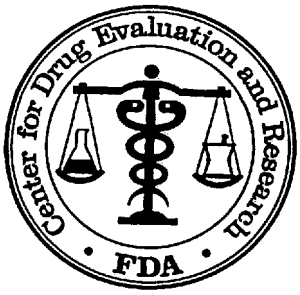



US Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# Statistical Review and Evaluation

## New Drug Application

### Clinical Studies

| | |
|---|---|
| **NDA/Serial Number**: | 50-819 |
| **Drug Name**: | IDP-110 |
| **Indication(s)**: | Treatment of acne vulgaris |
| **Applicant**: | Dow Pharmaceutical Sciences |
| **Dates**: | Submitted: December 26, 2007 |
| | PDUFA: October 24, 2008 |
| **Review Priority**: | Standard Review |
| **Biometrics Division**: | Division of Biometrics III |
| **Statistics Reviewer**: | Clara Y. Kim, Ph.D. |
| **Concurring Reviewer**: | Mohamed Alosh, Ph.D. |
| **Medical Division**: | Division of Dermatology and Dental Products |
| **Clinical Team**: | Brenda Vaughan, M.D./Markham Luke, M.D., Ph.D. |
| **Project Manager**: | Tamika White |
| **Keywords**: | Acne vulgaris, combination product |

# Contents

# 1 Executive Summary

## 1.1 Conclusions and Recommendations

Combination drug, IDP-110 has been demonstrated to be statistically superior to its monads, clindamycin and benzoyl peroxide (BPO), and its vehicle in two studies (Study 012 and Study 017) in the treatment of moderate to severe acne vulgaris. Efficacy was evaluated using the Evaluator's Global Severity Score (EGSS) and mean absolute change in inflammatory and non-inflammatory lesion counts. The protocol stated that efficacy would be demonstrated if at Week 12: (i) IDP-110 was superior to each monad and vehicle in EGSS and both lesion counts; (ii) IDP-110 was superior to each monad and vehicle in mean absolute change in inflammatory lesions; and (iii) IDP-110 was superior to vehicle in mean absolute change in non-inflammatory lesion counts. Tables 1 and 2 present the summary of the co-primary endpoint results. All co-primary endpoints that were required to establish efficacy were statistically significant in both studies with p-values less than 0.012.

Table 1: Primary Efficacy Results - Number (%) of Successes on EGSS at Week 12 (ITT)

| | Study 012 | | | |
|---|---|---|---|---|
| | IDP-110 n=399 | Clindamycin n=408 | BPO n=406 | Vehicle n=201 |
| Number of successes (%) | 131 (32.8%) | 100 (24.5%) | 96 (23.6%) | 38 (18.9%) |
| p-value† | NA | 0.002 | 0.001 | <0.0001 |

| | Study 017 | | | |
|---|---|---|---|---|
| | IDP-110 n=398 | Clindamycin n=404 | BPO n=403 | Vehicle n=194 |
| Number of successes (%) | 147 (36.9%) | 114 (28.2%) | 114 (28.3%) | 27 (13.9%) |
| p-value† | NA | 0.009 | 0.009 | <0.0001 |

† P-values were calculated using logistic regression with treatment, analysis center, dichotomized skin type, and baseline severity as factors.

Missing values were imputed using LOCF

Source: Study Report DPSI-06-22-2006-012, pg. 67; Study Report DPSI-06-22-2006-017, pg. 65; and reviewer analysis.

Table 2: Primary Efficacy Results - Mean Absolute Change in Lesion Counts at Week 12 (ITT)

| | Study 012 | | | |
|---|---|---|---|---|
| | IDP-110 n=399 | Clindamycin n=408 | BPO n=406 | Vehicle n=201 |
| **Inflammatory lesions** | | | | |
| Mean absolute change (sd) | 14.8 (10.8) | 12.2 (11.6) | 13.0 (10.4) | 9.0 (11.9) |
| p-value† | NA | <0.001 | 0.012 | <0.001 |
| **Non-inflammatory lesions** | | | | |
| Mean absolute change (sd) | 22.1 (21.2) | 17.9 (19.9) | 20.6 (22.0) | 13.2 (20.4) |
| p-value† | NA | 0.005 | 0.134 | <0.001 |

| | Study 017 | | | |
|---|---|---|---|---|
| | IDP-110 n=398 | Clindamycin n=404 | BPO n=403 | Vehicle n=194 |
| **Inflammatory lesions** | | | | |
| Mean absolute change (sd) | 13.7 (10.5) | 11.3 (11.7) | 11.2 (10.6) | 5.7 (12.6) |
| p-value† | NA | 0.003 | 0.001 | <0.001 |
| **Non-inflammatory lesions** | | | | |
| Mean absolute change (sd) | 19.0 (19.9) | 14.9 (18.8) | 15.2 (19.0) | 8.3 (19.8) |
| p-value† | NA | 0.007 | 0.016 | <0.001 |

† P-values were calculated using ANCOVA with the baseline inflammatory count as covariate and treatment, analysis center, dichotomized skin type, and baseline severity as factors. Each arm was tested against IDP-110.

Missing values were imputed using LOCF.

Source: Reviewer analysis.

The proportion of subjects who experienced at least one adverse event was highest in the benzoyl peroxide (BPO) arm and IDP-110 arm in Studies 012 and 017, respectively. The most common adverse events were upper respiratory tract infection and nasopharyngitis.

## 1.2 Brief Overview of Clinical Studies

The sponsor conducted two phase 3 studies (Study 012 and Study 017) to evaluate the safety and efficacy of IDP-110 compared to its monads (clindamycin and BPO) and vehicle in the treatment of moderate to severe acne vulgaris. Studies 012 and 017 randomized a total of 1414 and 1399 subjects, respectively, to either IDP-110, clindamycin, benzoyl peroxide (BPO) or vehicle in a 2:2:2:1 ratio. The treatment duration was 12 weeks. Efficacy was evaluated at

Week 12 for the following primary endpoints: (i) a two grade improvement from baseline on the Evaluator's Global Severity Score (EGSS); and (ii) mean absolute change from baseline in inflammatory and non-inflammatory lesion counts. Thirty-three (33) investigative sites in Study 012 were from the US, 1 from Canada, and 1 from Central America, whereas all 35 investigative sites in Study 017 were from the US.

### 1.3 Statistical Issues and Findings

The sponsor conducted two studies (Study 012 and Study 017) under the protocol that was agreed upon with the Agency in terms of study design and endpoints. Efficacy was evaluated at Week 12 using the proportion of successes based on the Evaluator's Global Severity Score (EGSS) and the mean absolute change in inflammatory and non-inflammatory lesion count from baseline. The protocol stated that efficacy would be demonstrated if (i) IDP-110 is superior to each monad and vehicle in EGSS and both lesion count; (ii) IDP-110 is superior to each monad and vehicle in mean absolute change in inflammatory lesions; and if (iii) IDP-110 is superior to vehicle in mean absolute change in non-inflammatory lesion count. The differences in the success rates based on EGSS in all comparisons, IDP-110 versus clindamycin, benzoyl peroxide (BPO) and vehicle were statistically significant in both studies (p-values$<$0.009). The differences in the mean absolute change in inflammatory lesion counts were also statistically significant in all comparisons in both studies (p-values$<$0.012). The differences in the mean absolute change in non-inflammatory lesion counts were statistically significant in the comparisons required to establish efficacy, IDP-110 compared to vehicle in both studies (p-values$<$0.001). Within each study, the efficacy results were relatively consistent across subgroups and investigative sites. However, most of the overall treatment effect was observed in the White subjects. Also, the success rate was higher in subjects with 'Severe' baseline disease severity. In Study 012, the success rates based on EGSS and mean absolute change in lesion count were marginally higher in the BPO arm than the IDP-110 in subjects with baseline EGSS of 'Severe' (4). However, this result was not replicated in Study 017.

## 2 Introduction

### 2.1 Overview

IDP-110 (clindamycin 1% and benzoyl peroxide 2.5%) is a combination product intended to treat moderate to severe acne vulgaris. Currently approved clindamycin and benzoyl peroxide combination products for acne vulgaris are BenzaClin® Topical Gel and Duac™ Topical Gel. Both products combine clindamycin 1% with benzoyl peroxide 5%. According to the sponsor, these products are effective, but may be irritating to the skin due to the concentration of

benzoyl peroxide. The sponsor's intention of developing IDP-110 was to provide an efficacious treatment for acne with a lower concentration of benzoyl peroxide to lessen skin irritation than other clindamycin/benzoyl peroxide products.

The sponsor met with the Division for an End of Phase 2 (EOP 2) meeting on September 19, 2006. At this meeting, the Division requested that the sponsor seek a broader indication in "acne vulgaris" (b) (4) . Also, agreement on primary efficacy endpoints was reached after reviewing the sponsor's phase 2 study results and extensive discussion. The following in italic is an excerpt from the EOP 2 meeting minutes.

> *Success will be demonstrated if (i) the sponsor's combination product is superior to vehicle in inflammatory and non-inflammatory lesion counts and the global severity score; and (ii) the sponsor's combination product demonstrates superiority to both monads in global severity score and inflammatory counts. Non-inflammatory lesion counts will be assessed for each of the arms, however, the dyad will not have to demonstrate superiority over the monads for this endpoint.*

Other essential comments conveyed at this meeting regarding the Statistical Analysis Plan (SAP) were (i) the Evaluator's Global Severity Score (EGSS) should be on a 5-grade scale instead of a 6-grade scale; (ii) stratification should be limited to factors that are expected to be highly correlated to the efficacy result; and (iii) stratification factors should be included in the analysis model.

Through the EOP 2 meeting and consequent communications, the sponsor and the Division came to an agreement on endpoints and most aspects of the study design. It should be noted that the sponsor assessed EGSS on a 6-grade scale instead of the Division's recommended 5-grade scale. The 6 grades were 'Clear', 'Almost Clear', 'Mild', 'Moderate', 'Severe', and 'Very Severe'. Table 3 presents the clinical studies (Study 012 and Study 017) on which the sponsor's efficacy claims are based, and the number of subjects enrolled in each of these studies. This review includes thorough evaluation of the efficacy and safety of IDP-110 in the clinical studies listed below.

Table 3: Overview of Pivotal Clinical Studies

| Study | Study Period | Enrollment | | | | |
|---|---|---|---|---|---|---|
| | | IDP-110 | Clindamycin 1% | Benzoyl Peroxide 2.5% | Vehicle | Total |
| 012 | 10/04/06 – 8/21/07 | 399 | 408 | 406 | 201 | 1414 |
| 017 | 10/05/06 – 8/13/07 | 398 | 404 | 403 | 194 | 1399 |

## 2.2 Data Sources

This reviewer evaluated the sponsor's clinical study reports and clinical summaries, as well as the proposed labeling. This submission was submitted in eCTD format and was entirely electronic. The data sets used in this review are archived at \\Cdsesub1\evsprod\NDA050819\0000 \m5\53-clin-stud-rep\535-rep-effic-safety-stud\acne-vulagris\5351-stud-rep-contr\study-report-dpsi-06-22-2006-012\datasets and \\Cdsesub1\evsprod\NDA050819\0000 \m5\53-clin-stud-rep\535-rep-effic-safety-stud\acne-vulagris\5351-stud-rep-contr\study-report-dpsi-06-22-2006-017\datasets.

