CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 50-781

MEDICAL REVIEW(S)

Amendt to
Dental Officer's Original Review of NDA 50-781

Drug: ARESTIN™ (minocycline 1mg. Periodontal Therapeutic System)

Sponsor: OraPharma, Inc.
732 Louis Drive
Warminster, PA 18974

Proposed Indication: ARESTIN™ is indicated as an adjunct to scaling and root planing procedures for reduction of pockets in patients with adult periodontitis.

Submission Date: February 16, 2000
Received Date: February 18, 2000
Review Date: June 22, 2000
Second Review Date: October 27, 2000
Third Review Date: December 5, 2000
Fourth Review Date: February 7, 2001

Reviewer: Clarence C. Gilkes, D.D.S.

Project Manager: Kalyani Bhatt, M. Sc.

Background:

The purpose to this amendment to the clinical review of this product is to comment on the conclusions of the audit, by FDA's Division of Scientific Investigations (DSI), of the San Antonio site of Study 103A. The following is the Financial Disclosure section from the original review of this NDA"

> "Financial Disclosure:
>
> The Sponsor has provided the required certification (Form FDA 3454) regarding financial interests and arrangements of clinical investigators. The Sponsor has certified that the value of compensation to the investigator was not influenced by the outcome of the study. One investigator has received a $1000/ month consulting retainer since February 1997. Four other investigators had stock or stock options in OraPharma valued at over $100,000 each, based on the stock price at the time of this review. The Biostatistics reviewer was asked to re-evaluate those sites to determine if there was anything unusual about the reported results and to assess the impact of those sites on the overall studies. In one instance, San Antonio (Study 103A), the mean baseline pocket depth for the active arm was the highest among all sites in the study and the mean baseline pocket depth for the S/RP arm was the lowest among all sites. Since we know that the deeper the pocket at baseline, the better the response is expected to be, the

situation described would likely favor the active arm. In fact, the delta between the active and S/RP arms at that site was the second highest among all sites in that study. If that site is dropped from the analysis, the p-value for the comparison goes from .047 to .237. This site did enroll a large number subjects, so dropping it would be expected to have some effect on the p-value, but it seems unlikely that the change would be so dramatic based on the number of subjects alone. Based on the unusual nature of the data and the fact that the investigator received substantial compensation, the Division has asked the Division of Scientific Investigations (DSI) to audit the site prior to making a final decision about the approvability of this NDA."

A memo from Jose A. Carreras, M.D., of DSI, dated January 30, 2001 reported the results of the audits of clinical study sites that were conducted. His conclusion was that, "No objectionable conditions were found in the above sites which would preclude the use of their data submitted in support of the pending NDA."

Recommendation:

Based on the DSI audit of the San Antonio site, this reviewer concludes that the data from that site should be included in the efficacy analysis for this product. Therefore, NDA 50-781 for ARESTIN™ (minocycline hydrochloride), Microspheres, 1 mg is approvable with the labeling changes recommended in the original clinical review dated December 18, 2000.

/S/ D.D.S.
Clarence C. Gilkes, D.D.S.

DFS 2-12-01

Original to NDA 50-781
HFD-540 Division File
HFD-540 Wilkin
HFD-540 Gilkes
HFD-540 Kelsey 2/9/01
HFD-540 Hyman
HFD-540 Bhatt
HFD-540 Jacobs
HFD-540 See 2/15/01
HFD-833 DeCamp
HFD-833 Gautam-Basak
HFD-725 Al-Osh
HFD-725 Rahman
HFD-880 Bashaw
HFD-880 Ghosh
HFD-520 Marsik

DFS 2/16/01

DEC 18 [illegible]

ARESTIN™ (minocycline hydrochloride) Microspheres, 1 mg.

NDA 50-781

Sponsor: OraPharma, Inc.

Clinical Review
Clarence Gilkes, D.D.S.
December 5, 2000

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Dental Officer's Original Review of NDA 50-781

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Third Review Date: December 5, 2000

Reviewer: Clarence C. Gilkes, D.D.S.

Project Manager: Kalyani Bhatt, M. Sc.

Materials Utilized in Review:

NDA 50-781, Vols. 1.1, 1.20 – 1.23, 1.26, 1.27, 1.32, 1.34, 1.40, 1.46, 1.90 – 1.94, 1.97, 1.99

Background and Regulatory History:

Periodontal disease is a pathogenic cascade which occurs at the supporting structures of the teeth and which, if untreated, results in the loss of connective tissue attachment, alveolar bone, and ultimately the teeth. Periodontal disease is a multifactorial process, the etiology of which may include the presence of dental plaque, microorganisms, occlusal trauma, nutritional deficiencies, and endocrinologic and hematologic influences. Some success in treating the disease or in slowing its progress has been achieved through several therapies, including surgical removal of diseased tissue, reduction of pathogens in the mouth, and reduction of the inflammatory response associated with periodontal destruction.

The most common treatment for periodontal disease is subgingival debridement combined with scaling and root planing (S/RP) and plaque control. As the pocket deepens, however, scaling and root planing may become less effective and a significant amount of bacteria may remain, exacerbating the tissue destruction that accompanies periodontal disease. Use of an agent that reduces bacteria in the pocket could be helpful in preventing the progression of periodontitis by reducing the inflammation that accompanies bacterial presence. This reduction in inflammation may also help to break the cycle of further bacterial accumulation by maintaining or reducing the depth of the gingival pocket (which traps the bacteria), thereby making the pocket more accessible for cleansing. This has caused clinicians and researchers to investigate the use of antimicrobials and host modulating drugs as both adjuncts to S/RP and as stand-alone products in the treatment of periodontitis. Systemic antibiotics do have a number of shortcomings for treatment of periodontitis including poor patient compliance, overgrowth of opportunistic organisms and development of resistant strains of bacteria. Also, periodontitis is a chronic disease requiring prolonged use of these drugs. For these reasons there have been efforts to develop locally delivered, sustained release antimicrobials. Studies have been reported using doxycycline, minocycline, metronidazole, chlorhexidine and tetracycline delivered in gels, polymers, chips, strips, rinses and fibers in the treatment of periodontitis.

To date, the Agency has approved four related products. Actisite®, which is a tetracycline impregnated ethylene/vinyl acetate monofilament fiber, was approved on March 25, 1994, as an adjunct to scaling and root planing for reduction of pocket depth and bleeding on probing in patients with adult periodontitis. PerioChip®, which is a bioresorbable gelatin chip containing chlorhexidine gluconate was approved letter on November 25, 1997, as an adjunct to scaling and root planing procedures for reduction of pocket depth in patients with adult periodontitis. On January 30, 1998 FDA approved Atridox™, 10% doxycycline (8.5% w/w) in a bioabsorbable polymer as a stand-alone therapy in the treatment of chronic adult periodontitis. On September 30, 1998 the Agency approved Periostat® (doxycycline hyclate 20 mg.) for the treatment of adult periodontitis. Periostat® is a sub-antimicrobial concentration of doxycycline, which the sponsor believes has an anti-inflammatory mechanism of action.

The sponsor of the NDA currently under review has studied Arestin™ (minocycline 1 mg. Periodontal Therapeutic System [ARESTIN]) in a bioabsorbable polymer as an adjunctive therapy to scaling and root planing in the reduction of pocket depths in patients with chronic adult periodontitis. This product is intended to be a prescription item. Biodegradable, time release microsphere capsules (a dry powder) are inserted into the periodontal pockets by the dentist using a syringe-like dispenser. ARESTIN has not been marketed in any country. Minocycline hydrochloride is a tetracycline derivative and has been clinically used for more than 15 years.

IND —— for Minocycline Periodontal Therapeutic System, (ARESTIN) was originally filed ———— by Lederle Laboratories, a division of American Cyanamid Company. Phase 1 and 2 studies were carried out from 1988-1991. Lederle Laboratories requested inactivation of IND —— on January 16, 1995. Transfer of the inactive IND to OraPharma, Inc. was accomplished June 17, 1997. OraPharma reactivated the IND on January 30, 1998 and conducted the Phase 3 studies that are the basis of this NDA submission. NDA —— was submitted on February 16, 2000 – the number was subsequently changed to 50-781. OraPharma Inc. has received a small business waiver of the user fee. The 10-month target date for this submission is December 17, 2000.

