

**A randomized placebo-controlled single center pilot study of the safety and efficacy of tralokinumab in subjects with moderate to severe alopecia areata**

**PI: Emma Guttman**

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Amendment #2: September 30, 2015

## **HYPOTHESES:**

### **Primary Hypothesis:**

1. It is hypothesized that IL-13 is involved in the pathogenesis of alopecia areata (AA).

### **Secondary Hypothesis:**

1. Tralokinumab is superior to placebo for induction of hair regrowth in patients with moderate to severe alopecia areata, and will result in improved clinical outcomes for subjects with concomitant atopic dermatitis (AD).

## **OBJECTIVES and ENDPOINTS:**

### **Primary objective**

- 1) This is a pilot study intended to look at IL-13 associated cellular and molecular markers in the skin of patients with alopecia areata and to gain some insight into whether blocking IL-13 with Tralokinumab will affect those markers and hair regrowth

### **Secondary objectives**

- 1) To study the safety of tralokinumab in patients with moderate to severe alopecia areata.
- 2) Study the safety of tralokinumab in patients with concomitant moderate to severe alopecia areata and atopic dermatitis.
- 3) Study the mechanism of action of tralokinumab in patients with moderate to severe alopecia areata.
- 4) Study the mechanism of action of tralokinumab in patients with concomitant moderate to severe alopecia areata and atopic dermatitis.

### **Primary endpoints**

- 1) Change from baseline in cellular, and molecular markers in skin biopsies after treatment.

### **Secondary endpoints**

- 1) Percentage change from Baseline in the Severity of Alopecia Tool (SALT) at Week 24.
- 2) Percentage of patients achieving 50% or greater improvement in their SALT score (SALT<sub>50</sub>) at Week 24, compared to Baseline.
- 3) Percentage change from baseline in the Alopecia Areata Symptom Impact Scale (AASIS) at Week 24.
- 4) Percentage change from Baseline in the Alopecia Areata Quality of Life questionnaire (AA-QoL) at Week 24.

## **Exploratory endpoints**

- 1) Percentage change from Baseline in the objective SCORAD at Week 24.
- 2) Percentage change from Baseline in the EASI score at Week 24.
- 3) Percentage change from Baseline in the Investigator Global Assessment (IGA) score at Week 24, and time points up to Week 24.

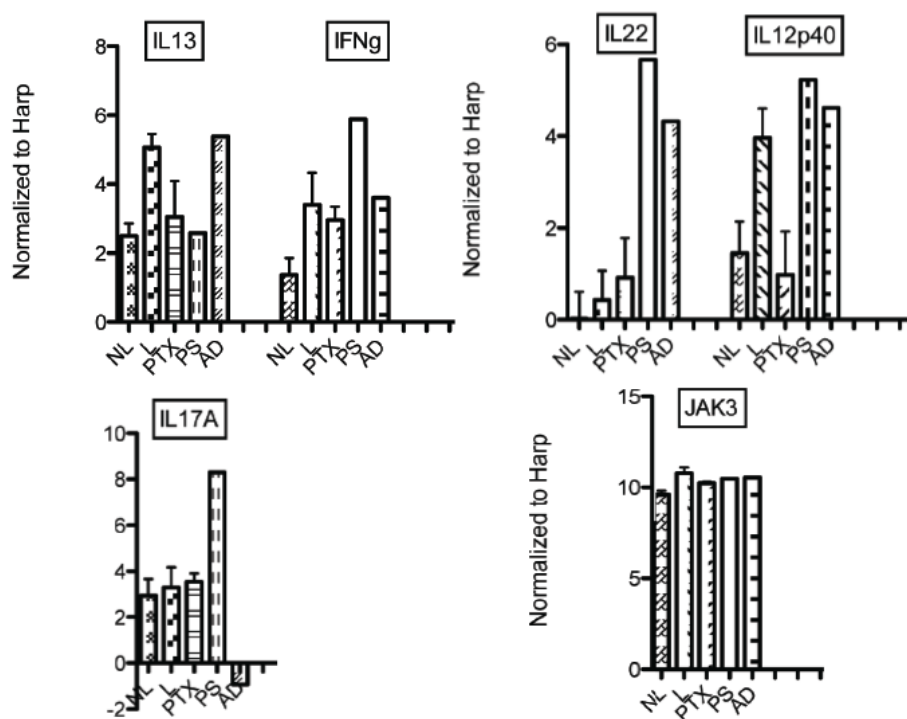
## **INTRODUCTION:**

Alopecia areata (AA) is an auto-immune disease characterized by non-scarring hair loss that can sometimes progress to total loss of all scalp and body hair.<sup>1</sup> The life-time risk of AA has been reported to be 1.7%.<sup>2</sup> AA can cause tremendous emotional and psychosocial distress in affected patients and their families. There is a lack of effective treatments for patients with alopecia areata. Topical treatments are usually not very effective, probably because of limited penetration. Intralesional injections of corticosteroids are effective but can only be considered for patients with limited involvement. Immunotherapy with diphencyprone or squaric acid dibutyl is effective in some patients but is usually limited to treatment of scalp involvement and can cause significant pruritus and dermatitis. None of these therapies are targeted to the underlying mechanism for disease pathogenesis. There is a need for new treatment options for patients with alopecia areata especially based on the recently evolving understanding of the disorder.

