The Effects of Dupilumab on Allergic Contact Dermatitis

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PROTOCOL SYNOPSIS

Protocol Title:	The Effects of Dupilumab on Allergic Contact Dermatitis
Site Numbers & Names:	001 Brigham and Women's Hospital, Department of Dermatology
Research Hypothesis:	Dupilumab will most likely benefit patients who have persistent allergic contact dermatitis to allergens that primarily elicit a Th2 immune response (ie rubber and fragrance) but may also benefit patients who have sensitivities to allergens that primarily elicit Th1, Th17 and Th22 immune responses (ie nickel).
Study Schema: **Drugs / Doses / Length of Treatment)**	Dupilumab 300 mg/2mL; 7 doses; 10 weeks of treatment
Study Objectives: • **Primary:** • **Secondary:**	• Primary endpoint 1: Number of patients who achieve a reduction in patch test site reactions from 2+-3+ at baseline to "?" or no reaction at week 12. • Secondary endpoint 1: Number of patients who achieve a reduction in investigator global assessment (IGA; IGA = vIGA-AD) from 3 or greater at screen and baseline to 0 or 1 at Week 6 and at Week 12. • Secondary endpoint 2a: To quantify the inflammatory markers (Th1, Th2, Th17, Th22 immune pathways) in the blood and skin of patients before and after dupilumab. Secondary endpoint 2b: Changes in IGA from baseline to week 12. Other secondary endpoints: Change in baseline eczema-area-and-severity-index (EASI), body surface area (BSA), numerical rating scale (NRS) itch, dermatology life quality index (DLQI), and SLEEPYQ from baseline to Week 6 and Week 12. • Secondary endpoint 3: Changes in IGA from baseline to Week 6 and to Week 12. • Secondary endpoint 4: To identify and quantify the top T cell clones by T-cell receptor high-throughput sequencing in the skin and blood before therapy and quantify their abundance after therapy. • Other secondary endpoints: Change in baseline eczema-area-and-severity- index (EASI), body surface area (BSA), numerical rating scale (NRS) itch, dermatology life quality index (DLQI), and SLEEPYQ from baseline to Week 6 and to 12.

Study Design:	We will recruit 30 patients with allergic contact dermatitis 18 years of age and older up to 18 months after patch testing with a documented IGA of at least 3 at baseline and screening visits, and at least one 2+ (strong) or 3+ (extreme) reaction on patch testing to participate in this open-label pilot study. If more than one 2+ (strong) or 3+ (extreme) reactions are present, up to two may be selected for evaluation in the study. Priority will be given to nickel, fragrance mix I or II, and rubber as these allergens have been studied previously with respect to their preferential T helper cell skewing. At the initial screening visit, demographic information will be obtained, inclusion and exclusion criteria as detailed in Section 4.2 will be reviewed, and informed consent obtained for those deemed eligible for enrollment. A single subcutaneous dose of 600 mg will be self-administered at week 0 +72-120 hours and 300 mg every 2 weeks thereafter for a total 10 weeks of therapy. Subjects will be evaluated for improvement in primary and secondary endpoints using clinical examination and questionnaires during initial and follow-up visits at Week 0, Week 6, and Week 12 as per Time and Events Schedule below. Patch test site reactions will also be evaluated 72 hours after the Week 0 and Week 12 visits. Skin biopsies will be taken at these two time points from both the patch test site reaction and from normal skin taken from a non-dermatitic area on the contralateral side of the body. For the Week 12 patch placement, a site contralateral to the Week 0 patch placement site will be chosen. If an area of persistent dermatitis other than the patch test site(s) is also present at week 12+72-120 hours an additional biopsy will be taken unless in an anatomic location not amenable to biopsy (face, hands, elbows, knees, genitals, feet). Serum samples will be obtained at four time-points including Week 0 (prior to patch placement), Week 0 +72-120 hours, Week 12 (prior to patch placement), and Week 12 +72-120 hours. If subjects do not mount a 2+ (strong) or 3+ extreme reaction to the tested allergens at the Week 0 +72 hour visit they will be discontinued from the study and will not receive dupilumab. These patients will be considered screen fails. Week 10 +72-120 hours will conclude the end of the treatment portion of the study. Week 12 +72-120 hours will conclude the subjects' participation in the study.
Accrual Goal: **(Total number of subjects)**	30 subjects
Accrual Rate: **(Number of subjects expected per month)**	1 subject/month
FPFV: **LPFV:** **Follow Up:** **(dd-mm-yy)**	FPFV: 09-01-18; LPFV: 05-01-20; Follow Up: 3 months after FV

Correlative Studies: **(PK/PD, etc.)**	
Inclusion Criteria:	1. At least 18 years of age 2. At least one contact allergen with a 2+ (strong) or 3+ (extreme reaction) confirmed by patch testing within 18 months of the baseline visit that can be duplicated at the initiation of the study (placement at Week 0 and patch test reaction read at Week 0 +72-120 hours). 3. Allergic contact dermatitis diagnosed clinically by the principle investigators who have expertise in allergic contact dermatitis 4. Investigator's global assessment score of at least 3 (range 0-4) at the screening and baseline visits 5. Documented recent history (within 18 months of patch testing) of inadequate response to treatment with topical medications and allergen avoidance 6. Able and willing to provide informed consent, participate in study visits, and undergo visit procedures.

Exclusion Criteria:	1. Prior dupilumab use 2. Treatment with a systemic immune-regulating medication within 3 months of the baseline visit or the patient's prior patch testing, whichever is longer. Examples of these medications include azathioprine, methotrexate, mycophenolate mofetil, Janus kinase inhibitors, and phototherapy (including tanning booths). Cyclosporine or prednisone may not have been used within 1 month of the baseline visit. 3. Treatment with other biologic agents, such as TNF inhibitors, anti-IL 17 agents, anti-IL 12/23 agents, or anti-IL 23 agents, within 4 months of baseline visit or the patient's prior patch testing, whichever is longer. 4. Use of rituximab within at 6 months (or until lymphocyte counts have normalized if longer than 6 months) of the baseline visit or the patient's prior patch testing, whichever is longer. 5. Treatment with topical corticosteroids, topical phosphodiesterase inhibitors or topical calcineurin inhibitors within 1 week before the baseline visit 6. Other active conditions, such as psoriasis, that may confound clinical evaluations of dermatitis and patient-reported symptoms.

