NIH Natl Inst Diabetes & Digest & Kidney
Clinical Research Protocol
KIDNEY AND PERIODONTAL DISEASE (KAPD) STUDY

Protocol Number:	12-09801 **NCT01802216**
Version Date:	12/20/2013
Investigational Product:	MINOCYCLINE HYDROCHLORIDE, ARESTIN
Sponsor:	Dr. Vanessa Grubbs, MD, MPH 1001 Potrero Ave, SFGH 100 San Francisco CA 94143
Funding Organization:	National Institutes of Health, Robert Wood Johnson Foundation
Principal Investigator:	Dr. Vanessa Grubbs, MD, MPH 415-206-5649 grubbsv@medsfgh.ucsf.edu

Approval:

12/20/13

PI or Sponsor Signature (Name and Title)

Date

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing NIH with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: 12-09801

Protocol Title: Kidney and Periodontal Disease Study

Protocol Date: 12/20/2013

12/20/13

Investigator Signature *Date*

Vanessa Grubbs, MD, MPH

Print Name and Title

Site # _____

Site Name San Francisco General Hospital

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LIST OF ABBREVIATIONS

AE	Adverse event
CFR	Code of Federal Regulations
CRF	Case report form
CRP	C-reactive protein
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
eGFR	Epidermal growth factor receptor
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
PI	Principal Investigator
SAE	Serious adverse experience

PROTOCOL SYNOPSIS

TITLE	Kidney and Periodontal Disease (KAPD) Study
SPONSOR	Dr. Vanessa Grubbs, MD MPH
FUNDING ORGANIZATION	NIH Natl Inst Diabetes & Digest & Kidney
NUMBER OF SITES	1
RATIONALE	The purpose of this study is (1) to determine whether a 12-month trial of patients from underserved communities with clinically significant gum disease and kidney disease randomly assigned to intensive gum disease treatment or delayed treatment is feasible and (2) to determine the variability of various tests of kidney function and inflammation in response to intensive gum disease treatment.
STUDY DESIGN	This is an unblinded, randomized, controlled pilot trial with 2 intent-to-treat treatment arms.
PRIMARY OBJECTIVE	Aim 1: To assess the feasibility of recruiting patients to this pilot trial.
SECONDARY OBJECTIVES	Aim 2: To determine the variability of kidney biomarkers in response to periodontal disease treatment.
NUMBER OF SUBJECTS	51
SUBJECT SELECTION CRITERIA	Inclusion Criteria: 1. Age 20 to 75 years 2. Speaks English or Spanish 3. At least 2 estimated glomerular filtration (eGFR) rate measurements of 15-59 mL/min/1.73 m2 within the preceding 12 mo 4. No eGFR increase by ≥ 50% in the preceding 6 months 5. Moderate/severe periodontal disease in accordance with the CDC and Prevention/American Academy of Periodontology definition AND at least 30% sites with bleeding on probing Exclusion Criteria: 1. Under age 20 or over age 75 2. Unable to understand and provide informed consent 3. Currently receiving dialysis 4. Receiving current immunosuppressant therapy 5. Receiving current anticoagulation therapy resulting in an elevated prothrombin time or an International Normalized Ratio (INR) greater than 2.0

	6. Pregnant
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Those assigned to the Intensive Intervention Group will undergo intensive treatment to include administration of local anesthetic to up to 2 oral quadrants for scaling and root planing with ultrasonic and hand instruments. Arestin (minocycline HCl) will be applied to any sites with probing depth ≥ 5 mm. Women with positive urine pregnancy tests (ie, have become pregnant while on-study) who are assigned to the Intervention Group will not receive Arestin.
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	Subjects assigned to the Rescue Treatment Group will undergo assessment and documentation of the levels of periodontal disease throughout the oral cavity. They will have extraction of hopeless teeth plus scaling and root planing only to sites of disease progression (3 mm or more) since screening examination. No administration of the product until the end of the study.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be on study for up to 12 months: Screening visit Baseline visit 4 month visit 8 month visit 12 month (last visit) The total duration of the study is expected to be 12 months from the time of recruitment.
CONCOMMITANT MEDICATIONS	Allowed: Prohibited:
EFFICACY EVALUATIONS	
PRIMARY ENDPOINT	Repeated scaling and root planing to resolution of periodontal disease (no sites with probing depths >3mm and <10% bleeding on probing among all sites).
SECONDARY ENDPOINTS	This is a pilot study intended to determine the variability of various renal and inflammatory biomarkers in response to intensive periodontal disease treatment as a means of establishing the pathophysiologic mechanism(s) of periodontal pathogen injury.

