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STUDY TITLE

An Open-Label Phase 4 Safety and Efficacy Trial of ACZONE (Dapsone) Gel, 7.5% in 9 to 11 Year-Old Patients With Acne Vulgaris

Protocol Number:	1679-401-006
Phase:	4
Name of Investigational Product:	ACZONE (Dapsone, AGN-225678) Gel, 7.5%
Sponsor:	Allergan (North America) 2525 Dupont Drive Irvine, California 92612 +1-714-246-4500 +1-800-347-4500
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Allergan Medical Safety Physician Contact Information:	PPD Tel (office): PPD Tel (mobile): PPD Fax: PPD Email: PPD
Allergan Signatory:	PPD PPD Refer to the final page of this protocol for electronic signature and date of approval.

The following information can be found on FDA Form 1572 and/or study contacts page: Name and contact information of Allergan study personnel and Emergency Telephone Numbers; name, address, and statement of qualifications of each investigator; name of each subinvestigator working under the supervision of the investigator; name and address of the research facilities to be used; name and address of each reviewing IRB; US 21 CFR 312.23 section 6(iii)b.

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INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR:

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.
- Maintain all information supplied by Allergan in confidence and, when this information is submitted to an Institutional Review Board (IRB), Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.
- Ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

I have read this protocol in its entirety and I agree to all aspects.

Investigator Printed Name	Signature	Date

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Protocol Summary

Study Compound: ACZONE (Dapsone, AGN-225678) Gel, 7.5%

Phase: 4

Study Objectives:

To evaluate the safety and tolerability of ACZONE Gel, 7.5% (hereafter referred to as ACZONE 7.5%) administered topically once-daily for 12 weeks in 9 to 11 year-olds with acne vulgaris

To evaluate the peak and trough plasma drug concentrations in 9 to 11 year-olds with acne vulgaris following once-daily dosing of ACZONE 7.5% under maximal use conditions for the first 8 days (+ 2 days)

To explore the efficacy of ACZONE 7.5% administered topically once-daily in 9 to 11 year-olds with acne vulgaris

Study Design

Structure: Multicenter, open-label, non-comparative trial

Duration: Patient participation is up to approximately 16 weeks from screening to trial exit; treatment duration is up to 12 weeks

Study Treatment Groups: ACZONE 7.5%

Controls: No control group

Dosage/Dose Regimen: All patients will receive treatment with ACZONE 7.5% once-daily

Pharmacokinetic (PK) Cohort (at least 16 evaluable PK patients): For the first 8 days (+ 2 days), study drug will be administered once-daily under maximal use condition (~2 grams/day) to the entire face, neck, upper chest, upper back and shoulders as instructed by the study site. The study drug should be rubbed in gently and completely. On Day 1, the study drug will be administered on site. From Day 2 through Day 7, the study drug will be administered in the morning at home by the patient's legally authorized representative. At the Week 1/Visit 3 [Day 8 (+2 days)], the study drug will be administered on site in the morning. After the Week 1/Visit 3, patients or the patient's legally authorized representative will apply a pea-sized amount of study drug in a thin layer to the patient's face, once-daily, at home for the remaining 11 weeks, the same as the dose regimen for the Non-PK Cohort. Acne-affected areas on the upper chest, upper back, and shoulders should also be treated with a thin layer during the final 11 weeks. Evaluable PK patients are defined as those that are administered at least 8 days of study drug under maximal use conditions, and provided PK samples for analysis without any major protocol deviations.

Non-PK Cohort (approximately 84 patients): Patients or the patient's legally authorized representative will apply a pea-sized amount of study drug in a thin layer to the patient's face once-daily for 12 weeks as instructed by the study site. Acne-affected areas on the upper chest, upper back, and shoulders should also be treated with a thin layer.

Randomization/Stratification: No randomization; all patients will receive ACZONE 7.5%. Assignment to PK or Non-PK Cohort will be based on patient/legally authorized representative choice and investigator's judgment.

Visit Schedule includes up to 7 scheduled study visits (see Table 1 for further details):

- Visit 1: Screening (-30 to day -1)
- Visit 2: Day 1 (Baseline)[a]
- Visit 3: Week 1 (Day 8 + 2 days)
- Visit 4: Week 2 (±3 days)
- Visits 5 and 6: Weeks 4 and 8 (±7 days)
- Visit 7: Week 12 / Early Exit (±7 days)

[a] Can be combined with the screening visit if no washout period is required.

Study Population Characteristics

Number of Patients:

For the PK Cohort, at least 16 subjects will be enrolled to ensure 16 evaluable PK subjects at the Week 1 visit.

For the Non-PK Cohort, approximately 84 patients will be enrolled.

Condition/Disease: Patients with mild, moderate, or severe facial acne vulgaris who are otherwise in good health.

Key Inclusion Criteria: Male or female, 9 to 11 years of age, with a score of 2 (mild), 3 (moderate), or 4 (severe) on the Investigator's Global Assessment (IGA) scale and 20-100 total lesions (noninflammatory and/or inflammatory) on the face, including the nose.

Key Exclusion Criteria: Patients with uncontrolled systemic disease(s); patients with severe cystic acne, acne conglobata, acne fulminans, or secondary acne (chloracne, drug-induced acne, etc); patients who have used topical dapsone within 1 month prior to the screening visit, oral dapsone within 2 months prior to the screening visit, or have any allergy or sensitivity to the study drugs or their components.

Response Measures

Safety:
Adverse events; physical examination; vital signs (heart rate, blood pressure, respiratory rate, and body temperature); urine pregnancy tests for female patients.

Tolerability:

- Investigator's or trained designee's assessment: dryness, scaling, and erythema
- Patient's assessment: stinging/burning

Pharmacokinetics:
For patients in the PK Cohort who will be dosed under maximal use conditions for the first 8 days (+ 2 days), blood samples will be collected at the Week 1/Visit 3 30 min prior to dosing at the site in the morning and at approximately 10 hours post dose (± 3 hour) to determine the peak and trough plasma concentrations of dapsone, N-acetyl dapsone (NAD), dapsone hydroxylamine (DHA), and other metabolites or analytes (if warranted).

Efficacy:
Lesion counts (face only); IGA (face only)

General Statistical Methods and Types of Analyses:

Three analysis populations will be utilized as follows:

1. The safety population includes all patients who are treated with at least 1 application of study drug.
2. The modified intent-to-treat (mITT) population includes all enrolled patients who have a baseline assessment and at least 1 postbaseline assessment.
3. The PK population will be defined as all patients who received applications of study drug for at least 8 days under maximal use conditions and have evaluable blood samples for PK analyses. This population will be used for pharmacokinetic analyses.

Safety analyses will be based on the safety population. Efficacy analyses will be based on the mITT population. No imputation for missing data will be performed for safety or efficacy analyses.

Safety Analyses: Safety variables are treatment-emergent adverse events (TEAEs), including new findings from physical examinations, local (dermal) tolerability, and vital signs.

For TEAEs, the number and percentage of patients reporting each TEAE at least once will be tabulated in descending order of incidence rate by primary system organ class (SOC) and preferred term (PT), and by primary SOC, PT, and severity. Treatment-related TEAEs will be analyzed in the same manner. Local (dermal)

tolerability data will be summarized using descriptive statistics, and frequency distributions. Positive pregnancy test results will be listed.

Efficacy Analyses: The frequency distribution of patients with a Grade 0 or Grade 1 on the IGA will be summarized by visit. Descriptive statistics will be used to summarize change from baseline in each of the following by visit: inflammatory lesion counts, non-inflammatory lesion counts, and total lesion counts.

Pharmacokinetic Data Analysis: For patients in the PK Cohort who will be dosed under maximal use conditions for the first 8 days (+ 2 days), the peak and trough plasma concentrations of dapsone, NAD, DHA, and other metabolites or analytes (if warranted) at Week 1/Visit 3 will be summarized using descriptive statistics, if applicable.

Sample Size Calculation: The sample size for this trial was determined empirically, and is consistent with that requested by the FDA in the postmarketing requirement for ACZONE 7.5%.

Table 1 Schedule of Visits and Procedures

Study Period	**Screening[a]**	**Baseline/Day 1[a]**	**Week 1**	**Week 2**	**Weeks 4 and 8**	**Week 12/ Early Exit**
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5 and Visit 6**	**Visit 7**
Visit Windows	**Day -30 to Day -1**	**N/A**	**Day 8 (+ 2 days)**	**Day 15 (± 3 days)**	**Day 29 (± 7 days) and Day 57 (± 7 days)**	**Day 85 (± 7 days)**
Informed consent/authorization and minor assent[b]	X					
Inclusion/exclusion criteria	X	X				
Medical/surgical history	X					
Demographics	X					
Skin phototype assessment	X					
Physical examination includes vital signs, height and weight[c]	X					X
Pregnancy test (urine)[d]	X	X			X	X
IGA	X	X	X	X	X	X
Lesion count	X	X	X	X	X	X
Enrollment		X				
PK Cohort: Dispense study drug, training on application/return[e]		D	R/D		R/D	R
Non-PK Cohort: Dispense study drug, training on application/return[f]		D			R/D	R
Standardized photographs[g]		X				X
Local tolerability[h]		X	X	X	X	X
Concomitant medications	X	X	X	X	X	X

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Study Period	**Screening[a]**	**Baseline/Day 1[a]**	**Week 1**	**Week 2**	**Weeks 4 and 8**	**Week 12/ Early Exit**
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5 and Visit 6**	**Visit 7**
Visit Windows	**Day -30 to Day -1**	**N/A**	**Day 8 (+ 2 days)**	**Day 15 (± 3 days)**	**Day 29 (± 7 days) and Day 57 (± 7 days)**	**Day 85 (± 7 days)**
Concomitant procedures	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X
PK sampling[i]			X			

D = dispense; IGA = Investigator's Global Assessment; N/A = not applicable; R = return; PK= pharmacokinetic

[a] If a washout period is not required, then screening and baseline visits can occur on the same day, and the procedures required to be repeated at both visits should be performed once.

