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MARINER Study: Mechanisms of benefit of IL4Ra inhibition in CRSwNP and Aspirin-Exacerbated Respiratory Disease (AERD)

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Study Protocol and Statistical Analysis Plan

Mass General Brigham

Institutional Review Board
Intervention/Interaction Detailed Protocol

Principal Investigator: Tanya M. Laidlaw, MD

Project Title: MARINER Study: Mechanisms of benefit of IL4Ra inhibition in CRSwNP and Aspirin-Exacerbated Respiratory Disease (AERD)

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1. Background and Significance

1.2 **A lack of mechanistic knowledge limits therapeutic options for CRSwNP and AERD.** Aspirin-exacerbated respiratory disease (AERD) is a disease characterized by chronic rhinosinusitis with nasal polyposis (CRSwNP), loss of sense of smell, difficult-to-control asthma, and reactions to aspirin and all cyclooxygenase-1 inhibitors. AERD affects 7-14% of adults with asthma,[1] or about ~1 million patients in the U.S. AERD is associated with significant medical resource consumption and detrimental effects on patient quality-of-life and productivity. There are few effective therapies for patients with either aspirin-tolerant CRSwNP or AERD, and neither the cause of the disease nor the mechanism by which any of our existing therapies actually work, are known. Both aspirin-tolerant CRSwNP and AERD are typified by sinonasal dysfunction, asthma, eosinophilic respiratory tract inflammation, overproduction of cysteinyl leukotrienes (cysLTs), and persistent release of mast cell products, along with chronic mucous production and loss of epithelial cell barrier integrity within the sinuses.

Our preclinical and in vitro data suggest that the abnormal function of mast cells and epithelial cells may cause the type 2 inflammation that contributes to the pathogenesis of CRSwNP. Additional insights into disease mechanism are needed to identify improved and targeted CRSwNP therapies.

1.3 **Biology of IL-4Rα in CRSwNP and AERD.** Interluekin-4 **(**IL-4) and Interleukin-13 (IL-13) are cytokines that drive type 2 inflammation and the resulting inflammatory response. They share overlapping functions due to their use of a shared receptor subunit (IL-4Rα). IL-4Rα signaling promotes goblet cell metaplasia, chemokine expression, Immunoglobulin E (IgE) class-switching, tissue fibrosis, and mast cell hyperplasia, reflecting actions across multiple cell types.[2] The efficacy of IL-4Rα inhibition with dupilumab for the treatment of severe asthma[3] and CRSwNP[4] reflects the broad importance of IL-4Rα pathways in type 2 inflammation-associated diseases. However, the key cellular targets responsible for the efficacy of dupilumab and inhibition of IL-4Rα remain largely unknown. AERD participants have very high levels of type 2 inflammation-associated biomarkers, suggesting influences of IL-4Rα signaling.[5]

1.4 **Preclinical and Clinical Experience.** Dupilumab is a human monoclonal IgG4 antibody that inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab is approved by the Food and Drug Administration (FDA) for the treatment of CRSwNP and severe asthma and has been shown to be particularly efficacious to treat patients with CRSwNP and the constellation of symptoms that constitute AERD. The robust response to dupilumab in AERD, and the expression of IL-4Rα on multiple relevant cell types, provide the opportunity to identify the cell targets that are most essential for IL-4Rα to drive inflammation, and are most responsible for causing the underlying inflammation that leads to AERD. Blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13 cytokine-induced inflammatory responses, including the release of proinflammatory cytokines, chemokines, nitric oxide, and IgE, and several of these outcomes may contribute to therapeutic benefit in CRSwNP in general and in AERD specifically. However, it is not yet known which of these immunologic changes are the most important improvements that lead to the clinical benefit that patients with CRSwNP experience in response to dupilumab treatment.

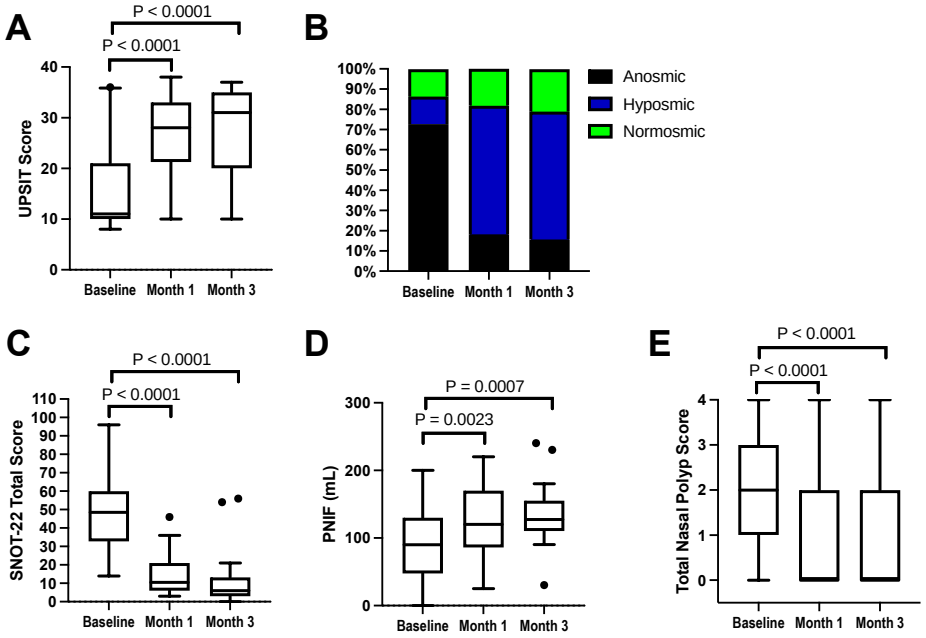


Figure 1: Dupilumab-induced changes in clinical upper respiratory outcomes. Smell identification level as measured by UPSIT is shown as raw scores (A) or as summarized levels of anosmia, hyposmia, or normosmia (B) at the pre-dupilumab baseline, and after 1 and 3 months of treatment with dupilumab. SNOT-22 scores (C), PNIF (D), and TPS (E) are shown for the same timepoints. Data in A, C-E are shown as Tukey's box-and-whisker

In a large, phase 3 study of patients with uncontrolled moderate-to-severe asthma, dupilumab was shown to reduce annualized severe asthma exacerbations by almost 50%, improve lung function, and improve asthma-related quality of life.[6] In two international phase 3 studies including 724 patients with CRSwNP treated with dupilumab vs. placebo, patients that received dupilumab had improved nasal polyp size (LS mean change from baseline in bilateral nasal polyp score), reduced need for systemic corticosteroids and sinus surgery, improved sinonasal symptoms/nasal congestion, and improved sense of smell compared to placebo.[7] A nested analysis of 19 AERD patients receiving either dupilumab or placebo in a phase 2a, randomized controlled trial (NCT01920893) showed that for the patients with AERD who had greater sinus opacification, worse sense of smell, and poorer lung function at baseline than did the aspirin-tolerant patients with CRSwNP, dupilumab specifically showed improvement in both upper and lower airway outcomes, suggesting particular efficacy in this difficult-to-treat subgroup of patients.[8] However, it is not yet known why patients with AERD respond so well to dupilumab, or whether a more narrowly targeted therapeutic medication could work just as well.

