A Pilot Study to Evaluate the Efficacy and Safety of Secukinumab in the Treatment of Moderate to Severe Atopic Dermatitis.

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INTRODUCTION/BACKGROUND

Atopic Dermatitis is the most common inflammatory skin disease with increasing prevalence.(1) Recent studies show at least 4-7% of adults and 15-25% of the pediatric population to be affected, with a 1/3 considered moderate to severe patients. 80% of the AD patients are extrinsic AD patients with elevated IgE levels while 20% are intrinsic patients, with normal IgE levels, and usually lacking family history of atopy.(2)

The disease poses a large unmet need for more effective topical and systemic therapeutics. Dupilumab, a fully human monoclonal antibody targeting the IL-4 receptor-α, blocking both IL-4 and IL-13 signaling, is a newly developed agent, and the first targeted treatment to show successful results in early clinical trials for AD.(3) Dupilumab has significant dose-dependent clinical efficacy in AD, irrespective of serum IgE levels. Agents currently in clinical trials for AD include antagonists of Th22 (anti IL-22/ILV-094), Th17/IL-23 (anti IL-23p40/ustekinumab), and innate (anti PDE4) immunity. Selection of immune targeted therapeutics for patients with different degrees of disease severity or recognized AD phenotypes should not be done by serendipity but should be guided by defining the extent of activation of polar immune circuits in skin and blood. Based on preliminary data we believe that different therapeutics may be required to effectively treat subsets of AD patients.

Our recent studies (below) suggest that the intrinsic (normal IgE levels) and extrinsic (high IgE levels) AD phenotypes are associated with distinct patterns of activation (or suppression) of polar immune axes and corresponding tissue responses:(2)

I) <u>Different AD phenotypes (e.g intrinsic and extrinsic AD) demonstrate differential cytokine polarity. A significantly higher state of Th22 and Th17 immune activation characterizes Intrinsic vs. Extrinsic AD.(2)</u> We have studied a group of extrinsic (n=43, high level of IgE and usually an atopic background) and intrinsic (n=9, normal levels of IgE and usually without an atopic background) AD

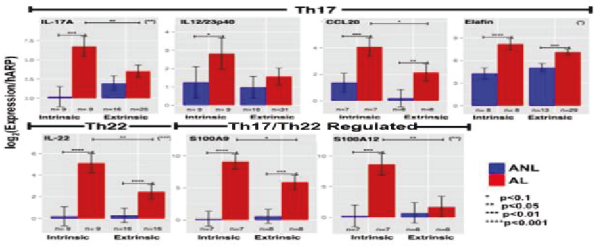

Fig. 1. Measures of mRNA levels (normalized to hARP mRNA) for specific Th17/IL-23 and Th22 cytokines and inflammatory products in non-lesional (ANL) and lesional AD (AL) skin from patients with intrinsic versus extrinsic disease. Number of patients in each comparison is shown in the graph. Expression is given in logarithmic scale.

patients with similar disease severity (mean scoring of AD/SCORAD of 53 and 54 in

extrinsic and intrinsic AD, respectively). As shown in Fig. 1, there is significantly higher mRNA expression of IL-17 and IL-22 cytokines in intrinsic compared with extrinsic skin lesions (~8 fold), with corresponding increases in CCL20, Elafin/PI3 and S100A proteins (these products are induced in keratinocytes by IL-17). Higher expression of IL-23p40 mRNA was also detected in intrinsic AD lesions.

The Th17 immune skewing in intrinsic AD has important therapeutic implications, suggesting that targeting this axis might preferentially benefit intrinsic AD patients. Despite high levels of IgE in extrinsic AD, similar expression levels of Th2-related products were observed in both extrinsic and intrinsic AD, suggesting that these phenotypes might have similar responses to Th2 antagonism, as recently shown in the NEJM paper with dupilumab, a fully human monoclonal antibody that blocks IL-4 and IL-13.(3)

Therefore, we hypothesize that blocking IL-17 would be able to clinically and mechanistically reverse atopic dermatitis effectively in AD patients.

HYPOTHESIS:

Primary Hypothesis:

1. It is hypothesized that IL-17 is involved in the pathogenesis of atopic dermatitis (AD).

Secondary Hypothesis:

1. Secukinumab is superior to placebo in the treatment of patients with moderate to severe AD.

OBJECTIVES:

Primary objective: To evaluate the efficacy of secukinumab in the treatment of intrinsic and extrinsic atopic dermatitis by measuring reduction in epidermal thickness at Week 16.

Secondary objectives:

1. To evaluate reduction in K16 expression at Week 16 compared to Baseline.
2. To evaluate the efficacy of secukinumab in the treatment of intrinsic and extrinsic atopic dermatitis by measuring different scoring systems (SCORAD, EASI, and IGA, see appendix) for AD.
3. To determine response biomarkers to secukinumab in treated patients with AD, which can be followed in future trials.
4. To define the cellular and molecular immune profiles of patients with AD as compared with non-lesional skin (from AD patients), and normal skin.