A recent study performed in medical centers across Boston, that included a review of 3568 patients with alopecia areata (over 11 years) found that 38.2% of patients with AA also had atopic dermatitis (AD) and/or other atopic conditions (asthma, allergic rhinitis, etc.), with another 35.9% having contact dermatitis or other types of eczema (which might represent misdiagnosed AD as well).<sup>3</sup> The main condition associated with AA was AD. Family or personal history of AD was found to be the number one risk factor for AA. A recent publication showed that patients with AA with concomitant AD show a genomic profile, highlighting a set of genes that overlap with AD (biopsies of AD skin were not available).<sup>4</sup> These include T-cell related and Th2-pathway related genes that modulate epidermal differentiation and drive abnormal T-cell responses. Furthermore, 5 of the 6 transcriptional “hot spots” found within the AA blood and skin gene expression signatures coincide with regions previously reported to be relevant to atopic dermatitis (AD) susceptibility. It was also shown that FLG mutations are significantly associated with the presence of AD among AA patients, and with a more severe clinical presentation of AA.<sup>4</sup> These data support evidence of a shared genetic background and pathophysiology for patients with AA and AD.

Preliminary analyses from our laboratory (Fig. 1) showed an elevation of IL-13 mRNA expression by RT PCR. However, in order to correctly characterize the overall inflammatory networks in AA and to evaluate how they relate to those in AD, a much larger sample size is needed. In addition to the clinical reversal of the alopecia, we need to also evaluate the tissues effects of Th2/IL-13 antagonism and changes in the immune and cellular markers in affected skin.

**Figure 1**



**Fig 1.** Figure 1 shows comparable cytokine expression of the defining Th2 cytokine/IL-13, the defining Th1 cytokine/IFN gamma, and the Th17/IL-23 cytokines/IL-17A and IL12/23p40 in AA and AD. Lesional psoriasis skin tissues show a significantly higher expression of both IL-17A and IFN gamma, with significantly lower expression of IL-13 as compared with both AA and AD. Significant decreases in mRNA expression of IL-13, and IL12/23p40 are seen after treatment with intralesional corticosteroids, without significant changes in the other cytokines. P value= 0.0002 for the IL-13, and p=0.1 for the IFN gamma lesional vs non-lesional alopecia skin comparisons. JAK3 shows similar activation in AA, AD, and Psoriasis. NL- non lesional skin from scalp of AA patients; L- lesional skin from scalp of AA patients; PTX- post intralesional steroid treatment skin from scalp of AA patients; PS-psoriasis lesional skin; AD- AD lesional skin. N=6 patients for both NL and L, and 4 for PTX.

## **STUDY DESIGN:**

This is a randomized, double-blind, placebo-controlled pilot study of a total of 30 subjects with moderate to severe alopecia areata involving 30-100% of the scalp. We expect 50% of these subjects to have concomitant alopecia areata (AA) and atopic dermatitis (AD).

Subjects with AA alone (15 subjects) will be randomized (2:1) to either receive tralokinumab 300 mg (150 mg/ml) or placebo via subcutaneous injection using 2 pre-filled syringes Q2W for 24 weeks. Subjects with concomitant alopecia areata and atopic dermatitis (15 subjects) will be randomized separately in a 2:1 ratio to receive tralokinumab 300 mg (150 mg/ml) or placebo via subcutaneous injection using 2 pre-filled syringes Q2W for 24 weeks.

After providing informed consent, subjects will be assessed for study eligibility at the Screening visit (day -28 to day -1), which includes: limited physical examination (including vital signs); assessment of regrowth pattern; SALT scoring; electrocardiogram (ECG); review of medical history and concomitant medications as well as prior medications/treatments; and serum pregnancy test (if applicable). Laboratory tests will be performed for Complete Blood Count (CBC with differentials (basophils, eosinophils, lymphocytes, monocytes, neutrophils), serum chemistry (albumin, alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), creatinine, potassium, sodium and total bilirubin), as well as hepatitis B surface antigen (HbsAg), hepatitis C antibody, and undergo testing for human immunodeficiency virus (HIV). Subjects will also undergo tuberculin purified protein derivative (PPD) or QuantiFERON TB-Gold test (QFT) testing.

Subjects who meet eligibility criteria (meeting all inclusion and exclusion criteria) will undergo Baseline / Day 0 assessments. These assessments include vital signs, assessment of regrowth pattern, SALT scoring, questionnaires (AASIS and AA-QoL), clinical photography, urine pregnancy test (if applicable), and blood collection for chemistry, hematology, mechanistic studies, DNA analysis, RNA analysis, proteomic analysis, anti-drug antibody (ADA) measurement, and serum tralokinumab levels. In addition, SCORAD, EASI and IGA scores will be performed in subjects with AD only. Two scalp biopsies will be obtained (one from an involved area of the scalp and one from an uninvolved area). Subjects with concomitant AD will have two additional skin biopsies (one from involved skin and one from uninvolved skin). Concomitant medications and any adverse events will be assessed.

Subjects will then undergo randomization, and will receive the first dose (300 mg SC) of study drug (tralokinumab or placebo). Subjects will continue to receive bi-weekly injections of study drug (300 mg tralokinumab or placebo) through Week 24.

Subjects will return for visits every two weeks to have the following performed: vital signs will be taken prior to every study drug administration; concomitant medications and any adverse events will be assessed; and a urine pregnancy test will be performed (if applicable).

