Title:	**Efficacy of dupilumab on facilitated food introduction in Eosinophilic Esophagitis**
Short Title	Dupilumab Food Introduction in Eosinophilic Esophagitis
Drug or Device Name(s):	Dupilumab
FDA IND	Not applicable
Regulatory Sponsor:	Children's Hospital of Philadelphia
eIRB Number	19416
Protocol Date:	December 29, 2022
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Amendment 2 Date:	August 3, 2022
Amendment 3 Date:	October 6, 2022
Amendment 4 Date:	

Sponsor CHOP

NCT Number: NCT05247866

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TABLE OF CONTENTS

Abbreviations and Definitions of Terms

°C	Degrees centigrade
AE	Adverse event
EGD	Esophagogastroduodenoscopy
EoE	Eosinophilic Esophagitis
EREFS	EoE Endoscopy Reference Score
Eos	Eosinophils
GCP	Good Clinical Practice
HPF	High Power Field
ICH	International Conference on Harmonization
IgE	Immunoglobulin E
PEESS	Pediatric Eosinophilic Esophagitis Symptom Score
PPI	Proton Pump Inhibitor
QOL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SOC	Standard of Care
T2	Type 2
TCS	Topical corticosteroids
TEAE	Treatment-emergent adverse event

ABSTRACT

Context:

Eosinophilic Esophagitis is a food driven non-IgE mediated disease involving eosinophils and type 2 inflammation. Current therapies include diet and the off-label use of medications including proton pump inhibitors, topical steroids, or biologics. Food elimination creates a decrease quality of life in many children. The goal of the study is to examine a T2 inhibitor (dupilumab) can allow successful reintroduction of allergic EoE foods into the diet.

Objectives:

Evaluate the efficacy of Dupilumab, a humanized anti-IL4 receptor alpha monoclonal antibody to allow Eosinophilic Esophagitis trigger foods into a diet based on symptoms and histologic endpoints

Study Design:

Open label pilot exploratory study

Setting/Participants:

This will be a single outpatient site at Children's Hospital of Philadelphia.

There will be 30 patients ages 6 to 25 years of age with food induced Eosinophilic Esophagitis.

Study Interventions and Measures:

Study drug: Dupilumab

Main study outcome measures:

Primary Efficacy Endpoint: The primary efficacy endpoint will be the change in peak eosinophil counts on esophageal biopsies between 1st and 2nd endoscopy after food introduction in the same patient

- Eosinophils per high power field in the esophagus after food introduction
- Eosinophilic Esophagitis symptom score measured by validated measure
- Esophageal compliance measured by Endoflip

PROTOCOL SYNOPSIS

Study Title	Dupilumab for Facilitated food introduction in Eosinophilic Esophagitis
Funder	Development funds (Donated medication from Regeneron and Sanofi-Pasteur)
Clinical Phase	Not applicable
Study Rationale	Eosinophilic esophagitis (EoE) is a chronic, debilitating, allergic/immune-mediated disease due to chronic esophageal inflammation with the development of dysphagia that affects food intake and quality of life. The disease is characterized by symptoms related to esophageal dysfunction and by eosinophil-predominant inflammation of the esophageal mucosa. While eosinophils are present in specific regions of the gastrointestinal (GI) tract, they are not normally found in the esophagus. Patients with EoE demonstrate esophageal tissue infiltration of significant numbers of eosinophils and other pro-inflammatory cells characterized by an enrichment of CD4+ T regulatory and type 2 cytokine producing effector type 2 T helper (Th2) cells. This infiltrating cellular profile along with over expression of cytokines, particularly interleukin-13 (IL-13) and interleukin-5 (IL-5), strongly suggests that EoE is a type 2 cell-mediated inflammatory disease. The treatment options for EoE include diet avoidance, and off-label use of topical steroids or proton pump inhibitors. Diet avoidance can be successful in eliminating symptoms and leading to normalization of the esophageal eosinophilia. However, six-food elimination diet which has success rate of 70% and elemental diet with a success rate of 90% have a tremendous amount of patient and family burden. Patients have a very restricted diet with increased costs to the family and reduced quality of life. The new biologics, in particular, dupilumab has shown to high rate of clinical and histologic remission in 2/3 of patients in treatment of EoE in adolescents and adults. Dupilumab is approved for the treatment of atopic dermatitis and asthma for children greater than or equal to 6 years of age. The goal of this study is to show that foods can be safely added to diet when on dupilumab without exacerbation of Eosinophilic Esophagitis when on standard of care treatment for EoE.
Study Objective	To determine if dupilumab can allow EoE trigger foods without inducing flares of EoE (histological or symptomatic)

Study Endpoint(s)	**Primary** - The primary efficacy endpoint will be the change in peak eosinophil counts on esophageal biopsies between 1st and 2nd endoscopy after food introduction in the same patient. **Secondary** - Maintenance of resolution (<15 eosinophils/HPF on peak measurements) of eosinophilia observed on esophageal biopsies - Maintenance of remission (<6 eosinophils/HPF on peak measurements) - Change in mean esophageal eosinophil count from baseline to the end of treatment. - Change in symptoms scores at the end of treatment compared to baseline - Interval change on a validated endoscopic scoring system, EREFS - Interval change on esophageal compliance and distensibility measured by EndoFlip - Interval change in mRNA transcriptome profile (esophageal tissue), Th2 phenotype (peripheral blood), blood eosinophilia, and total serum IgE. - Change in the Eosinophilic Esophagitis Quality of Life Score from baseline to the end of treatment
Test Article(s) *(If Applicable)*	Dupilumab (anti-IL4 receptor alpha)
Study Design	Open label exploratory pilot study
Subject Population **key criteria for Inclusion and Exclusion:**	**Inclusion Criteria** 1) Subjects age 6 – 25 years of age 2) Diagnosis of Eosinophilic Esophagitis 3) History of endoscopy with a peak count of >15 eosinophils per high powered field meeting consensus criteria for Eosinophilic Esophagitis[1] 4) History of either milk, egg, soy, or wheat induced EoE based on the following criteria in the last two years

	a) Addition of a single food lead to exacerbation of esophageal eosinophilia (increase of greater than 15 eos/hpf) or b) Removal of a single food lead to normalization of biopsy (esophageal eosinophilia showed less than 6 eos/hpf) AND c) History of either milk, egg, soy, or wheat induced EoE based on introduction of the food and symptoms in the last 12 months 5) Maintained on stable dose of PPI throughout the trial **Exclusion Criteria** 1. Patients with other Eosinophilic Gastrointestinal disease 2. Tracheo-esophageal fistulas, inflammatory bowel disease, Barrett's disease, or other significant inflammatory disease of the gastrointestinal tract 3. Biopsy evidence of eosinophilic infiltration in any other organ system 4. History of significant esophageal procedures e.g., sclerotherapy or esophagectomy 5. Systemic immunosuppressant usage in prior 3 months 6. Narrow caliber esophagus defined as the inability to pass a 9.5 mm endoscopy into the esophagus 7. IgE mediated reaction to food (milk, egg, soy, or wheat) being introduced in the last 12 months 8. No change in the dose of swallowed steroids for Eosinophilic Esophagitis for 2 months prior to starting the study and throughout the study (their current standard of care EoE treatments)
Number Of Subjects	30 patients
Study Duration	Each subject's participation will last 52 weeks
Study Phases **Disease Control** **Food introduction**	1) The first phase is the initial disease control in patients with Eosinophilic Esophagitis. Subjects will be treated with dupilumab for 12 weeks (per current proposed dosing in EoE clinical trials)

	a. At the end of the 12 weeks, subjects will have endoscopy showing resolution of EoE 2) **Food introduction:** If subjects do not have active esophageal biopsies (defined by greater than 15 eos/hpf) and have decreased symptoms per EoE symptom score, the subjects will continue dupilumab at current dosing regiment a. They will introduce one food (per food introduction guideline) for 12 weeks, then, upper endoscopy with biopsy will be done to examine EoE disease status b. If biopsies are normal, second food can be added, final endoscopy will be performed at week 51 to determine the stability of food introduction on dupilumab i. If a 3rd food was shown to be causative, it can be added at week 38.
Efficacy Evaluations	Esophageal Biopsy (Eosinophils/high power field) Esophageal Symptom Scores
Pharmacokinetic Evaluations	Not applicable
Safety Evaluations	Safety measures including symptom score, adverse events from dupilumab and endoscopies will be collected at each visit.
Statistical And Analytic Plan	The primary statistical efficacy endpoint will be tested using a Paired T-test on the change in peak eosinophil counts on esophageal biopsies between 1st and 2nd endoscopy after food introduction in the same patient. If peak eosinophil counts do not satisfy the assumption of normality, instead the Wilcoxon Signed-Rank test will be used for the primary.
DATA AND SAFETY MONITORING PLAN	The principal investigator will be responsible for the safety and monitoring of the study and data validation of the study.

TABLE 1: SCHEDULE OF STUDY PROCEDURES

Study Phase	**Disease Control**				**Food introduction**												**Follow-up**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6***	**7***	**8**	**9**	**10***	**11***	**12**	**13**	**14***	**15***	**16**	**17**
Study weeks	**1**	**3**	**8**	**12**	**13**	**15**	**20**	**25**	**26**	**28**	**33**	**38**	**39**	**41**	**46**	**51**	**52**
Informed Consent/Assent	X																
Review Inclusion/Exclusion Criteria	X																
Demographics/Medical History	X																
Physical Examination	X	X	X	X	X	X		X	X	X		X	X	X		X	X
Vital Signs: BP, HR, RR	X	X	X	X	X	X		X	X	X		X	X	X		X	
Height and Weight	X	X	X	X	X	X		X	X	X		X	X	X		X	
EGD and biopsy				X				X[a]				X[a]				X[a]	
EREFS				X				X[b]				X[b]				X[b]	
EoE Symptom Score	X	X	X	X	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X
EoE QOL	X			X				X				X					X
Food Introduction[#]					X				X				X				
Pregnancy Test	X																
Prior/Concomitant Medications	X																
Research laboratory	X			X				X				X				X	
CBC (safety)	X			X				X				X				X	

T cell phenotype, PBMC RNAseq	X			X				X				X				X	
Dispense Study Drug	X	X	X	X	X	X		X	X	X		X	X	X			
Drug Compliance		X	X	X	X	X		X	X	X		X	X	X		X	
Adverse Event Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

EREFS-EoE Endoscopy Reference Score

EoE QOL-Eosinophilic Esophagitis Quality of Life measure

*Visits can be done via remote research visit

a-EGDs are standard of care biopsies for food introduction

b-SOC procedures

Food Introduction

Foods in phase 1 will be introduced as one serving size at week 13. If biopsy at week 25 are less than 6 eosinophils/HPF, the subjects will have one of 2 options

- Increase the serving size to 2 servings a day or
- Add an additional EoE trigger food

