

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-751

MEDICAL REVIEW(S)



combination of (1) and (2).

Periodontitis usually develops as a sequel to persistent chronic gingivitis and has an identical etiology. Inflammation and bacterial products spread from the gingiva to the alveolar process along the neurovascular bundle of the interdental canal at the crest of the septum. Inflammation spreads along the course of the vascular channels because the loose connective tissue surrounding the neurovascular bundles offers less resistance than the dense fibers of the periodontal ligament. Extension of the chronic inflammatory process into the

alveolar bone is marked by infiltration of the marrow by leukocytes, new blood vessels, and proliferating fibroblasts. There is marked osteoclastic activity.

The most common treatment for periodontal disease is subgingival debridement combined with scaling and root planing 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 would 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 scaling and root planing (SRP) and as stand-alone products in the treatment of periodontitis. Systemic antimicrobials have shown some benefit in treating periodontitis, especially in patients with early-onset forms of the disease, or those unresponsive to standard treatment, though there are no systemic antibiotics currently approved for periodontal indications in the United States. 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. The sponsor of this NDA has studied ATRIDOX™, 10% doxycycline (8.5% w/w) in a bioabsorbable polymer as a stand-alone therapy in the treatment of chronic adult periodontitis.

Background and Regulatory History

Doxycycline is a broad-spectrum antibiotic synthetically derived from oxytetracycline and available as doxycycline hyclate. It has been marketed throughout the World for many years.

for treatment of infections caused by susceptible microorganisms. Doxycycline is known to be active against a variety of periodontal pathogens including Bacteroides and Actinomyces species. The safety profile of the product when taken systemically is well known. Atrix Laboratories, Inc. believed that doxycycline delivered directly to the periodontal pocket via a controlled-release formulation would be useful in treating adult periodontal disease and opened IND for the purpose of investigating the safety and efficacy of ATRIDOX™ (doxycycline hyclate in the Atrigel® delivery system).

To date, the Agency has approved or given "approvable" status to two 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 received an approvable letter on November 25, 1997, "as an adjunct to scaling and root planing procedures for reduction of pocket depth in patients with adult periodontitis."

Atrix Laboratories has received approval/clearance for, or is currently developing several related products. ATRISORB® GTR Barrier is a guided tissue regeneration (GTR) barrier that has been cleared for marketing by the Center for Devices and Radiological Health [510(k): K955838] and utilizes a resorbable polymer similar to that used in ATRIDOX™. GTR barriers are used in the surgical treatment of advanced periodontal disease. The barrier isolates the healing bone and periodontal ligament, giving these slower-growing cells an opportunity to regenerate. Atrix is developing ATRISORB® GTR Barrier with doxycycline added, as well as one with growth factors added. Atrix also has a license agreement with for a product which is identical to the subject of this NDA, for treating periodontal disease in companion animals. New Animal Drug Application (NADA) 141-082 was approved on November 11, 1997 for use of this product for the treatment and control of periodontal disease in dogs.

An End-of-Phase 2 meeting was held on February 18, 1994 between the sponsor and HFD-160, the Division where dental products were reviewed at that time. There was discussion about the need for an oral hygiene arm as a negative control and an SRP arm as a positive control. SRP is standard therapy for moderate to severe periodontal disease. Also discussed were appropriate endpoints, blinding and the criteria for stratifying by baseline pocket depth.

A teleconference between FDA and the sponsor was held on November 23, 1994 at which time various issues of study design were discussed. These included agreement on what would be considered clinically significant improvements in the efficacy parameters, and agreement on study length.

A teleconference was held with the sponsor on March 15, 1996. The principal topic of discussion was the labeling and intended use of the product - the sponsor was seeking to use the product in a different way than it was used in the pivotal trials. In the pivotal trials, the

product was retained by Coe-Pak™ periodontal dressing and was removed after seven days. The sponsor was proposing to label the product to be left in the pocket until it is bioabsorbed or is expelled by brushing and flossing. Also Octyldent™, a dental adhesive, was to be used for retention, rather than the Coe-Pak™. During t-cons held on 3/15/96, 3/29/96, and 7/18/96 the Division agreed that the sponsor could receive approval for the requested indication based on results of a single trial of nine months duration if the pivotal studies using Coe-Pak™ supported approval. Details of the agreements are include in the review of Study AGD 9603 on p. 32 of this document. Octyldent™ has been cleared for marketing as a medical device under the 510(k) mechanism (K884652).

A pre-NDA meeting was held on January 7, 1997. A number of content and format issues were discussed. In addition, there was discussion about the timing of the submission of the study results of AGD 9603, the bridging study using the Octyldent™ adhesive and leaving the material in the pocket to biodegrade or be expelled naturally. This NDA submission was received on April 7, 1997 and accepted for filing on May 6, 1997. The User Fee date is April 7, 1998.

On 12/31/98 the sponsor submitted an amendment to the NDA which included the results of the bridging study (AGD 9603) using the Octyldent™ adhesive and leaving the material in the pocket to biodegrade or be expelled naturally. Also included were the results of three bioequivalence studies. Study AGD 9607 compared the levels of doxycycline in gingival crevicular fluid (GCF) when the product was mixed using different methods. This was done to support a change in labeling to use a mixing method different than the one used in the pivotal trials. Study AGD 9701 looked at use of the product without a retention method. Finally, AGD 9705 assessed drug availability from product near its expiration date. This study was conducted to support proposed product release specifications.

Executive Summary

The sponsor of this NDA has studied ATRIDOX™, 10% doxycycline (8.5% w/w) in a bioabsorbable polymer as a stand-alone therapy in the treatment of chronic adult periodontitis. The sponsor conducted a total of 11 clinical trials involving 1827 subjects in support of this application. The subjects studied in the three pivotal clinical trials ranged in age from had chronic adult periodontal disease defined as moderate to severe disease characterized by at least two quadrants of the mouth, each containing at least four pockets which measured 5mm or greater and bled on gentle probing. Subjects also could not have substantial calculus, defined as no more than 20% of the tooth surfaces having detectable calculus. Subjects were stratified into three groups at baseline by pocket depth. The primary endpoint was gain in attachment level and the secondary endpoints were reduction in probing pocket depth and reduction in bleeding on probing. The studies were nine months in duration.

Change in Use of the Product

A shortcoming in the development of this product was the fact that the sponsor decided to label the product for use in a different way than it had been used in the pivotal clinical trials. In the original studies (ACS-34 & ACS-35), ATRIDOX™ was covered by Coe-Pak™ periodontal dressing and product and dressing were removed after seven days. The sponsor then decided that they would prefer to label the product to be left in the pocket until it biodegraded or was expelled by brushing and flossing. Also Octyldent™, a dental adhesive, was to be used for retention, rather than the Coe-Pak™, because the Octyldent™ could be brushed and flossed off, thereby obviating the need for a return visit to the dentist. The Division viewed this as similar to a "line extension" and agreed that the sponsor could receive approval for that indication based on results of a single three arm trial of nine months duration, if the pivotal studies using Coe-Pak™ (which at that time had not been completed), supported approval. This would be a three arm trial as follows: 1) ATRIDOX™ with Coe-Pak™ removed after 7 days as in the pivotal trails, 2) ATRIDOX™ with Octyldent™ left to biodegrade as in the proposed labeling, 3) Vehicle control with Octyldent™ left to biodegrade as in the proposed labeling. The primary efficacy endpoint was change in attachment level at nine months. Secondary efficacy endpoints were change in pocket depth (PPD) and Bleeding on Probing (BOP). In order to "win," the Octyldent™ arm had to be equivalent to the Coe-Pak™ arm and both had to be superior to vehicle. The study, AGD 9603, successfully demonstrated that the two methods were equivalent.

