Fabrication of a Definitive CAD/CAM Titanium Abutment Prior to Guided Surgery: A Pilot Study

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List of Abbreviations

CAD/CAM – Computer Aided Design/ Computer Aides Milling
CBCT – Cone Beam Computer Tomography
IV –Intravenous
UNC – University of North Carolina
SOD – School of Dentistry
PI – Primary Investigator
CRF – Case Report Form
PHI – Personal Health Information

Study Summary

Title	Fabrication of a Definitive CAD/CAM Titanium Abutment Prior to Guided Surgery: A Pilot Study
Protocol Number	IRB#13-2376
Methodology	Randomized trial/cohort with 2 arms (experimental) groups
Study Duration	7 months
Study Center(s)	Single Center
Objectives	To determine if a custom fabricated, patient specific, CAD/CAM titanium abutment that ideally supports the hard and soft tissues with both esthetics and function can be fabricated prior to guided surgery using computed tomography and diagnostic gypsum models
Number of Subjects	*24*
Diagnosis and Main Inclusion Criteria	Single edentulous space seeking tooth replacement with dental implant
Statistical Methodology	Fisher's Exact test

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Conventional dental implant therapy as described by Branemark and colleagues over 3 decades ago involves 3-6 months of healing prior to functional loading following surgical endosseous dental implant placement (Branemark 1983). In the protocol, the implants are buried under the gingival tissues until full healing is completed. Improved dental implant surface technology and osseointegration potential, along with improved understanding of the biology and mechanics of dental implants has led to loading protocols that involve less time for implant healing prior to functional loading. Commonly for single dental implants, loading is completed at 8 weeks, termed early loading (Bornstein et al. 2005, Cooper et al. 2001).

Although dental implants typically are not loaded with function (occlusion) until 8-12 weeks, immediate provisionalization is a procedure commonly provided in the course of dental implant therapy (Cornelini et al. 2005, Degidi et al. 2006, Drago et al. 2004). This protocol involves placing a provisional restoration on the implant that is out of function during the healing period further reducing the time for a patient to have a fixed tooth in the edentulous area.

Although dental implant therapy is considered the gold standard for tooth replacement therapy in most clinical situations, a common concern among practitioners and patients preventing the application of the procedure is the time involved to completion. Even when provisionalization of the implant is completed immediately, a conventional final impression is needed following healing of the dental implant. The patient is then reappointed for delivery of the final abutment and indirect crown restoration. Depending on the loading protocol, treatment can take as long as 3-5 months to complete.

Using cone beam computed tomography, software is available allowing precise virtual placement of an implant and creation of a milled guide from the plan (D'haese et al. 2010). This milled surgical guide allows the surgeon to place the implant precisely as planned using the patient's CBCT information. Utilizing this virtual plan, it is theoretically possible to fabricate a CAD/CAM patient specific abutment prior to surgery. This allows delivery of the abutment either at surgery or at delivery of the crown following osseointegration. Ultimately, fabrication of the final abutment prior to surgery removes that current necessity of appointing the patient for the final impression. Following surgical implant placement, the next appointment for the patient would be delivery of the final crown. Dental implant therapy could be reduced to 8 weeks of total therapy and 2 total appointments.

While guided surgery for the placement of the implant fixture is extremely precise and is milled from the virtual plan using the patient's CBCT information, surgical guides can have minor error leaving the implant in a position slightly different from the information in the virtual software (Turbush et al. 2012, Sarment et al. 2003). If the abutment and/or crown are produced prior to surgery, these slight differences in the virtual vs. actual position of the implant may provide an abutment and/or crown that either doesn't fit or is esthetically unpleasing.

It is the interest of this study to investigate the possibility of creating a patient specific abutment and provisional crown prior to surgery that is functionally and esthetically pleasing. With this treatment possibility, the time and expense involved with single tooth dental implant therapy will be reduced allowing a better experience for both patient and provider.

