

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-744

STATISTICAL REVIEW(S)

JAN 29 1997

Statistical Review and Evaluation

NDA/ Drug Class: 50-744 / 3S

Applicant: CollaGenex Pharmaceuticals, Inc.
301 South State Street
Newtown, PA 18940

Name of Drug: Periostat™ (doxycycline hyclate) 20 mg Capsules

Documents Reviewed: NDA Index and Summary sections (Vols. 2.1 and 2.2) and Statistical sections (Vols. 2.21-2.110) dated August 30, 1996, and diskettes containing SAS data sets provided by the sponsor.

Type of Report: Statistical

Indication: Periostat™ is indicated for use as part of a professional oral health program to promote attachment gain and reduce bone loss, pocket depth, and bleeding-on-probing in patients with adult periodontal disease.

Clinical Input: Dr. Gilkes (HFD-540)

I. Introduction

Periostat™ is capsule formulation of doxycycline hyclate equivalent to 20 mg of doxycycline. It is intended for oral administration twice daily. Doxycycline is a member of the tetracycline class of antibiotics and has been approved for approximately 30 years for use in the United States as an antibiotic for the treatment of a variety of infections caused by susceptible microorganisms. For antibiotic uses, doxycycline is administered in doses of 100-200 mg. Daily doses of 100 mg for up to 5 months are approved for malaria prophylaxis and often for several years, for acne therapy. Doxycycline hyclate, at a dose of 20 mg BID, is not effective as an antimicrobial agent, but exerts beneficial actions in the treatment of periodontal disease via mechanisms independent of antibacterial activity.

The primary symptoms of periodontitis are inflammation, loss of attachment of the tooth supporting structures, and the formation of gingival and bony pockets around the affected teeth. The extent of periodontal disease is routinely assessed via measurements of attachment level (ALv), which is the level on the tooth root at which the

junctional epithelium, connective tissue, and bone remains intact. ALv values of <4 mm are usually defined as normal. ALv values of 4-6 mm are considered to be indicative of mild-to-moderate periodontal disease, and ALv values ≥ 7 mm are representative of severe periodontal disease.

For adequate disease assessment, the ALv is measured at six sites around each tooth. Each site can yield a different value for ALv depending on the particular characteristics of tissue loss around that tooth. ALv can be measured using either a manual probe or an automated electronic probe, such as the Florida probe. The ALv obtained from the manual probe is often referred to as clinical ALv (cALv) and the measurement obtained from the Florida probe is called the relative ALv (rALv).

Secondary measures of supportive value in determining the extent of periodontal disease include pocket depth (PD), bleeding-on-probing (BOP), and gingival index (GI). PD provides a hybrid assessment of both the inflammation of the gums and the degeneration of the bone.

Three randomized, multi-center, placebo-controlled, double-blind, parallel clinical trials of Periostat™ in patients with adult periodontal disease were conducted. Each study was 12 months in duration and was identical with respect to patient recruitment, design, and methodology except as otherwise noted. The treatment groups included in these trials were Placebo and Periostat™ dosing regimens of 10 mg QD (used only in two of the three trials), 20 mg QD, and 20 mg BID. A total of 437 patients were enrolled in the three Phase III trials at 11 dental schools across the United States.

The objective of each Phase III trial was to determine the safety and efficacy of various dosing regimen of doxycycline on the clinical indices (attachment level, pocket depth, modified gingival index, and bleeding-on-probing) of involved teeth in patients with periodontitis. This objective is similar to the indication stated in the proposed label.

The sponsor performed efficacy analyses on variables created from efficacy measures at Baseline and at the post-Baseline visits. Since it was not practical to conduct Florida probe measurement of the whole mouth, two to four specific tooth sites per patient were selected to be measured with the Florida probe throughout the course of the study. Treatment comparisons on the selected site Florida probe variables were carried out at Baseline and at Months 3, 6, 9, and 12. Treatment comparisons on the full-mouth, manual probe variables were carried out at Baseline and at Months 6 and 12. The set of efficacy parameters created for each selected tooth site and each full-mouth tooth site within each patient are described in Table 1.

Table 1
Phase III Efficacy Parameters
Created for Each Tooth Site by the Sponsor

Population/Parameter
Selected Sites (Florida Probe)
- Change in rALv from Baseline
- BOP (yes/no)
Full-Mouth Sites (Manual Probe)
- Change in cALv from Baseline
- ALs \geq 2 mm from Baseline (yes/no)
- ALs \geq 3 mm from Baseline (yes/no)
- Change in PD from Baseline
- PD increase \geq 2 mm from Baseline (yes/no)
- PD increase \geq 2 mm from Baseline (yes/no)
- BOP (yes/no)

Baseline PD is used as the determinant of initial disease status. Therefore, for the full-mouth sites, the efficacy analysis is based on the results obtained within each Baseline PD strata. The efficacy parameters in Table 2 were created using the efficacy parameters in Table 1. These parameters are for each patient rather than each tooth site.

Table 2
Phase III Efficacy Parameters
Created for Each Patient by the Sponsor

Population/Parameter
Selected Sites (Florida Probe)
- Average Change in rALv from Baseline
- Proportion of sites with BOP
Full-Mouth Sites (Manual Probe)
- Average Change in cALv from Baseline
- Proportion of sites with ALs \geq 2 mm from Baseline
- Proportion of sites with ALs \geq 3 mm from Baseline
- Average Change in PD from Baseline
- Proportion of sites with PD increase \geq 2 mm from Baseline
- Proportion of sites with PD increase \geq 2 mm from Baseline
- Proportion of sites with BOP

The original analysis plan stated in the protocol proposed that treatment comparisons be performed only on the per patient parameters and did not envisage

including analyses of the per site parameters. With the recent availability of statistical methods and software appropriate for analyzing the per site parameters, while taking into account that the sites within a given patient may be correlated, a decision was made by the sponsor to perform analyses on the per-site efficacy parameters as well as on the per patient efficacy parameters. Treatment comparisons on the per site efficacy parameters were carried out using generalized estimating equation (GEE) regression techniques. Treatment comparisons on the per patient efficacy parameters were carried out using general linear models (ANOVA and ANCOVA).

II. Efficacy Evaluation

After discussion with the medical reviewer for the purpose of this review, the primary efficacy variables are chosen to be change in ALv from baseline at Month 12, change in PD from baseline at Month 12, and BOP at Month 12. These variables are chosen because they are the variables claimed in the indication of the label. also included in the indication. However, subtraction radiography which is used to determine alveolar bone height was only performed at two study centers, one each from Protocols E and F, and on a total of 23 patients at Month 12. Therefore, no evaluation of is made in this review.

Reviewer's Comment: Since is not evaluated clinically or statistically for a sufficient number of patients, it is recommended that be removed from the indication of the proposed label.

Statistical significance must be obtained at the 0.05 level for all three primary efficacy variables. The primary probe for which data will be analyzed is the manual probe. The manual probe is chosen over the Florida probe because it has measurements for each of the primary efficacy variables. The Florida probe does not include measurements for the change in PD. For this review and as stated in the original protocol, treatment comparisons of Periostat™ 20 mg to Placebo are based on per patient efficacy parameters rather than the per site efficacy parameters. These comparisons are carried out using ANCOVA for the mean change in ALv from baseline, the mean change in PD, and the proportion of sites per patient with BOP at Month 12 adjusting for investigator and for average baseline ALv and PD, and proportion of sites with BOP at baseline, respectively. All efficacy treatment comparisons are performed on the Intent-to-Treat/Last Observation Carried Forward (ITT/LOCF) population. This population includes all patients who were dispensed a study treatment and had a baseline value. For completeness, the results of the sponsor's per site GEE analyses for the primary efficacy variables stated above were evaluated.