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

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

[d] Female patients only. The urine pregnancy test can also be performed at any timepoint during the course of the trial at the investigator's discretion. If a patient misses a menstrual cycle, a urine pregnancy test must be performed.

[e] Patients in the PK cohort will be dispensed 1 kit with 14 tubes on Baseline/Day 1 (Visit 2). All patients in the PK cohort will start dosing on Day 1 using the 2.0 gram tubes dispensed for individual application.PK Cohort patients will return used study drug at Week 1/Visit 3. At Week 1/Visit 3, Week 4 (Visit 5) and Week 8 (Visit 6) the patients in the PK Cohort are dispensed 60-gram pumps. Dispensed and returned study drug will be weighed at the study center.

[f] All patients will start dosing on day 1. The patients in the Non-PK Cohort are dispensed 60-gram pumps on Baseline/Day 1 (Visit 2), Week 4 (Visit 5) and Week 8 (Visit 6). Dispensed and returned study drug will be weighed at the study center.

[g] At select centers, patients may have photographs taken of their face for illustration or presentation purposes. Patients who consent to being photographed will be required to remove any make-up at least 20 minutes prior to having photographs taken.

[h] Local tolerability will be assessed prior to drug administration on day 1, as well as postdose on the face only.

[i] Only applies to patients in the PK Cohort at the Week 1/Visit 3. Blood samples will be collected within 30 minutes prior to dosing in clinic in the morning and at approximately 10 hours post dose (± 3 hour) (patients are allowed to leave and come back if needed) under maximal use conditions to determine the peak and trough plasma drug concentrations.

Table 2 Detailed Schedule of Procedures Specific to the PK Cohort

Study Period	**Screening**	**Baseline/Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8 (+ 2 Days) Week 1**
Visit Number	**Visit 1**	**Visit 2**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**Visit 3**
PK Sampling									X[a]
On-Site dose administration		X							X[b]
At home dose administration[b]			X	X	X	X	X	X	

NA= not applicable; PK= pharmacokinetic.

[a] Two PK samples will be collected. Samples will be collected within 30 minutes prior to dosing in clinic in the morning and at approximately 10 hours post dose (± 3 hour).

[b] Dosing for the PK cohort should always occur at approximately the same time in the morning.

1. Background and Clinical Rationale

1.1 Introduction

Acne vulgaris is a complex skin disorder involving multiple abnormalities of the pilosebaceous unit, including hyperkeratinization (leading to obstruction of the follicle), increased sebum production (stimulated by androgens), bacterial proliferation (*Propionibacterium acnes,* an anaerobic diphtheroid bacterium), and inflammation (Fleischer et al, 2010, Longshore and Hollandsworth, 2003). The disease is characterized by papules, pustules, comedones, nodules, and cysts. The face, upper chest, and upper back are most commonly affected related to a greater concentration of sebaceous glands in these areas.

Acne vulgaris is estimated to affect approximately 40 to 50 million people in the United States alone (Bhate and Williams, 2013). It affects 80% of adolescents, but may also be observed in 54% of adult women and 40% of adult men (Ramos-e-Silva and Carneiro, 2009). For many patients, acne poses a significant psychosocial burden, negatively affecting mood, self-esteem, body image, and perceived levels of social isolation (Bhate and Williams, 2013). Successful treatment of acne significantly reduces symptoms of anxiety and depression and improves acne patients' quality of life (Klassen et al, 2000, Rubinow et al, 1987).

Pharmacological treatment options for acne vulgaris may be directed at reducing comedone formation, inflammation, *P. acnes* levels, or sebum production. Dapsone is a sulfone that has anti-inflammatory properties including inhibition of neutrophil myeloperoxidase and eosinophil peroxidase and suppression of hypochlorous acid production (Bozeman et al, 1990). Dapsone scavenges reactive oxygen species and minimizes associated inflammation, suppresses neutrophil recruitment and local production of toxic respiratory and secretory products, and inhibits chemoattractant-induced signal transduction (Debol et al, 1997).

Oral dapsone has been available for over 60 years and used for the treatment of leprosy and skin disorders such as dermatitis herpetiformis and nodulocystic acne. However, its clinical use is limited by hematologic reactions, including hemolysis, methemoglobinemia, and agranulocytosis. In patients treated with oral dapsone, hemolysis and Heinz body formation may be exaggerated in individuals with glucose-6-phosphate dehydrogenase (G6PD) (Dapsone Tablets Package Insert, 2011). The hemolytic process is most likely related to metabolites of dapsone (particularly the N-hydroxylamine product) rather than the parent compound. These hematologic reactions are much less likely with topical treatment due to considerably lower systemic exposure.

ACZONE® (dapsone) Gel, 5% (hereafter referred to as ACZONE 5%), administered twice-daily, and ACZONE® (dapsone) Gel, 7.5% (hereafter referred to as ACZONE 7.5%), administered once-daily, are both approved by the FDA for topical treatment of acne vulgaris in patients 12 years of age and older (ACZONE [dapsone] Gel, 5% package insert, 2015, ACZONE [dapsone] Gel, 7.5% package insert, 2016). ACZONE 7.5% simplifies the dosage regimen from the twice-daily dosing of ACZONE 5% to once-daily and thereby potentially enhances patient adherence to therapy. In vehicle-controlled, phase 3, pivotal trials, ACZONE 7.5% was safe and well tolerated, and was statistically superior to its vehicle for the percent of Global Acne Assessment Score (GAAS) successes and the reduction in all lesion counts for the protocol-defined primary analysis as well as all supportive and sensitivity analyses at the end of the treatment period. In clinical trials with either ACZONE 5% and ACZONE 7.5%, there was no evidence of clinically relevant hemolysis or anemia in patients treated with dapsone gel including patients who were G6PD-deficient.

1.2 Clinical Pharmacokinetics of Dapsone

Dapsone absorption after once-daily ACZONE 7.5% administration in patients with acne vulgaris results in low systemic exposure to dapsone and its metabolites. Systemic exposure to dapsone from ACZONE 7.5% is expected to be about 1% of that from a typical oral dose of dapsone 100 mg. Mean maximum plasma concentration (C_{max}) and area under the plasma-concentration time curve from time 0 to 24 hours postdose of dapsone at steady-state after once-daily dosing of dapsone 7.5% were approximately 28.6% and 28.7% lower than those following twice-daily dosing of ACZONE 5%, respectively (NDA 21-794). The volume of distribution of dapsone is about 1.5 to 2.5 L/kg. It is distributed throughout total body water and present in all tissues, especially liver, muscle, kidney, and skin. Its protein binding is 70% to 90%, and the acetylated dapsone metabolite has a protein binding of ~99%. Dapsone is acetylated by N-acetyl transferase in the liver to its major metabolite, N-acetyl dapsone (NAD). The acetylation of dapsone is reversible, resulting in a relatively constant ratio of NAD to dapsone in plasma during the elimination phase. Dapsone is also N-hydroxylated via cytochrome (CYP) P4502E1 and CYP3A4 to dapsone hydroxylamine (DHA) in the liver, which appears to be responsible for the drug's hematologic toxicity. The C_{max} and area under the concentration-time curve for DHA are approximately 5% of those of the parent compound. The relationship between oral and topical exposure for DHA is expected to be similar to the relationship observed for the dapsone parent compound. The apparent terminal half-life ($T_{1/2}$) values of dapsone and NAD are estimated to be similar and the mean/median values are in the range of 30 to 44 hours after multiple doses of dapsone. The DHA is primarily excreted in urine (~85%), with a small percentage excreted in feces. Consistent

with lower systemic exposures, urinary excretion of DHA after topical dapsone is about 1% of that obtained with the oral formulation.

1.3 Rationale for the Study

The FDA approval of ACZONE 7.5% included a post-marketing requirement (PMR 3017-1) to assess the product in patients 9 to 11 years of age, including pharmacokinetic (PK) evaluation in a subset of patients (FDA Letter, 2016).

Preadolesecent acne tends to be uncommon, mild, and predominantly noninflammatory (Lucky et al, 1991, Lucky et al, 1994, Friedlander et al, 2011). Compared to the more substantial acne typical of older patients, preadolescent acne tends to be less likely to precipitate patients to seek medical care and is more frequently be left untreated (Eichenfield et al, 2012). Nevertheless, there have been recent suggestions that preadolescent acne may become more common and/or recognized (Eichenfield et al, 2013-Pediatrics, Eichenfield et al, 2013-J Drugs of Dermatol, Eichenfield et al, 2012, Goldberg et al, 2011, Friedlander et al, 2010).

