CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-805

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	50-805 / 000
Drug Name:	Oracea™ (doxycycline [redacted] capsules) 40 mg
Indication(s):	Inflammatory Lesions of Rosacea
Applicant:	Collagenex Pharmaceuticals, Inc.
Date(s):	Received 8/01/2005, user fee (10 months) 6/01/2006
Review Priority:	Standard
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Keywords:	Analysis of covariance, Cochran-Mantel-Haenszel

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1. EXECUTIVE SUMMARY

Oracea™ (doxycycline capsules) 40 mg is intended for oral administration to be taken once daily to inflammatory lesions in patients with rosacea. The Sponsor submitted the results from two Phase 3 studies, COL-101-ROSE-301 and COL-102-ROSE-302 (referred to as either ROSE-301 and ROSE-302, or Study 301 and 302, respectively). This report summarizes the analyses of these studies.

1.1 Conclusions and Recommendations

For both Phase 3 studies the primary efficacy endpoint specified in the protocols was the change from baseline in inflammatory lesion count. In Study ROSE-301, at baseline the mean number of lesions in the Oracea group was 19.5 versus 20.3 in the Placebo group. In the intent-to-treat (ITT) population, using last observation carried forward (LOCF) imputation for dropouts, the Week 16 mean changes from this baseline count were -11.8 and -5.9, respectively. Using a simple ANOVA model, the difference in this change from baseline was statistically significant ($p \leq 0.0020$). In Study ROSE-302, at baseline the mean numbers of lesions were 20.5 and 21.2 in the Oracea and Placebo groups, respectively. So in both studies, while the difference was not statistically significant, the baseline lesion count was higher (i.e., worse) in the placebo group than the corresponding Oracea group. In ROSE-302, the corresponding Week 16 mean changes from this baseline count were -9.5 and -4.3, respectively. Again, as in ROSE-301, the difference in these changes from baseline was statistically significant ($p < 0.0001$). A preliminary Bayesian analysis using growth curve models confirmed these results. By week 12, the posterior probability at least 0.98 that a patient using Oracea would be expected to have at least three lesions less than when using Placebo (Please see Appendix 9).

In response to a request by the Division for a static Investigator Global Assessment (IGA), measuring global rosacea (except possibly erythema), the Sponsor provided an endpoint that is basically a grouped data version of the inflammatory lesion count (Please see section 2.1.2 and Appendix 6 for more on this.) At Week 16 in the intent-to-treat (ITT) population in Study ROSE-301, according to the Sponsor's IGA, 11 of the 127 Oracea patients versus 10 of the 124 Placebo patients were clear, i.e., had no inflammatory lesions. For statistical analysis, the Division recommended dichotomizing this endpoint so that a "success" was defined as an IGA of "Clear" or "Near Clear." At Week 16, in ROSE-301, 16.5% of the Oracea patients and 10.4% of the Placebo patients were scored as successes on this endpoint. In Study ROSE-302, at Week 16, only two of the 142 Oracea patients versus none of the 144 Placebo patients were scored as "Clear," while 8.5% of the Oracea patients versus 3.4% of the Placebo patients were scored as "Clear" or "Near Clear." These treatment differences in success rates were statistically significant ($p \leq 0.0361$ and $p \leq 0.012$, in Studies ROSE-301 and ROSE-302, respectively). In an attempt to provide a static overall IGA the Medical team defined a post hoc extended IGA, incorporating erythema. (please see Appendix 7). There were no statistically significant treatment differences on this endpoint.

1.2 Brief Overview of Clinical Studies

Studies ROSE-301 and ROSE-302 were randomized, double-blind, placebo-controlled, parallel group, multicenter, 16 week Phase 3 trials conducted in the United States with a total of 537 rosacea patients in both studies, 269 of whom were treated with Oracea. Study ROSE-302 included a further four week extension without treatment. Patients were randomized 1:1 to Oracea and Placebo. The study protocols defined the total inflammatory lesion counts as the sum of papule, pustule, and nodule counts. The primary efficacy endpoint was the Week 16 change from baseline in this inflammatory lesion count. The Division also requested that an Investigator Global Assessment (IGA) of the overall rosacea status be defined as a co-primary endpoint. The Sponsor argues that since the proposed indication is "to ___ inflammatory lesions in patients with rosacea" only the change from baseline in lesion count should be used as a primary endpoint. The analyses presented here follow the original Division recommendation.

1.3 Statistical Issues and Findings

Statistical Issues

1. Perhaps the most important issue with this submission is whether or not the IGA is defined appropriately, and is suitable as a primary endpoint. As discussed in section 2.1.2 for a rosacea indication, the division requested a global assessment of rosacea. The Sponsor provided an endpoint that is a grouped data version of the lesion count in Study 301 and largely a grouped data version in Study 302. Note the Sponsor argues that since the proposed indication is "to ___ inflammatory lesions in patients with rosacea" only the change from baseline in lesion count is needed as a primary endpoint. Both endpoints were analyzed in this review.

2. The protocols specify that the changes from baseline in lesion counts are to be analyzed with an analysis of variance (ANOVA) model with factors for treatment and center. The protocol also specified that if the residuals are not normal a van Elteren test is to be used to compare median scores of the treatment group. This reviewer's opinion is that in all cases in these studies the data do not seem to be sufficiently skewed to invalidate the assumption of approximate normality in the distribution of cell means. Thus ANOVA would be appropriate. However since this was specified in the protocol, results from both statistical tests are reported here, and are always essentially equivalent.

3. The IGA was measured on a 0-4 scale, but the guidelines indicate the corresponding associated range of inflammatory lesions are 0, 1-2, 3-10, 11-19, or 20+, respectively. For analysis the Division recommended dichotomizing the IGA so that treatment "success" was defined as a score of 0 or 1, otherwise it was a "failure". This endpoint was used in the analyses in this report. The Sponsor's protocol indicates that the second analysis of this endpoint should be based on the change from baseline. This change from baseline is summarized in Appendix 2; however, note that the difference in IGA scores between 0 and 1 (i.e., between 0 and 1-2 lesions) is not particularly commensurable with the nominally equal difference between 3 and 4 (i.e.,

between 11-19 and 20+ lesions). This would suggest that the change from baseline in this endpoint is not a particularly useful measure.

4. Several centers recruited only a small number of patients into the study. Pooling of subjects for the analysis was specified in amendment to the protocol issued on April 26, 2005, after completion of both studies. This is clearly a post hoc adjustment. However, this pooling was deemed to be acceptable, and for convenience was followed in the Agency analysis.

Statistical Findings

In Study ROSE-301, at baseline the mean number of lesions in the Oracea group was 19.5 versus 20.3 in the Placebo group. In Study ROSE-302, at baseline the mean numbers of lesions were 20.5 and 21.2 in the Oracea and Placebo groups, respectively. So in both studies, while the difference was not statistically significant, the baseline score was higher in the Placebo group. In the ITT-LOCF ROSE-301 population, the Week 16 mean changes from this baseline count were -11.8 and -5.9 for Oracea and Placebo, respectively. Using a simple ANOVA model, the difference in this change from baseline was statistically significant ($p \leq 0.0002$). In ROSE-302, the corresponding Week 16 mean changes from this baseline count were -9.5 and -4.3, respectively. Again, as in Study 301, the difference in these changes from baseline was statistically significant ($p < 0.0001$).

At Week 16 in the ITT population in Study ROSE-301, according to the Sponsor's IGA, 11 of the 127 Oracea patients versus 10 of the 124 Placebo patients were clear, i.e., had no inflammatory lesions. For analysis, the Division recommended dichotomizing this endpoint so that a "success" was defined as an IGA of "Clear" or "Near Clear." At Week 16, in Study 301, 16.5% of the Oracea patients and 10.4% of the Placebo patients were scored as successes on this endpoint. In Study ROSE-302, at Week 16, only two of the 142 Oracea patients versus none of the 144 Placebo patients were scored as "Clear," while 8.5% of the Oracea patients versus 3.4% of the Placebo patients were scored as "Clear" or "Near Clear." These treatment differences in success rates were also statistically significant ($p \leq 0.0361$ and $p \leq 0.012$, in Studies ROSE-301 and ROSE-302, respectively).

Results were generally consistent in the Per Protocol population and seemed to be generally consistent for each gender, and overall, across age groups. Few patients were non-Caucasian, but among these few patients, there was no particular evidence that treatment efficacy was greater than placebo.

2. INTRODUCTION

2.1 Overview

According to the Sponsor: "The clinical development program for Oracea™ included two pilot pharmacokinetic studies, a multiple-dose steady state bioequivalence study comparing Oracea™ with Periostat®, a food-effect study, and two Phase 3 studies, Oracea-ROSE-301 and

Oracea-ROSE-302 (referred to as 301 and 302, or ROSE-301 and ROSE-302, respectively). All of these studies used the same formulation of the drug product proposed for marketing. The randomized, double-blind, placebo-controlled, parallel group, multicenter, Phase 3 trials included 537 patients with rosacea, 269 of whom were treated with Oracea™ for up to 16 weeks. All of these studies were conducted in the United States." (page 78, volume 1.1, module 2)

2.1.1 Design

Both Studies ROSE-301 and ROSE-302 are described as multicenter, randomized, double-blind placebo controlled, parallel group, Phase 3 studies, each conducted at 14 investigational centers. Patients were randomly assigned 1:1 to Oracea™ (doxycycline [redacted] capsules) to be taken for 16 weeks. Patients were evaluated at baseline, and at Weeks 3, 6, 12, and 16. Study 302 included an extra evaluation at Week 20. Study 301 was initiated on 22 June 2004 and the last patient completed on 1 April 2005. Study 302 was initiated on 24 June 2004 and completed on 4 April 2005. Please see Section 2.1.2, below, for details on the regulatory history. Summaries of patient disposition and demographics are given in Section 3.1.2.

2.1.2 Regulatory History:

1. Pre-IND/End of Phase 2 Meeting (January 28, 2002), FDA minutes (sent to the Sponsor on February 13, 2002):

The Sponsor initially requested a claim for both [redacted] and rosacea, requesting one study of each condition. However, the FDA stated that since these were considered to be separate diseases, "The Sponsor should conduct two, adequate, placebo-controlled trials for each indication." (page 3 of minutes)

Further, for an indication of rosacea:
"i. The Agency supports the following two primary efficacy endpoints: the Investigator's (Clinician's) Global Assessment and lesion counts. The Investigator's Global Assessment should be a static assessment at efficacy endpoint and not a change from baseline. The Investigator's Global Assessment should be dichotomized a priori to success and failure. As presented in the briefing package the Agency would support success as a score of '0' on the assessment scale." (page 4 of minutes)

"If the Sponsor can be more precise in its description of the difference between score 1 and 2, ... then the Agency might consider adding category 1 to success." (page 4 of minutes)

"ii. There should be a statistically significant reduction in inflammatory lesions at endpoint. For approval, success must be demonstrated in both the Investigator's Global Assessment and in lesion counts." (page 4 of minutes)

2. Pre-IND/End of Phase 2 Meeting (May 3, 2004), FDA minutes (sent to the Sponsor on May 27, 2004):

The Sponsor indicated that the requested indication was the treatment of papules and pustules of ——— rosacea, but not erythema. However, the Division commented that the Sponsor did not conduct adequate dose ranging. Also, the Division stated that "The Agency recommends that the Clinician's Global Severity Score be modified to include static clinical descriptors and categories (e.g., Clear, Almost Clear, Mild, Moderate, and Severe). The Clinician's Global Severity Score appears to be similar to an Investigator's Global Assessment (IGA) scale; however, as an IGA the Agency recommends use of clinical descriptors (e.g., papules, nodules, slight pinkness, fiery redness, telangiectasia, etc.) The Sponsor's Clinician's Global Severity Score includes an area specific "score" which is not a clinical global assessment." (page 5 of minutes)

The Agency agreed that erythema could be removed from the Clinician's Global Severity Scale and be evaluated as a secondary endpoint. Note that the Clinician's Global Severity Scale was renamed to the Investigator's Global Assessment in this submission, but is largely or essentially only a grouped data version of the lesion count.

Further, the Agency reminded the Sponsor that "The endpoints are not as recommended at the January 28, 2002, Pre-IND/End of Phase 2 Meeting to support the rosacea indication.
i. The Agency recommends the following two primary efficacy endpoints for demonstrating efficacy in treatment of rosacea: 1) inflammatory lesion counts (papules, pustules, and nodules) and 2) the investigator's static global assessment (IGA). Clinical signs (erythema and telangiectasia) should be incorporated into the static global assessment.
ii. As noted above, the Agency recommends that the IGA be a static scoring system. The IGA should be dichotomized a priori to success and failure.
iii. For approval, success must be demonstrated in both the IGA and in lesion counts. There should be a statistically significant reduction in inflammatory lesions at study endpoint.
iv. The Sponsor proposes a Clinician's Erythema Score . . . obtained at endpoint as a sum obtained from evaluation of five facial areas (scale of 0 to 4). The Sponsor is reminded that if a reduction of erythema is sought as part of the indication, then this parameter should be incorporated into the IGA." (page 6 of minutes)

Further, in the Biostatistics comments:
"The protocol includes a large number of secondary endpoints. The Sponsor should consider a limited number of clinically relevant endpoints or an adjustment for multiplicity may be needed. During the meeting the Sponsor said that it could classify clinically relevant secondary endpoints into two groups: a small number that might be considered for labeling, and those with only exploratory interest." (page 7 of minutes)

3. The Protocol review dated September 27, 2004, reiterated these comments. It was noted that "instead of a secondary endpoint the IGA should be defined as a co-primary endpoint." Further, telangiectasia should be included in the IGA.

4. Pre-NDA Meeting (March 30, 2005), FDA minutes (sent to the Sponsor on May 27, 2005):

The Division again stated that the "analysis of the dichotomized IGA as a secondary variable is not acceptable. The Agency stands by the recommendation for use of co-primary efficacy endpoints for rosacea provided to the sponsor at the January 28, 2002, Pre-IND/End of Phase 2 meeting, May 3, 2004, End of Phase 2 Meeting, and protocol comments of September 27, 2004. As it is too late to modify the prespecified analysis plan, the Agency recommends the following analyses be submitted:
a. Submit data analysis as pre-specified in your statistical analysis plan in your protocol.
b. Submit data analysis as was recommended by the Agency." (pages 7-8 of minutes)

"Two primary efficacy endpoints are needed for demonstrating efficacy in treatment of rosacea: a): inflammatory lesion counts . . . and b) the investigator's static global assessment (IGA). . . . For approval, success must be demonstrated in both the Investigator's Global Assessment and in lesion counts. Subjects enrolled with an IGA in the win category (i.e. clear or almost clear) should not be included in the analysis. It was discussed that erythema and telangiectasia are not included in the Investigator's global assessment scale, will be addressed as secondary variables and should not get worse." (page 8 of minutes) Note that no such subjects with an IGA in the success category were actually enrolled at baseline, and that the Division thus confirmed that the clear and almost clear categories in the IGA are to be used to define "success".

5. The Sponsor states (in their response to the FDA 74 day letter, received 2 November 2005) that "Per the instruction of Dr. Jonathan Wilkin, Division Director, HFD-540 during the Pre-NDA meeting, the Sponsor was to maintain the IGA 'as a secondary endpoint' and file the results as requested by the Agency." This particular claim does not seem to be confirmed by the FDA minutes of that meeting.