Each Phase III study was a placebo-controlled, double-blind, parallel study with a 12 month scheduled duration of treatment. Protocol E was a six-center, four-treatment study; Protocol F was a four-center, four-treatment study; and Protocol G was a four-

center, three-treatment study (10 mg QD was not evaluated). Protocol E, however, had three investigators who also were included in Protocol F. This occurred because one center in Protocol E withdrew for administrative reasons prior to the initiation of the study so the number of patients who were to be treated at this site were distributed among one of the remaining investigators in Protocol E and among three Protocol F investigators. Since the three investigators from Protocol F included in Protocol E contributed no more than three patients to each treatment group and the total sample size was still sufficient, the patients from the Protocol F investigators were excluded from the analyses performed for Protocol E.

Patient Demographics:

Once the investigators common to both Protocols E and F were removed, Protocol E had 3 investigators and 33 patients randomized to each treatment. Protocol F had 40 patients randomized to each treatment group except for the 10 mg QD which only had 39 randomized patients. Protocol G had 39 patients randomized to each of the 3 treatment groups studied in that protocol.

The following tables contain the demographic characteristics for each protocol by treatment group for all randomized patients. As can be seen from Tables 3.1 to 3.3, distributions of these variables are similar across treatment groups ($p > 0.1$). The only exception is in the distribution of gender across the three treatment groups studied in Protocol G ($p = .014$). In Protocol G, the majority of patients in each treatment group were female and the Placebo group had the largest percentage of females. The descriptive variables, race (white versus others) and gender, were evaluated using Cochran-Mantel-Haenszel (CMH) tests stratified on investigator. Age was evaluated using ANOVA with investigator effects.

Tables 3.1 to 3.3
Patient Demographics
By Protocol

Table 3.1: Protocol E

	Placebo	10 mg QD	20 mg QD	20 mg BID	P-value
# Patients	33	33	33	33	
Age mean(SD)	49.3(10.0)	49.2(47.8)	47.8(7.9)	50.7(11.9)	.755
Race (N)					
Caucasian	26	25	30	27	.421
Black	5	6	2	3	
Asian	0	0	0	1	
Hispanic	1	2	1	2	
Other	1	0	0	0	
Gender(N)					
Male	19	14	17	21	.362
Female	14	19	16	12	

Table 3.2: Protocol F

	Placebo	10 mg QD	20 mg QD	20 mg BID	P-value
# Patients	40	39	40	40	
Age mean(SD)	49.1(9.8)	49.4(10.3)	50.5(10.6)	50.0(11.5)	.932
Race (N)					
Caucasian	34	35	35	34	.889
Black	5	2	5	5	
Asian	1	0	0	1	
Hispanic	0	2	0	0	
Gender(N)					
Male	17	22	15	24	.139
Female	23	17	25	16	

Table 3.3: Protocol G

	Placebo	20 mg QD	20 mg BID	P-value
# Patients	39	39	39	
Age mean(SD)	46.2(8.7)	45.3(8.7)	48.2(8.8)	.513
Race (N)				
Caucasian	35	31	36	.194
Black	2	5	1	
Asian	0	0	1	
Hispanic	2	3	1	
Gender(N)				
Male	6	18	13	.014
Female	33	21	26	

Analysis Results

The following table contains a summary of the results of the treatment comparisons for each of the primary efficacy variables. Included in the table are the mean values for the Placebo and 20 mg BID treatment groups adjusted for the parameters discussed above, the difference of the 20 mg BID group from the Placebo group, and the p-value from the pairwise comparison of Placebo vs. 20 mg BID of Periostat™.

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Table 4
Summary of Per Patient Efficacy Parameters from Phase III Studies
Placebo vs. 20 mg BID at Month 12
ITT/LOCF Population

Parameter	Placebo	20 mg BID	Difference	P-value
Mean Change in ALv (mm)				
•Sites with Baseline PD of 0-3 mm				
Protocol E	-.027	-.002	(.025)	.7600
Protocol F	.053	-.028	.081	.1698
Protocol G	.219	.135	.084	.2447
•Sites with Baseline PD of 4-6 mm				
Protocol E	-.422	-.562	.140	.2579
Protocol F	-.468	-.586	.118	.2719
Protocol G	-.256	-.406	.150	.1860
•Sites with Baseline PD of ≥ 7 mm				
Protocol E	-.929	-1.02	.091	.7062
Protocol F	-1.02	-.867	(.153)	.6276
Protocol G	-.621	-1.19	.569	.0540
Mean Change in PD (mm)				
•Sites with Baseline PD of 0-3 mm				
Protocol E	-.013	-.090	.077	.1496
Protocol F	.077	-.035	.112	.0201*
Protocol G	.215	.146	.069	.2173
•Sites with Baseline PD of 4-6 mm				
Protocol E	-.511	-.672	.161	.1984
Protocol F	-.447	-.600	.153	.1440
Protocol G	-.258	-.420	.162	.1213
•Sites with Baseline PD of ≥ 7 mm				
Protocol E	-.961	-1.23	.269	.2512
Protocol F	-1.01	-.950	(.06)	.8452
Protocol G	-.570	-1.21	.640	.0172*
Proportion of Sites Per Patient with BOP				
•Sites with Baseline PD of 0-3 mm				
Protocol E	.424	.374	.050	.2061
Protocol F	.359	.337	.022	.4704
Protocol G	.249	.168	.081	.0136*
•Sites with Baseline PD of 4-6 mm				
Protocol E	.695	.604	.091	.0227*
Protocol F	.615	.553	.062	.1496
Protocol G	.505	.405	.100	.0533
•Sites with Baseline PD of ≥ 7 mm				
Protocol E	.856	.770	.086	.1168
Protocol F	.803	.712	.091	.2281
Protocol G	.694	.602	.092	.2669

*Indicates significance at the 0.05 level.

Note 1: For ALv and PD, a negative value indicates a decrease from baseline and is indicative of improvement from baseline.

Note 2: Differences in parentheses indicate that Placebo was "better" than 20 mg BID.

Note 3: The pairwise comparison p-values adjust for Investigator and the baseline value for the respective parameter and are based on the model comparing all treatments simultaneously

Based on the results contained in Table 4, statistical significance is not achieved in two out of the three protocols within any baseline PD stratum for any of the three primary efficacy parameters. There is a trend favoring the 20 mg BID group over the Placebo. The 20 mg BID patients with a baseline PD of 4-6 mm showed an attachment gain about 0.14 mm more than the Placebo group and a pocket depth decrease of 0.16 mm more. As baseline PD increased in severity, the differences between the 20 mg BID and Placebo group increased, favoring the 20 mg BID group. For any baseline PD group, the 20 mg BID group had 5% to 10% fewer sites per patient with BOP than did the Placebo group. However, these results are not clinically significant either per discussion with the medical reviewer.

The following table includes the results of the sponsor's GEE analysis on the per site efficacy parameters. It is to be noted for Protocol E that these results include the three investigators that were not included in the analyses which lead to the results in Table 4.

