CUTANEA LIFE SCIENCES, INC.

STATISTICAL ANALYSIS PLAN

Investigational Product:	Omiganan topical gel[redacted]
Protocol No.:	CLS001-CO-PR-004
Protocol Title:	*A Phase 3, Randomized, Vehicle-Controlled, Double-Blind, Multicenter Study to Evaluate the Safety and Efficacy of a Once-Daily CLS001 Topical Gel Versus Vehicle Administered for 12 Weeks to Subjects with Papulopustular Rosacea with an Open-Label Safety Extension*
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Cutanea Life Sciences, Inc.
Protocol CLS001-CO-PR-004

A Phase 3, Randomized, Vehicle-Controlled, Double-Blind, Multicenter Study to Evaluate the Safety and Efficacy of a Once-Daily CLS001 Topical Gel Versus Vehicle Administered for 12 Weeks to Subjects with Papulopustular Rosacea with an Open-Label Safety Extension

Signature Page

This Statistical Analysis Plan has been reviewed and approved by the following personnel:

Version Number	Date	Revision
1.0	25-Aug-2015	Original Approved Document
2.0	29-Jun-2017	The following revisions were made to this Statistical Analysis Plan: 5.2: Clarify the populations to be used for summaries of the Open-Label study period. 5.4.1: Clarify that the Open-Label study period "may" (instead of "will") be ongoing at the time of unblinding. 5.4.2: Remove physical examination summaries, since only dates of exams are collected; clinically significant findings are recorded as medical history. Update to include summary of medical history and baseline signs and symptoms of rosacea. 5.4.3: Add baseline covariate to inflammatory lesion ANCOVA model. Clarify that subgroups (gender, age, race, center) are summarized only (no statistical testing) 5.4.5: Remove physical examination summaries, since only dates of exams are collected; clinically significant findings are recorded as adverse events. Remove immunogenicity summaries as these are not handled in the analysis plan. Clarify the subjects that will contribute to 6 month and 1 year exposure. 5.4.6: Clarify the definition of Open-Label period adverse events and the planned displays for Open-Label summaries. Remove physical examination summaries, since only dates of exams are collected; clinically significant findings are recorded as adverse events. 6.1: Add rules for handling Week 12 and Week 52 visits for subjects who discontinued early. 6.2: Add details regarding Multiple Imputation methodology. 7.0: Add section to describe deviation from protocol.

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1.0 Introduction

Rosacea is a chronic dermatologic disorder that primarily affects the facial skin. An estimated 16 million Americans have rosacea. The clinical signs and symptoms of rosacea are: facial flushing, telangiectasia, facial erythema, central facial inflammatory papules and pustules, hypertrophy of the sebaceous glands of the nose and ocular changes. Rosacea has been classified into four different subtypes; Subtype 1: erythematotelangiectatic, Subtype 2: papulopustular, Subtype 3: phymatous and Subtype 4: ocular. Each subtype has severity grades ranging from mild to severe.

Currently, there is no cure for rosacea and the etiology is poorly understood. Many theories regarding the cause of rosacea have been highlighted in the literature. The pathology of rosacea may be multifactorial: abnormal vascular and immune system responses; hair follicle mite Demodex folliculorum; bacteria such as Helicobacter pylori; prolonged steroid use and other aggravating trigger factors like sun and stress. Gallo and his colleagues found an abnormally high level of the naturally occurring antimicrobial peptide cathelicidins upon histopathological staining in the skin of patients with rosacea.

Cutanea Life Sciences is developing omiganan topical gel for the treatment of papulopustular rosacea. The exact cause of rosacea is unknown and may be in due in part to an inflammatory process. Recent research has shown that cationic peptides such as omiganan may have anti-inflammatory properties and may play a role in inhibiting the inflammatory response. Omiganan may also prevent the inflammatory cascade that is theorized to lead to the signs and symptoms of rosacea. A possible anti-inflammatory activity of omiganan is suggested by the observation of a reduction in inflammatory acne lesion counts with omiganan in two Phase 2 clinical trials. However, the exact mechanism of action is undetermined.

Two previous clinical studies of omiganan in rosacea were conducted. CLS001-R-001 was a double-blind, multicenter, randomized, vehicle-controlled, parallel group study in 240 adult subjects with subtype 2 papulopustular rosacea. Eligible subjects were randomized to 5 treatment groups in a 2:2:2:1:1 ratio. The treatment arms were Omiganan topical gel at 1% QD, 2.5% QD, 2.5% BID, and Vehicle QD and Vehicle BID. Subjects were treated for 9 weeks. In the Modified Intent-to-Treat (MITT) analysis, all efficacy variables improved compared with Baseline in all treatment groups. The reductions from Baseline tended to be greatest in the omiganan 2.5% QD group; however, there were no statistically significant differences between the active treatment groups and the combined vehicle group for any efficacy variable at the Week 9/end of treatment endpoint for the MITT population.