# 3 Statistical Evaluation

## 3.1 Evaluation of Efficacy

### 3.1.1 Study Design

To evaluate the efficacy and safety of IDP-110 in the treatment of moderate to severe acne, the sponsor submitted results from two phase 3 trials (Study 012 and Study 017). Studies 012 and 017 were conducted under identical protocols, which was evaluated by the Division in September, 2006. Both studies were designed as multicenter, randomized, double-blind, 4-arm, vehicle-controlled trials. The protocol planned to enroll approximately 1400 subjects from 32 sites in each study. The actual enrollment was 1414 and 1399 subjects in Studies 012 and 017, respectively. Study 012 enrolled 33 investigative sites from the US, one from Canada, and one from Central America (Belize). Study 017 enrolled 33 investigative sites, all from the US. Subjects enrolled in this study were to be between the ages of 12 and 70, with moderate to severe acne vulgaris based on EGSS scale (a score of 3 (moderate) or 4 (severe)), 17 - 40 inflammatory lesions (papules, pustules, and nodules), 20 - 100 non-inflammatory lesions (open and closed comedones), and $\leq 2$ nodules on the face at baseline.

Subjects were stratified by skin phototype based on the Fitzpatrick scale (phototypes I, II, and III vs. phototypes IV, V, and VI) and baseline disease severity based on the EGSS (EGSS of 3 vs. 4). Treatment was randomized using permuted blocks within each of the four stratum. The enrolled subjects were randomly assigned in a 2:2:2:1 ratio to receive one of the following 4 treatments: IDP-110; clindamycin, 1% gel; benzoyl peroxide (BPO), 2.5% gel; and IDP-110 vehicle. The actual randomization of Study 012 resulted in 399, 408, 406, and 206 subjects in IDP-110, clindamycin, BPO, and vehicle arms, respectively and that of Study 017 resulted in 398, 404, 403 and 194 subjects for those arms.

The protocol indicated that efficacy would be demonstrated if

- the combination test product IDP-110 was superior to vehicle for

  - mean absolute change from baseline at Week 12 in
    - inflammatory lesion count
    - non-inflammatory lesion count
  - dichotomized Evaluator's Global Severity Score (EGSS) at Week 12; and if

- the combination test product IDP-110 was superior to the monads, clindamycin and BPO, at Week 12 for
  - mean absolute change from baseline at Week 12 in inflammatory lesion count
  - dichotomized EGSS.

The protocol included analyses for percent change in the inflammatory and non-inflammatory lesions as supportive analyses. Also, comparison of IDP-110 to each monad in mean absolute change in non-inflammatory lesion count was included as supportive analysis. It should be noted that the sponsor proposed to analyze the absolute change from baseline to Week 12 using a visual analogue scale (VAS), completed by the evaluators. The Division conveyed to the sponsor at the Guidance meeting, dated June 27, 2006 that the VAS would have limited regulatory utility. Therefore, this review does not include analysis of the VAS. Inflammatory lesions included pustules, papules, and nodules, whereas non-inflammatory lesions included open and closed comedones. Success based on the EGSS was defined as at least a two grade improvement at Week 12 compared to baseline. The 6-grade EGSS scale is defined as the following.

| **Score** | **Grade** | **Description** |
|---|---|---|
| 0 | Clear | Normal, clear skin with no evidence of acne vulgaris |
| 1 | Almost Clear | Rare non-inflammatory lesions present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red) |
| 2 | Mild | Some non-inflammatory lesions are present, with few inflammatory lesions (papules/pustules only; no nodulocystic lesions) |
| 3 | Moderate | Non-inflammatory lesions predominate, with multiple inflammatory lesions evident; several to many comedones and papules/pustules, and there may or may not be one small nodulocystic lesion |
| 4 | Severe | Inflammatory lesions are more apparent, many comedones and papules/pustules, there may or may not be a few nodulocystic lesions |
| 5 | Very Severe | Highly inflammatory lesions predominate, variable number of comedones, many papules/pustles and many nodulocystic lesions |

The protocol defined the intent-to-treat (ITT) population as all subjects who were enrolled and assigned to a treatment regimen. The per-protocol (PP) population was defined as all subjects who completed the 12-week evaluation without noteworthy study protocol violations. The following were reasons for exclusion from the PP population.

- Did not attend the Week 12 visit, with the exception of a discontinuation from the study due to an adverse event related to study treatment or documented lack of treatment effect;

- Missed more than 1 study visit (excluding the Week 12 visit);
- Missed more than five consecutive days of dosing and did not apply 80-120% of the expected doses;
- Week 12 visit was outside the visit window of -3/+5 days.

The analysis methods proposed in the protocol are the following. Unless stated otherwise, the analysis methods proposed in the protocol were used in the submission and this review.

- Analysis for the absolute change and percent change from Baseline in inflammatory and non-inflammatory lesions analyzed using an Analysis of Covariance (ANCOVA) model with factors of treatment and analysis center and the respective baseline lesion count, dichotomized skin type (I, II, III, vs. IV, V, VI), and baseline severity as covariates. In the case that the treatment by center interaction term was statistically significant, this interaction term was included in the model.
- The protocol stated the Cochran-Mantel-Haenszel test, stratified by analysis center as the primary analysis for the EGSS in the protocol. The Division conveyed to the sponsor via comments that were faxed on April 26, 2007 that the primary analysis model should include all stratification factors. In this submission, a logistic regression with factors of treatment and analysis center and the stratification factors of dichotomized skin type (I, II, III, vs. IV, V, VI) and baseline severity was used as the primary analysis for the EGSS. EGSS was analyzed using logistic regression also in this review.
- Missing observations were imputed using last observation carried forward (LOCF). To ensure that efficacy results were not driven by the imputation method, sensitivity analyses were conducted on the primary endpoints. Missing observations were imputed as the following in the sensitivity analyses.
  - EGSS:
    - All missing values were imputed as failures.
    - All missing values were imputed as successes.
  - Lesion counts:
    - All missing values were imputed as the mean absolute change in lesion counts for the respective treatment group.
    - Subjects who were missing Week 12 evaluation were excluded from the analysis.
- Investigative sites that did not have a minimum of 8 subjects in each active treatment arm were pooled with other investigative sites and were referred to as “analysis centers”. The site with the smallest enrollment was combined with the largest sites. If there was a

further need to combine data, the data from the investigative site with the second largest enrollment was combined. Investigative sites were pooled into 28 sites in both studies.

### 3.1.2 Subject Disposition

Study 012 enrolled 1414 subjects who met the inclusion criteria and randomized 399 subjects to IDP-110, 408 subjects to clindamycin, 406 subjects to BPO, and 201 to vehicle, at 35 investigative sites. Study 017 enrolled 1399 subjects and randomized 398 subjects to IDP-110, 404 subjects to clindamycin, 403 subjects to BPO, and 194 to vehicle, at 32 investigative sites. The number of subjects who discontinued the study was 194 (13.7%) in Study 012 and 127 (9.1%) in Study 017. Table 4 presents the reasons for discontinuation by treatment arm.

The proportion of subjects who discontinued was largest in the vehicle arm and smallest in the IDP-110 arm in both studies. The most common reason for discontinuation was due to lost to follow up in all four arms in both studies. The second common reason was discontinuation at the subject's request. A larger proportion of subjects in the vehicle arm requested to discontinue the study than any other arm, whereas that proportion was lowest in the IDP-110 arm.

### 3.1.3 Baseline and Demographic Data

Baseline demographic variables and disease severity were generally balanced across treatment arms. The details can be found in Appendix A.1.

### 3.1.4 Primary Efficacy Endpoints

#### 3.1.4.1 ITT Analyses

The protocol indicated that efficacy of IDP-110 would be demonstrated if

- the combination test product IDP-110 was superior to vehicle for
  - mean absolute change from baseline at Week 12 in
    - inflammatory lesion count
    - non-inflammatory lesion count
  - dichotomized Evaluator's Global Severity Score (EGSS) at Week 12; and if
- the combination test product IDP-110 was superior to the monads, clindamycin and BPO, at Week 12 for
  - absolute change from baseline in inflammatory lesion count
  - dichotomized EGSS.

Table 4: Number (%) of Subjects Who Discontinue the Study: Classified by the Reason for Discontinuation (ITT)

| | Study 012 | | | |
|---|---|---|---|---|
| | IDP-110 n=399 | Clindamycin n=408 | BPO n=406 | Vehicle n=201 |
| **Subjects who discontinued** | **42 (10.5%)** | **55 (13.5%)** | **63 (15.5%)** | **34 (16.9%)** |
| *Reason* | | | | |
| Adverse event | 1 (<1%) | 3 (1%) | 6 (1.5%) | 0 (0%) |
| Subject request | 13 (3.3%) | 16 (3.9%) | 16 (3.9%) | 12 (6.0%) |
| Protocol violation | 5 (1.3%) | 0 (0%) | 2 (<1%) | 2 (1.0%) |
| Lost to follow-up | 20 (5.0%) | 29 (7.1%) | 33 (8.1%) | 16 (8.0%) |
| Pregnancy | 0 (0%) | 1 (<1%) | 0 (0%) | 0 (0%) |
| Lack of efficacy | 1 (<1%) | 2 (<1%) | 4 (1%) | 1 (<1%) |
| Other | 2 (1.0%) | 7 (1.7%) | 2 (<1%) | 3 (1.5%) |

| | Study 017 | | | |
|---|---|---|---|---|
| | IDP-110 n=398 | Clindamycin n=404 | BPO n=403 | Vehicle n=194 |
| **Subjects who discontinued** | **31 (7.8%)** | **33 (8.2%)** | **35 (8.7%)** | **28 (14.3%)** |
| *Reason* | | | | |
| Adverse event | 6 (1.5%) | 1 (<1%) | 2 (<1%) | 2 (1.0%) |
| Subject request | 6 (1.5%) | 11 (2.7%) | 15 (3.7%) | 12 (6.2%) |
| Protocol violation | 2 (1.0%) | 0 (0%) | 0 (0%) | 1 (1.0%) |
| Lost to follow-up | 12 (3.0%) | 20 (5.0%) | 16 (4.0%) | 11 (5.7%) |
| Pregnancy | 2 (1.0%) | 0 (0%) | 0 (0%) | 1 (1%) |
| Lack of efficacy | 2 (1.0%) | 1 (<1%) | 0 (0%) | 1 (1.0%) |
| Other | 1 (<1%) | 0 (0%) | 1 (<1%) | 1 (1.0%) |

Source: Study Report DPSI-06-22-2006-012, pg. 115; Study Report DPSI-06-22-2006-017, pg. 115 and Reviewer analysis.

Table 5 presents this reviewer's results of the EGSS analysis. Approximately 33% of the IDP-110 arm subjects had a two grade improvement from baseline at Week 12 in Study 012. At the same time point in the same study, the success rate in both monad arms was approximately 24%, where the vehicle's success rate was approximately 19%. The success rates were approximately 37% in the IDP-110 arm, 28% in both monads, and 14% in the vehicle arm in Study 017. Based on the EGSS score, the differences in the success rates of IDP-110 compared to each monad and vehicle were statistically significant with p-values less than 0.01 in both studies.