The original discussion for this submission seems to be addressed for a ——— However, the Sponsor argues that since the proposed indication is more limited, i.e., "to ———inflammatory lesions in patients with rosacea" only the change from baseline in lesion count should be used as a primary endpoint. This analysis follows the original Division recommendation and uses both primary endpoints.

2.2 Data Sources

Data for the pivotal study was downloaded from the FDA Electronic Data Room as SAS transport files, located in the following link:

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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Efficacy results are based on the data from two similar Phase 3 studies, labeled COL-101-ROSE-301 and COL-101-ROSE-302 (i.e., Studies ROSE-301 and ROSE-302, or 301 and 302), respectively, each study titled:

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Clinical Trial to Determine the Effects of 40 mg Doxycycline Monohydrate Modified Release Capsules (COL-101) Administered Once Daily Versus a Placebo Control Administered Once Daily for the Treatment of Rosacea.

The Sponsor reports that ROSE-301 was initiated on June 22, 2004, and completed April 1, 2005, while ROSE-302 was initiated on June 24, 2004, and completed April 4, 2005. The Sponsor reports that final protocols for both studies were issued on May 7, 2004.

3.1.1 Study Design and Endpoints

Two very similar Phase 3 studies, ROSE-301 and ROSE-302, or for brevity labeled as Studies 301 and 302, respectively, were conducted. The only difference between the two studies was that ROSE-302 included a 4-week extension period without treatment. The Sponsor describes these as: "Both studies were outpatient, multicenter, randomized, double-blind, placebo-controlled, parallel group trials to evaluate the safety and efficacy of Oracea™ for reducing total inflammatory lesions compared with placebo. Patients were to take one capsule of study medication once daily every morning for 16 weeks. Study visits were at Baseline and Weeks 3, 6, 12, and 16, and in Study 302 also at Week 20 (patients stopped treatment at Week 16)." (page 78, volume 1.1, module 2) Patients were randomized 1:1 to Oracea or placebo (i.e., vehicle).

Primary Efficacy Endpoints

The primary efficacy endpoint identified in the protocols was the Week 16 change from baseline in total inflammatory lesion count. Total inflammatory lesion count was defined as the sum of papule, pustule, and nodule counts. As discussed in Section 2.1.2, the Division recommended a static Investigator Global Assessment as a co-primary endpoint. The Sponsor argues that since the proposed indication is "to [redacted] inflammatory lesions in patients with rosacea" only the change from baseline in lesion count should be used as a primary endpoint. This analysis will follow both the original Division recommendation and the protocol definition.

The Investigator's Global Assessment was measured at Weeks 3, 6, 12, and 16, and is defined as follows. Note that for entry to the studies patients had to score at least a "2" (i.e., a score of "Mild") on the IGA. Most patients entered with a score of 3 (i.e., "Moderate").

Investigator's Global Assessment (IGA):

Score	Grade	Definition	Guideline
0	Clear	No signs or symptoms present	Skin clear of inflammatory lesions
1	Near Clear	One or two papules	1 or 2 small, non-inflammatory lesions
2	Mild	Some papules/pustules	3 to 10 papules/pustules
3	Moderate	Moderate number of papules/pustules	11 to 19 papules/pustules
4	Severe	Numerous papules/pustules; nodules	≥20 papules/pustules and nodules

For the analysis, following the Division recommendation, "success" on this endpoint is defined as a grade of "Near Clear" or "Clear", i.e., a score of 0 or 1. However, this endpoint, unlike the IGA recommended by the Division, is primarily a grouped data version of the inflammatory lesion count. With a single exception in Study ROSE-301, at each visit the lesion counts fall within the ranges assigned by the IGA. In Study ROSE-302, the matching between ranges of lesion counts and levels of the IGA is somewhat less consistent, but generally the lesion counts also fall within the ranges assigned by the IGA. Following the Division recommendation, the Week 16 score on this assessment is considered as a primary endpoint.

The Sponsor's analysis is based on the change from baseline in this IGA. Note that the computed differences in the IGA scores do not correspond to equal counts in lesions. For example, in the "natural" metric a one unit difference between IGA scores of 0 and 1 correspond to 1 or 2 lesions, while say a one unit difference between IGA scores of 2 and 3 correspond to between 1 to 16 lesions. This suggests that an analysis of the actual IGA scores would be more interpretable than the analysis based on change from baseline. For the FDA analysis the actual scores, dichotomized so that "success" is an IGA of 0 or 1, is used in the primary analysis, however the protocol specified analysis using change from baseline is provided in Appendix 2.

Secondary Efficacy Endpoints

An erythema score was defined for each of the forehead, chin, nose, right check, and left check, each facial region assessed on the following scale:

Erythema Score:

Score	Grade	Definition
0	None	No redness present
1	Mild	Slight pinkness
2	Moderate	Definite redness
3	Significant	Marked erythema
4	Severe	Fiery redness

The Clinician's Erythema Assessment is then defined as the sum of these five erythema scores.

The secondary efficacy parameters specified in the protocol are the following:

1. The Week 16 change from baseline in the Clinician's Erythema Assessment.

2. The Week 16 change from baseline in the Investigator's Global Assessment (IGA).

3. The Protocol defined two other endpoints based on the IGA, both labeled "Treatment Responders." 1) patients with an IGA of 0 ("Clear") and 2) patients with an IGA of 0 or 1 ("Near Clear"). As noted at the March 30, 2005 Pre-NDA meeting the latter definition corresponds to the FDA definition of "success" on the IGA. The Week 16 values of these variables are secondary endpoints.

4. The Week 12 change from baseline in inflammatory lesions.

Other Exploratory Analyses

The protocols specify the following additional "ancillary analysis parameters":

1. The Week 3, 6, and 12 change from baseline in the inflammatory lesion count.

2. The Week 3, 6, and 12 change from baseline in the IGA.

3. The Week 3, 6, and 12 change from baseline in the Clinician's Erythema Assessment.

4. The Week 3, 6, 12, and 16 changes in each of papule, pustule, and nodule counts.

The last of these is not included in this review.

3.1.2 Statistical Methodology

The protocols specified that, provided the data were normally distributed, the change from baseline in lesion counts would be analyzed with an analysis of variance (ANOVA) model with factors for treatment and center.

Change from baseline = treatment + pooled center.

A second analysis was to incorporate treatment by center interaction. If the data were not normally distributed, the protocol specified that a van Elteren test stratified on center would be used.

The Sponsor specified the change from baseline in the IGA score was to be used for analysis. This is presented in Appendix 2, however, as discussed in section 3.1.1 above, this version of the endpoint may be problematical. The FDA results are presented using a dichotomization of the IGA so that a score of 0 or 1 was defined as a treatment success. This was analyzed using a CMH test with table scores stratifying on center.

For this analysis, the dichotomized IGA is treated as a primary endpoint. Because of problems in interpretation (see Section 1.3), the change from baseline in the IGA is only analyzed descriptively. With only two remaining secondary endpoints it was felt that no adjustment for multiplicity was needed.

3.1.3 Patient Disposition, Demographics and Baseline Characteristics.

The following table displays the final disposition of patients entering the two trials:

Table 1. Patient Disposition

	ROSE-301		ROSE-302	
	Oracea	Placebo	Oracea	Placebo
Number of Patients Enrolled	127	124	142	144
Number of Patients Completed (%)	101 (80%)	101 (83%)	115 (81%)	118 (82%)
Number of Patients Discontinued (%)	26 (20%)	21 (17%)	27 (19%)	26 (18%)
Reason for Discontinuation N (%)				
Adverse Event	10 (8%).	4 (3%).	9 (6%).	7 (5%).
Other Illness	1 (1%)	1 (1%)	1 (1%)	0
Uncooperative	5 (4%)	4 (3%)	2 (1%)	1 (1%)
Protocol Violation	2 (2%)	2 (2%)	4 (3%)	5 (3%)
Loss to Follow-up	4 (3%)	2 (2%)	5 (4%)	5 (3%)
Treatment Failure	2 (2%)	2 (2%)	1 (1%)	4 (3%)
Other	2 (2%)	6 (5%)	5 (4%)	4 (3%)

In Study 302, 84 patients in the Oracea group and 76 in the Placebo group were enrolled in the four week follow-up period. All completed this follow-up.

Patient demographic and baseline characteristics are summarized below:

Table 2. Subject Demographics

	ROSE-301		ROSE-302	
	Oracea (n=127)	Placebo (n=124)	Oracea (n=142)	Placebo (n=144)
Gender N (%)				
Male	36 (28.3 %)	29 (23.4 %)	48 (33.8 %)	49 (34.0 %)
Female	91 (71.7 %)	91 (76.6 %)	94 (66.2 %)	95 (66.0 %)
Age in Years				
Mean (Std Dev)	46.8 (13.2)	47.6 (11.5)	46.3 (12.7)	47.6 (13.3)
Range (Min-Max)	22 – 90	19 – 84	20 – 80	19 – 82
Age group N (%)				
18-35	26 (20.5 %)	16 (12.9 %)	30 (21.1 %)	27 (18.8 %)
36-50	58 (45.7 %)	60 (48.4 %)	64 (45.1 %)	57 (39.6 %)
51-70	35 (27.6 %)	44 (35.5 %)	43 (30.3 %)	52 (36.1 %)
> 70	8 (6.3 %)	4 (3.2 %)	5 (3.5 %)	8 (5.6 %)
Race N (%)				
Caucasian	108 (85.0 %)	107 (86.3 %)	135 (95.1 %)	141 (97.9 %)
Black	0	0	2 (1.4 %)	0
Asian	1 (0.8 %)	0	1 (0.7 %)	1 (0.7 %)
Other (mostly Hispanic)	18 (14.2 %)	17 (13.7 %)	4 (2.8 %)	2 (1.4 %)

Note that within each study, demographic groups seem to be relatively balanced.

3.1.4 Reviewer Results and Conclusions

Following the Division recommendation, but not the Protocol (See Section 2.1.2) there were two primary endpoints, each evaluated at Week 16 or time of early termination: 1) the mean change from baseline in lesion counts, and 2) the dichotomized Investigator Global Assessment (IGA). However, the IGA defined by the Sponsor is basically a grouped data version of the lesion count (see Appendix 5) and does not fit the recommendation of the Division. Results are given for each primary endpoint in turn, followed by a section discussing the secondary endpoints. While significance levels associated with tests of treatment differences are provided at each nominal visit in tables 3-11 below, only the Week 16 values should be given any strong interpretation.

3.1.4.1 Total Lesion Count/Change from Baseline in Lesion Count

Mean changes from baseline in lesion count and total lesion count in the intent to treat population are given below for Study 301 (Table 3) and Study 302 (Table 4), along with the tests of treatment differences:

Table 3. ROSE-301 (ITT-LOCF) Mean Change from Baseline in Lesion Count

	Visit				
	Baseline	Week 3	Week 6	Week 12	Week 16
Change from Baseline					
Oracea (N=127)					
Mean	.	-6.54	-9.61	-10.80	**-11.82**
Std Dev	.	9.08	8.84	9.77	9.78
Placebo (N=124)					
Mean	.	-2.82	-3.96	-5.50	**-5.94**
Std Dev	.	10.79	9.87	11.95	13.91
p-value					
ANOVA	.	0.0048	<0.0001	0.0002	**0.0003**
van Elteren	.	0.0074	<0.0001	0.0001	**0.0020**
Total Lesions					
Oracea (N=127)					
Mean	19.54	13.01	9.94	8.75	**7.72**
Std Dev	8.78	9.95	8.73	8.54	7.96
Placebo (N=124)					
Mean	20.33	17.51	16.37	14.83	**14.39**
Std Dev	10.37	13.00	14.49	14.28	16.42
p-value					
ANOVA	0.4535	0.0011	<0.0001	0.0001	**0.0001**
van Elteren	0.7987	0.0027	0.0002	0.0050	**0.0008**

Similar results for Study ROSE-302 are given below:

Table 4. ROSE-302 (ITT-LOCF) Mean Change from Baseline in Lesion Count

	Visit Baseline	Week 3	Week 6	Week 12	Week 16	Week 20
Change from Baseline						
Oracea (N=142)						
Mean	.	-5.59	-7.22	-8.28	**-9.48**	-8.30
Std Dev	.	8.47	9.86	10.71	9.63	10.60
Placebo (N=144)						
Mean	.	-3.47	-3.65	-4.20	**-4.31**	-4.69
Std Dev	.	7.63	10.78	11.31	11.57	10.66
p-value						
ANOVA	.	0.0165	0.0005	<0.0001	**<0.0001**	0.0008
van Elteren	.	0.0051	<0.0001	<0.0001	**0.0001**	0.0022
Total Lesions						
Oracea (N=142)						
Mean	20.45	14.86	13.23	12.17	**10.97**	12.15
Std Dev	11.68	11.72	12.03	11.98	11.29	11.65
Placebo (N=144)						
Mean	21.19	17.72	17.55	16.99	**16.89**	16.51
Std Dev	12.51	11.93	13.41	13.79	14.69	14.66
p-value						
ANOVA	0.5119	0.0202	0.0011	0.0004	**<0.0001**	0.0014
van Elteren	0.6562	0.0044	0.0002	<0.0001	**<0.0001**	0.0052

Both studies show statistically significant differences favoring Oracea over Placebo, for both change from baseline and total lesion counts, using both the ANOVA and van Elteren tests (all eight tests have $p \leq 0.0020$). However, in both studies the Placebo group starts off with an overall slightly higher mean lesion count than the Oracea group, even though these differences are not statistically significant. This is possibly an artifact of the randomization, and differences remain statistically significant (in the ANOVA) even when one includes the baseline value as a covariate.

Similar results for the Per Protocol population are provided in Appendix 1. Statistical tests in the Per Protocol group show results similar to those in the ITT population. Again, both studies show statistically significant differences in favor of Oracea over Placebo. In this population, however, the mean scores in the Placebo treatment groups and the Oracea treatment groups are much closer at baseline.

3.1.4.2 Investigator's Global Assessment

Recall that the guidelines in the definition of the IGA indicate that this is essentially just a grouped data version of the lesion count (see Section 3.1.1), and is not a global evaluation of rosacea status as originally recommended by the Division. In an attempt to provide a static overall IGA, at an internal meeting on February 7, 2006, the Medical team defined a post hoc

extended IGA, incorporating erythema (please see Appendix 7). There were no statistically significant treatment differences on this endpoint.

As with the mean change from baseline in actual lesion count, in both studies, the Week 16 treatment differences in the Sponsor's IGA were statistically significant, ($p \leq 0.0361$ and $p \leq 0.0120$, respectively). Differences using mean scores were highly statistically significant ($p \leq 0.0014$ and $p < 0.0001$). However, the analysis using mean scores was a post hoc addition, and was not specified in the protocol.

Results on this endpoint in the Per Protocol population are summarized in Appendix 3.