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Table 5
Summary of Per Site Efficacy Parameters from Phase III Studies
Placebo vs. 20 mg BID at Month 12
ITT/LOCF Population

Parameter	Placebo	20 mg BID	P-value
Change in ALV (mm)			
•Sites with Baseline PD of 0-3 mm			
Protocol E	0.00	.01	.886
Protocol F	.12	-.01	.051
Protocol G	.28	.15	.037*
•Sites with Baseline PD of 4-6 mm			
Protocol E	-.51	-.76	.054
Protocol F	-.52	-.75	.040*
Protocol G	-.27	-.49	.051
•Sites with Baseline PD of ≥ 7 mm			
Protocol E	-1.40	-1.62	.420
Protocol F	-.85	-1.03	.469
Protocol G	-.59	-1.08	.057
Change in PD (mm)			
•Sites with Baseline PD of 0-3 mm			
Protocol E	0.00	-.06	.244
Protocol F	.10	-.03	.011*
Protocol G	.25	.16	.092
•Sites with Baseline PD of 4-6 mm			
Protocol E	-.61	-.88	.022*
Protocol F	-.52	-.75	.030*
Protocol G	-.25	-.50	.017*
•Sites with Baseline PD of ≥ 7 mm			
Protocol E	-1.39	-1.83	.096
Protocol F	-.93	-1.08	.510
Protocol G	-.57	-1.18	.005*
Proportion of Sites with BOP			
•Sites with Baseline PD of 0-3 mm			
Protocol E	42.4%	31.9%	.090
Protocol F	33.1%	34.7%	.631
Protocol G	19.7%	34.7%	.631
•Sites with Baseline PD of 4-6 mm			
Protocol E	70.6%	58.2%	.002*
Protocol F	63.3%	58.9%	.430
Protocol G	48.1%	39.0%	.110
•Sites with Baseline PD of ≥ 7 mm			
Protocol E	84.2%	71.3%	.144
Protocol F	83.0%	73.1%	.339
Protocol G	72.5%	63.1%	.138

*Indicates significance at the 0.05 level.

Note: The pairwise comparison p-values adjust for Investigator and the baseline value for the respective parameter and are based on the model comparing all treatments simultaneously.

With the GEE analysis, statistical significance is achieved or approached in a couple more of the comparisons, specifically, the comparisons of change in ALv and change in PD made for patients with mild/moderate disease (baseline PD of 4-6 mm). These results still do not show statistical significance across all three of the primary efficacy parameters in at least two of three protocols. Again, there is a trend that favors the 20 mg BID group over the Placebo group but the trend is not clinically significant either.

Subset Analysis

To investigate possible differences among demographic subsets, subgroups of patients were formed by gender, race (white vs. others), and age (≤ 55 years, > 55 years). The analyses performed for each of the primary efficacy variables were done using ANCOVA as before. In order to test for interactions of the given subset with treatment, the given subset and its respective interaction with treatment were added to the model. At the 0.10 level for the interaction term, there were no statistically significant differences across levels of gender, levels of race, or levels of age (results not shown here) for any of the primary efficacy variables. Within each subgroup, there are trends favoring the 20 mg BID group over the Placebo group which is consistent with the overall analyses, however, statistically significant differences between the 20 mg BID and Placebo groups are not achieved for two out of three protocols for any primary efficacy variable.

III. Safety Evaluation

The following is an analysis of the safety data provided by the sponsor. It is to be noted that this analysis contain all patients who were enrolled in the three studies. That is, the patients from Protocol E who were excluded from the efficacy analyses are included in the safety analysis.

Treatment Emergent Adverse Events

The following tables summarize the reported treatment emergent adverse events for each protocol. From these tables, it can be seen that the difference between the four treatment groups relative to the number of patients with adverse events was not statistically significant for any protocol ($p > 0.70$).

Tables 6.1 to 6.3
Treatment Emergent Adverse Events
By Protocol

Table 6.1: Protocol E

	Placebo	10 mg QD	20 mg QD	20 mg BID	P-value
Total # Patients	40	40	40	40	
# (%) Patients with Adverse Event	35 (87.5%)	36 (90.0%)	36 (90.0%)	30 (90%)	0.978

Table 6.2: Protocol F

	Placebo	10 mg QD	20 mg QD	20 mg BID	P-value
Total # Patients	40	39	40	40	
# (%) Patients with Adverse Event	29 (72.5%)	27 (69.2%)	30 (75.0%)	26 (65.0%)	0.783

Table 6.3: Protocol G

	Placebo	20 mg QD	20 mg BID	P-value
Total # Patients	39	39	39	
# (%) Patients with Adverse Event	32 (82.1%)	30 (76.9%)	29 (74.1%)	0.707

Treatment Emergent Adverse Events Related to Study Drug

Table 7 presents the treatment adverse events that were considered possibly or probably related to the study drug. Since the number of these events in each study was relatively small, the data for Protocols E, F, and G were pooled together. From this table, it can be seen that the difference between the four treatment groups relative to the number of patients with drug related adverse events was not significant ($p=0.073$).

Table 7

Treatment Emergent Adverse Events Possibly or Probably Related to Study Drug
All Protocols Combined

	Placebo	10 mg QD	20 mg QD	20 mg BID	P-value
Total # Patients	119	79	119	119	
# (%) Patients with Adverse Event	29 (24.4%)	13 (16.5%)	22 (18.5%)	36 (30.3)	0.073

Discontinued Patients

Table 8 contains a summary of the patients who discontinued from the study before the completion of the study.

Table 8
Number of Discontinued Patients

	Placebo	10 mg QD	20 mg QD	20 mg BID
Protocol E	13 (33%)	10 (25%)	11 (28%)	10 (25%)
Protocol F	12 (30%)	9 (23%)	6 (15%)	12 (30%)
Protocol G	9 (23%)	N/A	11 (28%)	6 (15%)
Total	33 (28%)	19 (24%)	28 (24%)	28 (24%)

Note. Percentages are based on the total number of study participants.

The following table contains the reasons for discontinuation from the study.

Table 9
Reasons for Discontinuation
All Protocols Combined

	Placebo	10 mg QD	20 mg QD	20 mg BID
Adverse Event	8 (25%)	1 (5%)	3 (11%)	6 (21%)
Illness Not Related to Drug	4 (21%)	2 (11%)	2 (7%)	6 (21%)
Uncooperative	5 (15%)	3 (16%)	9 (32%)	3 (11%)
Protocol Violation	4 (12%)	5 (26%)	9 (32%)	4 (14%)
Lost to Follow-Up	6 (18%)	2 (11%)	2 (7%)	5 (18%)
Treatment Failure	3 (9%)	3 (16%)	2 (7%)	2 (7%)
Other	3 (9%)	3 (16%)	1 (4%)	2 (7%)

Note: Percentages are based on the total number of participants who did not complete the study.

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Reviewer's Conclusions (which may be conveyed to the sponsor) ^{in THE ACTION LETTER}

1. *Three randomized, multicenter, double blind studies were provided to support the claim of efficacy of Periostat™ 20 mg BID versus Placebo in the treatment of adult periodontitis.*
2. *This review used an intent-to-treat population based on every subject who was dispensed a study treatment at baseline. Thus, the tables included in this report based on reviewer performed analyses differ from the sponsor tables because the sponsor's definition of the intent-to-treat population included only those patients dispensed a study treatment who had at least one post baseline visit. The overall conclusions drawn, however, do not differ.*
3. *For the reviewer performed efficacy analyses of Protocol E, the investigators who also had patients in Protocol F were not included in the Protocol E analyses.*
4. *This review was based on the per patient efficacy variables, as stated in the original protocol, rather than the sponsor submitted per-site efficacy variables.*
5. *Statistical significance must be met at the 0.05 level in at least two of the three protocols for each of the three primary efficacy variables, change in ALv from baseline at Month 12, change in PD from baseline at Month 12, and the proportion of sites with BOP at Month 12.*
6. *Since [redacted] is not evaluated clinically or statistically for a sufficient number of patients, [redacted] should be removed for the indication of the proposed label.*
7. *Based on the efficacy analyses performed and those submitted by the sponsor, it has not been demonstrated that Periostat™ 20 mg BID is statistically significantly (or clinically significantly per discussion with the medical reviewer) more effective than Placebo for the treatment of adult periodontitis.*

/S/

U
Cheryl Dixon, Ph.D.
Biostatistician, DOB IV

1/29/97


1/29/97Concur: R. Srinivasan
Team Leader, DOB IV

cc:

Archival NDA 50-744 Periostat

HFD-540

HFD-540/ Dr. Wilkin

HFD-540/ Dr. Kelsey

HFD-540/ Dr. Gilkes

~~HFD-540/ Dr. Blatt~~

HFD-725/ Dr. Harkins

HFD-725/ Dr. Srinivasan

HFD-725/ Dr. Dixon

HFD-344/ Dr. Carreras

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APR 16 1998

STATISTICAL CONSULTATION

NDA# 50-744 (major amendment)

Applicant: Collagenex Pharmaceuticals, Inc.