Executive Summary:

Periodontal disease is very prevalent and will likely become more so as the population ages. There are currently only four products approved in the U.S. for this condition and additions to the clinician's armamentarium would be welcome. This product contains an antibiotic that has not been incorporated into any of the approved products, but like Atridox and PerioChip is applied locally to the periodontal pocket.

The Sponsor has chosen to use this product as an adjunct to the standard of care for treating periodontal disease, scaling and root planning. In addition, the sponsor elected to seek the "lesser" periodontal indication of, "reduction in pocket depth in patients with adult periodontitis."

The Sponsor has conducted two well controlled (n=499) and one open label study (n=423) in support of approval of their product as an adjunct to scaling and root planning in the for the reduction of pocket depth in patients with adult periodontitis. The data presented support approval. The Sponsor has demonstrated a statistically significant difference in pocket depth reduction in the S/RP + ARESTIN group over the S/RP Alone group at 9 months. There was also a statistically significant difference in the percentage of pockets that were reduced ≥ 2 mm. in the S/RP + ARESTIN group over the S/RP Alone group at 9 months. Additional secondary endpoints were supportive, though did not achieve statistical significance.

The safety profile of this product appears benign. There were two deaths and 23 serious adverse events during the studies, none of which seem to be attributable to the study medication. In general the frequency and types of adverse events were reported by similar numbers of patients across the three treatment groups.

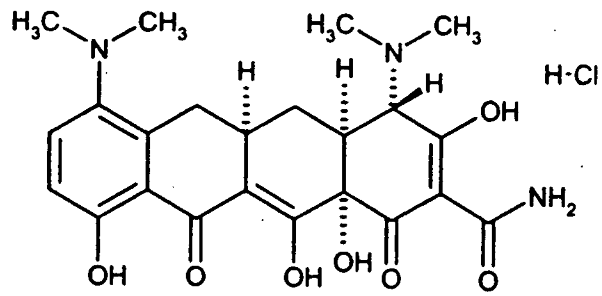
The review of this application was relatively straightforward. The Sponsor's proposed labeling required substantial revision.

One significant issue that arose late in the review concerns disclosure of financial interests of the investigators. Four investigators had stock or stock options in OraPharma valued at over $100,000 each, based on the stock price at the time of this review. The Biostatistics reviewer was asked to re-evaluate those sites. One site in particular was found to have unusual data, and that site is also critical to the success of that study. The Division has asked the Division of Scientific Investigations (DSI) to audit the site prior to making a final decision about the approvability of this NDA.

Chemistry, Manufacturing and Controls Summary:

Minocycline hydrochloride is a yellow crystalline powder of molecular weight 493.94. Its molecular formula is $C_{23}H_{27}N_3O_7 \bullet HCl$. It has four ionizable groups with pKa's of 2.8, 5.0, 7.8 and 9.5, making its solubility in water a complex function of pH. Solubility in water is at a minimum at pH 4.0. No polymorphic forms have been reported.

Chemical Structure of Minocycline HCl:



Minocycline HCl in the dry powder state is stable at room temperature for at least four years. The primary modes of

The drug substance is manufactured

and the analysis of minocycline HCl is conducted by Applied Analytical, Inc. (AAI) in North Carolina. AAI also manufactures the drug product.

The drug product, ARESTIN, 1 mg., consists of minocycline hydrochloride encapsulated in a bioresorbable polymer, poly(glycolide-co-di-lactide). This is similar to the polymers used in resorbable sutures and depot preparations. It is supplied in a unit dose dispenser that delivers 1 mg. of minocycline. Exposure to moisture in the periodontal pocket triggers hydrolysis of the polymer and release of the active ingredient. It is a sustained release product.

The primary packaging of the product consists of a dispenser with a narrow hollow delivery tip that fits into the periodontal pocket. The drug product resides in the barrel. There is a plunger with thumb-ring that fits inside the barrel above the powder. Applying pressure to the thumb-ring expresses the powder into the pocket.

Reviewer's Comment: The delivery of this product differs from Atridox in that it is a powder that is dispensed into the periodontal pocket, while Atridox is a viscous liquid, that is created by mixing the polymer liquid with the antibiotic powder immediately before inserting it into the periodontal pocket.

See Dr. Gautam-Basak's CMC review.

Pharmacology and Toxicology Summary:

Quoting Dr. See's review, "The Division, working in concert with personnel at the office level, agreed with the Sponsor long ago that, in view of the extensive clinical database available to support the safety of minocycline with respect to systemic toxicity and with the product with respect to local toxicity, that nonclinical data needed to support a NDA for the product could be limited to a suitable battery of genetic toxicology studies. Note that the clinical database for minocycline includes exposure at much higher levels and for much longer periods than proposed under NDA 50-781, and that minocycline bears the tetracycline class labeling for pregnancy category."

Dr. See reviewed six studies conducted in support of this NDA submission. These were:

1. Dermal sensitization study of a microcapsule formulation in the guinea pig.
2. A local tolerance study of minocycline hydrochloride applied topically to the gingiva of dogs daily for five days.
3. Bacterial reverse mutation assay
4. *In vitro* mammalian cell gene mutation test.
5. *In vitro* mammalian chromosome aberration test
6. Mammalian erythrocyte micronucleus test

The results of the genetic toxicology studies provided no evidence that the test substance is mutagenic or clastogenic. The product was non-sensitizing in a dermal sensitization study in the guinea pig. Finally, a five-day local tolerance study in dogs showed no irritation or other signs of toxicity, and the drug product did not delay healing of induced lesions.

Dr. See concludes that the proposed exposure to the drug product is safe. See Pharm./Tox review.

Pharmacokinetics Summary:

This section summarizes the known pharmacokinetics of systemically administered minocycline as well as the results of three trials of ARESTIN. Systemically administered minocycline is well absorbed in less than 3 hours. It is widely distributed and is metabolized to microbiologically inactive metabolites. It has a half-life in humans of about 16 hours and is 60-80% excreted in feces, and 2-9% in urine.

The sponsor conducted one human pharmacokionetic and bioavailability study (OPI-105) with ARESTIN. This was a two-center, open-label, single dose trial in 18 patients with moderate to advanced periodontal disease. After full mouth S/RP, ARESTIN was administered to at least 30 sites of 5 mm or greater pocket depth. Blood and saliva samples were collected pre-dose and at .5, 1, 2, 3, 6, 9, 18, 24, 48, 72, 168, and 336 hours post dose. Various pharmacokinetic parameters were measured. The half-life in serum was about 24 hours and in saliva about 45 hours. The study demonstrated that drug concentrations in saliva were much higher than in serum. C_{max} was .005 µg/mL for serum and 5.55 µg/mL for saliva. This is consistent with the rationale of developing high concentrations at the site of action while avoiding the problems associated with chronically high serum concentrations.

In addition, information on minocycline concentrations in gingival crevicular fluid that was obtained in the early Lederle studies was provided.

See Dr. Ghosh's Biopharmaceutics review.

Microbiology Summary:

The Sponsor collected microbiological data in three studies. In the pivotal safety/efficacy studies (OPI-103A and OPI-103B) plaque microbiology was monitored to determine if there was growth of opportunistic organisms. Plaque was collected from a single pocket of 6-9mm depth in each patient. Changes in the relative proportions of plaque microorganisms were assessed, as was the post-treatment expression of minocycline resistant organisms in plaque. The proportion of plaque microorganisms was determined by the percentage of total DNA detected by each of 40 DNA probes. For all of the DNA probes, the proportion of organisms was consistent across the three treatment groups (S/RP, vehicle + S/RP and ARESTIN + S/RP).

Treatment emergent antimicrobial resistance was assessed using serial agar dilution culture techniques on plaque samples from two study sites (San Antonio and Buffalo). The results of these analyses are in Table 1.

