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STATISTICAL REVIEW AND EVALUATION

NEW DRUG APPLICATION

CLINICAL STUDIES

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Drug Name: SOLODYN (minocycline hydrochloride) modified release , 45 mg, 90 mg, 135 mg.

Indication(s): Inflammatory lesions associated with moderate to severe acne vulgaris

Applicant: Medicis

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1 Executive Summary

1.1 Conclusions and Recommendations

Two studies demonstrate that minocycline ~~are~~ are statistically superior to placebo in the treatment of inflammatory lesions of acne as assessed by the two primary endpoints, percent reduction in inflammatory lesions and success (clear or almost clear) on the Evaluator's Global Severity Assessment (EGSA) after 84 days (12 weeks) of treatment. The two studies were designed to assess the effect of minocycline on inflammatory lesions only. In Study 04, minocycline subjects had a mean percent reduction in inflammatory lesions of 43% versus 32% for placebo. Similarly, in Study 05, minocycline subjects had a mean percent reduction in inflammatory lesions of 46% versus 31% for placebo. Both studies had p-values <0.001 for the percent reduction in inflammatory lesions. On the EGSA, 17% of minocycline subjects and 8% of placebo subjects were clear or almost clear at Day 84 in Study 04 (p=0.006). In Study 05, 16% of minocycline subjects and 9% of placebo subjects were clear or almost clear on the EGSA at Day 84 (p=0.018). Non-inflammatory lesions were evaluated as a secondary endpoint. The studies also demonstrated that minocycline is non-inferior to placebo in terms of non-inflammatory lesions with a non-inferiority margin of 15% (97.5% lower confidence bounds of -10.2% for Study 04 and +4.8% for Study 05.)

1.2 Brief Overview of Clinical Studies

The sponsor conducted two Phase 3 efficacy and safety studies and one Phase 2 dose ranging study to evaluate minocycline in the treatment of inflammatory lesions of moderate to severe acne vulgaris. The dose ranging study (MP-0104-01) evaluated three doses: 1 mg/kg, 2 mg/kg, and 3 mg/kg once daily. Of the three doses, the 1 mg/kg dose had the most favorable benefit/risk profile, no trend for increasing efficacy with increasing dose was observed. Therefore, the sponsor evaluated the 1 mg/kg dose once daily in Phase 3 trials. The Phase 3 trials (MP-0104-04 and MP-0104-05) were randomized, double-blind, 12-week studies comparing minocycline to placebo. Subjects were to have moderate to severe acne at baseline (based on the Evaluator's Global Severity Assessment (EGSA) which focused on inflammatory lesions), 20 to 75 inflammatory lesions and fewer than 2 nodules/cysts.

The primary efficacy endpoints were the percent change in inflammatory lesions from baseline to Day 84 and success (clear or almost clear) on the EGSA at Day 84. The secondary efficacy endpoints were the percent change in non-inflammatory lesions, two grades reduction on the EGSA, and success (clear or almost clear) on a second global assessment that took into account both inflammatory and non-inflammatory lesions. All investigative centers were in the United States. Study 04 enrolled 300 minocycline and 151 placebo subjects. Study 05 enrolled 315 minocycline and 158 placebo subjects.

1.3 Statistical Issues and Findings

Studies 04 and 05 were designed to assess minocycline in the treatment of inflammatory lesions of acne vulgaris rather than the full acne vulgaris indication. As such, the primary efficacy endpoints were the percent change in inflammatory lesions and an EGSA which

focused on inflammatory lesions. As a secondary endpoint, the study assessed the non-inferiority of non-inflammatory lesions relative to placebo. The study met all of its pre-specified efficacy objectives. All primary efficacy endpoints were statistically significant in both studies and the results are summarized in Table 1. The distribution of the percent reduction in inflammatory lesions was highly skewed and therefore the primary analysis was based on the ranks. The analyses based on the original data (non-transformed percent reductions) as well as the analyses based on the absolute change in lesions lead to the same conclusions as the analyses based on the ranks ($p \leq 0.004$). The study also met its prespecified non-inferiority criteria for non-inflammatory lesions with lower confidence bounds of -10.2% and +4.8% for the difference (minocycline – placebo) in the percent reduction in non-inflammatory lesions. Efficacy across subgroups (gender, race, age, and baseline severity) varied slightly in terms of both the treatment effect (minocycline – placebo) and the individual treatment estimates with females, adult subjects, and subjects with moderate disease often faring better than males, adolescent subjects, and subjects with severe disease. However, the differences were not extreme and in nearly every subgroup minocycline had better results than placebo.

Table 1 – Primary Efficacy Results

	Study 04		Study 05	
	Minocycline N=300	Placebo N=151	Minocycline N=315	Placebo N=158
Mean Percent Change in Inflammatory Lesions	43.1%	31.7%	45.8%	30.8%
	$p < 0.001$		$p < 0.001$	
No. (%) of Subjects Clear or Almost Clear on the EGSA	52 (17.3%)	12 (7.9%)	50 (15.9%)	15 (9.5%)
	$p = 0.006$		$p = 0.018$	

During the protocol planning stage, the Division and sponsor engaged in discussions about the most appropriate type of global evaluation to support an indication of inflammatory lesions. During the discussions the Division recommended using a global evaluation that incorporated both inflammatory and non-inflammatory lesions. The sponsor was not able to incorporate such a global before the study started, but added a second global assessment via an amendment after the study began. Consequently not all subjects have evaluations on the global that encompasses both lesion types. The two global evaluations are highly correlated ($r = 0.9$) among subjects with both evaluations. Since (1) the Division's current thinking is that it may be acceptable to use a global evaluation that emphasizes one lesion type when targeting an indication for only that lesion type as noted in the draft acne guidance, and (2) the comprehensive global was added to the protocol after the study started, the prespecified EGSA that focuses on inflammatory lesions only will be considered the primary endpoint.

Compliance and adverse event rates were similar for the minocycline and placebo treatment groups. Most individual adverse events occurred at similar rates for the two arms. Two events that occurred at slightly higher rates on the minocycline arm were fatigue (9.6% vs. 6.5%) and dizziness (8.1% vs. 4.5%). Other vestibular function related events (nausea, vomiting, tinnitus, vertigo) occurred at similar rates for both the minocycline and placebo arms.

2 Introduction

2.1 Overview

Solodyn (minocycline hydrochloride) is an oral antibiotic that has modified release characteristics relative to currently marketed versions of minocycline. Other approved minocycline products, such as Dynacin and Minocin, include as part of the indication “in severe acne, minocycline may be useful adjunctive therapy”. The Dynacin label does not specifically recommend a dosing regimen for acne, but it states that the usual dosage of Dynacin is 200 mg initially followed by 100 mg every 12 hours. The proposed dosage for Solodyn is once daily dosing of 45 mg, 90 mg, and 135 mg strength — dosed as 1 mg/kg. The proposed indication is the treatment of inflammatory lesions associated with moderate to severe acne vulgaris.

To support the use of Solodyn in the treatment of inflammatory lesions associated with moderate to severe acne vulgaris, the applicant conducted a Phase 2 dose-ranging study and two Phase 3 trials. The three clinical trials are listed in Table 2. All study centers were in the United States.

Table 2 – Clinical Studies for Solodyn

Study	Type	Doses	No. of Subjects
MP-0104-01	Dose Ranging	1 mg/kg,	59
		2 mg/kg,	59
		3 mg/kg,	60
		placebo	55
MP-0104-04	Efficacy and Safety	1 mg/kg,	300
		placebo	151
MP-0104-05	Efficacy and Safety	1 mg/kg,	315
		placebo	158

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 datasets used in this review are archived at \\Cdesub1\evsprod\N050808\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\acne vulgaris\5351-stud-rep-contr.

3 Statistical Evaluation

This review will focus primarily on the two Phase 3 studies and will only briefly discuss the Phase 2 dose ranging study.

3.1 Evaluation of Efficacy

3.1.1 Study Design

Studies MP-0104-04 (Study 04) and MP-0104-05 (Study 05) are identical randomized, double-blind, placebo-controlled Phase 3 studies. Subjects aged 12 and older were randomized to either minocycline or placebo in a 2:1 ratio. Subjects were to have between 25 and 75 inflammatory lesions, fewer than 2 nodules/cysts, and an Evaluator's Global Severity Assessment (EGSA) of moderate or severe.

Subjects were evaluated at baseline, Day 28, Day 56, and Day 84. After completing the 12-week treatment period in Studies 04 and 05, subjects were eligible to enter an open-label two-year, long-term follow-up study, taking minocycline 'as needed' (as determined by the investigator). Subjects not entering the long-term follow-up study were to return four weeks later at Day 112 for post-treatment follow-up. The target minocycline dose was 1 mg/kg once daily using strengths of 45 mg, 90 mg, and 135 mg. To achieve this dosing, subjects weighing 99-131 pounds were assigned to 45 mg, subjects weighing 132-199 pounds were assigned to 90 mg, and subjects weighing 200-300 pounds were assigned to 135 mg.

The primary efficacy endpoints were the percent reduction in inflammatory lesions and success on the EGSA (clear or almost clear) at Day 84. The secondary endpoints were the number of subjects with at least two grades reduction on the EGSA, the percent reduction in non-inflammatory lesions, and the number of clear/almost clear subjects on a second evaluator's global severity assessment that took into account both inflammatory and non-inflammatory lesions (EGSA-NI). The two global assessment scales are presented in Table 3 and Table 4. The EGSA-NI scale was added to the protocol after the studies started and not all subjects have evaluations on the EGSA-NI.