Name of Drug: Periostat (Doxycycline hyclate)

Documents Reviewed: From the major amendment of NDA--Response to FDA questions on stability

Type of Report: Consult

Chemistry Input: James Vidra , Ph.D. (HFD-830)

Introduction

In the submission of NDA 20-642, the stability analyses on the data, for the estimation of expiration date, from four lots (94213A, 94214A, 94215A, and 95057A) showed positive slope, hence, resulting a very long estimated expiration date (48 months).

The data contained time points at 0 , 3, 6, 9, 12 months. At each time point, drug samples were taken from the lots and tested for their release rate. The value of release rates from the samples are thus random variables. Hence, although on average, the release rates should decline with time, it is possible to get higher values of release rates from samples taken at a later time than the ones obtained at earlier time points. When this happens, and when data points are few (thus allow the higher release rates obtained at later time points to have stronger influence on the estimation of the slope) , the resulting regression line may have a positive slope. When more data at later time point is available, the slope from the regression analysis with added data points may change again, and possibly to negative. Besides, the slope is only an approximation of the trend of change of the average release rate. This means that the estimated slope based on 12 month data is the estimation of the change of the average release rate during the first 12 month only. The estimated expiration date from the slope is based on extrapolation. As mentioned above, more data at later time points may result in different slope, and hence different estimation of the expiration date. Therefore, the information from the first 12 months can not reliably predict the release rates at 48 months, and a expiration date of 48 months should not be granted. However, some extrapolation for a shorter time period may still be reasonable, and an expiration date of at least

18 months may be granted. An longer expiration date should be based on more data from more time points.

/S/

4/16/98

Ping Gao, Ph.D.

Mathematical Statistician, Biometrics IV

 April 16, '98

Concur: Rajagopalan Srinivasan, Ph.D.
Team Leader, Biometrics IV

Archival NDA 50-744

HFD-540

HFD-540/Dr. Blay

HFD-540/Dr. Wilkin

HFD-540/Dr. Kelsey

HFD-540/Dr. Gilkes

HFD-830/Dr. DeCamp

HFD-830/Dr. Vidra

HFD-725/Dr. Huque

HFD-725/Dr. Srinivasan

HFD-725/Dr. Gao

HFD-344/Dr. Carreras

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Statistical Review and Evaluation
of Amendment to Original NDA

JUN 23 1998

NDA/ Drug Class: 50-744 / 3S

Applicant: CollaGenex Pharmaceuticals, Inc.
301 South State Street
Newtown, PA 18940

Name of Drug: Periostat™ (doxycycline hyclate) 20 mg Capsules

Documents Reviewed: NDA Amendment Vols. S12.1- S12.15 dated April 1, 1998 and diskettes containing SAS data sets provided by the sponsor.

Type of Report: Statistical review of Study H

Indication: Periostat™ is indicated for use as an adjunct to supra- and sub-gingival scaling and root planing to promote and maintain attachment level gain and reduce pocket depth in patients with adult periodontal disease. *(Revised from original submission)*

Clinical Input: Dr. Gilkes (HFD-540)

I. Introduction

The original NDA, #50-744, for Periostat™ was submitted on August 31, 1996. The statistical review of this submission was dated January 29, 1997. On August 27, 1997, a non-approvable letter was issued for this submission. A meeting with the sponsor was held on November 17, 1997 to discuss the non-approvable decision. Following this meeting, a second letter restating the original non-approvable decision was issued on December 31, 1997. Another meeting with the sponsor was held on March 12, 1998. At this meeting, the Agency agreed that the results of Protocol H could be submitted as an amendment to the NDA. The results of this study would be reviewed as to support a claim for Periostat™ as an adjunct to scaling and root planing (SRP).

The purpose of this review is to evaluate the results of Protocol H and determine whether these results support a claim for Periostat™ as an adjunct to SRP. Protocol H was entitled: 'A 9-Month, Multicenter, Double-Blind, placebo-Controlled Trial Evaluating the Effect of Periostat™ (20 mg doxycycline hyclate capsules) BID in Conjunction with Scaling and Root Planing on Attachment Level and Pocket Depth in Patients with Adult Periodontitis.'

The objective of Protocol H is to evaluate the clinical effects of Periostat™ capsules 20 mg BID in conjunction with SRP versus placebo capsules BID in conjunction with SRP in order to support a claim that the administration of Periostat™ following SRP significantly increases the benefit of SRP in promoting attachment level (AL) gain and in reducing pocket depth (PD) and bleeding-on-probing (BOP). Protocol H was a multi-center, placebo-controlled, double-blind, parallel study of Periostat™ in patients with adult periodontitis. Five university dental centers enrolled patients. The study permitted the enrollment of 190 patients such that, after allowing for attrition and disqualification of patients approximately 70 patients in each of the two treatment groups would complete the study.

Reviewer's Comment: Protocol H is designed to support only the sub-gingival SRP portion of the revised indication stated in the proposed label submitted April 1, 1998.

Reviewer's Comment: No formal sample size calculation was stated in the original protocol for Protocol H. However, the study report for Protocol H states that 70 completed patients per treatment group would provide at least 80% power to detect a difference of 0.4 mm between the SRP + Placebo and SRP + Periostat™ groups with respect to the change in AL from Baseline.

To qualify for the study, patients had to have at least two tooth sites in each of two quadrants with pocket depths and attachment levels between 5 mm and 9 mm. At Baseline, patients were randomly assigned to one of the two treatment groups and SRP was performed on the two qualifying quadrants. Each treatment group took either Periostat™ 20 mg or Placebo twice daily for 9 months. Evaluations of AL, PD, BOP, gingival index, and safety were made at Months 3, 6, and 9. Patients who experienced an attachment loss > 2mm were to have that site treated locally with mechanical therapy.

The UNC-15 manual probe was used to measure clinical AL, PD, and BOP at 6 tooth sites about each tooth in the full mouth at the Baseline, Month 3, Month 6, and Month 9 visits. Full mouth data were collected for ethical reasons in order to monitor for rapid progression of disease in the non-qualifying quadrants. For the purpose of this review, however, only data from the qualifying quadrants which were SRP'd are used in the analyses.

As stated in the protocol, the primary efficacy parameters for the SRP quadrants are the average change in AL from baseline at 9 months, the average change in PD from baseline at 9 months, and the percentage of tooth sites exhibiting BOP at month 9. Supportive efficacy parameters include the percentage of tooth sites with attachment loss ≥ 2 mm and ≥ 3 mm from baseline and the percentage of tooth sites with PD increase ≥ 2 mm and ≥ 3 mm from baseline.

Reviewer's Comment: The study report of protocol H states that the primary efficacy parameters are the average change in AL and PD from Baseline only.

All treatment group comparisons are carried out for the Intent-to-treat (ITT) population using a last-observation-carried-forward (LOCF) approach. This population includes all patients who were dispensed a study treatment and had a baseline value. The efficacy analyses on AL, PD, and BOP were performed on tooth sites stratified by disease severity as measured by baseline PD. A tooth site with baseline PD of 0-3 mm was considered normal or non-diseased; tooth sites with baseline PD 4-6 mm were considered mildly to moderately diseased; and tooth sites with baseline PD ≥ 7 mm were considered severely diseased. Within each stratum, treatment group comparisons were performed on the per-patient average change in AL and PD, and on the per-patient percentage of sites experiencing BOP using ANOVA and ANCOVA.