Table 1: Percent Resistant Organisms; Studies OPI-103A & OPI-103B

	OPI-103A		OPI-103		COMBINED	
	Base.	Mo.9	Base	Mo.9	Base.	Mo.9
ARESTIN + S/RP	0.1%	0.5%	0.3%	3.0%	0.2%	1.7%
Vehicle + S/RP	0.2%	0.1%	1.4%	0.7%	0.8%	0.4%
S/RP	0.2%	0.2%	0.3%	0.6%	0.2%	0.3%

In Study OPI-105 the Sponsor assessed whether the local application of ARESTIN caused changes in the gastrointestinal microbiota. Stool specimens were monitored for changes in a) the total anaerobic flora, b) the proportion of flora resistant to the drug, and c) the levels of pathogens present. No statistically significant differences were detected in the total anaerobic counts, in the number of minocycline-resistant counts or in the proportion of minocycline-resistant counts. Also, no significant differences were detected in the three opportunistic pathogens enumerated (*Candida*, enteric bacteria, *Staphylococcus aureus*).

The Microbiology reviewer concludes that the Sponsor has failed to show a difference in the microbiological content of plaque from the S/RP + ARESTIN and the S/RP alone groups and therefore cannot make any statements in labeling correlating the microbiological and clinical outcomes. He goes on to say that the data submitted on minocycline-resistant organisms in plaque and the GI track were not a cause for concern. He recommends approval with labeling changes.

See Dr. Marsik's Microbiology review.

Clinical Studies:

Summary of Phase 1 and Phase 2 Studies:

Clinical Pharmacology:

Lederle Laboratories, the original sponsor of the IND conducted 2 dose tolerance studies and 4 therapeutic response studies during 1988 and 1989. Synopses of the studies follow.

Lederle Study 15-16-1

This was a randomized, evaluator-blind, 2-arm, parallel group study in 32 patients. Each patient received a single treatment on a single periodontal pocket of at least 5 mm. as an adjunct to S/RP. The treatments were S/RP plus ARESTIN or saline plus ARESTIN. The study objectives were to evaluate the clinical and histological response to the subgingival deposition of ARESTIN in periodontal pockets, and to assess the release of minocycline into the gingival crevicular fluid (GCF). Patients were assessed weekly for hypersensitivity, gingival irritation, tooth staining, bacterial or fungal overgrowth for 28 days. Patients were also asked about pain, irritation, taste and smell of the product. Patients were assessed for a number of clinical parameters at baseline and again at 28 days, including gingival inflammation, pocket depth (PD), plaque index (PI), gingival index (GI), bleeding index (BI) and dental hypersensitivity. Gingival biopsies were also obtained at 28 days. The Sponsor reported that the biopsies showed no abnormalities and no significant AEs were attributable to the drug or vehicle.

Lederle Study 15-19-1

This study was conducted to evaluate the safety of the polymer vehicle. It was a randomized, evaluator blind, two-arm study in 20 patients. A single treatment was applied to a single site 6 mm or deeper. Patients received S/RP followed by either vehicle polymer or saline. Patients were assessed for pain, alterations in taste or smell and signs of periodontitis at multiple time points during the 28 day study. Patient assessments of clinical indices (GI, PD, PI, BI) were conducted at Baseline and Day 28. Assessment of the free gingival margin (FGM), attached gingiva (AG) and alveolar mucosa (AM) were conducted to assess safety. Pre- and post-treatment plaque samples were compared to assess microbial growth. Pre- and post-treatment blood and urine samples were collected. Gingival biopsies were conducted at Day 28. The Sponsor reports that no significant adverse experiences were attributed to the vehicle in this study.

Lederle Study 15-18-1

This was a randomized, evaluator-blind, parallel study in 56 patients lasting six months. Two periodontal pockets, one ≥ 5mm and one ≥ 7mm were treated in each patient. The two arms were S/RP + ARESTIN and S/RP + saline. Clinical and safety assessments as were used in the previous studies were conducted at Baseline, 1, 3 and 6 months, but in addition, clinical attachment level (CAL) was measured. Plaque samples were collected for microbiological analysis on the same schedule. Blood and urine analysis were done at screening, 1 month and 3 months. Adverse event information was solicited at two weeks, 1 month and 3 months post-treatment. The Sponsor reported that both treatments resulted in a lowering of GI, PI, BI and dental hypersensitivity. Mean PD reduction was greater in the S/RP + ARESTIN group than in the S/RP + saline group though the difference was not statistically significant. However, no difference was observed between groups in the clinical attachment level (CAL).The Sponsor reported little difference in tissue changes, staining, laboratory values or adverse events between treatment groups.

Lederle Study 15-26-1

This was a randomize, evaluator-blind, three-arm, parallel, vehicle-controlled study in 79 patients for 6 months. Patients received treatment in one quadrant, which had to have at least 2 pockets ≥ 7mm. in depth. The treatments were: 1) S/RP + ARESTIN, 2) S/RP + vehicle, and 3) S/RP alone. The study was intended to evaluate the clinical and microbiological efficacy of ARESTIN in deep periodontal pockets. Clinical evaluations (PD, CAL, BI, PI, GI and dental hypersensitivity) were done at Baseline and 1, 3 and 6 months. Assessment of tooth staining, local irritation, patient assessment of adverse events, and changes in sense of taste or smell were conducted at each visit. Bacteriological assessments were conducted. Routine laboratory assessments of blood and urine were performed at screening and at one month. The sponsor reported that the efficacy data trended in favor of the active treatment arm and that there were no noticeable differences among groups in terms of safety. Overall, there appeared to be numerically larger decreases from baseline in the proportion of cultivable flora in the ARESTIN group.

Lederle Study 15-20-2

This was a randomized, evaluator-blind, four-arm parallel group study in 49 patients. Each patient had a single treatment of two teeth, with at least one site ≥ 6 mm in depth. In addition, the PGE_2 level in the crevicular fluid had to be greater than 66.2 ng/mL. Patients received one of four treatments: 1) S/RP + ARESTIN, 2) S/RP, 3)ARESTIN or 4) no treatment. The study lasted six months. Clinical assessments included those conducted in the previously mentioned studies. Microbiological samples were taken at Baseline, 3 and 6 months. Stain and local irritation were assessed; blood and urine samples were taken as in the previously mentioned studies. In addition, minocycline levels in the GCF were measured at multiple timepoints. The Sponsor reported that there were statistically significant differences between the S/RP + ARESTIN group and both S/RP and no treatment at 3 months. The subset of pockets ≥ 5mm and < 6mm also showed statistically significant differences in favor of the active at six months. Differences among treatment groups with respect to CAL were only marginally significant, according to the Sponsor. The Sponsor reported problems with the microbiological and GCF analyses. AEs, local irritation and extent of tooth staining were comparable across groups.

Lederle Study 15-27-1

This was a randomized, evaluator-blind, four-arm, parallel 6-month study in 57 patients. Patients received a single treatment in in one quadrant with 2 pockets ≥ 7mm in depth. At lease one of those sites had to be positive for one of three organisms by culture: *Bacteroides gingivalis, Prevotella intermedia, of Actinomyces actinomycetemcomitans.* Clinical assessments as in the previous studies were performed at Day 1 and Months 3 and 6. Bacteriological sampling of plaque for various periodontopathic organisms was done at Day 1 and Months 1, 3 and 6. Routine laboratory analysis of blood and urine were done for safety. Adverse event data were collected at Week 2 and Months 1, 3 and 6. In addition to the Lederle analysis which was of the evaluable population, the Sponsor presented the results of an ITT analysis that was conducted as part of a paper on this study: Jones AA, Kornman KS, Newbold DA, Manwell MA. *Clinical and microbiological effects of controlled-release locally delivered minocycline in periodontitis.* J Periodontol 1994;65:1058-1066. The S/RP + ARESTIN group trended better than the other groups with respect to PD. Of note, at Months 3 and 6, significantly greater gains in CAL were observed in the S/RP group compared to the S/RP + ARESTIN group. There were no consistent, substantial differences among groups for any of the other indices. The study gave no indication of potential safety problems.