The results from the Sponsor's Investigator's Global Assessment are presented in Tables 5 and 6 below:

Table 5. ROSE-301 (ITT-LOCF) Investigator's Global Assessment

Visit		Baseline	Week 3	Week 6	Week 12	Week 16
Oracea						
0. Clear	N	.	2	3	8	**11**
	%	.	1.7	2.7	8.1	9.4
1. Near Clear	N	.	4	19	15	**27**
	%	.	3.4	17.3	15.2	23.1
2. Mild	N	8	58	54	57	52
	%	6.3	50.0	49.1	57.6	44.4
3. Moderate	N	67	28	24	12	18
	%	52.8	24.1	21.8	12.1	15.4
4. Severe	N	52	24	10	7	9
	%	40.9	20.7	9.1	7.1	7.7
Placebo						
0. Clear	N	.	1	3	5	**10**
	%	.	0.9	2.7	5.0	8.8
1. Near Clear	N	.	2	6	13	**14**
	%	.	1.8	5.4	13.0	12.4
2. Mild	N	10	35	44	40	42
	%	8.1	31.8	39.6	40.0	37.2
3. Moderate	N	65	38	24	18	22
	%	52.4	34.5	21.6	18.0	19.5
4. Severe	N	49	34	34	24	25
	%	39.5	30.9	30.6	24.0	22.1
P-value						
Success (0,1)		.	0.3359	0.0079	0.2124	**0.0361**
Mean Score		0.7267	0.0086	<0.0001	0.0008	0.0014

For analysis of similar IGAs the Division has often recommended a dichotomization so that "success" is defined as a "Clear" or "Near Clear" at study end with a change from baseline of a least two units. That is, for a score of "success" a subject with a baseline IGA of 3 or 4

would require an IGA of 0 or 1 at study endpoint, while a subject with a baseline IGA of 2 would require an endpoint IGA of 0. With this definition, using LOCF in the ITT population at Week 16 there were 36 successes in the Oracea group versus 23 in the placebo group ($p \leq 0.0642$).

Table 6. ROSE-302 (ITT-LOCF) Investigator's Global Assessment

	Visit	Baseline	Week 3	Week 6	Week 12	Week 16	Week 20
Oracea							
0. Clear	N	.	.	.	3	**2**	6
	%	.	.	.	2.5	1.5	4.5
1. Near Clear	N	.	3	5	12	**19**	12
	%	.	2.3	4.0	10.2	14.4	9.1
2. Mild	N	17	57	66	59	63	56
	%	12.0	43.2	52.8	50.0	47.7	42.4
3. Moderate	N	77	49	38	33	32	41
	%	54.2	37.1	30.4	28.0	24.2	31.1
4. Severe	N	48	23	16	11	16	17
	%	33.8	17.4	12.8	9.3	12.1	12.9
Placebo							
0. Clear	N	.	.	2	2	.	3
	%	.	.	1.5	1.7	.	2.3
1. Near Clear	N	.	3	4	5	**9**	10
	%	.	2.2	3.0	4.2	7.0	7.8
2. Mild	N	7	40	43	40	49	51
	%	4.9	29.9	32.6	33.3	38.0	39.5
3. Moderate	N	80	52	43	46	41	33
	%	55.6	38.8	32.6	38.3	31.8	25.6
4. Severe	N	57	39	40	27	30	32
	%	39.6	29.1	30.3	22.5	23.3	24.8
P-value							
Success (0,1)		.	0.9974	0.9949	0.0285	**0.0120**	0.9790
Mean Score		0.0207	0.0035	0.0003	<0.0001	<0.0001	0.0740

Using the dichotomization so that "success" is defined as a "Clear" or "Near Clear" at study end with a change from baseline of a least two units, in the ITT-LOCF population at Week 16 there were 15 successes in the Oracea group versus 8 in the placebo group ($p \leq 0.1122$).

One of the protocol definitions of "Treatment Responder" was the number of patients with a score of clear (i.e. "0") on the IGA. In both studies, the treatment differences using this endpoint are not nearly statistically significant. Using the Division definition of "Success" on the IGA, i.e., a score or "0" or "1", differences were statistically significant ($p \leq 0.0361$ and $p \leq 0.0120$ in Studies 301 and 302, respectively).

3.1.4.3 Secondary Endpoints:

The Sponsor defined five secondary endpoints (discussed in Section 3.1.1). One of these was a score of "Clear" on the IGA, an endpoint that showed no statistically significant difference between treatment groups. Another corresponded to "Success" on the IGA and was considered as a primary endpoint, and is analyzed above. A third secondary endpoint was the change from baseline in the IGA, and due to problems of interpretation, is only summarized descriptively in Appendix 2. Results for fourth secondary endpoint, the Week 12 change from baseline in inflammatory lesions are also given in tables 4-5 above (both $p \leq 0.0002$). Results for the fifth secondary endpoint, change from baseline in the Clinician's Erythema Scores, are given below in tables 7 and 8. The Week 16 value was specified as the secondary endpoint. Treatment differences were statistically significant in ROSE-301 ($p \leq 0.0164$) but not in ROSE-302 ($p \leq 0.4278$).

Table 7. ROSE-301 (ITT-LOCF) Mean Change from Baseline in Erythema Score

	Visit				
	Baseline	Week 3	Week 6	Week 12	Week 16
Change in Total Erythema Score					
Oracea (N=127)					
Mean	.	-1.39	-2.15	-2.20	**-2.75**
Std Dev	.	2.48	2.73	2.91	3.25
Placebo (N=124)					
Mean	.	-0.89	-1.39	-1.75	**-1.85**
Std Dev	.	2.27	2.39	2.62	2.89
p-value					
ANOVA	.	0.0745	0.0130	0.1867	**0.0164**
van Elteren	.	0.0362	0.0255	0.2157	**0.0299**
Total Erythema Score					
Oracea (N=127)					
Mean	9.72	8.32	7.57	7.52	**6.97**
Std Dev	2.97	3.34	3.36	3.42	3.69
Placebo (N=124)					
Mean	9.52	8.63	8.13	7.77	**7.67**
Std Dev	2.72	2.83	3.22	3.51	3.53
p-value					
ANOVA	0.6152	0.3531	0.1283	0.4814	**0.0847**
van Elteren	0.7402	0.2504	0.3602	0.6448	**0.1032**

As noted previously, to control overall statistical significance levels, only the Week 16 significance levels should be given credence. In this study, ROSE-301, note that while the Week 16 treatment difference in change from baseline in total erythema scores was statistically significant ($p \leq 0.0164$), the treatment difference in total score was not ($p \leq 0.0847$).

Table 8. ROSE-302 (ITT-LOCF) Mean Change from Baseline in Erythema Score

	Visit Baseline	Week 3	Week 6	Week 12	Week 16	Week 20
Change in Total Erythema Score						
Oracea (N=142)						
Mean	.	-0.64	-0.58	-1.28	**-1.40**	-1.28
Std Dev	.	2.41	2.42	2.60	2.69	2.98
Placebo (N=144)						
Mean	.	-0.73	-0.76	-0.99	**-1.22**	-0.99
Std Dev	.	2.48	2.63	2.70	3.02	2.92
p-value						
ANOVA	.	0.8633	0.6588	0.2804	**0.4278**	0.2764
van Elteren	.	0.5912	0.8175	0.5563	**0.5271**	0.6984
Total Erythema Score						
Oracea (N=142)						
Mean	9.52	8.88	8.94	8.24	**8.12**	8.24
Std Dev	2.89	3.13	3.11	3.21	3.16	3.52
Placebo (N=144)						
Mean	9.15	8.42	8.39	8.15	**7.93**	8.15
Std Dev	2.47	2.91	3.10	3.09	3.26	3.22
p-value						
ANOVA	0.3834	0.3372	0.2430	0.8433	**0.9735**	0.7938
van Elteren	0.4104	0.4327	0.3500	0.5688	**0.6334**	0.9052

In this study, ROSE-302, there was no evidence of any statistically significant differences in either the Week 16 change from baseline in total erythema score or the actual total score ($p \leq 0.2764$ and $p \leq 0.7938$, respectively).

3.1.5 Sponsor Results and Conclusions

The Sponsor results are generally consistent with those in the FDA analysis. The Sponsor's results for the Week 16 primary and erythema endpoints in the ITT population are summarized in Tables 9-11 below:

Table 9. Sponsor Results on Inflammatory Lesions (ITT population)

	ROSE-301		ROSE-302	
	Oracea	Placebo	Oracea	Placebo
Baseline Total Lesions	19.5 (8.78)	20.2 (10.37)	20.5 (11.68)	21.2 (12.51)
Week 16 Total Lesions	7.7 (7.96)	14.4 (16.42)	11.0 (11.29)	16.9 (14.69)
Change from Base	-11.8 (9.78)	-5.9 (13.91)	-9.5 (9.63)	-4.3 (11.57)
p-value Change from Base	<0.001		<0.001	

The Sponsor noted that since the hypothesis of normality in the distribution of the residuals was rejected, the p-values are from a van Elteren test. In both studies, Week 16 treatment differences were highly statistically significant (both $p<0.001$).

As recommended by the Division, "success" on the Investigator's Global Assessment was defined as a score of "Clear" or "Near clear." The Sponsor reported values are summarized in Table 10 below:

Table 10. Sponsor Reported Success on Investigator's Global Assessment (ITT)

	ROSE-301		ROSE-302	
	Oracea	Placebo	Oracea	Placebo
Week 16 Success (0 or 1)	39	24	21	9
Week 16 No Success (2,3,4)	88	100	121	135
p-value CMH test	0.036		0.012	

In both Study ROSE-301 and ROSE-302, Week 16 treatment differences using a Cochran-Mantel-Haenszel test were statistically significant ($p \leq 0.036$ and $p \leq 0.012$, respectively).

The Sponsor's Week 16 change from baseline in erythema assessment score in the ITT population are summarized below (in Table 11):

Table 11. Sponsor Results on Erythema Assessment Score (ITT population)

	ROSE-301		ROSE-302	
	Oracea	Placebo	Oracea	Placebo
Baseline Total Score	9:7 (2.97)	9.5 (2.72)	9.5 (2.89)	9.1 (2.47)
Week 16 Total Score	7.0 (3.69)	7.7 (3.53)	8.1 (3.16)	7.9 (3.26)
Change from Base	-2.7 (3.25)	-1.8 (2.89)	-1.4 (2.69)	-1.2 (3.02)
p-value Change from Base	0.017		0.428	

As can be seen in both the Sponsor's and the Agency analysis, treatment differences were equivocal, statistically significant in Study 301 ($p \leq 0.017$) but not in Study 302 ($p \leq 0.428$). While the computed statistics are consistent with those from the FDA analysis, the p-values in Study 301 do differ slightly from those in the FDA analysis.

3.2 Evaluation of Safety

A table of reported adverse events and the number of subjects experiencing the adverse events (AEs) is presented in Appendix 8. Following the recommendation of the Medical team, several of the Sponsor defined events were pooled into single AEs. One possible statistical approach to the analysis of AEs would be to pool the results of the studies, and analyze the total subjects with each of these analyzable AEs using a multiplicity adjusted test of treatment differences. For this particular analysis, also at the recommendation of the Medical team, an AE that occurred in more than 1% of the Oracea subjects was considered to be appropriate for analysis. Since there are many different AEs and the studies are not powered to test for adverse events, any such statistical analysis of AEs should be interpreted as a "post hoc" analysis, with the possible problems associated with such post hoc analyses.

Of 25 AEs that satisfy the criteria above, only two showed statistical significance before adjusting for multiplicity (using a Fisher Exact test), and none after adjustment. The only two statistically significant comparisons are given below:

AE	Frequencies		Significance Levels	
	Oracea	Placebo	Unadjusted	Adjusted
Gastrointestinal Disorders GI Discomfort	13/269	4/268	0.0456	0.4865
Infections and Infestations Upper Respiratory Infection	9/269	21/268	0.0250	0.2199

Note that the incidence of upper respiratory infections actually favors Placebo over Oracea. However, adjusting for multiplicity using the techniques of Westfall and Young, neither AE displayed a statistically significant treatment difference ($p \leq 0.4865$ and $p \leq 0.2199$, respectively).

In summary, assessing adverse events is primarily a matter of clinical judgment, but if the AE categories are appropriate, then from a purely statistical point of view it seems safe to conclude these studies show no statistically significantly higher adverse event rate in the Oracea group than in the Placebo group.

For further details about the adverse events, please see the Medical Division Review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

To summarize the results in the following tables, in general, Oracea seems to be consistently more efficacious than placebo across gender and age groups, as well as in the subgroup of Caucasian patients. Although few patients were non-Caucasian, in general, among the non-Caucasian subjects there seemed to no particular evidence that Oracea was more efficacious than placebo. Not surprisingly, when the number of baseline lesions is small, the treatment differences between Oracea and Placebo are small, while when the baseline count is relatively higher, treatment differences are larger.

The following tables illustrate these points with simple summaries of the primary endpoints in the ITT-LOCF population. Lesion counts used pooled data, while the IGA is restricted to Week 16, but with results presented separately for each study.

4.1 Gender, Race and Age

4.1.1 Stratification on Gender:

Table 12. Change in Total Inflammatory Lesions Score by Gender

	Week 3	Week 6	Week 12	Week 16
Female				
Oracea (N=185)				
Mean	-5.69	-8.02	-9.47	**-10.10**
Std Dev	8.51	9.45	10.07	9.45
Placebo (N=190)				
Mean	-3.44	-3.54	-5.08	**-5.63**
Std Dev	9.97	11.67	12.40	13.38
Male				
Oracea (N=84)				
Mean	-6.80	-9.07	-9.46	**-11.65**
Std Dev	9.31	9.47	10.96	10.37
Placebo (N=78)				
Mean	-2.51	-4.40	-4.13	**-3.68**
Std Dev	7.04	6.05	9.43	10.85

So results in mean change from baseline in lesion counts seem to be consistent across genders.

Table 13. Week 16 Investigator Global Assessment by Gender

		ROSE-301				ROSE-302			
		Female		Male		Female		Male	
		Oracea	Placebo	Oracea	Placebo	Oracea	Placebo	Oracea	Placebo
0. Clear	N	7	5	5	5	1	.	1	.
	%	7.7	5.3	13.9	17.2	1.1	.	2.1	.
1. Near Clear	N	15	10	12	4	12	8	7	1
	%	16.5	10.5	33.3	13.8	12.8	8.4	14.6	2.0
2. Mild	N	42	34	12	10	44	38	21	11
	%	46.2	35.8	33.3	34.5	46.8	40.0	43.8	22.4
3. Moderate	N	18	22	4	3	25	24	12	23
	%	19.8	23.2	11.1	10.3	26.6	25.3	25.0	46.9
4. Severe	N	9	24	3	7	12	25	7	14
	%	9.9	25.3	8.3	24.1	12.8	26.3	14.6	28.6
All	N	91	95	36	29	94	95	48	49

Note that treatment relative success rate on the IGA (i.e., a score of "0" or "1") comparing Oracea to placebo in ROSE-301 was higher among males than among females. Results were more consistent across gender in ROSE-302. So this observation is not verified across studies, and may well be just an artifact of the study.

4.1.2 Stratification on Race:

Most patients were Caucasian, so the patient population was split into only two subgroups. Pooling over centers, for the mean change in lesion count we find the following profiles:

Table 14. Change in Total Inflammatory Lesions by Race by Week

	Week 3	Week 6	Week 12	Week 16
Caucasian				
Oracea (N=243)				
Mean	-5.78	-8.36	-9.47	**-10.54**
Std Dev	8.85	9.57	10.55	9.93
Placebo (N=248)				
Mean	-3.23	-3.75	-4.72	**-4.60**
Std Dev	9.21	10.51	11.75	12.94
Other				
Oracea (N=26)				
Mean	-8.42	-8.23	-9.42	**-11.00**
Std Dev	7.71	8.44	8.15	8.03
Placebo (N=20)				
Mean	-2.40	-4.30	-5.85	**-10.80**
Std Dev	9.42	8.29	9.83	7.39

Possibly due to the small number of non-Caucasian subjects, we see that in this subgroup there seems to be no difference in change from baseline between treatments. That is, Week 16 observed treatment differences only seem to occur among Caucasian subjects.

