# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-451**

## STATISTICAL REVIEW(S)

# STATISTICAL REVIEW AND EVALUATION — NDA
# CLINICAL STUDIES

**Medical Division**: Anesthetic, Critical Care, and Addiction Drug Products (HFD-170)
**Biometrics Division**: Division of Biometrics II (HFD-715)

**STATISTICAL KEY WORDS**:Hodge s-Lehmann estimate, Wilcoxon test
**NDA #**: 21-451
**SERIAL NUMBER**:
**DATE RECEIVED BY CENTER**: January 23, 2002
**DRUG NAME**:Oraqix (lidocaine 2.5% and prilocaine 2.5%) Periodontal Gel
**INDICATION**: Localized anesthesia in periodontal pocket for scaling and/or root planing
**SPONSOR**:Dentspl y Pharmaceutical
**DOCUMENTS REVIEWED**: Vol. 1, 47-74 Dated January 22, 2001
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# 1. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

## 1.1 Conclusion and Recommendation

Study 0003 demonstrated that Dental Gel 5% statistically significantly reduced pain from scaling/root planing (SRP) compared to placebo. But the treatment difference was 13.2 mm in mean in overall VAS in favor of Dental Gel 5%. The overall VRS pain score was statistically significantly lower in the Dental Gel 5% group than in the placebo group.

Study 0004 also demonstrated Dental Gel 5% statistically significantly reduced pain from SRP compared to placebo. But, the treatment effect (8.0 mm in median and 6.4 mm in mean, and 5.0 mm in Hodges-Lehmann estimate in overall VAS score) was minimal. Furthermore, there was statistically significant interaction between treatment and center. There was no consistent trend in favor of Dental Gel 5% over centers. The significant overall result was driven by Center 1. There was no statistically significant treatment difference in overall VRS pain score.

For pain-sensitive patients, study 0007 demonstrated that Dental Gel 5% statistically significantly reduced pain from SRP compared to placebo. But, the treatment effect (16.0 mm in median and 11.2 mm in mean, and 12.0 mm in Hodges-Lehmann estimate in overall VAS score) was modest. The reduction was statistically significant in tooth with the deepest pocket ? 6 mm. But the treatment effect was about 8.6 mm in mean, 10.6 mm in median, and 6.5 in Hodges-Lehmann estimate. The overall VRS pain score was statistically significantly lower in the Dental Gel 5% group than in the placebo group.

## 1.2 Overall of the Clinical Program and Studies Reviewed

In the current NDA, the sponsor is seeking approval of Oraqix for the production of localized anesthesia in periodontal pockets for _____ , scaling and/or root planing.

The sponsor has submitted three clinical trials (SP-DGA-0003, SP-DGA-0004, and SP-DGA-0007) supporting the use of Oraqix for the production of localized anesthesia in periodontal pockets for _____ scaling and/or root planing.

Two of the studies (SP-DGA-0003 and SP-DGA-0007) were carried out in the United States and the third (SP-DGA-0004) was carried out in Canada.

All three studies were randomized, double-blind, placebo-controlled, multi-centered studies of patients undergoing routine periodontal procedures including the probing of pocket depth, scaling and root planing.

All three trials used two widely accepted method of pain assessment: namely, the visual analogue scale method (VAS) and the verbal rating scale method (VRS).

### 1.2.1 Brief Description for Study Design for Studies SP-DGA-0003 and SP-DGA-0004

The study design of studies SP-DGA-003 and SP-DGA-004 was similar. Study SP-DGA-0003 was conducted in U.S. Study SP-DGA-0004 was conducted in Canada. The inclusion criterion for eligibility for Study SP-DGA-0004 was slightly different from that for Study SP-DGA-0003. In Study 0003, the quadrant contained a minimum of 5 natural teeth, of which 1 contained at least 1 pocket with a depth of ? 6 mm and at least 2 other teeth each contained at least 1 pocket with a depth of ? 5 mm. But, in Study 0004 the quadrant contained a minimum of 5 natural teeth, of which 3 each contained at least 1 pocket with a depth of ? 5 mm.

The primary objective of these studies was to determine the local anesthetic efficacy of Dental Gel 5% compared with placebo by means of assessing overall pain from scaling/root planing (SRP) using a Visual Analogue Scale (VAS).

Patients were screened for eligibility and randomized to receive Dental Gel 5% or Dental Gel placebo prior to SRP.

At the end of the SRP procedure, even if stopped prematurely, all patients were given a VAS ruler and asked to rate their overall pain perception on the VAS and VRS.

The primary efficacy variable was the overall pain score from the SPR procedure. The overall pain was assessed using a 100 mm horizontal upgraded VAS, with left end point marked 'no pain" and the right end point marked "worst pain imaginable."

The secondary efficacy parameter was the overall pain from SRP assessed using a 5 point Verbal Rating Scale (VRS); no pain, mild, moderate, severe, and very severe pain.

### 1.2.2 Brief Description for Study Design for Study 0007

This study was a multi-center (4 centers), randomized, double-blind, placebo controlled study comparing Dental Gel 5% (Dental Gel) and placebo gel for periodontal pocket anesthesia in conjunction with dental scaling and root planing in pain-sensitive patients.

The primary objective of this study was to determine the local anesthetic efficacy of Dental Gel 5% compared with placebo by means of assessing overall pain from scaling/root planing (SRP) using a Visual Analogue Scale (VAS) in pain-sensitive patients.

The study comprised one screening visit, one treatment visit and a telephone follow-up.

At the screen visit patients requiring periodontal SRP in at least one quadrant of the mouth that had not been scaled/root planed within the previous six months were enrolled in the run-in phase of the study. The selected quadrant should contain 5-8 natural teeth.

The enrolled patient was screened for pain sensitivity by probing the buccal side of the selected quadrant. The probing was done with a force sufficient to enable the investigator to accurately measure the depth of pockets and bleeding. Patients reporting pain score ?30 mm upon probing on a 100 mm VAS and with at least two teeth each containing at least one probing site ?5 mm, and at least one other tooth containing at least one probing site ?6 mm were entered into the treatment phase of the study.