Based upon the results of the first Phase 2 study in rosacea, Cutanea determined that the dose-response relationship of omiganan warranted further exploration. An additional Phase 2B study CLS001-CO-PR-001 investigated the safety and efficacy of once-daily omiganan 1%, 1.75% and 2.5% compared to vehicle gel. Again this was a double-blind, multicenter, randomized, vehicle-controlled, parallel group study in 240 adult subjects with subtype 2 papulopustular rosacea. Subjects were randomized into 4 test groups at a 1:1:1:1 ratio and observed over the course of 12 weeks. In addition to the primary analysis of the change from baseline in inflammatory lesion counts for the Intent-to-Treat (ITT) population, several strata based on baseline lesion counts were also evaluated in post hoc analyses. The efficacy signal was improved with increasing baseline lesion count, and was best for the [redacted] omiganan treatment group.

2.0 Study Design

This study will be conducted as a double-blind, multicenter, randomized, vehicle-controlled, parallel group study at approximately 50 centers (whenever possible, about 16 subjects will be enrolled per center), involving 450 subjects with severe subtype 2, papulopustular rosacea. After giving informed consent, each subject will be screened for study eligibility according to specific inclusion/exclusion criteria. Eligible subjects will be randomized to one of two treatment groups in a 1:1 ratio. The treatment arms are either: omiganan [redacted] topical gel or vehicle once daily.

Omiganan or vehicle will be topically applied once daily to the entire facial area; cheeks, chin, forehead and nose, avoiding contact with the eyes, mouth, and inside the nose.

Following baseline testing and evaluation for acceptance into the study, the subjects will be supervised during the first test drug application on Day 1 to ensure that the study treatment is applied correctly. Thereafter, each subject will apply the study treatment at home (unsupervised) once daily for 12 weeks in the double-blind study period. Subjects will then be asked to consent to continue in the open-label safety extension period for 3 months. In the open-label extension, subjects will apply omiganan [redacted] topical gel. No concurrent rosacea therapy of any kind, especially over the counter antimicrobial soaps or soapless cleansers, prescription topical and/or systemic antibacterial agents, will be allowed during the course of the study. No changes in topical soaps should occur. Other concurrent therapies will be recorded throughout the study. Subjects will have scheduled office visits at Weeks 1, 3, 6, 9, and 12 (Final Visit). Additional open-label safety extension visits occur at Weeks 16, 26, 39 and the final extension visit at Week 52. An unscheduled visit may occur in the event that the investigator determines that the subject should be seen for safety reasons.

3.0 Randomization

Subjects providing written informed consent and having met all inclusion and exclusion criteria will be randomized to 1 of 2 treatment groups in a 1:1 ratio during the double-blind portion of the study, according to a predetermined computer-generated randomization code.

Subjects will be randomized to treatment using an Interactive Web Response System (IWRS). The randomization scheme will include investigative center. The randomization will be performed using permuted blocks.

4.0 Study Objectives

The primary objective of this study is to evaluate the safety and efficacy of once-daily topical application of omiganan [redacted] topical gel compared to vehicle gel in subjects with severe papulopustular rosacea (IGA Grade 4 with baseline inflammatory lesion count ≥ 30).

Secondary objectives include the evaluation of long term safety of omiganan [redacted] topical gel.

5.0 Statistical Methodology

All statistical analyses will be performed using SAS® software version 9.3. Unless otherwise specified, all statistical tests will be two-sided with a significance level of 0.05. Continuous parameters will be summarized by N (number of non-missing observations), mean, standard deviation, median, minimum, and maximum. Categorical parameters will be summarized by count and percent.