Reviewer's Comment: *As will be discussed later in this review, the Sponsor was given the option of using either PD or CAL as the primary endpoint of the pivotal studies, subject to certain limitations. The Sponsor chose to use PD, presumably due to the clinical experience in these early studies.*

Human Pharmacokionetic and Bioavailability Study (OPI-105):

This was a two-center, open-label, single dose trial in 18 patients with moderate to advanced periodontal disease. After full mouth S/RP, ARESTIN was administered to at least 30 sites of 5 mm or greater pocket depth. The study had three stated objectives as follows:

- To document the pharmacokinetic profile of minocycline in serum and saliva following subgingival delivery of ARESTIN
- To assess the development of minocycline resistance in the gastrointestinal flora
- To evaluate the safety of ARESTIN in patients with generalized moderate to advanced adult periodontitis

Blood and saliva samples were collected pre-dose and at .5, 1, 2, 3, 6, 9, 18, 24, 48, 72, 168, and 336 hours post dose. Various pharmacokinetic parameters were measured as summarized in Table 1. Safety assessments including vital signs, adverse event and examination of the oral cavity were conducted at Days 0, 1, 2, 3, 7, 14, 28 and 56. Laboratory assessments were made at screening and Day 56. Fecal specimens were obtained at Days 0, 28 and 56 for assessment of minocycline resistance.

Table 2: Summary of Pharmacokinetic Results (Mean %CV)

Pharmacokinetic Parameter	Serum Data			Saliva data		
	Site A (n=10)	Site B (n=8)	All (n=18)	Site A (n=10)	Site B (n=8)	All (n=18)
AUC 0-t/Dose (µg·h/mL)	0.163 (25.2)	0.108 (53.5)	0.139 (40.0)	14.9 (33.9)	19.0 (48.6)	17.5 (45.3)
AUCinf/Dose (µg·h/mL) or $AUCinf_{sal}$/Dose (µg·h/mL)	0.200 (26.9)	0.131 (50.8)	0.169 (40.0)	15.1 (33.1)	19.2 (48.0)	17.6 (44.7)
Cmax/Dose (µg/mL)	0.00550 (31.3)	0.00412 (45.0)	0.00488 (38.2)	5.13 (28.9)	5.82 (56.2)	5.55 (47.9)
Tmax (h)	5.10 (39.7)	4.50 (35.6)	4.83 (37.7)	0.800 (83.9)	0.715 (73.4)	0.748 (74.8)
K_{sal} or kel	0.0298 (27.2)	0.0353 (37.5)	0.0322 (33.2)	0.0208 (32.1)	0.0165 (46.0)	0.0181 (40.2)
Half-life (h)	25.3 (36.0)	21.8 (31.7)	23.8 (34.5)	35.8 (26.8)	50.3 (43.9)	44.7 (42.9)
CL/F (L/h)	5.35 (27.4)	9.32 (48.3)	7.12 (51.8)	NC	NC	NC
Varea/F (L)	185 (23.2)	270 (39.2)	223 (38.7)	NC	NC	NC

NC = not calculated

As can be seen, the maximum minocycline concentrations in saliva were much higher than in serum. This is consistent with the rationale of developing high concentrations at the site of action while avoiding the problems associated with chronically high serum concentrations. There were no serious adverse events reported in this study and the vital signs and laboratory parameters pre- and post-dose showed no significant differences.

The Sponsor assessed whether the local application of ARESTIN caused changes in the gastrointestinal microbiota. Stool specimens were monitored for changes in a) the total anaerobic flora, b) the proportion of flora resistant to the drug, and c) the levels of pathogens present. No statistically significant differences were detected in the total anaerobic counts, in the number of minocycline-resistant counts or in the proportion of minocycline-resistant counts. Also, no significant differences were detected in the three opportunistic pathogens enumerated (*Candida*, enteric bacteria, *Staphylococcus aureus*).

<u>Summary of Phase 3 Studies:</u>

Well-controlled Safety and Efficacy Studies (OPI-103A and OPI-103B):

Study design:

The Sponsor conducted two pivotal Phase 3 safety and efficacy studies, which were identical in design. These were multicenter, randomized, single-blind, vehicle-controlled studies with three parallel arms as follows:

1. S/RP plus subgingival application of ARESTIN (S/RP + M)
2. S/RP plus subgingival application of vehicle (S/RP + V)
3. S/RP alone (S/RP)

The investigators and their sites were:

Study 103A:

Dr. Amitage	University of California, San Francisco
Dr. Caton	Eastman Dental Center, Rochester, NY
Dr. Cochran	University of Texas, San Antonio
Dr. Fiorellini	Harvard University
Dr. Giannoble	University of Michigan, Ann Arbor
Dr. Georgia K. Johnson	University of Iowa, Iowa City
Dr. Magnuson	University of Florida, Gainsville
Dr. Oringer	SUNY at Stony Brook, NY
Dr. Persson	University of Washington, Seattle

Study 103B:

Dr. Adams	Oregon Health Science University –Portland
Dr. Drisko	University of Louisville
Dr. Genco	SUNY at Stony Brook NY
Dr. Killoy	University of Missouri at Kansas City
Dr. Lamaster	Columbia University, NY
Dr. Paquette	University of North Carolina at Chapel Hill
Dr. Socransky	Forsyth Dental Center
Dr. Van Dyke	Boston University
Dr. Wolff	University of Minnesota

Patients were randomized to one of three treatment arms via permuted blocks with stratification according to center and smoking status (yes or no), yielding blocks of six.

The vehicle was a true placebo - it differed from the active only in that it did not contain any minocycline. Although the active and vehicle were formulated to be indistinguishable, those patients in the S/RP group received no medication, therefore the patient was not blinded to treatment and the study was single blind. The evaluator was blinded to treatment.

A total of 748 patients were enrolled in both studies; 368 in Study OPI-103A and 380 in Study OPI-103B). Patients had to have at least ten teeth remaining in the functional dentition, excluding third molars, and at least four teeth with periodontal pocket depth

(PD) of 6-9 mm and bleeding on probing (BOP) on all four qualifying teeth. Clinical examinations, measurement of PD, and microbial assessments were performed at Baseline (prior to S/RP and treatment), and at Days 30, 90, 180 and 270. Study treatments (ARESTIN or vehicle) were reapplied at Days 90 and 180 at all sites initially treated at Baseline and at any new periodontal sites that had PD ≥ 5 mm. S/RP was only performed at Baseline in this study.

Inclusion Criteria (Verbatim from Sponsor):

1. Patients must be adult males or females 30 years or older.

2. ~~Patients must be able and willing to follow study procedures and instructions~~

3. Patients must have read, understood and signed an informed consent form.

4. Patients must have generalized, moderate to advanced adult periodontitis - American Dental Association Class 3 or 4 - as determined by the investigator or designee during the screening periodontal examination.

5. Patients must present with at least 10 teeth in the functional dentition, excluding third molars.

6. Each patient must have at least four teeth with periodontal pocketing (PD = 6-9 mm) and BOP on all four qualifying teeth as determined by single-pass probing depth measurements in order to qualify for the study. In addition, all sites with PD ≥ 5 mm will be treated in the study.

<u>Reviewer's Comments</u>: *It is noted that only 20 patients out of 748 had an average pocket depth greater than 7 mm, ranging from 7 mm to 8.38 mm.*

Exclusion Criteria (Verbatim from Sponsor):

Patients will be excluded from the study for any of the following reasons:

1. Patients chronically treated (i.e., two weeks or more) with any medication known to affect periodontal status (e.g., phenytoin, calcium antagonists, cyclosporin, coumadin, and nonsteroidal anti-inflammatory drugs) within one month of the screening examination. Prophylactic use of aspirin (≤ 325 mg daily) for cardiovascular indications will be permitted in patients. All other medications for chronic medical conditions should be initiated at least two months prior to enrollment.

2. Patients who have received quadrant or maintenance S/RP, and/or periodontal surgical therapy within 6 months prior to enrollment.

3. Patients who have been treated with antibiotics for medical or dental reasons within 3 months prior to enrollment.

4. Patients having clinically significant or unstable organic disease; patients having compromised healing potential such as those with diabetes (Type I) or connective tissue disorders; patients having heart murmurs, histories of rheumatic fever, valvular disease or prosthetic joint replacement necessitating antibiotic prophylaxis. Patients with type II diabetes (non-insulin-dependent diabetes) can be included if no medication changes occurred during the 3 months prior to screening, as these patients are considered stable.

5. Female patients who are pregnant (as determined by a positive urine pregnancy test at baseline) or lactating, or female patients who are of childbearing potential and who are not using hormonal, barrier methods of birth control (e.g., oral or parenteral contraceptives, diaphragm plus spermicide, condoms), or abstinence. Patients who use hormonal contraceptives must have started the method not fewer than 30 days prior to the baseline examination.

