Clinical Research Protocol and Statistical Analysis Plan: Characterization of the response to secukinumab in plaque psoriasis using novel immunologic and genetic profiling

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Clinical Research Protocol

Characterization of the response to secukinumab in plaque psoriasis using novel immunologic and genetic profiling

Protocol Number:	CAIN457AUS04T
Version Date:	October 14, 2015
Investigational Product:	Secukinumab
Sponsor/Principle Investigator:	Wilson Liao, MD 2340 Sutter St. Rm N426 San Francisco, CA 94115 Telephone: (415) 476-8364 Fax: (415) 476-8837 E-mail: wilson.liao@ucsf.edu
Funding Organization:	Novartis Pharmaceuticals

Approval:

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

This confidential information about an investigational product is provided for the exclusive use of investigators of this product and is subject to recall at any time. The information in this document may not be disclosed unless federal or state law or regulations require such disclosure. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, with the obligation not to further disseminate this information.

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 Novartis 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: CAIN457AUS04T

Protocol Title: Characterization of the response to secukinumab in plaque psoriasis using novel immunologic and genetic profiling

Protocol Date: August 10, 2015

_____ _____

Investigator Signature *Date*

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Print Name and Title

Site # _____

Site Name _____

Address _____

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Phone Number _____

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CRF	case report form
CXR	chest X-ray
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL-17	Interleukin-17
IRB	Institutional Review Board
IUD	Intrauterine device
PASI	Psoriasis Area and Severity Index
PGA	Physician Global Assessment
PI	Principal Investigator
PK	Pharmacokinetic
QOL	Quality of life
RNA-seq	RNA-sequencing
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	serious adverse experience
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamate pyruvate transaminase
SQ	subcutaneously
Th-17	T-helper 17

PROTOCOL SYNOPSIS

TITLE	Characterization of the response to secukinumab in plaque psoriasis using novel immunologic and genetic profiling
SPONSOR	Wilson Liao, MD
FUNDING	Novartis Pharmaceuticals
STUDY DESIGN & OVERVIEW	This is a single-arm, open-label study, which will examine the effect of secukinumab on the immunologic and genetic environment within psoriatic lesions.
PRIMARY OBJECTIVE	Perform quantitative analysis of the immunologic changes in immune cell populations after secukinumab treatment in 15 patients at weeks 2, 4, and 12 compared to baseline week 0. The immunologic profiles in psoriasis patients will also be compared to healthy control skin surgical discard specimens (n=10).
SECONDARY OBJECTIVES	Quantify the number of differentially expressed genes in each cell population by RNA-seq at weeks 2, 4, 12 after secukinumab compared to baseline.
NUMBER OF SUBJECTS	15
SUBJECT SELECTION CRITERIA	Inclusion Criteria: 1. Ability to provide written informed consent and comply with the protocol. 2. At least 18 years of age. 3. Diagnosis of predominately plaque psoriasis for at least 6 months prior to enrollment. 4. Subject is considered a candidate for phototherapy or systemic therapy 5. PASI $\geq$ 12 6. PGA $\geq$ 3 7. Subject has a negative Quantiferon Gold, or if positive undergoes CXR. If CXR negative, subject initiated prophylactic therapy with isoniazid for a course of 9 months with one month of therapy completed prior to first dose of secukinumab. 8. Subject does not have active or chronic hepatitis B or C. 9. Subject does not have HIV (human immunodeficiency virus). 10. Subject is unlikely to conceive due to male, post-menopausal, or using adequate contraceptive (barrier, hormonal, implant, or permanent sterilization methods). 11. Physical exam within clinically acceptable limits. Exclusion Criteria: 1. Subject is unable to provide written informed consent or comply with the protocol. 2. Subject is younger than 18 years of age.

	3. Subject has predominately non-plaque form of psoriasis. 4. Subject with mild psoriasis (PASI<12 and PGA<3) or is not a candidate for phototherapy or systemic treatments. 5. Subject has drug-induced psoriasis. 6. Subject with current, or a history of, severe psoriatic arthritis well controlled on current therapy. 7. Subjects with a serum creatinine level exceeding 176.8 µmol/L (2.0 mg/dl). 8. Screening total white blood cell (WBC count) < 2,500/µl, platelets < 100,000/µl, neutrophils < 1,500/µl, or hemoglobin <8.5 g/dl. 9. Evidence of active tuberculosis infection as defined by a positive QuantiFERON TB-Gold test (QFT) with a positive chest X-ray at screening, or untreated latent tuberculosis defined by positive QFT with a negative chest X-ray without prophylactic therapy with isoniazid for a course of 9 months with one month of therapy completed prior to first dose of secukinumab. 10. History of an active, ongoing, chronic or recurrent infectious disease including past medical history record of HIV, hepatitis B or hepatitis C. 11. Subjects possess other diagnoses that, in the investigator's opinion, preclude him/her from safely participating in this study or interfere with the evaluation of the subject's psoriasis. 12. History of known or suspected intolerance to any of the ingredients of the investigational study product. 13. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (>10 mIU/mL). 14. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unwilling to use effective contraception during the study and for 6 weeks after stopping treatment.
STUDY TREATMENT	Secukinumab (Cosentyx™) 300mg SQ at weeks 0, 1, 2, 3, 4, and every 4 weeks thereafter until week 48.
STUDY DURATION	The total duration of the study is expected to be 78 weeks: 26 weeks for recruitment and 52 weeks for site visits.
PRIMARY ENDPOINT	Percentage of CD4+ T effector cells expressing IL17 at weeks 2, 4, 12 after secukinumab compared to baseline.
SECNDARY ENDPOINT	Number of differentially expressed genes in each cell population by RNA-seq at weeks 2, 4, 12 after secukinumab compared to baseline.
SAFETY EVALUATIONS	Safety and tolerability will be assessed by adverse events, vital signs, physical examinations (including skin examinations and injection-site evaluations), and concomitant medication review. Laboratory assessments will be performed at screening.