For the first four doses of Investigational Product (IP), subjects will be monitored after IP

administration for immediate drug reactions for a minimum of 2 hours with vital signs taken every 30 minutes or until stable, whichever is later. For the fifth and subsequent doses of IP, subjects will be monitored after IP administration for a minimum of 1 hour with vital signs taken every 30 minutes or until stable, whichever is later.

At Week 2, subjects will return for assessment of regrowth pattern, SALT scoring, study product administration, vital signs, assessment of concomitant medications, adverse events, and pregnancy test (if applicable).

At Week 4, subjects will return for assessment of regrowth pattern, SALT scoring, AASIS, AA-QoL, SCORAD, EASI and IGA scores (in subjects with AD only), clinical photography, vital signs, study product administration, assessment of concomitant medications, adverse events, pregnancy test (if applicable), and blood tests for chemistry, hematology, ADA measurement, and serum tralokinumab levels.

At Week 6, subjects will return for assessment of regrowth pattern, SALT scoring, vital signs, study product administration, assessment of concomitant medications, adverse events, and pregnancy test (if applicable).

At Week 8, subjects will undergo assessment of regrowth pattern, SALT scoring, AASIS, AA-QoL, SCORAD, EASI and IGA scores (in subjects with AD only), clinical photography, vital signs, study product administration, assessment of concomitant medications, adverse events, and pregnancy test (if applicable).

At Week 10, subjects will return for assessment of regrowth pattern, SALT scoring, vital signs, study product administration, assessment of concomitant medications, adverse events, and pregnancy test (if applicable).

At Week 12, subjects will undergo limited physical examination, assessment of regrowth pattern, SALT scoring, AASIS, AA-QoL, SCORAD, EASI and IGA scores (in subjects with AD only), vital signs, study product administration, assessment of concomitant medications, adverse events, pregnancy test (if applicable), clinical photography, and blood tests for chemistry and hematology, mechanistic studies, RNA, proteomic analysis, anti-drug antibody (ADA) measurement, and serum tralokinumab levels. Optional biopsies of the scalp (close to the area that was biopsied at Baseline) and skin (in those with AD only, and close to the area that was biopsied at Baseline) may be performed.

At Week 14, subjects will return for vital signs, study product administration, assessment of concomitant medications, adverse events, and pregnancy test (if applicable).

At Week 16, subjects will return for assessment of regrowth pattern, SALT scoring, AASIS, AA-QoL, SCORAD, EASI and IGA scores (in subjects with AD only), clinical photography, vital signs, study product administration, assessment of concomitant medications, adverse events, and pregnancy test (if applicable).

At Week 18, subjects will return for vital signs, study product administration, assessment of concomitant medications, adverse events, and pregnancy test (if

applicable).

At Week 20, subjects will return for assessment of regrowth pattern, SALT scoring, AASIS, AA-QoL, SCORAD, EASI and IGA scores (in subjects with AD only), clinical photography, vital signs, study product administration, assessment of concomitant medications, adverse events, and pregnancy test (if applicable).

At Week 22, subjects will undergo vital signs, assessment of concomitant medications, adverse events, pregnancy test (if applicable), and the final study product administration.

At Week 24, subjects will undergo limited physical examination, assessment of regrowth pattern, SALT scoring, AASIS, AA-QoL, SCORAD, EASI and IGA scores (in subjects with AD only), vital signs, clinical photography, assessment of concomitant medications, assessment of adverse events, and blood tests for chemistry and hematology, mechanistic studies, RNA, proteomic analysis, anti-drug antibody (ADA) measurement, and serum tralokinumab levels. In addition, biopsies of the scalp (one biopsy close to the area that was biopsied at Baseline) and skin (in subjects with AD only, one biopsy close to the area that was biopsied at Baseline) will be performed.

Follow-up visits will be conducted at Weeks 32 and 40 for safety analysis, at which the following will be performed: limited physical examination, assessment of regrowth pattern, SALT scoring, AASIS, AA-QoL, SCORAD, EASI and IGA scores (in subjects with AD only), clinical photography, and assessment of concomitant medications and adverse events. In addition, at Week 32 only, blood tests for chemistry and hematology, and an ECG will be performed.

If a subject is being discontinued prior to Week 24, the following procedures should be performed for the Early Termination visit: limited physical examination, pregnancy test (if applicable), assessment of regrowth pattern, SALT scoring, AASIS, AA-QoL, SCORAD, EASI and IGA scores (in subjects with AD only), clinical photography, assessment of concomitant medications, assessment of adverse events, and blood tests for chemistry and hematology, mechanistic studies, RNA, proteomic analysis, anti-drug antibody (ADA) measurement, and serum tralokinumab levels. In addition, biopsies of the scalp (one biopsy close to the area that was biopsied at Baseline) and skin (in subjects with AD only, one biopsy close to the area that was biopsied at Baseline) will be performed.

If a subject is being discontinued prior to Week 40 (but has completed Week 24), the following procedures should be performed for the Early Termination visit: limited physical examination, ECG (if not completed at Week 32), assessment of regrowth pattern, SALT scoring, AASIS, AA-QoL, SCORAD, EASI and IGA scores (in subjects with AD only), clinical photography, assessment of concomitant medications, assessment of adverse events, and blood tests for chemistry and hematology.

Subjects will not receive any other active treatment for alopecia areata or atopic dermatitis (outside of the study drug) while participating in the study.

Safety, laboratory, and clinical assessments will be performed at specified clinic visits. A



serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed at Baseline and every 2 weeks prior to administration of the IP dose, if applicable.