1.4 Rationale for the Study Design

This 12-week phase 4 trial will enroll a total of approximately 100 patients aged 9 to 11 years with mild, moderate, or severe acne, including a subset of at least 16 evaluable PK patients who are to be treated once-daily with 2 grams of the ACZONE 7.5% under maximal use conditions during the first 8 days in order to obtain blood samples for PK assessment. Evaluable PK patients are defined as those who are administered at least 8 days of study drug under maximal use conditions, and provided PK samples for analysis without any major protocol deviations.

Several elements of the trial design were included because of the predominantly noninflammatory nature of the preadolescent acne and the challenging nature of recruiting this population into a clinical trial, particularly the subset receiving PK assessment:

- Given that preadolescence acne tends to be predominately noninflammatory, the trial will (1) enroll patients with 20 to 100 total lesions on the face, and (2) use a modified global assessment corresponding to the more noninflammatory nature of preadolescence acne, consistent with a recent trial in this population (Eichenfield et al, 2012).

- For the subset of patients with PK assessments (PK Cohort; at least 16 evaluable PK patients), study drug will be administered once-daily for the first 8 days under maximal use condition (~2 grams/day) to the entire face, neck, upper chest, upper back and shoulders. On Day 1, the study drug will be administered on site. From Day 2 through Day 7, the study drug will be administered in the morning at home by the patient's legally authorized representative. At the Week 1/Visit 3 [Day 8 (+2 days)], the study drug will be administered on site in the morning. After the Week 1/Visit 3, patients or the patient's legally authorized representative will apply a pea-sized amount of study drug in a thin layer to the patient's face, once-daily, at home for the remaining 11 weeks, the same as the dose regimen for the Non-PK Cohort. In order to minimize the number of blood draws, blood samples will be collected at 2 timepoints corresponding to the peak and trough steady-state concentrations at Week 1/Visit 3 for steady-state pharmacokinetic assessment.

2. Study Objectives and Clinical Hypotheses

2.1 Study Objectives

To evaluate the safety and tolerability of ACZONE 7.5% administered topically once-daily for 12 weeks in 9 to 11 year-olds with acne vulgaris.

To evaluate the peak and trough plasma drug concentrations in 9 to 11 year-olds with acne vulgaris following once-daily dosing of ACZONE 7.5% under maximal use conditions for the first 8 days (+ 2 days).

To explore the efficacy of ACZONE 7.5% administered topically once-daily in 9 to 11 year-olds with acne vulgaris.

2.2 Clinical Hypotheses

ACZONE 7.5% is safe and well tolerated when administered topically once-daily for 12 weeks to 9 to 11 year-old patients with acne vulgaris.

3. Study Design

This study is a multicenter, open label, non-comparative, 12-week trial to evaluate the safety, tolerability, pharmacokinetics, and efficacy of ACZONE 7.5% in 9 to 11 year-old patients with mild, moderate, or severe acne vulgaris.

Patient participation is up to approximately 16 weeks. Patients will attend up to the following 7 visits: Screening, Baseline/Day 1 (Screening and Baseline/Day 1 may be combined if no washout is needed), and Weeks 1, 2, 4, 8, and 12/early exit. The total treatment duration of trial participation for each patient is up to 12 weeks. Safety measures include adverse events, physical examination, and vital signs. Efficacy measures include the Investigator's Global Assessment (IGA) and lesion counts in the face.

The 2 cohorts will enroll concurrently; the PK cohort and the non-PK Cohort.

The PK Cohort will include at least 16 evaluable PK patients. Evaluable PK patients are defined as those that are administered at least 8 applications of study drug under maximal use conditions, and provided PK samples for analysis without any major protocol deviations. For the first 8 days, study drug will be administered once-daily under maximal use condition (~2 grams/day) to the entire face, neck, upper chest, upper back and shoulders as instructed by the study site. The study drug should be rubbed in gently and completely. On Day 1, the study drug will be administered on site. From Day 2 through Day 7, the study drug will be administered in the morning at home by the patient's legally authorized representative. At the Week 1/Visit 3 [Day 8 (+2 days)], the study drug will be administered on site in the morning. After the Week 1/Visit 3, patients or the patient's legally authorized representative will apply a pea-sized amount of study drug in a thin layer to the patient's face, once-daily, at home for the remaining 11 weeks, the same as the dose regimen for the Non-PK Cohort. Acne-affected areas on the upper chest, upper back, and shoulders should also be treated with a thin layer during the final 11 weeks.

For the Non-PK Cohort (approximately 84 patients), patients or the patient's legally authorized representative will apply a pea-sized amount of study drug in a thin layer to the patient's face once-daily at home for 12 weeks as instructed by the study site. Acne-affected areas on the upper chest, upper back, and shoulders should also be treated with a thin layer.

4. Study Population and Entry Criteria

4.1 Number of Patients

For the PK Cohort, at least 16 subjects will be enrolled to ensure 16 evaluable PK subjects at the Week 1 visit. For the Non-PK Cohort, approximately 84 additional patients will be enrolled in the study for a total of approximately 100 patients. PK Cohort patients who discontinue from the trial prior to either of the PK blood draws scheduled at Week 1/Visit 3

(or who otherwise do not have evaluable PK samples) will be replaced. Assuming an attrition rate of 15%, approximately 85 patients are expected to complete the 12-week trial.

4.2 Study Population Characteristics

Study participants will be 9 to 11 year-old male and female patients with mild, moderate, or severe acne vulgaris who are otherwise in good health. **For the PK Cohort**, mild, moderate, or severe acne vulgaris patients will be enrolled for PK characterization until at least 16 evaluable PK patients are enrolled. After 16 evaluable PK patients are enrolled, additional patients with moderate or severe acne vulgaris may continue to be enrolled in the PK Cohort.

4.3 Inclusion Criteria

The following are requirements for entry into the trial:

1. Written informed consent has been obtained from the patient's legally authorized representative prior to any trial related procedure
2. Written assent has been obtained from the patient (a minor) in accordance with local laws and IRB/IEC requirements
3. Written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable (eg, Written Authorization for Use and Release of Health and Research Study Information for US centers)
4. Male or female patients, 9 to 11 years of age
5. Patients with acne vulgaris who have minimum of 20 but not more than 100 total inflammatory (papules, pustules, cysts, nodules) or noninflammatory (open or closed comedones) lesions on the face (including the nose) at screening and baseline
6. Patients with an acne grade of 2 (mild), 3 (moderate), or 4 (severe) using the IGA as assessed by the investigator at screening and baseline. **For the PK Cohort only:** after at least 16 PK patients are enrolled, additional patients with acne grades of 3 (moderate) or 4 (severe) using the IGA as assessed by the investigator at screening and baseline may continue to be enrolled in the PK Cohort unless specified by the Sponsor to refrain
7. Negative urine pregnancy test result for females at the Screening and Day 1 visits

8. Patient is in good health as determined by medical history, physical examination, and vital signs

9. Patient is willing to follow study instructions, complete study assessments without any assistance, and likely to complete all required visits

4.4 Exclusion Criteria

The following are criteria for exclusion from participating in the trial:

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 using systemic immunosuppressive drugs within 4 weeks prior to screening or anticipated use of any systemic therapy with the potential to affect acne during the trial

4. Any of the following topical procedures or treatments on the face occurring in the specified period prior to baseline (day 1):

   - 1 week: antibacterials (eg, clindamycin), salicylic acid, sulfur, sodium sulfacetamide, phototherapy devices (eg, ClearLight™), energy-based devices, adhesive cleansing strips (eg, Pond's®, Biore®), or cosmetic procedures (eg, facials, peeling, comedo extraction)

   - 2 weeks: anti-inflammatory drugs, corticosteroids, benzoyl peroxide-containing products (eg, benzamycin), retinoids, other topical acne treatments (eg, photodynamic therapy)

     note: No washout is required for alpha hydroxy acid products, astringents, antiseptics, devices used for cleansing and/or exfoliating the skin (eg, scrubs, pads, brushes), or preparations with alcohol for astringent effects, but they are not permitted at any time during the trial.