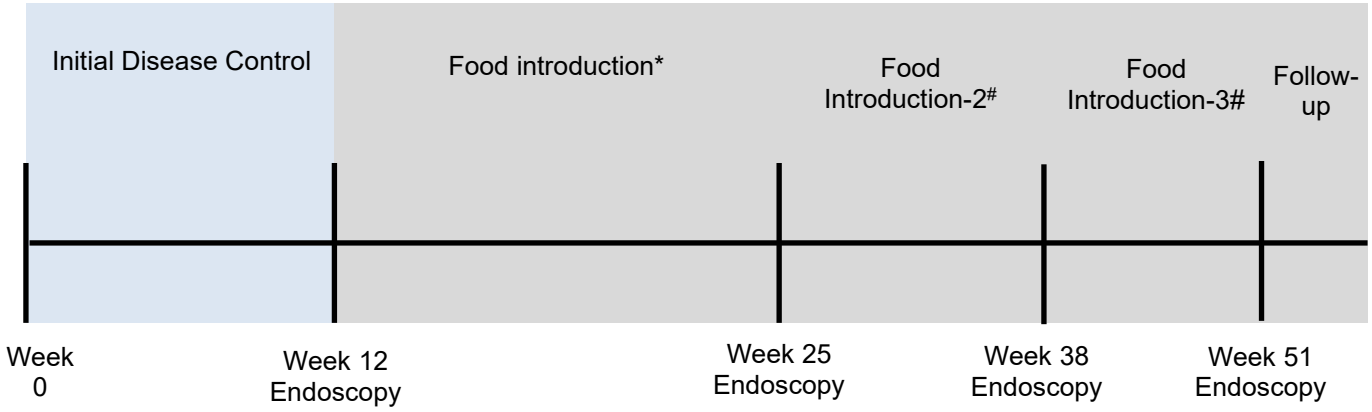
If the week 25 biopsy show 6-15 eosinophils/hpf, the diet will remain the same
If the week 25 biopsy show >15 eosinophils, the diet will decrease to ½ serving size a day
For the week 38 endoscopy with biopsy, the three scenarios are

If the biopsy show < 6 eosinophils/hpf, the three options are

- Increase the serving size to ad lib (if one food) or
- Add a 3rd EoE trigger food or
- Increase the serving size of 1st and 2nd foods to 2 serving size a day

If the biopsy shows 6-15 eosinophils/hpf, the plan is to remain at the current diet
If the biopsy show >15 eosinophils/hpf, the plan is to decrease the serving size by 50%

FIGURE 1: STUDY DIAGRAM



1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

Eosinophilic esophagitis (EoE) is a chronic, debilitating, allergic/immune-mediated disease due to chronic esophageal inflammation with the development of dysphagia that affects food intake and quality of life[1]. The disease is characterized by symptoms related to esophageal dysfunction and by eosinophil-predominant inflammation of the esophageal mucosa. EoE is a food allergy as removal of the foods can resolve the symptoms and histology.[2] But, it is not IgE mediated food allergy[3] and appears to be more driven by T cell mediated food allergy.[4, 5] The pathology of EoE is driven by eosinophils isolating to the esophagus. While eosinophils are present in specific regions of the gastrointestinal (GI) tract, they are not normally found in the esophagus. Patients with EoE demonstrate esophageal tissue infiltration of significant numbers of eosinophils and other pro-inflammatory cells, including mast cells and B and T lymphocytes[6], the latter characterized by an enrichment of CD4+ T regulatory and type 2 cytokine producing effector type 2 T helper (Th2) cells [7]. This infiltrating cellular profile along with over expression of cytokines, particularly interleukin-13 (IL-13) and interleukin-5 (IL-5), strongly suggests that EoE is a type 2 cell-mediated inflammatory disease. Many patients with EoE have other atopic diseases including asthma and food allergies, supporting the view that EoE likely represents a disease in which type 2 cells and eosinophils play key pathogenic roles[8].

The treatment options for EoE include diet avoidance, and off-label use of topical steroids or proton pump inhibitors[9]. Diet avoidance can be successful in eliminating symptoms and leading to normalization of the esophageal eosinophilia. However, six-food elimination diet which has success rate of 70% and elemental diet with a success rate of 90% have a tremendous amount of patient and family burden. Patients have a very restricted diet with increased costs to the family and reduced quality of life (QOL). The new biologics dupilumab has shown to high rate (67%) of clinical and histologic remission in treatment of EoE in adolescents and adults[10, 11]. The goal of this study is to show that foods can be safely added to diet when on dupilumab without exacerbation of Eosinophilic Esophagitis.

1.2 Name and Description of Investigational Product or Intervention

Dupilumab is an interleukin-4 receptor alpha antagonist It is approved for 6 years and above for the treatment of atopic dermatitis and asthma and approved for chronic rhinosinusitis with nasal polys for 18 years and above.

1.3 Findings from Non-Clinical and Clinical Studies

1.3.1 Clinical Studies

1.3.1.1 Eosinophilic Esophagitis

Dupilumab has been studied in Eosinophilic Esophagitis in phase 2 and 3 clinical trials. In the phase 2 clinical trial, subjects were randomly assigned to groups that received weekly subcutaneous injections of dupilumab (300 mg, n = 23) or placebo (n = 24) for 12 weeks. Dupilumab reduced the peak esophageal intraepithelial eosinophil count by a mean 86.8 eosinophils per high-power field (reduction of 107.1%; P < .0001 vs placebo), the EoE-histologic scoring system (HSS) severity score by 68.3% (P < .0001 vs placebo), and the endoscopic

reference score by 1.6 (P = .0006 vs placebo). Dupilumab increased esophageal distensibility by 18% vs placebo (P < .0001).[11]

In the phase 3 clinical trial, 81 subjects (12 years and older) were randomized 1:1 to dupilumab 300 mg weekly versus placebo. At 12 weeks, 64% of subjects treated with dupilumab versus 8% of the placebo subjects had less 15 eosinophils/hpf in the esophageal biopsies. Both groups had a similar adverse event profile with no serious adverse events in either group and 86% having adverse events in the active group and 84% in the placebo group. [12]

Dupilumab was approved for the treatment of EoE in patients greater than 12 years of age on May 24, 2022. We will be using the approved doses in this study.

In our published data of 45 children[13] (6-18) with eosinophilic esophagitis that were being treated with dupilumab for asthma or atopic dermatitis per approved indications. 39/41 patients (95%) had clinical improvement and 22/26 (85%) with follow-up endoscopies with biopsies had complete remission with esophageal eosinophil count of less 6 eosinophils/HPF.

1.3.1.2 Clinical Studies in Children

The drug is approved for clinical use in children with atopic dermatitis down to 6 years of age. It has been studied down to 1 year of age in atopic dermatitis and Eosinophilic Esophagitis and asthma to 6 years of age.

In the pivotal phase 3 study for the treatment of atopic dermatitis, 367 patients 6-11 years of age were randomized 1:1:1 to 300 mg dupilumab every 4 weeks (300 mg q4w), a weight-based regimen of dupilumab every 2 weeks (100 mg q2w, baseline weight <30 kg; 200 mg q2w, baseline weight ≥30 kg), or placebo. In both the q4w and q2w dupilumab + topical corticosteroid (TCS) regimens resulted in clinically meaningful and statistically significant improvement in signs, and symptoms of atopic dermatitis versus placebo + TCS in all prespecified endpoints. For q4w, q2w, and placebo, 32.8%, 29.5%, and 11.4% of patients, respectively, achieved Investigator's Global Assessment scores of 0 or 1; 69.7%, 67.2%, and 26.8% achieved ≥75% improvement in Eczema Area and Response to therapy was weight-dependent: optimal dupilumab doses for efficacy and safety were 300 mg q4w in children <30 kg and 200 mg q2w in children ≥30 kg.[14]

In the pediatric trial of 6 months to 6 years, 40 children were given open label dosing. At week 3, treatment with 3 and 6 mg/kg dupilumab reduced scores of mean Eczema Area and Severity Index by -44.6% and -49.7% (older cohort) and -42.7% and -38.8% (younger cohort) and mean Peak Pruritus NRS scores by -22.9% and -44.7% (older cohort) and -11.1% and -18.2% (younger cohort), respectively. At week 4, improvements in most efficacy outcomes diminished in both age groups, particularly with the lower dose. The safety profile was comparable to that seen in adults, adolescents, and children.[15]

In the asthma phase 3 trials for dupilumab in children 6-11 years of age, it was a randomized, double-blind, placebo-controlled trial of 408 children aged 6 to <12 years old with uncontrolled moderate-to-severe asthma. They were given dupilumab versus placebo plus their standard care of therapy. The population was split into two arms with 259 patients with baseline

(peripheral blood eosinophil count ≥300 cells/μl) and 350 patients with markers of type 2 inflammation (baseline peripheral blood eosinophil count ≥150 cells/μl or FeNO ≥20 ppb). During the 52-week treatment period, patients received subcutaneous injections of dupilumab 100 mg or 200 mg every two weeks, based on weight (100 mg for ≤30 kg, 200 mg for >30 kg), or placebo every two weeks. The primary endpoint assessed the annualized rate of severe asthma attacks. Dupilumab arm had reduced rate of severe asthma attacks, with a 65% ($p<0.0001$) and 59% ($p<0.0001$) average reduction over one year compared to placebo (0.24 and 0.31 events per year for dupilumab vs. 0.67 and 0.75 for placebo, respectively). The dupilumab arm had improved lung function at 12 weeks compared to baseline by 10.15 and 10.53 percentage points for Dupixent vs. 4.83 and 5.32 percentage points for placebo (least squares mean difference for Dupixent vs. placebo of 5.3 and 5.2 percentage points, $p=0.0036$ and $p=0.0009$), respectively, as measured by percent predicted FEV_1.[16]

1.3.1.3 Package Inserts

Package inserts for dupilumab for asthma eosinophilic Esophagitis and atopic dermatitis are in separate appendix.

1.4 Selection of Drugs and Dosages

We use the current dosing used in the phase 3 Eosinophilic Esophagitis clinical trials (see section 6.1.1-6.1.3). We are using the approved doses for 12 years and older and if a specific dose for EoE is approved during the trial for 6-11 yo, we will transition all patients to the FDA approved dose.

1.5 Relevant Literature and Data

The diagnosis of Eosinophilic Esophagitis will be made by the current international guidelines, where patients have symptoms of esophageal dysfunction and greater than 15 eosinophils/hpf isolated to the esophagus.[1] Other causes of esophageal eosinophilia will be ruled out.

The current consensus treatment options for EoE were based on peer reviewed and expert opinion and include diet elimination and medication use (topical corticosteroids (CS) and proton pump inhibitors (PPI)[10]. For diet elimination therapy, the most common foods are milk, egg, soy, and wheat based on multiple clinical trials (retrospective and prospective studies).[17, 18] Diet therapies have been successful in 40-70% depending on whether 1 or 4 foods were removed. When, patients are placed on elemental diets, the response rate with normalization of biopsies and symptoms in >95% of patients.[19]

For medical therapy, dupilumab is the first approved medication for EoE patients greater than 12 yo as in phase 2 and 3 trials with the use of dupilumab in adolescents in adults in 12 year and old found that 67% of the patients showed resolution of their EoE.[11] There are several phase 2 and 3 clinical trials examining the use of biologics and swallowed steroids for the use in EoE. Recent completed phase 3 clinical trial in patients in 12 years and old with EoE showed that swallowed budesonide is effective in about 50% of the patients.[20]

In our cohort of 3500 patients seen at Children's Hospital of Philadelphia, 70% are treated with a combination of two or three of the current therapies of diet elimination, topical steroids, or PPI.