The sponsor then decided that it would be desirable to use the product without retention, and the Division agreed to a bioequivalence study comparing the doxycycline concentration in the gingival crevicular fluid (GCF) using ATRIDOX™ when retained with Octyldent™ and ATRIDOX™ when no retentive material is used. A third arm, vehicle retained with Octyldent™, was also included.

Efficacy

The sponsor conducted three trials which are considered pivotal - one of these was the bridging study to the new method of retention and leaving the product in the pocket to biodegrade or be expelled naturally.

The conclusion of this review is that the sponsor met all the decision rules with respect to the primary efficacy variable, attachment level. The attachment level gains reported for ATRIDOX™ in the three pivotal trials were between .68 and .86 mm. at nine months for the Intent-to-Treat (ITT) population. This was comparable to the gains achieved by SRP in these studies. The results with respect to the secondary endpoints, though lesser in magnitude, demonstrated that the product is also efficacious in reducing pocket depths and bleeding on probing.

Subset analysis concluded that sex, age, race and smoking status did not appear to be correlated with either efficacy of this product or associated adverse events.

Safety

In all of the clinical trials, a total of 919 subjects received doxycycline, 472 vehicle, 226 oral hygiene and 210 SRP.

The ATRIDOX™ and vehicle groups had statistically significantly higher rates of adverse events in the digestive, endocrine, nutritional, metabolic, genitourinary, mental, musculoskeletal, and respiratory systems, and among ill-defined conditions. It seems unlikely that topically applied doxycycline or vehicle would have such broad ranging systemic effects, and it must be remembered that the subjects were not blinded to treatment.

In the Circulatory System category 16 subjects in the ATRIDOX™ group were reported as having an adverse event coded as, "unspecified essential hypertension." The difference between the ATRIDOX™ group and the other groups was statistically highly significant. The sponsor was queried about this finding and said that they had no reason to believe that there was any association between essential hypertension and the topical use of doxycycline. They believe that these results were a chance occurrence.

One concern that was raised by leaving the product in the pocket to bioabsorb or be expelled naturally was that there would be adverse events associated with prolonged retention of the product. In reviewing adverse events, most were observed in the first 8 days following placement of the product, rather than farther in time from placement of the product. This result suggests that leaving the product in the pocket does not result in a disproportionate number of adverse events.

Another concern that was raised by FDA was the possibility that the presence of doxycycline in the periodontal pocket might result in tooth sensitivity due to the fact that the hyclate salt of doxycycline has a low pH. To address this question, the sponsor added a question regarding tooth sensitivity in the bridging study (AGD 9603). While it cannot be ruled out that the vehicle causes increased sensitivity, the doxycycline does not appear to increase tooth sensitivity.

Two subjects treated with vehicle experienced an apparent localized allergic response. This is a 0.14% incidence of occurrence of allergic response to this product. Three subjects reported an adverse taste associated with the doxycycline hyclate product; this constituted 1.4% of the study subjects.

Sex, age, race and smoking status did not appear to be correlated with adverse events.

Labeling

Chemistry and Manufacturing Controls (CMC) Summary

The initial CMC review of this submission identified deficiencies in Manufacturing and Packaging, Drug Product Specifications and Methods, Stability and Microbiology. The sponsor was provided with a list of deficiencies, and satisfactorily addressed all of them except one involving the release specification for constituted product. The sponsor had proposed a specification. The Chemistry reviewer found this unacceptable and suggested a specification with a range of %. The sponsor countered with a suggestion that the range for the specification should be %. The Division found this unacceptable and suggested that the sponsor consider a different closure system that would better prevent moisture from contacting the product since that is the cause of degradation of the product. Ultimately, the sponsor accepted the % specification and the NDA was

given an approval by Chemistry. See the Chemistry reviews.

The initial review by the Microbiology Staff of the Office of New Drug Chemistry (ONDC) found the submission deficient in two specifics. Before the product could be approved, it was required that microbial limits should be established as part of the product specification that comply with the USP standard for topical, non-sterile drug products. In addition, preservative effectiveness testing (PET) should be part of the stability program. The sponsor agreed to these requirements. See the ONDC Chemistry review.

The CDER Labeling and Nomenclature Committee recommended that the two syringes be labeled as to their contents ("450 mg. of Atrigel® Delivery System" and "50 mg. of doxycycline hyclate"), but that the name ATRIDOX™ should not appear on the individual syringes. This was intended to prevent possible confusion that either syringe alone constituted the entire product. The sponsor has labeled the syringes "Syringe A - 450 mg. of Atrigel® Delivery System," and "Syringe B - 50 mg. of doxycycline hyclate," but has included the name ATRIDOX™ on each syringe.

Reviewer's Comment: In this reviewer's opinion the drug name should be on each syringe as there are many products in syringe delivery systems in use in dental offices and if the product name is not on the syringe it could be confused with an entirely different product system.

Pharmacology/Toxicology Summary

See the Pharmacology review for this NDA for a detailed discussion of the pharmacodynamics and toxicology of ATRIDOX™. The following evaluation is taken verbatim from the pharmacology review written by Dr. Norman See. "Although ATRIDOX™ may be used more than once in a given individual (at four month intervals), use of the ATRIDOX™ product would entail very low-level exposure to the drug substance for only 7 to 10 days per treatment episode, with an estimated lifetime exposure to doxycycline as a result of use of 21 to 30 days. The product is not indicated for chronic use. Studies in which either ATRIDOX™ or the vehicle in ATRIDOX™ was administered on a single occasion into either a periodontal pocket of a dog or into the subcutis of a rabbit demonstrated that the test materials did not cause excessive toxicity (including local irritation or inflammation). In view of the database accumulated during 30 years of human use of doxycycline and the low level of exposure proposed (2mg/kg/dose or less of doxycycline in a 50kg individual, followed by a 4 month wash-out period), the existing nonclinical data are adequate to support the safety of NDA 50-751." He goes on to say that NDA 50-751 is approvable in regard to pharmacologic and toxicologic concerns and recommends changes in the product label. See Dr. See's review for the specific changes that are recommended.

Pharmacokinetic Summary

See the Biopharmaceutics review for this NDA for a discussion of the Pharmacokinetics of

ATRIDOX™

Microbiology Summary

A single study was conducted to evaluate the effects of treatment with this product on the development of resistant bacteria. The study also sought to observe the effect of doxycycline on normal microbiota, periodontal pathogens and possible overgrowth of opportunistic organisms. The Microbiology reviewer concluded that, "The use of doxycycline hyclate in the manner and dose proposed while having the potential to bring about populations of bacteria resistant to doxycycline, other tetracyclines, as well as other antimicrobials and to cause alterations in the microflora of the gastrointestinal tract would appear to present no more of a potential health threat than the use of tetracyclines used at the recommended doses for the treatment of bacterial infections." See the Clinical Microbiology review for this NDA.

Clinical Trials

The first part of this section of the review contains a summary of phase 2 studies and a non-pivotal phase 3 study, as well as two bioequivalence studies. The second part contains a detailed discussion of the pivotal trials, ACS-34 and ACS-35. That is followed by discussion of Study AGD 9603, which is also considered pivotal. This is the study that was conducted to permit a change in the retention method and to leave the product in the pocket to bioabsorb or be expelled.