Exclusion Criteria (continued)	7. Increased risk of infection or reactivated infection, including history of human immunodeficiency virus, hepatitis B, hepatitis C, endoparasitic infections, receipt of a live attenuated vaccine within 3 months of the baseline visit, chronic or acute infection requiring treatment within 4 weeks of the baseline visit, immunosuppressed status (ie recurrent or resistant opportunistic infections) 8. Malignancy within 5 years of the screening visit excluding local cutaneous squamous cell carcinoma, basal cell carcinoma or cervical carcinoma in situ that has been fully treated. 9. Women who are or plan to become pregnant or breastfeed during study participation or are unable or not willing to use birth control during the study and for 4 months after the last dose of dupilumab. Options for birth control include abstinence, double barrier (ie male condom and female diaphragm), vasectomy, intrauterine device, and hormonal contraception. Females who have not had menses within 1 year of the baseline, bilateral tubal ligation, hysterectomy, and/or bilateral oophorectomy visit do not require additional methods contraception during study participation. 10. Unstable condition or status, as per study investigator's judgment, that may lead to more likely discontinuation from the study including but not limited to major, recurrent medical illnesses that may require hospital admission and/or discontinuation of dupilumab, surgery that would require discontinuation of dupilumab and/or major rehabilitation, inability to participate in all study visits and administer dupilumab. 11. Resident outside of Massachusetts, Connecticut, Rhode Island, New Hampshire, Maine or Vermont state. 12. Unable to use Zoom videoconferencing.
Criteria for Evaluation: **(Efficacy, safety, stopping rules, etc.)**	
Statistics:	

1 INTRODUCTION

1.1 Background on Allergic Contact Dermatitis

Allergic contact dermatitis (ACD) is a chronic, inflammatory dermatitis affecting millions of Americans yearly and has significant negative impacts on patient quality of life and the economy. Contact dermatitis has an estimated prevalence rate of 13.6 cases per 1000 population, with 8.4 million office visits, 4 million workdays, and $400 million lost yearly in the United States.[1,2,3] Identification of allergens through patch testing and subsequent avoidance is the first-line treatment along with topical corticosteroids. However, in certain patients, such as those with implantable devices or occupational exposures, allergen avoidance is difficult or impossible and represents a major unmet clinical need. Dupilumab is a promising treatment for allergic contact dermatitis through its blockade of the cytokines IL-4 and IL-13 that are central in the differentiation and maintenance of Th2 cells and its ability to also normalize Th1, Th17, and Th22-mediated immune pathways.[4] Blockade of this pathway in ACD patients and the study of their skin and blood before and after treatment offers a unique opportunity to improve our understanding of disease mechanisms in human ACD and the potential role for dupilumab in addressing this unmet need.

1.2 Role of T cells in Allergic Contact Dermatitis and Dupilumab

Current treatment strategies for ACD include allergen avoidance and the use of topical or systemic immunosuppressive agents. However, for many patients allergen avoidance can negatively affect quality of life or be inadequate, particularly in cases of unavoidable occupational exposures or implanted devices. While allergic contact dermatitis was originally posited to be a Th1-predominant disease, the important roles played by Th2, Th17 and Th22 cells is increasingly recognized. Activation of inflammatory pathways in ACD can be allergen specific, with differential upregulation of innate immune, Th1, Th2, Th17, and/or Th22 signaling. Specifically, nickel induces a strong Th1, Th17 and Th22 response, while fragrance and rubber have preferential TH2 stimulation. This is in contrast to atopic dermatitis, a predominantly Th2-mediated inflammatory reaction driven by the cytokines IL-4, IL-5 and IL-13. In atopic dermatitis, the cytokines IL-4 and IL-13 are the main pathogenic cytokines. These instructive cytokines both induce activated naïve T cells to become Th2 cells and maintain the survival of Th2-derived memory T cells. These cytokines can also alter chemokine expression and trafficking to inflamed tissue. The IL-4 and IL-13 receptors share the common subunit IL-4Rα. Dupilumab, an inhibitor of IL-4Rα, is FDA-approved for the treatment of atopic dermatitis. Despite its specific targeting of Th2-mediated pathology, it has also been shown to normalize Th1-,

and Th17-related gene expression in the skin of patients with atopic dermatitis. Therefore, we hypothesize that dupilumab will most likely benefit patients who have persistent allergic contact dermatitis to allergens that primarily elicit a Th2 immune response (ie rubber and fragrance), but may also benefit patients who have sensitivities to allergens that primarily elicit Th1, Th17, and Th22 immune responses (ie nickel). We propose to test this hypothesis by treating patients who have failed allergen avoidance and skin directed therapy with dupilumab and monitoring their responses in the following ways before and after therapy: using well-established clinical parameters addressing skin inflammation and quality of life issues, assessing whether the most abundant T cell clones (defined as the top 5 most abundant clones present in the skin at patch test site before therapy) can still traffic to the skin after therapy, and quantifying the changes in the inflammatory Th1, Th2, Th17 and Th22-specific immune gene signatures before and after treatment.

1.3 Summary of Results of Investigational Program

1.3.1 Pharmacology of Dupilumab

Dupilumab is a human monoclonal IgG4 antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the Type I receptor and both IL-4 and IL-13 signaling through the Type II receptor.

Blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13 cytokine-induced responses, including the release of proinflammatory cytokines, chemokines and IgE.