Table 3- Evaluator's Global Severity Assessment [Inflammatory Lesions] (EGSA)

Score	Grade	Description
0	Clear	No evidence of papules or pustules (inflammatory lesions)
1	Almost clear	Rare (eg, <5) non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red)
2	Mild	Few (eg, <10) inflammatory lesions (papules/pustules only; no nodulocystic lesions)
3	Moderate	Multiple (eg, between 25 and 40) inflammatory lesions present; many papules/pustules; there may or may not be a few nodulocystic lesions
4	Severe	Inflammatory lesions are more apparent, many papules/pustules (eg, between 40 and 75); there may or may not be a few nodulocystic lesions
5	Very Severe	Highly inflammatory lesions predominate, many papules/pustules, and many nodulocystic lesions

Table 4 – Evaluator’s Global Severity Assessment [Non-Infl. and Infl.] (EGSA-NI)

Score	Grade	Description
0	Clear	Normal, clear skin with no evidence of acne vulgaris
1	Almost clear	Rare noninflammatory lesions present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red)
2	Mild	Some noninflammatory lesions are present, with few inflammatory lesions (papules/pustules only; no nodulocystic lesions)
3	Moderate	Noninflammatory 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/pustules and many nodulocystic lesions

The protocol stated that the success rates on the global assessments would be analyzed with Cochran-Mantel-Haenszel tests stratified by investigator. Treatment by center interaction would be assessed with the Breslow-Day test. For the analysis of the percent change in inflammatory lesions, if the test for skewness (Zar, 1984) did not reject at 0.01, then the percent change was to be analyzed with an ANOVA with terms for treatment and pooled center. If the test for skewness was rejected, then the ranks of the percent changes were to be analyzed. Treatment by center interaction was to be assessed at 0.10, by adding the interaction term to the ANOVA model. Confidence intervals for the percent change in non-inflammatory lesion counts were to be constructed with least squares means and the mean square for error adjusted for center. The confidence intervals for the percent change in non-inflammatory lesions were to be compared to a non-inferiority margin of 15%. For all analyses, centers with fewer than 10 subjects per treatment arm were to be pooled in the analysis with the smallest center pooled with the largest center, etc. among the centers that had fewer than 10 subjects per arm.

The ITT population was defined as all subjects receiving study drug. Missing data in the ITT population was handled with LOCF. The per protocol population was defined as all subjects who completed treatment through Day 84 within a window of -3 to +5 days, were at least 80% compliant with study medication, and who took no prohibited concomitant medications. Subjects discontinuing due to adverse events at least possibly related to the study drug were also included in the per protocol population.

3.1.2 Protocol Discussions and Amendments

The sponsor and the Agency had a number of discussions regarding the study design during the protocol development stage. Although the sponsor and Agency agreed on most aspects of the protocol, the sponsor did not incorporate two of the Agency’s recommendations at the start of the trials. The Agency had recommended using an evaluator’s global that incorporated both inflammatory and non-inflammatory lesions and had recommended using a margin smaller than 15%, if feasible, to assess the non-inferiority of minocycline to placebo in terms of non-inflammatory lesions. The sponsor attempted to address the issue of the evaluator’s global by amending the protocol to add a

second global (the EGSA-NI) that incorporated both types of lesions as a secondary endpoint. As this amendment was instituted after the study began, not all subjects have evaluations on the EGSA-NI. Regarding the recommendation to use a non-inferiority margin smaller than 15%, the sponsor contended that any margin smaller than 15% would require an unreasonable increase in the sample size and designed the protocol with a 15% margin.

Since the time that the discussion with the sponsor was held regarding endpoints, the Agency has published a draft guidance on acne trials (Acne Vulgaris: Developing Drugs for Treatment) that states that for therapies targeting a single type of lesion the emphasis in the global on the non-target lesion type can be modified from what would be needed for a therapy targeting both types of lesions. In light of the Agency's current view on global assessments for targeted therapy and the fact that the sponsor added the EGSA-NI to the protocol after the study started, this reviewer agrees that the primary global assessment endpoint specified in the protocol, the EGSA, should be considered the primary global assessment, with the EGSA-NI as supportive. This reviewer agrees that it does not seem reasonable to require a non-inferiority margin for the non-targeted lesion type (secondary endpoint) that would require a substantial increase in sample size from what is needed to establish the efficacy for the targeted lesion type, and will review the analysis of the percent change in non-inflammatory lesions using the 15% margin specified in the protocol.

3.1.3 Subject Disposition

Subjects were enrolled in Studies 04 and 05 in a 2:1 ratio of minocycline to placebo. Study 04 enrolled 451 subjects (300 minocycline and 151 placebo) and Study 05 enrolled 473 subjects (315 minocycline and 158 placebo). Approximately 11% of subjects discontinued the study, with a slightly higher percentage of placebo subjects discontinuing versus minocycline (12% versus 10%). The most common reasons for discontinuation were loss to follow-up and withdrawal of consent and were similar for the two arms. The reasons for study discontinuation are presented in Table 5.

Table 5 – Reason for Study Discontinuation

	Study 04		Study 05	
	Minocycline	Placebo	Minocycline	Placebo
Number of Subjects	300	151	315	158
Subjects who Discontinued	34 (11%)	20 (13%)	28 (9%)	17 (11%)
<i>Adverse Event</i>	9 (3%)	2 (1%)	8 (3%)	3 (2%)
<i>Protocol Violation/Non-Compliance</i>	2 (<1%)	2 (1%)	2 (<1%)	2 (1%)
<i>Withdrawal of Consent</i>	11 (4%)	7 (5%)	7 (2%)	8 (5%)
<i>Lost to Follow-up</i>	10 (3%)	8 (5%)	11 (4%)	4 (3%)
<i>Other¹</i>	2 (<1%)	1 (<1%)	--	--

¹ Other = pregnancy (1 minocycline, 1 placebo) or subject moved (1 minocycline).

Note: There were 5 reported pregnancies in Study 04 (3 minocycline, 2 placebo). In addition to the subjects discontinued as 'Other' due to pregnancy, one subject (placebo) was classified as discontinuing due to an adverse event. The remaining two subjects (both minocycline) were considered to have completed the study. There were no pregnancies reported in Study 05.

Source: Table 9.1.1, pg 44 of file study-report-mp-0104-04 and pg 45 of file study-report-mp-0104-05.

Two subjects had screening data that is not included in any analyses. In Study 04, Subject 44017 was randomized to the study on March 12, 2004 but was not dispensed study drug because the subject was taking Zithromax (a prohibited medication). After a washout period, the subject was re-screened and re-randomized as Subject 44030 on April 19, 2004. The subject was randomized to minocycline both times. Data for Subject 44030 is included in analyses. In Study 05, Subject 61012 was lost to follow-up after the screening visit and did not return for the baseline visit and was never randomized.

3.1.4 Baseline and Demographic Data

The baseline demographic variables were generally balanced across treatment arms, though in Study 04, the placebo arm had slightly more black subjects and adult subjects than the minocycline arm. The studies enrolled more male than female subjects, more adolescent subjects than adult subjects, and mostly white subjects. Demographic data is presented in Table 6.

Table 6 –Demographic Data

		Study 04		Study 05	
		Minocycline N=300	Placebo N=151	Minocycline N=315	Placebo N=158
Gender	Male	171 (57%)	85 (56%)	182 (58%)	88 (56%)
	Female	129 (43%)	66 (44%)	133 (42%)	70 (44%)
Race	White	214 (71%)	97 (64%)	237 (75%)	121 (77%)
	Black	26 (9%)	22 (15%)	37 (12%)	17 (11%)
	Hispanic	51 (17%)	29 (19%)	26 (8%)	11 (7%)
	Am/AK Native	0 (0%)	2 (1%)	0 (0%)	0 (0%)
	Asian	4 (1%)	0 (0%)	7 (2%)	7 (4%)
	Other	5 (2%)	1 (<1%)	8 (3%)	2 (1%)
Age	Mean (SD)	19.2 (6.6)	21.3 (8.2)	20.0 (7.8)	19.6 (7.7)
	Range	12 - 63	12 - 45	12 - 51	12 - 53
	12 - 17	188 (63%)	80 (53%)	196 (62%)	95 (60%)
	≥ 18	112 (37%)	71 (47%)	119 (38%)	63 (40%)
Weight	99 – 131 lbs	65 (22%)	36 (24%)	80 (25%)	42 (27%)
	132 – 199 lbs	186 (62%)	96 (64%)	184 (58%)	97 (61%)
	200 – 300 lbs	49 (16%)	19 (13%)	51 (16%)	19 (12%)

Source: Table 9.4.1, pg 46, file study-report.mp-0104-04, and pg 47, file study-report.mp-0104-05.

Subjects were to have a score of moderate or severe on the EGSA at baseline. Approximately 73% of subjects were enrolled with a score of moderate. One subject in Study 05 was enrolled with a score of mild and two subjects in Study 04 were enrolled with scores of very severe. The inclusion criteria stated that subjects were to have between 25 and 75 inflammatory lesions and there were no restrictions on the number of non-inflammatory lesions. A few subjects were enrolled with inflammatory counts outside the 25 to 75 lesion range. Baseline severity in terms of the EGSA, inflammatory and non-inflammatory counts is balanced across the minocycline and placebo arms. The baseline acne endpoints are presented in Table 7.

Table 7 – Baseline Acne Endpoints

	Study 04		Study 05	
	Minocycline N=300	Placebo N=151	Minocycline N=315	Placebo N=158
<i>EGSA</i>				
0=Clear	0	0	0	0
1=Almost Clear	0	0	0	0
2=Mild	0	0	1 (<1%)	0
3=Moderate	210 (70%)	105 (70%)	237 (75%)	121 (77%)
4=Severe	89 (30%)	45 (30%)	77 (24%)	37 (23%)
5=Very Severe	1 (<1%)	1 (<1%)	0	0
<i>Inflammatory</i>				
Mean (SD)	39.1 (13.3)	38.7 (13.0)	38.9 (11.7)	38.4 (11.8)
Range	24-81	23-87	20-82	25-82
<i>Non-Inflam.</i>				
Mean (SD)	47.3 (33.6)	46.7 (34.2)	44.4 (21.5)	44.4 (20.7)
Range	0-196	0-234	0-128	5-109

Source: Reviewer analysis.