Table 5: Primary Efficacy Results - Number (%) of Successes on EGSS at Week 12 (ITT)

| | Study 012 | | | |
|---|---|---|---|---|
| | IDP-110 n=399 | Clindamycin n=408 | BPO n=406 | Vehicle n=201 |
| Number of successes (%) | 131 (32.8%) | 100 (24.5%) | 96 (23.6%) | 38 (18.9%) |
| p-value† | NA | 0.002 | 0.001 | <0.0001 |

| | Study 017 | | | |
|---|---|---|---|---|
| | IDP-110 n=398 | Clindamycin n=404 | BPO n=403 | Vehicle n=194 |
| Number of successes (%) | 147 (36.9%) | 114 (28.2%) | 114 (28.3%) | 27 (13.9%) |
| p-value† | NA | 0.009 | 0.009 | <0.0001 |

† P-values were calculated using logistic regression with treatment, analysis center, dichotomized skin type, and baseline severity as factors.

Missing values were imputed using LOCF

Source: Study Report DPSI-06-22-2006-012, pg. 67; Study Report DPSI-06-22-2006-017, pg. 65; and reviewer analysis.

Tables 6 presents this reviewer's results of the mean absolute change from baseline in inflammatory and non-inflammatory lesion count at Week 12. The mean absolute change in inflammatory lesion count was approximately 15 in the IDP-110 arm, 12 and 13 in the clindamycin and BPO arms, and 9 in the vehicle arm in Study 012. In Study 017, the mean absolute change was approximately 14 in the IDP-110 arm, 11 in both monad arms, and 6 in the vehicle arm. The differences in mean absolute change from baseline at Week 12 of IDP-110 compared to each monads and vehicle were statistically significant with p-values less than 0.012 in both studies.

The mean absolute change in non-inflammatory lesion count was approximately 22 in the IDP-110 arm, 18 and 21 in the clindamycin and BPO arms, and 13 in the vehicle arm in Study 012. In Study 017, the mean absolute change was approximately 19 in the IDP-110 arm, 15 in both monad arms, and 8 in the vehicle arm. The differences in mean absolute change from baseline at Week 12 of IDP-110 compared to clindamycin and vehicle were statistically significant with p-values less than 0.007 in both studies. The difference of IDP-110 compared to BPO was not statistically significant with a p-value of 0.134 in Study 012. It should be noted that statistical significance in non-inflammatory lesion count of IDP-110 compared to each monad was not required to establish efficacy of IDP-110.

Table 6: Primary Efficacy Results - Mean Absolute Change in Lesion Counts at Week 12 (ITT)

| | Study 012 | | | |
|---|---|---|---|---|
| | IDP-110 n=399 | Clindamycin n=408 | BPO n=406 | Vehicle n=201 |
| **Inflammatory lesions** | | | | |
| Mean absolute change (sd) | 14.8 (10.8) | 12.2 (11.6) | 13.0 (10.4) | 9.0 (11.9) |
| p-value† | NA | <0.001 | 0.012 | <0.001 |
| **Non-inflammatory lesions** | | | | |
| Mean absolute change (sd) | 22.1 (21.2) | 17.9 (19.9) | 20.6 (22.0) | 13.2 (20.4) |
| p-value† | NA | 0.005 | 0.134 | <0.001 |

| | Study 017 | | | |
|---|---|---|---|---|
| | IDP-110 n=398 | Clindamycin n=404 | BPO n=403 | Vehicle n=194 |
| **Inflammatory lesions** | | | | |
| Mean absolute change (sd) | 13.7 (10.5) | 11.3 (11.7) | 11.2 (10.6) | 5.7 (12.6) |
| p-value† | NA | 0.003 | 0.001 | <0.001 |
| **Non-inflammatory lesions** | | | | |
| Mean absolute change (sd) | 19.0 (19.9) | 14.9 (18.8) | 15.2 (19.0) | 8.3 (19.8) |
| p-value† | NA | 0.007 | 0.016 | <0.001 |

† P-values were calculated using ANCOVA with the baseline inflammatory count as covariate and treatment, analysis center, dichotomized skin type, and baseline severity as factors. Each arm was tested against IDP-110.

Missing values were imputed using LOCF.

Source: Reviewer analysis.

The protocol indicated that in the case of non-normality of the ANCOVA residuals, an ANCOVA analysis on the ranked inflammatory and non-inflammatory lesion count would be conducted. Normality was tested using Shapiro-Wilks test on inflammatory and non-inflammatory lesion count. The p-value of these tests were less than 0.001 and the residuals from the models were determined to be non-normal. Table 7 presents the p-values from the ranked ANCOVA analysis. The results from the ranked ANCOVA analysis were similar to that of the un-ranked ANCOVA analysis.

Table 7: P-values from the Ranked ANCOVA of Mean Absolute Change in Lesion Counts at Week 12

| | Study 012 | | | Study 017 | | |
|---|---|---|---|---|---|---|
| | Clindamycin n=408 | BPO n=406 | Vehicle n=201 | Clindamycin n=404 | BPO n=403 | Vehicle n=194 |
| Inflammatory | <0.001 | 0.002 | <0.001 | <0.001 | <0.001 | <0.001 |
| Non-inflammatory | 0.005 | 0.091 | <0.001 | 0.024 | 0.008 | <0.001 |

P-values were calculated using ranked ANCOVA with the baseline inflammatory count as covariate and treatment, analysis center, dichotomized skin type, and baseline severity as factors. Each arm was tested against IDP-110.

The number of subjects in IDP-110 arms was 399 and 398 in Studies 012 and 017, respectively.

Missing values were imputed using LOCF.

Source: Reviewer analysis.

#### 3.1.4.2 Sensitivity Analysis of the Primary Efficacy Endpoint

Per protocol, last observation carried forward (LOCF) was used to impute missing data in the primary analyses (previous section). The detailed numbers and proportions of missing observations in each treatment arm over time is provided in Appendix A.2.

The protocol defined sensitivity analyses regarding missing data imputation is the following:

- EGSS:
  - All missing values as failures;
  - All missing values as successes;
- Lesion count:
  - All missing value as the mean absolute change in lesion counts for the respective treatment group;
  - Exclude subjects with missing Week 12 evaluation.

Table 8 presents the efficacy results when missing observations were imputed as either all successes or as all failures. In Study 012, the differences in proportion of successes based on EGSS was not statistically significant at the 0.05 level when all missing observations were imputed as successes. The p-values from the comparisons of IDP-110 to clindamycin, BPO and vehicle were 0.113, 0.136, and 0.067, respectively. The proportion of missing observations at Week 12 was 9.5% in the IDP-110 arm, compared to 13.5%, 14.5% and 17.4% in the clindamycin, BPO and vehicle arms, respectively. Since the proportion of missing observations imputed as successes

was largest in the vehicle arm and smallest in the IDP-110 arm, this imputation method yields a smaller treatment effect. Consequently, this approach is very conservative. In Study 017, the differences in proportion of successes based on EGSS in IDP-110 compared to the monads and vehicle were statistically significant regardless of the missing observations imputation method.

Table 8: Sensitivity Analyses - Number (%) of Successes on EGSS at Week 12 (Missing Observations Imputed as All Successes or All Failures)

| | Study 012 | | | |
|---|---|---|---|---|
| | IDP-110 n=399 | Clindamycin n=408 | BPO n=406 | Vehicle n=201 |
| **Number of imputed subjects** | 38 (9.5%) | 55 (13.5%) | 59 (14.5%) | 35 (17.4%) |
| Number of successes (%)[§] | 169 (42.4%) | 154 (37.7%) | 152 (37.4%) | 72 (35.8%) |
| p-value[†] | NA | 0.113 | 0.136 | 0.067 |
| Number of successes (%)[§§] | 131 (32.8%) | 99 (24.3%) | 93 (22.9%) | 37 (18.4%) |
| p-value[†] | NA | 0.002 | 0.001 | <0.001 |

| | Study 017 | | | |
|---|---|---|---|---|
| | IDP-110 n=398 | Clindamycin n=404 | BPO n=403 | Vehicle n=194 |
| **Number of imputed subjects** | 30 (7.5%) | 32 (7.9%) | 36 (8.9%) | 28 (17.4%) |
| Number of successes (%)[§] | 174 (43.7%) | 144 (35.6%) | 148 (36.7%) | 55 (28.4%) |
| p-value[†] | NA | 0.024 | 0.047 | <0.001 |
| Number of successes (%)[§§] | 144 (36.2%) | 112 (27.7%) | 112 (27.7%) | 27 (13.9%) |
| p-value[†] | NA | 0.011 | 0.011 | <0.001 |

[†] P-values were calculated using logistic regression with treatment, analysis center, dichotomized skin type, and baseline severity as factors.

[§] All missing values were imputed as successes

[§§] All missing values were imputed as failures

Source: Study Report DPSI-06-22-2006-012, pg. 74; Study Report DPSI-06-22-2006-017, pg. 72; and reviewer analysis.

Table 9 presents the efficacy results based on the absolute change in lesion counts from baseline at Week 12 when missing observations were imputed as the mean of the respective treatment group. This imputation method implies that drop-outs are missing at random, which is generally not the case. The results using this imputation method was similar to that of the primary efficacy analysis. All endpoints required to show statistical significance to establish efficacy had p-values less than 0.05.

Table 9: Sensitivity Analyses - Mean Absolute Change in Lesion Count (Mean Imputation)

| | Study 012 | | | |
|---|---|---|---|---|
| | IDP-110 n=399 | Clindamycin n=408 | BPO n=406 | Vehicle n=201 |
| **Number of imputed subjects** | 38 (9.5%) | 55 (13.5%) | 59 (14.5%) | 35 (17.4%) |
| **Inflammatory lesions** | | | | |
| Mean absolute change | 16.0 (9.5) | 13.4 (10.8) | 14.5 (9.4) | 10.8 (10.9) |
| p-value† | NA | <0.001 | 0.016 | <0.001 |
| **Non-inflammatory lesions** | | | | |
| Mean absolute change | 23.8 (21.7) | 20.1 (19.8) | 23.7 (21.9) | 15.4 (21.1) |
| p-value† | NA | 0.025 | 0.670 | <0.001 |

| | Study 017 | | | |
|---|---|---|---|---|
| | IDP-110 n=398 | Clindamycin n=404 | BPO n=403 | Vehicle n=194 |
| **Number of imputed subjects** | 30 (7.5%) | 32 (7.9%) | 36 (8.9%) | 28 (14.4%) |
| **Inflammatory lesions** | | | | |
| Mean absolute change | 14.5 (10.1) | 12.2 (10.6) | 12.2 (10.0) | 6.9 (12.0) |
| p-value† | NA | 0.001 | 0.002 | <0.001 |
| **Non-inflammatory lesions** | | | | |
| Mean absolute change | 19.5 (20.2) | 15.7 (18.8) | 16.5 (19.4) | 10.2 (19.3) |
| p-value† | NA | 0.015 | 0.085 | <0.001 |

† P-values were calculated using ANCOVA with the respective baseline lesion count as covariate and treatment, analysis center, dichotomized skin type, and baseline severity as factors. Each arm was tested against IDP-110.

Missing values were imputed as the mean absolute change in lesion counts for the respective treatment group.

Source: Reviewer analysis.

Table 10 presents the efficacy results based on the absolute change in lesion counts from baseline at Week 12 when subjects with missing Week 12 assessments were excluded from the analysis. The results when excluding subjects with missing Week 12 assessment were also similar to that of the primary efficacy analysis. All endpoints required to show statistical significance to establish efficacy had p-values less than 0.05. The sensitivity analysis results suggest that the efficacy results were not due to the missing data imputation method used.