1.3.2 Human Pharmacokinetics of Dupilumab

Absorption

Following an initial subcutaneous (SC) dose of 600 mg, dupilumab reached peak mean ±SD concentrations (Cmax) of 70.1±24.1 mcg/mL by approximately 1 week post dose.

Steady-state concentrations were achieved by Week 16 following the administration of 600 mg starting dose and 300 mg dose either weekly (twice the recommended dosing frequency) or every other week. Across clinical trials, the mean ±SD steady-state trough concentrations ranged from 73.3±40.0 mcg/mL to 79.9±41.4 mcg/mL for 300 mg administered every 2 weeks and from 173±75.9 mcg/mL to 193±77.0 mcg/mL for 300 mg administered weekly. The bioavailability of dupilumab following a SC dose is estimated to be 64%. Distribution The estimated total volume of distribution was approximately 4.8±1.3 L.

Elimination The metabolic pathway of dupilumab has not been characterized. As a human monoclonal IgG4 antibody, dupilumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. After the last steady-state dose of 300 mg Q2W or 300 mg QW dupilumab, the median times to non-detectable concentration (<78 ng/mL) are 10 and 13 weeks, respectively.

Dose Linearity Dupilumab exhibited nonlinear target-mediated pharmacokinetics with exposures increasing in a greater than dose-proportional manner. The systemic exposure increased by 30-fold when the dose increased 8-fold following a single dose of dupilumab from 75 mg to 600 mg (i.e., 0.25times to 2-times the recommended dose). Weight Dupilumab trough concentrations were lower in subjects with higher body weight. Immunogenicity Development of antibodies to dupilumab was associated with lower serum dupilumab concentrations. A few subjects who had high antibody titers also had no detectable serum dupilumab concentrations.

Specific Populations

Geriatric Patients

In subjects who are 65 years and older, the mean ±SD steady-state trough concentrations of dupilumab were 69.4±31.4 mcg/mL and 166±62.3 mcg/mL, respectively, for 300 mg administered every 2 weeks and weekly. No dose adjustment in this population is recommended.

Renal or Hepatic Impairment

No formal trial of the effect of hepatic or renal impairment on the pharmacokinetics of dupilumab was conducted.

Drug Interaction Studies

Drug interaction studies have not been conducted with DUPIXENT.

1.3.3 Clinical Safety with Dupilumab SC Formulation

1.3.3.1 Drug-Related Adverse Events

Conjunctivitis

During the 52-week treatment period of concomitant therapy trial (Trial 3), conjunctivitis was reported in 16% of the DUPIXENT 300 mg Q2W + TCS group (20 per 100 subject-years) and in 9% of the placebo + TCS group (10 per 100 subject-years) [see Warnings and Precautions (5.2)].

Eczema Herpeticum and Herpes Zoster

The rate of eczema herpeticum was similar in the placebo and DUPIXENT groups.

Herpes zoster was reported in <0.1% of the DUPIXENT groups (<1 per 100 subject-years) and in <1% of the placebo group (1 per 100 subject-years) in the 16-week monotherapy trials. In the 52-week DUPIXENT + TCS trial, herpes zoster was reported in 1% of the DUPIXENT + TCS group (1 per 100 subject-years) and 2% of the placebo + TCS group (2 per 100 subject-years).

Hypersensitivity Reactions

Hypersensitivity reactions were reported in <1% of DUPIXENT-treated subjects. These included serum sickness reaction, serum sickness-like reaction, and generalized urticaria [see Contraindications (4), Warnings and Precautions (5.1), and Adverse Reactions (6.2)].

Eosinophils

DUPIXENT-treated subjects had a greater mean initial increase from baseline in eosinophil count compared to subjects treated with placebo in the monotherapy trials. Eosinophil counts declined to near baseline levels by Week 16. The initial increase in eosinophils was not observed in the 52-week DUPIXENT + TCS trial.

In Trials 1, 2, and 3, the incidence of treatment-emergent eosinophilia (≥500 cells/mcL) was similar in DUPIXENT and placebo groups. In Trials 1, 2, and 3, treatment-emergent eosinophilia (≥5,000 cells/mcL) was reported in <1% of DUPIXENT-treated patients and none in placebo-treated patients. In most cases, eosinophil counts declined to near baseline during study treatment.

1.4 Research Hypothesis

Dupilumab will most likely benefit patients who have persistent allergic contact dermatitis to allergens that primarily elicit a Th2 immune response (ie rubber and fragrance) but may also benefit patients who have sensitivities to allergens that primarily elicit Th1, Th17 and Th22 immune responses (ie nickel).

1.5 Study Rationale

One of the most innovative aspects of this proposal is the proposed combination of clinical and translational science to address a potential new cohort of patients that may benefit from the use of dupilumab. By ascertaining the efficacy of dupilumab in a cohort of patients using a combination of robust, well-characterized, clinical scoring and state-of-the-art technologies to identify and quantify changes in T cell trafficking and inflammatory gene and protein signatures, we will determine the extent to which dupilumab dampens the T-cell

response to allergens. Not only are these studies novel in this disease, blockade of IL-4 and IL-13 will lead to a better understanding of allergen-specific disease pathogenesis.

2 STUDY OBJECTIVES

2.1 Primary Objective

To measure the degree to which 2+(strong)-3+(extreme) patch test site reactions are reduced by dupilumab. Based on the International Contact Dermatitis Research Group scoring system (? as a doubtful reaction, + as a mild reaction, possible erythema, infiltration, and papules, ++ as a strong reaction, erythema, infiltration, papules and vesicles, +++ as a very strong reaction, intense erythema, infiltration, and coalescing vesicles, IR as an irritant reaction), we will measure patch test site reactions at two time points, both prior to starting dupilumab (Week 0 +72-120 hours) and 12 weeks after starting dupilumab.