The treatment visit took place 2 days to 4 weeks later. Patients were randomized to receive either Dental Gel 5% or placebo gel prior to SRP. The gel was first applied on the gingival margin around the selected tooth and to the gingival margin of the approximal surfaces of the adjacent teeth. After a waiting period of 30-45 seconds, the gel was applied to the corresponding gingival pockets. After a further 30-45 seconds, SRP of the actual tooth commenced. The procedure continued on the next anterior tooth in sequential fashion until the quadrant was finished. If there was an interruption due to pain, one reapplication of the gel per tooth was allowed. If the patient requested another interruption after the reapplication on the same tooth, the treatment would be stopped and the patient would be classified as needing rescue anesthetic.

At the end of the SRP of each tooth, the patient was asked to rate the intensity of pain perceived during the procedure on a 100 mm VAS ruler. Approximately five minutes after the SRP of the selected quadrant had finished, all patients were asked to rate their overall pain using the VAS and VRS.

The pain from the SRP procedure were assessed by the patient on a 100-mm horizontal, ungraded visual analogue scale (VAS), with the left end-point marked "no pain" and the right end-point marked "worst pain imaginable." Pain from the procedure was also assessed using a 5-point verbal rating scale (VRS): no pain, mild, moderate, severe and very severe pain.

### 1.3 **Principal Findings**

Study 0003 demonstrated that there was statistically significant difference of overall VAS pain score for ITT analysis. But the treatment difference (10.0 mm in median and 13.2 mm in mean, and 8 mm in Hodges-Lehmann estimate overall VAS) was modest. The overall VRS pain score was statistically significantly lower in the Dental Gel 5% group than in the placebo group.

In Study 0004, there was statistically significant difference of overall VAS pain score for ITT analysis. But the treatment effect (8.0 mm in median, 6.4 mm in mean, and 5.0 mm in Hodges-Lehmann estimate in overall VAS score) was minimal. However, statistically significant interaction between treatment and center was observed ($p=0.0358$) for overall VAS score. There was no consistent trend in favor of Dental Gel 5% among centers. The significant overall result was driven by Center 1. P-value would be 0.2358 from GLM (General Linear Model) with treatment, center, and treatment by center interaction effects included and 0.1294 from stratified Wilcoxon test if Center 1 was excluded. Furthermore, if Center 1 was excluded, the Hodges-Lehmann estimate would be 2.0 mm with 95%

confidence interval (-1.0mm, 7.0mm). The treatment difference was not statistically significant in overall VRS pain score.

Study 0007 demonstrated that in pain sensitive patients, there was statistically significant difference of overall VAS pain score for ITT analysis. But the treatment effect (16.0 mm in median, 11.2 mm in mean, and 12.0 mm in Hodges-Lehmann estimate in overall VAS score) was modest. Treatment effect was statistically significant for VAS pain scores per tooth with the deepest pocket ?6 mm or ? 5 mm. The treatment difference of VAS pain scores per tooth was 8.6 mm in mean and 4.4 mm in mean for the deepest pocket ?6 mm and ? 5 mm, respectively. The overall VRS pain score was statistically significantly lower in the Dental Gel 5% group than in the placebo group.

## 2. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

### 2.1 Background

In the current NDA, the sponsor is seeking approval of Oraqix for the production of localized anesthesia in periodontal pockets , scaling and/or root planing.

The sponsor has submitted three clinical trials (SP-DGA-0003, SP-DGA-0004, and SP-DGA-0007) supporting the use of Oraqix for the production of localized anesthesia in periodontal pockets for scaling and/or root planing.

Two of the studies (SP-DGA-0003 and SP-DGA-0007) were carried out in the United States and the third study (SP-DGA-0004) was carried out in Canada.

All three studies were randomized, double-blind, placebo-controlled, multi-centered studies of patients undergoing routine periodontal procedures including the probing of pocket depth, scaling and root planing.

All three trials used two widely accepted method of pain assessment: namely, the visual analogue scale method (VAS) and the verbal rating scale method (VRS).

### 2.2 SP-DGA-0003

#### 2.2.1 Description of Study

This study was a multi-center (8 centers), randomized, double-blind, placebo controlled study to evaluate the efficacy of Lidocaine, Prilocaine Dental Gel 5% (Dental Gel) for periodontal pocket anesthesia in conjunction with dental scaling and root planing. This study was conducted in United States

The primary objective of this study was to determine the local anesthetic efficacy of Dental Gel 5% compared with placebo by means of assessing overall pain from scaling/root planing (SRP) using a Visual Analogue Scale (VAS).

The patients at each center were randomized in balanced blocks within each center. The first two blocks were size six and the remaining block size four.

Patients were screened for eligibility and randomized to receive Dental Gel 5% or Dental Gel placebo prior to SRP. At least one quadrant of the jaw had not been scaled within the previous 12 months. The quadrant contained a minimum of 5 natural teeth, of which 1 contained at least 1 pocket with a depth of ? 6 mm and at least 2 other teeth each contained at least 1 pocket with a depth of ? 5 mm. All teeth in the chosen quadrant were scaled/root planed.

The gel was left in the periodontal pocket of each tooth between 30 seconds and 2 minutes, whereupon the SRP commenced.

For Dental Gel 5%, one quadrant of the mouth was treated with dose ranging from ¼ to 1¼ cartridges (approx. 0.4 - 2.2 g). For Dental Gel placebo, one quadrant of the mouth was treated with doses ranging from ¼ to 1½ cartridges (approx. 0.4-2.7 g). Dental syringes with blunt applicators were used to apply the drug.

If there was an interruption of the SRP procedure due to pain, the time was recorded, re-application of Gel directly into the pockets of the same tooth would occur, and the SRP would be resumed 30 seconds later. If the SRP was still painful, no further re-application of the Gel to the same tooth was allowed. Another anesthetic agent of the dentist/hygienist choice might then be given in order to complete the procedure. If the SRP, after this first re-application was not interrupted due to pain, the procedure would continue in sequential fashion.

At the end of the SRP procedure, even if stopped prematurely, all patients were given a VAS ruler and asked to rate their overall pain perception on the VAS and VRS.

The primary efficacy variable was the overall pain score from the SPR procedure. The overall pain was assessed using a 100 mm horizontal upgraded VAS, with left end point marked 'no pain" and the right end point marked "worst pain imaginable."

