PREDICTING INFLAMMATORY SKIN DISEASE RESPONSE TO IL-23 BLOCKADE (NCT04541329)
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JEFFREY CHENG

Clinical Research Protocol

PREDICTING INFLAMMATORY SKIN DISEASE RESPONSE TO IL23 BLOCKADE

Protocol Number:	**19-29813**
Version Date:	
Investigational Product:	
IND Number:	
Development Phase:	
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Funding Organization:	
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Medical Monitor:	Name: Telephone: Fax: E-mail:
Coordinating Center:	If applicable

Approval:

PI or Sponsor Signature (Name and Title) *Date*

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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 Raymond Cho (myself) 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: 19-29813

Protocol Title: Predicting inflammatory skin disease response to IL23 blockade

Protocol Date: TBD

_____ _____

Investigator Signature *Date*

_____

Print Name and Title

Site # _____

Site Name _____

Address _____

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_____

_____

Phone Number _____

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LIST OF ABBREVIATIONS

none

PROTOCOL SYNOPSIS

TITLE	**PREDICTING TREATMENT RESPONSE FOR INFLAMMATORY SKIN DISEASE**
SPONSOR	self
FUNDING ORGANIZATION	none
NUMBER OF SITES	1
RATIONALE	To develop a predictive algorithm to determine whether a given patient with psoriasis will respond to one of the multiple specific pathway blocking FDA-approved psoriasis biologic medications.
STUDY DESIGN	interventional trial with molecular profiling of skin samples
PRIMARY OBJECTIVE	To obtain pre-treatment psoriatic skin samples for molecular profiling prior to treatment with tildrakizumab to correlate with and to predict treatment response
SECONDARY OBJECTIVES	
NUMBER OF SUBJECTS	10
SUBJECT SELECTION CRITERIA	Inclusion Criteria: > 18 years of age, Patients with moderate-severe psoriasis or atypical psoriasis with either non-biologic treatment failure or > 5% body surface area affected. Exclusion Criteria: tuberculosis, active serious infection, active systemic malignancy, or received a systemic medication for psoriasis within 3 months of study screening.
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Tildrakizumab 100 mg subcutaneous injection
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	n/a

DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	The time commitment for the first visit will be approximately 1.5 hours to discuss the study, consent the patient, and perform the biopsy. The second visit will last approximately 15 minutes The third and fourth visits will last approximately 30 minutes. With a total time committment of ~ 2 hrs 45 minutes
CONCOMMITANT MEDICATIONS	Allowed: Prohibited: other systemic medications for psoriasis
EFFICACY EVALUATIONS	
PRIMARY ENDPOINT	• molecular gene expression profiling of skin cell populations.
SECONDARY ENDPOINTS	• Psoriasis Area and Severity Index (PASI) score
OTHER EVALUATIONS	
SAFETY EVALUATIONS	Re-evaluation of biopsy site at follow-up visit in 14 days for wound infection In person medical visit for physical exam and history 4 weeks and 16 weeks after start of medication
PLANNED INTERIM ANALYSES	When approximately 50% of patients have completed the study through Visit 4, an interim analysis for safety will be conducted by the investigator. Serious adverse events will be monitored by the committee on an ongoing basis throughout the study.
STATISTICS **Primary Analysis Plan**	We will rely heavily on RNA-seq analysis, in some cases complemented with DNA sequencing and protein assessments. The RNAseq data will be normalized and compared in diseased vs normal skin and differential expression discerned at a significance level of 5% in a single test, in a two-group comparison, using a Negative Binomial mode. Numerous qualitative analyses will be performed as well.
Rationale for Number of Subjects	Bulk RNA-seq studies have required ~100 patients to distinguish markers for different inflammatory skin diseases. We anticipate with single cell RNA-seq, fewer patients may be necessary. This is also a pilot trial and due to the cost of the molecular profiling will start with an initially smaller # of patients.

1 BACKGROUND

Cutaneous inflammation represents the most common skin pathology, placing pervasive burdens on health care cost and quality of life. Biologic immunomodulatory therapies now enable improvement of major rashes such as psoriasis and atopic dermatitis; however, a significant minority of patients do not adequately respond to these medications. Given the multiple medication options that target different inflammatory pathways, significant expense and serious side effects of these immunomodulatory medications, it is imperative that we develop mechanisms to better predict whether a patient will respond to a given drug.

1.1 . Overview of Non-Clinical Studies

1.1 We will be collecting skin tissue from psoriatic patients for the purposes of analyzing gene activity in these samples.