Table 10: Sensitivity Analyses - Mean Absolute Change in Lesion Count (Subjects with Week 12 Assessment)

| | Study 012 | | | |
|---|---|---|---|---|
| | IDP-110 n=361 | Clindamycin n=353 | BPO n=347 | Vehicle n=167 |
| **Inflammatory lesions** | | | | |
| Mean absolute change | 16.0 (9.7) | 13.5 (11.3) | 14.5 (9.8) | 10.9 (11.5) |
| p-value† | NA | 0.002 | 0.022 | <0.001 |
| **Non-inflammatory lesions** | | | | |
| Mean absolute change | 23.6 (21.4) | 20.1 (19.6) | 23.5 (21.9) | 15.1 (21.1) |
| p-value† | NA | 0.025 | 0.693 | <0.001 |

| | Study 017 | | | |
|---|---|---|---|---|
| | IDP-110 n=368 | Clindamycin n=372 | BPO n=367 | Vehicle n=166 |
| **Inflammatory lesions** | | | | |
| Mean absolute change | 14.5 (10.3) | 12.3 (10.9) | 12.1 (10.2) | 6.5 (12.6) |
| p-value† | NA | 0.008 | 0.005 | <0.001 |
| **Non-inflammatory lesions** | | | | |
| Mean absolute change | 19.8 (20.1) | 15.8 (18.9) | 16.2 (19.3) | 10.0 (19.3) |
| p-value† | NA | 0.015 | 0.052 | <0.001 |

† P-values were calculated using ANCOVA with the respective baseline lesion count as covariate and treatment, analysis center, dichotomized skin type, and baseline severity as factors. Each arm was tested against IDP-110.

Subjects who did not have the Week 12 assessment were excluded from the analysis.

Source: Reviewer analysis.

#### 3.1.4.3 Per Protocol Analysis

The per protocol (PP) population included subjects who completed the Week 12 evaluation, who did not miss more than 1 study visit, applied 80-120% of expected doses and did not miss more than five consecutive days of dosing. A total of 467 subjects were excluded from the PP

population, 281 (19.9%) and 186 (13.3%) subjects in Studies 012 and 017, respectively. Table 11 presents the efficacy results based on the proportion of successes on EGSS at Week 12 in the PP population. The proportion of successes based on EGSS was higher in the PP population than the ITT population for all arms in both studies. The treatment effect in the PP population, when IDP-110 was compared to vehicle, was similar to that of the ITT population. These results supports the superiority of IDP-110 over its monads and vehicle.

Table 11: Per Protocol - Number (%) of Successes on EGSS at Week 12

| | Study 012 | | | |
|---|---|---|---|---|
| | IDP-110 n=330 | Clindamycin n=329 | BPO n=325 | Vehicle n=149 |
| Number of successes (%) | 119 (36.1%) | 93 (28.3%) | 89 (27.4%) | 32 (21.5%) |
| p-value† | NA | 0.008 | 0.007 | <0.001 |

| | Study 017 | | | |
|---|---|---|---|---|
| | IDP-110 n=353 | Clindamycin n=352 | BPO n=348 | Vehicle n=160 |
| Number of successes (%) | 137 (38.8%) | 106 (30.1%) | 107 (30.7%) | 27 (16.9%) |
| p-value† | NA | 0.013 | 0.011 | <0.001 |

† P-values were calculated using logistic regression with treatment, analysis center, dichotomized skin type, and baseline severity as factors.

Source: Reviewer analysis.

Table 12 presents the mean absolute change from baseline in inflammatory and non-inflammatory lesion count at Week 12 in the PP population. Similar to the PP population EGSS results, the mean absolute changes in the inflammatory and non-inflammatory lesion counts in the PP population were greater than that of the ITT population in all arms and in both studies. The p-value from the comparison of IDP-110 to BPO in Study 012 was 0.083 and no longer statistically significant at the 0.05 level. In the ITT population analysis, the treatment effect of IDP-110 to BPO in mean absolute change was 1.8, IDP-110 14.8 and BPO 13.0 and the p-value was 0.012. In the PP population, the same treatment effect was 1.2, with a p-value of 0.083. Analysis on this population not being powered to detect statistical significance. Therefore, it is difficult to draw statistical inference from this analysis.

Table 12: Per Protocol - Mean Absolute Change in Lesion Count

| | Study 012 | | | |
|---|---|---|---|---|
| | IDP-110 n=330 | Clindamycin n=329 | BPO n=325 | Vehicle n=149 |
| **Inflammatory lesions** | | | | |
| Mean absolute change | 15.9 (9.9) | 13.5 (10.9) | 14.7 (9.8) | 11.0 (11.6) |
| p-value† | NA | 0.001 | 0.083 | <0.001 |
| **Non-inflammatory lesions** | | | | |
| Mean absolute change | 23.5 (21.0) | 19.7 (20.2) | 23.6 (22.4) | 15.4 (21.1) |
| p-value† | NA | 0.012 | 0.650 | <0.001 |

| | Study 017 | | | |
|---|---|---|---|---|
| | IDP-110 n=353 | Clindamycin n=352 | BPO n=348 | Vehicle n=160 |
| **Inflammatory lesions** | | | | |
| Mean absolute change | 14.3 (10.5) | 11.9 (11.6) | 12.2 (10.2) | 6.3 (12.6) |
| p-value† | NA | 0.008 | 0.008 | <0.001 |
| **Non-inflammatory lesions** | | | | |
| Mean absolute change | 20.0 (20.1) | 15.8 (19.0) | 16.1 (18.9) | 9.6 (20.2) |
| p-value† | NA | 0.022 | 0.053 | <0.001 |

† P-values were calculated using ANCOVA with the respective baseline lesion count as covariate and treatment, analysis center, dichotomized skin type, and baseline severity as factors. Each arm was tested against IDP-110.

Source: Reviewer analysis.

### 3.1.5 Secondary Efficacy Endpoints

The protocol defined analyses of percent change in the inflammatory and non-inflammatory lesion count as supportive. The sponsor also proposed to analyze the absolute change from baseline to Week 12 using a visual analogue scale (VAS), completed by evaluators. Since the Division conveyed to the sponsor that the VAS would have limited regulatory utility, this review does not include analysis of the VAS. Table 13 presents the results of the mean percent change in lesion counts analysis. The differences in lesion count percent change were all statistically significant in both lesion types with p-values less than 0.037 in both studies.

Table 13: Secondary Endpoint Analysis - Mean Percent Change in Lesion Count

| | Study 012 | | | |
|---|---|---|---|---|
| | IDP-110 n=399 | Clindamycin n=408 | BPO n=406 | Vehicle n=201 |
| **Inflammatory lesions** | | | | |
| Mean percent change | 55.0% (39.9%) | 47.1% (39.1%) | 49.3% (36.5%) | 34.5% (43.8%) |
| p-value† | NA | 0.001 | 0.013 | <0.001 |
| **Non-inflammatory lesions** | | | | |
| Mean absolute change | 45.3% (38.8%) | 38.0% (37.3%) | 40.2% (37.9%) | 43.8% (41.7%) |
| p-value† | NA | 0.002 | 0.037 | <0.001 |

| | Study 017 | | | |
|---|---|---|---|---|
| | IDP-110 n=398 | Clindamycin n=404 | BPO n=403 | Vehicle n=194 |
| **Inflammatory lesions** | | | | |
| Mean absolute change | 54.2% (39.1%) | 45.3% (44.0%) | 45.7% (43.8%) | 23.3% (52.2%) |
| p-value† | NA | 0.002 | 0.002 | <0.001 |
| **Non-inflammatory lesions** | | | | |
| Mean absolute change | 41.2% (37.8%) | 34.3% (41.4%) | 34.5% (42.0%) | 19.2% (44.6%) |
| p-value† | NA | 0.013 | 0.019 | <0.001 |

† P-values were calculated using ANCOVA with the respective baseline lesion count as covariate and treatment, analysis center, dichotomized skin type, and baseline severity as factors. Each arm was tested against IDP-110.

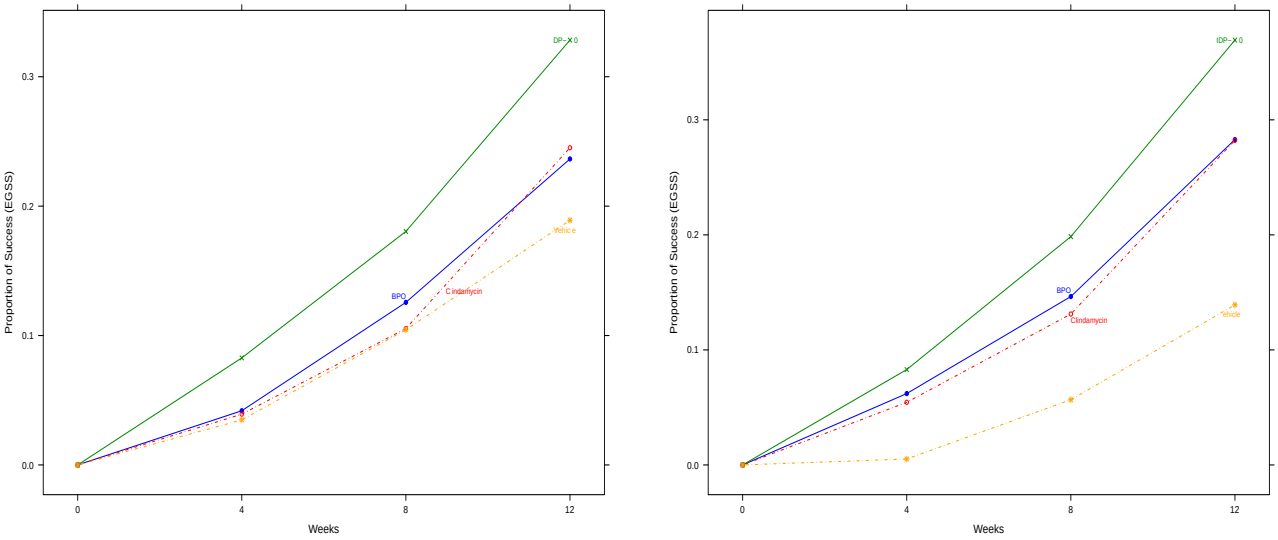
Missing values were imputed using LOCF.

Source: Study Report DPSI-06-22-2006-012, pg. 194-195; Study Report DPSI-06-22-2006-017, pg. 193-194; and Reviewer analysis.