1.2 Clinical Data to Date

There is no available clinical data that pertains to this study in which this protocol developed by Astra-Tech is used to fabricate custom Atlantis abutments prior to guided surgery.

2 Study Objectives

Purpose: To evaluate the possibility of fabricating an ideal CAD/CAM custom abutment that adequately supports the hard and soft tissues in a single edentulous space prior to guided surgery. Evaluation of the custom abutment will be completed at 2 intervals post operatively, with abutment exposure being the primary outcome at follow-up. With knowledge of fabricating the definitive CAD/CAM abutment prior to surgery, soft tissue development can begin immediately and restoration of the implant can be completed without subsequent soft tissue trauma during crown fabrication.

Participants: The study will seek 24 patients with a minimum of 20 teeth who have a bound edentulous space who seek restoration with a dental implant crown.

Procedures (methods): This is a convenience sample, we will recruit subjects who present to the graduate prosthodontics clinic or inquire about the study will be eligible to receive dental implant surgery with subsequent definitive abutment and provisional crown delivery at eight weeks. The group will then be randomly split with half of the group receiving a custom abutment with margin placement .5mm sub-gingivally and half of the group receiving a custom abutment with margin placement 1.5 mm sub-gingivally. Final impression for the definitive e-max all-ceramic crown will be completed at eight weeks with final crown delivery at eleven weeks. Follow-up and data collection will be completed at eight weeks, eleven weeks, and twenty-four weeks post operatively.

Primary Objective
Abutment margin exposure

Secondary Objective
Provisional crown fit.

3 Study Design

3.1 General Design

The general design of the study is a cohort study with 2 arms in which subjects are randomly assigned to one of 2 experimental groups. The expected duration of subject participation is 7 months. The subjects will complete 7 appointments within this 7 months span that includes initial screening, CBCT evaluation of the site, surgical placement of the dental implant, restoration of the dental implant and associated follow-ups at 7 days, 8 weeks, 11 weeks and 24 weeks.

3.2 Primary Study Endpoints

The primary objective is to compare differences in margin exposure of the abutment between baseline to 6 months later.

3.3 Secondary Study Endpoints

Secondary Objectives include measurement of the soft tissue response based on the condition of the peri-implant mucosa (bleeding on probing) as well as provisional crown fit.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

1. Partially edentulous with single edentulous space seeking dental implant tooth replacement therapy

2. Age 18-99

3. Edentulous site where previous tooth has been extracted for at least 2 months

4. Minimum of 20 teeth present in mouth

5. Consent to Participate in Clinical Trial

6. Able to tolerate dental implant surgical and restorative procedures

4.2 Exclusion Criteria

1.ASA Class 3+, Immunocompromised, Contraindicated for dental implant therapy in the UNC Department of Prosthodontics

2.Present drug abuse, Pregnant or plans to be pregnant at any point during trial

3. Patients in need of lateral window sinus graft

4. Patients in need of grafting prior to implant placement

5. Patients in need of extensive grafting at time of implant placement

6. Tooth is present or extracted within the last 2 months

7. History of IV bisphosphonate use or oral bisphosphonate use contraindicating dental implant therapy

8. Untreated caries or periodontal disease

9. Severe bruxism

10. Smoker within the past 6 months

11. Unlikely to be able to comply with the study procedures according to investigators

12. Known allergy to any materials used in dental implant surgery

4.3 Subject Recruitment and Screening

Patient will be identified by 2 methods. Patients will self-identify themselves for the study if they are interested in participation via response to mass-email and website inquiries. Patient will also be identified and inquired about possible inclusion in the study if they present to the school of dentistry with qualifying inclusion criteria.

Patients will be recruited through e-mail correspondence and advertisement on the UNC Department of Prosthodontics website. Patients will also be recruited in person if patients present with qualifying inclusion criteria. It is the belief of the primary investigator that no problems will be encountered in recruiting the allotted number of patients to complete the study. Inquiries about the study will be answered and the investigators only will conduct enrollment in the study. Subjects will be contacted during the study by telephone or direct mail.