5. Any of the following systemic medications in the specified period prior to baseline (day 1):

   - 4 weeks: antibacterials (except penicillins used for 2 weeks or less)

- 6 months: other acne treatments (eg, isotretinoin, anti-androgens such as spironolactone)

6. Patients who are using or have used hormonal contraceptives and therapies
7. Patients who have used topical dapsone within 1 month prior to the screening visit or oral dapsone within 2 months prior to the screening visit
8. Patients who have any allergy or sensitivity to the study drug or its components
9. Patients with underlying diseases or other dermatologic conditions such as, but not limited to, atopic dermatitis, perioral dermatitis or rosacea, which require the use of topical or systemic therapy that may interfere with the study assessments in the opinion of the investigator
10. Skin abnormalities (other than acne vulgaris), excessive hair, or other physical characteristics in or around the test sites that could confound the trial results based on the investigator's judgment
11. Patients who anticipate the need for surgery or hospitalization during the trial
12. Females who are pregnant, nursing, or think they may be pregnant at the start of the trial
13. Current enrollment in an investigational drug or device study, or participation in such a study within 30 days prior to screening for this trial
14. Patients who have a clinically significant finding or condition, or are in a situation which, in the investigator's opinion, may put the patients at significant risk, may confound the trial results, or may interfere significantly with patient's participation in the trial
15. Patients who have a medical history of hepatitis B, hepatitis C or human immune deficiency virus (HIV) infection
16. Patients with a history of liver or kidney disease
17. Patient who is an immediate family member (eg, partner, offspring, parents, siblings, or sibling's offspring) of an employee (eg, of sites, the Sponsor, or vendors) involved in the trial

4.5 Permissible and Prohibited Medications/Treatments

4.5.1 Permissible Medications/Treatments

Therapy considered necessary for the patient's welfare may be given at the discretion of the investigator. If concomitant medications may have an effect on trial outcomes, those medications should be administered in dosages that remain constant throughout the course of the trial. If the permissibility of a specific medication/treatment is in question, please contact the Sponsor.

Patients should maintain their usual skin care regimen, eg, non-medicated soaps, throughout the trial (with the exception of prohibited products).

4.5.2 Definition of Females of (Non-)Childbearing Potential and/or Acceptable Contraceptive Methods

For purposes of this study, all females will be considered of childbearing potential. If a patient misses a menstrual cycle, a urine pregnancy test must be performed.

If a female becomes pregnant during the study, the investigator will notify the sponsor immediately after the pregnancy is confirmed and the study treatment should be discontinued. The patient will be exited from the study after appropriate safety follow-up. The investigator will (1) notify the patient's physician that the patient was being treated with ACZONE 7.5%, and (2) follow the progress of the pregnancy. The investigator must document the outcome of the pregnancy and provide a copy of the documentation to the Sponsor.

4.5.3 Prohibited Medications/Treatments

The decision to administer a prohibited medication/treatment is done with the safety of the patient as the primary consideration. When possible, the Sponsor should be notified before the prohibited medication/treatment is administered.

Medications requiring washout (Section 4.4) must not be used during the study. Patients must not use topical drugs or treatments on acne affected areas. Patients must not use hormonal therapies or contraceptives.

For patients in the PK Cohort, use of any concomitant systemic medications that could affect PK outcomes is not permitted from 2 weeks prior to Day 1 through the Week 1/Visit 3 [Day 8 (+ 2 days)].

All patients are not permitted to use phototherapy devices, cosmetic procedures, or other topical acne treatments (eg, photodynamic therapy, laser therapy, or medicated soap).

Certain systemic medications (such as rifampin, anticonvulsants, St. John's Wort, and trimethoprim-sulfamethoxazole) may increase the formation of DHA, 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. Concomitant use of ACZONE 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.

4.5.4 Special Diet or Activities

All patients, and their legally authorized representative(s), will be instructed that throughout the trial they must refrain from:

- Intensively scratching their body at any areas of treatment
- Swimming or bathing up to 8 hours following drug application
- Tattooing their skin or body piercings to the areas of study drug application

Patients will be instructed to maintain their regular skin care regimen (with the exception of prohibited products) during the trial and must not use new products on treated areas while in the trial.

For patients in the PK Cohort, from Day 1 through the Week 1/Visit 3 [Day 8 (+ 2 days)], patients should not bathe, shower, swim, or wash face for at least 8 hours following administration of study drug.

5. Study Treatments

5.1 Study Treatments and Formulations

The study drug will be ACZONE 7.5% Gel (formulation number 11080X) consisting of dapsone 7.5%, diethylene glycol monoethyl ether (DGME) CCI [redacted], methylparaben, and purified water.

5.2 Methods for Masking/Blinding

This trial will be an open-label trial, and therefore blinding of the study drug is not required.

5.3 Method for Assignment to Treatment Groups/Randomization

Prior to initiation of study drug, each patient who has informed consent (provided by the legally authorized representative) will be assigned a patient number that will serve as the patient identification number on all study documents throughout the study.

All enrolled patients will receive ACZONE 7.5% treatment.

Study drug will be labeled with medication kit numbers generated by the Sponsor's Biostatistics group. An automated interactive web(-based) response system (IWRS) will provide the site with the specific medication kit number(s) for each enrolled patient at the time of study drug administration. Sites will dispense study drug according to the IWRS instructions. Sites will also log onto the IWRS at subsequent visits, as required, to obtain a study drug kit number for dispensing study drug. Sites will receive the IWRS confirmation notifications for each transaction. All notifications are to be maintained with the study source documents.

Assignment to the PK Cohort or the non-PK Cohort will be based on patient/legally authorized representative choice and the investigator's judgment.

5.4 Treatment Regimen and Dosing

5.4.1 Conduct of the Study

For all patients, the first dose of study drug will be administered at the study site on Day 1. Administration of the first dose of study drug will need to be supervised by study site personnel.

To ensure maximal use conditions for the PK Cohort for the first 8 days, study drug will be provided in individual usage tubes containing approximately 2 grams each. One individual usage tube will be used each day for the first 8 days. The patients will be dispensed 1 kit with 14 tubes on Baseline/Day 1 (Visit 2). PK Cohort patients will return used study drug on Week 1/Visit 3.

For the first 8 days, study drug will be administered once-daily under maximal use condition (~2 grams/day) to the entire face, neck, upper chest, upper back and shoulders as instructed by the study site. The study drug should be rubbed in gently and completely. On Day 1, the study drug will be administered on site. From Day 2 through Day 7, the study drug will be administered in the morning at home by the patient's legally authorized representative. At the Week 1/Visit 3 [Day 8 (+2 days)], the study drug will be administered on site in the morning. After the Week 1/Visit 3, patients or the patient's legally authorized representative will apply a pea-sized amount of study drug in a thin layer to the patient's face, once-daily, at home for the remaining 11 weeks, the same as the dose regimen for the Non-PK Cohort. Acne-affected areas on the upper chest, upper back, and shoulders should also be treated with a thin layer during the final 11 weeks. Evaluable PK patients are defined as those that are administered at least 8 days of study drug under maximal use conditions, and provided PK samples for analysis without any major protocol deviations.

For the non-PK Cohort, patients or the patient's legally authorized representativewill apply the study drug to the patient's entire face once-daily at home for the entire trial. The patients in the non-PK Cohort will be dispensed 60-gram pumps on Baseline/Day 1 (Visit 2), Week 4 (Visit 5) and Week 8 (Visit 6). Acne-affected areas on the neck, upper chest, upper back, and shoulders (where the patient can reach) should also be treated.

5.4.2 Stopping Rules

The safety and tolerability data for each patient will be monitored throughout the trial by the investigator and the Sponsor's Medical Safety Physician. In the event that a patient experiences unacceptable safety and/or dermal tolerability as designated by either the patient, the patient's legally authorized representative, or investigator, treatment should be discontinued.

5.5 Storage of Study Medications/Treatments

The study drug must be stored in a secure area and administered only to patients entered into the clinical trial, at no cost to the patient, in accordance with the conditions specified in this protocol.

The study drug must be stored at controlled room temperature, 20°to 25°C (68°to 77°F). Sites must report any temperature excursions as described in the Study Reference Manual or contact the Sponsor or its designee for further instructions.

5.6 Treatment Administration

For the PK Cohort, at the Day 1 visit, patients and their legally authorized representative(s) will be instructed how to administer the study drug, and the study drug will be administered on site. For Days 2 thorugh 7, study drug should be applied at approximately the same time in the morning (ie, before noon) at home by the patient's legally authorized representative. On Day 8 of the trial, study drug will be administered on site and in the morning.

After the skin on the face is gently washed and patted dry, legally authorized representative(s) of the patients will apply the contents of an individual usage tube containing 2 grams of study drug. The study drug will be applied to the patient's face, neck, upper chest, upper back, and shoulders. Wearing gloves, legally authorized representative(s) will spread the product on the patient's face, on the area between the mandibular line, and the hairline edge, taking care to avoid the areas around the eyes and the lips. The legally authorized representative(s) will also spread the study drug on the patient's neck, shoulders, upper chest, and upper back. New gloves will need to be used each day when applying the study drug. The product should be applied evenly to the entire face, neck, upper chest, upper back, and shoulders of the patient, and rubbed in gently and completely. All study drug should be rubbed in until no visible mass of the gel is observed on the surface of the skin. All patients and their legally authorized representatives will be provided with written instructions on the application of the study drug. Adherence to these instructions will be assessed at subsequent visits, with retraining performed as needed for noncompliant patients. Documentation of patient and legally authorized representative(s) training by site staff will be noted. See the non-PK Cohort section for information on PK Cohort patient dosing from the Week 1/Visit 3 until the end of study visit.