6. Patients with documented allergies to tetracyclines.

7. Patients with active infectious diseases such as hepatitis, human immunodeficiency virus or tuberculosis.

8. Patients diagnosed with human immunodeficiency virus (HIV) or patients that are immunocompromised as determined by the investigator.

9. Patients taking steroid medications except for acute topical treatment.

10. Patients with severe, unrestored caries, or any condition that is likely to require antibiotic treatment during the trial.

11. Patients who have taken an investigational drug within 30 days of enrollment.

Demographic Characteristics:

Table 3: Selected Demographics, Studies 103A & 103B

	Treatment Group		
Subgroup	**ARESTIN (n=249)**	**Vehicle (n=249)**	**S/RP (n=250)**
Gender			
Males	134	144	132
Females	115	105	118
Age			
≤ 50 years	142	168	167
> 50 years	107	81	83
Race			
Caucasian	195	181	191
Black	30	39	29
Others	24	29	30
Smoking Status			
Smokers	90	90	91
Non-smokers	159	159	159
CV Disease Hx.			
CV Disease	36	29	36
No CV Disease	213	220	214

For the combined pivotal studies, 103A & 103B, 249, 249 and 250 patients were randomized to receive ARESTIN, Vehicle and S/RP, respectively. Of the randomized patients, 54.8% (410/748) were male, 75.8% (567/748) were Caucasian, 32.6% (271/748) were smokers, and 63.8% (477/748) were ≤ 50 years of age. The demographic variables were well balanced among the three treatment groups, except for age. The ARESTIN group had a higher percentage of patients > 50 years of age (39.0%, 30% and 31% for ARESTIN, Vehicle and SR/P groups respectively).

The severity of periodontal disease at baseline was balanced across the three treatment groups. Severity of periodontal disease was moderate in 61.2% (458/748) of patients, and advanced in 38.8% (290/748) of patients.

Reviewer's Comments: The primary endpoint in these studies was change in pocket depth from baseline at 9 months. Baseline PD was balanced across the three treatment groups in each pivotal study. In Study 103A, the mean pocket depths at baseline were 5.88 mm for scaling and root planing, 5.91 mm for S/RP + vehicle and 5.88 mm for S/RP + ARESTIN. In study 103B mean pocket depths at baseline were 5.85 mm, 5.89 mm and 5.84 respectively.

Rationale for Treatment Schedule:

Quoting the Sponsor, "Data from Phase 2 studies indicate that ARESTIN suppresses putative periodontal pathogens for at least one month following a single administration as an adjunct to S/RP. Study 15-18-1 (Walker, University of Florida at Gainesville) reported that patients receiving adjunctive ARESTIN demonstrated lower mean proportions of dark-pigmented Bacteroides species, *Pi*, and *Ec* for at least one month.

Furthermore, Jones et al. reported significant depressions in subgingival *Pg* for at least one month with ARESTIN alone or ARESTIN therapy plus S/RP as compared to S/RP alone or no treatment. Therefore, despite the presence of therapeutic drug levels in the gingival crevicular fluid for 14 days or longer after application, evidence indicates that ARESTIN can alter the subgingival flora for a time period longer than one month. These findings are consistent with reports on the antimicrobial effects of other locally delivered periodontal therapeutics (e.g., Actisite fiber). In addition, retreatment at 3 and 6 months follows the standard of care for delivering periodic maintenance therapy to patients with moderate to advanced adult periodontitis."

Reviewer's Comments:

1. *The retreatment schedule is similar to that used in the Atridox™ studies and corresponds to the typical recall schedule for periodontitis patients.*

2. *As is noted in Dr. Ghosh's Biopharmaceutics review, the concentration of minocycline in the pocket immediately after placement is approximately 1000 times the MIC for the common periodontal pathogens. That may be more minocycline than is necessary, but the Agency has accepted that dosing level throughout the development of this product and it is similar to that which was achieved with Atridox™.*

Study Procedures:

Table 4: Schedule of Procedures by Visit, Studies OPI-103A and OPI-103B

	Visit 1 Screening	Visit 2 Baseline	Visit 3	Visit 4	Visit 5	Visit 6
Day	-30 to -1	0	30 ± 5	90 ± 7	180 ± 10	270 ± 14
Procedure:						
Informed consent	√					
Medical/periodontal history	√					
Examination of oral cavity	√	√	√	√	√	√
Vital signs	√	√	√	√	√	√
Urine pregnancy test (females)		√		√	√	
Scaling and root planing		√				
Obtain plaque samples		√*	√	√**	√**	√
Clinical periodontal assessments		√*	√	√**	√**	√
Study treatment administration		√		√	√	
Post-treatment instructions		√		√	√	
Record adverse events		√	√	√	√	√
Record concurrent medications	√	√	√	√	√	√

[1]Baseline may consist of up to 3 visits: 2 visits to complete full mouth S/RP and an additional visit to apply study treatments if bleeding has not subsided within a reasonable amount of time after S/RP has been completed. Study treatments must be administered within 48 hours of completion of S/RP. The time at which study treatments are administered will be designated Baseline (Day 0) of the study.
*Must be performed PRIOR to S/RP at Baseline.
**Must be performed PRIOR to re-treatment of the sites.

Scaling and root planing was performed only at baseline. Following baseline examinations, patients received one of three treatments. Treatments were administered to all sites with mean probing depths of 5 mm or greater. Pocket depths were measured using the University of North Carolina manual probe. Re-treatment occurred at 3 and 6 months after initial treatment and any new site with pocket depth (PD) greater than 5 mm also received treatment. Subgingival administration was accomplished by inserting the unit dose tip to the base of the periodontal pocket and then pressing the thumb ring in the handle mechanism to expel the powder while gradually withdrawing the tip from the base of the pocket.

Data Analysis Plan:

The patient's PD changes from baseline were analyzed using ANCOVA. The ANCOVA model included factors for treatment group, center (pooled), baseline response, age, disease severity and smoking status." Further, "As a supportive analysis, treatment comparisons for the primary and secondary efficacy parameters were undertaken with the non-parametric covariance adjusted extended Mantel-Haenszel test."

Reviewer's Comment: As is noted in Dr. Rahman's Biostatistics review, the Agency requested a change in the data analysis plan at the pre-NDA meeting because the Biostat. reviewer at that time, Dr. Thomson, concluded that the two step procedure that the Sponsor had originally proposed was ambiguous, possibly biased and hard to interpret. The data analysis plan that was argreed upon was, "For primary efficacy analysis, the patient was the unit of analysis.

The primary efficacy analysis was conducted on the ITT popultation. The Sponsor had defined the ITT as all patients who were randomized and had at least one post-baseline measurement. The Agency defines ITT as al patients randomized and dispensed medication. Dr. Rahman went to the data and found that there was no difference between the two analyses in this case.

Results:

Primary Efficacy Variable (PD):

The primary endpoint for these studies was change from baseline in within subject averaged pocket depth at nine months. ARESTIN + S/RP had to be statistically significantly better than both Vehicle + S/RP and S/RP alone.

Reviewer's Comments:

1. *The Sponsor was given the option of using PD or CAL as the primary endpoint. CAL is considered the "higher hurdle," and is generally regarded as a better surrogate for periodontal disease. The Division has approved the indication of "treatment of periodontitis" for products that have used CAL as the primary endpoint. Because the Division has also previously approved the indication, "reduction in pocket depth in patients with periodontal disease," that endpoint is permitted, but the Sponsor was told that if the "lower hurdle" of PD was chosen, the "higher hurdle" of CAL could not be a secondary endpoint. The Division felt that it would not be fair to sponsors who had demonstrated that their product met the higher hurdle to have competitors get on the market by meeting a lower efficacy standard and then be able to make claims regarding CAL in promotion and advertising.*

2. *CAL data was collected as a safety parameter as had been done in the PerioChip studies. The rationale was that it would be possible to have a reduction in pocket depth achieved by reducing soft tissue edema, while at the same time a worsening of attachment level was occuring. This would not be desirable and did not occur in these studies.*

3. *The Sponsor submitted an analysis of the CAL data, but did not show a statistically significant difference between S/RP + ARESTIN and S/RP alone in two studies as would be required for approval if CAL were the primary endpoint.*

Table 5: Probing Pocket Depth at Baseline and Change in Pocket Depth at 9 Months, Studies OPI-103A and OPI-103B