STATISTICS **Primary Analysis Plan**	Flow Cytometry: One sample paired t test comparing mean change in lesional IL-17A positive, CD4+ T lymphocytes compared to baseline. RNA-seq: Identification of differentially expressed genes compared to baseline within each immune population studied using the statistical program EdgeR (paired analysis).
ETHICAL CONSIDER-ATIONS	This study will be conducted in accordance with applicable laws and regulations and according to the recommendations of International Conference on Harmonization Good Clinical Practice (ICH GCP) guidelines and those of the Declaration of Helsinki (Edinburgh, 2000); only after approval for the study has been obtained from the relevant regulatory authority and relevant independent ethics committee (IEC). The institutional review board (IRB)/IEC must review and approve the protocol and informed consent form (ICF) before any subjects are enrolled. The subject must be consented using the approved ICF before any procedures specified in the protocol are performed.

1 BACKGROUND

Secukinumab is the first FDA-approved therapy for moderate to severe plaque psoriasis in the class of recombinant high-affinity, fully human monoclonal antibody of the IgG1/kappa isotype that selectively targets Interleukin-17A (IL-17A). In the psoriatic skin, IL-17A is thought to be produced by infiltrating Th17 cells, neutrophils and mast cells. Upon activation of keratinocytes by IL-17A along with other synergistic inflammatory cytokines, further recruitment and activation of neutrophils, lymphocytes and myeloid cells eventually lead to a sustained local cutaneous inflammation that drives the psoriatic epidermal changes mediated by keratinocytes. This includes increase in epidermal thickness (acanthosis), increase in outer stratum corneum (hyperkeratosis) and retention of nuclei in the cornified layer (parakeratosis) (Martin 2013).

Secukinumab interferes in this pathologic process by selectively binding to IL-17A, thereby preventing IL-17A interaction with the IL-17 receptor expressed on keratinocytes. By its mechanism of action, secukinumab prevents and reverses key pathologic processes in psoriasis leading to normalization of skin histology.

Non-clinical studies have not shown any impediment to using secukinumab administered subcutaneously in man.

The approval of secukinumab (Cosentyx™) is based on the safety and efficacy outcomes from 10 Phase II and Phase III studies, which included over 3,990 patients with moderate-to-severe plaque psoriasis. This included the four pivotal Phase III trials – ERASURE, FIXTURE, FEATURE and JUNCTURE.

For more detail refer to the Prescribing Information.

2 STUDY RATIONALE

The University of California San Francisco Psoriasis Center has dual expertise in both immunologic and genetic analyses of psoriasis. Therefore, this unique proposal will examine the effect of secukinumab on the immunologic and genetic environment within psoriatic lesions.

2.1 Rationale for Flow Cytometry and RNA-Seq

Regarding understanding the impact of biologics on the molecular profile of psoriatic skin, a fundamental question that has not yet been adequately answered is: What is the response of specific cell populations in lesional skin to biologic treatment? A number of recent studies have used techniques such as RT-PCR, gene microarrays, and immunohistochemistry to evaluate changes in lesional skin in response to treatment with biologic agents (Zaba, Krueger, Hendriks, Johnston, Russell). These studies are limited by the use of bulk skin tissue, which does not permit precise quantitative analysis of individual cell types, and by the reliance on limited gene probe libraries used in RT-PCR or microarray analysis. Ideally, in order to understand the fundamental biology of how a biologic medication improves psoriasis, one would like to be able to isolate the different cell populations and study their individual characteristics. Until now, this has not been possible.

At UCSF, we have developed innovative technologies to characterize individual skin cell populations at the protein and RNA level. Using a novel flow cytometry protocol, we are able to separately analyze distinct skin populations such as CD4+ T cells, CD8+ T cells, regulatory T cells, and myeloid dendritic cells and measure the production of proteins such as IL-17, TNF-α, IFN-γ, and IL-2 in parallel (Figure 1). Because this technique is based on protein expression, it offers a truly functional view of the activity of cell populations in psoriasis, as methods using microarrays can measure only mRNA production, which does not necessarily accurately reflect protein expression (Villarino).

