

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

Baseline EGSS		Study 012			
		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%)

Baseline EGSS		Study 017			
		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.

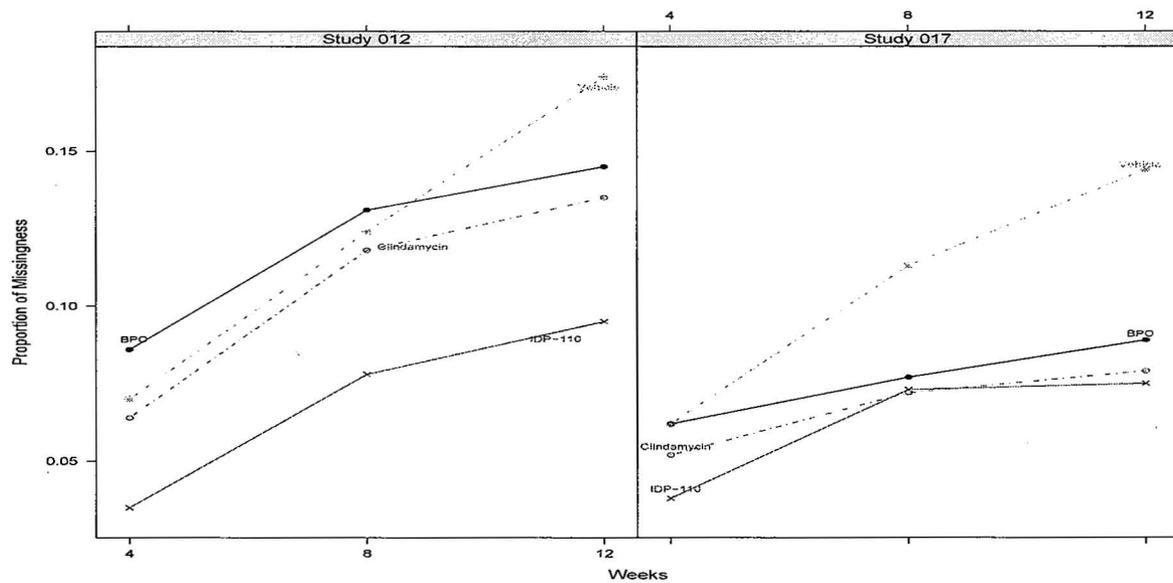
Baseline EGSS was fairly balanced between the four arms in both studies. The majority of

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.

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