

Evaluating Acne Treatment Success in Investigational Settings vs. Clinical Practice



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Acne affects an estimated 40 to 50 million Americans each year and is one of the most common reasons that patients visit dermatologists.^{1,2} In the office, dermatologists have a variety of medications in their acne treatment toolbox. Clinical trials provide safety and efficacy data for a particular drug. While understanding the data from clinical trials is important, the data must be interpreted and applied to clinical practice. This paper will discuss FDA guidelines for evaluating acne treatment efficacy in clinical trials and provide perspectives on criteria to consider when treating acne in practice. Furthermore, clinical trial data for topical dapsone gel 5% will be reviewed.

In 2005, the FDA drafted a guidance report for industry outlining requirements for developing new drugs for acne.³ In the report, the FDA specifically discussed types of studies needed as well as required endpoints to bring new drugs to the US market.

Currently, both lesion counts (inflammatory, non-inflammatory, and total lesion count reductions) and investigator's global assessments (IGA) are viewed as necessary co-primary endpoints.

Counting acne lesions is a long-standing method used to evaluate efficacy of acne therapies in clinical trials and was

first described in the 1960s.⁴ Given the multiple lesion types, even subtle differences in lighting and head position can affect counts because of altered appearance of lesions at different evaluation time points. Formal evaluator training and continued practice are necessary to generate reliable data.⁵

While individual lesion counts have often been employed in the investigational setting, using them as the only method may be less reliable to assess efficacy. Therefore, a universally-accepted global severity scale like the IGA and lesion count can allow for a more comprehensive approach to evaluate acne severity from a clinical and investigational application.

IGA performed by the study investigator is an efficacy evaluation that takes into account the overall severity of acne.³ Global assessment ratings take into account the collection of lesions, their individual severity, and the overall surface area of involvement.^{3,6} The most recent FDA guidance suggested a 5-point IGA scale, as described below.³

Combining the two approaches of ordinal global assessment scale and lesion count assessments allows for a balanced approach toward the evaluation of acne severity.

IMPORTANCE OF A BALANCED TREATMENT EXPERIENCE—EFFICACY AND TOLERABILITY OF DAPSONE GEL 5%

As prescribers, dermatologists must find balance between drug efficacy and tolerability. Findings from clinical trials play a key role in establishing this balance. In pivotal phase III trials for

ACZONE® (dapsone) Gel 5%

ACZONE® (dapsone) Gel 5% is indicated for the topical treatment of acne vulgaris.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hematological effects. Oral dapsone treatment has produced dose-related hemolysis and hemolytic anemia. Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are

more prone to hemolysis with the use of certain drugs. There was no evidence of clinically relevant hemolysis or anemia in patients treated with ACZONE® Gel 5%, including patients who were G6PD deficient. Some subjects with G6PD deficiency using ACZONE® Gel 5% developed laboratory changes suggestive of mild hemolysis. If signs and symptoms suggestive of hemolytic anemia occur, ACZONE® Gel 5% should be discontinued. ACZONE® Gel 5%

should not be used in patients who are taking oral dapsone or antimalarial medications because of the potential for hemolytic reactions. Combination of ACZONE® Gel 5% with trimethoprim/ sulfamethoxazole (TMP/SMX) may increase the likelihood of hemolysis in patients with G6PD deficiency.

Peripheral neuropathy. Peripheral neuropathy (motor loss and muscle weakness) has been reported with oral dapsone treat-

2005 FDA SUGGESTED IGA SCALE FOR ACNE VULGARIS

- 0 = Clear skin with no inflammatory or noninflammatory lesion;
- 1 = Almost clear, rare noninflammatory lesions with no more than one small inflammatory lesion
- 2 = Mild, some noninflammatory lesions, no more than a few inflammatory lesions
- 3 = Moderate, up to many noninflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion
- 4 = Severe, up to many noninflammatory and inflammatory lesions, but no more than a few nodular lesions

dapsone gel 5%, both co-primary endpoints for efficacy were evaluated per the FDA guidance described above. Safety studies provided further evidence for FDA approval of dapsone gel 5% for the topical treatment of acne in males and females 12 years of age and older.

