical anesthetic agents (lidocaine, prilocaine and benzocaine).[1] However, these agents are often administered to mucosal surfaces which would likely have a different absorption profile compared with dapsone applied to skin affected by acne vulgaris. The half-life of methemoglobin is 55 minutes.[2] Regarding benzocaine-induced methemoglobinemia, most cases resolve within 24 to 36 hours after clearing of residual benzocaine.[3] The applicant reports lab work being performed almost two and a half months after exposure which would be too long for detection if the half-life of methemoglobin is 55 minutes.

Comment: These two cases are not definitive regarding an association between use of ACZONE Gel, 7.5% and methemoglobinemia. Metheomoglobinemia has been previously added to labeling for NDA 21794, ACZONE® (dapsone) Gel, 5% based on the case reported in the literature by MN Sunilkumar et al. (see footnote 2 below) and a spontaneous report from the Allergan Global Safety Database.

Subject 224:
The subject was a 29-year-old, Black/African American, non-Hispanic, female who had a history of polycystic ovarian syndrome. She had patches of test product applied to her back on May 16, 2014 (day 1) and May 19, 2014 (day 4). On May 19, 2014 (day 4), she experienced pin prick sensations (application site paraesthesia) and excessive itching (application site pruritus) at the application sites, and removed the patches that night. The skin sites were not graded on May 20, 2014 (day 5) as the patches had not been in contact with the skin since the previous day. The subject was discontinued from the study. These TEAEs were reported as resolved on May 20, 2014 (day 6; application site paraesthesia) and May 23, 2014 (day 8; application site pruritus). These TEAEs were considered moderate and definitely related to study treatment.

Subject 139:
The subject was a 39-year old, White, non-Hispanic male who had a history of hypercholesterolemia and hypertension. He had patches of test product applied to his back on April 30, 2014 (day 1), May 2, 2014 (day 3), May 5, 2014 (day 6), May 7, 2014 (day 8), May 9, 2014 (day 10), May 12, 2014 (day 13), May 14, 2014 (day 14), and May 16, 2014 (day 17). On May 19, 2014 (day 20), he had irritant dermatitis (application site dermatitis) at the dapsone 7.5% gel and vehicle skin sites. The subject had skin irritation ratings of 3 (with itching) at the dapsone 7.5% site; 6 (with itching) at the vehicle site; and 2 (with itching) at the negative control (saline) site. The dapsone 7.5% gel and vehicle sites had significant epidermal damage and the investigator decided to remove the subject from the study. The TEAE was reported as resolved on June 9,

[1] Gupta PM, Lala DS and Arsura EL. 2000. Benzocaine-Induced Methemoglobinemia. Southern Medical Journal. 93(1):83-86.
[2] Coleman MD and Coleman NA. 1996. Drug-Induced Methaemoglobinemia. Treatment Issues. Drug Safety. 14(6):394-405.
[3] Gupta PM, Lala DS and Arsura EL. 2000. Benzocaine-Induced Methemoglobinemia.

2014 (day 41). The TEAE was considered moderate, and probably related to study treatment.

Trial 225678-11(photoallergy): A total of 5 subjects (58 randomized) discontinued the trial due to TEAEs. One subject, #34, withdrew because of a serious TEAE, stress cardiomyopathy (This event is discussed with serious TEAEs above).

- Subjects 1, 8, 16: These three subjects discontinued due to application site reactions of moderate severity that were considered related to study treatment. Two out of the 3 subjects (Nos. 001 and 008) developed application site irritation in the Induction Phase and patches were relocated twice. Per protocol, the subjects were discontinued. Subject 008 was also discontinued because of a moderate laceration on her index finger that was unrelated to study treatment. One subject (No. 016) developed application site reaction at all sites, 24 hours after patch application, in the Challenge Phase. The subject was not irradiated and was discontinued.
- Subject 12: withdrew as a result of urticaria of moderate severity that occurred bilaterally on the upper cheeks and also on the upper neck (distant from the patch sites) and was considered to be possibly related to study treatment.

Details of cases of interest for subjects discontinued from trial 225678-011:
Subject 1:
The subject was a 62-year-old, White, non-Hispanic female who had a history of hypercholesterolemia and celiac disease. The subject had patches of study material applied to her back on April 28, 2014 (day 1), May 1, 2014 (day 4), May 5, 2014 (day 8), May 8, 2014 (day 11), and May 12, 2014 (day 15). On 5 May 5, 2014 (day 8), all patch sites were moved using occlusive patches and on May 8, 2014 (day 11), all patch sites were moved for a second time using semi-occlusive patches. The subject's final patch application occurred on May 12, 2014. The subject was withdrawn from treatment due to observed reactions (moderate erythema, superficial damage to the epidermis) on left sites 1 and 2 and right sites 1 and 2; the reactions were observed with both dapsone 7.5% gel and its vehicle. Since the subject developed application site irritation reactions and the patch sites were relocated twice, as per protocol the subject was discontinued. The reactions were recorded as resolved on May 19, 2014. The TEAE of application site reaction was considered moderate and definitely related to study treatment.

Subject 8:
The subject was a 48-year-old White, non-Hispanic female who reported no relevant medical history. The subject received applications of study material to her back on April 28, 2014 (day 1), May 1, 2014 (day 4), May 5, 2014 (day 8), May 8, 2014 (day 11), and May 12, 2014 (day 15). On May 5, 2014 (day 8), all patch sites were moved using occlusive patches and on May 8, 14 (day 11), all patch sites were moved for a second time using semi-occlusive patches. The subject's final patch application occurred on May 12, 2014. The subject was withdrawn from treatment on May 13, 2014 (day 16) due to observed reactions of moderate erythema and definite edema with

erosion/vesiculation on left sites 1 and 2 and right site 2. Since the subject developed application site irritation reactions and the patch sites were relocated twice, as per protocol the subject was discontinued. The reactions were recorded as resolved on May 19, 2014. The TEAE of application site reaction was considered moderate in severity and related to study treatment.

Subject 16:
The subject was a 21-year-old White, Hispanic female who had an innocent heart murmur. The subject received applications of study material to her back on April 28, 2014 (day 1), May 1, 2014 (day 4), May 5, 2014 (day 8), May 8, 2014 (day 11), May 12, 2014, (day 15), and May 15, 2014 (day 18). The subject entered the Challenge Phase and challenge patches were applied on June 2, 2014. The subject developed application site reaction at all sites (moderate to severe erythema; definite edema with erosion/vesiculation) 24 hours after patch application. The subject was not irradiated and was discontinued from the study on June 10, 2014. The reactions were recorded as resolved on June 24, 2014. The TEAE of application site reaction was considered moderate in severity and related to study treatment.

Subject 12:
The subject was a 53-year-old White, Hispanic female who had a history of bilateral tubal ligation (1999), seasonal (spring) allergies (ongoing since 1993). The subject received applications of study material to her back on April 28, 2014 (day 1), May 1, 2014 (day 4), May 5, 2014 (day 8), May 8, 2014 (day 11), May 12, 2014 (day 15), May 15, 2014 (day 18), and May 19, 2014 (day 22). The subject reported urticarial patches that occurred bilaterally on her upper cheeks and also on her upper neck (distant from the patch sites) with onset on May 24, 2014 (day 27). These TEAEs (urticarial patches) were considered moderate in severity and possibly related to treatment. They were reported as resolved on June 2, 2014 (day 36), and the subject was discontinued from the study. The TEAE of urticarial patches was considered moderate in intensity and possibly related to study medication.

7.3.4 Significant Adverse Events

Phase 3 Trials:
In the pooled safety trials, severe TEAEs in those exposed to ACZONE Gel, 7.5% gel included; viral gastroenteritis and headache in 2 patients each, and, in 1 patient each, food poisoning, peritoneal hematoma, urinary tract infection, tooth abscess, appendicitis, otitis externa, helicobacter infection, sunburn, alcoholism, application site dermatitis, axillary pain, pain in jaw, and migraine.

> The application site dermatitis occurred in subject 16018-1953 in trial 006 and was discussed earlier in this review under section 7.3.2 (nonfatal SAEs). The event was not considered related to study medication.

In the vehicle group, severe TEAEs included, in 1 patient each; upper abdominal pain, pyrexia, application site acne, gastroenteritis viral, appendicitis, tooth infection, headache, abortion spontaneous, ovarian cyst, pneumothorax spontaneous, lumbar vertebral fracture, dehydration, depression, anxiety, and affective disorder.

> The application site acne occurred in subject 27005-5027 in trial 007. The subject was a 15 year old Caucasian male randomized to vehicle on January 2, 2014. The patient's relevant past medical history included acne (2009) and no relevant concomitant medications were reported. On January 3, 2014 (Day 2), a nonserious adverse event of application site acne of severe intensity was reported. Study medication was withdrawn as a result of the application site acne. The patient last used the study medication on January 13, 2014. The application site acne resolved on January 16, 2014. The investigator considered the application site acne to be related to study treatment. The patient was discontinued from the study on January 16, 2014 (Day 17) as a result of the adverse event.

Phase 1 Trials:

●Trial 225678-004 PK (Phase 1, 4-arm, active controlled): TEAEs were severe in 1 subject in the DAP-11079 (a formulation of dapsone 7.5% that was studied but not selected for further development) group; Subject 1539 developed severe diarrhea and upper abdominal pain 27 days after treatment and approximately 10 days after an upper respiratory tract infection. The diarrhea and abdominal pain resolved the same day and were not considered treatment related.

●Trial 225678-009 dermal safety (Phase 1, RIPT sensitization): No TEAEs were assessed as severe. One serious TEAE of elective abortion was reported for 1 subject (discussed earlier in this review under section 7.3.2, non-fatal Serious Adverse Events).

●Trial 225678-10 dermal safety (Phase 1, phototoxicity): No TEAEs were reported.

●Trial 225678-011 dermal safety (Phase 1, photoallergy): One TEAE was reported of severe intensity, stress cardiomyopathy. This TEAE was also classified as a SAE, non-treatment related. This was discussed earlier in this review under section 7.3.2, nonfatal serious adverse events.

7.3.5 Submission Specific Primary Safety Concerns

Approved labeling for topical dapsone, ACZONE® (dapsone) Gel, 5%, includes the following, excerpted from Warnings and Precautions (July 2015).

1) Methemoglobinemia: Cases of methemoglobinemia, with resultant hospitalization, have been reported postmarketing in association with ACZONE® Gel, 5% treatment. Patients with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic

methemoglobinemia are more susceptible to drug-induced methemoglobinemia. Dapsone can cause elevated methemoglobin levels particularly in conjunction with methemoglobin-inducing agents.
2) 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. Some subjects with G6PD deficiency using ACZONE® Gel developed laboratory changes suggestive of hemolysis. (b) (4)

3) Peripheral Neuropathy: Peripheral neuropathy (motor loss and muscle weakness) has been reported with oral dapsone treatment. No events of peripheral neuropathy were observed in clinical trials with topical ACZONE® Gel, 5% treatment.
4) Skin: Skin reactions (toxic epidermal necrolysis, erythema multiforme, morbilliform and scarlatiniform reactions, bullous and exfoliative dermatitis, erythema nodosum, and urticaria) have been reported with oral dapsone treatment. These types of skin reactions were not observed in clinical trials with topical ACZONE® Gel, 5% treatment.

Regarding methemoglobinemia:
With ACZONE Gel, 7.5% events occurred in two subjects in trial 225678-009 dermal safety (Phase 1, RIPT sensitization) experienced events of possible cyanosis which is usually the first presenting symptom of methemoglobinemia. These two cases were not definitive regarding an association between use of ACZONE Gel, 7.5% and methemoglobinemia. The applicant conducted an aggregate review of cumulative global safety reports of methemoglobinemia occurring with the use of dapsone 5% gel. Labeling for ACZONE Gel, 5% was modified in July 2015 to include the information that cases of methemoglobinemia, with resultant hospitalization, have been reported postmarketing in association with ACZONE Gel, 5% treatment.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 27: Overview of Adverse Events – TEAEs (Pooled Safety Trials)

	ACZONE Gel, 7.5% n = 2161	Vehicle n = 2175
Event	Subjects (%)	Subjects (%)
Serious TEAEs	7 (0.3%) 7 Serious TEAEs	9 (0.4%) 9 Serious TEAEs
D/C due to TEAE	6 (0.3%)	7 (0.3%)
TEAEs*	396 (18.3%)	409 (18.8%)
Treatment related TEAEs	75 (3.5)	73 (3.4)

Source: Applicant's NDA from Module 2.7.4, Summary of Clinical Safety, pp. 33, 38, 43, & 48.

Frequencies of TEAEs were similar between ACZONE Gel, 7.5% treated and vehicle treated subjects. TEAEs were reported in 18.3% (396/2161) of subjects in the ACZONE Gel, 7.5% group and 18.8% (409/2175) of patients in the vehicle group. The most common TEAEs (ie, those occurring in ≥ 1% of subjects in any treatment group) in decreasing frequency are shown in the next table:

Table 28: Most Common TEAEs (Pooled Safety Trials)

Adverse event	ACZONE Gel, 7.5% n = 2161	Vehicle n = 2175
Preferred term	Subjects (%)	Subjects (%)
Nasopharyngitis	40 (1.9)	48 (2.2)
Headache	34 (1.6)	26 (1.2)
Upper resp. tract infection	32 (1.5)	34 (1.6)
Application site dryness	26 (1.2)	22 (1.0)
Application site pruritus	23 (1.1)	14 (0.6)
Application site pain	11 (0.5)	33 (1.5)

Source: Applicant's NDA from Module 2.7.4, Summary of Clinical Safety, p 33.

The frequency of application site TEAEs was similar between ACZONE Gel, 7.5% treated and vehicle treated subjects (see table above). The most common application site TEAEs (i.e., those occurring in ≥ 1% of subjects in any treatment group) were: application site dryness (1.2% in the ACZONE Gel, 7.5% group versus 1.0% in the vehicle group), application site pruritus (1.1% versus 0.6%), and application site pain (0.5% versus 1.5%).