3.1.5 Primary Efficacy Endpoints

The sponsor designed Studies 04 and 05 to support the more limited indication of inflammatory lesions of acne. The studies had two primary efficacy endpoints, the percent change in inflammatory lesions and success (clear/almost clear) on the Evaluator's Global Severity Assessment [Inflammatory Lesions] (EGSA). Non-inflammatory lesions were assessed as a secondary endpoint.

3.1.5.1 Inflammatory Lesions

At each efficacy evaluation the investigator counted the number of inflammatory lesions on the forehead, nose, chin, and right and left cheeks. Inflammatory lesions were analyzed as the percent reduction in inflammatory lesions from baseline to Day 84. Since a test for the skewness of the distribution applied to the residuals from an ANOVA with factors of treatment and center was significant at 0.01 in both studies (Zar, 1984), per the protocol the sponsor analyzed the ranks of the percent reduction with ANOVA with factors of treatment and center. The results of the rank-transform analysis, as well as the results of the analysis on the original data for the ITT population are presented in Table 8. The conclusions for the two analyses are very similar, and the p-values for the rank-transform analysis (primary analysis) are <0.001 in both studies. In Study 04, the percent reduction in inflammatory lesions was 43% for minocycline versus 32% for placebo. In Study 05 the percent reduction in inflammatory lesions was 46% for minocycline versus 31% for placebo.

The conclusions were similar for the absolute reduction in inflammatory lesions. The results of the analysis of the absolute reduction are also presented in Table 8. In Study 04 minocycline reduced an average of 4 more inflammatory lesions than placebo (16.5 vs. 12.3) and in Study 05 minocycline reduced an average of 6 more inflammatory lesions

than placebo (17.2 vs. 11.3). The p-values for the analysis on the absolute change ($p \leq 0.004$) are comparable to those of the analysis on the rank-transformed percent change and the analysis on the original scale for the percent change. The results for the per protocol population are similar to those from the ITT population and are presented in Table 9. Treatment by center interaction was not significant in the analysis of the rank-transformed data in either study. However, in Study 05, the treatment by center interaction term was significant ($p < 0.10$) for the absolute and percent reduction in lesions analyses on the original scale. See Section 3.1.9 for additional discussion on the effect of center.

Table 8 –Inflammatory Lesion Efficacy Results at Day 84 (ITT)

	Study 04			
	Minocycline N=300	Placebo N=151	p-value ¹ (Ranked)	p-value ² (Unranked)
Change from Baseline	16.5 (15.1)	12.3 (15.8)	0.001	0.004
Percent Change from Baseline	43.1% (36.7%)	31.7% (40.3%)	<0.001*	0.002
	Study 05			
	Minocycline N=315	Placebo N=158	p-value ¹ (Ranked)	p-value ³ (Unranked)
Change from Baseline	17.2 (13.6)	11.3 (18.1)	<0.001	<0.001
Percent Change from Baseline	45.8% (34.8%)	30.8% (47.0%)	<0.001*	<0.001

* Primary Analysis

Values given are *Mean (SD)*

¹p-value based on ANOVA on the ranks with terms for treatment and center

²p-value based on ANOVA on the original data with terms for treatment and center

³p-value based on ANOVA on the original data with terms for treatment, center, and treatment by center interaction (significant interaction: $p < 0.001$)

Source: Table 10.2.1.1.1, pg 48, file study-report-mp-0104-04, and pg 49, file study-report-mp-0104-04, and reviewer analysis.

Table 9 –Inflammatory Lesion Efficacy Results at Day 84 (PP)

	Study 04			
	Minocycline N=300	Placebo N=151	p-value ¹ (Ranked)	p-value ² (Unranked)
Change from Baseline	17.6 (15.6)	14.3 (15.5)	0.017	0.054
Percent Change from Baseline	46.3% (37.6%)	36.4% (39.2%)	0.006	0.023
	Study 05			
	Minocycline N=315	Placebo N=158	p-value ¹ (Ranked)	p-value ³ (Unranked)
Change from Baseline	17.9 (13.0)	11.7 (19.2)	<0.001	<0.001
Percent Change from Baseline	48.3% (33.8%)	31.0% (49.4%)	<0.001	<0.001

Values given are *Mean (SD)*

¹p-value based on ANOVA on the ranks with terms for treatment and center

²p-value based on ANOVA on the original data with terms for treatment and center

³p-value based on ANOVA on the original data with terms for treatment, center, and treatment by center interaction (significant interaction: $p < 0.001$)

Source: Reviewer analysis.

3.1.5.2 Evaluator's Global Severity Assessment (Inflammatory Lesions)

The Evaluator's Global Severity Assessment focused on inflammatory lesions. The EGSA is presented again in Table 10. Subjects were to have a score or moderate (3) or severe (4) at baseline. Success at Day 84 was defined as a score of clear (0) or almost clear (1).

Table 10- Evaluator's Global Severity Assessment [Inflammatory Lesions] (EGSA)

Score	Grade	Description
0	Clear	No evidence of papules or pustules (inflammatory lesions)
1	Almost clear	Rare (eg, <5) non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red)
2	Mild	Few (eg, <10) inflammatory lesions (papules/pustules only; no nodulocystic lesions)
3	Moderate	Multiple (eg, between 25 and 40) inflammatory lesions present; many papules/pustules; there may or may not be a few nodulocystic lesions
4	Severe	Inflammatory lesions are more apparent, many papules/pustules (eg, between 40 and 75); there may or may not be a few nodulocystic lesions
5	Very Severe	Highly inflammatory lesions predominate, many papules/pustules, and many nodulocystic lesions

Success on the EGSA was statistically significant in both Studies 04 and 05 ($p \leq 0.018$). For the ITT population, in Study 04 the success rate on minocycline was 17% versus 8% for placebo and in Study 05 the success rate on minocycline was 16% versus 9% for placebo. Day 84 results for the EGSA in the ITT population are presented in Table 11. Results for the per protocol population are similar and are presented in Table 12.

Table 11 – Evaluator's Global Severity Assessment (EGSA) at Day 84 (ITT)

	Study 04		Study 05	
	Minocycline N=300	Placebo N=151	Minocycline N=315	Placebo N=158
0=Clear	3 (1%)	1 (<1%)	8 (3%)	0 (0%)
1=Almost Clear	49 (16%)	11 (7%)	42 (13%)	15 (9%)
2=Mild	110 (37%)	47 (31%)	109 (35%)	48 (30%)
3=Moderate	113 (38%)	68 (45%)	129 (41%)	72 (46%)
4=Severe	22 (7%)	23 (15%)	27 (8%)	21 (13%)
5=Very Severe	3 (1%)	1 (<1%)	0 (0%)	2 (1%)
Success ¹	52 (17%)	12 (8%)	50 (16%)	15 (9%)
p-value	0.006		0.018	

¹ Clear or Almost Clear. P-value based on the CMH test stratified on center.

Source: Reviewer analysis.

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Table 12 – Evaluator’s Global Severity Assessment (EGSA) at Day 84 (PP)

	Study 04		Study 05	
	Minocycline N=215	Placebo N=113	Minocycline N=258	Placebo N=126
0=Clear	3 (1%)	1 (1%)	6 (2%)	0 (0%)
1=Almost Clear	41 (19%)	10 (9%)	39 (15%)	13 (10%)
2=Mild	81 (38%)	36 (32%)	94 (36%)	37 (29%)
3=Moderate	72 (33%)	50 (44%)	99 (38%)	55 (44%)
4=Severe	16 (7%)	15 (13%)	20 (8%)	19 (15%)
5=Very Severe	2 (1%)	1 (1%)	0 (0%)	2 (2%)
Success ¹	44 (20%)	11 (10%)	45 (17%)	13 (10%)
p-value	0.014		0.034	

¹ Clear or Almost Clear. P-value based on the CMH test stratified on center.

Source: Reviewer analysis.

3.1.6 Secondary Efficacy Endpoints

3.1.6.1 Non-inflammatory Lesions

The effect of minocycline on non-inflammatory lesions was analyzed as a secondary endpoint. The sponsor pre-specified a non-inferiority margin of 15% to assess the non-inferiority of minocycline to placebo for the percent reduction in non-inflammatory lesions. Both studies met the non-inferiority criterion for the percent reduction in lesions for the ITT and per protocol populations. In Study 04, the 97.5% lower confidence bound for the treatment difference (minocycline – placebo) was -10.2% (15.6% for minocycline and 14.3% for placebo) for the ITT population. In Study 05 the 97.5% lower confidence bound for the treatment difference (minocycline – placebo) was +4.8% (13.8% for minocycline and -1.6% for placebo) for the ITT population. The results in the per protocol population are similar. In the two studies, the minocycline arms behaved similarly, but the placebo arms were more dissimilar. Subjects on the placebo arm showed some improvement on average for non-inflammatory lesions in Study 04, but demonstrated worsening in Study 05. The finding of worsening on average on the placebo arm in Study 05 is due to the presence of a few extreme outliers, as the median is positive. The non-inflammatory lesion results are presented in Table 13 for the ITT population and in Table 14 for the per protocol population.

The confidence intervals are constructed from least squares means adjusted for center. The confidence bounds calculated by the reviewer differ slightly from those calculated by the sponsor. This appears to be due to the standard error used in the calculation. The reviewer’s intervals are constructed with the mean square for error, while the sponsor’s appear to be computed using the individual standard deviation estimates for the two treatment arms. The protocol states that the mean square for error is to be used in the calculation. The sponsor’s intervals are slightly wider than those calculated by the reviewer. Since the non-inferiority criterion was met in both studies, we can conclude that minocycline does not cause a substantial (> 15%) worsening of non-inflammatory lesions relative to placebo.