### 3.1.6 Efficacy Results over Time

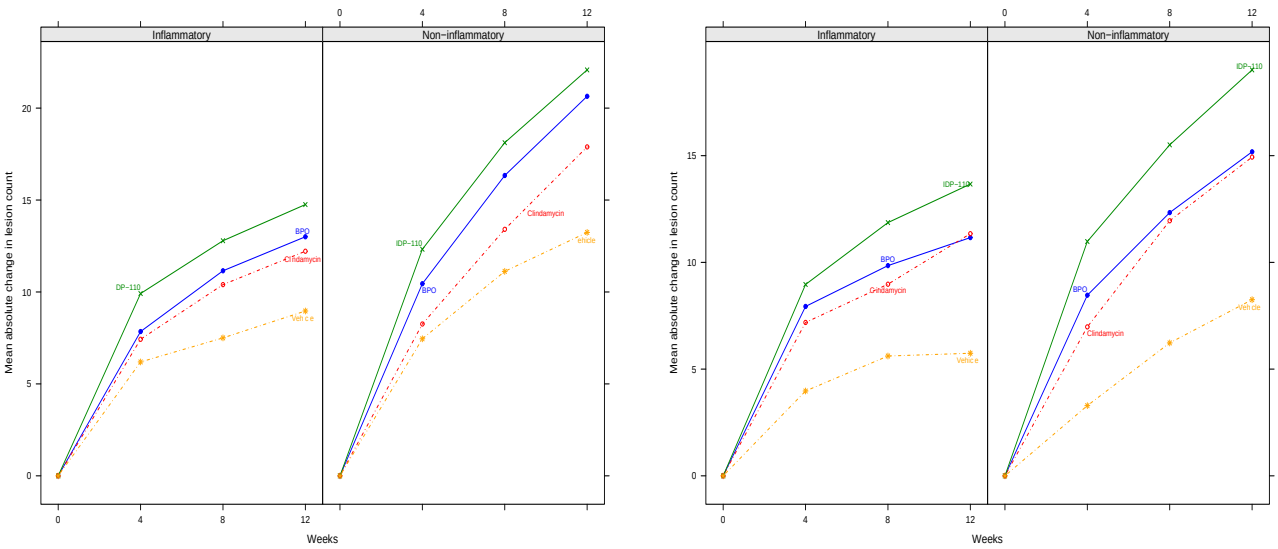
Subjects were treated for 12 weeks. Subjects' EGSS and lesion count were evaluated at baseline, Weeks 4, 8 and 12. Figure 1 and 2 present the success rates based on EGSS scores and mean absolute change in inflammatory and non-inflammatory lesion count over time. The efficacy of IDP-110 increased over time.

Figure 1: EGSS Over Time




(a) Study 012 (b) Study 017

Figure 2: Mean Absolute Change in Lesion Counts Over Time




(a) Study 012 (b) Study 017

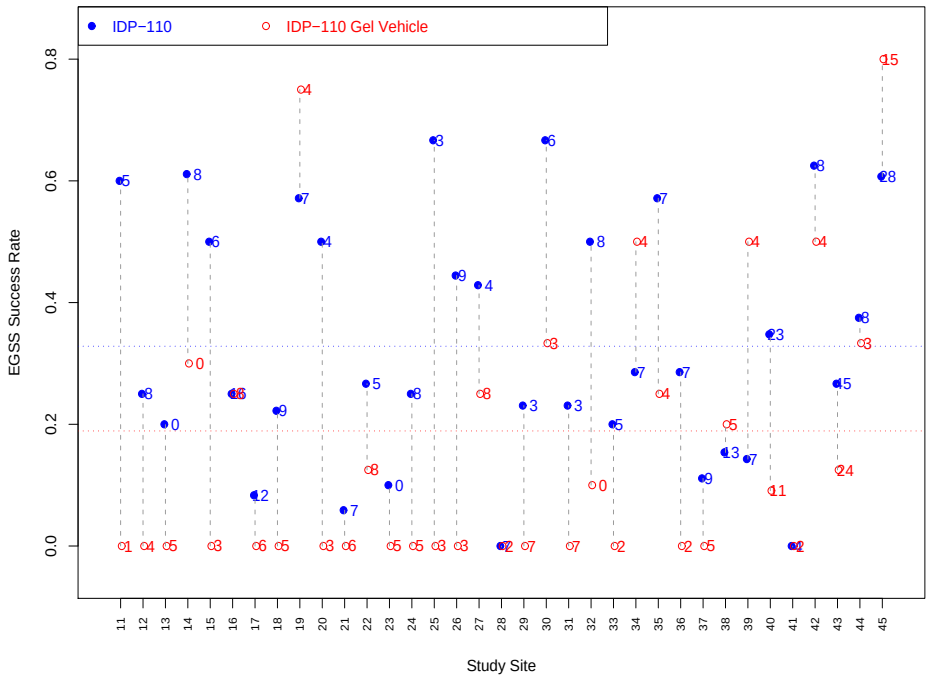
### 3.1.7 Efficacy Results by Center

Study 012 enrolled subjects from a total of 35 investigative sites, 33 from the US, 1 from Canada, and 1 from Central America (Belize). Study 017 enrolled subjects from 33 investigative sites, all from the US. The maximum number of enrollment by one site was 162 (11.4% of the total number of subjects) and 92 (6.5%) in Studies 012 and 017, respectively. In both studies, investigative sites were pooled into 28 pooled centers.

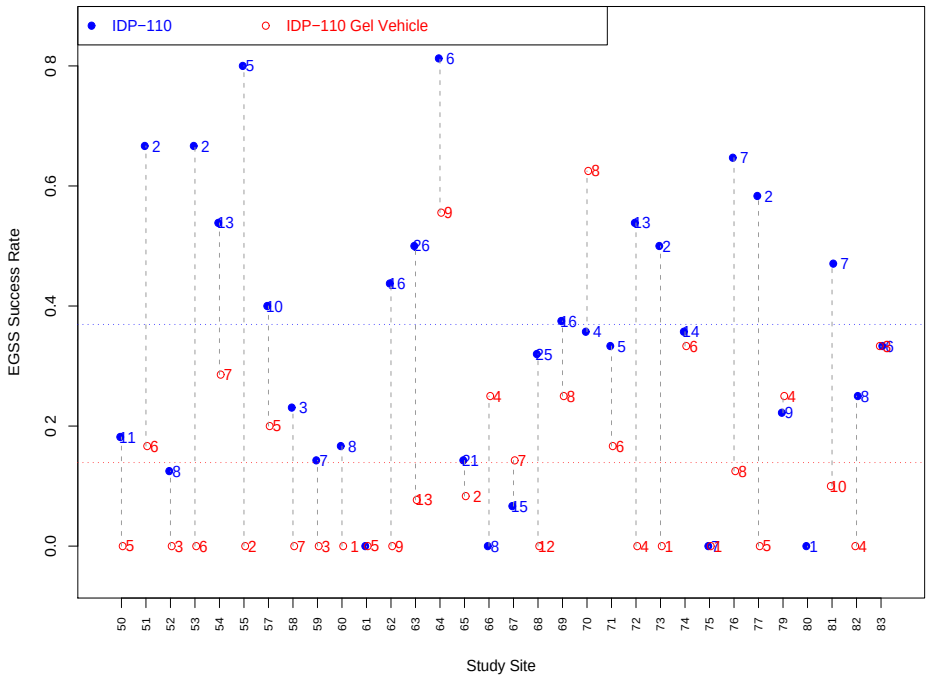
Figure 3 presents the success rate based on EGSS and number of subjects enrolled by each investigative site in the IDP-110 and vehicle arms. The treatment effect appeared to be relatively consistent across the pooled sites, and therefore the results do not seem to be driven by extreme sites.

Figure 4 and 5 present the mean absolute change in inflammatory and non-inflammatory lesion counts at Week 12 from baseline by site in the IDP-110 and vehicle arms. The treatment effect on both lesion types appeared to be consistent across the investigative sites. The results do not seem to be driven by extreme sites.

Figure 3: EGSS by Investigative Site

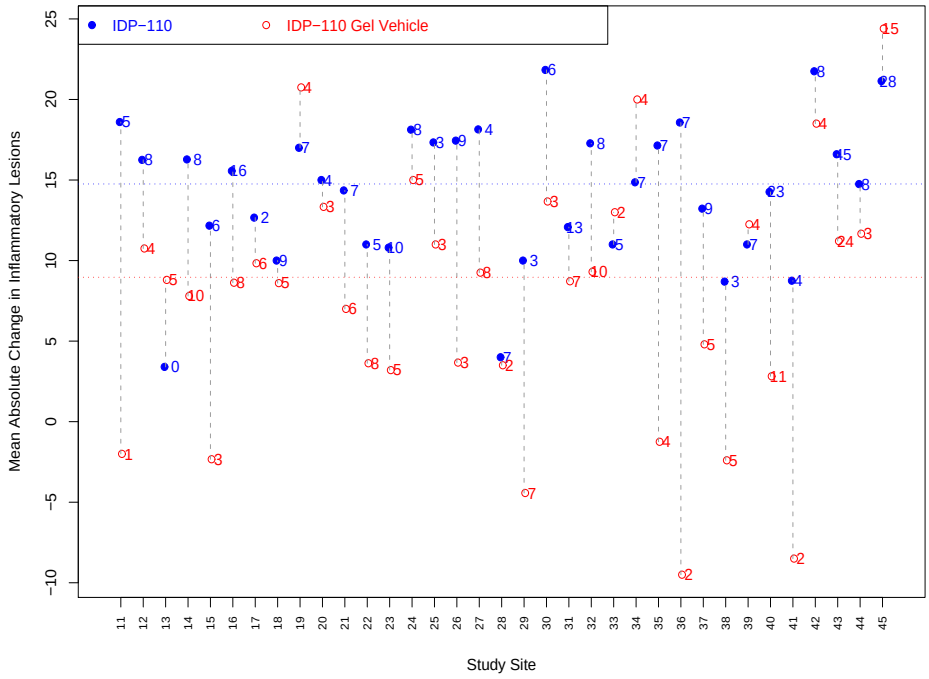



(a) Study 012

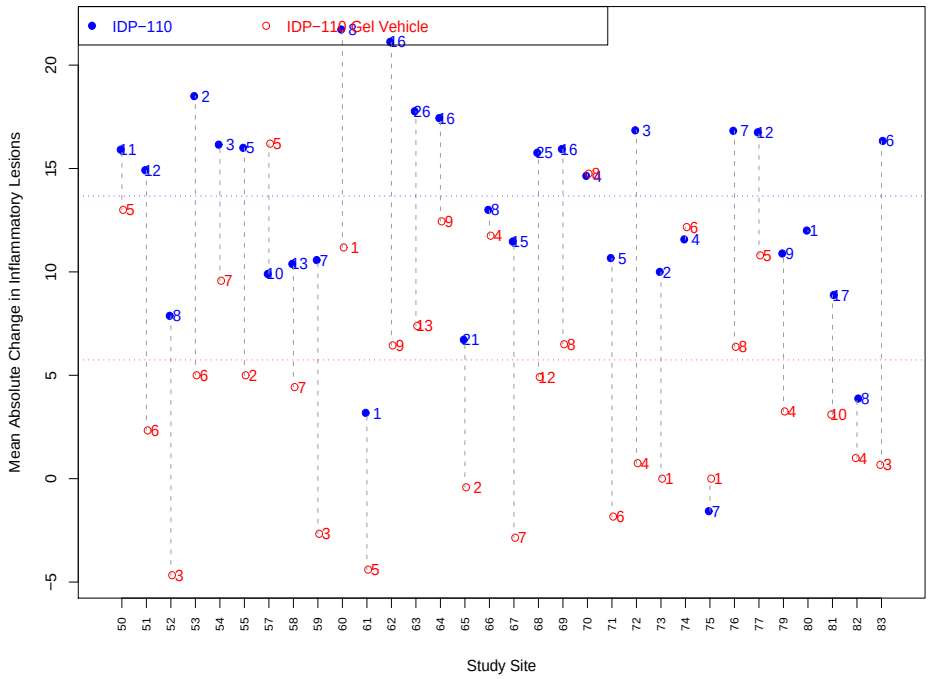



(b) Study 017

Figure 4: Mean Absolute Change in Inflammatory Lesion Count from Baseline by Investigative Sites