ENDPOINTS:

Primary endpoint: Change in epidermal thickness of lesional skin after 16 weeks of treatment.

Secondary endpoints:

1. Change in K16 expression of lesional skin after 16 weeks of treatment.
2. The proportion of patients who achieve an improvement of 50% or greater from their Baseline objective SCORAD at Week 16 of secukinumab treatment.
3. The proportion of patients who achieve an improvement of 50% or greater from their Baseline EASI score at Week 16 of secukinumab treatment.
4. The proportion of patients who achieve a score of "clear-0" or "almost clear-1" in the static IGA score at Week 16 as compared to Baseline.
5. Percentage decrease in SCORAD/EASI scores at Week 16.
6. The proportion of patients who achieve an improvement of 50% or greater from their Baseline objective SCORAD at Week 32 of secukinumab treatment.
7. The proportion of patients who achieve an improvement of 50% or greater from their Baseline EASI score at Week 32 of secukinumab treatment.
8. The proportion of patients who achieve a score of "clear-0" or "almost clear-1" in the static IGA score at Week 32 as compared to Baseline.
9. The proportion of patients who achieve an improvement of 50% or greater from their Baseline objective SCORAD at Week 52 of secukinumab treatment.
10. The proportion of patients who achieve an improvement of 50% or greater from their Baseline objective EASI score at Week 52 of secukinumab treatment.
11. The proportion of patients who achieve a score of "clear-0" or "almost clear-1" in the static IGA score at Week 52 as compared to Baseline.
12. To determine the safety of secukinumab in the treatment of intrinsic and extrinsic AD.

Secondary (Translational) Endpoints

1. Change of IL-17 regulated keratinocyte products (elafin/Pi3, CCL20, CXCL1, S100A7, A8, A9, A12) at Week 16 of treatment (as compared with Baseline). This will be assessed by a reduction of the mRNA gene expression levels of elafin/Pi3, CCL20, CXCL1, S100A7, A8, A9, A12 after 16 weeks of treatment by RT-PCR.

Exploratory Aims

1. To determine the effect of secukinumab therapy on suppression of immune driven inflammation, and related inflammatory cells (T-cells, dendritic cells (DCs), eosinophils), cytokines, and chemokines in lesional and non-lesional skin biopsies. Skin infiltration by T-cells (CD3, CD8), DCs (myeloid/CD11c,

IDECs/fcEpsilonRI, CD206, Langerhans cells/CD1a) will be assessed in pre- and post lesional and non-lesional skin biopsies after 16-weeks post first treatment with secukinumab by immunohistochemistry.

2. To determine what immune pathways are suppressed during treatment with secukinumab. Suppression of Th2, and Th22 immune pathways will be assessed by changes in Th2 inflammatory cytokines (including IL-13, IL-31, IL-10), and Th22/IL-22 cytokine and downstream response genes of IL-22 (including S100A7, and A8 that are co regulated by IL-17 and IL-22). We will also assess for gene modulation during treatment of Th1 and Th17 inflammatory cell markers (such as IFN-gamma, CXCL9, CXCL10/Th1, and IL-17A, IL-17F, IL-23p19 IL-23p40, CCL20, CXCL1, Elafin/PI3/Th17). RT-PCR will be used to determine these markers.
3. To determine the effect of treatment on the epidermal pathology that consists of epidermal hyperplasia and barrier/terminal differentiation abnormalities. The epidermal hyperplasia will be measured by epidermal thickness, K16, and Ki67 {by IHC, RT PCR (K16) and arrays}. Major differentiation genes such as loricrin, filaggrin, and periplakin will be measured before and after 16-week treatment with secukinumab on lesional and non-lesional AD skin by IHC (filaggrin), RT-PCR (filaggrin, loricrin and periplakin), and gene array.
4. In the group of patients that will respond to treatment by a reduction of at least 50% in SCORAD (“responders”), as well as in the non-responders, we will evaluate the correlation between clinical response to therapy with secukinumab (as measured by the SCORAD) with suppression of the pathologic epidermal and immune phenotypes. The epidermal hyperplasia will be measured by epidermal thickness and protein as well as gene expression of K16. The immune phenotype will be measured by gene expression changes in Th17/IL-17A, IL-23p40, IL-23p19, elafin/PI3, CXCL1, CXCL2), Th2/IL4 and/IL-13, and “T22”/IL-22, S100A7, and S100A8. We will also correlate the reduction in epidermal hyperplasia with the overall suppression of immune responses by a multivariate analysis.

RESEARCH DESIGN

This is a randomized, double-blind, pilot study of a total of 44 subjects with AD (22 with intrinsic and 22 with extrinsic AD) consisting of 2 phases. Subjects will be randomized (2:1) to either receive secukinumab 300 mg or placebo via subcutaneous injection using 2 prefilled syringes.

