15 December 2022
EMA/6467/2023
Human Medicines Division

CHMP extension of indication variation assessment report

Dupixent

dupilumab

Procedure no: EMEA/H/C/004390/II/0062

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AAS	Anti-drug antibody analysis set
Ab	Antibody
ABPA	Allergic bronchopulmonary aspergillosis
ACQ-5	Juniper Asthma Control Questionnaire-5
AD	Atopic dermatitis
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical Therapeutic Classification
BMI	Body mass index
COVID-19	Coronavirus Disease 2019
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CRSwNP	Chronic rhinosinusitis with nasal polyps
CSR	Clinical study report
DSQ	Dysphagia Symptom Questionnaire
EC	Ethics Committee
ECG	Electrocardiogram
EDP	Eosinophilic esophagitis diagnostic panel
EoE	Eosinophilic esophagitis
EoE-EREFS	Eosinophilic Esophagitis-Endoscopic Reference Score
EoEHSS	Eosinophilic Esophagitis Histology Scoring System
EoE-IQ	Eosinophilic Esophagitis Impact Questionnaire
EoE-SQ	Eosinophilic Esophagitis Symptom Questionnaire
EOS	Eosinophils
EREFS	Endoscopic Reference Score
eTMF	electronic Trial Master File
FLG	Filaggrin
HLT	High-level term
HPF	High power field
IBD	Inflammatory bowel disease
ICF	Informed consent form
ICH	International Council for Harmonisation
IgE	Immunoglobulin E
IgG4	Immunoglobulin G4
IL	Interleukin
IL-4Rα	Interleukin-4 receptor alpha
iNKTs	invariant natural killer T cells
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing antibody
NAS	Neutralizing antibody analysis set
NEC	Not elsewhere classified
NES	Normalized Enrichment Scores
PCSV	Potentially clinically significant value
PD	Pharmacodynamic
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity

PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
POEM	Patient-Oriented Eczema Measure
PPI	Proton pump inhibitor
PRN	Per required need (as needed)
PRO	Patient-Reported Outcomes
PT	Preferred term (MedDRA)
Q1	Quartile 1
Q3	Quartile 3
QOL	Quality of life
QW	Once weekly
RBM	Risk-Based Monitoring
RQLQ(s)+12	Rhinoconjunctivitis Quality of Life Questionnaires for 12 years and older
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SDR	Source data review
SDV	Source data verification
SE	Standard error
SMQ	Standardized MedDRA query
SOC	System organ class
SPRR3	Small proline-rich protein 3
STC	Swallowed Topical Steroids
TARC	Thymus and activation-regulated chemokine

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, sanofi-aventis groupe submitted to the European Medicines Agency on 1 April 2022 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of eosinophilic esophagitis (EoE) in adults and adolescents 12 years and older who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy, based on the pivotal Study R668-EE-1774. This is an ongoing phase 3, randomized, double-blind, placebo-controlled, 3-part (A, B, C) safety and efficacy study with an initial 24-week treatment period in adults (≥18 years of age) and adolescents (≥12 to <18 years of age) with EoE, and which includes an extended treatment period to a total of 52 weeks. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.
Version 8.0 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0059/2020) on the agreement of a paediatric investigation plan (PIP). A modification to the agreed PIP has been submitted to the EMA and approved (P/0361/2021).

At the time of submission of the application, the PIP P/0361/2021 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The MAH received Scientific Advice on the development for their product Dupilumab for treatment of adult and adolescent patients with eosinophilic esophagitis from the CHMP on 28 June 2018

(EMEA/H/SA/2744/7/2018/II). The Scientific Advice pertained to the clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Finbarr Leacy

Timetable	Actual dates
Submission date	1 April 2022
Start of procedure	23 April 2022
CHMP Rapporteur Assessment Report	20 June 2022
PRAC Rapporteur Assessment Report	20 June 2022
CHMP Co-Rapporteur Critique	29 June 2022
PRAC members comments	29 June 2022
PRAC Outcome	7 July 2022
CHMP members comments	11 July 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	14 July 2022
Request for supplementary information (RSI)	21 July 2022
CHMP Rapporteur Assessment Report	17 October 2022
PRAC Rapporteur Assessment Report	14 October 2022
PRAC Outcome	27 October 2022
CHMP members comments	28 October 2022
Updated CHMP Rapporteur Assessment Report	3 November 2022
Request for supplementary information (RSI)	10 November 2022
Joint Rapporteur's assessment report circulated on:	30 November 2022
Joint Rapporteur's updated assessment report on the MAH's responses circulated on	8 December 2022
CHMP opinion	15 December 2022
The CHMP adopted a report on similarity of Dupixent with JORVEZA	15 December 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Eosinophilic esophagitis (EoE) is a serious, chronic, type 2 inflammatory, immune-mediated disease of the esophagus.

The MAH's initially claimed therapeutic indication was:

"Dupixent is indicated for the treatment of eosinophilic esophagitis in adults and adolescents 12 years and older who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy."

Epidemiology

The prevalence of EoE is estimated at 22.7 per 100,000 worldwide and has been increasing. Eosinophilic esophagitis has been reported in all ages. However, most cases are in children and adults younger than 50 years. Gender differences in EoE have been consistently reported, with males affected 3 to 4 times more often than females, but there are no known gender-related differences in disease biology, clinical manifestations, severity, or natural history of the disease.

Aetiology and pathogenesis

The disease is characterized by type 2 inflammation with esophageal eosinophilia leading to symptoms of esophageal dysfunction. Growing evidence suggests that a type 2 cytokine-mediated immune response plays an important role in the development of EoE. Patients with EoE have increased levels of esophageal inflammatory infiltrates, including eosinophils, T-lymphocytes, mast cells, and basophils, as well as type 2-associated chemokines and cytokines, such as eotaxin-3, interleukin (IL)-4, IL-5, and IL-13. In particular, mRNA expression of IL4, IL-5, and IL-13 is increased in the esophagus of patients with EoE compared with in controls. Esophageal biopsies and blood samples of patients with active EoE have increased levels of the type 2 prototypical cytokines and chemokines including IL-4, IL-5, and IL-13. Eosinophilic esophagitis is also distinguished by the expression of a unique esophageal transcriptome and the interplay of early life environmental factors with distinct genetic susceptibility elements at 5q22 (thymic and stromal lymphopoietin [TSLP]) and 2p23 (calpain 14 [CAPN14]). CAPN14 is overexpressed by the esophageal epithelia in patients with EoE. Unlike TSLP, which is associated with multiple allergic disorders, CAPN14 may account for the tissue specificity of esophageal disease in EoE because CAPN14 invokes a pathway that alters basic epithelial cell functions, including barrier integrity.

The induction of eotaxin-3, an eosinophil chemoattractant, is thought to be an important factor in EoE pathogenesis. The two most up-regulated genes in esophageal biopsies from EoE patients (compared to normal controls) encode eotaxin-3 and periostin, another protein induced by type 2 cytokines and thought to promote inflammation and remodeling. Furthermore, esophageal biopsies and blood samples of patients with active EoE have increased levels of cytokines and chemokines associated with

type 2 inflammation, including IL-4 and IL-13, TSLP, and eotaxin-3 secreted by cells involved in allergic inflammation: T cells, mast cells, basophils, invariant natural killer T cells, and esophageal epithelial cells. Mutations in the eotaxin-3 and TSLP genes, whose functions propagate type 2 inflammation, have been associated with EoE risk.

Clinical presentation, diagnosis

The primary clinical manifestations of EoE in both adults and children over 10 years of age are dysphagia and food impaction. Other clinical manifestations such as heartburn, diarrhea and weight loss have also been reported. The symptoms lead to substantially impaired quality of life (QOL). Patients with advanced fibrostenotic disease live with frequent symptoms while eating as well as anxiety and fear regarding meals. As the disease progresses, the fibrosis/strictures that develop may result in food impaction in the esophagus. Food impaction is a traumatic event for patients and often requires medical intervention, including emergency room visits for manual removal to relieve the impaction. Eosinophilic esophagitis (EoE) is the underlying cause of approximately 50% of the food impaction cases that present in the emergency department.

Complications of EoE include food impaction, strictures, esophageal dysmotility, increased esophageal infections, aspiration, and spontaneous esophageal rupture. Food impaction can occur at any stage of the disease, either as an initial manifestation of EoE or after many years of EoE disease duration. Dysphagia, food impaction and regurgitation may increase the risk for aspiration, including aspiration pneumonia. Esophageal inflammation in EoE may also result in esophageal perforation. Most cases of esophageal perforation are due to undiagnosed or untreated EoE. Although fungal infections are a complication of topical corticosteroids, esophageal candidiasis may also occur spontaneously in patients with EoE.

Diagnostic criteria for EoE include the presence of clinical symptoms and ≥15 eosinophils per high-power field (eos/hpf; 400X) in mucosal esophageal biopsies. Approximately 90% of patients have associated endoscopic findings, including fixed or transient concentric rings, longitudinal furrows, white plaques, edema, fragile or crepe-like mucosa, and/or stricture. Edema, rings and furrows are common endoscopic features, seen in at least half of patients. The severity of esophageal rings scored using the EoE Endoscopic Reference Score is correlated with the risk of food impaction.

Patients with EoE have substantially impaired QOL. Reduction in the quality of life may be due to: 1) symptoms, such as dysphagia or food impaction, which may result in the need to cough, gag, or vomit to dislodge food, 2) diagnostic procedures, including the repeated endoscopic probing of the esophagus, and 3) behaviours to avoid symptoms, such as dietary modification (food avoidance) and prolongation of meal times, leading to avoidance of social dining. The true burden of disease for patients is likely underestimated due to compensatory behaviours. These dietary modifications and compensatory behaviours can cause psychosocial issues for patients. Overall, this serious disease results in substantial morbidity for the affected patient and impairs several aspects of quality of life including social functioning, emotional well-being, and productivity by disrupting one of the basic activities of daily living, namely eating.

Management

Management of EoE is complex and requires a multidisciplinary approach. Current therapeutic approaches include chronic dietary elimination, conventional medicinal therapies, and esophageal dilation. The combination of diet modification and conventional medicinal therapies (swallowed topical corticosteroid formulations [orodispersible budesonide (Jorveza)]) can be effective in the management

of some patients with EoE. However, long term compliance is often a challenge, and when these approaches are stopped, patients typically experience a recurrence of symptoms. As many as 25% of patients may have significant ongoing symptoms, despite treatment with dietary modification and corticosteroids. Furthermore, a significant portion of patients do not respond to corticosteroids, and those who do respond may not have sustained benefit, a critical limitation for this chronic disease. Endoscopic dilation can provide immediate relief but carries a risk (albeit low) of serious complications due to esophageal perforation and does not have any impact on the underlying inflammatory pathology of EoE.

Diet modification can be an effective way to manage EoE by removing immunogenic dietary antigens or triggers of inflammation and thereby reduce symptoms of disease. However, these diets are very difficult for patients to adhere to, and can lead to decreased QoL and feelings of social isolation. Therefore, diet modification is limited as a long-term solution for management of EoE.

Conventional medicinal therapy for EoE typically includes off-label proton-pump inhibitor (PPI) usage and use of systemic or topical corticosteroids. Proton-pump inhibitors are an important conventional treatment option for EoE. In addition to acid-suppression properties, PPIs have anti-inflammatory properties that impact the pathobiology of EoE. Proton-pump inhibitors inhibit IL-4-stimulated eotaxin-3 expression in EoE esophageal cells and block STAT6 binding to the promoter. Studies have shown approximately 50% of EoE patients respond to treatment with high-dose PPIs. Long-term use of PPIs, however, has been associated with an increased risk of chronic kidney disease and may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. There are no prospective, double-blind, randomized trials comparing the efficacies of corticosteroids to PPI or elimination diet to PPI.

Topical corticosteroids are the mainstay of treatment and other presentations (e.g., inhaler) have been adapted off-label worldwide to allow oral administration via swallowing: fluticasone is used orally as a spray from a metered-dose inhaler, and budesonide as a viscous preparation. Jorveza (budesonide) is an orodispersible tablet specifically formulated for swallowed topical use and is approved only in the EU for treatment of patients 18 years of age and older with EoE. While swallowed topical corticosteroids are often effective in quickly reducing eosinophilic esophageal inflammation, as shown in randomized controlled trials, there are limited data on long-term safety or efficacy of such agents.

Chronic inflammation of the esophagus leads to fibrosis, tissue damage, and tissue remodelling. Studies have shown that the presence of more severe endoscopic findings is associated with food-impaction history and that those findings also correlated with impaired esophageal distensibility. In patients with fibrostenotic phenotype (fixed rings or strictures), esophageal dilation is often necessary to relieve symptoms. Balloons or wire-guided bougies are used to induce a mucosal tear to mechanically open the esophagus in order to improve symptoms. Esophageal dilations are not a cure for EoE but rather provide temporary relief of dysphagia by increasing the patency of the esophagus. However, this improvement in esophageal patency is not long-lived if the underlying disease remains untreated.

In summary, the current available medicinal therapies for EoE are limited due to variable response rates and variable symptom improvement, relapse after therapy cessation, failure to show sustained benefit, the potential for side effects and adverse effects on QoL. Therefore, an unmet need is seen for safe and effective treatment options that address the underlying inflammation of EoE to prevent the disease progression and improve clinical symptoms in adults and adolescents 12 years and older inadequately controlled by, intolerant to, or who are not candidates for conventional medicinal therapy.

2.1.2. About the product

Dupilumab is a human monoclonal immunoglobulin G4 (IgG4) antibody that inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4 receptor alpha (IL-4Rα) subunit shared by the IL-4 and IL-13 receptor complexes. It inhibits IL-4 signaling via the type I receptor (IL-4Rα/γc), and both IL-4 and IL-13 signaling through the type II receptor (IL-4Rα/IL-13Rα). Blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13 type 2 cytokine-induced responses, including the release of pro-inflammatory cytokines, chemokines, and IgE.

Dupilumab is currently approved for the following indications: atopic dermatitis (AD), asthma, and chronic rhinosinusitis with nasal polyps (CRSwNP) and prurigo nodularis (PN) (commission decision pending).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

A Scientific Advice, with implications for the present Application was received from the CHMP in 2018 (EMEA/H/SA/2744/7/2018/II).

2.1.4. General comments on compliance with GCP

The MAH states that the clinical studies presented in this dossier were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Council for Harmonisation guidelines for Good Clinical Practice and applicable regulatory requirements.

2.2. Quality aspects

No new quality data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Justification regarding existing Drug-Device Combination

In *3.2.R Regional information* justifications have been provided regarding the use of the existing Medical Device Part of the Drug-Device Combination (DDC) 300 mg PFS, PFS-S and PFP for the introduction of the Eosinophilic esophagitis indication for the adolescent (12 to 17 years of age) and adult patient population.

Change assessment towards MDR Article 117 (PFS, PFS-S, PFP)

The MAH has determined that there are no changes to the design or intended purpose of the device (part), nor is there a new medical device being introduced. Therefore, a Notified Body opinion is not required. The details of the MAH´s assessment are as follows:

• There is no impact on the medical device clinical use; as it will still be administered with the same procedure and at the same injection sites (abdomen, upper thigh regions and upper arm).

• There are no changes to the medical device instructions for use related to the new therapeutic indication.

• There is no change to the intended users; the self-administration patient characteristics (functional capabilities/impairment such as perceptual, cognitive, manual dexterity, other comorbidities) are equal to the currently approved population.

Table 1 Intended users and patient populations of Dupilumab 300 mg PFS, PFS-S and PFP for the new therapeutic indication

Dupixent® 300 mg (2mL) PFS, PFS-S and PFPs for the Eosinophilic Esophagitis indication	
Intended Users	Healthcare Professionals (HCP) & Lay Caregivers Patient self-administration: Adults and Adolescents (12 to 17 years of age – under adult supervision)
Patient population	Adults and Adolescents (12 to 17 years of age)

Usability Studies

The MAH has determined that there is no need for additional Usability Studies.

The quality, safety and/or efficacy of the DDC product are not affected as the assessment results conclude the following:

• There are no changes to the medical device instructions for use related to the new therapeutic indication.

• There are no changes to the performance requirements, nor the specifications of the medical device.

• No new or different risks in relation to the medical device use have been identified, therefore no new mitigations need to be introduced. The existing Risk Management File will be updated as part of the life cycle management activities. The hazard list is already covering this new therapeutic indication.

No need for additional Usability Studies; usability for the PFS, PFS-S and PFP is supported by human factors data that may be bridging data to the same identical device part used with the patient populations tested to support the approved indications.

The intended user population is unchanged versus the DDC currently authorised, as the self-administration patient characteristics (functional capabilities/impairment such as perceptual, cognitive, manual dexterity, other comorbidities) are equivalent to the currently approved populations. Therefore, the bridging data demonstrated the effective use of the DDC by the same intended user population.

2.2.2. Discussion on quality

No new quality data have been submitted in this application.

The proposed new Eosinophilic esophagitis indication for the adolescent (12 to 17 years of age) and adult patient population does not result in the introduction of a new medical device or a modification to the design, or aforementioned intended use/purpose of the medical device part of the Drug Device Combination (DDC). Therefore, it is agreed that the variation application supporting the new therapeutic indication does not require a Notified Body Opinion (NBOp) for the currently authorised DDC.

The age group of the intended patient population of adults and 12 to 17-year-old adolescents is covered by authorised indications.

It is agreed that there is no need for additional Usability Studies as the new therapeutic indication has no impact on the 1) intended users, 2) the clinical use, and 3) use-related risks. In addition, there is no difference in the medical device instructions for use compared with the authorised instructions.

From a quality point of view, the MAH's justifications regarding the use of the existing Medical Device Part of the DDC 300 mg PFS, PFS-S and PFP for the new therapeutic indication in the adolescent (12 to 17 years of age) and adult patient population is accepted.

2.2.3. Conclusion on the quality aspects

The available quality data do not raise concern in the indication.

2.3. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3.1. Ecotoxicity/environmental risk assessment

A claim of exclusion from submission of environmental risk assessment studies is made according to Section 2 of the 2006 CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (ERA Guideline corr 2) because dupilumab is a monoclonal antibody consisting of linked naturally occurring amino acids. Per the ERA Guideline, vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempt from ERA study requirements because by their nature they are unlikely to result in significant risk to the environment.

2.3.2. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application.

The claim for ERA exemption by the MAH is justified and in conformity with the ERA guideline since the type II variation request concerns a monoclonal antibody consisting of naturally occurring amino acids. Dupilumab is significantly metabolized in-vivo and is expected to be readily and rapidly degraded in wastewater treatment systems and in the environment. The antibody's structure and mode of action do not indicate any specific risk to the environment.

2.3.3. Conclusion on the non-clinical aspects

The available non-clinical data do not raise concern in the indication.

There are no new non clinical data submitted in support of this indication. Dupilumab is a monoclonal antibody consisting of naturally occurring amino acids. The intended use does not lead to a significant increase in environmental exposure.

- Considering the above data, dupilumab is not expected to pose a risk to the environment.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study / Clinical Study Report (CSR) Location/ Study Status	Study Population/Analysis Set	Primary Efficacy-related Objectives	Study Design and Duration	Treatment: Dose, Route of Administration, Frequency (number of participants randomized in the Full Analysis Set)
R668-EE-1324 Module 5.3.5.1 R688-EE-1324 Completed (Database lock date 26 Jul 2017)	Adult males and females ≥18 to 65 years of age at the time of study entry with EoE. Documented diagnosis of EoE by endoscopy prior to or at screening. The full analysis set (FAS) included all randomized participants.	To assess the clinical efficacy of repeat SC doses of dupilumab, compared with placebo, to relieve symptoms in adult participants with active, moderate-to-severe EoE.	Phase 2, multicenter, double-blind, randomized, placebo-controlled study investigating the efficacy, safety, tolerability, pharmacokinetics (PK), and immunogenicity of dupilumab in adult participants with EoE. After the 12-week double-blind treatment phase, participants were followed for an additional 16 weeks post-treatment.	• Placebo (N=24) • Dupilumab 300 mg QW[1] (N=23)
R668-EE-1774 Module 5.3.5.1 R668-EE-1774 Completed (Data cutoff date/Database lock date for CSR): Part A (08 May 2020/20 May 2020) Part A/C (18 Nov 2020/17 Dec 2020) Part B (09 Sep 2021/30 Sep 2021) Ongoing: Part B/C (Not yet reported)	Adult males and females ≥18 years of age and adolescent males and females ≥12 to <18 years of age at the time of study entry with EoE. Confirmed diagnosis of EoE that was not responsive to high-dose proton pump inhibitor (PPI) therapy. Part A and Part B were carried out as 2 separate parts with distinct participants enrolled in both parts. For Part B, of the total study population, at least 10% were adolescents and at least 30% had a history of prior use of swallowed topical corticosteroids. The FAS included all randomized participants.	**Part A:** To determine the treatment effect of dupilumab compared with placebo in adult and adolescent participants with EoE after 24 weeks of treatment as assessed by histological and clinical measures. **Part B:** To demonstrate the efficacy of dupilumab treatment compared with placebo in adult and adolescent participants with EoE after 24 weeks of treatment as assessed by histological and clinical measures. **Part C:** To assess the safety and efficacy of dupilumab treatment in adult and adolescent participants with EoE for additional 28 weeks (up to a total of 52 weeks of treatment) as assessed by histological and clinical measures.	Randomized, double-blind, multi-center, 3-part, phase 3 study: Part A and Part B (each consisting of a 24-week double-blind treatment period), Part C (a 28-week extended active treatment period), and a 12-week post-treatment follow-up period following the end of the extended active treatment period for participants who enter into Part C or following the end of Parts A or B of the double-blind treatment period for participants who do not enter Part C. Study participation began with enrollment into Part A. Enrollment for Part B began immediately after the last patient was enrolled in Part A. Participants in Part A were not eligible to participate in Part B.	**Part A** • Placebo (N=39) • Dupilumab 300 mg QW (N=42) **Part A/C** • Dupilumab 300 mg QW (N=77) **Part B** • Placebo (N=79) • Dupilumab 300 mg QW (N=80) • Dupilumab 300 mg Q2W (N=81)

[1]R668-EE-1324- A loading dose of 600 mg was administered on study day 1, followed by weekly doses 300 mg from week 1 to week 11.

2.4.2. Pharmacokinetics

The PK of functional dupilumab in serum has previously been extensively described in healthy subjects and in participants with AD, asthma, or CRSwNP. The PK of dupilumab is characterized as non-linear with parallel linear and target-mediated elimination pathways, with the target-mediated pathway expressing a high degree of non-linearity. As drug concentrations increase and become sufficient to saturate the target-mediated pathway, the PK of dupilumab moves to a linear and dose-proportional profile.

The presence and type of type 2 inflammatory disease studied to date does not influence the PK or PD of dupilumab. Dupilumab is well absorbed after SC administration, characterized by parallel non-saturable catabolic and target-mediated disposition; the estimated bioavailability of 61% to 64% has

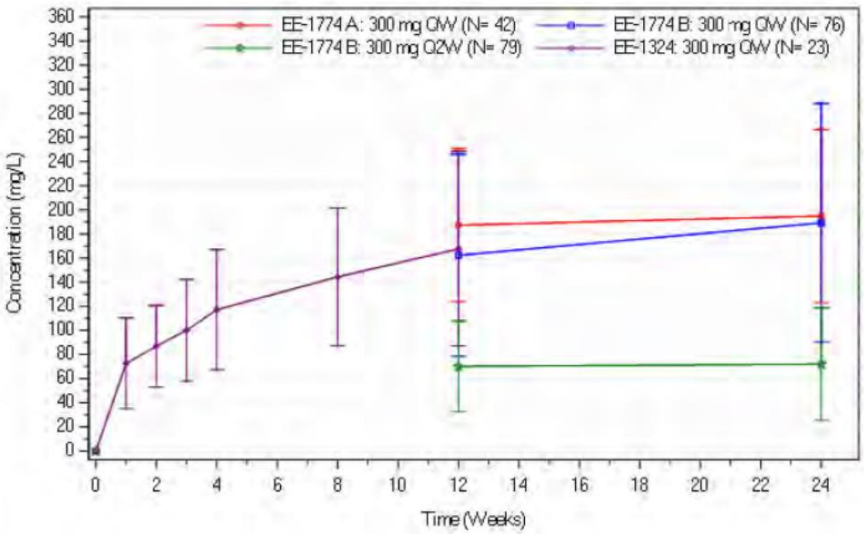
consistently been reported in patients with type 2 inflammatory conditions. Body weight is the primary covariate influencing the distribution and elimination of dupilumab. After accounting for body weight in adults and paediatric participants ≥6 years, age does not affect the PK of dupilumab.

The PK of dupilumab in adult and adolescent participants with EoE was assessed in the supportive phase 2 study R668-EE-1324, phase 3 pivotal study R668-EE-1774 Part A, Part B, and Part A/C, population PK (PopPK) analysis and comparison analyses of PK across studies.

Dupilumab Drug Concentrations in Serum Across EoE Studies

Trough concentration-time profiles for functional dupilumab concentrations across study R668-EE-1774 Part A and Part B and study R668-EE-1324 are shown in the Figure below. Trough concentrations at steady state in EoE study participants following either the dupilumab 300 mg QW or 300 mg Q2W regimen were consistent with those observed in other indications.

Figure 1 Mean (SD) Concentrations of Functional Dupilumab in Serum by Time and Treatment Group in Adult and Adolescent Participants with Eosinophilic Esophagitis Receiving Dupilumab 300 mg QW or 300 mg Q2W (R668-EE-1774 Part A and Part B and R668-EE-1324, PKAS)



Treatment Group	Week 0	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Week 24
	Number of Participants							
R668-EE-1774 A: 300 mg QW	41	-	-	-	-	-	42	37
R668-EE-1774 B: 300 mg QW	73	-	-	-	-	-	65	63
R668-EE-1774 B: 300 mg Q2W	77	-	-	-	-	-	67	68
R668-EE-1324: 300 mg QW	22	22	23	20	22	21	23	-

Abbreviations: N=number of participants; PKAS=pharmacokinetic analysis set; Q2W=once every 2 weeks; QW=once weekly; SD=standard deviation

Note: The table below the figure shows the number of participants at each time point by treatment group. Participants in R668-EE-1774 received dupilumab 300 mg QW for 24 weeks in Part A and dupilumab 300 mg QW or 300 mg Q2W for 24 weeks in Part B. Participants in R668-EE-1324 received dupilumab 300 mg QW for 12 weeks with a 600 mg loading dose on day 1. Concentration data were sampled only at week 12 and week 24 for R668-EE-1774 Parts A and B.

Mean trough concentration in participants treated with dupilumab 300 mg QW, measured 1 week after the initial 600 mg loading dose was 72.7 mg/L. Upon weekly dosing, trough concentrations increased to 171 mg/L at week 12. The week 12 concentrations of dupilumab in serum were similar across EoE Studies R668-EE-1324 and R668-EE-1774 Parts A and B.

Similarity between mean dupilumab concentrations at weeks 12 and 24 in Part A and Part B of Study R668-EE-1774 for participants treated with dupilumab suggest that concentrations are at or near

steady-state within 12 weeks of initiating treatment with dupilumab 300 mg QW and 300 mg Q2W when administered without a loading dose.

The consistency in trough concentration at week 12 between study R668-EE-1324, which included a dupilumab 600 mg loading dose, and study R668-EE-1774, in which no loading dose was used, shows that the loading dose had no influence on the steady-state trough concentration obtained at week 12. The consistency in trough concentration with dupilumab 300 mg QW is illustrated again at week 24 when comparing the mean concentrations from Part A and Part B of study R668-EE-1774.

Considering the difference in dosing interval between the dupilumab 300 mg QW and 300 mg Q2W dosing regimens, the steady-state trough concentration observed at week 12 and week 24 for the 300 mg Q2W dosing regimen are as predicted from a model-based analysis and consistent with dupilumab concentrations following the 300 mg QW dosing regimen.

Absorption

Dupilumab is generally well absorbed following SC administration with an estimated absolute bioavailability of 61% to 64% based on a previous population PK analysis of healthy subjects and participants with asthma or AD. Given the ability of the global population PK model to accurately and effectively describe the PK in the patient population with EoE, the model confirms similar bioavailability in the EoE population.

Distribution

The estimated volume of distribution at steady state (Vss) for the EoE population from the population PK model was 4.49 L. This value is similar to the value obtained for the previous population PK analysis of healthy subjects and participants with asthma or AD. For more detail on the absorption and distribution profile of dupilumab, refer to the initial AD marketing application.

Elimination

Linear and non-linear clearance parameters in participants with EoE are consistent with that observed following administration of dupilumab in AD and asthma patient populations and, therefore, the time to reach non-detectable concentrations after the last steady-state dose is the same across adult and adolescent populations.

Dose proportionality and time dependencies

Dupilumab is characterized by parallel linear and non-linear target-mediated kinetics. This non-linear PK profile is observed at drug concentrations below that required to saturate the target-mediated pathway, resulting in a greater than dose proportional increase in exposure. As drug concentrations increase to levels greater than those required to saturate the target-mediated pathway, the PK profile reverts to a linear and dose-proportional profile. For further details of dose proportionality, refer to the initial adult AD marketing application.

Participants receiving dupilumab 300 mg QW or 300 mg Q2W, including participants in study R668-EE-1774 Part A, Part B, and Part A/C, achieved concentrations saturating the non-linear clearance pathway throughout the duration of the dosing interval. This is demonstrated by the approximate dose-proportionality (as measured by steady-state area under the concentration-time curve [AUC] over a normalized 2-week dose interval) between the 300 mg Q2W and 300 mg QW regimens.

Saturation of the non-linear clearance pathway can be considered a necessary but insufficient criterion to maximize target engagement and may not always translate to full efficacy, if, for example, drug distribution to a deeper tissue compartment is required for complete efficacy

Trough concentrations of functional dupilumab were at or near steady state by week 12 in participants receiving dupilumab 300 mg Q2W or 300 mg QW based on simulated profiles of the entire concentration-time course over 24 weeks using the re-estimated population PK model, which included 22 pooled studies including EoE data.

For adults (≥18 years of age) and adolescents (≥12 to <18 years of age) with EoE, the proposed dose regimen is 300 mg QW without a loading dose. The proposed posology is supported by results of study R668-EE-1774 (Part A, Part B, and Part A/C), in which no loading dose was administered. A total loading dose of 600 mg SC was administered in study R668-EE-1324. The decision to not use a loading dose in the phase 3 study R668-EE-1774 was informed by the well-established observation that a loading dose, while effective at achieving higher systemic concentrations sooner and reducing the time and number of dosing intervals needed to achieve steady state, has no influence on the steady-state concentrations and, hence, efficacy at week 24.

Despite the limitation that the measures of dysphagia were different between study R668-EE-1324 (Straumann Dysphagia Instrument [SDI]) and study R668-EE-1774 (Dysphagia Symptom Questionnaire (DSQ) total score), changes from baseline relative to placebo followed a similar time course indicating that administration of a loading dose did not impact onset of effect for the 300 mg QW regimen. Lack of the loading dose in the phase 3 study R668-EE-1774 is not related to the observed lack of efficacy in reducing dysphagia symptoms at week 24 with the 300 mg Q2W regimen. Administration of a loading dose reduces the time to reach steady state but does not affect steady-state exposures (maximum concentration, trough concentration, AUC). This is demonstrated by similarity of the week 12 concentration of dupilumab in serum across EoE studies R668-EE-1324 (loading dose) and R668-EE-1774 Part A and Part B (no loading dose).

The implication for DSQ response is that loading dose, in the best case, may potentially result in a greater response earlier for the 300 mg Q2W regimen but will not affect the magnitude of response at week 24. Given that the PK of an mAb is characterized by relatively slow clearance, the dose-response of the 300 mg QW regimen (without a loading dose) over the first 4 weeks of therapy can be taken as a surrogate of the dose response of 300 mg Q2W regimen with a loading dose. The relatively small difference between the dupilumab 300 mg QW and 300 mg Q2W regimens in the DSQ total score mean change from baseline response at week 4 does not explain the large difference in mean change from baseline response observed at week 24 between these regimens.

Intrinsic and Extrinsic Factors Affecting Pharmacokinetics

- Body Weight

PK assessments identified body weight as the primary covariate affecting the PK of dupilumab, with an increase in concentration with a decrease in body weight. Across studies, dupilumab 300 mg QW has been studied in adult participants with AD (phases 2 and 3), asthma (phase 2), or CRSwNP (phase 2) with body weight as low as 42 kg. Supportive safety data from the studies using the 300 mg QW dose regimen in adults (≥42 kg), provided the rationale for the use of dupilumab 300 mg QW dose regimen in adult and adolescent participants with EoE with body weight ≥40 kg. Dupilumab 300 mg QW has not been studied in EoE participants with a body weight <40 kg as patients (adults or adolescents) with body weight <40 kg were excluded from study R668-EE-1774.

- Age

Population PK analyses of dupilumab across adult (≥18 years), adolescent (≥12 to <18 years), and paediatric (≥6 to <12 years) patients with AD have demonstrated that after accounting for body weight, age did not have a clinically meaningful impact on the PK of dupilumab. This is further confirmed by the ability of the global population PK model to describe dupilumab PK in the EoE population where body weight and not age was a covariate in the model. Based on observed data, once weight differences between adults and adolescents are accounted for, drug concentrations in serum are similar between both age groups.

To facilitate a comparison of dupilumab exposure in adult and adolescent participants of lighter body weights, mean steady state trough concentrations of dupilumab following administration of 300 mg QW were compared across studies of adult and adolescent participants with EoE, asthma, AD or CRSwNP weighing <70 kg.

Table 2 Summary of Mean (SD) Concentrations of Functional Dupilumab in Serum by Study for Adult and Adolescent Participants <70 kg with Atopic Dermatitis, Asthma, Chronic Rhinosinusitis with Nasal Polyps, or Eosinophilic Esophagitis Receiving Dupilumab 300 mg QW

	Concentration of Functional Dupilumab in Serum (mg/L) and Baseline Body Weight (kg)					
	300 mg QW			300 mg Q2W		
Study	n	Mean (SD) Concentration	Mean (SD) Body Weight	n	Mean (SD) Concentration	Mean (SD) Body Weight
Adults		(N=351)			(N=512)	
ACT11457 (Asthma)	11	225 (58.1)	59.8 (6.02)	0	-	
EFC13579 (Asthma)	0	-	-	128	95.8 (36.6)	60.1 (6.75)
EFC13691 (Asthma)	0	-	-	29	82.3 (27.6)	59.3 (6.48)
ACT12340 (CRSwNP)	4	202 (94.7)	63.4 (6.68)	0		
EFC14146 (CRSwNP)	0	-	-	34	103 (39.6)	59.2 (7.19)
EFC14280 (CRSwNP)	0	-	-	86	62.7 (47.8)	60.4 (7.41)
R668-AD-1117 (AD)	20	185 (94.5)	60.9 (3.68)	0		
R668-AD-1224 (AD)	134	225 (86.0)	60.0 (6.09)	46	103 (42.7)	59.0 (5.63)
R668-AD-1334 (AD)	64	216 (88.8)	59.4 (6.96)	84	96.9 (38.9)	59.3 (7.15)
R668-AD-1416 (AD)	83	242 (74.2)	59.2 (7.31)	89	99.0 (32.9)	59.8 (7.15)
R668-EE-1324 (EoE)	7	227 (104)	59.7 (8.54)	0	-	
R668-EE-1774 Part A (EoE)	5	254 (28.2)	61.5 (4.56)	0	-	
R668-EE-1774 Part A/C (EoE)	11	164 (78.1)	66.5 (4.69)	0	-	
R668-EE-1774 Part B (EoE)	15	227 (91.6)	60.7 (7.35)	16	91.3 (40.9)	61.4 (6.14)
Adolescents		(N=54)			(N=55)	
EFC13579 (Asthma)	0	-	-	17	116 (48.8)	47.4 (10.75)
EFC13691 (Asthma)	0	-	-	1	118 (---)	65.0 (---)
R668-EE-1774 Part A (EoE)	9	228 (68.5)	56.0 (9.92)	0	-	-
R668-EE-1774 Part A/C (EoE)	16	176 (87.6)	58.0 (10.74)	0	-	-
R668-EE-1774 Part B (EoE)	18	243 (99.4)	55.3 (8.11)	16	86.9 (71.0)	54.0 (8.07)

Abbreviations: AD=atopic dermatitis; CRSwNP=chronic rhinosinusitis with nasal polyps; EoE=eosinophilic esophagitis; n=number of participants; Part A/C=Part C (participants from Part A); PKAS=pharmacokinetic analysis set; Q2W=every 2 weeks; QW=once weekly; SD=standard deviation

Note: Trough concentrations of participants receiving dupilumab 300 mg QW at Week 12 (R668-EE-1324, R668AD-1117, ACT11457), Week 16 (R668-AD-1334, R668-AD-1416, ACT12340), Week 24 (R668-EE-1774 Part A and Part B), or Week 52 (R668AD1224, R668-EE-1774 Part A/C [placebo or dupilumab in Part A]). Participants received dupilumab 300 mg Q2W at Week 16 (R668-AD-1334, R668-AD-1416), Week 24 (R668EE1774 Part B, EFC14146, EFC13691), or Week 52 (R668-AD-1224, EFC13579, EFC14280).

Dupilumab 300 mg QW was administered as a 600 mg loading dose on day 1 in studies R668AD-1334, R668AD1416, R668-AD-1224 (AD), R668-EE-1324 (EoE), ACT12340 (CRSwNP), EFC13691 (asthma), and without a loading dose in studies R668AD1117 (AD), ACT11457 (asthma), and R668-EE-1774 (EoE).

Concentrations include the subset of adult (≥18 years of age) and adolescents (≥12 to <18 years of age) participants <70 kg at baseline.

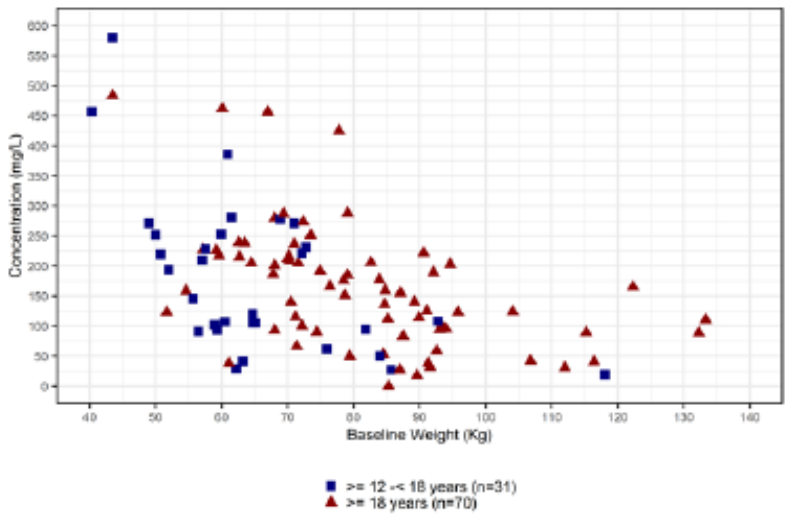
Source: T_PC_SUM2

Mean (SD) steady-state trough concentrations of dupilumab at Week 52 for adolescent participants (aged ≥12 to <18 years; mean [SD] baseline body weight 61.1 [13.7] kg) with EoE that received dupilumab 300 mg QW in R668-EE-1774 Part A/C were 176 ±83.2 mg/L (N=18). These observed mean dupilumab concentrations were within the range of variability for dupilumab concentrations at Week 52 in adult participants with EoE (≥18 years; mean [SD] baseline body weight 86.4 [19.0] kg) who also received dupilumab 300 mg QW in R668-EE-1774 Part A/C (134 ±69.8 mg/L, N=49).