Time	Study OPI-103A N=368			Study OPI-103B N=380		
	S/RP Alone N=124	**S/RP + Vehicle N=123**	**S/RP + ARESTIN N=121**	**S/RP Alone N=126**	**S/RP + Vehicle N=126**	**S/RP + ARESTIN N=128**
PD (mm) at Baseline, mean ± SD	5.88 ± 0.45	5.91 ± 0.54	5.88 ± 0.50	5.79 ± 0.37	5.82 ± 0.48	5.81 ± 0.42
PD (mm) Change from Baseline at 9 months, mean (SD)	-1.04 (0.81)	-0.90 (0.70)	-1.20*•• (0.79)	-1.32 (0.80)	-1.30 (0.81)	-1.63**•• (0.80)

SD = standard deviation, S/RP = scaling and root planing, PD = pocket depth
Significantly different from S/RP alone*($p \leq 0.05$); ** ($p \leq 0.001$)
Significantly different from S/RP + Vehicle • ($p \leq 0.05$); •• ($p \leq 0.001$)

<u>Reviewer's Comment</u>: *In both study OPI-103A and OPI-103B, ARESTIN plus scaling and root planing showed a statistically significant improvement in pocket depth reduction when compared to scaling and root planing alone. Because this product is being used as an adjunct to standard therapy any statistically significant improvement is considered clinically significant.*

Secondary Efficacy Variables:

The secondary efficacy variables that the Sponsor looked at in studies OPI-103A & OPI-103B were:

1. Clinical response
2. PD Extent
3. Bleeding on Probing
4. Need for Rescue Therapy

The data analysis plan for the secondary endpoints was essentially the same as for the primary endpoints

Clinical response was based on the percent of sites in each patient that had PD reductions of ≥ 1 mm, ≥ 2 mm, and ≥ 3 mm respectively.

Table 6: Numbers (percentage) of Pockets Showing a Change of Pocket Depth ≥ 2 mm and ≥ 3 mm at 9 months from Two Multicenter U.S. Clinical Trials

	Study OPI-103A			**Study OPI-103B**		
	S/RP Alone	**S/RP + Vehicle**	**S/RP + ARESTIN**	**S/RP Alone**	**S/RP + Vehicle**	**S/RP + ARESTIN**
Pockets ≥ 2mm (% of total)	1046 (31.1%)	927 (25.7%)	1326 (36.5%)	1692 (42.2%)	1710 (40.0%)	2082 (51.0%)
Pockets ≥ 3mm (% of total)	417 (12.4%)	315 (8.7%)	548 (15.1%)	553 (13.8%)	524 (12.3%)	704 (17.3%)

Reviewer's Comment: The Agency encourages this type of analysis because it may help clinicians and patients to understand the clinical utility of a product more than does reporting of means. In this case, changes in pocket depths of 2 or 3 mm may affect treatment decisions, e.g. retreatment or surgery.

Table 7: Mean Pocket Depth Change in Patients with Mean Baseline PD ≥ 5 mm, ≥ 6 mm and ≥ 7 mm at 9 months from Two Multicenter U.S. Clinical Trials

Mean Baseline Pocket Depth	Study OPI-103A			Study OPI-103B		
	S/RP Alone	**S/RP + Vehicle**	**S/RP + ARESTIN™**	**S/RP Alone**	**S/RP + Vehicle**	**S/RP + ARESTIN™**
≥ 5mm (n)	-1.04mm (124)	-0.90mm (123)	-1.20mm* (121)	-1.32mm (126)	-1.30mm (126)	-1.63mm* (128)
≥ 6mm (n)	-0.91mm (34)	-0.77mm (46)	-1.40mm* (45)	-1.33mm (37)	-1.46mm (40)	-1.69mm* (25)
≥ 7mm (n)	-1.10mm (4)	-0.46mm (5)	-1.91mm (3)	-1.72mm (3)	-1.11mm (3)	-2.84mm (2)

*Statistically significant comparison between S/RP + ARESTIN™ and S/RP Alone

The PD extent analysis looked at the treatment effect in pockets of ≥ 5 mm, ≥ 6 mm, and ≥ 7 mm respectively. ARESTIN + S/RP was statistically significantly better than S/RP alone at baseline depths of ≥ 5 mm, ≥ 6 mm. The differences in the ≥ 7 mm group not statistically significant, though there was a favorable trend and the numbers were small. In patients with these baseline pocket depths, the deeper the pocket, the greater the reduction in pocket depth with therapy. These results support the conclusion that the product is efficacious.

Bleeding on probing showed reductions at nine months for all treatment groups. ARESTIN + S/RP trended better than S/RP alone in one study, but the difference was not statistically significant.

The final secondary endpoint addressed in these studies was the need for rescue therapy. In Section 8.2, Discontinuation of Teeth and Patients Due to Rescue, the protocol states that, "Any site that exhibits a PD increase of 3 mm or more will result in the rescue of that tooth. That tooth will be discontinued from study treatment at the time of rescue, and the increased PD will be considered an adverse event (AE). Affected teeth will be locally treated with S/RP, and will continue to be monitored clinically. For time points following such tooth discontinuation, site-specific responses for that tooth will be censored from the analysis. If periodontal breakdown is extensive and necessitates more than local mechanical debridement in the opinion of a periodontist, the whole patient will be rescued and discontinued from study participation."

Reviewer's Comment: The percent of teeth that deteriorated 3 mm or more was very low in all three treatment groups in both studies, ranging from 2.1% to 5.1%. There were no statistically significant differences among groups. In one study the ARESTIN + S/RP arm had the smallest percentage of discontinued teeth, while in the other the S/RP alone group had the smallest percentage of discontinued teeth. It is this reviewer's opinion that this secondary endpoint does not impact one way or the other on the determination that the product is efficacious but does support the safety of the product.

Table 8: Mean Pocket Depth Changes (SE) in Subpopulations, Studies 103A and 103B Combined

	S/RP Alone	S/RP + Vehicle	S/RP + ARESTIN
Smokers	N = 91 -0.96±0.09 mm	N = 90 -0.98±0.07 mm	N = 90 -1.24±0.09 mm**
Non Smokers	N = 159 -1.31±0.06 mm	N = 159 -1.17±0.07 mm	N = 159 -1.53±0.06 mm**
Patients > 50 YOA	N = 21 -1.07±0.09 mm	N = 81 -0.92±0.08 mm	N = 107 -1.42±0.08 mm**
Patients ≤ 50 YOA	N = 167 -1.24±0.06 mm	N = 168 -1.19±0.06 mm	N = 142 -1.43±0.07 mm*
Patients with CV Disease	N = 36 -0.99±0.13 mm	N = 29 -1.06±0.14 mm	N = 36 -1.56±0.14 mm**
Patients w/o CV Disease	N = 214 -1.22±0.06 mm	N = 220 -1.11±0.05 mm	N = 213 -1.40±0.06 mm**

S/RP = scaling and root planing, YOA = Years of Age, CV = cardiovascular
* S/RP v. S/RP + ARESTIN™ $p \leq 0.05$; ** S/RP v. S/RP + ARESTIN™ $p \leq 0.001$

Smokers, patients over and under 50 years of age, and patients with a previous history of cardiovascular disease were the subpopulations pre-specified for analysis. When studies 103A and 103B are combined, S/RP + ARESTIN™ resulted in significantly greater reductions in PD than S/RP alone for all groups. The results of the combined studies are presented in Table 3. In smokers, the mean reduction in pocket depth at nine months was less in all treatment groups than in non-smokers, but the reduction in mean pocket depth at 9 months with S/RP + ARESTIN™ was significantly greater than with S/RP + vehicle or S/RP alone.

Safety results:

The Sponsor addressed the safety of the product through evaluation of adverse events, vital signs, clinical laboratory evaluations, microbiological evaluations and assessment of changes in clinical attachment levels. Studies OPI-103A and OPI-103B as well as the open label study (OPI-104) had very similar results with respect to safety and safety data from these studies will be reported in the Integrated Summary of Safety.