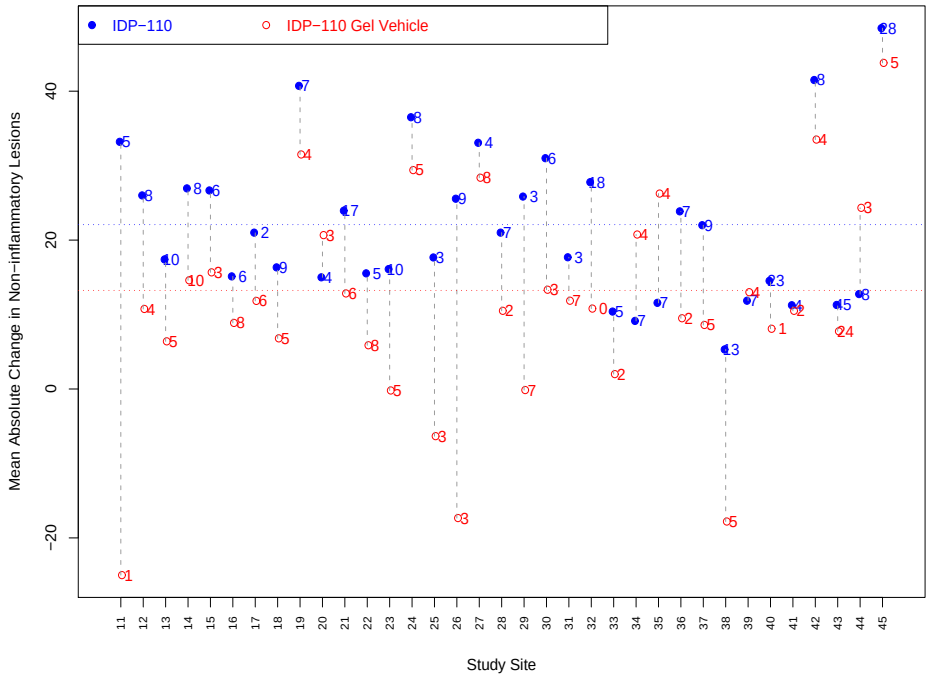



(a) Inflammatory: Study 012

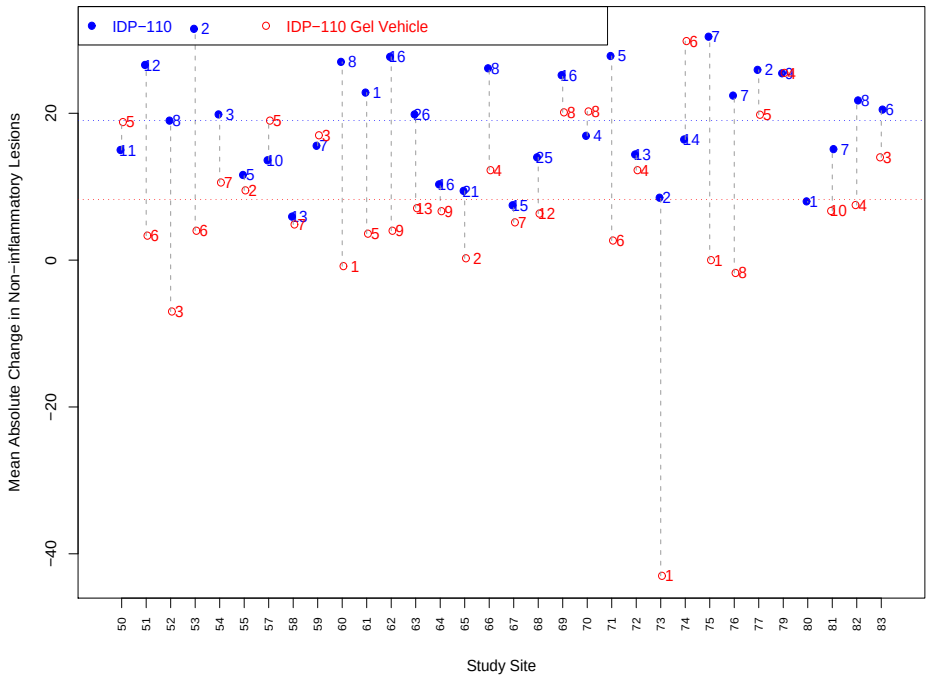



(b) Inflammatory: Study 017

Figure 5: Mean Absolute Change in Non-Inflammatory Lesion Count from Baseline by Investigative Sites




(a) Non-inflammatory: Study 012




(b) Non-inflammatory: Study 017

## 3.2 Evaluation of Safety

Subjects who had documented use of study medication and at least one post-Baseline evaluation were included in the safety evaluation. There were 1335 and 1352 subjects in Studies 012 and 017, respectively that were evaluated for safety. This section includes the extent of drug exposure and adverse events.

### 3.2.1 Extent of Exposure

The duration of treatment was defined as (date of last application date)-(date of baseline visit)+1. Most subjects in all four arms used the treatment for 84 days (12 weeks). In both studies and all treatment arms, the median treatment duration was 84 days. In Study 012, the mean treatment duration was 82.9 (range 9 - 116 days) in the IDP-110 arm, 82.2 (2 - 119 days) and 81.8 (4 - 135 days) in the clindamycin and BPO arms, and 80.8 (9 - 120 days) in the vehicle arm. The mean treatment duration was very similar across treatment arms in Study 017: 82.8 (range 1 - 102 days) in the IDP-110 arm, 84.0 (6 - 109 days) and 82.9 (1 - 115 days) in the clindamycin and BPO arms, and 81.4 (11 - 99 days) in the vehicle arm.

### 3.2.2 Adverse Events

A total of 339 (25.4%) and 301 (22.3%) subjects in Studies 012 and 017, respectively reported at least one adverse event. The proportion of subjects who experienced such AEs was highest in the BPO arm (28.5%), followed by IDP-110 (27.5%), vehicle (26.6%) and clindamycin (19.7%) in Study 012. In Study 017, the proportion of subjects who experienced at least one AE was highest in IDP-110 arm (24.8%), followed by clindamycin (22.3%), vehicle (21.6%) and BPO (20.5%). Table 14 presents AE rates by system organ classes (SOC) that at least 1% of the subjects per treatment arm experienced.

The most common AEs in the infections and infestations class were nasopharyngitis and upper respiratory tract infection in both studies. The proportion of subjects who experienced nasopharyngitis was highest in BPO subjects (5.3%) in Study 012 and in IDP-110 (3.4%) in Study 017. Upper respiratory tract infection was highest in the IDP-110 arm (4.7%) in Study 012 and in BPO (6.5%) in Study 017. Headache was the most common AE among the nervous system disorders. The sponsor defined serious adverse events (SAE) as any event that resulted in death, a life-threatening event, required hospitalization or prolonged an existing hospitalization, caused a persistent or significant disability/incapacity, resulted in congenital anomaly or birth defect, or was considered a medically important event. In Study 012 four SAEs were reported. In the IDP-110 arm, the reported SAE was uterine leiomyoma which was considered by the sponsor as not related to the study drug. Possible congestive heart failure, gun shot wound and breast cancer were reported as SAE in the clindamycin and BPO arms. In Study 017, 6 SAEs were reported. Depression and oppositinal defiant disorder were reported in the IDP-110 arm,

Table 14: AEs by System Organ Class in at Least 1% of Subjects per Treatment Arm

| | Study 012 | | | |
|---|---|---|---|---|
| SOC | IDP-110 n=386 | Clindamycin n=385 | BPO n=376 | Vehicle n=188 |
| Infections and infestations | 56 (15.0%) | 41 (10.6%) | 62 (16.5%) | 29 (15.4%) |
| Nervous system disorders | 12 (3.1%) | 11 (2.9%) | 10 (2.7%) | 5 (2.7%) |
| Respiratory, thoracic and mediastinal disorders | 8 (2.1%) | 8 (2.1%) | 12 (3.2%) | 3 (1.6%) |
| Gastroinetestinal disorders | 6 (1.6%) | 8 (2.1%) | 5 (1.3%) | 7 (3.7%) |
| Injury, poisoning and procedural complications | 12 (3.1%) | 7 (1.8%) | 11 (2.9%) | 6 (3.2%) |
| Psychiatric disorders | 5 (1.3%) | 4 (1.0%) | 3 (0.8%) | 0 (0.0%) |
| Skin and subcutaneous tissue disorders | 3 (0.8%) | 3 (0.8%) | 9 (2.4%) | 3 (1.6%) |
| General disorders and administration site conditions | 2 (0.5%) | 3 (0.8%) | 5 (1.3%) | 2 (1.1%) |
| Musculoskeleta and connective tissue disorders | 4 (1.0%) | 2 (0.5%) | 4 (1.1%) | 2 (1.1%) |

| | Study 017 | | | |
|---|---|---|---|---|
| SOC | IDP-110 n=387 | Clindamycin n=385 | BPO n=385 | Vehicle n=185 |
| Infections and infestations | 54 (14.0%) | 52 (13.5%) | 54 (14.0%) | 18 (9.7%) |
| Respiratory, thoracic and mediastinal disorders | 17 (4.4%) | 14 (3.6%) | 5 (1.3%) | 10 (5.4%) |
| Gastroinetestinal disorders | 6 (1.6%) | 7 (1.8%) | 7 (1.8%) | 1 (0.5%) |
| Injury, poisoning and procedural complications | 5 (1.3%) | 7 (1.8%) | 5 (1.3%) | 4 (2.2%) |
| Nervous system disorders | 16 (4.1%) | 5 (1.3%) | 6 (1.6%) | 4 (2.2%) |
| General disorders and administration site conditions | 2 (0.5%) | 4 (1.0%) | 3 (0.8%) | 3 (1.6%) |
| Skin and subcutaneous tissue disorders | 4 (1.0%) | 2 (0.5%) | 5 (1.3%) | 4 (2.2%) |
| Surgical and medical procedures | 1 (0.3%) | 0 (0.0%) | 4 (1.0%) | 0 (0.0%) |

Source: Study Report DPSI-06-22-2006-012, pg. 301-308; and Study Report DPSI-06-22-2006-017, pg. 300-306.

which were both considered as unrelated or unlikely related to the study drug by the sponsor. Other SAEs were moderate events of appendicitis and cellulitis, small intestinal obstruction and gallstones in the clindamycin and BPO arms, which the sponsor considered as unrelated or unlikely related to the study drug. No deaths were reported in either study.

# 4 Findings in Special/Subgroup Populations

## 4.1 Gender, Race, and Age

In this section, the efficacy of IDP-110 was evaluated by subgroup based on the EGSS. Table 15 presents the EGSS success rates by gender. The success rate in the IDP-110 arm was highest

in both females and males. In Study 012, the success rate in females was higher than in males in the active treatment arms: IDP-110, clindamycin and BPO arms. In Study 017, females had higher success rates in IDP-110 and clindamycin arms. The success rates in the BPO arm were similar in both genders.

Table 15: Number (%) of Successes on EGSS by Gender

| | | Study 012 | | | |
|---|---|---|---|---|---|
| Gender | | IDP-110 n=399 | Clindamycin n=408 | BPO n=406 | Vehicle n=201 |
| Female | Total | 215 | 215 | 239 | 94 |
| | Success (%) | 79 (36.7%) | 56 (26.0%) | 61 (25.5%) | 16 (17.0%) |
| Male | Total | 184 | 193 | 167 | 107 |
| | Success (%) | 52 (28.3%) | 44 (22.8%) | 35 (21.0%) | 22 (20.6%) |

| | | Study 017 | | | |
|---|---|---|---|---|---|
| Gender | | IDP-110 n=398 | Clindamycin n=404 | BPO n=403 | Vehicle n=194 |
| Female | Total | 193 | 205 | 216 | 98 |
| | Success (%) | 75 (38.9%) | 64 (31.2%) | 60 (27.8%) | 16 (16.3%) |
| Male | Total | 205 | 199 | 187 | 96 |
| | Success (%) | 72 (35.1%) | 50 (25.1%) | 54 (28.9%) | 11 (11.5%) |

Source: Reviewer analysis.

