Perelman School of Medicine
University of Pennsylvania

PHASE IV OPEN LABEL STUDY OF THE EFFECTS OF SECUKINUMAB ON NAIL PSORIASIS AND NON-INVASIVE MEASURES OF ENTHESITIS

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List of Abbreviations

AE: Adverse Event
CTSA: Clinical and Translational Science Award
GRAPPA: Group for Research and Assessment of Psoriasis and Psoriatic
IA; Inflammatory Arthritis
IDEOM: International Dermatology Outcome Measures
PPACMAN: Psoriasis and Psoriatic Arthritis Clinics Multicenter Advancement Network
PsA: Psoriatic arthritis
PARC: Psoriatic Arthritis Research Collaboration (PARC)
PsO: Psoriasis
RA: Rheumatoid arthritis
S.C.: Subcutaneous

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Study Summary

Title	Effects of Secukinumab on Nail Psoriasis and non-invasive measures of enthesitis
Short Title	IL17i and Nail PsO
IRB Number	834149
Phase	Phase IV
Methodology	Open Label
Study Duration	One Screening visit followed by 24 Week Intervention
Study Center(s)	Single-Center
Objectives	Primary: • To identify predictors of nail disease response at 24 weeks. Secondary: • To examine the validity, responsiveness and basic metrics of the available outcome measures for nail disease. • To examine correlation among MRI and US for nail bed inflammation and for matrix inflammation • To examine subclinical enthesitis or signs of psoriatic arthritis among patient with psoriasis and nail disease without known PsA.
Number of Subjects	50 subjects may be consented and screened to ensure that 40 subjects complete baseline
Main Eligibility Criteria	Inclusion Criteria: • Active psoriatic nail disease defined as a Minimum 4 or more fingernails OR NAPSI>20 • Active skin psoriasis currently (no minimum PASI or BSA) or skin psoriasis in the past documented by a dermatologist • Age 18-85 Exclusion Criteria: • History of IL-17 inhibitor use (other therapies including TNF inhibitors or non-biologics DMARDS in the past are acceptable) • Inflammatory bowel disease • Metal implants or other concerns for use of MRI • Active infection • Patients may have a history of self-reported psoriatic arthritis but may not have active PsA at the time of screening. • We will exclude patients with onychomyosis of the fingernails on clippings • Age >85 or age <18

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Investigational Product (drug, biologic, device, etc.) **For Drug, food, cosmetic, etc. include the dose, route of administration and dose regiment**	Secukinumab (Cosentyx) 300 mg- Every 4 weeks after loading dose (Loading Dose-300 mg once weekly for 5 weeks) Subcutaneous Injection
Duration of administration (if applicable)	24 Weeks
Reference therapy	Open label, no reference therapy
Statistical Methodology	For predictive models with the continuous outcome (NAPSI), we will examine the association between each exposure of interest and the outcome. For objectives in which the goal is to understand factors at baseline associated with response, we will use linear regression models (for continuous outcomes; logistic regression for binary response) and for objectives in which we are examining the change in a particular factor between weeks 0 and 4 and the relationship to the outcome, we will use generalized estimating equations.
Safety Evaluations	Primary measurements for safety will include measurement of injection site reactions, gastrointestinal complaints, respiratory infections, and oral thrush. Serious adverse events will include hospitalizations or emergency room visits.
Data and Safety Monitoring Plan	Dr. Ogdie, the PI, will monitor the study on a day-to-day basis. In addition, we will appointment a Data Safety Monitoring officer(DSMO). Please see Data and Safety Monitoring Plan Appendix for a detailed description of the complete plan.

1. Background and Study Rationale

This study will be conducted in full accordance all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations including *[as applicable include the following regulations as they apply 45 CFR 46, 21 CFR Parts 50, 54, 56, 312, 314 and 812 and Good Clinical Practice: Consolidated Guidelines approved by the International Conference on Harmonisation (ICH).*

1.1 Introduction

The proposed study will identify predictors of nail response among patients with psoriatic nail disease, evaluate the validity and responsiveness of a range of outcome measures for nail disease, and examine imaging modalities to measure nail disease including subclinical measures of distal interphalangeal (DIP) joint enthesitis and how these subclinical measures are impacted by secukinumab prior to achieving clinical response. This study will provide novel insights into the kinetics of secukinumab response in nail disease while identifying surrogate markers that can better guide treatment of psoriatic nail disease.

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1.2 Background and Relevant Literature

Nail psoriasis causes significant functional impairment and emotional distress in patients, but the precise effects of systemic psoriasis therapy on nail disease is rarely studied. Overall, little is known about nail psoriasis, including how to best measure it. Furthermore, nail psoriasis is often very slow to improve. Knowledge of predictors of treatment response such as early imaging features of nail improvement could substantially shorten trials of nail psoriasis and may improve clinical management. Thus, studies to identify optimal instruments for measurement of nail disease activity and predictors of response are needed.

In addition, nail psoriasis may also be associated with development of psoriatic arthritis (PsA) or may be a key early feature in PsA, a potentially destructive inflammatory arthropathy. The hypothesized mechanism is that inflammation begins where the enthesis inserts into the nail unit and extends to distal interphalagneal joint. However, nail disease is common in both psoriasis patients without joint disease and patients with PsA so the role of nail disease in development of inflammatory arthritis is not clear. The presence of nail features alone is not sufficient to define an association with PsA. However, development of tools to examine nail bed enthesitis may assist in defining who is at risk for development of PsA. Ultimately, treating this early form of inflammation may likewise be beneficial for preventing further development of PsA.

1.3 Name and Description of the Investigational Product

Secukinumab is an IL-17A inhibitor that is FDA approved for the treatment of moderate to severe plaque psoriasis and psoriatic arthritis (PsA). It has already been extensively used in psoriasis and PsA but only limited studies have addressed psoriatic nail disease which occurs in both psoriasis and PsA. Furthermore, limited studies have addressed a) the earliest phases of the PsA or b) nail disease is a potential predictor of early PsA.

1.3.1 Nonclinical Data

Preclinical data demonstrated the effectiveness of IL17 inhibitors in diminishing the inflammatory characteristics of spondyloarthritis-like illness in mice. Because the clinical data is more relevant for this protocol, we have not provided extensive preclinical background.

1.3.2 Clinical Data to Date

Numerous randomized controlled trials have been conducted including secukinumab as one of the target agents (see Table below). Most relevant to this proposal, there have been two clinical trials that have addressed nail disease. TRANSFIGURE, a phase IIIB study, reported a statistically significant improvement in nail psoriasis at week 16 among patients treated with secukinumab 300 mg versus placebo. Additionally, a post-hoc analyses of FUTURE II, a phase III study for secukinumb in PsA, found similar results. The primary outcomes used in TRANSFIGURE and FUTURE II were the nail psoriasis severity index (NAPSI) and the modified NAPSI, respectively. Therefore, these studies provide a strong rationale for treating psoriatic nail disease with secukinumab, but still very little is known about the predictors and kinetics of nail disease response. In other words, the nail generally takes about 6 months to grow, so patients are often told that their nail disease should respond by 6 months. This, however, is a long waiting period to know the effectiveness of a drug. Early imaging, therefore, may be helpful for defining biomarkers or response and/or non-response. Early imaging may be helpful for defining biomarkers of response and/or non-response.