In adolescents initially randomized to receive placebo during the double-blind treatment period followed by dupilumab 300 mg QW upon entering Part C (Placebo/Dupilumab 300 mg QW), mean (SD) steady state concentrations of dupilumab at Week 52 were 141 ±97.5 mg/L (N=10) compared to 155 ±97.0 mg/L (N=27) in adults. The mean (SD) weight of the adolescent participants was 71.5 ±20.7 kg (range 50 to 118 kg) and the mean (SD) weight of the adults was 83.0 ±17.9 kg (range 60.1 to 132 kg). In adolescent participants who received dupilumab 300 mg QW throughout the entire study period, mean (SD) steady state trough concentrations of dupilumab at Week 52 were 201 ±142 mg/L (N=21) compared to 164 ±108 mg/L in adults (N=45) receiving the same regimen. Mean (SD) weight of the adolescent and adult participants was 61.8 ±11.5 kg (range 40.3 to 92.8 kg) and 79.8 ±18.1 kg (range 43.5 to 133 kg), respectively.

A scatter plot of the steady state concentrations at Week 52 by baseline body weight and age group in adult and adolescent participants with EoE who received dupilumab 300 mg QW in R668-EE-1774 Part B/C is presented below:

Figure 2 Scatter Plot of Concentrations of Functional Dupilumab in Serum at Week 52 by Baseline Body Weight and Age Group in Adult and Adolescent Patients with Eosinophilic Esophagitis Receiving 300 mg QW (Study R668-EE-1774, Part B/C)



Based on the scatter plot of Week 52 trough dupilumab concentrations, adolescents and adults with similar body weight exhibited similar dupilumab exposures following administration of 300 mg QW. The 52-week data in adolescent EoE participants who received 300 mg QW in Part B/C are therefore consistent with the data previously reported for Part A/C, and are also within the range of variability previously reported for the 300 mg QW regimen in adults (≥18 years).

In addition, a pooled analysis of mean steady state trough concentrations of dupilumab by body weight category has also been conducted for participants receiving dupilumab 300 mg QW. Although mean trough concentrations of dupilumab in participants weighing ≥40 kg to ≤50 kg were higher than trough

concentrations in participants weighing >50 kg, individual data indicated that adolescents and adults with similar body weight exhibited overlapping exposure.

2.4.3. Pharmacodynamics

Mechanism of action

Dupilumab treatment provides a marked reduction in downstream effectors of the type 2 immune response and in EoE-associated inflammation. Both Thymus and activation-regulated chemokine (TARC) and eotaxin-3 responses were similar across EoE studies and were indiscriminatory of dose regimen (300 mg QW versus 300 mg Q2W).

The magnitude and time course of TARC response in EoE participants were similar to that observed in asthma and CRSwNP participants. However, the magnitude of TARC response was markedly higher in AD participants (2-fold higher percent change from baseline), indicating a higher sensitivity of the biomarker to drug effect in AD.

Exposure-Response Relationships

Exposure-response (E-R) relationships on both histologic infiltration of eosinophils in the esophagus and the absolute and percent change from baseline in DSQ total score show that the dupilumab 300 mg QW regimen is associated with histologic and clinical efficacy in EoE participants. In contrast, dose-response and E-R relationships showed that the dupilumab 300 mg Q2W regimen was not differentiated from placebo on change from baseline in DSQ total score response but showed similar differentiation to the 300 QW regimen on histologic endpoints.

Exposure-safety analysis showed little evidence for an E-R relationship between dupilumab trough concentration and AESIs at week 24.

Immunogenicity

The incidence of treatment-emergent ADA-positive responses was low, <5% in all treatment groups. The available immunogenicity data did not show a clinically significant effect of ADA on safety. There was no clear association between injection site reactions or other commonly related treatment-emergent adverse events and the development of ADA. However, due to the small number of participants who were ADA positive, meaningful conclusions cannot be drawn.

In Pool 2a (phase 3 placebo-controlled pooled study parts), a transient, treatment-emergent ADA-positive response was seen in 1.5% (3/195) of participants receiving dupilumab and 0.8% (1/118) in the dupilumab 300 mg QW group. In Pool 2b (phase 2 and phase 3 placebo-controlled pooled study parts), a transient treatment-emergent ADA-positive response was seen in 1.4% (3/218) of participants receiving dupilumab and 0.7% (1/141) in the dupilumab 300 mg QW group.

2.4.4. PK/PD modelling

A population modelling analysis was performed to characterize the pharmacokinetics (PK) of dupilumab in patients with EoE, including data from the Phase 2 study (Study R668-EE-1324) in adults with EoE and the Phase 3 Study (R668-EE-1774) in adult (≥18 years old) and adolescent EoE patients (≥12 to <18 years old).

A global population PK (PopPK) model was previously developed to characterize dupilumab concentration data from healthy subjects and patients with AD or asthma. This model, developed from a large dataset in three different populations, was intended to serve as a robust starting point for PopPK analyses of dupilumab in other Th2- mediated inflammatory diseases, such as EoE. In the current analysis, an external visual predictive check (VPC) was performed to assess whether dupilumab PK is consistent between patients with EoE and other populations. Dupilumab PK data from patients with EoE was subsequently combined with PK data from previous dupilumab studies in healthy subjects and patients with AD or asthma, and the previous population PK model was re-fit to the combined data-set including patents with EoE.

The primary objectives of the population pharmacokinetic (PopPK) analysis were to:

- Assess the PK of dupilumab in patients with eosinophilic esophagitis (EoE) using an external validation approach with a PopPK model developed for dupilumab in healthy subjects and patients with asthma or AD;
- Update the PopPK model developed for dupilumab in healthy subjects and patients with asthma or AD with the addition of PK data in patients with EoE;
- Investigate the effects of selected EoE covariates on PK parameters;
- Generate individual subject PK parameters and exposure predictions across patient populations.

Studies Included in the Population Modelling Analysis

Dupilumab concentration-time data from 20 clinical studies (eight Phase 1, seven Phase 2, and five Phase 3 studies) in healthy adult subjects, adult patients with AD, and adult (≥18 years old) and adolescent (≥12 to <18 years old) patients with asthma supported the previously developed global population PK model. Two additional studies, a Phase 2 study in adult patients with EoE and a Phase 3 study in adult and adolescent patients with EoE were included in the analysis.

Covariates

- BLWT – baseline body weight (kg)
- AGEY – baseline age (years)
- ADA3 – ADA peak titer category; ADA3=0 for patients with negative ADA or pre-existing ADA that was not boosted by treatment; ADA3 = 1 for treatment-emergent or treatment-boosted ADA peak titer 0 < to < 1000; ADA3 = 2 for treatment-emergent or treatment-boosted ADA peak titer ≥1000 to < 10000; ADA3 = 3 for treatment-emergent or treatment-boosted ADA peak titer ≥10000
- POP – study population; POP = 0 for healthy subjects; POP = 1 for patients with asthma; POP = 2 for patients with atopic dermatitis; POP = 3 for patients with eosinophilic esophagitis

Additional covariates were described in the dataset for patients with EoE in Studies R668-EE-1324 and R668-EE-1774. The covariates below were used in an exploratory assessment using the final updated model. These covariates were listed as missing for all other studies.

- SEX – character/numeric sex
- RACE – character/numeric race
- HGTBL – baseline height (cm)

- BMIBL – baseline BMI (kg/m2)
- ADAMTC – ADA status/maximum titer category (=0 if negative or missing, =1 if positive with ADA peak titer 0 < to < 1000 [low titer], = 2 if positive with ADA peak titer ≥1000 to < 10000 [moderate titer], =3 if positive with ADA peak titer ≥10000)
- ALABL – baseline alanine aminotransferase (U/L)
- ASTBL – baseline aspartate aminotransferase (U/L)
- ALPBL – baseline alkaline phosphatase (U/L)
- EEOSBL – baseline peak esophageal intraepithelial eosinophil count (eos/high power field [hpf]; x400)
- EREFSBL – baseline Eosinophilic Esophagitis-Endoscopic Reference Total Score

  o Study R668-EE-1324 used an EREFBL measurement instrument with a scale score of 0-9.

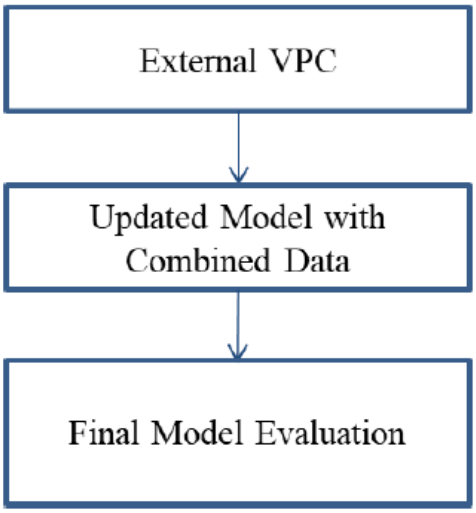
  o Study R668-EE-1774 used an EREFBL measurement instrument with a scale score of 0-18.
- HSSGRBL – baseline Eosinophilic Esophagitis Histology Scoring System (aka Collins Histology Score) mean grade score (Scale 0-3)
- HSSSTBL - baseline Eosinophilic Esophagitis Histology Scoring System (aka Collins Histology Score) mean stage score (Scale 0-3)
- DSQBL – Dysphagia Symptom Questionnaire (DSQ) total score at baseline (Scale 0 – 84), note: available for patients in R668-EE-1774 only.

Data were classified as outliers using the population conditional weighted residuals (CWRES) and individual weighted residuals (IWRES). Observations with |CWRES|>6 or |IWRES|>6 were considered potential outliers. The influence of these outliers was evaluated by comparing estimates of the key model parameters (i.e., linear elimination constant [KEL] and distribution volume of the central compartment [Vc]) from model fits on data with and without the outliers. The outliers were considered influential if key parameter estimates differed by more than 15%.

Modelling Methodology

The general approach of this modelling analysis was to perform an external VPC to assess the consistency of dupilumab PK in patients with EoE with other populations, using the previously developed PopPK global model for dupilumab in healthy subjects and patients with asthma or AD. Following the external VPC, the population PK model was re-fit to an updated dataset combining data from patients with EoE with the pooled dataset from the global model. Parameter re-estimation included determining the impact of the previously evaluated demographic covariate of body weight in the updated pooled dataset. In addition, covariate effects to explain potential differences in dupilumab PK between patient populations were to be evaluated, if necessary. An internal VPC was performed on the updated final model following the re-estimation of the parameter effects to verify the predictive performance of the updated final model was adequate. Finally, the updated final model was used to generate post-hoc estimates of individual PK parameters and exposure predictions for each of the patient populations (i.e., EoE, asthma and AD). An exploratory assessment of covariates specific to EoE was performed.

Figure 3 Flow Chart of Planned Model Development



Model development was based on the following criteria:

- Successful minimization and completion of covariance steps in NONMEM®;
- Precision of parameter estimates;
- Assessment of standard goodness-of-fit plots;
- Reductions in NONMEM® objective function value (OFV) for hierarchical models; and,
- Reductions in residual variability.

In addition, the stability of the models throughout the model development process was monitored. To avoid ill-conditioning, inspection of the covariance matrix of estimates at every stage of model development was performed in order to verify that extreme pairwise correlations ($\rho > 0.95$) of the parameters were not encountered. The condition number of the correlation matrix of the parameter estimates (i.e., the ratio of the largest to smallest eigenvalues) was also assessed to ensure values less than 1000. Values greater than 1000 are indicative of a severely ill-conditioned model. If during the course of model development convergence or covariance estimation problems occurred, ad hoc NONMEM® runs were to be performed to evaluate the nature of the ill-conditioning.

An external visual predictive check (VPC) was performed using the previously developed model (two compartment disposition model with parallel linear and Michaelis-Menten elimination and first-order SC absorption) to predict dupilumab concentrations in EoE patients. Parameter estimates were fixed to their final values from the previous global model and used to simulate 500 datasets which replicated the designs, subject populations, dose regimens, sample sizes and covariate distributions from Study R668-EE-1324 and Study R668-EE-1774. Appropriate statistical intervals (e.g., median, 5th percentile, and 95th percentile) of dupilumab concentrations were computed at nominal PK time points in the observed and each of the simulated datasets. The observed summary measures were then compared to the statistical intervals (e.g., median, 5th and 95th percentiles) of the simulated summary measures and plotted in order to provide a visual assessment of the predictive performance of the previous PK model in patients with EoE. The data for patients with EoE were combined with data from the previous PopPK model (global model) developed using dupilumab data from healthy subjects and patients with asthma or AD, and the population PK model was re-analysed with the combined dataset. Parameter estimates for the PopPK model with combined data from all 22 studies were compared with those from the previous model.

Accounting of Subjects and Samples

The dataset included a total of 4396 unique subjects, of which 4307 were included in the analysis (251 patients with EoE, 2015 patients with asthma, 1839 patients with atopic dermatitis, and 202 healthy volunteers) and 29515 quantifiable PK samples, of which 29184 were included. A total of 5910 post-dose PK samples were below the limit of quantification (BLQ; 16.8%), of which 52 (6.9%) were from Studies R668-EE-1324 and R668-EE-1774 and the rest were from the 20 studies in healthy subjects and patients with asthma or AD. All BLQ samples were excluded from the analysis. Subjects and PK samples that were previously excluded in the 20 studies used to develop the global PopPK model were also excluded in this analysis, including 11 patients with asthma and 74 patients with AD. There were 331 quantifiable PK samples in the dataset that were excluded from the analysis. Additionally, in the updated PopPK model there were 4 subjects excluded from Study R668-EE-1774 due to all post-dose concentrations being BLQ. No quantifiable PK samples were excluded from the EoE population.

Table 3 Summary of Subjects and PK Samples by Population

Population	Included in Analysis		Summary of Subjects and Samples in the Dataset					
	Subjects	Included Samples	Subjects	Subjects Excluded	Total Quantifiable Observations	Excluded Quantifiable Observations	Post-dose BLQ Observations	Post-dose BLQ%[a]
EoE	251	700	255	4	700	0	52	6.9%
Asthma	2015	13118	2026	11	13143	25	2827	17.7%
Atopic Dermatitis	1839	13417	1913	74	13723	306	2237	14.3%
Healthy Subjects	202	1949	202	0	1949	0	794	29.0%
TOTAL	4307	29184	4396	89	29515	331	5910	16.8%

PK = Pharmacokinetic; BLQ = Below the limit of quantification; EoE = Eosinophilic esophagitis
[a] Post-dose BLQ% = Post-dose BLQ/(Included Samples + Post-dose BLQ)*100
Note: Subjects and sample exclusions for asthma[9] and atopic dermatitis[10] were previously reported.

Summaries of Covariates and Baseline Demographics

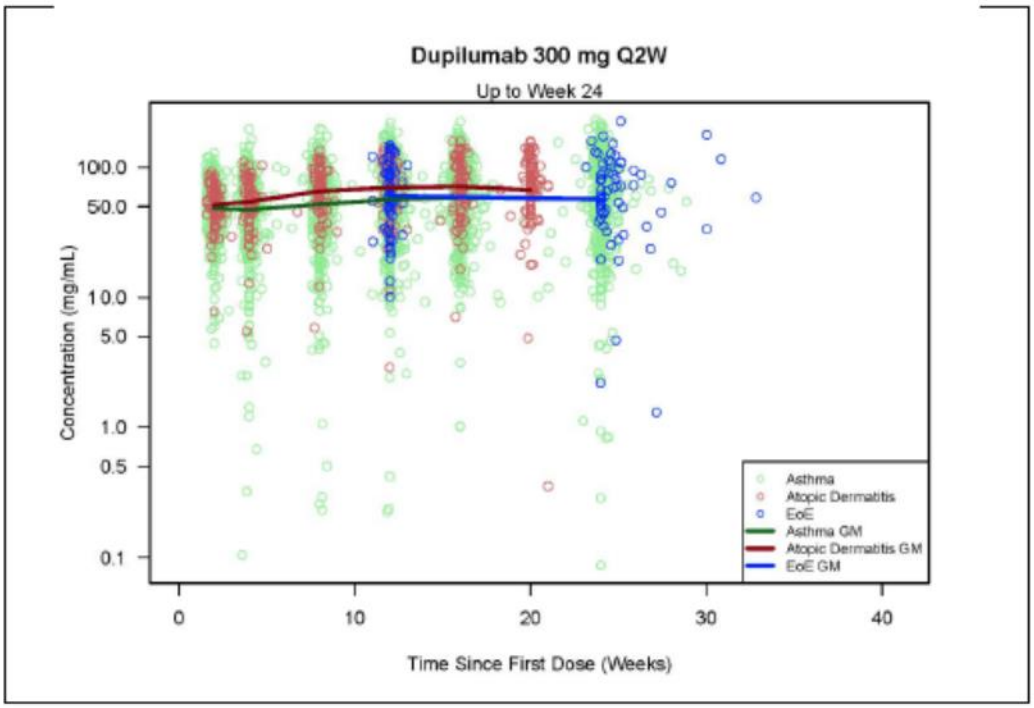
In the pooled analysis, most subjects were adults (96.8%) with only the asthma (69 subjects) and EoE (68 subjects) patient populations including adolescents. The median (range) age for all populations was 42 years (12 to 88 years). Patients with EoE had the lowest median age of 28 years, healthy subjects (32 years) and patients with AD (36 years) had similar median ages, and patients with asthma had the highest median age of 50 years. The median weights for each of the populations were similar with the pooled populations having a median (range) of 76.0 kg (32.0 kg to 185.6 kg). The majority (86.1%) of the pooled populations had no treatment-emergent or treatment-boosted ADA response to dupilumab, 12.3% had a low ADA titer, 1.2% had a moderate ADA titer, and 0.4% had a high ADA titer. Patients with EoE comparatively had less of an immunological response, with 96% having no/negative ADA status, 3.2% with a low ADA titer, and 0.8% with a moderate ADA titer. None of the EoE patients had a high ADA titer.

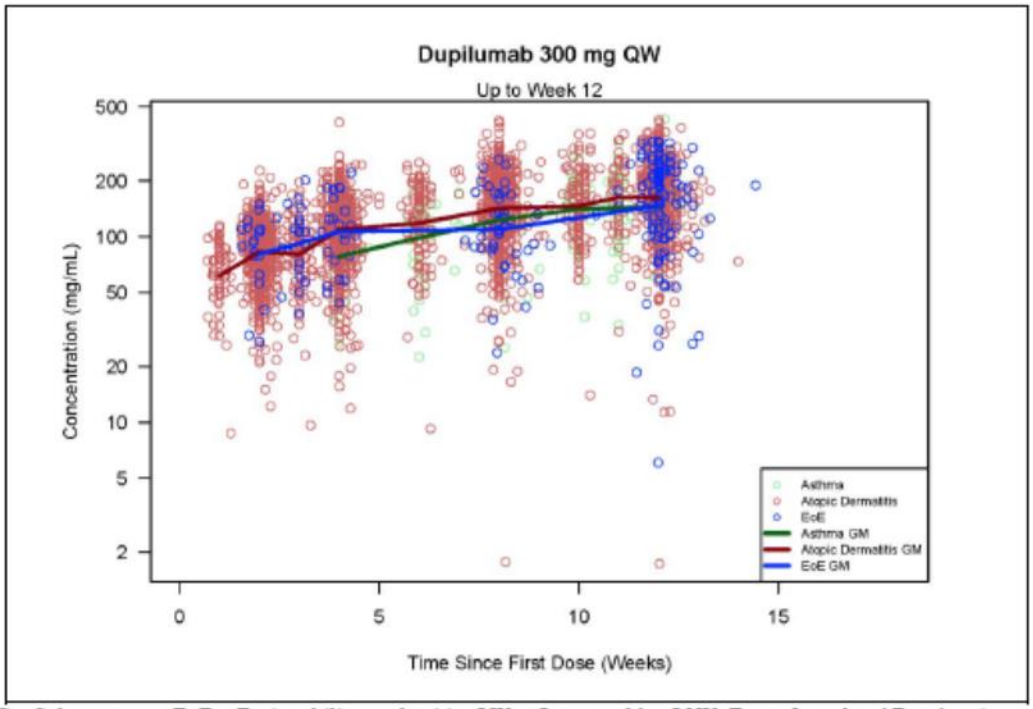
Results

Exploratory plots comparing dupilumab concentration over time for matched dosing regimens across populations (i.e., patients with atopic dermatitis, asthma, and EoE) are shown below. The plots illustrate the individual observed concentrations and the geometric mean for each population receiving dupilumab 300 mg Q2W to the end of treatment (week 24 for Part B) and 300 mg QW through week

12 on a semi-log scale. The open circles indicate the observed concentration data, with green representing patients with asthma, red, patients with atopic dermatitis and blue, patients with EoE. In general, the distributions of the observed concentrations for each of the patient populations are similar and the geometric means seem to be overlapping, suggesting that dupilumab PK in patients with EoE is similar to other patient populations.

Figure 4 Observed Dupilumab Concentration vs. Time for SC Dose Administration in Different Patient Populations



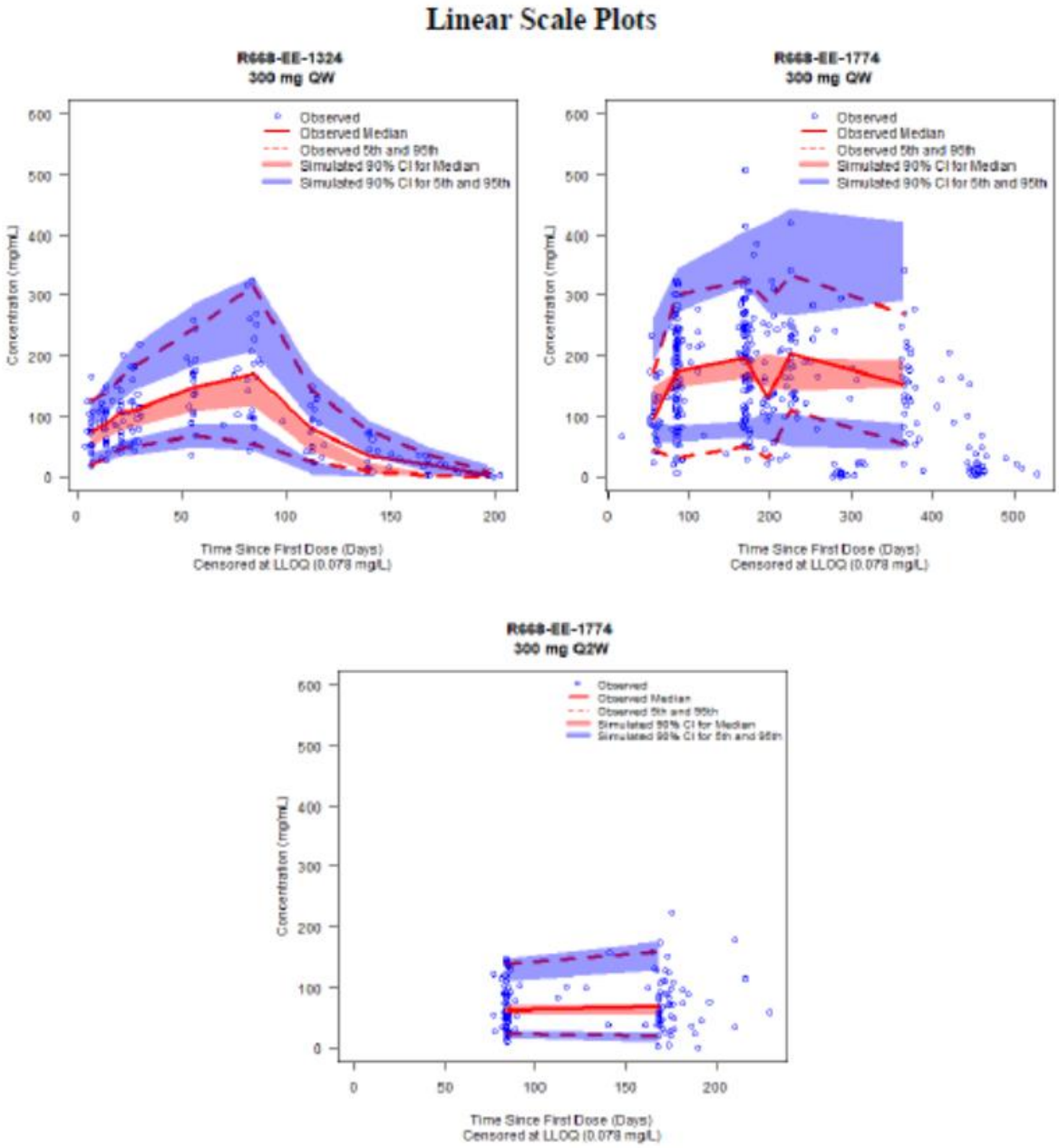


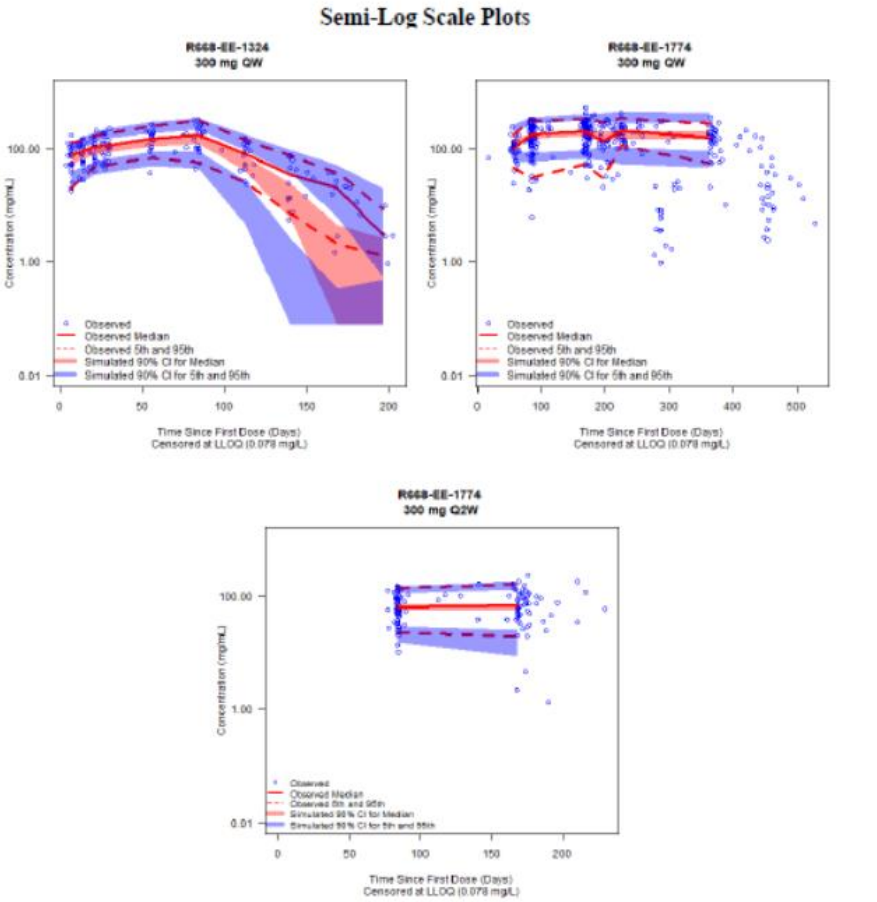
SC = Subcutaneous; EoE = Eosinophilic esophagitis; QW = Once weekly; Q2W; Every 2 weeks; AD = Atopic dermatitis; GM = Geometric mean

Note: Patient populations are identified by color: asthma (green), atopic dermatitis (red); and EoE (blue). Open circles are observed concentrations and lines represent geometric mean at nominal times. The dupilumab 300 mg QW plot (up to 12 weeks) only included studies with a 300 mg QW regimen of 12 weeks or longer (included: ACT11457, R668-AD-1117, R668-AD-1021, R668-AD-1314, R668-AD-1334, R668-AD-1416, R668-AD-1224, R668-EE-1324, R668-EE-1774). Shorter studies were excluded from the exploratory plot.

Visual predictive check (VPC) plots stratified by dose illustrate that concentrations predicted by the previous global model are consistent with the observed dupilumab concentrations in patients with EoE in Studies R668-EE-1324 and R668-EE-1774.

Figure 5 External Visual Predictive Check of Studies R668-EE-1324 and R668-EE-1774 Stratified by Study and Dose





QW = Every week; Q2W = Every 2 weeks; CI = Confidence interval
Blue circles indicate observed data (using actual time); the solid red line represents the observed median; the red dashed lines represent the 5th and 95th percentiles of the observed data; the red shaded region represents the simulated 90% CI for the median; and the blue shaded regions represent the simulated 90% CIs for the 5th and 95th percentiles of simulated data. The model predicted values used nominal time, based on the treatment periods in the protocols.

Population PK Model Update

As the global model was adequate to describe EoE patient data from Studies R668-EE-1324 and R668-EE-1774, dupilumab concentration data from patients with EoE were combined with the original dataset consisting of 20 studies, and parameters were re-estimated in the PopPK global model. With the inclusion of the EoE data, a condition number of >180,000 was observed. Therefore, minor modifications were implemented to address potential model instability suggested by the high condition number.

Table 4 Model Update Development Steps

Model	Description	OFV	Minimization	CN
Global Model[4]	Previous final model with 20 studies	170666.6	Successful	NA[a]
Run 3	All Data; including EoE (22 studies)	176550.3	Successful; but problems occurred	181,482
Run 4	**All Data (22 studies) Fixed F1 and Removed IIV on F1**	**176596.8**	**Successful**	**299**

OFV = Objective function value; CN = Condition number; EoE = Eosinophilic esophagitis; F1 = Bioavailability; IIV = Inter-individual variability; NA = Not applicable
[a] No eigenvalues reported
Note: Model identified in bold type was chosen as the updated final model.

PK parameter estimates for the original 20 studies (global model) and for the combined 22 studies (updated final model) are presented below. The structural parameter estimates for the updated final model were within 17% of the previous global model and the confidence intervals (CI) for the two models mostly overlapped, suggesting that dupilumab PK is consistent between patients with EoE in Studies R668-EE-1324 and R668-EE-1774 and the previously pooled populations (20 studies) which included patients with asthma or AD.

Table 5 Final PopPK Model Comparison

Parameters	Global Model Estimates [a] 20 Studies (Bootstrap 95%CI) [b]	Updated Final Model Estimates 22 Studies (95% CI)	Percent Difference
Fixed Effects			
K_{EL} (day^{-1})	0.041 (0.037, 0.044)	0.040 (0.038, 0.041)	-2.4%
Vc (L)	2.79 (2.63, 2.97)	2.93 (2.84, 3.02)	5.0%
K_{CP} (day^{-1})	0.089 (0.06, 0.11)	0.080 (0.073, 0.086)	-10.1%
K_{PC} (day^{-1})	0.15 (0.13, 0.17)	0.15 (0.14, 0.15)	0.0%
V_{MAX} (mg/L/day)	1.48 (1.24, 1.61)	1.39 (1.33, 1.46)	-6.1%
Km (mg/L)	2.52 (1.84, 3.01)	2.41 (2.01, 2.82)	-4.4%
KA (day^{-1})	0.25 (0.22, 0.29)	0.26 (0.25, 0.27)	4.0%
F1	0.628 (0.536, 0.680)	0.628 FIX	--
CL (L/day)	0.114	0.117	--
V3 (L)	1.66	1.56	--
WT on Vc (ref: 76 kg)	0.72 (0.67, 0.75)	0.73 (0.70, 0.76)	1.4%
WT on V_{MAX} (ref: 76 kg)	0.33 (0.22, 0.44)	0.32 (0.25, 0.40)	-3.0%
WT on K_{EL} (ref: 76 kg)	0.12 (0.05, 0.20)	0.14 (0.08, 0.20)	16.7%
IIV (CV%) [Shrinkage%]			
K_{EL}	21.7 [41%]	22.9 [40%]	
Vc	8.09 [63%]	17.5 [23%]	
V_{MAX}	29.1 [43%]	33 [41%]	
KA	44.0 [58%]	45.8 [60%]	
F1	41.9 [31%]	0 FIX	
Residual Error			
Proportional (%)	0.17	0.17	
Additive (mg/L)	2.06	2.0	

K_{EL} = Linear elimination rate constant; Vc = Volume of the central compartment; K_{CP} = Inter-compartment distribution rate constant from central to peripheral; K_{PC} = Inter-compartment distribution rate constant from peripheral to central; V_{MAX} = Maximum target mediated rate of elimination; Km = Concentration of half-maximal nonlinear clearance (Michaelis constant); KA = Absorption rate constant; F1 = Bioavailability; CL = clearance (derived value); V3 = Vp = Volume of the peripheral compartment (derived value); WT = Body weight; IIV = Inter-individual variability; CV% = Percent coefficient of variation; OFV = Objective function value; ref = Reference value for body weight

[a] Model estimates are from SAR2311893/POH0668 PopPK Report (Table 6).

[b] Bootstrapped 95% CI are from SAR2311893/POH0668 PopPK Report (Table 7; [2.5th, 97.5th])

Model Applications

- Comparison of Steady-State Exposure Predictions Across Indications

Simulations using the updated final model and individual ETAs were performed to generate steady-state exposure predictions (i.e., Ctrough,ss, Cmax,ss, and AUC2wk,ss). In order to compare exposures between different treatment regimens with QW and Q2W dosing intervals, an AUC was computed over a 2-week time period at steady-state (AUC2wk,ss) for each population. The AUC2wk,ss exposure metric was consistent among patients with EoE, asthma and AD for 300 mg QW and Q2W treatment regimens.

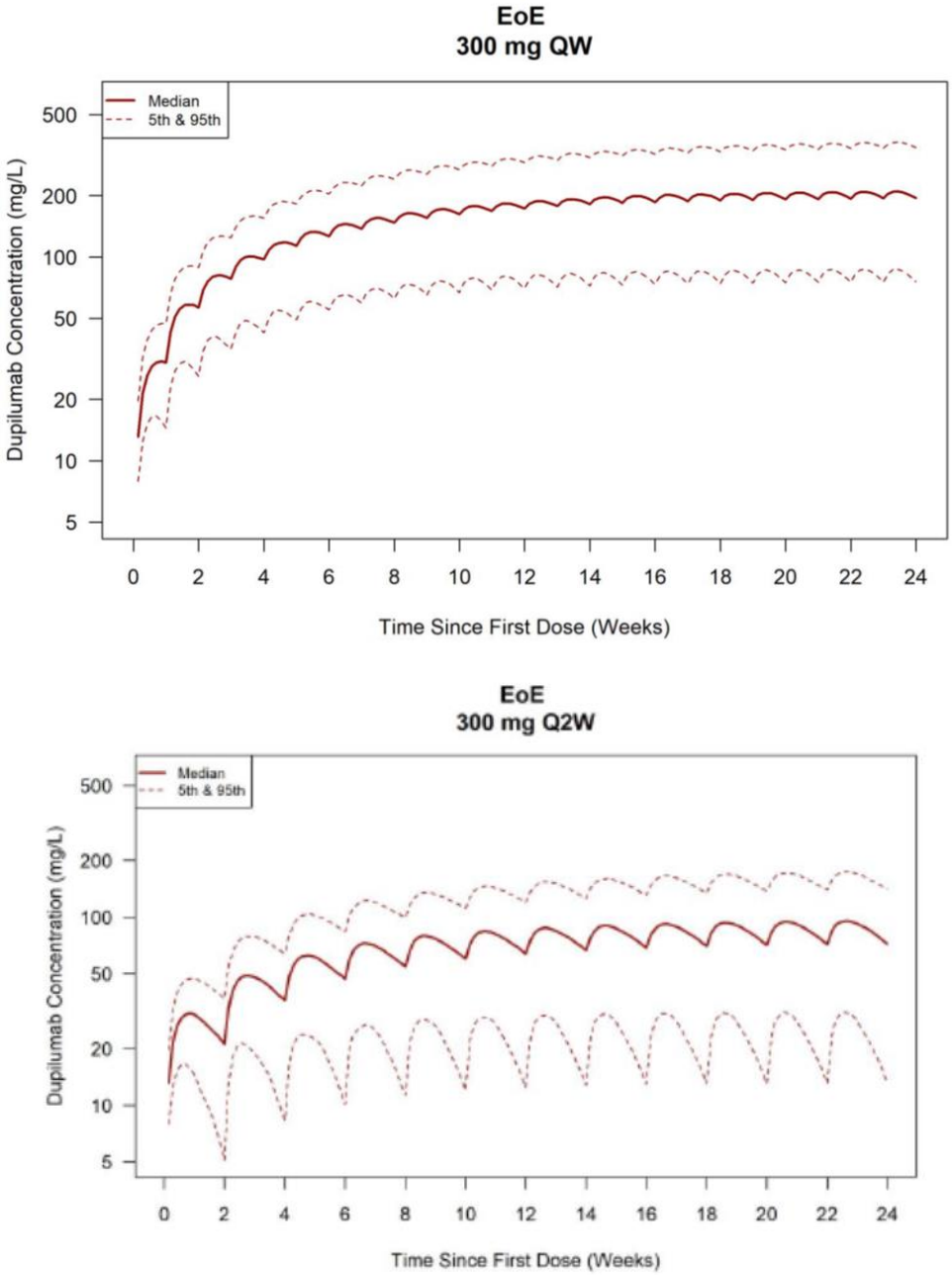
Predicted median Ctrough,ss values for patients with EoE were 73 mg/L (dupilumab 300 mg Q2W) and 198 mg/L (dupilumab 300 mg QW) which were similar to predicted Ctrough,ss for the other populations (mean range for dupilumab 300 mg Q2W is 69 to 73 mg/L; 300 mg QW is 192 to 199 mg/L).

- Steady-State Concentration-Time Profiles and Ctrough Exposure Predictions for Patients with EoE

The predicted Week 24 concentration-time profiles for patients with EoE are shown below. Note that observed data included patients with EoE receiving 12, 24, 28 or 52 weeks of dupilumab treatment; therefore, PK profiles are extrapolated for patients with 12 weeks of treatment. Also, in Study R668-EE-1324, there was a 600 mg loading dose, whereas the simulations were done without a loading dose for all patients with EoE.

PK profiles at the 5th and 95th percentiles suggested an asymmetrical pattern, with a larger separation of the 5th percentile from the median. However, mean and median values were nearly equivalent which would not support a skewed distribution, although the random effects may not be balanced as some patients were noted to have low C_{trough} values.