Open-label Safety Study (OPI-104):

Study design:

This was an open label study in patients with moderate to severe adult periodontitis that enrolled 174 patients at five centers. The primary intent of the study was to assess safety in order to meet the target of 300 patients on active for at least six months. All patients received S/RP + ARESTIN. S/RP was performed at baseline, and for new treatment sites only, at Months 1, 3 and 6. Application of study treatment occurred at Baseline, Month 1 (new sites only) and Months 3 and 6 as indicated (sites ≥ 5 mm). The primary efficacy variable was PD reduction from baseline at 9 months. The secondary variables were: 1) PD extent scores, 2) % bleeding on probing, 3) need for rescue therapy and 4) clinical response. Clinical assessments were at Baseline and Months 1, 3, 6, and 9. Safety was assessed through monitoring of adverse events, vital signs, CAL and examination of oral tissues.

Inclusion Criteria (Verbatim from Sponsor):

1. Patients must be adult males or females 30 years or older.

2. Patients must be able and willing to follow study procedures and instructions.

3. Patients must have read, understood and signed an informed consent form.

4. Patients must have generalized, moderate to advanced adult periodontitis - American Dental Association Class 3 or 4 - as determined by the investigator or designee during the screening periodontal examination.

5. Patients must present with at least 10 teeth in the functional dentition, excluding third molars.

6. Each patient must have at least four teeth with periodontal pocketing (PD = 6-9 mm) and BOP on all four qualifying teeth as determined by single-pass probing depth measurements in order to qualify for the study. In addition, all sites with PD ≥ 5 mm will be treated in the study.

Exclusion Criteria (Verbatim from Sponsor):

Patients will be excluded from the study for any of the following reasons:

1. Patients chronically treated (i.e., two weeks or more) with any medication known to affect periodontal status (e.g., phenytoin, calcium antagonists, cyclosporin, coumadin, and nonsteroidal anti-inflammatory drugs) within one month of the screening examination. Prophylactic use of aspirin (≤ 325 mg daily) for cardiovascular indications will be permitted in patients. All other medications for chronic medical conditions should be initiated at least one month prior to enrollment.

2. Patients who have received quadrant or maintenance S/RP, and/or periodontal surgical therapy within 6 months prior to enrollment.

3. Patients having clinically significant or unstable organic disease; patients having compromised healing potential such as those with diabetes (Type I) or connective tissue disorders; patients having heart murmurs, histories of rheumatic fever, valvular disease or prosthetic joint replacement necessitating antibiotic prophylaxis. Patients with type II diabetes (non-insulin-dependent diabetes) can be included if no

medication changes occurred during the 3 months prior to screening, as these patients are considered stable.

4. Female patients who are pregnant (as determined by a positive urine pregnancy test at baseline) or lactating, or female patients who are of childbearing potential and who are not using hormonal, barrier methods of birth control (e.g., oral or parenteral contraceptives, diaphragm plus spermicide, condoms), or abstinence. Patients who use hormonal contraceptives must have started the method not fewer than 30 days prior to the baseline examination.

5. Patients with documented allergies to tetracyclines.

6. Patients with active infectious diseases such as hepatitis, human immunodeficiency virus or tuberculosis.

7. Patients diagnosed with human immunodeficiency virus (HIV) or patients that are immunocompromised as determined by the investigator.

8. Patients taking steroid medications except for acute topical treatment.

9. Patients with severe, unrestored caries, or any condition that is likely to require antibiotic treatment during the trial.

10. Patients who have taken an investigational drug within 30 days of enrollment.

Reviewer Comment: The inclusion/exclusion criteria differed little from those for the pivotal efficacy trials (OPI-103A & 103B). The Sponsor did drop the requirement to exclude, "Patients who have been treated with antibiotics for medical or dental reasons within 3 months prior to enrollment." In addition, the time for which a patient must have been on a chronic medication before enrollment was dropped from two months to one month.

Demographic Characteristics:

The demographics for the Study, OPI-104 were as follows:

Table 9: Selected Demographics, Study OPI-104, ITT Population

Subgroup	ARESTIN (n=173)	Percent
Gender		
Males	92	53.2
Females	81	46.8
Age		
≤ 50 years	101	58.4
> 50 years	72	41.6
Race		
Caucasian	146	84.4
Black	15	8.7
Asian	5	2.9
Hispanic	7	4.0
Smoking Status		
Smokers	71	41.0
Non-smokers	102	59.0
Disease Severity		
Moderate	107	61.8
Advanced	66	38.2

Reviewer's Comment: The demographic distribution in Table 8 above reflects the distribution of periodontal disease in the population, with the exception of race. Blacks and Hispanics are known to have a higher prevalence of periodontal disease, yet the numbers of those racial groups in this study underrepresent the population.

The severity of periodontal disease at baseline was virtually the same as in studies OPI-103A and OPI-103B

Study Procedures:

Table 10: Schedule of Procedures by Visit, Studies OPI-104

	Visit 1 Screening [A]	Visit 2 Baseline [B]	Visit 3	Visit 4	Visit 5	Visit 6
Day	**-30 to -1**	**0**	**30 ± 5**	**90 ± 7**	**180 ± 10**	**270 ± 14**
Month	-1	0	1	3	6	9
Procedure:						
Informed consent	√					
Medical/periodontal history	√					
Examination of oral cavity	√	√	√	√	√	√
Vital signs	√	√	√	√	√	√
Urine pregnancy test (females)		√	√[C]	√	√	
Scaling and root planing		√	√[D]	√[D]	√[D]	
Clinical periodontal assessments		√[E]	√	√[F]	√[F]	√
Study treatment administration		√	√[C]	√	√	
Post-treatment instructions		√	√[C]	√	√	
Record adverse events		√	√	√	√	√
Record concurrent medications	√	√	√	√	√	√

[A] Screening and Baseline procedures may have been combined on the same day
[B] Baseline may consist of up to 3 visits: 2 visits to complete full mouth S/RP and an additional visit to apply study treatments if bleeding has not subsided within a reasonable amount of time after S/RP has been completed. Study treatments must be administered within 48 hours of completion of S/RP. The time at which study treatment was first administered was designated Day 1 of the study.
[C] Performed if new periodontal sites had been identified
[D] S/RP of new treatment sites
[E] Performed PRIOR to S/RP at Baseline.
[F] Performed PRIOR to re-treatment of the sites or PRIOR to treatment of new sites.

Efficacy Results:

As this was an open label study, it cannot be used as a pivotal study to support efficacy of the product. The mean pocket depth at baseline was 5.88 mm. The mean pocket depth was reduced, relative to baseline, at all time points, with the greatest reduction occurring at month nine. PD reductions were similar to those for the S/RP + ARESTIN in studies OPI-103A and OPI-103B.

Safety Results:

As noted above, adverse events for all three studies, OPI-103A, OPI-103B and OPI-104 will be reported together in the Integrated Summary of Safety.

Integrated Summary of Safety:

Patient Exposure:

For all three studies, OPI-103A, OPI-103B and OPI-104, 922 patients were randomized to treatment and assigned as follows:

Table 11: Patients randomized, Studies OPI-103A, OPI-103B and OPI-104

Study	Treatment Group (Total = 922)		
	S/RP + ARESTIN	S/RP + Vehicle	S/RP Alone
OPI-103A	121	123	124
OPI-103B	128	126	126
OPI-104	174	0	0
Total	423	249	250

Of the 922 patients who were enrolled in the combined studies, 397 patients were exposed to ARESTIN at 3 month intervals for at least nine months.

<u>Reviewer's Comment</u>: *The label will reflect the experience in the clinical studies. Because 397 patients received thee treatments at 3 month intervals and completed at least nine months of follow-up, the database should be adequate to assess the safety of this product.*

Deaths and Study Withdrawals Due to an Adverse Event:

Two deaths were reported among the patients in the three principal studies reviewed for this NDA (103A, 103B and 104). One patient died of carcinoma of the neck, lung and lower back. This death was not attributed to the study medication. The second patient died of an aneurism 190 days after completing the final dose of study treatment. This death was also not attributed to study medication.

Three patients withdrew from the three studies due to serious adverse events. Two were the patients mentioned in the previous paragraph who died. The other patient withdrew due to a myocardial infarction not related to treatment.

Serious Adverse Events:

Twenty-three of the 922 patients in studies OPI-103A and OPI-103B and OPI-104 experienced serious adverse events (SAE's). These were distributed evenly among treatment groups and showed no pattern that would be of concern.