Table 29: Application Site TEAEs (Pooled Safety Trials) Occurring in at Least 1 Subject in ACZONE Gel, 7.5% Group

Adverse event	ACZONE Gel, 7.5% n = 2161	Vehicle n = 2175
Preferred term	Subjects (%)	Subjects (%)
Application site dryness	26 (1.2)	22 (1.0)
Application site pruritus	23 (1.1)	14 (0.6)
Application site erythema	16 (0.7)	13 (0.6)
Application site exfoliation	12 (0.6)	14 (0.6)
Application site pain	11 (0.5)	33 (1.5)
Application site paresthesia	5 (0.2)	7 (0.3)
Application site dermatitis	4 (0.2)	2 (0.1)
Skin tightness	3 (0.1)	1(<0.1)
Application site irritation	3 (0.1)	0 (0)
Application site acne	2 (0.1)	4 (0.2)
Skin irritation	2 (0.1)	3 (0.1)

Acne	2 (0.1)	2 (0.1)
Seborrhea	2 (0.1)	2 (0.1)
Impetigo	2 (0.1)	0 (0)
Application site bruise	1 (<0.1)	2 (0.1)
Application site erosion	1 (<0.1)	1(<0.1)
Application site papules	1 (<0.1)	1 (<0.1)
Application site photosensitivity reaction	1 (<0.1)	1 (<0.1)
Application site rash	1 (<0.1)	1 (<0.1)
Application site discoloration	1 (<0.1)	0 (0)
Application site discomfort	1 (<0.1)	0 (0)
Application site eczema	1 (<0.1)	0 (0)
Application site reaction	1 (<0.1)	0 (0)
Application site swelling	1 (<0.1)	0 (0)
Application site vesicles	1 (<0.1)	0 (0)
Burning sensation	1 (<0.1)	0 (0)
Hair growth abnormal	1 (<0.1)	0 (0)

All application site treatment-emergent adverse events are represented, regardless of relationship to treatment. Preferred terms are sorted by descending frequencies of treatment groups from left to right. Within each preferred term, a patient is counted at most once.

Source: Applicant's NDA from Module 2.7.4, Summary of Clinical Safety, adapted from Table 11, p 35.

Treatment-related TEAEs, considered by this reviewer to be adverse drug reactions, were reported in 3.5% (75/2161) of subjects in the ACZONE Gel, 7.5% group and 3.4% (73/2175) of patients in the vehicle group. The most common treatment related TEAEs (i.e., those occurring in ≥ 0.9% of subjects in any treatment group) were application site events: application site dryness (1.1% in the ACZONE Gel, 7.5% group versus 1.0% in the vehicle group), application site pruritus (0.9% versus 0.5%), and application site pain (0.4% versus 1.4%).

For labeling, regarding adverse reactions, it is proposed that the most common treatment related TEAEs be included (i.e., those occurring in ≥ 0.9% of subjects and at a rate greater than vehicle) : application site dryness (1.1% in the ACZONE Gel, 7.5% group versus 1.0% in the vehicle group) and application site pruritus (0.9% versus 0.5%).

Table 30: Treatment Related TEAEs (Pooled Safety Trials)

	ACZONE Gel, 7.5%	**vehicle**
System Organ Class (SOC)	N = 2161	N = 2175
Preferred Term[1]	n (%)	n (%)
Eye disorders		
Eyelid rash	1 (<0.1)	0 (0)
Lacrimation increased	1 (<0.1)	0 (0)
Blepharitis	0 (0)	1 (<0.1)

System Organ Class (SOC)	ACZONE Gel, 7.5% N = 2161	vehicle N = 2175
Preferred Term[1]	n (%)	n (%)
SOC total	2 (0.1)	1 (<0.1)
Gastrointestinal disorders		
Chapped lips	1 (<0.1)	0 (0)
SOC total	1 (<0.1)	0 (0)
General disorders and administration site conditions		
Application site dryness	24 (1.1)	21 (1.0)
Application site pruritus	20 (0.9)	11 (0.5)
Application site erythema	14 (0.6)	13 (0.6)
Application site pain	9 (0.4)	31 (1.4)
Application site exfoliation	9 (0.4)	14 (0.6)
Application site paresthesia	5 (0.2)	7 (0.3)
Application site irritation	3 (0.1)	0 (0)
Application site acne	2 (0.1)	2 (0.1)
Application site dermatitis	1 (<0.1)	1 (<0.1)
Application site discomfort	1 (<0.1)	0 (0)
Application site photosensitivity reaction	1 (<0.1)	0 (0)
Application site reaction	1 (<0.1)	0 (0)
Application site swelling	1 (<0.1)	0 (0)
Application site vesicles	1 (<0.1)	0 (0)
Application site papules	0 (0)	1 (<0.1)
Application site warmth	0 (0)	1 (<0.1)
SOC total	69 (3.2)	70 (3.2)
Nervous system disorders		
Dizziness	1 (<0.1)	0 (0)
SOC total	1 (<0.1)	0 (0)
Psychiatric disorders		
Depression	0 (0)	1 (<0.1)
SOC total	0 (0)	1 (<0.1)
Skin and subcutaneous tissue disorders		
Skin tightness	3 (0.1)	1 (<0.1)
Seborrhea	2 (0.1)	1 (<0.1)
Pruritus	1 (<0.1)	0 (0)
Skin irritation	0 (0)	1 (<0.1)
Sticky skin	0 (0)	1 (<0.1)
SOC total	6 (0.3)	4 (0.2)
Total number of Subjects	75 (3.5)	73 (3.4)

Treatment-related adverse events include those that in the investigator's opinion may have been caused by the study product with reasonable possibility. Within each system organ class, preferred terms are sorted by descending frequencies of treatment groups from left to right. Within each preferred term, a patient is counted at most once.

Source: Applicant's NDA, Module 2.7.4, Summary of Clinical Safety, Table 13, p 39.

Local tolerability
The local dermal tolerability assessment for the face was performed by the investigators or appropriately trained designee and by the patient at baseline and at weeks 1, 2, 4, 8, and 12. Assessments included dryness, scaling, and erythema (assessed by the investigator) and stinging/burning (assessed by the patient). Each assessment used 4-point scales: 0 = none, 1 = mild, 2 = moderate, 3 = severe.

Cutaneous irritation evaluations, presented in Table 2, were conducted at each study visit in the two clinical trials. Incidences of erythema, scaling, dryness, and stinging/burning were similar between ACZONE Gel, 7.5 % and vehicle.

Table 31: Local Cutaneous Irritation by Maximum Severity in Subjects with Acne Vulgaris Whose Irritation Score was Higher than at Baseline

	ACZONE Gel, 7.5% (N = 2161)			Vehicle (N = 2175)		
Local Cutaneous Irritation	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Erythema	9.7%	2.7%	0.2%	11.3%	3.6%	0%
Scaling	12.4%	1.3%	0.2%	14.9%	2.0%	<0.1%
Dryness	17.7%	2.0%	0.2%	18.9%	2.4%	0
Stinging/ burning	23.5%	5.6%	1.0%	31.5%	11.4%	2.2%

Source: Applicant's NDA, Module 5.3.5.3, Integrated Summary of Safety (Tables), adapted from Tables 4 - 11, 4 - 10, 4 - 9, 4 - 8, pp 401, 399, 397, 395.

7.4.2 Laboratory Findings

Phase 3 trials 225678-006 & 225678-007: No laboratory assessments were stipulated in the protocols for the pivotal Phase 3 trials. The Agency stated in an advice letter dated 12/13/2013 that the planned Phase 3 studies did not include an assessment of systemic safety (e.g. laboratory analysis or ECG monitoring). The Agency further stated that if both peak and trough systemic levels are lower for ACZONE GEL, 7.5% once daily than that of the twice daily 5% approved strength, then relying on the systemic safety of ACZONE 5% gel appears reasonable. In trial 225678-004 (PK, 4-arm, active controlled) it was found that mean plasma concentrations of dapsone (including mean peak and trough concentrations) following application of ACZONE Gel, 7.5% once-daily were consistently lower than those following application of ACZONE Gel, 5% twice-daily.

It is noted that in the End of Phase 2 Meeting Briefing Package submitted to Investigational New Drug application (IND) 054440, 26 July 2013, the applicant stated the following:

- Laboratory assessment of the hematological safety of ACZONE Gel, 7.5% was not deemed necessary in the phase 3 studies.
- Allergan did not plan to conduct a study in glucose 6-phosphate dehydrogenase (G6PD)-deficient patients

At the End of Phase 2 Meeting of August 28, 2013, the applicant posed the query: "Does the Division agree that the proposed phase 3 studies will meet the requirements for the potential approval of an NDA Supplement?" The Division replied that: "We anticipate that the development program you outline would be sufficient for filing if you adequately address Agency comments provided." No comments were provided regarding assessment of the hematological safety of ACZONE Gel, 7.5% gel in the phase 3 studies or regarding Allergan's plan not to conduct a study in in glucose 6-phosphate dehydrogenase (G6PD)-deficient patients.

Phase 1 Trials 225678-009, 225678-010, and 225678-011: No laboratory assessments were stipulated in the protocols for these Phase 1 trials. In trial 225678-009 unscheduled blood tests that were performed for 2 subjects who both reported the TEAEs of skin discoloration ("blue hands") and tremor. These subjects had follow-up procedures performed because the investigator suspected an episode of dapsone-induced methemoglobinemia. Additional investigations did not reveal findings relevant to these TEAEs. These two cases are discussed in detail under section 7.3.3 of this review.

Phase 1 Trial 225678-004(PK, 4-arm, active controlled): Laboratory data was collected including hematology, chemistry, urinalysis at screening, Days1, 7, 14, 21, 28, and 35/or early exit. Methemoglobin was measured at Days 1, 7, 14, 21, 28, and 35/or early exit. For this trial a total of 77 subjects were randomized and 72 completed treatment. For this trial, treatment groups included DAP-1178 (20 randomized and 17 completed), DAP-11079 (19 randomized and 18 completed), and DAP-11080(This was formulation to be developed commercially – 19 randomized and 18 completed), and Aczone 5% gel (19 randomized and 18 completed).

Hematology parameters evaluated included: hematocrit, hemoglobin, haptoglobin, red and white cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red blood cell morphology, reticulocyte count, platelet count, neutrophil count, lymphocyte count, monocyte count, eosinophil count, and basophil count.

Chemistry parameters evaluated included: alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, albumin, alkaline phosphatase, bilirubin (total, direct, and indirect), urea, calcium, cholesterol, chloride, creatinine, glucose,

phosphorus, potassium, bicarbonate, total protein, sodium, triglycerides, uric acid, and creatine phosphokinase.

Urinalysis parameters evaluated included: Urine dipstick analysis will be performed, including color (appearance), specific gravity, pH, glucose, protein, ketone, urobilinogen, nitrite, occult blood, and bilirubin. If abnormal results are obtained, a microscopic examination will be also performed.

The applicant provided line listings (all values and abnormal values) and shift tables for the above parameters. These were examined in detail for subjects exposed to the DAP 11080 formulation (used for commercial development) and for ACZONE Gel, 5% formulation. Clinically significant changes over the course of trial 225678-004 were not seen.

Methemoglobin:
Clinically significant changes in methemoglobin levels over the course of trial 225678-004 (PK, 4-arm, active controlled) were not seen. Mean methemoglobin levels at baseline were 0.76%, and 0.74% in the DAP-11080 (formulation same as ACZONE Gel, 7.5 %), and ACZONE Gel, 5 % gel groups, respectively, and at day 28 mean change from baseline was -0.02, and -0.02 in each group, respectively.

Table 32: Methemoglobin – Baseline and Change from Baseline (Trial 004)

	Dap 11080	**ACZONE Gel, 5%**
	N = 19	N = 19
Baseline /# of subjects	19	19
Mean	0.76	0.74
SD	0.217	0.287
Median	0.80	0.80
Min - Max	0.1 – 1.2	0.2 – 1.2
Day 7 # of subjects	19	18
Mean **change from baseline**	0.12	0.17
SD	0.177	0.413
Median	0.10	0.0
Min - Max	-0.4 – 0.4	-0.4 1.2
Day 14 # of subjects	19	18
Mean **change from baseline**	0.11	0.83
SD	0.346	0.356
Median	0.10	0.0
Min - Max	-0.5 – 1.1	-0.6 – 0.7

	Dap 11080	ACZONE Gel, 5%
	N = 19	N = 19
Day 21 # of subjects	19	18
Mean **change from baseline**	0.16	0.09
SD	0.192	0.383
Median	0.20	0.05
Min - Max	-0.2 – 0.5	-0.6 – 1.2
Day 28 # of subjects	19	18
Mean **change from baseline**	-0.02	-0.02
SD	0.366	0.373
Median	0.0	0.0
Min - Max	-0.6 – 0.8	-0.8 – 0.7
Day 35 # of subjects	19	19
Mean **change from baseline**	0.05	0.10
SD	0.293	0.414
Median	0.10	0.20
Min - Max	-0.4 – 0.9	-0.8 – 1.2

Source: Applicant's NDA, Clinical Study Report 225678-004, adapted from Table 14.3-33.2, pp 721-722.

7.4.3 Vital Signs

Phase 1:
●Trial 225678-004 (PK, 4-arm, active controlled): Systolic and diastolic blood pressure (mm Hg), pulse rate (beats/minute), respiratory rate (breaths/minute), and body temperature (ºC) were to be recorded at screening and day 35/exit. No vital signs data were reported as a TEAE. Clinically significant changes in vital signs (for formulation DAP 11080 – chosen to be developed commercially and for ACZONE Gel, 5%) from screening to day 35 were not observed, this included changes in mean and median values.

●Trial 225678-009 (Phase 1, RIPT, sensitization): No vital signs were collected.
●Trial 225678-010 dermal safety (Phase 1, phototoxicity): No vital signs were collected.
●Trial 225678-011 dermal safety (Phase 1, photoallergy): No vital signs were collected.