For the Non-PK Cohort at the Day 1 visit, patients and their legally authorized representative(s) will be instructed regarding how to administer the study drug for the

remainder of the trial. If dosing of the patient is performed by the patient's legally authorized reppersentative, they should wear gloves, and new gloves should be used each day. If dosing is performed by the patient, the patient must wash his/her hands before and after each application. After the patient's skin on the face is gently washed and patted dry, the patient or the patient's legally authorized representativewill apply an approximately pea-sized amount of study drug in a thin layer to the patient's entire face. The product should be rubbed in gently and completely. Acne-affected areas on the neck, upper chest, upper back, and shoulders (where the patient can reach) should also be treated by applying enough to cover the affected areas, then rubbing in gently and completely. All study drug should be rubbed in until no visible mass of the gel is observed on the surface of the skin. All patients and their legally authorized representatives will be provided with written instructions on the application of the study drug. Adherence to these instructions will be assessed at subsequent visits, with retraining performed as needed for noncompliant patients. Documentation of patient and legally authorized representative(s) training by site staff will be noted.

6. Response Measures and Summary of Data Collection Methods

6.1 Pharmacokinetics

6.1.1 Pharmacokinetic Sampling Timepoints

For patients in the PK Cohort who will be dosed under maximal use conditions for the first 8 days, blood samples will be collected prior to dosing and at approximately 10 hours post dose (± 3 hours) (patient can leave the site in between blood samples) at Week 1/Visit 3 [Day 8 (+ 2 days)] to determine the peak and trough plasma concentrations of dapsone, NAD, DHA, and other metabolites or analytes (if warranted).

6.1.2 Pharmacokinetic Sample Collection and Processing

Detailed instructions on sample collection, processing, and storage of plasma samples for drug assay are given in the Procedure Manual.

6.1.3 Pharmacokinetic Sample Bioanalysis

Plasma concentrations of dapsone, NAD, DHA, and other metabolites or analytes (if warranted) will be determined using a validated liquid chromatography-tandem mass spectrometry method.

6.2 Efficacy Measures

Each patient's overall severity of acne vulgaris will be evaluated by a 5-point IGA. The IGA assessment must be performed by an investigator.

The lesion counts will be conducted on the face only. Lesion counts may be performed by an investigator or trained designated study personnel.

Assessments should be performed in a well-lit room under consistent lighting at each study visit. When possible, the evaluator(s) performing the IGA and/or lesion counts at an individual study center should perform these evaluations for all patients throughout the trial. If the same evaluator performs both IGA and lesion counts, the IGA assessment should be performed prior to lesion count assessment. In the rare event there is a change in the assigned evaluator for a given patient, the reason for change must be documented. If it is not possible to use the same evaluator to follow a given patient, the Sponsor recommends that evaluations between the primary and subsequent evaluator overlap (both evaluators should examine the patient together and discuss findings) for at least one visit; this should be documented.

6.2.1 Investigator's Global Assessment

The IGA will be evaluated at screening, baseline, and on weeks 1, 2, 4, 8 and 12/early exit. Patients' acne severity will be evaluated by the investigator using a 5-point IGA scale as shown in Table 3. This assessment must be performed by an investigator, ie, the principal investigator or subinvestigator. Only the face of the patient will be evaluated using the IGA.

Table 3 Investigator's Global Assessment

Grade		Description
0	Clear	• No comedones, papules or pustules • Residual hyperpigmentation and erythema may be present
1	Almost Clear	• Rare comedones • No more than a few small papules and pustules
2	Mild	• Easily recognizable comedones in limited numbers • +/- Presence of small papules and pustules
3	Moderate	• Many comedones • +/- Easily recognizable small and medium-sized papules • No nodules or cysts.
4	Severe	• Widespread and numerous comedones • Many small, medium-sized and large papules and pustules • Nodules or cysts may or may not be present.

(Eichenfield et al, 2013, J of Dermatol)

6.2.2 Lesion Count

The lesion counts will be performed at screening, baseline, and at weeks 1, 2, 4, 8, and 12/early exit. The lesion counts will be performed by the investigator or an appropriately trained designee.

For each area, the following lesion types will be 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 – a circumscribed, elevated, solid lesion generally more than 1.0 cm in diameter with palpable depth

  Cyst – a smooth, dome-shaped, elevated, freely moveable, skin colored, round to ovoid lesion greater than 0.7 cm in diameter

- Noninflammatory Lesions

  Open Comedone – a pigmented dilated pilosebaceous orifice (blackhead)

  Closed Comedone – a tiny white papule (whitehead)

Total lesions will be the sum of inflammatory lesion counts and noninflammatory lesion counts. In addition, the presence of truncal acne will be documented.

6.2.3 Other Measures

6.2.3.1 Skin Phototype

At screening, Fitzpatrick skin phototype will be rated (FDA Federal Register, 1999):

I: Always burns easily; never tans (sensitive)
II: Always burns easily; tans minimally (sensitive)
III: Burns moderately; tans gradually (light brown) (normal)
IV: Burns minimally; always tans well (moderate brown) (normal)
V: Rarely burns; tans profusely (dark brown) (insensitive)
VI: Never burns; deeply pigmented (insensitive)

6.3 Safety Measures

The following safety measures will be collected:

- Adverse events
- Physical examination
- Height
- Weight
- Vital signs (heart rate, blood pressure, respiratory rate, and body temperature)
- Urine pregnancy tests for females
- Local dermal tolerability assessments (stinging/burning rated by the patient; dryness, scaling, and erythema rated by an investigator or appropriately trained designee)

6.3.1 Adverse Events

An adverse event is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. In addition, during the screening period, adverse events will be assessed regardless of the administration of a pharmaceutical product.

Note: Adverse events must be collected once informed consent has been obtained, regardless of whether or not the patient has been administered study drug.

The investigator will question the patient to ascertain whether any adverse events were experienced since the previous visit. All pertinent information regarding adverse events (ie, date and time of onset and stop, duration, outcome, severity, relation to study drug, action or treatment required) will be obtained and recorded in the source documents and appropriately transcribed on the electronic case report form (eCRF) page.

6.3.2 Suspected Sensitization

If the patient experiences a skin reaction of such nature or severity that a contact allergy is suspected, the patient should discontinue the study drug. The event should be documented as an adverse event. The patient should be re-challenged using the assigned study drug to confirm or rule out contact dermatitis. If the diagnosis of allergic contact dermatitis is confirmed the patient may have an additional patch test with the study drug and the individual study drug ingredients. The patch test will be performed at least 2 weeks after discontinuation of the study drug. Patches will be applied to untreated areas on the back for 48 hours. Readings will be performed approximately 15 to 30 minutes and 48 hours following the removal of the patches. At the investigator's discretion, a facultative additional reading might be performed at 96 or 120 hours after removal of the patches if an equivocal reaction is observed at the previous reading.

6.3.3 Unscheduled Visits

If a patient is seen for an unscheduled visit, an assessment and record of adverse events should be completed. Additional evaluations should be performed as necessary, and the appropriate eCRFs should be completed.

6.3.4 Local Tolerability

Local (dermal) tolerability examination will be performed at timepoints given in Table 1 and will include assessments of stinging/burning (rated by the patient), dryness, scaling, and erythema (rated by an investigator, or appropriately trained designee). Dryness, scaling, and erythema must be assessed by the same person throughout the trial whenever possible. Local tolerability will be assessed on the face and will be rated as none, mild, moderate, or severe based on the detailed descriptions that follow.

Patient-rated

Stinging/Burning: prickling pain sensation after dosing (also performed predose on Day 1).

None (0) = No stinging/burning

Mild (1) = Slight warm, tingling/stinging sensation; not really bothersome

Moderate (2) = Definite warm, tingling/stinging sensation that is somewhat bothersome

Severe (3) = Hot, tingling/stinging sensation that has caused definite discomfort

Investigator-rated

Dryness: brittle and/or tight sensation

None (0) = No dryness

Mild (1) = Slight but definite roughness

Moderate (2) = Moderate roughness

Severe (3) = Marked roughness

Scaling: abnormal shedding of the stratum corneum

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: abnormal redness of the skin

None (0) = No erythema

Mild (1) = Slight pinkness present

Moderate (2) = Definite redness, easily recognized

Severe (3) = Intense redness

If any sign or symptom is judged to be an adverse event in the opinion of the investigator, it will be captured on the patient's adverse event source document and eCRF.

6.4 Other Study Supplies

The following will be provided by the Sponsor:

- The central laboratory will provide vacutainer tubes and polypropylene tubes for plasma collection for pharmacokinetic analysis if not already present at the site
- At selected sites, standardized cameras and photographic equipment which will be supplied by a qualified third party vendor

The following will be provided by the Investigator:

- Urine pregnancy test kits with a sensitivity of at least 25 mIU/mL for human chorionic gonadotropin
- Patch test supplies
- Gloves for legally authorized representative(s) performing dosing
- Scale with a readability of 0.1 gram or lower to weigh study drug
- Equipment for collection of vital signs
- Freezer set to maintain -20ºC for storage of PK samples

6.5 Summary of Methods of Data Collection

This trial will use eCRFs using remote electronic data capture. The data will be entered on the eCRFs in a timely manner on an ongoing basis. The investigator is responsible for ensuring that data are properly recorded on each patient's eCRFs and related documents. An investigator who has signed the protocol signature page should personally electronically sign for the case report forms (CRFs; as indicated in the eCRFs) to ensure that observations and findings are recorded on the eCRFs correctly and completely. A certified electronic copy of the eCRFs including data corrections will be provided to the site for archiving at the end of the trial.