Table 16 presents the EGSS success rates by age groups. The 25%, 50%, and 75% quantile of age was approximately 15.2, 16.9, and 21.1, respectively. Age groups were formed based on these quantiles. The success rate did not show a trend across age groups and were relatively consistent across age groups.

Table 16: Number (%) of Successes on EGSS by Age Group

| | | Study 012 | | | |
|---|---|---|---|---|---|
| | | IDP-110 | Clindamycin | BPO | Vehicle |
| Age Group | | n=399 | n=408 | n=406 | n=201 |
| 12 - 15 | Total | 148 | 132 | 154 | 76 |
| | Success (%) | 42 (28.4%) | 29 (22.0%) | 38 (24.7%) | 9 (11.8%) |
| 16 - 17 | Total | 90 | 112 | 94 | 44 |
| | Success (%) | 28 (31.1%) | 29 (25.9%) | 24 (25.5%) | 11 (25.0%) |
| 18 - 21 | Total | 74 | 73 | 65 | 27 |
| | Success (%) | 29 (39.2%) | 24 (32.9%) | 11 (16.9%) | 8 (29.6%) |
| 22 - | Total | 87 | 91 | 93 | 54 |
| | Success (%) | 32 (36.8%) | 18 (19.8%) | 23 (24.7%) | 10 (18.5%) |

| | | Study 017 | | | |
|---|---|---|---|---|---|
| | | IDP-110 | Clindamycin | BPO | Vehicle |
| Age Group | | n=398 | n=404 | n=403 | n=194 |
| 12 - 15 | Total | 159 | 155 | 186 | 80 |
| | Success (%) | 61 (38.4%) | 37 (23.9%) | 44 (23.7%) | 9 (11.3%) |
| 16 - 17 | Total | 96 | 96 | 88 | 45 |
| | Success (%) | 31 (33.3%) | 25 (26.0%) | 33 (37.5%) | 1 (2.2%) |
| 18 - 21 | Total | 67 | 61 | 52 | 30 |
| | Success (%) | 25 (37.3%) | 19 (31.1%) | 16 (30.8%) | 3 (10.0%) |
| 22 - | Total | 76 | 92 | 77 | 39 |
| | Success (%) | 30 (39.5%) | 33 (35.9%) | 21 (27.3%) | 14 (35.9%) |

Source: Reviewer analysis.

Table 17 presents the EGSS success rates by race. The majority of the subjects were White (See Table 21 in Appendix A.1), in which the success rate of the IDP-110 arm was higher than other arms in both studies. Success rate was highest in the Clindamycin arm in 'Other' subgroup in both studies. In Asians, the success rate was highest in the BPO arm. Asian and 'Other' subjects were only a small proportion of the sample and therefore inference from these subgroups has limited meaning.

Table 17: Number (%) of Successes on EGSS by Race

| Race | | Study 012 IDP-110 n=399 | Clindamycin n=408 | BPO n=406 | Vehicle n=201 |
|---|---|---|---|---|---|
| White | Total | 308 | 311 | 295 | 155 |
| | Success (%) | 115 (37.3%) | 78 (25.1%) | 72 (24.4%) | 27 (17.4%) |
| Black | Total | 65 | 70 | 82 | 34 |
| | Success (%) | 13 (20.0%) | 13 (18.6%) | 17 (20.7%) | 9 (26.5%) |
| Asian | Total | 8 | 16 | 8 | 6 |
| | Success (%) | 2 (25.0%) | 5 (31.3%) | 3 (37.5%) | 1 (16.7%) |
| Other | Total | 22 | 16 | 24 | 12 |
| | Success (%) | 2 (9.1%) | 5 (31.3%) | 4 (16.7%) | 2 (16.7%) |

| Race | | Study 017 IDP-110 n=398 | Clindamycin n=404 | BPO n=403 | Vehicle n=194 |
|---|---|---|---|---|---|
| White | Total | 310 | 317 | 303 | 150 |
| | Success (%) | 122 (39.4%) | 90 (28.4%) | 90 (29.7%) | 22 (14.7%) |
| Black | Total | 63 | 63 | 83 | 34 |
| | Success (%) | 22 (34.9%) | 18 (28.6%) | 23 (27.7%) | 4 (11.8%) |
| Asian | Total | 9 | 11 | 10 | 5 |
| | Success (%) | 2 (22.2%) | 1 (9.1%) | 3 (30.0%) | 1 (20.0%) |
| Other | Total | 21 | 19 | 15 | 6 |
| | Success (%) | 4 (19.0%) | 6 (31.6%) | 1 (6.7%) | 0 (0%) |

Source: Reviewer analysis.

## 4.2 Other Special/Subgroup Populations

The proportion of success rates based on EGSS were explored by baseline disease severity based on EGSS. Table 18 presents the success rates across baseline EGSS. The majority of subjects had moderate disease severity at baseline (EGSS of 3). (See Table 22 in Appendix A.1.) The success rate in the IDP-110 arm was higher than in other arms in subjects with baseline EGSS of 'Moderate' (3). In Study 012, the success rate in the IDP-110 arm in subjects with baseline severity of 'Severe' (4) was slightly lower than that of the BPO subjects. However, the treatment effect of IDP-110 compared to BPO in Study 017 was 17%, in favor of IDP-110 . In Study 012,

the success rates in subjects with severe baseline disease were higher than that of subjects with moderate baseline disease in all four arms. However, this trend was not replicated in Study 017. The success rate was higher in subjects with baseline EGSS of 4 was higher than in subjects with baseline EGSS of 3.

Table 18: Number (%) of Successes on EGSS by Baseline Disease Severity

| | | Study 012 | | | |
|---|---|---|---|---|---|
| Baseline EGSS | | IDP-110 n=399 | Clindamycin n=408 | BPO n=406 | Vehicle n=201 |
| 3 | Total | 328 | 332 | 341 | 163 |
| | Success (%) | 101 (30.8%) | 70 (21.1%) | 67 (19.6%) | 26 (16.0%) |
| 4 | Total | 71 | 76 | 65 | 38 |
| | Success (%) | 30 (42.3%) | 30 (39.5%) | 29 (44.6%) | 12 (31.6%) |

| | | Study 017 | | | |
|---|---|---|---|---|---|
| Baseline EGSS | | IDP-110 n=398 | Clindamycin n=404 | BPO n=403 | Vehicle n=194 |
| 3 | Total | 315 | 321 | 326 | 156 |
| | Success (%) | 107 (34.0%) | 89 (27.7%) | 90 (27.6%) | 21 (13.5%) |
| 4 | Total | 83 | 83 | 77 | 38 |
| | Success (%) | 40 (48.2%) | 25 (30.1%) | 24 (31.2%) | 6 (15.8%) |

Source: Reviewer analysis.

Tables 19 and 20 present the mean absolute change in inflammatory and non-inflammatory lesion counts by baseline EGSS. The results were similar to that of EGSS, regarding the BPO subjects with severe baseline disease severity resulting in a greater decrease in mean absolute lesion count than the IDP-110 arm. The difference in mean absolute lesion count between the two baseline severity was more apparent in non-inflammatory lesions than inflammatory lesions.

Table 19: Mean Absolute Change in Inflammatory Lesion Count by Baseline Disease Severity

| Baseline EGSS | | Study 012 IDP-110 n=399 | Clindamycin n=408 | BPO n=406 | Vehicle n=201 |
|---|---|---|---|---|---|
| 3 | Total | 328 | 332 | 341 | 163 |
| | Mean change (SD) | 14.8 (10.6) | 11.8 (11.3) | 12.5 (9.6) | 8.9 (11.7%) |
| 4 | Total | 71 | 76 | 65 | 38 |
| | Mean change (SD) | 14.7 (11.7) | 13.9 (12.8) | 15.7 (13.6) | 9.2 (12.9) |

| Baseline EGSS | | Study 017 IDP-110 n=398 | Clindamycin n=404 | BPO n=403 | Vehicle n=194 |
|---|---|---|---|---|---|
| 3 | Total | 315 | 321 | 326 | 156 |
| | Mean change (SD) | 13.4 (9.8) | 11.0 (11.6) | 11.3 (10.3) | 5.6 (12.4) |
| 4 | Total | 83 | 83 | 77 | 38 |
| | Mean change (SD) | 14.6 (12.9) | 12.7 (12.0) | 10.7 (11.8) | 6.2 (13.3) |

Source: Reviewer analysis.

Table 20: Mean Absolute Change in Non-Inflammatory Lesion Count by Baseline Disease Severity

| Baseline EGSS | | Study 012 IDP-110 n=399 | Clindamycin n=408 | BPO n=406 | Vehicle n=201 |
|---|---|---|---|---|---|
| 3 | Total | 328 | 332 | 341 | 163 |
| | Mean change (SD) | 21.6 (20.9) | 17.5 (19.1) | 19.8 (20.7) | 12.3 (18.8) |
| 4 | Total | 71 | 76 | 65 | 38 |
| | Mean change (SD) | 24.4 (22.8) | 19.4 (23.1) | 25.1 (27.5) | 17.4 (25.8) |

| Baseline EGSS | | Study 017 IDP-110 n=398 | Clindamycin n=404 | BPO n=403 | Vehicle n=194 |
|---|---|---|---|---|---|
| 3 | Total | 315 | 321 | 326 | 156 |
| | Mean change (SD) | 18.0 (20.4) | 14.4 (18.8) | 14.3 (17.9) | 7.8 (20.1) |
| 4 | Total | 83 | 83 | 77 | 38 |
| | Mean change (SD) | 22.9(17.2) | 17.2 (18.8) | 18.8 (22.7) | 10.3 (18.6) |

Source: Reviewer analysis.

# 5 Summary and Conclusions

## 5.1 Statistical Issues and Collective Evidence

The sponsor conducted two studies (Study 012 and Study 017) under the protocol that was agreed upon with the Agency in terms of study design and endpoints. Efficacy was evaluated at Week 12 using the proportion of successes based on the Evaluator's Global Severity Score (EGSS) and the mean absolute change in inflammatory and non-inflammatory lesion count from baseline. The protocol stated that efficacy would be demonstrated if (i) IDP-110 is superior to each monad and vehicle in EGSS and both lesion count; (ii) IDP-110 is superior to each monad and vehicle in mean absolute change in inflammatory lesions; and if (iii) IDP-110 is superior to vehicle in mean absolute change in non-inflammatory lesion count. The differences in the success rates based on EGSS in all comparisons, IDP-110 versus clindamycin, benzoyl peroxide (BPO) and vehicle were statistically significant in both studies (p-values<0.009). The differences in the mean absolute change in inflammatory lesion counts were also statistically significant in all comparisons in both studies (p-values<0.012). The differences in the mean absolute change in non-inflammatory lesion counts were statistically significant in the comparisons required to establish efficacy, IDP-110 compared to vehicle in both studies (p-values<0.001). Within each study, the efficacy results were relatively consistent across subgroups and investigative sites. However, most of the overall treatment effect was observed in the White subjects. Also, the success rate was higher in subjects with 'Severe' baseline disease severity. In Study 012, the success rates based on EGSS and mean absolute change in lesion count were marginally higher in the BPO arm than the IDP-110 in subjects with baseline EGSS of 'Severe' (4). However, this result was not replicated in Study 017.