1.5 **Efficacy and mechanistic insights from open-label pilot study:** We previously followed 22 patients with AERD and CRSwNP who initiated dupilumab treatment, as an early observational pilot study to investigate the efficacy of dupilumab in patients with AERD. The patients were treated with dupilumab for 3 months for clinically indicated treatment of their asthma and/or CRSwNP. Upper and lower airway symptoms, smell identification, nasal flow, and lung function were assessed prior to initiation of dupilumab and at one and three months after initiation of dupilumab. As shown in **Figures 1-2**, there were striking and rapid improvements in all clinical parameters tested, with most patients reporting clinical improvement in their symptoms within the first 1 month of treatment, including improvement in sense of smell, sinonasal symptoms, asthma symptoms and lung function. Dupilumab treatment led to decreases led to decreases in nasal and urinary leukotriene E4 (LTE4) and as the majority of the cysteinyl leukotriene production in patients with AERD is presumed to be derived from mast cells, this suggests an effect of dupilumab on decreasing mast cell activation in the respiratory tissue.

Further, with our pilot study, we also investigated possible surrogate biomarkers for epithelial barrier integrity. Nasal albumin levels significantly fell after 1 month of dupilumab, suggesting an improvement in the "leakiness" of the epithelial barrier. Therefore, dupilumab-induced improvement in the epithelial barrier function for these patients could play a large role in its clinical efficacy but has not been fully explored.

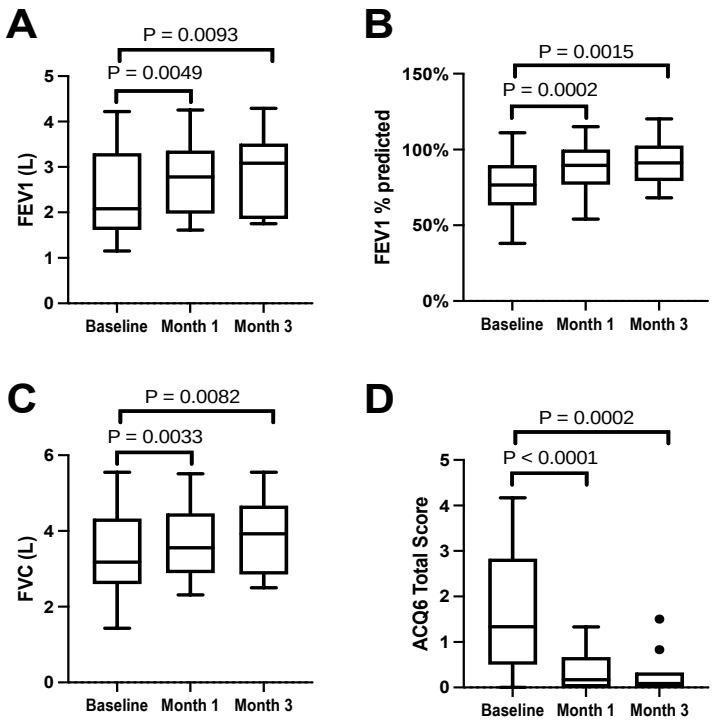


Figure 2: Dupilumab-induced changes in pulmonary outcomes. Pulmonary function and asthma control as measured by liters of FEV1 (A), FEV1 % predicted (B), liters of FVC (C), and ACQ6 (D) are shown at the pre-dupilumab baseline and after 1 and 3 months of treatment with dupilumab. Data are shown as Tukey's box-and-whisker plots.

Given the widespread expression of IL-4Rα on multiple potentially relevant cell types, the rapid clinical improvement noted in the early pilot study is likely due to several concomitant mechanistic changes, including a reduction in cysteinyl leukotrienes, an increase in local nasal PGE_2, and an improvement in airway epithelial barrier integrity. However, the exact effector cells most influenced by IL-4Rα are not yet known. While there are multiple potential mechanisms by which dupilumab may lead to clinical improvement in patients with CRSwNP, with or without AERD, it is not yet known which mechanistic changes are the principal drivers of disease resolution, nor which are the result of direct vs indirect effects of IL-4Rα blockade. These determinations will require further analyses, which are the focus of this proposed study.

The remarkable therapeutic improvement provided by IL-4Rα inhibition with dupilumab in patients with AERD may be due in large part to the drug's anti-mast cell and pro-epithelial cell effects. Furthermore, it is suspected that an early dupilumab-induced decrease in local nasal mast cell mediators and increase in epithelial barrier integrity will correlate with later clinically-measurable therapeutic improvement, which would add greatly to the existing knowledge of dupilumab's mechanism of therapeutic benefit.

The proposed research addresses a significant clinical and research need for asthma, CRSwNP, and AERD in the following ways. **(1)** First, it would identify the specific mechanism of benefit afforded by dupilumab treatment for patients with CRSwNP with or without AERD, and yield new insights into CRSwNP with or without AERD pathobiology, deepening the understanding of this disease and its treatment. **(2)** Second, it would establish whether specific mast cell-related or epithelial cell-related biomarkers of therapeutic response to dupilumab (exploratory mechanistic objectives) could be of high clinical significance. The successful completion of this observational study would represent a step forward in the knowledge, and clinical management, of CRSwNP with or without AERD, and would lay the groundwork for a future large prospective clinical trial of dupilumab specifically targeted at patients with CRSwNP with or without AERD.

2. Specific Aims and Objectives

2.2 Study Hypotheses

The **clinical hypothesis** is that treatment with anti-IL-4Rα (dupilumab) will provide symptomatic improvement for patients with CRSwNP with or without AERD by the 8-week treatment timepoint, with some early and rapid onset of clinical effectiveness starting at the 2-week treatment timepoint. The **mechanistic hypotheses** are that the rapid onset of clinical improvement provided by IL-4Rα inhibition with dupilumab in CRSwNP with our without AERD is due in large part to the drug's direct effects on both mast cells and epithelial cells, and that dupilumab will decrease the activation of or total cell burden of respiratory tissue mast cells and will increase the integrity of the nasal epithelial barrier in participants with CRSwNP with or without AERD by the 8-week treatment timepoint. For some patients, we expect that the immunologic changes and the clinical improvement will be evident by the 2-week treatment timepoint. With this study we aim to understand which effector cell pathways and mediators are the dominant drivers of chronic respiratory inflammation in these patients.

2.3 Study Objective(s)

The **primary clinical objective** is to determine if 8 weeks of treatment with anti-IL-4α (dupilumab) decreases the extent of nasal polyp burden and improves the sense of smell in patients with CRSwNP with or without AERD in a prospective open-label observational study of CRSwNP with or without AERD patients who are initiating dupilumab as part of their standard medical care for the treatment of CRSwNP, as approved by the FDA. Although dupilumab is not FDA-approved specifically to treat AERD, as all patients with AERD have chronic rhinosinusitis with nasal polyposis, and the dupilumab given during this study will have been prescribed as an add-on maintenance treatment for inadequately controlled chronic rhinosinusitis with nasal polyposis, the use of dupilumab will be for an FDA-approved indication.