Summary of Non-Pivotal Phase 2 and Phase 3 studies**Clinical Pharmacology (Study ACS-32)**

This was a Phase 2, two-center, open label, randomized, parallel design, feasibility study. The primary purpose of the study was to determine whether the levels of doxycycline released in the GCF of subjects were comparable across the various retentive methods proposed. Safety was also assessed. The study included 40 subjects, age with chronic adult periodontitis. All subjects received the two-phase, to-be-marketed active drug product: ATRIDOX™ Atrigel® Delivery System with 10% doxycycline hyclate, equivalent to 8.5% w/w doxycycline). Twelve subjects were assigned to each of the following three treatment groups:

1. ATRIDOX™ retained with Coe-Pak™
2. ATRIDOX™ retained with Octyldent™
3. ATRIDOX™ with no retentive material

The study duration for the treatment groups was 28 days. The Coe-Pak™ was removed at day 7 and the remaining Octyldent™ and any product remaining at day 28 were removed. Four additional subjects were enrolled to provide training for investigators in GCF sampling

procedures. The duration of their portion of the study was 6 hours. Pharmacokinetics was evaluated by doxycycline release into GCF. Retention was assessed visually. Safety was evaluated by periodontal exams at days 0 and 28 which included measurement of probing depths and assessment of bleeding on probing. Adverse event reports were also collected.

Considerable variation in doxycycline concentration in the GCF was observed at the time points where the concentration was greatest. The sponsor reported that mean levels for doxycycline were above the MIC of periodontal pathogens at day 7, though not at days 14 and 28. No significant difference was observed in retention of product between Coe-Pak™ and Octyldent™ adhesive groups. No polymer had been lost at Hour 2, however, one subject in the no retentive material group had lost polymer by Hour 4. No subjects in the Coe-Pak™ and Octyldent™ groups lost polymer until Day 3, when one subject in the Octyldent™ group lost polymer. By Day 7, two subjects each in the Coe-Pak™ and Octyldent™ groups and six subjects in the no retention group had lost polymer in at least one of the two sites. Though not powered to show statistical significance, the sponsor reported that pocket depths and bleeding probing scores were reduced in all three treatment groups during the 28 day study. No serious adverse events were reported. The sponsor concluded that though there was variability in the retention of the product between the retention and no retention groups, the data on concentration of doxycycline in the GCF support the use of any of the three methods. The sponsor interpreted the safety data to support the fact that there is no additional risk incurred by leaving the product in the pocket for 28 days.

Clinical Pharmacology (Study ACS-38)

This was a Phase 2, single-center, single-blind, randomized, parallel group pharmacokinetic study. Thirty-two subjects, age 25-75, with chronic adult periodontitis were enrolled. The primary objective of this study per the sponsor was to characterize the release profile of doxycycline in GCF, saliva and serum. Secondary objectives were: 1) comparison of doxycycline release between subjects receiving active but using the two different retention materials, 2) comparison with doxycycline administered orally at an approved dosage, 3) comparison of doxycycline in GCF, serum and saliva respectively between the approved oral dosage and the to-be-marketed formulation, 4) comparison of data between treated and untreated sites, 5) determination of the approximate amount of doxycycline delivered from the drug product, 6) comparison of doxycycline levels in GCF, saliva and serum within each treatment group.

The treatments were assigned as follows:

1. ATRIDOX™ retained with Coe-Pak™ - Coe-Pak™ and the drug product removed at Day 7
2. ATRIDOX™ retained with Octyldent™ - any remaining Octyldent™ and drug product removed at Month 3
3. Vibramycin® Hyclate, 100 mg PO, at hours 0 and 12, then daily through Day 8

Samples of GCF, saliva and serum were evaluated for doxycycline concentration using For each subject C_{max} , T_{max} , and AUC for each body fluid were calculated. Safety was assessed by collecting adverse event reports and through clinical measurement of attachment levels, probing depth and bleeding on probing. Measurements were taken at baseline and day 7 for the Coe-Pak™ group, baseline and month 3 for the Octyldent™ group and baseline and day 8 for the Vibramycin® group.

Following treatment with ATRIDOX™ doxycycline levels in GCF peaked at two hours in both the Coe-Pak™ (mean value = 1500 $\mu\text{g}/\text{ml}$) and Octyldent™ (mean value = 2000 $\mu\text{g}/\text{ml}$) groups. By Day 7 the doxycycline levels were 317 $\mu\text{g}/\text{ml}$ and 148 $\mu\text{g}/\text{ml}$ in the Coe-Pak and Octyldent groups respectively. In contrast the GCF levels for the orally administered doxycycline peaked at 2.5 $\mu\text{g}/\text{ml}$ at 12 hours following the initial oral dose.

In saliva, mean levels of doxycycline also peaked at 2 hours at 4 $\mu\text{g}/\text{ml}$ for Coe-Pak™ and 9 $\mu\text{g}/\text{ml}$ for Octyldent™. Minimal doxycycline (0.12 $\mu\text{g}/\text{ml}$) was detected in saliva of the oral doxycycline group at Hour 18 and Day 1.

In serum, low levels were detectable in both groups receiving the ATRIDOX™. Mean levels of approximately 0.1 $\mu\text{g}/\text{ml}$ were detected 2 to 8 hours post application. After Day 2, serum levels dropped below the limit of detection (.04 $\mu\text{g}/\text{ml}$). In contrast, the subjects receiving oral doxycycline had levels ranging from $\mu\text{g}/\text{ml}$ over the eight days of oral doxycycline administration. The results of this study support the sponsor's assertion that a single treatment using ATRIDOX™ provides high local levels of doxycycline at 7 days with less systemic exposure than that observed following an 8 day regimen of oral doxycycline.

Though the study was not powered to detect statistically significant differences among treatment groups and there was no control group, the sponsor reported that all three groups showed reductions in both probing depths and bleeding on probing at the final clinical visit as compared to baseline. The sponsor reported that the clinical results were comparable between the Coe-Pak™ and Octyldent™ treatment groups and supported not removing the product, but rather allowing it to biodegrade and be expelled. No remaining product was noted at Month 3. There were three adverse events that the investigator considered to be treatment related. All consisted of mild discomfort after product placement and resolved within a day after placement.

Efficacy/Safety (STUDY ACS-28)

This was a nine month, Phase 2, multicenter, parallel group, randomized, modified double-blind trial. The investigators who administered the treatment were unblinded because the treatments were dissimilar. A total of 180 subjects years old with chronic adult periodontitis were enrolled at five sites. Subjects received one of the following treatments:

1. Atrigel® Delivery System with 5% (w/w) sanguinarine chloride (SaCl)

2. Atrigel® Delivery System with 10% (w/w) doxycycline hyclate (ATRIDOX™)
3. Vehicle Control (Atrigel® Delivery System without drug)

Sanguinarine chloride was a new drug substance being investigated by the sponsor. For all groups, test articles were applied at baseline and four months as in the pivotal trials, the Coe-Pak™ dressing was used and treatment duration was 7 days. The doxycycline product was the uniphase form.

Reviewer's Comment: Early in the development of this product a single-phase dosage form was used. It was found that mixing the doxycycline with the polymer resulted in degradation of the doxycycline over time so a two syringe system was introduced and is the to-be-marketed product. It has exactly the same composition as the uniphase system, but the doxycycline and the polymer are in separate syringes which are joined and the product is mixed at the time of use.

The objective of this study was to compare the safety, tolerability and efficacy of the three treatments in patients with moderate to severe periodontitis. The primary clinical efficacy endpoint was attachment level gain, with probing depth reduction and reduction in bleeding on probing as secondary efficacy endpoints. These endpoints were the same as in the pivotal studies. The statistical methodology used to analyze the endpoints was also the same as in the pivotal trials. The active product, VR-303-ABS (ATRIDOX™), was statistically significantly superior to vehicle with respect to both attachment level gain and probing depth reduction at Months 4, 6 and 9 (See Table 1).