Figure 6 Exposure Predictions Over Time for Patients with EoE in Studies R668-EE-1324 and R668-EE-1774 Stratified by Treatment Regimens



QW = Every week; Q2W = Every 2 weeks; EoE = Eosinophilic esophagitis
Note: The plots are in semi-log scale.

Table 6 Final Population PK Model Comparison with and without EoE Studies R668-EE-1324 and R668-EE-1774

Parameters	Global Model Estimates [a] 20 studies without EoE (Bootstrap 95%CI)	Updated Final Model Estimates 22 studies including EoE (95% CI)	Percent Difference
Fixed Effects			
K_{EL} ($days^{-1}$)	0.041 (0.037, 0.044)	0.040 (0.038, 0.041)	-2.4%
Vc (L)	2.79 (2.63, 2.97)	2.93 (2.84, 3.02)	5.0%
KCP ($days^{-1}$)	0.089 (0.06, 0.11)	0.080 (0.073, 0.086)	-10.1%
KPC ($days^{-1}$)	0.15 (0.13, 0.17)	0.15 (0.14, 0.15)	0.0%
Vmax (mg/L/day)	1.48 (1.24, 1.61)	1.39 (1.33, 1.46)	-6.1%
KM (mg/L)	2.52 (1.84, 3.01)	2.41 (2.01, 2.82)	-4.4%
KA ($days^{-1}$)	0.25 (0.22, 0.29)	0.26 (0.25, 0.27)	4.0%
F1	0.628 (0.536, 0.680)	0.628 FIX	--
WT on Vc (ref: 76 kg)	0.72 (0.67, 0.75)	0.73 (0.70, 0.76)	1.4%
WT on Vmax (ref: 76 kg)	0.33 (0.22, 0.44)	0.32 (0.25, 0.40)	-3.0%
WT on K_{EL} (ref: 76 kg)	0.12 (0.05, 0.20)	0.14 (0.08, 0.20)	16.7%
IIV (CV%) [Shrinkage%]			
K_{EL}	21.7 [41%]	22.9 [40%]	-
Vc	8.09 [63%]	17.5 [23%]	-
Vmax	29.1 [43%]	33 [41%]	-
KA	44 [58%]	45.8 [60%]	-
F1	41.9 [31%]	0 FIX	-
Residual Error			
Proportional (%)	0.17	0.17	-
Additive (mg/L)	2.06	2.0	-
OFV	170666.554	176596.839	-

Abbreviations: CI=confidence interval; CV%=percent coefficient of variation; EoE=eosinophilic esophagitis; FI=bioavailability; IIV=inter-individual variability; KA=absorption rate constant; KCP=inter-compartment distribution rate constant from central to peripheral; K_{EL}=linear elimination rate constant; KM=Michaelis constant; KPC=inter-compartment distribution rate constant from peripheral to central; LLOQ=lower limit of quantification; OFV=objective function value; PK=pharmacokinetics; Q2W=every 2 weeks; QW=every week; Vc=volume of central compartment; Vmax=maximum target mediated rate of elimination; WT=body weight; ref=reference value for body weight

[a]Model estimates are from SAR231893/POH0688 PopPK Report

Post-Hoc Assessment of Covariates

The updated final model (including 22 studies) was used in a post-hoc covariate analysis to investigate if there were any additional covariates of interest, which might impact dupilumab PK in patients with EoE. Predicted values of linear CL and Vc were plotted by covariate category or covariate value (for continuous covariates). The only covariate that illustrated a trend with linear clearance (CL) and volume of the central compartment (Vc) was body size (i.e., body weight, height, and BMI) on linear CL and Vc, which is consistent with covariate effects of body weight on linear CL and Vc demonstrated in the PopPK model. Height and BMI are correlated with body weight and therefore only body weight was tested in the model. There were no major trends in the plots of predicted linear CL and Vc values or individual random effect (ETA) values versus other categorical or continuous covariates, including markers of EoE disease severity. The results of the post-hoc analysis suggest that there are no covariates of interest that are not accounted for in the model, and no further covariates were explored.

2.4.5. Discussion on clinical pharmacology

In participants with EoE, the PK of dupilumab is characterized by parallel linear and target-mediated elimination pathways, with the target-mediated pathway expressing a high degree of non-linearity.

The observed concentrations over time in the population of participants with EoE are consistent with those observed in previously studied patient populations with type 2 disease, such as AD, asthma, and CRSwNP.

Exposure-response relationships for efficacy show that the dupilumab 300 mg QW regimen is associated with efficacy in EoE participants with a positive E-R on both histologic and symptomatic outcome measures at week 24. In contrast, dose-response and E-R relationships for the dupilumab 300 mg Q2W dosing regimen showed similar differentiation to the dupilumab 300 mg QW regimen on the infiltration of eosinophils in the esophagus, but showed a flat E-R that was not differentiated from placebo on DSQ total score response. The cause of failure of the 300 mg Q2W regimen to achieve efficacy on reducing dysphagia is not likely due to insufficient drug distribution to the esophageal mucosa. Results of the phase 3 studies indicate that reducing eosinophilic infiltration to the esophagus is necessary but not adequate in improving dysphagia symptoms. Therefore for the treatment of EoE, the recommended dose regimen is 300 mg QW.

The PK and sources of variability in the EoE population are accurately and effectively described by the existing integrated global population PK model based on data from patients with AD, asthma, and CRSwNP. Body weight remains the single most influential source of variability in exposure for both adolescents and adults.

At the CHMP request, the MAH provided additional data on the PK of adolescents (particularly lighter adolescents) compared to adults. While the mean concentrations are slightly higher in the adolescents than in the adults weighing less than 70kg, (likely due to the fact that adolescents are lighter than the adults), it is agreed by the CHMP that the observed difference is minimal and results considered as overall comparable.

The MAH also provided further PK data from 31 adolescents dosed with 300mg QW in Part B/C and compared their mean dupilumab concentrations with those from adults in the same studies. In adolescents initially randomized to receive placebo during Part B followed by dupilumab 300 mg QW upon entering Part C (Placebo/Dupilumab 300 mg QW), mean (SD) steady state concentrations of dupilumab at Week 52 were 141 ±97.5 mg/L (N=10) compared to 155 ±97.0 mg/L (N=27) in adults, which is considered comparable. In adolescent who received dupilumab 300 mg QW throughout the entire study period, mean (SD) steady state trough concentrations of dupilumab at Week 52 were 201 ±142 mg/L (N=21) compared to 164 ±108 mg/L in adults (N=45) receiving the same regimen, which is a higher concentration than seen in the adults. However, this concentration still lies in the range observed in adults patients weighting less than 70kg based on data from 14 studies in various indications. In conclusion it is agreed that overall the PK data suggest that adolescents and adults of similar weights have similar exposures.

A population modelling analysis was performed to characterize the PK of dupilumab in patients with EoE, including data from the Phase 2 study (Study R668-EE-1324) in adults with EoE and the Phase 3 Study (R668-EE-1774) in adult (≥18 years old) and adolescent EoE patients (≥12 to <18 years old).

The global population PK (PopPK) model which was previously developed from a large dataset in three different populations, was intended to serve as a robust starting point for PopPK analyses of dupilumab in other Th2- mediated inflammatory diseases, such as EoE. In the current analysis, an external visual predictive check (VPC) was performed to assess whether dupilumab PK is consistent between patients with EoE and other populations. Dupilumab PK data from patients with EoE was subsequently combined with PK data from previous dupilumab studies in healthy subjects and patients with AD or asthma, and the previous population PK model was re-fit to the combined data-set including patents with EoE.

The external validation analysis demonstrated that dupilumab PK in patients with EoE is consistent with AD and asthma patient populations. Dupilumab PK was described by a 2-compartment disposition model with first order SC absorption, parallel linear and non-linear elimination and body weight-dependent elimination and distribution volume. The re-estimated final model, which included pooled data from 22 studies including patients with EoE, resulted in similar primary dupilumab PK parameter estimates as the previous final model without EoE data.

The integrated final model (including all 22 studies) predicted steady-state exposures that were comparable for all indications, including EoE, AD and asthma, suggesting no differences in dupilumab PK across the studied populations.

Post-hoc covariate analysis identified no new covariates that might impact dupilumab PK in patients with EoE, in addition to the existing effects of body weight on linear CL and Vc in the updated global PopPK model. No further covariates were explored in this analysis.

Consistent with the incidence of ADA, the incidence of treatment-emergent ADA in the population of participants with EoE was low and consistent between Study R668-EE-1324 and R668-EE-1774 with an incidence of 1.3% and 2.6%, respectively. In participants who received dupilumab 300 mg QW or Q2W for 24 weeks in Part B of Study R668-EE-1774 of 1.3% and 0.7% in all participants who received 300 mg QW in EoE Studies R668-EE-1324 and R668-EE-1774 (Parts A and B). Most participants who developed treatment-emergent ADA exhibited a low titer and transient response.

The additional data from Part B/C and the pooled analysis of data for participants with AD and EoE receiving 300 mg QW dupilumab are consistent with the data presented, that after accounting for body weight, age is not a clinically meaningful covariate of dupilumab PK. Furthermore, the results indicate that it does not have an impact on safety, as presented later in the Clinical Safety section.

2.4.6. Conclusions on clinical pharmacology

Overall, the clinical pharmacology data evaluated for the population of participants with EoE are consistent with those observed in previously studied patient populations with type 2 disease. The data support the use of dupilumab 300 mg QW for the treatment of patients with EoE weighing at least 40 kg. The following dose recommendation for EoE patients is therefore added in section 4.2 of the SmPC: *The recommended dose of dupilumab for patients 12 years of age and older is 300 mg given every week (QW).*

2.5. Clinical efficacy

2.5.1. Dose response study

No dose response studies in patients with EoE have been performed.

2.5.2. Main study

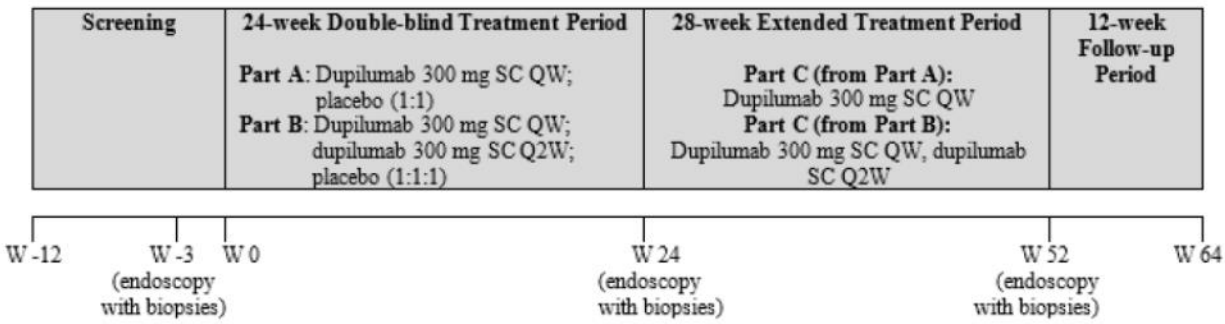
Study R668-EE-1774 A Phase 3, Randomized, 3-Part Study to Investigate the Efficacy and Safety of Dupilumab in Adult and Adolescent Patients with Eosinophilic Esophagitis (EoE)

Methods

Study Design

Study R668-EE-1774 was a randomized, double-blind, multi-centre, pivotal phase 3 study to evaluate the efficacy of dupilumab treatment compared with placebo in adult and adolescent patients with EoE. This study consisted of 3 parts. Part A and Part B consisted of a 24-week double-blind treatment period each, Part C of a 28-week extended active treatment period. A 12-week post treatment follow-up period followed at the end of Part C or at the end of Parts A or B of the for participants who did not enter Part C. Data for participants from Part A who entered Part C are presented in this application. Part C for participants from Part B was still ongoing at the time of submission, additional results from part B/C were submitted at CHMP's request and are presented below. Of note, participants who participated in Part A were not eligible to participate in Part B.

Figure 7 Study Flow Diagram



Abbreviations: Q2W=every 2 weeks; QW=once weekly; SC=subcutaneous; W=week.
Note: For participants who did not have at least 11 daily entries during the 14 days immediately preceding the planned randomization date (baseline), randomization was to be postponed until this requirement was met, but without exceeding the 85-day maximum duration for screening.

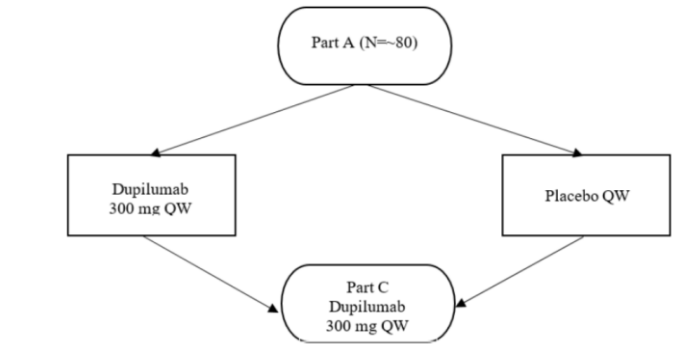
After a screening period (up to 12 weeks), participants in Part A were randomized in a 1:1 ratio to dupilumab 300 mg QW or placebo administered SC. In Part B, participants were randomized in a 1:1:1 ratio to dupilumab 300 mg QW, dupilumab 300 mg Q2W, or placebo administered SC.

Randomization of participants was stratified by age (≥18 vs ≥12 to <18 years of age) and use of PPI at randomization .

If medically necessary, rescue medications (systemic and/or swallowed topical corticosteroids) or emergency esophageal dilation were allowed. An endoscopy with biopsies was to be performed prior to the initiation of rescue therapy unless COVID-19 restrictions prohibited this procedure. If the endoscopy with biopsies could not occur due to COVID-19 restrictions, rescue treatment was not to be delayed and these participants were eligible for Part C. Part C treatment was to be initiated per the schedule of events and only at an in-clinic visit. Participants receiving rescue therapy were able to continue to receive study drug. They remained blinded and returned to all remaining study treatment visits and participated in all study assessments. However, they did not undergo any scheduled endoscopy/biopsies subsequent to the date of rescue. Participants on a food-elimination diet must remain on the same diet throughout the study.

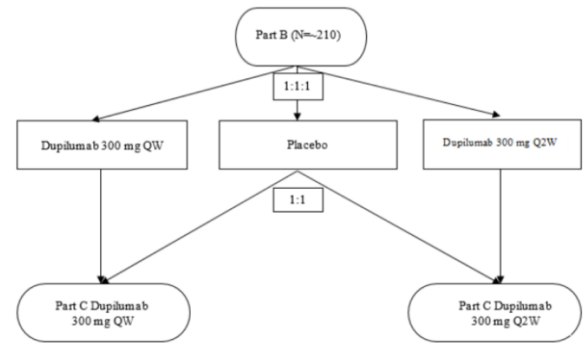
At the end of the 24-week double-blind treatment period, eligible participants in Part A and Part B had the option to enter Part C a 28-week extended active treatment period where all participants from Part A received dupilumab 300 mg QW.

Figure 8 Study Design for Participants Enrolled in Part A



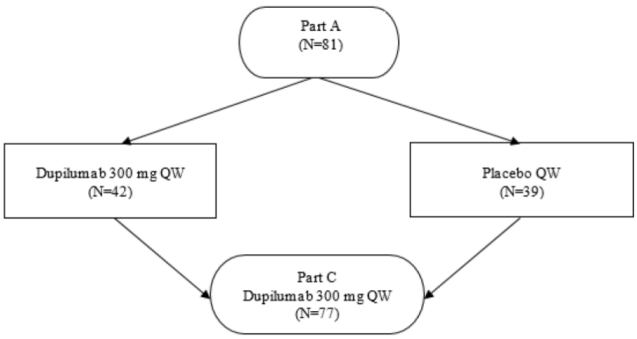
Abbreviations: QW=once weekly

Figure 9 Study Design for Participants Enrolled in Part B



Abbreviations: Q2W=every 2 weeks; QW=once weekly.
Note: At the end of Part B, eligible participants were provided with an option to enter Part C to receive dupilumab 300 mg Q2W or dupilumab 300 mg QW in a blinded fashion for an additional 28 weeks. Participants who did not enter Part C entered a 12-week post-treatment follow-up period immediately after Part B.

Figure 10 Study Design of Part C (Participants from Part A Only)



Abbreviations: QW=once weekly

Study participants

Part A

In Part A, 81 participants met the eligibility criteria and were randomized in a 1:1 ratio. 39 participants were in the placebo group and 42 participants in the dupilumab 300 mg QW group.

The study population in Part A consisted of adult males and females ≥18 years of age and adolescent males and females ≥12 to <18 years of age at the time of study entry with EoE. Approximately 25% of participants enrolled in Part A were to be adolescents ≥12 to <18 years of age. Study participants were required to have a confirmed diagnosis of EoE that was not responsive to high-dose proton pump inhibitor (PPI) therapy. Participants who were receiving PPIs during the screening period and eligible to enrol in the study were to continue a high-dose PPI regimen during the study. All participants were required to have an endoscopy with biopsies at the baseline visit (visit 2) which demonstrated ≥15 intraepithelial eos/hpf in at least 2 of 3 esophageal regions (proximal, mid, and distal).

The clinical study report describes the results of the primary analysis with a data cut-off date of 08 May 2020. The addendum to the Part A Clinical study report (CSR) describes data from 4 participants who had not completed their Part A week 24 biopsy at the time of the data cut-off, due to not being able to attend study visits because of the COVID-19 pandemic.

Part B

In Part B, 240 participants were randomized to 1 of 3 treatment regimens: 80 in the dupilumab 300 mg QW group, 81 in the dupilumab 300 mg Q2W group and 79 in the placebo group.

The study population consisted of adult males and females ≥18 years of age and adolescent males and females ≥12 to <18 years of age at the time of study entry with EoE. At least 10% of participants enrolled in Part B were to be adolescents ≥12 to <18 years of age. At least 30% of participants enrolled in Part B must have had a history of prior use of Swallowed Topical Steroids (STCs) for the treatment of EoE. Study participants were required to have a confirmed diagnosis of EoE that was not responsive to high-dose PPI therapy. Participants who were receiving PPIs during the screening period and eligible to enrol in the study were to continue a high-dose PPI regimen during the study. Participants were also required to have a history of an average of at least 2 episodes of dysphagia per week in the 4 weeks prior to screening and at least 4 episodes of dysphagia in the 2 weeks prior to baseline. Participants must also have completed at least 11 of 14 days of the DSQ e-diary data entry in the 2 weeks prior to the baseline visit (visit 3) and have a baseline DSQ score ≥10.

The efficacy and safety primary analysis data evaluated for this submission with a database lock date of 30 Sep 2021 are considered final for Part B.

Part C

At the end of the double-blind treatment period (week 24), eligible participants in Part A and Part B had the option to enter a 28-week extended active treatment period (Part C) where all participants received dupilumab.

- Participants from Part A

The study population of Part C (participants who entered from Part A) consisted of adult males and females ≥18 years of age and adolescent males and females ≥12 to <18 years of age with EoE at the time of study entry into Part A. Participants who developed a serious or drug related adverse event during Parts A or B, which in the opinion of the investigator could indicate that continued treatment may have presented an unreasonable risk for the participant, poor compliance or inability to complete required study assessments, became pregnant, prematurely discontinued from study, did not undergo

endoscopy with biopsies prior to receiving rescue treatment or systemic hypersensitivity to dupilumab or the excipients were excluded.

All 77 participants who continued into Part C of the study were treated with SC dupilumab 300 mg QW, regardless of randomized treatment received in Part A. All 77 participants received at least 1 dose of dupilumab 300 mg QW during Part C (37 placebo/dupilumab 300 mg QW and 40 dupilumab 300 mg QW/dupilumab 300 mg QW) and are included in the Part C SAF.

The completed R668-EE-1774 Part A-C clinical study report contained the analysis of data from the 28-week extended active treatment phase enrolling patients from Part A. The report contained all data through 18 Nov 2020 (data cut-off). The database lock occurred on 17 Dec 2020.

At the time of data cut-off, 66 of 77 participants (85.7%) completed week 52 (end of Part C; week 52 visit), 5 of 77 participants (6.5%) discontinued Part C and 6/77 participants (7.8%) were continuing in Part C (including 1 participant who completed the 28 weeks of study drug in Part C but had not completed the final visit in Part C).

An addendum was submitted summarizing the data from the 6 ongoing participants in Part C obtained after the data cut-off. Individual patient data profiles are provided that include all data from 18 Nov 2020 up to last patient last visit (LPLV) (27 May 2021).

- Participants from Part B

With the responses to the Request for Supplementary Information, the MAH submitted the data from study Part B/C as requested by CHMP. These additional data include 24 adolescents who completed 52 weeks on dupilumab 300 mg QW, which is the planned dose for registration for this indication.

Of the 240 participants randomized to receive dupilumab 300 mg QW, dupilumab 300 mg every 2 weeks (Q2W) or placebo in Part B, 227 entered Part C. Participants, who received placebo during the double-blind treatment period of Part B were re-randomized in a 1:1 ratio to dupilumab 300 mg QW or dupilumab 300 mg Q2W. All other Part B participants remained on the same dupilumab dose regimen upon entering Part C. Of the 227 participants, 111 participants received dupilumab 300 mg QW in Part C (37 received placebo and 74 received dupilumab 300 mg QW in Part B), and 116 participants received dupilumab 300 mg Q2W in Part C (37 received placebo and 79 received dupilumab 300 mg Q2W in Part B). Of the 79 adolescent participants enrolled in Part B (approximately 33% of the study population in Part B), 75 adolescents entered Part C (26/27 from the dupilumab 300 mg Q2W group, 24/26 from the dupilumab 300 mg QW group and 25/26 from the Part B placebo group). Four Part B patients discontinued study and did not participate in Part C.

Treatments

Part A: Study drug was dupilumab 300 mg or matching placebo QW administered SC on day 1 followed by maintenance SC injections for the following 24 weeks.

Part B: Study drug was dupilumab 300 mg QW, dupilumab 300 mg Q2W, or matching placebo administered SC on day 1 followed by maintenance SC injections for the following 24 weeks.

Part C:

- All participants entering Part C from Part A received dupilumab 300 mg QW SC, regardless of randomized treatment received during Part A.
- Participants entering Part C from Part B, who received placebo during the double-blind treatment period of Part B were re-randomized in a 1:1 ratio to dupilumab 300 mg QW or

dupilumab 300 mg Q2W. All other Part B participants remained on the same dupilumab dose regimen upon entering Part C.

Objectives

Part A Objectives:

Primary

- To determine the treatment effect of dupilumab compared with placebo in adult and adolescent participants with EoE after 24 weeks of treatment as assessed by histological and clinical measures, and to inform/confirm the final sample size determination for Part B.

Secondary

- To evaluate the safety, tolerability, and immunogenicity of dupilumab treatment for up to 52 weeks in adult and adolescent participants with EoE
- To explore the relationship between dupilumab concentration and responses in adult and adolescent participants with EoE, using descriptive analyses
- To evaluate the effects of dupilumab on transcriptomic signatures associated with EoE and type 2 inflammation

Part B Objectives

Primary

- To demonstrate the efficacy of dupilumab treatment compared with placebo in adult and adolescent patients with EoE after 24 weeks of treatment as assessed by histological and clinical measures.

Secondary

- To evaluate the safety, tolerability, and immunogenicity of dupilumab treatment for up to 52 weeks in adult and adolescent participants with EoE
- To explore the relationship between dupilumab concentration and responses in adult and adolescent participants with EoE, using descriptive analyses
- To evaluate the effects of dupilumab on transcriptomic signatures associated with EoE and type 2 inflammation
- To demonstrate the efficacy of dupilumab treatment compared to placebo after 24 weeks of treatment in adult and adolescent patients with EoE who have previously received swallowed topical corticosteroids

Part C Objectives

Primary

- To assess the safety and efficacy of dupilumab treatment in adult and adolescent participants with EoE after up to 52 weeks of treatment as assessed by histological and clinical measures.

Secondary

- To evaluate the safety, tolerability, and immunogenicity of dupilumab treatment for up to 52 weeks in adult and adolescent participants with EoE
- To explore the relationship between dupilumab concentration and responses in adult and adolescent participants with EoE, using descriptive analyses

- To evaluate the effects of dupilumab on transcriptomic signatures associated with EoE and type 2 inflammation

Outcomes/endpoints

Part A Endpoints

The **co-primary endpoints** for Part A of the study were:

- Proportion of participants achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24
- Absolute change in DSQ score from baseline to week 24

The **key secondary endpoints** for Part A of the study were:

- Absolute change in EoE-EREFS from baseline to week 24
- Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to week 24
- Absolute change in EoE Grade Score from the EoEHSS from baseline to week 24
- Absolute change in EoE Stage Score from the EoEHSS from baseline to week 24

Part B Endpoints

The **co-primary** endpoints for Part B of the study were:

- Proportion of participants achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24
- Absolute change in DSQ score from baseline to week 24

The **key secondary** endpoints for Part B of the study were:

- Absolute change in EoE-EREFS from baseline to week 24
- Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to week 24
- Absolute change in EoE Grade Score from the EoEHSS from baseline to week 24
- Absolute change in EoE Stage Score from the EoEHSS from baseline to week 24

Part C Endpoints

- Proportion of participants achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 52
- Absolute change in DSQ score from baseline to week 52
- Absolute change in EoE-EREFS from baseline to week 52
- Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to week 52
- Absolute change in EoE Grade Score from the EoEHSS from baseline to week 52
- Absolute change in EoE Stage Score from the EoEHSS from baseline to week 52
- Proportion of participants achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf at week 52
- Proportion of participants achieving peak esophageal intraepithelial eosinophil count of ≤1 eos/hpf at week 52

- Percent change in DSQ from baseline to week 52
- NES for the relative change from baseline to week 52 in the EDP transcriptome signature
- eNES for the relative change from baseline to week 52 in the type 2 inflammation transcriptome signature
- Absolute change from baseline to week 52 in health-related QOL as measured by EoE-IQ
- Absolute change from baseline to week 52 in severity and/or frequency of EoE symptoms other than dysphagia
- Proportion of participants who receive rescue medications or procedures during the treatment period

Sample size

Part A: 81 patients (61 were adults and 20 were paediatric patients 12 to 17 years of age)
The planned sample size for Part A was approximately 40 patients in each treatment group such that for the comparison of each dupilumab dose regimen to placebo:

- This sample size will yield >99% power to detect a treatment difference of 62% in the proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24 (placebo 3% vs. dupilumab 65%) at a 2-sided significance level of 5% using Fisher's exact test.
- With respect to the treatment group difference in the mean change from baseline in DSQ total score, assuming a common SD of 13.0, this sample size is expected to generate a 95% confidence interval whose half-width is 5.7. If the true treatment difference is -9.0 points, the statistical power for the co-primary endpoint of DSQ will be 80% using a two-sample t-test.

Part B: 240 patients (161 were adults and 79 were paediatric patients 12 to 17 years of age)

Based on the Part A study results, the planned sample size for Part B was approximately 70 patients in each treatment group such that for the comparison of each dupilumab dose regimen to placebo:

- This sample size will yield >99.9% power to detect a treatment difference of 55.4% in the proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24 between placebo (5.1%) and each dupilumab treatment group (59.5%) at a 2-sided significance level of 5% using Fisher's exact test.
- This sample size will provide >99.9% power to detect a treatment difference of -12.3 points in the mean change from baseline in the total DSQ score to week 24 at a 2-sided significance level of 5% using a two-sample t-test, assuming a common SD of 15.0.

Randomisation

Part A: randomised 1:1 to receive either 300 mg dupilumab every week (N=42) or placebo (N=39), stratified by age (≥18 vs. ≥12 to <18 years of age) and use of PPI at randomization (yes vs. no).

Part B: randomised 1:1:1 to receive either 300 mg dupilumab every week (N=80), 300 mg dupilumab every other week (N=81; the 300 mg every other week dosage regimen is not approved for EoE) or placebo (N=79) stratified by age (≥18 vs ≥12 to <18 years of age) and use of PPI at randomization (yes vs. no).

Part C, all patients who previously participated in Part A received 300 mg 'TM' (N=77) every week. Of the patients who previously participated in Part B, those who received 'TM' in Part B continued their dosing regimen in Part C and those who received placebo were randomised to either dosing regimen.

Blinding (masking)

Double-blind study (both parts A and B) until week 24 (co-primary endpoint).

Statistical methods

The full analysis set (FAS) population that includes all randomised patients was utilised in the evaluation of efficacy in study R668 EE 1774. The study-part specific per protocol set (PPS) includes all patients in the corresponding FAS except for those who are excluded due to important protocol violations. For Part A and Part B, the study part-specific safety analysis set (SAF) includes all randomized patients who received any study drug; it is based on the treatment received (as treated).

Analysis of the co-primary efficacy endpoints:

Histologic response (binary endpoint):

The proportion of patients achieving a histologic response of peak esophageal intraepithelial eosinophil count (from all 3 regions) of ≤6 eos/hpf at week 24 was analysed using the Cochran-Mantel-Haenszel (CMH) test to assess the difference in the proportion of responders in the FAS adjusting for the randomization stratification factors (age group [≥18 vs. ≥12 to <18 years of age] and use of PPI at randomization [yes vs. no]).

DSQ total score (continuous endpoint):

The absolute change from baseline in the DSQ total score at week 24 was analysed using an analysis of covariance (ANCOVA) model for the FAS with treatment group, randomization stratification factor, and baseline endpoint measurement as covariates included in the model.

Missing values, sensitivity analyses:

Data may have been collected after the participant discontinued treatment and was included in the analyses. Participants were considered as non-responders after rescue treatment. Multiple imputation (MI) was used if participants had dosing interruption due to COVID-19. Participants with missing peak esophageal intraepithelial eosinophil count at week 24 were considered as non-responders if missingness was not due to COVID-19 and were imputed by MI if missingness was due to COVID-19.

Sensitivity analyses were performed using different imputation methods for the peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24 and for the absolute change in DSQ total score from baseline to week 24.

Multiplicity (Hierarchical Testing):

Statistical significance of both co-primary efficacy endpoints was required before drawing inferential conclusions about any secondary efficacy endpoints. If both co-primary endpoints were statistically significant, the testing was to proceed to the key and other secondary efficacy endpoints following a hierarchical procedure.

Table 7 Statistical hierarchy for co-primary and secondary endpoints for R668-EE-1774 Part A and Part B

	Endpoints	Hierarchical Testing Position		
		Dupilumab		
		Part A	Part B	
		300mg QW group	300mg Q2W group	300mg QW group
Co-Primary endpoints	Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24 Absolute change in DSQ score from baseline to week 24	1	3	1
Secondary endpoints	Percent change in DSQ from baseline to week 24	7	4	2
	Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to week 24	2	8	5
	Absolute change in EoEHSS mean grade score from baseline to week 24	3	9	6
	Absolute change in EoEHSS mean stage score from baseline to week 24	4	10	7
	Absolute change in EoE EREFS total score from baseline to week 24	5	12	11
	Proportion of patients achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf at week 24	6	14	13
	NES for the relative change from baseline to week 24 in the EoE diagnostic panel (EDP) transcriptome signature	8	17	15
	NES of the relative change from baseline to week 24 in the type 2 inflammation transcriptome signature	9	18	16

Analysis of Secondary Efficacy Endpoints in Part A and Part B

Binary endpoints:

Secondary efficacy endpoints that measure binary responses at week 24 were analysed in the same fashion as the co-primary endpoint of histologic response of peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf, including the method to handle missing data and planned sensitivity analyses.

Continuous endpoints:

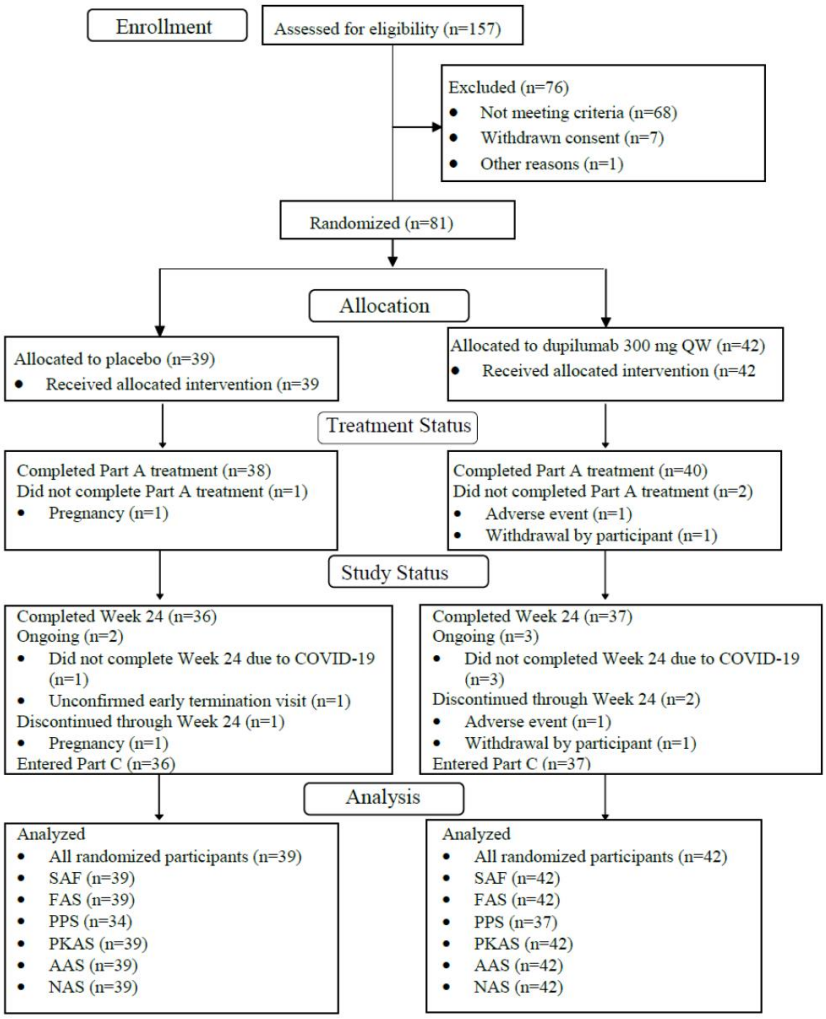
During an endoscopy procedure, EoE-EREFS was completed by the investigator for Parts A and B. In addition to the investigator reading, video imaging was to be collected during Part B for EoE-EREFS analysis and scoring by a centralized reading center. However, during the course of the study, it was noted that there were technical and image quality issues associated with the central reading of EoE-EREFS. Per the Part B SAP, given centralized readings were introduced for the first time for Part B participants of this study, if the centralized reading was not possible for a given proportion of the FAS (e.g., >20% patients in FAS with either baseline or week 24 unavailable), the EoE-EREFS performed in Part B would be based on the investigator reading, as was consistent with Part A.

No interim analysis was planned according to the protocol and no interim analysis was performed accordingly.

Results

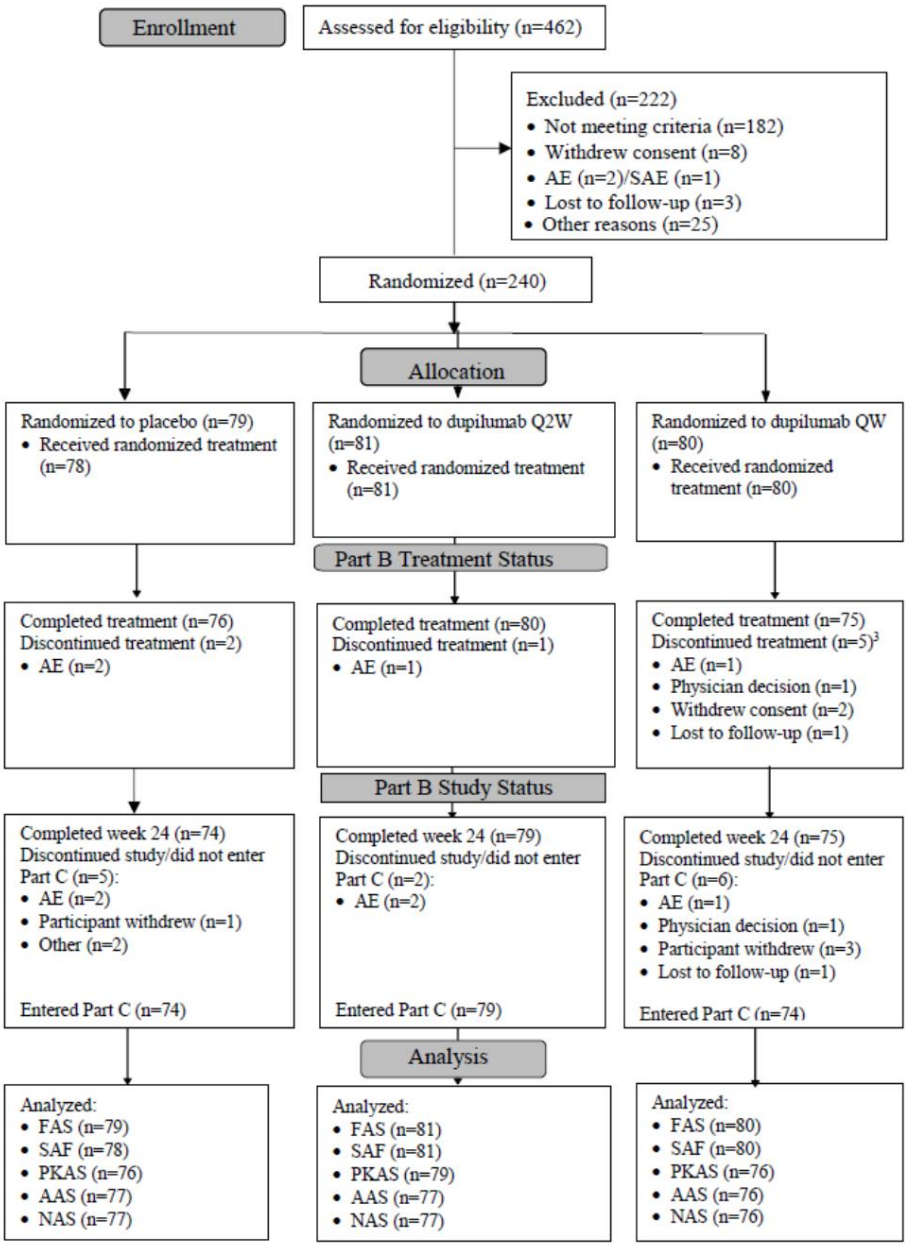
Participant flow

Part A



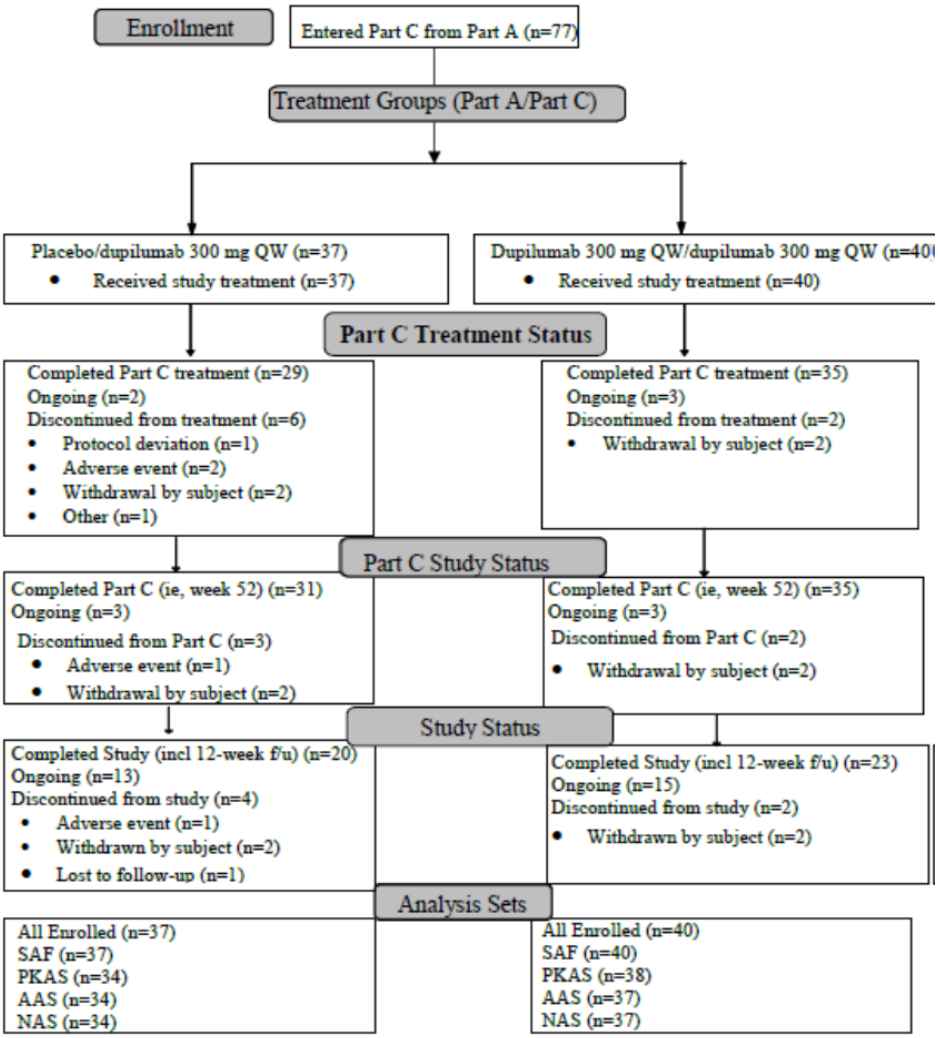
Source: PTTs 1.1.1/3A, 1.1.2/1A, 1.1.2/2A, 1.1.2/3A, and 3.1.1/1A
Abbreviation: AAS=anti-drug antibody analysis set; COVID-19=Coronavirus Disease-2019; FAS=full analysis set; NAS=neutralizing antibody analysis set; PKAS=pharmacokinetic analysis set; PPS=per protocol analysis set; QW=once weekly; SAF=safety analysis set.