1.2 Overview of Clinical Studies

Patient will be assessed for improvement in their psoriasis using the Psoriasis Area and Severity Index (PASI) score. Patients will be administered tildrakizumab (a FDA-approved medication for psoriasis) following manufacturer's and FDA indications and dosing schedule.

2 STUDY RATIONALE

The researchers want to find a way to predict whether a person with psoriasis will respond to a given medication. In this study, patient will start tildrakizumab (a FDA-approved medication for psoriasis). Prior to treatment, a small piece of psoriasis-affected skin will be sampled and molecularly profiled. We will then analyze the molecular profiles and compare to patient tildrakizumab treatment response to predict which future patients will best respond to this medication.

2.1 Risk / Benefit Assessment

Regarding the tildrakizumab treatment, this is a FDA approved medication for psoriasis. The same risks/benefits assessment for a psoriatic patient in our clinics as to whether to start this medication apply.

Regarding the skin biopsy, there is minimal risk to patients as punch biopsies are standard dermatologic procedures that are performed frequently with minimal side effects, which include bleeding, pain, infection, scar, changes in skin coloration, and allergic reaction to anesthesia. Knowledge may be gained about health conditions and patient may derive a feeling of contribution to knowledge in the health field

3 STUDY OBJECTIVES

3.1 Primary Objective

Our primary objective is to identify the genes that are differentially expressed in psoriatic skin between patients that do and do not respond to tildrakizumab

3.2 Secondary Objectives

There is no secondary objective.

4 STUDY DESIGN

4.1 Study Overview

This is a single center study in which patients with psoriasis or atypical psoriasis will donate small samples of that skin and/or normal tissue prior to treatment with the FDA-approved psoriasis medication, tildrakizumab.

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

We will evaluate if there are genes which are statistically significantly upregulated or downregulated in specific cell populations, based on RNA sequencing.

For assessment of psoriasis improvement, we will use the Psoriasis Area and Severity Index (PASI) scoring system.

5.2 Secondary Efficacy Endpoints

- There are no secondary endpoints.

5.3 Safety Evaluations

- The biopsy site will be evaluated at time of suture removal for any signs of superficial infection.
- Patients will have standard follow-up visits to assess efficacy and side effects of tildrakizumab, as would any of our non-trial patients started on this medication.

6 SUBJECT SELECTION

6.1 Study Population

Subjects with a diagnosis of psoriasis or atypical psoriasis who meet the inclusion and exclusion criteria will be eligible for participation in this study.

6.2 Inclusion Criteria

1. Male or female ≥18 years of age at clinic visit.
2. Documentation of moderate-severe psoriasis or atypical psoriasis.
3. Written informed consent (and assent when applicable) obtained from subject or subject's legal representative and ability for subject to comply with the requirements of the study.

6.3 Exclusion Criteria

4. 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 (e.g. tuberculosis, active serious infection, active systemic malignancy)
5. tuberculosis, active serious infection, active systemic malignancy,
6. or received a systemic medication for psoriasis within 3 months of study screening

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.

6.4 Allowed Medications and Treatments

Prohibited Medications and Treatments

The following medications are prohibited during the study and administration will be considered a protocol violation.

phototherapy, systemic medications for psoriasis (e.g. corticosteroids, other biologic medications, methotrexate, cyclosporine)

7 STUDY TREATMENTS

7.1 Method of Assigning Subjects to Treatment Groups

All patients in the trial are treated.

7.2 Blinding

None

7.3 Formulation of Test and Control Products

Standard manufacturer formulation

7.3.1 Formulation of Test Product

Standard manufacturer formulation

7.3.2 Formulation of Control Product

none

7.3.3 Packaging and Labeling

Standard manufacturer formulation

7.4 Supply of Study Drug at the Site

7.4.1 Dosage/Dosage Regimen

100 mg subcutaneous injection at 0, 4, and 16 weeks.

7.4.2 Dispensing

physician administered in clinic, From the investigational pharmacy at UCSF.

7.4.3 Administration Instructions

physician administered in clinic

7.5 Supply of Study Drug at the Site

physician administered in clinic

7.5.1 Storage

From the investigational pharmacy at UCSF.

7.6 Study Drug Accountability

By the investigational pharmacy at UCSF.

7.7 Measures of Treatment Compliance

physician administered in clinic

8 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 or subject's legal representative. If appropriate, assent must also be obtained prior to conducting any study-related activities.