Table 13 –Non-Inflammatory Lesion Results at Day 84 (ITT)

	Study 04		97.5% LCL
	Minocycline N=300 ¹	Placebo N=151 ¹	
<i>Change from Baseline</i>			
Median	8	7	
Mean (SD)	9.2 (21.4)	8.2 (22.3)	
LSMean (LS-SD)	9.8 (21.6)	8.7 (21.4)	-3.1 ²
<i>Percent Change from Baseline</i>			
Median	25.0%	21.6%	
Mean (SD)	13.7% (59.9%)	12.6% (58.1%)	
LSMean (LS-SD)	15.6% (59.8%)	14.3% (59.2%)	-10.2% ²
	Study 05		97.5% LCL
	Minocycline N=315 ¹	Placebo N=158	
<i>Change from Baseline</i>			
Median	10	3.5	
Mean (SD)	9.3 (19.0)	4.8 (18.5)	
LSMean (LS-SD)	8.8 (20.3)	4.4 (19.4)	1.0 ²
<i>Percent Change from Baseline</i>			
Median	23.1%	11.0%	
Mean (SD)	14.5% (53.5%)	-0.9% (65.0%)	
LSMean (LS-SD)	13.8% (62.4%)	-1.6% (59.5%)	4.8% ²

LCL = Lower Confidence Limit. Least squares means (LSMeans) are adjusted for center.

¹ One subject in each marked treatment group had 0 non-inflammatory lesions at baseline and percent change cannot be computed

² The reported bounds are from the reviewer’s analysis. The sponsor reports lower bounds of -3.1 (Change, Study 04), -10.4% (%Change, Study 04), 0.7 (Change, Study 05), and 3.8% (%Change, Study 05).

Source: Reviewer analysis and Table 10.3.1.1, pg 53, file study-report-mp-0104-04, and pg 54, file study-report-mp-0104-05.

Table 14 –Non-Inflammatory Lesion Results at Day 84 (PP)

	Study 04		97.5% LCL
	Minocycline N=215 ¹	Placebo N=113	
<i>Change from Baseline</i>	11.0 (22.5)	8.9 (22.1)	-2.9
<i>Percent Change from Baseline</i>	19.8% (61.7%)	15.4% (60.8%)	-9.4%
	Study 05		97.5% LCL
	Minocycline N=258 ¹	Placebo N=126	
<i>Change from Baseline</i>	9.2 (20.0)	5.9 (19.2)	-0.5
<i>Percent Change from Baseline</i>	16.1% (58.8%)	0.2% (56.5%)	4.8%

LCL = Lower Confidence Limit.

Table displays least squares means and standard deviations adjusted for center.

¹ One subject in each marked treatment group had 0 non-inflammatory lesions at baseline and percent change cannot be computed

Source: Reviewer analysis

3.1.6.2 Two Grades Improvement on the EGSA

In addition to the primary analysis of defining success as clear or almost clear at Day 84, the sponsor analyzed the proportion of subjects with at least two grades improvement on the EGSA. The results of this analysis are presented in Table 15. The success rates increase in both arms relative to the primary analysis with the inclusion of subjects who went from severe to mild, but the treatment effect between the two arms (8-10%) is roughly the same as for the primary analysis where success was defined as achieving clear or almost clear.

Table 15 – At Least Two Grades Improvement on the EGSA at Day 84 (ITT)

	Study 04		Study 05	
	Minocycline N=300	Placebo N=151	Minocycline N=315	Placebo N=158
Success ¹	71 (24%)	21 (14%)	62 (20%)	19 (12%)
p-value	0.011		0.012	

¹ Success is defined as at least two grades improvement from baseline. P-value is from the CMH test stratified by center.

Source: Table 10.3.2.1.1 pg 55, file study-report-mp-0104-04, and pg 56, file study-report-mp-0104-05.

3.1.7 Post hoc Efficacy Endpoints

Based on the Agency's feedback, the sponsor added a global assessment that took into account both inflammatory and non-inflammatory lesions and did not include any references to lesion count ranges, the EGSA-NI. Refer to Table 4 for the definition of the EGSA-NI. The EGSA-NI was incorporated into Protocols 04 and 05 after patient recruitment had begun, therefore, not all subjects were evaluated on the EGSA-NI. Results for success (clear/almost clear) on the EGSA-NI on the observed data population are presented in Table 16. The success rates are similar to those observed for the EGSA. Among subjects with both an EGSA and an EGSA-NI evaluation, the correlation between the two scores is 0.93 in Study 04 and 0.88 in Study 05 at Day 84. The p-value for success on the EGSA-NI in Study 05 is greater than 0.05 (p=0.065), which may be partially due to the reduced sample size for this endpoint.

Table 16 – Evaluator's Global Severity Assessment (Inflammatory and Non-Inflammatory Lesions) [EGSA-NI] at Day 84 (Observed Data)

	Study 04		Study 05	
	Minocycline N=279	Placebo N=136	Minocycline N=283	Placebo N=141
0=Clear	4 (1%)	1 (<1%)	1 (<1%)	0 (0%)
1=Almost Clear	46 (16%)	13 (10%)	29 (10%)	7 (5%)
2=Mild	97 (35%)	35 (26%)	102 (36%)	41 (29%)
3=Moderate	110 (39%)	65 (48%)	129 (46%)	72 (51%)
4=Severe	20 (7%)	19 (14%)	21 (7%)	20 (14%)
5=Very Severe	2 (<1%)	3 (2%)	1 (<1%)	1 (<1%)
Success ¹	50 (18%)	14 (10%)	30 (11%)	7 (5%)
p-value	0.040		0.065	

¹ Clear or Almost Clear

Source: Reviewer analysis.

3.1.8 Efficacy Results over Time

The percent reduction in lesion counts generally increased throughout the study (from Day 28 to Day 84), with the treatment effect for inflammatory lesions staying either fairly constant (Study 04) or slightly increasing (Study 05) over time. Figure 1 and Figure 2 present the percent change in inflammatory and non-inflammatory lesions over time for the two studies.

Figure 1 – Percent Change in Lesion Counts from Day 28 to Day 84 (Study 04)

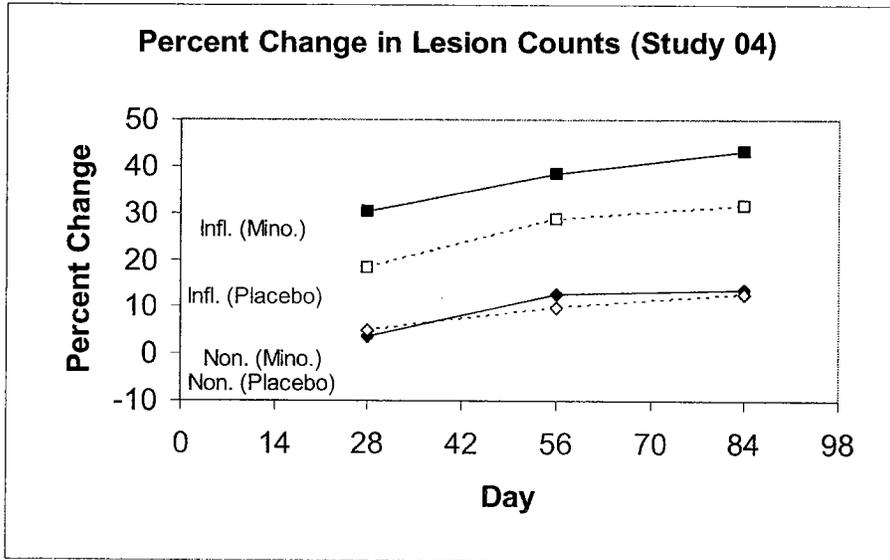
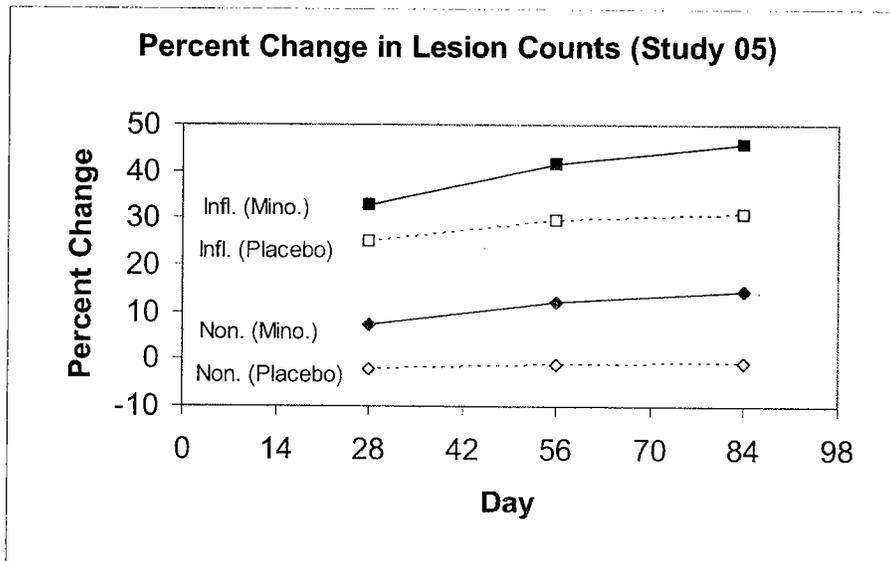


Figure 2 – Percent Change in Lesion Counts from Day 28 to Day 84 (Study 05)



The Agency asked the sponsor to follow-up subjects post-treatment to observe the effects following cessation of treatment. Some subjects were rolled over into a long-term open-label safety study where minocycline was to be used “as needed” (based on the EGSA

and investigator judgment) over a two-year period. Subjects electing not to enter the long-term study were supposed to return for a 4-week follow-up visit at Day 112. Approximately half of the subjects returned for the Day 112 visit. Comparisons of Day 84 (end of treatment) and Day 112 (post-treatment) efficacy results are presented in Table 17. Since only half of the subjects returned for a Day 112 visit, missing values were not imputed, only results for observed cases are presented. To present a fair comparison, the Day 84 results are presented only among the subset of subjects with a Day 112 evaluation. Note that subjects with a Day 112 evaluation tend to have slightly higher reductions in inflammatory lesions than the study population as a whole (refer back to Table 8). It appears that among the subjects who had both a Day 84 and Day 112 evaluation, the subjects regained an average of 1-3 inflammatory lesions or about 4-8% of their baseline inflammatory lesions during the off-treatment follow-up period. In terms of the EGSA, the number of minocycline subjects with scores of clear/almost clear actually increased between Day 84 and Day 112.