Moreover, we are able to perform RNA-sequencing on distinct cell populations. RNA-seq is a novel technique of quantifying gene expression in which RNA species are sequenced rather than hybridized as in microarrays. RNA-seq provides greater sensitivity than microarrays, particularly for low-expressed transcripts (Li et al). RNA-seq can also identify the expression of coding and noncoding transcripts that are absent on microarray platforms. Utilizing our innovative skin biopsy digestion protocol and cell sorting protocol described above, we are now able to perform RNA-seq on individual cell populations (Figure 2), permitting an understanding of the genetic and immunologic profile of individual cell types within psoriatic lesions. Importantly, this cell type-level RNA-seq analysis has never previously been utilized to evaluate changes in patients undergoing biologic therapy.

Flow cytometry panel: Live/dead, CD45, CD3, CD4, CD8, Foxp3, IL-2, IL-17A, IL17-F, TNF-α, IFN-γ, IL-21, IL-22 and IL-23

RNA-seq cell types: CD4+ T effectors, CD4+ T Regs, CD8+ T effectors

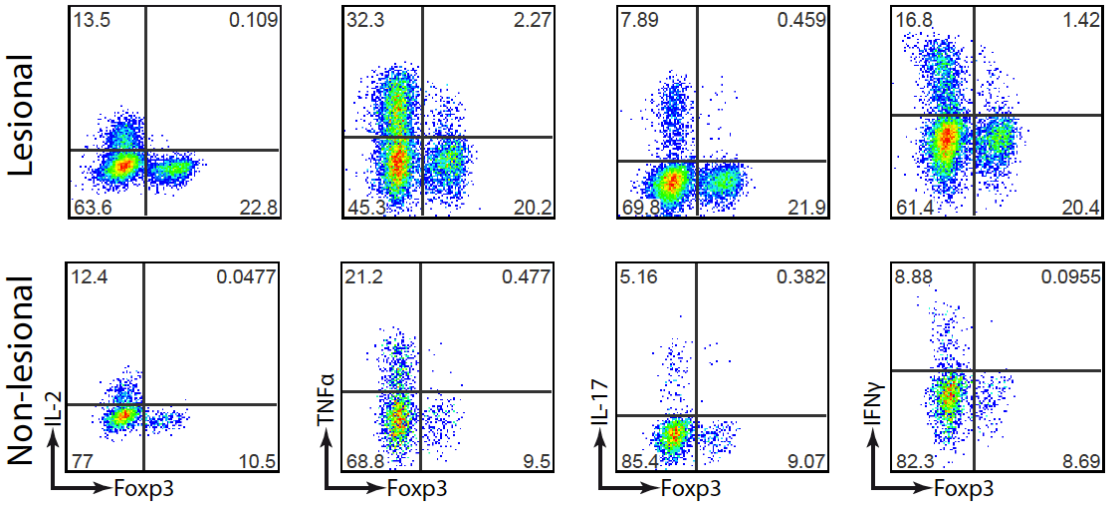

Figure 1. Multi-parameter flow cytometry of punch biopsies obtained from patients with psoriasis. We have recently developed and optimized a new flow cytometric-based protocol for comprehensively studying leukocyte populations isolated from human skin (Sanchez Rodriguez et al). Traditional approaches have relied on culturing skin biopsy specimens for 10-20 days in the presence of growth factors, to allow infiltrating leukocytes to expand in response to these factors. It is becoming increasingly appreciated that lymphocytes cultured for this length of time can alter their functional capabilities and may not accurately reflect *in vivo* differentiation and function. Using a single 4mm punch biopsy of freshly isolated human skin, we are now able to isolate lymphocytes and monocytes and immediately assess their functional activities in the absence of growth factors. We perform 15-color flow cytometry on these specimens, allowing for the quantification of multiple cytokine, chemokine, and cell surface and intracellular differentiation/activation markers at the protein level. Using this technique on 5mm skin punch biopsy specimens, we have analyzed the intracellular cytokine expression patterns from T cells infiltrating lesional and non-lesional skin of a patient with psoriasis (shown above). This data shows increased Tregs (denoted by Foxp3 expression) and increased TNF-α, IL-17 and IFN-γ production from T cells infiltrating lesional psoriatic plaques when compared to non-lesional (normal appearing) skin from the same patient. All graphs are pre-gated on live CD3+CD4+ T cells. Numbers indicate percentage of cells per quadrant.