OTHER EVALUATIONS	Feasibility and process outcomes: assessment of enrollment, randomization, adherence to study protocol, participant and study coordinator input.
SAFETY EVALUATIONS	Adverse events will be ascertained at each study visit. Ascertainment will include the event start and stop date, severity, outcome, whether it was expected, relationship to study intervention, and any actions taken regarding the study intervention.
PLANNED INTERIM ANALYSES	When approximately 50% of patients have completed the study through study month 4, an interim analysis for safety will be conducted by an independent data monitoring committee. Serious adverse events will be monitored by the committee on an ongoing basis throughout the study. The DSMB will meet twice a year during the intervention phases of the randomized controlled trial (approximately an 18-month period). This Chairperson will be responsible for overseeing the meetings and developing the agenda in consultation with the PI and will also serve at the Safety Officer. The Chair is the contact person for the DSMB and for severe adverse event reporting.
STATISTICS **Primary Analysis Plan**	We will calculate descriptive statistics (mean, standard deviation) of each clinical outcome which will include a traditional marker of kidney function (serum creatinine), cystatin C, markers of kidney structure {as glomerular injury (albuminuria) and tubular injury [neutrophil gelatinase-associated lipocalin (NGAL)]}; a marker of vascular endothelial injury [asymmetrical dimethylarginine (ADMA)]; and markers of systemic inflammation (IL-6 and C-reactive protein) measured at baseline, study month 4, and study month 12. We will use repeated-measures generalized estimating equations (GEE) to compare changes in clinical outcomes over time within each treatment group and to compare differences between treatment groups taking individual change over time into account.
Rationale for Number of Subjects	This is a pilot study. To our knowledge, there are no existing data of the anticipated effect size of periodontal treatment to inform sample size calculations. However, because a primary aim is to determine the variability of various renal and inflammatory biomarkers, we seek to enroll at least 30 subjects in the intervention arm of the trial. We assume 25% of patients screened will meet all inclusion/exclusion criteria and enroll in the study.

1 BACKGROUND

Chronic kidney disease (CKD) remains a prevalent public health issue despite intense efforts targeting traditional risk factors. Periodontal disease, both common and modifiable, has been implicated as a promising novel focus for impacting CKD. A few recent studies, including our work, have collectively found that subjects with significant periodontal disease were 1.5 to 2-fold more likely to have CKD than those without periodontal disease**.** Underserved (poor/uninsured) populations are differentially impacted by both CKD and periodontal disease.

Although periodontal disease is an infection of the oral cavity, periodontal pathogens can access systemic circulation through normal oral health procedures like tooth brushing and even chewing**.** As a result, the circulating bacterial coating can bind specific receptors found throughout the kidney. Once bound to the bacterial coating, the receptors are activated to launch an inflammatory cascade that may lead to deterioration in renal function.

1.1 Overview of Clinical Studies

This pilot study will be conducted among an underserved patient population. Therefore, we expect the prevalence of significant periodontal disease to be due to low rates of dental care. In our recently published manuscript[21] in which we examined a cohort of 2,235 and 4,263 adult (≥ 20 years) patients with without CKD, respectively, and at least 1 year of follow-up between 2005 and 2010 within the San Francisco Department of Public Health Community Health Network, we found that only 245 (11.0%) patients with and 741 (17.4%) patients without CKD had at least one outpatient dental visit within the Network throughout the study period. Those with CKD had a 25% lower likelihood of having a dental visit [HR = 0.75, 95% CI (0.64-0.88)] than those without CKD adjustment for age, gender, race/ethnicity, language, insurance, and monthly income.