Phase 3:
●Trials 225678-006 & 007pivotal (Phase 3, 2-arm vehicle controlled): In the Phase 3 trials vital signs were assessed at screening and at the Week 12/early exit visit. Vital signs assessed included heart rate, blood pressure, and body temperature. For the Phase 3 trials, changes in mean and median heart rate from screening to Week 12/early exit visit, blood pressure, and body temperature were small and similar across treatment

groups (ACZONE Gel, 7.5 % and vehicle). Unusual deviations or changes were not noted.

7.4.4 Electrocardiograms (ECGs)

ECGs were collected only in trial 225678-004 (PK, 4-arm, active controlled).

Time-matched ECGs were collected in triplicate on days -1 and 28 at 0 (predose), 1, 2, 4, 8, and 12 hours postdose. Mean changes from baseline in QTC (both QTcB and QTcF) interval were noted for all treatment groups but these were small indicating no clinically significant effect on the QTc interval by any of the 7.5% dapsone gel formulations (DAP-11078, DAP-11079 and DAP-11080 = formulation chosen for commercial development for ACZONE Gel, 7.5%). An independent cardiologist review of changes from baseline to day 28 in heart rate, PR interval, QRS interval, and QTcF interval indicated that none of the 4 treatments (DAP-11078, DAP-11079, DAP-11080, and ACZONE Gel, 5%) was associated with a large or clinically significant mean change from baseline in QTc at any timepoint.

In the independent cardiologist review, it was concluded that an electrocardiographic or proarrhythmic effect of any of the dapsone formulations is extremely unlikely. The conclusion was based on the following four points:

- Large oral doses of dapsone have been used chronically for multiple indications in severely ill patients, but over 50 years of this experience has yielded no reports in the literature of proarrhythmia due to dapsone.
- Allergan's dapsone gel formulations resulted in very low plasma concentrations, with maximum plasma concentration (C_{max}) shown to be < 1% of that associated with a 100 mg oral dose.
- Dapsone has been used topically in dozens of studies with no reported ECG changes or arrhythmias.
- ECG analysis of Protocol 225678-004 showed no clinically significant ECG changes in 72 patients.

In addition, this reviewer notes that for NDA 21794 ACZONE® (dapsone) Gel 5%, ECG data were collected in study DA9903, a 28 day multicenter, dose-ranging PK trial of topical dapsone gel in 48 subjects with acne vulgaris. This trial included the 5% twice a day topical dapsone gel formulation (ACZONE Gel, 5%) and did not show any correlation between ECG abnormalities and plasma dapsone levels.

It is further noted that, trial 225678-004 (PK, 4-arm, active controlled) demonstrated that mean plasma concentrations of dapsone (including mean peak and trough concentrations) following application of ACZONE Gel, 7.5% once-daily were consistently lower than those following application of ACZONE Gel, 5% twice-daily.

Request for a Waiver of the Requirement for a Thorough QT/QTc Study:
In the current application, Module 1.12.5, the applicant requests a waiver for the conduct of a Thorough QT/QTc study. At the End of Phase 2 meeting (August 28, 2013) the possibility of waiving the Thourough QT/QTc study was discussed and the Division stated that the applicant's rationale based on low plasma concentration, historical clinical use and relative bioavailability data to (dapsone) Gel, 5% seemed reasonable to support a waiver to conduct a thorough QT/QTc study for (dapsone) Topical Gel, 7.5%.

The applicant's request for a waiver of a Thorough QT/QTc study is based on the following points:

- Dapsone has been in clinical use for over 50 years. During this period of time, many patients have been exposed to large clinical doses or unintentional overdoses administered orally, yet there are no reports of cardiac arrhythmias or cardiac adverse events known to be associated with QT prolongation or torsades de pointes in the medical literature. The applicant considers that the duration of dapsone use, and its use in multiple conditions (leprosy, Pneumocystis pneumonia and toxoplasmosis encephalitis prophylaxis in immunocompromised patients, including those with HIV infection, malaria, dermatitis herpetiformis, vasculitis, spider bites, and acne vulgaris) make it very unlikely that a proarrhythmic signal would not have become apparent by now.
- Arrhythmogenic effects of all known proarrhythmic drugs are dose related, and in nearly all cases, larger doses and plasma concentrations are associated with increased risk. ACZONE (dapsone) Gel, 7.5% administered topically resulted in 100-fold lower exposures than occur during therapeutic oral dosing (100 mg orally) and perhaps 1000-fold lower than after overdose oral administration. The results of the phase 1 PK study (CSR 225678-004) indicate that both average peak and trough concentrations to dapsone from ACZONE (dapsone) Gel, 7.5% applied once daily are lower than from ACZONE Gel, 5% applied twice daily. According to the applicant, since the administration of ACZONE (dapsone) Gel, 7.5% for the treatment of acne in patients 12 years of age and older will result in very low plasma concentrations of dapsone, arrhythmogenicity is extremely unlikely.
- ECG methodology was included in clinical Study 225678-004 comparing ACZONE (dapsone) Gel, 7.5% formulations to ACZONE Gel, 5% under maximized use conditions. Pre- and post-dose ECGs were performed in triplicate at multiple time points within a day, and day-to-day timing of ECG acquisition was precisely monitored. Independent cardiologist review of summary data (heart rate, PR interval, QRS interval, and QTcF interval) in this study from baseline to day 28 indicated that none of the 4 treatments were associated with a clinically significant mean change from baseline at any time point, and that an electrocardiographic or proarrhythmic effect of any of the dapsone formulations is extremely unlikely.

- Absence of cardiac or electrocardiographic adverse events in the ACZONE Gel, 5% or the ACZONE (dapsone) Gel, 7.5% development programs

The Division accepts the request for a waiver to submit data from a thorough QT/QTc on the basis of low systemic exposure, and absence of a safety signal for cardiac events for the moiety dapsone.

7.4.5 Special Safety Studies/Clinical Trials

For the current application, three special safety trials were conducted:

1) Trial 225678-009 dermal safety (Phase 1, RIPT sensitization)
2) Trial 225678-010 dermal safety (Phase 1, phototoxicity)
3) Trial 225678-011 dermal safety (Phase 1, photoallergy)

1) Trial 225678-009: "Combined Cumulative Irritation Potential and Repeat Insult Patch Test of Dapsone 7.5% Gel in Healthy Volunteers"

Objective: To determine the cumulative irritation potential and sensitization potential of ACZONE Gel, 7.5% after repeat applications on the skin of healthy volunteers.

Trial Design: Single-center, randomized, evaluator-blinded, vehicle-controlled, within-subject comparison trial utilizing a cumulative irritation and sensitization (repeat insult patch test [RIPT]) combination study design

Number of healthy volunteers: 237 subjects were randomized; 202 completed the trial

Key Inclusion Criteria: General good health between 18 and 65 years of age with Fitzpatrick skin type of I through IV; were willing to avoid sun exposure and refrain from applying lotions, topical medications, and other products to the test sites for the duration of the study; and females of childbearing potential were willing and able to practice an acceptable contraceptive method during the study

Key Exclusion Criteria: Clinically significant chronic illness; females who were pregnant or nursing; compromised skin or skin disease, had excessive hair, tattoos, pigmentation, scars, moles, or other conditions at the areas to be patched which could have interfered with patch application, confounded study results, or interfered with study evaluations; had a disease or therapy leading to a potential for immunosuppression; had a history of sensitivity to adhesive bandages, tapes, and any ingredients of the study products; subject had received, applied, or taken certain specified treatments within the specified timeframe prior to first patch application

Trial Methodology:
The study population was divided into 2 subsets:

- subset 1 (cumulative irritation) 40 subjects

- subset 2 (repeat insult patch test RIPT) 197 subjects

Induction Phase (21 days):
Subset 1, Cumulative Irritation
Each subject received, under occlusive patches on the left upper back) approximately 200 µL of:

- ACZONE Gel, 7.5%
- Vehicle
- Positive control (0.2% sodium lauryl sulfate [SLS])
- Negative control (0.9% saline)

The test products were applied to the same site(s)/zone(s) on a given subject during the 21-day Irritation/Induction Phase of the study, unless a ≥ 3 combined dermal response score occurred (see following Tables 33 and 34), in which case that study material was applied to a new adjacent naïve site. The patch applications for this subset were made daily for an approximately 24-hour wear time. Over the 21-day Induction Phase, there were a total of 21 applications.

Subset 2, RIPT
Each subject received, under occlusive patches on the left upper back) approximately 200 µL of:

- ACZONE Gel, 7.5%
- Vehicle
- Negative control (0.9% saline)

The study treatments were applied to the same site(s) on a given subject for approximately 48 or 72 hours over the 21-day Induction Phase for a total of 9 applications, unless a ≥ 3 combined dermal response score occurred (see following Table 33 and 34), in which case that study material was applied to a new adjacent naive site.

For Both Subsets: If the patch application sites were moved because of ≥ 3 combined dermal response score, the test product was applied under semi-occlusive conditions for the remaining period of the study applications in consultation with the investigator and the study sponsor.

Evaluation of dermal response at the application sites was assessed clinically using a visual scale, the skin irritation scale of Berger and Bowman, that rated the degree of erythema, edema, and other signs of cutaneous irritation.

According to protocol, skin responses to each patch application were to be examined and graded under light supplied by a 100-watt incandescent blue bulb. The patch site evaluator was to be blinded as to treatment assignments and any previous scores. The same individual was to conduct all skin evaluations of the test sites but a qualified back-up individual was to be available if needed. The Evaluator was to evaluate irritancy

signs of skin reaction at each test site at approximately 30 minutes after the patch was removed.

Table 33: Scoring of Dermal Response

Score	Skin Appearance
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible; or minimal edema; or minimal papular response
3	Erythema and/or papules
4	Definite edema
5	Erythema and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test (ie, application) site

Source: Applicant's NDA, Module 5.3.5.4, Clinical Study Report 225678-009, p 27

Table 34: Scoring of Other Effects

Score	Numeric Equivalent	Observation
A	(0)	Slight glazed appearance
B	(1)	Marked glazed appearance
C	(2)	Glazing with peeling and cracking
F	(3)	Glazing with fissures
G	(3)	Film of dried serous exudates covering all or part of the patch site
H	(3)	Small petechial erosions and/or scabs

Source: Applicant's NDA, Module 5.3.5.4, Clinical Study Report 225678-009, p 27

Rest Period, Subsets 1 and 2:

During the rest period of approximately 10 to 17 days, subjects did not receive application of any study materials.

Contact Sensitization Challenge, Subsets 1 and 2:

To be eligible for the contact sensitization Challenge Phase, subjects must have received the minimum required induction applications (9 for the RIPT subset, 20 for the cumulative irritation subset; both subsets having completed a 21-day application period). Subjects in the Challenge Phase received a single application of dapsone 7.5% gel and its corresponding vehicle on separate occlusive patches applied to previously nonpatched naive sites (right upper back) for 48 hours.

After the 48-hour challenge, the patches were removed and the sites assessed after 30 minutes and 24, 48, and 72 hours. Sensitization was assessed on completed cases. If, in the opinion of the investigator (who was a dermatologist), any signs suggestive of contact sensitization (erythema and/or papulation) were observed at any of the evaluations following the removal of the challenge patch, the subjects were to undergo a Rechallenge Phase with the appropriate investigational product(s) at least 2 weeks after the 72-hour timepoint of the Challenge Phase and after the signs of previous reaction(s) have resolved. The rechallenge procedure was identical to the challenge procedure with application to a naive skin site. Rechallenge patches were to remain in place for 48 hours and patch sites were to be evaluated approximately 30 minutes and 24, 48, and 72 hours after removal.

The same sensitization reaction scoring system was used for both the Challenge and Rechallenge Phases.

Table 35: Sensitization Reaction Scoring

Score	Definition
0	Negative
1	Equivocal
2	Positive

Source: Applicant's NDA, Module 5.3.5.4, Clinical Study Report 225678-009, p 28

The dermatologist justified and documented these reactions. The judgment was based on criteria that included:

- Presence of itching
- Spreadability of lesions
- Presence of vesicles
- Crescendo reaction
- Reproducible upon rechallenge, if rechallenge was performed

Results:
Disposition of subjects:
Subset 1: Of the 63 subjects who were screened in subset 1, 40 subjects were randomized, and 32 subjects (80.0%) completed the study. Eight subjects in subset 1 did not complete the study: 5 subjects withdrew consent and 3 subjects were lost to follow-up. Subjects withdrew their consent for the following reasons: scheduling conflicts (3), no longer wanted to participate (1), and missed two visits (1; this subject completed the end-of-study procedures and withdrew after receiving a lost-to-follow-up letter).

Subset 2: Of the 284 subjects who were screened in subset 2, 197 subjects were randomized, and 170 subjects (86.3%) completed the study. Twenty-seven subjects in subset 2 did not complete the study: 13 subjects withdrew consent, 8 subjects were lost to follow-up, and 6 subjects were discontinued due to AEs. Subjects withdrew their

consent for the following reasons: scheduling conflicts or work schedule (6), did not want to continue (2), missed two visits (2), had to leave the state for an emergency (1), car trouble (1), and did not want to wear patches for 48 hours (1).

Demographics:
The safety population (both subset 1 and subset 2) included 237 subjects, of whom 184 (77.6%) were females and 53 (22.4%) were males. Overall, 168 subjects (70.9%) were White, 65 subjects (27.4%) were Black or African, 3 subjects (1.3%) were Asian, and one subject (0.4%) was "Other". One hundred seventy-five subjects (73.8%) were not Hispanic or Latino, and 62 subjects (26.2%) were Hispanic or Latino. Subjects ranged in age from 18 to 65 years with a mean age of 42.2 years.

Analysis Populations:
Safety Population
The safety population included all subjects who received at least one treatment dose. Analysis of AEs was performed using the safety population.

Skin Irritation and Sensitization Populations
Analyses of dermal sensitization potential and cumulative irritation potential were performed using the PP population. The analysis populations were defined separately for cumulative irritation and contact sensitization, and were defined per skin site (per treatment) rather than per subject.

The PP population consisted of 32 subjects for the analysis of cumulative irritation and 203 subjects (subjects from subset 1 and subset 2 who completed the Challenge Phase) for the sensitization analysis.