The **secondary clinical objectives** are to determine the effects of 8 weeks of treatment with dupilumab on additional clinical measures of disease severity in CRSwNP with or without AERD, including nasal congestion, respiratory-related quality of life, lung function, and asthma control.

The **exploratory clinical objectives** are to determine the effects of 2 weeks of treatment with dupilumab on nasal polyp burden, sense of smell, nasal congestion, respiratory-related quality of life, lung function, and asthma control.

The **exploratory mechanistic objectives** are to determine if 2 or 8 weeks of treatment with dupilumab induces immunologic changes in any of the following, and to determine if any of those immunologic changes correlate with changes in any of the clinical endpoints listed above, with a particular interest in any immunologic changes that correlate with treatment-induced improvement in sense of smell (UPSIT):

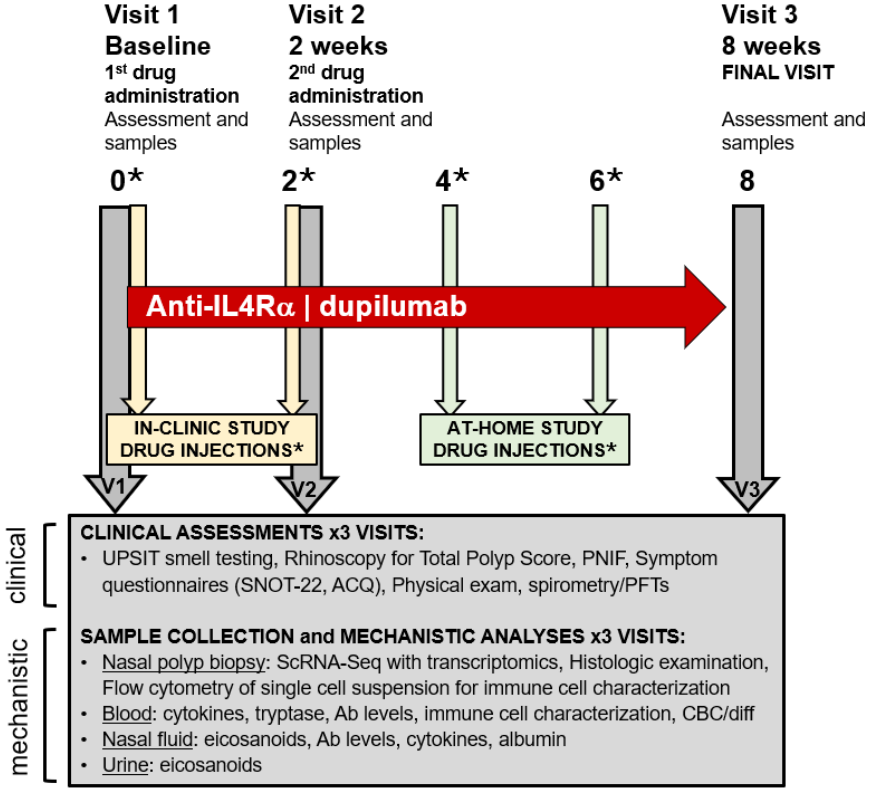
1. Mast cell and epithelial cell function within the sinuses.
2. Levels of circulating immune cells (eosinophils, basophils, ILC2s, Th2 cells, and mast cell progenitors)
3. Eosinophil burden in the nose and blood.
4. Sinus tissue barrier integrity and immune cell composition.
5. Tuft cell number and activation within the sinuses.

3. General Description of Study Design

The study involves an 8-week open-label observational study of subcutaneous dupilumab (300mg) for patients with CRSwNP with or without AERD who are initiating treatment with dupilumab as part of their standard medical care for severe CRSwNP **(Figure 3)**.

Participants will receive 4 total doses of study drug during the study period, with each dose administered every 2 weeks, as per usual prescribing practices. Doses 1 and 2 will be administered at the clinical research center (Visits 1-2), with in-person patient education so that the patients then feel comfortable administering the rest of their treatment doses at home, which is the standard practice in our Allergy and Immunology Clinic at the BWH AERD Center. Doses 3 and 4 will be self-administered by the patients at home at weeks 4 and 6. There will be full

Figure 3. Study schema summary for the 8-week observational trial. Participants will receive dupilumab for 8 weeks, with sample collections at Baseline (V1), Week 2 (V2), and Week 8 (V3).



clinical assessments and biospecimen collections at Baseline (Visit 1), Week 2 (Visit 2), and Week 8 (Visit 3).

The study population will consist of individuals with CRSwNP with or without AERD referred to the BWH Asthma Center, BWH Allergy or Otolaryngology clinics, or the BWH AERD Center for evaluation and treatment of nasal polyposis. 33 individuals with CRSwNP with or without AERD will be enrolled in this study with the anticipation that there will be 30 participants who complete 8 weeks of therapy. All participants will have a clinical history consistent with CRSwNP with or without AERD (asthma, nasal polyposis, and a history of a reaction to a nonselective cyclooxygenase (COX) inhibitor). Participants may be on standard therapy for persistent asthma, which may include some combination of inhaled glucocorticoids, oral glucocorticoids, long- and short-acting β-agonists, and $CysLT_1R$ antagonists, and standard therapy for CRSwNP, which may include daily intranasal steroids (INS).

Following completion of the study, the patients will continue on their every-other-week dupilumab therapy at home as prescribed and will follow-up with their prescribing physician.

4. Subject Selection

4.2 Recruitment methods

Our study population will consist of individuals with CRSwNP with or without AERD referred to the Brigham and Women's Hospital (BWH) AERD Center, BWH Asthma Center, Allergy clinics, or otolaryngology clinics for evaluation and treatment. Patients seen in evaluation for CRSwNP with or without AERD in either the Allergy or ENT Clinics at BWH for whom treatment with dupilumab is clinically indicated will be identified by their allergist or rhinologist, and if interest is expressed in the initiation of dupilumab use and in participation in the study, they will be offered the opportunity to take home the Consent Form and call back if they wish to participate. Only patients who meet criteria for the FDA-approved use of dupilumab (every-other-week 300mg subcutaneous injections) for standard-of-care treatment of uncontrolled CRSwNP will be approached and offered participation. Scheduling of the first study visits will occur only after the patient has received their first shipment of their prescribed dupilumab (standard clinical practice is for approved patients to have their dupilumab doses shipped to their homes by a specialty pharmacy on a monthly basis, and to then bring their dupilumab to a scheduled clinic for an in-person teaching visit for the first two administered injections).

Rationale for Study Population

Since CRSwNP and AERD are virtually always an adult-onset disease, adults will comprise all of the study participants. CRSwNP and AERD affects both sexes and all races; no exclusions will be made based on sex or ethnicity. Both CRSwNP in general and AERD specifically are slightly more common in women than in men, so we anticipate that there will be ample representation of women. The proportion of minorities in our clinical practice reflects the patient mix at BWH, roughly 10% Latino, 20% African American, 10% Asian or Pacific Islander.

Inclusion Criteria

Only individuals who meet <u>all</u> of the criteria will be eligible for enrollment.