1.3.2.1 Human Pharmacokinetics

Secukinumab is selective for human IL-17A and potently neutralizes the bioactivity of this cytokine. IL-17A is the central cytokine in multiple autoimmune and inflammatory processes. It is being recognized as one of the principal pro-inflammatory cytokines in autoimmune diseases such as psoriasis, PsA, AS, and uveitis and is thought to play a role in other inflammatory conditions.

Secukinumab shows a dose-proportional pharmacokinetic (PK) behavior, which is typical for an IgG antibody that interacts with a soluble target like IL-17A. The distribution volume and clearance are low, the

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elimination half-lives are comparable in psoriasis, PsA, and AS patients (i.e. in the range between 25 and 27 days), and the median Tmax is shortly after the end of infusion in the case of intravenous (i.v.) administration. After s.c. administration, median Tmax is in the range between six and eight days. Based on population PK analysis in psoriasis, PsA, and AS patients, the absolute bioavailability after s.c. administration is in the range between 73% and 85%.

1.3.2.2 Clinical Studies in Adults

Trial	First Author	Comparator	N	Dosing
JUNCTURE	Paul	Placebo	404	Secukinumab 150 mg SC single administration at week 0, or 150 mg SC at weeks 0, 1, 2, 4, or 150 mg SC at weeks 0, 4, 8, or placebo
FEATURE	Blauvelt	Placebo	177	Secukinumab 150 mg or 300 mg SC once weekly between weeks 0 and 4, and once again at week 8, or placebo
ERASURE	Langley	Placebo	738	Secukinumab 150 mg or 300 mg SC once weekly for 5 weeks then every 4 weeks, or placebo
FIXTURE	Langley	Etanercept	1306	Secukinumab 150 mg or 300 mg SC once weekly for 5 weeks then every 4 weeks, or etanercept SC twice weekly for 12 weeks then once weekly, or placebo
ERASURE subanalysis	Ohtsuki	Placebo	87	Secukinumab 150 mg or 300 mg SC once weekly for 5 weeks then every 4 weeks, or placebo
SCULPTURE	Mrowietz	Placebo	966	Secukinumab 150 mg or 300 mg SC weekly for 5 weeks then once at week 8, then at week 12 patients achieving PASI75 were re-randomized to either 150 mg or 300 mg SC given at fixed interval or retreatment as-needed regimen
STATURE	Thaci	Placebo	43	Secukinumab 10 mg/kg IV at baseline, weeks 2 and 4, or 300 mg SC at baseline and week 4
CLEAR	Thaci	Ustekinumab	676	Secukinumab 300 mg SC at weeks 0, 1, 2, 3, and every 4 weeks starting at week 4, or ustekinumab 45 mg or 90 mg SC (depending on subject body weight at baseline) at weeks 0 and 4 and then every 12 weeks
FUTURE 1	Mease	Placebo	606	All patients assigned to receive an IV loading dose of secukinumab at a dose of 10 mg/kg at 0, 2, and 4 weeks followed by secukinumab SC at a dose of either 150 mg or 75 mg every 4

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				weeks or placebo. Placebo group was switched to secukinumab SC at a dose of 150 mg or 75 mg at week 16 or 24 depending on the clinical response.
FUTURE 2	McInnes	Placebo	397	Secukinumab 300 mg or 150 mg or 75 mg SC to receive once a week from baseline and then every 4 weeks from week 4
FUTURE 2 sub analysis	Gottlieb	Placebo	279	secukinumab 300 mg, 150 mg, 75mg or PBO
TRANSFIGURE	Reich	Placebo	198	secukinumab 300 mg, 150 mg, or placebo in patients with moderate-to-severe plaque and nail psoriasis.
FUTURE 3	Nash	Placebo	414	secukinumab 300 mg, 150 mg, or placebo in patients with active psoriatic arthritis
FUTURE 5	Mease	Placebo	996	secukinumab 300 mg or 150 mg with loading dose (LD), 150 mg without LD or placebo in patients with active psoriatic arthritis
2 PRECISE	Mrowietz	Placebo	237	Patients with palmoplantar pustular psoriasis (PPP) treated with Secukinumab 300 mg or 150 mg or placebo
PSARTROS	Kampylafka	None	20	Open label study of 20 patients with inflammation and bone changes in joints affected by PsA.
CHOICE		Placebo		
MEASURE 1 & 2		Placebo		

Adapted from Table 1 from Abrouk M, Gandy J, Nakamura M, Lee K, Brodsky M, Singh R, Zhu H, Farahnik B, Bhutani T, Koo J. Secukinumab in the Treatment of Psoriasis and Psoriatic Arthritis: A Review of the Literature. Skin Therapy Lett. 2017 Jul;22(4):1-6. Review. PubMed PMID: 28732152.

1.1 **Dose Rationale**

We will be treating all patients with secukinumab 300 mg as this is the approved dose for psoriasis.

2. Study Objectives

2.1 Primary Objective

- To identify predictors of nail disease response at 24 weeks.
  a) Identify non-invasive imaging predictors of response in nail psoriasis to secukinumab at week 24 defined by a 25% improvement in NAPSI (one such hypothesized risk factor is MRI response at week 4)

2.2 Secondary Objectives

- Examine the validity, responsiveness and basic metrics of the available outcome measures for nail disease.
  a) Examine the proportion of responders and rate of response in nail psoriasis depending upon the outcome measures used.

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b) Examine correlation among imaging scores, clinical nail scores, and patient reported outcomes.

- Examine correlation among MRI and ultrasound for nail bed inflammation and for matrix inflammation.

- Examine subclinical enthesitis or signs of psoriatic arthritis among patient with psoriasis and nail disease without known PsA.
  a) Determine the prevalence of symptomatic and asymptomatic (preclinical) nail bed enthesitis on ultrasound and MRI among patients with nail psoriasis.
  b) Examine change in nail bed enthesitis between 0 and 4 weeks on MRI and US.

3. Investigational Plan

This study will be an open label study of secukinumab for the treatment of nail psoriasis. Patients will be screened for eligibility and then will undergo 7 visits from baseline through week 24. More details on procedures occurring during each phase will be included in subsequent sections of the protocol.

3.1 General Design

Phase IV open label trial of secukinumab for the treatment of nail psoriasis.

3.1.1 Screening Phase

Patients will be recruited using the following methods: a) flyers in the clinics, b) physician referrals, c) advertisements on radio or in the subway if needed, d) electronic message through “My Penn Medicine” (Epic My Chart) if needed.

Informed consent will be explained and signed at the screening visit prior to any study procedures. Inclusion and exclusion criteria will be reviewed. A past medical history (to elicit comorbidities), social history, treatment history (all systemic medications for psoriasis and PsA will be reviewed) will be recorded to ensure eligibility. A nail exam will be performed. CASPAR criteria and inflammatory back pain criteria will be reviewed. Vital signs will be taken. Patients will undergo a baseline blood draw (CBC, CMP, CRP, quantiferon gold) to determine whether they are able to receive secukinumab. Blood for storage for further testing will also be obtained. Fingernail clippings of at least one involved nail will be obtained to test for onychomycosis. Imaging visits for weeks 0 and 4 will be scheduled so that all study activities occur on a single day.