2 STUDY RATIONALE

To our knowledge, there are no existing data of the anticipated effect size of periodontal treatment to inform sample size calculations. Further, the pathophysiologic mechanism(s) of periodontal pathogen injury has not been established. Therefore, in addition to measuring creatinine as a traditional marker of kidney function, we will measure cystatin C; markers of kidney structure {as glomerular injury (albuminuria) and tubular injury [neutrophil gelatinase-associated lipocalin (NGAL)]}; vascular endothelial injury [asymmetrical dimethylarginine (ADMA)]; and systemic inflammation (IL-6 and C-reactive protein) to both predict the effect of treatment and determine the specific mechanisms through which the periodontal pathogen may exert effects. Though kidney failure (eGFR <15 ml/min/1.73m2 or the initiation of renal replacement therapy) would be a definitive clinical end point for a trial evaluating the effect of intensive periodontal disease treatment on CKD progression, it is impractical as a primary outcome within the time and resource constraints of the career development award funding this project.

2.1 Risk / Benefit Assessment

This study involves an increase over minimal risk. The study requires blood draws; data collection from medical records; a periodontal exam; and periodontal therapy consisting of administration of systemic oral antibiotics, scaling and root planing and treatment with local delivery minocycline antibiotics (Arestin). The probability and magnitude of harm or discomfort anticipated in this research study presents low risks and improved dental care compared to subject baseline that is reasonably commensurate with current medical or dental practice. The likelihood of serious harm to subjects is low.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to test the feasibility of conducting this trial among an underserved population (mostly poor and/or low literacy).

3.2 Secondary Objectives

The secondary purpose is to determine the variability of renal and inflammatory biomarkers in response to intensive periodontal therapy over a 12-month period among participants with both chronic kidney disease (CKD) and significant periodontal disease.

4 STUDY DESIGN

4.1 Study Overview

This is an unblinded, randomized, controlled pilot trial with 2 intent-to-treat treatment arms: immediate intensive periodontal therapy or delayed intensive periodontal therapy.

Randomization will be stratified with respect to diabetes (a strong risk factor for causing/aggravating both CKD and periodontal disease) to prevent an imbalance between the 2 arms. The accrual target is 51 patients from the San Francisco General Hospital (SFGH) Renal Clinic. Participants will be assigned 2:1 to the Intensive Intervention Group for the intensive periodontal treatment protocol (n = 34) or to the Rescue Treatment Group for rescue periodontal treatment only with intensive treatment at the end of the study (n = 17).

Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study.

Subjects who meet oral study criteria and CDC/AAP definition for moderate/severe periodontal disease will be randomized 2:1 to either an intensive intervention cohort or a rescue treatment cohort [1,2] in blocks of 3, with stratification by presence of diabetes to ensure balance between groups.

Total duration of subject participation will be 12 months. Total duration of the study is expected to be 18 months.

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

Repeated scaling and root planing to resolution of periodontal disease (no sites with probing depths >3mm and <10% bleeding on probing among all sites).

5.2 Secondary Efficacy Endpoints

This is a pilot study intended to determine the variability of various renal and inflammatory biomarkers in response to intensive periodontal disease treatment as a means of establishing the pathophysiologic mechanism(s) of periodontal pathogen injury.

5.3 Safety Evaluations

Adverse events will be ascertained at each study visit. Ascertainment will include the event start and stop date, severity, outcome, whether it was expected, relationship to study intervention, and any actions taken regarding the study intervention.