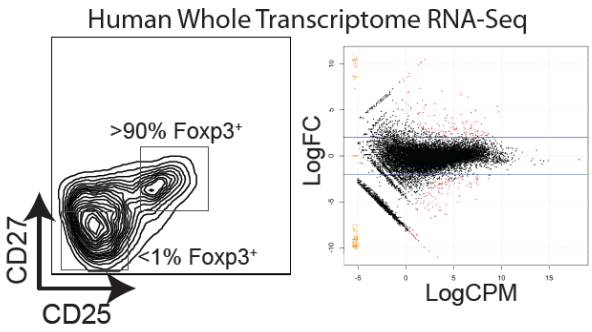

Figure 2. RNA-sequencing studies at UCSF. Whole transcriptome RNA-sequencing of CD4+ Tregs and Teffs isolated from normal human skin. Tregs and Teffs were sorted from normal skin using expression of CD25 and CD27. RNA was isolated from these purified cell fractions and subjected to whole transcriptome RNA-sequencing. Scatter plot shows grouped Treg vs. Teff comparisons.

2.2 Risk / Benefit Assessment

Details of the risk and benefits of secukinumab are outlined in the Prescribing Information. Side effects of secukinumab include nasopharyngitis (11.4%), diarrhea (4.1%), and upper respiratory infections (2.5%). Serious side effects include anaphylaxis and exacerbation of Crohn's disease. The risk to subjects in this trial will be minimized by compliance with the inclusion/exclusion criteria, proper study design, and close clinical monitoring.

In regards to skin biopsy procedures, as in any surgical procedure, there are certain inherent risks including bleeding, post-operative pain, infection, reactions to sutures, anesthetics or topical antibiotics, and scarring. All reasonable efforts will be made to minimize the possibility of these potential complications.

The benefit to subjects is that they will be receiving an approved therapy for moderate-to-severe psoriasis. Although it cannot be guaranteed, secukinumab has shown to be safe and effective in moderate-to-severe psoriasis. An additional benefit to patients is that they are contributing to society by helping the enhancement of science.

3 STUDY OBJECTIVES

3.1 Primary Objective

Perform quantitative analysis of the immunologic and genetic changes in immune cell populations after secukinumab treatment in 15 patients at weeks 2, 4, 12 compared to baseline week 0. The immunologic profiles in psoriasis patients will also be compared to healthy control skin surgical discard specimens (n=10).

3.2 Secondary Objectives

Quantify the number of differentially expressed genes in each cell population by RNA-seq at weeks 2, 4, 12 after secukinumab compared to baseline.

4 STUDY DESIGN

4.1 Study Overview

This is a single center, open-label study. 15 subjects are planned. 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. Each subject will be administered FDA approved dose of secukinumab 300mg subcutaneously at weeks 0, 1, 2, 3, 4, then every 4 weeks thereafter until week 48. All 15 patients will undergo skin biopsies at weeks 0, 2, 4, and 12 for molecular profiling. Total duration of subject participation will be 52 weeks. Total duration of the study is expected to be 78 weeks, which includes 26 weeks of recruitment.

5 CRITERIA FOR EVALUATION

5.1 Primary Analysis Endpoint

Percentage of CD4+ T effector cells expressing IL17 at weeks 2, 4, 12 after secukinumab compared to baseline.

5.2 Secondary Analysis Endpoint

Number of differentially expressed genes in each cell population by RNA-seq at weeks 2, 4, 12 after secukinumab compared to baseline.

5.3 Safety Evaluations

Safety and tolerability to secukinumab will be assessed by adverse events, vital signs, physical examinations (including skin examinations and injection-site evaluations), and concomitant medication review. Laboratory assessments will be performed at screening.

6 SUBJECT SELECTION

6.1 Study Population

Subjects with a diagnosis of predominately plaque psoriasis for at least 6 months prior to enrollment who meet the inclusion and exclusion criteria will be eligible for participation in this study.

6.2 Inclusion Criteria

1. Ability to provide written informed consent and comply with the protocol.
2. At least 18 years of age.
3. Diagnosis of predominately plaque psoriasis for at least 6 months prior to enrollment.
4. Subject is considered a candidate for phototherapy or systemic therapy
5. PASI $\geq$ 12
6. PGA $\geq$ 3
7. Subject has a negative Quantiferon Gold, or if positive undergoes CXR. If CXR negative, subject initiated prophylactic therapy with isoniazid for a course of 9 months with one month of therapy completed prior to first dose of secukinumab.
8. Subject does not have active or chronic hepatitis B or C.
9. Subject does not have HIV (human immunodeficiency virus).
10. Subject is unlikely to conceive due to male, post-menopausal, or using adequate contraceptive (barrier, hormonal, implant, or permanent sterilization methods).
11. Physical exam within clinically acceptable limits.

6.3 Exclusion Criteria

1. Subject is unable to provide written informed consent or comply with the protocol.
2. Subject is younger than 18 years of age.
3. Subject has predominately non-plaque form of psoriasis.
4. Subject with mild psoriasis (PASI<12 and PGA<3) or is not a candidate for phototherapy or systemic treatments.