Table 1: Clinical Results (ACS-28)

Parameter	Treatment Arm	N	Baseline Mean	Mean Change from Baseline		
				Month 4	Month 6	Month 9
Attachment Level Gain (mm.)	VR-303-ABS (ATRIDOX™)	56	5.3	0.9* p=.035	1.2* p=.014	1.0* p=.029
	Vehicle Control	53	5.6	0.6	0.8	0.6
	SaCl	54	5.5	0.8	0.8	0.6
Probing Depth Reduction (mm.)	VR-303-ABS (ATRIDOX™)	56	6.0	1.5* p<.001	1.9* p<.001	1.8* p<.001
	Vehicle Control	53	6.0	1.0	1.2	1.2
	SaCl	54	6.0	1.2	1.2	1.1

The safety data showed that most of the common adverse events were associated with the mouth. One subject had an ulceration of the lower lip that was believed to be treatment

related. It was thought to have resulted from the doxycycline leaking onto the lip, possibly in an area that had been mechanically traumatized. Because there were no control arms, it was impossible to draw conclusions about the relative risk of using the product. However, the adverse events were generally mild and did not result in discontinuation of study subjects.

Microbiology (STUDY ACS-33)

This was an antimicrobial resistance study that looked at possible overgrowth of doxycycline-resistant organisms and opportunistic and putative periodontal pathogens following administration of the product. This study showed that there was no significant increase in doxycycline-resistant organisms in subgingival plaque and only a transient increase in saliva. No resistance to putative periodontal pathogens was observed. See the Clinical Microbiology review for details of this study.

Training (STUDY ACS-30)

This was a 28 day open-label training program for the Phase 3 trials. All of the 103 patients who were enrolled (17 centers) received ATRIDOX™. The product was removed at 7 days post-treatment. Because the recording of standardized measurements of safety and efficacy was part of the program, efficacy variables were analyzed, but the analysis was limited to descriptive statistics. The mean changes in attachment level and pocket depth were consistent with the other studies reported for this product. There were no serious adverse events reported from this study.

Product Mixing Technique (Study AGD 9607)

This bioequivalence study was conducted to support a change in the way the product is mixed prior to placement. The to-be-marketed product is provided in two syringes, one of which contains the doxycycline powder and the other the polymer vehicle. The two syringes are joined and the contents are then pushed from one syringe to the other until thoroughly mixed. In the pivotal studies (ACS-34 & ACS-35) the product was mixed using 100 mixing cycles, followed by a 15 minute wait and then an additional 10 mixing cycles. In this study the product was mixed using only 100 mixing cycles and then used immediately. Octyident™ was used for retention in both cases. The sponsor had conducted an in vitro comparison of the two mixing methods and had shown them to be equivalent. AGD 9607 was conducted to confirm that the concentration of doxycycline in vivo, in the GCF is equivalent using either of the mixing methods.

This was a single-center, single-blind, parallel design, Phase 3 bioequivalence study comparing the drug release characteristics of ATRIDOX™ using the two mixing regimens. Twenty-five subjects ages with chronic adult periodontitis were randomly assigned to two groups. The objective of the study was to characterize the release profile of doxycycline in GCF in subjects with chronic adult periodontitis. The study duration was seven days and

all product was removed at the conclusion of the study.

The Biopharmaceutics review concluded that the extreme variability of the data from this study precluded a showing of bioequivalence. Inspection of individual data showed high day to day variability which may be due to the sampling strip coming into contact with retained product. See Dr. Wang's Biopharmaceutics review for discussion of this issue.

There was one treatment related adverse event of note in this study. One subject reported "superficial soft tissue necrosis" that resolved after five days and did not result in withdrawal from the study.

Shelf Life (Study AGD 9705)

This single center, open label study was designed to determine whether levels of doxycycline in GCF with product approaching the end of its proposed shelf-life are comparable to levels in product used in a previous pharmacokinetic study (ACS-38). The sponsor undertook this study because the product was experiencing degradation during storage.

This study assessing the release characteristics of the product at a point near the end of its shelf life was conducted in twelve subjects age with chronic adult periodontitis. Product was retained with Octyldent™, the study duration was seven days and the drug product was removed at the end of the study period. The GCF samples collected were evaluated using and C_{max} , T_{max} , and AUC were calculated for each subject. Adverse events were collected by observing and interviewing the subjects.

The results of this study were also highly variable and therefore of little regulatory utility. Ultimately the FDA agreed on a range of release specifications for the product which are discussed in the Chemistry review. See Dr. Wang's Biopharmaceutics review.

Reviewer's Comment: The sponsor's Phase 2 studies addressed the question of microbial overgrowth, collected adverse event data and established that the product was likely to be efficacious at the concentration studied for the endpoints of attachment level gain, probing depth reduction and bleeding on probing. In retrospect, it would have been simpler for the sponsor to have conducted the pivotal studies using the mixing and retention methods ultimately sought.

SUMMARY OF PIVOTAL STUDIES

Studies ACS-34 & 35 were submitted as pivotal. Because the protocols for ACS-34 and ACS-35 were identical, they will be reviewed together. Results will be identified by trial number. AGD9603 was conducted to show equivalence between the two methods of retention and use, and the results will be reflected in the labeling, so it is also pivotal. AGD9603 will be reviewed separately and the Discussion Section of this review will address the conclusions

from all of the trials. Safety data from all of the trials will be presented together and the question of the safety of leaving the product in the pocket to biodegrade or be expelled naturally will be discussed at that point.

STUDIES ACS-34 and ACS-35

These were 4-arm, randomized, controlled, parallel group, single-blind trials which enrolled patients between _____ years of age with chronic adult periodontitis. A total of 833 subjects were enrolled at 22 centers. The four arms were as follows:

1. ATRIDOX™ (VR-303-ABS) retained with Coe-Pak™
2. Vehicle (VR-303-P) retained with Coe-Pak™
3. SRP (Positive Control)
4. Oral Hygiene (Negative Control)

The sponsor states that the primary objective for ACS-34 and ACS-35 was to compare ATRIDOX™ drug product to vehicle control and oral hygiene (OH) with respect to periodontal attachment level (PAL) gain. The primary efficacy endpoint was change in attachment level at nine months. Secondary efficacy objectives were to compare active treatment to vehicle and oral hygiene (OH) with respect to reduction in periodontal probing depth (PPD) and bleeding on probing (BOP). Safety data was also collected in these trials. An additional objective that the sponsor refers to as secondary was to compare active to scaling and root planing (SRP) with respect to PAL, PPD and BOP.

Reviewer Comment: It is the policy of the Division to require that, for a "stand-alone" indication for treatment of periodontitis, the product must not only be statistically significantly superior to both vehicle and oral hygiene (negative control) with respect to attachment level gain, but also 75% as good as SRP (positive control). In this application the sponsor refers to the comparisons with SRP as an "additional objective," when in fact showing that the product is 75% as good as SRP was required for a win on the endpoints. The issue is moot because the sponsor achieved the 75% of SRP requirement.

Inclusion Criteria:

1. Subject signed the informed consent agreement. If the subject required someone to read and/or interpret any or all of the informed consent, a statement of this fact was included.
2. Subject had chronic adult periodontitis as characterized by at least two quadrants of the mouth, each containing at least four pockets that measured 5 mm or greater and bled on gentle probing. Two of the qualifying sites had probing depths of 7 mm or greater. If two 7 mm sites did not exist within the selected side of the mouth (one side of the mouth was selected for treatment), they were present at other locations distributed around the dentition.