6 SUBJECT SELECTION

6.1 Study Population

Subjects with at least 2 estimated glomerular filtration (eGFR) rate measurements of 15-59 mL/min/1.73 m^2 within the preceding 12 months and who meet the inclusion and exclusion criteria will be eligible for participation in this study.

6.2 Inclusion Criteria

1. Age 20 to 75 years
2. Speaks English or Spanish
3. At least 2 estimated glomerular filtration (eGFR) rate measurements of 15-59 mL/min/1.73 m^2 within the preceding 12 months
4. No eGFR increase by ≥ 50% in the preceding 6 months
5. Moderate/severe periodontal disease in accordance with the Centers for Disease Control and Prevention/American Academy of Periodontology definition AND at least 30% sites with bleeding on probing

6.3 Exclusion Criteria

1. Pregnant, breastfeeding, or unwilling to practice birth control during participation in the study.
2. Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.
3. Under age 20 or over age 75
4. Unable to understand and provide informed consent
5. Currently receiving dialysis
6. Receiving current immunosuppressant therapy

7. Receiving current anticoagulation therapy resulting in an elevated prothrombin time or an International Normalized Ratio (INR) greater than 2.0

7 CONCURRENT MEDICATIONS

All subjects should be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies.

7.1 Allowed Medications and Treatments

Standard therapy for CKD is allowed except for treatments noted in the exclusion criteria described above and as noted in the prohibited medications section below.

Prohibited Medications and Treatments

The following medications are prohibited during the study and administration will be considered a protocol violation. Subjects who begin taking these medications will be withdrawn from the study.

Warfarin (Coumadin)

Immunosuppressant medications:

Prednisone

Cellcept/Mycophenolate/Mofetil/MMF

Cyclophosphamide/Cytoxan

Tacrolimus/Prograf

Siroimus/Rapamune

Azathioprine/Imuran/Azasan

Cyclosporine/Gengraf/Neoral/Sandimmune

Any DMARD: Methotrexate, Etanercept, Adalimumab, Infliximab, Leflunomide, Sulfasalazine, Hydroxychloroquine

8 STUDY TREATMENTS

8.1 Method of Assigning Subjects to Treatment Groups

Randomization will be stratified with respect to diabetes (a strong risk factor for causing/aggravating both CKD and periodontal disease) to prevent an imbalance between the 2 arms. The accrual target is 51 patients from the San Francisco General Hospital (SFGH) Renal Clinic. Participants will be assigned 2:1 to the Intensive Intervention Group for the intensive periodontal treatment protocol (n = 34) or to the Rescue Treatment Group for rescue periodontal treatment only with intensive treatment at the end of the study (n = 17). At the end of the study the Rescue Treatment Group will receive the full intensive treatment.

8.2 Supply of Study Drug at the Site

Orapharma, Inc. will ship Arestin to the investigational site. The Investigator will store the drug in a locked office at room temperature.

8.2.1 Dispensing

Investigator and Study Research Coordinator will have access to Arestin and will dispense to Study Hygienist as needed for study intervention.

8.2.2 Administration Instructions

The Study Hygienist will apply Arestin to periodontal pockets probing 5mm or more at each study visit for subjects in the Intervention Group and at the last study visit for subjects in the Rescue Control Group. An exception will be Intervention Group subjects who become pregnant during the study. They will not be given Arestin due to risk of teratogenicity.

8.3 Supply of Study Drug at the Site

Orapharma will ship Arestin to the investigational site in batches agreed upon with Investigator.

8.3.1 Storage

Study drug should be stored by the study site at controlled room temperature, 15 to 30ºC (59 to 86ºF). If the temperature of study drug storage in the clinic/pharmacy exceeds or falls below this range, this should be reported to the Sponsor or designee and captured as a deviation. Subjects will be instructed to store the medication in original packaging (foil pouch and protected from light) at room temperature according to the instructions outlined on the Drug Administration Instructions.

8.4 Study Drug Accountability

An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The number of study drug dispensed and returned by the subject will be recorded on the Investigational Drug Accountability Record. The study monitor will verify these documents throughout the course of the study.