5.1 Sample Size Determination

The primary objective of the study is to show superiority of Omiganan [redacted] over vehicle for the treatment of rosacea in patients with severe papulopustular rosacea (IGA Grade 4 with baseline inflammatory lesion count $\geq$ 30). A sample size calculation was made for two co-primary endpoints. For change from baseline in inflammatory lesions, it is assumed that in the Omiganan [redacted] treatment arm, subjects will have an average reduction of 13.5 inflammatory lesions, compared to 4 in the vehicle arm. The standard deviation is assumed to be 12. For 95% power, a sample size of 86 subjects (43 per group) is needed. For IGA, it is assume that Clear or Almost clear (IGA of 0 or 1) at Week 12 has lesser power than 2 point reduction. It is also assumed that 17% of the subjects in the Omiganan [redacted] treatment arm versus 6% in the vehicle arm will have IGA of clear or almost clear at Week 12. For 95% power and using a Fisher's Exact test, 450 subjects (225 in each arm) are needed. Therefore, the number of subjects needed to ensure at least 95% power for both endpoints is 450.

The sample sizes were calculated using 95% power in order to ensure 90% power across two Phase 3 studies.

5.2 Analysis Populations

The Intent-to-Treat (ITT) analysis population will include all randomized subjects. The ITT population will be the primary population for all efficacy analyses. Subjects will be analyzed based on the randomized treatment group, regardless of the treatment actually received.

The All-Treated analysis population will consist of all subjects receiving at least one application of study medication. All safety analyses will be performed on the all-treated population. Subjects will be analyzed based on the treatment actually received, regardless of the treatment group to which they were randomized.

The Per-Protocol (PP) population will include all subjects in the ITT population who provide Baseline and Week 12 efficacy data for all primary endpoints and complete the 12-week treatment period without any major deviations from the protocol. The subjects to be included in the PP population will be determined by the Sponsor/CRO prior to the unblinding of the study. The PP population will be secondary for the co-primary endpoints only.

The Open-Label Intent-to-Treat (ITT) analysis population will include all randomized subjects who complete the Double-Blind Study Period and continue into the Open-Label Extension. The Open-Label ITT population will be the primary population for all Open-Label Study Period efficacy analyses. Subjects will be analyzed based on the randomized treatment group

as assigned at randomization during the Double-Blind Study Period, regardless of the treatment actually received.

The Open-Label All-Treated analysis population will consist of all subjects receiving at least one application of study medication during the Open-Label Study Period. All safety analyses during the Open-Label Study Period will be performed on the Open-Label all-treated population. Subjects will be analyzed based on the treatment received during the Double-Blind Study Period, regardless of the treatment group to which they were randomized.

5.3 Efficacy Endpoints

The co-primary endpoints are:

- The absolute change from baseline to Week 12 in inflammatory lesions (papules and pustules).
- IGA at Week 12: 2 point reduction; Clear or Almost Clear (IGA 0, 1).

Secondary endpoints are:

- The absolute change from baseline to Week 9 in inflammatory lesions (papules and pustules).
- The absolute change from baseline to Week 6 in inflammatory lesions (papules and pustules).
- IGA at Week 9: 2 point reduction; Clear or Almost Clear (IGA 0, 1).
- IGA at Week 6: 2 point reduction; Clear or Almost Clear (IGA 0, 1).

Exploratory endpoints:

- The absolute change from baseline to Weeks 1 and 3 in inflammatory lesions (papules and pustules).
- Percentage of subjects with an IGA of clear or almost clear (0 or 1) at Weeks 1 and 3.
- Percentage of subjects with a 2 point IGA reduction at Weeks 1 and 3.
- Percentage of subjects with an Investigator Assessment of Erythema (IAE) of clear or almost clear (0 or 1) at each visit.
- Percentage of subjects with telangiectasia score of none or mild (0 or 1) at each visit.
- Percentage of subjects with scaling/peeling score of none or mild (0 or 1) at each visit.
- Percentage of subjects with pruritus score of none or mild (0 or 1) at each visit.

5.4 Statistical Analysis

5.4.1 Unblinding at Completion of Double-Blind Study Period

Unblinding of the study will occur when all double-blind study data has been entered into the database and the double-blind database is locked. The open-label extension may be ongoing at the time of double-blind lock and unblinding.

5.4.2 Subject Accounting, Demographic, and Baseline Characteristics

Demographic, baseline characteristics (including vital signs and laboratory parameters), medical history, baseline subject reported signs and symptoms of rosacea, and prior and

concomitant medications will be summarized by treatment. Study completion status and reasons for discontinuation will also be displayed by treatment.

Previous rosacea therapies taken within the last five years will only be presented in the listings.

5.4.3 Efficacy Analysis

The co-primary endpoint of absolute change from baseline in inflammatory lesions will be analyzed using an Analysis of Covariance (ANCOVA) model, with treatment as a main effect, and baseline inflammatory lesions and pooled center as covariates. To investigate consistency of efficacy results across study centers, treatment by center interaction will be tested at 0.1 level of significance, and if significant, it will be further be explored.