Table 17 – Day 84 and Day 112 Efficacy Results

	Study 04			
	Day 84		Day 112	
	Minocycline N=148 ¹	Placebo N=76 ¹	Minocycline N=148 ¹	Placebo N=76 ¹
<i>Inflammatory Lesions</i>				
Change from Baseline	18.5	14.2	16.6	13.1
Percent Change from Baseline	51.1%	40.0%	45.7%	36.3%
Clear/Alm. Clear on the EGSA	27 (18.2%)	10 (13.2%)	30 (20.3%)	8 (10.5%)
	Study 05			
	Day 84		Day 112	
	Minocycline N=170 ¹	Placebo N=76 ¹	Minocycline N=170 ¹	Placebo N=76 ¹
<i>Inflammatory Lesions</i>				
Change from Baseline	20.3	11.0	19.2	14.6
Percent Change from Baseline	54.2%	29.4%	50.4%	38.6%
Clear/Alm. Clear on the EGSA	33 (19.4%)	10 (13.2%)	37 (21.8%)	15 (19.7%)

¹ Computations for both visits are taken only over subjects with a Day 112 visit.

Source: Reviewer Analysis

3.1.9 Efficacy Results by Center

Study 04 did not have any evidence of a treatment by center interaction. For success on the EGSA, the p-value for the Breslow-Day test was 0.907. For the analysis of the percent reduction in inflammatory lesions based on the ranks, the p-value for the treatment by center interaction was 0.800. Study 05 did not have evidence of treatment by center interaction for the two primary efficacy analyses. For success on the EGSA the p-value for the Breslow-Day test was 0.116. For the analysis of the percent reduction in inflammatory lesions based on the ranks, the p-value for the treatment by center interaction was 0.363. Study 05 did, however, have some evidence of a treatment by center interaction in the analysis of the change and percent change in inflammatory lesions when the original data rather than the ranks were analyzed ($p < 0.001$).

Graphs of the mean reduction in inflammatory lesions and EGSA success rates are presented in Figure 3 through Figure 6. Most notable on these graphs is that two centers in Study 05 had substantial worsening of inflammatory lesions on the placebo arm, though these two centers were relatively small (10 and 18 subjects). At Center 61, 2 out of 3 placebo subjects worsened from baseline and at Center 62, 3 out of 6 placebo subjects worsened, including one subject who worsened by over 300%. Overall in Study 05, approximately 10% of minocycline and 14% of placebo subjects had worsening inflammatory lesion counts at the end of treatment. These two centers appear to contribute to the significant treatment by center interaction that is observed when the percent change and change in inflammatory lesions on the original scale, as opposed to the ranks, are analyzed.

Figure 3 – Percent Reduction in Inflammatory Lesions by Center (Study 04)

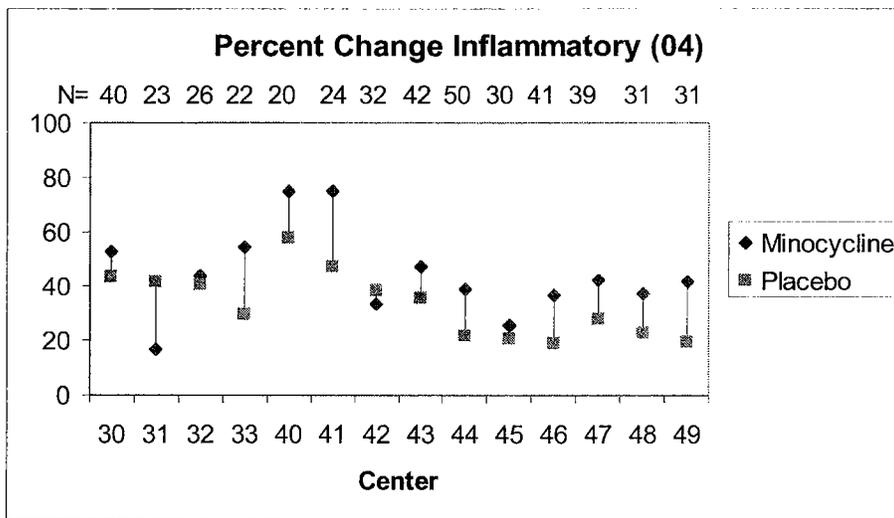
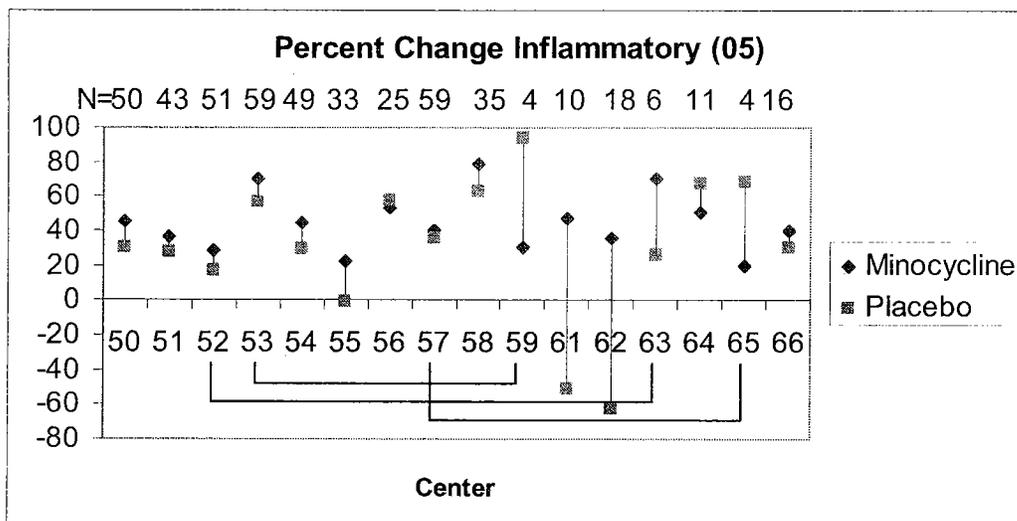


Figure 4 – Percent Reduction in Inflammatory Lesions by Center (Study 05)



Note: Brackets indicate the centers pooled in the sponsor's analysis.

Figure 5 – Success on the EGSA by Center (Study 04)

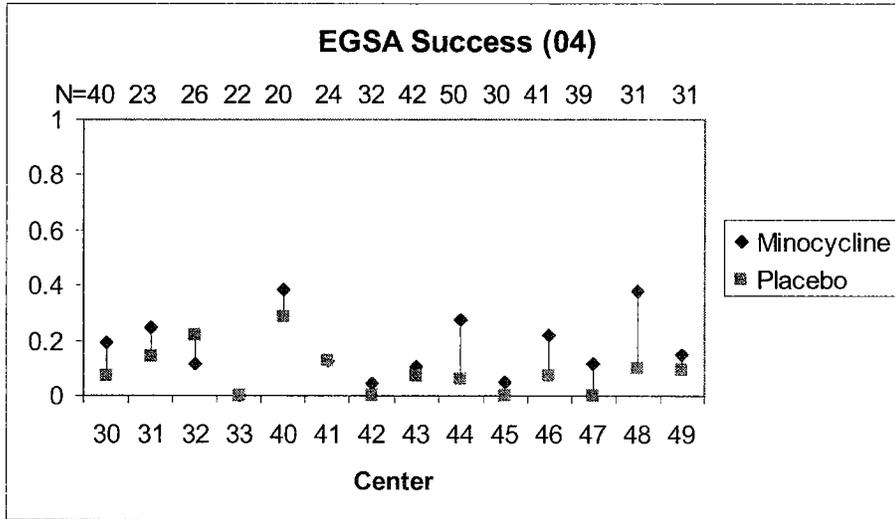
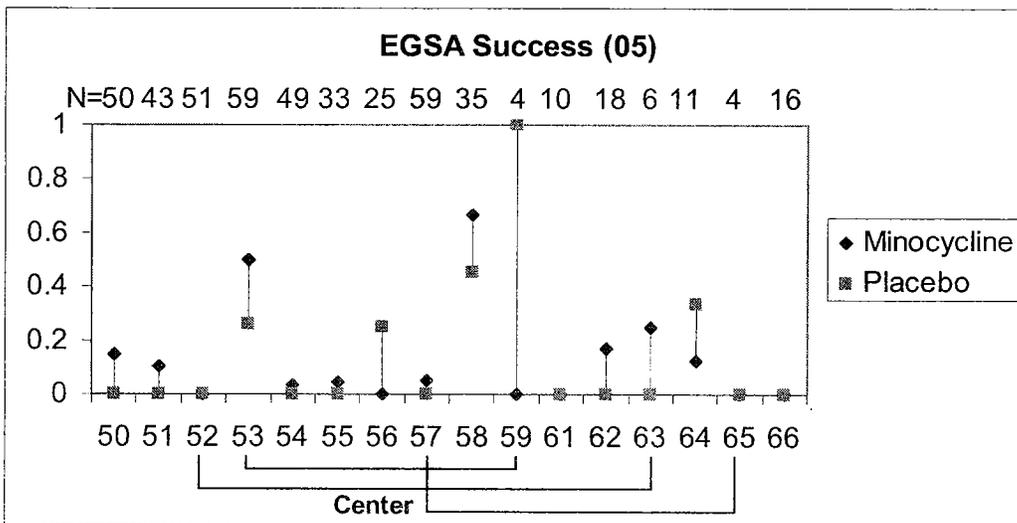


Figure 6 – Success on the EGSA by Center (Study 05)



Note: Brackets indicate the centers pooled in the sponsor's analysis.