2.2 Secondary Objectives

Secondary endpoint 1: Number of patients who achieve a reduction in investigator global assessment (IGA) from 3 or greater at screen and baseline to 0 or 1 at Week 6 and Week 12.

Secondary endpoint 2a: To quantify the inflammatory markers (Th1, Th2, Th17, Th22 immune pathways) in the blood and skin of patients before and after dupilumab. Using novel nanostring-based gene expression assays and multispectral immunofluorescence we will quantify changes in key genes that are specific for the Th1, Th2, Th17, Th22 immune pathways in the skin and blood of patients before and after treatment with dupilumab. Secondary endpoint 2b: Changes in IGA from baseline to week 12. Other secondary endpoints: Change in baseline eczema-area-and-severity-index (EASI), body surface area (BSA), numerical rating scale (NRS) itch, dermatology life quality index (DLQI), and SLEEPYQ from baseline to Week 6 and Week 12.

Secondary endpoint 3: To measure the reductions in the severity of clinical skin disease and quality of life scores with dupilumab treatment. We will measure changes in investigator global assessment (IGA; scored on a scale of 0-5 with 0 being no disease and 5 being the most severe disease) from baseline to Week 6 and Week 12.

Secondary endpoint 4: To address whether dupilumab affects T cell trafficking, use high-throughput sequencing of the T-cell receptor (TCR HTS) to identify the unique

CDR3 sequence of the likely pathogenic T cell clones before therapy and quantify their relative frequency in the skin after dupilumab therapy.

3 ETHICAL CONSIDERATIONS

3.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH) and in accordance with the ethical principles underlying the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50). Study procedures and guidelines are outlined in this protocol and any changes to the protocol or informed consent forms will be submitted for IRB approval prior to their use. Any serious breaches in GCP, such as those leading to risks to patients or study validity, will be reported to Regeneron. All team members involved in the study will have appropriate qualifications to complete their responsibilities. Anyone with a history of scientific misconduct or fraud or anyone against whom sanctions have been invoked will not participate in the study.

3.2 Institutional Review Board/Independent Ethics Committee

The IRB will review and approve all study materials including the protocol, informed consent form, and any other written information provided to subjects. A copy of the Investigator Brochure or product labeling information provided to subjects should be given to the IRB. Other information required by institutional procedures or regulatory agencies should also be given to the IRB.

3.3 Informed Consent

Informed consent requires that patients are clearly and fully informed about the purpose, risks, and any other important information related to the study in which they are agreeing to participate. The rights, safety, and well-being of individual patients take prescience over other considerations including those of scientific investigation and society.

Investigators must provide a copy of the informed consent form, signed and dated by the subject and the investigator who conducted the discussion of informed consent. The informed consent form should be written in lay language that is easy to understand and must be approved by the IRB prior to its use. All revisions to the informed consent form, which should be done when new, pertinent information

related to subject consent arises, also require IRB approval. All subjects participating in the study should be notified of the changes to the informed consent form and discuss with the investigator whether they plan to continue in the study. During the informed consent process, adequate time must be given to subjects so that they may review and ask questions about the study. The investigator should document all discussions regarding informed consent.

4 INVESTIGATIONAL PLAN

4.1 Study Design and Duration

Patients previously seen at the Contact Dermatitis and Occupational Dermatology Program at Brigham and Women's Hospital that meet the inclusion criteria will be recruited. In addition, patients will be invited to participate in the study directly during their clinical visit. Patients may be identified and provided information about the study at the time of their patch testing visits and/or follow-up appointments. Additionally, patients who have been patch tested that inform us they are not improving following the allergen avoidance recommendations may also be provided information about the study.

A cover letter describing the study, signed by PI will be sent to the subjects at least a week in advance of their scheduled study visit with the PI or Co-Investigator. In addition, an informed consent document will be sent with the letter to them to read over and discuss with family and others (including their healthcare providers). If interested in participating in the study, the subject will be asked to bring the informed consent document to the visit with the PI or Co-Investigator.

Patients identified directly during the office visit will be approached by a study staff other than PI. They will be provided with a cover letter and the informed consent document to take home and read and discuss with family members. Subsequent follow-up may include contact via mail, post or phone calls to patients to provide additional information about the study.
Patients who read the consent form at the clinic and feel comfortable enough to consent to participate in the study, may be enrolled right away.

It will be emphasized that participation is purely voluntary and will not influence the care or ability to get care within our institution any provider.

In person study visits will take place at the clinical rooms of the Center for Clinical Investigations (CCI), the Ambulatory Clinical Center at 221 Longwood Avenue. In

addition, virtual study visits will take place using Healthcare Secure Zoom. Prior to their scheduled study visits, a research assistant will prepare the administrative paperwork informed consent, information materials, prospective visit schedule and the physician questionnaires.

We will recruit 30 patients with allergic contact dermatitis 18 years of age and older up to 6 months after patch testing with a documented IGA of at least 3 at baseline and screening visits, and at least one 2+ (strong) or 3+ (extreme) reaction on patch testing to participate in this open-label pilot study. If more than one 2+ (strong) or 3+ (extreme) reactions are present, up to two may be selected for evaluation in the study. Priority will be given to nickel, fragrance mix I or II, and rubber as these allergens have been studied previously with respect to their preferential T helper cell skewing. At the initial screening visit, demographic information will be obtained, inclusion and exclusion criteria as detailed in Section 4.2 will be reviewed, and informed consent obtained for those deemed eligible for enrollment. A single subcutaneous dose of 600 mg will be self-administered at week 0 +72-120 hours and 300 mg every 2 weeks thereafter for a total 10 weeks of therapy. Subjects will be evaluated for improvement in primary and secondary endpoints using clinical examination and questionnaires during initial and follow-up visits at Week 0, Week 6, and Week 12 as per Time and Events Schedule. Patch test site reactions will also be evaluated 72 hours after the Week 0 and Week 12 visits. Skin biopsies will be taken at these two time points from both the patch test site reaction and from normal skin taken from a non-dermatitic area on the contralateral side of the body. For the Week 12 patch placement, a site contralateral to the Week 0 patch placement site will be chosen. If an area of persistent dermatitis other than the patch test site(s) is also present at week 12+72-120 hours an additional biopsy will be taken unless in an anatomic location not amenable to biopsy (face, hands, elbows, knees, genitals, feet). Serum samples will be obtained at four time-points including Week 0 (prior to patch placement), Week 0 +72-120 hours, Week 12 (prior to patch placement), and Week 12 +72-120 hours. If subjects do not mount a 2+ (strong) or 3+ extreme reaction to the tested allergens at the Week 0 +72-120 hour visit they will be discontinued from the study and will not receive dupilumab. These patients will be considered screen fails. Week 10 +72-120 hours will conclude the end of the treatment portion of the study. Week 12 +72-120 hours will conclude the subjects' participation in the study.

