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STATISTICAL REVIEW AND EVALUATION  
NEW DRUG APPLICATION  
CLINICAL STUDIES

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# 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 <sup>†</sup>	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 <sup>†</sup>	NA	0.009	0.009	<0.0001

<sup>†</sup> 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
<b>Inflammatory lesions</b>				
Mean absolute change (sd)	14.8 (10.8)	12.2 (11.6)	13.0 (10.4)	9.0 (11.9)
p-value <sup>†</sup>	NA	<0.001	0.012	<0.001
<b>Non-inflammatory lesions</b>				
Mean absolute change (sd)	22.1 (21.2)	17.9 (19.9)	20.6 (22.0)	13.2 (20.4)
p-value <sup>†</sup>	NA	0.005	0.134	<0.001

  

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

<sup>†</sup> 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<sup>®</sup> Topical Gel and Duac<sup>™</sup> 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

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## 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