3.1.2 Study Intervention Phase

If patients are eligible based on the screening visit, they will be scheduled for a baseline visit. At the baseline visit (week 0), the patient will complete the study Patient Reported Outcomes (PROs)/surveys: DLQI, RAPID3, PSAID, pain VAS, NAPPA, and patient global assessment of nail disease. We are capturing psoriatic arthritis indices as well as psoriasis and nail disease outcome measures as one of the aims of the study is to examine subclinical PsA. Vitals will be obtained, and pictures of the nails will be taken. An investigator will perform a nail exam (NAPSI, mNAPSI, nail PGA*), skin exam (PASI, BSA, PGA), joint examination (66/68 joint count, SPARCC enthesitis count, and dactylitis count) and a Physician Global Assessment of Overall Health. For the nail exam, in addition to capturing the necessary information for NAPSI and mNAPSI, we will also capture onycholysis, oil drops, pitting, crumbling, nail bed hyperkeratosis, and Beau’s lines for each nail graded as 0-3 scale, for the Nijmegen-Nail Psoriasis Activity Index tooL (N-NAIL) outcome measure. Patients will then undergo MRI of the target hand ('target' hand will be the one with the most nail disease as determined from the exam) and US of both target hands with particular attention to the nail beds and nail matrix. The first dose of drug will be administered.

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Patients will be educated on how to complete the next loading dose injections prior the week 4 visit. They will have the option to choose to come in for the weekly injections if they wish.

Patients will return for a Week 4 visit where all the study activities from the baseline will be repeated: vital signs, pictures of the nails, a nail exam (mNAPSI, NAPSI, nail PGA), skin exam (PASI, BSA, PGA), joint examination (66/68 joint count, SPARCC enthesitis count, dactylitis count), Physician Global Assessment of Overall Health, and patient completion of PROs/surveys (RAPID3, DLQI, PSAID, NPQ10, pain VAS, and patient global assessment of nail disease). Patients will again undergo MRI of the target hand and US of both hands.

Patients will return every 4 weeks (Week 8, 12, 16, 20) for a nail exam (NAPSI, mNAPSI, nail PGA). Patients will complete PROs/surveys (RAPID3, DLQI, PSAID, NPQ10, pain VAS, and patient global assessment of nail disease) at each visit.

The Week 24 visit will be the final visit of the study. Vital signs, pictures of the nails, a nail exam (NAPSI, mNAPSI, nail PGA), skin exam (PASI, BSA, PGA), joint examination (66/68 joint count, SPARCC enthesitis count, dactylitis count), and Physician Global Assessment of Overall Health will all be performed. The patients will also complete the set of PROs a final time (RAPID3, DLQI, PSAID, pain VAS, NPQ10, and patient global assessment of nail disease). The patient will not receive the drug at this visit.

3.1.3 Follow Up Phase

There will be a safety follow-up phone call at 52 Weeks to determine whether the participant is still using the investigational product from this study, if there have been any adverse events related to the study, and also to see if the patient has developed Psoriatic Arthritis.

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

In this study, the primary outcome is the NAPSI (continuous score) response at 24 weeks. Nail disease takes several months to fully respond. If there were markers of early response, the patient could be encouraged to stay on therapy to maintain response or alternatively, the therapy could be adjusted earlier to improve outcomes.

3.2.2 Secondary Study Endpoints

NAPSI, mNAPSI, varied cut offs of NAPSI/mNAPSI, physician global assessment of nail disease, PASI, DLQI, patient nail VAS, Imaging evidence of inflammation in the nail bed (MRI/USD), nail matrix (MRI/USD), subcutaneous tissue (MRI), enthesial inflammation (MRI), and bone inflammation (MRI) at baseline, and change from baseline at 24 weeks. Change in each measure will be plotted over time; We will calculate mean time to resolution and mean time to 25%, 50%, 75%, and 90% improvement in NAPSI, mNAPSI, physician nail global assessment and patient nail global assessment. Correlation between outcome measures will be assessed at baseline and correlation among change in the outcomes from 0 to 24 weeks will be calculated using Spearman’s correlation coefficients (assuming a non-parametric distribution). Among patients with and without imaging inflammation in the individual structures, we will examine mean values in physician-assessed and patient-reported outcomes

Nail bed and nail matrix inflammation on MRI (presence or absence) and US Doppler (positive or negative) will be examined for each digit at baseline and 4 weeks.

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3.2.3 Primary Safety Endpoints

The primary safety endpoint will be the adverse events related to the investigational product as recorded during the study. Other measurements for safety will include measurement of injection site reactions, gastrointestinal complaints, respiratory infections, and oral thrush. Serious adverse events will include hospitalizations or emergency room visits.

4. Study Population and Duration of Participation

The population for this study is adult patients with psoriasis and psoriatic nail disease.

4.1 Inclusion Criteria

- Active skin psoriasis currently (no minimum PASI or BSA) or skin psoriasis in the past documented by a dermatologist
- Active psoriatic nail disease defined as a Minimum 4 or more fingernails OR NAPSI>20
- Age 18-85

4.2 Exclusion Criteria

- History of IL-17 inhibitor use (other therapies including TNF inhibitors or non-biologics DMARDS in the past are acceptable)
- Inflammatory bowel disease
- Metal implants or other concerns for use of MRI
- Active infection
- Patients may have a history of self-reported psoriatic arthritis but may not have active PsA at the time of screening.
- We will exclude patients with onychomyosis of the fingernails on clippings
- Age <18 or age >85
- Currently pregnant or actively trying to conceive

4.3 Subject Recruitment

Patients will be recruited using the following methods: a) flyers in the clinics, b) physician referrals, c) advertisements on radio or in the subway if needed, d) electronic message through “My Penn Medicine” (Epic My Chart) if needed.

4.4 Duration of Study Participation

Screening visit followed by 24-week intervention with a safety follow-up phone call at Week 52.

4.5 Total Number of Subjects and Sites

50 patients may be consented and screened at one center (UPenn) to account for screen failures and to ensure that 40 participants complete the baseline visit. For a predictor with a prevalence of 33%, 36 patients are needed. Assuming 10% drop out or are loss to follow up, we aim to have a total of 40 patients complete the baseline visit and 36 complete the study.

4.6 Vulnerable Populations

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

Although not directly targeted, mentally disabled persons, economically or educationally disadvantaged persons, and/or employees or students of the recruiting institutions will not be denied enrollment and any special protections and/or additional safeguards will be undertaken in order to protect the rights and welfare of these subjects from coercion or undue influence as appropriate.

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5. Study Intervention

The study intervention will be the FDA approved drug Secukinumab. Secukinumab (Cosentyx®) is a prescription medicine that has been approved by the FDA for the treatment of plaque psoriasis, active psoriatic arthritis, and active ankylosing spondylitis in adults.

5.1 Description

Secukinumab comes in an auto-injector that patients generally give themselves at home. In this trial, the clinical research nurse will deliver the injections, or the patient may give themselves the injection after they have received training by the site.

5.2 Intervention Regimen

Secukinumab will be given at the currently approved dose for psoriasis which is 300 mg s.c. every 4 weeks with a loading regimen of 300 mg at Weeks 0, 1, 2, 3, and 4. The Secukinumab will be administered in two 150 mg subcutaneous (s.c) injections. Patients will self-administer all secukinumab doses after they have received training by the site. While patients are encouraged to self-inject, continued assistance by the site or home nurse is acceptable. All assessments at the scheduled visit will be performed before the patients receive the injection with the appropriate study medication for that visit.

If the patient has an active infection, the dose will be held for one week. If a participant withdraws from the study at the visit, no dose will be given.

5.3 Receipt

The investigational product will be shipped in bulk from Novartis and received by the Investigational Drug Service (IDS) staff at University of Pennsylvania Hospital. The shipment will be assessed to verify that all drug has been accounted for and that the drug has been shipped at the correct temperature and is viable for the study. IDS staff will record the receipt and condition of drug. IDS will store the product on site according to UPenn and Novartis policy.

