

STUDY SYNOPSIS

Name of finished product: Arestin® Name of active ingredient: Minocycline HCl

Title of study:

EFFECT OF ADJUNCTIVE TREATMENT WITH ARESTIN ON THE SUBGINGIVAL MICROFLORA IN PATIENTS WITH MODERATE TO ADVANCED PERIODONTITIS

Study centers: Five centers participated in this study. They are identified as follows:

Table S-1 Centers participating in the study, the number of subjects enrolled at each and the investigators

| Center Code | Center | Center Description | Subjects Enrolled | Investigators |
|-------------|--------|--|-------------------|-------------------|
| A | 1 | Forsyth Institute Boston, MA | 11 | J. Max Goodson |
| B | 2 | University of Maryland, Baltimore, MD | 37 | John C. Gunsolley |
| C | 3 | Private Practice, Los Angeles, CA | 17 | Joan Otomo-Corgel |
| D | 4 | University of Tennessee, Memphis, TN | 16 | Paul Bland |
| E | 5 | SUNY at Buffalo, Buffalo, NY | 49 | Sara Grossi |
| Total | | | 130 | |

Publication(s): There are no publications to date.

Study period: First subject enrolled: 21-Jan-2004 Last subject completed: 12-Aug-2004

Development phase: IV

Objectives: To measure the antimicrobial effects of Arestin in subjects with moderate to advanced periodontal disease

Methodology: This was a multi-center, stratified, single-blind, randomized, 30 day clinical trial with two parallel arms:

- 1) Test Group: Arestin plus scaling and root planing (SRP)
- 2) Control Group: Scaling and root planing alone

Microbial and clinical assessments were performed at baseline and at 30 days.

Number of subjects: One hundred thirty (130) subjects were enrolled and randomly assigned to a treatment group. One hundred twenty seven (127) subjects were available for complete microbiological and clinical analyses. Three (3) subjects were excluded from the efficacy analysis, two (2) because of periodontal abscess formations (both Arestin group) and one (1) because no post therapy microbiology samples were obtained (Control group). All one hundred thirty (130) subjects were included in the safety analysis.

Indication and main criteria for inclusion:

- At least 16 teeth excluding 3rd molars and implants
- Five sites with probing depths of ≥ 5 mm in 5 non-adjacent interproximal spaces, excluding the distal of terminal teeth

The population was comprised entirely of outpatients of unrestricted gender or ethnicity and with no serious systemic diseases. Subjects were stratified by smoking status. A smoker was defined as an individual who had smoked ≥ 10 cigarettes on a daily basis within the past 12 months.

Investigational drug: Arestin (minocycline HCl) Microspheres, 1mg.

Reference therapy: Scaling and root planing alone

Duration of treatment: All treatments were administered at a single visit. Results were evaluated at baseline before treatment and again at 30 days.

Criteria for evaluation:

Efficacy: The primary outcome variable was the change in the mean sum of primary pathogens: *Porphyromonas gingivalis* (*P. gingivalis*), *Tannerella forsythensis* (*T. forsythensis*), and *Treponema denticola* (*T. denticola*).

The secondary outcome variables were:

- Change in mean numbers of individual primary pathogens *P. gingivalis*, *T. forsythensis* and *T. denticola*
 - Prevalence of individual primary pathogens (proportions)
 - Change in probing depth
 - Change in clinical attachment level
 - Change in bleeding on probing
-

Safety: All volunteered, elicited and observed adverse events were documented.

Statistical methods: Outcome measures were assessed for underlying distributional characteristics and transformations were performed as necessary. Analyses of variance and covariance were used to evaluate mean differences in measures from baseline to 30 days between treatment groups, as well as for possible differences between centers and interaction between the two effects. No interim analyses were performed. No further analyses to correct for baseline or center bias is anticipated.

Results: The primary outcome variable in this study was reduction in red complex bacteria. Two measures of red complex bacterial changes were evaluated. The red complex proportions are the percentage of bacteria measured (Section 6.1.1) and the red complex bacteria numbers are the numbers of bacteria in a scaler sample (Section 6.1.2). Both were significantly reduced by the test treatment (Arestin + SRP) relative to the control therapy (SRP Alone). These results are summarized in the following table.

Table S-2 Summary of primary outcome variable measurements

| Parameter | Arestin + SRP | SRP Alone | p-value |
|------------------------------|-----------------------|-----------------------|---------|
| Red complex Proportions | 6.49% | 5.03% | 0.0005 |
| Red complex bacteria Numbers | 9.4 x 10 ⁵ | 5.1 x 10 ⁵ | 0.002 |

The secondary outcome variables included reduction in numbers and proportions of each of the red complex bacterium individually, as indicated in the following table.