4.3.1 When and How to Withdraw Subjects

Subjects may withdraw at any point during study. There are no circumstances for discontinuation unless CBCT reveals that a dental implant is not possible in the site or a subject becomes pregnant during the study period.

4.3.2 Data Collection and Follow-up for Withdrawn Subjects

Even though subjects may be withdrawn prematurely from the study, it is imperative to collect at least survival data on such subjects throughout the protocol defined follow-up period for that subject (though careful thought should be give to the full data set that should to be collected on such subjects to fully support the analysis). If a subject withdraws consent to participate in the study, attempts will be made to obtain permission to record at least survival data up to the protocol-described end of subject follow-up period.

4.4 Method for Assigning Subjects to Treatment Groups

Subjects will be assigned to treatment groups through randomization methods.

4.5 Preparation and Administration of Study Drug

N/A

4.6 Subject Compliance Monitoring

N/A

4.7 Prior and Concomitant Therapy

N/A

4.8 Blinding of Study Drug (if applicable)

N/A

4.9 Receiving, Storage, Dispensing and Return

4.9.1 Receipt of Drug Supplies

An IIS is submitted to AstraTech and supplies for study will be supplied by the company that include implant surgical supplies, implants, and impression copings, among other items needed to conduct protocol.

Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

4.9.2 Storage

N/A

4.9.3 Dispensing of Study Drug

N/A

4.9.4 Return or Destruction of Study Drug

N/A.

5 Study Procedures

5.1 Visit 1 (1 hour)

Appointment 1: Screening Exam (1 hour), Prior to inclusion into study

All patients will receive standard care for their initial clinical appointment. This appointment is not research-driven. Standard care includes:

- General extraoral and intraoral exam
- Maxillary and mandibular alginate impressions
- Standardized radiographs (panoramic film)
- Standardized photographs
- Completion of the dental implant surgery consent form
- Completion of the treatment in the graduate Prosthodontic clinic consent form

If the patient is eligible for the research study, s/he will be introduced to the study and given a copy of the consent form to take home. If the potential subject is interested in participating in the study, the consent form will be signed at the beginning of visit 2 and the subject will be enrolled.

5.2 Visit 2

Appointment 2: Completion of consent for inclusion into study, CBCT with scanning appliance

CBCT will be obtained of surgical site to be used for planning and surgical guide fabrication. This procedure is the standard of care for implant patients within the school of dentistry.

5.3 Visit 3

Appointment 3: Place implant in healed alveolar ridge

Each patient will have the opportunity to ask remaining questions about the surgery protocol. Each patient will use a pre-operative rinse of antibacterial mouth rinse (Peridex).

Standard UNC Graduate Prosthodontics clinic protocol for implant placement will be used including full body sterile drape of patient as well as surgical scrub of both operator and assistant. Local anesthetic will be used at

surgical site (2% lidocaine 1:100,000 Epinephrine).

An Astra Tech dental implant will be placed using standard clinical protocol. The dental implant will be covered with a cover screw to allow soft tissue healing. A post-operative radiograph will be made to edemonstrate proper placement of the implant in bone.

The patient will be prescribed normal post-operative medications including analgesics and anti-bacterial mouth rinse (peridex).All procedures listed are the standard of care for implant placement.

5.4 Visit 4

Appointment 4: Follow-up (1 week post-op)

Usual and customary follow-up to be completed to verify adequate and acceptable healing of surgical site. This procedure is the standard of care for implant placement.

5.5 Visit 5

Appointment 5: Final impression (8 weeks post-op) for full coverage crown

Final impression for crown fabrication of the abutment will be completed at 8 weeks post surgery using standard clinical protocol. Provisional restorations will be placed onto final abutments delivered at same appointment. These procedures are standard of care for all participants. Research-driven data to include abutment exposure will be collected from subjects regarding fit of the provisional restoration.A peri-apical radiograph of the implant in bone is produced to demonstrate the proper connection of the abutment to the implant at the time of placement of the abutment.