METHODS

Informed consent will be obtained at the study site at the time of the first consultation for participation in this study.

Phase 1:
After providing informed consent, subjects will be assessed for study eligibility at the Screening visit (day -28 to day -1). At the Screening visit the following procedures will be performed by the blinded investigator:

1. medical history and concomitant as well as prior medications/treatments will be reviewed
2. physical examination will be performed (including vital signs)
3. skin examination will be performed (including assessment of SCORAD, EASI, and IGA)
4. electrocardiogram (ECG) will be performed
5. approximately 9 cc (approximately 2 teaspoons) of blood will be drawn for a chemistry panel (including renal function tests, electrolytes, liver function tests) and complete blood count (including MCV).
6. approximately 6 cc (approximately 1 ¼ teaspoons) of blood will be drawn for a QuantiFERON TB-Gold test (QFT) assay; or subjects will undergo tuberculin purified protein derivative (PPD) testing.
7. HIV, hepatitis B surface antigen (HBsAg) and hepatitis C (HCV) antibody testing will be done in subjects deemed at risk. These include subjects with a history of injection drug use, homosexual subjects, and subjects with known sexual contact with an HIV positive partner.
8. females of child bearing potential will have a serum pregnancy test performed. This test must be negative in order to qualify for the study.

Subjects will be deemed eligible as per inclusion/exclusion criteria. Qualified subjects meeting all the inclusion and exclusion criteria will be randomized at Day 0 by an unblinded research staff member (designated drug dispenser) to either the secukinumab group or placebo group (within 28 days of signing the consent form). Female subjects of child-bearing potential will have 2 teaspoons of urine collected for a pregnancy test prior to randomization (only if the Screening visit was more than 7 days prior to randomization).

Assessments at this Baseline visit include skin examination, assessment of SCORAD, EASI and IGA scores, clinical photographs, bloods tests for chemistry and hematology (6 cc - approximately 1 ¼ teaspoons), as well as for mechanistic studies, and two punch biopsies (4.5 mm in size) will be obtained from involved and uninvolved skin.

Subjects with intrinsic AD (22 subjects) will be randomized (2:1) to either receive secukinumab (300 mg) or placebo via subcutaneous injection using 2 prefilled syringes at Weeks 0, 1, 2, 3, 4 and every 4 weeks thereafter through and including Week 12. Subjects with extrinsic AD (22 subjects) will be randomized separately (2:1) to either receive secukinumab (300 mg) or placebo via subcutaneous injection using 2 prefilled syringes at Weeks 0, 1, 2, 3, 4 and every 4 weeks thereafter through and including Week 12. Study drug will be administered subcutaneously by a blinded study investigator or designated research staff member in the Dermatology department.

At Week 1, subjects will return for study product administration, assessment of concomitant medications and adverse events.

At Week 2, subjects will undergo skin assessment (including SCORAD, EASI, and IGA), study product administration, assessment of concomitant medications and adverse events.

At Week 3, subjects will return for study product administration, assessment of concomitant medications and adverse events.

At Week 4, subjects will undergo skin assessment (including SCORAD, EASI, and IGA), study product administration, assessment of concomitant medications and adverse events, a urine pregnancy test (if applicable), laboratory tests for mechanistic studies, and one biopsy from involved skin only, close to the area that was biopsied at Baseline.

At Week 8, subjects will undergo skin assessment (including SCORAD, EASI, and IGA), study product administration, assessment of concomitant medications and adverse events, a urine pregnancy test (if applicable), and clinical photography.

At Week 12, subjects will undergo skin assessment (including SCORAD, EASI, and IGA), study product administration, assessment of concomitant medications and adverse events, and a urine pregnancy test (if applicable).

Concomitant treatments prohibited prior to randomization and during the study are listed below. Subjects will be allowed to drop out of the study if they complete all required assessments and visits through and including Week 4. At Week 16, the primary endpoint will be assessed.

<u>Phase 2:</u>
At Week 16, all subjects will be eligible to enter into the second phase of the study, in which all subjects will receive secukinumab (300 mg). In order to maintain the initial blind, subjects who had been randomized to secukinumab in Phase 1 will continue to receive secukinumab at a dose of 300 mg SQ every 4 weeks starting Week 16 until Week 52 (Weeks 16, 20, 24, 28, 32, 36, 40, 44, and 48), however, they will also receive two saline injections at Weeks 17, 18, and 19, so that neither the subject nor the assessor knows if the subject had received secukinumab or placebo in phase 1. Subjects, who had been randomized to placebo in Phase 1, will receive secukinumab at a dose of 300 mg SQ at weeks 16, 17, 18, 19, and 20, followed by every 4 weeks until Week 48 (Weeks 24, 28, 32, 36, 40, 44, and 48). The final study visit will be at Week 52.