5.4 Storage

Secukinumab Solution for Subcutaneous Injection will be provided in prefilled syringes (PFS). Single syringes will be packed in individual boxes. The boxes containing the safety prefilled syringes with study treatment solution should be kept at 2 to 8°C (36°F and 46°F) and protected from light. IDS will store the product on site according to UPenn and Novartis policy.

5.5 Preparation and Packaging

Secukinumab Solution for Subcutaneous Injection will be provided in prefilled syringes (PFS). Prior to administration the boxes containing the safety prefilled syringes with study treatment solution should be allowed to come to room temperature unopened for about 20 minutes before administration. Used safety syringe should be disposed of in a sharps container immediately after use.

5.6 Administration and Accountability

Patients will be instructed at baseline by the site staff on how to self-inject the secukinumab. At each visit, the injections will be self-administered into the appropriate site of the body (thighs, arms, abdomen), and each injection should be given at a different injection site. Each new injection should be given at least one inch from the previously used site. If subject chooses the abdomen, 2 inches area around navel should be avoided. Investigational drug should not be injected into areas where the skin is tender, bruised, red, or hard, or where subject has scars or stretch marks. Injection sites should be changed to reduce the risk of reaction.

All study treatment will be self-administered subcutaneously after visit study assessments have

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been completed. While patients are encouraged to self-inject, continued assistance by the site or home nurse is acceptable.

The Investigator will maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Product reconciliation will be completed on a regular basis and include information on product administration, such as: date administered, amount administered and to which subjects, product remaining, product damaged/destroyed and date of damage/destruction, product returned and date of return, etc. The Penn Investigational Drug Service will be used for this study and will assist with drug accountability including maintaining temperature and dispensing logs.

5.7 Subject Compliance Monitoring

For the visits at Weeks 0, 4, 8, 12, 16, and 20, the injections of the investigational product will be completed on site, so site staff will ensure that the injection has been done correctly. At the baseline visit (Week 0), patients will be educated on how and where to inject the product along with how often it should be done. At Weeks 1, 2, and 3, the study staff will call patients to check whether the patient has completed the injection and to help with any issues or questions. Patients can also choose to come to the site for the injection if they wish. The call or patient visit date will be recorded to ensure that the patient was compliant and study procedure was followed correctly

5.7.1 Return or Destruction of Investigational Product

At the conclusion of the study, and as appropriate during the course of the study, the Investigator will destroy any unused/expired study product on site as per the Investigational Drug Service (IDS) SOP. If unused/expired study product cannot be destroyed on site, then it may be sent to Novartis for destruction.

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6. Study Procedures

Table 1: Schedule of Study Procedures

	Screening	Baseline (Week 0)	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Informed Consent (PHY)	X							
Inclusion/Exclusion (PHY/N)	X							
Medical History (PHY/N)	X							
CASPAR Criteria (PHY/N)	X	X						
Nail Exam (NAPSI, mNAPSI, PGA) (PHY/N)	X	X	X	X	X	X	X	X
Nail Pictures	X	X	X					X
Skin Exam (PASI, BSA, PGA) (PHY/N)	X	X	X					X
Joint Exam (66/68 Joint Count) (PHY/N)		X	X					X
SPARCC Enthesitis Count (PHY/N)		X	X					X
Dactylitis Count (PHY/N)		X	X					X
Physician Global Assessment (PGA) of Overall Health	X	X	X					X
Demographics (Participant)		X						
Comorbid Conditions (Participant)		X						
DLQI (Participant/PRO)		X	X	X	X	X	X	X
RAPID3 (Participant/PRO)		X	X		X			X
PROMIS 10 (Participant/PRO)		X	X		X			X
Global assessment of nail disease (Participant/PRO)		X	X	X	X	X	X	X
NAPPA (Participant/PRO)		X	X	X	X	X	X	X
Global assessment of improvement (Participant/PRO)			X		X			X
PEST (Participant/PRO)		X						
MRI of Target Hand (TECH)		X	X					
US of Both Hands (TECH)		X	X					
Handheld US of Four Fingers		X	X					
Vital Signs (C/N)	X	X	X	X	X	X	X	X
Blood Draw (CBC, CMP, CRP, TB Qgold, etc) (C/N)	X							
Urine Pregnancy Test	X	X	X	X	X	X	X	X
Fingernail Clipping (C/N)	X							
On Site Drug Injection (Participant/N?)		X	X	X	X	X	X	***
Payment (C/N)		$25+P	$25+P	$25+P	$25+P	$25+P	$25+P	$25+P
Give Medication to Participant for home injection		3 doses						

PHY/N= PHYSICIAN OR NURSE, C/N= CRC or Nurse
**** Investigational Product will NOT be administered at this visit. Patients may choose to continue using Secukinumab clinically.*

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6.1 Screening

- Explanation and signature of Informed Consent,
- Review of inclusion and exclusion criteria,
- Review of past medical history (to elicit comorbidities), social history, and treatment history (including all systemic medications for psoriasis and PsA)
- Review of CASPAR criteria and inflammatory back pain criteria,
- Vital signs, (Height, Weight, Blood Pressure, Heart Rate)
- Pictures of the nails,
- Nail exam (NAPSI, mNAPSI, nail PGA*),
- Fingernail clipping (of at least one involved nail to test for onychomycosis)
- Skin exam (PASI, BSA, PGA),
- Physician Global Assessment of Overall Health
- Blood draw (CBC, CMP, CRP, TB Qgold, etc),
- Urine Pregnancy Test
- Scheduling of imaging for Baseline (Week 0) and Week 4 visits.

6.2 Study Intervention Phase

6.2.1 Visit 1 (Baseline visit, Week 0)

- Vital signs, (Blood Pressure, Heart Rate)
- Demographics,
- Comorbid conditions,
- Pictures of the nails,
- Nail exam (NAPSI, mNAPSI, nail PGA*),
- Skin exam (PASI, BSA, PGA),
- Joint exam (66/68 joint count, SPARCC enthesitis count, dactylitis count),
- Physician Global Assessment of Overall Health
- Patient Reported Outcomes (DLQI, RAPID3**, PROMIS 10, global assessment of nail disease, NAPPA, PEST),
- Urine Pregnancy Test
- MRI of the target hand (SOC),
- US of both hands with particular attention to the nail beds and nail matrix,
- Handheld US of Four Fingers (Optional)
- Administration of first dose of investigational product,
- Patient education on how to complete the next loading dose injections prior to the Week 4 visit.

6.2.2 Visit 2 (Week 4)

- Vital signs, (Blood Pressure, Heart Rate)
- Assessment of possible adverse events,
- Review of medication changes and updates,
- Pictures of the nails,
- Nail exam (NAPSI, mNAPSI, nail PGA*),
- Skin exam (PASI, BSA, PGA),
- Joint exam (66/68 joint count, SPARCC enthesitis count, dactylitis count),
- Physician Global Assessment of Overall Health
- Patient Reported Outcomes (DLQI, RAPID3**, PROMIS 10, global assessment of nail disease, NAPPA, global assessment of improvement),
- Urine Pregnancy Test
- MRI of the target hand (SOC),
- US of both hands with particular attention to the nail beds and nail matrix

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- Handheld US of Four Fingers (Optional)
- Administration of investigational product.

6.2.3 Visit 3 (Week 8)

- Vital signs, (Blood Pressure, Heart Rate)
- Assessment of possible adverse events,
- Review of medication changes and updates,
- Pictures of the nails,
- Nail exam (NAPSI, mNAPSI, nail PGA*),
- Patient Reported Outcomes (DLQI, global assessment of nail disease, NAPPA),
- Urine Pregnancy Test
- Administration of investigational product.