Part B



Note: Participants may have discontinued from study treatment, but completed the week 24 visit (ie, end of double-blind treatment period) or completed study treatment but discontinued the study prior to completing the week 24 visit. Participants were also allowed to continue Part B study treatment beyond the planned 24 week treatment period if the visit 11/week 24 endoscopy with biopsies and/or entry into Part C was delayed due to the COVID-19 pandemic.
Abbreviations: AAS=anti-drug antibody analysis set; COVID-19=Coronavirus Disease-2019; FAS=full analysis set; NAS=neutralizing antibody analysis set; PKAS=pharmacokinetic analysis set; Q2W=every 2 weeks; QW=once weekly; SAE=serious adverse event; SAF=safety analysis set.
Source: PTTs 1.1.1/3B, 1.1.2/1B, 1.1.2/2B, and 3.1.1/1B

Part C *for Participants Who Entered from Part A*



Abbreviations: AAS=anti-drug antibody analysis set; f/u=follow-up; NAS=neutralizing antibody analysis set; PKAS=pharmacokinetic analysis set; QW=once weekly; SAF=safety analysis set.
Source: PTT 1.1.1/1C, 1.1.2/1C, 1.1.2/2C, 3.1.1/1C

Recruitment

Part A

24 Sep 2018 (date of first consent) to 08 May 2020 (date of last week 24 visit in Part A). The analyses presented in the CSR are based on a database lock date of 20 May 2020.

Part B

12 Aug 2019 (date of first consent for first screened participant in Part B) to 09 Sep 2021 (date of last week 24 visit in Part B). The analyses presented in the CSR are based on a database lock date of 30 Sep 2021.

Part C

24 Sep 2018 (date of first consent) to 18 Nov 2020 (data cut-off date). The analyses presented in the CSR are based on a database lock date of 17 Dec 2020.
Time Period in which Addendum Data were collected: 18 Nov 2020 (data cut-off for Part C Final Analysis) to LPLV (27 May 2021).

Conduct of the study

The study was conducted during the COVID-19 pandemic, which lead to numerous protocol deviations.

- **Amendments**

Five protocol amendments were implemented for study R668-EE-1774. All changes in the conduct of the study were implemented by protocol amendments.

The main purpose of **Amendment 1** was to revise several exclusion criteria.

The main purpose of **Amendment 2** was to add additional secondary endpoints for proportion of patients who receive rescue medications or procedures, revision of several sections related to patient screening and eligibility criteria, change design of Part C as per Health Authority request.

The main purpose of **Amendment 3** was to add transcriptome sequencing for analysing RNA expression of eosinophilic EoE and type 2 inflammation to the study secondary objectives and endpoints, to add the EQ-5D-3L Questionnaire, to revise the EoE-EREFS procedure for Part B patients to allow for centralized reading and scoring.

The main purpose of protocol **Amendment 4** was to protect participant safety and data integrity during the COVID-19 pandemic by allowing for certain study procedures to occur at delayed time points and/or outside of the clinic environment. All temporary mechanisms utilized, deviations from planned study procedures were documented and remained in effect only for the duration of the public health emergency. At the time of protocol Amendment 4, Part A of the study was fully enrolled and mostly complete.

Most important deviations implemented on Study R668-EE-1774 due to the impacts of COVID-19 were:

- to allow shipments of IP direct to the participant. This process was implemented on 01 April 2020.
- To extend Part A IP dosing was for 4 participants (1 placebo and 3 dupilumab 300 mg QW) who could not make their visit 11 appointment. The endoscopy that is performed during visit 11 is one of the co-primary endpoints for Part A the study and must be done before active drug (dupilumab) is given at visit 11 (Part C of the study). Visit 11 is end of treatment period for Part A and the start of the extended treatment period in Part C. It was decided to extend blinded Part A dosing until week 24 endoscopy visits could be performed for these participants. Thus, these 4 participants were to continue Part A treatment after the 24-week treatment period and entry into Part C was delayed. Three of these 4 participants took extended doses up to 08 May 2020.
- To allow Patient Reported Outcomes (PRO) questionnaires to be completed via interviews over the phone during a call between the study participants and relevant site personnel (not for Part A).
- To allow for remote site qualification, the conduct of a comprehensive remote Site Initiation Visit (via telephone/Skype), the remote review of data (in countries where this practice is permissible), remote routine monitoring visits to support protocol delivery and compliance (not for Part A).

The main purpose of **Amendment 5** was to adjust the sample size for Part B based on the results of Part A of the study and to add an additional database lock after all patients in Part A complete study week 52 of Part C.

- **Protocol deviations**

Part A

A total of 428 protocol deviations were reported for 68 (84.0%) participants during Part A. Of these, 101 protocol deviations in 47 (58.0%) participants were considered important protocol deviations.

As most participants had already completed Part A of the study, very few participants (n=2) had protocol deviations related to COVID-19. No participants had important protocol deviations related to COVID-19.

Protocol: R668-EE-1774 Part A/C

Table 2.1.1/1A Summary of Protocol Deviations in Part A
(All Randomized Patients in Part A)

	Placebo (N=39)	Dupilumab 300 mg QW (N=42)
Number of Protocol Deviations	211	217
Number of Important Protocol Deviations	48	53
Number of Minor Protocol Deviations	163	164
Number of Protocol Deviations due to COVID-19 Pandemic	1	1
Number of Important Protocol Deviations	0	0
Number of Minor Protocol Deviations	1	1
Patients with Any Protocol Deviations, n (%)	35 (89.7%)	33 (78.6%)
Patients with Any Important Protocol Deviation, n (%)	26 (66.7%)	21 (50.0%)
Patients with Any Minor Protocol Deviation, n (%)	33 (84.6%)	29 (69.0%)
Patients with Any Protocol Deviations due to COVID-19 Pandemic, n (%)	1 (2.6%)	1 (2.4%)
Patients with Any Important Protocol Deviation, n (%)	0	0
Patients with Any Minor Protocol Deviation, n (%)	1 (2.6%)	1 (2.4%)

The proportion of participants with important protocol deviations was similar in both treatment groups with 211 in the placebo and 217 in the dupilumab 330 mg QW group. Ten participants (5 in the placebo group and 5 in the dupilumab 300 mg QW group) were excluded from the PPS due to specified important protocol deviations during Part A.

Part B

During Part B, 2483 protocol deviations were reported from 225/240 participants (93.8%). Participants may have had more than 1 protocol deviation. Of these 2483 deviations, 430 (17.3%) were reported as important protocol deviations from 153/240 participants (63.8%). The most frequently reported important protocol deviation overall was in the category of procedure not performed (50.4%), which was reported for 49.4% to 51.9% of participants across treatment groups. Important protocol deviations related to procedure not performed included DSQ assessment missed >6 times in a 14-day period, urine or serum pregnancy test(s) not performed, baseline PGIS assessment not collected, EoE-EREFS not performed or incomplete, baseline physical examination not done, and esophageal biopsy collection not performed or insufficient samples collected.

The most frequently reported procedure not performed was DSQ e-diary not completed by participants >6 times in a 14-day period after the baseline visit, which was reported for 38.8% to 45.7% of participants across treatment groups. This protocol deviation was further evaluated to determine any impact on the DSQ primary endpoint. A minimum of 8 diary entries was required for each 14-day

period to derive a standardized DSQ total score for the analysis. Across each 14-day block at baseline and at week 24, most participants had 8 days or more of DSQ e-diary entries completed (only 0.4% at baseline and 16.3% at week 24 were missing due to <8 days of DSQ completion).

For participants who had <8 days of DSQ completion at week 24, the primary analysis considered these data missing and results were imputed (multiple imputations [MI]). Further, sensitivity analyses regardless of the assumptions used for missing data and supplemental analysis including averaging the DSQ total score over 7 days instead of over 14 days were performed using different DSQ scoring algorithms to assess the robustness of the primary analysis. The results of these analysis were consistent with the primary analysis. This supports the conclusion that this deviation did not impact the efficacy results of the study. The next most frequently reported important protocol deviation categorized as procedure not performed was urine pregnancy testing not performed at 1 or more specified visits (10.0%), which was reported for 13.8% of the participants in the dupilumab 300 mg QW group, 7.4% in the dupilumab 300 mg Q2W group, and 7/79 participants 8.9% in the placebo group. No pregnancies were reported during this study.

Part C

A total of 892 protocol deviations were reported for 74 participants (96.1%) during Part C and the 12-week follow-up period. Of these, 109 protocol deviations reported in 59 participants were considered important protocol deviations.

Important protocol deviations during Part C included procedures not performed (i.e., missing DSQ assessments, urine pregnancy test not performed, EoE-EREFS not performed, esophageal biopsy collection not performed), wrong treatment or incorrect dose received by 6 participants, prohibited treatment received by 5 participants or other treatment compliance in 3 participants.

Thirty-two participants (41.6%) had at least 1 visit impacted by COVID-19. These included primarily missed study visits, remote study visits, or hybrid study visits due to travel restrictions, site closures, limited site personnel, and participant/guardian under quarantine. A total of 493 protocol deviations due to the COVID-19 pandemic were reported for 51 participants (66.2%) during Part C.

Baseline data

Part A

Demographic characteristics were generally balanced between the 2 treatment groups. The majority of participants were male (60.5%) and most participants were white (96.3%) and not Hispanic or Latino (93.8%). The mean age of participants was 31.5 (14.31) years with 24.7% of participants ≥12 to <18 years of age, 43.2% of participants ≥18 to <40 years of age, and 32.1% of participants ≥40 to <65 years. No enrolled participants were ≥65 years of age. The mean (SD) weight of participants was 77.8 (20.95) kg. Most participants (96.3%) were from the United States, with 3.7% from Spain. The placebo group had a higher percentage of female participants than the dupilumab 300 mg QW group (46.2% vs 33.3%, respectively), more participants ≥18 to <40 years of age (56.4% vs 31.0%, respectively), and fewer participants ≥40 to <65 years of age (20.5% vs 42.9%, respectively).

Baseline disease characteristics were generally balanced between the 2 treatment groups and indicated a highly symptomatic population, with most participants having previously used swallowed topical corticosteroids for the treatment of EoE (74.1%) and almost half of participants having prior esophageal dilations (43.2%).

Thirty-seven percent of participants had a history of both swallowed topical corticosteroid use for the treatment of EoE and prior esophageal dilations. Overall, 56.8% of participants had been on a food

elimination diet in the past. The mean peak eosinophil count of 3 esophageal regions (proximal, mid, and distal) at baseline was 89.3 (48.29) eos/hpf. The mean EREFS total score (including stricture – proximal + distal regions) at baseline was 6.3 (2.83) points. The mean DSQ score at baseline was 33.6 (12.41), indicating multiple days of dysphagia every 2 weeks (14 days). The mean number of days with dysphagia at baseline was 10.0 (3.19) days out of 14 days, with more than half of participants (49/81, 60.5%) having dysphagia for ≥10 out of 14 days. More than 70% of participants had a baseline blood peripheral eos count ≥0.30 giga/L (58/81, 71.6%). A number of participants had other type 2 co-morbidities, including atopic dermatitis (19.8%), asthma (35.8%), and allergic rhinitis (60.5%).

Participants in the dupilumab 300 mg QW group had numerically lower peak and mean esophageal eosinophil counts from the 3 esophageal regions (82.6 eos/hpf and 58.71 eos/hpf, respectively) at baseline than the placebo group (96.5 eos/hpf and 70.30 eos/hpf, respectively). Although the mean total IgE was higher in the placebo group than in the dupilumab 300 mg QW group, the median IgE levels were similar. The mean total IgE values differed due to participant in the placebo group with a very high IgE value (19993 IU/mL).

The majority of participants (85.2%) had at least 1 atopic/allergic condition other than EoE. The most frequently reported allergic condition was allergic rhinitis (59.3%).

Seventy-eight of the 81 participants in Part A used at least 1 prior medication (other than PPIs used to treat EoE). The most frequently reported ATC Therapeutic Classes of prior medications were Anesthetics (75.3%), Drugs for Obstructive Airway Diseases (55.6%), Antidiarrheals, Intestinal Anti-inflammatory / Anti-infective Agents (48.1%) and Antihistamines for Systemic Use (46.9%).

Prior procedures were reported for 80 participants (98.8%; 39 [100%] in the placebo group and 41 [97.6%] in the dupilumab 300 mg QW group). The most frequently reported procedure aside from endoscopies and esophagogastroduodenoscopies, required for the diagnosis and monitoring of the underlying condition, was the esophageal dilation procedure (42.0%).

There was some variability in the use of concomitant medications (other than PPI) during the study. However, the use was generally comparable between the 2 treatment groups.

Seventy-six participants (38 in the placebo group and 38 in the dupilumab 300 mg QW group) in Part A reported using at least 1 concomitant medication (other than PPI for EoE) during the study. The most frequently reported medications were Anesthetics (23 in the placebo group and 21 in the dupilumab 300 mg QW group), Antihistamines for systemic use (20 in the placebo group and 19 in the dupilumab 300 mg QW group), Antiemetics and Antinauseants (11 in the placebo group and 7 in the dupilumab 300 mg QW group).

Table 8 Concomitant medications (other than PPIs for EoE) taken by more than 20% of participants in either treatment group during Part A 24-week treatment period (Part A SAF)

Therapeutic Class Chemical Class	Placebo (N=39)	Dupilumab 300 mg QW (N=42)	Total (N=81)
Patients with at least one concomitant medication	38 (97.4%)	38 (90.5%)	76 (93.8%)
Anesthetics	23 (59.0%)	21 (50.0%)	44 (54.3%)
Other General Anesthetics	21 (53.8%)	17 (40.5%)	38 (46.9%)
Amides	15 (38.5%)	12 (28.6%)	27 (33.3%)
Opioid Anesthetics	9 (23.1%)	5 (11.9%)	14 (17.3%)
Antihistamines For Systemic Use	20 (51.3%)	19 (45.2%)	39 (48.1%)
Piperazine Derivatives	13 (33.3%)	13 (31.0%)	26 (32.1%)
Other Antihistamines For Systemic Use	5 (12.8%)	10 (23.8%)	15 (18.5%)
Drugs For Obstructive Airway Diseases	17 (43.6%)	12 (28.6%)	29 (35.8%)
Selective Beta-2-Adrenoreceptor Agonists	14 (35.9%)	9 (21.4%)	23 (28.4%)
Blood Substitutes And Perfusion Solutions	16 (41.0%)	12 (28.6%)	28 (34.6%)
Solutions Affecting the Electrolyte Balance	13 (33.3%)	8 (19.0%)	21 (25.9%)
Antiemetics and Antinauseants	11 (28.2%)	7 (16.7%)	18 (22.2%)
Serotonin (5HT3) Antagonists	11 (28.2%)	7 (16.7%)	18 (22.2%)
Antiinflammatory and Antirheumatic Products	8 (20.5%)	9 (21.4%)	17 (21.0%)
Propionic Acid Derivatives	8 (20.5%)	6 (14.3%)	14 (17.3%)

WHO DRUG Global IB3 March, 2020 dictionary applied.
Sorted by decreasing frequency at all levels in the dupilumab group
Anesthetics include those taken for endoscopy with biopsy.
Abbreviations: Abbreviations: EoE=eosinophilic esophagitis; PPI=proton-pump inhibitor; QW=once weekly; SAF=safety analysis set; WHO DRUG=World Health Organization Drug Dictionary
Source: PTT 4.4.2/1A

During the Part A 24-week treatment period, 4 participants on placebo (10.3%) received rescue medication with glucocorticoids (3 with swallowed topical corticosteroids and 1 with systemic corticosteroids) and 1 participant on placebo (2.6%) underwent a esophageal dilation procedure.

No participants in the dupilumab group received rescue medication or underwent a rescue procedure.

Overall, 7 participants (3 placebo participants, 7.7%, and 4 dupilumab participants, 9.5%) in the Part A SAF population used a prohibited medication during the 24-week treatment period. Prohibited medications used were glucocorticoids, corticosteroids acting locally, systemic glucocorticoids, PPI (administered for nausea) and corticosteroids. Two participants had prohibited initiation, discontinuation, or change of PPI use for EoE. Of the participants who used a prohibited medication during the Part A, 4 participants (2 in the placebo and 2 in the dupilumab group) were excluded from the PPS for receiving a prohibited medication considered a specified important protocol deviation.

Overall, 33 participants (16 placebo participants and 17 dupilumab participants) in Part A had at least 1 food eliminated in their diet at baseline for either allergies or EoE. Food elimination diets were being utilized by 8.6% of participants for EoE at baseline compared with 34.6% of participants for allergies.

Adolescent (≥12 to <18 years) Participants for Part A

A total of 20 participants were ≥12 and <18 years of age. The mean age of the adolescent subgroup was 14.9 years. The majority (80.0%) were male and most participants were white (90.0%). The mean weight and BMI of adolescent participants was 58.9 kg and 20.8 kg/m2, respectively with 35.0% ≥60 kg. All adolescent participants (100.0%) were from the US.

Baseline disease characteristics were generally balanced between the 2 treatment groups. The majority of adolescent participants having previously used STCs for the treatment of EoE (85.0%) and 10.0% having prior esophageal dilations with a mean of 2.5 previous dilations. Over half (55.0%) of adolescent participants were receiving PPIs at the time of randomization. Overall, 85.0% adolescent participants had been on a food elimination diet in the past and 75.0% were on a food elimination diet at screening.

The mean peak eosinophil count of 3 esophageal regions (proximal, mid, and distal) at baseline was 50.18 eos/hpf. The mean EREFS total score at baseline was 3.5 points. The mean DSQ score at baseline was 36.8, indicating substantial symptom burden of dysphagia in the preceding 2 weeks (14 days).

Part B

Demographic characteristics of participants included in the Part B FAS were generally balanced across the 3 treatment groups.

The majority of participants were male (63.8%) and most participants were White (90.4%) and not Hispanic or Latino (94.2%). The mean age of participants was 28.1 years with 32.9% of participants ≥12 to <18 years of age, 46.3% of participants ≥18 to <40 years of age, and 20.0% of participants ≥40 to <65 years. Two participants (0.8%) were ≥65 years of age. The mean weight of participants was 76.2 kg with 77.1% of participants ≥60 kg. Most participants (80.8%) were from the US followed by Australia (4.2%), Canada (3.8%), Italy (2.9%), and Spain (2.5%). The placebo group had a higher percentage of male participants (73.4%) than in either of the dupilumab 300 mg groups (QW: 62.5%; Q2W: 55.6%) and a smaller percentage (15.2%) of participants <60 kg (dupilumab 300 mg QW: 26.3%; dupilumab 300 mg Q2W: 27.2%).

Baseline disease characteristics

The baseline disease characteristics indicated a highly symptomatic population, with the majority of participants having previously used STCs for the treatment of EoE (73.3%) and 35.4% having prior esophageal dilations with a mean of 2.3 previous dilations. Overall, 29.2% had a history of both STC used for EoE and prior esophageal dilation. Only 30.0% reported STCs as being effective for EoE. A total of 49.2% had a history of an inadequate response, intolerance, and /or contraindication to STCs. Almost three-fourths of participants were receiving PPIs at the time of randomization. Overall, 59.6% had been on a food elimination diet in the past and 37.1% were on a food elimination diet at screening. The mean peak eosinophil count of 3 esophageal regions (proximal, mid, and distal) at baseline was 87.1 eos/hpf. The mean EREFS total score at baseline was 7.2 points. The mean DSQ score at baseline was 36.7, indicating substantial symptom burden of dysphagia. The mean number of days with dysphagia at baseline was 10.7 days out of 14 days with 71.25% having dysphagia for ≥10 out of 14 days. Several participants had other type 2 co-morbidities, including atopic dermatitis (25.8%), asthma (44.6%) and allergic rhinitis (63.8%). Overall, 90.0% had a history of at least 1 atopic/allergic condition other than EoE, including 89.1% with a current history.

Prior and Concomitant Medications (Other Than PPI for EoE)/Procedures

A total of 98.7% in the Part B used at least 1 prior medication with 97.5% in the dupilumab 300 mg QW group, all participants in the dupilumab 300 mg Q2W group and 98.7% in the placebo group. The most frequently reported ATC Therapeutic Classes of prior medications were Anesthetics (67.8%), Drugs for Obstructive Airway Diseases (57.3%), Antidiarrheals, Intestinal Anti-inflammatory/ Anti-infective Agents (53.6%) and Antihistamines for Systemic Use (46.4%). Prior procedures were reported for 96.2% of the participants with 93.8% in the dupilumab 300 mg QW group, 96.3% in the dupilumab 300 mg Q2W group, and 98.7% in the placebo group. The most frequently reported

procedure aside from esophagogastroduodenoscopies (37.7%) and endoscopies (27.2%) required for the diagnosis and monitoring of the underlying condition, was the esophageal dilation procedure (35.6%).

Concomitant Medications (Other Than PPI for EoE)/Procedures

Two hundred thirty-two of the 239 participants in the Part B SAF reported using at least 1 concomitant medication during the study: 97.5% in the dupilumab 300 mg QW group, 97.5% in the dupilumab 300 mg Q2W group, and 96.2% in the placebo group.

During the Part B 24-week treatment period, 5 participants in the Part B received rescue treatment.

One participant in the placebo group (1.3%) received concomitant medications in both the Corticosteroids for Systemic Use (prednisone) and Antidiarrheals, Intestinal Anti-inflammatory/Anti-infective Agents (budesonide) therapeutic classes as rescue medication.

One participant in the dupilumab 300 mg QW group (1.3%) received concomitant medications in both the Corticosteroids for Systemic Use (prednisolone sodium phosphate) and Drugs for Obstructive Airway Disease (fluticasone propionate) therapeutic classes as rescue medication and to treat a TEAE of abdominal pain.

Three participants (1 in each treatment group) underwent a rescue procedure during the Part B treatment period. Rescue procedures included esophageal dilation procedure in 2 participants (1 in the placebo group and 1 in the dupilumab 300 mg Q2W group) and pylorus dilation procedure in 1 participant (in the dupilumab 300 mg QW group).

All participants in the Part B received at least 1 prior high dose PPI for EoE either prior to screening or during the screening period per protocol.

73.2% in the Part B used at least 1 prior swallowed topical/systemic corticosteroid for EoE, including 68.8% in the dupilumab 300 mg QW group, 80.2% in the dupilumab 300 mg Q2W group and 70.5% in the placebo group. Most participants (73.2%) used prior STCs, while only 3.3% used prior systemic corticosteroids. Treatment with STCs was deemed not effective in 43.1%, with 59.8% reporting recurrence of EoE symptoms within 3 months.

During the Part B 24-week treatment period 72.4% used at least 1 concomitant PPI for EoE, including 72.5% in the dupilumab 300 mg QW group, 70.4% in the dupilumab 300 mg Q2W group and 74.4% in the placebo group. The most frequently used PPI overall was omeprazole followed by pantoprazole. 8.4% of the participants in the Part B used a prohibited medication during the 24-week treatment period: 10,3% of the placebo participants, 8.8% of dupilumab 300 mg QW participants and 6,2% of the dupilumab 300 mg Q2W participants. The most frequently used prohibited medications overall were Corticosteroids for Systemic Use. All systemic corticosteroids were given ≥10 days prior to the week 24 biopsy.

Adolescent Participants in Part B

The majority of adolescent participants were male (72.2%) and most were White (81.0%) and not Hispanic or Latino (96.2%). The mean age of adolescent participants was 15.0 years. The mean weight of adolescent participants was 64.3 kg with 53.2% ≥60 kg. Most adolescent participants (89.9%) were from the US followed by Canada (7.6%), Australia (1.3%), and Spain (1.3%).

The majority of adolescent participants having previously used STCs for the treatment of EoE (72.2%) and 6.3% having prior esophageal dilations with a mean of 2.8 previous dilations. A history of both STCs used for the treatment of EoE and prior esophageal dilation was reported for 6.3% of the adolescent participants. Only 25.3% reported STCs as being effective for EoE. About half of adolescent

participants (51.9%) had a history of an inadequate response, intolerance, and /or contraindication to prior STCs. Almost 70% of adolescent participants were receiving PPIs at the time of randomization. Overall, 52/79 adolescent participants (65.8%) had been on a food elimination diet in the past. Forty-three of 79 adolescent participants (54.4%) were on a food elimination diet at screening, including 21/79 adolescent participants (26.6%) for EoE.

Part C

- Participants from Part A

At the start of Part C, demographic characteristics for participants from Part A who enrolled in Part C were consistent with that for participants from the Part A FAS. The majority of participants were male (61.0%) and most participants were white (96.1%) and not Hispanic or Latino (93.5%). The mean age of participants at study entry was 31.8 years with 24.1% of participants ≥12 to <18 years of age, 41.6% of participants ≥18 to <40 years of age, and 33.8% of participants ≥40 to <65 years of age. No participants in Part C were ≥65 years of age. Most participants were from the United States (96.1%), with 3.9% from Spain. Demographic characteristics for participants from Part A who enrolled in Part C were consistent with that for participants from the Part A FAS.

At the start of Part C, the mean peak esophageal intraepithelial eosinophil count of 3 esophageal regions was 66.7 eos/hpf in the placebo/dupilumab 300 mg QW group and 12.3 eos/hpf in the dupilumab 300 mg QW/ dupilumab 300 mg QW group.

A total of 98.7% in the Part C (Participants from Part A) used at least 1 medication prior to Part C of the study (other than PPIs for EoE). The most frequently reported ATC Therapeutic Classes of prior medications were Anesthetics (80.5%), Antihistamines for Systemic Use (57.1%), Drugs for Obstructive Airway Disease (57.1%), Antidiarrheals, Intestinal Anti-inflammatory / Anti-infective Agents (55.8%), and Blood Substitutes and Perfusion Solutions (44.2%). The most frequently reported procedure aside from endoscopies and esophagogastroduodenoscopies, was the esophageal dilation procedure (42.9%), which was done for treatment of EoE.

- Participants from Part B

At the start of Part C, demographic characteristics for participants from Part B who enrolled in Part C were consistent with that for participants from the Part B FAS.

The majority of participants were male (63.9%) and most participants were White (90.7%) and not Hispanic or Latino (94.3%). The mean age of participants was 28.1 years with 33% of participants ≥12 to <18 years of age, 45.4% of participants ≥18 to <40 years of age, 20.7% of participants ≥40 to <65 years and 0.9% were older than 65 years. The mean weight was 75.5 kg at baseline, while 24.2% were less than 60 kg.

Numbers analysed

Part A

All 81 participants were treated as randomized and, therefore, included in both the Part A FAS and Part A SAF. Analyses on the Part A FAS are considered to be the primary analyses for efficacy. The Part A SAF is the basis for Part A safety analyses. 10 participants (5 in each treatment group) were excluded from the Part A PPS due to important protocol violations.

Table 9 Summary of Study Analysis Set (All Randomized Participants in Part A)

	Placebo	Dupilumab 300 mg QW	Total
All Randomized Patients, n	39	42	81
Patients Included in the Safety Analysis Set (SAF), n(%)	39/39 (100%)	42/42 (100%)	81/81 (100%)
Patients Who Entered The Safety Follow-up Period Immediately after Part A, n(%)	0/39	0/42	0/81
Patients included in the Full Analysis Set (FAS), n(%)	39/39 (100%)	42/42 (100%)	81/81 (100%)
Patients Included in the Per Protocol Set (PPS), n(%)	34/39 (87.2%)	37/42 (88.1%)	71/81 (87.7%)
Patients Excluded from PPS, n (%)	5/39 (12.8%)	5/42 (11.9%)	10/81 (12.3%)
Patients included in the PK Analysis Set (PKAS), n(%)	39/39 (100%)	42/42 (100%)	81/81 (100%)
Patients included in the ADA Analysis Set (AAS), n(%)	39/39 (100%)	42/42 (100%)	81/81 (100%)
Patients included in the Neutralizing Antibodies Analysis Set (NAS), n (%)	39/39 (100%)	42/42 (100%)	81/81 (100%)

The percentage is based on the number of randomized patients in each treatment group as denominator
Abbreviations: AAS=anti-drug antibody analysis set; ADA=anti-drug antibody; FAS=full analysis set; NAS=neutralizing antibody analysis set; PKAS=pharmacokinetic analysis set; PPS=per-protocol analysis set; QW=once weekly; SAF=safety analysis set.

Part B

Analyses on the Part B FAS are considered to be the primary analyses for efficacy. The Part B SAF is the basis for Part B safety analyses.

Table 10 Summary of Study Analysis Set (All Randomized Participants in Part B)

		Dupilumab 300 mg			
	Placebo	Q2W	QW	Combined	Total
All Randomized Patients, n	79	81	80	161	240
Patients Included in the Safety Analysis Set (SAF), n(%)	78/79 (98.7%)	81/81 (100%)	80/80 (100%)	161/161 (100%)	239/240 (99.6%)
Patients Excluded from SAF, n(%)	1/79 (1.3%)	0/81	0/80	0/161	1/240 (0.4%)
Patients Who Entered The Safety Follow-up Period Immediately after Part B, n(%)	0/79	0/81	1/80 (1.3%)	1/161 (0.6%)	1/240 (0.4%)
Patients included in the Full Analysis Set (FAS), n(%)	79/79 (100%)	81/81 (100%)	80/80 (100%)	161/161 (100%)	240/240 (100%)
Patients included in the PK Analysis Set (PKAS), n(%)	76/79 (96.2%)	79/81 (97.5%)	76/80 (95.0%)	155/161 (96.3%)	231/240 (96.3%)
Patients included in the ADA Analysis Set (AAS), n(%)	77/79 (97.5%)	77/81 (95.1%)	76/80 (95.0%)	153/161 (95.0%)	230/240 (95.8%)
Patients included in the Neutralizing Antibodies Analysis Set (NAS), n (%)	77/79 (97.5%)	77/81 (95.1%)	76/80 (95.0%)	153/161 (95.0%)	230/240 (95.8%)

The percentage is based on the number of randomized patients in each treatment group as denominator.
Abbreviations: AAS=anti-drug antibody analysis set; ADA=anti-drug antibody; FAS=full analysis set; NAS=neutralizing antibody analysis set; PKAS=pharmacokinetic analysis set; Q2W=every 2 weeks; QW=once weekly; SAF=safety analysis set.

Part C

Table 11 Summary of Study Analysis Set (All Randomized Participants in Part A Who Entered Part C)

	Placebo / Dupilumab 300 mg QW	Dupilumab 300 mg QW / Dupilumab 300 mg QW	Total
Patients enrolled, n	37	40	77
Patients Included in the Safety Analysis Set (SAF), n(%)	37/37 (100%)	40/40 (100%)	77/77 (100%)
Patients Who Entered the Safety Follow-up Period after Part C, n(%)	23/37 (62.2%)	27/40 (67.5%)	50/77 (64.9%)
Patients included in the PK Analysis Set (PKAS), n(%)	34/37 (91.9%)	38/40 (95.0%)	72/77 (93.5%)
Patients included in the ADA Analysis Set (AAS), n(%)	34/37 (91.9%)	37/40 (92.5%)	71/77 (92.2%)
Patients included in the Neutralizing Antibodies Analysis Set (NAS), n(%)	34/37 (91.9%)	37/40 (92.5%)	71/77 (92.2%)

Note: Percentages are based on number of enrolled patients.
Abbreviations: AAS=anti-drug antibody analysis set; ADA=anti-drug antibody; NAS=neutralizing antibody analysis set; PKAS=pharmacokinetic analysis set; QW=once weekly; SAF=safety analysis set

Outcomes and estimation

Part A

Table 12 Co-primary, Key Secondary, and Other Secondary Efficacy Endpoint Results in the Prespecified Statistical Hierarchy (Part A FAS)

Endpoints at Week 24 (in prespecified hierarchy)	Placebo (N=39)	Dupilumab 300 mg QW (N=42)	Difference vs Placebo LS Mean (95% CI)	P-value
Co-Primary Efficacy Endpoints				
Proportion of participants who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24, n (%)[1]	2 (5.1)	25 (59.5)	55.3 (39.58, 71.04)	<0.0001
Baseline DSQ total score, mean (SD)	35.13 (12.113)	32.25 (12.661)	-	-
Absolute change from baseline in DSQ total score at week 24, LS mean (SE)[2,3]	-9.60 (2.785)	-21.92 (2.526)	-12.32 (-19.107, -5.537)	0.0004
Key Secondary Efficacy Endpoints				
Baseline peak esophageal intraepithelial eosinophil count, mean (SD)	96.5 (54.69)	82.6 (41.02)	-	-
Percent change from baseline in peak esophageal intraepithelial eosinophil count at week 24, LS mean (SE)[4]	-2.98 (7.596)	-71.24 (6.948)	-68.26 (-86.896, -49.615)	<0.0001
Baseline EoEHSS mean grade score, mean (SD)	1.324 (0.4676)	1.260 (0.4088)	-	-
Absolute change from baseline in EoEHSS mean grade score at week 24, LS mean (SE)[4]	-0.001 (0.0588)	-0.761 (0.0573)	-0.759 (-0.9061, -0.6127)	<0.0001
Baseline EoEHSS mean stage score, mean (SD)	1.376(0.3972)	1.299 (0.3334)	-	-
Absolute change from baseline in EoEHSS mean stage score at week 24, LS mean (SE)[4]	-0.012 (0.0571)	-0.753 (0.0557)	-0.741 (-0.8842, -0.5978)	<0.0001
Baseline EoE-EREFS total score, mean (SD)	6.0 (2.38)	6.5 (3.20)	-	-
Absolute change from baseline in EoE-EREFS total score at week 24, LS mean (SE)[4]	-0.3 (0.41)	-3.2 (0.41)	-2.9 (-3.91, -1.84)	<0.0001
Other Secondary Efficacy Endpoints				
Proportion of participants who achieved peak esophageal intraepithelial eosinophil count <15 eos/hpf at week 24, n (%)[1]	3 (7.7)	27 (64.3)	57.5 (41.69, 73.33)	<0.0001
Baseline DSQ total score, mean (SD)	35.13 (12.113)	32.25 (12.661)	-	-
Percent change from baseline in DSQ total score at week 24, LS mean[3]	-31.68 (8.092)	-69.17 (7.354)	-37.48 (-57.222, -17.745)	0.0002
NES for the relative change from baseline to week 24 in the EDP, median (n)[5]	-0.160 (29)	-2.660 (31)	-2.250 (-2.7200, -1.7300)	<0.0001
NES for the relative change from baseline to week 24 in the type 2 inflammation signature, median (n)[5]	-0.320 (29)	-1.970 (31)	-1.590 (-1.7400, -1.2700)	<0.0001

[1] Participants in Part A missing endoscopy with biopsies at week 24 were imputed by the MI if due to COVID-19. Otherwise, participants were treated as non-responder in the analysis if missingness is not due to COVID-19.
[2] For the change from baseline in DSQ score at week 24, with respect to a Health Authority's comments during the SAP review, a modified scoring algorithm was also used as a sensitivity analysis to calculate the DSQ score by requiring a minimum number of 4 reported diary entries each week for 2 weeks rather than using a minimum of 8 reported diary entries over a 14-day period. Using the modified DSQ scoring algorithm, the LS mean change from baseline in DSQ score at week 24 was -21.14 in dupilumab QW group, compared with -9.64 in placebo (LS mean difference (95% C.I.) is -11.49 (-18.236, -4.748) and nominal p=0.0008) (PTT 6.1.2.1/11A).
[3] Missing value due to any reasons are imputed by MI.
[4] Missing value were imputed by WOCF if not due to COVID-19 and by MI if due to COVID-19).
[5] n= number of patients with NES score in Part A. Difference and its CI are based on the Hodges-Lehmann estimator. P-values were based on Wilcoxon rank-sum test. Missing values were imputed by LOCF.
Abbreviations: CI=confidence interval; COVID-19=Coronavirus Disease-2019; DSQ= Dysphagia Symptom Questionnaire; EDP=EoE diagnostic panel; EoE-EREFS=Eosinophilic Esophagitis-Endoscopic Reference Score; eos/hpf=eosinophils/high-power field; EoEHSS=Eosinophilic Esophagitis Histology Scoring System; FAS=full analysis set; LOCF=last observation carried forward; LS=least squares; MI=multiple imputation; NES=Normalized Enrichment Score; QW=once weekly; SAP=statistical analysis plan; SD=standard deviation; SE=standard error; WOCF=worst observation carried forward.