Subset 1 (Cumulative Irritation):
The test scores were a combination of a numerical and letter score (referred to as combined induction irritation score), which were transformed to numerical equivalents for the statistical analyses. For the analysis of cumulative irritation (subset 1), the transformed patch test scores provided an overall mean score for each test article for all assessments during Induction Phase (Mean Cumulative Irritancy Index [MCII]).

Table 36: Mean Cumulative Irritancy Index during Induction (Subset 1 PP Population)

	Number of Subjects	Mean (SD)	Wilcoxon Signed Rank P-value[a]		
			B	C	D
A. Dapsone 7.5% Gel	32	0.5 (0.55)	0.469	<0.001[b]	<0.001[b]
B. Vehicle	32	0.5 (0.67)		<0.001[b]	<0.001[b]
C. Negative Control	32	0.0 (0.08)			<0.001[b]
D. Positive Control	32	2.2 (0.62)			
Overall p-value, Friedman Rank Sum Text		<0.001			

SD = standard deviation
[a] Significant if less than 0.0083
[b] Significant
Source: Applicant's NDA, Module 5.3.5.4, Table 12-3, Clinical Study Report 225678-009, p 54.

The mean MCII scores for ACZONE Gel, 7.5% (0.5) and its vehicle (0.5) were significantly different from those of the negative control (0.0; $p < 0.001$). The MCII was greater at the positive control patch site (2.2) than at any of the other sites, and these differences were statistically significant ($p < 0.001$). There was no statistically significant difference in MCII between ACZONE Gel, 7.5% and the vehicle ($p = 0.469$).

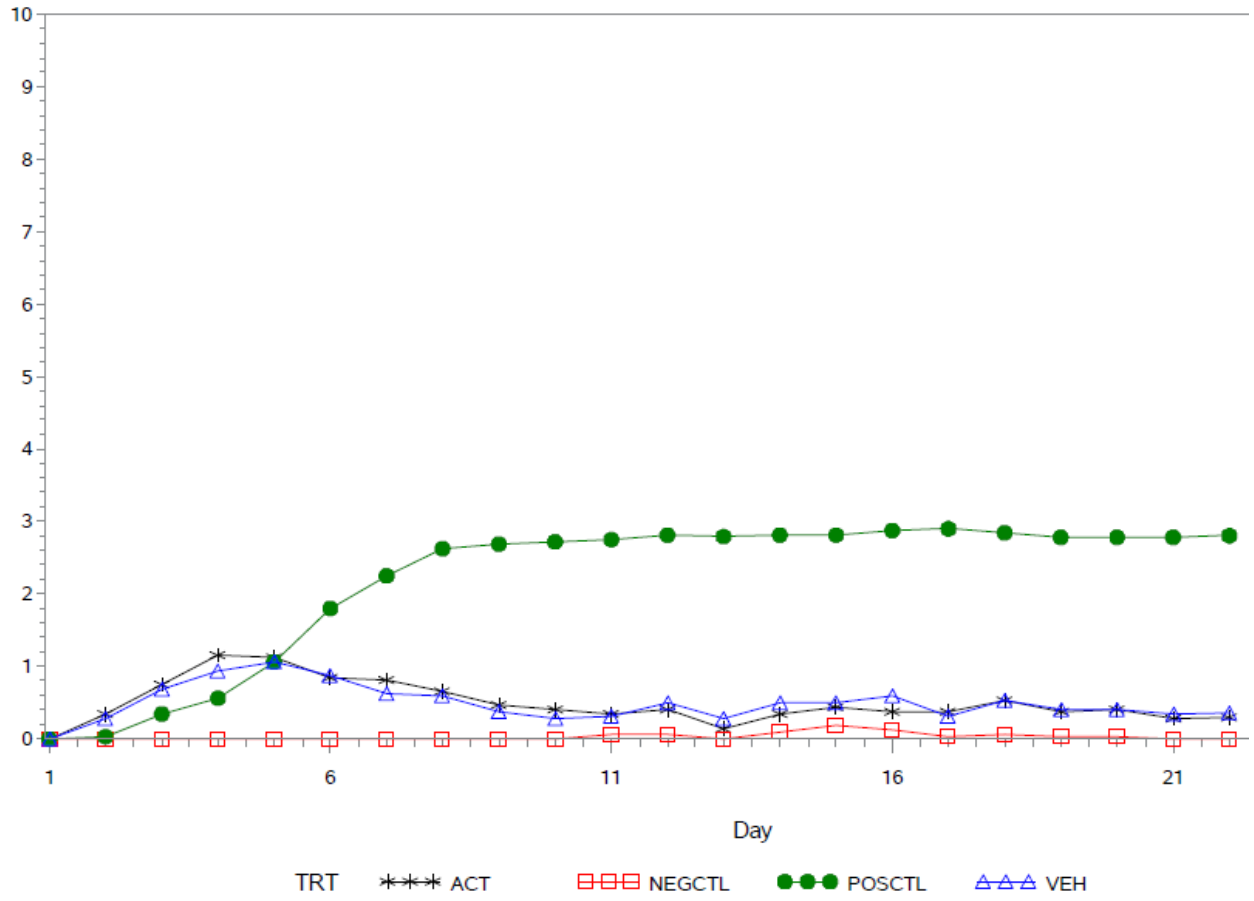
As shown in the following table, the worst combined score (including scores at both the original and moved sites) was a "4" in the ACZONE (dapsone) Gel, 7.5% group, a "6" in the vehicle group, a "2" in the negative control group, and a "4" in the positive control group.

Table 37: Frequency of Worst Combined Score Post-Baseline during Induction (Subset 1 PP Population)

Combined Scores	N (%)			
	Dapsone 7.5% Gel N = 32	Vehicle N = 32	Negative Control N = 32	Positive Control N = 32
0	3 (9.4%)	3 (9.4%)	25 (78.1%)	1 (3.1%)
1	10 (31.3%)	12 (37.5%)	5 (15.6%)	0
2	17 (53.1%)	15 (46.9%)	2 (6.3%)	2 (6.3%)
3	1 (3.1%)	1 (3.1%)	0	28 (87.5%)
4	1 (3.1%)	0	0	1 (3.1%)
5	0	0	0	0
6	0	1 (3.1%)	0	0
7	0	0	0	0
8	0	0	0	0
9	0	0	0	0
10	0	0	0	0

Source: Applicant's NDA, Module 5.3.5.4, Table 12-4, Clinical Study Report 225678-009, p 55.

Figure 1: Induction Irritation Scores for Subset 1 (Cumulative Irritation) PP Population



Y axis = Mean Score
Source: Applicant's NDA, Module 5.3.5.4, Figure 1-1, Clinical Study Report 225678-009, p 142.

Throughout the induction period, the mean combined induction irritation scores for ACZONE Gel, 7.5% (TRT above) were similar to those for the vehicle. The highest mean score occurred at day 4 for ACZONE Gel, 7.5% (1.2) and at day 5 for the vehicle (1.1). After these peaks the mean scores subsequently decreased.

After day 5, the mean scores were highest for the positive control, ranging from 1.8 on day 6 to a peak of 2.9 on day 16 and day 17. Throughout the study, the lowest mean scores occurred in the negative control group, ranging from 0.0 to a peak of 0.2 on day 15.

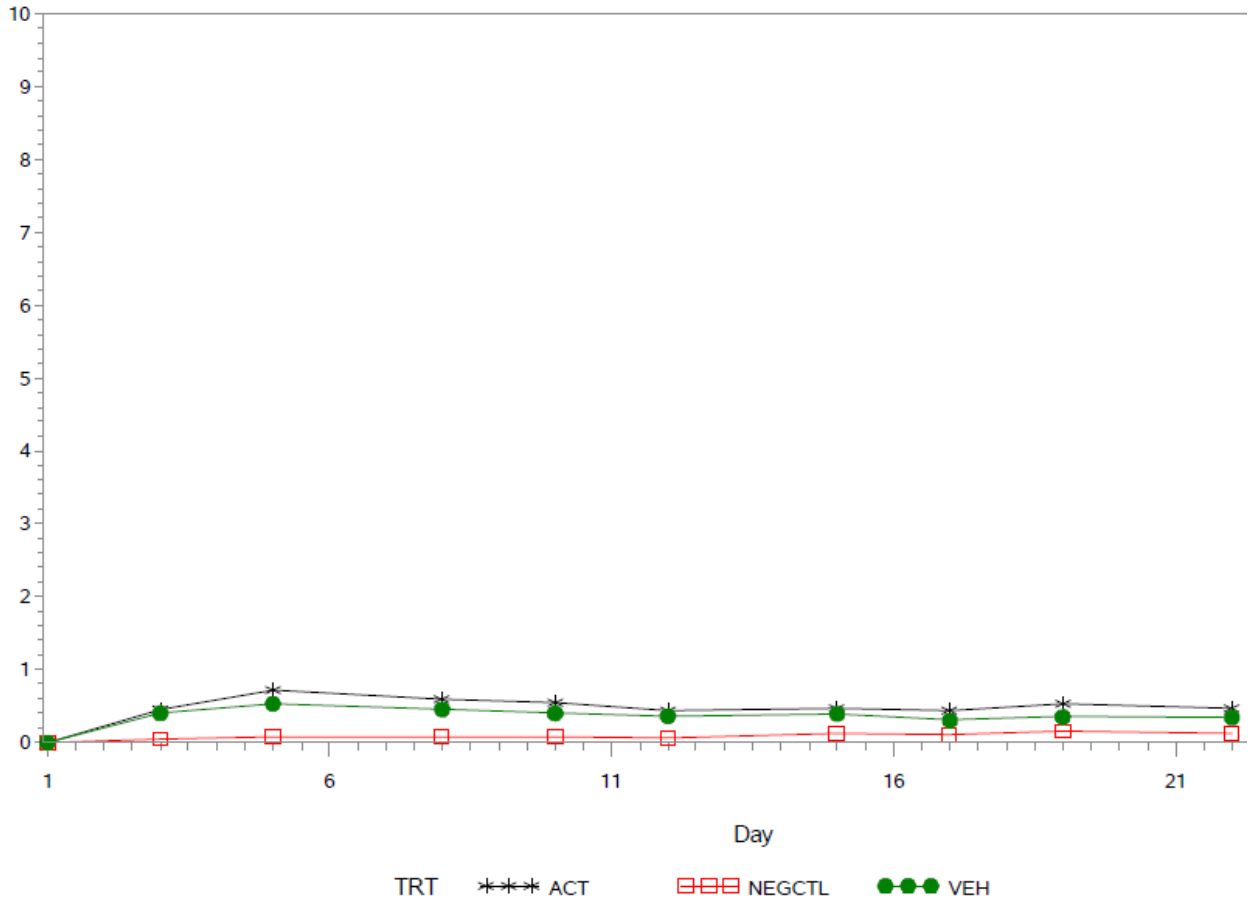
Subset 2(RIPT):
The worst combined score (including scores at both the original and moved sites) was a "5" in the ACZONE (dapsone) Gel, 7.5% group, a "5" in the vehicle group, and a "5" in the negative control group.

Table 38: Frequency of Worst Combined Score Post-Baseline during Induction (Subset 2 – PP Population)

	N (%)		
Combined Scores	Dapsone 7.5% Gel	Vehicle	Negative Control
.	N = 171	N = 171	N = 171
0	53 (31.0%)	70 (40.9%)	125 (73.1%)
1	58 (3.9%)	58 (33.9%)	29 (17.0%)
2	49 (28.7%)	35 (20.5%)	16 (9.4%)
3	3 (1.8%)	3 (1.8%)	0
4	5 (2.9%)	4 (2.3%)	0
5	3 (1.8%)	1 (0.6%)	1 (0.6%)
6	0	0	0
7	0	0	0
8	0	0	0
9	0	0	0
10	0	0	0

Percentages are calculated as % = 100 * n/N.
Combined score is numerical "Dermal response" score + numeric equivalent for the "Other Effects" lettered score (A = 0,
B = 1, C = 2, and F, G, and H = 3).
Worst combined score includes Original, M (first move), and M1 (second move) sites.
Source: Applicant's NDA, Module 5.3.5.4, Table 12-6, Clinical Study Report 225678-009, p 58.

Figure 2: Induction Irritation Scores (Subset 2 RIPT – PP Population)



Y axis = Mean Score
Source: Applicant's NDA, Module 5.3.5.4, Figure 1-2, Clinical Study Report 225678-009, p 143.

The combined irritation scores for subset 2 (PP population) during the Induction period are presented graphically in Figure 2. The mean combined irritation scores tended to be mildly higher for ACZONE Gel, 7.5% than for the vehicle group. The lowest irritation scores occurred for the negative control. Overall these results appear consistent with those found for Subset 1.

Sensitization:
A total of 203 subjects in the PP population were included in the sensitization analysis during the Challenge Phase.

Table 39: Incidence of Sensitization (Subsets 1&2 – PP Population)

Phase	Score	Dapsone 7.5% n (%)	Vehicle n (%)
Primary Test	Total Number of Observations	203	203
	Negative	201 (99.0%)	201 (99.0%)
	Equivocal	2 (1.0%)	2 (1.0%)
	Positive	0	0
Re-test	Total Number of Observations	2	2
	Negative	2 (100.0%)	2 (100.0%)
	Equivocal	0	0
	Positive	0	0
Combined Result[a]	Total Number of Observations	203	203
	Negative	202 (99.5%)	203 (100.0%)
	Equivocal	1 (0.5%)	0
	Positive	0	0

Primary Test = initial challenge; Re-test = rechallenge for some subjects
[a] Initial testing data with rechallenge data replacing initial challenge results.
Source: Applicant's NDA, Module 5.3.5.4, Table 12-2, Clinical Study Report 225678-009, p 53.

As shown above, the primary challenge test results were negative for ACZONE (dapsone) Gel, 7.5% and vehicle for 201 of 203 skin sites (99.0%). The primary challenge test results were equivocal for 2 ACZONE Gel, 7.5% skin sites (Subject Nos. 051 and 281) and for 2 vehicle skin sites (Subject Nos. 051 and 104).