In the pivotal phase III studies, dapsone gel 5% was studied in two identical clinical trials involving a total of 3,010 patients. The aim of the study was to assess the safety and efficacy of dapsone gel 5% in the treatment of acne vulgaris. The combined results of the two trials are presented here. Participants were randomized 1:1 to receive active drug (n=1506) or vehicle (n=1504). Study medication was applied to the face twice daily for 12 weeks. For inclusion in the study, patients had to be at least 12 years old with 20-50 inflammatory lesions and 20-100 noninflammatory lesions at baseline. At baseline, 58% of patients were considered to have moderate acne and 33% mild acne.⁷

Co-primary endpoints in the study were mean percent reduction in acne lesions and treatment success ("clear or almost clear") based on IGA scores. Success for acne lesion counts was defined as statistically greater mean percent reductions at week 12 in at least two of the three types of lesion counts (inflammatory, noninflammatory, and total) in the dapsone gel-

ment. No events of peripheral neuropathy were observed in clinical trials with topical ACZONE® Gel 5% treatment.

Skin. Skin reactions (toxic epidermal necrolysis, erythema multiforme, morbiliform and scarlatiniform reactions, bullous and exfoliative dermatitis, erythema nodosum, and urticaria) have been reported with oral dapsone treatment. These types of skin reactions were not observed in clinical trials with topical ACZONE® Gel

5% treatment.

ADVERSE REACTIONS

The most common adverse reactions of ACZONE® Gel 5% (incidence ≥ 10%) are oiliness/peeling, dryness, and erythema at the application site.

DRUG INTERACTIONS

Topical application of ACZONE® Gel followed by benzoyl peroxide in subjects with acne vulgaris resulted in a temporary

local yellow or orange discoloration of the skin and facial hair (reported by 7 out of 95 subjects in a clinical study) with resolution in 4 to 57 days.

For more information on ACZONE®, please see the accompanying full Prescribing Information, including Patient Labeling.

MEAN PERCENT CHANGE IN LESION COUNTS

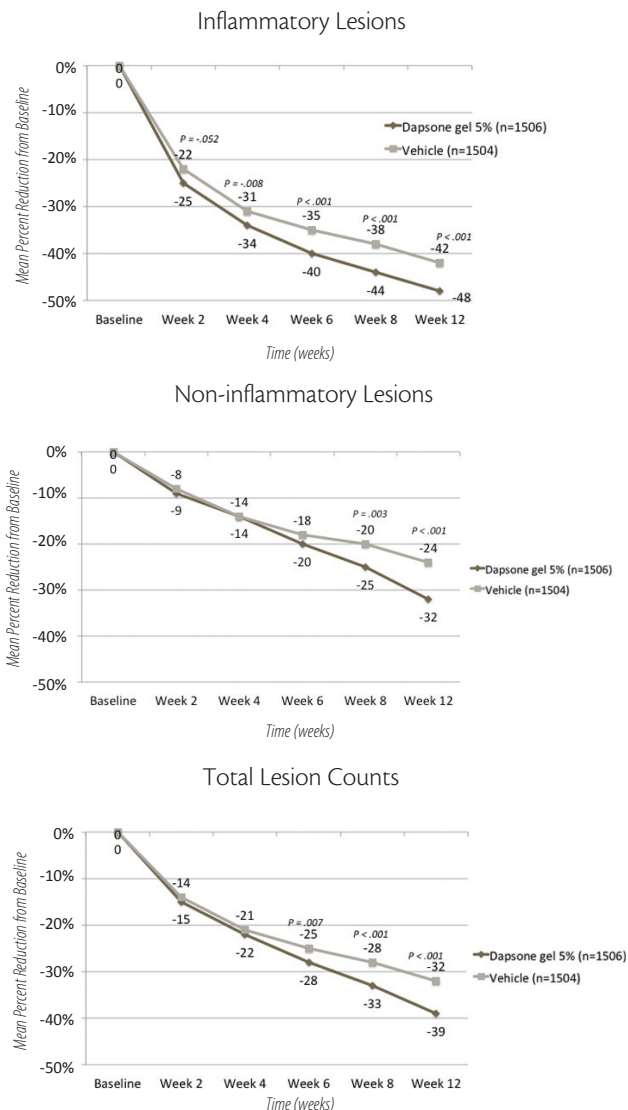


Fig. 2. Lesion reductions in clinical trials of ACZONE® (dapsone) Gel 5% (n=1506) versus vehicle gel (n=1504).⁷