Co-Primary Efficacy Endpoints

- **Proportion of Participants Achieving Peak Esophageal Intraepithelial Eosinophil Count ≤6 eos/hpf at Week 24**

Participants must have had a peak intraepithelial eosinophil count ≥15 eos/hpf in at least 2 of the 3 esophageal regions sampled to be eligible for the study. The proportion of participants who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24 (which indicates reduced esophageal inflammation) was significantly greater (p<0.0001) in the dupilumab 300 mg QW group (25/42 [59.5%] participants) versus the placebo group (2/39 [5.1%] participants). Mean (SD) peak eosinophil count of 3 regions at baseline was 89.3 (48.29)/hpf and ranged from 16 to 228/hpf.

Table 13 Proportion of Participants Achieving Peak Esophageal Intraepithelial Eosinophil Count ≤6 eos/hpf in All 3 Regions at Week 24 (Part A FAS)

Treatment	Participants with Peak Esophageal Intraepithelial Eosinophil Count of ≤6 eos/hpf at Week 24, n (%)	95 % CI [1]	Difference (95% CI) [2]	P-value [3]
Dupilumab 300 mg QW (N=42)	25 (59.5)	(43.28, 74.37)	55.3 (39.58, 71.04)	<0.0001
Placebo (N=39)	2 (5.1)	(0.63, 17.32)		

Values after first rescue treatment use were set to missing (censoring). Participants with missing peak esophageal intraepithelial eosinophil count at week 24 were considered as a non-responders if missing was not due to COVID-19 and were imputed by MI if missing was due to COVID-19. .
[1] CI is calculated using exact binomial distribution.
[2] Difference is Dupilumab minus Placebo. CI calculation stratified by age group (≥12 to <18 vs ≥18) and use of PPI at randomization (Yes vs No).
[3] P-values were derived by CMH test stratified by age group (≥12 to <18 vs ≤18) and use of PPI at randomization (Yes vs No).
Abbreviations: CI=confidence interval; CMH= Cochran-Mantel-Haenszel; COVID-19=Coronavirus Disease-2019; eos/hpf=eosinophils/high-power field; FAS=full analysis set; MI=multiple imputation; PPI= PPI=proton pump inhibitor ; QW=once weekly

Sensitivity analyses, using different imputation methods, yielded the same results as the primary analysis and confirmed that, regardless of the assumptions used for missing data, treatment with dupilumab produced a greater clinical effect size in comparison with placebo. These sensitivity analyses include:

- Last observation carried forward (LOCF)-MI: data were set to missing post rescue. Participants missing endoscopy with biopsies at week 24 were imputed by MI if due to the COVID-19 pandemic. Otherwise missing values were imputed by LOCF if missingness was not due to the COVID-19 pandemic closures.
- All observed values, regardless of rescue treatment use, were included in the analysis. Participants with missing data were considered as non-responder, regardless of whether missingness was due to the COVID-19 pandemic closures or not.
- Data were set to missing post rescue. Participants with missing data were considered as non-responders, regardless of whether missingness was due to the COVID-19 pandemic closures or not.

Subgroup Analysis

Descriptive analyses were performed on the primary endpoint results to summarize the treatment effects across the subgroups of age (≥12 to <18 years or ≥18 years), sex, baseline body weight (<60 kg or ≥60 kg), BMI (<25 kg/m2 or ≥25-<30 kg/m^2), and baseline disease characteristics, history of prior swallowed topical steroid use for EoE, treatment with PPI at randomization per IWRS or per EDS, history of esophageal dilations and food elimination.

A trend of dupilumab treatment benefit versus placebo was observed in all the subgroups analysed, and logistic regression modelling did not demonstrate any nominally statistically significant p-values for the treatment by subgroup interactions that were evaluated.

- **Absolute Change from Baseline in DSQ Total Score**

Treatment with dupilumab 300 mg QW resulted in improvement in DSQ total score compared to placebo at week 24 in participants with EoE. The least squares (LS) mean change (reduction [i.e., improvement]) from baseline in DSQ total score at week 24 was significantly greater (p=0.0004) in the dupilumab 300 mg QW group (-21.92 points) versus the placebo group (-9.60 points). Mean baseline DSQ scores were approximately 34 points.

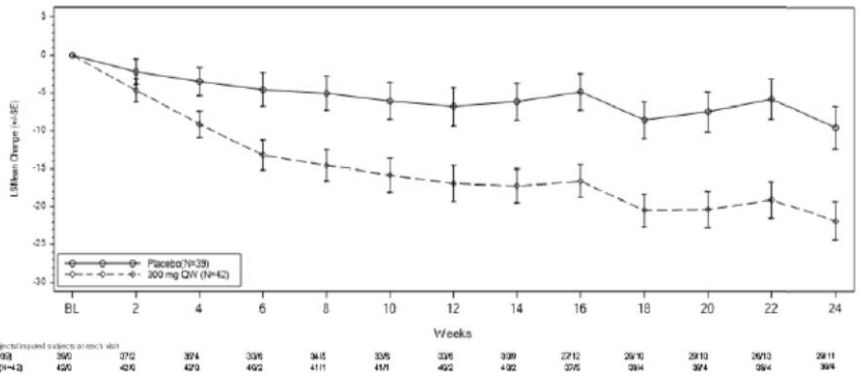
A nominally statistically significant effect in LS mean change in DSQ was noted by week 4 of dupilumab 300 mg QW treatment and was sustained for the remainder of the 24-week treatment period.

Table 14 Absolute Change From Baseline in DSQ Total Score at Week 24, MI Method with Data Set to Missing After Rescue Treatment Use (Part A FAS)

Treatment	LS Mean Change (SE)	LS Mean Change 95% CI	Mean Change (SD)	Baseline Mean (SD)	Num. of Subjects/ Imputed Subjects	Contrast	LS Mean Difference (95% CI)[1]	P-value [1]
Dupilumab 300 mg QW (N=42)	-21.92 (2.526)	(-26.870, -16.967)	-20.45 (14.552)	32.25 (12.661)	38/4	Dupilumab 300 mg QW vs Placebo	-12.32 (-19.107, -5.537)	0.0004
Placebo (N=39)	-9.60 (2.785)	(-15.056, -4.136)	-8.78 (15.180)	35.13 (12.113)	28/11			

Values after first rescue treatment use were set to missing (censoring), then MI was used to impute missing values.
[1] The CI with p-value is based on treatment difference (Dupilumab group vs Placebo) of the LS mean change using ANCOVA model with baseline measurement as covariate and the treatment, age group [≥12 to <18 vs ≥18] and PPI use at randomization (Yes vs No) strata as fixed factors.
Note: For the change from baseline in DSQ score at week 24, with respect to a Health Authority's comments during the SAP review, a modified scoring algorithm was also used as a sensitivity analysis to calculate the DSQ score by requiring a minimum number of 4 reported diary entries each week for 2 weeks rather than using a minimum of 8 reported diary entries over a 14-day period. Using the modified DSQ scoring algorithm, the LS mean change from baseline in DSQ score at week 24 was -21.14 in dupilumab QW group, compared with -9.64 in placebo (LS mean difference (95% C.I.) is -11.49 (-18.236, -4.748) and nominal p=0.0008) (PTT 6.1.2.1/11A).
Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; DSQ=Dysphagia Symptom Questionnaire; eos/hpf=eosinophils/high-power field; FAS=full analysis set; LS=least squares; MI=multiple imputation; PPI=proton pump inhibitor; QW=once weekly; SAP=statistical analysis plan; SD=standard deviation; SE=standard error

Figure 11 LS Mean (SE) in Absolute Change From Baseline in DSQ Total Score to Week 24, MI Method with Data Set to Missing After Rescue Treatment Use (Part A FAS)



Abbreviations: ANCOVA=analysis of covariance; BL=baseline; DSQ=Dysphagia Symptom Questionnaire; FAS=full analysis set; LS=least square; MI=multiple imputation; PPI=proton pump inhibitor; QW=once weekly; SE=standard error

Note: Values after first rescue treatment used were set to missing (censoring), then MI was used to impute missing values.

LS mean (SE) is based on ANCOVA model with baseline measurement as covariate and the treatment. Age group (≥12 to <18 vs ≥18) and PPI use at randomization (Yes vs No) strata as fixed factors.

The results of all sensitivity analyses were consistent with the primary analysis.

Subgroup Analysis

Descriptive analyses were performed on the primary endpoint results to summarize the treatment effects across the subgroups of age (≥12 to <18 years [adolescents] or ≥18 years [adults]), sex, baseline body weight (<60 kg or ≥60 kg), BMI, and baseline disease characteristics (including duration of EoE [<5 years or ≥5 years], history of prior swallowed topical steroid use for EoE, treatment with PPI at randomization by EDC and by IWRS, history of esophageal dilations, food elimination. A trend of dupilumab treatment benefit versus placebo was observed in all the subgroups analysed.

Key Secondary Endpoints

- **Percent Change from Baseline in Peak Esophageal Intraepithelial Eosinophil Count (eos/hpf)**

The percent change from baseline in peak esophageal intraepithelial eosinophil count at week 24 was significantly greater (p<0.0001) in the dupilumab 300 mg QW group (-71.24%) versus the placebo group (-2.98%). Sensitivity analysis also demonstrated a percent change from baseline in peak esophageal intraepithelial eosinophil count at week 24 that was nominally significantly greater (nominal p<0.0001 for both analyses) in the dupilumab 300 mg QW group versus the placebo group.

Subgroup analyses were performed to summarize the treatment effects across the subgroups of age (≥12 to <18 years or ≥18 years), sex, baseline body weight (<60 kg or ≥60 kg), BMI, and baseline disease characteristics. A trend of dupilumab treatment benefit versus placebo was observed in all the subgroups analysed and ANCOVA modelling of treatment-by-subgroup did not demonstrate any nominally statistically significant p-values <0.05 for the different subgroups that were evaluated.

- **Absolute Change from Baseline in EoEHSS Mean Grade Score**

Treatment with dupilumab 300 mg QW resulted in an improvement in Eosinophilic Esophagitis Histology Scoring System (EoEHSS) mean grade score compared to placebo at week 24. The LS mean change (reduction [i.e. improvement]) from baseline in EoEHSS mean grade score at week 24 was

significantly greater (p<0.0001) in the dupilumab 300 mg QW group (-0.761 points) versus the placebo group (-0.001 points). Sensitivity analysis also demonstrated an absolute change from baseline in EoEHSS mean grade score at week 24 that was greater (nominal p<0.0001 for both analyses) in the dupilumab 300 mg QW group versus the placebo group.

- **Absolute Change from Baseline in EoEHSS Mean Stage Score**

Treatment with dupilumab 300 mg QW resulted in an improvement in EoEHSS mean stage score compared to placebo at week 24. The LS mean change from baseline in EoEHSS mean stage score at week 24 was greater (p<0.0001) in the dupilumab 300 mg QW group (-0.753 points) versus the placebo group (-0.012 points). Sensitivity analysis also demonstrated an absolute change from baseline in EoEHSS mean stage score at week 24 that was nominally significantly greater (nominal p<0.0001 for both analyses) in the dupilumab 300 mg QW group versus the placebo group. Subgroup analyses showed a trend of dupilumab treatment benefit versus placebo in all the subgroups analysed.

- **Absolute Change from Baseline in EoE-EREFS Total Score**

Treatment with dupilumab 300 mg QW resulted in a significant improvement in EoE-EREFS total score compared to placebo at week 24. The LS mean change from baseline in EoE-EREFS total score at week 24 was significantly greater (p<0.0001) in the dupilumab 300 mg QW group (-3.2 points) versus the placebo group (-0.3 points). The results of the inflammation subscore at week 24 was greater in the dupilumab 300 mg QW group than in the placebo group (nominal p<0.0001), but the remodelling subscores did not demonstrate nominally significant p-values. Sensitivity analysis also demonstrated an absolute change from baseline in EoE-EREFS at week 24 that was greater in the dupilumab 300 mg QW group versus the placebo group (nominal p<0.0001 for both analyses). A trend of dupilumab treatment benefit versus placebo was observed in all the subgroups analysed.

- **Other Secondary Endpoints**

Due to high number of endpoints evaluated in the study not all results are described in detail. However, all other evaluated endpoints showed similar results to the above presented endpoints.

➢ Part B

Table 15 Co-primary, Key Secondary, and Other Secondary Efficacy Endpoint Results in the Prespecified Statistical Hierarchy (Part B FAS)

Endpoints at Week 24 (in prespecified hierarchy) *(baseline values provided as applicable)*	Placebo (N=79)	Dupilumab 300 mg Q2W (N=81)		Dupilumab 300 mg QW (N=80)		Rank Q2W	Rank QW
		Value	Difference vs Placebo LS Mean (95% CI) P-value	Value	Difference vs Placebo LS Mean (95% CI) P-value		
Co-Primary Efficacy Endpoints							
Proportion of participants achieving peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24, n (%)[1,2]	5 (6.3)	49 (60.5)	**56.0 (43.44, 68.54) <0.0001**	47 (58.8)	**53.5 (41.20, 65.79) <0.0001**	3	1
Baseline DSQ total score, mean (SD)[3]	*36.09 (10.550)*	*35.56 (12.239)*	-	*38.36 (10.705)*	-	-	-
Absolute change in DSQ total score from baseline to week 24, LS mean change (SE)[3,4,5]	-13.86 (1.909)	-14.37 (1.861)	-0.51 (-5.423, 4.406) 0.8393	-23.78 (1.861)	**-9.92 (-14.811, -5.022) <0.0001**	3	1
Secondary Efficacy Endpoints (*indicates key secondary)							
Percent change in DSQ total score from baseline to week 24, LS mean % change (SE)[5,7]	-41.43 (5.261)	-45.78 (5.038)	-4.35 (-17.734, 9.038) 0.5243	-64.32 (5.072)	**-22.89 (-36.272, -9.513) 0.0008**	4	2
Baseline peak esophageal intraepithelial eosinophil count, mean (SD)	*84.3 (41.20)*	*87.7 (49.37)*	-	*89.2 (46.67)*	-	-	-
Percent change in peak esophageal intraepithelial eosinophil count from baseline to week 24*, LS mean % change (SE)[5,6]	8.38 (10.089)	-70.84 (8.292)	-79.22 (-103.098, -55.338) <0.0001	-80.24 (8.340)	-88.62 (-112.194, -65.046) <0.0001	8	5
Baseline EoEHSS mean grade score, mean (SD)	*1.226 (0.3996)*	*1.245 (0.3721)*	-	*1.305 (0.3882)*	-	-	-
Absolute change in EoEHSS mean grade score from baseline to week 24*, LS mean change (SE)[5,6]	-0.148 (0.0456)	-0.814 (0.0419)	-0.666 (-0.7773, -0.5538) <0.0001	-0.830 (0.0427)	-0.682 (-0.7929, -0.5707) <0.0001	9	6
Baseline EoEHSS mean stage score, mean (SD	*1.216 (0.3608)*	*1.248 (0.3182)*	-	*1.294 (0.3256)*	-	-	-
Absolute change in EoEHSS mean stage score from baseline to week 24*, LS mean change (SE)[5,6]	-0.132 (0.0436)	-0.793 (0.0400)	-0.661 (-0.7674, -0.5540) <0.0001	-0.804 (0.0409)	-0.672 (-0.7778, -0.5655) <0.0001	10	7
Baseline EoE-EREFS total score, mean (SD)	*7.2 (3.34)*	*7.5 (3.14)*	-	*6.8 (2.96)*	-	-	-
Absolute change in EoE-EREFS total score from baseline to week 24*, LS mean change (SE)[5,6]	-0.6 (0.38)	-4.6 (0.34)	-3.9 (-4.86, -3.02) <0.0001	-4.5 (0.36)	-3.8 (-4.77, -2.93) <0.0001	12	11
Proportion of participants achieving peak esophageal intraepithelial eosinophil count <15 eos/hpf at week 24, n (%)[1,2]	6 (7.6)	64 (79.0)	72.4 (61.05, 83.70) <0.0001	66 (82.5)	74.9 (64.25, 85.50) <0.0001	14	13
NES for the relative change from baseline to week 24 in the EDP transcriptome signature, median change (n)[8,9]	-0.730 (41)	-2.675 (44)	-1.840 (-2.4200 , -1.1100) <0.0001	-2.665 (40)	-1.850 (-2.4400 , -1.1500) <0.0001	17	15
NES for the relative change from baseline to week 24 in the type 2 inflammation transcriptome signature, median change (n)[8,9]	-0.640 (41)	-1.950 (44)	-1.255 (-1.7300 , -1.0500) <0.0001	-1.930 (40)	-1.275 (-1.8200 , -1.0700) <0.0001	18	16

- **Co-Primary Efficacy Endpoints**

Proportion of Participants Achieving Peak Esophageal Intraepithelial Eosinophil Count ≤6 eos/hpf at Week 24

The proportion of participants who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24 (which indicates histological remission) was greater in the dupilumab 300 mg QW (47/80; 58.8%) and 300 mg Q2W (49/81; 60.5%) groups than in the placebo group (5/79; 6.3%; p<0.0001 vs placebo for both).

Table 16 Primary Analysis of Proportion of Participants Achieving Peak Esophageal Intraepithelial Eosinophil Count ≤6 eos/hpf in All 3 Regions at Week 24, Participants Considered Non-Responder After Rescue Treatment Use and MI Method for Missing or Dosing Interruption Due to COVID-19 (Part B FAS)

Treatment	Patients with Peak Esophageal Intraepithelial Eosinophil Count of ≤6 eos/hpf at Week 24, n(%)	95 % CI[1]	Difference (95% CI)[2]	P-value[3]
Dupilumab 300 mg QW (N=80)	47 (58.8)	(47.18, 69.65)	53.5 (41.20, 65.79)	<0.0001
Dupilumab 300 mg Q2W (N=81)	49 (60.5)	(49.01, 71.19)	56.0 (43.44, 68.54)	<0.0001
Placebo (N=79)	5 (6.3)	(2.09, 14.16)		

Patients were considered as non-responders after rescue treatment. MI was used if patients had dosing interruption due to COVID-19. Patients with missing peak esophageal intraepithelial eosinophil count at week 24 were considered as non-responders if missing is not due to COVID-19 and were imputed by MI if missing is due to COVID-19.
[1] CI is calculated using exact binomial distribution.
[2] Difference is dupilumab minus placebo. CI stratified by age group (≥12 to <18 vs ≥18) and use of PPI at randomization (Yes vs No).
[3] P-values were derived by CMH test stratified by age group (≥12 to <18 vs ≥18) and use of PPI at randomization (Yes vs No).
Abbreviations: CI=confidence interval; CMH=Cochran-Mantel-Haenszel; COVID-19=Coronavirus Disease-2019; eos/hpf=eosinophils/high-power field; FAS=full analysis set; MI=multiple imputations; PPI=proton pump inhibitor ; Q2W=every 2 weeks; QW=once weekly

Sensitivity analyses, using different imputation methods, showed similar results as the primary analysis and confirmed that, regardless of the assumptions used for missing data, treatment with dupilumab 300 mg QW and Q2W produced a greater clinical effect size in comparison with placebo.

Descriptive analyses were performed on the co-primary endpoint to summarize the treatment effects across several subgroups e.g. age (≥12 to <18 years or ≥18 years), sex, baseline body weight (<60 kg or ≥60 kg), BMI (<25 kg/m2 or ≥25 to <30 kg/m2, ≥30 kg/m2), and baseline disease characteristics, history of prior STC use for treatment of EoE and use of PPI at randomization. A consistent trend of dupilumab treatment benefit (Q2W and QW) versus placebo was observed in all the subgroups analysed.

Absolute Change from Baseline in DSQ Total Score

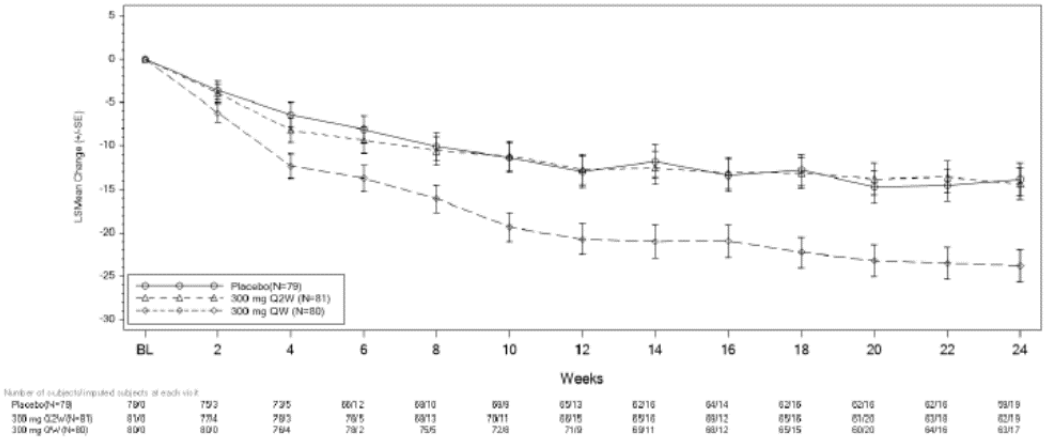
The DSQ e-diary was to be completed daily. The daily score ranged from 0 to 6 and biweekly total DSQ score from 0 to 84. A higher score indicates worse dysphagia. A minimum of 8 diary entries was required for each 14-day period to derive a standardized DSQ total score for the primary analysis. Mean baseline DSQ scores across the treatment groups were comparable.

Treatment with dupilumab 300 mg QW, but not dupilumab 300 mg Q2W, resulted in a significant improvement in DSQ total score compared to placebo at week 24 in participants with EoE. The least square (LS) mean absolute change from baseline in DSQ total score at week 24 was −23.78 points in the dupilumab 300 mg QW group (p<0.0001 vs placebo), −14.37 in the dupilumab 300 mg Q2W group (p=0.8393 vs placebo), and −13.86 points in the placebo group.

An improvement in DSQ was noted by week 4 of dupilumab 300 mg QW treatment and was sustained for the remainder of the 24-week treatment period. No significant difference versus placebo was noted with dupilumab 300 mg Q2W at any time point.

Sensitivity analyses of the absolute change from baseline in DSQ total score, using different imputation methods for handling missing data.

Figure 12 Primary Analysis of LS Mean (SE) in Absolute Change from Baseline in DSQ Total Score to Week 24, MI Method with Data Set to Missing After Rescue Treatment Use (Part B FAS)



Sensitivity analyses, using different imputation methods, supported the primary analysis and confirmed that, regardless of the assumptions used for missing data, treatment with dupilumab 300 mg QW produced a clinically meaningful greater response compared to placebo.

Supplemental analyses, using alternative strategies for the calculation of the DSQ biweekly total scores supported the primary analysis and confirmed that the treatment with dupilumab 300 mg QW produced a greater response in comparison with placebo.

Table 17 Summary of Supplemental Analyses of Absolute Change From Baseline in DSQ Total Score at Week 24 (Part B FAS)

	Statistics	Placebo (N=79)	Dupilumab 300 mg Q2W (N=81)	Dupilumab 300 mg QW (N=80)
Primary Analysis				
ANCOVA 14-day Prorated Score MI Method With Data Set to Missing After Rescue Treatment Use	**LS Mean Change (SE)**	-13.86 (1.909)	-14.37 (1.861)	-23.78 (1.861)
	LS Mean Change 95% CI	(-17.605, -10.120)	(-18.018, -10.723)	(-27.427, -20.131)
	Number of Subjects/Imputed Subjects	59/19	62/19	63/17
	LS Mean Difference (95% CI)	-	-0.51 (-5.423, 4.406)	-9.92 (-14.811, -5.022)
	P-value	-	0.8393	<0.0001
Supplemental Analyses				
ANCOVA Composite strategy for rescue WOCF-MI Method	**LS Mean Change (SE)**	-13.63 (1.925)	-14.20 (1.867)	-23.68 (1.871)
	LS Mean Change 95% CI	(-17.407, -9.859)	(-17.859, -10.539)	(-27.344, -20.007)
	Number of Subjects/Imputed Subjects	59/19 (17)	62/19 (18)	63/17 (15)
	LS Mean Difference (95% CI)	-	-0.57 (-5.476, 4.345)	-10.04 (-14.984, -5.100)
	P-value	--	0.8215	<0.0001
ANCOVA Treatment policy for rescue MI Method Regardless of Rescue	**LS Mean Change (SE)**	-13.96 (1.841)	-14.27 (1.811)	-24.35 (1.814)
	LS Mean Change 95% CI	(-17.565, -10.347)	(-17.819, -10.717)	(-27.902, -20.791)
	Number of Subjects/Imputed Subjects	61/17	63/18	65/15
	LS Mean Difference (95% CI)	--	-0.31 (-5.080, 4.456)	-10.39 (-15.165, -5.615)
	P-value	--	0.8979	<0.0001
ANCOVA 7-day Prorated Score MI Method with Data Set to Missing After Rescue Treatment Use	**LS Mean Change (SE)**	-7.82 (0.976)	-7.70 (0.934)	-12.85 (0.937)
	LS Mean Change 95% CI	(-9.737, -5.911)	(-9.532, -5.870)	(-14.689, -11.014)
	Number of Subjects/Imputed Subjects	59/19	58/21	60/20
	LS Mean Difference (95% CI)	--	0.12 (-2.399, 2.646)	-5.03 (-7.501, -2.554)
	P-value	--	0.9238	<0.0001

ANCOVA 7-day Un-prorated Score MI Method with Data Set to Missing After Rescue Treatment Use	**LS Mean Change (SE)**	-1.12 (0.139)	-1.10 (0.133)	-1.84 (0.134)
	LS Mean Change 95% CI	(-1.391, -0.844)	(-1.362, -0.839)	(-2.098, -1.573)
	Number of Subjects/Imputed Subjects	59/19	58/21	60/20
	LS Mean Difference (95% CI)	-	0.02 (-0.343, 0.378)	-0.72 (-1.072, -0.365)
	P-value	-	0.9238	<0.0001
ANCOVA 14-day Un-prorated Score MI Method with Data Set to Missing After Rescue Treatment Use	**LS Mean Change (SE)**	-0.99 (0.136)	-1.03 (0.133)	-1.70 (0.133)
	LS Mean Change 95% CI	(-1.257, -0.723)	(-1.287, -0.766)	(-1.959, -1.438)
	Number of Subjects/Imputed Subjects	59/19	62/19	63/17
	LS Mean Difference (95% CI)	-	-0.04 (-0.387, 0.315)	-0.71 (-1.058, -0.359)
	P-value	-	0.8393	<0.0001

Note: p-values are nominal in this table.
MI was also used to impute missing values using seed: 6681774 with imputation size 50. Missing baseline was not imputed by MI. The CI with p-value is based on treatment difference (dupilumab group vs placebo) of the LS mean change using ANCOVA model with baseline measurement as covariate and the treatment, age group [≥12 to <18 vs ≥18] and PPI use at randomization [Yes vs No] strata as fixed factors.
Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; DSQ=Dysphagia Symptom Questionnaire; FAS=full analysis set; LS=least squares; MI=multiple imputations; Q2W=every 2 weeks; QW=once weekly; SE=standard error; WOCF=worst observation carried forward

In descriptive analyses a consistent treatment benefit versus placebo was noted for dupilumab 300 mg QW but not for dupilumab 300 mg Q2W across subgroups (e.g. age, sex, baseline body weight (<60 kg or ≥60 kg), BMI (<25 kg/m2 or ≥25 to <30 kg/m2, ≥30 kg/m2), and baseline disease characteristics).

- **Key Secondary Endpoints**

Percent Change from Baseline in Peak Esophageal Intraepithelial Eosinophil Count (eos/hpf)

The LS mean percent change from baseline in peak esophageal intraepithelial eosinophil count at week 24 showed greater decrease in count (i.e. improvement) in both the dupilumab 300 mg QW (−80.24%) and 300 mg Q2W (−70.84%) groups than in the placebo group (+8.38%; nominal p<0.0001 vs placebo for both).

Absolute Change from Baseline in EoEHSS Mean Grade Score

The EoEHSS evaluates more detailed histologic changes than are captured by the co-primary endpoint of peak intraepithelial eosinophil counts. Severity (grade) and extent (stage) of abnormalities were scored by blinded, central pathologists using a 4-point scale (0 normal; 3 maximum change) for eight features: eosinophil density, basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, dilated intercellular spaces, surface epithelial alteration, dyskeratotic epithelial cells and lamina propria fibrosis (absent/present). Higher score indicates greater severity and extent of histological abnormalities.

Treatment with either dupilumab 300 mg QW or 300 mg Q2W resulted in greater decrease (i.e. improvement) in Eosinophilic Esophagitis Histology Scoring System (EoEHSS) mean grade score compared to placebo at week 24. The LS mean reduction from baseline in EoEHSS mean grade score at week 24 was substantially greater in the dupilumab 300 mg QW (−0.830 points) and 300 mg Q2W (−0.814 points) groups than in the placebo group (−0.148 points; nominal p<0.0001 vs placebo for both).

Absolute Change from Baseline in EoEHSS Mean Stage Score

Treatment with either dupilumab 300 mg QW or Q2W resulted in a nominally greater decrease (i.e. improvement) in EoEHSS mean stage score compared to placebo at week 24. The LS mean absolute

reduction from baseline in EoEHSS mean stage score at week 24 was substantially greater in the dupilumab 300 mg QW (−0.804 points) and 300 mg Q2W (−0.793 points) groups than in the placebo group (−0.132 points; nominal p<0.0001 vs placebo for both).

Absolute Change from Baseline in EoE-EREFS Total Score

The EoE-EREFS is a validated endoscopic scoring system for inflammatory and remodelling features of EoE including oedema, rings, exudates, furrows, and stricture; the score was assessed in the proximal and distal esophageal regions with each region scored from 0 to 9 with total scores possibly ranging from 0 to 18. Higher score indicates worse endoscopic inflammatory and remodelling findings.

Treatment with both dupilumab 300 mg QW and dupilumab 300 mg Q2W resulted in improvement (i.e., decrease) in EoE-EREFS total score compared to placebo at week 24. The LS mean reduction from baseline in EoE-EREFS total score at week 24 was substantially greater in both the dupilumab 300 mg QW (−4.5 points) and 300 mg Q2W (−4.6 points) groups than in the placebo group (−0.6 points; nominal p<0.0001 vs placebo for both) (Table 30). The results of the inflammation and remodelling subscores at week 24 also showed greater improvement in both the dupilumab 300 mg QW and 300 mg Q2W groups than in the placebo group (nominal p<0.0001 vs placebo for both).

- **Other Secondary Efficacy Endpoints**

Due to high number of endpoints evaluated in the study not all results are described in detail. However, the results of the other secondary endpoints are in line with the results of the key secondary endpoints showing greater improvement of signs and symptoms in participants with EoE in the dupilumab 300 mg QW treatment group compared to placebo.

Biomarker

Eotaxin-3 (also known as CCL26), a chemokine important in directing the migration of eosinophils into tissue, is up-regulated in esophageal mucosa of EoE patients relative to controls. Near maximal reductions from baseline were observed in the dupilumab 300 mg QW and Q2W treatment groups as early as week 4, the first post-treatment time point assessed in the study. These reductions remained sustained through week 24. Much smaller median reductions were noted in the placebo group compared to the dupilumab groups. At week 24, 56.23% and 55.49% reductions from baseline in median concentrations were observed in the dupilumab 300 mg QW and Q2W groups, respectively.

Thymus and Activation Regulated Chemokine (TARC): Interleukin-4 and IL-13 induce the mRNA expression of TARC, a type 2 chemokine that attracts inflammatory cells to tissue. near maximal reductions from baseline were observed in the dupilumab 300 mg QW and Q2W treatment groups as early as week 4, the first post-treatment time point assessed in the study. These reductions were sustained through week 24, and slightly greater in the dupilumab Q2W group than QW group. Much smaller median reductions were noted in the placebo group compared to both dupilumab groups. At week 24, 26.61% and 36.14% reductions from baseline in median concentrations were observed in the dupilumab 300 mg QW and Q2W groups, respectively, relative to 7.55% median reduction observed in the placebo group.

Total IgE: Significant median reductions from baseline were observed in the dupilumab 300 mg QW and Q2W treatment groups as early as week 4, the first post-treatment time point assessed in the study. The serum total IgE levels in both dupilumab groups continued to decrease through week 24 compared to much smaller median reductions in the placebo group. At week 24, 49.22% and 50.17% reductions from baseline in median concentrations were observed in the dupilumab 300 mg QW and Q2W groups relative to 3.67% median reduction observed in the placebo group.

- **Part C**
  - Participants from Part A

Table 18 Results for Selected Secondary Efficacy Endpoints at Part C Baseline (end of Part A) and Week 52 (end of Part C), All Observed Values (Part C SAF – Participants from Part A)

Efficacy Endpoints 52[a]	Part A / Part C Treatment				
	Part C Baseline (end of Part A)		Week 52 (End of Part C)		
	Placebo/ Dupi 300 mg QW (N=37)	Dupi 300 mg QW/ Dupi 300 mg QW (N=40)	Placebo/ Dupi 300 mg QW (N=37)	Dupi 300 mg QW/ Dupi 300 mg QW (N=40)	Total (N=77)
Proportion of participants who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf, n/N1 (%)	2/33 (6.1%)	26/38 (68.4%)	18/30 (60.0%)	19/34 (55.9%)	37/64 (57.8%)
Absolute change from Part A baseline in DSQ total score, mean (SD)	N1=37 -10.16 (16.175)	N1=40 -21.15 (14.581)	N1=23 -21.71 (17.143)	N1=29 -23.44 (16.149)	N1=52 -22.68 (16.453)
% change from Part A baseline in peak esophageal intraepithelial eosinophil count, mean (SD)	N1=33 -22.41 (50.829)	N1=38 -85.14 (27.634)	N1=30 -83.76 (24.996)	N1=34 -88.59 (13.506)	N1=64 -86.33 (19.724)
Absolute change from Part A baseline in EoEHSS mean grade score, mean (SD)	N1=33 -0.140 (0.4114)	N1=38 -0.866 (0.3555)	N1=30 -0.873 (0.5506)	N1=34 -0.873 (0.3537)	N1=64 -0.873 (0.4529)
Absolute change from Part A baseline in EoEHSS mean stage score, mean (SD)	N1=33 -0.144 (0.3394)	N1=38 -0.857 (0.3166)	N1=30 -0.874 (0.4630)	N1=34 -0.891 (0.2770)	N1=64 -0.883 (0.3727)
Absolute change from Part A baseline in EREFS total score, mean (SD)	N1=32 -0.8 (3.00)	N1=38 -4.1 (3.77)	N1= 30 -3.9 (2.74)	N1=35 -4.1 (3.37)	N1=65 -4.0 (3.07)
Peak esophageal intraepithelial eosinophil count <15 eosinophils/hpf, n/N1(%)	3/33 (9.1%)	29/38 (76.3%)	21/30 (70.0%)	28/34 (82.4%)	49/64 (76.6%)
% change from Part A baseline in DSQ score, mean (SD)	N1=37 -31.23 (48.958)	N1=40 -70.06 (38.587)	N1=23 -65.87 (49.705)	N1=29 -75.93 (36.892)	N1=52 -71.48 (42.877)
NES for relative change from Part A baseline in EDP, median	N1=29 -0.160	N1=31 -2.660	N1=27 -2.580	N1=30 -2.670	N1=57 -2.650
NES for relative change from Part A baseline in type 2 inflammation signature, median	N1=29 -0.320	N1=31 -1.970	N1=27 -1.940	N1=30 -1.970	N1=57 -1.960

[a] For endpoints measured by absolute or % change, changes were calculated from study baseline (ie, start of Part A).
N1 = number of participants with observed data.
Abbreviations: DSQ= Dysphagia Symptom Questionnaire; EDP=EoE diagnostic panel; EoE-EREFS=Eosinophilic Esophagitis-Endoscopic Reference Score; eos/hpf=eosinophils/high-power field; EoEHSS=Eosinophilic Esophagitis Histology Scoring System; NES=Normalized Enrichment Score; QW=once weekly; SAF=safety analysis set; SD=standard deviation.
Note: Endpoints included above were the co-primary and secondary efficacy endpoints included in the testing hierarchy in Part A. There were no primary efficacy endpoints in Part C.

Table 19 Key Efficacy Parameters at Week 52 in the Adolescents Versus Adults, All Observed Values Regardless of Rescue Treatment Use (Part C SAF – Participants from Part A)

Efficacy Endpoints at Week 52[a]	Part A / Part C Treatment					
	Adolescents (≥12 to <18 years of age)			Adults (>18 years of age)		
	Placebo/ Dupi 300 mg QW (N=9)	Dupi 300 mg QW/ Dupi 300 mg QW (N=10)	Total (N=19)	Placebo/ Dupi 300 mg QW (N=28)	Dupi 300 mg QW/ Dupi 300 mg QW (N=30)	Total (N=58)
Proportion of participants who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf, n/N1 (%)	6/8 (75.0%)	3/9 (33.3%)	9/17 (52.9%)	12/22 (54.5%)	16/25 (64.0%)	28/47 (59.6%)
Absolute change from Part A baseline in DSQ total score, mean (SD)	N1=5 -25.45 (22.460)	N1=6 -25.57 (18.339)	N1=11 -25.52 (19.234)	N1=18 -20.68 (16.012)	N1=23 -22.88 (15.935)	N1=41 -21.92 (15.806)
% change from Part A baseline in peak esophageal intraepithelial eosinophil count, mean (SD)	N1=8 -91.99 (14.480)	N1= 9 -83.40 (12.944)	N1=17 -87.45 (13.965)	N1=22 -80.77 (27.526)	N1=25 -90.46 (13.463)	N1=47 -85.92 (21.549)
Absolute change from Part A baseline in EoEHSS mean grade score, mean (SD)	N1=8 -1.076 (0.5582)	N1=9 -0.933 (0.3099)	N1=17 -1.000 (0.4356)	N1=22 -0.799 (0.5416)	N1=25 -0.851 (0.3717)	N1= 47 -0.827 (0.4546)
Absolute change from Part A baseline in EoEHSS mean stage score, mean (SD)	N1=8 -1.016 (0.5656)	N1=9 -0.905 (0.1778)	N1=17 -0.957 (0.3987)	N1=22 -0.822 (0.4230)	N1=25 -0.886 (0.3080)	N=47 -0.856 (0.3636)
Absolute change from Part A baseline in EoE-EREFS total score, mean (SD)	N1= 8 -3.5 (2.56)	N1=9 -4.8 (2.49)	N1=17 -4.2 (2.53)	N1=22 -4.0 (2.85)	N1=26 -3.8 (3.63)	N1= 48 -3.9 (3.26)

[a] For endpoints measured by absolute or % change, changes were calculated from study baseline (ie, start of Part A).
N1 = number of participants with observed data.
Abbreviations: DSQ= Dysphagia Symptom Questionnaire; EoE-EREFS=Eosinophilic Esophagitis-Endoscopic Reference Score; eos/hpf=eosinophils/high-power field; EoEHSS=Eosinophilic Esophagitis Histology Scoring System; QW=once weekly; SAF=safety analysis set; SD=standard deviation.