1. Participant must be able to understand and provide informed consent

2. Age between 18 and 75 years
3. Physician-diagnosed CRSwNP, with or without AERD.
4. Visible nasal polyps bilaterally on otoscope physical exam at the time of screening.
5. For patients with asthma, their asthma must be stable, no glucocorticoid burst for at least 4 weeks prior to screening, and no hospitalizations or ER visits for asthma for at least the prior 3 months).
6. Prescribed dupilumab, 300mg subcutaneous injections every-other-week for the FDA-approved treatment of uncontrolled CRSwNP, with either insurance approval for drug coverage or patient self-pay for standard-of-care use of dupilumab.
7. Confirmation that participant will continue their intranasal steroid (INS) regimen or lack thereof throughout the study period. For patients currently using INS, this is defined as consistent (daily) use for at least 4 weeks prior to screening. For participants with asthma who require daily controller therapy with an inhaled corticosteroid (ICS), they should have a consistent inhaled corticosteroid regimen for the 4 weeks prior to screening, with confirmation that participant will continue with the same inhaled steroid regimen throughout the study period.
8. No current smoking (not more than one instance of smoking in the last 3 months), to be assessed per participant report with a Screening questionnaire.
9. For females: Practicing FDA-approved methods of birth control for the duration of the study. Female participants of childbearing potential must have a negative pregnancy test upon study ***entry***

Exclusion Criteria

Individuals who meet any of these criteria will ***not*** be eligible for enrollment

1. Inability or unwillingness of a participant to give written informed consent or comply with study protocol
2. Use of respiratory investigational drugs within 12 weeks of screening.
3. Use of any biologic agent within 4 months prior to screening.
4. Use of systemic (enteral or injected) glucocorticoids within 4 weeks prior to screening.
5. History of any sinonasal surgery within 4 months prior to screening.
6. Current use of zileuton (which blunts the production of cysLTs and may confound biologic treatment-induced changes in cysLTs and mast cell activation)
7. Current use of high-dose aspirin therapy (no more than 325 mg aspirin per day will be allowed)
8. Pregnant, nursing, or planning to become pregnant
9. Known hypersensitivity to dupilumab or any of its excipients
10. Known current helminth infection
11. Planning to receive any live vaccines during the study period
12. History of malignancy within the last 5 years prior to screening, except for completely treated in situ carcinoma of the cervix and/or completely treated and resolved nonmetastatic squamous or basal cell carcinoma of the skin.
13. Evidence of acute or chronic infection requiring systemic treatment with antibacterial, antiviral, antifungal, antiparasitic, or antiprotozoal medications within 4 weeks before screening.
14. Suspicion of acute coronavirus disease 2019 (COVID-19) infection at screening or known exposure to acute COVID-19 within 2 weeks prior to screening; known history of COVID-19 infection within 4

weeks prior to screening; history of requiring mechanical ventilation or extracorporeal membrane oxygenation secondary to COVID-19 within 6 months prior to screening; participants who have had a known COVID-19 infection prior to screening who have not yet sufficiently recovered to participate in the procedures of a clinical trial.

15. Past or current medical problems, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality of data obtained from the study.

5. Subject Enrollment

Pre-screening. All subjects will be pre-screened over the phone prior to scheduling the formal Screening/Visit 1 to ensure that they understand and are interested in participation, meet all patient-reportable inclusion criteria, meet criteria for the FDA-approved use of dupilumab for treatment of CRSwNP, and have been prescribed dupilumab by their treating physician (allergist or rhinologist) as part of their standard medical care.

Once prescription approval has been confirmed and the first shipment of dupilumab has been received by the patient, they will be scheduled for their first study visit. This will serve as both the Screening Visit and, provided that the patient signs consent to proceed and all inclusion criteria are met, also the baseline Visit 1 at which baseline assessments will be collected and the first dupilumab injection will be administered.

At the Screening/Visit 1, the study will be thoroughly reviewed and written consent will be obtained by a study physician. The research study will be explained in lay terms to each potential research participant. The potential participant will sign an informed consent form before undergoing any study procedures. The participants will be given ample time to consider their participation before making their final decision. No electronic consenting procedures will be used. All participants will be adults and no participants will be enrolled who are unable to provide consent.

As several of the investigators conducting this study are recognized as specialists in the management of patients with CRSwNP with or without AERD, it is likely that a high proportion of patients with CRSwNP with or without AERD will be identified from within their own clinical practice and referral base at BWH. To minimize the possibility that these patients will feel obligated to participate because it is their own physician who is asking, those investigators will initially present the study during a regular clinical patient visit and will offer a Consent Form to take home, and then ask a physician study colleague or study coordinator to re-contact the potential study participant. Further, for patients for whom their primary physician prescribing dupilumab is also a study investigator, efforts will be made so that the study physician at the at the Screening/Visit 1 who reviews and explains the consent form is not the patient's primary treating/prescribing physician, but is one of the other physician study colleagues.

6. STUDY PROCEDURES

6.1 Detailed description of all study visits, procedures, and data collections

Screening and baseline Visit 1: The purpose of this visit is to confirm eligibility to continue in the study, and if confirmed, to proceed with baseline assessments and dupilumab administration.

The following procedures, assessments, and laboratory measures will be conducted first, in order to determine participant eligibility:

- A physical exam to confirm presence of visible bilateral nasal polyps
- Spirometry to assess lung function
- Urine pregnancy, if indicated
- Assessment of asthma control (ACQ score, which evaluates asthma control over the proceeding 1 week)
- Assessment of nasal symptoms (SNOT-22 score, which assesses nasal symptoms over the proceeding 2 weeks)
- Assessment of sense of smell impairment [University of Pennsylvania Smell Identification Test (UPSIT)]

Provided that the participant meets eligibility requirements, the following additional procedures and assessments will then be conducted as the baseline assessments:

- Peak Nasal Inspiratory Flow (PNIF).
- Blood will be drawn for CBC/differential and the cellular profiling and activation assays.
- A urine sample will be collected for eicosanoid metabolites (if urine sample was already collected for pregnancy testing, this sample can also be used for the research assessments).
- Nasal fluid for cytokine, Ab levels, albumin, and eicosanoid measurements, and nasal epithelial cell brushings for cell phenotyping and characterization.
- Rhinoscopy will be performed for Total Polyp Score (TPS) measurement, along with a nasal polyp biopsy for transcriptomic analysis, histologic examination, and flow cytometry for immune cell characterization.
- Patients will be counseled that it is recommended to avoid administration of live vaccines during treatment with dupilumab.
- Participants will then receive their first dupilumab (300mg subcutaneous injection) dose administered at the end of Visit 1, followed by a 30-minute observation period.

Visit 2: Two weeks after dose 1 (Visit 1), participants will come into the clinical research center for their 2-week assessment, 2nd administration of dupilumab, and sample collection (Visit 2).

The following procedures, assessments, and laboratory measures will be conducted:

- Interval history, physical exam, ACQ-6, SNOT-22, UPSIT, and spirometry will be recorded, along with PNIF.
- Blood will be drawn for CBC/differential and the cellular profiling and activation assays.
- A urine sample will be collected for pregnancy (if indicated) and eicosanoid metabolites.

- Nasal fluid for cytokine, Ab levels, albumin, and eicosanoid measurements, and nasal epithelial cell brushings for cell phenotyping and characterization.
- Rhinoscopy will be performed for Total Polyp Score (TPS) measurement, along with a nasal polyp biopsy for with transcriptomic analysis, histologic examination, and flow cytometry for immune cell characterization.
- Administration of the second injection of dupilumab at the end of Visit 2.
- Participants will be instructed on proper technique for at-home administration for their next 2 doses of dupilumab.