Biopsies from the scalp will be performed on all subjects at Baseline and Week 24 or Early Termination visit. At Baseline, biopsies will be obtained from involved and uninvolved areas of the scalp. At Week 24 or Early Termination visit, the biopsy will be performed in the vicinity of the involved area biopsied at Baseline. An optional biopsy will be performed at Week 12, close to the area that was involved and biopsied at Baseline.

Subjects with concomitant AD will have two additional skin biopsies at Baseline (one from involved skin and one from uninvolved skin), and one additional biopsy at Week 24 or Early Termination visit (in the vicinity of the involved area biopsied at Baseline). An optional biopsy will be performed at Week 12, close to the area that was involved and biopsied at Baseline. All biopsies will be 4.5 mm in diameter.

Our experience in AD<sup>12-14</sup>, and past experience in psoriasis<sup>15, 16</sup> showed that biomarker studies in skin tissues are critical to the understanding of key pathogenic pathways that are upregulated in each disease and how well they are suppressed with effective treatment. These mechanistic studies coupled with clinical trials are key in the disease to shed light on important disease mechanisms, and to explain which molecules are suppressed by each therapeutic target. We now have data that shows that IL-13 is significantly upregulated in both AD and AA lesions compared to nonlesional skin. It is very important to associate the clinical responses with suppression of this cytokine and related molecules as well as other pathway cytokines in skin tissues. Both the whole genomic profiling and individual molecular and cellular markers are very important in order to understand how well anti-IL-13 will change/suppress AA-associated pathways and compare with those that will be suppressed in AD.

At Baseline, serum will be obtained for DNA (1 PaxGene), RNA (2 PaxGene), and proteomic analysis (2 tubes serum). Studies of RNA and proteomic analysis will further be performed at Weeks 12 and 24. Serum levels of various biomarkers such as interferon gamma, IL-2, IL-12, IL-13, IL-17A, IL-5, IL-10, IL-31 and IL-4 have been shown to be elevated in patients with alopecia areata. Therefore we will assess these Th1, including interferon gamma, Th2, Th17, and Th22 markers in serum before and after tralokinumab treatment. Measurements of serum anti-drug antibodies (ADA) including neutralizing antibodies (nAb), as well as serum tralokinumab levels will be performed at Baseline, Weeks 4, 12, and 24 and at Early Termination visit if it occurs prior to Week 24.

Mechanistic blood analyses including RNA, DNA, and proteomic analysis, as well as ADA and serum drug levels will be conducted collaboratively with Medimmune/Astra Zeneca.

## **INCLUSION CRITERIA:**

1. Male or female, aged from 18 to 75 years, inclusively at the time of signing the informed consent document.
2. Subject has provided written informed consent prior to any study specific procedures.
3. Body weight of  $\geq 40$  and  $< 150$  kg at enrollment.
4. Subject has a history of alopecia areata for at least 3 months.
5. Subject has extensive patchy alopecia areata (at least 30% scalp hair loss).
6. No evidence of hair regrowth at Baseline.
- Women of childbearing potential (WOCBP) (after menarche), including adolescent females, must use a highly effective form of birth control (confirmed by the investigator). Highly effective forms of birth control includes: true sexual abstinence, a vasectomised sexual partner, Implanon, female sterilization by tubal occlusion, any effective intrauterine device/system (IUD/IUS), Depo-Provera injections, oral contraceptive, and Evra Patch or Nuvaring. WOCBP must agree to use highly effective method of birth control, as defined above, from enrolment, throughout the study duration and within 16 weeks after last dose of investigational product (IP), and have negative serum pregnancy test result at Visit 1.

Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrheic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age specific requirements apply:

- a. Women  $< 50$  years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone (FSH) levels in the postmenopausal range.
  - b. Women  $\geq 50$  years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatment.
7. For WOCBP only: have a negative urine pregnancy test prior to administration of the IP.
  8. For inclusion in the voluntary pharmacogenetic research, subjects should fulfil the following criterion:

- a. Provision of a signed and dated written informed consent for the pharmacogenetic sample and analysis. If a subject declines to participate in the pharmacogenetic research, there will be no consequence or loss of benefit to the subject. The subject will not be excluded from the other aspects of the study described in the protocol, as long as they consent to participate in the study.
9. 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 performed at Screening.
10. Subjects may be naïve to treatment or unresponsive to intralesional steroids or other treatments for alopecia areata.

**EXCLUSION CRITERIA:**

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. History of male or female pattern hair loss Ludwig stage III or Hamilton > stage V.
2. Subjects in whom the diagnosis of alopecia areata is in question.
3. Any disorder, including but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, psychiatric, or major physical impairment that is not stable in the opinion of the Investigator and could:
  - Affect the safety of the subject throughout the study
  - Influence the findings of the studies or their interpretations
  - Impede the subject's ability to complete the entire duration of study
4. Known history of allergy or reaction to any component of the IP formulation.
5. History of anaphylaxis following any biologic therapy.
6. The following treatments within 4 weeks before the Baseline visit, or any condition that, in the opinion of the investigator, will likely require such treatment(s) at any time during the study:
  - Systemic corticosteroids
  - Immunosuppressive/immunomodulating drugs (eg, cyclosporine, mycophenolate-mofetil, IFN- $\gamma$ , Janus kinase (JAK) inhibitors, azathioprine or methotrexate), Ultra-Violet (UV) B phototherapy; and/or Psoralen Ultra-Violet A (PUVA) therapy.
7. Treatment with topical corticosteroids, tacrolimus and/or pimecrolimus within 1 week before the Baseline visit.
8. Subject has taken enzyme-modifying drugs that are moderate inhibitors/potent inducers of cytochrome P450 3A4 or potent inhibitors of cytochrome P450 2C19

enzymes (such as cimetidine, quinidine, erythromycin, ciprofloxacin, fluconazole, ketoconazole etc...) and strong inducers of CYP enzymes (such as rifampin etc...), in the previous 28 days before day 0.