Families have strong desire for simple therapy and improved quality of life with expansion of foods into their diet.

In preliminary data for this study[13], we performed a retrospective chart review of patients with EoE using dupilumab for approved indications (asthma or atopic dermatitis). We identified 45 patients age 6 to 19 years of age and we have follow-up data for 41 patients. 39/41 patients showed improvement in EoE symptoms and we have follow-up endoscopies in 26 endoscopies showing normalization of histology in 22 patients and maintenance of normal endoscopy and histology in one additional patient while stopping their other medications to treat their EoE. However, 80% of the patients were still on a combination of medications and diet to treat their EoE. This current study will examine if the use of dupilumab for the treatment of Eosinophilic Esophagitis will allow expansion of their diet. The goal of expansion of diet will improve quality of life, nutrition without negatively affecting their EoE. We will examine EoE using validated EoE measures for disease activity and nutrition status by weight (z-scores).

The validated measures for endpoints in Eosinophilic Esophagitis to be used include

- Pediatric Eosinophilic Esophagitis Symptom Score[21]
- EoE Endoscopy Reference Score[22]
- EoE Quality of Life[23]
- EoE Histology Scale[24]
- Esophageal Compliance (Endoflip)[25]
- Height and Weight, calculated z-scores

We would also examine if the use of dupilumab will normalize the esophageal transcriptome by examining esophageal biopsy mRNA transcriptome. In EoE, there is an altered esophageal transcriptome with an increase expression of specific esophageal and T2 cytokines.[26] Both T cell profile and peripheral blood eosinophilia and eosinophil progenitors have shown correlation with esophageal biopsy and maybe a non-invasive marker of disease.[4, 27] We will examine these research bloods to explore potential non-invasive markers of disease and/or mechanism of dupilumab on disease activity.

The goal of this study is to see if dupilumab can facilitate food introduction while patients on standard of care EoE therapies. They will maintain their EoE therapies, which can include PPIs, swallowed steroids, or diet elimination. throughout the study except for food introduction as indicated by the protocol.

We are examining food introduction in this age group for the following reasons.

1) Dupilumab is approved for children 6 years and above for asthma and atopic dermatitis
2) Dupilumab has been shown to be clinical effective in phase 2 and 3 clinical trials for 12 years and above and recently approved in May 24, 2022
3) Dupilumab has been shown to be effective in our published observational study looking at patients 6 years and older being treated with dupilumab for their co-existing asthma and/or atopic dermatitis. We found that their EoE had improvements in both clinical symptoms and histology. In addition, many patients were able to add foods into their diet.

4) Foods triggers have been primarily identified in pediatrics as almost all the dietary trials were done in pediatrics. The proposed biomarker studies have only been done in pediatrics.

Therefore, the study medication is safe and effective in this age group of 6 years and above. There are insufficient patients in the adult group with identified food triggers to complete this trial.

1.6 Compliance Statement

This study will be conducted in full accordance all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, and the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonization (ICH) and all relevant FDA regulations. All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with The Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

The purpose of the study is to determine if dupilumab can allow introduction of EoE triggered foods to be added reintroduced back into the diet without causing exacerbation of disease.

2.1 Primary Aim

1) Evaluate the efficacy of Dupilumab, a humanized anti-IL4 receptor alpha monoclonal antibody, to allow successful food introduction into diet
2) Assess changes in clinical (symptoms, QOL) and biologic parameters after food introduction.

The secondary Endpoint:

- Maintenance of resolution (<15 eosinophils/HPF on peak measurements) of eosinophilia observed on esophageal biopsies
- Maintenance of remission (<6 eosinophils/HPF on peak measurements)
- Change in mean esophageal eosinophil count from baseline to the end of treatment.
- Change in symptoms scores at the end of treatment compared to baseline
- Interval change on a validated endoscopic scoring system, EREFS
- Interval change on esophageal compliance and distensibility measured by EndoFlip
- Interval change in mRNA transcriptome profile (esophageal tissue), Th2 phenotype (peripheral blood), blood eosinophilia, and total serum IgE.

- Change in the Eosinophilic Esophagitis Quality of Life Score from baseline to the end of treatment

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

This study is an open label exploratory study to examine if patients controlled with dupilumab can successful introduce EoE trigger foods back into their diet.

In the initial 12-week period, patients will be start on dupilumab on the doses used in the phase 3 trials to control disease. If disease is controlled based on histologic and symptom control at week 12 endoscopy, patients will be start on EoE trigger food. The trigger foods will be based on both a combination of history and histology results. The food will have trigger EoE by histology in the last 2 years and symptoms in the last year when reintroduced into the diet. The study will focus on the four most common foods that trigger EoE: milk, egg, wheat, and soy. For the initial food introduction, the subjects will add one serving size of the food daily for 12 weeks. After 12 weeks, the subjects will have a 2nd endoscopy if the 2nd endoscopy is normal, the subjects will increase the trigger food to 2 serving sizes a day or add an additional trigger food. A 3rd endoscopy will be done if the patients increase the food amount or adds a new food at week 38 (12 weeks after adding the new food). If the subject does not increase or add new foods at week 25, the 3rd endoscopy will not be obtained. All subjects will have end of study endoscopy at week 51.

If the subjects have abnormal endoscopy or increase in symptoms, the amount food will be reduced by 50% and repeat endoscopy will be obtained at the same time schedule-12 weeks later. (See Figure 1 and Table 1)

Screening Phase

Potential subjects will be screened using the protocol inclusion and exclusion criteria based on review of their medical records.

Parental/guardian permission (informed consent) and, if applicable, child assent, will be obtained prior to any study related procedures being performed. After consent is obtained, research blood samples will be drawn to confirm eligibility based on clinical laboratory parameters. Females of child bearing potential will have an urine pregnancy test.

3.1.1 Disease Control

At the initial phase, research subjects will start on dupilumab based on the dosage used in the 2 phase 3 clinical trials. Based on previous data, patients respond within 12 weeks, therefore, a baseline endoscopy showing a clinical and histologic response will be obtained at week 12. If patients show clinical response with dupilumab as defined as esophagus biopsy with less 6 eosinophils/hpf. If the biopsy does not improve such that eosinophil count is still greater than 15 eosinophils/hpf, the subject will exit the study. If the biopsy is between 6-15 eosinophils/hpf, the subject will be treated for an additional 12 weeks on dupilumab. If the biopsy is still not less than six eosinophils/hpf, the subject will exit the study. If the subjects have biopsy have less than six eosinophils/hpf (FDA definition of remission), the subjects will advance to food introduction phase of the study.

3.1.2 Food Introduction

If research subjects have a clinical response to dupilumab, they will introduce an EoE trigger food at one serving size per day. After 12 weeks, repeat EGD and symptoms score will be obtained. 12 weeks is being used as determined clinical and histologic responses can be seen at that time point in previous clinical studies[18].

The foods (milk, egg, soy, and wheat) to be introduced after having caused exacerbation of their EoE by standard definitions:

- Addition of a single food lead to exacerbation of esophageal eosinophilia (increase of greater than 15 eos/hpf) or
- Removal of a single food lead to normalization of biopsy (esophageal eosinophilia showed less than 6 eos/hpf)
- AND
- History of either milk, egg, soy, or wheat induced EoE based on introduction of the food and symptoms in the last 12 months

Foods in phase 1 will be introduced as one serving size at week 13. If biopsy at week 25 are less than 6 eosinophils/HPF, the subjects will have one of 2 options

- Increase the serving size to 2 servings a day or
- Add an additional EoE trigger food

If the week 25 biopsy show 6-15 eosinophils/hpf, the diet will remain the same

If the week 25 biopsy show >15 eosinophils, the diet will decrease to ½ serving size a day

For the week 38 endoscopy with biopsy, the three scenarios are

If the biopsy show < 6 eosinophils/hpf, the three options are

- Increase the serving size to ad lib (if one food) or
- Add a 3rd EoE trigger food or
- Increase the serving size of 1st and 2nd foods to 2 serving size a day

If the biopsy shows 6-15 eosinophils/hpf, the plan is to remain at the current diet

If the biopsy show >15 eosinophils/hpf, the plan is to decrease the serving size by 50%

3.1.3 Follow-up Phase

The follow-up phase will continue for up to 14 days to monitor for adverse events.

3.2 Allocation to Treatment Groups and Blinding

All patients will receive active drug.

3.3 Study Duration, Enrollment and Number of Sites

3.3.1 Duration of Subject Study Participation

If subjects complete all phases, the study will last 52 weeks. 51 weeks of treatment and 1 week of follow-up. If the subject does not meet study criteria (response to dupilumab), they will exit the study at week 13.

3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at approximately 1 investigative site in the United States.

3.4 Study Population

Children, adolescent, and adults with Eosinophilic Esophagitis

3.4.1 Inclusion Criteria

3.4.2 Index/Case Subject Inclusion Criteria

1) Males or females age 6 to 25 years
2) Diagnosis of Eosinophilic Esophagitis based on the most recent international consensus definition (Dellon et al, Gastroenterology 2019)
    a) History of endoscopy with a peak count of >15 eosinophils per high powered field meeting consensus criteria for Eosinophilic Esophagitis[1]
3) History of either milk, egg, soy, or wheat induced EoE based on the following criteria in the last two years
    a) Addition of a single food lead to exacerbation of esophageal eosinophilia (increase of greater than 15 eos/hpf) or
    b) Removal of a single food lead to normalization of biopsy (esophageal eosinophilia showed less than 6 eos/hpf)

       AND

    c) History of either milk, egg, soy, or wheat induced EoE based on introduction of the food and symptoms in the last 12 months
4) Weight $\geq$ 10 kg
5) Ability to remain on stable dose of PPI therapy throughout the study
6) Women with child bearing potential must have a negative urine/serum pregnancy test.
7) Parental/guardian permission (informed consent) and if appropriate, child assent.