Table 15. Week 16 Investigator Global Assessment by Race

		ROSE-301				ROSE-302			
		Caucasian		Other		Caucasian		Other	
		Oracea	Placebo	Oracea	Placebo	Oracea	Placebo	Oracea	Placebo
0. Clear	N	11	9	1	1	2	.	.	.
	%	10.2	8.4	5.3	5.9	1.5	.	.	.
1. Near Clear	N	25	9	2	5	17	9	2	.
	%	23.1	8.4	10.5	29.4	12.6	6.4	28.6	.
2. Mild	N	47	39	7	5	64	47	1	2
	%	43.5	36.4	36.8	29.4	47.4	33.3	14.3	66.7
3. Moderate	N	15	23	7	2	34	47	3	.
	%	13.9	21.5	36.8	11.8	25.2	33.3	42.9	.
4. Severe	N	10	27	2	4	18	38	1	1
	%	9.3	25.2	10.5	23.5	13.3	27.0	14.3	33.3
All	N	108	107	19	17	135	141	7	3

Again, for each study, the treatment differences in the IGA seem to be solely in the Caucasian subjects.

4.1.3 Stratification on Age Group:

Table 16. Change in Total Inflammatory Lesions by Age Group and Week

	Week 3	Week 6	Week 12	Week 16
Age Group=19-35				
Oracea (N=56)				
Mean	-6.95	-8.27	-10.09	**-10.18**
Std Dev	8.87	9.43	10.75	9.76
Placebo (N=43)				
Mean	-3.81	-5.70	-4.79	**-5.00**
Std Dev	9.03	10.01	11.01	12.24
Age Group=36-50				
Oracea (N=122)				
Mean	-5.23	-7.25	-8.24	**-9.86**
Std Dev	9.38	10.31	11.15	10.02
Placebo (N=117)				
Mean	-3.15	-2.36	-4.84	**-5.70**
Std Dev	10.38	11.81	12.97	12.39
Age Group=51+				
Oracea (N=91)				
Mean	-6.56	-9.87	-10.74	**-11.80**
Std Dev	7.78	8.04	8.73	9.37
Placebo (N=108)				
Mean	-2.94	-4.58	-4.77	**-4.40**
Std Dev	7.93	8.52	10.30	13.30

Again, mean changes seem to be consistent across the three age subgroups.

Table 17. Week 16 Investigator Global Assessment by Age Group

		ROSE-301						ROSE-302					
		19-35		36-50		51+		19-35		36-50		51+	
		Oracea	Placebo	Oracea	Placebo	Oracea	Placebo	Oracea	Placebo	Oracea	Placebo	Oracea	Placebo
Clear	N	1	.	5	2	6	8	1	.	.	.	1	.
	%	3.8	.	8.6	3.3	14.0	16.7	3.3	.	.	.	2.1	.
Near Clear	N	3	4	11	7	13	3	2	1	6	4	11	4
	%	11.5	25.0	19.0	11.7	30.2	6.3	6.7	3.7	9.4	7.0	22.9	6.7
Mild	N	9	5	28	21	17	18	12	6	27	24	26	19
	%	34.6	31.3	48.3	35.0	39.5	37.5	40.0	22.2	42.2	42.1	54.2	31.7
Moderate	N	8	3	10	13	4	9	10	8	21	14	6	25
	%	30.8	18.8	17.2	21.7	9.3	18.8	33.3	29.6	32.8	24.6	12.5	41.7
Severe	N	5	4	4	17	3	10	5	12	10	15	4	12
	%	19.2	25.0	6.9	28.3	7.0	20.8	16.7	44.4	15.6	26.3	8.3	20.0
All		26	16	58	60	43	48	30	27	64	57	48	60

Oracea efficacy assessed by the IGA in Study 301 seems concentrated in the two higher age groups. However, this is not replicated in Study 302, where efficacy seems concentrated in the lowest and highest age groups. Again these seem to be due to vagaries of studies where the results are not overwhelmingly strong.

4.2 Other Special/Subgroup Populations: Stratification on Baseline Lesion Count

Table 18. Change in Total Inflammatory Lesions by Baseline Score by Week

	Week 3	Week 6	Week 12	Week 16
Baseline lesion count = 10-20				
Oracea (N=169)				
Mean	-3.41	-5.07	-5.57	**-6.66**
Std Dev	6.56	6.87	7.52	6.08
Placebo (N=162)				
Mean	-2.01	-3.28	-3.81	**-4.01**
Std Dev	7.98	8.83	9.18	9.28
Baseline lesion count = 21-105				
Oracea (N=100)				
Mean	-10.48	-13.89	-16.05	**-17.22**
Std Dev	10.16	10.60	11.11	11.13
Placebo (N=106)				
Mean	-4.95	-4.57	-6.31	**-6.68**
Std Dev	10.62	12.32	14.48	16.56

Not surprisingly, when the number of baseline lesions is small, the treatment differences between Oracea and Placebo are small, while they are much larger when the baseline number of lesions is relatively large.

Table 19. Week 16 Investigator Global Assessment by Baseline Score

		ROSE-301				ROSE-302			
		10-20		21-105		10-20		21-105	
		Oracea	Placebo	Oracea	Placebo	Oracea	Placebo	Oracea	Placebo
0. Clear	N	9	8	3	2	.	.	2	.
	%	11.7	10.5	6.0	4.2	.	.	4.0	.
1. Near Clear	N	20	12	7	2	17	8	2	1
	%	26.0	15.8	14.0	4.2	18.5	9.3	4.0	1.7
2. Mild	N	32	35	22	9	47	37	18	12
	%	41.6	46.1	44.0	18.8	51.1	43.0	36.0	20.7
3. Moderate	N	15	14	7	11	23	28	14	19
	%	19.5	18.4	14.0	22.9	25.0	32.6	28.0	32.8
4. Severe	N	1	7	11	24	5	13	14	26
	%	1.3	9.2	22.0	50.0	5.4	15.1	28.0	44.8
All	N	77	76	50	48	92	86	50	58

Results using the Week 16 IGA are similar to those associated with the mean change from baseline in lesion counts. As would be expected, for both studies, treatment differences are much more pronounced when the baseline number of lesions is larger.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Statistical Issues

1. Perhaps the most important issue with this submission is whether or not the investigator global assessment is defined appropriately, and is suitable as a primary endpoint. As discussed in Section 2.1.2, for an indication of "rosacea", the division requested a global assessment of the disease. The Sponsor provided an endpoint that is a grouped data version of the lesion count in Study 301 and largely a grouped data version in Study 302. The Sponsor asserts that since the proposed indication is "to [redacted] inflammatory lesions in patients with rosacea" only the change from baseline in lesion count is needed as a primary endpoint. Both endpoints were analyzed in this review.

2. The protocols specified that the changes from baseline in lesion counts be analyzed with an analysis of variance (ANOVA) model with factors for treatment and center. The protocol also specified that if the residuals were not normal, a van Elteren test was to be used to compare treatment groups. It is this reviewer's opinion that in all cases here, the data do not seem to be sufficiently skewed to invalidate the assumption of approximate normality in the distribution of cell means. Thus ANOVA would be appropriate. However since this was specified in the protocol, results from both the ANOVA and the van Elteren statistical tests are reported here, and were in all cases essentially equivalent. In a few cases the reported significance levels for the Sponsor's van Elteren tests do seem to generally differ slightly from those computed by this reviewer, but the differences are never enough to change conclusions.

3. The Investigator's Global Assessment was measured on a 0-4 scale, but the guidelines indicate the associated range of inflammatory lesions are 0, 1-2, 3-10, 11-19, or 20+. The Sponsor's protocol indicates the second analysis of this endpoint should be based on the change from baseline. This change from baseline is summarized in Appendix 1; however, note that the difference in IGA scores between 0 and 1 (i.e., between 0 and 1-2 lesions) is not particularly commensurable with the nominally equal difference between 3 and 4 (i.e., between 11-19 and 20+ lesions). This would suggest that the change from baseline in this endpoint is not a particularly useful measure. The Division recommended a measure based on dichotomizing the IGA so that a treatment "success" was defined as a score of 0 or 1. This endpoint was used here.

4. Several centers only recruited a small number of patients into the study. Pooling of subjects for the analysis was specified in amendment to the protocol issued on April 26, 2005. This is clearly a post hoc adjustment. However, this pooling was deemed to be acceptable, and for convenience was followed in the Agency analysis.

Collective Evidence

For both Phase 3 studies the primary efficacy endpoint specified in the protocols was the change from baseline in inflammatory lesion count. In Study ROSE-301, at baseline the mean number of lesions in the Oracea group was 19.5 versus 20.3 in the Placebo group. In the intent to treat population, using last observation carried forward (LOCF) imputation for dropouts, the Week 16 mean changes from this baseline count were -11.8 and -5.9, respectively. Using a simple ANOVA model, the difference in this change from baseline was statistically significant ($p \leq 0.0001$). In Study ROSE-302, at baseline the mean lesion counts were 20.5 and 21.2 in the Oracea and Placebo groups, respectively. So in both studies, while the difference was not statistically significant, the baseline lesion count was larger in the Placebo group. In Study 302, the corresponding Week 16 mean changes from this baseline count were -9.5 and -4.3, respectively. Again, as in Study 301, the difference in these changes from baseline was statistically significant ($p < 0.0001$). A preliminary Bayesian analysis using a linear growth curve models confirmed these results. By week 12 the posterior probability at least 0.98 that a patient using Oracea would be expected to have at least three lesions less than when using Placebo (Please see Appendix 9).

In response to a request by the Division for a static Investigator Global Assessment (IGA), measuring global rosacea (except possibly erythema), the Sponsor provided an endpoint that is basically a grouped data version of the inflammatory lesion count (see section 2.1.2 for more on this). At Week 16 in the intent-to-treat (ITT) population in Study ROSE-301, according to the Sponsor's IGA, 11 of the Oracea patients versus 10 of the Placebo patients were clear, i.e., had no inflammatory lesions. For analysis, the Division recommended dichotomizing this endpoint so that a "success" was defined as an IGA of "Clear" or "Near Clear." At Week 16, in ROSE-301, 16.5% of the Oracea patients and 10.4% of the Placebo patients were scored as successes on this endpoint. In Study ROSE-302, at Week 16, only two of the Oracea patients versus none of the Placebo patients were scored as "clear," while 8.5% of the Oracea patients versus 3.4% of the Placebo patients were scored as "clear" or "near clear." These treatment differences in success rates were statistically significant ($p \leq 0.0361$ and $p \leq 0.012$, in Studies 301 and 302, respectively).

Possibly due to the fine breakdown in adverse event categories, there was no statistically significant evidence of treatment differences in adverse event rates.

5.2 Conclusions and Recommendations

For both Phase 3 studies the primary efficacy endpoint specified in the protocols was the change from baseline in inflammatory lesion count. In Study ROSE-301 the Week 16 mean changes from this baseline in lesion counts were -11.8 and -5.9, for Oracea and Placebo, respectively ($p \leq 0.0001$). In Study ROSE-302, the corresponding Week 16 mean changes from this baseline count were -9.5 and -4.3, respectively ($p < 0.0001$). The proportion of patients who achieved "Clear" or "Near Clear" according to the Sponsor defined Investigator Global Assessment in both studies was statistically significantly higher in the Oracea treatment group

than in the Placebo treatment group. In an attempt to provide a static overall IGA as repeatedly requested by the Agency the Medical team defined a post hoc extended IGA, incorporating erythema. (Please see Appendix 7). There were no statistically significant treatment differences on this endpoint ($p \leq 0.7868$ and $p \leq 0.6211$, for studies 301 and 302 respectively).

APPENDICES:

Appendix 1. Per Protocol Analysis of Total Lesion Count/Change from Baseline in Lesion Count

The following tables show the results on inflammatory lesion counts in the Per Protocol population. In both studies, results from the Per Protocol population are similar to those in the ITT population. Both studies show statistically significant treatment differences favoring Oracea over Placebo ($p \leq 0.0001$ in both studies). In this population, however, compared to the ITT population, the mean baseline scores in the Placebo treatment groups and the Oracea treatment groups are much closer.

Table A.1.1 ROSE-301 (Per Protocol) Mean Change from Baseline in Lesion Count

Visit	Baseline	Week 3	Week 6	Week 12	Week 16
Change from Baseline					
Oracea					
Mean	.	-7.21	-10.83	-12.50	**-12.69**
Std Dev	.	8.57	8.65	9.06	9.48
Placebo					
Mean	.	-2.79	-3.88	-6.06	**-5.46**
Std Dev	.	9.38	9.51	10.72	14.53
p-value					
ANOVA	.	0.0013	<0.0001	<0.0001	**0.0001**
van Elteren	.	0.0024	<0.0001	0.0005	**0.0037**
Total Lesions					
Oracea					
N	97	94	90	86	95
Mean	19.32	11.96	8.28	6.72	**6.58**
Std Dev	8.67	8.79	7.50	6.29	6.88
Placebo					
N	99	92	94	89	97
Mean	19.20	16.20	14.90	12.74	**13.63**
StdDev	8.50	11.09	12.80	12.46	16.67
p-value					
ANOVA	0.8542	0.0015	<0.0001	<0.0001	**0.0002**
van Elteren	0.7121	0.0012	<0.0001	0.0070	**0.0109**

Results for Study 302 given below:

Table A.1.2 ROSE-302 (Per Protocol) Mean Change from Baseline in Lesion Count

	Visit Baseline	Week 3	Week 6	Week 12	Week 16	Week 20
Change from Baseline						
Oracea						
Mean	.	-5.64	-7.71	-9.84	**-9.64**	-8.87
Std Dev	.	8.25	10.03	9.45	9.30	10.11
Placebo						
Mean	.	-2.94	-3.04	-4.02	**-3.68**	-3.79
Std Dev	.	7.04	10.60	9.17	12.29	10.02
p-value						
ANOVA	.	0.0069	0.0005	<0.0001	**<0.0001**	0.0074
van Elteren	.	0.0032	0.0002	<0.0001	**0.0005**	0.0059
Total Lesions						
Oracea						
N	111	106	101	98	109	70
Mean	19.17	13.70	11.48	9.42	**9.61**	10.31
Std Dev	7.53	8.51	8.54	6.92	7.51	7.68
Placebo						
N	111	109	109	103	106	66
Mean	19.41	16.40	16.23	14.98	**15.42**	14.61
Std Dev	7.71	9.44	12.18	10.83	13.01	10.84
p-value						
ANOVA	0.7814	0.0234	0.0006	<0.0001	**0.0001**	0.0123
van Elteren	0.7970	0.0113	0.0006	<0.0001	**0.0008**	0.0218

As in ROSE-301 there are statistically significant differences favoring Oracea over Placebo.

Recall that in both studies,the Week 16 values would define the main endpoint of interest.

Appendix 2. Change from Baseline in Investigator's Global Assessment

The protocol specified that the change from baseline in the IGA will be a secondary endpoint. Note that these IGA scores represent grouped data values with different ranges of lesions for each level of the IGA, so the change from baseline scores represent different numbers of changes in lesions, for example, changes of -1 can represent very different number changes in the number of lesions. Thus these values are, strictly speaking, not particularly comparable.