At Week 16, subjects will undergo vital signs, skin assessment (including SCORAD, EASI, and IGA), study product administration, assessment of concomitant medications, adverse events, pregnancy test (if applicable), clinical photography,

blood tests for mechanistic studies. Two skin biopsies will be performed, in the vicinity of the involved and uninvolved areas biopsied at Baseline.

At Week 17, subjects will return for study product administration, assessment of concomitant medications and adverse events.

At Week 18, subjects will return for skin assessment (including SCORAD, EASI, and IGA), study product administration, assessment of concomitant medications and adverse events.

At Week 19, subjects will return for study product administration, assessment of concomitant medications and adverse events.

At Week 20, subjects will undergo skin assessment (including SCORAD, EASI, and IGA), study product administration, assessment of concomitant medications and adverse events, and pregnancy test (if applicable).

At Week 24, subjects will undergo skin assessment (including SCORAD, EASI, and IGA), study product administration, assessment of concomitant medications and adverse events, pregnancy test (if applicable), clinical photography, and bloods tests for chemistry and hematology.

At Week 28, subjects will undergo skin assessment (including SCORAD, EASI, and IGA), study product administration, assessment of concomitant medications and adverse events, pregnancy test (if applicable).

At Week 32, subjects will undergo skin assessment (including SCORAD, EASI, and IGA), study product administration, assessment of concomitant medications and adverse events, pregnancy test (if applicable), and clinical photography.

At Weeks 36, 40, and 44, subjects will undergo skin assessment (including SCORAD, EASI, and IGA), study product administration, assessment of concomitant medications and adverse events, and pregnancy test (if applicable).

At Week 48, subjects will undergo skin assessment (including SCORAD, EASI, and IGA), study product administration, assessment of concomitant medications and adverse events, pregnancy test (if applicable), and laboratory tests for chemistry and hematology.

At Week 52, subjects will return for skin assessment (including SCORAD, EASI, and IGA), assessment of concomitant medications and adverse events, clinical photography, blood tests for mechanistic studies, and one optional biopsy will be performed (in the vicinity of the involved areas biopsied at Baseline).

Adverse events and changes in concomitant medications will be assessed at each visit (through and including Week 52).

We will recruit patients at the Dermatology department at MSSM. Patients will be informed of the study when attending the Dermatology department, if they qualify for

the study. Potential subjects will further be recruited from our database of patients who have requested to be contacted for future studies, and they will be referred by in-house residents and affiliated attendings

In order to identify the molecular and cellular immune profile of AD at Baseline and identify treatment response biomarkers, we include blood analyses at Baseline, Week 4, 16 and Week 52, in addition to punch biopsies (4.5 – 5.0 mm in size) at Baseline (one from involved skin and one from uninvolved skin), at Week 4 (one biopsy from involved skin only, close to the area that was biopsied at Baseline), at Week 16 (two biopsies, in the vicinity of the involved and uninvolved areas biopsied at baseline), and at Week 52, one optional biopsy will be performed (in the vicinity of the involved areas biopsied at Baseline).

Blood analyses of IL-17, IL-22 and IL-13 cytokines (by Singulex) and chemokines (by MSD-a Th1, Th2 panel) will be performed at baseline, Week 4, Week 16, and Week 52 or Early Termination visit. Gene expression studies (RT-PCR and gene arrays) and immunohistochemistry of biopsy samples will be conducted. The expression levels of markers in different immune pathways, including: Th1 (IFN-gamma, CXCL9, CXCL10, MX-1, STAT1), Th17 (IL-17, IL23p19, IL23p40, CCL20, CXCL1), Th2 (IL-13, IL-5, IL-10, CCL17, CCL18, CCL22, CCL5), T22/IL-22 cytokine and IL-17/IL-22 regulated S100s genes (S100A7, A8), Th9/IL-9, and Treg/FOXP3 will be evaluated using RT-PCR. We will also assess for modulation of IL-17 regulated antimicrobial peptides (i.e LL-37, elafin, lipocalin 2, hBD2), inflammatory markers (i.e MMP12, S100A12), and innate immune genes (IL1b) by RT-PCR. Additionally, skin infiltration by T-cells, DCs, eosinophils, mast cells, and neutrophils will be assessed by immunohistochemistry. The following markers will be used: CD3 and CD8 for T cells, Langerin for Langherans cells, CD11c for myeloid DCs, TRAIL for inflammatory DCs, CD83/DC-LAMP as markers of mature activated DCs, MBP to identify eosinophils, and neutrophil elastase to identify neutrophils. Epidermal thickness will also be assessed by immunohistochemistry. Finally, gene arrays, particularly the Affymetrix U133A Plus 2 gene array platform, will also be performed. This same platform is being used in our other studies involving lesional/affected and non-lesional/normal skin of AD patients.