3.4.3 Exclusion Criteria

1. Tracheo-esophageal fistulas, inflammatory bowel disease, Barrett's disease, or other significant inflammatory disease of the gastrointestinal tract
2. Biopsy evidence of eosinophilic infiltration in any other organ system

3. History of significant esophageal procedures e.g., sclerotherapy or esophagectomy
4. Systemic immunosuppressant usage in prior 3 months and throughout the study
5. Narrow caliber esophagus defined as the inability to pass a 9.5 mm endoscopy into the esophagus
6. IgE mediated reaction to food (milk, egg, soy, or wheat) being introduced in the last 12 months
7. Therapy with biologic molecule (e.g., omalizumab, infliximab) in prior 12 months
8. Any factors that may pose a significant risk for undergoing anesthesia/sedation
9. Subjects undergoing any type of immunotherapy to any food (oral immunotherapy, sublingual immunotherapy, specific oral tolerance induction) within 3 months prior to Visit 1.
10. Active IgE- mediated milk, egg, wheat, or soy allergy based on skin test or history (if those foods are being introduced back into the diet).
11. Allergy or known hypersensitivity to the dupilumab.
12. Subjects (or parents of subjects) with obvious excessive anxiety and unlikely to cope with the conditions of an upper Endoscopy and biopsy.
13. No change in the dose of swallowed steroids for Eosinophilic Esophagitis for 2 months prior to starting the study and throughout the study (their current standard of care EoE treatments
14. Past or current disease(s), which in the opinion of the Investigator or the Sponsor, may affect the subject's participation in this study, including but not limited to active autoimmune disorders, immunodeficiency, malignancy, uncontrolled diseases (hypertension, psychiatric (especially anxiety), cardiac), or other disorders (e.g., liver, gastrointestinal, kidney, cardiovascular, pulmonary disease, or blood disorders).
15. Participation in another clinical intervention study in the three months prior to Visit 1.
16. Subjects unable to follow the protocol and the protocol requirements.
17. Subjects on any experimental drugs or treatments.
18. Subjects unable to read/understand English or follow the protocol and the protocol requirements.
19. Treatment with a live (attenuated) vaccine within 4 weeks before the baseline visit or throughout the trial
20. Major elective surgeries are prohibited during the study
21. Female patients who are pregnant, breastfeeding, or planning to become pregnant or breastfeed during the study
22. Women of children bearing potential (WOCBP) who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 12 weeks after the last dose. This includes female patients who experience menarche during the study duration and who are unwilling to follow the precautions for WOCBP.

23. Chronic or acute infection requiring treatment with systemic antibiotic, antivirals, or antifungal within 2 weeks of baseline visits

    a. Patients maybe rescreened after infection resolves

24. Participants with active or suspected parasitic infection are excluded.

3.4.4 Individual stopping rules

Subjects may withdraw from the study/schedule of assessments for any of the following reasons:

- Patients will be stopped if they have severe adverse reaction from a serious adverse event from injection reaction
- The Investigator decides that it is the subject's best interest to be withdrawn from the study.
- The subject is unwilling to continue in the study (consent withdrawal).
- Lack of compliance with protocol requirements and procedures.
- The Sponsor- Investigator or Regulatory Authorities, for any reason, stops the study.
- The subject fails to return to the clinic for scheduled visits and does not respond to telephone or written attempts at contact (lost to follow-up).
- Subject's death

The reason for withdrawal will be recorded in the clinical records and the electronic Case Report Form (eCRF). All subjects who are withdrawn or discontinue should be provided with alternative medical care, if applicable.

4 STUDY PROCEDURES

Eosinophilic Esophagitis History

Physical examination

Esophagogastroduodenoscopy with biopsy with conscious sedation:

Eosinophilic Esophagitis Symptom Score:

Pediatric Eosinophilic Esophagitis Symptom Score

Pediatric Eosinophilic Esophagitis Symptom Questionnaire

Eosinophilic Esophagitis Quality of Life Measures

- PedsQL™ Eosinophilic Esophagitis Module Version 3 Teen Report (ages 13-18)
- PedsQL™ Eosinophilic Esophagitis Module Version 3 Child Report (ages 8-12)
- PedsQL™ Eosinophilic Esophagitis Module Version 3 Parent Report for Child (ages 8-12)
- PedsQL™ Eosinophilic Esophagitis Module Version 3 Parent Report for Young Child (ages 5-7)

Esophageal Compliance measured by Endoflip

Research esophageal biopsies-6 additional esophageal biopsies

Blood draws for exploratory markers (RNAseq transcriptome of blood, T cell proliferation, peripheral blood eosinophils and progenitors)-15 ml per blood draw

Diet records

Study Drug administration

4.1 Study Treatment Phase: EoE disease control

4.1.1 Visit 1

Visit 1: Baseline Visit, Study enrollment

- Informed consent obtained,
- Inclusion and exclusion criteria reviewed,
- Medical Records reviews
- Physical exam including vital signs with height and weight
- Eosinophilic Esophagitis Symptom Score-Pediatric Eosinophilic Esophagitis Symptom Score (PEESS and PESQ)
- EoE Quality of life (QOL)
- Research labs (T cell phenotype, PBMC RNAseq, peripheral blood eosinophils and progenitors, proteomics)-15 ml
- First dose of Dupilumab

4.1.2 Visit 2

2 weeks from visit 1 (+/- 3 days)

- EoE Symptom Score-PEESS and PESQ
- Drug disposition
- Monitor drug compliance
- AE assessment
- Physical Examination including vital signs with height and weight

4.1.3 Visit 3

5 weeks from visit 2 (+/- 4 days)

- EoE Symptom Score-PEESS and PESQ
- Drug disposition
- Monitor drug compliance
- AE assessment
- Physical Examination including vital signs with height and weight

4.1.4 Visit 4

4 weeks from visit 3 (+/- 4 days)

- Upper Endoscopy with biopsy with 4 esophageal biopsies for histology
- EoE Symptom Score-PEESS and PESQ
- EoE QOL
- Drug disposition
- Monitor drug compliance

- AE assessment
- Physical Examination including vital signs with height and weight
- Endoflip and/or esophageal impedance
- Research bloods (T cell phenotype, PBMC RNAseq. peripheral blood eosinophils and progenitors, proteomics)-15 ml of blood
- Research Biopsies (esophageal RNAseq)-6 esophageal biopsies for research samples

4.2 Phase 2: Food Introduction

4.2.1 Visit 5, 9, 13

1 week (+/- 3 days) after visit 4, 8 and 12

- EoE Symptom Score-PEESS and PESQ (SOC procedure)
- Drug disposition
- New food introduction
- Monitor drug compliance
- AE assessment
- Physical Examination including vital signs with height and weight

4.2.2 Visit 6, 10, 14

2 weeks (+/- 4 days) after preceding visit. This visit can be done by remote research visit.

- EoE Symptom Score-PEESS and PESQ (SOC procedure)
- Drug disposition
- Review food diary
- Monitor drug compliance
- AE assessment
- Physical Examination including vital signs with height and weight

4.2.3 Visit 7, 11, 15

5 weeks (+/- 4 days) after preceding visit. This visit can be done by remote research visit.

- EoE Symptom Score-PEESS and PESQ (SOC procedure)
- Review food diary
- Monitor drug compliance
- AE assessment

4.2.4 Visit 8, 12, 16

- Upper Endoscopy with biopsy-4 esophageal biopsies (SOC procedure)
- EoE Symptom Score-PEESS and PESQ
- EoE QOL
- Review food diary
- Drug disposition (except for visit 16)
- Monitor drug compliance

- AE assessment
- Physical Examination including vital signs with height and weight
- Endoflip and/or esophageal impedance
- Research bloods: (T cell phenotype, PBMC RNAseq. peripheral blood eosinophils and progenitors, proteomics)-15 ml of blood
- Research Biopsies: Esophageal biopsy RNAseq-6 esophageal biopsies
- AE assessment

4.3 Follow-up Phase

4.3.1 Visit 17: End of Study

- AE assessment
- Physical Examination including vital signs with height and weight

4.4 Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reasons as warranted.

4.5 Concomitant Medication

All prior and concomitant medications used within 14 days prior to the screening visit and through the end of the study will be recorded. The dates of administration, dosage, and reason for use will be included.

4.6 Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to study treatment or visit schedules, AEs, or due to lack of response to dupilumab as defined by esophageal biopsy greater than 15 eosinophils/high power field at week 12. The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the CRF.

4.6.1 Early Termination Study Visit

Subjects who withdraw from the study will have all procedures enumerated for Visit 8 as the early termination visit.

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Screening and Monitoring Evaluations and Measurements

5.1.1 Medical Record Review

Prior to screening visit, previous upper endoscopy and biopsy results and diet history will be reviewed. This information will be collected as part of routine clinical care.

5.1.2 Medical History

Complete medical history will include history and duration of all allergies (including milk. Egg, soy, or wheat allergy) and current medical conditions, number of allergic reactions and treatments in the previous 12 months, past or present cardiovascular, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatological, psychiatric, and genitourinary disorders, drug and surgical history and any other diseases or disorders.

5.1.3 Physical Examination

Physical examinations will be performed by a physician or nurse practitioner and will include examination of the following: general appearance, head, ears, eyes, nose and throat, neck, complete skin examination, cardiovascular system, respiratory system, abdominal system, and nervous system. For each body system an assessment of normal or abnormal will be recorded in the eCRF at screening and the abnormality will be documented. During the study, any clinically relevant changes observed during physical examinations will be reported as AEs.

Physical examinations must be performed before the upper endoscopy/biopsy.

5.1.4 Vital Signs

Vital signs will include sitting systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature. Systolic blood pressure and diastolic blood pressure will be measured on the same arm after the subject has been in a sitting position for 5 minutes. Heart rate will be recorded simultaneously with blood pressure measurements, followed by respiratory rate and body temperature.

Body weight (kg) will be measured without shoes or jacket. Height (cm) will be determined at without shoes.

During the study, the measurement of vital signs may be repeated at the discretion of the Investigator for safety reasons. Clinically relevant abnormal findings will be reported as AEs.

Vital signs must be performed before the upper endoscopy/biopsy.

5.1.5 Eosinophilic Esophagitis Quality of Life

Quality of life is a measurement of a subject's overall well-being. QOL will be measured by the validated age specific Eosinophilic Esophagitis tool for 5-7 years of age, 8-12 years of age, and 13-18 years of age developed by Franciosi and colleagues based on the age of the subject at Visit 1.

The subjects will complete the same questionnaire throughout the study.

5.1.6 Upper Endoscopy with Biopsy

All subjects will undergo a maximum of six upper endoscopies with biopsies during their participation in the study (biopsies will include three each of proximal and distal, plus any inflamed areas) as per standard clinical practice). The samples will be processed by the Department of Pathology at The Children's Hospital of Philadelphia and the number of eosinophils will be counted using hematoxylin and eosin stain. The handling of samples will be done following ASGE Standard on Endoscopic Mucosal Tissue Sampling.[28]

Six research biopsies will be obtained in addition to the clinical biopsies. The biopsies will be taken from other areas of the esophagus compared to the clinical biopsies.

Upper endoscopy will be scored using a validated standardized measure. [22] The measure examines four major esophageal features (rings, furrows, exudates, and edema) and the presence of minor features of narrow caliber esophagus, feline esophagus, stricture, and crepe paper esophagus. The features are graded:

- Rings (0-none, 1 mild, 2-moderate, 3-severe)
- Exudates (0-none, 1-mild, 2-severe)
- Furrows- (0-none, 1-present)
- Edema- (0-none, 1-present)
- Stricture (0-none, 1-present)
- Crepe paper esophagus (0-none, 1-present)

Endoscopy and biopsy are standard of care after food introduction.

