# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 207154Orig1s000

# STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

| | |
|---|---|
| **NDA/BLA #:** | NDA 207154 |
| **Drug Name:** | ACZONE (dapsone) gel 7.5% |
| **Indication(s):** | Acne Vulgaris |
| **Applicant:** | Allergan, Inc. |
| **Date(s):** | Letter Date: 4/28/2015 |
| | PDUFA Date: 2/28/2016 |
| **Review Priority:** | Standard |
| | |
| **Biometrics Division:** | Division of Biometrics III |
| **Statistical Reviewer:** | Matthew Guerra, Ph.D. |
| **Concurring Reviewers:** | Mohamed Alosh, Ph.D. |
| | |
| **Medical Division:** | Division of Dermatology and Dental Products |
| **Clinical Team:** | Patricia Brown, M.D. / Gordana Diglisic, M.D. |
| **Project Manager:** | Strother Dixon / Cristina Attinello |

**Keywords:** Acne vulgaris, superiority trial, multiple imputation

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# 1 EXECUTIVE SUMMARY

The applicant has developed ACZONE® (dapsone) gel, 7.5% for the topical treatment of acne vulgaris in patients 12 years of age and older. ACZONE® (dapsone) gel, 5% was approved on July 7, 2005 for the indication of topical treatment of acne vulgaris. It should be noted that the approved dose regimen for ACZONE® (dapsone) gel, 5% is twice daily and the proposed dose regimen for ACZONE® (dapsone) gel, 7.5% is once daily.

The applicant submitted data from two identically-designed, randomized, multicenter, vehicle-controlled, parallel-group, Phase 3 trials (Trials 006 and 007). For enrollment, the protocol specified the following key inclusion criteria: 12 years of age or older, a Global Acne Assessment Score (GAAS) of 3 (moderate), 20-50 inflammatory lesions (papules and pustules) on the face, and 30-100 non-inflammatory lesions (open comedones and closed comedones) on the face. The protocol-specified co-primary efficacy endpoints were the proportion of subjects achieving a GAAS score of 0 (none) or 1 (minimal) at Week 12 and the absolute change in inflammatory and non-inflammatory lesion counts from baseline to Week 12. Secondary efficacy endpoints included percent change in inflammatory and non-inflammatory lesion counts from baseline to Week 12.

Table 1 presents the results of the co-primary efficacy endpoints and the secondary efficacy endpoints of percent change in inflammatory and inflammatory lesion counts from baseline to Week 12. In both trials, ACZONE gel, 7.5% was statistically superior (p-values $\leq 0.004$) to vehicle gel for all endpoints presented in Table 1.

**Table 1: Results for the Co-Primary and Secondary Efficacy Endpoints at Week 12**

| | Trial 006 | | Trial 007 | |
|---|---|---|---|---|
| **Endpoints** | **ACZONE (N=1044)** | **Vehicle (N=1058)** | **ACZONE (N=1118)** | **Vehicle (N=1120)** |
| **Co-Primary:** | | | | |
| GAAS (none or minimal): n (%) | 30% | 21% | 30% | 21% |
| Absolute Change in: | | | | |
| Inflammatory Lesions: Mean | 16.1 | 14.3 | 15.6 | 14.0 |
| Non-Inflammatory Lesions: Mean | 20.7 | 18.0 | 20.8 | 18.7 |
| **Secondary:** | | | | |
| Percent Change in: | | | | |
| Inflammatory Lesions: Mean | 56% | 49% | 54% | 48% |
| Non-Inflammatory Lesions: Mean | 45% | 39% | 46% | 41% |

Source: Reviewer's Analysis (same as Applicant's Analysis)

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

# 2 INTRODUCTION

## 2.1 Overview

The applicant, Allergan, is developing ACZONE® (dapsone) gel, 7.5% for the topical treatment of acne vulgaris in patients 12 years of age and older. ACZONE® (dapsone) gel, 5% was approved on July 7, 2005 for the indication of topical treatment of acne vulgaris. It should be noted that the approved dose regimen for ACZONE® (dapsone) gel, 5% is twice daily and the proposed dose regimen for ACZONE® (dapsone) gel, 7.5% is once daily.

### 2.1.1 Regulatory History

On August 28, 2013, the Agency and the applicant met for an End-of-Phase 2 (EOP2) meeting to discuss the development plan for ACZONE (dapsone) gel, 7.5%. The applicant proposed to conduct two identically-designed Phase 3 trials (Trials 006 and 007) and submitted the protocol for these trials in the meeting package. The applicant proposed the co-primary efficacy endpoints of proportion of subjects with success on the GAAS (i.e., score of 0 or 1) at Week 12 and absolute change in lesion counts (inflammatory, non-inflammatory, and total) from baseline to Week 12. The Agency recommended that the co-primary endpoints regarding lesion counts be absolute change in inflammatory and non-inflammatory lesion counts from baseline to Week 12 (i.e., not include total as a co-primary endpoint). The Agency also commented that several of the secondary endpoints are closely related and some of the secondary endpoints might not be clinically relevant for labeling. The Agency stated that the secondary endpoints of percent change in inflammatory and non-inflammatory lesion count from baseline to Week 12 are acceptable. In addition, the Agency stated that the proposed patient reported outcomes may have limited utility for eventual product labeling. The Agency also provided comments regarding the handling of missing data (i.e., recommended a more scientifically sound approach, such as multiple imputation or modeling approach, instead of the last observation carried forward (LOCF) approach).

On October 7, 2013, the applicant submitted amended protocols for the Phase 3 trials proposed during the EOP2 meeting. An advice letter was sent to the applicant on January 15, 2014. The Agency reiterated the comments from the EOP2 meeting regarding the absolute change in total lesion counts as a co-primary endpoint and the limited utility of the proposed patient reported outcomes (i.e., the Acne Symptom and Impact Scale (ASIS)).

On February 11, 2014, the applicant submitted their responses to the Agency's comments conveyed in the advice letter sent on January 15, 2014. In addition, on February 18, 2014, the applicant submitted their Patient Reported Outcomes (PRO) Questions Document, a new Acne Symptom and Impact Scale (ASIS) PRO Dossier and a draft statistical analysis plan (SAP) for their pivotal Phase 3 trials. An advice letter regarding these two submissions was sent to the applicant on June 13, 2014. The Agency provided extensive comments regarding the ASIS. For any PRO endpoints that are proposed to support labeling claims, the Agency recommended pre-specifying an appropriate responder definition, making appropriate adjustments for multiple endpoints, and discussing these considerations with the Agency.

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