The secondary efficacy parameter was the overall pain from SRP assessed using a 5 point Verbal Rating Scale (VRS); no pain, mild, moderate, severe, and very severe pain.

Stratified Wilcoxon rank-sum test, stratified by center was used for VAS and VRS pain scores. The 95% confidence interval and Hodges-Lehmann point estimate of the difference between treatment group was evaluation. The test was two-sided with statistical significance if the p-value was = 0.05. The results for need for rescue anesthetic were evaluated by descriptive statistics.

The minimum clinically relevant difference in the primary efficacy parameter, overall VAS pain score, to be detected was defined as 15 mm. Assuming a standard deviation of 25 mm, a sample size of 59 evaluable patients per group was required to detect a statistically significant difference with power of at least 90%.

In these power consideration, a simple unstratified two-sample t-test with significance level 0.05 was used under assumption of normality. This should have provided a reasonable approximation of the sample size required for the stratified Wilcoxon test.

### 2.2.2 Sponsor's Analysis

A total of 122 patients, 63 in the Dental Gel 5% group and 59 in the placebo group, were recruited from eight periodontal clinics. All of the recruited patients completed the study and were valid for the all patients treated (APT) analysis. Three patients, all in the Dental Gel 5% group had major protocol violations and were excluded from the per protocol analysis. 119 patients were valid for the per protocol analysis (PP).

#### 2.2.2.1 Treatment Group Comparability

The demographic and baseline characteristics of all randomized patient population are summarized in Attached Table 1. As seen from Attached Table 1, the demographic and baseline characteristics were similar between two treatment groups with regard to age, sex, race, time of last SRP, VAS score upon probing, and extent of disease.

#### 2.2.2.2 Sponsor's Analysis of Primary Efficacy Variable

The primary efficacy variable was the overall VAS pain score. The results of analysis of overall VAS pain score are given below.

**Overall VAS Pain Score**
**Per Protocol Analysis**
**Study 0003**

| Treatment | N | Mean (SD) | Median | Hodges-Lehmann point estimate of difference (95% C.I.) | p-value |
|---|---|---|---|---|---|
| GEL 5% | 60 | 11.6 (12.0) | 7.0 | 8.0 (2.0, 13.0) | <0.0005 |
| Placebo | 59 | 25.4 (24.7) | 17.0 | | |

Copied from Tables 9 and 10, page 008-008-046
p-value obtained using Wilcoxon rank test.

### 2.2.2.3 Sponsor's Analysis of Secondary Efficacy Variable

The secondary efficacy variable was the verbal rating scale.

#### 2.2.2.3.1 Pain Assessment, Verbal Rating Scale (VRS)

The results of analysis of verbal rating scale are given below.

**Overall VRS Pain Score**
**All Patient Treated Analysis**
**Study 0003**

| Treatment | No pain | Mild pain | Moderate pain | Severe pain | Very Severe pain | p-value |
|---|---|---|---|---|---|---|
| Gel 5% | 22 (35%) | 35 (55%) | 5 (8%) | 1 (2%) | 0 (0%) | 0.0008 |
| Placebo | 12 (20%) | 26 (44%) | 14 (24%) | 6 (10%) | 1 (2%) | |

Copied from Table 11, page 008-008-049
p-value obtained by this reviewer using Mantel-Haenszel Chi-Square test for ordinal data.

As seen from table above, the overall VRS pain score was statistically significantly lower in the Dental Gel 5% group than in the placebo group.

#### 2.2.2.3.2 Need for Rescue Medication

In the Dental Gel 5% group 7 out 63 (11%) patients needed rescue anesthetic, that is, they had a second interruption due to pain or had rescue medication given. In the placebo group the corresponding figure was 10 out 59 (17%) patients. The number of teeth with first and second interruption due to pain is given below.

**Number of Teeth with First and Second Interruption(s) Due to Pain**
**Study 0003**

| Treatment | N | First Interruption(s) | p-value | Second Interruption | p-value |
|---|---|---|---|---|---|
| Dental Gel 5% | 398 | 49 (12%) | 0.9109 | 7 (2%) | 0.4622 |
| Placebo | 356 | 42 (12%) | | 10 (3%) | |

Copied from Table 18, page 008-0008-050
P-values were obtained by this reviewer using Fisher's exact test.

### 2.2.3 Reviewer's Evaluation

#### 2.2.3.1 Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Variable

The sponsor's analysis of primary efficacy variable was based on per protocol analysis. In the PP analysis, there were three patients, all in the Dental Gel 5% group, were excluded from the per protocol analysis. So, this analysis may be biased in favor of test

drug. This reviewer re-analyzed primary efficacy variable based on ITT analysis using StatXact 5. The result from ITT analysis is given below.

**Overall VAS Pain Score**
**All Patient Treated Analysis**
**Study 0003**

| Treatment | N | Mean (SD) | Median | Hodges-Lehmann point estimate of difference (95% C.I.) | p-value |
|---|---|---|---|---|---|
| GEL 5% | 63 | 12.2 (12.8) | 7.0 | 8.0 (2.0, 15.0) | 0.0005 |
| Placebo | 59 | 25.4 (24.7) | 17.0 | | |

Compiled by this reviewer.
p-value was obtained from StatXact 5 using stratified Wilcoxon-Mann-Whitney rank test .

As seen from table above, there was statistically significant difference for ITT analysis. However, the treatment difference was reduced to 13.2 mm in mean from 13.8 mm resulting from per protocol analysis.

2.2.3.2 **Subgroup Analysis**

This reviewer performed subgroup analyses by center, gender and age. The results of subgroup analyses are given below.