9. A helminth parasitic infection diagnosed within 6 months prior to the date informed consent or assent obtained that has not been treated with, or has failed to respond to, standard of care therapy.
10. History of clinically significant infection, including acute upper or lower respiratory infections, requiring antibiotics or antiviral medication within 30 days prior to the date informed consent or assent is obtained or during the run-in period.
11. Tuberculosis requiring treatment within the 12 months prior to enrolment (Visit 1).
12. Any clinically significant abnormal findings in physical examination, vital signs, ECG, hematology, clinical chemistry, or urinalysis during the run-in period, which in the opinion of the Investigator, may put the subject at risk because of his/her participation in the study, or may influence the results of the study, or the subject's ability to complete entire duration of the study.
13. History of chronic alcohol or drug abuse within 12 months of the enrolment visit, or a condition associated with poor compliance as judged by the Investigator.
14. Positive hepatitis B surface antigen or hepatitis C virus antibody serology. Subjects with a history of hepatitis B vaccination without a history of hepatitis B are allowed to be enrolled.
15. History of any known primary immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test at enrolment, or the subject taking antiretroviral medications as determined by medical history and/or subject's verbal report.
16. Current tobacco smoking (smoking must have stopped for  $\geq 3$  months prior to enrollment) or a history of tobacco smoking for  $\geq 10$  pack-years (one pack year = 20 cigarettes smoked per day for 1 year).
17. History of cancer:
  - a. Subjects who have had basal cell carcinoma, localized squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible provided that the subject is in remission and curative therapy was completed at least 12 months prior to the date informed consent was obtained
  - b. Subjects who have had other malignancies are eligible provided that the subject is in remission and curative therapy was completed at least 5 years prior to the date informed consent was obtained
18. Use of immunosuppressive medication (including but not limited to: methotrexate, toleandomycin, cyclosporine, azathioprine, systemic corticosteroids including regular treatment with OCS or intramuscular long-acting

depot corticosteroids, or any experimental anti-inflammatory therapy) within 3 months prior to the date informed consent or assent is obtained.

19. Clinically significant asthma exacerbation, in the opinion of the Investigator, including those requiring use of oral corticosteroids 30 days prior to the date of informed consent or during the screening/run-in period.
20. Receipt of immunoglobulin or blood products within 30 days prior to the date informed consent or assent is obtained.
21. Receipt of any marketed or investigational biologic agent within 4 months or 5 half-lives prior to the enrolment visit, whichever is longer.
22. Receipt of live attenuated vaccines 30 days prior to the date of randomization and during the study including the follow-up period
  - a. Receipt of inactive/killed vaccinations (eg, inactive influenza) are allowed, provided they are not administered within 5 days before/after any study visit.
23. Receipt of any investigational non-biologic agent within 30 days or 5 half lives prior to informed consent or assent being obtained, whichever is longer.
24. Previous receipt of tralokinumab (CAT-354).
25. Initiation of new allergen immunotherapy or change in existing immunotherapy is not allowed within 30 days prior to the date of informed consent. However allergen immunotherapy initiated prior to this period may be continued provided there is a span of at least 5 days between the immunotherapy and IP administration.
26. Current use of oral or ophthalmic non-selective  $\beta$ -adrenergic antagonist (eg, propranolol).
27. Current use of five- lipoxygenase inhibitors (eg, Zileuton) or roflumilast.
28. Major surgery within 8 weeks prior to the enrolment visit, or planned in-subject surgery or hospitalization during the study period.
29. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level  $\geq 2.5$  times the upper limit of normal (ULN) at enrolment
30. Pregnant, currently breast-feeding, or lactating women.
31. Previous randomization in the present study.
32. Concurrent enrollment in another clinical study where the subject is receiving an IP.

33. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
34. Employees of the clinical study site or any other individuals directly involved with the planning or conduct of the study, or immediate family members of such individuals.
35. Individuals who are legally institutionalized.

For exclusion from the voluntary pharmacogenetic research:

36. Previous allogeneic bone marrow transplant.
37. Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection.

### **SAFETY OF TRALOKINUMAB**

Several trials have been conducted with tralokinumab in people with Asthma, Ulcerative Colitis, Idiopathic Pulmonary Fibrosis and in Healthy Volunteers. This is the first time that tralokinumab has been given to subjects with alopecia areata.

In the largest study of tralokinumab to date, a total of 452 subjects with severe, uncontrolled asthma were given tralokinumab 300mg or placebo as an injection under the skin over a 52-week dosing period. Half of the subjects received 300mg tralokinumab or placebo every 2 weeks for the entire study, whereas the other half received 300mg tralokinumab or placebo every 2 weeks for the first 12 weeks, and then every 4 weeks for the rest of the study. Overall, 301 subjects received tralokinumab and 151 subjects received placebo. Side effects occurring more frequently in subjects receiving tralokinumab (5% more frequently) were injection site redness and allergic rhinitis or “hay fever”. Other side effects such as asthma, cold-like symptoms, bronchitis, flu-like illness and headache were common in both the placebo and tralokinumab groups. Injection site reactions were experienced by subjects in all groups, but those receiving tralokinumab every 2 weeks experienced reactions the most frequently (35 of 150 subjects [23%] compared to 7 of 76 subjects [9.2%] receiving placebo every 2 weeks). The most common types of symptoms experienced at the injection site in all groups were pain, itching, redness and rash. Three subjects receiving tralokinumab (out of a total of 301) stopped receiving study drug due to reactions at the injection site (redness, rash and urticaria or “hives”). The reactions in all 3 subjects were mild to moderate in severity and occurred after they had received more than one dose of tralokinumab.