6.2.4 Visit 4 (Week 12)

- Vital signs, (Blood Pressure, Heart Rate)
- Assessment of possible adverse events,
- Review of medication changes and updates,
- Pictures of the nails,
- Nail exam (NAPSI, mNAPSI, nail PGA*),
- Patient Reported Outcomes (DLQI, RAPID3**, PROMIS 10, global assessment of nail disease, NAPPA, global assessment of improvement),
- Urine Pregnancy Test
- Administration of investigational product.

6.2.5 Visit 5 (Week 16)

- Vital signs, (Blood Pressure, Heart Rate)
- Assessment of possible adverse events,
- Review of medication changes and updates,
- Pictures of the nails,
- Nail exam (NAPSI, mNAPSI, nail PGA*),
- Patient Reported Outcomes (DLQI, global assessment of nail disease, NAPPA),
- Urine Pregnancy Test
- Administration of investigational product.

6.2.6 Visit 6 (Week 20)

- Vital signs, (Blood Pressure, Heart Rate)
- Assessment of possible adverse events,
- Review of medication changes and updates,
- Pictures of the nails,
- Nail exam (NAPSI, mNAPSI, nail PGA*),
- Patient Reported Outcomes (DLQI, global assessment of nail disease, NAPPA),
- Urine Pregnancy Test
- Administration of investigational product.

6.2.7 Visit 7: End of Study Visit (Week 24)

- Vital signs, (Blood Pressure, Heart Rate, Weight)
- Assessment of possible adverse events,
- Review of medication changes and updates,
- Pictures of the nails,

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- Nail exam (NAPSI, mNAPSI, nail PGA*),
- Skin exam (PASI, BSA, PGA),
- Joint examination (66/68 joint count, SPARCC enthesitis count, dactylitis count),
- Physician Global Assessment of Overall Health
- Patient Reported Outcomes (DLQI, RAPID3**, PROMIS 10, global assessment of nail disease, NAPPA, global assessment of improvement),
- Urine Pregnancy Test

*** Investigational Product will NOT be administered at this visit. Patients may choose to continue using Secukinumab clinically.*

6.3 Follow Up Phase of the Study

6.3.1 Safety Follow-Up

There will be a safety follow-up phone call from the coordinator to the patient at Week 52.

- Discuss and assess possible adverse events,
- Is the patient still using the investigational product as a clinical treatment?
- Has the patient developed Psoriatic Arthritis?
- Address any follow-up questions or concerns.

6.4 Rescue Therapy [if applicable]

Rescue medication is not permitted during the study. Patients will be free to discontinue participation in the study at any time.

6.5 Unscheduled Visits

Patients may be seen at any time for an unscheduled visit if they experience deterioration or AEs that in the opinion of the investigator need intervention or repeat laboratory testing. The assessment(s) performed at an unscheduled visit should include: an assessment of concomitant medication and procedures/significant non-drug therapies, vital signs, and an AE/SAE assessment. Any additional assessments performed are at the investigator/qualified site staff's discretion. During an unscheduled visit, study treatment will not be administered.

6.6 Subject Withdrawal

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to intervention or study procedures or visit schedules, or in the case of certain AEs. The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study.

6.6.1 Data Collection and Follow-up for Withdrawn Subjects

Subjects who withdraw early will be asked to complete the safety follow up call to collect additional information and check on any adverse events.

6.7 Early Termination Visits

It will be documented if a participant withdraws, leaves the study early, or is asked to cease participation. Subjects who withdraw or ends participation early will be asked to complete the safety follow up call to collect additional information and to check on any adverse events.

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7. Study Evaluations and Measurements

7.1 Medical Record Review

- Date of birth
- Relevant psoriasis, psoriatic arthritis, and general medical history/current medical condition data: date of symptom onset, date of diagnosis, targeted medical history events related to PsA and PsO
- A past medical history (to elicit comorbidities)
- Social history
- Medication and Treatment History (previous therapies, current medications, all systemic medications for psoriasis and PsA will be reviewed)

7.2 Physical Examination

Demographic and baseline characteristic data to be collected on all patients and to be recorded in the CRF include:

- Age, sex, race, ethnicity
- Vital signs (Height, Weight, Blood Pressure, Heart Rate)
- Pictures of the nails,
- Nail exam (NAPSI, mNAPSI, nail PGA*),
    - *For the nail exam, in addition to capturing the necessary information for NAPSI and mNAPSI, we will also capture onycholysis, oil drops, pitting, crumbling, nail bed hyperkeratosis, and Beau's lines for each nail graded as 0-3 scale, for the Nijmegen-Nail psoriasis Activity Index tooL (N-NAIL) outcome measure.
- Skin exam (PASI, BSA, PGA),
- Joint examination** (66/68 joint count, SPARCC enthesitis count, and dactylitis count).
- Physician Global Assessment of Overall Health
    - **We are capturing psoriatic arthritis indices as well as psoriasis and nail disease outcome measures as one of the aims of the study is to examine subclinical PsA.

7.3 Laboratory Evaluations

There will be a baseline blood draw to determine whether participants are able to receive secukinumab

- Complete Blood Count (CBC) (1 Lavender Top- 3 ml)
- A Comprehensive Metabolic Panel (CMP) (1 SST Tube Red/Black- 8.5 ml)
- C-Reactive Protein (CRP) (1 Gold Top- 5 ml)
- Quantiferon Gold to test for TB (4 tubes x 1 ml each)
- Blood for storage will also be obtained (Serum, Plasma, and DNA) (10 ml Red Top, 10 ml Purple Top EDTA, 8.5 PAXgene)
- Total = 49 ml

7.4 Pregnancy Testing

A urine pregnancy test will be performed at every visit for female subjects 18 years of age to 60 years of age.

7.5 Other Evaluations, Measures

<u>Patient Reported Outcomes (PROs):</u>
The patient will complete the following:

- Dermatology Life Quality Index (DLQI)
- Routine Assessment of Patient Index Data 3 (RAPID3)
- Psoriatic Arthritis Impact of Disease (PSAID)

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- Pain Visual Analogue Scale (Pain VAS)
- Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPPA)
- Patient Global Assessments of Nail Disease
- PEST (Psoriasis Epidemiology Screening Tool)
- Global Assessment of Improvement

Imaging

- Magnetic Resonance Imaging (MRI) of the target hand(s)- These will be standard of care (SOC) MRIs without contrast agents or any investigational sequences or coils.
- Ultrasound (US) of the both hand(s) with particular attention to the nail beds and nail matrix.
- Handheld Ultrasound (US) of four fingers and the four nails on those fingers.

7.6 Efficacy Evaluations

The efficacy of the study intervention will be measured primarily based upon the NAPSI and the physician global assessment of nail disease.

7.7 Genetic Testing

This study will include a blood draw (serum, plasma and DNA) for storage and later testing. These tests may include exploratory genetic components but samples will be de-identified and results will not be returned to patients.

7.8 Safety Evaluations

Vital signs will be recorded at each visit for safety. Women ages 18 - 60 will complete a urine pregnancy test at each visit to ensure that it is safe for them to continue using the study drug. Adverse events related to the investigational product will be recorded as safety evaluations. These adverse events and safety measurements will include measurement of injection site reactions, gastrointestinal complaints, respiratory infections, and oral thrush. Serious adverse events will include hospitalizations or emergency room visits.