Periodontal pockets in which the depth of the pocket corresponded to the apex of the tooth, as in a possible endodontic/periodontic condition, were not treated or evaluated. Implants were not treated.

3. Subject was 25 - 75 years of age and in good general health according to a medical history, blood pressure and pulse rate, and clinical judgement.
4. Subject was able to follow written and verbal instructions, perform oral hygiene according to the protocol, and return to the center for specified study visits.
5. Subject met the blocking requirements for the enrolling center.

Exclusion Criteria:

1. Subject who had never had scaling instrumentation. (Subject with negative history of dental treatment may not be compliant.)
2. Subject who received scaling and root planing therapy less than two months prior to the Baseline examination. (Clinical conditions at the sites may not have stabilized following the last SRP.)
3. Subject with substantial accumulation of subgingival calculus defined as 80% or greater surfaces of the dentition having detectable calculus. (May alter ability to measure clinical parameters.)
4. Subject with a compromised heart condition requiring subacute bacterial endocarditis (SBE) prophylaxis. (Prophylactic antibiotics could possibly affect clinical efficacy.)
5. Subject having taken systemic cancer therapy and/or radiation at any time. (Unknown effect on clinical parameters. Unknown if a subject's disease state is stable.)
6. Subject with compromised renal function. (May be systemically compromised to the point that the subject cannot meet appointment criteria or clinical responses may be affected.)
7. Subject with a history of rheumatic fever. (Subject may require prophylactic antibiotic treatment which could possibly affect clinical efficacy.)
8. Subject with clinically significant acute or concurrent illness such as hepatitis. (Subject may be immunocompromised or systemically compromised to level that clinical outcomes are affected.)
9. Subject with clinically significant chronic illness such as cardiovascular disease, diabetes, cancer, HIV positive, etc. (Subject with severe medical complications may not be able to meet study appointments, may be immunocompromised and at greater risk to develop future illness.)
10. Subject with disease of the connective tissue, such as systemic lupus erythematosus, lichen planus, rheumatoid arthritis and ankylosing spondylitis. (Treatments associated with these diseases may alter clinical parameters.)
11. Subject with joint replacements. (May require prophylactic antibiotic treatment as a part of therapy that could possibly affect clinical efficacy.)
12. Subject with a history of oral candidiasis. (Use of doxycycline may increase the

- potential for oral candidiasis in subjects prone to this condition.)
13. Subject with allergies to doxycycline hyclate or other tetracyclines. (Subjects require treatment with doxycycline if randomized to the test group.)
 14. Subject taking phenytoin or cyclosporine, which could cause gingival hyperplasia, within one month prior to the Baseline examination. (These medications may alter the clinical parameters associated with periodontitis.)
 15. Subject using mouthwash with known antibacterial properties (i.e., Peridex[®], Listerine[®], Viadent[®]) regularly within one month prior to Baseline examination. (May alter clinical parameters at Baseline.)
 16.
 - a. Subject taking antimicrobials within the two weeks prior to the Baseline examination. (May alter clinical parameters.)
 - b. Subject taking antimicrobials for greater than three consecutive days between two and six weeks prior to Baseline examination. (May alter clinical parameters.)
 17. Subject taking ibuprofen or indomethacin within the two weeks prior to Baseline examination. (May alter clinical entry criteria at Baseline.)
 18. Subject taking sulfasalazine within the three months prior to the Baseline examination. (May alter clinical parameters associated with periodontitis.)
 19.
 - a. Subject taking steroids within the two weeks prior to the Baseline examination. (May alter clinical entry criteria at baseline.)
 - b. Subject taking steroids for greater than three consecutive days between the two and six weeks prior to Baseline examination. (May alter clinical entry criteria at baseline.)
 20. Subject taking continuous low doses of tetracyclines for the four months prior to Baseline examination. (May alter clinical parameters.)
 21. Subject taking an investigational drug within one month prior to Baseline examination. (Unknown effect on clinical parameters.)
 22. Female, nonsterile subject who is pregnant, lactating or not using an acceptable method of birth control (only birth control pills, IUD, Norplant[®] system, Depo Provera[®], diaphragm, or condom plus foam are acceptable). All females 55 years old and younger will have a pregnancy test performed prior to Baseline treatment, or have written documentation from a physician that they have been surgically sterilized or are post-menopausal. Negative test results or this written documentation must be obtained prior to the Baseline treatment. (Risks of product use with pregnancy undefined.)
 23. Subject who, in the investigators opinion would not comply with study procedures. (Noncompliance may alter clinical outcomes.)

For subjects in the SRP arm of the studies, the treated side of the mouth and any selected 7 mm. sites on the untreated side of the mouth received a thorough supra- and sub-gingival scaling using an ultrasonic scaler and currettes until the root surfaces were smooth and hard on examination with an explorer.

Subjects randomized to the Oral Hygiene arm received instruction in and demonstration of proper brushing and flossing technique at baseline and at 4 months. Oral hygiene consisted of brushing and flossing twice daily using toothbrush, dentifrice and floss provided.

Subjects were enrolled at each center using a randomized blocks design based on their history of scaling instrumentation as follows:

- Scaling at least 2, but less than 6 months prior
- Scaling at least 6, but less than 12 months prior
- Scaling more than 12 months prior

The exclusion criteria required the subjects to have had prior experience with scaling, but not in the two months immediately prior to enrollment.

The investigator who administered the treatment and the subjects were unblinded since the treatments were dissimilar, and during the first week and the first week of Month 4 it was not possible to blind all study personnel because the product was in place. However, the examiner was unaware of the treatment and all other personnel involved in making clinical measurements were blinded. Examiners were not present during treatment, did not enter any data on the case report forms, and did not discuss treatments or adverse events with subjects or investigational staff. The person who collected adverse event data could not necessarily be blinded because some of the adverse events might be related to the test material itself. In order to minimize any bias in collecting adverse event data, the sponsor created a script to be used in collecting adverse event information in a standardized manner.

Reviewer's Comment: Given the fact that it was impossible to conduct a completely blinded investigation of this product using this design, the sponsor's efforts to reduce potential bias on the part of the examiner seem reasonable.

Study Procedures:

Pretreatment Evaluation

The subject's medical and periodontal history was taken, as was history of tobacco use, concomitant medications. Blood pressure and pulse were taken. Assessment of the periodontal entry criteria was performed.

Baseline (Day 0) Evaluation

The baseline visit followed the screening by 1 to 4 weeks. Radiographs were taken if none had been taken in the past six months. Medical history, medication usage, blood pressure and pulse were again taken. A plaque sample was taken from the treatment side of the mouth for microbiological testing. Clinical measurement of attachment

levels, periodontal pocket depths, BOP and a plaque index were performed. Four or five sites that qualified based on pocket depth were identified and the examiner measured attachment levels at those sites. The treatment side of the mouth was identified. The amount of subgingival calculus was measured throughout the dentition. Pregnancy tests were conducted if required. Subjects meeting all entry criteria were assigned a study number.

Subjects received the appropriate treatment, based on the randomization scheme. Subjects receiving active or vehicle covered by a periodontal dressing were instructed not to brush or floss during the first seven days, until the dressing had been removed.

Day 7

If the dressing on either the active or vehicle subjects was lost during the first seven days, the subject was asked to return to the clinic, at which time the investigator would replace dressing as indicated. All subjects returned to the clinic at Day 7 at which time the polymer and dressing were removed from those subjects that had received this treatment (active and vehicle control arms). Subgingival plaque samples were collected on all subjects. All subjects received oral hygiene instruction.