5. Subject has drug-induced psoriasis.
6. Subject with current, or a history of, severe psoriatic arthritis well controlled on current therapy.
7. Subjects with a serum creatinine level exceeding 176.8 µmol/L (2.0 mg/dl).
8. Screening total white blood cell (WBC count) < 2,500/µl, platelets < 100,000/µl, neutrophils < 1,500/µl, or hemoglobin <8.5 g/dl.
9. Evidence of active tuberculosis infection as defined by a positive QuantiFERON TB-Gold test (QFT) with a positive chest X-ray at screening, or untreated latent tuberculosis defined by positive QFT with a negative chest X-ray without prophylactic therapy with isoniazid for a course of 9 months with one month of therapy completed prior to first dose of secukinumab.
10. History of an ongoing, chronic or recurrent infectious disease including past medical history record of HIV, hepatitis B or hepatitis C.
11. Subjects possess other diagnoses that, in the investigator's opinion, preclude him/her from safely participating in this study or interfere with the evaluation of the subject's psoriasis.
12. History of known or suspected intolerance to any of the ingredients of the investigational study product.
13. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (>10 mIU/mL).
14. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unwilling to use effective contraception during the study and for 6 weeks after stopping treatment. Effective contraception is defined as either:

Barrier method: Condom or occlusive cap (diaphragm or cervical/vault caps) with spermicide (where available). Spermicides alone are not a barrier method of contraception and should not be used alone.

The following methods are considered more effective than the barrier method and are also acceptable:

- Total abstinence: When this is in line with the preferred and usual lifestyle of the subject (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception)
- Female sterilization: have had a surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male partner sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomised male partner should be the sole partner for that subject.
- Use of established oral, injected or implanted hormonal methods of contraception, intrauterine device (IUD) or intrauterine system (IUS)

NOTE: Women are considered post-menopausal and not of child bearing potential if they have had: 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels >40 mIU/mL and estradiol <20 pg/mL or surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone - only when the reproductive status of the woman has been confirmed.

7 CONCURRENT MEDICATIONS

7.1 Allowed Medications and Treatments

All prior concomitant medications must be on a stable dose for at least 4 weeks before the first study treatment administration. All subjects should be maintained on the same medications throughout the entire study period, as medically feasible. Any changes in medications and medication dosing will be recorded on the CRF. After the screening period, the use of concomitant medication for psoriasis in all body regions is restricted to bland emollients and other non-medicated interventions.

7.2 Prohibited Medications and Treatments

The following are prohibited during the study and prior to the study for a set duration as follows:

- Systemic anti-psoriatic treatments including methotrexate, cyclosporine, corticosteroids, and cyclophosphamide: 4 weeks.
- Biological immunomodulating agents including infliximab, etanercept, and adalimumab: 12 weeks
- Ustekinumab: 6 months
- Other systemic psoriasis treatments including retinoids: 4 weeks
- Photochemotherapy: 4 weeks
- Phototherapy (UVA/UVB): 2 weeks
- Topical treatment that is likely to impact signs and symptoms of psoriasis such as corticosteroids, vitamin D analogues, pimecrolimus, retinoids, salicylic acid, lactic acid, tacrolimus, tar, urea, α-hydroxy or fruit acids: 2 weeks
- Live vaccinations: 6 weeks
- Any investigational treatment or participation in any interventional trial: 4 weeks or 5 half-lives, whichever is longer

8 STUDY TREATMENTS

Secukinumab (Cosentyx™)

8.1 Supply of Study Drug at the Site

Novartis will ship the study drug to the investigational sites. The study drug is supplied in a carton of one 150 mg/mL (300 mg dose) Sensoready pens. Each kit of study drug will be labeled with the required FDA warning statement, the protocol number, and directions for use and storage.

8.2 Storage

Secukinumab Sensoready pens must be refrigerated at 2ºC to 8ºC (36ºF to 46ºF). The medication will be kept in a temperature-monitored refrigerator at the study site. The product will be kept in the original carton until the time of use.

8.3 Dosage/Dosage Regimen

Secukinumab will be administered at a dose of 300mg subcutaneously through the study, which a FDA-approved and recommended dose for secukinumab. There is no weight-based dosing. The dosing schedule will be as follows: secukinumab 300mg subqutaneously once a week at weeks 0, 1, 2, 3, and 4, then every four weeks thereafter until week 48.

8.4 Administration Instructions

All doses of study treatment will be administered at the study site after the study assessments for the visit have been completed at visits occurring between week 1 and 16. After week 16 subjects will administer the medication independently every 4 weeks only after they have shown the competency to self-administer the treatment outside of the study site. There will be no medication given after week 48.

The subject should be instructed to contact the investigator if he/she is unable for any reason to attend a study visit as scheduled. All dates and times of injections done to the subject during the study must be recorded on the Dosage Administration Record CRF. The investigator will promote compliance by instructing the subject to attend the study visits as scheduled and by stating that compliance is necessary for the subject's safety and the validity of the study.