PATIENT POPULATION:

Prior to enrollment, all subjects must meet the following inclusion and exclusion criteria:

Inclusion criteria:

1. Male or female subject at least 18 years of age
2. If female, the subject is not pregnant or nursing
3. Subject is able to provide written informed consent and comply with the requirements of this study protocol.
4. Chronic (>6 months) atopic dermatitis (intrinsic disease with IgE levels that are below 500, and extrinsic disease with IgE levels above 500).

5. Moderate to severe AD (SCORAD index ≥25, and IGA index≥3).
6. Subjects who are women of childbearing potential must have a negative urine pregnancy test at screening and must be practicing an adequate, medically acceptable method of birth control for at least 30 days before Day 0 and at least 6 months after the last study drug administration. Acceptable methods of birth control include intrauterine device (IUD); oral, transdermal, implanted or injected hormonal contraceptives (must have been initiated at least 1 month before entering the study); tubal ligation; abstinence and barrier methods with spermicide. Otherwise, if not of childbearing potential, subjects must: have a sterile or vasectomized partner; have had a hysterectomy, a bilateral oophorectomy or be clinically diagnosed infertile; or be in a menopausal state for at least a year.
7. Tuberculin purified protein derivative (PPD) or QuantiFERON TB-Gold test (QFT) negative at the time of screening, or if patient has a history of positive PPD or QuantiFERON, he/she has completed the appropriate prophylaxis.
8. Subject is judged to be in good general health as determined by the principal investigator based upon the results of medical history, laboratory profile, and physical examination.
9. Patients with stable chronic asthma, treated with inhaled corticosteroids, will be allowed to participate.

Exclusion criteria:

1. Any subject who is pregnant or refuses to practice an acceptable method of birth control (as stated in inclusion criterion # 6)
2. History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis infection as defined by a positive tuberculin purified protein derivative (PPD) or QuantiFERON TB-Gold test (QFT) at Screening. Subjects with a positive or indeterminate PPD or QFT test may participate in the study if a full tuberculosis work up (according to local practice/guidelines) is completed within 12 weeks prior to randomization and establishes conclusively that the subject has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment must have been initiated at least for 4 weeks prior to randomization and the course of prophylaxis is planned to be completed.
3. Skin colonization by S. aureus is expected in a high percentage of AD patients with active disease and will not be considered an exclusion criterion.
4. Active Crohn's disease
5. Known hypersensitivity to latex
6. Subjects with a history of HIV, or history of positive HCV or HBV
7. Previous exposure to Secukinumab or other drug targeting IL-17A or its receptor
8. Use of phototherapy (i.e. UVB, UVA) or systemic immunosuppressive drugs (including cyclosporine, corticosteroids, mycophenolate mofetil, azathioprine, methotrexate) within four weeks prior to Baseline/Randomization (Visit 2).

9. Use of interferon-γ within 12 weeks prior to Baseline/Randomization (Visit 2).

10. Use of abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, or tocilizumab within 12 weeks prior to Baseline/Randomization (Visit 2).

11. Use of omalizumab, rituximab, ustekinumab, alefacept, briakinumab, or other therapeutic antibody products within 24 weeks prior to Baseline/Randomization (Visit 2).

12. Use of any investigational drug within four weeks or five PK or PD half lives (whichever is longer) prior to Baseline/Randomization (Visit 2).

13. Use of topical corticosteroid preparations, topical calcineurin inhibitors, or other topical preparations with immunomodulatory properties within 2 weeks prior to Baseline/Randomization (Visit 2).

14. Serious concomitant illness that could require the use of systemic corticosteroids or otherwise interfere with the patient's participation in the trial.

15. Clinically important deviation as judged by the investigator (such as >3 times the norm for LFTs, or, WBC< 3) from normal limits in physical examination, vital sign measurements, 12-lead electrocardiograms (ECGs), or clinical laboratory tests results, not associated with a chronic, well-controlled medical condition.

STATISTICAL METHODS

Determination of Sample Size

This is a pilot study, and therefore the sample size has been kept relatively low. No formal analysis of statistical power for the primary endpoint of the trial lies behind this decision; however the consequence on precision of the parameter of interest is described in the following paragraph assuming the use of a 1-sided alpha of 0.05 in the Fisher's exact test:

The sample size estimation is driven by the primary endpoint, namely the epidermal thickness change observed at Week 16. Prior studies with Cyclosporine [4, 5] show a reduction of 90 on epidermal thickness with 62.79 as standard deviation after 12 weeks of treatment. To be conservative about the effect of Secukinumab we will assume a reduction of 85 on treatment group and no change on placebo group after 16 weeks of treatment. The same standard deviation will be considered for both groups. Under these assumptions, a sample size of 30:14 (Treatment/Placebo) will allow testing the hypothesis that the change in the Treatment group is different than the change in the Placebo group. This sample size will be able to detect an effect size equal to 1.35 with 96% power. For the subgroup analysis, based on IgE status, a

sample size of 15:7 in each subgroup (Intrinsic/Extrinsic) will allow to detect the same effect size with 80% power.