All of the centers in Study 04 were large enough that no pooling was needed for the analysis. The smallest center in Study 04 had 13 minocycline and 7 placebo subjects. Study 05, however, had several small centers that were pooled in the analyses involving center. The three smallest centers which had 6 or fewer subjects each were each pooled with the three largest centers. The centers that were combined in the analysis are indicated by the brackets in Figure 4 (52/63, 53/59, and 57/65). The sponsor's pooling differed slightly from the algorithm in the statistical analysis plan. The algorithm stated that the smallest center with fewer than 10 subjects *per treatment arm* would be pooled with the largest center *with fewer than 10 subjects per treatment arm*, and so on. The

actual algorithm used by the sponsor was to pool the smallest center with fewer than 10 *total* subjects with the center with the largest enrollment (not restricted among the small centers), and so on. The impact of this change is minimal. If the centers are pooled according to the statistical analysis plan algorithm (pooling centers with fewer than 10 subjects per minocycline arm) the pooled centers in Study 05 would be: 59/64 and 61/63/65. The conclusions of a significant treatment effect for success on the EGSA and percent change in inflammatory lesions (rank analysis) are unchanged. The only interpretation change is that the Breslow-Day test for the EGSA analysis which was not significant under the sponsor's pooling algorithm ($p=0.116$) is significant under the algorithm that more closely follows the statistical analysis plan ($p=0.026$) in Study 05. The increased significance of the Breslow-Day test for the EGSA may be due to the pooled center 59/64, as both of these centers favored placebo over minocycline for the EGSA success, whereas in the sponsor's analysis, Center 59 was pooled with a much larger center that favored minocycline.

3.1.10 Dose Response (Study 01)

Prior to conducting the Phase 3 studies, the sponsor conducted a dose-ranging study (MP-0104-01) comparing 1 mg/kg, 2 mg/kg, and 3 mg/kg doses to placebo. The study was 12 weeks in duration and enrolled 233 treated subjects (59-1 mg/kg, 59-2 mg/kg, 60-3 mg/kg, and 55 placebo). The primary efficacy endpoint was the reduction in inflammatory lesions. One of the secondary endpoints was success (clear or almost clear) on the Static Global Assessment. The scale for the Static Global Assessment differed from the EGSA used in the Phase 3 trials and is defined in Table 18.

Table 18 – Static Global Assessment (Study 01)

Score	Grade	Description
4	Clear	No signs or symptoms of acne
3	Almost clear	Only minimal signs and symptoms of acne
2	Mild	Few to several papules/pustules
1	Moderate	Several to many pustules
0	Severe	Numerous and/or extensive papules/pustules

Baseline severity was not balanced across the treatment groups at baseline with the 2 mg/kg dose group having substantially higher baseline inflammatory counts than the other three dose groups. No dose-response trend for efficacy is observed as the two higher doses did not appear to have any efficacy benefit over the low dose (1 mg/kg) group. It is possible that the baseline imbalance may have contributed to the lack of observed trend.

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Table 19 – Efficacy Results at Day 84 for Study 01 (ITT)

	Minocycline 1 mg/kg N=59	Minocycline 2 mg/kg N=59	Minocycline 3 mg/kg N=60	Placebo N=55
<i>Inflammatory (mean)</i>				
Baseline	38.8	47.0	39.1	40.3
Change from BL	21.8	23.7	18.3	17.2
% Ch. from BL	56.8%	49.3%	46.6%	39.4%
SGA Success ¹	14 (23.7%)	10 (16.9%)	18 (30.0%)	8 (14.5%)

¹ Success is defined as Clear or Almost Clear

Source: Table 10.2.1, pg 35 and Table 14.2.5.1 pg 149 of file study-report-mp-0104-01.

Although there was no apparent trend for efficacy with increasing doses of minocycline, the adverse event rates were higher for some events in the higher dose arms. The 3 mg/kg dose arm had the highest number of subjects with adverse events (78% vs. 68%-71% for the other three arms). The adverse event rates for events occurring in at least 5% of the study subjects are presented in Table 20. The adverse events that had generally increased incidence with higher doses include vertigo, nausea, fatigue, malaise, dizziness, and headache. Based on the efficacy and safety results from this study, the sponsor elected to pursue the 1 mg/kg dose in Phase 3 trials.

Table 20 – Adverse Events (at least 5% Incidence) (Study 01)

	Minocycline 1 mg/kg N=59	Minocycline 2 mg/kg N=59	Minocycline 3 mg/kg N=60	Placebo N=55
All Adverse Events	41 (70%)	40 (68%)	47 (78%)	39 (71%)
Vertigo	1 (2%)	1 (2%)	5 (8%)	1 (2%)
Diarrhea	3 (5%)	1 (2%)	3 (5%)	1 (2%)
Gastrointestinal Pain	2 (3%)	3 (5%)	4 (7%)	7 (13%)
Nausea	4 (7%)	9 (15%)	13 (22%)	9 (16%)
Vomiting	1 (2%)	1 (2%)	3 (5%)	4 (7%)
Fatigue	3 (5%)	3 (5%)	6 (10%)	4 (7%)
Malaise	4 (7%)	6 (10%)	7 (12%)	3 (6%)
Upper Resp. Inf.	2 (3%)	4 (7%)	3 (5%)	4 (7%)
Sinusitis	0 (0%)	1 (2%)	0 (0%)	3 (6%)
Seasonal Allergy	0 (0%)	1 (2%)	0 (0%)	3 (6%)
Dizziness	9 (15%)	13 (22%)	14 (23%)	3 (6%)
Headache	21 (36%)	23 (39%)	25 (42%)	15 (27%)
Migraine	0 (0%)	3 (5%)	1 (2%)	0 (0%)
Mood Alterations	0 (0%)	3 (5%)	4 (7%)	3 (6%)
Nasopharyngitis	6 (10%)	2 (3%)	4 (7%)	4 (7%)
Acne Aggravated	1 (2%)	1 (2%)	3 (5%)	0 (0%)
Pruritus	1 (2%)	3 (5%)	2 (3%)	2 (4%)

Source: Table 11.2.1, pg 47 of file study-report-mp-0104-01.

3.2 Evaluation of Safety

3.2.1 Extent of Exposure

In Studies 04 and 05, compliance and the duration of exposure were similar for the two treatment arms. In Study 04, 85% of minocycline and 84% of placebo subjects took at least 80% of scheduled doses. The average number of dosing days was 82 on minocycline (range 6 – 117) and 81 on placebo (range 1 – 106) in Study 04. In Study 05, 89% of minocycline and 85% of placebo subjects took at least 80% of scheduled doses. The average number of dosing days was 82 on minocycline (range 1 – 120) and 81 on placebo (range 14 – 99).

3.2.2 Adverse Events

Approximately half of subjects in Studies 04 and 05 experienced adverse events throughout the study, with slightly more minocycline than placebo subjects experiencing adverse events. The events occurring in at least 5% of subjects in either treatment arm are presented in Table 21. For these most common events, fatigue and dizziness occurred more often among minocycline subjects than placebo subjects.

Table 21 – Adverse Events (at least 5% Incidence)

	Study 04		Study 05	
	Minocycline N=300	Placebo N=151	Minocycline N=315	Placebo N=158
All Adverse Events	160 (53%)	73 (48%)	178 (57%)	85 (54%)
Diarrhea	14 (5%)	8 (5%)	18 (6%)	12 (8%)
Gastrointestinal Pain	14 (5%)	11 (7%)	18 (6%)	7 (4%)
Nausea	25 (8%)	16 (11%)	35 (11%)	17 (11%)
Fatigue	25 (8%)	9 (6%)	34 (11%)	11 (7%)
Dizziness	21 (7%)	8 (5%)	29 (9%)	6 (4%)
Headache	57 (19%)	30 (20%)	74 (24%)	38 (24%)
Insomnia	7 (2%)	2 (1%)	7 (2%)	8 (5%)
Pruritus	15 (5%)	5 (3%)	15 (5%)	9 (6%)

Source: Table 11.2.1.1, pg 65 of file study-report-mp-0104-04 and pg 66 of file study-report-mp-0104-05.

Of particular interest with minocycline are the vestibular function related adverse events (nausea, dizziness, vomiting, tinnitus, and vertigo). The sponsor was particularly interested in these events during the first 5 dosing days and subjects were to record any of these symptoms in patient diaries over the first 5 days. The incidences of these 5 events, at any point during the study, are presented in Table 22. Figure 7 displays Kaplan-Meier curves for the two studies combined for the time to the first occurrence of any one of the five vestibular function related events. By the end of the study, a higher percentage of minocycline subjects than placebo subjects had experienced at least one vestibular related event, though during the first 5 dosing days, the curves for the two treatment arms are difficult to distinguish.