Two of the 3 subjects with equivocal results (Nos. 051 and 104) were rechallenged, and their rechallenge results were negative at both the ACZONE Gel, 7.5% and vehicle skin sites. No rechallenge was performed for the third subject (No. 281), who was lost to follow-up.

Table 40: Summary of Subjects Rechallenged

Subject No. #	Test	ACZONE Gel, 7.5%	Vehicle
051	Primary Challenge	Equivocal	Equivocal
	Rechallenge	Negative	Negative
104	Primary Challenge	Negative	Equivocal
	Rechallenge	Negative	negative
281	Primary Challenge	Equivocal	Negative
	Rechallenge	Not done	Not done

Source: Applicant's NDA, Module 5.3.5.4, Clinical Study Report 225678-009, p 53.

Conclusions:

- Under the conditions of this study, ACZONE Gel, 7.5% and its vehicle did not show potential for sensitization.

- The MCIIs for ACZONE Gel, 7.5% (0.5) and its vehicle (0.5) were statistically significantly higher compared with the negative-control MCII, and they were statistically significantly lower than that for the positive control (0.5 versus 2.2). Under the conditions of this study, these results indicate that ACZONE Gel, 7.5% and its vehicle are unlikely to cause clinically meaningful irritation under normal use conditions.

Adverse Events:
There were no deaths in the trial. One serious TEAE was reported, an elective abortion, following a positive UPT on study day 41; this subject previously had a negative UPT on study day 36. This event was considered to be not related to study treatment. This event is also discussed further in section 7.3.2 (Nonfatal Serious Adverse Events) of this review.

A total of 11 subjects reported 16 TEAEs. These were reported as mild or moderate in severity and all were reported as resolved. Seven subjects had 12 TEAEs that were considered (definitely, probably, possibly, or unlikely) to be related to study treatment; these included skin discoloration, tremor, pyrexia, application site events (application site reaction, paresthesia, pruritus, and dermatitis), myalgia, and dyspnea. It is noted that the myalgia and dyspnea were considered unlikely related to study treatment. A total of 4 subjects had 4 events that were considered to have no relation to study treatment; 014-tape reaction, 122- acne on face, 123-cold, and 280-abortion (discussed further in section 7.3.2 of this review (nonfatal Serious Events).

A total of 6 subjects in subset 2 (RIPT 197 randomized) had study drug withdrawn and were discontinued because of non-serious TEAEs.

- Two subjects (Nos. 109 and 111) discontinued due to skin discoloration and tremor, both moderate in intensity, that were considered related to study treatment.
- One subject (No. 224) discontinued due to events of application site pruritus and paraesthesia that were moderate in intensity and considered related to study treatment.
- One subject (No. 139) discontinued due to application site dermatitis that was considered moderate and probably related to study treatment.
- One subject (No. 100) discontinued due to myalgia and dyspnea that were considered mild and unlikely related to study treatment.
- One subject (No. 014) discontinued due to contact dermatitis (a “tape reaction”) that was considered moderate in intensity and not related to study treatment.

Subjects 109 and 111 are discussed further under section 7.3.3 of this review (Dropouts and/or Discontinuations).

Subject 224:
The subject was a 29-year-old, Black/African American, non-Hispanic, female who had a history of polycystic ovarian syndrome. She had patches of test product applied to her back on May 16, 2014 (day 1) and May 19, 2014 (day 4). On May 19, 2014 (day 4), she experienced pin prick sensations (application site paraesthesia) and excessive itching (application site pruritus) at the application sites, and removed the patches that night. The skin sites were not graded on May 20, 2014 (day 5) as the patches had not been in contact with the skin since the previous day. The subject was discontinued from the study. These TEAEs were reported as resolved on May 20, 2014 (day 6; application site paraesthesia) and May 23, 2014 (day 8; application site pruritus). These TEAEs were considered moderate and definitely related to study treatment.

Subject 139:
The subject was a 39-year old, White, non-Hispanic male who had a history of hypercholesterolemia and hypertension. He had patches of test product applied to his back on April 30, 2014 (day 1), May 2, 2014 (day 3), May 5, 2014 (day 6), May 7, 2014 (day 8), May 9, 2014 (day 10), May 12, 2014 (day 13), May 14, 2014 (day 14), and May 16, 2014 (day 17). On May 19, 2014 (day 20), he had irritant dermatitis (application site dermatitis) at the ACZONE Gel, 7.5% and vehicle skin sites. The subject had skin irritation ratings of 3 (with itching) at the ACZONE Gel, 7.5% site; 6 (with itching) at the vehicle site; and 2 (with itching) at the negative control (saline) site. The ACZONE Gel, 7.5% and vehicle sites had significant epidermal damage and the investigator decided to remove the subject from the study. The TEAE was reported as resolved on 09 June 2014 (day 41). The TEAE was considered moderate and probably related to study treatment.

While these cases are suggestive of an irritant reaction to ACZONE Gel, 7.5% and/or vehicle their clinical significance is uncertain in view lack of grading of the sites for the first case and possible" excited skin syndrome" (in the presence of a strongly positive reaction, a state of skin hyper reactivity in which other patch test sites become reactive, especially to marginal irritants) for the second case.

2) Trial 225678-010: "Phototoxicity Test of Dapsone 7.5% Gel in Healthy Volunteers"

Objective: To determine the potential of ACZONE Gel, 7.5% and its vehicle to cause a phototoxic reaction after a single topical application followed by irradiation to the skin of healthy volunteers under controlled conditions.

Trial Design: Single-center, randomized, double-blinded, within-subject comparison study of investigational products ACZONE Gel, 7.5% and its vehicle under occlusive patch conditions

Number of heathy volunteers: A total of 33 subjects were randomized and 32 completed the trial.

Key Inclusion Criteria:
General good health between 18 years to 65 years of age with a Fitzpatrick skin type of I, II, or III; were willing to avoid sun exposure and refrain from applying lotions, topical medications, and other products to the test sites for the duration of the study; and females of childbearing potential were willing and able to practice an acceptable contraceptive method during the study.

Key Exclusion Criteria:
Clinically significant chronic illness; females who were pregnant or nursing; compromised skin or skin disease, excessive hair, tattoos, pigmentation, scars, moles, or other conditions at the areas that were patched which may have interfered with patch application, confounded study results or interfered with study evaluations; had a disease or therapy leading to a potential for immunosuppression; had a history of sensitivity to adhesive bandages, tapes, and any ingredients of the study products; subject had received, applied, or taken certain specified treatments within the specified timeframe prior to first patch application.

Trial Methodology:
A defined area (approximately 50 cm^2) on each subject's upper back (area above the infrascapular region) was irradiated to determine the minimal erythemal dose (MED) of ultraviolet (UV) light. A trained evaluator was to determine the MED for each subject.

All subjects were to have 4 application sites (2 irradiated and 2 nonirradiated) on the area above the infrascapular region of the back designated for application of investigational products and irradiation (if applicable) and 1 untreated irradiated control site (5 sites in total)..

On day 1, investigational products ACZONE Gel, 7.5% (.2 g) and vehicle (.2g) were each applied under occlusive patch conditions to 1 site designated for irradiation and 1 site designated for nonirradiation.

On day 2, the patches were removed and the sites designated for irradiation (including 1 untreated control site) were exposed to irradiation. The sites designated for irradiation were to receive 16 J/cm^2 of UVA radiation followed by 0.5 times the MED of UVA/UVB irradiation, using a filtered light source.

On Day 3, approximately 24 hours after irradiation, on day 3 (approximately 48 hours following patch application), all application sites and the untreated control site were evaluated.

On Day 4, approximately 48 hours after irradiation, on day 4 (approximately 72 hours following patch application) all application sites and the untreated control site were evaluated.

Dermal reactions at the application sites were evaluated by a trained, experienced evaluator using a visual scale for the degree of erythema, edema, and other signs of cutaneous irritation (see Table 41 and Table 42 below). These results were interpreted as indicating either a negative, equivocal or positive phototoxic reaction by a dermatologist. Retests were required to confirm any potential phototoxicity.

Table 41: Response Grading

Response	Symbol	Numerical Equivalent Score
Erythema		
No reaction	-	0
Mild, but definite erythema	+	1.0
Moderate erythema	++	2.0
Marked/severe erythema	+++	3.0
Edema		
Mild, but definite edema	**	1.0
Definite edema with erosion/vesiculation	***	1.5

Source: Applicant's NDA, Module 5.3.5.4, Table 9-4, Clinical Study Report 225678-010, p 25.

Table 42: Effects on Superficial Layers of Skin

Response/Comment	Notation
Hyperpigmentation	Hr
Hypopigmentation	Ho
Vesiculation	V
Papular response	p
Papulovesicular response	pv
Damage to epidermis: oozing, crusting and/or superficial erosions	D
Itching	I
Spreading of reaction beyond patch study site (ie, reaction where material did not contact skin)	S
Follicular irritation with or without pustule formation (folliculitis)	f
Subject absent	X
Patch dislodged	PD
Not patched	NP

Source: Applicant's NDA, Module 5.3.5.4, Table 9-5, Clinical Study Report 225678-010, p 25.

Results:

Subject Disposition: Forty-one subjects were screened for the study, 33 subjects were randomized, and 32 subjects (97.0%) completed the study. One subject was discontinued from the study due to noncompliance with study drug application instructions. On day 2, the subject came into the study site and stated that the patches had come off her back on the same day as patch application. The patches had been reapplied by the subject, but were no longer on the assigned sites making this subject ineligible for further study participation.

Analysis Populations: The safety population included all subjects with at least one patch applied, a total of 33 subjects. The evaluation of phototoxicity and local tolerability was based on the per protocol (PP) population, which included all subjects who wore the patch for at least 23 hours before irradiation, received the full irradiation dose administered, and completed day 3 or day 4 of the evaluation. A total of 32 subjects were included in the PP population.

Demographics: The safety population included 28 (84.8%) females and 5 (15.2%) males, all of whom were White. Thirty subjects (90.9%) were Not Hispanic or Latino, and 3 subjects (9.1%) were Hispanic or Latino. Subjects ranged in age from 18 to 65 years with a mean age of 44.1 years. Sixteen subjects (48.5%) had Fitzpatrick Skin Type II, 16 subjects (48.5%) had Fitzpatrick Skin Type III, and 1 subject (3.0%) had Fitzpatrick Skin Type I.

Adverse Events: There were no adverse events reported in this trial.

Phototoxicity Testing:
On day 4 (48 hours post-irradiation), mean irritation score for erythema, edema, erythema + edema (combined) were similar across the ACZONE Gel, 7.5% and vehicle irradiated and nonirradiated skin sites. Mean erythema scores ranged from 0.7 to 1.0 in these treatment groups. Mean edema scores ranged from 0.0 to 0.1. These erythema and edema scores were slightly higher than what was observed in the untreated irradiated control sites (0.2 for mean erythema score and 0.0 for mean edema score).

At the end of the initial testing (day 4), results of phototoxicity testing were negative for 31 of 32 subjects, and the result for 1 subject was considered to be equivocal. The subject underwent a retest for phototoxicity, which yielded a negative result. Therefore, of the 32 subjects analyzed, no subject was considered to have had a phototoxic reaction to ACZONE Gel, 7.5% or to its vehicle.

Conclusion: Under the conditions of the trial, the investigational products ACZONE Gel, 7.5% and its vehicle did not show potential for phototoxicity in healthy human subjects.

3) Trial 225678-011: "Evaluation of Photoallergy Potential of Dapsone 7.5% Gel in Healthy Volunteers"

Objective: To determine the potential of ACZONE Gel, 7.5% and its vehicle to cause a photoallergic reaction after repeated topical application and irradiation to the healthy skin of humans under controlled conditions.

Trial Design: Single-center, double-blind, controlled, randomized, within-subject comparison study of ACZONE Gel, 7.5% and its vehicle under occlusive patch conditions.

Number of Healthy Volunteers: 58 subjects were enrolled and randomized, 49 subjects completed the trial

Key Inclusion Criteria: General good health, between18 years and 65 years of age with Fitzpatrick skin type of I, II, or III; were willing to avoid sun exposure and refrain from applying lotions, topical medications, and other products to the test sites for the duration of the study; and females of childbearing potential were willing and able to practice an acceptable contraceptive method during the study.

Key Exclusion Criteria: Clinically significant chronic illness; females who were pregnant or nursing; had compromised skin or skin disease, excessive hair, tattoos, pigmentation, scars, moles, or other conditions at the areas that were to be patched that might have interfered with patch application, confounded study results, or interfered with study evaluations; had a disease or therapy leading to a potential for immunosuppression; had a history of sensitivity to adhesive bandages, tapes, or any ingredients in the study products; had received, applied, or taken certain specified treatments within the specified timeframe prior to first patch application.

Trial Methodology:

MED Determination

Each subject had an area (approximately 50 cm^2 and divided into 6 equal sites) defined on the upper back (area above the infrascapular region) irradiated to determine the minimal erythemal dose (MED) of ultraviolet (UV) light. Each of the skin sites was irradiated with full spectrum UV light (consisting of UVB plus UVA), with each exposure having differed from the next by a factor of 1.25 (ie, each irradiated site was exposed for 25% longer than the previous site). The MED was defined as the length (in time) of light exposure required to produce a minimal erythema reaction approximately 16 to 24 hours after irradiation using a standardized filtered UV light source that emitted UVB (290 to 320 nm) as part of its emission spectrum.

Induction Phase (Day1, Weeks 1-3):

For application of ACZONE Gel, 7.5% and its vehicle, a total of 4 sites on each subject's back were selected. Of the 4 sites, 2 were designated as "irradiated sites" (1 for

ACZONE Gel, 7.5% and 1 for vehicle) and 2 were designated as “nonirradiated sites” (1 for ACZONE Gel, 7.5% and 1 for vehicle). The areas involved in MED determination were independent of the application sites on which investigational products were applied.