8.5 Study Drug Accountability

The qualified site personnel will maintain an accurate record of the shipment and dispensing of study treatment in a treatment accountability log. All study treatment kits assigned to the subject during the study will be recorded.

8.6 Measures of Treatment Compliance

Subjects will be given scheduled doses of secukinumab at each visit from visit 0 (week 1) until visit 8 (week 16). After week 16, subjects will be given a dosing diary to record their scheduled injections administered at home every 4 weeks.

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.

All clinical assessments will take place at the study site: 515 Spruce St., San Francisco,

CCA 94118

All blood draws will take place at Health Exams, Inc laboratory: 3580 California St., San Francisco, CA 94118.

9.1 Clinical Assessments

9.1.1 Medical History

Relevant medical history, including history of current disease, and information regarding underlying diseases will be recorded at Screening.

11.1.2 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at Screening, at every site visit, and at early termination when applicable. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.3 Demographics

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

9.1.4 Physical Examination

A complete physical examination will be performed by either the investigator or a sub-investigator who is a physician at screening and weeks 0, 12, 24, and 52. 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 all site visits.

9.1.6 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).

9.1.7 PASI and PGA

Psoriasis Area and Severity Index (PASI) and Physician Global Assessment (PGA) will be completed at screening and weeks 0, 4, 8, 12, 24, 36, and 52.

9.1.8 Photography

Photographs (full front and back) will be taken at weeks 0, 2, 4, 12, and 52.

9.2 Clinical Laboratory Measurements

9.2.1 Hematology

Blood will be obtained and sent to the clinical hematology lab for a complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, white blood cell

differential, and platelet count) determinations for assessment of systemic evidence for infection and/or inflammation at Screening.

9.2.2 Blood Chemistry Profile

Blood will be obtained and sent to the clinical chemistry lab for determination of electrolyte levels, serum BUN, creatinine, AST, ALT, and alkaline phosphatase at screening.

9.2.3 Pregnancy Test

A urine pregnancy test will be obtained at the study site for female subjects of childbearing age at screening and weeks 0, 4, 8, 12, 16, 24, 36, and 52.

9.2.4 Hepatitis B/C and HIV Testing

Blood will be obtained and sent to the clinical lab for determination of hepatitis B and C and HIV status at Screening.

9.2.5 Quantiferon Gold with or without chest X-ray

Blood will be obtained and sent to the clinical lab for determination of tuberculosis infection at Screening. If positive, a chest X-ray will be obtained to assess for active vs. latent tuberculosis status.

10 EVALUATIONS BY VISIT

See Appendix 1.

1.1 Visit 0 (Screening)

1. Review inclusion/exclusion criteria.
2. Review the study with the subject and obtain written informed consent and HIPAA authorization and assent, if appropriate.
3. Assign the subject a unique screening number.
4. Record demographics data.
5. Record medical history, including a history of plaque psoriasis, diagnosis date, and prior treatments for psoriasis.
6. Record concomitant medications.
7. Perform a complete physical examination.
8. Perform PASI and PGA.
9. Perform and record vital signs.
10. Collect blood for clinical laboratory tests (CBC, serum electrolytes, BUN, Creatinine, AST, ALT, alkaline phosphatase, Hepatitis B/C, HIV, Quantiferon Gold with/without CXR).
11. Perform urine pregnancy test (if applicable).

1.2 Visit 1 (Week 0)

1. Record any Adverse Experiences.
2. Concomitant medications review.
3. Perform a complete physical examination.
4. Perform and record vital signs.

5. Perform PASI and PGA.
6. Perform urine pregnancy test (if applicable)
7. Perform skin biopsy procedure.
8. Obtain photographs.
9. Dispense study medication.

1.3 Visit 2 (week 1)

1. Record any Adverse Experiences.
2. Concomitant medications review.
3. Perform and record vital signs.
4. Dispense study medication.

10.4 Visit 3 (week 2)

1. Record any Adverse Experiences
2. Concomitant medications review.
3. Perform and record vital signs.
4. Perform skin biopsy procedure.
5. Obtain photographs.
6. Dispense medication.

10.5 Visit 4 (week 3)

1. Record any Adverse Experiences.
2. Concomitant medication review.
3. Perform and record vital signs.
4. Dispense study medication.

10.6 Visit 5 (week 4)

1. Record any Adverse Experiences.
2. Concomitant medications review.
3. Perform and record vital signs.
4. Perform PASI and PGA.
5. Perform urine pregnancy test (if applicable)
6. Perform skin biopsy procedure.
7. Obtain photographs.
8. Dispense study medication.

10.7 Visit 6 (week 8)

1. Record any Adverse Experiences.
2. Concomitant medications review.
3. Perform and record vital signs.
4. Perform PASI and PGA assessments.
5. Perform urine pregnancy test (if applicable).
6. Dispense study medication.