The endoscopy will be done under moderate conscious sedation. Moderate sedation is defined as a drug-induced depression of consciousness during which patients respond purposefully to verbal command that is accompanied by light tactile stimulation. No interventions are required to maintain a patent airway and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.

Conscious sedation will be done by CHOP standard protocol: Policy: Protocol Sedation: http://intranet.chop.edu/patcare/patcarman/tx-5-01.pdf

5.1.7 Histological Evaluation

Esophageal biopsy samples will be evaluated to confirm eligibility. Biopsy samples will be stained with hematoxylin and eosin stain. Intraepithelial eosinophils will be counted in all HPFs using 400X light microscopy. A HPF will be counted only if at least half of the field is occupied by tissue. The maximum eosinophil count per HPF will be reported for each esophageal biopsy site (at each

of 2 levels) with a minimum of 2 biopsies at each level. In addition to the evaluation for eosinophilia, all biopsy samples will be assessed for other histologic changes including epithelial hyperplasia, intercellular edema, and fibrosis.

Specimens will be examined with respect to the maximum eosinophil counts and other histologic changes. Together with the EoE Clinical Symptom Score, the maximum eosinophil count per HPF for each specimen (from the total of all specimens) will be used to determine response to treatment.

The maximum eosinophil count will be defined as the highest number of eosinophils observed in any single HPF from an esophageal specimen. All specimens from all esophageal sites will be considered in determining the resolution of eosinophilia. A maximum eosinophil count will be recorded for the esophagus. The highest peak counts at a given timepoint will be referred to as the maximum eosinophil count for that timepoint.

5.1.8 Endoflip

Esophageal distensibility utilizing the endolumenal functional lumen imaging probe (EndoFLIP, Medtronic, USA) will be performed with measurements taken as part of the esophagogastroscopy procedure. The EndoFLIP procedure must be performed before biopsies are collected. Procedural order should be: EREFS/imaging, EndoFLIP, then biopsies. The EndoFLIP device is a catheter-based procedure that measures the cross-sectional area at multiple sites along the esophagus with simultaneous intraluminal pressure recordings during volumetric distension of the esophagus. The analyses of cross-sectional area versus pressure relationships of the esophagus allow for determination of esophageal compliance as well as the distensibility plateau. The distensibility plateau has been shown to be significantly reduced in adult patients with EoE compared to healthy controls[29]. Moreover, the esophageal distensibility has been associated with outcomes of both food impaction and need for esophageal dilation[25]. Endoflip has also been shown to correlate with symptoms in pediatric cohorts.[30]

Endoflip are standard of care at the time of endoscopy to measure esophageal function.

Esophageal epithelial integrity is affected by the presence of dilated intercellular spaces (DIS), or spongiosis (intercellular edema), which affects paracellular permeability of the esophageal lumen. DIS is an important histologic feature in GERD and EoE which inversely correlates with MI measurements (i.e., lower impedance values with increasing DIS).

Patients with EoE have shown to decreased impedance compared to GERD or achalasia.[31] Esophageal impedance will be measured by MiVu.

5.1.9 Diet Diary

Subjects will indicate the duration and amount of food taken on a daily basis during the food reintroduction period.

5.1.10 Pregnancy testing

A urine pregnancy test will be performed for female subjects who are physically capable of becoming pregnant.

5.1.11 Pregnancy

If a subject becomes pregnant during the trial, they will immediate stop receiving dupilumab. They will not be followed as there no published reports of adverse events from pregnancy, fetus and dupilumab.

If the subject becomes pregnant, we will enroll them in a pregnancy exposure registry for women who take DUPIXENT during pregnancy. The purpose of this registry is to collect information about the health of subject and her baby. The registry is https://mothertobaby.org/ongoing-study/dupixent/.

5.1.12 Research Laboratory Tests

The differential gene expression profiles of esophageal biopsies of EoE patients shows a marked difference compared to healthy controls and is the EoE disease transcriptome[32]. This disease gene expression signature was further refined to a smaller gene set to be used as an EoE diagnostic panel (EDP)[33]. A gene signature representing type 2 inflammation has been curated from the literature, preclinical experiments performed at Regeneron, and dupilumab response signatures from atopic dermatitis and a phase 2 and 3 study of EoE (Regeneron unpublished data).

In a phase 2 study of EoE (R668-EE-1324), dupilumab significantly decreased the disease, EDP, and type 2 transcriptome signatures. Normalized Enrichment Score (NES) reflects the degree to which the activity level of a set of transcripts is overrepresented at the extremes (top or bottom) of the entire ranked list of transcripts within a sample and is normalized by accounting for the number of transcripts in the set[34, 35].

The research bloods that will be collect include:
T cell phenotyping for T1/T2/Th17 expression, blood eosinophilia (CBC) and eosinophilic progenitor cells measured by flow cytometry in peripheral blood.

We will collect patient 6 biopsies and 15 ml peripheral blood at the time of study endoscopy. Patient samples will be provided to laboratory and CAG staff using the deidentified study code. Biopsy tissue will be dissociated in media containing RNAse inhibitors and single cell RNA expression libraries will be generated following 10x genomics manufacturer protocols. Peripheral blood mononuclear cell samples will be isolated from patient blood samples and single cell RNA expression libraries will be generated following 10x genomics manufacturer protocols. Single cell RNA libraries will be pooled and sequenced to a minimum depth of 20,000 reads per cell using next generation sequencing (Illumina) at CHOP Center for Applied Genomics (CAG).

Patient sequencing data will be stored using deidentified study codes and will not be associated with patient names or any protected health information. Sequencing data will be transferred

from the CAG to study staff for analysis and stored using CHOP IT managed laboratory data drives (i.e.: SMB://ressmb). Sequencing data will not be stored on personal devices. Data analysis will be performed on CHOP managed devices and on the CHOP high performance computing cluster.

Research blood will be done at the following visits 1, 4, 8, 12, and 16

Research esophageal biopsies will be collected at visit 4, 8, 12 and 16.

5.2 Safety Evaluation

Subject safety will be monitored by adverse events, vital signs, physical examinations and endoscopy and biopsy.

If a public health emergency is declared that limits or prevents on-site study visits, regular phone call or virtual calls can occur for safety monitoring and discussion of the patient's health until it is safe for the participant to visit the site again.

5.3 STATISTICAL CONSIDERATIONS

5.3.1 Primary Endpoint

The primary efficacy endpoint will be the change in peak eosinophil counts on esophageal biopsies between 1st and 2nd endoscopy after food introduction in the same patient.

5.3.2 Secondary Endpoints

Secondary endpoints will include the following:

- Maintenance of resolution (<15 eosinophils/HPF on peak measurements) of eosinophilia observed on esophageal biopsies
- Maintenance of remission (<6 eosinophils/HPF on peak measurements)
- Change in mean esophageal eosinophil count from baseline to the end of treatment.
- Change in symptoms scores at the end of treatment compared to baseline
- Interval change on a validated endoscopic scoring system, EREFS
- Interval change on esophageal compliance and distensibility measured by EndoFlip
- Interval change in mRNA transcriptome profile (esophageal tissue), Th2 phenotype (peripheral blood), blood eosinophilia
- Change in the Eosinophilic Esophagitis Quality of Life Score from baseline to the end of treatment

5.4 Statistical Methods

5.4.1 Analysis Populations

An Intent to Treat population (ITTP) will be used as the primary analysis population. This will include all patients that were enrolled in the study.

A Per Protocol population (PPP) will be used as a sensitivity analysis population. This will include all patients that did not have a major protocol violation.

5.4.2 Demographics and Baseline Characteristics Analysis

Demographic and baseline characteristics will be described descriptively. For continuous (including age, height, weight, and maximum Esophageal Eosinophil Count), means, standard deviations, medians, and ranges and for categorical (including race, ethnicity, medical history) frequency counts and percentages.

All individual subject demographic and baseline characteristic data will be listed.

5.4.3 Efficacy Analysis

The efficacy analysis will focus on changes from baseline measure to follow-up measures.

5.4.3.1 Primary Efficacy Analysis

The primary statistical efficacy endpoint will be tested using a Paired T-test on the change in peak eosinophil counts on esophageal biopsies between 1st and 2nd endoscopy after food introduction in the same patient.

If peak eosinophil counts do not satisfy the assumption of normality, instead the Wilcoxon Signed-Rank test will be used for the primary.

5.4.3.2 Descriptive analysis

Descriptive statistics will be presented by time point, and changes from baseline. Tables will use means, standard deviations, medians, and ranges for continuous variables and frequency counts and percentages for the categorical variables. Graphs will use box plots for continuous variables, and barplots for categorical variables.

All individual subject data will be listed.

Biostatistical core of Westat will help with the analysis.

5.4.3.3 Univariate testing

For measures with multiple time points, Paired statistical tests will be used with Baseline being compared to the other time points. Specifically, the statistical method will be the most appropriate of paired T-test, Wilcoxon Sign-Rank, or McNemar's tests.

5.4.3.4 Statistical Modeling

Modeling using categorical time points as the explanatory variable will be conducted with baseline as the reference category. The model will be estimated using generalized estimating equations with a covariance structure assumed for time points from the same subject. The appropriate distribution and covariance structure will be selected based on the data.

5.4.3.5 Operationalization of Variables

Distribution of the continuous outcomes will be evaluated using density and histograms. Transformation and categorization of some of these continuous variables will be performed wherever deemed more appropriate.

Re-categorization of categorical variables will be considered when appropriate.

5.4.3.6 Eosinophilic Esophagitis Symptom Score

Improvement in symptom scores will be defined as a decrease in total symptom scores of two or

more from baseline to end of treatment. Subjects will be categorized based on whether they improved their symptoms. Subjects who improved their symptom scores were considered as responders and patients who did not improve their symptom scores were considered as non-responders.

The responses will be divided into three categories as suggested: Poor <30% improvement, good 30-70% improvement and excellent >70% improvement from baseline.

5.4.3.7 Vital Signs

The analysis of vital signs will focus on the incidence of clinically relevant abnormalities.

5.4.4 Pharmacokinetic Analysis

Not applicable, no pharmacokinetic assessments will be performed during this study.

5.4.5 Safety Analysis

All AEs will be coded by system organ class and preferred term using MedDRA.

Treatment-emergent AEs (TEAEs) will be defined as any AEs, regardless of relationship to study drug, which occur during AE collection period of study drug or any event already present that worsens in either intensity or relationship to study drug following exposure to the dupilumab. If relationship information is missing, the TEAE will be considered drug related.

An overall summary of TEAEs will be provided showing the number and percentage of subjects in each treatment group with any TEAE, any potentially drug related TEAE, any severe TEAE, any serious TEAE, any TEAE leading to discontinuation, and any TEAE leading to death. The number of events will also be presented.