We developed a contingency plan in case there is a resurge of COVID, a pandemic, closure of facilities or other act of God that prevents the study visit schedule to be completed in person. In such case, we will add a virtual visit component to our in-person visits to complete some of the research activities related to that visit**.**

Please see the Time and Events Schedule for full details.

4.2 Study Population

For entry into the study, the following criteria MUST be met.

4.2.1 Inclusion Criteria

The following inclusion criteria are required for patient participation in the study:

1. At least 18 years of age

2. At least one contact allergen with a 2+ (strong) or 3+ (extreme reaction) confirmed by patch testing within 18 months of the baseline visit that can be duplicated at the initiation of the study (placement at Week 0 and patch test reaction read at Week 0 +72-120 hours).

3. Allergic contact dermatitis diagnosed clinically by the principle investigators who have expertise in allergic contact dermatitis

4. Investigator's global assessment score of at least 3 (range 0-4) at the screening and baseline visits

5. Documented recent history (within 18 months of patch testing) of inadequate response to treatment with topical medications and allergen avoidance

6. Able and willing to provide informed consent, participate in study visits, and undergo visit procedures.

4.2.2 Exclusion Criteria

Any of the following exclusion criteria would prohibit patient participation in the study:

1. Prior dupilumab use

2. Treatment with a systemic immune-regulating medication within 3 months of the baseline visit or the patient's prior patch testing, whichever is longer. Examples of these medications include azathioprine, methotrexate, mycophenolate mofetil, Janus kinase inhibitors, and phototherapy (including tanning booths). Cyclosporine or prednisone may not have been used within 1 month of the baseline visit.

3. Treatment with other biologic agents, such as TNF inhibitors, anti-IL 17 agents, anti-IL 12/23 agents, or anti-IL 23 agents, within 4 months of baseline visit or the patient's prior patch testing, whichever is longer.

4. Use of rituximab within at 6 months (or until lymphocyte counts have normalized if longer than 6 months) of the baseline visit or the patient's prior patch testing, whichever is longer.

5. Treatment with topical corticosteroids, topical phosphodiesterase inhibitors or topical calcineurin inhibitors within 1 week before the baseline visit

6. Other active conditions, such as psoriasis, that may confound clinical evaluations of dermatitis and patient-reported symptoms.

7. Increased risk of infection or reactivated infection, including history of human immunodeficiency virus, hepatitis B, hepatitis C, endoparasitic infections, receipt of a live attenuated vaccine within 3 months of the baseline visit, chronic or acute infection requiring treatment within 4 weeks of the baseline visit, immunosuppressed status (ie recurrent or resistant opportunistic infections)

8. Malignancy within 5 years of the screening visit excluding local cutaneous squamous cell carcinoma, basal cell carcinoma or cervical carcinoma in situ that has been fully treated.

9. Women who are or plan to become pregnant or breastfeed during study participation or are unable or not willing to use birth control during the study and for 4 months after the last dose of dupilumab. Options for birth control include abstinence, double barrier (ie male condom and female diaphragm), vasectomy, intrauterine device, and hormonal contraception. Females who have not had menses within 1 year of the baseline, bilateral tubal ligation, hysterectomy, and/or bilateral oophorectomy visit do not require additional methods contraception during study participation.

10. Unstable condition or status, as per study investigator's judgment, that may lead to more likely discontinuation from the study including but not limited to major, recurrent medical illnesses that may require hospital admission and/or discontinuation of dupilumab, surgery that would require discontinuation of dupilumab and/or major rehabilitation, inability to participate in all study visits and administer dupilumab.

11. Resident outside of Massachusetts, Connecticut, Rhode Island, New Hampshire, Maine or Vermont state.

12. Unable to use Zoom videoconferencing**.**

4.2.2 Discontinuation of Subjects from Treatment

Patients may withdraw from the study for any reason and at any time and will not

be subject to consequences because of their withdrawal. The investigators may also withdraw a patient from the study for any reason such as to protect patient safety, administrative changes, or protocol deviation. Patients who withdraw or are withdrawn from the study will undergo early termination study assessments.

5 TREATMENTS

5.1 Study Treatment: Dupilumab

Patients will receive dupilumab subcutaneously 300 mg every 2 weeks during the 10-week treatment period following a loading dose of 600 mg at Week 0 +72-120 hours. The study staff will demonstrate to the patient administration of study drug at Week 0 +72-120 hours through Zoom video conference and will administer the first loading dose injection at the in-person portion of the visit on the same day. The study staff will observe the patient self-administer the second loading dose injection. After the initial dose dupilumab will be self-administered by patients off-site. Injection sites may include the four quadrants of the abdomen (avoiding the umbilicus and waist), upper thigh, and upper arms. The same site should not be injected for two consecutive doses of dupilumab. A dupilumab administration log will also be provided to patients.