The safety of tralokinumab has been tested in monkeys following intravenous (directly into the bloodstream) and subcutaneous (under the skin) administration at doses higher than those being used in this study. No toxic effects were seen following weekly intravenous doses of tralokinumab for up to 6 months of dosing.

## **ADVERSE EVENTS**

During a previous study where 301 subjects with asthma were given tralokinumab, the following side effects were reported (greater than or equal to 10% occurrence): asthma, nasopharyngitis (cold symptoms), bronchitis, upper respiratory tract infection, and headache. Similar frequencies of side effects were seen in subjects receiving placebo.

Events that were judged to be related to the study drug by the investigator were primarily injection site reactions (redness, itching and pain). There have also been occasional reports of serious side effects in people participating in clinical studies with tralokinumab, but it has not been established that the study drug caused these effects.

There is a small chance of anaphylaxis to tralokinumab. Such reactions have been observed following the use of antibodies to treat human diseases, including asthma; such reactions have been described as occurring rarely (likely to affect fewer than 1 in every 1000 subjects). Anaphylaxis may cause a serious drop in blood pressure; wheezing; difficulty in breathing; a feeling of dread; swelling around the mouth, throat, or eyes; a fast pulse; sweating; severe hives (itchy rash); and sometimes death. Subjects will be monitored after administration of the study drug, and will have medications available to treat any allergic reactions that might occur. Less serious allergic reactions, such as skin rash with or without itching and swelling, may also occur within hours to days after receiving the drug. These effects usually get better without treatment. One person with asthma experienced a rapid allergic reaction known as an acute hypersensitivity reaction (increased wheezing, shortness of breath and facial swelling) after being given tralokinumab intravenously, i.e. administered through the vein.

Additional potential risks include the development of anti-drug antibodies. Anti-drug antibodies could result in an immune complex disease that can include symptoms such as joint pain, serum-sickness, inflammation of arteries and veins called vasculitis, autoimmunity, or it can change the amount of drug in blood or the way the drug works.

Other potential risks include an increased risk for tumors, such as breast cancer and prostate cancer, and an increased risk for severe infections like opportunistic infections and parasitic worm infection. These side effects have not been seen in other tralokinumab studies.

The effects of tralokinumab on the unborn fetus are not known. Some drugs cause premature birth or birth defects. There is a potential risk of miscarriage with tralokinumab though this has not been seen in animal studies. In the Tralokinumab Asthma Study five pregnancies were reported. Of these, four mothers and one father were taking part in the Tralokinumab Asthma Study. One of these four mothers who was taking part in the Tralokinumab Asthma Study had a miscarriage. However, this mother was found to be taking placebo and so this miscarriage was not related to tralokinumab.

It is very important that women taking part in the study practice birth control to prevent pregnancy during this study. The acceptable methods of birth control have been

described previously in this document. Women who are pregnant or nursing mothers are not allowed to be in the study as the safety of tralokinumab administration during pregnancy and to nursing children is unknown. Women who become pregnant during the study will have to terminate the study. The study doctor or study staff may ask for information about the pregnancy and the child's health at birth and may share this information with the sponsor.

There may be other side effects of tralokinumab that are unknown, which include the condition getting worse. Subjects will be monitored by the Study Doctor and, in the event that the results show conditions that may need following, the subject will be followed by the Study Doctor, their own doctor, or a specialist. This may require the release of records to a non-study doctor. In this case, subjects will be asked for their consent (permission).

It is possible that receiving tralokinumab may change how subjects' regular medications, vaccines, or supplements work. Subjects will be asked to tell the Study Doctor about any medications, supplements, or vaccines before taking them during the study.

### **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.

### **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 Early Termination visit for the procedures listed in the Schedule of Events table.



Considering there is no current treatment that is very effective in treating alopecia areata, these subjects are highly motivated to participate in any study that may provide a treatment option. Thus, we have accounted for a 10% drop out rate, and plan to enroll 30 subjects in order to have 27 subjects complete the study.

### **INVESTIGATIONAL DRUG SUPPLY**

In this double-blind study, the investigator will supply tralokinumab (formulated at 150 mg/ml in an isotonic sodium acetate buffer at pH 5.5 in accessorized prefilled syringes for subcutaneous injection) 300 mg for up to 20 subjects and placebo for up to 10 subjects. The tralokinumab and placebo will be provided by MedImmune as 150 mg tralokinumab (and matching placebo) prefilled syringes. Both the 150 mg tralokinumab and the matching placebo prefilled 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°C. 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.