A qualified central laboratory will be used to store samples drawn for PK analysis and samples will be stored until shipment to a qualified bioanalytical laboratory.

A qualified bioanalytical laboratory will be used to determine the plasma concentrations of dapsone, DHA, NAD, and other metabolites or analytes (if warranted). Pharmacokinetic data will be transferred to the Sponsor by the end of the trial.

At selected sites, for patients who consent to photographs, facial photographs will be taken by study personnel for illustration or presentation purposes using standardized cameras and photographic equipment which will be supplied by a qualified third party vendor. Each selected site will receive documented training and instructions on taking photographs. The photographs will be uploaded to a secure server via the internet. All photographs will be transferred to the Sponsor at the end of the study. The sponsor will process the photographs and shall have full ownership rights to any photographs derived from the study.

7. Statistical Procedures

A detailed analysis plan will be approved prior to database lock. Database lock will follow completion of data entry, verification and validation, database audit, and data clarification resolution.

7.1 Analyses Populations

The following 3 analysis populations will be utilized:

1. The safety population includes all patients who are treated with at least one application of study drug.

2. The modified intent-to-treat (mITT) population includes all enrolled patients who have a baseline assessment and at least one post-baseline assessment.

3. The PK population will be defined as all patients who received applications of study drug for at least 8 days under maximal use conditions and have evaluable blood samples for PK analysis. This population will be used for PK analyses.

Safety analyses will be based on the safety population. Efficacy analyses will be based on the mITT population. No imputation for missing data will be performed for safety or efficacy analyses.

7.2 Pharmacokinetic Analysis

For patients in the PK Cohort who will be dosed under maximal use condition for the first 8 days, the peak and trough plasma concentrations of dapsone, NAD, DHA, and other metabolites or analytes (if warranted) at Week 1/Visit 3 will be summarized using descriptive statistics, if applicable.

No formal inferential statistics will be performed with the PK data. However, if warranted, graphical methods may be used to examine the relationships between systemic drug concentrations and the changes in lesion counts and safety parameters. Details of these analyses will be described in the PK data analysis plan.

7.3 Efficacy Analysis

All efficacy analyses are considered exploratory and will be performed using the mITT population. All efficacy summaries will use data from both study cohorts combined.

For lesion counts, change and percent change from baseline in inflammatory lesion counts will be summarized using descriptive statistics. Baseline is the predose measurement on Day 1. Inflammatory lesion counts include papules, pustules, nodules and cysts. The same summarizations will be done for noninflammatory lesion counts and total lesion counts. Noninflammatory lesion counts include open and closed comedones, and total lesion counts include inflammatory and noninflammatory lesion counts.

If a number of patients have fewer than 5 inflammatory or noninflammatory lesions at baseline, an additional analysis may be conducted for that lesion type including only those patients with at least 5 lesions of that type at baseline.

A frequency distribution will be used to summarize the proportion of patients with none (0) or minimal (1) score on the IGA at each visit. In addition, a frequency distribution will be used to summarize the proportion of patients with none (0) or minimal (1) score plus at least a 2-grade improvement on the IGA at each visit.

7.3.1 Safety Analyses

Safety variables are treatment-emergent adverse events (TEAEs), inlcuding new findings from physical examinations, local (dermal) tolerability, and vital signs.

All adverse events will be coded from the verbatim text to the lower level term and mapped to preferred term (PT) and primary system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA).

All TEAEs will be listed by patient. For TEAEs regardless of causality, and for treatment-related TEAEs, the number and percentage of patients reporting the TEAEs at least once will be tabulated by descending order of incidence rate by PT within primary SOC, and by primary SOC, PT, and severity.

Local (dermal) tolerability data will be summarized using descriptive statistics and frequency distributions. Vital signs will be summarized using descriptive statistics. Positive pregnancy test results will be listed.

More detailed analyses for the safety measures will be described in the analysis plan.

7.4 Other Analysis

Skin phototype will be summarized by frequency distributions. Further details will be provided in the analysis plan.

7.5 Subgroup Analyses

Key safety analyses and summaries will be performed as described in the detailed analysis plan.

7.6 Sample Size Calculation

The sample size for the trial was determined empirically, and is consistent with that requested by the FDA in the postmarketing requirement for ACZONE 7.5%.

7.7 Interim Analyses

There is no planned interim analysis.

8. Study Visit Schedule and Procedures

Please see Table 1 for a schematic of the schedule of visits and procedures.

8.1 Patient Entry Procedures

8.1.1 Overview of Entry Procedures

Prospective patients as defined by the criteria in Sections 4.3, and 4.4 (inclusion/exclusion criteria) will be considered for entry into this study.

8.1.2 Informed Consent and Patient Privacy

The study will be discussed with the patient's legally authorized representative(s) and they must give informed consent and the patients must give written assent prior to any study-related procedures. Additionally, for those patients in the PK Cohort, the legally authorized representatives will provide a written informed consent prior to the patient participating in PK sampling procedures. See also Section 10.1.

Each patient enrolled in to the study will be assigned a patient number that will be used on patient documentation throughout the study.

8.2 Washout Intervals

Drugs requiring a washout period (Section 4.4) should not be used during the study. Please see Section 4.5.3 for prohibited medications.

8.3 Procedures for Final Study Entry

See Section 5.3 for the method for assignment to treatment groups.

8.4 Visits and Associated Procedures

This study consists of visits at screening (days -30 to -1), day 1 (baseline), and weeks 1, 2, 4, 8, and 12/early exit.

After obtaining informed consent and authorization the patient's legally authorized representative and assent from the patient, patients will undergo a series of screening procedures to assess qualification for the study. Final eligibility for the study will be determined at the day 1 (baseline) visit. The following is a description of the procedures to be performed at each visit from screening to week 12/early exit. To the extent possible, procedures should occur in the order presented below.

8.4.1 Screening Visit (Days -30 to -1)

- Informed consent/authorization and minor assent obtained
- Inclusion/exclusion eligibility criteria reviewed – ongoing throughout visit
- Demographics obtained
- IGA performed (should be performed before lesion count)
- Lesion count performed
- Medical/surgical history status obtained
- Skin phototype assessed
- Urine pregnancy test administered for females
- Physical examination completed and vital sign measurements obtained, including height and weight (not required for screen failures)

- Adverse events recorded
- Concomitant medications and concomitant procedures recorded

8.4.2 Baseline/Day 1 (Visit 2)

Procedures (May be combined with the Screening Visit if no washout period is required)

- IGA performed (should be performed before lesion count)*
- Lesion count performed*
- Inclusion/exclusion eligibility criteria re-evaluated*
- Urine pregnancy test administered for females prior to administration of study drug*
- Local tolerability assessed on the face prior to study drug administration on day 1
- Standardized photography performed at selected centers (make up must be removed at least 20 minutes prior to photography)
- Training on study drug application
- Study drug weighed
- Study drug administered on site and dispensed for at-home use for the PK Cohort. Patients will receive 2.0 gram tubes for daily application from Baseline to Day 8 (+ 2 days) and then 60-gram pumps will be dispensed from Week 1/Visit 3 onwards.
- Study drug administered on site and dispensed for at-home use for the non-PK Cohort. Patients will receive 60-gram pumps starting on Baseline/Day 1.
- Local tolerability performed on the face, postdose
- Adverse events recorded
- Concomitant medications and concomitant procedures recorded*

* These may not need to be repeated if the baseline and screening visits occur on the same day.

8.4.3 Week 1/Visit 3 [Day 8 (+ 2 days)] and Week 2/Visit 4 (Day 15 ± 3 days)

- IGA performed (should be performed before lesion count)
- Lesion count performed
- Local tolerability assessed on the face only
- Adverse events recorded
- Concomitant medications and concomitant procedures recorded
- Study drug is dispensed for the PK Cohort
- Study drug returned will be assessed for the PK Cohort only at Week 1/ Visit 3 [Day 8 (+ 2 days)]-sites need to verify dosing compliance, retraining to be completed if needed
- At Week 1/Visit 3 [Day 8 (+ 2 days)] only, PK samples will be collected for the PK Cohort patients (see below)

At Week 1/Visit 3 [Day 8 (+ 2 days)] Procedures for the PK Cohort only

Blood samples will be collected within 30 minutes prior to dosing in clinic in the morning and at approximately 10 hours post dose (± 3 hour) under maximal use conditions at the Week 1/Visit 3 [Day 8 (+ 2 days)] to determine the peak and trough plasma drug concentrations. Dosing of the study drug will occur on site in the morning on Week 1/Visit 3.