Table A.2.1 ROSE-301: Change from Baseline in IGA

			Week 3	Week 6	Week 12	Week 16
Oracea	-4	N	1	1	2	4
		%	0.9	0.9	2.0	3.4
	-3	N	2	5	9	13
		%	1.7	4.5	9.1	11.1
	-2	N	18	31	33	39
		%	15.5	28.2	33.3	33.3
	-1	N	48	50	39	39
		%	41.4	45.5	39.4	33.3
	0	N	41	21	15	20
		%	35.3	19.1	15.2	17.1
	1	N	5	2	1	2
		%	4.3	1.8	1.0	1.7
	2	N	1	.	.	.
		%	0.9	.	.	.
Placebo	-4	N	.	.	1	2
		%	.	.	1.0	1.8
	-3	N	1	2	5	9
		%	0.9	1.8	5.0	8.0
	-2	N	4	14	20	21
		%	3.6	12.6	20.0	18.6
	-1	N	44	40	35	40
		%	40.0	36.0	35.0	35.4
	0	N	52	48	33	35
		%	47.3	43.2	33.0	31.0
	1	N	9	7	6	6
		%	8.2	6.3	6.0	5.3

Assuming these scores are actually interpretable, Oracea treatment is generally associated with general a larger decrease in IGA than with Placebo.

Table A.2.2 ROSE-302: Change from Baseline in IGA

			Week 3	Week 6	Week 12	Week 16	Week 20
Oracea	-4	N	.	.	.	2	3
		%	.	.	.	1.5	2.3
	-3	N	.	.	5	2	3
		%	.	.	4.2	1.5	2.3
	-2	N	13	21	22	28	22
		%	9.8	16.8	18.6	21.2	16.7
	-1	N	53	54	56	57	53
		%	40.2	43.2	47.5	43.2	40.2
	0	N	58	42	27	37	44
		%	43.9	33.6	22.9	28.0	33.3
	1	N	7	7	7	5	6
		%	5.3	5.6	5.9	3.8	4.5
	2	N	1	1	1	1	1
		%	0.8	0.8	0.8	0.8	0.8
Placebo	-4	N	.	1	1	.	.
		%	.	0.8	0.8	.	.
	-3	N	.	2	1	1	2
		%	.	1.5	0.8	0.8	1.6
	-2	N	7	9	12	22	21
		%	5.2	6.8	10.0	17.1	16.3
	-1	N	48	44	42	44	42
		%	35.8	33.3	35.0	34.1	32.6
	0	N	70	66	57	49	53
		%	52.2	50.0	47.5	38.0	41.1
	1	N	9	9	7	13	9
		%	6.7	6.8	5.8	10.1	7.0
	2	N	.	1	.	.	.
		%	.	0.8	.	.	.

As found in ROSE-301 (Table A.2.1), the Oracea treatment is associated with a generally larger decrease in the IGA than the Placebo treatment.

Appendix 3. Per Protocol Analyses of the Investigator's Global Assessment

The following tables display the observed IGA values in the Per Protocol population in both studies. Significance levels for the Week 16 CMH test of treatment differences in success rates (i.e., a score of 0 or 1) are also given. The Week 16 treatment differences in success rates in the Per Protocol population were close to being statistically significant ($p \leq 0.0541$). However, in Study 302, Week 16 treatment differences in the corresponding population are statistically significant ($p \leq 0.0169$).

Table A.3.1. ROSE-301 (Per Protocol) Investigator's Global Assessment

		Visit Baseline	Week 3	Week 6	Week 12	Week 16
Oracea						
0. Clear	N	.	1	1	6	**8**
	%	.	1.1	1.1	7.0	8.4
1. Near Clear	N	.	2	18	13	**25**
	%	.	2.1	20.0	15.1	26.3
2. Mild	N	7	49	48	53	41
	%	7.2	52.1	53.3	61.6	43.2
3. Moderate	N	51	24	18	9	16
	%	52.6	25.5	20.0	10.5	16.8
4. Severe	N	39	18	5	5	5
	%	40.2	19.1	5.6	5.8	5.3
Placebo						
0. Clear	N	.	1	2	5	**10**
	%	.	1.1	2.1	5.6	10.3
1. Near Clear	N	.	2	4	12	**13**
	%	.	2.2	4.3	13.5	13.4
2. Mild	N	8	28	39	33	33
	%	8.1	30.4	41.5	37.1	34.0
3. Moderate	N	54	34	21	17	19
	%	54.5	37.0	22.3	19.1	19.6
4. Severe	N	37	27	28	22	22
	%	37.4	29.3	29.8	24.7	22.7
p-value						
0,1 success						**0.0541**

Again, Week 16 treatment differences using this endpoint in the Per Protocol population were close to statistically significant ($p \leq 0.0541$).

Table A.3.2. ROSE-302 (Per Protocol) Investigator's Global Assessment

		Visit Baseline	Week 3	Week 6	Week 12	Week 16	Week 20
Oracea							
0. Clear	N	.	.	.	2	**2**	4
	%	.	.	.	2.0	1.8	5.7
1. Near Clear	N	.	2	5	12	**17**	4
	%	.	1.9	5.0	12.2	15.6	5.7
2. Mild	N	14	49	52	50	50	35
	%	12.6	46.2	51.5	51.0	45.9	50.0
3. Moderate	N	60	37	33	25	26	20
	%	54.1	34.9	32.7	25.5	23.9	28.6
4. Severe	N	37	18	11	9	14	7
	%	33.3	17.0	10.9	9.2	12.8	10.0
Placebo							
0. Clear	N	.	.	1	1	.	3
	%	.	.	0.9	1.0	.	4.5
1. Near Clear	N	.	2	3	5	**6**	5
	%	.	1.8	2.8	4.9	5.7	7.6
2. Mild	N	6	33	39	34	40	23
	%	5.4	30.3	35.8	33.0	37.7	34.8
3. Moderate	N	65	43	34	39	35	18
	%	58.6	39.4	31.2	37.9	33.0	27.3
4. Severe	N	40	31	32	24	25	17
	%	36.0	28.4	29.4	23.3	23.6	25.8
p-value							
0,1 success						**0.0169**	

However, in contrast to Study ROSE-301, in Study ROSE-302, Week 16 treatment differences in this population were statistically significant ($p \leq 0.0169$).

Appendix 4. Sensitivity Analysis to Centers in Study ROSE-301

The following table displays the number of subjects per center in the ITT-LOCF group at Week 16 in the ROSE -301 study:

Table A.4.1 Number of Subjects per Center (ITT-LOCF) in ROSE-301

	Investigator ID													
Treatment	100	200	300	400	500	600	700	800	900	1000	1100	1200	1300	1400
Oracea	1	12	16	7	11	12	15	8	11	10	11	10	2	1
Placebo	2	12	16	6	12	12	15	8	11	9	11	6	2	2

The following table displays mean change from baseline in the primary endpoint, total inflammatory lesion count. Note that a decrease in this count (i.e., a negative number), is favorable to the treatment arm.

Table A.4.2 Mean Change in Lesion Counts per Center (ITT-LOCF) in ROSE-301

	Investigator ID													
	100	200	300	400	500	600	700	800	900	1000	1100	1200	1300	1400
Oracea	-6.0	-16.9	-10.2	-14.1	-9.5	-14.3	-11.6	-10.4	-11.9	-15.2	-9.2	-8.9	-6.5	-11.0
Placebo	-1.0	0.4	-9.3	-2.8	-3.7	-8.6	-4.5	-6.5	-7.3	-7.3	-6.6	-5.5	-12.0	-15.5

Center 200 has the largest decrease from baseline and also the highest difference between treatment groups. While Centers 1300 and 1400 actually favor placebo over the active treatment, these are small centers with 2 or fewer subjects per arm.

One way to analyze the impact of a center is to investigate the effect of deleting that center. The following table displays the effect of deleting centers on the protocol specified primary endpoint, total inflammatory lesion count.

Table A.4.3 Effect of Deleting Centers on lesion Counts (ITT-LOCF) in ROSE-301

Deleted Center	Ora N	Pla N	Ora Mean	Ora STD	Pla Mean	Pla STD	F	ANOVA PROB	van Elteren PROB
None	127	124	-11.8189	9.7788	-5.94355	13.9093	14.5687	0.00017	0.0009
200	115	112	-11.2870	9.4625	-6.62500	10.8662	11.4217	0.00087	0.0044
300	111	108	-12.0541	9.9780	-5.44444	14.3581	15.1061	0.00014	0.0002
500	116	112	-12.0431	9.9890	-6.18750	14.3599	12.5518	0.00049	0.0027
600	115	112	-11.5565	9.6584	-5.66071	14.4082	12.7049	0.00045	0.0032
700	112	109	-11.8482	9.3772	-6.13761	14.0234	12.4004	0.00053	0.0019
800	119	116	-11.9160	9.8931	-5.90517	13.4229	14.9735	0.00014	0.0012
900	116	113	-11.8103	9.9555	-5.81416	14.2951	13.2232	0.00035	0.0011
1000	117	115	-11.5299	9.5697	-5.83478	13.9170	12.9277	0.00040	0.0014
1100	116	113	-12.0690	9.9247	-5.87611	14.5339	13.7973	0.00026	0.0010
1200	117	118	-12.0684	10.0170	-5.96610	14.2054	13.7595	0.00027	0.0019
1400	127	124	-11.8189	9.7788	-5.94355	13.9093	14.5687	0.00017	0.0009
5000	123	118	-11.9593	9.8824	-5.76271	14.0279	15.3405	0.00012	0.0009

Again, Center 200 seems to have the highest impact on final conclusions.

Note that for this analysis, Centers 100, 1300, and 1400 were pooled to a single center, labeled 5000. This is not as strict a pooling algorithm as that specified by the Sponsor, but is designed to show the impact of each center. The protocol specified the use of ANOVA if the data were normally distributed, and van Elteren's stratified Wilcoxon if not. The change from baseline in lesion counts are highly skewed, and are extremely non-normal. Cell means seem to be more normally distributed, so ANOVA is appropriate, and is arguably more readily interpretable. However, since the protocol specified van Elteren's test, results showing the impact of deleting the specified center are presented for both methods of analysis. The choice of either method of analysis would have no real impact on efficacy conclusions.

The protocol specified the investigator global assessment (IGA) as a secondary endpoint, however the Division recommended an IGA as a co-primary endpoint (Please see section 2.1.2 for details on this). Note that the Sponsor's IGA ranges from 0 "Clear" to 4 "Severe". The following table displays the Week 16 IGA scores for each center. Note that two p-values are presented. The "Success p-value" corresponds to the test of success deleting that center. The "Mean p-value" corresponds to a test of mean rank scores. The p-values under the "All" column correspond to no deletion of any center.

Table A.4.4 Distribution of IGA and the Effect of Deleting Centers in ROSE-301

Investigator:	200		300		400		500		600		700		800	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Oracea														
Clear	2	16.7	1	6.3	.	.	.	.	1	8.3	2	13.3	.	.
Near Clear	2	16.7	2	12.5	.	.	2	18.2	5	41.7	4	26.7	3	37.5
Mild	4	33.3	5	31.3	3	42.9	6	54.5	4	33.3	5	33.3	4	50.0
Moderate	3	25.0	6	37.5	1	14.3	3	27.3	1	8.3	2	13.3	1	12.5
Severe	1	8.3	2	12.5	3	42.9	.	.	1	8.3	2	13.3	.	.
Placebo														
Clear	.	.	1	6.3	.	.	.	.	1	8.3	4	26.7	.	.
Near Clear	1	8.3	4	25.0	.	.	3	25.0	.	.	3	20.0	1	12.5
Mild	2	16.7	4	25.0	.	.	4	33.3	7	58.3	2	13.3	3	37.5
Moderate	5	41.7	3	18.8	3	50.0	3	25.0	2	16.7	3	20.0	1	12.5
Severe	4	33.3	4	25.0	3	50.0	2	16.7	2	16.7	3	20.0	3	37.5
Test of Success														
p-value	0.0865		0.0102		0.0374		0.0212		0.1559		0.0142		0.0639	
Test of Mean														
p-value	0.0171		0.0011		0.0047		0.0031		0.0110		0.0013		0.0095	

Table A.4.4 (cont.) Distribution of IGA and the Effect of Deleting Centers in ROSE-301

900	1000		1100		1200		5000		All			
	n	%	n	%	n	%	n	%	n	%	n	%
Oracea												
Clear	2	18.2	3	30.0	.	.	1	10.0	.	.	12	9.4
Near Clear	1	9.1	2	20.0	.	.	4	40.0	2	50.0	27	21.3
Mild	8	72.7	4	40.0	8	72.7	3	30.0	.	.	54	42.5
Moderate	.	.	.	.	2	18.2	2	20.0	1	25.0	22	17.3
Severe	.	.	1	10.0	1	9.1	.	.	1	25.0	12	9.4
Placebo												
Clear	1	9.1	2	22.2	.	.	.	.	1	16.7	10	8.1
Near Clear	2	18.2	.	.	.	.	.	.	.	.	14	11.3
Mild	3	27.3	2	22.2	11	100.0	4	66.7	2	33.3	44	35.5
Moderate	.	.	2	22.2	.	.	.	.	3	50.0	25	20.2
Severe	5	45.5	3	33.3	.	.	2	33.3	.	.	31	25.0
Test of success												
p-value	0.0282		0.0742		0.0374		0.1114		0.0577		0.0374	
Test of mean												
p-value	0.0086		0.0087		0.0008		0.0096		0.0023		0.0031	

Using the change in significance level as a measure of the impact on the IGA of deleting center, it would seem that, given the other centers, that deleting Centers 600, 1200, and 200 (in that order) has the highest impact.

The protocol specified that the IGA was to be analyzed as change from baseline. However that is not the analysis recommended by the FDA (please see the analysis for "success" in the preceding table). The p-values in the following table correspond to a CMH/van Elteren test, where the p-value under each center corresponds to the effect of deleting that center, and the p-value under the "All" column is the corresponding omnibus test stratified on all centers with no center deleted.

Table A.4.5 Distribution of Change from Baseline in IGA and the Effect of Deleting Centers in ROSE-301

Investigator:

	200		300		400		500		600		700		800	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Oracea														
-4	2	16.7	.	.	.	.	.	.	.	.	1	6.7	.	.
-3	2	16.7	1	6.3	.	.	.	.	4	33.3	3	20.0	.	.
-2	2	16.7	3	18.8	3	42.9	3	27.3	4	33.3	4	26.7	4	50.0
-1	3	25.0	8	50.0	1	14.3	6	54.5	2	16.7	3	20.0	1	12.5
0	3	25.0	4	25.0	3	42.9	2	18.2	1	8.3	4	26.7	3	37.5
1	.	.	.	.	.	.	.	.	1	8.3	.	.	.	.
Placebo														
-4	.	.	.	.	.	.	.	.	.	.	.	.	.	.
-3	.	.	3	18.8	.	.	.	.	1	8.3	3	20.0	.	.
-2	2	16.7	2	12.5	.	.	3	25.0	3	25.0	3	20.0	2	25.0
-1	3	25.0	6	37.5	2	33.3	3	25.0	4	33.3	3	20.0	2	25.0
0	6	50.0	4	25.0	4	66.7	4	33.3	4	33.3	5	33.3	4	50.0
1	1	8.3	1	6.3	.	.	2	16.7	.	.	1	6.7	.	.
p-value for protocol test:	0.0017		<0.0001		0.0005		0.0006		0.0009		0.0004		0.0004	

Investigator:

	900		1000		1100		1200		5000		All	
	n	%	n	%	n	%	n	%	n	%	n	%
Oracea												
-4	.	.	1	10.0	.	.	.	.	.	.	4	3.1
-3	2	18.2	1	10.0	.	.	1	10.0	.	.	14	11.0
-2	4	36.4	5	50.0	2	18.2	4	40.0	2	50.0	40	31.5
-1	5	45.5	2	20.0	7	63.6	2	20.0	.	.	40	31.5
0	.	.	1	10.0	1	9.1	3	30.0	2	50.0	27	21.3
1	.	.	.	.	1	9.1	.	.	.	.	2	1.6
Placebo												
-4	.	.	1	11.1	.	.	.	.	1	16.7	2	1.6
-3	1	9.1	1	11.1	.	.	.	.	.	.	9	7.3
-2	3	27.3	1	11.1	.	.	1	16.7	1	16.7	21	16.9
-1	2	18.2	2	22.2	8	72.7	3	50.0	2	33.3	40	32.3
0	4	36.4	4	44.4	3	27.3	2	33.3	1	16.7	45	36.3
1	1	9.1	.	.	.	.	.	.	1	16.7	7	5.6
p-value for protocol test:	0.0010		0.0006		0.0004		0.0004		0.0002		0.0003	

Note that deleting no one particular center has a major impact upon conclusions of efficacy using this endpoint, however Center 200 would again have the largest effect.