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject. If appropriate, assent must also be obtained prior to conducting any study-related activities.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at Baseline/Screening and Study Visits 4 months, 8 months, 12 months and at early termination when applicable. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded at Baseline.

9.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded at Baseline.

9.1.4 Physical Examination

A complete physical examination will be performed by either the study nurse at Baseline. Qualified staff (MD, NP, RN, and PA) may complete the abbreviated physical exam at all other visits. New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

9.1.5 Vital Signs

Body temperature, blood pressure, pulse and respirations will be performed after resting for 5 minutes at Baseline, months 4, 8, and 12.

9.1.6 Oral Examination

At baseline and every study visit, Mark Ryder/Periodontal Residents will conduct a complete oral examination in the SFGH Oral Surgery Clinic including determination of PD and CAL at 6 sites per tooth, assessment of BOP, Plaque Index, Gingival Index, and determination of hopeless teeth. Per standard of care, confirmation that teeth are hopeless will be on the basis of a Panorex radiograph performed for that purpose.

9.1.7 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates), outcome, treatment and relation to study drug will be recorded on the case report form (CRF).

9.2 Clinical Laboratory Measurements

9.2.1 Hematology

Blood for Hemoglobin A1c (HbA1c, a marker for diabetes) will be sent to the SFGH Lab at baseline study visit.

9.2.2 Pregnancy Test

A urine pregnancy test will be obtained from female subjects who are of childbearing age prior to their participation in the study and at each study visit.

9.2.3 Urinalysis

Urine will be obtained at study visits baseline, month 4, and month 12 and sent to the SFGH clinical laboratory for microalbumin quantification and the UCLA Clinical and Research Laboratory for NGAL. Urine for tobacco metabolites (Cotinine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol [NNAL, a metabolite of the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and biomarker for tobacco use) will be sent to the Clinical Pharmacology Laboratory at UCSF/SFGH.

9.3 Research Laboratory Measurements (include sections as appropriate)

Blood will be obtained at study visits baseline, month 4, and month 12 for Creatinine, Cystatin C, Neutrophil gelatinase-associated lipocalin (NGAL, a marker of renal tubular injury), Assymetrical dimethylargine (ADMA, a marker of endothelial injury), Interleukin 6 (IL-6, a biomarker of systemic inflammation), Cotinine (a metabolite of nicotine and biomarker for exposure to tobacco smoke), and serum C-reactive protein (CRP) and IL-6 determinations for assessment of systemic evidence for infection and/or inflammation. Specimens will be collected in appropriate vials, labeled and shipped overnight in batches to the UCLA Clinical and Research Laboratory except for ADMA, which will be shipped to the Oxonon Laboratory in Oakland, California. Samples will be stored at -70°C while waiting to be shipped.

Dental measurements include collection of saliva, plaque and gingival crevicular fluid at each study visit. Samples will be collected in sterile specimen cups, placed in an ice cup and kept in an ice cup until delivery to laboratory for processing (within 2 hours) or stored a -70°C.

10 EVALUATIONS BY VISIT

10.1 Visit 1 (Screening)

1. Review the study with the subject and obtain written informed consent and HIPAA authorization and assent, if appropriate.
2. Assign the subject a unique screening number.
3. Record demographics data.
4. Record concomitant medications.
5. Administer questionnaires.
6. Oral examination/screening.
7. Schedule subject for Baseline visit and provide payment.
8. Randomize subject.

10.2 Visit 2 (Baseline)

1. Concomitant medications review.
2. Perform physical examination.
3. Perform and record vital signs.
4. Collect blood and urine sample.
5. Administer questionnaires.
6. Perform Panorex mouth x-ray.
7. Oral exam and assess disease progression
8. Writes order for extractions, full mouth deep cleaning, & (Arestin if Intensive Intervention Group).
9. Provide brushing and flossing education
10. Performs scaling & planing in areas of disease progression.
11. If needed, extract hopeless teeth and provides aftercare instructions.
12. Schedules next appointment and provide visit payment.