The co-primary endpoint of IGA will be tested in the following manner: the 2 point reduction and the Clear or Almost Clear (0, 1) will be tested using the Hochberg procedure as follows: Statistical significance will be concluded if both endpoints are significant at a two-sided 0.05 level, or if either endpoint is significant at a two-sided 0.025. Both IGA endpoints will be analyzed using a Cochran–Mantel–Haenszel (CMH) test with center as the stratification factor. If the overall IGA response rates are less than 10%, a Fisher's Exact test will be used to corroborate the CMH test. All tests of the co-primary endpoints will be analyzed.

If the co-primary endpoints of absolute lesion reduction and the two IGA endpoints (2 point reduction, and Clear or Almost Clear (0, 1)) are significant, the secondary endpoints will be tested sequentially in the order listed as follows:

- Test first secondary endpoint at 0.05. If not significant, stop; otherwise,
- Test second secondary endpoint at 0.05. If not significant, stop; otherwise,
- Test third secondary endpoint at 0.05 using Hochberg (similar to the primary method). If not both IGA (0,1) and IGA 2 point reduction are significant, stop; otherwise,
- Test fourth secondary endpoint at 0.05 using the Hochberg method.

For all efficacy analyses, small centers may be pooled in order to ensure sufficient cell counts for statistical testing.

Subgroup summaries (e.g. Gender, Age, Race, and Center) of the co-primary endpoints will be performed.

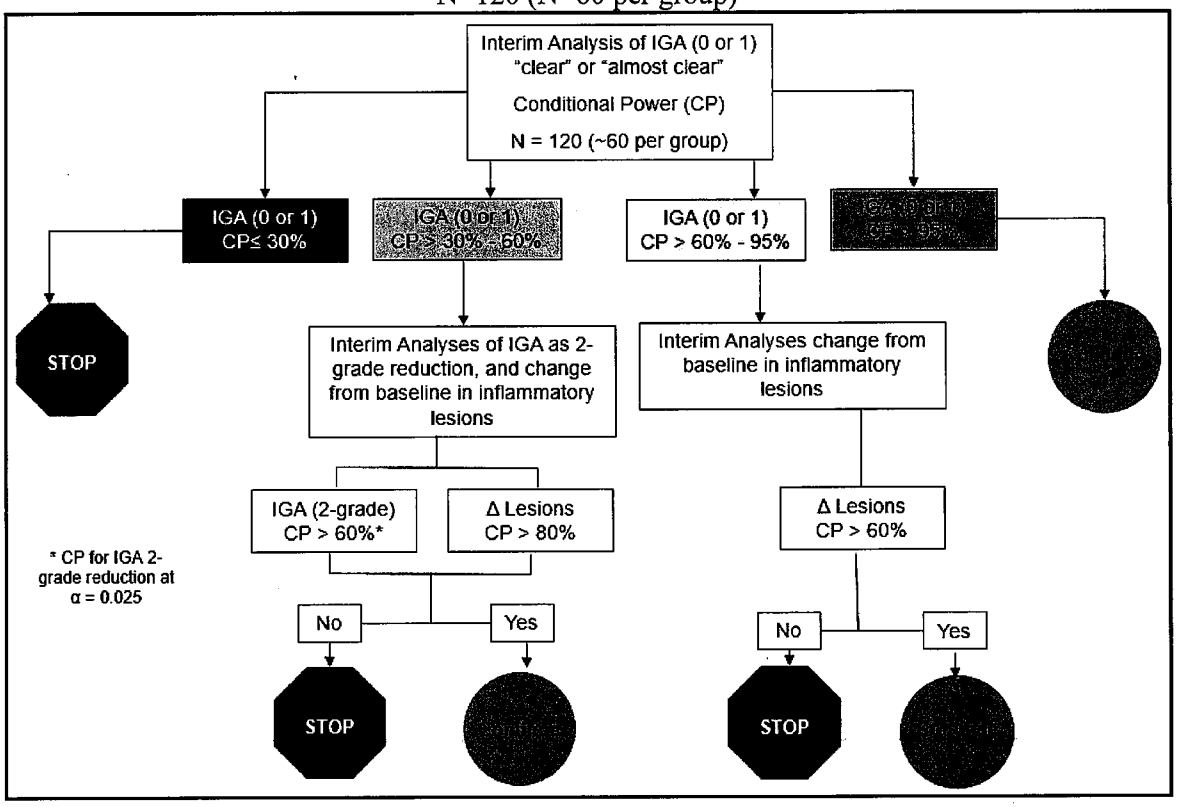
5.4.4 Interim Analysis

An interim analysis for futility will be conducted by an independent statistician. The purpose of the interim analysis is to help make a decision whether to continue the trial to the planned sample size, or to stop the trial for futility. No increase or decrease to the sample size will be performed, except to stop the trial for futility, therefore no adjustment to type-1 error is indicated. The interim analysis will be based on conditional power analysis when approximately 60 subjects (per group) have completed the study. Only