**Subgroup Analysis**
**Study 0003**

| | Placebo | | Gel 5% | | Treatment | |
|---|---|---|---|---|---|---|
| Subgroup | N | Mean | N | Mean | Difference | 95% C.I. |
| Center 1 | 8 | 20.0 | 8 | 8.9 | -11.1 | (-24.6, 2.4) |
| Center 2 | 6 | 6.5 | 6 | 5.8 | -0.7 | (-9.0, 7.6) |
| Center 4 | 8 | 14.6 | 10 | 2.2 | -12.4 | (-26.7, 1.9) |
| Center 5 | 8 | 15.1 | 9 | 13.3 | -1.8 | (-14.9, 11.3) |
| Center 6 | 6 | 12.8 | 6 | 8 | -4.8 | (-20.1, 10.4) |
| Center 7 | 8 | 49.4 | 9 | 28 | -21.4 | (-37.3, -5.5) |
| Center 8 | 6 | 37.2 | 6 | 20.5 | -16.7 | (-50.7, 17.4) |
| Center 9 | 9 | 40.6 | 9 | 11 | -29.6 | (-52.8, -6.3) |
| Male | 31 | 29.3 | 25 | 11.4 | -17.9 | (-29.1, -6.9) |
| Female | 28 | 21.0 | 38 | 12.8 | -8.2 | (-17.4, 0.9) |
| Age <65 | 55 | 25.8 | 61 | 12.1 | -13.7 | (-21.0, -6.4) |
| Age ?65 | 4 | 20.0 | 2 | 16.5 | -3.5 | (-25.8, 18.8) |
| Age<55 | 48 | 24.4 | 52 | 12.3 | -12.1 | (-19.8, -4.5) |
| Age?55 | 11 | 29.5 | 11 | 11.8 | -17.6 | (-36.8, 1.5) |
| Age<45 | 29 | 28.1 | 41 | 12.9 | -15.3 | (-24.1, -6.4) |
| Age?45 | 30 | 22.7 | 22 | 11 | -11.7 | (-23.6, 0.2) |

Compiled by this reviewer.

As seen from table above, there was a trend in favor of Dental Gel 5% in all subgroups. Treatment effect varied from center to center ranging from 0.7 to 29.6 mm.

### 2.2.3.3 Reviewer's Comments on Sponsor's Analysis of Overall VRS Pain Score

The overall pain from SRP was assessed using a 5 point Verbal Rating Scale (VRS); no, mild, moderate, severe, and very severe pain. The response variable for VRS is ordinal. So, the data is categorical data. The commonly used method for analyzing ordinal data is Mantel-Haenszel method.

### 2.2.3.4 Reviewer's Analysis of Overall VRS Pain Score

As requested by Medical officer, alternative analysis of overall VRS pain score was performed using Fisher's exact test. In this analysis "no pain" was combined with "mild pain." The result from this analysis is given below.

**Overall VRS Pain Score**
**Study 0003**

| Treatment | No Pain or Mild Pain | p-value |
|---|---|---|
| Gel 5% | 57/63 (90.5%) | 0.0008 |
| Placebo | 38/59 (64.4%) | |

p-value obtained by this reviewer using Fisher's exact test.

As seen from table above, there was statistically significant difference in favor of Dental Gel for overall VRS pain score.

## 2.3 SP-DGA-0004

### 2.3.1 Study Design

The study design of this study was similar to that for Study SP-DGA-0003. This study was conducted in Canada. The inclusion criterion for eligibility for this study was slightly different from that for Study SP-DGA-0003. In Study 0003, the quadrant contained a minimum of 5 natural teeth, of which 1 contained at least 1 pocket with a depth of ? 6 mm and at least 2 other teeth each contained at least 1 pocket with a depth of ? 5 mm. But, in this study the quadrant contained a minimum of 5 natural teeth, of which 3 each contained at least 1 pocket with a depth of ? 5 mm.

### 2.3.2 Sponsor's Analysis

A total of 131 patients were enrolled into the study and randomized to one of the two treatment groups (64 in Dental Gel and 67 in placebo). One patient in Dental Gel group (no. 505) did not receive any study drug and was therefore, not valid for any analysis.

### 2.3.2.1Treatment Group Comparability

The demographic and baseline characteristics of all randomized patient population are summarized in Attached Table 2. As seen from Attached Table 2, the demographic and baseline characteristics were similar between two treatment groups with regard to age, sex, race, time of last SRP, VAS score upon probing, and extent of disease.

### 2.3.2.2 Sponsor's Analysis of Primary Efficacy Variable

The primary efficacy variable was the overall VAS pain score. The results of analysis of overall VAS pain score are given below.

**Overall VAS Pain Score**
**Study 0004**

| Treatment | N | Mean (SD) | Median | Hodges-Lehmann point estimate of difference (95% C.I.) | p-value |
|---|---|---|---|---|---|
| GEL 5% | 63 | 12.8 (17.9) | 5.0 | 4.0 (0.0, 10.0) | 0.015 |
| Placebo | 67 | 19.2 (19.2) | 13.0 | | |

Copied from Tables 9 and 10, page 008-011-047, 050
p-value obtained using stratified Wilcoxon rank test.

### 2.3.2.3 Sponsor's Analysis of Secondary Efficacy Variable

The secondary efficacy variable was the verbal rating scale.

#### 2.3.2.3.1 Pain Assessment, Verbal Rating Scale (VRS)

The results of analysis of verbal rating scale are given below.

**Overall VRS Pain Score**
**Study 0004**

| Treatment | No pain | Mild pain | Moderate pain | Severe pain | Very Severe pain | p-value |
|---|---|---|---|---|---|---|
| Gel 5% | 23 (37%) | 26 (41%) | 11 (17%) | 3 (5%) | 0 (0%) | 0.3878 |
| Placebo | 17 (25%) | 34 (51%) | 13 (19%) | 3 (5%) | 0 (0%) | |

Copied from Table 11, page 008-011-050
p-value obtained by this reviewer using Mantel-Haenszel Chi-Square test for ordinal data.

As seen from table above, the treatment difference was not statistically significant in overall VRS pain score.

### 2.3.2.3.2 Need for Rescue Medication

In the Dental Gel 5% group 4 out 63 (6%) patients needed rescue anesthetic, that was, they had a second interruption due to pain or had rescue medication given. In the placebo group the corresponding figure was 7 out 67 (10%) patients. The number of teeth with first and second interruption due to pain is given below.

**Number of Teeth with First and Second Interruption(s) Due to Pain**
**Study 0004**

| Treatment | N | First Interruption(s) | p-value | Second Interruption | p-value |
|---|---|---|---|---|---|
| Dental Gel 5% | 409 | 22 (5%) | 0.1040 | 5 (1%) | 0.7742 |
| Placebo | 436 | 36 (8%) | | 7 (2%) | |

Copied from Table 18, page 008-0008-050
P-values were obtained by this reviewer using Fisher's exact test.