Phone Call 1: There will be a telephone encounter (Phone Call 1) +/- 2 days prior to planned administration of dose 3 of the study medication to remind participants of upcoming scheduled dose for at-home administration at week 4.

Phone Call 2: There will be a telephone encounter (Phone Call 2) +/- 2 days prior to planned administration of dose 4 of the study medication to remind participants of next scheduled dose for at-home administration at week 6.

Visit 3: Eight weeks after dose 1 (Visit 1), participants will come into the clinical research center for their final study visit for 8-week assessment and sample collection (Visit 3).

The following procedures, assessments, and laboratory measures will be conducted:

- Interval history, physical exam, ACQ-6, SNOT-22, UPSIT, and spirometry will be recorded, along with PNIF.
- Blood will be drawn for CBC/differential and the cellular profiling and activation assays.
- A urine sample will be collected for pregnancy (if indicated) and eicosanoid metabolites.
- Nasal fluid for cytokine, Ab levels, albumin, and eicosanoid measurements, and nasal epithelial cell brushings for cell phenotyping and characterization.
- Rhinoscopy will be performed for Total Polyp Score (TPS) measurement, along with a nasal polyp biopsy for with transcriptomic analysis, histologic examination, and flow cytometry for immune cell characterization.
- Participants will be instructed to continue their regular every-other-week schedule of at-home administration as per their prescribing clinician's recommendation, and to schedule a follow-up clinical appointment with their primary provider within the next 2 months.

Unscheduled visits

If disease activity increases or other concerns arise between regularly scheduled visits, participants will be instructed to contact study personnel and may be asked to return to the study site for an "unscheduled" visit.

If any participants with asthma experience an exacerbation of their asthma (an asthma exacerbation will be defined as the development of an increase in symptoms of cough, chest tightness, or wheezing requiring treatment with oral glucocorticoids) during the study, he or she will be advised to notify the clinical center as soon as possible, preferably within 72 hours of the event.

If a participant needs to stop dupilumab prior to the end of the study, we will ask them to come in for one final visit. During this visit we will ask the participant to return all unused medication, perform a physical examination, obtain spirometry testing, and obtain one final pregnancy test (if applicable). If the participant does not return for this final visit, a study investigator will attempt to speak to the participant by telephone, and if unreachable at their preferred contact number, a clear message regarding the importance of follow-up and study investigator contact information will be left. If a participant experiences an adverse event that results in discontinuation from the study, we will follow the participant until the event is resolved or until the participant is discharged to alternate care.

Table of study visits and procedures:

Study Phase		**Treatment Period**				
Week		0	2	4	6	8
Visit		Screen/ V1	V2			V3
Consent, Verify eligibility		+				
Phone Call				+	+	
Dupilumab injection in clinical research center		+	+			
Dupilumab injection at home (self-injection)				+	+	
Physical Exam and Spirometry/PFTs		+	+			+
Symptom questionnaires (ACQ, SNOT-22, etc)		+	+			+
Olfaction testing (UPSIT)		+	+			+
Nasal rhinoscopy for Total Polyp Score		+	+			+
Nasal polyp biopsy and nasal fluid & cell collection		+	+			+
Urine for:	Pregnancy	+	+			+
	Mechanistic studies	+	+			+
Blood for:	CBC/differential	+	+			+
	Mechanistic studies	+	+			+
Adverse event assessment		+	+			+

6.2 Definition of primary and secondary outcomes/endpoints

The **co-primary clinical outcomes** are the change from baseline in the rhinoscopic Total Polyp Score (TPS) and in the sense of smell (UPSIT) at Week 8.

The **secondary clinical outcomes** are the change from baseline at Week 8 in:

- Peak Nasal Inspiratory Flow (PNIF) as a measure of nasal congestion
- Quality-of-life (22-Item Sino-Nasal Outcome Test [SNOT-22])
- Lung function (FEV1)
- Asthma control (ACQ-6).

The **exploratory clinical outcomes** are the change from baseline at Week 2 in:

- Total Polyp Score (TPS)
- Sense of smell (UPSIT)
- Peak Nasal Inspiratory Flow (PNIF) as a measure of nasal congestion
- Quality-of-life (22-Item Sino-Nasal Outcome Test [SNOT-22])
- Lung function (FEV1)
- Asthma control (ACQ-6).

The **exploratory mechanistic outcomes** are change from baseline at Weeks 2 and 8 in the following mechanistic assays, and correlation between those immunologic changes and changes in the clinical endpoints listed above, with a particular interest in any immunologic changes that correlate with treatment-induced improvement in sense of smell (UPSIT):

1. Mast cell and epithelial cell function within the sinuses.
2. Eicosanoid levels, including cysLTs (LTC4, LTD4, and LTE4), prostaglandin D2 metabolites, and prostaglandin E2 metabolites will be measured in both nasal fluid and in urine by mass spectrometry, as markers of mast cell activation and epithelial cell function.
3. Tryptase levels in the serum, as a systemic marker of mast cell burden and activation, will also be measured, as will IgE levels in nasal fluid and plasma, by Enzyme Linked Immunoassay (ELISA).
4. Levels of circulating immune cells (eosinophils, basophils, ILC2s, Th2 cells, and mast cell progenitors).
5. Numbers and activation levels of eosinophils, basophils, ILC2s, Th2 cells, and mast cell progenitors in the blood will be assessed by flow cytometry.
6. Eosinophil burden in the nose and blood.
7. Nasal fluid eosinophilic cationic protein (ECP) will be analyzed by ELISA as a measure of local eosinophil burden and activity.
8. Plasma levels of IL-5 and plasma and nasal levels of IL-13 and CCL26 will be measured by ELISA as markers of treatment response and as a possible surrogate biomarker of mucosal eosinophil infiltration.
9. Sinus tissue barrier integrity and immune cell composition.
10. Sinus tissue epithelial integrity, goblet cells, and eosinophil burden will be assessed by histologic examination of nasal polyp biopsies, and nasal fluid albumin will be assessed as a marker of plasma exudate and epithelial barrier function.
11. Nasal polyp mast cell, epithelial cell, and B cell/plasma cell populations from nasal polyp biopsies will be assessed by scRNA-seq and by flow cytometry, and any changes in T cell populations and ILC2s will be assessed by scRNA-seq.
12. In addition to RNA sequencing, genetic material will be available for genome sequencing should that become relevant to scientific hypotheses.

6.3 Description of planned genetic research.

13. Blood and tissue samples will be taken, from which cell populations will be isolated for genetics studies. The relevant tissue specimens and isolated cell populations for the genetics studies will be labeled with a unique numerical identification code. Subject name or other identifiers will not be placed on the genetics specimens. The key to the code will connect the subject's name to the subject's study information and specimens. The key to the code will be kept in a separate electronic database file and subject's genetic specimens will always remain coded and their identity will remain confidential.
14. Transcriptomic expression analyses are planned as part of this protocol. Whole genome sequencing may be performed on blood or nasal polyp cells as well, should the mechanistic results suggest that this would be relevant to scientific hypotheses. Information from this testing will not be shared with the patients or their families, as it is experimental and not considered part of clinical care. Furthermore, the results of any genetic testing in this study will not be entered into the participant's medical records.
15. No immortalized cell lines are expected to be created from this study.