### **EFFICACY EVALUATIONS**

The following efficacy parameters will be obtained at the previously specified visits:

1. Investigator evaluation of alopecia on the scalp (efficacy of the drug) using the following tools:

**Severity Alopecia Tool (SALT)<sup>5</sup> score:**

The SALT score is a mathematical approach to the determination of hair loss and hair regrowth.<sup>6</sup> The percentage of scalp hair loss in each of the sides, back and top of the scalp are determined independently, and are multiplied by the percentage scalp covered in that area of the scalp and the products of each section summed for a final total percentage hair loss, designated as the SALT score. (Appendix 1)

2. Quality of life will be evaluated using the **Alopecia Areata Symptom Impact scale (AASIS)<sup>7</sup>** and the **Alopecia Areata Quality of Life Index (AA-QLI)<sup>8</sup>**. Safety will be assessed by evaluation of adverse events, physical examinations and laboratory parameters. (Appendices 2 and 3)
3. **SCORing for Atopic Dermatitis (SCORAD) Index** (only applicable to subjects with concomitant AD).<sup>9</sup>

The most widely accepted clinical assessment tool for AD disease severity index is known as SCORAD: 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. (Appendix 4)

4. **The Eczema Area and Severity Index (EASI) score** (only applicable to subjects with concomitant AD):<sup>10</sup> 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. (Appendix 5)
5. **Investigator's Global Assessment (IGA) index** (only applicable to subjects with concomitant AD):<sup>11</sup> a static IGA 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. (Appendix 5)

The SCORAD, EASI, and IGA indices will only be undertaken in those subjects who have concomitant AA and AD.

## **BIOPSY SPECIMENS**

The skin site(s) selected for biopsy are anesthetized by injection of 1-2% lidocaine with epinephrine. Two punch biopsies (4.5 mm each; one from involved skin and one from uninvolved skin) prior to initiating study drug and one additional punch biopsy will be repeated at Week 24 or Early Termination Visit (in the vicinity of the involved area

biopsied at Baseline). An optional biopsy will be performed at Week 12 (in the vicinity of the involved area biopsied at Baseline).

Subjects with concomitant AD will have two additional skin biopsies at Baseline (one from involved and one from uninvolved skin), and one additional biopsy at Week 24 or Early Termination visit (in the vicinity of the involved area biopsied at Baseline). An optional biopsy will be performed at Week 12 (in the vicinity of the involved area biopsied at Baseline). All skin biopsies will be 4.5 mm in diameter. The wounds will be sutured and sterile dressings applied. This procedure leaves a small and permanent scar.

The tissue samples will be handled and processed according to the Standard Operating Procedures of the Laboratory for Inflammatory Skin Diseases.

Since this study is designed to gain basic knowledge rather than to yield information directly related to patient care, the results are not entered in the participants' medical records. If, at a later date, correlations of in-vitro tests and the patients' clinical situation suggest that the results do bear on the patients' health, an amended protocol will be submitted to the IRB so that results can be made available to the medical record. As all tissue is obtained for research purposes and not for routine clinical tests, the above outlined blood and skin samples may be stored until used. Skin and/or blood cells will be studied and de-identified samples may be shared with collaborating investigators at Mount Sinai in the future for further histology and immunochemistry, FACS analysis, PCR studies, cell cultures, and gene chip analyses. The samples will be stored indefinitely and will primarily be used for the scope of this study.

### **LABORATORY SPECIMENS**

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

Mechanistic blood analyses including RNA, DNA, and proteomic analysis, as well as ADA will be conducted collaboratively with MedImmune/AstraZeneca.

### **INSTITUTIONAL REVIEW BOARD**

Prior to beginning this study, approval for all study related documents (protocol, consent form, advertising) would 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.

### **DATA ANALYSES:**

This is an exploratory study therefore sample size has been kept relatively low. Data collected from this study will be used to obtain estimates of differences and variability, of the change in treatment for IL-13. If the variability of the Post vs Pre differences are of the magnitude of the LS vs NL differences observed in preliminary data (SE=0.46) then the size of the confidence interval in differences could be observed in this study would be 0.58. As for the secondary outcome, the spontaneous regrowth rate in alopecia areata is 4%. To demonstrate efficacy of the study drug, a response rate of at least 50% is required. To be statistically significant, we would require a minimum of 10 subjects in the study, with an expected response rate of 0 or 1 subject in the placebo group.

### **MECHANISTIC STUDIES DATA ANALYSES:**

For the comparisons of expression levels of lesional, and non-lesional AA skin, we will use RT-PCR, and gene-arrays. RT-PCR values will be normalized to the housekeeping gene hARP (validated in all our AD studies) and log2-transformed prior to analysis. Microarray data will be preprocessed using standard pipeline (exhaustively used by our group in a large number of studies) and log-2 transformed expressions. Adjustments by batch effect and clinical variables will be carried out if needed using ComBat. Mixed effect model on R's *limma* framework will be used and p-values for the moderated t-tests and paired-t-test will be adjusted by Benjamini-Hochberg procedure.

Extensive bioinformatics tools will be employed to gain insights on the results and test hypotheses that are generated in the "data mining stage". This will include (but is not be limited to) pathway and gene-set enrichment analyses using Ingenuity software, GSEA, the R package GSEA (Gene Set Variation Analysis) and other in-house codes produced by our group.

To define cellular and molecular biomarkers of AA in skin biopsies, biomarkers will be divided into those that show significant group differences and those that do not. Multiple regression models will be used to determine the best set of biomarkers that predict disease activity and response. Similar approaches will be carried out for blood analyses.

Gene expression changes in Th2/IL-13, "T22"/IL-22, S100A7 and S100A8, Th1/IFN-gamma, and Th17/IL-17A will be jointly correlated with clinical responses by multivariate analysis using multivariate u-statistics and R package muStat, as we have previously reported.