There were no primary efficacy endpoints for Part C of the study.

Efficacy endpoints assessed at week 24 for Part A were assessed at week 52 as secondary endpoints for Part C of the study and summarized for Part C SAF participants who entered Part C from Part A as a single group, as well as based on the treatment assignment in Part A (as randomized).

Secondary Endpoints

- **Proportion of Participants Achieving Peak Esophageal Intraepithelial Eosinophil Count of ≤6 eos/hpf**

At the baseline of Part C, the mean peak esophageal intraepithelial eosinophil count of 3 regions was lower in the dupilumab 300 mg QW/dupilumab 300 mg QW group (12.3 eos/hpf) than in the placebo/dupilumab 300 mg QW group (66.7 eos/hpf).

At the baseline of Part C, 26 of 38 (68.4%) participants in the dupilumab 300 mg QW/dupilumab 300 mg QW group achieved a peak esophageal intraepithelial eosinophil count ≤6 eos/hpf. Six participants had their week 24 biopsy performed after their first Part C dose of study drug (ranged from 2 to 17 days) due to the COVID-19 pandemic. Data from these biopsies were not considered as Part C baseline.

After an additional 28 weeks of dupilumab 300 mg QW treatment in Part C (i.e., through week 52), 55.9% of participants in the dupilumab 300 mg QW/dupilumab 300 mg QW group had a peak esophageal intraepithelial eosinophil count ≤6 eos/hpf in all 3 regions, indicating a maintenance of effect with continued treatment. 6 participants achieved histological remission at week 24 (peak esophageal intraepithelial eos/hpf ≤6) which was not maintained at week 52, although all participants had peak intraepithelial eosinophils/hpf well below baseline. Five of these 6 participants maintained peak esophageal eosinophils below 15 eos/hpf and all maintained or improved their DSQ. Five of the 6

also maintained or improved their EREFS scores. Therefore, this slight increase in the esophageal eosinophilic count did not correlate with worsening of symptoms or anatomical changes. Additional 3 participants achieved histological remission at week 24 but histological assessments were unavailable at week 52. Two other participants dupilumab 300 mg QW/dupilumab 300 mg QW group did not achieve histological remission at week 24 but achieved it at week 52

For participants in the placebo/dupilumab 300 mg QW group who started dupilumab treatment in Part C, 18 of 30 (60.0%) participants achieved a peak esophageal intraepithelial eosinophil count ≤6 eos/hpf in all 3 regions at week 52. This finding is consistent with the effect seen in the dupilumab group during Part A.

Table 20 Proportion of Participants Achieving Peak Esophageal Intraepithelial Eosinophil Count ≤6 eos/hpf in All 3 Regions at Week 52, All Observed Values Regardless of Rescue Treatment Use (Part C SAF -Participants from Part A)

Visit	Placebo / Dupilumab 300 mg QW (N=37) n/N1 (%)	Dupilumab 300 mg QW / Dupilumab 300 mg QW (N=40) n/N1 (%)	Total (N=77) n/N1 (%)
Baseline of Part C	2/33 (6.1%)	26/38 (68.4%)	28/71 (39.4%)
Week 52	18/30 (60.0%)	19/34 (55.9%)	37/64 (57.8%)

N1 stands for number of participants with non-missing values at each visit.
Abbreviations: eos/hpf=eosinophils/high-power field; QW=once weekly; SAF=safety analysis set.

Adolescents

A consistent trend of dupilumab treatment benefit was observed when evaluated for the subgroups of age (≥12 to <18 years and ≥18 years). 3 of 9 (33.3%) adolescent participants in the dupilumab 300 mg QW/dupilumab 300 mg QW group and 6/8 (75.0%) in the placebo/dupilumab 300 mg QW group achieved a peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 52. Two adolescent participants in the dupilumab 300 mg QW/dupilumab 300 mg QW group achieved a peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at baseline of Part C but were no longer responders at week 52.

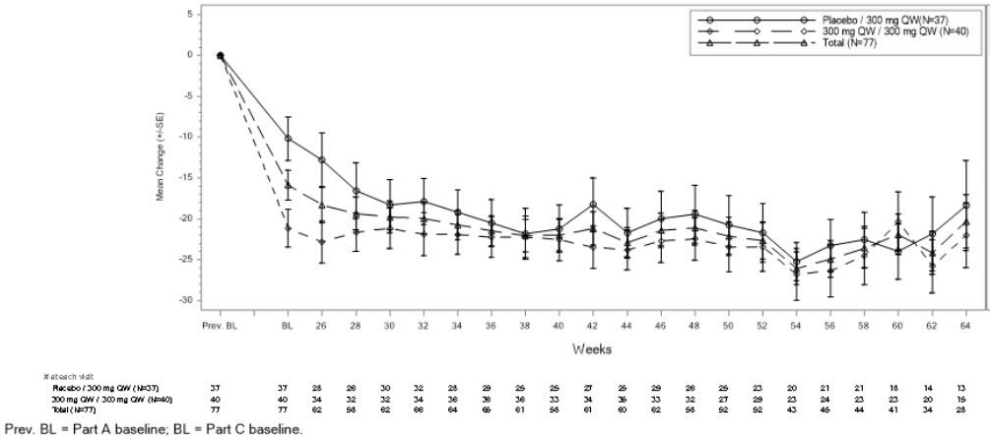
- **Absolute Change from Baseline in DSQ Total Score**

Absolute Change from Part A Baseline

Participants in the dupilumab 300 mg QW/dupilumab 300 mg QW group maintained their improvement (decrease in score) in DSQ total score (possible score ranges from 0 to 84) from Part A during Part C. In the dupilumab 300 mg QW/dupilumab 300 mg QW group, the mean (SD) change from the Part A baseline was -21.15 points at the Part C baseline (week 24) and -23.44 points at week 52.

Participants in the placebo/dupilumab 300 mg QW group who started dupilumab treatment in Part C showed progressive improvement during Part C. The mean change from the Part A baseline was -21.71 points at week 52. This change was similar to that noted for the dupilumab 300 mg QW/dupilumab 300 mg QW group at the Part C baseline.

Figure 13 Mean (±SE) of Absolute Change in DSQ Total Score to Each Visit from Baseline of Part A, All Observed Values (Part C SAF – Participants From Part A)



Prev. BL = Part A baseline; BL = Part C baseline.

There was also a trend of a slight increase in total DSQ score after discontinuation of dupilumab during the post-treatment 12-week follow-up period.

Absolute Change from Part C Baseline

The mean change in DSQ total score from the Part C baseline was -1.75 for participants in the dupilumab 300 mg QW/dupilumab 300 mg QW group showing a maintenance of effect from the end of Part A. Participants in the placebo/dupilumab 300 mg QW group showed progressive improvement from the start of dupilumab treatment in Part C. The mean change from the Part C baseline was -9.79 points at week 52.

A consistent trend of dupilumab treatment benefit was observed when evaluated for the subgroups of age (≥12 to <18 years and ≥18 years) and history of prior use of swallowed topical steroid for EoE.

- **Absolute Change from Baseline in EoE-EREFS Total Score**

The EoE-EREFS is a validated classification and grading system designed to standardize nomenclature for the major endoscopically identified esophageal features of EoE (edema, rings, exudates, furrows, and strictures).

Absolute Change from Part A Baseline

The participants in the dupilumab 300 mg QW/dupilumab 300 mg QW group showed maintenance of effect in EoE-EREFS total score (possible score ranges from 0 to 18) with continued treatment. The mean change from the Part A baseline total score was -4.1 points at the Part C baseline (week 24) and -4.1 points at week 52. Participants in the placebo/dupilumab 300 mg QW group who started dupilumab treatment in Part C also showed improvement in EoE-EREFS total score. The mean change from the Part A baseline was -0.8 points at week 24 and -3.9 points at week 52 similar to that in the dupilumab 300 mg QW/dupilumab 300 mg QW group at the Part C baseline.

Absolute Change from Part C Baseline

The mean change in EoE-EREFS total score at week 52 was 0.0 points from the Part C baseline for participants in the dupilumab 300 mg QW/dupilumab 300 mg QW group showing a maintenance of effect from the end of Part A, and -3.4 points from the Part C baseline for participants in the placebo/dupilumab 300 mg QW group showing progressive improvement from start of dupilumab treatment in Part C.

A consistent trend of dupilumab treatment benefit was observed when evaluated for the subgroups of age (≥12 to <18 years and ≥18 years) and history of prior use of swallowed topical steroid for EoE.

- **Percent Change from Baseline in EoE-EREFS Total Score from Part A Baseline**

In the dupilumab 300 mg QW/dupilumab 300 mg QW group; the mean percent change in EoE-EREFS total score from the Part A baseline was −48.51% at the Part C baseline (week 24) and −62.06% at week 52. Participants in the placebo/dupilumab 300 mg QW group who started dupilumab treatment in Part C showed consistent improvement. The mean percent change from the Part A baseline was −65.54% at week 52.

- **Percent Change from Baseline in Peak Esophageal Intraepithelial Eosinophil Count**

The mean percent change from the Part A baseline was −85.14% at the Part C baseline (week 24; N=38) and −88.59% at week 52 showing sustained improvement in participants in the dupilumab 300 mg QW/dupilumab 300 mg QW group with continued dupilumab treatment. Participants in the placebo/dupilumab 300 mg QW group who started dupilumab treatment in Part C showed similar improvement at week. The mean percent change from the Part A baseline in the placebo/dupilumab 300 mg QW group was -83.76% at week 52.

The median percent change from the Part C baseline was -15.56% at week 52 for participants in the dupilumab 300 mg QW/dupilumab 300 mg QW group, and -93.26% for participants in the placebo/dupilumab 300 mg QW-group who started dupilumab treatment in Part C

A consistent trend of dupilumab treatment benefit was observed when evaluated for the subgroups of age (≥12 to <18 years and ≥18 years) and history of prior use of swallowed topical steroid for EoE.

- **Absolute Change from Baseline in EoEHSS Mean Grade Score**

EoE Grade and Stage Scores evaluate eight histological features in the esophageal biopsy specimens: eosinophil density, basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, dilated intercellular spaces, surface epithelial alteration, dyskeratotic epithelial cells, and lamina propria fibrosis (absent/present). Severity (grade) and extent (stage) of abnormalities were scored using a 4-point scale (0 normal; 3 maximum change).

Participants in the dupilumab 300 mg QW/dupilumab 300 mg QW group showed sustained improvement in EoEHSS mean grade score during Part C. The mean change from the Part A baseline was -0.866 points at the Part C baseline (week 24) and −0.873 points at week 52.

Participants in the placebo/dupilumab 300 mg QW group who started dupilumab treatment in Part C showed improvement in EoEHSS mean grade score at week 52. The mean change from the Part A baseline was -0.873 points at week 52. The improvement in the placebo/dupilumab 300 mg QW group at week 52 was therefore similar to the improvement in the dupilumab 300 mg QW/dupilumab 300 mg QW group during Part A.

At week 52, the mean change in EoEHSS mean grade score was −0.006 points from the Part C baseline for participants in the dupilumab 300 mg QW/dupilumab 300 mg QW group, which indicates maintenance of efficacy. Participants in the placebo/dupilumab 300 mg QW group showed improvement from start of dupilumab treatment in Part C with a mean change in EoEHSS mean grade score at week 52 of -0.723 points from the Part C baseline.

- **Proportion of Participants Achieving Peak Esophageal Intraepithelial Eosinophil Count of <15 eos/hpf**

28 of 34 (82.4%) participants in the dupilumab 300 mg QW/dupilumab 300 mg QW group achieved a peak esophageal intraepithelial eosinophil count <15 eos/hpf at week 52, suggesting sustained reduction of esophageal eosinophilic inflammation with continued dupilumab treatment. For participants in the placebo/dupilumab 300 mg QW group who started dupilumab treatment in Part C,

21 of 30 (70.0%) participants achieved a peak esophageal intraepithelial eosinophil count <15 eos/hpf in all 3 regions at week 52.

- **Proportion of Participants Achieving Peak Esophageal Intraepithelial Eosinophil Count of ≤1 eos/hpf**

10 of 34 (29.4%) participants in the dupilumab 300 mg QW/dupilumab 300 mg QW group achieved a peak esophageal intraepithelial eosinophil count ≤1 eos/hpf at week 52. For participants in the placebo/dupilumab 300 mg QW group who started dupilumab treatment in Part C, 8/30 participants (26.7%) achieved a peak esophageal intraepithelial eosinophil count ≤1 eos/hpf in all 3 regions at week 52.

- **Absolute Change from Baseline in Health-related QOL Average Score by EoE Impact Questionnaire (EoE-IQ)**

The EoE-IQ is a disease-specific measure of health-related QOL that measures impact of EoE on emotional, social, work and school, and sleep aspect of a patient. Score ranges from 1 to 5 with higher score indicating worse HRQOL.

Participants in the dupilumab 300 mg QW/dupilumab 300 mg QW group maintained improvement in health-related QOL average score by EoE-IQ from Part A with continued dupilumab treatment in Part C. The mean change from the Part A baseline was -0.628 points at the Part C baseline (week 24) and -0.911 points at week 52. Participants in the placebo/dupilumab 300 mg QW group who started dupilumab treatment in Part C showed progressive improvement; the mean change from the Part A baseline was −0.954 points at week 52.

- **Other Secondary Endpoints**

Due to high number of endpoints evaluated in the study not all results are described in detail. However, all other evaluated endpoints showed similar results to the above presented endpoints with maintenance of the treatment effect in in the dupilumab 300 mg QW/dupilumab 300 mg QW group and improvement of signs and symptoms in the placebo/dupilumab 300 mg QW group at week 52 similar to the results seen in the dupilumab group in Part A.

Eotaxin-3 (from heparinized plasma), TARC, and IgE (total and allergen-specific) are believed to be relevant to the pathophysiology of EoE and response to treatment (i.e., assessment of type 2 inflammation). Consistent with the results of Part A, dupilumab treatment in Part C maintained reductions in plasma eotaxin-3, as well as serum TARC and total IgE from the Part A baseline in the dupilumab 300 mg QW/dupilumab 300 mg QW group and showed reductions in these biomarkers in the placebo/dupilumab 300 mg QW group.

As in Part A, median reductions from the Part A baseline were observed in allergen-specific IgEs (cow's milk, dermatophagoides farina, dermatophagoides pteronyssinus, egg white, peanuts, soybean) and sIgG4s (egg white, peanuts, soybean, and wheat) in both the dupilumab 300 mg QW/dupilumab 300 mg QW and placebo/dupilumab 300 mg QW treatment groups. These median reductions in allergen-specific IgEs and IgG4s continued through week 52.

- Participants from Part B

Table 21 R668-EE-1774 Part B/C - Results for Selected Secondary Efficacy Endpoints at Week 52 (Part B/C SAF)

Endpoints at Week 52[a] using OC regardless of rescue treatment	EE-1774 Part C[B] (Week 52) (N=227)			
	Placebo/ Dupilumab 300 mg q2w (N=37)	Placebo/ Dupilumab 300 mg qw (N=37)	Dupilumab 300 mg q2w/ Dupilumab 300 mg q2w (N=79)	Dupilumab 300 mg qw/ Dupilumab 300 mg qw (N=74)
Proportion of Peak Eos Count ≤6/hpf, n/N1 (%)	23/32 (71.9%)	25/37 (67.6%)	54/73 (74.0%)	**55/65 (84.6%)**
Absolute Change in DSQ total score [0-84], Mean (SD), [N1]	-23.69 (13.737), [27]	-27.25 (11.457), [24]	-20.87 (16.387), [52]	**-30.26 (15.389), [54]**
% change in DSQ total score [0-84], Mean (SD), [N1]	-71.01 (37.256), [27]	-78.13 (31.003), [24]	-61.19 (44.447), [52]	**-80.74 (32.866), [54]**
% change in peak eos count, Mean (SD), [N1]	-91.20 (13.037), [32]	-84.21 (42.169), [37]	-84.78 (40.973), [73]	**-95.85 (4.037), [65]**
Absolute Change in EoEHSS mean grade score [0-3], Mean (SD), [N1]	-0.779 (0.4292), [32]	-0.906 (0.3936), [37]	-0.838 (0.4039), [73]	**-0.968 (0.4293), [65]**
Absolute Change in EoEHSS mean stage score [0-3], Mean (SD), [N1]	-0.710 (0.3783), [32]	-0.871 (0.3510), [37]	-0.809 (0.3434), [73]	**-0.932 (0.3730), [65]**
Absolute Change in EREFS total score [0-18] (local reads), Mean (SD), [N1]	-4.3 (3.21), [31]	-6.1 (3.60), [37]	-5.2 (3.40), [73]	**-5.3 (2.85), [63]**
Peak Eos Count <15/hpf, n/N1 (%)	28/32 (87.5%)	29/37 (78.4%)	61/73 (83.6%)	**65/65 (100%)**
NES for EDP, median, [N1]	-2.39, [8]	-2.58, [14]	-2.65, [32]	**-2.72, [27]**
NES for T2INF, median, [N1]	-1.83, [8]	-1.96, [14]	-1.96, [32]	**-1.98, [27]**

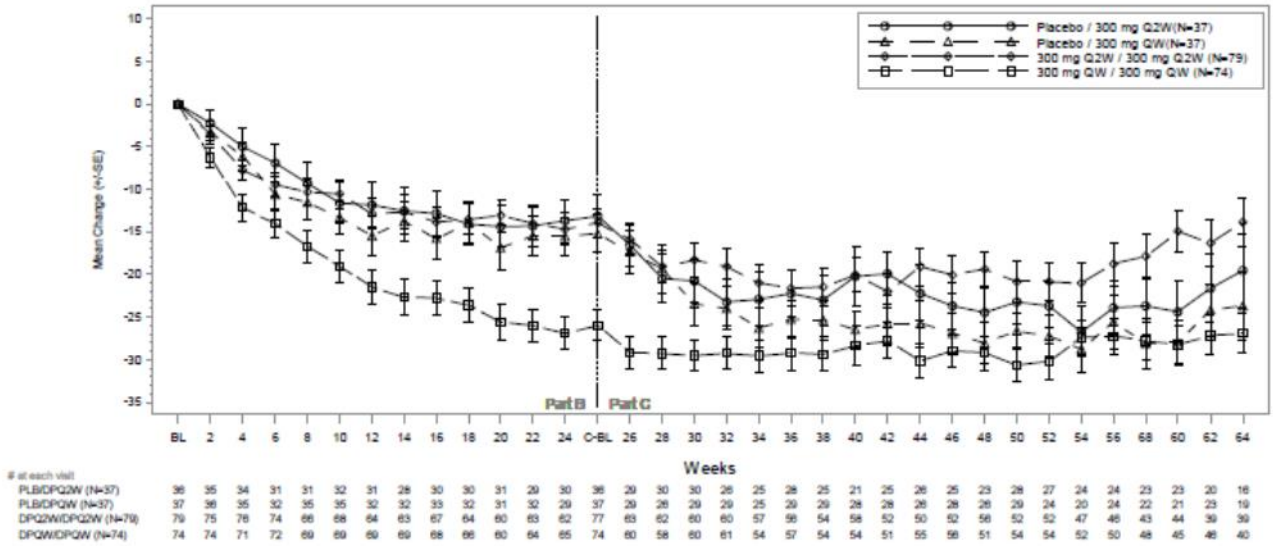
Abbreviations: DSQ=Dysphagia Symptom Questionnaire; EDP= the EoE diagnostic panel; EoE=eosinophilic esophagitis; EoEHSS=EoE Histology Scoring System; EREFS=Endoscopic Reference Score; NES=Normalized Enrichment Scores; Q2W=every 2 weeks; QW=every week; SD=standard deviation; T2INF=type 2 inflammation signature.
N=number of patients enrolled in Part C from Part B; N1=number of patients with observed data.
a For endpoints measured by absolute or % change, changes were calculated from study baseline (ie, start of Part B).

In Part B/C, numerically greater effects in all endpoints were observed in participants treated with dupilumab 300 mg QW for 52 weeks (dupilumab 300 mg QW/dupilumab 300 mg QW group) compared with those treated with dupilumab 300 mg Q2W (dupilumab 300 mg Q2W/dupilumab 300 mg Q2W group).

Furthermore, efficacy in the dupilumab 300 mg QW/dupilumab 300 mg QW group continued to improve during Part C. In Part B 58.8% of participants had achieved peak esophageal intraepithelial eosinophil count ≤6/hpf at Week 24, while 84.6% had achieved this after 52 weeks. In addition, 100% of participants achieved an eos count of <15/hpf at 52 weeks on 300 mg QW (74.9% after 24 weeks).

Similarly, DSQ scores continued to improve in Part B participants treated with dupilumab 300 mg QW/ dupilumab 300 mg QW group from -23.78 at 24 weeks to -30.26 at 52 weeks.

Figure 14 Summary of Absolute Change in DSQ Total Score From Part B Baseline to Week 64, All Observed Values Regardless of Rescue Treatment Use (R668-EE-1774 Part C Safety Analysis Set - Patients from Part B)



The participants who previously received placebo achieved improvements after 28 weeks on dupilumab 300 mg QW in Part C that were similar to those observed for participants who received 24 weeks of dupilumab treatment during Part B.

In summary, the additional Part B/C efficacy data for up to one year provide further evidence that treatment with dupilumab 300 mg QW shows clinically meaningful efficacy in the treatment EoE patients.

Ancillary analyses

- **Subgroup Analyses by age**

Adolescent Participants

PART A

Table 22 Co-Primary and Key Secondary Endpoints: Adolescent Participants (R668 EE-1774 Part A FAS)

	Endpoints (at Week 24)	Placebo (N=9)	Dupilumab QW (N=11)	Difference vs Placebo LS mean (95%CI)	P value (treatment by age group interaction)
Co-primary Endpoints	Proportion of participants achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf, n(%)[1]	0 (0.0)	4 (36.4)	36.5 (8.11, 64.95)	0.9804
	Baseline total DSQ score, mean (SD)	36.04 (10.357)	37.48 (11.783)	-	-
	Absolute change in DSQ score[2] (0-84), LS mean (SE)[2]	-15.93 (5.250)	-23.84 (4.767)	-7.91 (-21.770, 5.951)	0.4024
Key Secondary Endpoints	Baseline peak esophageal intraepithelial eosinophil count, mean (SD)	106.3 (70.11)	108.0 (52.95)	-	-
	Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline, LS mean (SE)[3]	1.42 (14.712)	-58.87 (13.399)	-60.30 (-99.186, -21.411)	0.5857
	Baseline EoEHSS mean grade score, mean (SD)	1.491 (0.5666)	1.477 (0.3421)	-	-
	Absolute change in mean EoEHSS grade score from baseline, LS mean (SE)[3]	0.041 (0.1173)	-0.836 (0.1098)	-0.877 (-1.1904, -0.5634)	0.3399
	Baseline EoEHSS mean stage score, mean (SD)	1.495 (0.5125)	1.446 (0.2142)	-	-
	Absolute change in mean EoEHSS stage score from baseline, LS mean (SE)[3]	-0.006 (0.1184)	-0.754 (0.1104)	-0.748 (-1.0641, -0.4314)	0.5228
	Baseline EoE-EREFS total score, mean (SD)	5.7 (2.40)	6.7 (2.05)	-	-
	Absolute change in EoE-EREFS from baseline, LS mean(SE)[3]	0.0 (0.82)	-3.0 (0.77)	-3.0 (-5.25, -0.80)	0.3097
Other Selected Secondary Endpoints	NES for the relative change from baseline to week 24 in the EDP, median (n)[4]	-0.050 (5)	-2.705 (6)	-2.655 (-4.0800, -1.1500)	0.0081
	NES for the relative change from baseline to week 24 in the type 2 inflammation signature, median (n)[4]	-0.170 (5)	-1.980 (6)	-1.810 (-3.1300, -0.8500)	0.0081

[1] Participants in Part A missing endoscopy with biopsies at week 24 were imputed by the MI if due to COVID-19. Otherwise, participants were treated as non-responder in the analysis if missingness is not due to COVID-19.
[2] Missing value due to any reasons are imputed by MI
[3] Missing value are imputed by WOCF if not due to COVID-19 and by MI if due to COVID-19.
[4] n= number of patients with NES score in Part A. Difference and its CI are based on the Hodges-Lehmann estimator. P-values were based on Wilcoxon rank-sum test. Missing values were imputed by LOCF.
Note: All p-values in this table are nominal.
Abbreviations: COVID-19=Coronavirus Disease-2019; CI=confidence interval; DSQ=Dysphagia Symptom Questionnaire; EoE=eosinophilic esophagitis; EoE-EREFS=Eosinophilic Esophagitis-Endoscopic Reference Score; eos/hpf=eosinophils/high-power field; EoEHSS=Eosinophilic Esophagitis Histology Scoring System; LS=least squares; MI=multiple imputation; PPI=proton pump inhibitor; QW=once weekly; SE=standard error; WOCF=worst observation carried forward.

- Co-primary endpoints

Eosinophil Count ≤6 eos/hpf at Week 24

The proportion of adolescent participants (≥12 to <18 years) who achieved a peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24 was greater in the dupilumab 300 mg QW (04/11; 36.4%) group than in the placebo group (0/9; 0%). The proportion of patients is lower than in the Dupilumab 300 mg QW group in Part B and in adult participants treated with dupilumab.

Absolute Change from Baseline in DSQ Total Score

The improvement from baseline in DSQ total score at week 24 for adolescent participants (≥12 to <18 years) was greater in the dupilumab 300 mg QW (−23.48) group than in the placebo group (−15.93).

PART B

Table 23 Co-Primary and Key Secondary Endpoints: Adolescent Participants (R668 EE-1774 Part B FAS)

			Dupilumab 300 mg Q2W (N=27)		Dupilumab 300 mg QW (N=26)	
	Endpoints (at Week 24)	**Placebo (N=26)**	**Value**	**Difference vs Placebo LS mean (95%CI)[1]**	**Value**	**Difference vs Placebo LS mean (95%CI)**
Co-primary Endpoints	Proportion of participants achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf, n(%)	2 (7.7)	13 (48.1)	42.1 (18.87, 65.41)	15 (57.7)	52.2 (30.08, 74.36)
	Baseline DSQ total score, mean (SD)	32.54 (10.188)	36.13 (13.959)	-	39.94 (10.884)	-
	Absolute change in DSQ total score (0-84), LS mean change (SE)	-16.42 (3.600)	-12.14 (3.444)	4.28 (-5.102, 13.665)	-19.54 (3.574)	-3.12 (-12.795, 6.554)
Key Secondary Endpoints	Baseline peak esophageal intraepithelial eosinophil count, mean (SD)	74.1 (37.18)	86.9 (37.70)	-	80.6 (56.26)	-
	Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline, LS mean % change (SE)	5.66 (21.412)	-46.32 (19.456)	-51.98 (-106.485, 2.523)	-74.56 (19.529)	-80.22 (-134.483, -25.963)
	Baseline EoEHSS mean grade score, mean (SD)	1.202 (0.4591)	1.336 (0.3981)	-	1.250 (0.4416)	-
	Absolute change in mean EoEHSS grade score from baseline, LS mean (SE)	-0.180 (0.0875)	-0.750 (0.0796)	-0.570 (-0.7925, -0.3477)	-0.773 (0.0815)	-0.593 (-0.8093, -0.3760)
	Baseline EoEHSS mean stage score, mean (SD)	-0.059 (0.4316)	1.363 (0.3172)	-	1.247 (0.3475)	-
	Absolute change in mean EoEHSS stage score from baseline, LS mean (SE)	-0.142 (0.0842)	-0.741 (0.0775)	-0.599 (-0.8149, -0.3829)	-0.748 (0.0786)	-0.606 (-0.8148, -0.3975)
	Baseline EoE-EREFS total score, mean (SD)	6.0 (3.07)	6.7 (3.01)		5.7 (3.07)	

			Dupilumab 300 mg Q2W (N=27)		Dupilumab 300 mg QW (N=26)	
	Endpoints (at Week 24)	**Placebo (N=26)**	**Value**	**Difference vs Placebo LS mean (95%CI)[1]**	**Value**	**Difference vs Placebo LS mean (95%CI)**
	Absolute change in EoE-EREFS total score from baseline, LS mean (SE)	-0.0 (0.64)	-4.1 (0.56)	-4.1 (-5.68, -2.52)	-3.7 (0.61)	-3.6 (-5.19, -2.07)

Values after first rescue treatment were assigned using MI. MI was also used to impute missing values using seed: 6681774 with imputation size 50. Missing baseline was not imputed by MI.

[1] The CI with p-value is based on treatment difference (dupilumab group vs. placebo) of the LS mean change using ANCOVA model with baseline measurement as covariate and the treatment, age group [≥12 to <18 vs ≥18] (except for the subgroup analysis by age group) and PPI use at randomization (Yes vs. No) (except for the subgroup analysis by PPI use) strata as fixed factors.

Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; DSQ=Dysphagia Symptom Questionnaire; EoE-EREFS=Eosinophilic Esophagitis-Endoscopic Reference Score; eos/hpf=eosinophils/high-power field; EoEHSS=Eosinophilic Esophagitis Histology Scoring System; FAS=full analysis set; LS=least squares; MI=multiple imputation; PPI=proton pump inhibitor; Q2W=every 2 weeks; QW=once weekly; SD=standard deviation; SE=standard
error.

- Co-primary endpoints

Eosinophil Count ≤6 eos/hpf at Week 24

The proportion of adolescent participants (≥12 to <18 years) who achieved a peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24 was greater in both the dupilumab 300 mg QW (15/26; 57.7%) and 300 mg Q2W (13/27; 48.1%) groups than in the placebo group (2/26; 7.7%). The improvements in the dupilumab groups followed a similar pattern to those in adult participants (≥18 years).

Absolute Change from Baseline in DSQ Total Score

The improvement from baseline in DSQ total score at week 24 for adolescent participants (≥12 to <18 years) was greater in the dupilumab 300 mg QW (−19.54) group than in the placebo group (−16.42). However, the improvement in the dupilumab 300 mg Q2W (−12.14) group was less than that in the placebo group.

Overall, in adult participants (≥18 years), the effect of treatment on DSQ total score at week 24 was greater than in adolescents in both dupilumab 300 mg groups (QW and Q2W) than in the placebo group. This difference might be a function of a greater change from baseline in the placebo group observed in adolescents relative to adult participants.

Table 24 Absolute Change from Baseline in DSQ Total Score at Week 24 by Age Group, MI Method with Data Set to Missing After Rescue Treatment Use (Part B FAS)

Treatment	LS Mean Change (SE)	LS Mean Change 95% CI	Mean Change (SD)	Baseline Mean (SD)	Num. of Subjects/ Imputed Subjects	Contrast	LS Mean Difference (95% CI)[1]
Age Group: ≥12-<18 years							
Dupilumab 300 mg QW (N=26)	-19.54 (3.574)	(-26.548, -12.538)	-19.57 (19.882)	39.94 (10.884)	18/8	Dupilumab 300 mg QW vs Placebo	-3.12 (-12.795, 6.554)
Dupilumab 300 mg Q2W (N=27)	-12.14 (3.444)	(-18.891, -5.391)	-11.68 (15.475)	36.13 (13.959)	20/7	Dupilumab 300 mg Q2W vs Placebo	4.28 (-5.102, 13.665)
Placebo (N=26)	-16.42 (3.600)	(-23.480, -9.365)	-15.46 (11.783)	32.54 (10.188)	21/5		
Age Group: ≥18 years							
Dupilumab 300 mg QW (N=54)	-26.68 (2.067)	(-30.730, -22.629)	-26.97 (14.062)	37.59 (10.635)	45/9	Dupilumab 300 mg QW vs Placebo	-13.30 (-18.959, -7.650)
Dupilumab 300 mg Q2W (N=54)	-16.42 (2.133)	(-20.603, -12.240)	-16.27 (14.246)	35.28 (11.414)	42/12	Dupilumab 300 mg Q2W vs Placebo	-3.05 (-8.829, 2.737)
Placebo (N=53)	-13.38 (2.163)	(-17.616, -9.134)	-13.72 (13.134)	37.87 (10.370)	38/14		

Values after first rescue treatment were assigned using MI. MI was also used to impute missing values using seed: 6681774 with imputation size 50. Missing baseline was not imputed by MI.

- Selected Key Secondary endpoints

Percent Change from Baseline in Peak Esophageal Intraepithelial Eosinophil Count (eos/hpf)

The percent decrease from baseline in peak esophageal intraepithelial eosinophil count at week 24 in adolescents (≥12 to <18 years) was greater in the dupilumab 300 mg QW (-74.56%) and 300 mg Q2W (−46.32%) groups than in the placebo group (+5.66%). These improvements in adolescent participants for the dupilumab 300 mg regimen were similar to those in the adult participants.

Absolute Change from Baseline in EoE-EREFS Total Score

The LS mean decrease from baseline in EoE-EREFS total score at week 24 in adolescent participants (≥12 to <18 years) was greater in the dupilumab 300 mg QW (−3.7 points) and 300 mg Q2W (−4.1 points) groups than in the placebo group (−0.0 points). Overall, the LS mean placebo-corrected decreases in adolescent participants were consistent with those in the adult participants for both dupilumab regimens.

Absolute Change from Baseline in EoEHSS Mean Grade Score

The LS mean absolute change from baseline in EoEHSS mean grade score at week 24 in adolescent participants (≥12 to <18 years) showed greater reduction in the dupilumab 300 mg QW (−0.773 points) and 300 mg Q2W (−0.750 points) groups than in the placebo group (−0.180 points).

Part C

- Participants from Part A

Table 25 Key Efficacy Parameters at Week 52 in the Adolescents Versus Adults, All Observed Values Regardless of Rescue Treatment Use (Part C SAF – Participants from Part A)

Efficacy Endpoints at Week 52[a]	Part A / Part C Treatment					
	Adolescents (≥12 to <18 years of age)			Adults (>18 years of age)		
	Placebo/ Dupi 300 mg QW (N=9)	Dupi 300 mg QW/ Dupi 300 mg QW (N=10)	Total (N=19)	Placebo/ Dupi 300 mg QW (N=28)	Dupi 300 mg QW/ Dupi 300 mg QW (N=30)	Total (N=58)
Proportion of participants who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf, n/N1 (%)	6/8 (75.0%)	3/9 (33.3%)	9/17 (52.9%)	12/22 (54.5%)	16/25 (64.0%)	28/47 (59.6%)
Absolute change from Part A baseline in DSQ total score, mean (SD)	N1=5 -25.45 (22.460)	N1=6 -25.57 (18.339)	N1=11 -25.52 (19.234)	N1=18 -20.68 (16.012)	N1=23 -22.88 (15.935)	N1=41 -21.92 (15.806)
% change from Part A baseline in peak esophageal intraepithelial eosinophil count, mean (SD)	N1=8 -91.99 (14.480)	N1= 9 -83.40 (12.944)	N1=17 -87.45 (13.965)	N1=22 -80.77 (27.526)	N1=25 -90.46 (13.463)	N1=47 -85.92 (21.549)
Absolute change from Part A baseline in EoEHSS mean grade score, mean (SD)	N1=8 -1.076 (0.5582)	N1=9 -0.933 (0.3099)	N1=17 -1.000 (0.4356)	N1=22 -0.799 (0.5416)	N1=25 -0.851 (0.3717)	N1= 47 -0.827 (0.4546)
Absolute change from Part A baseline in EoEHSS mean stage score, mean (SD)	N1=8 -1.016 (0.5656)	N1=9 -0.905 (0.1778)	N1=17 -0.957 (0.3987)	N1=22 -0.822 (0.4230)	N1=25 -0.886 (0.3080)	N=47 -0.856 (0.3636)
Absolute change from Part A baseline in EoE-EREFS total score, mean (SD)	N1= 8 -3.5 (2.56)	N1=9 -4.8 (2.49)	N1=17 -4.2 (2.53)	N1=22 -4.0 (2.85)	N1=26 -3.8 (3.63)	N1= 48 -3.9 (3.26)

[a] For endpoints measured by absolute or % change, changes were calculated from study baseline (ie, start of Part A).
N1 = number of participants with observed data.
Abbreviations: DSQ= Dysphagia Symptom Questionnaire; EoE-EREFS=Eosinophilic Esophagitis-Endoscopic Reference Score; eos/hpf=eosinophils/high-power field; EoEHSS=Eosinophilic Esophagitis Histology Scoring System; QW=once weekly; SAF=safety analysis set; SD=standard deviation.

Proportion of Participants Achieving Peak Esophageal Intraepithelial Eosinophil Count ≤6 eos/hpf

3 of 9 (33.3%) adolescent participants in the dupilumab 300 mg QW/dupilumab 300 mg QW group and 6/8 (75.0%) in the placebo/dupilumab 300 mg QW group achieved a peak esophageal intraepithelial eosinophil count ≤6 eos/hpf in all 3 regions at week 52. Two adolescent participants in the dupilumab 300 mg QW/dupilumab 300 mg QW group achieved a peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at baseline of Part C but were no longer responders at week 52.

Table 26 Proportion of Adolescent Participants Achieving Peak Esophageal Intraepithelial Eosinophil Count ≤6 eos/hpf in All 3 Regions at Week 52, All Observed Values Use (Part C SAF - Participants from Part A)

Visit	Placebo / Dupilumab 300 mg QW (N=9) n/N1 (%)	Dupilumab 300 mg QW / Dupilumab 300 mg QW (N=10) n/N1 (%)	Total (N=19) n/N1 (%)
Baseline of Part C	0/7	5/9 (55.6%)	5/16 (31.3%)
Week 52	6/8 (75.0%)	3/9 (33.3%)	9/17 (52.9%)

N1 stands for number of participants with non-missing values at each visit.
Abbreviations: eos/hpf=eosinophils/high-power field; QW=once weekly; SAF=safety analysis set.

Absolute Change from Baseline in DSQ Total Score

Adolescent participants in the dupilumab 300 mg QW/dupilumab 300 mg QW group maintained improvement in DSQ total score with continued treatment during Part C. The mean change from the Part A baseline (36.21) was -24.80 points at the Part C baseline (week 24; N=10) and −25.57 points at week 52 (N=6). Adolescent participants in the placebo/dupilumab 300 mg QW group who started dupilumab treatment in Part C showed progressive improvement. The mean change from the Part A baseline (36.04) was -25.45 points at week 52 (N=5).

The mean change in DSQ total score at week 52 was -3.97 points from the Part C baseline (11.41 points) for the dupilumab 300 mg QW/dupilumab 300 mg QW group (N=6) showing maintained

improvement with continued treatment during Part C and -10.68 points from the Part C baseline (21.06 points) in the placebo/dupilumab 300 mg QW group (N=5) showing progressive improvement from start of dupilumab treatment in Part C.