Months 1 & 2

All subjects returned at these time points and were interviewed regarding adverse events, use of concomitant medications and compliance with oral hygiene procedures. PPD, BOP and a plaque index were performed on all teeth and attachment levels were measured at the selected sites. At the Month 2 visit, plaque samples were taken from the selected sites for microbial analysis.

Month 4

All subjects returned at this point and were interviewed regarding adverse events, use of concomitant medications and compliance with oral hygiene procedures. PPD, BOP and a plaque index were performed on all teeth and attachment levels were measured at the selected sites. Plaque samples were taken from the selected sites for microbial analysis. Pregnancy tests were again performed as appropriate. All subjects received a repeat of the treatment that they had received at Day 0.

Day 7 Post-Reapplication

The intermittent and Day 7 visits mimicked the corresponding visits after the first application.

Months 5, 6, 8, and 9

These visits mimicked the Month 1 & 2 visits. Samples for microbiological testing were taken at Months 6 & 9. In addition, at Month 9 pregnancy tests were again performed as appropriate and all subjects were scheduled for a scaling and root planing. They were also advised of any additional periodontal treatment needs.

At the completion of the study all subjects were offered an ultrasonic debridement and root planing and were advised of the need for any additional periodontal treatment.

Proposed Statistical Methodology

Quoting the sponsor's application, "Change from baseline in attachment level, probing depth and bleeding on probing score means for each subject for all on-study efficacy time points were analyzed using datasets. Analysis of covariance (ANCOVA) was to be the primary analysis used in this study, but ANOVA was used as the primary analysis due to heterogeneity of slopes." See Dr. Gao's Biostatistics review.

Results:

Primary Efficacy Variable

The primary outcome variable for the pivotal studies was change in attachment level at 9 months. The decision rules were that the active treatment had to be statistically significantly superior to vehicle and oral hygiene (negative control) and had to be at least 75% as good as SRP (positive control).

Reviewer's Comment: It is the policy of the Division to accept attachment level change as a surrogate for bone change, which is the ultimate endpoint in periodontal disease.

Reviewer's Comment: The natural history of periodontal disease is slow loss of attachment, punctuated by periods of more rapid loss. Slowing the progression of the disease is a positive outcome. Reversal of the disease process, attachment gain, is better still. The results of these studies reflect gains in attachment level, rather than a slowing of attachment loss.

Scaling and root planing is the standard first line therapy for patients with moderate to severe periodontitis. Products to treat periodontitis are generally positioned as either "adjunctive" or "stand alone," depending whether they are intended to be used in conjunction with SRP. In the case of an adjunctive indication, the Division only requires that the product be statistically superior to SRP. In the case of a "stand-alone" periodontitis indication the decision is more complicated. The Proposed guidelines for American Dental Association acceptance of products for professional, non-surgical treatment of adult periodontitis, as developed by the Taskforce on Design and Analysis in Dental and Oral Research addresses the issues concerning acceptance of "stand alone" products in a thoughtful way and provides the basis on which the Division has made decisions regarding such indications. The paper addresses

the fact that it might be desirable to have products available that could be used to, "...increase the efficiency of clinical care by partially substituting for SRP." They go on to say however, "To accept products, however, based solely on statistical superiority to a weak positive control was widely viewed as too permissive for evaluating an anti-periodontitis agent to be used in any setting. By acceptance of products with statistically significant but small effects compared to a weak positive control, the ADA would risk endorsing products which informed members of the periodontal community might disdain to recommend because of insufficient benefit." They go on to recommend such an effect be expressed as a fraction of the effect of SRP. The studies would have to include a weak positive control and the decision rules would be that the active arm would have to beat the weak positive control and vehicle as well as achieving an effect that is at least a fraction of the effect of SRP. At the End-of-Phase 2 meeting held on February 18, 1994, the Division agreed to accept 75% as good as scaling and root planing as a decision rule for comparison of the active and SRP arms.

Mean pocket depths at baseline ranged from 5.6 - 6.2 mm. There were somewhat more men than women in each study. Study ACS-34 had the greater difference in gender with a 55.5:44.5 ratio of men to women.

Both studies ACS-34 and ACS-35 demonstrated that the active treatment, ATRIDOX™, was statistically significantly superior to both vehicle and oral hygiene, the weak positive control, with respect to the primary efficacy variable, mean change in attachment level at 9 months. ATRIDOX™ also met the criterion of 75% as good as SRP with regard to attachment level change at nine months. Therefore, the sponsor has met the requirements for demonstrating efficacy with respect to the primary efficacy endpoint. See Dr. Gao's Statistical Review. Table 3 shows the Mean Attachment Level Gain from baseline for the various arms for ACS-34 and ACS-35 at nine months.

Reviewer's Comment: By 75% as good as we mean that the 95% confidence interval for the mean of the active treatment group should lie above 75% of the mean of the SRP group. See Dr. Gao's Biostatistics review.

Reviewer's Comment: The tables that follow that present the efficacy results of the sponsor's studies are abstracted from Dr. Gao's Biostatistics review. Data are presented for both the Intent to Treat (ITT) and Efficacy Evaluable datasets. Data were adjusted for center, block, center by block interaction, as well as center by treatment interaction and block by treatment interaction.

Table 2: Mean Attachment Level Gain at Nine Months (ACS-34 & ACS-35)

ACS-34	Treatment	N	Gain (mm.)	p-values
ITT Population		402		
	ATRIDOX™ (A)	99	0.68	
	Oral Hygiene (OH)	99	0.39	A vs. OH: 0.0135*
	SRP (SRP)	102	0.63	A vs. SRP: 0.6730
	Vehicle (V)	102	0.40	A vs. V: 0.0125*
Efficacy Population		329		
	ATRIDOX™ (A)	80	0.77	
	Oral Hygiene (OH)	83	0.31	A vs. OH: 0.0012*
	SRP (SRP)	84	0.63	A vs. SRP: 0.2941
	Vehicle (V)	82	0.13	A vs. V: 0.0001*
ACS-35	Treatment	N	Gain (mm.)	p-values
ITT Population		399		
	ATRIDOX™ (A)	100	0.80	
	Oral Hygiene (OH)	97	0.53	A vs. OH: 0.0101*
	SRP (SRP)	103	0.87	A vs. SRP: 0.4430
	Vehicle (V)	99	0.47	A vs. V: 0.0021*
Efficacy Population		355		
	ATRIDOX™ (A)	85	0.81	
	Oral Hygiene (OH)	89	0.53	A vs. OH: 0.0117*
	SRP (SRP)	98	0.86	A vs. SRP: 0.6647
	Vehicle (V)	83	0.46	A vs. V: 0.0022*

Of note is a treatment by center interaction involving the Loma Linda VA site in Study ACS-34. Data from that center showed a loss of attachment in all four treatment groups, even though an increase in attachment was observed for all four treatment groups for all nine of the other centers. The sponsor speculates that, "The unusual data for this center is likely related to either examiner error at Baseline or a change in the reference location for attachment levels Post-Baseline." In any event, statistically and clinically significant results were achieved in spite of the data reported from the Loma Linda site.

Secondary Efficacy Variables

The sponsor selected two secondary efficacy variables, Probing Pocket Depth (PPD) and Bleeding on Probing (BOP); these are appropriate secondary endpoints and are common in periodontitis studies. A Gingival Index (GI) was done to assess compliance with oral hygiene procedures.