As a comment, note that the protocol states that this change from baseline is to be analyzed stratifying on baseline, but the statistical analysis plan states that stratification will be on center. Since center is a restriction on randomization it makes more sense to stratify on center as was done here.

Appendix 5. Sensitivity Analysis to Centers in Study ROSE-302

The following table displays the number of subjects in each treatment arm in each center in the ITT-LOCF group in the ROSE -302 study:

Table A.5.1 Number of Subjects per Center (ITT-LOCF) in ROSE-302

	Investigator ID													
Treatment	100	200	300	400	500	600	700	800	900	1000	1100	1200	1300	1400
Oracea	23	4	12	.	10	16	12	16	7	7	9	10	1	15
Placebo	23	5	11	1	9	14	12	17	7	7	15	6	2	15

The following table displays the corresponding Week 16 mean change from baseline in the lesion count:

Table A.5.2 Mean Change in Lesion Counts per Center (ITT-LOCF) in ROSE-302

	Investigator ID													
	100	200	300	400	500	600	700	800	900	1000	1100	1200	1300	1400
Oracea	-10.7	-2.3	-6.8	.	-12.4	-11.2	-9.3	-4.1	-11.7	-19.3	-15.7	-6.5	-13.0	-6.3
Placebo	-3.7	-8.4	4.1	-22.0	-5.3	-4.1	-7.8	-3.8	-2.9	-12.9	-7.1	-5.3	-13.5	1.3

Center 300 has the largest difference between treatment groups. Also, note that Centers 200 and 1300 actually favor placebo over the active treatment, but these are relatively small centers.

As in the preceding analysis, the following table displays the effect of deleting centers on the primary endpoint. In this analysis Centers 200, 400, and 1300 were pooled to create Center 5000.

Table A.5.3 Effect of Deleting Centers on lesion Counts (ITT-LOCF) in ROSE-302

Deleted Center	Ora N	Pla N	Ora Mean	Ora STD	Pla Mean	STD Pla	F	ANOVA PROB	van Elteren PROB
None	142	144	-9.4789	9.62688	-4.30556	11.5718	19.7747	0.00001	0.0002
100	119	121	-9.2353	9.79338	-4.42975	11.4301	14.9959	0.00014	0.0007
300	130	133	-9.7308	9.95088	-5.00000	10.7464	15.7587	0.00010	0.0009
400	142	144	-9.4789	9.62688	-4.30556	11.5718	19.7747	0.00001	0.0002
500	132	135	-9.2576	9.48170	-4.23704	11.6146	17.9855	0.00003	0.0007
600	126	130	-9.2619	9.65085	-4.33077	11.7351	16.2822	0.00007	0.0009
700	130	132	-9.5000	9.52048	-3.99242	11.7509	20.5766	0.00001	0.0001
800	126	127	-10.1667	9.36525	-4.37795	12.0495	21.3628	0.00001	0.0003
900	135	137	-9.3630	9.72657	-4.37956	11.0747	18.6722	0.00002	0.0002
1000	135	137	-8.9704	9.36247	-3.86861	11.5139	18.3877	0.00003	0.0004
1100	133	129	-9.0602	9.40967	-3.98450	12.0889	15.7894	0.00009	0.0009
1200	132	138	-9.7045	9.75637	-4.26087	11.8076	19.7075	0.00001	0.0002
5000	137	136	-9.6642	9.68950	-3.88971	11.6725	22.4909	0.00000	<0.0001

Using the van Elteren test the impact of deleting center 300 seems to be large. The even larger impact of center 100 in the ANOVA results is due to using Type II sums of squares for the ANOVA and the fact this center is considerably larger than the other centers.

Again, the FDA recommended that "success" on the IGA should be a co-primary endpoint. The following table displays the Week 16 IGA scores for each center. For the Division recommended analysis is based on the dichotomized success scores. As before, the "Success p-value" corresponds to the test of that dichotomized success deleting the particular center. The "Mean p-value" corresponds to a test of mean rank scores. The p-values under the "All" column correspond to no deletion of any center.

Table A.5.4 Distribution of IGA and the Effect of Deleting Centers in ROSE-302

Investigator	100		300		500		600		700		800		900	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Oracea														
Clear	1	4.3	.	.	.	.	.	.	.	.	.	.	.	.
Near Clear	5	21.7	2	16.7	1	10.0	1	6.3	1	8.3	1	6.3	1	14.3
Mild	9	39.1	8	66.7	2	20.0	8	50.0	5	41.7	8	50.0	4	57.1
Moderate	5	21.7	2	16.7	5	50.0	5	31.3	2	16.7	5	31.3	1	14.3
Severe	3	13.0	.	.	2	20.0	2	12.5	4	33.3	2	12.5	1	14.3
Placebo														
Near Clear	1	4.3	.	.	.	.	.	.	1	8.3	1	5.9	.	.
Mild	8	34.8	5	45.5	.	.	3	21.4	4	33.3	8	47.1	1	14.3
Moderate	4	17.4	2	18.2	4	44.4	8	57.1	4	33.3	4	23.5	1	14.3
Severe	10	43.5	4	36.4	5	55.6	3	21.4	3	25.0	4	23.5	5	71.4
Test of success														
p-value	0.0745		0.0240		0.0161		0.0160		0.0083		0.0085		0.0164	
Test of mean														
p-value	0.0011		0.0005		0.0003		0.0003		<0.0001		<0.0001		0.0003	

Investigator	1000		1100		1200		1400		5000		All	
	n	%	n	%	n	%	n	%	n	%	n	%
Oracea												
Clear	1	14.3	.	.	.	.	.	.	.	.	2	1.4
Near Clear	.	.	3	33.3	2	20.0	2	13.3	.	.	19	13.4
Mild	4	57.1	3	33.3	4	40.0	8	53.3	2	40.0	65	45.8
Moderate	1	14.3	2	22.2	3	30.0	3	20.0	3	60.0	37	26.1
Severe	1	14.3	1	11.1	1	10.0	2	13.3	.	.	19	13.4
Placebo												
Near Clear	1	14.3	1	6.7	.	.	1	6.7	3	37.5	9	6.3
Mild	4	57.1	5	33.3	5	83.3	2	13.3	4	50.0	49	34.0
Moderate	1	14.3	9	60.0	1	16.7	8	53.3	1	12.5	47	32.6
Severe	1	14.3	.	.	.	.	4	26.7	.	.	39	27.1
Test of success												
p-value	0.0085		0.0360		0.0195		0.0129		0.0019		0.0109	
Test of mean												
p-value	<0.0001		0.0001		<0.0001		0.0005		<0.0001		<0.0001	

Unlike Study 301, note that only deleting Center 100 would move the significance level of "success" from statistical significance to statistical non-significance (though only barely non-

significant), and, as noted previously, that is due to the relatively large size of that particular center.

Again, the protocol specified analysis for the IGA was change from baseline, as summarized in the following table:

Table A.5.5 Distribution of Change from Baseline in IGA and the Effect of Deleting Centers in ROSE-302

Investigator

	100		300		500		600		700		800		900	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Oracea														
-4	1	4.3	.	.	.	.	.	.	.	.	.	.	.	.
-3	1	4.3	.	.	.	.	.	.	.	.	.	.	.	.
-2	5	21.7	1	8.3	3	30.0	5	31.3	2	16.7	1	6.3	3	42.9
-1	10	43.5	8	66.7	3	30.0	7	43.8	4	33.3	9	56.3	1	14.3
0	6	26.1	3	25.0	4	40.0	4	25.0	5	41.7	4	25.0	2	28.6
1	.	.	.	.	.	.	.	.	.	.	2	12.5	1	14.3
2	.	.	.	.	.	.	.	.	1	8.3	.	.	.	.
Placebo														
-3	1	4.3	.	.	.	.	.	.	.	.	.	.	.	.
-2	3	13.0	1	9.1	.	.	2	14.3	3	25.0	3	17.6	.	.
-1	8	34.8	4	36.4	1	11.1	5	35.7	4	33.3	4	23.5	1	14.3
0	9	39.1	3	27.3	8	88.9	6	42.9	4	33.3	8	47.1	5	71.4
1	2	8.7	3	27.3	.	.	1	7.1	1	8.3	2	11.8	1	14.3
p-value for protocol test:	0.0194		0.0121		0.0183		0.0146		0.0019		0.0048		0.0102	

Investigator

	1000		1100		1200		1400		5000		All	
	n	%	n	%	n	%	n	%	n	%	n	%
Oracea												
-4	1	14.3	.	.	.	.	.	.	.	.	2	1.4
-3	.	.	.	.	.	.	1	6.7	.	.	2	1.4
-2	3	42.9	.	.	4	40.0	1	6.7	.	.	28	19.7
-1	2	28.6	6	66.7	2	20.0	5	33.3	2	40.0	59	41.5
0	1	14.3	2	22.2	3	30.0	7	46.7	3	60.0	44	31.0
1	.	.	1	11.1	1	10.0	1	6.7	.	.	6	4.2
2	.	.	.	.	.	.	.	.	.	.	1	0.7
Placebo												
-3	.	.	.	.	.	.	.	.	.	.	1	0.7
-2	4	57.1	1	6.7	.	.	1	6.7	4	50.0	22	15.3
-1	2	28.6	3	20.0	5	83.3	5	33.3	3	37.5	45	31.3
0	1	14.3	10	66.7	1	16.7	6	40.0	1	12.5	62	43.1
1	.	.	1	6.7	.	.	3	20.0	.	.	14	9.7
p-value for protocol test:	0.0047		0.0105		0.0046		0.0067		0.0009		0.0048	

Thus no one center seems to have a major impact on the results, though the largest center, Center 100 and Center 300 might be considered somewhat extreme.

Appendix 6. Association between the IGA and the Inflammatory Lesion Count

Note the guidelines in the protocol for the Sponsor's investigator global assessment (IGA) indicate ranges of lesion counts for each of the levels of the IGA. In Study ROSE-301, with the exception of one subject at a pre-Week 16 visit, for each subject the computed lesion count falls within the range of values specified by the guidelines for the corresponding level of the IGA. That is, in Study 301, with that single exception previously noted, the observed level of the IGA is just a grouped data version of the inflammatory lesion count. In Study ROSE-302, the association is less precise, but the computed lesion count still primarily falls within the range of values specified by the guidelines for the corresponding IGA. To illustrate this, the following table displays, for each study, the Week 16 count of ITT cases assigned to each level of the IGA, the number of those cases that exceed the bounds associated with that level of IGA (both lower and upper); and, for reference, the minimum, median, and maximum lesion count values at that IGA level.

Table A.6.1 ROSE-301 Association Between the Week 16 IGA and the total lesion count

IGA	Range	Counts			Quantiles		
level	Low-high	N	# < low	# > high	minimum	median	maximum
0	0 - 0	22	-	0	0	0	0
1	1- 2	41	0	0	1	2	2
2	3-10	98	0	0	3	5	10
3	11-19	47	0	0	11	15	19
4	≥ 20	43	0	-	20	28	111

Thus for example, every case assigned to IGA level 3 had lesion counts between 11 and 19. The guidelines were less consistently followed in Study ROSE-302, as illustrated in the following table:

Table A.6.2 ROSE-302 Association Between the Week 16 IGA and the total lesion count

IGA	Range	Counts			Quantiles		
level	Low-high	N	# < low	# > high	minimum	median	maximum
0	0 – 0	2	-	0	0	0	0
1	1- 2	28	0	4	1	2	7
2	3-10	114	1	2	2	6	13
3	11-19	84	3	2	7	14	26
4	≥ 20	58	1	-	17	28.5	105

So for example, only five (of 84) subjects were assigned an IGA level of 3, but had lesion counts outside the 11-19 range.

These observations would seem to justify the claim that the observed IGA is essentially just a measure of observed lesion count.

Appendix 7. Sensitivity Analysis: Extended Investigator's Global Assessment

In response to a request by the Division for a static Investigator Global Assessment (IGA), measuring global rosacea (except possibly erythema), the Sponsor provided an endpoint scored with labels as follows:

0. Clear 1. Near Clear 2. Mild 3. Moderate 4. Severe

However the guidelines indicate, as is confirmed in Appendix 6, that this is (in Study 301) or largely is (in Study 302) merely a grouped data version of the inflammatory lesion count. The Sponsor also evaluated erythem a for each of the forehead, chin, nose, right check, and left check, each facial region assessed on the following scale:

0. None 1. Mild 2. Moderate 3. Significant 4. Severe

At Clinical/Biostatistics internal Agency meeting on 7 February 2006, the Medical team recommended a sensitivity analysis using an Extended IGA (XIGA), which, for analysis, was defined as follows:

Score	Description
0. Clear	If IGA=0 and each of the 5 erythema scores are 0.
1. Near Clear	If IGA=1 and each of the 5 erythema scores are 0 or 1.
2. Other	Otherwise

For analysis the 0 and 1 scores were to be pooled to define a dichotomized success variable, however, in both studies, no subject achieved an XIGA of 0. The following tables display the XIGA in the ITT population at each scheduled time in each study. Since there no treatment differences at any timepoint on the XIGA it was felt that significance levels for the tests of treatment differences would be superfluous, however for consistency with other endpoints the significance levels for the Week 16 test of differences are presented.

Table A.7.1. ROSE-301 Extended Investigator's Global Assessment

	Visit	Baseline	Week 3	Week 6	Week 12	Week 16
Oracea						
1. Near Clear	N	.	1	4	5	**8**
	%	.	0.8	3.1	3.9	6.3
2. Other	N	127	126	123	122	**119**
	%	100.0	99.2	96.9	96.1	93.7
Placebo						
1. Near Clear	N	.	1	3	4	**7**
	%	.	0.8	2.4	3.2	5.6
2. Other	N	124	123	121	120	**117**
	%	100.0	99.2	97.6	96.8	94.4
p-value						**0.7868**

Table A.7.2. ROSE-302 Extended Investigator's Global Assessment

		Visit Baseline	Week 3	Week 6	Week 12	Week 16	Week 20
Oracea							
1. Near Clear	N	.	1	.	2	**5**	2
	%	.	0.7	.	1.4	3.5	1.4
2. Other	N	142	141	142	140	**137**	140
	%	100.0	99.3	100.0	98.6	96.5	98.6
Placebo							
1. Near Clear	N	.	.	1	3	**4**	2
	%	.	.	0.7	2.1	2.8	1.4
2. Other	N	144	144	143	141	**140**	142
	%	100.0	100.0	99.3	97.9	97.2	98.6
p-value						**0.6211**	

Again, please note that there are no statistically significant treatment differences in the XIGA either study ($p \leq 0.7868$ and $p \leq 0.6211$, respectively).