Reviewer's Comment: The ITT/LOCF definition used for the reviewer performed analyses differ from the sponsor's analyses. In order to be included in the sponsor's ITT population, a patient had to have at least one post-baseline measurement in addition to receiving at least one day of study drug.

II. Efficacy Evaluation

For the purpose of this review, the primary efficacy variables are chosen to be change in ALv from baseline at Month 12 and change in PD from baseline at Month 12. These variables are chosen because they are the variables claimed in the indication of the label. The results of BOP at Month 12 will also be presented for completeness.

Statistical significance must be obtained at the 0.05 level for each of primary efficacy variables. Treatment comparisons of SRP + Periostat™ to SRP + Placebo are based on per patient efficacy parameters. These comparisons are carried out using ANCOVA for the mean change in ALv from baseline, the mean change in PD from baseline, and the proportion of sites per patient with BOP at Month 12 adjusting for investigator and for average baseline ALv and PD, and proportion of sites with BOP at baseline, respectively.

Patient Demographics:

There were 96 and 94 patients enrolled at Baseline in the SRP + Placebo and SRP + Periostat™ treatment groups, respectively. The following table contains the demographic characteristics by treatment group for all randomized patients. As can be seen from Table 1, distributions of sex and age are similar across treatment groups ($p > 0.29$). The difference between treatment groups with respect to race was marginally significant ($p = .054$). This difference, however, was not expected to affect efficacy results. The descriptive variables, race (white versus others) and gender, were evaluated using Cochran-Mantel-Haenszel (CMH) tests stratified on investigator. Age was evaluated using ANOVA with investigator effects.

Table 1
Patient Demographics

	SRP + Placebo	SRP + Periostat™	P-value
# Patients	96	94	
Age mean(SD)	48.1 (11.13)	46.5 (10.24)	.298
Race (N)			
Caucasian	66	74	.054
Black	24	17	
Asian	2	3	
Hispanic	4	0	
Gender(N)			
Male	51	46	.600
Female	45	48	

Analysis Results

The following table contains a summary of the results of the treatment comparisons for each of the efficacy variables. Included in the table are the mean values for the SRP + Placebo and SRP + Periostat™ treatment groups adjusted for the parameters discussed above, the difference of the SRP + Periostat™ group from the SRP + Placebo group, and the p-value from the pairwise comparison of SRP + Placebo vs. SRP + Periostat™.

Table 2
Summary of Per Patient Efficacy Parameters
SRP + Placebo vs. SRP + Periostat™ at Month 9
ITT/LOCF Population

Parameter	SRP + Placebo	SRP + Periostat™	Difference	P-value
Mean Change in ALv (mm)				
•Sites with Baseline PD of 0-3 mm	-.191	-.238	.047	.324
•Sites with Baseline PD of 4-6 mm	-.839	-.979	.14	.071
•Sites with Baseline PD of ≥ 7 mm	-1.14	-1.50	.35	.046*
Mean Change in PD (mm)				
•Sites with Baseline PD of 0-3 mm	-.045	-.154	.109	.002*
•Sites with Baseline PD of 4-6 mm	-.669	-.905	.236	.001*
•Sites with Baseline PD of ≥ 7 mm	-1.16	-1.61	.45	.009*
Proportion of Sites Per Patient with BOP				
•Sites with Baseline PD of 0-3 mm	.464	.390	.074	.007*
•Sites with Baseline PD of 4-6 mm	.694	.641	.053	.042*
•Sites with Baseline PD of ≥ 7 mm	.797	.752	.045	.330

*Indicates significance at the 0.05 level.

Note 1: For ALv and PD, a negative value indicates a decrease from baseline and is indicative of improvement from baseline..

Note 2: The pairwise comparison p-values adjust for Investigator and the baseline value for the respective parameter.

Based on the results contained in Table 2, statistical significance at the 0.05 level is achieved for mean change in AL for tooth sites with severe baseline PD, for mean change in PD for tooth sites in all baseline PD stratum, and for the proportion of sites per patient with BOP in tooth sites with normal and mild/moderate baseline PD. The mean change in AL for tooth sites with mild/moderate baseline PD is marginally statistically significant ($p=0.071$). For all efficacy variables and baseline PD strata, the SRP + Periostat™ treatment group shows improvement over the SRP + Placebo group. As baseline PD increased in severity, the differences between the SRP + Periostat™ and the SRP + Placebo group increased for change in AL and PD, favoring the SRP+ Periostat™ group. The reverse is true for the proportion of sites with BOP but the trend favors the SRP+ Periostat™ group.

Table 3 includes the results of the analyses of the Sponsor's ITT/LOCF population. The Sponsor's ITT/LOCF population includes 93 patients in the SRP + Placebo group and 90 patients in the SRP + Periostat™ group. Using the Sponsor's ITT/LOCF population, the mean change in AL for patients with mild/moderate baseline PD is now statistically significant at the 0.05 level. All other conclusions are the same as those drawn from Table 2.

Table 3
Summary of Per Patient Efficacy Parameters
SRP + Placebo vs. SRP + Periostat™ at Month 9
Sponsor's ITT/LOCF Population

Parameter	SRP + Placebo	SRP + Periostat™	Difference	P-value
Mean Change in ALv (mm)				
•Sites with Baseline PD of 0-3 mm	-.20	-.25	.05	.275
•Sites with Baseline PD of 4-6 mm	-.86	-1.03	.17	.031*
•Sites with Baseline PD of ≥ 7 mm	-1.17	-1.55	.38	.037*
Mean Change in PD (mm)				
•Sites with Baseline PD of 0-3 mm	-.05	-.16	.11	.002*
•Sites with Baseline PD of 4-6 mm	-.69	-.95	.26	<.001*
•Sites with Baseline PD of ≥ 7 mm	-1.20	-1.68	.48	.007*
Percentage of Sites Per Patient with BOP				
•Sites with Baseline PD of 0-3 mm	46%	39%	7%	.006*
•Sites with Baseline PD of 4-6 mm	70%	64%	6%	.027*
•Sites with Baseline PD of ≥ 7 mm	80%	75%	5%	.281

*Indicates significance at the 0.05 level.

Note 1: For ALv and PD, a negative value indicates a decrease from baseline and is indicative of improvement from baseline..

Note 2: The pairwise comparison p-values adjust for Investigator and the baseline value for the respective parameter.

Table 4 contains the Sponsor's results of the analyses for the supportive efficacy parameters. The mean per-patient percentage of tooth sites with ALs ≥ 2 mm from baseline, ALs ≥ 3 mm from Baseline, PD increase (PDi) ≥ 2 mm from baseline, and PD

increase ≥ 3 mm from Baseline is small overall. The SRP + Periostat™ group had lower mean per-patient percentages than the SRP + Placebo for all of the efficacy parameters and every Baseline PD stratum. The only statistically significant difference was the difference of the groups mean per-patient percentage of tooth sites with ALs ≥ 2 mm from baseline for severely diseased tooth sites.