Reviewer's Comment: It is expected that changes in PAL and PPD will be highly correlated. PAL is the distance from the cemento-enamel junction (CEJ) to the gingival attachment, which is at the base of the pocket. PPD is the distance from the free gingival margin to the gingival attachment. Unlike the CEJ, which is a fixed anatomical landmark on the tooth, the free gingival margin changes as the gingiva becomes more or less edematous. Because changes in both the gingiva and changes in attachment level affect PPD, it is viewed as a composite indicator. PPD can improve due to resolution of inflammation of the gingiva without affecting attachment level. While attachment level change is widely accepted as a surrogate for alveolar bone loss, which is the ultimate outcome in periodontitis, PPD is not universally regarded as an appropriate surrogate. However, reduction of pocket depths is thought to be desirable. It has been the policy of the Division since the approval of Actisite[®] to grant a "lesser indication" of "reduction in pocket depths in patients with periodontitis," in cases where pocket depth changes, but not attachment level changes, have been demonstrated. The recent approvable decision for the PerioChip[™] NDA was based on pocket depth data. In order to get a "treatment of periodontitis" indication, a difference in attachment level must be demonstrated.

Probing Pocket Depth (PPD)

ATRIDOX[™] showed statistically significantly greater reduction in pocket depth than both vehicle and oral hygiene in both pivotal studies, ACS-34 and ACS-35. ATRIDOX[™] met the requirement of 75% as good as SRP in this parameter in both of the studies. Therefore, based on the decision rules, the sponsor has shown efficacy for this endpoint. See Dr. Gao's Statistical Review. Table 3 shows the Mean Pocket Depth Reduction for the various arms for ACS-34 and ACS-35 at nine months.

Table 3: Mean Pocket Depth Reduction at Nine Months (ACS-34 & ACS-35)

ACS-34	Treatment	N	Reduction (mm.)	p-values
ITT Population		402		
	ATRIDOX™ (A)	99	1.05	
	Oral Hygiene (OH)	99	0.59	A vs. OH: 0.0001*
	SRP (SRP)	102	0.96	A vs. SRP: 0.3002
	Vehicle (V)	102	0.77	A vs. V: 0.0016*
Efficacy Population		329		
	ATRIDOX™ (A)	80	1.13	
	Oral Hygiene (OH)	83	0.51	A vs. OH: 0.0001*
	SRP (SRP)	84	0.93	A vs. SRP: 0.0504
	Vehicle (V)	82	0.80	A vs. V: 0.0012*
ACS-35	Treatment	N	Reduction (mm.)	p-values
ITT Population		399		
	ATRIDOX™ (A)	100	1.30	
	Oral Hygiene (OH)	97	0.91	A vs. OH: 0.0001*
	SRP (SRP)	103	1.33	A vs. SRP: 0.7991
	Vehicle (V)	99	0.92	A vs. V: 0.0001*

Efficacy Population		355—		
	ATRIDOX™ (A)	85	1.27	
	Oral Hygiene (OH)	89	0.87	A vs. OH: 0.0001*
	SRP (SRP)	98	1.31	A vs. SRP: 0.7649
	Vehicle (V)	83	0.95	A vs. V: 0.0008*

Bleeding on Probing (BOP)

BOP is another common efficacy endpoint in periodontitis studies, but like PPD is not viewed by this Division as a surrogate endpoint for treatment of periodontitis. As reported in the *World Workshop in Periodontics*, "...the presence of BOP had low positive predictive and very high negative predictive value with respect to the development of additional attachment loss." (Armitage, G.C., Periodontal Diseases: Diagnosis, *Annals of Periodontology* 1996;1:46).

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Table 4: Mean Reduction in Bleeding on Probing at Nine Months (ACS-34 & ACS-35)

ACS-34	Treatment	N	Reduction (Index)	p-values
ITT Population		402		
	ATRIDOX™ (A)	99	0.50	
	Oral Hygiene (OH)	99	0.38	A vs. OH: 0.0260*
	SRP (SRP)	102	0.50	A vs. SRP: 0.9776
	Vehicle (V)	102	0.46	A vs. V: 0.4820
Efficacy Population		329		
	ATRIDOX™ (A)	80	0.50	
	Oral Hygiene (OH)	83	0.36	A vs. OH: 0.0231*
	SRP (SRP)	84	0.48	A vs. SRP: 0.7504
	Vehicle (V)	82	0.48	A vs. V: 0.7695
ACS-35	Treatment	N	Reduction (Index)	p-values
ITT Population		399		
	ATRIDOX™ (A)	100	0.62	
	Oral Hygiene (OH)	97	0.44	A vs. OH: 0.0066*
	SRP (SRP)	103	0.58	A vs. SRP: 0.5365
	Vehicle (V)	99	0.45	A vs. V: 0.0071*
Efficacy Population		355		
	ATRIDOX™ (A)	85	0.61	
	Oral Hygiene (OH)	89	0.42	A vs. OH: 0.0060*
	SRP (SRP)	98	0.58	A vs. SRP: 0.5852
	Vehicle (V)	83	0.45	A vs. V: 0.0177*

BOP was ascertained per the study protocol as follows. After withdrawing the periodontal probe from the pocket, the examiner observed the area for 30 seconds for the presence of bleeding and scored the site using the following scale:

- 0 - No bleeding
- 1 - Single bleeding point or a fine line of blood
- 2 - Interdental triangle or direct margin filled with blood
- 3 - Profuse bleeding observed immediately after probing

Both studies ACS-34 and ACS-35 demonstrated that the active treatment, ATRIDOX™, was statistically significantly superior to oral hygiene, the weak positive control, with respect to the secondary efficacy variable, mean reduction in BOP at 9 months. ATRIDOX™ also met the criterion of 75% as good as SRP with regard to attachment level change at nine months.

However, the comparison between ATRIDOX™ and vehicle differed markedly between the studies, with ACS-34 showing almost identical reductions for ATRIDOX™ and vehicle, while ACS-35 showed a statistically significant difference. See Dr. Gao's Statistical Review for a more detailed discussion. In this case, the decision rules were not met. Table 4 shows the Mean Reduction in Bleeding on Probing in Studies ACS-34 & 35.

Gingival Index (GI)

This consisted of performing a Silness and Løe Plaque Index on six surfaces on all teeth in the dentition at Baseline and months 1,2,4,5,6,8 and 9. This was not an outcome variable, but these data were collected to measure oral hygiene compliance. The Silness and Løe Plaque Index is the one most commonly used in periodontitis research. The sponsor reported that there were no statistical differences among the four treatment groups at all timepoints, indicating similar levels of plaque control.

Demographic Characteristics

The demographic characteristics of the subjects studied in ACS-34 and ACS-35 are presented in Tables 5 & 6 below. These data are from the efficacy evaluable dataset. Study ACS-34 included a total of 411 subjects. The overall percentage of males was 55.5% and ranged from % by treatment group. The overall mean age was 48.65 years and the range of means across treatment groups was years. Though not detailed in the tables, the largest proportion of the subjects were in the years age group followed by the years age group. The breakdown by race was as follows: 74% White, 14% Black and 12% Other. The range across treatment groups for these groups was as follows: % for Whites, % for Blacks and % for Other. Subjects who smoked 10 or more cigarettes per day comprised 31%, 7% smoked fewer than 10 cigarettes per day and 62% were non-smokers. Across treatment groups the range of smokers who smoked more than 10 cigarettes per day was 28.7% - 32.7%.