absolute lesion reduction count and IGA data (2 point reduction, and Clear or Almost Clear (0, 1)) will be analyzed following the same statistical approaches as pre-specified in the Efficacy Analysis section.

Conditional power for differences in proportions will be calculated using a Normal approximation, two-sided alpha of 0.05, assuming future data will follow the current trend. The decision rules and algorithm for interim analysis are shown in Figure 1.

Figure 1
Graphical Illustration of Interim Analysis Algorithm
N=120 (N=60 per group)



The independent unblinded statistician will receive the interim study data and the randomization information confidentially from the CRO. The independent statistician will then follow the algorithm above and make a recommendation accordingly. This recommendation will be reviewed by designated sponsor's representatives who will make the final decision as to continue the trial as planned or stop for futility. Upon receiving the recommendation, the sponsor may ask the independent statistician to examine additional data before the final decision is made. All communications between the unblinded statistician and the sponsor's representatives will be kept confidential and unknown to all personnel involved in the trial (other sponsor's personnel, CRO, and clinical center personnel). A charter will be written to describe in detail the process and roles related to

this interim analysis. This charter will name the independent statistician to conduct the interim analysis, and the sponsor's designated personnel that will make final decisions.

5.4.5 Safety Analysis

Adverse events will be categorized by system organ class and Preferred Term from the current version of MedDRA. Treatment-emergent adverse events will be summarized overall and by seriousness, severity, and relationship to treatment using frequencies and percentages. Adverse events will be considered treatment-emergent if the onset date is on or after the first dose of study medication.

Changes from baseline in vital signs and laboratory parameters, and shifts from baseline in laboratory parameters will be summarized by treatment.

Safety summaries will be presented for the double-blind study period. Additional summaries will be presented for the open-label extension study period, based on the treatment received during the double-blind study period.

In addition, all safety data for omiganan treatment whether from the double-blind or open-label extension period of this study will contribute to the overall long-term safety database for omiganan which will be reported according to ICH-E1 and FDA guidance. Subjects who continue into the open-label extension study period will be included in the planned 300 subjects to be exposed for 6 months and 100 subjects exposed for one year based on their duration of omiganan treatment.

5.4.6 Open-Label Extension Summaries (Safety Extension Period: Week 16, 26, 39, and 52)

Summary statistics for the open-label extension study period will include baseline demographics, disposition, exposure, safety, and efficacy variables.

Efficacy summaries will include:

- The absolute change from baseline to Weeks 26 and 52 in inflammatory lesions (papules and pustules).
- IGA at Weeks 16, 26, 39, and 52: 2 point reduction; Clear or Almost Clear (IGA 0, 1).

Safety summaries will include:

- concomitant medications
- adverse events that were emergent during the open-label extension study period
- vital signs and laboratory tests at Week 52.

All efficacy and safety summaries in the open-label extension study period will be performed by the original double blind randomized treatment group, and overall.

5.4.7 Compliance (Study Product Utilization and Exposure)

The total number of days product was applied during the double-blind study period from the study medication diary will be summarized by treatment. Per day product usage will be estimated for each dispensing interval and overall as the weight of product used divided by the number of days product was applied. The total number of days product was applied and the per day product usage will be summarized by N, mean, standard deviation, median, minimum, and maximum.

6.0 Data Handling Conventions

This section contains the data handling conventions that will be used to carry out the statistical analyses.

6.1 Baseline and Follow-Up Visits

Visits and time points (Double-blind period: baseline, interim [Weeks 1, 3, 6 and 9], final visit [Week 12]; Safety extension period: Weeks 16, 26, 39 and Week 52) for all analyses will be as record on the eCRFs , except as noted below. Baseline will be the later of the non-missing values from the Screening and Baseline/Day 1 visits scheduled to occur prior to receiving study medication. Unscheduled visits will not be used in any analyses but will be included on data listings.