8. Statistical Plan

8.1 Primary Endpoint

In this study, the primary outcome is the NAPSI (continuous score) response at 24 weeks.

	Objective	**Endpoint**
Primary	Objective 1: Identify predictors of nail disease response at 24 weeks. a) Identify noninvasive imaging predictors at week 4 of response in nail psoriasis to secukinumab at week 24 defined by a 25% improvement in NAPSI. *Rationale*: Nail disease takes several months to fully respond. If there were markers of early response, the patient could be encouraged to stay on therapy to maintain response or alternatively, the therapy could be adjusted earlier to improve outcomes. In this objective, we	*Outcomes*: The primary outcome will be response defined as change in NAPSI from 0 to 24 weeks (continuous outcome, range 0-80). In sensitivity analyses, we will examine other response outcomes including a cut off of >25% (as well as >50% and > 75%) improvement in NAPSI, change in mNAPSI, proportion change in mNAPSI, resolution of nail disease. *Analysis*: First, we will describe the imaging features of nail disease on MRI and US among the cohort at baseline. We will then examine change in MRI and US between baseline and week 4

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	will identify such predictors. Additionally, we will examine a variety of imaging features and how they are associated with response.	(e.g., change in US Doppler score, presence and/or degree of inflammation in nail bed, surrounding soft tissue or bone edema on MRI). These variables will be used as predictors for NAPSI response. (see statistical analysis) *Timepoint*: 24 weeks

8.2 Secondary Endpoints

Secondary/ Exploratory	Objective 2: Examine the validity, responsiveness and basic metrics of the available outcome measures for nail disease. 9. Examine the proportion of responders and rate of response in nail psoriasis depending upon the outcome measures used 10. Examine correlation among imaging scores, clinical nail scores and patient reported outcomes.	*Outcomes*: NAPSI, mNAPSI, varied cut offs of NAPSI/mNAPSI, physician global assessment of nail disease, PASI, DLQI, patient nail VAS, Imaging evidence of inflammation in the nail bed (MRI/USD), nail matrix (MRI/USD), subcutaneous tissue (MRI), enthesial inflammation (MRI), bone inflammation (MRI). *Analysis*: Change in each measure will be plotted over time; We will calculate mean time to resolution and mean time to 25%, 50%, 75%, and 90% improvement in NAPSI, mNAPSI, physician nail global assessment and patient nail global assessment. Correlation between outcome measures will be assessed at baseline and correlation among change in the outcomes from 0 to 24 weeks will be calculated using Spearman's correlation coefficients (assuming a non-parametric distribution). Among patients with and without imaging inflammation in the individual structures, we will examine mean values in physician-assessed and patient-reported outcomes *Timepoint*: Baseline, and change from baseline at 24 weeks _____ *Variables*: Nail bed and nail matrix inflammation on MRI (presence or absence) and US Doppler (positive or negative) will be examined for each digit.

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	Objective 3: Examine correlation among MRI and US for nail bed inflammation and for matrix inflammation.	*Analysis*: We will descriptively report the prevalence of each imaging feature by patient and by nail. We will examine the proportion of nails with clinically involvement that have inflammation and the proportion of nails without visible nail changes where imaging inflammation is present. We will report the association between inflammation and symptoms. We will examine the mean NAPSI score (by nail) among fingers with and without inflammation. Additionally, we will calculate a kappa statistic at each time point (0, 4 weeks) for agreement between the two instruments for each outcome. *Time points*: Baseline and 4 weeks
		Outcome: Nail bed inflammation or nail unit/DIP enthesitis defined by (USD, MRI, and for enthesitis, enlargement or swelling within the enthesis) *Analysis*: We will examine the prevalence of enthesial or finger, hand, or wrist joint inflammation on imaging. Additional features of PsA or OA on imaging will also be descriptively reported (i.e., erosions, osteophytes, junxtaarticular new bone formation). We will descriptively report change in each feature from 0 to 4 weeks on secukinumab *Time point(s)*: Baseline and 4 weeks
	Objective 4: Examine subclinical enthesitis or signs of psoriatic arthritis among patient with psoriasis and nail disease without known PsA. a) Determine the prevalence of symptomatic and asymptomatic (preclinical) nail bed enthesitis on ultrasound and MRI among patients with nail psoriasis. b) Examine change in nail bed enthesitis between 0 and 4 weeks on MRI and US.	*Outcomes*: We will use the same outcome measures described in Objective 1. *Analysis*: We will examine the association of hypothesized predictors at baseline with response at 24 weeks: age, sex, BMI, imaging features including high inflammation (positive Doppler US of nail bed, or nail bed or

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		soft tissue inflammation or adjacent bone edema on MRI), type of nail lesions (pitting, oil spots, onycholysis), baseline NAPSI, presence of inflammatory joint or enthesial lessions on MRI at baseline *Time point(s)*: Baseline and 4 weeks
	Exploratory objective A: Identify clinical predictors of nail psoriasis response to secukinumab at 24 weeks (e.g., NAPSI change at week 4)	Outcomes: Prior to study initiation, we will meet with an MSK radiologist, MRI specialist, US specialist, and experimental radiologists to develop a standardized imaging protocol that will allow for ideal image analysis. In this exploratory phase, we will use computer software to identify predictors of response. We will examine markers of intensity, texture, and other MR features within the regions of interest (nail bed, nail matrix, DIP joint). We may extract several hundred different markers. We will divide the images into two sets. One set will be used as a training set to identify the imaging feature or features (which may include baseline only or change from baseline to four weeks) most strongly associated with response using bioinformatics methods such as classification tree, CART, or latent class analysis. We will validate the set of features in the second set of images. We will examine continuous response at 24 weeks as the outcome as well as binary response. Time points: outcome at 24 weeks, images from 0 and 4 weeks
	Exploratory objective B: Examine exploratory measures for quantifying MRI inflammation in the nail bed and nail bed entheses and whether these are also predictors of response.	

8.3 Sample Size and Power Determination

The primary objective is identification of predictors for response to therapy at 24 weeks. We are deriving a sample size from the response rates in the two previous studies of nail disease with secukinumab. The TRANSFIGURE study was conducted among patients with moderate-to-severe psoriasis, with nail involvement defined as NAPSI>=16 and >=4 fingers involved, and PASI >=12 and BSA >=10%. In this population, the mean improvement was -45.5% (SD not given in the primary publication, the SD at baseline is 15) from baseline in the NAPSI score at week 16 among patients receiving secukinumab 300 mg. Our study will enroll a similar population of patients (from the nail perspective) and will use the same outcome measure, although we do not have the requirement for severe psoriasis. If we assume that patients with a predictor of response (with prevalence 50%) have a mean improvement of -40 with SD 15 and those without the predictor have mean improvement of -25 with SD 15, we need 32 patients to achieve a power of 80%. For a predictor with a prevalence of 33%, 36 patients are needed. Assuming 10% drop out or loss to follow

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up, we may consent a total of 50 patients for screening in order to ensure that 40 patients complete the baseline visit.

We are also appropriately powered for the mNAPSI as a continuous outcome. In FUTURE2, among patients with PsA the mNAPSI mean at baseline was 18.6 and the change at week 24 was -12.3 for 300 mg and -4.1 for placebo. We assume that the change for all treated patients will be approximately -12.3. Patients with a predictor (e.g. elevated CRP, assume prevalence is 50%) will change by -14 and those without the predictor (e.g. normal CRP) will change by -10, with SD -4 (which is quite large), then 34 patients must complete the study to achieve 80% power. If the prevalence of the risk factor is lower (e.g., 33%), the sample size decreases to 24.