Table 4
Summary of Supportive Per Patient Efficacy Parameters
SRP + Placebo vs. SRP + Periostat™.at Month 9
Sponsor's ITT/LOCF Population

Parameter	SRP + Placebo	SRP + Periostat™	P-value
Mean % of Sites with ALs ≥ 2mm from Baseline			
•Sites with Baseline PD of 0-3 mm	2.2%	1.9%	.640
•Sites with Baseline PD of 4-6 mm	2.4%	1.3%	.083
•Sites with Baseline PD of ≥ 7 mm	3.6%	0.3%	.029*
Mean % of Sites with ALs ≥ 3 mm from Baseline			
•Sites with Baseline PD of 0-3 mm	.64%	.49%	.614
•Sites with Baseline PD of 4-6 mm	.72%	.46%	.465
•Sites with Baseline PD of ≥ 7 mm	.63%	.17%	.281
Mean % of Sites with PDi ≥ 2 mm from Baseline			
•Sites with Baseline PD of 0-3 mm	1.5%	.6%	.109
•Sites with Baseline PD of 4-6 mm	1.6%	.9%	.117
•Sites with Baseline PD of ≥ 7 mm	2.7%	.6%	.151
Mean % of Sites with PDi ≥ 3 mm from Baseline			
•Sites with Baseline PD of 0-3 mm	.60%	.20%	.373
•Sites with Baseline PD of 4-6 mm	.48%	.42%	.869
•Sites with Baseline PD of ≥ 7 mm	.43%	.16%	.470

*Indicates significance at the 0.05 level.

III. Safety Evaluation

The following is an analysis of the safety data provided by the sponsor.

Treatment Emergent Adverse Events

Table 5 summarizes the reported treatment emergent adverse events. There was no significant difference between treatment groups ($p=0.26$) with respect to the number of patients who experienced at least one treatment emergent adverse event.

Table 5
Treatment Emergent Adverse Events

	SRP + Placebo	SRP + Periostat™	P-value
Total # Patients	96	94	
# (%) Patients with Adverse Event	78 (81%)	70 (74%)	0.260

The most frequent treatment emergent adverse events were the common cold, headache, flu, toothache, and sinus congestion. Those adverse events which occurred in $\geq 5\%$ of patients in either treatment group are summarized in Table 6.

Table 6
Treatment Emergent Adverse Events
Occurring in $\geq 5\%$ of Patients in Either Treatment Group

Event	SRP + Placebo (N=96)	SRP + Periostat™ (N=94)
Common Cold	28 (29%)	27 (29%)
Headache	26 (27%)	26 (28%)
Flu	17 (18%)	10 (11%)
Toothache	13 (14%)	9 (10%)
Sinus congestion	5 (5%)	8 (9%)
Abscess periodontal	8 (8%)	3 (3%)
Menstrual cramp	5 (5%)	6 (6%)
Sinusitis	7 (7%)	3 (3%)
Tooth disorder	5 (5%)	5 (5%)
Dyspepsia	2 (2%)	7 (7%)
Sinus headache	4 (4%)	5 (5%)
Sore throat	5 (5%)	4 (4%)

Treatment Emergent Adverse Events Related to Study Drug

Table 7 presents the treatment emergent adverse events that were considered possibly or probably related to the study drug. The incidence of treatment emergent adverse events related to study drug was small and the difference between treatment groups was not significant ($p=0.125$). The most frequent possibly or probably related treatment emergent adverse event was dyspepsia which was experienced by 4% of patients in the SRP + Periostat™ group compared to none in the SRP + Placebo group.

Table 7
Treatment Emergent Adverse Events Possibly or Probably Related to Study Drug

	SRP + Placebo	SRP + Periostat™	P-value
Total # Patients	96	94	
# (%) Patients with Adverse Event	6 (6%)	12 (13%)	0.125

Discontinued Patients

Table 8 contains a summary of the primary reasons for patients who discontinued from the study before the completion of the study.

Table 8
Reasons for Discontinuation

Reason	SRP + Placebo (N=96)	SRP + Periostat™ (N=94)
Adverse Event	2 (2%)	1 (1%)
Illness Not Related to Drug	2 (2%)	1 (1%)
Uncooperative	2 (2%)	1 (1%)
Protocol Violation	1 (1%)	1 (1%)
Lost to Follow-up	4 (4%)	3 (3%)
Other	1 (1%)	4 (4%)

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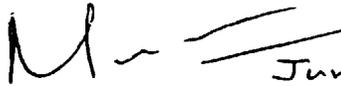
Reviewer's Conclusions (which may be conveyed to the sponsor)

1. *Protocol H is designed to support only the sub-gingival SRP portion of the revised indication stated in the proposed label submitted April 1, 1998.*
2. *This review used an intent-to-treat population based on every subject who was dispensed a study treatment at baseline. Thus, the tables included in this report based on reviewer performed analyses differ from the sponsor tables because the sponsor's definition of the intent-to-treat population included only those patients dispensed a study treatment who had at least one post baseline visit. The overall conclusions drawn, however, do not differ.*
3. *Based on the efficacy analyses performed and those submitted by the sponsor, it has been demonstrated that SRP + Periostat™ is statistically more effective than SRP + Placebo with respect to attachment gain and reduction in pocket depth in tooth sites with mild to moderate and severe disease at 9 months. The SRP + Periostat™ had a statistically significant lower percentage of tooth sites with BOP than the SRP + Placebo group for tooth sites with mild to moderate disease at 9 months.*
4. *The safety of Periostat™ has been demonstrated. There are no significant differences between the SRP + Periostat™ and the SRP + Placebo groups with respect to treatment emergent adverse events.*

/S/

6/24/98

Cheryl Dixon, Ph.D.
Biostatistician, DOB IV

 June 23, '98

Concur: R. Srinivasan, Ph.D.
Team Leader, DOB IV

cc:
Archival NDA 50-744 Periostat
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HFD-540/ Dr. Wilkin
HFD-540/ Dr. Kelsey
HFD-540/ Dr. Gilkes
HFD-540/ Dr. Blay
HFD-725/ Dr. Huque
HFD-725/ Dr. Srinivasan
HFD-725/ Dr. Dixon
Chron.

This review contains 9 pages.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-744

MICROBIOLOGY REVIEW(S)

MAY 15 1997

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
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NDA#: 50-744 MICROBIOLOGY REVIEW: #1 REVIEW DATE: 2/19/97

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL NDA	8/30/96	8/30/96	1/15/97

NAME & ADDRESS OF APPLICANT: COLLAGENEX PHARMACEUTICALS
301 SOUTH STATE STREET
NEWTON, PA 18940CONTACT PERSON: Christopher Powala
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DRUG PRODUCT NAME:

Proprietary: PERIOSTAT
Nonproprietary: Doxycycline Hyclate Caps (20mg)
Code names/#'s: NA
Chemical Type: Tetracycline
Therapeutic Class: S3

ANDA Suitability Petition/DES/Patent Status:

US Patent 4,704,383 (expires 11/3/2004) The Research Foundation
of State University of New York
US Patent 4,666,987 (expires 5/19/2004) The Research Foundation
of State University of New York
US Patent 34,656 (reissue) The Research Foundation of State
University of New York

PHARMACOLOGICAL CATEGORY/INDICATION(S):

Tetracycline/Adult Periodontal Disease
Mechanism of Action: Inhibitor of Collagenase ActivityDOSAGE FORM: Capsules
STRENGTH: 20mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: Rx

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CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: See Submission Vol.2, Section 2.1. The description in this section of the NDA is of a typical doxycycline hyclate moiety as described by the USP(1).

SUPPORTING DOCUMENTS: NA

RELATED DOCUMENTS: IND IND

CONSULTS: NA

REMARKS/COMMENTS:

This submission is for the use of doxycycline as an inhibitor of collagenase activity of host cell response to infection **not** as an antibiotic to treat bacterial infection.

CONCLUSIONS & RECOMMENDATIONS:

The data submitted by the applicant for the use of low-dose doxycycline not as an antibiotic but rather as an inhibitor of collagenase is in agreement with the published literature (11,12). The use of low-dose tetracycline while having a potential to bring about populations of bacteria resistant to tetracyclines as well as other antimicrobials and to cause alterations in the microflora of the gastrointestinal tract presents no more of a potential health threat than the use of tetracyclines at higher doses for the treatment of bacterial infections.

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COLLAGENEX PHARMACEUTICALS
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INTRODUCTION: This review is of the product Periostat, which is doxycycline, and its use *not* as an antibiotic for the treatment of adult periodontitis but as an inhibitor of the collagenase produced by host cells in response to periodontal infection.