Table S-3 Summary of secondary outcome variables-red complex bacteria reductions

| Parameter | Arestin + SRP | SRP Alone | p-value |
|------------------------------------|------------------------|--------------------------|---------|
| <i>P. gingivalis</i> proportions | 2.51% | 1.68% | 0.00007 |
| <i>T. forsythensis</i> proportions | 2.65% | 2.48% | 0.0009 |
| <i>T. denticola</i> proportions | 1.40% | 0.78% | 0.004 |
| <i>P. gingivalis</i> numbers | 3.71 x 10 ⁵ | 1.54 x 10 ⁵ | 0.0001 |
| <i>T. forsythensis</i> numbers | 4.32 x 10 ⁵ | 3.57 x 10 ⁵ | 0.07 * |
| <i>T. denticola</i> numbers | 1.40 x 10 ⁵ | -0.003 x 10 ⁵ | 0.01 |

*not statistically significant

These results indicate that Arestin reduced the proportions and numbers of each of the red complex bacteria individually. These reductions were all statistically significant except for

T. forsythensis numbers which were borderline significant. (Note: negative values indicate an increase from baseline to 30 days).

Clinical measurements were also considered secondary outcome variables in this study. These measurements included reduction in pocket depth, reduction in number of deep pockets, gain in tooth attachment and reduction in BOP, as indicated in the following table.

Table S-4 Summary of clinical measurements

| Parameter | Arestin + SRP | SRP Alone | p-value |
|-------------------------------------|---------------|-----------|---------|
| Pocket depth reduction | 1.38mm | 1.01mm | 0.00004 |
| Reduction in number of ≥5mm pockets | 12.40 | 10.60 | 0.01 |
| BOP reduction | 25.2 % | 13.8 % | 0.009 |
| Attachment gain | 1.16mm | 0.80mm | 0.0004 |

These results indicate that the addition of Arestin to SRP reduced pocket depth, reduced the number of deep pockets, reduced BOP, and increased clinically measured tooth attachment. These changes in clinical parameters were all statistically significant.

Secondary Analysis: Separate analysis on subjects who were currently smoking and who never smoked revealed that Arestin + SRP was significantly more effective in pocket depth reduction than SRP Alone.

| Smoking Status | Pocket Depth Reduction (baseline-30 days) | |
|----------------|---|-----------|
| | Arestin + SRP | SRP Alone |
| Never smoked | 1.40mm | 1.06mm |
| Current smoker | 1.28mm | 0.86mm |

Inclusion of Arestin significantly improved pocket depth reduction irrespective of smoking status.

Clinical Efficacy: The reduction in numbers of pockets that were ≥5mm at baseline is provided as a measure of clinical significance of the response. These data indicate that before treatment each subject had 24 to 28 (depending on the treatment group) periodontal pockets that were ≥5mm (of a possible maximum of 168 sites for fully dentate subjects). Following treatment, the number in subjects treated with Arestin + SRP fell to 12.40 pockets, 51.7% of the original number. By comparison, the number of ≥5mm pockets in subjects treated with SRP Alone fell by 10.6 pockets, 37.3% of the original number. This difference (51.7-37.3=14.4%) is the improvement in reducing pocket depth by the addition of Arestin to SRP. An alternative method of expressing this result is that the number of periodontal sites with pocket depth ≥5mm that the dentist needed to treat (NNT) to obtain one pocket more than treatment by SRP Alone was $1/0.144 = 6.9$. This means that in the average subject in this study with 26 pockets that were ≥5mm, 3.7 more pockets would have been eliminated by the addition of Arestin to SRP.

An association between bacterial reduction and attachment gain was investigated. Regression analysis between pocket depth reduction (a measure of clinical improvement) and red complex proportions (a measure of antibacterial effectiveness) resulted in a linear relationship described by the following equation:

$$\text{Pocket depth reduction (mm)} = -0.027 \times \text{Red complex (\%)} + 0.71$$

This equation predicts that by complete elimination of red complex bacteria (Red complex %= 0), one would expect 0.71mm pocket depth reduction. For all values of Red complex % > 26.6%, pocket depth reduction will be negative indicating a loss of attachment. This relation explained 37.6% of the observed variability ($r^2 = 0.376$) and was statistically significant ($p = 0.0001$). The remainder of the variability could be attributed to treatment variables, home care, genetics, diet, and other uncontrolled factors.

Safety: No serious adverse events were reported. Of 73 reported non-serious adverse events (AEs), nearly twice as many occurred in the SRP Alone group as in the Arestin + SRP group. On a percentage basis, both treatment groups experienced most AEs at equal frequency. A major exception, however, appeared in the category of oral pain which was 3 times more common in the SRP Alone group than in the Arestin + SRP group.

Of the one hundred thirty (130) subjects randomly assigned to a treatment group and included in the safety analysis, 36(27.7%) reported no concomitant medication usage. Of the 94(72.3%) subjects who reported using concomitant medications, the most common medications taken were analgesics, antihypertensives, hormones, and cholesterol lowering drugs.

Conclusions: The objective of this trial was to measure the antimicrobial effects of Arestin when used as an adjunct to scaling and root planing. The results demonstrate that, 30 days post-treatment, Arestin significantly reduced red complex periodontal pathogens and the effect was associated with a beneficial clinical response.

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