## 2.3.3 Reviewer's Evaluation

### 2.3.3.1 Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Variable

This reviewer used StatXact 5 to compute the Hodges-Lehmann estimate and its 95% confidence interval and p-value using stratified Wilcoxon-Mann-Whitney test. The resulting p-value was 0.0066 less than 0.015 reported by the sponsor. The resulting Hodges-Lehmann estimate was 5.0 mm with 95% confidence interval of (1.0mm, 10.0mm) which were slightly different from those obtained by the sponsor.

Statistically significant interaction between treatment and center was observed (p=0.0358). The overall VAS pain score by center is given below.

**Overall VAS Pain Score by Center**
**Study 0004**

| | Placebo | | Gel 5% | | Treatment | |
|---|---|---|---|---|---|---|
| Center | N | Mean | N | Mean | Difference | 95% C.I. |
| Center 1 | 13 | 34.4 | 12 | 11.9 | -22.5 | (-40.0, -5.0) |
| Center 2 | 17 | 10.8 | 16 | 8.7 | -2.1 | (-9.0, 4.7) |
| Center 3 | 8 | 36.3 | 8 | 23 | -13.3 | (-41.6, 15.1) |
| Center 4 | 15 | 10.9 | 15 | 13.9 | 2.9 | (-8.2, 14.0) |
| Center 5 | 8 | 13.4 | 6 | 21.3 | 8.0 | (-12.9, 28.8) |
| Center 6 | 6 | 16.2 | 6 | 0.7 | -15.5 | (-28.4, -2.6) |

Compiled by this reviewer.

As seen from table above, there was no consistent trend in favor of Dental Gel 5%. The significant overall result was driven by Center 1. P-value would be 0.2358 from GLM (General Linear Model) with treatment, center, and interaction between treatment and center effects included and 0.1294 from stratified Wilcoxon test if Center 1 was

excluded. Furthermore, if Center 1 was excluded, the Hodges-Lehmann estimate would 2.0 mm with 95% confidence interval (-1.0mm, 7.0mm).

### 2.3.3.2 Subgroup Analyses

This reviewer performed subgroup analyses by gender and age. The results of subgroup analyses are given below.

**Subgroup Analysis**
**Study 0004**

| | Placebo | | Gel 5% | | Treatment | |
|---|---|---|---|---|---|---|
| Subgroup | N | Mean | N | Mean | Difference | 95% C.I. |
| Male | 30 | 21.9 | 26 | 17.0 | -4.8 | (-16.4, 6.7) |
| Female | 37 | 17.1 | 37 | 9.8 | -7.3 | (-14.7, 0.1) |
| Age <65 | 58 | 20.4 | 56 | 14.1 | -6.3 | (-13.4, 0.9) |
| Age ?65 | 9 | 11.9 | 7 | 2.1 | -9.7 | (-19.1, -0.4) |
| Age <55 | 46 | 21.4 | 45 | 12.3 | -9.1 | (-16.8, -1.3) |
| Age ?55 | 21 | 14.5 | 18 | 14.0 | -0.5 | (-12.6, 11.5) |
| Age<45 | 33 | 20.6 | 29 | 13.3 | -7.3 | (-16.7, 2.1) |
| Age?45 | 34 | 17.9 | 34 | 12.4 | -5.6 | (-14.8, 3.6) |

Compiled by this reviewer.

As seen from table above, there was a positive trend in favor of Dental Gel 5% in each subgroup. The treatment effect was modest ranging from 0.5 to 9.7 mm in mean in VAS.

### 2.3.3.3. Reviewer's Analysis of Overall VRS Pain Score

As requested by Medical officer, alternative analysis of overall VRS pain score was performed using Fisher's exact test. In this analysis "no pain" was combined with "mild pain." The result from this analysis is given below.

**Overall VRS Pain Score**
**Study 0004**

| Treatment | No Pain or Mild Pain | p-value |
|---|---|---|
| Gel 5% | 49/63 (78.8%) | 0.8383 |
| Placebo | 51/67 (76.1%) | |

p-value obtained using Fisher's exact test.

As seen from table above, there was no statistically significant difference between treatment group in terms of no pain or mild pain for overall VRS pain score.

## 2.4 SP-DGA-0007

### 2.4.1 Study Design

This study was a multi-center (4 centers), randomized, double-blind, placebo controlled study comparing Dental Gel 5% (Dental Gel) and placebo gel for periodontal pocket anesthesia in conjunction with dental scaling and root planing in pain-sensitive patients. This study was conducted in United States.

The primary objective of this study was to determine the local anesthetic efficacy of Dental Gel 5% compared with placebo by means of assessing overall pain from scaling/root planing (SRP) using a Visual Analogue Scale (VAS) in pain-sensitive patients.

The study comprised one screening visit, one treatment visit and a telephone follow-up.

At the screen visit patients requiring periodontal SRP in at least one quadrant of the month that had not been scaled/root planed within the previous six months were enrolled in the run-in phase of the study. The selected quadrant should contain 5-8 natural teeth. The enrolled patient was screened for pain sensitivity by probing the buccal side of the selected quadrant. The probing was done with a force sufficient to enable the investigator to accurately measure the depth of pockets and bleeding. Patients reporting pain score ?30 mm upon probing on a 100 mm VAS and with at least two teeth each containing at least one probing site ?5 mm, and at least one other tooth containing at least one probing site ?6 mm were entered into the treatment phase of the study.

The treatment visit took place 2 days to 4 weeks later. Patients were randomized to receive either Dental Gel 5% or placebo gel prior to SRP. The gel was first applied on the gingival margin around the selected tooth and to the gingival margin of the approximal surfaces of the adjacent teeth. After a waiting period of 30-45 seconds, the gel was applied to the corresponding gingival pockets. After a further 30-45 seconds, SRP of the actual tooth commenced. The procedure continued on the next anterior tooth in sequential fashion until the quadrant was finished. If there was an interruption due to pain, one reapplication of the gel per tooth was allowed. If the patient requested another interruption after the reapplication on the same tooth, the treatment would be stopped and the patient would be classified as needing rescue anesthetic.

At the end of the SRP of each tooth, the patient was asked to rate the intensity of pain perceived during the procedure on a 100 mm VAS ruler. Approximately five minutes after the SRP of the selected quadrant had finished, all patients were asked to rate their overall pain using the VAS and VRS.