Table 5: Demographic Characteristics ACS-34 (All Subjects)

Baseline Characteristic		ATRIDOX™		Vehicle		Oral Hygiene		Scaling/ Root Planing	
		N	%	N	%	N	%	N	%
Sex	Male	51	50.5	59	56.7	56	54.9	62	59.6
	Female	50	49.5	45	43.3	46	45.1	42	40.4
Age	N	101		104		102		104	
	Mean	48.49		50.13		47.19		48.74	
	S.D.	10.74		10.20		10.22		10.72	
	Range								
Race	White	74	73.3	71	68.3	78	76.5	80	76.9
	Black	10	9.9	23	22.1	13	12.7	11	10.6
	Hispanic	12	11.9	9	8.7	9	8.8	10	9.6
	Asian	4	4.0	1	1.0	2	2.0	2	1.9
	Nat. Am./ Mixed	1	1.0	0	0.0	1	1.0	0	0.0
Smoking Status	Non- smoker	66	65.3	62	59.6	61	59.8	63	60.6
	≤ 9 Cigs/day	6	5.9	9	8.7	8	7.8	7	6.7
	≥ 10 Cigs/day	29	28.7	33	31.7	33	32.4	34	32.7

Study ACS-35 included a total of 422 subjects. The overall percentage of males was 52.4% and ranged from % across treatment groups. The overall mean age was 47.15 years and the range of means across treatment groups was years. The breakdown by race was as follows: 68% White, 23% Black and 9% Other. The range across treatment groups for groups with significant representation was as follows: 63.2% - 72.6% for whites and 23.5% - 29.2% for blacks. Subjects who smoked 10 or more cigarettes per day comprised 33%, 6% smoked fewer than 10 cigarettes per day and 61% were non-smokers. Across treatment groups the range of smokers who smoked more than 10 cigarettes per day was 33.0% - 35.3%.

Table 6: Demographic Characteristics ACS-35 (All subjects)

Baseline Characteristic		ATRIDOX™		Vehicle		Oral Hygiene		Scaling/ Root Planing	
		N	%	N	%	N	%	N	%
Sex	Male	53	50.0	48	45.3	57	55.9	62	58.5
	Female	53	50.0	58	54.7	45	44.1	44	41.5
Age	N	106		106		102		106	
	Mean	47.37		46.84		47.38		47.89	
	S.D.	8.63		10.33		10.79		10.24	
	Range								
Race	White	73	68.9	67	63.2	70	68.6	77	72.6
	Black	27	25.5	31	29.2	24	23.5	17	16.0
	Hispanic	2	1.9	4	3.8	3	2.9	5	4.7
	Asian	3	2.8	4	3.8	5	4.9	5	4.7
	Nat. Am./ Mixed	1	0.9	0	0.0	0	0.0	1	0.9
Smoking Status -	Non- smoker	67	63.2	64	60.4	60	58.8	68	64.2
	≤ 9 Cigs/day	4	3.8	5	4.7	6	5.9	8	7.5
	≥ 10 Cigs/day	35	33.0	37	34.9	36	35.3	30	28.3

Subgroup Analysis

In order to evaluate whether the demographic variables had any effect, subgroups of subjects were analyzed based on gender, age, race. No statistically significant interactions were observed for any of these variables.

Smoking

The sponsor reported that the subset of smokers was analyzed in studies ACS 34 & 35, but the

sponsor did not submit the data electronically, and because there is no discussion about smoking in the labeling, the data were not analyzed by the FDA. The sponsor reported that their analysis showed little difference in response to the various treatments between smokers and non-smokers. This result is not consistent with the effects of smoking reported in the literature. As discussed in the *Proceedings of the 1996 World Workshop in Periodontics*, *Annals of Periodontology*, 1:1, 1996, p.17, "A substantial body of evidence has demonstrated the detrimental effect of smoking on periodontal health." Because the findings in these studies were inconsistent with the literature, the sponsor was asked to speculate about why these results were observed. The sponsor responded that in their initial analysis, both former smokers and smokers who consumed nine or fewer cigarettes per day were included in the non-smoker group. The sponsor conducted a reanalysis that compared those who had never smoked to current and former smokers with respect to attachment level, probing depth, bleeding on probing and plaque index. They also looked at the effect of smoking on pockets of 5-6 mm and pockets ≥ 7 mm. The reanalysis reportedly showed a trend in which subjects in the SRP group who had never smoked responded better to treatment in terms of attachment level and probing depth than did former or current smokers.

Reviewer's Comment: Though the results observed with respect to smoking by treatment interaction in the initial analysis are not consistent with the literature on the impact of smoking on attachment level, the fact that the reanalysis showed at least a trend in favor of those who had never smoked over current and former smokers lends comfort regarding the validity of the trial. The sponsor does not make statements regarding smoking in the label.

The sponsor also looked at the subset of patients who were on maintenance therapy, which was defined as those who had had definitive therapy for periodontitis on a 2-6 month basis for at least one year. Again, the sponsor did not submit the data electronically and there was no reference to maintenance therapy in the proposed label, so there was no analysis performed by the FDA.

The sponsor analyzed the four well-controlled studies based on level of disease at baseline. Moderate disease was defined as probing depths of 5-6mm and severe disease as probing depths of 7 mm or more. The analysis showed that the greatest response to all treatments was in subjects with more severe disease. This is consistent with the literature.

STUDY AGD 9603:

Reviewer's Comment: This study was conducted by the sponsor to support labeling to use the product in a different way than it was used in the pivotal trials. In the pivotal trials, the product was covered by Coe-Pak™ periodontal dressing with product and dressing removed after seven days. The sponsor was proposing to label the product to be left in the pocket until it bioabsorbed or was expelled by brushing and flossing. Also Octylident™, a dental adhesive, was to be used for retention, rather than the Coe-Pak™. The Division agreed that the sponsor could receive approval for the requested indication based on results of a single trial of nine months duration if

the pivotal studies using Coe-Pak™ support approval. The sponsor could then label the product for use with Coe-Pak™ or Octyldent™ or both. The Division also asked that a question regarding hot and cold sensitivity be added to the adverse events questionnaire. Doxycycline hyclate has a low pH and there was concern about whether this might result in pulpal irritation. This question had not been included in the pivotal trials.

The Division also asked that in the Safety Analysis subsection of the Data Analysis section be modified to provide for tabulated listings of adverse events by time from the start of the study and that the events be summarized by time of the event. This was done to assess whether the adverse event profile differed when the product was left in the pocket to bioabsorb or be expelled naturally.

This was a 3-arm, randomized, controlled, parallel group, single blind trial which enrolled patients between _____ years of age with chronic adult periodontitis. A total of 605 subjects were enrolled at 14 centers. The three arms were as follows:

1. ATRIDOX™ with Coe-Pak™ removed after 7 days as in the pivotal trials
2. ATRIDOX™ with Octyldent™ left to bioabsorb as in the proposed labeling
3. Vehicle control with Octyldent™ left to bioabsorb as in the proposed labeling

The purpose of this study was to compare the product when retained with Coe-Pak™ and removed a 7 days with the product retained with Octyldent™ and left to biodegrade or be expelled naturally. The primary efficacy endpoint was change in attachment level at nine months. Secondary efficacy endpoints were change in pocket depth (PPD) and Bleeding on Probing (BOP). In order to “win,” the Octyldent™ arm had to be equivalent to the Coe-Pak™ arm and both had to be superior to vehicle.

The study followed a randomized blocks design at each study center employing two blocks; 1) subjects who had received scaling between eight weeks and eight months prior to the Baseline exam, and 2) those who had received scaling more than eight months prior to Baseline exam. Subjects who had received scaling less than eight weeks prior to the study were excluded, as were subjects who had never been scaled (due to concerns about compliance).

The investigator who administered the treatment and the subjects were unblinded since the treatments were dissimilar, but the examiners were blinded to treatment.

Inclusion Criteria:

The inclusion criteria for this study were identical to those for ACS-34 and ACS-35.

Exclusion Criteria:

The exclusion criteria for this study were very similar to those for ACS-34 and ACS-35.