- Participants from Part B

Proportion of Participants Achieving Peak Esophageal Intraepithelial Eosinophil Count ≤6 eos/hpf

Table 27 Summary of number of adolescent patients (%) with peak eosphageal intraepithelial eosinophil count of ≤6 eos/hpf in all three regions at week 52, all observed values regardless of rescue treatment use (Part C Safety Analysis Set – Patients from Part B)

Visit	Placebo/Dupilumab 300 mg Q2W (N=15) n/N1 (%)	Placebo/Dupilumab 300 mg QW (N=10) n/N1 (%)	Dupilumab 300 mg Q2W/ Dupilumab 300 mg Q2W (N=26) n/N1 (%)	Dupilumab 300 mg QW/ Dupilumab 300 mg QW (N=24) n/N1 (%)
Baseline of Part C	1/15 (6.7%)	1/10 (10.0%)	14/26 (53.8%)	16/24 (66.7%)
Week 52	10/14 (71.4%)	5/10 (50.0%)	15/25 (60.0%)	18/22 (81.8%)

Abbreviations: Q2W=every 2 weeks; QW=every week
N1 stands for number of patients with non-missing values at each visit

The dupilumab 300 mg QW/dupilumab 300 mg QW treated group demonstrated continued improvement in the proportion of adolescent participants who achieved a peak esophageal intraepithelial eosinophil count ≤6 eos/hpf in all 3 regions of the esophagus (histologic remission) at Week 52. At baseline of Part C (Week 24), 16/24 (66.7%) adolescents treated with dupilumab 300 mg QW achieved histologic remission. The results from Part B/C show continued improvement with 18/22 (81.8%) adolescent participants achieving histological remission at Week 52. The dupilumab 300 mg Q2W/dupilumab 300 mg Q2W group also demonstrated sustained improvement. Fourteen out of 26 (53.8%) participants treated with dupilumab 300 mg Q2W achieved histologic remission at Week 24, with 15/25 (60.0%) of participants achieving histological remission in all 3 regions at Week 52.

This observation is consistent with the Part B data, showing that highest rates in histologic response in adolescent participants are reached with the 300 mg QW dosing regimen.

Absolute Change from Baseline in Dysphagia Symptom Questionnaire (DSQ) Total Score

Table 28 Absolute change in DSQ total score from baseline of Part B to week 52 for adolescents, all observed values regardless of rescue treatment use (Part C Safety Analysis Set – Patients from Part B)

Visit	Placebo/Dupilumab 300 mg Q2W (N=15) Mean (SD), N1	Placebo/Dupilumab 300 mg QW (N=10) Mean (SD), N1	Dupilumab 300 mg Q2W/ Dupilumab 300 mg Q2W (N=26) Mean (SD), N1	Dupilumab 300 mg QW/ Dupilumab 300 mg QW (N=24) Mean (SD), N1
Baseline of Part C	-14.11 (16.073), [15]	-18.29 (13.613), [10]	-8.71 (14.433), [26]	-22.26 (18.783), [24]
Week 52	-18.07 (14.266), [11]	-25.02 (14.951), [7]	-17.00 (18.784), [16]	-26.86 (20.430), [15]

Abbreviations: DSQ=Dysphagia Symptom Questionnaire; Q2W=every 2 weeks; QW=every week; SD=standard deviation
N1 stands for number of patients with non-missing values at each visit
Note: To calculate the DSQ score, a minimum of 8 diary entries is required for each 14-day period to derive a standardized total score based on the cumulative scores through 14 days. If there are less than 8 diary entries for a 14-day period, the DSQ score is considered to be missing for that period.

The results from Part B/C show that adolescent participants in the dupilumab 300 mg QW/dupilumab 300 mg QW group maintained improvement in DSQ total score, with lower scores with continued treatment during Part C. The mean absolute change from the Part B baseline was -22.26 points at the Part C baseline (Week 24; N=24) and -26.86 points at Week 52 (N=15).

The adolescent participants in the dupilumab 300 mg Q2W/dupilumab 300 mg Q2W group also showed improvement at Week 52. However, the magnitude of improvements in DSQ total score achieved were lower than in the dupilumab 300 mg QW group, either at Week 24 or Week 52. The mean absolute change from the Part B baseline was -17.00 points at Week 52 (N=16).

Based on these results from the 300 mg Q2W treatment group, the treatment effect improves but the results are of lesser extent.

Pooled Analyses by age

Table 29 Subgroup Analysis of Proportion of Patients with Peak Esophageal Intraepithelial Eosinophil Count of ≤6 eos/hpf in All Three Regions at Week 24 by Age Group

Age Group: >= 12 -< 18 Years

Study	Treatment	Patients with Peak Esophageal Intraepithelial Eosinophil Count of <=6 eos/hpf at Week 24, n(%)	95 % CI [1]	Difference(95% CI) [2]
R668-EE-1774 Part A	Dupilumab 300 mg QW (N=11)	4 (36.4)	(10.93, 69.21)	36.5 (8.11, 64.95)
	Placebo (N=9)	0 (0.0)	(0.00, 33.63)	
R668-EE-1774 Part B	Dupilumab 300 mg QW (N=26)	15 (57.7)	(36.92, 76.65)	52.2 (30.08, 74.36)
	Dupilumab 300 mg Q2W (N=27)	13 (48.1)	(28.67, 68.05)	42.1 (18.87, 65.41)
	Placebo (N=26)	2 (7.7)	(0.95, 25.13)	
Pooled Analysis (Pool 1)	Dupilumab 300 mg QW (N=37)	19 (51.4)	(34.40, 68.08)	47.9 (29.96, 65.82)
	Placebo (N=35)	2 (5.7)	(0.70, 19.16)	

Age Group: >= 18 Years

Study	Treatment	Patients with Peak Esophageal Intraepithelial Eosinophil Count of <=6 eos/hpf at Week 24, n(%)	95 % CI [1]	Difference(95% CI) [2]
R668-EE-1774 Part A	Dupilumab 300 mg QW (N=31)	21 (67.7)	(48.63, 83.32)	61.4 (43.12, 79.69)
	Placebo (N=30)	2 (6.7)	(0.82, 22.07)	
R668-EE-1774 Part B	Dupilumab 300 mg QW (N=54)	32 (59.3)	(45.03, 72.43)	54.1 (39.14, 69.10)
	Dupilumab 300 mg Q2W (N=54)	36 (66.7)	(52.53, 78.91)	62.8 (48.21, 77.47)
	Placebo (N=53)	3 (5.7)	(1.18, 15.66)	
Pooled Analysis (Pool 1)	Dupilumab 300 mg QW (N=85)	53 (62.4)	(51.18, 72.64)	57.6 (45.76, 69.37)
	Placebo (N=83)	5 (6.0)	(1.98, 13.50)	

In Pool 1, the Co-Primary Endpoints were analysed by age.

The results show that in the ≥12 to <18 years of age group, the proportion of participants who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24 was 19/37 (51.4%) in the dupilumab 300 mg QW group versus 2/35 (5.7%) in the placebo group. In the ≥18 years of age group, the proportion of participants who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24 was 53/85 (62.4%) in the dupilumab 300 mg QW group versus 5/83 (6.0%) in the placebo group.

In the ≥12 to <18 years of age group, the improvement in DSQ total score from baseline to week 24 was -21.07 points in the dupilumab 300 mg QW group (n=37) and -17.23 points in the placebo group (n=35).

When compared to the ≥18 years of age subgroup, the improvement from baseline in DSQ total score at week 24 relative to placebo in the adolescent subgroup was numerically smaller than the adult subgroup likely due to a higher placebo effect.

In the ≥18 years of age group, the LS mean absolute change from baseline in DSQ total score at week 24 was -23.57 points in the dupilumab 300 mg QW group (n=85) and -10.06 points in the placebo group (n=83) (LS mean difference [95% CI]: -13.50 [-17.936, -9.073]).

- **Additional Data**

Part A

The R668-EE-1774 Part A Clinical Study Report contained the final analysis of data from the randomized, double-blind, placebo-controlled Part A of the study. The report contained all Part A data through 08 May 2020 (data cut-off). The final database lock for Part A occurred on 20 May 2020.

Four participants had not completed their Part A week 24 biopsy at the time of the data cut-off, due to not being able to attend study visits because of the Coronavirus Disease-2019 (COVID-19) pandemic. As a result, all 4 participants were allowed to extend their assigned Part A dose regimen of study drug beyond the week 23 injection until the post-baseline esophageal biopsy procedure(s) were performed. All 4 participants had some interruptions to study treatment and a delayed week 24 visit. Their data up to the Part A data cut-off were included in the Part A CSR, including their Dysphagia Symptom Questionnaire (DSQ) data though week 24 (which were not impacted by the COVID-19 pandemic) for the primary analysis.

One serious adverse event (SAE) that was reported approximately 14 months after the onset of the event, and hence after the data cut-off. 2 adverse events of Arthralgia were re-categorized as adverse events of special interest. A pregnancy was reported in a participant who had requested to withdraw from the study, but who could not attend an early termination visit due to the COVID-19 pandemic. These events have been included in the relevant sections of the AR.

No new analyses were performed or data summaries produced. The listed data from the 4 participants who completed Part A after data cut-off are consistent with the overall efficacy and safety conclusions in the Part A CSR.

Part C

The completed R668-EE-1774 Part A-C clinical study report contained the final analysis of data from the 28-week extended active treatment phase enrolling patients from Part A. The report contained all data through 18 Nov 2020 (data cut-off). The database lock occurred on 17 Dec 2020.

Six participants were ongoing in Part C at the time of the data cut-off for the Part A-C CSR. This addendum summarizes their Part C data obtained after the data cut-off. Individual patient data profiles were provided that include all data from 18 Nov 2020 up to last patient last visit (LPLV) (27 May 2021).

No new analyses were performed or data summaries were produced. Of the 6 participants, 2 had completed dosing with dupilumab at the time of the 18 Nov 2020 data cut-off. The 4 patients with Continued dosing had a range of 2-14 additional doses. For all 4 of the participants with additional DSQ data, DSQ scores remained below the Part A or Part C baseline values for the duration of the study. The data from the 6 participants who completed Part C after the data cut-off are consistent with the overall efficacy and safety conclusions in the Part A-C CSR.

Summary of main study

The following tables summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as

well as the benefit risk assessment (see later sections).

Table 30. Summary of Efficacy for trial R668-EE-1774 (Part A)

Title: A Phase 3, randomized, 3-part study to investigate the efficacy and safety of dupilumab in adult and adolescent patients with eosinophilic esophagitis.			
Study identifier	R668-EE-1774 (Part A)		
Design	Randomized, double-blind, placebo-controlled, parallel-group design		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks N/A N/A
Hypothesis	Superiority		
Treatments groups	Dupilumab 300mg QW		Dupilumab 300 mg SC QW for 24 weeks, N =42
	Matching placebo		Placebo QW for 24 weeks, N =39
Endpoints and definitions	Co-Primary endpoints	Peak eos count of ≤6 eos/hpf at week 24	Proportion of participants achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24
		Change in DSQ score to week 24	Absolute change in DSQ score from baseline to week 24
	Key Secondary endpoints	Percent change in peak eos count (eos/hpf) to week 24	Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to week 24
		Change in EoEHSS grade score to week 24	Absolute change in EoE Grade Score from the EoEHSS from baseline to week 24
		Change in EoEHSS stage score to week 24	Absolute change in EoE Stage Score from the EoEHSS from baseline to week 24
		Change in EoE-EREFS to week 24	Absolute change in EoE-EREFS from baseline to week 24
	Other Secondary endpoints	Peak eos count of <15 eos/hpf at week 24	Proportion of participants achieving peak esophageal intraepithelial eosinophil count <15 eos/hpf at week 24
		Percent change in DSQ score at week 24	Percent change from baseline in DSQ total score at week 24
		NES change to wk 24 in EDP	NES for the relative change from baseline to week 24 in the EoE Diagnostic Panel transcriptome signature
		NES change to wk 24 in T2 inflammation signature	NES for the relative change from baseline to week 24 in the type 2 inflammation transcriptome signature
Database lock	20 May 2020		
Results and Analysis			

Title: A Phase 3, randomized, 3-part study to investigate the efficacy and safety of dupilumab in adult and adolescent patients with eosinophilic esophagitis.			
Study identifier	R668-EE-1774 (Part A)		
Analysis description	**Primary endpoint analysis**		
Analysis population and time point description	Full Analysis Set Week 24		
Descriptive statistics and estimate variability	**Treatment group**	**Dupilumab 300mg QW**	**Placebo**
	Number of subjects	**42**	**39**
	Peak eos count of ≤6 eos/hpf at week 24 (n (%))	25 (59.5)	2 (5.1)
	95% CI (%)	(43.28, 74.37)	(0.63, 17.32)
	Change in DSQ score to week 24 (LS mean change)	-21.92	-9.60
	95% CI	(-26.870, -16.967)	(-15.056, -4.136)
Effect estimate per comparison	**Co-Primary endpoint:** Peak eos count of ≤6 eos/hpf at week 24	Comparison groups	Dupilumab 300 mg QW vs. Placebo
		Difference vs Placebo LS Mean (95% CI)	55.3 (39.58, 71.04)
		P-value	<0.0001
	Co-Primary endpoint: Change in DSQ score to week 24	Comparison groups	Dupilumab 300 mg QW vs. Placebo
		Difference vs Placebo LS Mean (95% CI)	-12.32 (-19.107, -5.537)
		P-value	0.0004
Analysis description	**Secondary endpoint analysis**		
Analysis population and time point description	Full Analysis Set Week 24		
Descriptive statistics and estimate variability	**Treatment group**	**Dupilumab 300mg QW**	**Placebo**
	Number of subjects	**42**	**39**
	Secondary Endpoint: Percent change in peak eos count (eos/hpf) to week 24 (LS mean % change)	-71.24	-2.98
	LS Mean % Change 95% CI	(-84.863, -57.613)	(-17.886, 11.921)
	Secondary Endpoint: Change in EoEHSS grade score to week 24 (LS mean change)	-0.761	-0.001
	LS Mean % Change 95% CI	(-0.8732 ,-0.6484)	(-0.1166 , 0.1139)

Title: A Phase 3, randomized, 3-part study to investigate the efficacy and safety of dupilumab in adult and adolescent patients with eosinophilic esophagitis.			
Study identifier	R668-EE-1774 (Part A)		
	Secondary Endpoint: Change in EoEHSS stage score to week 24 (LS mean change)	-0.753	-0.012
	LS Mean Change 95% CI	(-0.8627 , -0.6441)	(-0.1243 , 0.0995)
	Secondary Endpoint: Change in EoE-EREFS to week 24 (LS mean change)	-3.2	-0.3
	LS Mean Change 95% CI	(-3.98 ,-2.38)	(-1.11 , 0.50)
	Secondary Endpoint: Peak eos count of <15 eos/hpf at week 24 (n(%))	27 (64.3)	3 (7.7)
	95% CI	(48.03, 78.45)	(1.62, 20.87)
	Secondary Endpoint: Percent change in DSQ score at week 24 (LS mean % change)	-69.17	-31.68
	LS Mean % Change 95% CI	(-83.578, -54.752)	(-47.545, -15.818)
	Secondary Endpoint: NES change to wk 24 in EDP (median change (n^1))	-2.660 (31)	-0.160 (29)
	Secondary Endpoint: NES change to wk 24 in T2 inflammation signature (median change (n^1))	-1.970 (31)	-0.320 (29)
Effect estimate per comparison	**Secondary Endpoint** Percent change in peak eos count (eos/hpf) to week 24	**Comparison groups**	**Dupilumab 300 mg QW vs. Placebo**
		LS Mean Difference (95% CI)	-68.26 (-86.896, -49.615)
		P-value	<0.0001
	Secondary Endpoint Change in EoEHSS grade score to week 24	**Comparison groups**	**Dupilumab 300 mg QW vs. Placebo**
		Difference vs Placebo LS Mean (95% CI)	-0.759 (-0.9061, -0.6127)
		P-Value	<0.0001
	Secondary Endpoint	**Comparison groups**	**Dupilumab 300 mg QW vs. Placebo**

Title: A Phase 3, randomized, 3-part study to investigate the efficacy and safety of dupilumab in adult and adolescent patients with eosinophilic esophagitis.			
Study identifier	R668-EE-1774 (Part A)		
	Change in EoEHSS stage score to week 24	Difference vs Placebo LS Mean (95% CI)	-0.741 (-0.8842, -0.5978)
		P-value	<0.0001
	Secondary Endpoint Change in EoE-EREFS to week 24	**Comparison groups**	**Dupilumab 300 mg QW vs. Placebo**
		Difference vs Placebo LS Mean (95% CI)	-2.9 (-3.91, -1.84)
		P-value	<0.0001
	Secondary Endpoint Peak eos count of <15 eos/hpf at week 24	**Comparison groups**	**Dupilumab 300 mg QW vs. Placebo**
		Difference vs Placebo LS Mean (95% CI)	57.5 (41.69, 73.33)
		P-value	<0.0001
	Secondary Endpoint Percent change in DSQ score at week 24	**Comparison groups**	**Dupilumab 300 mg QW vs. Placebo**
		Difference vs Placebo LS Mean (95% CI)	-37.48 (-57.222, -17.745)
		P-value	0.0002
	Secondary Endpoint NES change to wk 24 in EDP	**Comparison groups**	**Dupilumab 300 mg QW vs. Placebo**
		Difference vs Placebo LS Mean (95% CI)	-2.250 (-2.7200, -1.7300)
		P-value	<0.0001
	Secondary Endpoint NES change to wk 24 in T2 inflammation signature	**Comparison groups**	**Dupilumab 300 mg QW vs. Placebo**
		Difference vs Placebo LS Mean (95% CI)	-1.590 (-1.7400, -1.2700)
		P-value	<0.0001

1. n= number of patients with NES score in Part A.

Abbreviations: CI=confidence interval; DSQ= Dysphagia Symptom Questionnaire; EDP=EoE diagnostic panel; EoE-EREFS=Eosinophilic Esophagitis-Endoscopic Reference Score; eos/hpf=eosinophils/high-power field; EoEHSS=Eosinophilic Esophagitis Histology Scoring System; LS=least squares; NES=Normalized Enrichment Score; QW=once weekly; T2=Type 2.

Table 31. Summary of efficacy for trial R668-EE-1774 (Part B)

Title: A Phase 3, randomized, 3-part study to investigate the efficacy and safety of dupilumab in adult and adolescent patients with eosinophilic esophagitis.		
Study identifier	R668-EE-1774 (Part B)	
Design	Randomized, double-blind, placebo-controlled, parallel-group design	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks N/A N/A
Hypothesis	Superiority	
Treatments groups	Dupilumab 300 mg QW	Dupilumab 300 mg QW for 24 weeks, N = 80
	Dupilumab 300 mg Q2W	Dupilumab 300 mg Q2W for 24 weeks, N = 81

Title: A Phase 3, randomized, 3-part study to investigate the efficacy and safety of dupilumab in adult and adolescent patients with eosinophilic esophagitis.				
Study identifier	R668-EE-1774 (Part B)			
	Matching placebo		Placebo QW or Q2W for 24 weeks, N =79	
Endpoints and definitions	Co-Primary endpoints	Peak eos count of ≤6 eos/hpf at week 24	Proportion of participants achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24	
		Change in DSQ score to week 24	Absolute change in DSQ total score from baseline to week 24	
	Key Secondary endpoints	Percent change in peak eos count (eos/hpf) to week 24	Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to week 24	
		Change in EoEHSS grade score to week 24	Absolute change in EoE Grade Score from the EoEHSS from baseline to week 24	
		Change in EoEHSS stage score to week 24	Absolute change in EoE Stage Score from the EoEHSS from baseline to week 24	
		Change in EoE-EREFS to week 24	Absolute change in EoE-EREFS total score from baseline to week 24	
	Other Secondary endpoints	Peak eos count of <15 eos/hpf at week 24	Proportion of participants achieving peak esophageal intraepithelial eosinophil count <15 eos/hpf at week 24	
		Percent change in DSQ score to week 24	Percent change in DSQ total score from baseline to week 24	
		NES change to wk 24 in EDP	NES for the relative change from baseline to week 24 in the EoE Diagnostic Panel transcriptome signature	
		NES change to wk 24 in T2 inflammation signature	NES for the relative change from baseline to week 24 in the type 2 inflammation transcriptome signature	
Database lock	30 Sept 2021			
Results and Analysis				
Analysis description	**Primary endpoint analysis**			
Analysis population and time point description	Full Analysis Set Week 24			
Descriptive statistics and estimate variability	**Treatment group**	**Dupilumab 300 mg QW**	**Dupilumab 300 mg Q2W**	**Placebo**
	Number of subjects	**80**	**81**	**79**
	Peak eos count of ≤6 eos/hpf at week 24 (n (%))	47 (58.8)	49 (60.5)	5 (6.3)
	95% CI (%)	(47.18, 69.65)	(49.01, 71.19)	(2.09, 14.16)
	Change in DSQ score to week 24 (LS mean change)	-23.78	-14.37	-13.86

Title: A Phase 3, randomized, 3-part study to investigate the efficacy and safety of dupilumab in adult and adolescent patients with eosinophilic esophagitis.				
Study identifier	R668-EE-1774 (Part B)			
	95% CI	(-27.427,-20.131)	(-18.018,-10.723)	(-17.605,-10.120)
Effect estimate per comparison	**Co-Primary endpoint:** Peak eos count of ≤6 eos/hpf at week 24	**Comparison groups**	**Dupilumab 300 mg QW vs. Placebo**	**Dupilumab 300 mg Q2W vs. Placebo**
		Difference vs Placebo LS Mean (95% CI)	53.5 (41.20, 65.79)	56.0 (43.44, 68.54)
		P-value	<0.0001	<0.0001
	Co-Primary endpoint: Change in DSQ score to week 24	Comparison groups	Dupilumab 300 mg QW vs. Placebo	Dupilumab 300 mg Q2W vs. Placebo
		Difference vs Placebo LS Mean (95% CI)	-9.92 (-14.811, -5.022)	-0.51 (-5.423, 4.406)
		P-value	<0.0001	0.8393*
Analysis description	**Secondary endpoint analysis**			
Analysis population and time point description	Full Analysis Set Week 24			
Descriptive statistics and estimate variability	**Treatment group**	**Dupilumab 300 mg QW**	**Dupilumab 300 mg Q2W**	**Placebo**
	Number of subjects	**80**	**81**	**79**
	Secondary Endpoint: Percent change in peak eos count (eos/hpf) to week 24 (LS mean % change)	-80.24	-70.84	8.38
	LS Mean % Change 95% CI	(-96.589, -63.895)	(-87.095,-54.585)	(-11.677, 28.433)
	Secondary Endpoint: Change in EoEHSS grade score to week 24 (LS mean change)	-0.830	-0.814	-0.148
	LS Mean % Change 95% CI	(-0.9136,-0.7463)	(-0.8958,-0.7317)	(-0.2379,-0.0584)
	Secondary Endpoint: Change in EoEHSS stage score to week 24 (LS mean change)	-0.804	-0.793	-0.132
	LS Mean Change 95% CI	(-0.8839, -0.7237)	(-0.8713,-0.7144)	(-0.2179 ,-0.0464)

Title: A Phase 3, randomized, 3-part study to investigate the efficacy and safety of dupilumab in adult and adolescent patients with eosinophilic esophagitis.				
Study identifier	R668-EE-1774 (Part B)			
	Secondary Endpoint: Change in EoE-EREFS to week 24 (LS mean change)	-4.5	-4.6	-0.6
	LS Mean Change 95% CI	(-5.17 , -3.77)	(-5.24 , -3.89)	(-1.37 ,0.12)
	Secondary Endpoint: Peak eos count of <15 eos/hpf at week 24 (n(%))	66 (82.5)	64 (79.0)	6 (7.6)
	95% CI	(72.38, 90.09)	(68.54, 87.27)	(2.84, 15.80)
	Secondary Endpoint: Percent change in DSQ score at week 24 (LS mean percent change)	-64.32	-45.78	-41.43
	LS Mean % Change 95% CI	(-74.267,-54.382)	(-55.658,-35.904)	(-51.749,-31.116)
	Secondary Endpoint: NES change to wk 24 in EDP (median change (n[1]))	-2.665 (40)	-2.675 (44)	-0.730 (41)
	Secondary Endpoint: NES change to wk 24 in T2 inflammation signature (median change (n[1]))	-1.930 (40)	-1.950 (44)	-0.640 (41)
Effect estimate per comparison	**Secondary Endpoint** Percent change in peak eos count (eos/hpf) to week 24	**Comparison groups**	**Dupilumab 300 mg QW vs. Placebo**	**Dupilumab 300 mg Q2W vs. Placebo**
		LS Mean Difference (95% CI)	-88.62 (-112.194,-65.046)	-79.22 (-103.098,-55.338)
		P-value	<0.0001*	<0.0001*
	Secondary Endpoint Change in EoEHSS grade score to week 24	**Comparison groups**	**Dupilumab 300 mg QW vs. Placebo**	**Dupilumab 300 mg Q2W vs. Placebo**
		Difference vs Placebo LS Mean (95% CI)	-0.682 (-0.7929,-0.5707)	-0.666 (-0.7773, -0.5538)
		P-Value	<0.0001*	<0.0001*
	Secondary Endpoint	**Comparison groups**	**Dupilumab 300 mg QW vs. Placebo**	**Dupilumab 300 mg Q2W vs. Placebo**

Title: A Phase 3, randomized, 3-part study to investigate the efficacy and safety of dupilumab in adult and adolescent patients with eosinophilic esophagitis.				
Study identifier	R668-EE-1774 (Part B)			
	Change in EoEHSS stage score to week 24	Difference vs Placebo LS Mean (95% CI)	-0.672 (-0.7778,-0.5655)	-0.661 (-0.7674, -0.5540)
		P-value	<0.0001*	<0.0001*
	Secondary Endpoint Change in EoE-EREFS to week 24	**Comparison groups**	**Dupilumab 300 mg QW vs. Placebo**	**Dupilumab 300 mg Q2W vs. Placebo**
		Difference vs Placebo LS Mean (95% CI)	-3.8 (-4.77,-2.93)	-3.9 (-4.86,-3.02)
		P-value	<0.0001*	<0.0001*
	Secondary Endpoint Eos count of <15 eos/hpf at week 24	**Comparison groups**	**Dupilumab 300 mg QW vs. Placebo**	**Dupilumab 300 mg Q2W vs. Placebo**
		Difference vs Placebo LS Mean (95% CI)	74.9 (64.25, 85.50)	72.4 (61.05, 83.70)
		P-value	<0.0001*	<0.0001*
	Secondary Endpoint Percent change in DSQ score at week 24	**Comparison groups**	**Dupilumab 300 mg QW vs. Placebo**	**Dupilumab 300 mg Q2W vs. Placebo**
		Difference vs Placebo LS Mean (95% CI)	-22.89 (-36.272, -9.513)	-4.35 (-17.734, 9.038)
		P-value	0.0008	0.5243*
	Secondary Endpoint NES change to wk 24 in EDP	**Comparison groups**	**Dupilumab 300 mg QW vs. Placebo**	**Dupilumab 300 mg Q2W vs. Placebo**
		Difference vs Placebo LS Mean (95% CI)	-1.850 (-2.4400,-1.1500)	-1.840 (-2.4200, -1.1100)
		P-value	<0.0001*	<0.0001*
	Secondary Endpoint NES change to wk 24 in T2 inflammation signature	**Comparison groups**	**Dupilumab 300 mg QW vs. Placebo**	**Dupilumab 300 mg Q2W vs. Placebo**
		Difference vs Placebo LS Mean (95% CI)	-1.275 (-1.8200,-1.0700)	-1.255 (-1.7300, -1.0500)
		P-value	<0.0001*	<0.0001*

*Nominal P-value

1. n= number of patients with NES score in Part B

Abbreviations: CI=confidence interval; DSQ= Dysphagia Symptom Questionnaire; EDP=EoE diagnostic panel; EoE-EREFS=Eosinophilic Esophagitis-Endoscopic Reference Score; eos/hpf=eosinophils/high-power field; EoEHSS=Eosinophilic Esophagitis Histology Scoring System;LS=least squares; NES=Normalized Enrichment Score; Q2W=every 2 weeks; QW=once weekly; T2=Type 2

Analysis performed across trials (pooled analyses and meta-analysis)

Pool 1

Pooling of data for Part A and Part B were performed to ensure an adequate sample size for subgroup analyses of efficacy for the co-primary efficacy endpoints (Pool 1). Pool 1 was used for analyses of the additional clinico-pathologic remission endpoint and for efficacy subgroup analyses of the histologic remission and clinical symptoms endpoints.

The clinico-pathological remission (defined as proportion of patients who achieved peak esophageal intraepithelial eos< 6 per hpf and ≥30% reduction (improvement) from baseline in DSQ total score at Week 24) evaluated treatment effects of dupilumab in improving both dysphagia symptom and esophageal histology concurrently. Responder analyses of the treatment effects on clinico-pathologic remission were performed on the FAS dataset of study R668-EE- 1774 for participants in Part A (dupilumab 300 mg QW vs. placebo), Part B (dupilumab 300 mg QW and 300 mg Q2W vs. placebo) and participants in Parts A and B pooled who received the proposed to-be-marketed dose of dupilumab 300 mg QW (referred to as Pool 1).

Table 32 Analysis of Proportion of Patients with Peak Esophageal Intraepithelial Eosinophil Count of ≤6 eos/hpf in All Three Regions and DSQ Improvement of ≥30% at Week 24 (Pool 1 - Full Analysis Set)

Study	Treatment	Peak Esophageal Intraepithelial Eosinophil Count of <=6 eos/hpf in All Three Regions and DSQ Improvement of >=30% at Week 24	95 % CI[1]	Difference(95% CI)[2]	P-value[3]
R668-EE-1774 Part A	Dupilumab 300 mg QW (N=42)	19 (45.2)	(29.85, 61.33)	42.3 (25.80, 58.72)	<0.0001
	Placebo (N=39)	2 (5.1)	(0.63, 17.32)		
R668-EE-1774 Part B	Dupilumab 300 mg QW (N=80)	31 (38.8)	(28.06, 50.30)	35.4 (23.68, 47.17)	<0.0001
	Dupilumab 300 mg Q2W (N=81)	25 (30.9)	(21.07, 42.11)	27.2 (16.32, 38.05)	<0.0001
	Placebo (N=79)	3 (3.8)	(0.79, 10.70)		
Pooled Analysis (Pool 1)	Dupilumab 300 mg QW (N=122)	50 (41.0)	(32.17, 50.25)	37.7 (28.13, 47.33)	<0.0001
	Placebo (N=118)	5 (4.2)	(1.39, 9.61)		

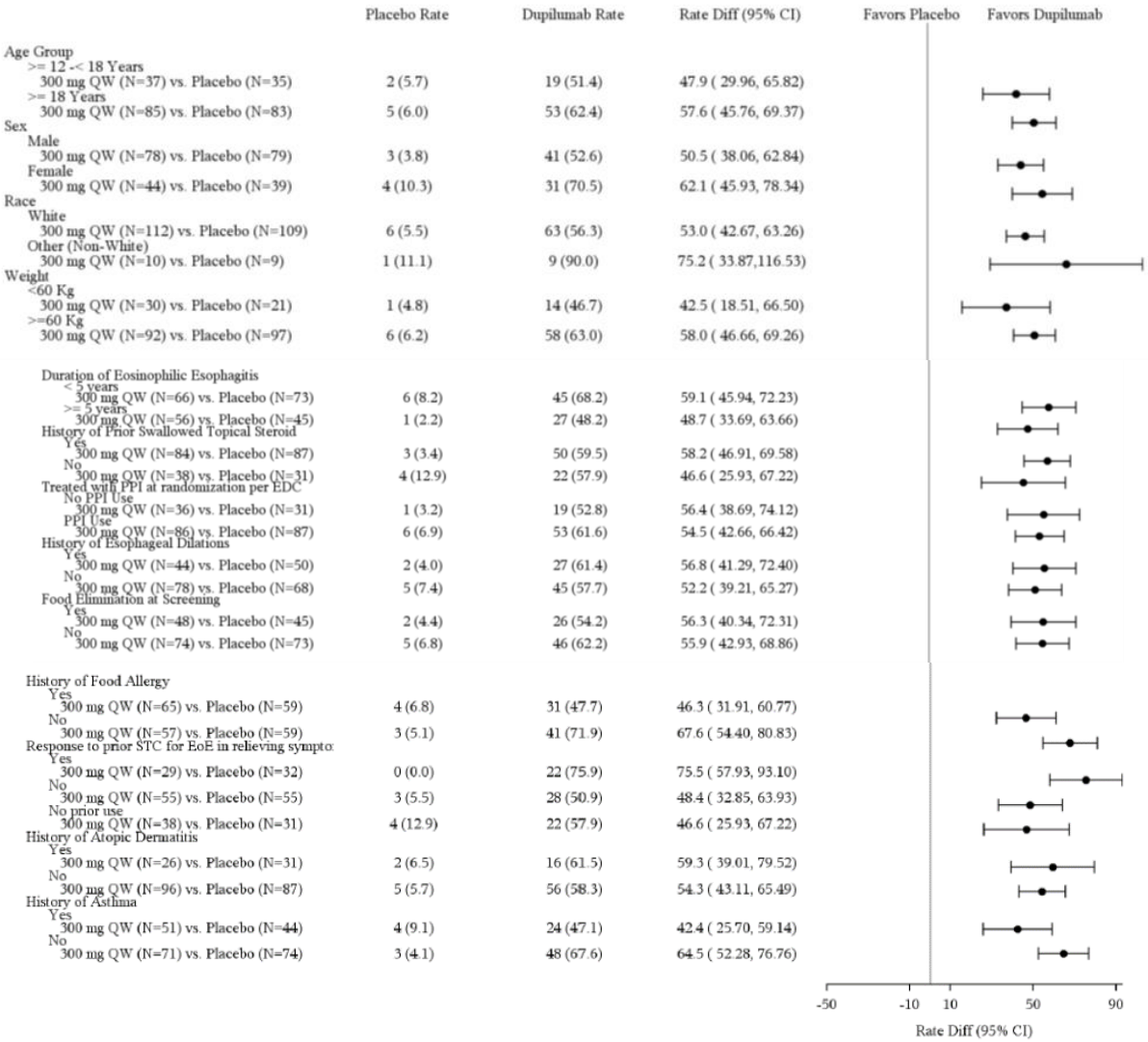
Pool 1 includes Part A and Part B of study EE-1774.
Values after first rescue treatment used were set to missing (censoring). Patients with missing peak esophageal intraepithelial eosinophil count at week 24 are considered as non-responders if missing is not due to COVID-19 and are imputed by MI if missing is due to COVID-19 (for Part A and Part B patients) or data were set to missing because of dosing interruption due to COVID-19 (for Part B patients). Patients with missing DSQ score at week 24 are considered as non-responders.
[1] CI is calculated using exact binomial distribution.
[2] Difference is Dupilumab minus Placebo. C.I. = Confidence interval stratified by age group (>=12 to <18 vs >=18) and use of PPI at randomization (Yes vs No). For pool 1 analysis, study identifier (Part A vs Part B) is included as an additional stratification factor.
[3] P-values are derived by Cochran-Mantel-Haenszel (CMH) test stratified by age group (>=12 to <18 vs >=18) and use of PPI at randomization (Yes vs No). For pool 1 analysis, study identifier (Part A vs Part B) is included as an additional stratification factor.

The results showed greater proportion of dupilumab-treated participants achieved clinico-pathologic remission compared to placebo-treated participants in Part A, Part B and the Pool 1 population. The results were consistent between Parts A and B and Pool 1, with a nominally significant difference observed (p<0.0001) compared to placebo.

Descriptive analyses were performed on the co-primary endpoints to summarize the treatment effects across 13 subgroups (e.g. Age (≥12 to < 18 years, ≥18 years), Sex (Male, Female), Race (White, Black or African American/Asian/Other/ Not Reported), Duration of EoE (<5 years, ≥5 years), Prior use

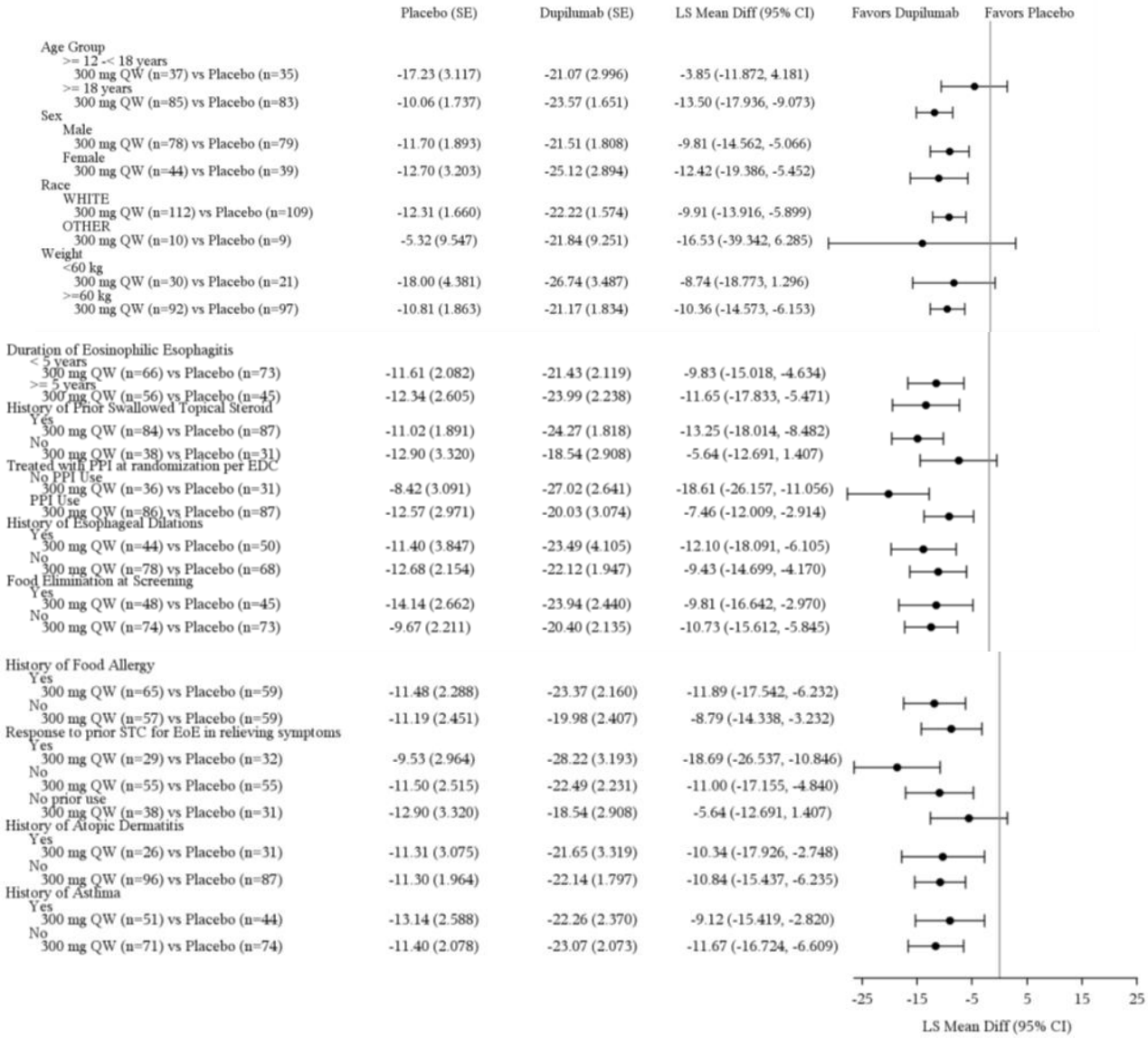
of swallowed topical steroids (STC) for the treatment of EoE (Yes, No)). Dupilumab 300 mg QW demonstrated a consistent effect on the proportion of participants in both Part A and Part B of R668-EE-1774 who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24 and absolute change in DSQ total score from baseline to week 24 compared to placebo across all subgroups assessed, including in particular age, gender, history of atopic dermatitis, history of asthma, history of food allergy, and previous use of STC for EoE.