The pain from the SRP procedure were assessed by the patient on a 100-mm horizontal, ungraded visual analogue scale (VAS), with the left end-point marked "no pain" and the right end-point marked "worst pain imaginable." Pain from the procedure was also

assessed using a 5-point verbal rating scale (VRS): no pain, mild, moderate, severe and very severe pain.

The assessment of the VAS pain score was made before the VRS pain score to avoid any influence from an already expressed verbal expression.

The VAS pain scores at screening and the overall VAS and VRS pain scores following treatment was be assessed by a separate evaluator and was be not assessed by the periodontist/dental hygienist performing the SRP procedure.

The primary efficacy variable was the overall VAS pain score. The secondary efficacy variables were the overall VRS pain score and the VAS pain scores per tooth.
The ITT (Intent-to-Treat) dataset was based on all patient included except those who did not receive any study drugs.

The Per Protocol dataset was a subset of the ITT dataset obtained by excluding patients in the event of major protocol violations.

The main analysis of the efficacy variables was based on the ITT dataset. In addition, an analysis of the efficacy variables was performed using the PP dataset.

The primary efficacy variable, the overall VAS pain score was compared between the two treatment groups using a stratified Wilcoxon rank-sum test stratifying by center. The corresponding 95% confidence interval and Hodges-Lehmann point estimate of the difference between the groups were also evaluated.

The same analysis was also carried out for the variable overall VRS. The proportions of patients needing rescue anesthetic in the treatment groups were compared using a Mantel-Haenszel test.

Two subgroups analyses of the VAS pain score per tooth were carried out to investigate the treatment effect differences for different pocket depths, one analysis for deep pockets (teeth with deepest probing site ? 6 mm) and one for shallow pockets (teeth with deepest probing site ? 5 mm).

Centers with fewer than six patients might be pooled with other small centers.

Missing data was assumed to be missing completely at random.

The minimum clinically relevant difference in the primary efficacy variable, overall VAS pain score, to be detected in defined as 15 mm. Based on previous studies a standard deviation of 20 mm was assumed. With this standard deviation a sample size of 39 evaluable patients per group was required to detect a statistically significant difference with a power of at least 90%.

The sponsor believes that in these power considerations, a simple unstratified two-sample t-test with ? =0.05 was used under assumptions of normality. This should have provided a reasonable approximation of the sample size required for the stratified Wilcoxon test.

### 2.4.2 **Sponsor's Analysis**

The study was first due to start in 1998 at center 1-4 and was put on hold for two years due stability issue. When study activities resumed in 2000, the plan was to recruit patients from centers 2-6; however, due to administrative reasons center 3 was unable to participate.

A total of 113 patients were screened for pain sensitivity upon probing. 87 of the screened patients met the inclusion criteria and were scheduled for a treatment visit. Two patients withdraw their consent between the screening visit and treatment visit. 85 patients, 43 in the Dental Gel 5% group and 42 in the placebo group, were randomized to treatment.

All randomized patients completed the study and were included for ITT. 80 patients were evaluable for PP analysis.

#### 2.4.2.1 **Treatment Group Comparability**

The demographic and baseline characteristics of all randomized patient population are summarized in Attached Table 3. As seen from Attached Table 3, the demographic and baseline characteristics were similar between two treatment groups with regard to age, sex, race, time of last SRP, VAS score upon probing, and extent of disease.

#### 2.4.2.2 **Sponsor's Analysis of Primary Efficacy Variable**

The primary efficacy variable was the overall VAS pain score. The results of analysis of overall VAS pain score are given below.

**Overall VAS Pain Score**
**Study 0007**

| Treatment | N | Mean (SD) | Median | Hodges-Lehmann point estimate of difference (95% C.I.) | p-value |
|---|---|---|---|---|---|
| GEL 5% | 43 | 17.3 (19.2) | 11.0 | 10.0 (4.0, 19.0) | 0.004 |
| Placebo | 42 | 28.5 (20.9) | 27.0 | | |

Copied from Tables 11 and 12, page 008-013-047
p-value obtained using Wilcoxon rank test.

### 2.4.2.3 Sponsor's Analysis of Secondary Efficacy Variables

The secondary efficacy variables were the overall VRS pain score and the VAS pain scores per tooth.

#### 2.4.2.3.1 Pain Assessment, Verbal Rating Scale (VRS)

The results from pain assessment using overall VRS pain score are given below.

**Overall VRS Pain Score**
**Study 0007**

| Treatment | No pain | Mild pain | Moderate pain | Severe pain | Very Severe pain | p-value |
|---|---|---|---|---|---|---|
| Gel 5% | 6 (14%) | 24 (56%) | 13 (30%) | 0 (0%) | 0 (0%) | 0.0023 |
| Placebo | 0 (0%) | 20 (48%) | 18 (43%) | 3 (7%) | 1 (2%) | |

Copied from Table 17, page 008-013-052
p-value obtained by this review using Mantel-Haenszel Chi-Square test for ordinal data.

As seen from table above, the overall VRS pain score was statistically significantly lower in the Dental Gel 5% group than in the placebo group.

#### 2.4.2.3.2 VAS Pain Scores Per Tooth

The results of VAS pain scores per tooth with the deepest pocket ?6 mm and ? 5 mm are given below.

**VAS Pain Scores Per Tooth with the Deepest Pocket ? 6mm**
**Study 0007**

| Treatment | N | Mean (SD) | Median | Hodges-Lehmann point estimate of difference (95% C.I.) | p-value |
|---|---|---|---|---|---|
| GEL 5% | 43 | 17.0 (16.8) | 11.7 | 6.5 (1.0, 14.5) | 0.017 |
| Placebo | 42 | 25.6 (21.5) | 22.3 | | |

Copied from Tables 13 and 14, page 008-013-049 – 008-013-050
p-value obtained using Wilcoxon rank test.

**VAS Pain Scores Per Tooth in Teeth with the Deepest Pocket ? 5 mm**
**Study 0007**

| Treatment | N | Mean (SD) | Median | Hodges-Lehmann point estimate of difference (95% C.I.) | p-value |
|---|---|---|---|---|---|
| GEL 5% | 39 | 12.4 (14.9) | 6.6 | 3.8 (0.2, 8.5) | 0.043 |
| Placebo | 36 | 16.8 (14.8) | 10.1 | | |

Copied from Tables 15 and 16, page 008-013-050 –008-013-051.
p-value obtained using Wilcoxon rank test.