8.4.4 Week 4/Visit 5 (Day 29 ± 7 days)) and Week 8/Visit 6 (Day 57 ± 7 days))

- IGA performed (should be performed before lesion count)
- Lesion count performed
- Local tolerability assessed on the face only
- Urine pregnancy test administered for females
- Adverse events recorded

- Concomitant medications and concomitant procedures recorded
- Study drug dispensed
- Study drug returned will be assessed

8.4.5 Week 12/Early Exit/Visit 7 (Day 85 ± 7 days)

- IGA performed (should be performed before lesion count)
- Lesion count performed
- Local tolerability assessed on the face only
- Adverse events are recorded
- Urine pregnancy test administered for females
- Physical examination completed and vital sign measurements obtained
- Standardized photography performed at selected centers
- Concomitant medications and concomitant procedures recorded
- Study drug returned will be assessed

8.5 Instructions for the Patients

Patients will be instructed to maintain their regular skin care regimen (with the exception of prohibited products) during the trial and must not use new products on treated areas while in the trial.

For patients in the PK Cohort, from Day 1 through Week 1/Visit 3, patients should not bathe, shower, swim, or wash face for at least 8 hours following administration of study drug.

Patients (or their legally authorized representative, if applicable) will be instructed to avoid all prohibited medications, treatments, and activities, as described in Section 4.5.4. In addition, patients (and their legally authorized representative, if applicable) should be instructed to arrive at the research unit approximately 30 minutes before any scheduled procedures.

8.6 Unscheduled Visits

Additional examinations may be conducted as necessary to ensure the safety and wellbeing of patients during the study period. Case report forms should be completed for each unscheduled visit.

8.7 Compliance With Protocol

Dispensed and returned study drug will be weighed at the study center. Patients will be asked questions to evaluate compliance with the medication regimen. At each visit, patients will be asked by site staff if they have complied with their instructions, dietary restrictions, and activity restrictions for a given visit.

8.8 Early Discontinuation of Patients

Patients may voluntarily withdraw from the study at any time. Notification of early patient discontinuation from the study and the reason for discontinuation will be made to the sponsor and will be clearly documented on the appropriate eCRFs.

8.9 Withdrawal Criteria

Patients should be discontinued from the study if any of the following criteria are met:

- Patient develops (or has an exacerbation of) any medical condition that, in the opinion of the investigator, would put the patient at an unacceptable medical risk or compromises the patient's ability to participate in the study.
- Patient is unable/unwilling to comply with study procedures.

Where possible, the decision to withdraw a patient from the study should be discussed with the Sponsor.

8.10 Study Termination

The study may be stopped at his/her study site at any time by the site investigator. The Sponsor may stop the study (and/or the study site) for any reason with appropriate notification.

9. Adverse Events

Adverse events occurring during the study will be recorded on an adverse event CRF page. If adverse events occur, the first concern will be the safety of the study participants.

9.1 Definitions

9.1.1 Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. In addition, during the screening period, adverse events will be assessed regardless of the administration of a pharmaceutical product.

Note: Adverse events must be collected once informed consent/assent has been obtained, regardless of whether or not the patient has been administered study drug.

Progression of treatment indication including new or worsening of anticipated clinical signs or symptoms, which are collected as clinical efficacy variables and assessed as unequivocally associated with the disease progression and /or lack of efficacy, should NOT be reported as adverse events unless the disease progression is greater than anticipated in the natural course of the disease.

Adverse events will be assessed, documented, and recorded in the CRF throughout the study (ie, after informed consent has been obtained). At each visit, the investigator will begin by querying for adverse events by asking each patient a general, non-directed question such as "How have you been feeling since the last visit?" Directed questioning and examination will then be done as appropriate. All reported adverse events will be documented on the appropriate CRF.

9.1.2 Serious Adverse Event

A serious adverse event is any adverse event occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be

life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (See Section 9.3 for procedures for reporting a serious adverse event.)

The Sponsor considers all cancer adverse events as serious adverse events. In addition, the Sponsor considers any abortion (spontaneous or nonspontaneous) as a serious adverse event.

Pre-planned surgeries or procedures for pre-existing, known medical conditions for which a patient requires hospitalization is not reportable as a serious adverse event.

Any pre-planned surgery or procedure should be clearly documented in the site source documents by the medically qualified investigator at the time of the patient's entry into the study. If it has not been documented at the time of the patient's entry into the study, then it should be documented as a serious adverse event and reported to the Sponsor.

9.1.3 Severity

A clinical determination will be made of the intensity of an adverse event. The severity assessment for a clinical adverse event must be completed using the following definitions as guidelines:

Mild	Awareness of sign or symptom, but easily tolerated.
Moderate	Discomfort enough to cause interference with usual activity.
Severe	Incapacitating with inability to work or do usual activity.

9.1.4 Relationship to Study Drug or Study Procedure

A determination will be made of the relationship (if any) between an adverse event and the study drug or study procedure, as applicable. A causal relationship is present if a determination is made that there is a reasonable possibility that the adverse event may have been caused by the study drug or study procedure.

9.2 Procedures for Reporting Adverse Events

Any adverse event must be recorded on the appropriate CRF.

All adverse events that are drug-related and unexpected (not listed as treatment-related in the current Investigator's Brochure) must be reported to the governing Institutional Review Board/Independent Ethics Committee (IRB/IEC) as required by the IRB/IEC, local regulations, and the governing health authorities.

Adverse events which are ongoing at exit and require follow-up include serious adverse events and any non-serious adverse events of special interest suggestive of methemoglobinemia, anemia, hemolysis, peripheral neuropathy, severe skin reactions, suicide attempt, tonic clonic movements, severe vomiting, pancreatitis, or severe pharyngitis.

9.3 Procedures for Reporting a Serious Adverse Event

Any serious adverse event occurring during the study period (beginning with informed consent) and for at least 28 days after the last dose of study drug must be immediately reported but no later than 24 hours after learning of a serious adverse event. Serious adverse events must be reported to the Sponsor(or Agent of the Sponsor) as listed on the Sponsor's Study Contacts Page and recorded on the serious adverse event form. All patients with a serious adverse event must be followed up and the outcomes reported. The investigator must supply the sponsor and the IRB/IEC with any additional requested information (eg, autopsy reports and discharge summaries).

In the event of a serious adverse event, the investigator must:

1. Notify the Sponsor immediately by fax or email using the serious adverse event form (contact details can be found on page 1 of the serious adverse event form); phone numbers and relevant Sponsor personnel contacts are also on the front page of protocol and Study Contacts Page.

2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.

3. Provide the Sponsor with a complete, written description of the adverse event(s) on the serious adverse event form describing the event chronologically, including any treatment given (eg, medications administered, procedures performed) for the adverse event(s). Summarize relevant clinical information about the event: signs, symptoms, diagnosis, clinical course and relevant clinical laboratory tests, etc. Include any additional or alternative explanation(s) for the causality which includes a statement as to whether the event was or was not related to the use of the investigational drug.

4. Promptly inform the governing IRB/IEC of the serious adverse event as required by the IRB/IEC, local regulations, and the governing health authorities.

9.4 Procedures for Unmasking of Study Medication

This is an open-label study.

10. Administrative Items

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines, eg, the ICH Guideline on GCP.

10.1 Protection of Human Patients

10.1.1 Compliance With Informed Consent Regulations (US 21 CFR Part 50) and Relevant Country Regulations

Written informed consent is to be obtained from the patient's legally authorized representative. the consent form must be signed by the legally authorized representative in accordance with the relevant country and local regulatory requirements.

A separate written minor assent (in accordance with any applicable state and local laws/regulations) are required prior to study enrollment or any study-related procedures.

10.1.2 Compliance With IRB or IEC Regulations

This study is to be conducted in accordance with IRB regulations (US 21 CFR Part 56.103) or applicable IEC regulations. The investigator must obtain approval from a properly constituted IRB/IEC prior to initiating the study and re-approval or review at least annually. The Sponsor is to be notified immediately if the responsible IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/IEC correspondence with the investigator should be provided to the Sponsor.

10.1.3 Compliance With Good Clinical Practice

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

10.1.4 Compliance With Electronic Records; Electronic Signatures Regulations (US 21CFR Part 11)

This study is to be conducted in compliance with the regulations on electronic records and electronic signature.

10.2 Changes to the Protocol

The investigator must not implement any deviation from or changes to the protocol without approval by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment, except where necessary to eliminate immediate hazards to study patients, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers).

10.3 Patient Confidentiality

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the patient's name will not be disclosed in these documents. The patient's name may be disclosed to the Sponsor of the study, the Sponsor, or the governing health authorities or the FDA if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

10.3.1 Patient Privacy

Written authorization (United States [US] sites only), and Personal Information Protection and Electronic Documents Act (PIPEDA; Canadian sites only), and other documentation in accordance with the relevant country and local privacy requirements (where applicable) were obtained from each patient prior to enrollment into the study, and/or from thepatient's legally authorized representative in accordance with the applicable privacy requirements (eg, HIPAA).

Samples of ICF and privacy documentation forms are on file in the sponsor's trial master file and are available upon request.

10.4 Documentation

10.4.1 Source Documents

Source documents may include a patient's medical records, hospital charts, clinic charts, the investigator's patient study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the CRFs serves as part of the investigator's record of a patient's study-related data.