6.4 Description of plans for sending and/or receiving specimens or data with research collaborators outside Mass General Brigham or with NIH.

16. De-identified samples of urine, blood, nasal fluid, and nasal biopsies will be stored and analyzed at BWH. Some subsets of samples may be sent for additional research analysis at specialized cores outside of Mass General Brigham, but no identifying information will be sent with the samples that could ever link the specimens to the individual subjects.
17. All clinical data will also be submitted to the NIAID Division of Allergy, Immunology and Transplantation-funded data repository known as the Immunology Database and Analysis Portal (ImmPort, www.immport.org), per NIAID stipulations, once the data for all prespecified outcomes has been collected, and the database has been cleaned and locked.
18. All transcriptomic data generated will be anonymized and shared by depositing these data into ImmPort, in accordance with the NIH Genomic Data Sharing (GDS) Policy.

6.5 Biospecimen and source data storage.

Biospecimen Storage. The following biospecimen types will be obtained with the intention to be analyzed within the context of this protocol, but in some cases, there may be excess sample volume left over after the specified analyses. In those cases, the excess volume would be stored within our divisional laboratory freezers.

19. Nasal fluid
20. Nasal polyp biopsies
21. Urine
22. Plasma
23. Serum
24. Immune cells isolated from the peripheral blood

Sample storage data will be accessible only to study investigators and study staff at BWH via clinical sample management software. Before patient visits, anticipated samples will be entered into the database and associated with the patient ID and the date and number of the visit so that labels for sample containers can be printed and applied. When samples are received, the entries will be updated to reflect the actual type and number of samples obtained, any aliquots of samples to be made for storage purposes will be accounted for, labels will be printed for the aliquot tubes, and space in a dedicated -80°C freezer will be assigned. This process will permit tracking of the history of all samples, as well as multi-parameter searches to identify and locate samples with the characteristics and thus minimize temperature fluctuations in the freezer when samples are sought.

Source Data. The Principal Investigator will keep accurate records to ensure that the conduct of the study is fully documented. Data derived from source documents will be transferred to protocol-specific CRFs. Hard copy results of the following clinical evaluations and clinical laboratory evaluations will be maintained in the participant's protocol-specific binder, housed on the 5th floor at BTM:

25. Patient medical histories, concomitant medications, adverse event forms (results written onto CRF)
26. CBC/differential (printed copy)
27. Pulmonary Function Tests (PFTs) (printed copy)
28. Pregnancy test (results written onto CRF by coordinator/investigator)
29. Physical exam (results written onto CRF by coordinator/investigator)
30. Patient questionnaires (results written onto CRF by patient)
31. Details of which biologic specimens collected at each visit (written onto CRF by coordinator/investigator)

The applicable clinical study data will be transferred to a password-secured REDCap database on a dedicated server. Data derived from research laboratory evaluations (flow cytometry, eicosanoid and cytokine levels, cellular assays) will be stored as a hard copy (as applicable) within laboratory notebooks, or within the appropriate assay-specific software program as required for each type of analysis.

6.6 Remuneration.
Participants will be compensated $100 per completed study visit, for a maximum total payment of $300 if all 3 study visits are completed.

7. Risks and Discomforts

7.1 Risks of dupilumab

The safety of dupilumab has been studied in 739 adult participants with atopic dermatitis, 617 children <18yo with atopic dermatitis, 2888 adult and adolescent participants with asthma, and 722 adult patients with CRSwNP. Hypersensitivity reactions (anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred very rarely following administration of dupilumab, reported in <1% of participants who received dupilumab in clinical trials. These reactions generally occur quickly after administration, but in some instances, have had a delayed onset. Conjunctivitis occurred more frequently in chronic rhinosinusitis with nasal polyposis (CRSwNP) participants who received dupilumab.

There were no cases of keratitis reported in the CRSwNP development program. Among asthma participants, the frequencies of conjunctivitis and keratitis were similar between dupilumab and placebo. There have been several reports of increased blood eosinophils in participants treated with dupilumab, which will be monitored at each of the visits. Cases of eosinophilic pneumonia were reported in adult patients who participated in the asthma development program and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis (EGPA) have been reported with dupilumab in adult patients who participated in the asthma development program as well as in adult patients with comorbid asthma in the CRSwNP development program. A causal association between dupilumab and these conditions has not been established. Overall, for patients with asthma, the most common adverse reactions (incidence ≥1%) are injection site reactions, oropharyngeal pain, and eosinophilia. For patients with CRSwNP, the most common adverse reactions (incidence ≥1%) are injection site reactions, eosinophilia, insomnia, toothache, gastritis, arthralgia, and conjunctivitis.

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to dupilumab during pregnancy. Available data from case reports and case series with dupilumab use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, dupilumab may be transmitted from the mother to the developing fetus. In an enhanced pre- and post-natal developmental study, no adverse developmental effects were observed in offspring born to pregnant monkeys after subcutaneous administration of a homologous antibody against IL-4Rα during organogenesis through parturition at doses up to 10-times the maximum recommended human dose.

7.2 Risks of Other Protocol-Specified Medications

Risks of corticosteroids. All participants will have been on intranasal corticosteroids prior to enrollment in the study, and some will have been maintained on inhaled corticosteroids. Corticosteroid dosing will not be changed for this study. Nonetheless, participants will be informed that when taken at high doses for extended periods, inhaled corticosteroids can produce hoarseness, sore throat, and thrush, as well as cause adrenal gland suppression, weight gain, bruising of the skin, and diabetes. Inhaled corticosteroids have also been associated with reduced growth velocity in children, but participants in our study will all be age 18 and over.

Risks of topical lidocaine. Intranasal topical lidocaine is routinely used to partially numb the lining of the nose/sinus prior to nasal rhinoscopy. Although the incidence of adverse effects with topical lidocaine are quite low, caution will be exercised to use the lowest, most effective dose, and doses will be administered by a trained otolaryngologist. Possible side effects include irritation, application site erythema, application site burning, or application site pruritus.

7.3 Risks of Study Procedures

Risk of blood draw. Risks associated with drawing blood include some pain when the needle is inserted. There is a small risk of bruising and/or infection at the place where the needle enters the arm. Some people may experience lightheadedness, nausea, or fainting. It is possible to develop an infection, but this is rare and can be treated.

Risk of spirometry. Occasionally, individuals may develop a slight dizzy feeling and/or temporary cough and/or chest discomfort when performing breathing tests. These tests are used in hundreds of laboratories throughout the world on a daily basis without harmful effects.

Risks of nasal fluid and cell collection. The nasal procedures that we will use to collect fluid and cells from the nose may be uncomfortable. Local irritation of the nostril is possible which could include blood-tinged discharge that is expected to resolve on its own. Risk for infection will be minimized by using sterile absorbent material for each collection. Common risks associated with collection of fluid and nasal cells from the nasal cavity are mild burning, pain, stinging, and nasal irritation.