8.1 Clinical Assessments

8.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at Baseline/Screening visit. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

8.1.2 Demographics

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

8.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent dermatologic history, review of systems, and information regarding underlying diseases will be recorded at Screening.

8.1.4 Physical Examination

A complete skin examination will be performed by either the investigator or a co-investigator who is a physician at Visit #1. 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. Photographic documentation of pre and post-treatment psoriatic lesions will be obtained.

8.1.5 Vital Signs

In standard clinical (non-research) dermatology visits, vital signs are not typically monitored prior to/after skin biopsies unless the patient complains of feeling unwell**.**

8.1.6 Oximetry

No oximetry will be taken for this skin study.

8.1.7 Spirometry

No spirometry will be taken for this skin study.

8.1.8 Other Clinical Procedures

No other clinical procedures will be taken for this skin study.

8.1.9 Adverse Events

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

8.2 Pharmacokinetic Measurements

No pharmacokinetic measurement will be taken for this skin study.

9 EVALUATIONS BY VISIT

9.1 Visit 1

1. Review the study with the subject (subject's legal representative) 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 medical history, including a history of rash, diagnosis date, and prior treatments.

5. Record concomitant medications.
6. Perform a complete skin examination.
7. Clean skin, anesthetize skin, take skin sample(s) (up to 2 6 mm punch biopsies), place suture.
8. Photograph of biopsied lesional skin and other psoriatic lesions
9. Part of the biopsied specimen will be sent for standard histopathology (if no previous histopathology from a similar representative lesion has been done)
10. Schedule subject for suture removal in 14 days.
11. Baseline routine bloodwork (CBC, quant gold, HIV, HB surface Ag, Anti-HB surface AB, anti-HB core AB, hepatitis C antibody, BUN/Creatinine, AST/ALT)

9.2 Visit 2 (2 weeks after Visit #1)

1. Remove suture.
2. Inspect biopsy site(s) to rule out infection.
3. Administration of tildrakizumab if normal baseline laboratory results, no interim medical issues, and/or histopathology consistent with psoriasis or atypical psoriasis (if no previous histopathology)

9.3 Visit 3 (4 weeks after Visit #2)

4. Interim medical history
5. Physical examination
6. Administration of tildrakizumab

9.4 Visit 4 (12 weeks after Visit #3)

7. Interim medical history
8. Physical examination
9. Administration of tildrakizumab

10 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

10.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a a pharmaceutical product and that does not necessarily have a causal relationship with the treatment.

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.

10.2 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.

10.2.1 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.

10.3 Medical Monitoring

Dr. Raymond J. Cho or Jeffrey Cheng should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone: (650) 520-0208

11 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

11.1 Early Discontinuation of Study 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)

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

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 should still be offered Visit 2 for suture removal.

12.4 Replacement of Subjects

Subjects who withdraw from the study will be replaced.

12 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject or investigator 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 investigator Jeffrey Cheng 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.

13 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.

13.1 Data Sets Analyzed

All eligible patients who consent to the study and have a skin sample taken will have data analyzed.

13.2 Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized: race, gender, age, rash type and biopsy site.

13.3 Analysis of Primary Endpoint

After RNA sequencing performs, standard distribution-based statistical test for significantly overexpressed or under-expressed genes will be applied.

13.4 Analysis of Secondary Endpoints

There are no secondary endpoints.

13.5 Interim Analysis

There are no interim analysis.

13.6 Sample Size and Randomization

10 samples will be collected for initial analysis. Distribution-based statistical analysis indicates that two-fold differences in gene transcription will be detected at this size.

14 DATA COLLECTION, RETENTION AND MONITORING

14.1 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) OR paper CRF 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 site number, subject number and initials.

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. For paper CRFs*:* If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

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.

14.2 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.

14.3 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.

14.4 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.

14.5 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.

14.6 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.

14.7 Subject Confidentiality

In order to maintain subject confidentiality, only a site number, subject number and subject initials 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.

15 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).

15.1 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.

15.2 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.

15.3 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 (or their legal representatives) 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 or legal representative of the subject and the original will be maintained with the subject's records.

15.4 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.

15.5 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 (Day 1)[a]	VISIT 2 (Day 15)[a]	VISIT 3 (DAY 43)*	VISIT 4 (DAY 127)*
Informed Consent	X			
Medical History	X	X	X	X
Skin Exam	X		X	X
Abbreviated Physical Exam		X		
Biopsy	X			
Suture removal and biopsy site check		X		
Treatment Administration		X	X	X
Baseline routine bloodwork	X			

[a] ± 5 days