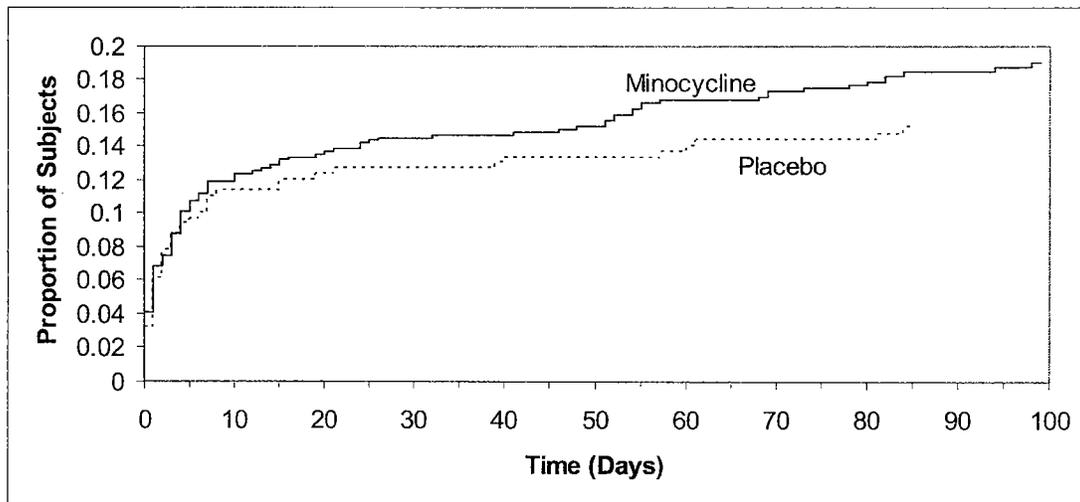
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Table 22 – Vestibular Function Related Adverse Events

	Study 04		Study 05	
	Minocycline N=300	Placebo N=151	Minocycline N=315	Placebo N=158
Nausea	25 (8.3%)	16 (10.6%)	35 (11.1%)	17 (10.8%)
Dizziness	21 (7.0%)	8 (5.3%)	29 (9.2%)	6 (3.8%)
Vomiting	7 (2.3%)	3 (2.0%)	6 (1.9%)	3 (1.9%)
Tinnitus	4 (1.3%)	2 (1.3%)	4 (1.3%)	2 (1.3%)
Vertigo	1 (0.3%)	0 (0%)	6 (1.9%)	3 (1.9%)

Source: Table 14.3.1.2, pg 224 of file study-report-mp-0104-04 and pg 235 of file study-report-mp-0104-05.

Figure 7 – Time to First Vestibular Event (Studies 04 and 05 Combined)



4 Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

The treatment effect for EGSA success was slightly larger for female subjects, while the treatment effect for the percent reduction in inflammatory lesions was slightly larger for male subjects. Males tended to have larger baseline inflammatory lesion counts than females. Efficacy results by gender are presented in Table 23.

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Table 23 – Efficacy Results by Gender (ITT)

	Study 04			
	Male		Female	
	Minocycline N=171	Placebo N=85	Minocycline N=129	Placebo N=66
<i>Inflammatory</i>				
Baseline	40.2 (13.9)	40.3 (13.1)	37.5 (12.1)	36.6 (12.7)
Change from BL	15.6 (15.1)	9.5 (17.2)	17.8 (15.0)	15.9 (13.0)
% Ch. from BL	38.0% (37.4)	23.5% (45.7)	49.8% (34.9)	42.2% (29.3)
EGSA Success	25 (14.6%)	7 (8.2%)	27 (20.9%)	5 (7.6%)
	Study 05			
	Male		Female	
	Minocycline N=182	Placebo N=88	Minocycline N=133	Placebo N=70
<i>Inflammatory</i>				
Baseline	40.9 (12.4)	40.6 (13.3)	36.1 (10.0)	35.7 (8.9)
Change from BL	17.6 (13.3)	11.3 (20.1)	16.6 (14.1)	11.2 (15.3)
% Ch. from BL	44.9% (33.1)	27.2% (53.0)	47.0% (37.2)	35.3% (37.9)
EGSA Success	25 (13.7%)	10 (11.4%)	25 (18.8%)	5 (7.1%)

Note: For lesion counts, values given are *Mean (SD)* and for EGSA success they are *Count (Percent)*.
Source: Reviewer analysis.

The treatment effect for white subjects was generally larger than for those of non-white subjects, though the number of non-white subjects was small relative to the number of white subjects. The efficacy results by race are presented in Table 24 and .

Table 24 – Efficacy Results by Race (Study 04) (ITT)

	White		Black	
	Minocycline N=214	Placebo N=97	Minocycline N=26	Placebo N=22
<i>Inflammatory</i>				
Baseline	40.0 (14.1)	40.5 (14.0)	36.2 (10.9)	34.2 (8.3)
Change from BL	15.6 (15.2)	11.1 (16.3)	15.1 (13.9)	15.5 (8.6)
% Ch. from BL	39.7% (37.1)	25.5% (37.7)	46.6% (39.4)	47.0% (26.7)
EGSA Success	40 (18.7%)	5 (5.2%)	4 (15.4%)	2 (9.1%)
	Hispanic		Other	
	Minocycline N=51	Placebo N=29	Minocycline N=9	Placebo N=3
<i>Inflammatory</i>				
Baseline	37.3 (11.4)	35.5 (11.2)	34.1 (4.2)	43.0 (17.8)
Change from BL	22.0 (14.8)	15.8 (12.6)	12.3 (11.0)	-5.0 (46.8)
% Ch. from BL	57.1% (31.9)	45.5% (37.3)	34.6% (31.0)	-15.6% (126.7)
EGSA Success	7 (13.7%)	4 (13.8%)	1 (11.1%)	1 (33.3%)

Note: For lesion counts, values given are *Mean (SD)* and for EGSA success they are *Count (Percent)*.
Source: Reviewer analysis.

Table 25 – Efficacy Results by Race (Study 05) (ITT)

	White		Black	
	Minocycline N=237	Placebo N=121	Minocycline N=37	Placebo N=17
<i>Inflammatory</i>				
Baseline	39.2 (11.6)	39.1 (11.7)	35.5 (10.5)	31.8 (5.4)
Change from BL	17.0 (14.0)	9.4 (18.2)	18.5 (13.7)	16.1 (10.8)
% Ch. from BL	45.0% (35.6)	26.1% (48.9)	51.1% (35.2)	51.2% (33.8)
EGSA Success	34 (14.4%)	9 (7.4%)	11 (29.7%)	3 (17.7%)
	Hispanic		Other	
	Minocycline N=26	Placebo N=11	Minocycline N=15	Placebo N=9
<i>Inflammatory</i>				
Baseline	41.8 (13.4)	42.7 (16.7)	35.9 (10.1)	37.1 (12.0)
Change from BL	18.7 (11.8)	17.4 (24.2)	14.2 (10.3)	20.0 (14.8)
% Ch. from BL	48.4% (31.8)	35.9% (46.7)	40.6% (31.2)	49.6% (26.7)
EGSA Success	3 (11.5%)	2 (18.2%)	2 (13.3%)	1 (11.1%)

Note: For lesion counts, values given are *Mean (SD)* and for EGSA success they are *Count (Percent)*.

Adult subjects tended to have better efficacy outcomes than adolescent subjects regardless of treatment assignment (minocycline or placebo). In Study 04 the treatment effect for the primary endpoints was similar for the two age groups. In Study 04, however, the observed treatment effect for EGSA success was larger for adult subjects, while the observed treatment effect for lesion counts was larger for adolescent subjects. Efficacy results by age group are presented in Table 26.

Table 26 –Efficacy Results by Age (ITT)

	Study 04			
	< 18 years		≥ 18 years	
	Minocycline N=188	Placebo N=80	Minocycline N=112	Placebo N=71
<i>Inflammatory</i>				
Baseline	40.3 (14.2)	41.0 (14.0)	37.0 (11.3)	36.0 (11.3)
Change from BL	14.2 (15.6)	9.7 (16.4)	20.4 (13.3)	15.3 (14.7)
% Ch. from BL	36.0 (38.4)	21.8 (40.4)	55.0 (30.3)	42.8 (37.5)
EGSA Success	27 (14.4%)	3 (3.8%)	25 (22.3%)	9 (12.7%)
	Study 05			
	< 18 years		≥ 18 years	
	Minocycline N=196	Placebo N=95	Minocycline N=119	Placebo N=63
<i>Inflammatory</i>				
Baseline	40.5 (12.3)	39.9 (12.3)	36.2 (10.0)	36.2 (10.7)
Change from BL	17.1 (14.0)	7.7 (19.7)	17.3 (13.1)	16.7 (13.9)
% Ch. from BL	43.5% (33.7)	21.1% (53.2)	49.5% (36.4)	45.4% (30.5)
EGSA Success	24 (12.2%)	7 (7.4%)	26 (21.9%)	8 (12.7%)

Note: For lesion counts, values given are *Mean (SD)* and for EGSA success they are *Count (Percent)*.

4.2 Other Special/Subgroup Populations

The treatment effect for both EGSA success and inflammatory lesions is larger for subjects with moderate disease at baseline than for those with severe disease. Efficacy results by baseline severity are presented in Table 27. Table 27 also presents the number of subjects achieving clear, almost clear, or mild on the EGSA at Day 84. Among subjects with severe disease at baseline this represents at least two grades reduction, and the treatment effect is roughly 5% for the two studies, which is smaller than the treatment effect observed for moderate baseline subjects for either the clear/almost clear or clear/almost clear/mild definition of success.

Table 27 – Efficacy Results by Baseline Severity (ITT)

	Study 04			
	Moderate		Severe	
	Minocycline N=210	Placebo N=105	Minocycline N=90	Placebo N=46
<i>Inflammatory</i>				
Baseline	33.3 (7.7)	32.7 (7.2)	52.5 (13.6)	52.3 (13.2)
Change from BL	15.1 (13.0)	9.5 (14.6)	19.9 (18.7)	18.8 (16.6)
% Ch. from BL	44.5% (37.8)	29.6% (43.8)	39.8% (34.0)	36.4% (30.8)
<i>EGSA</i>				
Clear/AC	45 (21.4%)	9 (8.6%)	7 (7.8%)	3 (6.5%)
Clear/AC/Mild	136 (64.8%)	48 (45.7%)	26 (28.9%)	11 (23.9%)
	Study 05			
	Moderate		Severe	
	Minocycline N=238	Placebo N=121	Minocycline N=77	Placebo N=37
<i>Inflammatory</i>				
Baseline	34.6 (8.2)	34.6 (8.2)	52.1 (10.8)	51.0 (13.2)
Change from BL	16.5 (12.4)	10.2 (18.4)	19.3 (16.8)	14.5 (16.7)
% Ch. from BL	48.2% (35.4)	31.7% (51.4)	38.4% (32.0)	27.8% (28.6)
<i>EGSA</i>				
Clear/AC	46 (19.3%)	13 (10.7%)	4 (5.2%)	2 (5.4%)
Clear/AC/Mild	143 (60.1%)	57 (47.1%)	16 (20.8%)	6 (16.2%)

Note: For lesion counts, values given are *mean (sd)* and for EGSA success they are *count (percent)*.
Source: Reviewer analysis.