5.1.1 Identification

Dupilumab injection is dispensed as a 300 mg/syringe (300 mg/2 mL) for subcutaneous administration, which contains L-arginine hydrochloride(10.5 mg), L-histidine (6.2 mg), polysorbate 80 (4 mg), sodium acetate (2 mg), sucrose (100 mg), and water for injection, pH 5.9.

5.1.2 Packaging and Labeling

Dupilumab SC is supplied in a box of 2 syringes with an open-label.

5.1.3 Handling and Dispensing

Dupilumab will be stored by the study pharmacy under refrigeration (approximately 2°C to 8°C).

5.2 Drug Ordering and Accountability

5.2.1 Initial Orders

Initial dupilumab orders will be placed through the Regeneron project manager.

5.2.2 Re-Supply

Re-supply dupilumab orders will be placed through the Regeneron project manager.

5.3 Timing of Dose for Each Subject

Two doses of dupilumab, 300 mg/2 mL, will be administered subcutaneously using the prefilled syringe at week 0 +72-120 hours and one dose dupilumab, 300 mg/2 mL, will be administered subcutaneously every two weeks thereafter continuing until week 10 +72-120 hours.

5.3.1 Dose Modifications

Not applicable.

5.4 Blinding/Unblinding

Not applicable.

5.5 Concomitant Treatments

See inclusion and exclusion criteria (4.2.1 and 4.2.2) for details on concomitant treatments allowed and not allowed for study participation.

5.6 Treatment Compliance

Patients will be given a dupilumab dosing diary that will be collected at the completion of the study to monitor treatment compliance.

6 STUDY ASSESSMENTS AND PROCEDURES

6.1 Time and Events Schedule

Time and events schedule is detailed in the table below:

Visit Number	1 Screening	2 Week 0	3 Week 0 +72-120 Hours	4 Week 6	5 12 Weeks	6 12 Weeks +72-120 hours	7 Early Termination /Unscheduled Visit

Day (+/- 3 days)	-34 to 0	1	4	42	84	87	N/A
Informed eConsent	X						
Inclusion/Exclusion Criteria	X						
Medical History	X						
Prior/Concurrent Medications	X						X
Safety Assessments							
Adverse Events		X	X	X	X	X	X
Clinical Efficacy Assessments							
Patch Test Site Reaction			X			X	
IGA	X	X		X	X		X
EASI		X		X	X		X
BSA		X		X	X		X
Patient-Reported Outcomes							
DLQI		X		X	X		X
NRS Itch		X		X			X
SLEEPYQ		X		X	X		X
Distribute Diaries (Allergen Avoidance and Dupilumab Dosing)		X					
Collect Diaries (Allergen Avoidance and Dupilumab Dosing)						X	X
Laboratory Assessments							
Pregnancy Test	X	X		X	X		X
Biomarker Skin Sample			X			X*	
Biomarker Serum Sample		X	X		X	X	
Medication Dosing							
In-Office Dosing			X				
Dispense Study Medication			X	X			
Patch Testing							
Patch Test Material Placement		X			X		
Patch Test Material Removal							
Photographs							
Patch Test Site Photographs		X	X		X	X	
Dermatitis Photographs			X			X	X

*In addition to the allergen patch site and normal skin, an additional biopsy will be done on an area of persistent dermatitis if present unless in an anatomic location not amenable to biopsy (face, hands, elbows, knees, genitals, feet).

6.2 Study Materials

Dupilumab will be provided by Regeneron at no cost.

6.3 Safety Assessments

All subjects who receive a dose of dupilumab will be evaluated for safety. Our clinical trials team will provide periodic audits internally for safety assessments. The investigator will determine the severity of each adverse event as mild, moderate, severe, or very severe. The relationship between the adverse event and study drug will also be determined. Dupilumab may be discontinued due to lack of effectiveness, patient is lost-to-follow-up or withdraws consent, protocol deviation, or adverse event that may cause severe or permanent harm according to the judgment of the study investigator or an adverse event of grade 2 or more related to dupilumab defined by the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (CTCAE: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm).

Notification will be provided to Regeneron if a patient discontinues dupilumab and the reason will be recorded in the patient's medical and study records.

6.4 Efficacy Assessments

6.4.1 Primary Efficacy Assessment

The following clinical assessments will provide outcome data:

Number of patients who achieve a reduction in patch test site reactions from 2+-3+ at baseline to "?" or no reaction at week 12 +72-120 hours.

6.4.2 Secondary Efficacy Assessments

6.4.2.1 Secondary Clinical Endpoints

Secondary endpoint 1: Number of patients who achieve a reduction in investigator global assessment (IGA) from 3 or greater at screen and baseline to 0 or 1 at Week 6, and Week 12.

Secondary endpoint 2a: To quantify the inflammatory markers (Th1, Th2, Th17, Th22 immune pathways) in the blood and skin of patients before and after dupilumab. Secondary endpoint 2b: Changes in IGA from baseline to week 12. Other secondary endpoints: Change in baseline eczema-area-and-severity-index (EASI), body surface area (BSA), numerical rating scale (NRS) itch, dermatology life quality index (DLQI), and SLEEPYQ from baseline to Week 6 and Week 12.

Secondary endpoint 3: Changes in IGA from baseline to Week 6 and Week 12.

Other secondary endpoints: Change in baseline eczema-area-and-severity-index (EASI), body surface area (BSA), numerical rating scale (NRS) itch, dermatology life quality index (DLQI), and SLEEPYQ from baseline to Week 6 and Week 12.

Secondary endpoint 4: Identification and quantification of the most prevalent T cell clones in the skin before therapy and how those clones change after therapy using high-throughput sequencing of the TCRB gene.