Appendix 8. Reported Adverse Events by Number of Events and Number of Subjects with Event

The following table displays summary counts of adverse events in both studies. Sponsor defined AEs are presented in all upper case, AEs specified to be pooled by the Medical team are labeled in mixed case.

Table A.8.1 Adverse Events: Number of Events and Number of Subjects (of 537 patients)

	Number of Events		Number of Subjects	
	Oracea	Placebo	Oracea	Placebo
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
ANAEMIA	1	2	1	2
CARDIAC DISORDERS				
CORONARY ARTERY DISEASE	2	0	1	0
PALPITATIONS	0	1	0	1
TACHYCARDIA	1	1	1	1
VENTRICULAR EXTRASYSTOLES	1	0	1	0
CONGENITAL, FAMILIAL AND GENETIC DISORDERS				
DERMOID CYST	1	0	1	0
EPIDERMAL NAEVUS	1	0	1	0
EAR AND LABYRINTH DISORDERS				
EAR CONGESTION	1	0	1	0
EAR PAIN	1	0	1	0
TYMPANIC MEMBRANE PERFORATION	0	1	0	1
VERTIGO	2	1	2	1
ENDOCRINE DISORDERS				
HYPERTHYROIDISM	1	1	1	1
THYROID NODULE	0	1	0	1
EYE DISORDERS				
PHOTOPHOBIA	1	0	1	0
UVEITIS	0	1	0	1
VISION BLURRED	1	0	1	0
GASTROINTESTINAL DISORDERS				
CONSTIPATION	2	2	2	2
DENTAL DISCOMFORT	1	0	1	0
DIARRHOEA	12	7	12	7
DRY MOUTH	3	0	3	0
DYSPEPSIA	0	1	0	1
DYSPHAGIA	1	0	1	0
FOOD POISONING	1	0	1	0
GASTROOESOPHAGEAL REFLUX DISEASE	2	2	2	2
GI Discomfort	19	5	13	4
GI Irritation	1	1	1	1
LARGE INTESTINE PERFORATION	1	0	1	0
LOOSE STOOLS	2	1	2	1
NAUSEA	5	12	5	9
PERITONITIS	1	0	1	0
TOOTH FRACTURE	1	0	1	0
TOOTHACHE	0	2	0	2
VOMITING	2	4	2	4
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
CHEST PAIN	2	1	2	1
DIFFICULTY IN WALKING	0	1	0	1
FATIGUE	0	1	0	1
INFLUENZA-LIKE ILLNESS	2	0	2	0
MALAISE	1	0	1	0
OEDEMA	1	0	1	0
OEDEMA PERIPHERAL	0	2	0	2
PAIN	4	1	4	1
PYREXIA	1	3	1	2
XEROSIS	0	1	0	1

Table A.8.1 (cont.) Adverse Events: Number of Events and Number of Subjects (of 537 patients)

	Number of Events		Number of Subjects	
	Oracea	Placebo	Oracea	Placebo
IMMUNE SYSTEM DISORDERS				
FOOD ALLERGY	1	0	1	0
SEASONAL ALLERGY	1	0	1	0
INFECTIONS AND INFESTATIONS				
BRONCHITIS	3	5	3	5
BRONCHITIS VIRAL	0	1	0	1
CANDIDIASIS	1	0	1	0
CELLULITIS	0	1	0	1
CYSTITIS	2	3	2	2
DIVERTICULITIS	0	1	0	1
EAR INFECTION	1	1	1	1
FUNGAL INFECTION	6	1	5	1
FURUNCLE	1	0	1	0
GASTROENTERITIS VIRAL	1	0	1	0
HERPES OPHTHALMIC	0	1	0	1
HERPES SIMPLEX	1	0	1	0
HORDEOLUM	0	1	0	1
INFLUENZA	5	4	5	4
KIDNEY INFECTION	2	0	1	0
LABYRINTHITIS	0	2	0	1
LOCALISED INFECTION	1	0	1	0
NASOPHARYNGITIS	13	10	13	10
OTITIS MEDIA	0	1	0	1
PARONYCHIA	1	0	1	0
PHARYNGITIS STREPTOCOCCAL	1	2	1	2
PNEUMONIA	1	3	1	3
RHINITIS	0	1	0	1
SEPSIS	1	0	1	0
SEPTIC SHOCK	1	0	1	0
SINUSITIS	8	2	7	2
SWEAT GLAND INFECTION	0	1	0	1
TOOTH ABSCESS	1	0	1	0
UPPER RESPIRATORY TRACT INFECTION	9	24	9	21
URINARY TRACT INFECTION	2	2	2	2
VAGINAL CANDIDIASIS	0	1	0	1
VAGINAL MYCOSIS	0	3	0	3
VAGINITIS	0	1	0	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS				
ANIMAL BITE	0	1	0	1
ANIMAL SCRATCH	1	0	1	0
ARTHROPOD BITE	2	0	2	0
FALL	1	0	1	0
FRACTURE	1	0	1	0
INJURY	1	1	1	1
LACERATION	1	1	1	1
LIMB INJURY	1	1	1	1
MENISCUS LESION	2	0	2	0
MOUTH INJURY	1	0	1	0
MUSCLE INJURY	0	1	0	1
MUSCLE STRAIN	1	1	1	1
POST PROCEDURAL PAIN	1	1	1	1
SUNBURN	2	1	2	1
THERMAL BURN	0	1	0	1
UPPER LIMB FRACTURE	0	1	0	1
INVESTIGATIONS				
ALANINE AMINOTRANSFERASE INCREASED	4	4	4	4
ASPARTATE AMINOTRANSFERASE INCREASED	6	2	6	2
BLOOD GLUCOSE INCREASED	3	0	3	0

Table A.8.1 (cont.) Adverse Events: Number of Events and Number of Subjects (of 537 patients)

	Number of Events		Number of Subjects	
	Oracea	Placebo	Oracea	Placebo
INVESTIGATIONS (cont.)				
BLOOD LACTATE DEHYDROGENASE INCREASED	4	1	4	1
BLOOD PRESSURE INCREASED	4	1	4	1
BLOOD UREA INCREASED	0	1	0	1
BLOOD URIC ACID INCREASED	2	2	2	2
PLATELET COUNT DECREASED	0	1	0	1
PLATELET COUNT INCREASED	0	1	0	1
SMEAR CERVIX ABNORMAL	1	0	1	0
WEIGHT INCREASED	1	0	1	0
METABOLISM AND NUTRITION DISORDERS				
ANOREXIA	1	0	1	0
DIABETES MELLITUS NON-INSULIN-DEPENDENT	1	0	1	0
GOUT	1	0	1	0
HYPERCHOLESTEROLAEMIA	1	0	1	0
HYPERLIPIDAEMIA	2	0	2	0
POLYDIPSIA	1	0	1	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
ARTHRALGIA	2	3	2	3
ARTHRITIS	1	0	1	0
BACK PAIN	4	1	3	1
BONE SPUR	1	2	1	2
FACIAL PAIN	0	1	0	1
GANGLION	0	1	0	1
MUSCLE CRAMP	2	1	2	1
MUSCLE SPASMS	0	3	0	3
MUSCULAR WEAKNESS	1	0	1	0
MYALGIA	0	3	0	3
NECK PAIN	1	0	1	0
PAIN IN EXTREMITY	1	0	1	0
TENDONITIS	2	1	2	1
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)				
BASAL CELL CARCINOMA	2	0	2	0
CYST	1	2	1	2
RENAL NEOPLASM	0	1	0	1
UTERINE CANCER	1	0	1	0
NERVOUS SYSTEM DISORDERS				
AGEUSIA	0	1	0	1
BALANCE DISORDER	1	0	1	0
DIZZINESS	1	4	1	4
DYSGEUSIA	2	0	2	0
HYPOAESTHESIA	0	1	0	1
Headache	20	23	17	19
MULTIPLE SCLEROSIS	0	1	0	1
PARAESTHESIA	0	2	0	2
PETIT MAL EPILEPSY	1	0	1	0
SYNCOPE	1	0	1	0
PSYCHIATRIC DISORDERS				
ANXIETY	4	0	4	0
DEPRESSION	2	2	2	2
INSOMNIA	1	1	1	1
PANIC ATTACK	0	1	0	1
RENAL AND URINARY DISORDERS				
MICTURITION URGENCY	1	0	1	0
NEPHROLITHIASIS	2	0	2	0
POLLAKIURIA	1	0	1	0
RENAL INSUFFICIENCY	1	0	1	0
RENAL TUBULAR NECROSIS	1	0	1	0

Table A.8.1 (cont.) Adverse Events: Number of Events and Number of Subjects (of 537 patients)

	Number of Events		Number of Subjects	
	Oracea	Placebo	Oracea	Placebo
REPRODUCTIVE SYSTEM AND BREAST DISORDERS				
AMENORRHOEA	0	1	0	1
BREAST PAIN	1	0	1	0
BREAST TENDERNESS	0	1	0	1
DYSMENORRHOEA	1	0	1	0
MENORRHAGIA	1	1	1	1
MENSTRUATION IRREGULAR	1	0	1	0
PROSTATITIS	1	0	1	0
VAGINAL DISCHARGE	1	0	1	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
ASTHMA	0	1	0	1
BRONCHOSPASM	3	0	1	0
COUGH	1	0	1	0
DYSPNOEA	1	1	1	1
HYPOXIA	1	0	1	0
NASAL CONGESTION	4	2	4	2
PHARYNGOLARYNGEAL PAIN	3	3	3	2
PULMONARY EMBOLISM	1	0	1	0
RESPIRATORY ARREST	1	0	1	0
RESPIRATORY TRACT CONGESTION	1	0	1	0
RHINITIS ALLERGIC	1	2	1	2
SINUS CONGESTION	3	3	3	3
SINUS PAIN	2	0	2	0
SNEEZING	1	0	1	0
TACHYPNOEA	1	0	1	0
UPPER RESPIRATORY TRACT CONGESTION	0	2	0	2
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
ACNE	0	1	0	1
DERMAL CYST	1	0	1	0
DERMATITIS	2	0	1	0
DERMATITIS ATOPIC	1	0	1	0
DERMATITIS CONTACT	4	1	3	1
DRY SKIN	2	2	2	2
ECCHYMOSIS	0	1	0	1
ECZEMA	0	1	0	1
FACE OEDEMA	3	0	1	0
HYPERHIDROSIS	0	1	0	1
HYPERKERATOSIS	1	0	1	0
PRURITUS	5	4	4	4
RASH	3	2	2	2
RASH PAPULAR	0	2	0	2
ROSACEA	2	1	2	1
SEBORRHOEIC DERMATITIS	0	1	0	1
SKIN BURNING SENSATION	1	0	1	0
SKIN DISORDER	1	0	1	0
SKIN REACTION	1	0	1	0
URTICARIA	2	0	1	0
SURGICAL AND MEDICAL PROCEDURES				
NASAL SINUS DRAINAGE	0	1	0	1
VASCULAR DISORDERS				
DEEP VEIN THROMBOSIS	1	0	1	0
HYPERTENSION	8	2	8	2

Appendix 9. Preliminary Bayesian Analysis

A number of possible alternative models are available. One possible analysis is based on a linear growth curve with treatment specific intercept and slope. Note that observations after initiation of treatment were observed at weeks 3, 6, 12, and 16.

These observations can be modeled as:

$$y_{it} = \beta_{1j} + \beta_{2j}\,time_t + \beta_3\,base_i + center_{k(i)} + e_{it}$$

for subject i=1,…,N, time point t=1,2,3,4, treatment j=1,2, center k=1,…,14.

The baseline score for subject i is denoted $base_i$ and the $center_{k(i)}$, for k=1,…,14, denotes the center for subject i. For simplicity the notation j(i) for treatment within subject is not used. The 1x4 error vector $\underline{e}_i$ is assumed to be distributed as normal with mean vector $\underline{0}$ and variance covariance matrix Σ, i.e., $\underline{e}_i \sim N(\underline{0}, \Sigma)$. Centers are treated as random N(0,1000). The prior for Σ is assumed Wishart(100 I(4),4), while the parameter priors are for j=1,2, $\beta_{1j} \sim N(20,1000)$, $\beta_{2j} \sim N(-1,1000)$, and $\beta_3 \sim N(-1,1000)$. Note these priors are quite dispersed and should be relatively non-informative. In the analysis, to increase numerical stability, times are centered.

To assess overall treatment differences, one possible parameter would be the expected treatment difference. For j=1 denoting Oracea and j=2 denoting Placebo, the expected treatment difference at each time point t is:

$$dift_t = \beta_{11} - \beta_{12} + (\beta_{21} - \beta_{22})\,time_t \text{ for } t = 1,\ldots,4$$ (for weeks 3,6,9, and 12, respectively).

Among other possibilities, two other related parameters in this model that might be of interest would be $diffb1 = \beta_{11} - \beta_{12}$ and $diffb2 = \beta_{21} - \beta_{22}$.

Using WINBUGS 1.4, in ROSE-301 the estimated posterior distributions of the mean parameters are summarized as follows:

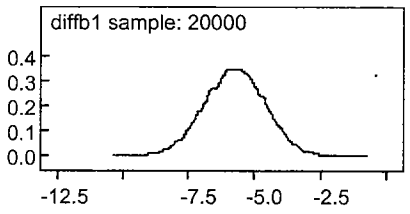
Table A.9.1 ROSE-301 Summaries of Posterior Distributions

	node	mean	sd	MC error	2.5%	median	97.5%	start	sample
	beta1[1]	-0.8682	4.685	0.2915	-10.13	-0.9925	7.882	5001	20000
	beta1[2]	4.866	4.651	0.289	-4.265	4.711	13.61	5001	20000
	beta2[1]	-0.2989	0.07274	6.414E-4	-0.4411	-0.2985	-0.1588	5001	20000
	beta2[2]	-0.2466	0.07292	6.232E-4	-0.3885	-0.2465	-0.1041	5001	20000
	beta3	0.6273	0.06345	0.001588	0.5026	0.6275	0.7523	5001	20000
	diffb1	-5.734	1.137	0.009847	-7.967	-5.729	-3.515	5001	20000
	diffb2	-0.05233	0.1032	9.088E-4	-0.2566	-0.05156	0.1473	5001	20000
	prdiffb1	1.0	0.0	7.071E-13	1.0	1.0	1.0	5001	20000
	prdiffb2	0.6933	0.4611	0.00379	0.0	1.0	1.0	5001	20000
t=3	dift[1]	-5.407	1.104	0.008082	-7.58	-5.395	-3.289	5001	20000
t=6	dift[2]	-5.564	1.073	0.008512	-7.669	-5.56	-3.495	5001	20000
t=12	dift[3]	-5.878	1.26	0.01146	-8.347	-5.867	-3.39	5001	20000
t=16	dift[4]	-6.087	1.519	0.01427	-9.05	-6.082	-3.097	5001	20000

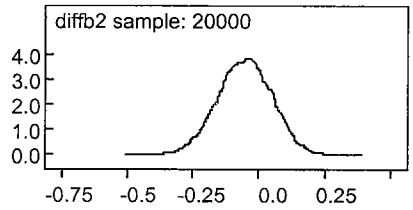
Note that at each time point the probability that the mean reduction is in lesions favoring Oracea over Placebo is more than 3 lesions, is at least 0.98.