10.3 Visit 3 (Month 4)

1. Record any Adverse Experiences.
2. Record changes to concomitant medications.
3. Perform and record vital signs.
4. Collect blood and urine sample.
5. Administer questionnaires.
6. Oral exam and assess disease progression.
7. If question of hopeless teeth schedule Panorex mouth x-ray.
8. Writes order for extractions (if needed), (full mouth deep cleaning, & Arestin if Intensive Intervention Group).
9. Performs scaling & planing in areas of disease progression.
10. If needed, extract hopeless teeth and provides aftercare instructions.
11. Schedule next appointment and provide payment.

10.4 Visit 4 (Month 8)

1. Record any Adverse Experiences.
2. Record changes to concomitant medications.
3. Perform and record vital signs.
4. Collects blood and urine sample.
5. Administer questionnaires.

6. Oral exam and assess disease progression.
7. If question of hopeless teeth schedule Panorex mouth x-ray.
8. Writes order for extractions (if needed), (full mouth deep cleaning, & Arestin if Intensive Intervention Group).
9. Performs scaling & planing in areas of disease progression.
10. If needed, extract hopeless teeth and provides aftercare instructions.
11. Schedule next appointment and provide payment.

10.5 Visit 5 (Month 12)

1. Record any Adverse Experiences.
2. Record changes to concomitant medications.
3. Perform and record vital signs.
4. Collects blood and urine sample.
5. Administer (end of study) questionnaires.
6. Oral exam and assess disease progression.
7. If question of hopeless teeth schedule Panorex mouth x-ray.
8. Writes order for extractions (if needed), (full mouth deep cleaning, & Arestin if Intensive Intervention Group).
9. Performs scaling & planing in areas of disease progression.
10. If needed, extract hopeless teeth and provides aftercare instructions.
11. Schedule next appointment and provide payment.

11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

11.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

11.2.1 Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per UCSF CHR Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

11.3 Medical Monitoring

Vanessa Grubbs should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone: (415) 206-5649
Pager: (415) 443-4406

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Discontinuation of Study and/or Drug

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents Refer to Section 10 for early termination procedures.

12.3 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. As noted above, subjects who discontinue study treatment early (i.e., they withdraw prior to Visit 5 (Month 12)) should have an early discontinuation visit. Refer to Section 10 for early termination procedures. Subjects who withdraw after Visit 1 (screening) but prior to Visit 5 (Month 12) should be encouraged to come in for a final visit (and the procedures to be followed would include those for their next scheduled visit).

12.4 Replacement of Subjects

Subjects who withdraw from the study treatment will not be replaced.

Subjects who withdraw from the study will not be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, investigator, or staff fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The Sponsor will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

14 DATA SAFETY MONITORING

The UCSF Data Safety Monitoring Board (DSMB) will establish a Data Monitoring Committee (DMC) to review data relating to safety and efficacy, to conduct and review interim analyses, and to ensure the continued scientific validity and merit of the study, according to the UCSF Data Safety Monitoring Board Operations Manual and a DMC Charter to be established for this protocol. There will be (number of reviews, if any) interim review(s) conducted by the DMC for the purpose of monitoring study conduct and assessing patient safety. Further details regarding the timing and content of the interim reviews is included in the statistical section below.

15 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

15.1 Data Sets Analyzed

Randomization will be stratified with respect to diabetes (a strong risk factor for causing/aggravating both CKD and periodontal disease) to prevent an imbalance between the 2 arms. Participants will be assigned 2:1 to the Intensive Intervention Group for the intensive periodontal treatment protocol (n = 34) or to the Rescue Treatment Group for rescue periodontal treatment only with intensive treatment at the end of the study (n = 17).

All eligible patients who are randomized into the study and receive at least one dose of the study drug (the Safety Population) will be included in the safety analysis.