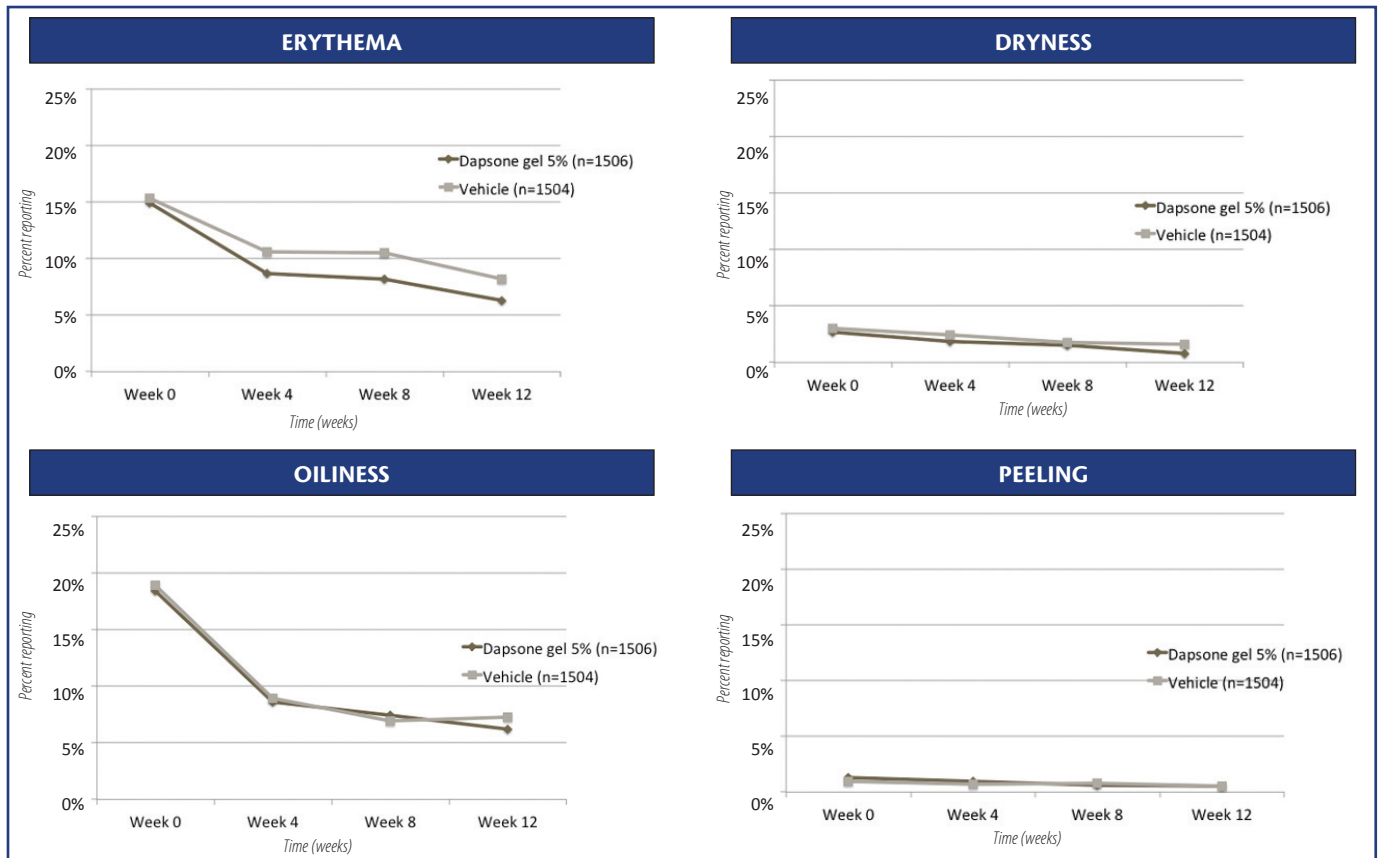


Fig. 2. Reported rates of adverse events (n = 2,898) during the clinical trials of ACZONE® (dapson) Gel 5%.⁷

treated patients compared with the vehicle gel-treated patients. Secondary efficacy endpoints included mean lesion counts for inflammatory, noninflammatory, and total acne lesions, as well as mean reduction from baseline at week 12 for all of these. Reductions in inflammatory lesions compared to vehicle were observable as early as week 4 ($P=0.008$), and continued to improve until week 12. At the conclusion of the study, there was a 48% (n=1506) mean reduction in inflammatory lesions, versus 42% (n=1504) in the vehicle arm, $P<0.001$, and a 32% reduction in non-inflammatory lesions, versus 24% in the vehi-

cle arm, $P<0.001$. Total lesion counts were reduced 39%, versus 33% in the vehicle arm, $P<0.001$. At week 12, treatment success according the IGA scale was achieved by 41% of patients in the dapson gel group compared to 33% of patients in the vehicle group ($P<0.001$).⁷ (Fig. 1)

In the phase 3 study no significant differences in adverse events emerged between the dapson and vehicle groups. The most common events reported from these studies include oiliness/peeling, dryness, and erythema.⁷ (Fig. 2) ACZONE® Gel 5% was also evaluated for 12 weeks in four controlled studies

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Peripheral neuropathy. Peripheral neuropathy (motor loss and muscle weakness) has been reported with oral dapson treat-



Fig. 3. Patients are shown at baseline (left) and 12 weeks (right) after treatment with ACZONE® (dapson) Gel 5%.

for local cutaneous events in 1,819 patients and less than 1% of patients had severe erythema, dryness, oiliness/peeling in these studies that evaluated safety. One percent of dapson gel patients discontinued due to treatment-related factors.⁸

OTHER CONSIDERATIONS WHEN EVALUATING THE SUCCESS OF AN ACNE TREATMENT