The Induction Phase consisted of a series of 6 applications of ACZONE Gel, 7.5% (200 µL) and vehicle (200µL) and subsequent evaluation and irradiation (if designated) of the application sites. Patches (occlusive) were applied twice a week for 3 consecutive weeks. The same product was to be applied to the same skin site throughout the Induction Phase, with the exception of the presence of irritation requiring a change in patch application site. Beginning with the first day of the Induction Phase, skin sites were evaluated immediately prior to product application. Approximately 24 hours following each product application, all patches were removed. The skin sites were evaluated using a scoring system that rated the intensity of any erythema or edema that was present; other effects on the skin (such as hyperpigmentation, site not patched, etc.) were also to be noted. See following tables. Twice a week during each week of the Induction Phase, the skin sites designated for irradiation received two times the subject’s MED using the full Xenon lamp spectrum (UVA/UVB).

Table 43: Response Grading

Response	Symbol	Numerical Equivalent Score
Erythema		
No reaction	-	0
Mild, but definite erythema	+	1.0
Moderate erythema	++	2.0
Marked/severe erythema	+++	3.0
Edema		
Mild, but definite edema	**	1.0
Definite edema with erosion/vesiculation	***	1.5

Source: Applicant’s NDA, Module 5.3.5.4, Table 9-3, Clinical Study Report 225678-011, p 22.

Table 44: Effects on Superficial Layers of Skin

Response/Comment	Notation
Hyperpigmentation	Hr
Hypopigmentation	Ho
Vesiculation	V
Papular response	p
Papulovesicular response	pv
Damage to epidermis: oozing, crusting and/or superficial erosions	D
Itching	I
Spreading of reaction beyond patch study site (ie, reaction where material did not contact skin)	S
Follicular irritation with or without pustule formation (folliculitis)	f
Subject absent	X
Patch dislodged	PD
Not patched	NP

Source: Applicant's NDA, Module 5.3.5.4, Table 9-4, Clinical Study Report 225678-011, p 22.

Rest Period (Weeks 4 and 5):
Duration approximately 10 to 17 days

Challenge Phase:
In the Challenge Phase, subjects who completed the Induction Phase and the Rest Period had ACZONE Gel, 7.5% and its vehicle applied to naive sites on the back. The skin sites were designated according to the randomization scheme. As in the Induction Phase, ACZONE Gel, 7.5% and its vehicle were each to be applied using occlusive patch conditions to 2 sites, one that was irradiated and one that remained nonirradiated. In addition, an untreated site was designated for irradiation (5 sites in total). The patches were to remain in place for approximately 24 hours. The clinical staff then removed the patches, evaluated the skin sites, and irradiated the designated skin sites (including the untreated site) with 6 J/cm^2 of UVA radiation followed by 0.5 times the MED of UVA/UVB radiation, obtained by using a filtered light source. Each site was evaluated again for dermal reactions at approximately 24, 48, and 72 hours post irradiation.

Rechallenge:
If the investigator determined that a rechallenge was required, the rechallenge patches were to be applied as soon as challenge reactions resolved or as determined as appropriate by the investigator. ACZONE Gel, 7.5% gel and its vehicle were to be applied to naive sites on the back using the same procedures as for the Challenge Phase.

At the last reading of the Challenge Phase, if applicable, the dermatologist gave his/her opinion concerning a possible photosensitization reaction, by comparing evaluation of

each irradiated site with the corresponding non-irradiated site and with the untreated irradiated site, using the following scale:

Table 45: Photosensitization Reaction Scoring

Score	Definition
0	Negative
1	Equivocal
2	Positive

Source: Applicant's NDA, Module 5.3.5.4, Clinical Study Report 225678-011, p 23

Results:
Disposition of Subjects:
A total of 78 subjects were screened for the study, 58 subjects were randomized and 49 subjects (84.5%) completed the study. Five subjects discontinued the study due to an AE and one subject discontinued due to non-compliance with study drug (see Section 12.3.3). Two subjects withdrew from the study, and one subject was lost to follow-up.

Demographics:
The safety population included 50 (86.2%) females and 8 (13.8%) males. Fifty-seven (98.3%) subjects were White, and one subject (1.7%) was Asian. Forty-four (75.9%) subjects were Not Hispanic or Latino, and 14 subjects (24.1%) were Hispanic or Latino. Subjects ranged in age from 19 to 64 years with a mean age of 46.0 years.

Analysis Populations:
Safety Population:
The safety population included all subjects (58) with at least one patch applied.

Per Protocol Population:
The PP population was defined per skin site and was established after a review of protocol deviations. The PP population (50 subjects representing 50 skin sites) was the primary analysis population for the evaluation of photosensitization and local tolerability.

Photosensitization:
At the last reading of the Challenge Phase, 49 of 50 subjects (98.0%, subjects in the PP population; 49 of 50 skin sites for ACZONE Gel, 7.5% and 49 of 50 sites for vehicle) were considered to have a negative photosensitization reaction at the irradiated sites, as assessed by a dermatologist.

One subject (No. 029) was considered to have an equivocal photosensitization reaction. In the opinion of the investigator, this subject's data were unusual as during Challenge worsening erythema was observed compared to the Induction Phase at both ACZONE Gel, 7.5% gel and vehicle irradiated sites at pre-irradiation, 24 hours, and 48 hours post-irradiation timepoints. The erythema subsided at 72 hours post-irradiation

timepoint. Edema reaction was also seen in this subject at pre-irradiation and 24 hours post-irradiation at both ACZONE Gel, 7.5% gel and vehicle irradiated sites. This equivocal response qualified the subject to be rechallenged; however, as the subject was lost to follow-up no rechallenge was conducted.

Conclusion:
Under the conditions of this study, ACZONE Gel, 7.5% gel and its vehicle did not show clinically significant potential for photoallergy in healthy subjects.

Adverse Events:
No deaths were reported in the trial. One serious TEAE was reported, stress cardiomyopathy, It was considered not to be related to study treatment. This event is discussed further in section 7.3.2 of this review (Nonfatal Serious Adverse Events).

A total of 11 subjects reported 17 TEAEs. Most of the TEAEs were mild or moderate in severity (see Table 12-3). Only 1 TEAE of severe intensity (stress cardiomyopathy) was reported. Five subjects had 7 adverse events that were considered (definitely, probably, possibly, or unlikely) to be related to study treatment. Three subjects, Nos. 001, 008, and 016 had application site reactions that were considered definitely related to study treatment and moderate in severity. Study product was withdrawn and all of the reactions resolved. One subject, No. 012, had urticarial patches in two locations (bilateral upper cheeks and upper neck). None of the subject's application sites received a combined erythema+edema score greater than 1. These events were considered to be possibly related to study treatment and moderate in severity. Study product was withdrawn and both TEAEs resolved. One subject, No. 019, had a rash on the dorsal aspect of her feet and bilaterally on her legs. These events were considered to be unlikely related to study treatment and mild in severity. No action was taken and both events resolved. A total of 7 subjects had 10 TEAEs that were considered to have no relation to study medication; 008-cut on finger, 027-mid back pain & upper respiratory infection, 034-stress cardiomyopathy, 042-cheek scratches, 043-cough, 45-contact dermatitis, and 62-vomiting & chills & stomach ache.

A total of 5 subjects (58 randomized) discontinued the trial due to TEAEs. One subject, number 34, withdrew because of a serious TEAE, stress cardiomyopathy (This event is discussed in section 7.3.2 of this review, Nonfatal Serious Adverse Events).

- Subjects 1, 8, 16: These three subjects discontinued due to application site reactions of moderate severity that were considered related to study treatment. Two out of the 3 subjects (Nos. 001 and 008) developed application site irritation in the Induction Phase and patches were relocated twice. Per protocol, the subjects were discontinued. Subject 008 was also discontinued because of a moderate laceration on her index finger that was unrelated to study treatment. One subject (No. 016) developed application site reaction at all sites, 24 hours after patch application, in the Challenge Phase. The subject was not irradiated and was discontinued.

- Subject 12: withdrew as a result of urticaria of moderate severity that occurred bilaterally on the upper cheeks and also on the upper neck (distant from the patch sites) and was considered to be possibly related to study treatment.

Details of cases of interest for subjects discontinued from trial 225678-011:
Subject 1:
The subject was a 62-year-old, White, non-Hispanic female who had a history of hypercholesterolemia and celiac disease. The subject had patches of study material applied to her back on April 28, 2014 (day 1), May 1, 2014 (day 4), May 5, 2014 (day 8), May 8, 2014 (day 11), and May 12, 2014 (day 15). On 5 May 5, 2014 (day 8), all patch sites were moved using occlusive patches and on 8 May 8, 2014 (day 11), all patch sites were moved for a second time using semi-occlusive patches. The subject's final patch application occurred on May 12, 2014. The subject was withdrawn from treatment due to observed reactions (moderate erythema, superficial damage to the epidermis) on left sites 1 and 2 and right sites 1 and 2; the reactions were observed with both ACZONE Gel, 7.5% and its vehicle. Since the subject developed application site irritation reactions and the patch sites were relocated twice, as per protocol the subject was discontinued. The reactions were recorded as resolved on May 19, 2014. The TEAE of application site reaction was considered moderate and definitely related to study treatment.

Subject 8:
The subject was a 48-year-old White, non-Hispanic female who reported no relevant medical history. The subject received applications of study material to her back on April 28, 2014 (day 1), May 1, 2014 (day 4), May 5, 2014 (day 8), May 8, 2014 (day 11), and May 12, 2014 (day 15). On May 5, 2014 (day 8), all patch sites were moved using occlusive patches and on May 8, 14 (day 11), all patch sites were moved for a second time using semi-occlusive patches. The subject's final patch application occurred on May 12, 2014. The subject was withdrawn from treatment on 13 May 13, 2014 (day 16) due to observed reactions of moderate erythema and definite edema with erosion/vesiculation on left sites 1 and 2 and right site 2. Since the subject developed application site irritation reactions and the patch sites were relocated twice, as per protocol the subject was discontinued. The reactions were recorded as resolved on May 19, 2014. The TEAE of application site reaction was considered moderate in severity and related to study treatment.

Subject 16:
The subject was a 21-year-old White, Hispanic female who had an innocent heart murmur. The subject received applications of study material to her back on April 2014 28, (day 1), May 1, 2014 (day 4), May 5, 2014 (day 8), May 8, 2014 (day 11), May 12, 2014, (day 15), and May 15, 2014 (day 18). The subject entered the Challenge Phase and challenge patches were applied on June 2, 2014. The subject developed application site reaction at all sites (moderate to severe erythema; definite edema with erosion/vesiculation) 24 hours after patch application. The subject was not irradiated

and was discontinued from the study on June 10, 2014. The reactions were recorded as resolved on June 24, 2014. The TEAE of application site reaction was considered moderate in severity and related to study treatment.

Subject 12:
The subject was a 53-year-old White, Hispanic female who had a history of bilateral tubal ligation (1999), seasonal (spring) allergies (ongoing since 1993). The subject received applications of study material to her back on April 28, 2014 (day 1), May 1, 2014 (day 4), May 5, 2014 (day 8), May 8, 2014 (day 11), May 12, 2014 (day 15), May 15, 2014 (day 18), and May 19, 2014 (day 22). The subject reported urticarial patches that occurred bilaterally on her upper cheeks and also on her upper neck (distant from the patch sites) with onset on 24 May 2014 (day 27). These TEAEs (urticarial patches) were considered moderate in severity and possibly related to treatment. They were reported as resolved on June 2, 2014 (day 36), and the subject was discontinued from the study. The TEAE of urticarial patches was considered moderate in intensity and possibly related to study medication.

7.4.6 Immunogenicity

This is not applicable since the drug is not a therapeutic protein.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The applicant did not provide an analysis for adverse events (TEAEs) versus dose of medication. Using a cut-off of approximately 120% of the mean daily medication, the FDA statistician has provided an analysis of TEAEs by amount of product used per day.

Table 46: Overview of Adverse Events Reported by Amount of Product Used (Pooled Trials; Safety Population)

	Averaged < 0.8 g/day		Averaged ≥ 0.8 g/day	
Subjects With:	**ACZONE (N=1561)**	**Vehicle (N=1559)**	**ACZONE (N=546)**	**Vehicle (N=573)**
Any Treatment-Emergent AEs	308 (20%)	314 (20%)	86 (16%)	92 (16%)
Any Drug-Related(1) AEs	52 (3%)	55 (4%)	22 (4%)	16 (3%)
Any Serious AEs	5 (<1%)	8 (<1%)	2 (<1%)	1 (<1%)
Any Treatment-Emergent AEs Leading to Discontinuation	5 (<1%)	6 (<1%)	1 (<1%)	1 (<1%)

(1) Assessed by investigator as possibly drug-related.

Source: Statistical review NDA 207154, Table 19, p.18.

Table 47: Treatment-Related(1) Treatment-Emergent Adverse Events by Amount of Product Used (Pooled Trials, Safety Population)

	Averaged < 0.8 g/day		Averaged ≥ 0.8 g/day	
System Organ Class / Preferred Term	**ACZONE (N=1561)**	**Vehicle (N=1559)**	**ACZONE (N=546)**	**Vehicle (N=573)**
Eye disorders				
Eyelid rash	1 (0.1%)	0	0	0
Lacrimation increased	0	0	1 (0.2%)	0
Blepharitis	0	1 (0.1%)	0	0
Gastrointestinal disorders				
Chapped lips	1 (0.1%)	0	0	0
General disorders and administration site conditions				
Application site dryness	16 (1.0%)	11 (0.7%)	8 (1.5%)	9 (1.6%)
Application site pruritus	14 (0.9%)	10 (0.6%)	5 (0.9%)	1 (0.2%)
Application site erythema	9 (0.6%)	10 (0.6%)	5 (0.9%)	3 (0.5%)
Application site pain	5 (0.3%)	25 (1.6%)	4 (0.7%)	5 (0.9%)
Application site exfoliation	8 (0.5%)	10 (0.6%)	1 (0.2%)	4 (0.7%)
Application site paraesthesia	4 (0.3%)	5 (0.3%)	1 (0.2%)	2 (0.3%)
Application site irritation	1 (0.1%)	0	2 (0.4%)	0
Application site acne	1 (0.1%)	2 (0.1%)	1 (0.2%)	0
Application site dermatitis	1 (0.1%)	1 (0.1%)	0	0
Application site discomfort	1 (0.1%)	0	0	0
Application site photosensitivity reaction	1 (0.1%)	0	0	0
Application site reaction	1 (0.1%)	0	0	0
Application site swelling	0	0	1 (0.2%)	0
Application site vesicles	0	0	1 (0.2%)	0
Application site papules	0	1 (0.1%)	0	0
Application site warmth	0	1 (0.1%)	0	0
Nervous system disorders				
Dizziness	1 (0.1%)	0	0	0
Psychiatric disorders				
Depression	0	1 (0.1%)	0	0
Skin and subcutaneous tissue disorders				
Skin tightness	2 (0.1%)	1 (0.1%)	1 (0.2%)	0
Seborrhoea	2 (0.1%)	0	0	1 (0.2%)
Pruritis	0	0	1 (0.2%)	0
Skin irritation	0	0	0	1 (0.2%)
Sticky skin	0	1 (0.1%)	0	0

(1) Assessed by investigator as possibly drug-related.