PRE-CLINICAL EFFICACY

SPECTRUM OF ACTIVITY AND MECHANISM(S) OF ACTION:

Periostat is a modified tetracycline known as doxycycline. The tetracycline class of antibiotics have a broad spectrum of activity against microorganisms including facultative, aerobic and anaerobic bacteria(2). This class of antibiotics is bacteriostatic with their main mechanism of action being to inhibit protein synthesis(2).

MECHANISMS OF RESISTANCE:

Tetracycline resistance is widespread among bacteria(3). This resistance may be do to: 1) limiting access of tetracycline to the ribosomes, 2) altering the ribosome to prevent effective binding of tetracycline, or 3) producing tetracycline-inactivating enzymes(4). Combinations of these mechanisms of resistance have been described (4).

Fourteen determinants coding for tetracycline resistance in bacteria are currently known. Of these *tet(A-E)*, *tet(G)*, *tet(K)*, *tet(L)*, and *tet(P)* encode proteins that mediate an efflux mechanism for tetracycline and the *tet(M)*, *tet(O)*, and *tet(Q)* genes encode proteins that prevent tetracycline from attaching to the ribosomes. A third class of genes, including *tet(X)*, encode proteins mediating the breakdown of tetracycline. The mechanism of the *tet(F)* determinant has not been conclusively determined(5). All but classes C, D, K, and L confer resistance to minocycline(5). *Tet(M)* confers resistance to both tetracycline and minocycline as well as all second generation tetracycline analogs(6). Many of the tetracycline genes from gram-negative

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bacilli are located on plasmids and are readily transmissible within and between species(5). Other transmissible tetracycline-resistance genes particularly those found in gram-positive organisms are located on transposable chromosomal elements that can be transferred between organisms by conjugation(7).

EPIDEMIOLOGY

Development of resistance to tetracycline among organisms isolated from the periodontal pockets is frequently seen in patients with periodontal disease treated with tetracycline(8). The presence of tetracycline-resistant organisms in the oral microflora of individuals with no periodontitis and not receiving tetracycline has also been described. These tetracycline-resistant bacteria have been shown to constitute between 2 - 6% of the viable count in subgingival samples(9).

APPEARS THIS WAY
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MICROBIOLOGY REVIEW

MICROBIOLOGY DATA SUBMITTED: (volumes 2.1, 2.2, 2.12, 2.13, 2.18,
2.19)

DOSAGE: 20mg b.i.d.

PHARMOKINETICS/BIOAVAILABILITY:

Plasma - Mean peak concentration
790 +/- 285ng/mL.

Average steady state concentration 482 +/-
142ng/mL.

Note: Doxycycline has been shown to concentrate in the gingival crevicular fluid two to three times the concentration found in plasma over the same time interval(10). This is believed in part to be due to doxycycline's affinity for calcium containing substances(10).

Elimination - Urine	% within	hr.
Stool	% over	days

CLINICAL EFFICACY

CLINICAL MICROBIOLOGY:

The uniqueness of this NDA submission is that the applicant is not claiming Periostat, which is doxycycline, as an antibiotic to eliminate periopathogenic organisms but rather as an inhibitor of collagenase released by the cells of the diseased host. Collagenase has been shown to cause tissue as well as bone damage(11). Tetracyclines have been shown to inhibit the activity of collagenase(10,12). This activity does not appear to be related to the antibiotic's antibacterial properties since modified tetracyclines with no antibacterial activity have been shown to exhibit anticollagenase activity(13).

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The non-claim of Periostat as an antibiotic is based on the daily dose of 20mg twice a day. This dose is well below the usual dosage of doxycycline (i.e. 200mg first day followed by 100mg for the next 7 to 10 days) given to eradicate bacteria at the site of infection(14).

OBJECTIVES OF REVIEW:

The intent of this review is not to assess the activity of doxycycline against periopathogenic bacteria. Therefore this review will not address "Isolates/relevance to approved indications", "Disk content studies", "MIC broth/agar dilution comparisons", "MIC/Disk diffusion Correlation Studies", "Quality Control Studies (MIC and Disk diffusion)", "Anaerobe studies", "Haemophilus and Neisseria Studies", "Bacteriological Efficacy", "Isolates Approved" and "Establishment of Interpretive Criteria".

This review will attempt to: 1) verify the summary presentation of the study data; 2) assess from the study data and from the published literature if the use of this product could potentially cause the occurrence of abnormally high concentrations of antibiotic-resistant bacteria in patients being treated with the product, and 3) whether there could be an alterations in the microbial ecology of various anatomical sites of the patient in such a way as to bring about adverse side effects.

STUDIES SUBMITTED:

Three (3) studies were conducted to address the issues of: 1) antimicrobial activity, and 2) assessment of bacterial resistance.

Data for different dosage regimens was submitted. The applicant is applying for a regimen of 20mg b.i.d. All microbiology comments in this review are based on the 20mg b.i.d. regimen.

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MICROBIOLOGY PHARMOKINETICS:

The mean Cmax levels for doxycycline normally required to eradicate infecting organisms is >1mcg/mL(15). While approximately 23% of the subjects given Periostat had Cmax levels exceeding the threshold effect of 1mcg/mL, the mean Cmax levels did not exceed 1mcg/mL.

The antimicrobial activity of Periostat was studied by characterizing the microbial flora of the gingival crevices of study patients at baseline and after 18 months of treatment with Periostat. These studies were done using either DNA probes or culture techniques to detect and quantitate organisms known to be associated with periodontal disease as well as those which are considered to be part of the "normal" microbial flora(16). None of the studies demonstrated any obvious changes in the distribution of Gram-positive or Gram-negative morphotypes isolated at baseline and after treatment. There were, however, some reductions in the numbers of certain bacteria in those individuals receiving Periostat. No overgrowth by opportunistic microorganisms such as the yeast was noted in any of the studies. Based on the "MICROBIOLOGY PHARMOKINETICS" and the characterization of the microbial flora studies Periostat given according to the applied for dosage regimen does not seem to act as an antibiotic.

DEVELOPMENT OF RESISTANT BACTERIA:

Studies submitted addressing the development of resistant bacteria at the site of infection showed a transient increase of tetracycline resistance in the marker organisms *Actinomyces viscosus* and *Fusobacterium nucleatum*. The increases occurred at 12 months for *A. viscosus* and 18 months for *F. nucleatum*. In both cases baseline values returned by 12 months for *A. viscosus* and 6 months for *F. nucleatum* post therapy. No cross resistance to ampicillin, benzylpenicillin, cefoxitin, erythromycin, or metronidazole were noted in the marker organisms *A. viscosus* or *F. nucleatum* during the studies. The data submitted with this

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application is consistent with the published literature which indicates that resistant populations of bacteria do not permanently develop as a result of treating adult periodontitis with tetracycline(17,18).

ALTERATIONS IN THE MICROBIAL FLORA:

No data were submitted addressing the issues of development of tetracycline-resistant bacteria in the gastrointestinal tract, genito-urinary tract or other body sites of individuals receiving Periostat.

No data were submitted in relation to the gastrointestinal tract specifically addressing alterations in the microflora of the gastrointestinal tract such as: 1) overgrowth of already present microorganisms such as yeast and *Clostridium difficile*; or 2) reduction in colonization resistance.