Table 12: Serious Adverse Events, Studies OPI-103A, OPI-103B and OPI-104

	Treatment Group		
	ARESTIN n=423	Vehicle N=249	S/RP N=250
Number (%) of Patients with an SAE	12(2.8)	6 (2.4)	5 (2.0)
Body as a Whole	2 (0.50)	2 (0.8)	3 (1.2)
Pain	0	0	1 (0.4)
Accidental Injury	0	1 (0.4)	1 (0.4)
Henia	0	1 (0.4)	0
Viral Infection	0	0	1 (0.4)
Carcinoma	1 (0.25)	0	0
Lumber Disc Repair	1 (0.25)	0	0
Cardiovascular	1(0.25)	2 (0.8)	1 (0.4)
Angina	1(0.25)	0	0
Tachycardia	0	1 (0.4)	0
Embolus	0	0	1 (0.4)
Myocardial Infarction	0	1 (0.4)	0
Digestive	4 (0.1)	0	0
Appendicitis	1 (0.25)	0	0
Colitis	1 (0.25)	0	0
Cholecystitis	1 (0.25)	0	0
Pancreatitis	1 (0.25)	0	0
Renal	1 (0.25)	0	0
Elective Surgery	1 (0.25)	0	0
Respiratory	2 (0.5)	1 (0.4)	0
Asthma	1 (0.25)	1 (0.4)	0
Pneumonia	1 (0.25)	0	0
Urogenital	1 (0.25)	1 (0.4)	1 (0.4)
Urinary Incontinence	0	1 (0.4)	0
Prostatic Carcinoma	0	0	1 (0.4)
Uterine Disorder	1 (0.25)	0	0

All Adverse Events:

The adverse events reported here are for three multi-center trials conducted in the U.S. In addition to Studies 103A and 103B which are submitted to support both safety and efficacy, safety data from an ongoing open label study, 104 are included.

Table 13: Adverse Events Reported in ≥ 3%, Studies OPI-103A, OPI-103B and OPI-104

	S/RP Alone N=250	S/RP + Vehicle N=249	S/RP + ARESTIN N=423
Number (%) of Patients Treatment Emergent AE	62.4%	71.9%	68.1%
Total Number of AEs	543	589	987
Periodontitis	25.6%	28.1%	16.3%
Tooth Disorder	12.0%	13.7%	12.3%
Tooth Caries	9.2%	11.2%	9.9%
Dental Pain	8.8%	8.8%	9.9%
Gingivitis	7.2%	8.8%	9.2%
Headache	7.2%	11.6%	9.0%
Infection	8.0%	9.6%	7.6%
Stomatitis	8.4%	6.8%	6.4%
Mouth Ulceration	1.6%	3.2%	5.0%
Flu Syndrome	3.2%	6.4%	5.0%
Pharyngitis	3.2%	1.6%	4.3%
Pain	4.0%	1.2%	4.3%
Dyspepsia	2.0%	0	4.0%
Infection Dental	4.0%	3.6%	3.8%
Mucous Membrane Disorder	2.4%	0.8%	3.3%

There were no clinically significant changes in vital signs attributed to study medication during either study.

Microbiological evaluations were conducted to address the question of whether ARESTIN promoted the development of minocycline resistant organisms. The conclusion is that it did not. See Microbiology review for a full discussion.

An additional parameter that was measured and that supports the safety of the product is clinical attachment level (CAL). The pocket depth (PD) is affected by the point where the periodontal apparatus attaches to the root of the tooth and by degree of edema in the soft tissue (free gingiva). It is conceivable that a product could reduce inflammation in the free ginigva, reducing pocket depth, while simultaneously causing a worsening of the periodontal attachment level. If the reduction in edema was greater that the worsening in attachment level, pocket depth would still be improved. Loss of attachment level would be a safety concern and for that reason this parameter was monitored in this study as it had been in the clinical studies supporting approval of PerioChip, which also used PD as the primary endpoint. Attachment level did not worsen during these studies of ARESTIN, supporting the safety of the product.

<u>Reviewer's Comment</u>: *As was discussed in the section on the primary efficacy endpoint, the Sponsor was given the option of using either PD or CAL as the primary endpoint. CAL is considered the "higher hurdle," and is generally regarded as a better surrogate for periodontal disease. The Division has approved the indication of "treatment of periodontitis" for products that have used CAL as the primary endpoint. Because the*

Division has also previously approved the indication, "reduction in pocket depth in patients with periodontitis," that endpoint is permitted, but the Sponsor was told that if the "lower hurdle" of PD was chosen, the "higher hurdle" of CAL could not be a secondary endpoint. The Division felt that it would not be fair to sponsors who had demonstrated that their product met the higher hurdle to have competitors get on the market by meeting a lower efficacy standard and then be able to make claims regarding CAL in promotion and advertising. It should be noted that, by the Sponsor's own analysis, the pairwise comparisons between ARESTIN + S/RP and S/RP alone were not statistically significant in one of the two pivotal studies and the product would not have been approved had CAL been the primary endpoint. The draft labeling submitted with the NDA included a table with CAL measurements from the combined studies, which has been deleted in the labeling review.

The sponsor reported only two patients on the test product experienced tooth staining.

Reviewer's Comment: *It is unclear why the Sponsor included the information about tooth staining. Staining is a concern with chlorhexidine products and a comment about staining was included in the label of PerioChip, which the Sponsor may have used as an example. Since we don't expect to see staining with this product and in fact saw no significant differences among groups, it seems superfluous and confusing to include in the label.*

Discussion:

The Sponsor has conducted two well controlled (n=499) and one open label study (n=423) in support of approval of their product as an adjunct to scaling and root planning for the reduction of pocket depth in patients with adult periodontitis. The data presented support approval. The Sponsor has demonstrated a statistically significant difference in pocket depth reduction in the S/RP + ARESTIN group over the S/RP Alone group at 9 months. There was also a statistically significant difference in the percentage of pockets that were reduced ≥ 2 mm. in the S/RP + ARESTIN group over the S/RP Alone group at 9 months. Additional secondary endpoints were supportive, though did not achieve statistical significance.

The safety profile of this product appears benign. There were two deaths and 23 serious adverse events during the studies, none of which seem to be attributable to the study medication. In general the frequency and types of adverse events were reported by similar numbers of patients across the three treatment groups.

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2. Slots J, Rams TE. 1990. Antibiotics in periodontal therapy: advantages and disadvantages. J Clin Periodontol 17: 479-493.

Financial Disclosure:

The Sponsor has provided the required certification (Form FDA 3454) regarding financial interests and arrangements of clinical investigators. The Sponsor has certified that the value of compensation to the investigator was not influenced by the outcome of the study. One investigator has received a $1000/ month consulting retainer since Februray 1997. Four other investigators had stock or stock options in OraPharma valued at over $100,000 each, based on the stock price at the time of this review. The Biostatistics reviewer was asked to re-evaluate those sites to determine if there was anything unusual about the reported results and to assess the impact of those sites on the overall studies. In one instance, ———— the mean baseline pocket depth for the active arm was the highest among all sites in the study and the mean baseline pocket depth for the S/RP arm was the lowest among all sites. Since we know that the deeper the pocket at baseline, the better the response is expected to be, the situation described would likely favor the active arm. In fact, the delta between the active and S/RP arms at that site was the second highest among all sites in that study. If that site is dropped from the analysis, the p-value for the comparison goes from .047 to .237. This site did enroll a large number subjects, so dropping it would be expected to have some effect on the p-value, but it seems unlikely that the change would be so dramatic based on the number of subjects alone. Based on the unusual nature of the data and the fact that the investigator received substantial compensation, the Division has asked the Division of Scientific Investigations (DSI) to audit the site prior to making a final decision about the approvability of this NDA.

Pediatric Waiver:

Adult periodontitis, as its name indicates, affects only adults, so no studies in children are indicated.

Recommendation:

NDA 50-781 for ARESTIN™ (minocycline hydrochloride), Microspheres, 1 mg is approvable with the labeling changes recommended above, contingent upon the DSI audit of the ———— site not resulting in the disqualification of the data from that site.

/S/ D.D.S 12-18-00
Clarence C. Gilkes, D.D.S.

fn DFS 12/18/00

Original to NDA 50-781