If a subject does not complete the Double-Blind Study Period, the final double-blind visit (Week 12) will be reassigned to a scheduled visit based on the relative day ranges in the following table (where Day 1 is the first day of dosing). If a result already exists for the calculated visit or the calculated visit was not a scheduled visit, the next scheduled visit will be assigned.

Study Day Range	Calculated Visit
$2 \leq$ Study Day ≤ 15	Week 1
$16 \leq$ Study Day ≤ 32	Week 3
$33 \leq$ Study Day ≤ 53	Week 6
$54 \leq$ Study Day ≤ 74	Week 9
Study Day ≥ 75	Week 12

If an Open-Label subject does not complete the study, the final open-label visit (Week 52) will be reassigned to a scheduled visit based on the relative day ranges in the following table. If a result already exists for the calculated visit or the calculated visit was not a scheduled visit, the next scheduled visit will be assigned.

Study Day Range	Calculated Visit
$89 \leq$ Study Day ≤ 148	Week 16
$149 \leq$ Study Day ≤ 228	Week 26
$229 \leq$ Study Day ≤ 319	Week 39
Study Day ≥ 320	Week 52

6.2 Missing Data

The primary method of dealing with missing data is multiple imputation (MI) technique. All co-primary and secondary endpoints will be analyzed using MI for missing data. As a sensitivity analysis, Observed Case and Baseline Observation Carried Forward (BOCF) will be utilized for the co-primary endpoints only.

The MI technique will be implemented as follows:

a) 100 imputed datasets will be generated to impute missing data using the below SAS code.

1) For inflammatory lesions

```
Proc MI NIMPUTE=100 SEED=20170531
MIN   = . 0 0 0 0 0 0
MAX   = . . . . . . .
ROUND = . 1 1 1 1 1 1;
class sex;
var sex base w1 w3 w6 w9 w12;
fcs reg(w1) reg(w3) reg(w6) reg(w9) reg(w12);
run;
```

2) For IGA

```
Proc MI NIMPUTE=100 SEED=20170531
MIN   = . 0 0 0 0 0
MAX   = . 4 4 4 4 4
ROUND = . 1 1 1 1 1;
class sex;
var sex w1 w3 w6 w9 w12;
fcs reg(w1) reg(w3) reg(w6) reg(w9) reg(w12);
run;
```

b) The 100 imputed datasets will each be analyzed separately by the methods described in Section 5.4.2.

1) For inflammatory lesions, individual LS means and associated standard errors as well as estimates and standard errors from the pairwise comparison of treatments from the analysis of each imputation will be combined into single estimates, standard errors, and p-value using PROC MIANALYZE as displayed below.

```
Proc MIANALYZE;
Modeleffects estimate;
Stderr stderr;
   run;
```

The p-value for the treatment by center interaction will be based on the average of p-values from each the analyses of each imputation.

2) For IGA, estimates of the event rates will be based on the average of rates from each imputation. The CMH test statistic from the analysis of each imputation will be converted to a Normal Z score by taking the square root and adjusting for direction (change to a negative value if Omiganan group is worse than Vehicle). These Z scores (with SE=1) will be combined into a single p-value using PROC MIANALYZE as displayed below:

```
Proc MIANALYZE;
Modeleffects estimate;
Stderr SE;
   run;
```

Similarly, the p-values for the one-sided Fisher's Exact test of each imputation will be converted to a Normal Z score using the inverse normal function. These Z scores (with SE=1) will be combined into a single p-value using the same PROC MIANALYZE code.

6.3 Multicenter Analysis

Approximately 50 centers are planned in this study; whenever possible, approximately 16 subjects will be enrolled per center. In the event a center has a low (< 16) number of subjects enrolled or no subject that meets either of the IGA co-primary endpoints, pooling of centers may be performed based on geographical center location until the pooled center has at least 16 subjects and at least one subject with an IGA of clear or almost clear and at least one subject with a 2 point reduction in IGA.

Centers that do not meet above criteria will be pooled according to the following priorities:
1. Within a state/territory/country;
2. Across states/territory/country.

The exact pools will be determined prior to unblinding according to the above methodology.

Descriptive summary statistics will be generated including center and pooled-center (when appropriate) by co-primary and secondary efficacy endpoints.

6.4 Unscheduled Data

Unscheduled data will not be used in the analyses, but will be presented in the listings.

7.0 Deviations from the Protocol

Because of the wide range of inflammatory lesions at baseline, the ANCOVA model for change in inflammatory lesions was revised to include a covariate for the baseline inflammatory lesions.