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COLLAGENEX PHARMACEUTICALS
PERIOSTAT CAPSULES

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/S/
5/15/97
Frederic J. Marsik, Ph.D.
Microbiology Reviewer

cc: Original 50-744

HFD-520 Division File
HFD-540/DO/C.Gilkes
HFD-540/Chem/J.Vidra
HFD-540/Pharm/Tox/N. See
HFD-720/Stat/C.Dixon,
HFD-880/Biopharm/D.Wang

Concurrence Only
HFD-520/Dep/Dir/L.Gavrilovich
HFD-520/GLMicro/ATSheldon

R 5/14/97

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DENTAL CONSULT

5/8/98

SUBMISSION TYPE **DOCUMENT DATE** **CDER DATE** **ASSIGNED DATE**
ND 50-744 3/31/98 4/1/98 4/8/98

NAME AND ADDRESS OF APPLICANT:

CollaGenex Pharmaceuticals, Inc.
301 South State Street
Newton, PA 18940

CONTACT PERSON:

Christopher V. Powala
Director, Drug Development & Regulatory
Affairs
CollaGenex Pharmaceuticals, Inc.
301 South State Street
Newton, PA 18940
Telephone #: 251-579-7619

DRUG PRODUCT NAME:

Proprietary:	Periostat™
Nonproprietary:	Doxycycline Hyclate Capsules USP
Code Name/#'s:	None
Chemical Name:	4-(dimethylamino-1,4,4a,5,5a,6,11,12a- -ocatahydro-3.5.10.12.12a-pentahydroxy- 6-methyl-1,11-dioxo-2- naphthacenecarboxamide monohydrochloride

INDICATIONS:

Treatment of Adult Periodontitis

DOSAGE FORM:

Capsule

STRENGTH:

20mg

ROUTE OF ADMINISTRATION:

Oral

RELATED DOCUMENTS:

IND
IND
AADA 62-374
AADA 62-839

REMARKS/COMMENTS: This review is of the answers by the applicant to the microbiology questions asked of the company in the initial review dated 2/19/97 (see

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attached pages 1-10 of original review). The initial review should be consulted for the "Spectrum of Activity and Mechanism of Activity", "Mechanisms of Resistance", "Epidemiology", "Clinical Microbiology", "Microbiology Pharmacokinetics", "Developments of Resistant Bacteria", "Alterations in the Microbial Flora", and "References".

QUESTION 1: "The potential for the development of tetracycline-resistant bacteria appearing in the gastrointestinal tract and/or the genitourinary tract in individuals taking Periostat needs to be addressed."

This question was asked because the applicant had not done fecal stool cultures on patients being treated with Periostat or placebo controls to look for the development of resistant bacteria.

The applicant has responded to this question by noting that they had submitted data in the original submission from studies looking for the development of resistant bacteria in the oral microflora of Periostat and placebo treated patients. These studies had been reviewed by this reviewer and the results were found to be consistent with the published literature and were acceptable. The applicant now states that because the organisms in the microbial flora of the oral cavity and the gastrointestinal tract are similar and their initial studies only detected a transient development of resistant bacteria in the oral cavity permanent colonization of the intestinal tract with resistant bacteria is very unlikely to occur. This reviewer after review of the published and in house data submitted (Study 5732.11H a multi-center, double-blinded controlled study of 78 patients receiving 20mg doxycycline hyclate bid to assess development of resistant bacteria) by the applicant concurs with the applicant that the potential for the gastrointestinal tract to become permanently colonized with resistant bacteria is highly unlikely. Even transient colonization by such bacteria is highly unlikely and if it were to occur has a extremely minimal chance of creating a medical problem. As for the potential that resistant bacteria may colonize the genitourinary tract of individuals treated with Periostat this reviewer believes that such a probability also is extremely low. One reason being that the dosage of Periostat is one-fifth to one-tenth that of the dosage normally given therapeutically treat bacterial infection. With such a low dose the potential for resistant bacteria to occur in the genitourinary tract has a very low possibility. A second reason being that in the female bacteria are often transferred from the intestinal tract to the genitourinary tract where colonization may occur. Since it is felt that the potential for the intestinal tract to be colonized for any extended period of time with resistant bacteria in patients treated with Periostat is minimal then the potential for transfer to the genitourinary tract is

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extremely low. Since the female because of her anatomy is more likely to be colonized colonization of the male is even less likely to occur.

QUESTION 2: "The potential for alterations in the microflora (e.g., overgrowth of yeast) or reduction in the colonization resistance of the gastrointestinal tract and/or genitourinary tract needs to be addressed."

The applicant in addressing this question states that their studies did not show any overgrowth in the oral cavity with any bacteria or yeasts in patients treated with Periostat. Thus they feel that such overgrowth is unlikely to occur in the intestinal tract or the genitourinary tract. They further state that their statistical analysis (Chi-Square test) showed no significant differences with regard to frequency of adverse events in any category within the digestive or genito-urinary system between any of the Periostat groups and placebo controls. While not direct evidence that colonization is or is not occurring such an analysis suggests that probably no medical problem is occurring due to colonization or overgrowth of bacteria or fungi.

The initial review of the data submitted by the applicant did not uncover any documentation of any overgrowth of the oral cavity by any particular bacteria or yeasts in patients treated with Periostat. The applicant in addressing this questions reiterates this again and notes that Periostat which is given at a dose of 20mg bid showed no clinically meaningful effect against *Actinobacillus actinomycetemcomitans*, *Prevotella intermedia*, or *Porphyromonas gingivalis*; or on total anaerobic, *Fusobacteria*, or *Actinomyces* counts. Furthermore there was no detectable shift from Gram-positive to Gram-negative flora, nor was there any replacement or major shift of any of the 40 obligate anaerobes compromising the predominant flora. This evidence is consistent as noted in the original review that Periostat is not acting like an antibiotic to eliminate periopathogenic organisms but probably as an inhibitor of collagenase released by the cells of the diseased host. Because of the fact that Periostat is administered at one-tenth to one-fifth of the dose of doxycycline used to treat bacterial infections the potential for a major change in the gastrointestinal or genitourinary tract flora is in the opinion of this reviewer unlikely to occur and if it does occur it would most likely be transient and its potential to cause medical problems is unlikely to occur.

The above remarks as they relate to development of resistant bacteria, reduction in the colonization resistance of the gastrointestinal and genitourinary tract, and overgrowth of bacteria or yeasts address only the immunocompetent population of patients. Not enough data was presented by the applicant in any study in relation to these areas in the

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immunocompromised patient. Thus this reviewer suggests that the following statements be incorporated under PRECAUTIONS in the labeling:

CONCLUSION:

The answers given by the applicant to the original microbiology concerns have been satisfactorily addressed. As noted in this review a statement in the labeling under "PRECAUTIONS" is required since the issues raised have not been adequately addressed by the applicant in immunocompromised patients.

/S/

4/17/98
FREDERIC J. MARIK, Ph.D.
Microbiology Reviewer

cc: Original 50-744
HFD-520 Division Files
HFD-540/DO/J. Kelsey
HFD-540/Chem/J. Vidra
HFD-540/Pharm/Tox/N. Sec
HFD-540/Stat/C. Dixon

Concurrence Only

HFD-520/Dep/Dir/L. Gavrilovich
HFD-520/TLMicro/A. T. Sheldon

RD 5/4/98
Final 5/7/98

16 5/2/98

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AUG 3 1998

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LABELING

Related documents: Microbiology Review - 2/19/97
Microbiology Review - 4/8/98

The following is suggested wording for the microbiology portion of the Periostat label.

FS/ 7/20/98
FREDERIC J. MARSIK, Ph.D.
Microbiology Reviewer

cc: Original 50-744

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NDA 50-744 3/31/98 4/1/98 7/22/98
LABELING

HFD-520 Division Files
HFD-540/DO/J. Kelsey
HFD-540/DO/C. Gilkes
HFD-540/Chem/J. Vidra
HFD-540/Pharm/Tox/N. See
HFD-540/Stat/C. Dixon
HFD-540/Biopharm/D. Wang
HFD-540/CSO/R. Blay
HFD-520/Micro/ F. Marsik

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8/3/98
8/3/98