8.4 Statistical Methods

We will examine a variety of predictors (clinical, imaging, and patient-reported) of improvement in nail disease with secukinumab. In addition, we have outlined several analyses aiming to better understand the measurement of nail disease. There are few studies addressing measurement of nail disease from these three perspectives, none addressing the objectives above. In some analyses, we will test the same exposures among multiple different outcomes to better understand how the outcome measure used affects the predictors defined. These will be considered sensitivity or exploratory analyses and will be labeled as such to address the concern for multiple testing.

For predictive models with the continuous outcome (NAPSI), we will examine the association between each exposure of interest and the outcome. Among those with a $p<0.1$, we will include these in a full model and remove one variable at a time until all variables in the model are significant (<0.05). If the remainder of the variables in the model change substantially, we will add it back to the model after removing other variables to retest. We will aim to create the most parsimonious model which also has the highest Akaike information criterion (AIC).

8.4.1 Baseline Data

For objectives in which the goal is to understand factors at baseline associated with response, we will use linear regression models (for continuous outcomes; logistic regression for binary response) and for objectives in which we are examining the change in a particular factor between weeks 0 and 4 and the relationship to the outcome, we will use generalized estimating equations.

8.4.2 Imaging Analysis

Ultrasounds will be performed by Dr. Ogdie or by an ultrasound technician trained in MSK US. The protocol will be standardized prior to subject enrollment. Nail bed, nail matrix and DIP entheses, and DIP joints will be imaged for all fingers at weeks 0 and 4. Images will be stored for each subject. The ultrasonographer will give a score to the image in real time and will record the nail bed, nail matrix, enthesis and joint scores for each finger. We will later ask a radiologist to re-read the images and from these scores will calculate an inter-rater reliability (intraclass correlation, or ICC). For 5 randomly selected patients, the ultrasonographer will rescan 4 fingers and from these repeat scans we will calculate intra-rater reliability for each type of measure using a kappa statistic.

Dr. Ogdie or trained study staff may also use a handheld ultrasound device to scan four fingers and the four nails on those fingers for comparison with standard ultrasound images. This will be an optional procedure so patients that do not wish to undergo the additional US will still be eligible to participate in the study. Images from each of the finger joints and nails will be captured and stored as de-identified images. Additionally, at the time of scanning, Dr. Ogdie or study staff will label the individual joint as inflamed or not inflamed (and similarly with the nail bed). After full data collection is complete, we will examine the concordance between the handheld ultrasound and the technician's ultrasound using a kappa statistic. The kappa will be calculated overall and by individual joint/nail.

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MRIs will be read in batch form blinded to subject ID and time point (0 or 4 weeks). An MSK radiologist will read the MRI using a standard clinical protocol (examining for erosions, osteophytes, junxta articular new bone formation). In addition, we will examine specific regions of interest (nail bed, nail matrix, nail unit/DIP enthesis) and these will be graded as having inflammation (yes or no), and when inflammation is present it will be rated from 1-3 (mild, moderate or severe) in each region. After reading approximately 15 MRIs, the study investigators will meet with the radiologists (MSK and experimental) to discuss images to discuss other potential regions of interest to add to the protocol. We will periodically review images throughout the study, blinded to subject and time point.

8.4.3 Safety Analysis

All subjects entered into the study and administered the drug at the baseline visit will have detailed information collected on adverse events for the overall study safety analysis

8.5 Subject Population(s) for Analysis

The subject population for analysis will be patients who received at least one dose for the primary analysis and those who received the full load for the secondary analysis.

9. Safety and Adverse Events

9.1 Definitions

9.1.1 Adverse Event

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

- *results in study withdrawal*
- *is associated with a serious adverse event*
- *is associated with clinical signs or symptoms*
- *leads to additional treatment or to further diagnostic tests*
- *is considered by the investigator to be of clinical significance*

Particular attention will be paid to adverse events that feature injection site reactions, gastrointestinal complaints, respiratory infections, and oral thrush. Pregnancy of participant will also be considered an adverse event.

For FDA regulated studies the FDA defines an adverse event as the following:

Adverse event means any untoward medical occurrence associated with the use of a drug in humans whether or not considered drug related.

9.1.2 Serious Adverse Event

Serious Adverse Event

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

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

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- *For this study, serious adverse events will include hospitalizations or emergency room visits.*

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

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

9.2 Recording of Adverse Events

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

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

9.3 Relationship of AE to Study

The PI will determine the relationship of each adverse event to the study procedures (definitely related, probably related, possibly related, unlikely or unrelated)

9.4 Reporting of Adverse Events and Unanticipated Problems

Investigators will conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible,

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

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

Additionally all other events (unanticipated problems, adverse reactions, unanticipated adverse device effects and subject complaints will be recorded and reported with respect to institutional and federal policies as described in the Penn Manual and below.

If a subject becomes pregnant after the first intake of any IMP, the subject will be withdrawn from the study and will not receive any further injections. A Safety Follow-Up Visit will be scheduled 20 weeks after the final dose of IMP.

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The Investigator will inform the subject of information currently known about potential risks and about available treatment alternatives. The pregnant subject will be asked if they would like to register with MotherToBaby Pregnancy Studies conducted by the Organization of Teratology Information Specialists (OTIS). This is a pregnancy registry that studies how psoriasis/psoriatic arthritis and its management can affect a pregnancy and a developing baby

The progression of the pregnancy and the eventual birth will be followed up to report on the health of the mother and of the child. Every reasonable attempt should be made to follow the health of the child for 30 days after birth for any significant medical issues. If the subject is lost to follow up and/or refuses to give information, written documentation of attempts to contact the subject needs to be provided

9.4.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

9.4.2 Investigator reporting: Notifying the study funder

The PI will be directly responsible for identifying and reporting all adverse events, protocol deviations or violations and unanticipated events to the IRBs and funding agency promptly, as appropriate. The PI will also report all adverse events, accrual rates, retention rates, and all other logistical issues to the study funder yearly.

The requirements for the transfer to Novartis of adverse event data collected from the trial, including timeframes, are defined in the IIT Agreement. For trials involving patients treated with a Novartis drug, the Novartis safety requirements include:

- Transfer to Novartis in an ongoing manner of reports of SAEs, drug misuse or abuse, reports of drug exposure during pregnancy, any other information that may suggest a change in the benefit-risk profile for the Novartis drug, and where required, copies of Investigator Notifications for suspected unexpected serious adverse events (SUSAR) and copies of the Development Safety Update Report
- Performing an adverse event reconciliation between the Sponsor's trial database and an output from the Novartis safety database periodically throughout the trial.

Once the study concept is approved and the IIT agreement is executed, please refer to the IIT agreement for exact requirements for the type of trial you are proposing.

☒ **WITH a Novartis Drug**
Must be collected: • All Serious Adverse Events (SAE) • All reports of drug exposure during pregnancy • All non-serious Adverse Events (AE) • All reports of misuse and abuse of the Novartis drug, other medication errors and uses outside of what is foreseen in the protocol (irrespective if a clinical event has occurred)

9.4.3 Investigator Reporting: Notifying the Penn IRB

This study will follow the Penn reporting requirements and timelines for reportable events and reporting timelines. http://www.upenn.edu/IRB/mission-institutional-review-board-irb/reportable-events.