10.8 Visit 7 (week 12)

1. Record any Adverse Experiences.
2. Concomitant medications review.

3. Perform complete physical exam.
4. Perform and record vital signs.
5. Perform PASI and PGA.
6. Perform urine pregnancy test (if applicable)
7. Perform skin biopsy.
8. Obtain photographs.
9. Dispense study medication

10.9 Visit 8 (week 16)

1. Record any Adverse Experiences.
2. Concomitant medications review.
3. Perform and record vital signs.
4. Perform PASI and PGA.
5. Perform urine pregnancy test (if applicable)
6. Dispense study medication

10.10 Visit 9 (week 24)

1. Record any Adverse Experiences.
2. Concomitant medications review.
3. Perform complete physical examination.
4. Perform and record vital signs.
5. Perform PASI and PGA.
6. Perform urine pregnancy test (if applicable).
7. Dispense study medication.

10.11 Visit 10 (week 36)

1. Record any Adverse Experiences.
2. Concomitant medications review.
3. Perform and record vital signs.
4. Perform PASI and PGA.
5. Perform urine pregnancy test (if applicable).
6. Dispense study medication.

10.12 Visit 11: END OF STUDY (week 52)

1. Record any Adverse Experiences.
2. Concomitant medications review.
3. Perform complete physical examination.
4. Perform and record vital signs.
5. Perform PASI and PGA.
6. Perform urine pregnancy test (if applicable).
7. Obtain photographs.

10.13 EARLY TERMINATION

1. Record any Adverse Experiences.
2. Concomitant medications review.
3. Perform complete physical examination.

4. Perform and record vital signs.
5. Perform PASI and PGA.
6. Perform urine pregnancy test (if applicable).
7. Obtain photographs.

11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1 Adverse Events

Definition of an AE: Any untoward medical occurrence in a subject administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the investigational medicinal product.

Investigational Medicinal Product (IMP) includes the drug under evaluation and the comparator drug(s) if specified as part of the research objective, given at any time during the study. Medical conditions/diseases present before starting the drug of interest are only considered adverse events if they worsen after starting the drug of interest.

The occurrence of adverse events will be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All adverse events will be recorded in the study database including the following information:

1. the severity grade (mild, moderate, severe)
2. its relationship to the drug(s) of interest (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

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 **Error! Reference source not found.** 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.

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)

A SAE is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is otherwise a significant medical event.

This includes any SAEs likely to arise from the trial indication or progression of underlying/concomitant illness(es) (e.g. progression of cancer in oncology trials), unless specified in the protocol as study specific exemptions.

Any SAE, irrespective of causality, occurring after the subject has provided informed consent and until four weeks after the subject has stopped study participation must be reported unless otherwise stated in the protocol. SAEs occurring after four weeks from ending study participation should only be reported if considered by the Investigator attributable to the exposure to the investigational drug(s) during the trial period. This includes the period in which the study protocol interferes with the standard medical treatment given to a subject, even if study treatment has not yet started (e.g. withdrawal of previous treatment during washout period, change in treatment to a fixed dose of concomitant medication).

11.3 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.

SAEs occurring after four weeks from ending study participation should only be reported if considered by the Investigator attributable to the exposure to the investigational drug(s) during the trial period. This includes the period in which the study protocol interferes with the standard medical treatment given to a subject, even if study treatment has not yet started (e.g. withdrawal of previous treatment during washout period, change in treatment to a fixed dose of concomitant medication).

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.

Timelines: All serious adverse events (SAEs) must be reported by the sites to Sponsor within 24 hours of occurrence of the SAE. The timelines for investigator initiated trials reporting to Novartis will be done as per Third Party Study/Investigator Initiated Trial Agreement.

Follow-up reports: SAEs will be followed until resolution or until it is judged to be permanent, and an assessment will be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the drug of interest, the interventions required to treat it, and the outcome.

The Sponsor shall support Novartis in the following-up of all SAEs so that complete information is available to maintain patient safety and also as part of any commitments by Novartis to any Health authority OR specific Health authority follow-up requests for the product under investigation.

Pregnancies: Any occurrences of a pregnancy in a patient (or a patients partner) during study participation will be collected. All pregnancies will be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 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)
- 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
- Sponsor request for early termination of study
- Positive pregnancy test (females)

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 10.13 for early termination procedures.

12.2 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 11) should have an early discontinuation visit. Refer to Section 10.13 for early termination procedures. Subjects who withdraw after Visit 1 but prior to Visit 52 should be encouraged to come in for a final visit (and the procedures to be followed would include those for their next scheduled visit). Subjects who sign the informed consent form (ICF) and who are discontinued or withdraw from the study before study product administration will be defined as screen failures. No data will be collected in the CRFs for screen failure subjects.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, investigator, or Sponsor 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.
- Non-compliance with study drug regimen.
- Non-compliance with study visit procedures.
- Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The PI 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 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.