As seen from tables above, treatment effect was statistically significant for VAS pain scores per tooth with the deepest pocket ?6 mm or ? 5 mm. The treatment difference of VAS pain scores per tooth was 8.6 mm in mean and 4.4 mm in mean for the deepest pocket ?6 mm and ? 5 mm, respectively.

2.4.2.3.3 **Need for Rescue Medication**

The number of patients with first and second interruption(s) due to pain is given below.

**Number of Patients with First and Second Interruption(s) Due to Pain**
**Study 0007**

| Treatment | N | First Interruption(s) | p-value | Second Interruption | p-value |
|---|---|---|---|---|---|
| Gel 5% | 43 | 12 (28%) | 0.1774 | 2 (5%) | 0.0887 |
| Placebo | 42 | 18 (43%) | | 7 (17%) | |

Copied from Table 18, page 008-013-054
P-values were obtained by this reviewer using Fisher's exact test.

As seen from table above, there was not statistical difference between treatment groups for first interruption and second interruption.

2.4.3 **Reviewer's Evaluation**

2.4.3.1 **Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Variable**

This reviewer used StatXact 5 to compute the Hodges-Lehmann estimate and its 95% confidence interval. The resulting Hodges-Lehmann estimate was 12.0 mm with 95% confidence interval of (3.0 mm, 19.0 mm) which were slightly different from those obtained by the sponsor.

As requested by Medical officer, alternative analysis of overall VAS pain score was performed using the GLM adjusted for center, the resulting p-value was 0.0137. The treatment difference was 11.1 mm in least square mean (LSMEAN).

### 2.4.3.2 Subgroup Analyses

This reviewer performed subgroup analyses by center, gender and age. The results of subgroup analyses are given below.

**Subgroup Analysis**
**Study 0007**

| | Placebo | | Gel 5% | | Treatment | |
|---|---|---|---|---|---|---|
| Subgroup | N | Mean | N | Mean | Difference | 95% C.I. |
| Center 2 | 8 | 24.9 | 9 | 12.0 | -12.9 | (-27.8, 2.1) |
| Center 4 | 10 | 33.0 | 10 | 16.7 | -16.3 | (-40.5, 7.9) |
| Center 5 | 12 | 31.0 | 12 | 21.6 | -9.4 | (-21.6, 2.8) |
| Center 6 | 12 | 24.5 | 12 | 17.5 | -7.0 | (-27.4, 13.4) |
| Male | 19 | 32.9 | 15 | 15.3 | -17.6 | (-30.9, -4.3) |
| Female | 23 | 24.7 | 28 | 18.4 | -6.4 | (-18.1, 5.4) |
| Age <65 | 38 | 28.9 | 41 | 18.0 | -10.9 | (-20.1, -1.7) |
| Age ?65 | 4 | 23.8 | 2 | 2.5 | -21.3 | (-51.3, 8.8) |
| Age <55 | 32 | 27.1 | 36 | 17.8 | -9.3 | (-19.2, 0.7) |
| Age ?55 | 10 | 32.8 | 7 | 14.6 | -18.2 | (-38.2, 1.8) |
| Age<45 | 16 | 26.6 | 20 | 16 | -10.6 | (-22.8, 1.7) |
| Age?45 | 26 | 29.6 | 23 | 18.4 | -11.2 | (-23.7, 1.4) |

Compiled by this reviewer.

As seen from table above, there was a consistent positive trend in favor of Dental Gel 5% among centers, gender, and age.

### 2.4.3.3 Reviewer's Comments on Sponsor's Analysis of Secondary Efficacy Variable

#### 2.4.3.3.1 Subgroup Analysis of Overall Pain Score for Per Tooth in Teeth with the Deepest Pockets ? 6mm and ? 5 mm

This reviewer performed simple t-tests for subgroup analysis of overall pain scores for per tooth in teeth with the deepest pockets ? 6mm and ? 5 mm yielded p-value of 0.043 and 0.204, respectively. The treatment differences were 8.6 mm and 4.4 mm in mean, for deepest pockets ? 6mm and ? 5 mm, respectively.

#### 2.4.3.3.2 Analysis of Overall VRS Pain Score

As requested by Medical officer, alternative analysis of overall VRS pain score was performed using Fisher's exact test. In this analysis "no pain" was combined with "mild pain." The result from this analysis is given below.

**Overall VRS Pain Score**
**Study 0007**

| Treatment | No Pain or Mild Pain | p-value |
|---|---|---|
| Gel 5% | 30/43 (69.8%) | 0.0485 |
| Placebo | 20/42 (47.6%) | |

p-value obtained using Fisher's exact test.

As seen from table above, Dental Gel 5% marginally statistical significantly reduced pain from SRP compared to placebo for overall VRS pain score in terms of "no pain or mild pain."

### 2.4.3.4 Reviewer's Comments on Sponsor's Explorative Analyses

These sponsor's explorative analyses are subgroup analyses and hypothesis generating.

## 3. OVERALL SUMMARY AND CONCLUSION

### 3.1 Summary and Conclusion

The Hodges-Lehmann estimator is the median of the all possible differences between two treatment groups. It is a robust competitor of the mean of treatment differences, less strong influenced by outlying observations.

Study 0003 demonstrated that Dental Gel 5% statistically significantly reduced pain from SRP compared to placebo. But, the treatment difference (10.0 mm in median, 13.2 mm in mean, and 8.0 mm in Hodges-Lehmann estimate in overall VAS) was modest. The overall VRS pain score was statistically significantly lower in the Dental Gel 5% group than in the placebo group.

Study 0004 also demonstrated Dental Gel 5% statistically significantly reduced pain from SRP compared to placebo. But, the treatment effect (8.0 mm in median, 6.4 mm in mean, and 5.0 mm in Hodges-Lehmann estimate in overall VAS score) was minimal. Furthermore, there was statistically significant interaction between treatment and center and there was no consistent trend in favor of Dental Gel 5% over centers. The significant overall result was driven by Center 1. There was no statistically significant treatment difference in overall VRS pain score.