15.2 Demographic and Baseline Characteristics

The expected study population age 20 to 75 years consists primarily of impoverished individuals who may have low health literacy and/or may speak primarily Spanish with low English literacy. Usual dental care in this population is essentially very limited or none until teeth have to be extracted, and perhaps not then.

15.3 Analysis of Primary Endpoint

Clinical assessment for resolution of periodontal disease (no sites with probing depths >3mm and <10% bleeding on probing among all sites) at each follow-up study visit.

15.4 Analysis of Secondary Endpoints

We will calculate descriptive statistics (mean, standard deviation) of each clinical outcome which will include a traditional marker of kidney function (serum creatinine), cystatin C, markers of kidney structure {as glomerular injury (albuminuria) and tubular injury [neutrophil gelatinase-associated lipocalin (NGAL)]}; a marker of vascular

endothelial injury [asymmetrical dimethylarginine (ADMA)]; and markers of systemic inflammation (IL-6 and C-reactive protein) measured at baseline, study month 4, and study month 12. We will use repeated-measures generalized estimating equations (GEE) to compare changes in clinical outcomes over time within each treatment group and to compare differences between treatment groups taking individual change over time into account.

Safety and tolerability data will be summarized by treatment group.

Adverse event rates will be coded by body system and MedDra classification term. Adverse events will be tabulated by treatment group and will include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to study drug.

15.5 Interim Analysis

When approximately 50% of patients have completed the study through study month 4, an interim analysis for safety will be conducted by an independent data monitoring committee.

15.6 Sample Size and Randomization

This is a pilot study. To our knowledge, there are no existing data of the anticipated effect size of periodontal treatment to inform sample size calculations. However, because a primary aim is to determine the variability of various renal and inflammatory biomarkers, we seek to enroll at least 30 subjects in the intervention arm of the trial. Subjects who meet oral study criteria and CDC/AAP definition for moderate/severe periodontal disease will be randomized 2:1 to either an intensive intervention cohort or a rescue treatment cohort in blocks of 3, with stratification by presence of diabetes to ensure balance between groups.

16 DATA COLLECTION, RETENTION AND MONITORING

16.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a subject number.

For eCRFs: If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for

completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

16.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

16.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

16.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

16.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

16.6 Monitoring

Monitoring visits will be conducted by representatives of the Sponsor according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and

appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

16.7 Subject Confidentiality

In order to maintain subject confidentiality, only a subject number will identify all study subjects on CRFs and other documentation submitted to the Sponsor. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

17 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

17.1 Protocol Amendments

Any amendment to the protocol will be written by the Sponsor. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

17.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to the Sponsor or designee prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

17.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject and the original will be maintained with the subject's records.

17.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

17.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

APPENDIX 1. EXAMPLE OF SCHEDULE OF STUDY VISITS

	VISIT 1 (Screening)[a]	VISIT 2 (Baseline)[a]	VISIT 3 (Month 4)[a]	VISIT 4 (Month 8)[a]	VISIT 5 (Month 12)
Informed Consent	X				
Medical History	X				
Complete Physical Exam					
Height		X	X	X	X
Weight		X	X	X	X
Vital Signs		X	X	X	X
Pregnancy Test (Urine or Serum)		X	X	X	X
Hematology		X	X	X	X
C-Reactive Protein		X	X	X	X
Urinalysis		X	X	X	X
Randomization	X				
Dispensing or Administration of Study Drug		X	X	X	X
Perform Panorex mouth x-ray	X				
Oral exam and assess disease progression	X	X	X	X	X
Writes order for extractions, full mouth deep cleaning, & (Arestin if Intensive Intervention Group).	X	X	X	X	X
Performs scaling & planing in areas of disease progression	X	X	X	X	X
Provide brushing and flossing education	X				
Tooth Extraction	X				
Concomitant Medication Review	X	X	X	X	X
Adverse Experiences	X	X	X	X	X

[a] ±2 week