Definition of Trial Analysis Sets

All subjects enrolled in the trial (i.e. subjects for whom informed consent has been obtained and who have been registered in a clinical trial) will be accounted for in the clinical trial report.

The inclusion/exclusion of subjects and/or subject data from the trial analysis sets will be documented in the statistical analysis plan before breaking the randomization code.

Analysis Populations

'MODIFIED INTENTION-TO-TREAT' ANALYSIS SET. The primary analysis population will be based on a modified intention-to-treat (mITT) population, which is defined as all randomized patients who received at least one dose of the randomized treatment. Because the loading dose is given at baseline, this should effectively include all the randomized patients.

Statistical Analysis

Random Allocation of Subjects

A randomized block design will be performed to guarantee a 15:7 Treatment/Placebo proportion within the Intrinsic/Extrinsic AD subgroups. The IgE status will be considered as a blocking factor. This means that subjects will be randomly allocated to each treatment (Secukinumab/Placebo) with a proportion 15:7 inside each level of the factor.

Disposition of Subjects

The reasons for leaving the trial will be presented for all randomized subjects by last visit attended and by treatment group. For patients who prematurely discontinued the trial the last observation carried forward (LOCF) will be considered by last visit attended.

Demographics and other Baseline Characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for all subjects. Demographics include age, sex, race, ethnicity, and skin type. Other baseline characteristics include height, weight, and vital signs, duration of atopic dermatitis, concurrent diagnoses (from medical history and indications for concomitant medication), concomitant medication, previous atopic dermatitis treatments and IgE.

Analysis of Primary Endpoint

The primary objective is to study the efficacy of secukinumab in the treatment of intrinsic atopic dermatitis by measuring change of epidermal thickness at Week 16

from baseline. To compare this endpoint between secukinumab versus placebo, a mixed-effect model will be used to estimate the means for outcomes at Phase 1 (Weeks 0-16). Observed measure at Week 4 will be considered in the model. Under the assumption of LOCF, a sensitivity analysis will be performed. A secondary analysis will be done, also including the outcomes at Phase 2 (Weeks 16-32) for subjects randomized as Placebo at Phase 1. For this cohort, observed measure at Week 20 will be considered in the model.

Analysis of Secondary Endpoints

For K16, the same analysis as for epidermal thickness will be performed.

To compare secukinumab versus placebo according to the proportion of patients who achieve an improvement of 50% or greater from their baseline for SCORAD, EASI and IGA ("clear-0" or "almost clear-1") at Week 16 a Fisher´s exact test for contingency tables analysis will be used. Additionally to Phase 1 data, the group who started with treatment at Week 16 in Phase 2 will be already included.

For long term efficacy analysis of secukinumab, Phase 1 and Phase 2 data will be used to calculate Confidence Intervals at 95% significance level for to the proportion of patients who achieve an improvement of 50% or greater from their baseline for SCORAD, EASI and IGA ("clear-0" or "almost clear-1").

Differences in change over time on SCORAD/EASI between treatment and placebo will be assessed using a Mixed-effect model repeated measures (MMRM) to detect any overall differences in the treatment effect as compared to placebo. Outcomes for Weeks 0 to 16 for all subjects from Phase 1 and the outcomes for Weeks 16 to 32 for subjects randomized with secukinumab in both phases will be considered. The model will include the fixed, categorical effects of treatment, and treatment-by visit interaction. Likelihood ratio tests and the AIC will be use to determine which covariance structure, CS or unstructured, provides the best fit to the data. Contrasts will be defined in the mixed-model to test for treatment differences at the different time points. Final results will be communicated as percentages change from baseline, calculated from the least square means of the model above. For patients who prematurely discontinued the trial missing values will be considered. Sensitive analysis will be performed treating them as: (a) LOCF, (b) data as observed.

Safety will be evaluated by tabulations of adverse events and will be presented with descriptive statistics at each visit for each treatment group. The statistical evaluations will be organized by Treatment Phase (Weeks 0-16 and 16-32), and Post-Treatment Phase (long-term follow-up), as appropriate. AEs will be coded using the CTCAE, Common Terminology Criteria for Adverse Events, V 4.0. The number and percentage of subjects experiencing an AE/SAE will be stratified by system organ class, or a preferred term, and severity of the adverse event, and recorded and tabulated overall by each sub-strata. Each subject will be counted only once within a system organ class or a preferred term using the adverse events with the highest severity within each category. All information pertaining to adverse events noted during the study will be listed by subject, detailing verbatim given by the investigator, preferred term, system organ class, date of onset, date of resolution, severity, and relationship to treatment. A tabulation of Serious Adverse Events (SAEs), will be

provided by subject within treatment groups. The proportion of subjects in each treatment group reporting adverse events that occur in ~ 5% in either treatment group will be compared using the Fisher's exact test. The specific system organ classes and preferred terms analyzed will be those that are reported by at least five percent of the subjects in either treatment group.