The number of AEs as well as the number and percentage of subjects who experienced at least one AE will be summarized by system organ class, preferred term, and time period. The incidence of the following events will be summarized:

- TEAEs: incidence, severity, and duration.
- Potentially drug related TEAEs
- Discontinuations due to TEAEs
- Physical examinations, and vital signs
- SAEs
- Potentially drug-related SAEs

In addition, TEAEs will be summarized by relationship to study drug and by severity. If a subject has more than one occurrence of the same TEAE with different severities or relationship to study drug, then the TEAE will be assigned to the highest severity category and/or most related relationship category. If the intensity or relationship is missing, then the ‘worst case’ will be assumed (i.e., severe for intensity and drug-related for relationship).

Time period of an AE will be determined based on the start time of the AE.

5.5 Significance level and alpha allocation

The significance level for all statistical testing in this study will be 0.05, and the alpha of 0.05 will all be allocated entirely to the primary efficacy endpoint. All other statistical testing will be considered exploratory.

5.6 Sample Size and Power

In the phase 2 clinical trial, 67% of the active treated with dupilumab had less 6 eosinophils per high power field compared to zero in the placebo group.[11] In phase 3 trial, 59.5% of the dupilumab had less 6 eos/hpf and only 5% of the placebo treated group had less than 6 eos/hpf.[36, 37]

Therefore, we would assume 64% efficacy rate (average between the 2 studies) from the initial enrollment allowing 19 evaluable subjects. A sample size of 20 with alpha of 0.05 and power 80% would allow detection of difference in eosinophil count of 11 (effect size of 0.7 based on 15 eosinophils/high power field being abnormal).

5.7 Interim Analysis

No interim analysis is planned.

6 STUDY MEDICATION (STUDY DEVICE OR OTHER STUDY INTERVENTION)

6.1 Description

Dupilumab, an interleukin-4 receptor alpha antagonist, is a human monoclonal antibody of the IgG4 subclass that binds to the IL-4Rα subunit and inhibits IL-4 and IL-13 signaling. Dupilumab has an approximate molecular weight of 147 kDa.

Dupilumab is produced by recombinant DNA technology in Chinese Hamster Ovary cell suspension culture.

DUPIXENT (dupilumab) Injection is supplied as a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution for subcutaneous injection. DUPIXENT is provided as either a single-dose pre-filled syringe with needle shield or a single dose pre-filled pen in a siliconized Type-1 clear glass syringe. The needle cap is not made with natural rubber latex.Available dupilumab dosing:

- Injection: 300 mg/2 mL solution in a single-dose pre-filled syringe with needle shield.
- Injection: 200 mg/1.14 mL solution in a single-dose pre-filled syringe with needle shield.
- Injection: 100 mg/0.67 mL solution in a singled-dose pre-filled syringe with needle shield
- Injection: 300 mg/2 mL solution in a single-dose pre-filled pen.
- Injection: 200 mg/1.14 mL solution in a single-dose pre-filled pen.

Pre-filled pen will be used in adults and pediatric patients aged 12 and older and the pre-filled syringe will be used for adults and pediatrics patients aged 6 years and older.

6.1.1 Labeling

Description of product label

6.1.2 Dosing

Dosing will be done based on current doses in phase 3 clinical trials for EoE. The dose will not be adjusted based on changes in weight during the study protocol.

Dupilumab Dosing Scale: per the current Eosinophilic Esophagitis trials (R668-EE-1877 and R668-EE-1774) and approved dosage for 12 yo > 40 kg:

	Weight	
≥12 years of age	**> 40 kg**	**300 mg SQ weekly**
	30-39.9 kg	**300 mg SQ Q2W**
	15-29.9 kg	**200 mg SQ Q2W**
6-11 years of age	**10-14.9 kg**	**100 mg SQ Q2W**
	> 15-29.9 kg	**200 mg SQ Q2W**
	≥ 30-60 kg	**300 mg SQ Q2W**
	≥ 60.1 kg	**300 mg SQ Q2W**

6.1.3 Treatment Compliance and Adherence

It is the Investigators' responsibility to ensure that subjects are correctly instructed on how to take their study medication. Records of study medication used and intervals between visits will be kept during the study. Subjects will be asked to return their unused medication (box(es)) when they come back for their study visits. All unused medication (boxes) should be returned at each study visit and the end of the study. The study drug will be dispensed by the Investigator, or by a qualified individual under the Investigator's supervision.

At each visit, prior to dispensing trial medication, previously dispensed trial medication will be retrieved by the Investigator and compliance assessed. A compliance of > 80% over the treatment period is sought. Subjects exhibiting poor compliance as assessed by counts and response to the question "Did you take your dupilumab regularly?" will be counseled on the importance of good compliance to the study dosing regimen.

Non-compliance is defined as taking less than 80% of trial medication during any evaluation period (visit to visit). Subjects who are persistently non-compliant may be withdrawn from the study.

6.1.4 Drug Accountability

All supplies of dupilumab will be accounted for in accordance with GCP. There will be an individual study drug accountability record for each subject and the Investigator will maintain accurate records of the disposition of all trial medication supplies received during the study. These records will include the amounts and dates that clinical drug supplies were received, dispensed to the subject, returned by the subject, and returned to the Investigator or destroyed on site. The unused dupilumab will be returned on subsequent study visits. The excessive and used study drug will be destroyed by The Children's Hospital of Philadelphia Research Pharmacy using standard protocols. The research pharmacist will provide a corresponding certificate of destruction.

7 SAFETY MANAGEMENT

7.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study.

7.2 Adverse Event Reporting

Unanticipated problems related to the research involving risks to subjects or others that occur during this study (including SAEs) will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that do not meet prompt reporting requirements will be summarized in narrative or other format and submitted to the IRB at the time of continuing review (if continuing reviews are required) or will be tracked and documented internally by the study team but not submitted to the IRB (if continuing reviews are not required).

7.3 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a subject who has received an intervention (drug, biologic, or other intervention). The occurrence does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All AEs (including serious AEs) will be noted in the study records and on the case report form with a full description including the nature, date and time of onset, determination of non-serious versus serious, intensity (mild, moderate, severe), duration, causality, and outcome of the event.

The severity of AEs will be graded according to the following scale:

Mild: Does not interfere in a significant manner with the patient's normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms but may be given because of personality of the patient.

Moderate: Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptoms may be needed.

Severe: Produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

Injection Site Reactions
The severity of injection site reactions will be graded according to the following scale (semi-colon indicates "or" within description of grade:

Mild: Pain that does not interfere with activity; mild discomfort to touch; <5 cm of erythema or induration that does not interfere with activity

Moderate: Pain that requires repeated use of non-narcotic pain reliever >24 hours or interferes with activity; discomfort with movement; 5.1 cm to 10 cm erythema or induration or induration that interferes with activity

Severe: Pain that requires any use of narcotic pain reliever or that prevents daily activity; significant discomfort at rest; >10 cm erythema or induration; prevents daily activity; requires emergency room visit or hospitalization; necrosis or exfoliative dermatitis

7.4 Causality

The investigator must provide causality assessment as to whether or not there is a reasonable possibility that the drug caused the AE, based on evidence or facts, his/her clinical judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

The following factors should be considered when assessing causality:
• Temporal relationship: time to onset versus time drug was administered
• Nature of the reactions: immediate versus long term
• Clinical and pathological features of the events
• Existing information about the drug and same class of drugs
• Concomitant medications
• Underlying and concurrent illnesses
• Response to dechallenge (drug discontinuation) or dose reduction
• Response to rechallenge (re-introduction of the drug) or dose increase, when applicable
• Patient's medical and social history

Causality to the study drug (including study drug administration):
• Related:
− The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the nature of the reaction, patient's clinical state (e.g., disease under study, concurrent diseases, concomitant medications), or other external factors.

Or

− The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its class of drugs, or is predicted by known pharmacology.

• Not Related:
− The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the nature of the reaction, patient's clinical state (e.g., disease under study, concurrent diseases, and concomitant medications) or other external factors.

Causality to the study conduct (protocol-specified procedure):

• Related:
− The AE follows a reasonable temporal sequence from a protocol-specified procedure, and cannot be reasonably explained by the nature of the reaction, patient's clinical state (e.g., disease under study, concurrent diseases, concomitant medications), or other external factors.

• Not Related:
− The AE does not follow a reasonable sequence from a protocol-specified procedure, or can be reasonably explained by the nature of the reaction, patient's clinical state (e.g., disease under study, concurrent diseases, and concomitant medications) or other external factors.

7.5 Definition of a Serious Adverse Event (SAE)

An SAE is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- death,
- a life-threatening event (at risk of death at the time of the event),
- requires inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant disability/incapacity, or
- a congenital anomaly/birth defect in the offspring of a subject.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A distinction should be drawn between serious and severe AEs. A severe AE is a major event of its type. A severe AE does not necessarily need to be considered serious. For example, nausea which persists for several hours may be considered severe nausea but would not be an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

7.5.1 Relationship of SAE to study drug or other intervention

The relationship of each SAE to the study intervention should be characterized using one of the following terms in accordance with CHOP IRB Guidelines: definitely, probably, possibly, unlikely, or unrelated.

7.6 IRB/IEC Notification of SAEs and Other Unanticipated Problems

The Investigator will promptly notify the IRB of all on-site unanticipated, serious Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed using the eIRB system and in accordance with the timeline below. External SAEs that are both unexpected and related to the study intervention will be reported promptly after the investigator receives the report.

Type of Unanticipated Problem	Initial Notification (Phone, Email, Fax)	Written Report
Internal (on-site) SAEs Death or Life Threatening	24 hours	Within 2 calendar days
Internal (on-site) SAEs All other SAEs	7 days	Within 7 business days
Unanticipated Problems Related to Research	7 days	Within 7 business days
All other AEs	N/A	Brief Summary of important AEs may be reported at time of continuing review

7.6.1 Follow-up report

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

7.7 STUDY ADMINISTRATION

7.7.1 Treatment Assignment Methods

7.7.2 Randomization

Not applicable, all patients are receiving active therapy

7.7.3 Blinding

Not applicable, all patients are receiving active therapy

7.8 Data Collection and Management

An eCRF will be used for the current study, and a data management plan will be prepared by the BDMC (Biostatistics and Data management Core) at CHOP managed by Westat. The data will be entered in REDCap (prepared by Westat).

Previous and concomitant medications will be coded using the latest available World Health Organization (WHO) Drug Reference Dictionary. Coexistent diseases and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by written agreement between the investigator and the Westat BioStat unit.

7.9 Confidentiality

No identifiable data will be used for future study without first obtaining IRB approval or determination of exemption. The investigator will obtain a data use agreement between the provider (the PI) of the data and any recipient researchers (including others at CHOP) before sharing a limited dataset (PHI limited to dates and zip codes).