## **DATA AND SAFETY MONITORING PLAN**

Since this is a phase II study, with few subjects and minimal risks, this project will be monitored by the principal investigator, sub-investigators, and independent DSMB. Both the principal investigator will provide safety data to an independent Data and Safety Monitoring Board every 12 months. This DSMB will be comprised of dermatologists who are not directly related to this study. The DSMB will review all the safety data and provide a report of their findings to the Principal Investigator.

All non-serious events will be reported to the IRB and FDA (on behalf of the IND) on a yearly basis. All serious events will be reported to the IRB and FDA within 24 hours of becoming aware of the event.

## Schedule of Events

Procedures	Screening (Day -28 to Day -1)	Baseline Day 0	Weeks 2, 6	Week 4	Week 8	Week 10	Week 12	Weeks 14 and 18	Weeks 16 and 20	Week 22	Week 24	Week 32	Week 40	Early Term Visit
Informed consent	X													
Inclusion/exclusion criteria	X	X												
Past Medical History (including demographic data and age on onset)	X													
ECG	X											X		X <sup>6</sup>
Limited Physical Examination	X						X				X	X	X	X
Vital Signs <sup>1</sup>	X	X	X	X	X	X	X	X	X	X	X			
Chemistry and hematology	X	X		X			X				X	X		X <sup>6</sup>
PPD or Quantiferon Gold	X													
HIV screening	X													
HBsAg, Anti-HBc antibody	X													
Pregnancy test <sup>2</sup>	X	X	X	X	X	X	X	X	X	X				X <sup>7</sup>
Assessment of Regrowth Pattern	X	X	X	X	X	X	X		X		X	X	X	X
SALT assessment	X	X	X	X	X	X	X		X		X	X	X	X
Subject Questionnaires AASIS and AA-QoL		X		X	X		X		X		X	X	X	X

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<i>Procedures</i>	Screening (Day -28 to Day -1)	Base- line Day 0	Weeks 2, 6	Week 4	Week 8	Week 10	Week 12	Weeks 14 and 18	Weeks 16 and 20	Week 22	Week 24	Week 32	Week 40	Early Term Visit
SCORAD, EASI, IGA <sup>3</sup>		X		X	X		X		X		X	X	X	X
Blood for mechanistic studies		X					X				X			X <sup>7</sup>
Blood DNA analysis		X												
Blood RNA and proteomic analysis		X					X				X			X <sup>7</sup>
ADA measurement		X		X			X				X			X <sup>7</sup>
Serum drug levels		X		X			X				X			X <sup>7</sup>
Clinical Photographs		X		X			X		X		X	X	X	X
Scalp Biopsies		X					X <sup>8</sup>				X			X <sup>7</sup>
Skin biopsies of atopic dermatitis (AD subset only)		X					X <sup>8</sup>				X			X <sup>7</sup>
Study product administration		X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>				
Prior and concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X

<sup>1</sup> vital signs will be taken prior to every study drug administration

<sup>2</sup> Serum pregnancy test for females of childbearing potential at screening and urine test at other visits.

- 3 These will be performed on subjects with concomitant AD only.
- 4 For the first four doses of Investigational Product (Baseline, Weeks 2, 4 and 6) subjects will be monitored after IP administration for immediate drug reactions for a minimum of 2 hours with vital signs taken every 30 minutes or until stable, whichever is later.
- 5 For the fifth and subsequent doses of IP, subjects will be monitored after IP administration for a minimum of 1 hour with vital signs taken every 30 minutes or until stable, whichever is later
- 6 Only if Early Term Visit occurs before Week 32.
- 7 Only if Early Term Visit occurs before Week 24.
- 8 Optional biopsies at Week 12.

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#### Amendment # 1

All Pages: The version date in the footer was changed to 8/11/15.

#### Page 1:

- Dr. Suarez-Farinas (Biostatistician) and Yasaman Mansouri, MD were removed as investigators because they are not considered key personnel;
- amendment #1 August 11, 2015 was listed.

Pages 5 - 9:

- The procedures for each visit on pages 5 through to 9 were clarified and checked against our schedule of events table.
- Electrocardiogram (ECG) was added to the assessments performed during the screening visit.
- Serum tralokinumab levels were added to the Baseline visit as recommended by the FDA.

Page 6 & 7:

- Serum tralokinumab levels and antidrug antibody (ADA) measurements were added to the Week 4 and Week 12 visits as recommended by the FDA.
- Serum tralokinumab levels were added to the Week 24 visit as recommended by the FDA.
- Blood tests for chemistry and hematology were changed from the Week 22 visit to the Week 24 visit.
- Two paragraphs explaining the procedures for Early Termination Visits were added.

Page 8:

- We clarified the language used regarding the location where the biopsies will be performed.
- In the last paragraph, we added the information regarding the serum drug levels that were suggested by the FDA.

Page 9:

- Inclusion Criteria: We revised the language for contraception to be used by women of childbearing potential.

Page 15 and 20:

- The Principal Investigator will provide safety data to an independent Data and Safety Monitoring Board every 12 months instead of every 6 months.

Page 16:

- We removed the paragraph listing the procedures to be performed at the Early Termination Visit, as this has been added under study design.

Pages 21-23:

- the table on pages 21 through 23 was updated to be consistent with the protocol, and the title of the table was changed from “flow chart” to “Schedule of Events”.