5.6 Visit 6

Appointment 6: Delivery final E-max crown restoration (11 weeks post-op)

Delivery of final crown will be completed using standard clinical protocol at 11 weeks post-surgery. Research driven data to include abutment exposure will be collected from all subjects regarding esthetics of the final abutment.

5.7 Visit 7

Appointment 7: Follow-up 24 weeks post-op

Follow-up of crown restorations will be completed at 6 months post surgery (24 weeks). Research driven data to include abutment exposure will be collected for all subjects. Bleeding on probing measurements will be made to evaluate soft tissue health around the abutments (Standard of Care). A peri-apical radiograph will be made for hard tissue evaluation of the abutment (Standard of Care). Photographs will be taken of restorations per standard protocol (photographs are standard of care). The patient will then be dismissed from the study.

6 Statistical Plan

6.1 Sample Size Determination

Sample size determination was based on obtaining a reasonable amount of subjects to have meaningful results that will allow completion of the study in time allotted.

6.2 Statistical Methods

Demographics and other baseline characteristics will be presented by means of descriptive statistics.

The primary objective is to compare differences in margin exposure of the abutment between baseline to 6 months later. The null hypothesis is that there is no difference in the margin exposure of the abutment between those 2 visits. Ho will be tested by means of Fisher's exact test, after each abutment margin is classified as it shows or not. A p-value less than 5% will be regarded statistically significant.

Secondary objectives include:

Measurement of the soft tissue response based on the condition of the peri-implant mucosa (bleeding on probing). Fisher's exact test will be used after the site has been evaluated for presence of bleeding or not. Provisional crown fit at delivery of provisional crown- Fisher's exact test will be used after the provisional crown is determined to fit or not.

6.3 Subject Population(s) for Analysis

The subject population for analysis is an all randomized population obtained through a convenience sample.

7 Safety and Adverse Events

7.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research,
- Serious (as defined below) "***Serious" is different than "severe" as reported in the CTC criteria that applies a grade to the AE.***

Adverse Event
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event

- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity

- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

7.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

7.3 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators and the protocol sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others
  (see definitions, section 8.1).

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Investigator reporting:

For reportable deaths, the initial submission to the UNC IRB may be made by contacting the IRB Director or Associate Director. The AE/Unanticipated Problem Form is required as a follow up to the initial submission.

Other Reportable events:
For clinical drug trials, the following events are also reportable to the UNC IRB:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

Sponsor reporting: Notifying the FDA

The study sponsor is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND safety reports. The following describes the safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 7 calendar days***
  Any study event that is:
  - associated with the use of the study drug
  - unexpected,
  - fatal or life-threatening, and

- ***Within 15 calendar days***
  Any study event that is:
  - associated with the use of the study drug,
  - unexpected, and
  - serious, but not fatal or life-threatening

-or-

– a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

Any finding from tests in laboratory animals that:

– suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Additional reporting requirements
Sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Reporting Process
Adverse events may be submitted on FDA Form 3500A or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section 8.3. The contact information for submitting IND safety reports is noted below:

8 Data Handling and Record Keeping

8.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

8.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

8.3 Case Report Forms (as applicable)

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR

WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

8.4 Records Retention

Records will be kept for 2 years.

9 Study Monitoring, Auditing, and Inspecting

9.1 Study Monitoring Plan

N/A

9.2 Auditing and Inspecting

N/A

10 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment ___ for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

11 Study Finances

11.1 Funding Source

The study will be funded through an IIS grant from AstraTech.

11.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of UNCsylvania investigators will follow the University conflict of interest policy.

11.3 Subject Stipends or Payments

There are no subject payments or stipends associated with participation in the study

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