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A reportable event is an adverse event or incident that has the potential to be classified by the IRB as an unanticipated problem posing risks to participants or others. An incident is determined to be reportable to the IRB when it is both:

- probably or definitely related to participation in the research
- unexpected in terms of nature, severity, or frequency

9.4.4 Sponsor reporting: Notifying the FDA

This study will be operating under an IND exemption.

9.5 Medical Monitoring

The Principal Investigator will oversee the safety of the study at the site with assistance from the Co-Investigators and study team. Dr. Ogdie, the PI, will monitor the study on a day-to-day basis. In addition, we will appointment a Data and Safety Monitoring Officer(DSMO). Please see Data and Safety Monitoring Plan Appendix for a detailed description of the complete plan. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above.

9.5.1 Data and Safety Monitoring Plan

Overall, we feel that the study is of low risk to participants, particularly as this is an FDA approved medication used at approved doses. The main safety concerns will be loss of confidentiality or data breaches. Other potential risks include known side effects from secukinumab. Informed consent, acknowledging these risks, will be completed prior to subject enrollment. Dr. Ogdie, the PI, will monitor the study on a day-to-day basis. In addition, we will appointment a Data and Safety Monitoring Officer(DSMO). Please see Data and Safety Monitoring Plan Appendix for a detailed description of the complete plan.

10. Study Administration, Data Handling, and Record Keeping

10.1 Confidentiality

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

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

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

10.2 Data Collection and Management

All research data for the study will be stored on the Way to Health Platform. Way to Health (W2H) is a software platform developed by the Penn Center for Health Incentives and Behavioral Economics (CHIBE) and is currently operated through a partnership between CHIBE and the Penn Medicine Center for Health Care Innovation. W2H is an integrated, cloud-based platform that blends behavioral science with scalable digital technology to improve clinical outcomes. W2H automates many research functions necessary for conducting randomized controlled trials of healthy behavior interventions. The platform facilitates online and mobile participant enrollment; survey administration; integrated biomedical device data transmissions; automated randomization in a variety of schemes; automated communication with participants/patients via voice, text and email; delivery of financial and social incentives; utilization of

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gamification strategies and much more. More details are available at https://waytohealth.org. Way to Health will also be used to send surveys/questionnaires directly to participants by text and/or email throughout the study.

The paper consent forms along with any other separate paper documentation will be kept in locked offices in the Division of Rheumatology at University of Pennsylvania. Any electronic tracking or additional documentation including electronic regulatory documents will be kept on the UPHS server and accessed using UPHS/UPenn logins on password protected computers.

10.3 Records Retention

This study will retain records as required by the University of Pennsylvania.

11. Study Monitoring, Auditing, and Inspecting

11.1 Study Monitoring Plan

Dr. Ogdie, the PI, will monitor the study on a day-to-day basis. In addition, we will appointment a Data Safety Monitoring officer (DSMO). Please see Data and Safety Monitoring Plan Appendix for a detailed description of the complete plan.

11.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the study funder, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

12. Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

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

12.1 Risks

Secukinumab (Investigational Drug)

The large safety dataset of secukinumab did not show unexpected safety issues relative to the known mode of action. Secukinumab was generally safe and well-tolerated. The most frequently reported adverse events (AEs) are non-serious mild to moderate infections, mainly upper respiratory tract infections with secukinumab relative to placebo. In addition, there was an increase in localized mucosal or cutaneous candidiasis with secukinumab compared with placebo, but the cases were generally mild or moderate in severity, non-serious, and responsive to standard treatment and did not require discontinuation of secukinumab. There was also a small increase in neutropenia cases with secukinumab compared with placebo. Most cases were mild to moderate, transient and reversible and without a temporal relationship to infections. Common Toxicity Criteria (CTC) AE grade 3 neutropenia (< 1.0-0.5 x 109/L) was uncommonly observed with secukinumab. Hypersensitivity reactions include urticaria and rare events of anaphylactic reaction to secukinumab have also been observed in clinical studies.

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Blood Draw
Occasionally there are risks associated with blood draws such as bruising, swelling, black and blue marks, fainting and/or infection at the site. Patients may also experience a decrease in hemoglobin and hematocrit (red blood cell number, called anemia) from having blood drawn frequently.

MRI
The risks of the MRI including flying objects, medical implants and foreign bodies, possibility of yet undiscovered pregnancy related risks, and incidental findings. These risks will be included in the consent form.

There is also a small risk of loss confidentiality but the study and data collection will be designed to avoid these as much as possible.

Reproductive Risks
Because of the effects of this drug, there could be serious harm to unborn children or children who are breast-feeding. These effects could also harm the mother. It is also possible that harmful side effects that are not yet known could happen to both the mother and unborn or breast-feeding child. Patients who are currently pregnant will not be able participate in the study. There will be a urine pregnancy test before entry into the study. While on the study, use of a contraceptive regimen will be required for patients who are able to conceive. Barrier methods (condoms, etc), oral, injected or implanted hormonal methods or placement of an intrauterine device (IUD) are all acceptable options for contraception during the study. Sterilization and/or total abstinence from sexual acts that could result in pregnancy are also acceptable.

If a subject becomes pregnant after the first intake of any IMP, the subject will be withdrawn from the study and will not receive any further injections. Pregnancy follow-up will occur according to Section 9.4.

12.2 Benefits

Direct
Nail psoriasis causes significant functional impairment and emotional distress in patients and this treatment could help improve nails and psoriasis outcomes. Secukinumab has shown efficacy in several inflammatory diseases and approved by the FDA and EMA for the treatment of adults with active AS, active PsA, and plaque psoriasis. Significant differences from placebo, etanercept, and ustekinumab have been demonstrated in the treatment of psoriasis (Langley 2014; Thaçi 2015), as well as significant difference from placebo in the treatment of joint pain, swelling, health-related quality of life, and radiographic progression in PsA. A recent Phase IIIB study, TRANSFIGURE, reported a statistically significant improvement in nail psoriasis at week 16 among patients treated with secukinumab 300 mg versus placebo.

Indirect
Knowledge of predictors of treatment response such as early imaging features of nail improvement and accurate measures of nail psoriasis could substantially shorten trials of nail psoriasis and may improve clinical management.

12.3 Risk Benefit Assessment

This study has greater than minimal risk. However, the expected risk profile of secukinumab is similar or improved compared to the approved inflammatory cytokine-targeting therapies. The risk to patients in this trial will be minimized by compliance to the study design along with close clinical and data monitoring. From the standpoint of the overall risk-benefit assessment, current trial with secukinumab is justified.

12.4 Informed Consent Process / HIPAA Authorization

Eligible patients may only be included in the study after providing written IRB-approved informed consent. The investigators will consent the patients in a private space. Patients will be encouraged to ask questions regarding any portion of the study they do not understand. Once all questions have been answered and the

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patient comprehends the nature of the study, the consent from will be signed. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent will be documented in the patient source documents.

Women of child bearing potential will be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

13. Study Finances

13.1 Funding Source

This study will be funded through a contract with Novartis.

13.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

13.3 Subject Stipends or Payments

Participants will be compensated $25 per visit for their time and effort in participating in the trial. They will also be given parking passes if needed for visits. Participants will be paid using the Clincard/Greenphire system.

14. Publication Plan

We will submit the results for presentation at meetings (AAD, SID, EULAR and/or ACR) and will submit manuscripts for publication at the end of the study. We anticipate two manuscripts: one on response to therapy by the various nail measures included, one on the validity of nail measures (construct validity and responsiveness), and one on imaging findings of subclinical PsA and response to therapy.

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