The distribution of the difference in the growth curve parameters can be estimated as follows:

For β_{11} - β_{12}:



For β_{21} - β_{22}:



Note that both distributions are concentrated below zero, favoring Oracea over Placebo, although the effect for β_{21} - β_{22} is less marked.

For the same model in Study ROSE-302 we get the following:

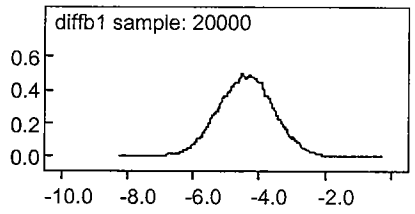
Table A.9.2 ROSE-302 Summaries of Posterior Distributions

	node	mean	sd	MC error	2.5%	median	97.5%	start	sample
	beta1[1]	-0.8124	1.35	0.04154	-3.48	-0.8086	1.825	5001	20000
	beta1[2]	3.579	1.384	0.04244	0.8457	3.582	6.274	5001	20000
	beta2[1]	-0.3046	0.05716	5.132E-4	-0.4154	-0.3053	-0.192	5001	20000
	beta2[2]	-0.08926	0.05745	4.434E-4	-0.2016	-0.0893	0.02471	5001	20000
	beta3	0.6029	0.04178	0.001141	0.5233	0.6028	0.6851	5001	20000
	diffb1	-4.392	0.831	0.006503	-6.009	-4.392	-2.77	5001	20000
	diffb2	-0.2153	0.08129	6.888E-4	-0.374	-0.2154	-0.05648	5001	20000
	prdiffb1	1.0	0.0	7.071E-13	1.0	1.0	1.0	5001	20000
	prdiffb2	0.9957	0.06543	3.987E-4	1.0	1.0	1.0	5001	20000
t=3	dift[1]	-3.046	0.8412	0.005847	-4.671	-3.051	-1.37	5001	20000
t=6	dift[2]	-3.692	0.7968	0.005784	-5.236	-3.688	-2.118	5001	20000
t=12	dift[3]	-4.984	0.9201	0.007589	-6.785	-4.98	-3.203	5001	20000
t=16	dift[4]	-5.845	1.119	0.009627	-8.045	-5.848	-3.665	5001	20000

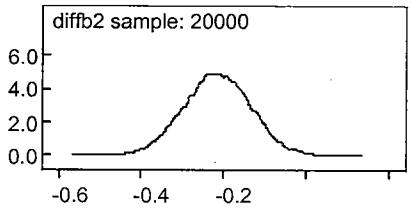
Here the posterior distribution indicates that by week 12, the probability that the Oracea treatment is associated with a reduction of at least 3 more lesions than Placebo is about 0.98 or more.

The distribution of the difference in the growth curve parameters can be estimated as follows:

For $\beta_{11} - \beta_{12}$:



For $\beta_{21} - \beta_{22}$:



Again, both distributions are concentrated below zero, favoring Oracea over Placebo.

In addition models assuming a first order autoregressive process were investigated. While the treatment differences were similar to those above, as might be expected with a autoregressive process, parameter mixing was slow, and convergence was not achieved. Due to time constraints this model was not investigated further.

This is not a full Bayesian analysis, due to time constraints only two of a number of feasible models were investigated, and only one model adequately, but results do seem to support the frequentist analysis in the remainder of the report.

The analyses above used the following program:

```
#Model 1 ;  Prior Precision Matrix = I(4)
model {for (i in 1:N){  y[i , 1:4] ~ dmnorm(mu[i,1:4], T[ , ])}
# priors
for( k in 1 :2) {beta1[k]  ~dnorm(20,0.001)
                 beta2[k] ~ dnorm(-1,0.001)}
beta3 ~ dnorm(-1,0.001)
for (k in 1:4) {  C[k,k] <- 0.01}
```

```
for (k in 1:3) { for (j in k+1:4) {C[k,j] <- 0 ; C[j,k] <- C[k,j]}}
                 T[1:4,1:4] ~ dwish(C[1:4,1:4],4)
# model
cntr[1]<-0.0
for( k in 2 :14) {cntr[k] ~dnorm(0.0,0.001)}
for (i in 1:N) {for (j in 1:4)
     {mu[i,j] <- beta1[trt[i]] + beta2[trt[i]]*t[j]+ beta3*base[i] +
                 cntr[ctr[i]]}}
for (k in 1:4) { for (j in 1:4) { Corr[k,j] <- V[k,j]/sqrt(V[k,k]*V[j,j])}}
     V[1:4,1:4] <- inverse(T[,])
# for (k in 1:4) { for (j in 1:4) { V[k,j] <- inverse(T[,],k,j)}}
diffb1<- beta1[1]-beta1[2]
diffb2<- beta2[1]-beta2[2]
prdiffb1 <- 1-step(diffb1)
prdiffb2 <- 1 -step(diffb2)
dift[1] <-  diffb1 + diffb2*t[1]
dift[2] <-  diffb1 + diffb2*t[2]
dift[3] <-  diffb1 + diffb2*t[3]
dift[4] <-  diffb1 + diffb2*t[4]
 }
Inits
list(beta1=c(0,0),beta2=c(-1,0),beta3=0)
list(beta1=c(10,20),beta2=c(-0.5,-0.8),beta3=-1)
list(beta1=c(-10,-20),beta2=c(1,2),beta3=1)

data
list(N=251,t=c(-6.25,-3.25,2.75,6.75))
ctr[ ] trt[ ] base[ ]  y[ ,1]  y[ ,2]  y[ ,3]  y[ ,4]
 1  1   17   19   11   NA   NA
 1  2   10   NA   11   14   13
 1  2   21   21   13   18   16
 2  1   17   24    7    7   13
 -  data -
13  2   24   18    7   17    0
13  1   22   20   NA   NA   NA
14  1   12    8    5    1    1
14  2   34   14   15   NA   10
14  2   13   NA    6    3    6  END
```

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/s/

Steven Thomson
4/12/2006 05:17:18 PM
BIOMETRICS

Mohamed Alosh
4/12/2006 05:25:38 PM
BIOMETRICS
Concur with review

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES-ADDENDUM/CORRECTION

NDA/Serial Number:	50-805 / 000
Drug Name:	Oracea™ (doxycycline [redacted] capsules) 40 mg
Indication(s):	Inflammatory Lesions of Rosacea
Applicant:	Collagenex Pharmaceuticals, Inc.
Date(s):	Received 8/01/2005, user fee (10 months) 6/01/2006
Review Priority:	Standard
Biometrics Division:	Division 3, HFD-725
Statistical Reviewer:	Steve Thomson, HFD-725
Concurring Reviewer:	Team Leader: Mohamed Alosh, Ph. D., HFD-725
Medical Division:	Dermatology and Dental Products, HFD-540
Clinical Team:	Clinical Reviewer: P. Brown, M.D.,HFD-540 Team Leader: M. Luke, M.D., Ph.D.,HFD-540
Project Manager:	S. Jain, HFD-540
Keywords:	Analysis of covariance, Cochran-Mantel-Haenszel

1. Summary

The original statistical review, placed in the Division File System (DFS) on April 12, 2006, included an analysis of the Sponsor's Investigator Global Assessment (IGA) as a co-primary endpoint. The IGA was a discrete, five level, 0-4 measure, and the review included frequency tables of these responses at various endpoints. As usual, for the Intent-to-Treat (ITT) data, missing values at certain time points were imputed using last observation carried forward (LOCF) techniques. The Sponsor's IGA data set had a separate record for each visit by a patient, including the baseline. For most cases, when the IGA was not assessed at a particular visit, there was no record corresponding to that visit. When the IGA was missing, LOCF imputation would take the value of the IGA at the closest previous visit, and use that value to impute a value for the missing IGA. However, for a few cases in the IGA data set there was a record for the visit, but the reported IGA value in the data set was a computer missing value code. When these missing value codes were then used for imputation using LOCF the missing value code was carried forward to subsequent cases. Under those circumstances, a missing value code, treated as missing, and thus not tabulated, would be used to impute the later missing value. So effectively, for those cases there was no imputation of the missing value by a valid value, and the missing value remained missing. This was noted early in the statistical analysis and supposedly corrected in the programs. However, several frequency tables in the statistical review seem to have been generated using the uncorrected programs.

The tables in error were tables 5 and 6 of the statistical review (pages 17 and 18, respectively), and tables A.2.1 and A.2.2 in Appendix 2 (pages 32 and 33). Due to the error in imputing some missing values, effectively, in these tables a few cases were dropped from the LOCF frequency counts at most time points. The programs used to provide test statistics and associated significance levels for the hypotheses of no treatment differences in these tables did employ the correct LOCF imputation, and thus, except for a transcription error at one of the non-primary time points, the reported significance levels in these tables are correct.

Unfortunately, the error in the frequency counts was not noted until early in the labeling discussions, after the review had been placed in DFS. Hence this correction/addendum is being added to the record.

Note that frequency counts in the remaining 14 tables dealing with the IGA do not have this error. However, for completeness the corrected incidence tables are displayed below. Again, the test statistics were correct and no conclusions presented in the review were changed.

Table 1 below should replace table 5 on page 17 of the original review.

Table 1. ROSE-301 (ITT-LOCF) Investigator's Global Assessment

Visit		Baseline	Week 3	Week 6	Week 12	Week 16
Oracea						
0. Clear	N	.	2	3	9	**12**
	%	.	1.6	2.4	7.1	**9.4**
1. Near Clear	N	.	4	20	18	**27**
	%	.	3.1	15.7	14.2	**21.3**
2. Mild	N	8	58	57	61	54
	%	6.3	45.7	44.9	48.0	42.5
3. Moderate	N	67	34	33	27	22
	%	52.8	26.8	26.0	21.3	17.3
4. Severe	N	52	29	14	12	12
	%	40.9	22.8	11.0	9.4	9.4
Placebols						
0. Clear	N	.	1	3	5	**10**
	%	.	0.8	2.4	4.0	**8.1**
1. Near Clear	N	.	2	6	14	**14**
	%	.	1.6	4.8	11.3	**11.3**
2. Mild	N	10	38	47	46	44
	%	8.1	30.6	37.9	37.1	35.5
3. Moderate	N	65	45	29	24	25
	%	52.4	36.3	23.4	19.4	20.2
4. Severe	N	49	38	39	35	31
	%	39.5	30.6	31.5	28.2	25.0
P-value						
Success (0,1)		.	0.3359	0.0079	0.2124	**0.0361**
Mean Score		0.7267	0.0086	<0.0001	0.0008	0.0014

Table 2 below should replace table 6 on page 18 of the original review.

Table 2. ROSE-302 (ITT-LOCF) Investigator's Global Assessment

	Visit	Baseline	Week 3	Week 6	Week 12	Week 16	Week 20
Oracea							
0. Clear	N	.	.	.	3	**2**	6
	%	.	.	.	2.1	**1.4**	4.2
1. Near Clear	N	.	3	6	13	**19**	12
	%	.	2.1	4.2	9.2	**13.4**	8.5
2. Mild	N	17	59	69	64	65	58
	%	12.0	41.5	48.6	45.1	45.8	40.8
3. Moderate	N	77	54	46	42	37	46
	%	54.2	38.0	32.4	29.6	26.1	32.4
4. Severe	N	48	26	21	20	19	20
	%	33.8	18.3	14.8	14.1	13.4	14.1
Placebo							
0. Clear	N	.	.	2	2	.	3
	%	.	.	1.4	1.4	.	2.1
1. Near Clear	N	.	3	4	5	**9**	10
	%	.	2.1	2.8	3.5	**6.3**	6.9
2. Mild	N	7	41	44	42	49	51
	%	4.9	28.5	30.6	29.2	34.0	35.4
3. Moderate	N	80	56	48	55	47	39
	%	55.6	38.9	33.3	38.2	32.6	27.1
4. Severe	N	57	44	46	40	39	41
	%	39.6	30.6	31.9	27.8	27.1	28.5
P-value							
Success (0,1)		.	0.9974	0.9949	0.0285	**0.0120**	0.1227
Mean Score		0.0207	0.0035	0.0003	<0.0001	<0.0001	0.0027

Appendix. Change from Baseline in Investigator's Global Assessment

Table A.1 below should replace Table A.2.1 on page 32 in Appendix 2 of the original review. Again, no comments or conclusions would change.

Table A.1 ROSE-301: Change from Baseline in IGA

			Week 3	Week 6	Week 12	Week 16
Oracea	-4	N	1	1	2	4
		%	0.8	0.8	1.6	3.1
	-3	N	2	6	12	14
		%	1.6	4.7	9.4	11.0
	-2	N	18	31	35	40
		%	14.2	24.4	27.6	31.5
	-1	N	48	54	44	40
		%	37.8	42.5	34.6	31.5
	0	N	52	33	32	27
		%	40.9	26.0	25.2	21.3
	1	N	5	2	2	2
		%	3.9	1.6	1.6	1.6
	2	N	1	.	.	.
		%	0.8	.	.	.
	All		127	127	127	127
Placebo	-4	N	.	.	1	2
		%	.	.	0.8	1.6
	-3	N	1	2	5	9
		%	0.8	1.6	4.0	7.3
	-2	N	4	14	20	21
		%	3.2	11.3	16.1	16.9
	-1	N	44	41	40	40
		%	35.5	33.1	32.3	32.3
	0	N	66	60	51	45
		%	53.2	48.4	41.1	36.3
	1	N	9	7	7	7
		%	7.3	5.6	5.6	5.6
	All	N	124	124	124	124

Again, Table A.2 below should replace Table A.2.2 (page 33) in the original report.

Table A.2 ROSE-302: Change from Baseline in IGA

			Week 3	Week 6	Week 12	Week 16	Week 20
Oracea	-4	N	.	.	.	2	3
		%	.	.	.	1.4	2.1
	-3	N	.	.	5	2	3
		%	.	.	3.5	1.4	2.1
	-2	N	13	22	23	28	22
		%	9.2	15.5	16.2	19.7	15.5
	-1	N	53	57	61	59	55
		%	37.3	40.1	43.0	41.5	38.7
	0	N	68	54	42	44	51
		%	47.9	38.0	29.6	31.0	35.9
	1	N	7	8	10	6	7
		%	4.9	5.6	7.0	4.2	4.9
	2	N	1	1	1	1	1
		%	0.7	0.7	0.7	0.7	0.7
		All	142	142	142	142	142
Placebo	-4	N	.	1	1	.	2
		%	.	0.7	0.7	.	1.4
	-3	N	.	2	1	1	2
		%	.	1.4	0.7	0.7	1.4
	-2	N	7	9	12	22	21
		%	4.9	6.3	8.3	15.3	14.6
	-1	N	48	45	46	45	43
		%	33.3	31.3	31.9	31.3	29.9
	0	N	80	77	75	62	66
		%	55.6	53.5	52.1	43.1	45.8
	1	N	9	9	9	14	10
		%	6.3	6.3	6.3	9.7	6.9
	2	N	.	1	.	.	.
		%	.	0.7	.	.	.
		All	144	144	144	144	144

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Date: 15 May 2006

Concurring Reviewer:

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/s/

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