Source: Statistical review NDA 207154, Table 20, p.19.
Clinically significant differences in TEAEs between the groups averaging < 0.8 g/day versus those using ≥ 0.8 g/day are not seen.

7.5.2 Time Dependency for Adverse Events

Most subjects experienced adverse events at the time of or shortly (days to Weeks) after product application. The pooled safety studies in this submission were not designed to evaluate the time dependency of adverse events.

7.5.3 Drug-Demographic Interactions

Adverse Events by Age:
The proportion of subjects experiencing TEAEs was similar among those aged 12 to 17 years of age as compared with those subjects ≥ 18 years of age. Within age subgroups the frequency of TEAEs was similar between the ACZONE Gel, 7.5 % and vehicle groups. For subjects 12 to 17 years of age, the overall frequency of TEAEs was 19.4% (207/1066) in the ACZONE Gel, 7.5% group versus 20.2% (219/1084) in the vehicle group. For subjects ≥ 18 years of age, the overall frequency of TEAEs was 17.3% (189/1095) in the ACZONE Gel, 7.5% group versus 17.4% (190/1091) in the vehicle group.

Table 48: Treatment Emergent Adverse Events, Primary SOC by Age Group (Pooled Safety Trials)

	12 < Age < 17 Years		**Age ≥ 18 years**	
	ACZONE 7.5%	**vehicle**	**ACZONE 7.5 %**	**vehicle**
System Organ Class (SOC)	N = 1066	N = 1084	N = 1095	N = 1091
	n (%)	n (%)		
Blood				
SOC total	0 (0)	1 (0.1)	0 (0)	3 (0.3)
Ear and labyrinth disorders				
SOC total	-	-	1 (0.1)	0 (0)
Endocrine disorders				
SOC total	-	-	3 (0.3)	0 (0)
Eye disorders				
SOC total	1 (0.1)	0 (0)	2 (0.2)	5 (0.5)
Gastrointestinal disorders				
SOC total	18 (1.7)	12 (1.1)	11 (1.0)	11 (1.0)
General disorders and administration site conditions				
SOC total	37 (3.5)	47 (4.3)	58 (5.3)	45 (4.1)
Hepatobiliary disorders				
SOC total	-	-	0 (0)	1 (0.1)
Immune system disorders				

	12 < Age < 17 Years		Age ≥ 18 years	
	ACZONE 7.5%	vehicle	ACZONE 7.5 %	vehicle
System Organ Class (SOC)	N = 1066	N = 1084	N = 1095	N = 1091
	n (%)	n (%)		
SOC total	2 (0.2)	1 (0.1)	0 (0)	2 (0.2)
Infections and infestations				
SOC total	88 (8.3)	87 (8.0)	72 (6.6)	70 (6.4)
Injury, poisoning and procedural complications				
SOC total	39 (3.7)	36 (3.3)	12 (1.1)	21 (1.9)
Investigations				
SOC total	1 (0.1)	0 (0)	0 (0)	1 (0.1)
Metabolism and nutrition disorders				
SOC total	1 (0.1)	0 (0)	2 (0.2)	2 (0.2)
Musculoskeletal and connective tissue disorders				
SOC total	11 (1.0)	0 (0)	10 (0.9)	7 (0.6)
Neoplasms benign, malignant, and unspecified				
SOC total	2 (0.2)	0 (0)	1 (0.1)	2 (0.2)
Nervous system disorders				
SOC total	26 (2.4)	11 (1.0)	19 (1.7)	21 (1.9)
Pregnancy, puerperium and perinatal conditions				
SOC total	-	-	0 (0)	1 (0.1)
Psychiatric disorders				
SOC total	2 (0.2)	5 (0.5)	4 (0.4)	8 (0.7)
Renal and urinary disorders				
SOC total	1 (0.1)	0 (0)	-	-
Reproductive system and breast disorders				
	-	-	0 (0)	2 (0.3)
Respiratory, thoracic and mediastinal disorders				
SOC total	31 (2.9)	37 (3.4)	22 (2.0)	20 (1.8)
Skin and subcutaneous tissue disorders				
SOC total	9 (0.8)	13 (1.2)	12 (1.1)	13 (1.2)
Surgical and medical procedures				
SOC total	-	-	0 (0)	1 (0.1)
Vascular disorders				
SOC total	0 (0)	1 (0.1)	0 (0)	2 (0.2)
Total number of Subjects	207 (19.4)	219 (20.2)	189 (17.3)	190 (17.4)

All treatment emergent adverse events are represented, regardless of relationship to treatment.
Within each preferred term, a patient is counted at most once. MedDRA Version 17.0.
Source: Applicant's NDA, Module 5.3.5.3, ISS adapted from Tables 3-7.1 and 3-7.2, pp. 305-325.

Adverse Events by Gender:
The proportion of subjects experiencing TEAEs was similar among male and female subjects and among those exposed to ACZONE Gel, 7.5 % compared with those exposed to vehicle. For male patients, the overall frequency of TEAEs was 17.4% (166/953) in the ACZONE Gel, 7.5% group versus 18.1% (175/965) in the vehicle group. For female subjects, the overall frequency of TEAEs was 19.0% (230/1208) in the ACZONE Gel, 7.5% group versus 19.3% (234/1210) in the vehicle group.

Table 49: Treatment Emergent Adverse Events, Primary SOC by Gender (Pooled Safety Trials)

	Male		Female	
	ACZONE 7.5%	**vehicle**	**ACZONE 7.5 %**	**vehicle**
System Organ Class (SOC)	N = 953	N = 965	N = 1095	N = 1091
	n (%)	n (%)		
Blood				
SOC total	0 (0)	2 (0.2)	0 (0)	2 (0.2)
Ear and labyrinth disorders				
SOC total	-	-	1 (0.1)	0 (0)
Endocrine disorders				
SOC total	-	-	3 (0.2)	0 (0)
Eye disorders				
SOC total	1 (0.1)	2 (0.2)	2 (0.2)	3 (0.2)
Gastrointestinal disorders				
SOC total	16 (1.7)	5 (0.5)	13 (1.1)	18 (1.5)
General disorders and administration site conditions				
SOC total	33 (3.5)	40 (4.1)	62 (5.1)	52 (4.3)
Hepatobiliary disorders				
SOC total	-	-	0 (0)	1 (0.1)
Immune system disorders				
SOC total	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.2)
Infections and infestations				
SOC total	72 (7.6)	65 (6.7)	88 (7.3)	92 (7.6)
Injury, poisoning and procedural complications				
SOC total	32 (3.4)	31 (3.2)	19 (1.6)	26 (2.1)
Investigations				
SOC total	1 (0.1)	0 (0)	0 (0)	1 (0.1)
Metabolism and nutrition disorders				
SOC total	-	-	3 (0.2)	2 (0.2)
Musculoskeletal and connective tissue disorders				
SOC total	8 (0.8)	7 (0.7)	13 (1.1)	13 (1.1)
Neoplasms benign, malignant, and unspecified				
SOC total	2 (0.2)	2 (0.2)	1 (0.1)	0 (0)
Nervous system disorders				
SOC total	20 (2.1)	8 (0.8)	25 (2.1)	24 (2.0)

	Male		Female	
	ACZONE 7.5%	**vehicle**	**ACZONE 7.5 %**	**vehicle**
System Organ Class (SOC)	N = 953	N = 965	N = 1095	N = 1091
	n (%)	n (%)		
Pregnancy, puerperium and perinatal conditions				
SOC total	-	-	0 (0)	1 (0.1)
Psychiatric disorders				
SOC total	2 (0.2)	4 (0.4)	4 (0.3)	9 (0.7)
Renal and urinary disorders				
SOC total	1 (0.1)	0 (0)	-	-
Reproductive system and breast disorders				
	-	-	4 (0.3)	8 (0.7)
Respiratory, thoracic and mediastinal disorders				
SOC total	22 (2.3)	32 (3.3)	31 (2.6)	25 (2.1)
Skin and subcutaneous tissue disorders				
SOC total	1 (0.1)	12 (1.2)	20 (1.7)	14 (1.2)
Surgical and medical procedures				
SOC total	-	-	0 (0)	1 (0.1)
Vascular disorders				
SOC total	-	-	0 (0)	3 (0.2)
Total number of Subjects	166 (17.4)	175 (18.1)	230 (19.0)	234 (19.3)

All treatment emergent adverse events are represented, regardless of relationship to treatment.
Within each preferred term, a patient is counted at most once. MedDRA Version 17.0.
Source: Applicant's NDA, Module 5.3.5.3, ISS adapted from Tables 3-8.1 and 3-8.2, pp. 326-346.

Adverse Events by Race:
The proportion of subjects experiencing TEAEs was similar among Caucasian and non-Caucasian subjects and among those exposed to Aczone 7.5 % gel compared with those exposed to vehicle. For Caucasian subjects, the overall frequency of TEAEs was 19.5% (243/1247) in the ACZONE Gel, 7.5% group versus 21.5% (267/1241) in the vehicle group. For non-Caucasian subjects, the overall incidence of TEAEs was 16.7% (153/914) in the ACZONE Gel, 7.5% group versus 15.2% (142/934) in the vehicle group.

Table 50: Treatment Emergent Adverse Events, Primary SOC by Race (Pooled Safety Trials)

	Caucasian		Non-Caucasian	
	ACZONE 7.5%	**vehicle**	**ACZONE 7.5 %**	**vehicle**
System Organ Class (SOC)	N = 1247	N = 1241	N = 1095	N = 1091
	n (%)	n (%)		
Blood				
SOC total	0 (0)	4 (0.3)	-	-
Ear and labyrinth disorders				
SOC total	-	-	1 (0.1)	0 (0)
Endocrine disorders				
SOC total	2 (0.2)	0 (0)	1 (0.1)	0 (0)
Eye disorders				
SOC total	1 (0.1)	3 (0.2)	2 (0.2)	2 (0.2)
Gastrointestinal disorders				
SOC total	24 (1.9)	16 (1.3)	5 (0.5)	7 (0.7)
General disorders and administration site conditions				
SOC total	47 (3.8)	52 (4.2)	48 (5.3)	40 (4.3)
Hepatobiliary disorders				
SOC total	-	-	0 (0)	1 (0.1)
Immune system disorders				
SOC total	1 (0.1)	2 (0.2)	1 (0.1)	1 (0.1)
Infections and infestations				
SOC total	109 (8.7)	113 (9.1)	51 (5.6)	44 (4.7)
Injury, poisoning and procedural complications				
SOC total	33 (2.5)	41 (3.3)	20 (2.2)	16 (1.7)
Investigations				
SOC total	1 (0.1)	1 (0.1)	-	-
Metabolism and nutrition disorders				
SOC total	3 (0.2)	2 (0.2)	-	-
Musculoskeletal and connective tissue disorders				
SOC total	15 (1.2)	12 (1.0)	6 (0.7)	8 (0.9)
Neoplasms benign, malignant, and unspecified				
SOC total	3 (0.2)	2 (0.2)	-	-
Nervous system disorders				
SOC total	28 (2.2)	13 (1.0)	17 (1.9)	19 (2.0)
Pregnancy, puerperium and perinatal conditions				
SOC total	-	-	0 (0)	1 (0.1)
Psychiatric disorders				
SOC total	3 (0.2)	10 (0.8)	3 (0.3)	3 (0.3)
Renal and urinary disorders				
SOC total	1 (0.1)	0 (0)	-	-
Reproductive system and breast disorders				
	1 (0.1)	5 (0.4)	3 (0.3)	3 (0.3)

	Caucasian		Non-Caucasian	
	ACZONE 7.5%	**vehicle**	**ACZONE 7.5 %**	**vehicle**
System Organ Class (SOC)	N = 1247	N = 1241	N = 1095	N = 1091
	n (%)	n (%)		
Respiratory, thoracic and mediastinal disorders				
SOC total	34 (2.7)	40 (3.2)	19 (2.1)	17 (1.8)
Skin and subcutaneous tissue disorders				
SOC total	12 (1.0)	18 (1.5)	9 (1.0)	8 (0.9)
Surgical and medical procedures				
SOC total	-	-	0 (0)	1 (0.1)
Vascular disorders				
SOC total	0 (0)	1 (0.1)	0 (0)	2 (0.2)
Total number of Subjects	243 (19.5)	267 (21.5)	153 (16.7)	142 (15.2)

All treatment emergent adverse events are represented, regardless of relationship to treatment.
Within each preferred term, a patient is counted at most once. MedDRA Version 17.0.
Source: Applicant's NDA, Module 5.3.5.3, ISS adapted from Tables 3-9.1 and 3-9.2, pp. 347-367.

7.5.4 Drug-Disease Interactions

All subjects entering the trial were to have moderate disease for trial entry. No formal analyses were performed for drug-disease interactions with this topical drug product.

7.5.5 Drug-Drug Interactions

No formal analyses were performed for drug-drug interactions with this topical drug product.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity was not assessed as part of the clinical development program. Controlled clinical trials were too short to allow for evaluation of carcinogenicity.