For pain-sensitive patients, Study 0007 demonstrated that Dental Gel 5% statistically significantly reduced pain from SRP compared to placebo. But the treatment effect (16.0 mm in median,11.2 mm in mean, and 12.0 mm in Hodges-Lehmann estimate in overall VAS score) was modest. The reduction was statistically significant in tooth with the deepest pocket ? 6 mm. But, the treatment effect was about 8.6 mm in mean, 10.6 mm in median, and 6.5 in Hodges-Lehmann estimate. The overall VRS pain score was statistically significantly lower in the Dental Gel 5% group than in the placebo group.

Among these three studies (0003, 0004, and 0007), both studies (0003 and 0004) failed to include 15 mm, minimum treatment difference in its 95% confidence interval for Hodges-Lehmann estimates. However, Study 0007 did, as 15 mm was included in the confidence interval.

## 3.2 Labeling

### 3.2.1 Clinical Studies

The labeling proposed by the sponsor for efficacy section for Clinical Study was based on the results from sponsor's alternative analysis. This alternative analysis is based on "log VAS values" instead of VAS value, pre-specified in the protocol. It seems to be troublesome to interpret the results. Furthermore, the labeling for efficacy should be based on results from efficacy analyses on primary endpoint, VAS value. The labeling for efficacy should be the Hodges-Lehmann point estimate of treatment difference and its 95% confidence interval, pre-specified in the protocol.

### 3.2.2 Geriatric Use

There were 28 (17 in placebo and 11 in Dental Gel) patients aged 65 and over were included in clinical studies. The differences in medians between two treatment groups were 3 mm, 8 mm, and 22 mm for studies 0003, 0004 and 0007, respectively. Thus, the data are just not adequate to provide reliable efficacy information regard geriatric patients.

Table 1 Summary of Demographic and Baseline Characteristics --- SP-DGA-0003

| Characteristics | Dental Gel 5% (N=63) | Placebo (N=59) | Between Treatment p-value |
|---|---|---|---|
| Sex | | | 0.1543 |
| Male | 25 (40%) | 31 (53%) | |
| Female | 38 (60%) | 28 (47%) | |
| Race | | | 0.5564 |
| Caucasian | 42 (67%) | 37 (63%) | |
| Black | 17 (27%) | 14 (24%) | |
| Oriental | 3 (5%) | 7 (12%) | |
| Other | 1 (2%) | 1 (2%) | |
| Age (yr) | | | 0.3856 |
| Mean (SD) | 43.3(11.2) | 45.1 (12.3) | |
| Pocket depth (mm) | | | |
| Mean (SD) | 3.6 (0.5) | 3.7 (0.5) | |
| Deepest pocket depth | | | |
| Mean (SD) | 4.9 (0.8) | 5.1 (0.7) | |
| Prop. of bleeding pockets | | | |
| Mean (SD) | 0.4 (0.3) | 0.4 (0.3) | |
| Prop of hypersensitive teeth | | | |
| Mean (SD) | 0.1 (0.2) | 0.1 (0.2) | |

P-value was obtained by this reviewer using Chi-square test for sex and race and using t-test for age.

Table 2 Summary of Demographic and Baseline Characteristics --- SP-DGA-0004

| Characteristics | Dental Gel 5% (N=63) | Placebo (N=67) | Between Treatment p-value |
|---|---|---|---|
| Sex | | | 0.6866 |
| Male | 26 (41%) | 30 (45%) | |
| Female | 37 (59%) | 37 (55%) | |
| Race | | | 0.1833 |
| Caucasian | 57 (90%) | 63 (94%) | |
| Black | 2 (3%) | 4 (6%) | |
| Oriental | 2 (3%) | 0 (0%) | |
| Other | 2 (3%) | 0 (0%) | |
| Age (yr) | | | 0.8120 |
| Mean (SD) | 48.0(11.9) | 48.5 (13.0) | |
| Pocket depth (mm) | | | |
| Mean (SD) | 3.5 (0.5) | 3.6 (0.5) | |
| Prop. of bleeding pockets | | | |
| Mean (SD) | 0.5 (0.3) | 0.5 (0.3) | |
| Prop of hypersensitive teeth | | | |
| Mean (SD) | 0.1 (0.2) | 0.1 (0.2) | |

P-value was obtained by this reviewer using Chi-square test for sex and race and using t-test for age.

Table 3 Summary of Demographic and Baseline Characteristics --- SP-DGA-0007

| Characteristics | Dental Gel 5% (N=43) | Placebo (N=42) | Between Treatment p-value |
|---|---|---|---|
| Sex | | | 0.3299 |
| Male | 15 (35%) | 19 (45%) | |
| Female | 28 (65%) | 23 (55%) | |
| Race | | | 0.5565 |
| Caucasian | 20 (47%) | 23 (55%) | |
| Black | 22 (51%) | 17 (40%) | |
| Oriental | 1 (2%) | 2 (5%) | |
| Age (yr) | | | 0.5605 |
| Mean (SD) | 45.6(11.0) | 47.2 (13.8) | |
| Time of last SRP | | | 0.5904 |
| 6-11 months ago | 5 (12%) | 4 (10%) | |
| 1-2 years ago | 12 (28%) | 11 (26%) | |
| 3-4 years ago | 4 (9%) | 1 (2%) | |
| ?5 years ago | 9 (21%) | 8 (19%) | |
| never | 13 (30%) | 18 (43%) | |
| VAS pain score | | | 0.7698 |
| Mean (SD) | 61.6 (17.0) | 62.7 (17.8) | |
| Pocket depth (mm) | | | |
| Mean (SD) | 4.0 (0.7) | 3.9 (0.9) | |
| Prop. of bleeding pockets | | | |
| Mean (SD) | 0.5 (0.3) | 0.5 (0.3) | |
| Prop of hypersensitive teeth | | | |
| Mean (SD) | 0.3 (0.2) | 0.3 (0.3) | |

P-value was obtained by this reviewer using Chi-square test for sex, race and time of last SRP and using t-test for age and VAS pain score.

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/s/
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Milton Fan
10/8/02 03:21:20 PM
BIOMETRICS

Please sign off

Thomas Permutt
10/9/02 10:05:40 AM
BIOMETRICS
concur