6.4.2.2 Secondary Non-Clinical Endpoints

Serum samples will be collected at baseline and week 12 prior to patch placement for analysis of inflammatory cells and markers. Additionally skin and serum

samples will be collected for analysis of inflammatory cells and markers 72 hours after patch placement at baseline and week 12. We will also collect one additional biopsy from an area of persistent, chronic dermatitis if present after the 10-week course of dupilumab. Skin biopsies will be collected at 72 hours after patch testing from the sites of allergen placement and will be initially placed in saline. Blood samples will also be collected on the same day. DNA and RNA will be isolated from PBMCs and 300 um of tissue. The isolated DNA will be subjected to TCR HTS of the TCRB gene before and after therapy. We will determine the CDR3 sequence of the top 5 most prevalent clones in the skin of patch tested skin before therapy, which likely represents at least one of the pathogenic T cell clones specific to the allergen. We will quantify the presence and abundance of those same clones in the blood and patch tested skin after therapy as a measure of T cell trafficking (ie ability of those same T cell clones being able to reenter skin at site of specific allergen placement may be inhibited after dupilumab therapy). The RNA will be subjected to multiplex gene expression analysis of 594 human immune genes to specifically characterize the Th1, Th2, Th17, and Th22 skewing of the immune microenvironment as well as quantify the expression of alarmins and proteases known to be important in the elicitation phase of allergic contact dermatitis. These gene signatures and immune cell subtypes analyses will be confirmed at the protein level with multispectral immunofluorescence on the skin and flow cytometry in the blood.

Novel Technologies to be used: High throughput sequencing of the T cell receptor CDR3 region (TCR HTS) is a powerful technology that measures the CDR3 sequences and the relative frequencies of all T cells in a biologic specimen, allowing study of individual T cell clones as well as studies of the entire T cell population in a patch tested skin lesion. Tyramide signaling amplification immunostaining/multi-spectral imaging and automated image analysis. This technology provides visualization of up to 6 proteins of interest for state-of-the-art phenotypic and functional analyses compared to standard IHC. Tyramide signaling amplification (TSA) allows for sequential immunostaining of the same tissue section for up to six different markers. We will utilize the revolutionary Perkin-Elmer Mantra Quantitative Pathology Imaging Microscope which scans each slide and extracts the data from each individual fluorescence channel so that each marker can be displayed in separate images. This imaging technology allows the equivalent of flow cytometry profiling on tissue sections and it works particularly well on FFPE samples, as shown below in Preliminary Studies. NanoString-based technologies. NanoString-based gene expression analysis using their human immunology panel allows robust and direct quantification of 594 mRNA sequences in FFPE tissues, allowing quantitative gene profiling studies utilizing our skin biopsy specimens. This panel allows for immune cell subset analysis of Th1, Th2, Th17 and Th22 cells by using a subset of genes whose expression is largely specific to certain immune cell populations. The underlying assumption from this

model is that these characteristic genes are expressed only in that cell type and are expressed at the same level in each cell (these are essentially reference genes specific to individual cell types). Under this model, a cell type's abundance can be measured as the average logscale expression of its characteristic genes that are concordant within the sample. This allows an unbiased comparison of relative abundance of cell types between sample groups. It also allows for comparisons between cell types.

7 ADVERSE EVENT REPORTING

7.1 Adverse Events

Adverse events include any new or worsening of a medical condition. Adverse events are not limited to those related to study drug.

7.1.1 Serious Adverse Events

A serious adverse event may include those that result in death, life-threatening events, inpatient hospitalization or prolonged hospitalization, disability/incapacity, congenital anomaly/birth defect, important medical event, suspected transmission of an infectious agent through the study drug, and the case of the current study pregnancy.

7.1.2 Non-serious Adverse Events

A non-serious adverse event includes adverse events that are not considered serious adverse events.

7.1.3 Assignment of Adverse Event Intensity and Relationship to Dupilumab

Adverse events are graded as mild (grade 1) for those that are noticeable but easily tolerated; moderate (grade 2) for those that cause enough discomfort that there is some interference with usual activity; severe (grade 3) for those that lead to an inability to perform usual activities; very severe (grade 4) for those that are debilitating causing significant incapacitation even with symptomatic treatment. An adverse event may be related (reasonable causal relationship between dupilumab administration and the event) or not related (no reasonable causal relationship between dupilumab administration and the event). A reasonable causal relationship denotes that there are facts or other arguments suggesting a positive causal relationship.

7.2 Collection and Reporting

When documenting adverse events the diagnosis if preferable to symptoms. Information that should be collected for adverse events include: onset, duration, intensity, and seriousness of the event, relationship between the event and dupilumab, resulting action taken, and any required treatments (should be documented in the medical record).

7.2.1 Serious Adverse Event Collecting and Reporting

Serious adverse event collection should begin at the time that informed consent is obtained. All serious adverse events must be collected and reported, including those that occur within 30 days after the final dupilumab dose. If a serious adverse event occurs after this period, but is related to dupilumab or procedures performed in the study these should also be reported. If there is uncertainty whether an event is a serious one, a serous adverse event report should be completed. All serious adverse events, whether related or not related to dupilumab, must be reported to Regeneron within 24 hours.

7.2.2 Non-Serious Adverse Events (NSAEs) Collecting and Reporting

Non-serious adverse event collection should begin at the time that dupilumab is first administered. These events should be monitored until they resolve or become stable. Non-serious adverse events may also become serious adverse events.

7.3 Pregnancy

Pregnancy should be considered a serious adverse event in the case when a subject is found to be pregnant while taking dupilumab.

8 DATA MONITORING COMMITTEE

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

Open label, pilot design: Descriptive statistics to report baseline subject characteristics A sample size of 11 participants achieves 80% power to detect a mean change of -1.0 (i.e., one less reaction on average) with an estimated standard deviation of 1.0 using a two-sided Wilcoxon test with significance level

α=0.05 and assuming the actual distribution of change is normal. Upweighting of 10-25% would add conservatively to our ability to detect a change and is reflected in the final sample size estimation of 14 subjects. Therefore, we need a minimum of 14 subjects who complete the study to have enough statistical power. In order to accomplish this, we will aim to enroll a maximum of 30 subjects.

