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.

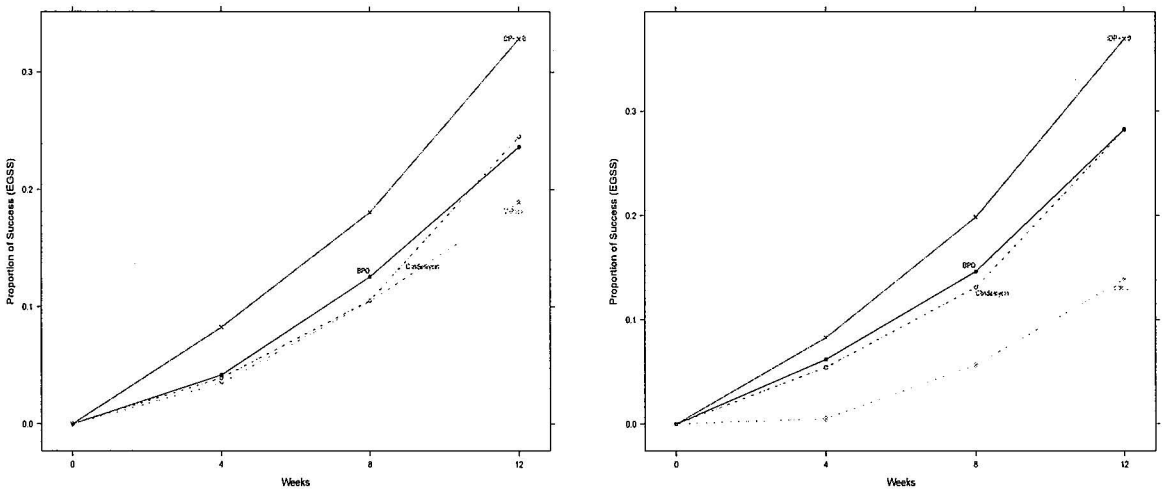
Missing values were imputed using LOCF.

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

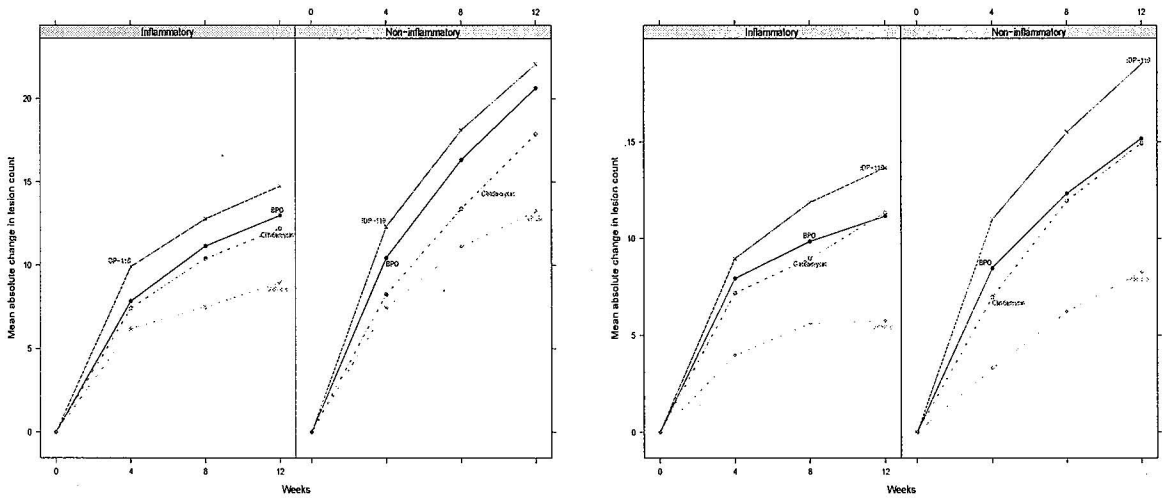
Subjects were treated for 12 weeks. Subjects' EGSS and lesion count were evaluated at baseline, Weeks 4, 8 and 12. Figure 1 and 2 present the success rates based on EGSS scores and mean absolute change in inflammatory and non-inflammatory lesion count over time. The efficacy of IDP-110 increased over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