14.1 Analysis of Primary Endpoint

Flow Cytometry: One sample paired t-test comparing mean change in lesional IL-17A positive, CD4+ T lymphocytes at weeks 2, 4, 12 compared to baseline.

14.2 Analysis Secondary Endpoint

RNA-seq: Identification of differentially expressed genes at weeks 2, 4, 12 compared to baseline within each immune population studied using the statistical program EdgeR (paired analysis).

14.3 Safety Data

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.

14.4 Sample Size

15 subjects will receive secukinumab for a treatment period of 52 weeks (i.e. last injection on week 48). All subjects will undergo skin biopsies for molecular profiling.

Sample size justification

Flow cytometry: Since these measurements using real-time flow cytometry have never been previously reported, we will have to estimate the minimum effect size that would be clinically relevant. Given the results of pilot testing of our methods using ustekinumab in plaque psoriasis, we believe a reduction in lesional IL-17A positive, CD4+ T lymphocytes of 10% is clinically meaningful (i.e., results in clinical improvement). The standard deviation of the change in lesional IL-17A positive, CD4+ T-lymphocytes in the patient population is estimated at 10% (also extrapolated from data generated with ustekinumab). Therefore, our standardized effect size is 1.00. For the statistical analysis, we will set alpha at 0.05, beta at 0.20 (power = 0.8). The resulting sample size estimate for a one sample paired.

RNA-seq: To determine statistical power to identify differentially expressed genes as measured by RNA-seq, we used the Scotty (Busby et al.) power calculator which uses a t-statistic and incorporates the variance attributable to read depth. Performing RNA-seq on 15 samples before and after treatment to a read depth of 50 million per sample as proposed here, we can detect >97% of transcripts displaying 2X fold change and >80% of transcripts displaying 1.5X fold change with $p<0.01$ (Figure 3).

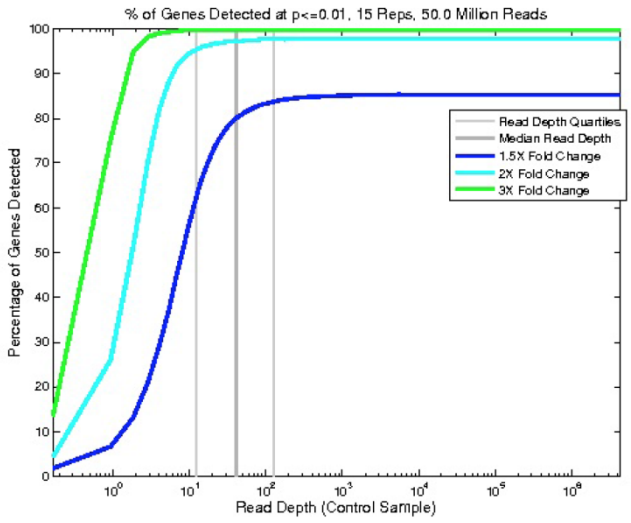

Fig 3. Power to detect differentially expressed genes using RNA-Seq.

15 DATA COLLECTION, RETENTION AND MONITORING

15.1 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. Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic or paper 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, but will be identified by a site number, subject number and initials.

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. If a correction is made on a paper 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.

15.2 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.

15.3 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. On eCRFs, queries are entered, tracked, and resolved through the EDC system directly. On paper, query reports (Data Clarification Requests) pertaining to data omissions and discrepancies will be forwarded to the Investigators and study monitors for resolution. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

15.4 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.

15.5 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.

15.6 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.

16 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).

16.1 Protocol Amendments

Any amendment to the protocol will be written by the PI or a sub-investigator with the PI's approval. 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.

16.2 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 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.

16.3 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 Harmonization 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.

16.4 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.

16.5 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.

11 Personally conduct or supervise the study (or investigation).

12 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.

13 Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.

14 Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

15 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).

16 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.

17 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).

18 Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.

19 Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

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APPENDIX 1. EVALUATION SCHEDULE

Visit number	0	1	2	3	4	5	6	7	8	9	10	11
Time of Visit	Screen-ing	wk 0	wk 1	wk 2	wk 3	wk 4	wk 8	wk 12	wk 16	wk 24	wk 36	wk 52
Inclusion/Exclusion criteria	x											
Informed consent	x											
Review Medical History	x											
Physical examination	x	x						x		x		x
Vital Signs	x	x	x	x	x	x	x	x	x	x	x	x
PASI and PGA	x	x				x	x	x	x	x	x	x
Laboratory assessments*	x											
Urine Pregnancy	x	x				x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x	x	x	x
Review con meds	x	x	x	x	x	x	x	x	x	x	x	x
Biopsy Procedures		x		x		x		x				
Photography		x		x		x		x				x
Dispense study medication		x	x	x	x	x	x	x	x	x	x	

*CBC with differential, BUN, Cr, AST/ALT/Alk Phos, Hep B/C screening, Quantiferon Gold +/- CXR