Analysis of Secondary (Translational) Endpoints

Outcomes for Weeks 0 to 16 for all subjects from Phase 1, and the outcomes for Weeks 16 to 32 for subjects randomized with placebo in Phase 1, and to secukinumab in Phase 2 will be considered.

Change of the pathological epidermal disease phenotype of lesional and non-lesional skin between baseline values and those after treatment at Week 16 will be estimated as a reduction of epidermal thickness and K16 expression using a two-tailed t-Student test for paired samples at 95% significance.

Analysis of Exploratory Endpoints

Mixed-effect model will be used to assess the change on cell counts and RT-PCR-derived expression levels after 16 weeks of treatment. The goal is to estimate the drug effect on both lesional and non-lesional biopsies. RT-PCR will be normalized to hARP and Log2 transformed prior the analysis.

To assess correlations between clinical resolution of disease and the treatment response of skin biomarkers Spearman correlation coefficient will be used. Additional multivariate methods such as multivariate regression, clustering algorithms and PCA will be used to explore patterns in the data such as biomarkers with the same resolution pattern and outliers. A variety of data mining tools may be used to further explore hypothesis generated on the analysis stage.

ADVERSE EVENTS

A total of 3430 psoriasis subjects were treated with secukinumab in controlled and uncontrolled clinical trials. Of these, 1641 subjects were exposed for at least 1 year. Side effects seen in studies with secukinumab that occurred in greater than 1% of subjects (greater than 1 in 100 patients) include nasopharyngitis, diarrhea, upper respiratory tract infection, rhinitis, oral herpes, pharyngitis, urticaria, and rhinorrhea. Side effects seen in studies with secukinumab that occurred in less than 1% of subjects (less than 1 in 100 patients) include hypersensitivity reactions, anaphylaxis, sinusitis, tinea pedis, conjunctivitis, tonsillitis, skin or oral candidiasis, impetigo, otitis media, otitis externa, inflammatory bowel disease, increased liver transaminases and neutropenia, various infections, worsening of Crohn's disease. Live vaccines should be avoided during treatment with secukinumab.

SAFETY MONITORING

The study will be conducted in accordance with our department's Standard Operating Procedures, which are based on US FDA Title 21 Code of Federal Regulations and ICH Good Clinical Practice guidelines.

An investigator will review all laboratory results and assess for adverse events. The principal investigator will be informed of all adverse events. In the event that a subject's safety is compromised, the investigator will discontinue the subject immediately.

The Principal Investigator will provide safety data to an independent Data and Safety Monitoring Board every 12 months. This DSMB will be comprised of board certified dermatologists who are not directly related to this study. The DSMB will review the data and provide a report of their findings to the Principal Investigator.

Pharmacovigilance requirements:

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)

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).

Timelines: All serious adverse events (SAEs) from interventional clinical trials must be reported by the sites to the 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.

All other AEs will be reported by the PI directly to the Icahn School of Medicine at Mount Sinai IRB in the annual report.
Should a temporary or permanent suspension occur, we would report the occurrence to all appropriate authorities.

EARLY TERMINATION

Any individual whose health or well being may be threatened by continuation in this study will be discontinued by the investigator.

If a female subject becomes pregnant at anytime during the study, she will be discontinued immediately. She will be asked to provide the investigator with medical updates throughout her pregnancy and on the final outcome of the pregnancy.

Any subject who chooses to discontinue the study, or is discontinued from the study by the investigator will be asked to return for a final visit to have some or all of the following procedures: a blood test; pregnancy test; skin photography; skin evaluation including SCORAD, EASI, and IGA; and biopsy.

INVESTIGATIONAL DRUG SUPPLY

In this double-blind study, the investigator will supply secukinumab 300 mg (two injections of 150 mg each) for up to 44 subjects and placebo (comprised of silica and/or cellulose) for up to 15 subjects. The secukinumab and placebo will be provided by Novartis as 150 mg secukinumab (and matching placebo) pre-filled syringes. Both the 150 mg secukinumab and the matching placebo pre-filled syringes will be of the same quality and identical in size and shape.
All study medication will be stored in a secure cool area between 2-8^{0}C (under refrigeration). Study drug will be administered to subjects at each visit, and any unused study drug will be kept at the study site. The number of missed doses will be documented for each subject. The investigative site will account for all study drug dispensed and stored during the study.

LABORATORY SPECIMEN

All blood and urine samples will be processed through the Mount Sinai Center for Clinical Laboratories, One Gustave Levy Place, New York, NY 10029.

INSTITUTIONAL REVIEW BOARD

Prior to beginning this study, approval for all study related documents (protocol, consent form, advertising) will be obtained from the Icahn School of Medicine at Mount Sinai Program for the Protection of Human Subjects (Institutional Review Board), One Gustave Levy Place, Box 1081, New York, NY 10029.