7.10 Regulatory and Ethical Considerations

7.10.1 Data and Safety Monitoring Plan

The principal investigator (PI) will monitor adverse events and other safety concerns during the study. As the drug is approved for this age group and has been studied in this indication, little new adverse events are expected. The main novel adverse event will be with food introduction while on dupilumab. The symptoms and side effects will be monitored at regular study visits for worsening EoE symptoms. In addition, the endoscopies at week 12 after the introduction will examine if active disease has returned and the food introduction will be adjusted.

The PI will ensure the accuracy, security, and validity of the data via oversight of data storage, integrity, and laboratory methodology including statistical analysis. The PI will provide oversight of study personnel to ensure the safety of enrolled subjects by enforcing the protections and safeguards outlined in the protocol.

7.10.2 Risk Assessment

7.10.2.1 Risks from Upper Endoscopy and Biopsy.

The safety of multiple biopsies is supported by studies on adult patients with Barrett's esophagus that have shown that multiple esophageal biopsies (as many as 35 to 120 esophageal biopsies in an individual patient) do not produce esophageal perforation or bleeding when performed by an experienced team of physicians, nurses, and technicians[38]. In addition, a recent NIH study demonstrated that obtaining multiple mucosal biopsies for research purposes during elective endoscopy is well-tolerated and appears to have no more than minimal risk without appreciably increasing the risk of otherwise routine endoscopy[39]. Importantly, there was no statistically significant association between the number of biopsies, type of procedure, anatomic location of research biopsies, endoscopist, or the use of nonsteroidal anti-inflammatory drugs and the risk of complications.

The incidence of perforation associated with upper endoscopy was recently reviewed in an 11-year retrospective study at CHOP. A total of 21,345 esophagogastroduodenoscopy (EGD) were performed between February 1998 and November 2008 including patients with esophageal strictures or crepe-paper esophagus. Three perforations occurred with EGD (0.02%, 95% CI 0-0.04%), and 2 with colonoscopy (0.04%, 95% CI 0-0.11%). Two of the three EGD-related perforations occurred after therapeutic EGD (foreign body removal, and dilatation of a proximal esophageal stricture and esophageal web removal), for an incidence of 0.18% (95% CI 0-0.47%). **None of the EGD-related perforations was the result of esophageal mucosal biopsies.** The presence of crepe-paper esophagus or strictures does not increase the risk for EGD-related perforations based on this review, thus these patients were not excluded from our proposed cohort. Identified risk factors for perforation on diagnostic (non-therapeutic) endoscopy were Crohn's disease (2 colonoscopy perforations) and severe hemorrhagic gastritis (1 EGD perforation of the stomach). The incidence of perforation associated with pediatric gastrointestinal endoscopy performed by pediatric gastroenterologists in this case series from CHOP was low and less than that previously reported in adults. Based upon this retrospective study, the estimated incidence of perforation from EGD at CHOP is 1 in 7,115 EGD procedures.[40, 41]

There are standard risks from moderate intravenous sedation or general anesthesia for research biopsy. To minimize the risks, all anesthesia will be done by pediatric anesthesiologist. For the intravenous sedation, the risk of assisted ventilation is 0.1-0.2% and no patients have required intubation and no history of permanent injury based on current literature. For general anesthesia, the overall risk for a serious adverse event is 1/250,000. Total adverse events with nausea and vomiting being the most common are seen in 1/29 cases[42-44].

Since the EGD procedure with biopsy is conducted under conscious sedation only, this needs to be considered for the total risk assessment. The investigative team considers the overall risk of the single research EGD procedure with biopsy under conscious sedation to be at most a minor increase above minimal risk[45].

7.10.2.2 Endoscopies after food introduction

For EoE, patients have standard care of endoscopies when foods are reintroduced into the diet. Routinely, patients have endoscopies 3-4 months after adding a new food into the diet and this is considered best practice. Therefore, it is not uncommon that patients have 3-4 standard of care (SOC) upper endoscopy with biopsies a year when food(s) are introduced into the diet. Patients in this study will have endoscopies that are no different in frequency than SOC endoscopies when foods are introduced into their diet.

Therefore, only the first endoscopy is research. The remaining endoscopies with biopsies are standard of care.

7.10.2.3 Risks from food introduction

The main risk from food introduction is exacerbation of Eosinophilic Esophagitis symptoms. Subjects will be monitored one week by phone for increasing symptoms and study visits for worsening symptoms by validated EoE questionnaires. In addition, the other risk is worsening esophageal histology and possible long-term fibrosis with untreated disease. Therefore, we monitor for worsening disease at 12 weeks after food introduction by upper endoscopy with biopsy.

7.10.2.4 Risk from dupilumab

Dupilumab is approved for asthma and atopic dermatitis at this age at Q2 week interval. The dosing from both Q1 and Q2 week were similar in atopic dermatitis pivot trial.[46]

Adverse Events (AE)			
	Placebo N=222	Dupilumab QOW N=229	Dupilumab QW N=218
Any AE	145 (63%)	167 (73%)	150 (69%)
Injection reaction	13 (6%)	19 (8%)	41(19%)
Infections	63(28%)	80(35%)	74(34%)
Conjunctivitis	2(1%)	12(5%)	7(3%)
Headache	13 (6%)	21 (9%)	11(5%)

The adverse event profile was from the pediatric clinical trials show a low AE rate:

For pediatric asthma

Adverse Reaction			
	Dupixent 200 mg Q2W + SOC N=779	Dupixent 300 mg Q2W + SOC N=788	Placebo N=792
Injection site reactions	111 (14)	144 (18)	50 (6)
Oropharyngeal pain	13 (2)	19 (2)	7 (1)
Eosinophilia	17 (2)	16 (2)	2 (<1)

For pediatric atopic dermatitis:

Adverse Reaction		
	DUPIXENT 200 mg or 300 mg Q2W (n=82)	PLACEBO (n=85)
Conjunctivitis	10%	5%
Injection site reaction	9%	4%
Gastroenteritis viral	4%	1%
Pharyngitis streptococcal	2%	0%
Viral upper respiratory tract infection	2%	1%
Bronchitis	2%	0%
Sinusitis bacterial	2%	0%
Fatigue	2%	0%

Oropharyngeal pain	2%	1%
Nausea	2%	1%
Abdominal pain upper	2%	1%
Ligament sprain	2%	0%
Procedural pain	2%	0%

For the concern of Qweek vs Q2week dosing as the study will be using Qweek dosing instead of Q2 week approved dosing. Both dupilumab 300 mg QW and Q2W have a well understood and favorable safety profile. Approximately 2500 atopic dermatitis patients were exposed to dupilumab in clinical trials; 645 atopic dermatitis patients have been exposed to 300 mg QW for ≥364 days, and 58 have been exposed to 300 mg Q2W for ≥364 days as of the 27 April 2016 biologics license application cut-off. In completed/unblinded Phase 2/3 studies of dupilumab in asthma patients (as of 30 September 2017), 2649 asthma patients were exposed to dupilumab; 1035 of these patients have been exposed to 300 mg Q2W for ≥1 year, 662 have been exposed for ≥1.5 years, and 473 have been exposed for ≥2 years.

From the Dupilumab investigator brochure-AD clinical trials comparing Q2 week to Qw showed similar AE rates:

Primary System Organ Class Preferred Term MedDRA Version 18.0	Placebo qw (N=517)	Dupilumab 300 mg q2w (N=529)	Dupilumab 300 mg qw (N=518)	Dupilumab Combined (N=1047)
Number of patients with at least 1 such Event, n (%)	359 (69.4)	366 (69.2)	357 (68.9)	723 (69.1)
Infections and infestations	167 (32.3)	175 (33.1)	177 (34.2)	352 (33.6)
Nasopharyngitis	52 (10.1)	55 (10.4)	58 (11.2)	113 (10.8)
Upper respiratory tract infection	15 (2.9)	18 (3.4)	24 (4.6)	42 (4.0)
Conjunctivitis	3 (0.6)	21 (4.0)	20 (3.9)	41 (3.9)
Oral herpes	8 (1.5)	20 (3.8)	13 (2.5)	33 (3.2)
Conjunctivitis bacterial	2 (0.4)	7 (1.3)	8 (1.5)	15 (1.4)
Herpes simplex	4 (0.8)	9 (1.7)	4 (0.8)	13 (1.2)
Folliculitis	10 (1.9)	4 (0.8)	8 (1.5)	12 (1.1)
Bronchitis	6 (1.2)	5 (0.9)	4 (0.8)	9 (0.9)
Urinary tract infection	9 (1.7)	7 (1.3)	2 (0.4)	9 (0.9)
Impetigo	8 (1.5)	5 (0.9)	3 (0.6)	8 (0.8)
Skin infection	7 (1.4)	5 (0.9)	2 (0.4)	7 (0.7)
Sinusitis	6 (1.2)	2 (0.4)	2 (0.4)	4 (0.4)
Skin and subcutaneous tissue disorders	187 (36.2)	109 (20.6)	102 (19.7)	211 (20.2)
Dermatitis atopic	158 (30.6)	70 (13.2)	62 (12.0)	132 (12.6)
Alopecia	4 (0.8)	3 (0.6)	9 (1.7)	12 (1.1)
Rash	2 (0.4)	6 (1.1)	2 (0.4)	8 (0.8)
Pruritus	10 (1.9)	1 (0.2)	6 (1.2)	7 (0.7)
Pruritus generalised	6 (1.2)	1 (0.2)	3 (0.6)	4 (0.4)
General disorders and administration site conditions	59 (11.4)	85 (16.1)	100 (19.3)	185 (17.7)
Injection site reaction	28 (5.4)	51 (9.6)	72 (13.9)	123 (11.7)
Fatigue	7 (1.4)	12 (2.3)	9 (1.7)	21 (2.0)
Injection site erythema	2 (0.4)	6 (1.1)	7 (1.4)	13 (1.2)
Pyrexia	6 (1.2)	6 (1.1)	5 (1.0)	11 (1.1)
Nervous system disorders	49 (9.5)	67 (12.7)	58 (11.2)	125 (11.9)
Headache	26 (5.0)	45 (8.5)	41 (7.9)	86 (8.2)
Dizziness	12 (2.3)	6 (1.1)	5 (1.0)	11 (1.1)
Musculoskeletal and connective tissue disorders	32 (6.2)	52 (9.8)	41 (7.9)	93 (8.9)
Back pain	12 (2.3)	9 (1.7)	12 (2.3)	21 (2.0)