## 5.2 Conclusions and Recommendations

Combination drug, IDP-110 has been demonstrated to be statistically superior to its monads, clindamycin and benzoyl peroxide (BPO), and its vehicle in two studies (Study 012 and Study 017) in the treatment of moderate to severe acne vulgaris. Efficacy was evaluated using the Evaluator's Global Severity Score (EGSS) and mean absolute change in inflammatory and non-inflammatory lesion counts. The protocol stated that efficacy would be demonstrated if at Week 12: (i) IDP-110 was superior to each monad and vehicle in EGSS and both lesion counts; (ii) IDP-110 was superior to each monad and vehicle in mean absolute change in inflammatory lesions; and (iii) IDP-110 was superior to vehicle in mean absolute change in non-inflammatory lesion counts. Tables 1 and 2 present the summary of the co-primary endpoint results. All co-primary endpoints that were required to establish efficacy were statistically significant in both studies with p-values less than 0.012.

The proportion of subjects who experienced at least one adverse event was highest in the

benzoyl peroxide (BPO) arm and IDP-110 arm in Studies 012 and 017, respectively. The most common adverse events were upper respiratory tract infection and nasopharyngitis.

# Appendix

## A.1 Baseline and Demographic Data

Table 21 present the baseline demographic data based on the ITT population and Table 22 presents the baseline EGSS and lesion counts by treatment arm.

Table 21: Baseline Demographics (ITT population)

| | Study 012 | | | |
|---|---|---|---|---|
| | IDP-110 n=399 | Clindamycin n=408 | BPO n=406 | Vehicle n=201 |
| **Age** (in years) | | | | |
| Mean (Std) | 19.3 (6.5) | 19.7 (7.2) | 19.4 (7.0) | 19.7 (7.1) |
| Median | 17.0 | 17.2 | 16.7 | 16.9 |
| Min, Max | 12.2, 46.6 | 12.1, 49.1 | 12.0, 53.8 | 12.2, 44.4 |
| **Gender** | | | | |
| Male | 184 (46.1%) | 193 (47.3%) | 167 (41.1%) | 107 (53.2%) |
| Female | 215 (53.9%) | 215 (52.7%) | 239 (58.9%) | 94 (46.8%) |
| **Race** | | | | |
| White | 308 (77.2%) | 311 (76.2%) | 295 (72.7%) | 155 (77.1%) |
| Black | 65 (16.3%) | 70 (17.2%) | 82 (20.2%) | 34 (16.9%) |
| Asian | 8 (2.0%) | 16 (3.9%) | 8 (2.0%) | 6 (3.0%) |
| Other | 22 (5.5%) | 16 (3.9%) | 24 (5.9%) | 12 (6.0%) |

| | Study 017 | | | |
|---|---|---|---|---|
| | IDP-110 n=398 | Clindamycin n=404 | BPO n=403 | Vehicle n=194 |
| **Age** (in years) | | | | |
| Mean (Std) | 19.1 (7.1) | 19.6 (7.4) | 18.9 (7.1) | 18.9 (6.5) |
| Median | 16.6 | 17.0 | 16.3 | 16.4 |
| Min, Max | 12.1, 54.7 | 12.1, 70.2 | 12.0, 48.4 | 12.3, 50.9 |
| **Gender** | | | | |
| Male | 205 (51.5%) | 199 (49.3%) | 187 (46.4%) | 187 (49.5%) |
| Female | 193 (48.5%) | 205 (50.7%) | 216 (53.6%) | 98 (50.5%) |
| **Race** | | | | |
| White | 310 (77.9%) | 317 (78.5%) | 303 (75.2%) | 150 (77.3%) |
| Black | 63 (15.8%) | 63 (15.6%) | 83 (20.6%) | 34 (17.5%) |
| Asian | 9 (2.3%) | 11 (2.7%) | 10 (2.5%) | 5 (2.6%) |
| Other | 21 (5.3%) | 19 (4.7%) | 15 (3.7%) | 6 (3.1%) |

Source: Study Report DPSI-06-22-2006-012, pg. 115; Study Report DPSI-06-22-2006-017, pg. 110; and Reviewer analysis.

Baseline demographic variables were generally balanced across treatment arms. The average ages of all subjects in Studies 012 and 017 were 19.5 and 19.1, respectively. Subjects' ages ranged from 12.0 to 53.8 in Study 012, and from 12.0 to 70.2 in Study 017. In both studies, the majority of subjects were White.

Table 22: Baseline Disease Severity

| | Study 012 | | | |
|---|---|---|---|---|
| | IDP-110 n=399 | Clindamycin n=408 | BPO n=406 | Vehicle n=201 |
| **EGSS** | | | | |
| 3 | 328 (82.2%) | 332 (81.4%) | 341 (84.1%) | 163 (81.1%) |
| 4 | 71 (17.8%) | 76 (18.6%) | 65 (16.0%) | 38 (18.9%) |
| Inflammatory lesion count | | | | |
| Mean (Std) | 26.8 (6.9) | 26.8 (6.8) | 26.3 (6.7) | 26.9 (6.9) |
| Median | 26 | 26 | 25 | 26 |
| Min, Max | 17, 42 | 17, 48 | 17, 42 | 16, 41 |
| Non-inflammatory lesion count | | | | |
| Mean (Std) | 48.4 (21.7) | 45.8 (20.3) | 48.9 (21.3) | 44.0 (20.2) |
| Median | 43 | 41 | 44 | 37 |
| Min, Max | 20, 100 | 20, 100 | 20, 100 | 20, 100 |

| | Study 017 | | | |
|---|---|---|---|---|
| | IDP-110 n=398 | Clindamycin n=404 | BPO n=403 | Vehicle n=194 |
| **EGSS** | | | | |
| 3 | 315 (79.1%) | 321 (79.5%) | 326 (80.9%) | 156 (80.4%) |
| 4 | 83 (20.9%) | 83 (20.5%) | 77 (19.1%) | 38 (19.6%) |
| Inflammatory lesion count | | | | |
| Mean (Std) | 26.0 (7.0) | 25.7 (6.8) | 25.3 (6.8) | 25.3 (6.4) |
| Median | 24.5 | 24 | 23 | 24 |
| Min, Max | 17, 41 | 17, 41 | 17, 42 | 17, 40 |
| Non-inflammatory lesion count | | | | |
| Mean (Std) | 46.5 (21.1) | 44.9 (20.1) | 44.7 (20.8) | 44.1 (18.2) |
| Median | 40 | 39 | 39 | 40 |
| Min, Max | 20, 100 | 20, 100 | 20, 100 | 20, 94 |

Source: Study Report DPSI-06-22-2006-012, pg. 134; Study Report DPSI-06-22-2006-017, pg. 130; and Reviewer analysis.

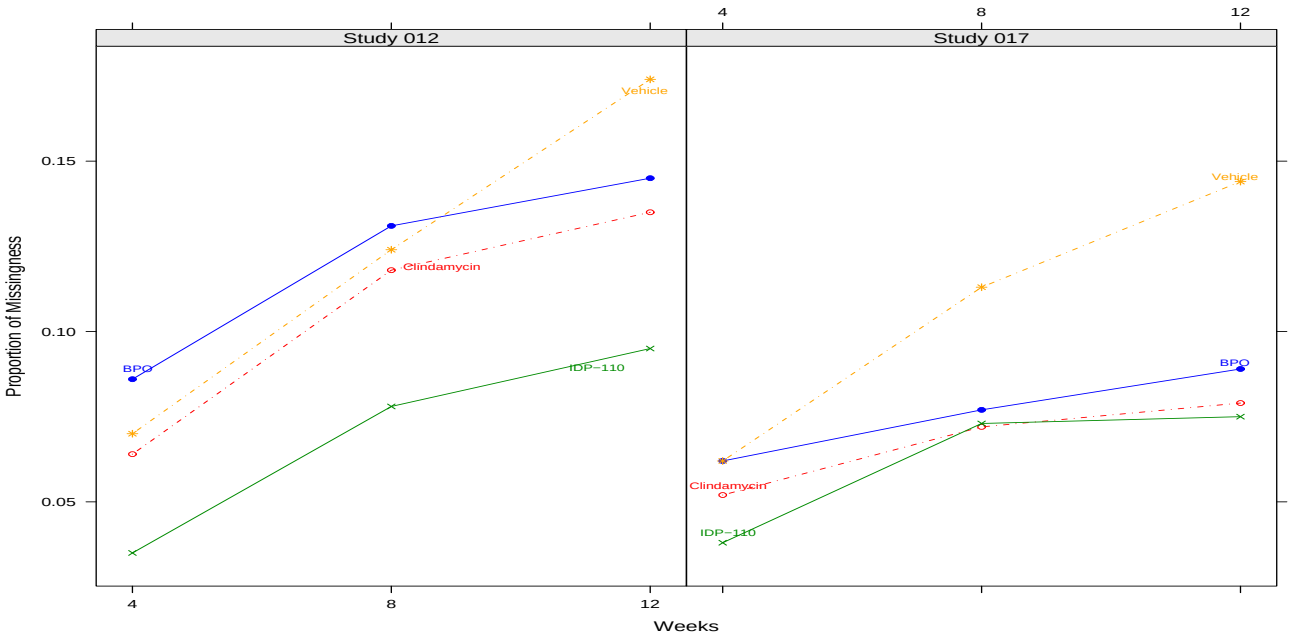
Baseline EGSS was fairly balanced between the four arms in both studies. The majority of

the subjects had baseline EGSS of 3 ('Moderate'), 82.3% and 79.9% in Studies 012 and 017, respectively. In Study 012, IDP-110 and BPO arms had marginally larger proportions of subjects who had baseline EGSS of 3 than clindamycin and vehicle arms. In Study 017, the proportion of subjects with baseline EGSS of 3 was higher in the BPO and vehicle arms. The mean baseline inflammatory and non-inflammatory lesion counts were very balanced across treatment arms in both studies.

## A.2 Number and Proportion of Missing Observations

Figure 6 presents the number and proportion of missing observations in each treatment arm over time.

Figure 6: Proportion of Missing Observations Over Time




The number of missing observations at Week 12 were a total of 187 (13.2%) and 126 (9.0%) subjects in Studies 012 and 017, respectively. Study 012 had more missing observations than Study 017 in general. In both studies, the proportion of missing observations was lowest in the IDP-110 arm throughout most of the study. The vehicle arm had the highest proportion of missingness at Week 12 in Study 012, and throughout the whole study in Study 017. The proportion of missingness was higher in the BPO arm than the clindamycin arm in both studies.

# Signatures/Distribution List

Primary Statistical Reviewer: Clara Y. Kim, Ph.D.
Date: June 24, 2008

Statistical Team Leader: Mohamed Alosh, Ph.D.

cc:
Archival NDA
DDDP/Walker
DDDP/Kukich
DDDP/Luke
DDDP/Vaughan
DDDP/White
OBIO/Nevius
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DBIII/Wilson
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June 24, 2008

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/s/
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Clara Kim
6/27/2008 10:29:29 AM
BIOMETRICS

Mohamed Alosh
7/29/2008 10:32:45 AM
BIOMETRICS