Risks of nasal polyp biopsy. Nasal polyp tissue (or area of hyperplastic nasal epithelium) biopsies will be obtained during the rhinoscopy procedure by a trained Ear, Nose and Throat doctor (ENT)/otolaryngologist. Under topical local anesthesia (which will have been used for the rhinoscopy at the visit), a directed biopsy of the polyp tissue or area of hyperplastic nasal epithelium to produce a specimen measuring from 2 mm to 1 cm of nasal polyp tissue will be obtained under endoscopic visualization. There is a low risk of bleeding, pain, and bruising at the site and, rarely, infections that may require antibiotic treatment. There may be some soreness around the biopsy site for 1-2 days after the anesthetic wears off, but the inflammatory nasal polyp tissue in CRSwNP is essentially non-innervated, so pain is very unlikely.

Risks of urine collection. There are no known risks for urine collection.

Risks of UPSIT smell test. The smell test involves scratch and sniff of forty microencapsulated odors and individuals, on occasion, may develop a headache depending on strength of sense of smell. This test is used frequently to assess anosmia and there are no lasting harmful effects.

Risks of ACQ-6 and SNOT-22 questionnaires. There are no risks associated with questionnaires.

7.4 Risks to privacy. The risk of loss of confidentiality will be minimized by the use of a unique study number and password protected and encrypted databases. Data extracted for analysis will also be de-identified and personal identifiers will only be available to study staff.

7.5 Relation of procedures to standard clinical care. This study will align closely with the standard of care for the treatment of patients with AERD who are initiating treatment with dupilumab. Spirometry and rhinoscopy are routine procedures used during follow-up evaluations for patients with AERD, as are in-person visits with a provider at the time of first injections of dupilumab in order to provide teaching and guidance.

8. Benefits

Dupilumab is known to provide clinical improvement (improved asthma control and reduced nasal polyposis) to the majority of patients with CRSwNP with or without AERD, and as such most patients in this study will be expected to derive clinical improvement of their symptoms during the study period.

However, as the dupilumab administered during the study period of the observational study would have otherwise been available clinically for the participants, there is no direct clinical benefit to the patients through their participation in this study.

The results from this study should yield important information pertaining to the pathophysiology of CRSwNP and AERD, and by providing a greater understanding on how dupilumab works, they should shed light on how to improve therapies for patients with CRSwNP with or without AERD and respiratory inflammation.

9. Statistical Analysis

9.1 Statistical Overview. This is a single-center open-label observational study of dupilumab treatment of patients with CRSwNP. This study will plan to enroll 33 study participants, to meet a target sample size of 30 to complete the 8-week study, with the objective to determine the underlying mechanistic changes induced by anti-IL-4α (dupilumab) that contribute to its quick-onset clinical efficacy in CRSwNP. All participants treated with at least one dose of dupilumab will be included in the analysis.

9.2 Analysis Plan

Primary Analysis of Primary Clinical Endpoint(s)/Outcome(s). Data will be summarized using descriptive statistics (N, Mean, Standard Deviation, Minimum, and Maximum) for TPS and UPSIT at baseline, week 2, week 8, a difference from baseline to week 2, and difference from baseline to week 8. We will use a paired t-test to assess the change from baseline to week 8 in TPS and UPSIT. We will check distributions of TPS and UPSIT before we apply paired t-tests. If the data has non-normal distribution, we will apply Wilcoxon signed-rank tests.

Analyses of Secondary and Other Clinical Endpoint(s)/Outcome(s). Data will be summarized using descriptive statistics (N, Mean, Standard Deviation, Minimum, and Maximum) for PNIF, SNOT-22, FEV1, and ACQ-6 at baseline, week 2, week 8, a difference from baseline to week 2, and difference from baseline to week 8. We will use a paired t-test to assess the change from baseline to week 8 in PNIF, SNOT-22, FEV1, and ACQ-6. We will check distributions of PNIF, SNOT-22, FEV1, and ACQ-6 before we apply paired t-tests. If the data has non-normal distribution, we will apply Wilcoxon signed-rank tests.

Analyses of Exploratory Mechanistic Endpoint(s)/Outcome(s). All numerical outcomes from mechanistic assays will also be summarized using descriptive statistics (N, Mean, Standard Deviation, Minimum, and Maximum) at baseline, week 2, week 8, a difference from baseline to week 2, and difference from baseline to week 8. We will use a paired t-test to assess the change from baseline to week 8 (or week 2) in mechanistic assay data. We will check distributions of data from mechanistic assay before we apply paired t-tests. If the data has non-normal distribution, we will apply Wilcoxon signed-rank tests.

The longitudinal analysis will use a restricted maximum likelihood-based repeated measures approach with a random intercept model. Visit will be analyzed as weeks since baseline. Mechanistic outcomes are expected to be skewed. If necessary, we will use log transformation for the outcomes. An unstructured covariance structure will be used to model the within-participant errors. If the analysis fails to converge, the other structures will be tested. The covariance structure converging to the best fit, as determined by Akaike's information criterion, will be used. The analysis will use all measurements

obtained over the 8-week study period, including those from any patients who discontinue study medication. We will assume that missing endpoints are "missing at random." Significance tests will be based on least squares means using a two-sided $\alpha = 0.05$ with standard error. Assumptions for models will be assessed by examining plots of the residual values. Further, a relationship between the change in each specific mechanistic measurement and the change in each clinical outcome will also be analyzed using a restricted maximum likelihood-based repeated measures approach with a random intercept model.

Descriptive Analyses. The number of participants reaching the milestones in the trial will show the number screened and reaching each visit, or study close, and the number dropped out and for what reasons. We will examine all treatment-emergent adverse events (AEs) by the type of event, as well as by body system class. The safety analysis population will include all participants who receive at least 1 dose of dupilumab as part of this study.

9.3 Sample Size Considerations and Power Calculations

With a sample size of 30 patients, and based on data from our prior observational pilot study with dupilumab, we estimate the below two primary co-endpoints:

10. **UPSIT:** Based on our preliminary observational pilot study with dupilumab, and the inclusion criteria for this study, we expect participants to have an average baseline UPSIT score of 10.2 ±1.6 (standard deviation, STDEV). We observed an average UPSIT score of 26.3 ± 6.9 in our pilot trial with dupilumab at month 1 (16.1-point improvement ± 7.3 STDEV). With our proposed sample size, we will have 100% power to detect an improvement of 10 points (10 more scents identified) at 0.025 level of significance, and 99.9% power to detect an improvement of 8 points (half of the difference found in the preliminary dupilumab pilot study).

11. **TPS:** Based on our preliminary observational pilot study with dupilumab, and the inclusion criteria for this study, we expect participants to have an average baseline TPS score of 5.5 ± 1.7 STDEV. We observed an average TPS score of 2.9 ± 2.5 in our pilot trial with dupilumab at month 1 (2.6-point improvement ± 1.5 STDEV). With our proposed sample size, we will have 100% power to detect an improvement in TPS of 2 points at 0.025 level of significance, and 98.9% power to detect an improvement of 1.3 points (half of the difference found in the dupilumab pilot study).

10. Monitoring and Quality Assurance

10.1 Overview

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. Adverse events that are classified as serious according to the definition of health authorities will be reported promptly to the Institutional Review Board (IRB).