An additional consideration when evaluating the success of an acne treatment, is understanding what the patient wants and expects out of therapy. In the author's practice, acne patients want to be engaged in the decision making process and help choose their own therapies. After the skin is closely examined, the conversation is framed within the context of acne. In a recent cross-sectional, web-based survey, investigators evaluated the concerns of adult females with acne. The survey demonstrated that most females have already attempted to address their acne before visiting the dermatologist. Other data from the same survey show that many females cannot differentiate between facts and myths about acne and can benefit from seeking professional medical advice regarding their skin.⁹ Given this data, dermatologist have a tremendous opportunity to educate and set realistic expectations for patients.

Building relationships with patients is critical. For some acne patients, your visit may be their first encounter with therapies for the skin. For others, you may be the fifth dermatologist they have seen.

Step 1: Establish trust. Discuss your treatment plan, involve the patient, and manage expectations.

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Step 2: Do no harm. Contrary to popular belief the skin of acne patients may be exquisitely sensitive. Ask the patient about previous experience and preferences to identify an appropriate regimen. Commonly in the author's Manhattan practice, patients report concerns about specific treatments, so alternative approaches must be taken before moving to

Step 3: Refine the regimen. Once the patient trusts you, you can discuss other optional therapies.

All we can do is apply available clinical trial data to our individual practices and patient needs. Topical dapson gel is a drug with a large amount of data supporting its use. In practice, it can be viewed as a balanced treatment experience providing efficacy and tolerability for many patients. ■

Dr. Zeichner is a consultant for Allergan, Inc. and has received an honorarium for his contribution to this publication.

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9. Data on file, Allergan, Inc., Irvine, CA.

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