7.6.2 Human Reproduction and Pregnancy Data

Phase 1:

●Trial 225678-004 (PK, 4-arm, active controlled): All pregnancy testing (UPT) was negative.

●Trial 225678-009 (Phase 1, RIPT, sensitization): A UPT was to be performed at the first visit of each study phase (Induction, Challenge, EOS (End of Study), and Rechallenge, if applicable) for females of childbearing potential. Test results were negative for all applicable subjects except one, No. 280. Subject No. 280, a female subject of childbearing potential, reported sexual abstinence and had a negative UPT result at Screening and Day 36, but had a positive UPT result at the EOS visit. This subject had a serious TEAE reported of elective abortion (discussed earlier in this review under section 7.3.2):

> The subject was a 22 year old Black/African American female. The subject had no relevant medical history and no concomitant medications were reported. The subject underwent the screening and day 1 procedures on May 21, 2014 (day 1), including a UPT that had a negative result. She was enrolled into subset 2, and underwent the RIPT procedures. She received 9 applications of study treatment (ACZONE Gel, 7.5%, vehicle, and saline [negative control]) over a 21-day induction period. On June 23, 2014 (day 34) she had a negative UPT and underwent the study challenge procedure, which included application of ACZONE Gel, 7.5% and its corresponding vehicle. On June 28, 2014 (day 28), 5 days after the challenge procedure, the subject had a positive UPT. Subsequently, she informed the site that she had undergone an abortion to terminate the pregnancy on July 2, 2014 (day 43). Study treatment had been completed prior to this event, so no action was taken regarding the study drug. The adverse event did not result in discontinuation from the trial. The investigator assessed the treatment emergent adverse event (TEAE) of abortion to be moderate in severity and not related to the study treatment.

●Trial 225678-010 dermal safety (Phase 1, phototoxicity): All pregnancy testing (UPT) was negative.

●Trial 225678-011 dermal safety (Phase 1, photoallergy): All pregnancy testing (UPT) was negative.

Phase 3:

●Trial 225678-006 pivotal (Phase 3, 2-arm vehicle controlled): There were 12 (later determined to be 10) subjects with positive urine pregnancy tests, all occurring at the week 12 or early exit visit: 5 (later determined to be 4) subjects in the ACZONE Gel, 7.5% group and 7 (later determined to be 6) subjects in the vehicle group. The study blind was broken, and subjects were discontinued from study treatment when the pregnancies were determined.

In the ACZONE Gel, 7.5 % group, 3 subjects discontinued the trial early due to pregnancy:

- Subject 16022-1385 was randomized to ACZONE Gel, 7.5% on February 12, 2014. She was found to have a positive pregnancy test 66 days later on April 18, 2014 and was discontinued from the trial on that date. Follow-up information received from the site indicated that the patient delivered a healthy baby on an unknown date).
- Subject 16035-2067 was randomized to ACZONE Gel, 7.5% on April 9, 2014. She was found to have a positive pregnancy test 34 days later on May 12, 2014 and was discontinued from the trial on that date. Follow-up information received from the site indicated that the patient had an elective abortion on May 13, 2014.
- Subject 16086-2638 was randomized to ACZONE Gel, 7.5% on 04 June 4, 2014. She was found to have a positive pregnancy test 59 days later on 01 August 1, 2014 and was discontinued from the trial on that date.

Subject 16019-1653 was found to have positive pregnancy results at the study exit visit. For the 4 subjects in the ACZONE Gel, 7.5% group having positive urine pregnancy test results, only 1 TEAE was reported during the trial which was skin irritation on the left shoulder for one subject (16019-1653: not in treatment area).

In the vehicle group, 2 subjects discontinued the trial early due to pregnancy and 1 subject was reported to have a serious TEAE of induced abortion at their trail exit visit.

- Subject 16039-2724 was randomized to vehicle treatment on June 10, 2014. She was found to have a positive pregnancy test 30 days later on July 9, 2014 and was discontinued from the study on that date.
- Subject 16039-3531 was randomized to vehicle treatment on 06 August 6, 2014. She was found to have a positive pregnancy test 63 days later on October 7, 2014 and was discontinued from the study on that date.
- Subject 16022-1741, a 27-year-old black female, was randomized to vehicle treatment on March 12, 2014 and had a negative pregnancy test on that date. The patient found out she was pregnant after taking a home pregnancy test. She had been voluntarily sexually active with a male partner and was not using any form of contraception. The estimated date of conception was April 2, 2014 and the estimated due date was December 24, 2014. An ultrasound on 03 June 3, 2014 showed a fetus of 10 weeks. The patient had elected not to continue the pregnancy as she “had too many kids” already. On day 85 of study treatment (04 June 4, 2014), the patient had gone to a Women’s Center and had the pregnancy terminated by elective abortion (reported as the serious TEAE of induced abortion). Treatment included oral misoprostol following the procedure. The event resolved without sequelae on the same day and she completed the study on June 17, 2014. No change was made to study medication. The induced abortion was considered to be serious as it was medically significant. The investigator considered the induced abortion not to be related to study treatment.

Subjects 16021-1273, 16030-2935, and 16047-1763 were found to have positive pregnancy test results at their trial exit visit. For the 6 subjects in the vehicle group having positive urine pregnancy tests, 3 TEAEs were reported; upper respiratory tract infection in 2 subjects (16030-2935 and 16039-5313) and induced abortion in 1 subject (16022-1741).

●Trial 225678-007 pivotal (Phase 3, 2-arm vehicle controlled): There were 9 subjects with positive urine pregnancy tests, all occurring at the week 12 or early exit visit: 6 subjects in the ACZONE Gel, 7.5% group and 3 subjects in the vehicle group. The study blind was broken, and subjects were discontinued from study treatment when the pregnancies were determined.

Of the 6 subjects in the ACZONE Gel, 7.5% group with positive pregnancy test results 2 subjects discontinued the trial early due to pregnancy:

- Subject 27038-5454 was randomized to ACZONE Gel, 7.5% on 10 March 10, 2014. She did an at-home pregnancy test which showed positive results and discontinued the study product 17 days later on March 27, 2014. She returned for the study exit visit on April 7, 2014.
- Subject 27507-6987 was randomized to ACZONE Gel, 7.5% on June 30, 2014. She was found to have a positive pregnancy test 50 days later on August 18, 2014 and was discontinued from the study on that date.

A total of 4 subjects (27016-5796, 27034-5416, 27043-6985, and 27050-5312) were found to have positive pregnancy test results at their final trial visit. For the 6 subjects in the ACZONE Gel, 7.5 % group with positive urine pregnancy tests, the only TEAE reported during the trial was nasopharyngitis in one subject (27038-5454).

Of the 3 subjects in the vehicle group with positive pregnancy test results, 1 subject (27035-5713) discontinued the study early due to pregnancy. This subject was randomized to vehicle on March 20, 2014. She was found to have a positive pregnancy test 47 days later on May 5, 2014 and was discontinued from the study on that date. The other 2 subjects (27016-6366 and 27099-6395) were found to have positive pregnancy test results at their study exit visit. For the 3 subjects in the vehicle group having positive urine pregnancy tests there were no TEAEs reported during the trial.

One subject (27069-5896) in the vehicle group had negative pregnancy results at the screening visit on 08 April 8, 2014; however, she later had a positive result on a home urine pregnancy test.

- This subject was randomized on April 8, 2014 to receive vehicle treatment. The subject's last menstrual period was March 16, 2014, and the type of contraception used was condom with spermicide. On April 20, 2014 and April 21, 2014, the subject completed two urine pregnancy tests at home. In response to the first positive pregnancy test, the subject stopped treatment with study medication on her own (last used on April 19, 2014). The subject came to the site

for the week 2 visit on April 22, 2014 and reported the positive pregnancy tests, but declined to receive a pregnancy test on site. On day 16 of the study (April 23, 2014), she was reported to have had a spontaneous abortion (reported as a serious TEAE) that resolved without sequelae within 8 days on April 30, 2014. Subsequent to the spontaneous abortion, upon agreement by Allergan and the investigator, the study medication was dispensed to the patient again at the week 4 visit on May 6, 2014; follow-up visits with an obstetrics-gynecology specialist were scheduled. She continued in the study and had negative pregnancy results at the study exit visit on day 81 (June 27, 2014) with no other adverse events reported.

7.6.3 Pediatrics and Assessment of Effects on Growth

The applicant submitted to IND 054440 an initial Pediatric Study Plan (iPSP) on October 17, 2013 and requested a partial waiver of the requirement to perform pediatric studies in patients from birth to 11 years of age for the indication of acne vulgaris.

The applicant stated that the reason for waiving pediatric studies is that necessary studies are impossible or highly impractical (because, for example, the number of patients in that age group is so small or patients in that age group are geographically dispersed). In addition the applicant stated that the drug or biological product (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group and (2) is not likely to be used by a substantial number of pediatric patients in that age group.

In a letter dated January 1, 2014, the Division concurred that dapsone 7.5% gel is unlikely to represent a meaningful therapeutic benefit over existing therapies for pediatric patients under the age of 12 and is not likely to be used by a substantial number of pediatric patients less than 12 years of age. The Division concurred with the sponsor request for a partial pediatric waiver with respect to the pediatric population from birth to (b) (4) years and 11 months of age.

The iPSP for dapsone 7.5% was presented a second time to the Pediatric Review Committee (PeRC) on March 5, 2014 who agreed with the iPSP. Agreement to the revised iPSP was communicated with the applicant in a letter dated March 24, 2014.

However, it is noted that epidemiology of acne is changing. Because of the existence of a sizeable population of children having acne in the age group 9 to 12 years of age, by law a pediatric assessment should be performed in that age group.

Acne vulgaris is increasing in prevalence in younger children. Its development is strongly linked to the onset of puberty.[1] A total of 10% of US girls are menstruating by

[1] Davis S A, et al. 2013. Treatment of Preadolescent Acne in the United States: An Analysis of Nationally

age 11.[1] The age of pubertal onset has been falling for boys and girls over the past several decades.[2] According to the National Ambulatory Medical Care Survey, between 1993 and 2009 there were a total of 55 million estimated visits for patients age 18 years and younger with a diagnosis of acne, of these, 4.8% or 2.6 million were for preadolescent acne, ages 7 to 11 years (Davis SA et al.). The above information suggests that there are sufficient numbers of patients with acne in the age group less than 12 years and therefore subjects younger than 12 years of age (e.g. 9 years old) should be assessed (unless there is a safety issue).

The applicant now requests a waiver from age 0 to < 9 years of age because studies are impossible or highly impractical (e.g. the number of pediatric subjects is so small or is geographically dispersed). The applicant requests a deferral for ages 9 years to 11 years 11 months because trials have been conducted in pediatric subjects aged 12 years to 16 years 11 months and the data from these trials are included in an NDA that is ready for approval.

There will therefore be a PREA PMR. A proposal for the PMR is as follows:

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

The request for a deferral and consequent PMR was communicated to the applicant in a teleconference November 23, 2015. The sponsor may contemplate submission of a PPSR.

This application was presented to the Pediatric Review Committee (PeRC) on December 2, 2015. The PeRC agreed with the Division to grant a partial waiver in patients ages birth to less than 9 years of age and to the deferral in patients 9 years to 11 years 11 months.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose:
Overdose was not reported as an adverse event in the clinical development program.

Representative Data. *Pediatric Dermatology*. 30 (6): 680-694.

[1] Chumlea W C, et al. 2003. Age at Menarche and Racial Comparisons in US Girls. *Pediatrics*. 111(1):110-113.

[2] Goldberg J L, et al. 2011. Changing Age of Acne Vulgaris Visits: Another Sign of Earlier Puberty? *Pediatric Dermatology*. 28 (6):645-648.

Drug Abuse:
No instances of drug abuse were reported in the clinical development program.

Withdrawal and Rebound:
The occurrence of rebound and relapse of disease after discontinuation of treatment with ACZONE Gel, 7.5% was not examined in the trials submitted for this application.

7.7 Additional Submissions / Safety Issues

- 120 Day Safety Update:

120 Day Safety Update: At the time of the NDA submission, the phase 3 clinical trials had been completed. No trials had been on-going and no additional trials had been initiated since the NDA submission, therefore, no new data was available. In addition, no new data relating to safety for dapsone was retrieved by the applicant from the literature.

- Long Term Safety:

In the End of Phase 2 Meeting Briefing Package submitted to Investigational New Drug application (IND) 054440, 26 July 2013, the applicant stated that they did not plan to conduct a long-term safety study because the safety data for ACZONE Gel, 5% that had been submitted under NDA 21794 would be referenced in the current submission.

The Division stated that they anticipated that the development program outlined by the applicant would be sufficient for filing if the applicant adequately addressed the Agency comments provided.

From currently approved labeling for ACZONE® (dapsone) Gel, 5%, section 6.1 Clinical Studies Experience: "…486 patients were evaluated in a 12 month safety study. The adverse event profile in this study was consistent with that observed in the vehicle-controlled studies."

It is noted that, trial 225678-004 (PK, 4-arm, active controlled) demonstrated that mean plasma concentrations of dapsone (including mean peak and trough concentrations) following application of ACZONE Gel, 7.5% once-daily were consistently lower than those following application of ACZONE Gel, 5% twice-daily.

8 Postmarket Experience

There are no postmarketing data for Aczone 7.5% gel.

9 Appendices

9.1 Literature Review/References

Literature references are cited in the body of the review.

9.2 Labeling Recommendations

The applicant submitted labeling that was reviewed and modified. The following sections of the revised draft labeling include important changes from labeling proposed by the applicant:

- **Section 5: Warnings and Precautions**
- **Section 6: Adverse Reactions**
- **Section 7: Drug Interactions**
- **Section 8: Use in Specific Populations**
- **Section 12: Clinical Pharmacology**
- **Section 13: Nonclinical Toxicology**
- **Section 14: Clinical Studies**

9.3 Advisory Committee Meeting

No advisory committee meeting was convened in response to this application.

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/s/

PATRICIA C BROWN
01/21/2016

GORDANA DIGLISIC
01/21/2016