This is an observational study evaluating the efficacy and mechanism of action of clinically indicated dupilumab. Safety will be assessed by the Principal Investigator and the study co-investigators. Even though this is an observational study and dupilumab is standard of care, safety will be assessed as-needed throughout the study period by monitoring of any adverse events (AEs). Participants will be instructed to call their individual physicians or the study physician if they experience any adverse event. The Principal Investigator and the co-investigators will review data and safety monitoring on a twice-yearly basis. The study will be terminated when the target enrollment is reached.

10.2 Definition of Adverse Event (AE). Defined as any untoward or unfavorable medical occurrence associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research.
For this study, an adverse event will include any untoward or unfavorable medical occurrence associated with:

- Dupilumab: any AEs occurring during the treatment period once the first dose of dupilumab is administered and for 14 days after completion or discontinuation from the study.
- Study mandated procedures:
    - Blood draw: Any AE occurring within 24 hours after blood collection.
    - Nasal biopsy/sample collection: Any AE occurring within 24 hours after procedure.

10.3 Unexpected Adverse Event. An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator Brochure or the Informed Consent Form, or is not listed at the specificity, severity, or rate of occurrence that has been observed.

10.4 Serious Adverse Event (SAE). An adverse event or suspected adverse reaction is considered "serious" if it results in any of the following outcomes (21 CFR 312.32(a)):

- Death.
- A life-threatening event: An AE is considered "life-threatening" if its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

10.5 Grading and Attribution of Adverse Events

Grading Criteria

The study site will grade the severity of adverse events experienced by the study participants according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. This document (referred to herein as the NCI-CTCAE manual) provides a

common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. The NCI-CTCAE has been reviewed by the Principal Investigator and has been deemed appropriate for the participant population to be studied in this protocol.
Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

Grade 1 = Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 = Moderate; minimal, local or noninvasive intervention indicated.
Grade 3 = Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated.
Grade 4 = Life-threatening consequences; urgent intervention indicated.
Grade 5 = Death related to AE.

Events grade 2 or higher will be recorded on the appropriate AE paper case report form for this study.

10.6 Attribution Definitions

The relationship, or attribution, of an AE to the study or study procedure(s) will be determined using the definitions provided in the below Table:

Code	Descriptor	Relationship (to primary investigational product and/or other concurrent mandated study therapy or study procedure)
UNRELATED CATEGORY		
1	Not Related	The adverse event is clearly not related: there is insufficient evidence to suggest a causal relationship.
RELATED CATEGORIES		
2	Possibly Related	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
3	Related	The adverse event is clearly related.

10.7 Collection and Recording of Adverse Events

Collection Period. Adverse events will be collected from the time of enrollment – which begins once the participant signs the consent form – through 14 days after completion of the study, or through 14 days after he/she prematurely withdraws (without withdrawing consent) or is withdrawn from the study if the participant has received at least one dose of dupilumab.

Collecting Adverse Events. Adverse events (including SAEs) may be discovered through any of these methods:

- Observing the participant.
- Interviewing the subject with specific questions about whether there has been any change in health status.
- Receiving an unsolicited complaint from the participant.
- Notification through the hospital medical record

Recording Adverse Events. Throughout the study, the investigator will record adverse events and serious adverse events on the appropriate AE/SAE paper CRF regardless of the relationship to study

therapy regimen or study procedure. Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or until the end of study participation, or until 30 days after the participant prematurely withdraws (without withdrawing consent)/or is withdrawn from the study, whichever occurs first.

10.8 Reporting of Adverse Events to the IRB
The investigators shall report adverse events, including expedited reports, in a timely fashion to the IRB in accordance with applicable regulations and guidelines. A cumulative report of all adverse events will be submitted annually to the IRB at continuing review. Adverse events that are unexpected and related/possibly related to the research will be reported to the IRB as an Expedited Safety Report within 5 working days/7 calendar days of the date the investigator first becomes aware of them.

10.9 Pregnancy Reporting
The Principal Investigator shall be informed immediately of any pregnancy in a study participant. A pregnant participant shall be instructed to stop taking dupilumab and contact their primary prescribing physician to discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant participant shall continue until the conclusion of the pregnancy.
All pregnancy complications that result in a congenital abnormality, birth defect, miscarriage, or medically indicated abortion will be considered a Severe Adverse Event.

10.10 Reporting of Other Safety Information
An investigator shall promptly notify the MGB IRB when an "unanticipated problem involving risks to participants or others" is identified, which is not otherwise reportable as an adverse event.

10.11 Study Stopping Rules. The Principal Investigator may terminate this study at any time. Reasons for termination may include but are not limited to the incidence or severity of AEs in this study indicating a potential health hazard to participants or unsatisfactory participant enrollment. Any serious and/or persistent noncompliance by the investigator with the protocol, or other local applicable regulatory guidelines in conducting the study may also be grounds for termination of the study. The Principal Investigator will promptly inform all other investigators conducting the study if the study is suspended or terminated for safety reasons and will also inform the IRB of the suspension or termination of the study and the reason(s) for the action.
Study enrollment, dupilumab administration, and study procedures will be suspended pending review of all pertinent data by the Principal Investigator and the IRB, if any one of the following occurs:

1. If any death occurs that is designated as related to dupilumab or to a study procedure.
2. If 3 CRSwNP enrolled trial participants experience serious non-fatal AEs related to dupilumab, or to a study procedure.

10.12 Participant Stopping Rules and Withdrawal Criteria. Participants may be prematurely terminated from the study for the following reasons:

1. The participant elects to withdraw consent from all future study activities, including follow-up.
2. The participant is "lost to follow-up" (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed, which will include at least 3 phone calls and at least 3 emailed attempts at contact).
3. The participant dies.

4. The Investigator no longer believes participation is in the best interest of the participant.
5. Individual safety stopping rules:
    a. Participant becomes pregnant during the study period.
    b. A participant requires treatment with systemic (oral or injected) glucocorticoids during the study period.

10.13 Monitoring of source data.
As this is an observational study, monitoring of source data and recordkeeping will be done internally. Quarterly Quality Management review activities will be completed every 3 months by the lead clinical study coordinator, and will be documented on a QM Quarterly Participant Data Review Tool:

- Review 100% of the consents that were executed since the previous Quarterly review, so that all consents are reviewed once.
- Review laboratory checklists and specimen storage logs for completeness and confirm that all protocol-required lab tests were performed.
- Review all AEs to ensure that they have been identified, recorded, and reported properly and within the specified timelines.
- Review source documentation CRFs to confirm that all entries have been signed and dated.
- All discrepancies identified will be discussed with the Principal Investigator for resolution.

Annual Quality Management review activities will be completed every 12 months by the lead clinical coordinator, and will be documented on the QM Annual Review Tool:

- Training Logs will be reviewed annually to verify training is current and properly documented.
- The Regulatory Binder materials, including licenses and certifications will be reviewed and kept up to date.

11. Privacy and Confidentiality

☒ Study procedures will be conducted in a private setting
☒ Only data and/or specimens necessary for the conduct of the study will be collected
☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
☒ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies

- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
- ☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
- ☐ Additional privacy and/or confidentiality protections

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