Primary System Organ Class Preferred Term MedDRA Version 18.0	Placebo qw + TCS (N=315)	Dupilumab 300 mg q2w + TCS (N=110)	Dupilumab 300 mg qw + TCS (N=315)	Dupilumab Combined + TCS (N=425)
Number of patients with at least 1 such Event, n (%)	214 (67.9%)	81 (73.6%)	227 (72.1%)	308 (72.5%)
Infections and infestations	111 (35.2%)	39 (35.5%)	108 (34.3%)	147 (34.6%)
Nasopharyngitis	33 (10.5%)	15 (13.6%)	37 (11.7%)	52 (12.2%)
Upper respiratory tract infection	20 (6.3%)	7 (6.4%)	21 (6.7%)	28 (6.6%)
Oral herpes	5 (1.6%)	3 (2.7%)	8 (2.5%)	11 (2.6%)
Sinusitis	3 (1.0%)	0	10 (3.2%)	10 (2.4%)
Viral upper respiratory tract infection	4 (1.3%)	2 (1.8%)	7 (2.2%)	9 (2.1%)
Conjunctivitis bacterial	2 (0.6%)	1 (0.9%)	6 (1.9%)	7 (1.6%)
Rhinitis	2 (0.6%)	1 (0.9%)	5 (1.6%)	6 (1.4%)
Herpes simplex	1 (0.3%)	1 (0.9%)	4 (1.3%)	5 (1.2%)
Molluscum contagiosum	1 (0.3%)	0	5 (1.6%)	5 (1.2%)
Folliculitis	5 (1.6%)	1 (0.9%)	2 (0.6%)	3 (0.7%)
Influenza	6 (1.9%)	1 (0.9%)	2 (0.6%)	3 (0.7%)
Furuncle	2 (0.6%)	2 (1.8%)	0	2 (0.5%)
Gastroenteritis	5 (1.6%)	1 (0.9%)	1 (0.3%)	2 (0.5%)
Eczema herpeticum	4 (1.3%)	1 (0.9%)	0	1 (0.2%)
Skin infection	7 (2.2%)	0	1 (0.3%)	1 (0.2%)
General disorders and administration site conditions	32 (10.2%)	20 (18.2%)	65 (20.6%)	85 (20.0%)
Injection site reaction	18 (5.7%)	11 (10.0%)	50 (15.9%)	61 (14.4%)
Fatigue	7 (2.2%)	1 (0.9%)	6 (1.9%)	7 (1.6%)
Pyrexia	4 (1.3%)	2 (1.8%)	1 (0.3%)	3 (0.7%)
Asthenia	1 (0.3%)	2 (1.8%)	0	2 (0.5%)
Skin and subcutaneous tissue disorders	110 (34.9%)	20 (18.2%)	63 (20.0%)	83 (19.5%)
Dermatitis atopic	84 (26.7%)	12 (10.9%)	25 (7.9%)	37 (8.7%)
Erythema	2 (0.6%)	1 (0.9%)	6 (1.9%)	7 (1.6%)
Acne	6 (1.9%)	0	6 (1.9%)	6 (1.4%)
Dermatitis contact	3 (1.0%)	1 (0.9%)	4 (1.3%)	5 (1.2%)
Urticaria	8 (2.5%)	1 (0.9%)	3 (1.0%)	4 (0.9%)
Pruritus	4 (1.3%)	1 (0.9%)	1 (0.3%)	2 (0.5%)
Eye disorders	19 (6.0%)	23 (20.9%)	59 (18.7%)	82 (19.3%)
Conjunctivitis allergic	10 (3.2%)	7 (6.4%)	22 (7.0%)	29 (6.8%)
Blepharitis	2 (0.6%)	5 (4.5%)	8 (2.5%)	13 (3.1%)
Eye pruritus	2 (0.6%)	2 (1.8%)	9 (2.9%)	11 (2.6%)
Dry eye	1 (0.3%)	2 (1.8%)	3 (1.0%)	5 (1.2%)
Eye irritation	2 (0.6%)	2 (1.8%)	3 (1.0%)	5 (1.2%)
Allergic keratitis	0	2 (1.8%)	1 (0.3%)	3 (0.7%)
Ocular hyperaemia	0	2 (1.8%)	0	2 (0.5%)

Overall, a higher incidence of injection site reactions has been observed in the dupilumab-treated subjects, consistent with the SC injection of a protein biologic. Most injection site reactions were mild to moderate in intensity, and less than 2% were severe or led to treatment discontinuation. The proportion of patients experiencing injection site reactions diminished over time during the treatment period.

The only known adverse event that has been seen is conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, blepharitis, dry eye, eye pruritus, herpes simplex (primarily mucocutaneous in nature), and oral herpes but only for the atopic dermatitis indication. These eye-related disorders and mucocutaneous herpes infections appear to be atopic dermatitis specific, as no increase in incidence of these events has been observed in clinical studies of other indications including EoE. Most events were mild in intensity and transient in nature and did not necessitate treatment discontinuation.

In the 52-week phase 3 clinical trial for EoE, 81 pts were randomized in Part A 1:1 to dupilumab (42) or placebo(39) for 24 weeks; 77 pts continued into Part C to dupilumab for a further 28 weeks (40 from dupilumab/dupilumab, 37 from placebo/placebo). The most common treatment-emergent adverse events for dupilumab/dupilumab arm and placebo/dupilumab arm were injection-site reactions (10.0% and 21.6%) and injection site erythema (10.0% and 13.5%). In part B of the phase 3 clinical trial, patients were randomized 1:1:1 to placebo, q weekly or q2 weekly dosing with 115 patients in each arm. There were no significant differences in adverse event rates. The overall rates of treatment-emergent adverse events were similar for dupilumab/placebo (83.8%/70.5%), the most common being injection-site reactions (MedDRA High-Level Term, 37.5%/33.3%).[11, 12]

The dosing from the 52 weeks clinical trial for EoE showed no novel adverse events compared to the adverse event for asthma or atopic dermatitis. There were lower rates of conjunctivitis in the EoE clinical trial compared to the atopic dermatitis clinical trial and similar rate to the asthma clinical trial.

To summarize, the most common risks that have identified in pediatric trials of dupilumab are injection site reaction, and conjunctivitis and there are no significant differences between Qweek and Q2week dosing.

It is also not predicted to be any difference in adverse events between patients 6-12 with asthma, atopic dermatitis or EoE based on

1) No difference was detected in subjects > 12 years of age in published phase 3 trials in asthma, atopic dermatitis and EoE
2) No difference in adverse events was seen in our patients > 6 years of age treated for asthma or atopic dermatitis with or without Eosinophilic Esophagitis
3) There are no biologic reasons to predict an increased risk of adverse events in patients with EoE at any age.

7.10.2.5 Risk from blood draws

The risks associated with drawing blood include discomfort, bleeding, bruising, or swelling where the needle is inserted, local infection, and, in rare cases, syncope. A local skin anesthetic (i.e., topical lidocaine/prilocaine cream) may be placed on the skin before the blood draw to reduce the pain of the stick. Side effects from this agent (mainly skin rash) may occur, including allergic reactions. The

7.10.2.6 Risk for Research laboratories

The risk from research laboratories are minimal. We are not collecting genetic data. We are only collecting lymphocyte function, expression, and eosinophil expression.

7.10.2.7 Risk from Questionnaires:

There is a possibility that the participant and/or parent/legal guardian too personal. A participant and/or parent/legal guardian may refuse to answer any questions that make them uncomfortable. There is also a possibility that answers may be read by others; however, the participants' records are carefully protected so this is very unlikely.

7.10.3 Potential Benefits of Trial Participation

Potential benefits for the subject include clinical and histologic improvement with the use of dupilumab. In addition, subjects may be able to add additional foods into their diet with improvement in quality of life, and nutritional status.

In the phase 2 clinical trial, 65.2% of active treated patients had less than 6 eosinophils per high power field compared to zero in the placebo group[11]. In the phase 3 clinical trial of dupilumab for EoE, at Week 24 endpoint, 58.8% of dupilumab- vs 6.3% placebo-treated patients achieved histological remission of less 6 eosinophils per hpf(P<0.0001).[12] Therefore, we would assume that over 50% will respond in the initial screening phase and benefit from dupilumab. In the previous EoE clinical trials, the patients were not allowed to add new foods into their diet. This proposed clinical trial will address an important family question and goal of adding foods back into their diet. In addition, patients' nutritional issue will improve as foods are added into their diet and patients benefit from improved quality of life.

7.10.4 Risk-Benefit Assessment

All subjects will have active therapy and therefore the risks are from three inventions: endoscopy, food introduction and dupilumab compared to the benefit of expansion of the foods into the diet are lower than the benefit of improved quality of life and nutritional status. The risk from endoscopy which is identical to standard of care endoscopy with food introduction is equivalent to SOC. The risk of food introduction is minimal and will be monitor closely by repeat clinical visits and endoscopy to ensure patient safety. The assumption of expanded diet will enhance nutritional status of patients and improve their quality of life. Dupilumab has low adverse event profile with minimal serious side effects. Therefore, the benefit of the study (adding new foods) significantly outweighs the risk of endoscopy, food introduction and dupilumab.

7.11 Recruitment Strategy

Subjects will be recruited from Children's Hospital of Philadelphia Eosinophilic Esophagitis Program. The program has over 3000 subjects in its clinical data base. All the information that is needed captured as routine standard of care.

7.12 Informed Consent/Assent and HIPAA Authorization

The Investigator is responsible for and will obtain informed consent from each subject in the study, in accordance with the ICH-GCP Guidelines, the Declaration of Helsinki, and applicable regulatory requirements.

Subjects will be informed of the nature of the study, its aim, possible risks and restrictions, its duration, and the compensation that they might receive. The protocol will be explained during a meeting prior to study enrollment, and each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time. The subject should read the ICF before signing and dating it and a copy of the signed document should be given to the subject. No subject can enter the study before his/her informed consent has been obtained. Children if able will sign assent. The parents or legal representative(s) of all children and adolescents regardless of

age must also sign the ICF.

The consent form may need to be revised during the study should important new information become available that may be relevant to the safety of the subject. In this instance approval should always be given by the CHOP IRB and existing subjects informed of the changes and re-consented. This is documented in the same way as previously described.

The Investigator should keep a copy of the consent of the subject, inform the subject's primary physician about participation in the clinical study.

The study physician will be available to explain the medical aspects of the study, risks and benefits of the intervention, and answer questions during the consent process

7.12.1 Screening

Patients will be screen through chart review for diagnosis of Eosinophilic Esophagitis and foods to be introduced. Patients will be approached during Allergy, Gastroenterology or Center for Pediatric Eosinophilic Disease Clinics.

7.12.2 Main Study

The consent will be completed in person to allow sufficient time to review the consent and answer all questions and concerns. Subjects and their families will also be emailed the consent prior to screening visit if requested by the family. All consent procedure will follow CHOP SOP and Division of Allergy and Immunology Research SOP. Obtaining and reviewing consents will be done in separate visits not part of standard of care visits. The visits will be done in the dedicated Allergy research room.

7.12.3 Consent/HIPAA Authorization Plan for Subjects Who Reach Age of Majority

At the next study visit after the subject turns 18 (age of majority), the subject will review the written consent/HIPPA authorization for their continued participation in the trial. The subject will continue in the study if they sign the consent.

7.13 Payment to Subjects/Families

7.13.1 Reimbursement for travel, parking, and meals

Subjects will be paid $35 per visit for travel, parking, and time. Subjects will be $125 for each endoscopy due to extended time.

8 PUBLICATION

We will publish the data upon completion of the study and finalization of the data basis and statistical plans. The data will be presented in national/international medical meetings and submitted for peer review publications.

9 REFERENCES

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