APPENDIX 1

Schedule of events:

Visit #	1 Screening	2 Baseline	3-5	6	7	8	9	10-12	13-15	16	17-20	21	Early Term Visit
Week		**0**	**1,2,3**	**4**	**8**	**12**	**16**	**17,18,19**	**20,24, 28**	**32**	**36,40, 44, 48**	**52**	
ICF	X												
Inc/Exc Criteria	X	X											
Past Med Hx	X												
Phys Exam	X												
ECG	X												
Vital Signs	X						X						
CBC, CMP	X								X[1]		X[2]		X[8]
Quantiferon Test	X												
HBsAg, HCV antibody, HIV screening (if deemed at risk)	X												
Clinical Assessment (incl. SCORAD, EASI, IGA)	X	X	X[3]	X	X	X	X	X[4]	X	X	X	X	X
Pregnancy Test[5]	X	X		X	X	X	X		X	X	X		X[9]
Disp Study Med		X	X	X	X	X	X	X	X	X	X		
Photographs		X			X		X		X[6]	X		X	X
Blood Sample for Mechanistic Studies		X		X			X					X	X
Biopsy		X		X			X					X[7]	X[10]
Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	X	X
AE	X	X	X	X	X	X	X	X	X	X	X	X	X

1 CBC and CMP at Weeks 24 only.
2 CBC and CMP at Weeks 48 only.
3 Clinical Assessment at Week 2 only.
4 Clinical Assessment at Week 18 only.

5 Serum pregnancy test at Screening and urine at other time points. Pregnancy test at Baseline only if Screening occurred more than 7 days prior.

6 Photographs at Week 24 only.
7 Optional biopsy at Week 52 from lesional skin only.
8 Only if Early Term Visit occurs before Week 48.

9 Only if Early Term Visit occurs before Week 48.
10 Only if Early Term Visit occurs before Week 32.

APPENDIX 2:

SCORAD Index(6): The most widely accepted clinical assessment tool for AD disease severity index is known as SCORAD (SCORing for Atopic Dermatitis). This tool combines clinical features of AD such as erythema, dryness, lichenification, percent body surface area, as well as quality of life issues such as pruritus and loss of sleep due to disease.

To measure the extent of AD, the rule of nines is applied on a front/back drawing of the patient's inflammatory lesions. The extent can be graded 0–100. The intensity part of the SCORAD index consists of six items: erythema, edema/papulation, excoriations, lichenification, oozing/crusts and dryness. Each item can be graded on a scale 0–3. The subjective items include daily pruritus and sleeplessness. Both subjective items can be graded on a 10-cm visual analogue scale. The maximum subjective score is 20. All items should be filled out in the SCORAD evaluation form. The SCORAD index formula is: A/5 + 7B/2 + C. In this formula A is defined as the extent (0–100), B is defined as the intensity (0–18) and C is defined as the subjective symptoms (0–20). The maximum SCORAD score is 103.

EASI score(7): The Eczema Area and Severity Index (EASI) is a validated tool to objectively assess dermatitis severity incorporating surface area involvement. It was designed by modifying the general scheme used in the PASI (psoriasis area and severity index) scoring system, which has been utilized effectively in the assessment of psoriasis. The EASI index assigns proportionate values to 4 body regions (head and neck, 10%; trunk, 30%; upper limbs, 20%; lower limbs, 40%. Each region is assessed separately for erythema, infiltration/papulation, excoriation, and lichenification. The average clinical severity of each sign in each of the 4 body regions is assigned a score of 0 to 3, indicating none, mild, moderate, and severe expression. This percentage of area involved for each of the four body regions is assigned a proportional score from 0 to 6 during the analysis: 0=no eruption; 1=10%; 2=10%–29%; 3=30%–49%; 4=50%–69%; 5=70%–89%; and 6=90%–100%. The buttocks and feet are counted as part of the lower extremities; the internal axillae and groin are counted as part of the trunk; and 3) the external axillae and hands are counted as part of the upper extremities. The total body score for each body region is obtained by multiplying the sum of the severity scores of the four key signs by the area score, then multiplying the result by the constant weighted value assigned to that body region. The sum of these scores gives the EASI total, which ranges from 0 to a maximum 72.

IGA index(8): a static IGA (Investigator's Global Assessment) score is widely used as a primary efficacy point of treatment success in many studies of dermatological diseases including AD. The static IGA score represents an overall static evaluation of dermatitis, performed by the investigator at each visit. It utilizes a scale of 6-points, ranging from 0 (clear) to 5 (very severe disease), with 0-clear, 1-almost clear, 2- mild disease, 3-moderate disease, 4-severe disease, and 5-very severe disease. IGA scores measure disease severity based on morphology, without referring back to the baseline state.

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