The following information should be entered into the patient's medical record:

- Patient’s name
- Patient’s contact information
- The date that the patient entered the study, patient number, and patient drug kit number dispensed and returned
- The study title and/or the protocol number of the study and the name of the Sponsor
- A statement that informed consent and assent was obtained (including the date). A statement that written authorization (US sites only), or other country and local patient privacy required documentation for this study has been obtained (including the date)
- Documentation that a patient met all of the inclusion and exclusion criteria for study entry, and the date when eligibility was confirmed
- Patient’s demographics, skin phototyping, and medical history, as collected at screening
- Documentation that females had a negative pregnancy test result at screening, baseline/Day 1 (Visit 2), Week 4/Visit 5, Week 8/Visit 6, and Week 12/early exit (Visit 7).
- Dates of all patient visits
- Occurrence and status of any adverse events
- The date the patient exited the study, and a notation as to whether the patient completed the study or reason for discontinuation

- Documentation of PK sample collection, processing, storage, and shipping for the patients in the PK Cohort
- Training on study drug administration, dispensing and weighing/confirming dosing compliance
- The results of laboratory tests performed by the site for an adverse event
- Key study variables such as:
    - Documentation of the patient's compliance with study restrictions, including activity restrictions
    - All concomitant medications (List all prescription and non-prescription medications being taken at the time of enrollment. At each subsequent visit, changes to the list of medications should be recorded.)
    - Concomitant procedures
    - Results of vital sign, body weight, and height measurements
    - Results of local tolerability assessments
    - IGA assessment
    - Lesion count results, including information on who the assessor is
    - Documentation confirming standardized photography has been completed at the selected sites

Source documentation practices must follow Section 4.0 of ICH E6,GCP: Consolidated Guidance and ALCOA; ie, records must be Attributable, Legible, Contemporaneous, Original and Accurate.

10.4.2 Case Report Form Completion

The investigator is responsible for ensuring that data are properly recorded on each patient's case report forms and related documents. An investigator who has signed the protocol signature page should personally sign for the case report forms (as indicated in the case report forms) to ensure that the observations and findings are recorded on the case report forms correctly and completely. The case report forms are to be submitted to the Sponsor in

a timely manner at the completion of the study, or as otherwise specified by the Sponsor and will be maintained in a central data repository.

10.4.3 Study Summary

An investigator's summary will be provided to the Sponsor within a short time after the completion of the study, or as designated by the Sponsor. A summary is also to be provided to the responsible IRB/IEC.

10.4.4 Retention of Documentation

All study related correspondence, patient records, consent forms, patient privacy documentation, records of the distribution and use of all investigational products, and copies of case report forms should be maintained on file.

For countries falling within the scope of the ICH guidelines, the sponsor-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

In addition, for countries not falling within the scope of the ICH guidelines, local regulatory requirements should be followed regarding the retention of clinical study documentation.

The Sponsor requires that it be notified in writing if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

10.5 Labeling, Packaging, and Return or Disposal of Study Medications/Treatments

10.5.1 Labeling/Packaging

All study drug will be packaged, labeled, and supplied by the Sponsor. To ensure maximal use conditions for the PK Cohort for the first 8 days, study drug will be provided in individual usage tubes containing approximately 2 grams each. Each weekly kit will contain 14 x 2-gram tubes. After Week 1/Visit 3 the maximal use condition portion of the trial for the

PK Cohort, study drug will be supplied in 60-gram pumps as it has been for the non-PK Cohort from the start of the study. The study drug will be identified as an investigational compound. The kit number will be identified on the unit label.

10.5.2 Clinical Supply Inventory

The investigator must keep an accurate accounting of the number of investigational units received from the Sponsor, dispensed or administered to the patients, the number of units returned to the investigator by the patient (if applicable), and the number of units returned to the Sponsor during and at the completion of the study. A detailed inventory must be completed for the study drug. The study drug must be dispensed or administered only by an appropriately qualified person to patients in the study. The drug is to be used in accordance with the protocol for patients who are under the direct supervision of an investigator.

10.5.3 Return or Disposal of Study Medications/Treatments and/or Supplies

All clinical study drugs/treatments and/or supplies will be returned to the Sponsor or the Sponsor's designee for destruction.

10.6 Monitoring by the Sponsor

A representative of the sponsor will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the study.

Authorized representatives of the Sponsor or regulatory authority representatives will conduct on-site visits to review, audit and copy study-related documents. These representatives will meet with the investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

10.7 Handling of Biological Specimens

Blood samples obtained at selected sites will be analyzed for dapsone, NAD, DHA, and other metabolites or analytes (if warranted) by a bioanalytical laboratory.

All samples will be returned to the Sponsor or the Sponsor's designee for destruction. The Sponsor shall have full ownership rights to any biological specimens/samples derived from the study.

10.8 Publications

The Sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and the Sponsor's personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with the Sponsor.

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12. Attachments

12.1 Examination Procedures, Tests, Equipment, and Techniques

Pharmacokinetic Measures

- Plasma concentrations of dapsone, its metabolites (NAD, DHA), and other metabolites or analytes (if warranted)

Detailed instructions on the collection, processing, and storage of pharmacokinetic samples are provided in the Procedure Manual.

Safety Measures

- Adverse events

The investigator will question the patient in order to ascertain whether any adverse events were experienced since the previous visit. All pertinent information regarding adverse events (ie, date of onset and stop, duration, outcome, severity, relationship to study drug, action or treatment required) will be obtained and recorded in the source documents and appropriately transcribed on the eCRF page.

- Urine pregnancy test

All females will be asked to provide a urine sample for pregnancy testing. Sample testing will be performed in accordance with the instructions provided in the pregnancy test kit.

- Vital signs

Heart rate (beats per minute) and respiratory rate: patients should be seated for at least 10 minutes, and heart rate and respiratory rate will be counted over 60 seconds, and recorded in the source document and eCRF.

Blood pressure (millimeters of mercury): patients should be seated for at least 10 minutes, and systolic/diastolic blood pressure will be measured with a sphygmomanometer.

Body temperature (°C): patients should have had no oral intake for 5 minutes before the body temperature is taken orally.

- Physical examination (PE)

The body systems listed below will be checked. The date of PE will be recorded, and any new PE findings will be recorded on the AE CRF.

1. General Appearance
2. HEENT (head, eyes, ears, nose, and throat)
3. Heart/Cardiovascular
4. Lungs
5. Abdomen
6. Neurologic
7. Extremities
8. Back
9. Musculoskeletal
10. Lymphatic
11. Skin
12. Other: _____

- Body weight and height

Efficacy Measures:

- **IGA**

Grade		**Description**
0	Clear	• No comedones, papules or pustules • Residual hyperpigmentation and erythema may be present
1	Almost Clear	• Rare comedones • No more than a few small papules and pustules
2	Mild	• Easily recognizable comedones in limited numbers • +/- Presence of small papules and pustules
3	Moderate	• Many comedones • +/- Easily recognizable small and medium-sized papules • No nodules or cysts.
4	Severe	• Widespread and numerous comedones • Many small, medium-sized and large papules and pustules • Nodules or cysts may or may not be present.

(Eichenfield et al, 2013, J of Dermatol)

- Local dermal tolerability assessment

The local tolerability examination of the face is to be performed by the investigator (or appropriately trained designee), who will assess dryness, scaling, and erythema, and the patient will assess stinging/burning. The assessor will examine the skin area where study drug is applied in comparison to the surrounding skin from day 1 to week 12. The same assessor will rate dryness, scaling, and erythema at each visit, where possible. Local tolerability signs and symptoms will be rated using a severity scoring of 0 (none), 1 (mild), 2 (moderate), or 3 (severe), as further defined below.

Based on the assessor's medical judgment, if a sign or symptom is clinically significant, it must be recorded on the adverse event eCRF. Other dermatological findings of clinical significance in the patient's treated area must also be reported as adverse events on the eCRF.

Patient-rated:

Stinging/Burning: prickling pain sensation immediately after (within 5 minutes of dosing, except baseline)

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

Investigator- (or designee) rated:

Dryness: brittle and/or tight sensation

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

Scaling: abnormal shedding of the stratum corneum

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: abnormal redness of the skin

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

- Fitzpatrick skin phototype (FDA Federal Register, 1999):

  I: Always burns easily; never tans (sensitive)
  II: Always burns easily; tans minimally (sensitive)
  III: Burns moderately; tans gradually (light brown) (normal)
  IV: Burns minimally; always tans well (moderate brown) (normal)
  V: Rarely burns; tans profusely (dark brown) (insensitive)
  VI: Never burns; deeply pigmented (insensitive)

- Photographs will be taken by a subset of study sites. Photographs will be transferred to the Sponsor on a periodic basis.

12.2 Handling of Biological Specimens

Details relating to the handling of biological samples are provided in the Procedure Manual.

12.3 Glossary of Abbreviations

Term/Abbreviation	Definition
CRF	case report form
C_{max}	maximum plasma concentration
DHA	dapsone hydroxylamine
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practices
G6PD	glucose-6-phosphate dehydrogenase
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IETD	investigator emergency treatment disclosure
IRB	Institutional Review Board
IVRS	interactive voice response system
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
NAD	N-acetyl dapsone
NSAID	nonsteroidal anti-inflammatory drug
PK	Pharmacokinetics
PT	preferred term
SOC	system organ class
TEAE	treatment-emergent adverse event
US	United States

ALLERGAN

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Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
23-Jun-2016 07:47 GMT-070	PPD	PPD Approval

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