9.2 Populations for Analyses

Study population will be subjects ages 18 years and older of any race/ethnicity and gender, with clinically diagnosed allergic contact dermatitis who have not improved following allergen avoidance and topical therapies within 6 months of patch testing.

9.3 Endpoint Definitions

Investigator's Global Assessment (IGA) score

The investigator's global assessment is a physician-reported global assessment of disease activity (range 0-4) with 0 being clear and 4 being severe.

Body Surface Area (BSA)

The body surface area is a physician-reported measure of the amount of disease involvement. The patient's palm size approximates 1% of body surface area involvement.

Eczema Area and Severity Index (EASI) score

The eczema-area-and-severity-index score is a composite score of disease severity and extent of disease distribution. It was initially developed for evaluation of eczema. Disease severity (range 0-3; 0 being no disease and 3 being severe disease) is a measure of redness, thickness/induration, scratching, and lichenification. Each characterization is measured separately for body regions (head and neck, trunk, upper extremities, and lower extremities) to calculate a regional score. The total score is a sum of the four body regions (range 0-72).

Numerical Rating Scale (NRS) itch

The numerical rating scale for itch is a patient-reported measure of itch (range 0-10) with 0 being no itch and 10 being the worst imaginable itch.

Dermatology Life Quality Index (DLQI)

The Dermatology Life Quality Index is a 10-question, patient-reported instrument to assess impact of skin diseases on patient quality of life.

SLEEPY-Q

The Sleepy-Q is a patient-reported questionnaire that consists of 18 questions. It assesses three dimensions of sleep in patients with inflammatory skin conditions: sleep disturbance, causes of sleep disturbance and impairment related to sleep disturbance.

9.4 Analyses

9.4.1 Demographics and Baseline Characteristics

Demographics and baseline disease characteristics including age, gender, ethnicity, age of onset of allergic contact dermatitis, body areas of dermatitis involvement, prior treatments for allergic contact dermatitis (including prescription therapies and prior recommended allergen avoidance strategies) will be documented at the initial screening visit.

9.4.2 Safety Analyses

Subjects will be questioned about experiencing any adverse events at every follow-up visit.

9.4.3 Efficacy Analyses

At the time of enrollment, clinical parameters will be measured and recorded including their prior positive patch test reactions type and strength, IGA, EASI, BSA, DLQI, NRS itch, and SLEEPYQ. Patients will also be provided with a diary to record their allergen avoidance strategies and dulpilumab dosing. A sample of blood will also be taken. At the week 0 +72-120 hours study visit their patch test site reaction will be recorded. Samples of skin will be placed on sterile, saline soaked gauze and transported back to the Clark laboratory at 221 Longwood Avenue. One portion of the skin will be embedded in OCT and frozen at -20°C for future cryosectioning and the second portion of the skin will be placed in culture for the isolation of skin T cells. T cells and dendritic cells will then be analyzed by molecular and cellular techniques including TCR sequencing, nanostring, and multiplex fluorescence. A second sample of blood will also be taken. DNA will be extracted from blood samples and TCR sequencing will be done through collaborators at Adaptive as a fee for service arrangement. Isolated DNA from biopsies and blood samples will be sent, these will be coded with no identifiable information shared. Any leftover samples may be stored for future projects if a subject provides this optional consent**.**

The primary clinical efficacy endpoint will be the number of patients who achieve a reduction in patch test site reactions from 2+-3+ at baseline to "?" or no reaction at week 12 +72-120 hours. Secondary endpoints will include number of patients who achieve a reduction in investigator global assessment (IGA) from 3 or greater at screen and baseline to 0 or 1 at Week 6, and Week 12; quantification of the inflammatory markers (Th1, Th2, Th17, Th22 immune pathways) in the blood and skin of patients before and after dupilumab; changes in IGA from baseline to week 12. Other secondary endpoints: Change in baseline eczema-area-and-severity-index (EASI), body surface area (BSA), numerical rating scale (NRS) itch, dermatology life quality index (DLQI), and SLEEPYQ from baseline to Week 6 and Week 12; changes in IGA from baseline to Week 6 and Week 12; changes in baseline eczema-area-and-severity-index (EASI), body surface area (BSA), numerical rating scale (NRS) itch, dermatology life quality index (DLQI), and SLEEPYQ from baseline to Week 6 and Week 12;i dentification and quantification of the most prevalent T cell clones in the skin before therapy and how those clones change after therapy using high-throughput sequencing of the TCRB gene.

10 STUDY MANAGEMENT

10.1 Compliance with the Protocol

10.1.1 Compliance with the Protocol and Protocol Revisions

Study procedures are performed according the protocol, approved by the IRB. Signed approval by the IRB should be sent to the study sponsor. If there is an immediate hazard to study subjects, deviation or change in the protocol may be made prior to IRB approval. The deviation or change should be submitted as soon as possible to the IRB for review, the study sponsor, and any regulatory authorities as required by local regulations.

If there is a study amendment that significantly changes the study design and/or potential subject risk, the informed consent form must be revised and approved by the IRB, informed consent must be obtained from all subjects in the study for those affected by the amendment and who agree to continue their participation, and used for all new subjects.

10.2 Records Retention

10.2.1 Records Retention

All study documents will be retained for the maximum period required by applicable regulations/guidelines or institution procedures, whichever is longer.

10.2.2 Study Drug Records

The research pharmacy will maintain a record of dupilumab study drug.

11 LIST OF ABBREVIATIONS

ACD	Allergic Contact Dermatitis
BSA	Body Surface Area
GCP	Good Clinical Practice
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Quality of Life Index
EASI	Eczema Area and Severity Index
HTS	High Throughput Sequencing
ICH	International Conference on Harmonization
IGA	Investigator's Global Assessment
IRB	Internal Review Board
NRS	Numerical Rating System
TNF	Tumor Necrosis Factor

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