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

Studies 04 and 05 were designed to assess minocycline in the treatment of inflammatory lesions of acne vulgaris rather than the full acne vulgaris indication. As such, the primary efficacy endpoints were the percent change in inflammatory lesions and an EGSA which focused on inflammatory lesions. As a secondary endpoint, the study assessed the non-inferiority of non-inflammatory lesions relative to placebo. The study met all of its pre-specified efficacy objectives. All primary efficacy endpoints were statistically significant

in both studies and the results are summarized in Table 28. The distribution of the percent reduction in inflammatory lesions was highly skewed and therefore the primary analysis was based on the ranks. The analyses based on the original data (non-transformed percent reductions) as well as the analyses based on the absolute change in lesions lead to the same conclusions as the analyses based on the ranks ($p \leq 0.004$). The study also met its prespecified non-inferiority criteria for non-inflammatory lesions with lower confidence bounds of -10.2% and +4.8% for the difference (minocycline – placebo) in the percent reduction in non-inflammatory lesions. Efficacy across subgroups (gender, race, age, and baseline severity) varied slightly in terms of both the treatment effect (minocycline – placebo) and the individual treatment estimates with females, adult subjects, and subjects with moderate disease often faring better than males, adolescent subjects, and subjects with severe disease. However, the differences were not extreme and in nearly every subgroup minocycline had better results than placebo.

Table 28 – Primary Efficacy Results

	Study 04		Study 05	
	Minocycline N=300	Placebo N=151	Minocycline N=315	Placebo N=158
Mean Percent Change in Inflammatory Lesions	43.1%	31.7%	45.8%	30.8%
	p < 0.001		p < 0.001	
No. (%) of Subjects Clear or Almost Clear on the EGSA	52 (17.3%)	12 (7.9%)	50 (15.9%)	15 (9.5%)
	p = 0.006		p = 0.018	

During the protocol planning stage, the Division and sponsor engaged in discussions about the most appropriate type of global evaluation to support an indication of inflammatory lesions. During the discussions the Division recommended using a global evaluation that incorporated both inflammatory and non-inflammatory lesions. The sponsor was not able to incorporate such a global before the study started, but added a second global assessment via an amendment after the study began. Consequently not all subjects have evaluations on the global that encompasses both lesion types. The two global evaluations are highly correlated ($r = 0.9$) among subjects with both evaluations. Since (1) the Division's current thinking is that it may be acceptable to use a global evaluation that emphasizes one lesion type when targeting an indication for only that lesion type as noted in the draft acne guidance, and (2) the comprehensive global was added to the protocol after the study started, the prespecified EGSA will be considered the primary endpoint.

Compliance and adverse event rates were similar for the minocycline and placebo treatment groups. Most individual adverse events occurred at similar rates for the two arms. Two events that occurred at slightly higher rates on the minocycline arm were fatigue (9.6% vs. 6.5%) and dizziness (8.1% vs. 4.5%). Other vestibular function related events (nausea, vomiting, tinnitus, vertigo) occurred at similar rates for both the minocycline and placebo arms.

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5.2 Conclusions and Recommendations

Two studies demonstrate that minocycline — are statistically superior to placebo in the treatment of inflammatory lesions of acne in terms of the percent reduction in inflammatory lesions and success (clear or almost clear) on the Evaluator's Global Severity Assessment (EGSA) after 84 days (12 weeks) of treatment. In Study 04, minocycline subjects had a mean percent reduction in inflammatory lesions of 43% versus 32% for placebo. Similarly, in Study 05, minocycline subjects had a mean percent reduction in inflammatory lesions of 46% versus 31% for placebo. Both studies had p-values were <0.001 for the percent reduction in inflammatory lesions. On the EGSA, 17% of minocycline subjects and 8% of placebo subjects were clear or almost clear at Day 84 in Study 04 (p=0.006). In Study 05, 16% of minocycline subjects and 9% of placebo subjects were clear or almost clear on the EGSA at Day 84 (p=0.018). The studies also demonstrated that minocycline is non-inferior to placebo in terms of non-inflammatory lesions with a non-inferiority margin of 15% (97.5% lower confidence bounds of -10.2% for Study 04 and +4.8% for Study 05.)

Appendix (Reference)

Zar JH. Biostatistical Analysis. Upper Saddle River, New Jersey: Prentice Hall, 1984.

Signatures/Distribution List

Primary Statistical Reviewer: Kathleen Fritsch, Ph.D.

Date: 3/17/2006

Statistical Team Leader: Mohamed Alosch, Ph.D.

cc:

Archival NDA

HFD-540/Kukich

HFD-540/Luke

HFD-540/Nikhar

HFD-540/Curtis

HFD-700/O'Neill

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HFD-725/Huque

HFD-725/Lin

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/s/

Kathleen Fritsch
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Mohamed Alesh
4/3/2006 09:02:42 AM
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**Statistical Review and Evaluation
Fileability Review**

NDA: 50-808/N-000
Name of Drug: SOLODYN (minocycline hydrochloride) modified release
 45 mg, 90 mg, and 135 mg
Applicant: Medicis
Indication: Inflammatory Lesions of Acne Vulgaris
Filing Date: August 22, 2005
Fileability Meeting Date: August 15, 2005
User Fee Date: May 8, 2006
Statistical Reviewer: Kathleen Fritsch, Ph.D.
Clinical Reviewer: Bindi Nikhar, M.D.

Clinical Studies: Phase 2 dose ranging: MP-0104-01; Phase 3: MP-0104-04, MP-0104-05; Long term safety: MP-0104-07

I. ORGANIZATION AND DATA PRESENTATION	YES/NO/NA
A. Is there a comprehensive table of contents with adequate indexing and pagination?	YES ¹
B. Are the original protocols, protocol amendments, and proposed label provided?	YES
C. Are the following tables/listings provided in each study report?	
1. Patient profile listings by center, for all enrolled patients.	YES
2. Discontinued subject tables by center (includes reason and time of loss).	YES
3. Subgroup analysis summary tables (gender, age, race, etc.)	YES
4. Adverse event listings by center and time of occurrence.	YES
D. Have the data been submitted electronically?	YES ²
1. Has adequate documentation of the data sets been provided?	YES
2. Do the data appear to accurately represent the data described in the study reports?	YES
3. Can the data be easily merged across studies and indications?	YES

¹ EDR loading problems have made navigation more difficult, but all parts of the application are accessible.

² The sponsor still needs to submit the data for the supplemental IGA (infl and non) and analysis datasets with derived variables would assist the reviewer.

II. STATISTICAL METHODOLOGY**YES/NO/NA**

A. Are all primary efficacy studies of appropriate design to meet basic approvability requirements within current Division policy, or to the extent agreed upon previously with the sponsor by the Division?	YES
B. For each study, is there a comprehensive statistical summary of the efficacy analyses which covers the intent-to-treat population and per protocol population?	YES
C. Based on the summary analyses of each study, 1. Are the analyses appropriate for the type of data collected, the study design, and the study objectives (based on protocol objectives and proposed labeling claims?)	YES
2. Are the intent-to-treat and per protocol patient analyses properly performed?	YES
3. Has missing data been appropriately handled?	YES
4. Have multiplicity issues (regarding endpoints, timepoints, or dose groups) been adequately addressed?	YES
5. If interim analyses were performed, were they planned in the protocol and appropriate significance level adjustments made?	NA
D. Were sufficient and appropriate references included for novel statistical approaches?	NO ³
E. Are all of the pivotal studies complete?	YES
F. Has the safety data been comprehensively and adequately summarized?	YES

³ A copy of Zar (1984) is requested.

III. FILEABILITY CONCLUSIONS

From a statistical perspective this submission, or indications therein, is reviewable with only minor further input from the sponsor.

IV. REQUEST FOR INFORMATION (to be conveyed to the sponsor)

Please submit the following items to the NDA, or indicate where these items can be located in the current submission:

1. Submit SAS transport datasets containing the Evaluator's Global Severity Assessment (Inflammatory and Noninflammatory Lesions) and a copy of the

annotated (blank) CRF containing the pages where evaluations of this endpoint were recorded for Studies MP-0104-04 and MP-0104-05.

2. Submit analysis datasets for Studies MP-0104-04 and MP-0104-05 that include the following derived variables: inflammatory lesion count, non-inflammatory lesion count, change from baseline in inflammatory lesions, change from baseline in non-inflammatory lesions, percent change from baseline in inflammatory lesions, percent change from baseline in non-inflammatory lesions, and success on the Evaluator's Global Severity Assessment (Inflammatory Lesions Only) (Clear/Almost clear), along with the variables for treatment, site, analysis center, race, age, gender, ITT status, and per protocol status. The primary endpoints (percent change in inflammatory lesions and success on the global assessment) should be presented as both observed cases and imputed for missing data (LOCF).
3. Submit a copy of the pages of Zar (1984, *Biostatistical Analysis*) relevant to the test for skewness of the distribution of percent change.
4. Provide additional background information and details about the interactive voice-recognition system (IVRS) and how the system generates randomization assignments.

Kathleen Fritsch, Ph.D.
Mathematical Statistician, Biometrics III

Concur: Mohamed Alosch, Ph.D.
Team Leader, Biometrics III

cc:
Archival NDA 50-808/N-000
HFD-540/Wilkin
HFD-540/Luke
HFD-540/Nikhar
HFD-540/Curtis
HFD-700/Anello
HFD-725/Huque
HFD-725/Alosch
HFD-725/Fritsch

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Kathleen Fritsch
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Mohamed Alesh
8/16/2005 01:32:59 PM
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Concur with review