Table 33 Forest Plot of Proportion of Participants with Peak Esophageal Intraepithelial Eosinophil Count of ≤6 eos/hpf in All Three Regions at Week 24 by Subgroup (Pool 1 FAS)



Pool 1 includes Part A and Part B of study EE-1774.
Values after first rescue treatment used were set to missing (censoring). Patients with missing peak esophageal intraepithelial eosinophil count at week 24 are considered as a non-responder if missing is not due to COVID-19 and are imputed by MI if missing is due to COVID-19 (for Part A and Part B patients) or data were set to missing because of dosing interruption due to COVID-19 (for Part B patients).
Difference is Dupilumab minus Placebo. C.I. = Confidence interval stratified by age group (>=12 to <18 vs >=18) (except for the subgroup analysis by age group) and use of PPI at randomization (Yes vs No) (except for the subgroup analysis by PPI use).For pool 1 analysis, study identifier (Part A vs Part B) is included as an additional stratification factor.

Table 34 Forest Plot of LS Mean Difference in Absolute Change From Baseline in DSQ Total Score at Week 24 by Subgroup (Pool 1 FAS)



Pool 1 includes Part A and Part B of study EE-1774.

Note: Values after first rescue treatment used were set to missing (censoring), then MI (multiple imputations) was used to impute missing values using seed: 6681774 with imputation size 50.

LS mean (SE) is based on ANCOVA with baseline measurement as covariate and the treatment, age group [>=12 to <18 vs >=18] (except for the subgroup analysis by age group) and PPI use at randomization (Yes vs. No) (except for the subgroup analysis by PPI use) strata as fixed factors. For pool 1 analysis, study part (Part A vs Part B) is included as an additional fixed factor.

Previous use of Swallowed Topical Steroids (STC) for EoE

In the Pool 1, when the co-primary endpoint was analysed by previous use of STC for EoE (yes or no), the results were consistent between those participants with or without prior STC use.

In the group with a prior history of STC use for EoE, the proportion of participants who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24 was 50/84 (59.5%) in the dupilumab 300 mg QW group versus 3/87 (3.4%) in the placebo group (difference 95% CI: 58.2 [46.91, 69.58]).

In the group without a prior history of STC use for EoE, the proportion of participants who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24 was 22/38 [57.9%] in the dupilumab 300 mg QW group versus 4/31 [12.9%] in the placebo group (difference 95% CI: 46.6 [25.93, 67.22])

In the Pool 1, the magnitude of response in the Absolute Change in DSQ Total Score From Baseline to Week 24 in the dupilumab 300 mg QW was numerically higher in the subgroup who had a prior history of STC use for EoE compared to the one without prior STC use. In the group with a prior history of STC use for EoE, the LS mean absolute change in DSQ total score from baseline to week 24 was -24.27 points in the dupilumab 300 mg QW group (n=84) and -11.02 points in the placebo group (n=87) (LS mean difference [95% CI]: -13.25 [-18.014, -8.482]). In the group without a prior history of STC use for EoE, the LS mean absolute change in DSQ total score from baseline to week 24 was −18.54 points in the dupilumab 300 mg QW group (n=38) and -12.90 points in the placebo group (n=31) (LS mean difference [95% CI]: -5.64 [-12.691, 1.407]).

Clinical studies in special populations

Adolescent participants see above.

Supportive study (R668-EE-1324)

Methods

Study design

Study R668-EE-1324 was a phase 2, multicenter, double-blind, randomized, placebo-controlled study investigating the efficacy, safety, tolerability, PK, and immunogenicity of dupilumab in adult patients with EoE.

After providing informed consent, patients were assessed at the screening visit (to occur between day -35 and day -1) for eligibility to participate in the study. Patients who met the eligibility criteria underwent day 1 baseline assessments and were randomized in a 1:1 ratio to receive dupilumab 300 mg QW or placebo during the 12-week double-blind treatment phase. The end of treatment period visit occurred at week 12, 1 week after the last dose of study drug. Patients were followed off-study drug for an additional 16 weeks. The end of study visit occurred at week 28.

Patients could receive concomitant medications (except for prohibited medications) as needed, at the discretion of the investigator, while continuing study treatment. Frequency of use and type of product were documented. If medically necessary, rescue medications (e.g., systemic and swallowed topical corticosteroids) or emergency esophageal dilation could be provided to study patients. Patients receiving rescue therapy were to be discontinued from study treatment. These patients were to remain blinded and to be asked to return to the clinic for all remaining study treatment visits and participate in all follow-up assessments according to the visit schedule.

- **Study participants**

Approximately 44 patients were planned to be enrolled at up to 20 study sites in the US.

Eligible for inclusion in the study were male or female patients from 18 to 65 years of age with a documented diagnosis of EoE by endoscopy prior to or at screening and history of on average at least 2 episodes of dysphagia (with intake of solids off anti-inflammatory therapy) per week in the 4 weeks prior to screening and on average at least 2 episodes of documented dysphagia per week in the weeks between screening and baseline. Furthermore a SDI PRO score ≥5 at screening and baseline documented history of or presence of allergic disease (e.g., allergic asthma, allergic rhinitis, AD, or food allergies), peripheral eosinophil counts ≥0.25 GI/L, or serum total IgE ≥100 kU/L were required. Excluded were patients with hypereosinophilic syndromes, Churg-Strauss vasculitis, eosinophilic

gastroenteritis, a history of achalasia, active Helicobacter pylori infection, Crohn's disease, ulcerative colitis, celiac disease, prior esophageal surgery prior to screening, any esophageal stricture unable to be passed with a standard upper endoscope or any critical esophageal stricture that requires dilation at screening, history of bleeding disorders or esophageal varices.

- **Treatments**

Patients were to receive **SC dupilumab 300 mg or matching placebo** during the 12-week double-blind treatment phase. Patients were to receive 2 injections (300-mg initial dose, followed by a 300-mg loading dose) on day 1, followed by **weekly** injections.

Dupilumab was provided in 5 mL vials. Each vial contained 2.5 mL (150 mg/mL) with a withdrawable volume of 2.0 mL or 300 mg of study drug.

Placebo matching dupilumab was prepared in the same formulation as dupilumab without the addition of protein (i.e., active substance, anti-IL-4R monoclonal antibody).

If medically necessary (e.g., for treatment of intolerable EoE symptoms) patients could be rescued with a prohibited medication or procedure including swallowed topical corticosteroids, systemic corticosteroids, start or dose change of systemic leukotriene inhibitors, topical, nasal, and/or inhaled corticosteroids, systemic treatment for EoE with an immunosuppressive substance (e.g. omalizumab, cyclosporine, mycophenolate-mofetil, azathioprine, methotrexate) and esophageal dilation.

- **Objectives**

The **primary objective** of the study was to assess the clinical efficacy of repeat SC doses of dupilumab, compared with placebo, to relieve symptoms in adult patients with active, moderate-to-severe EoE.

The **secondary objectives** of the study were:

- To assess the safety, tolerability, and immunogenicity of SC doses of dupilumab in adult patients with active, moderate-to-severe EoE
- To assess the effect of dupilumab on esophageal eosinophilic infiltration
- To evaluate the pharmacokinetics (PK) of dupilumab in adult patients with EoE

- **Outcomes/endpoints**

The **primary endpoint** in the study was the change in the SDI PRO score from baseline to week 10.

The **secondary endpoints** were:

- Percent change in weekly EEsAI PRO score from baseline to week 10
- Change in weekly EEsAI PRO score from baseline to week 10
- Percent change in weekly EEsAI PRO score from baseline to week 12
- Change in weekly EEsAI PRO score from baseline to week 12
- Percent change in the SDI PRO score from baseline to week 10
- Percent change in the SDI PRO score from baseline to week 12
- Change in the SDI PRO score from baseline to week 12
- Change in EoE-QOL-A PRO score from baseline to week 12
- Percentage of patients with SDI PRO response at week 10; where response was defined as a decrease of at least 3 points on the SDI compared to baseline
- Incidence of treatment-emergent AEs

- **Sample size**

A sample size of 18 patients per treatment arm was planned in order to provide 94% power to detect a treatment effect, with an expected mean difference of 3 points in change from baseline to week 12 in SDI score between dupilumab and placebo at a 2-sided t-test with 5% significance level and an assumed SD of 2.46. Considering the assumed 15% dropouts, 22 patients per treatment arm were planned to be enrolled.

- **Randomisation**

1:1 allocation to receive either dupilumab every week (loading dose 600mg, followed by 300 mg doses; N=23) or placebo (N=24), stratified by baseline SDI PRO score (≥5 and ≤7 versus >7; total possible score ranges from 0 to 9) that reflects EoE severity and frequency.

- **Blinding (masking)**

Double-blind study until week 12.

- **Statistical methods**

The full analysis set (FAS) included all randomized patients. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). This was the primary analysis population for efficacy analyses.

The primary efficacy endpoint, change in SDI score at week 10 from baseline, was analyzed in the FAS using multiple imputation (MI), with an analysis of covariance (ANCOVA) model with treatment group as fixed effect, and the baseline SDI value as continuous covariate (time point for the primary endpoint was changed from week 12 to week 10 in protocol amendment 4). Due to the substantial imbalance at baseline in the number of patients in the 2 randomization strata (only 12.8% patients in the strata of baseline SDI >7), the randomization strata was not used as a factor in the multiple imputation and ANCOVA model. Instead, as specified in the SAP, the baseline SDI was included as a continuous covariate in the MI and ANCOVA model.

Missing values, sensitivity analyses:

If a patient used rescue treatment during the 12-week treatment period, patients' efficacy data after rescue treatment were to be set to missing first, and then imputed by the MI method. No patients used a rescue medication or procedure during the study. Missing data from the FAS were imputed 50 times to generate 50 complete data sets.

In addition to the MI method described above, sensitivity analyses for the primary efficacy endpoint were conducted as described below:

1. All observed data with MI for imputing missing values: ANCOVA analysis based on all observed data no matter whether rescue medication was used. MI method was used to impute missing values. Because no patients used rescue treatment, this analysis was the same as the primary analysis.

2. Last-observation-carried-forward (LOCF) method: ANCOVA model with efficacy data set to missing after rescue medication was used. The post-baseline LOCF method was used to impute missing values.

3. Worst observation carried forward (WOCF) method: ANCOVA model with efficacy data set to missing after rescue medication was used. The post-baseline WOCF method was then be used to impute missing values.

4. All observed data without data imputation: ANCOVA model including all observed data no matter if rescue medication was used, without imputation for missing data.

No interim analysis was planned according to the protocol and no interim analysis was performed accordingly.

Results

- **Participant flow**

80 patients were screened, of whom 47 (58.7%) were enrolled at 14 sites. Thirty-three (41.3%) patients were considered screen failures as they did not meet all inclusion criteria or met one or more exclusion criterion (32 patients), or withdrew consent (1 patient). Of the 47 enrolled patients, 23 patients were randomized to receive dupilumab 300 mg QW and 24 patients were randomized to receive placebo.

Table 35 Summary of Patients Disposition (SAF)

	Placebo (N=24)	Dupilumab 300 mg QW (N=23)	Total (N=47)
Patients in Safety Analysis Set (SAF)	24 (100%)	23 (100%)	47 (100%)
Patients who completed treatment	20 (83.3%)	22 (95.7%)	42 (89.4%)
Patients withdrawn from treatment	4 (16.7%)	1 (4.3%)	5 (10.6%)
Adverse Event	0	1 (4.3%)	1 (2.1%)
Lack of Efficacy	0	0	0
Protocol Deviation	1 (4.2%)	0	1 (2.1%)
Other	3 (12.5%)	0	3 (6.4%)
OTHER REASON (SPECIFY):PREGNANCY	1 (4.2%)	0	1 (2.1%)
OTHER REASON (SPECIFY): SUBJECT WAS NOT ELIGIBLE FOR THE STUDY.	1 (4.2%)	0	1 (2.1%)
OTHER REASON (SPECIFY):SUBJECT WAS WITHDRAWN PER SPONSOR[1]	1 (4.2%)	0	1 (2.1%)
Patients who completed study	18 (75.0%)	18 (78.3%)	36 (76.6%)
Patients did not complete study	6 (25.0%)	5 (21.7%)	11 (23.4%)
Protocol Deviation	0	1 (4.3%)	1 (2.1%)
Adverse Event	0	1 (4.3%)	1 (2.1%)
Physician Decision	1 (4.2%)	1 (4.3%)	2 (4.3%)
Withdrawal by Subject	2 (8.3%)	0	2 (4.3%)
Lack of Efficacy	0	0	0
Lost to Follow-up	2 (8.3%)	1 (4.3%)	3 (6.4%)
Death	0	0	0
Other	1 (4.2%)	1 (4.3%)	2 (4.3%)
OTHER, SPECIFY: SUBJECT DID NOT MEET INCLUSION/ EXCLUSION CRITERIA	1 (4.2%)	0	1 (2.1%)
OTHER, SPECIFY: SUBJECT WAS INCARCERATED	0	1 (4.3%)	1 (2.1%)

[1] Patient 840011001 used inhaled steroids within 3 months of screening visit, which was an exclusion criterion, therefore, was withdrawn from the study due to this protocol violation (information from email communication among the sponsor, CRO, and study site).

The majority of the randomized patients completed the study treatment, with the percentage of patients in the dupilumab group (95.7% of patients) slightly higher than in the placebo group (83.3% of patients).

One patient in the dupilumab group discontinued study treatment due to an AE (Nail Disorder).

- **Recruitment**

  Start of the study: 12 May 2015

  End of the study: 10 July 2017

- **Conduct of the study**

Amendments

The purposes of **Amendment 1** (dated 15 Jan 2015) were to:

- Revise inclusion criterion #2 concerning past diagnosis of EoE by endoscopy

- Add SDI and EEsAI at telephone visits, and add a note to indicate that SDI and EEsAI should be performed by the patient electronically
- Add electronic patient diary in the list of electronic systems used in this study

The primary purpose of **Amendment 2** (dated 08 May 2015) was to update the number of study sites and the enrolment criteria based on the principal investigators' feedback.

The primary purposes of **Amendment 3** (dated 04 May 2016) were to modify inclusion criterion #2 and clarify inclusion criteria #6 and #10 and exclusion criteria #9 and #16.

The purposes of **Amendment 4** (dated 16 Oct 2016) were to modify the primary endpoint to have change from baseline to week 10 instead of to week 12 to ensure an adequate amount of data for analysis, due to failure with electronic diaries. The list of secondary endpoints was modified as a result of changing the primary endpoint to week 10. The statistical plan was updated accordingly to previous changes.

Protocol deviations

Overall, 3 patients in each treatment group had a major protocol deviation. The types of major protocol deviations were unlikely to impact the results of the study. Nonetheless, the primary efficacy endpoint was evaluated in the PPS as a supportive analysis, which excluded patients with major protocol violations.

Note: the missing patient-reported data due to failure of the eDiary were not defined as protocol deviations.

- **Baseline data**

Demographic characteristics were balanced between the dupilumab group and the placebo group except for the sex composition and body weight categories. There were more male patients (56.5%) in the dupilumab group while there were more female patients (58.3%) in the placebo group. In the dupilumab group there were a higher percentage of patients with body weight <70 kg (30.4% patients) or ≥100 kg (30.4% patients) than in placebo group (20.8% and 16.7%, respectively).

The baseline disease characteristics were balanced between the 2 treatment groups for most of the parameters, except mean/median serum total IgE, composition of patients with IgE <100 IU/mL or IgE ≥100 IU/mL. All patients had a baseline SDI PRO score ≥5, reflecting all patients met the inclusion criterion of SDI PRO score ≥5 at screening and baseline.

- **Numbers analysed**

Table 36 Study Analysis Sets by Treatment Group (All Enrolled Patients)

	Placebo (N=24)	Dupilumab 300 mg QW (N=23)	Total (N=47)
Patients enrolled	24 (100%)	23 (100%)	47 (100%)
Randomized, n (%)	24/24 (100%)	23/23 (100%)	47/47 (100%)
Patients included in the Full Analysis Set (FAS), n (%)	24/24 (100%)	23/23 (100%)	47/47 (100%)
Patients included in the Per Protocol Analysis Set (PPS)[1], n (%)	21/24 (87.5%)	20/23 (87.0%)	41/47 (87.2%)
Patients Included in the Safety Analysis Set (SAF), n (%)	24/24 (100%)	23/23 (100%)	47/47 (100%)
Patients included in the PK Analysis Set (PKAS), n (%)	24/24 (100%)	23/23 (100%)	47/47 (100%)
Patients included in the ADA Analysis Set (AAS), n (%)	23/24 (95.8%)	23/23 (100%)	46/47 (97.9%)

[1] All patients with any major protocol deviations were excluded from the per protocol analysis set.

- **Outcomes and estimation**

Table 37 Overview of Primary and Secondary Efficacy Results – FAS

Endpoints[1]	Placebo (N=24)	Dupilumab 300 mg QW (N=23)	Difference (95% CI)	P-value[2]
	n = # of observed patients[3]/ # of imputed patients	n = # of observed patients[3]/ # of imputed patients		
Primary Efficacy Endpoint				
LS mean (SE) change of SDI PRO total score from baseline to week 10 (score range 0 to 9)	n =14/10	n=17/6		
	-1.3 (0.6)	-3.0 (0.5)	-1.7 (-3.22, -0.16)	0.0304
Secondary Efficacy Endpoints				
LS mean (SE) % change of SDI PRO total score from baseline to week 10 (score range 0 to 9)	n=14/10	n=17/6		
	-18.6 (9.0)	-45.0 (8.4)	-26.5 (-50.52, -2.39)	0.0312
LS mean (SE) change of SDI PRO total score from baseline to week 12 (score range 0 to 9)	n=9/15	n=16/7		
	-2.2 (0.7)	-2.9 (0.6)	-0.8 (-2.48, 0.96)	0.3830
LS mean (SE) % change of SDI PRO total score from baseline to week 12 (score range 0 to 9)	n=9/15	n=16/7		
	-31.8 (10.7)	-42.8 (8.6)	-11.0 (-37.46, 15.47)	0.4147
Number (%) of patients with decrease of ≥3 points in SDI PRO total score from baseline to week 10	3 (12.5%)	9 (39.1%)	26.6 (-3.04, 51.05)	0.049
LS mean (SE) % change of weekly reported EEsAI PRO score from baseline to week 10 (score range 0 to 100)	n=13/11	n=17/6		
	-11.3 (9.9)	-34.6 (9.1)	-23.2 (-49.68, 3.21)	0.0850
LS mean (SE) change of weekly reported EEsAI PRO score from baseline to week 10 (score range 0 to100)	n=13/11	n=17/6		
	-9.0 (5.6)	-22.9 (5.0)	-13.9 (-28.54, 0.78)	0.0635
LS mean (SE) % change of weekly reported EEsAI PRO score from baseline to week 12 (score range 0 to 100)	n=8/16	n=15/8		
	-3.3 (12.7)	-37.0 (11.2)	-33.6 (-68.83, 1.54)	0.0608
LS mean (SE) change of weekly reported EEsAI PRO score from baseline to week 12 (score range 0 to 100)	n=8/16	n=15/8		
	-5.0 (7.1)	-26.1 (5.9)	-21.1 (-40.42, -1.86)	0.0318
Number (%) of patients achieving ≥40% improvement in weekly reported EEsAI score from baseline to week 10	2 (8.3)	6 (26.1)	17.8 (-11.54, 43.55)	0.1365
Number (%) of patients achieving ≥40% improvement in weekly reported EEsAI PRO score from baseline to week 12	1 (4.2)	9 (39.1)	35.0 (5.69, 58.34)	0.0044
LS mean (SE) change of EoE-QOL-A PRO total score from baseline to week 12 (score range 1 to 5)	n=21/3	n=23/0		
	0.47 (0.14)	0.80 (0.14)	0.33 (-0.05, 0.72)	0.0910
LS mean (SE) % change of overall peak esophageal intraepithelial eosinophils/high power field (eos/hpf) (400×) from baseline to week 12	n=22/2	n=23/0		
	14.2 (12.5)	-92.9 (12.1)	-107.1 (-141.22,-73.05)	<0.0001
LS mean (SE) change of EoE-EREFS total score including stricture (endoscopy visual anatomical score) from baseline to week 12 (score range 0 to 8)	n=22/2	n=23/0		
	-0.3 (0.3)	-1.9 (0.3)	-1.6 (-2.50, -0.68)	0.0006

[1] For continuous variables, multiple imputation (MI)/ANCOVA was used and LS mean (SE) were presented; for binary variables, patients with missing data were treated as non-responders and Fisher exact test was used for comparison; number and % of responders were presented.
[2] For the secondary endpoints, all p-values were nominal
[3] n represents # of patients with both baseline and post-baseline observed values.

- **Primary Efficacy Endpoint: Change in Patient-Reported Outcome of Straumann Dysphagia Instrument Score from Baseline to Week 10**

The absolute change in SDI total score from baseline to week 10 was significantly greater in the dupilumab group than in the placebo group. The LS mean change of -3.0 points in the dupilumab group indicates a clinically meaningful improvement. A reduction from baseline in SDI total score of ≥3 points is considered a clinical response, compared to a LS mean change of -1.3 points in the placebo

group. The difference in LS mean of absolute change from baseline between the 2 treatment groups was statistically significant (p-value = 0.0304).

Table 38 Primary Analysis of Absolute Change from Baseline in SDI Total Score at Week 10, MI Method with Data Set to Missing after Rescue Treatment Use - FAS

Treatment	LS Mean Change (SE)	Mean Change (SD)	Baseline Mean (SD)	Num. of Observed Patients/ Imputed Patients	Contrast	P-value [1]	LS Mean Difference (95% CI)
Dupilumab 300 mg QW (N=23)	-3.0 (0.53)	-3.0 (3.04)	6.4 (1.04)	17/6	Dupilumab 300 mg QW vs Placebo	0.0304	-1.7 (-3.22, -0.16)
Placebo (N=24)	-1.3 (0.57)	-1.3 (2.06)	6.4 (1.01)	14/10			

[1] The confidence interval (CI) with p-value is based on treatment difference (dupilumab vs. placebo) of the LS mean using ANCOVA model with baseline measurement as covariate and the treatment as fixed factor.

The results of all sensitivity analyses were consistent with the primary analysis.

A trend of dupilumab treatment benefit versus placebo was observed in majority of the subgroups. It is noted that for the female subgroup, the LS mean difference between dupilumab and placebo in change of SDI score from baseline at week 10 was close to zero (-0.1) and the associated 95% CI (-2.15, 2.01) included 0, while for the male subgroup the LS mean difference (95% CI) were -3.1 (-5.31, -0.95).

- **Secondary Efficacy Endpoints (selected)**

Percent Change in SDI PRO Total Score from Baseline to Week 10

The results of percent change in SDI total score from baseline to week 10 were similar to that of absolute change (decrease) in SDI total score from baseline to week 10. A greater percent change (decrease) from baseline to week 10 was observed in the dupilumab group (-45.05%) than in the placebo group (-18.59%).

Sensitivity analyses, using different imputation methods (LOCF, WOCF, and all observed data without data imputation) supported the same conclusions as those generated from the primary analysis.

Change in SDI Total Score from Baseline to Week 12

The results of absolute change in SDI total score from baseline at week 12 were similar to that at week 10. However, the numbers of patients with an observed value at week 12 were small, resulting in a wider 95% CI that contained 0 for the LS mean difference between the placebo and dupilumab groups.

Sensitivity analyses, using different imputation methods (LOCF, WOCF, and observed data without data imputation), showed results similar to those generated from the primary analysis.

Percent Change in SDI Total Score from Baseline to Week 12

The results of percent change in SDI total score from baseline at week 12 were similar to that of absolute change in SDI total score from baseline at week 12.

Sensitivity analyses supported the analyses.

Proportion of Patients Achieving a Reduction of ≥3 Points in SDI Total Score from Baseline at Week 10

During the study treatment period up to week 12, an upward trend in percentage of patients achieving a ≥3-point reduction in SDI total score was observed in the dupilumab group compared to the placebo

group. At week 10, 39.1% of patients in the dupilumab group achieved this responder status compared to 12.5 % in the placebo group.

Proportion of Patients Achieving a Reduction of ≥3 Points in SDI Total Score from Baseline at Week 12

The results in percentage of patients achieving a reduction of ≥3 points in SDI total score at week 12 were similar to that at week 10. At week 12, 34.8% of patients in the dupilumab group achieved this responder status compared to 4.2% in the placebo group.

Percent Change in Weekly Reported EEsAI from Baseline to Week 10

During the study treatment period up to week 12, a downward trend in LS mean percent change from baseline in weekly reported EEsAI was observed in the dupilumab group compared to the placebo group. At week 10, the LS mean (SE) percent change from baseline was -34.56% (9.076%) for the dupilumab group compared to -11.33% (9.915%) for the placebo group.

Change in Weekly Reported EEsAI from Baseline to Week 12

A downward trend in LS mean absolute change from baseline in weekly reported EEsAI was observed in the dupilumab group compared to the placebo group. At week 12, the LS mean (SE) absolute change from baseline was -26.1 (5.87) for the dupilumab group compared to -5.0 (7.06) for the placebo group.

Proportion of Patients Achieving ≥40% Improvement in Weekly Reported EEsAI from Baseline at Week 10

At week 10, 26.1% of patients in the dupilumab group achieved this responder status compared to 8.3% for the placebo group.

Proportion of Patients Achieving ≥40% Improvement in Weekly Reported EEsAI Score from Baseline at Week 12

The results in percentage of ≥40% EEsAI improvement responders at week 12 were similar to that at week 10, however, the difference between the dupilumab group and placebo group was greater. At week 12, 39.1% of patients in the dupilumab group achieved this responder status compared to 4.2% in the placebo group.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study R668-EE-1774 was a randomized, double-blind, multi-centre, pivotal phase 3 study to evaluate the efficacy of dupilumab treatment compared with placebo in adult and adolescent patients with EoE. This study consisted of 3 parts. Part A and Part B consisted of a 24-week double-blind treatment period each, Part C of a 28-week extended active treatment period. A 12-week post treatment follow-up period followed at the end of Part C or at the end of Parts A or B for participants who did not enter Part C.

Part A and Part B were carried out as 2 separate sequential independent parts and participants could only be enrolled in either Part A or Part B. Part A evaluated efficacy and safety of dupilumab 300 mg QW versus placebo. Part B evaluated efficacy and safety of dupilumab 300 mg QW and 300 mg Q2W versus placebo. Participants were stratified by age (≥18 years versus ≥12 to <18 years of age) and

use of PPI at randomization. The choice of placebo as a control was appropriate for the objective of this study as it provided the most robust assessment of the efficacy and safety of dupilumab.

Part C of Study R668-EE-1774 extended the treatment period for an additional 28 weeks. All participants who entered Part C from Part A were administered dupilumab 300 mg SC QW for 28 weeks during Part C. Participants who received dupilumab during Part B received the same dupilumab dose regimen in Part C (300 mg QW or Q2W) and participants who received placebo were re-randomized in a 1:1 ratio to receive dupilumab 300 mg QW or dupilumab 300 mg Q2W in Part C. The design for the extension period (Part C) allowed characterization of the efficacy and safety profile over a longer period. Rescue treatment with systemic and swallowed topical corticosteroids or emergency esophageal dilation was allowed.

The key eligibility criteria of study R668-EE-1774 Part A and Part B were similar. The study population consisted of adult males and females ≥18 years of age and adolescent males and females ≥12 to <18 years of age at the time of study entry with documented diagnosis of EoE by endoscopic biopsy that was not responsive to at least 8 weeks of treatment with high-dose PPI. All participants were required to have an endoscopy with biopsies at the baseline visit, which demonstrated ≥15 intraepithelial eos/hpf in at least 2 of 3 esophageal regions (proximal, mid, and distal).

A total of 81 participants met the eligibility criteria in **Part A** and were randomized in a 1:1 ratio with 39 participants in the placebo group and 42 participants in the dupilumab 300 mg QW group.
The majority of participants were male (60.5%) and most participants were white (96.3%). The mean age of participants was 31.5 years with 24.7% of participants ≥12 to <18 years of age, 43.2% of participants ≥18 to <40 years of age and 32.1% of participants ≥40 to <65 years. Baseline disease characteristics were generally balanced between the 2 treatment groups and indicated a highly symptomatic population, with most participants having previously used swallowed topical corticosteroids for the treatment of EoE (74.1%) and almost half of participants having prior esophageal dilations (43.2%). The mean peak eosinophil count of 3 esophageal regions (proximal, mid, and distal) at baseline was 89.3 eos/hpf. The mean DSQ score at baseline was 33.6, indicating multiple days of dysphagia every 2 weeks (14 days).
A total of 20 participants were adolescents (≥12 to <18 years of age). 11 adolescents were randomized to the dupilumab 300 mg QW and 9 to the placebo group. The mean age of the adolescent subgroup was 14.9 years. The majority were male (80.0%) and most participants were white (90.0%). The mean weight and BMI of adolescent participants was 58.9 kg and 20.8 kg/m2, respectively with 35.0% ≥60 kg. Baseline disease characteristics were generally balanced between the 2 treatment groups. The majority had previously used STCs for EoE (85.0%) and 10.0% had prior esophageal dilations with a mean of 2.5 previous dilations.
Overall, the demographic and baseline characteristics were comparable across treatment groups in Part A. All randomized participants received at least 1 dose of study drug in Part A and 96.3% completed Part A study drug. Three participants (3.7%) discontinued study drug during Part A.

In **Part B**, 240 participants were randomized in a 1:1:1 ratio to 1 of the 3 treatment groups: 80 participants in the dupilumab 300 mg QW group, 81 participants in the dupilumab 300 mg Q2W group and 79 participants in the placebo group.
The majority of participants were male (63.8%) and most participants were White (90.4%). The mean age of participants was 28.1 years with 32.9% of participants ≥12 to <18 years of age, 46.3% of participants ≥18 to <40 years of age, and 20.0% of participants ≥40 to <65 years. Two participants (0.8%) were ≥65 years of age. The mean weight of participants was 76.2 kg with 77.1% of participants ≥60 kg. 35.4% of participants had prior esophageal dilations and 72.5% of participants were receiving PPIs at the time of randomization. Most participants (73.2%) used prior swallowed

topical corticosteroids. Treatment with STCs was deemed not effective in 43.1%, with 59.8% reporting recurrence of EoE symptoms within 3 months. At baseline, participants had a mean esophageal peak eosinophil counts of 87.1 eos/hpf and elevated mean scores for the DSQ of 36.7 points.
A total of 79 (32.9%) participants were adolescents (≥12 to <18 years of age). 26 adolescents were enrolled in the dupilumab 300 mg QW group, 27 in the dupilumab 300 mg Q2W group and 26 in the placebo group. The majority of adolescent participants were male (72.2%) and most were white (81.0%). The mean age of adolescent participants was 15.0 years. The mean weight of adolescent participants was 64.3 kg with 53.2% ≥60 kg. The majority had previously used STCs for the treatment of EoE (72.2%) and 6.3% had prior esophageal dilations with a mean of 2.8 previous dilations. Only 25.3% reported STCs as being effective for EoE. About half of adolescent participants (51.9%) had a history of an inadequate response, intolerance, and /or contraindication to prior STCs.
Overall, the demographic and baseline characteristics were comparable across treatment groups in Part B and consistent with the Part A study population and published literature for an EoE population with a significant disease burden. Twelve participants (5 placebo, 5 dupilumab 300 mg QW, and 2 dupilumab 300 mg Q2W) discontinued the study through week 24 and another participant in the dupilumab 300 mg QW group discontinued from the study after completing week 24 but discontinued during the Part B follow-up period.

A total of 77 participants from Part A entered **Part C (Part A/C)**, 40 from the dupilumab 300 mg QW group and 37 from the placebo group. All participants received dupilumab 300 mg QW for 28 weeks during Part C. At the start of Part C, demographic characteristics for participants from Part A were consistent with that for participants from the Part A FAS. The majority of participants were male (61.0%) and most participants were white (96.1%). The mean age of participants at study entry was 31.8 years with 24.1% of participants ≥12 to <18 years of age, 41.6% of participants ≥18 to <40 years of age, and 33.8% of participants ≥40 to <65 years of age. The mean peak esophageal intraepithelial eosinophil count at baseline of Part C was 66.7 eos/hpf in the placebo/dupilumab 300 mg QW group and 12.3 eos/hpf in the dupilumab 300 mg QW/dupilumab 300 mg QW group. At the start of Part C, the mean DSQ total score was 24.7 in the placebo/dupilumab 300 mg QW group and 10.4 in the dupilumab 300 mg QW/dupilumab 300 mg QW group.

Of the 240 participants from Part B, 227 entered **Part C (Part B/C)**. Participants, who received placebo during the double-blind treatment period of Part B were re-randomized in a 1:1 ratio to dupilumab 300 mg QW or dupilumab 300 mg Q2W. All other Part B participants remained on the same dupilumab dose regimen upon entering Part C. Of the 227 participants, 111 participants received dupilumab 300 mg QW in Part C (37 received placebo and 74 received dupilumab 300 mg QW in Part B) and 116 participants received dupilumab 300 mg Q2W in Part C (37 received placebo and 79 received dupilumab 300 mg Q2W in Part B). Of the 79 adolescent participants enrolled in Part B, 75 adolescents entered Part C (26/27 from the dupilumab 300 mg Q2W group, 24/26 from the dupilumab 300 mg QW group and 25/26 from the Part B placebo group).

Study R668-EE-1774 was conducted during the COVID-19 pandemic. Several changes were implemented via amendment to protect patient safety and data integrity by allowing for certain study procedures to occur at delayed time points and/or outside of the clinic environment. The protocol amendments are considered adequate due to the restrictions during the pandemic and not to have affected the efficacy results.
A high number of protocol deviations have also been reported for all parts of the study with the most frequently reported important protocol deviation in the category of procedure not performed. The most frequently reported procedure not performed was DSQ e-diary not completed by participants >6 times in a 14-day period. Considering the high percentage of this protocol deviation observed during the study, this was further evaluated by the MAH to determine whether there would be any impact on the

DSQ primary endpoint. Sensitivity analyses were performed using different DSQ scoring algorithms to assess the robustness of the primary analysis. Results of these sensitivity analyses were consistent with the primary analysis. In conclusion, the CHMP agreed with the MAH that the deviations did not have an impact on study objectives, nor efficacy results or interpretation of study results.

No subjects weighting less than 40kg were included in study R668-EE-1774, therefore from an efficacy perspective, the evidence base for inclusion of patients weighting less than 40kg in the initially proposed indication was considered very limited. The MAH revised the indication during the procedure to exclude patients weighting less than 40kg to adequately reflect the studied population. In addition, the MAH updated section 4.2 to mention that Dupilumab has not been studied in patients weighting less than 40kg as requested by CHMP.
The co-primary endpoint in Part A and B were Proportion of Participants Achieving Peak Esophageal Intraepithelial Eosinophil Count ≤6 eos/hpf at week 24 and Absolute Change from Baseline in DSQ Total Score at week 24. Part C had no primary endpoint, but the peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf and Absolute change in DSQ score from baseline to week 52 were part of the key secondary endpoints.

The esophageal intraepithelial eosinophil count is a diagnostic criterion for EoE. DSQ is a well-defined, valid and reliable PRO measure, that has been developed and tested in both adults and adolescents with EoE. Therefore, the endpoints are considered adequate to evaluate the efficacy of dupilumab in patients with EoE.

The key secondary endpoints for Part A and B included Absolute change in EoE-EREFS from baseline to week 24, Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to week 24, Absolute change in EoE Grade and Stage Score from the EoEHSS from baseline to week 24. Further secondary endpoints were Percent change in DSQ from baseline to week 24, NES for the relative change from baseline to week 24 in the EDP transcriptome signature, NES for the relative change from baseline to week 24 in the type 2 inflammation transcriptome signature, Absolute change from baseline to week 24 in health-related QOL as measured by EoE-IQ. For Part B, Absolute change from baseline to week 24 in severity and/or frequency of EoE symptoms other than dysphagia was also evaluated.

Study R668-EE-1324 was submitted as supportive data. This study was a phase 2 proof of concept, multicenter, double-blind, randomized, placebo-controlled study investigating the efficacy, safety, tolerability, PK, and immunogenicity of dupilumab in adult participants with EoE. The participants were randomized in a 1:1 ratio to receive dupilumab 300 mg QW with a 600 mg loading dose or placebo during a 12-week treatment phase. Rescue treatment with systemic and swallowed topical corticosteroids or emergency esophageal dilation was allowed. Participants who met the eligibility criteria underwent day 1 baseline assessments and were randomized in a 1:1 ratio to receive dupilumab 300 mg QW or placebo. After the 12-week double-blind treatment phase, participants were followed for an additional 16 weeks.

A total of 47 participants were enrolled, 23 participants were randomized to receive dupilumab 300 mg QW, and 24 participants were randomized to receive placebo. Overall, the study design is considered appropriate..

Efficacy data and additional analyses

In **Part A** the proportion of participants who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24 was significantly greater in the dupilumab 300 mg QW group (59.55%)

compared to the placebo group (5.1%). The reduction [i.e., improvement] from baseline in DSQ total score at week 24 was greater in the dupilumab 300 mg QW group (-21.92 points) versus the placebo group (-9.60 points).

The results of the secondary endpoints evaluated show consistent improvement of EoE disease symptoms and health-related quality-of-life measures consistent with results of the primary endpoints. Consistent beneficial effects across this multiple histologic, endoscopic and patient-reported outcome measures of disease activity were seen, demonstrating efficacy for dupilumab 300 mg QW for treatment of patients with EoE in Part A.

In **Part B**, Dupilumab 300 mg QW demonstrated clinically meaningful improvement over placebo in the co-primary endpoints. The proportion of participants who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24 was greater in the dupilumab 300 mg QW group (58.8%) compared to placebo (6.3%). Higher improvement from baseline in DSQ total score at week 24 was seen in the dupilumab 300 mg QW group (−23.78 points) compared to placebo (−13.86 points).

Sensitivity analyses, using different imputation methods, showed similar results as the primary analysis and confirmed that regardless of the assumptions used for missing data, treatment with dupilumab 300 mg QW produced a greater clinical effect size in comparison with placebo.

The results of the high number of secondary endpoints also show greater improvement of EoE disease symptoms and health-related quality-of-life measures with Dupilumab 300 mg QW compared to placebo.

In contrast, the dupilumab 300 mg Q2W dosing regimen significantly reduced esophageal eosinophil counts ≤6 eos/hpf (60.5%) without meaningful effects on dysphagia (as measured by the absolute change from baseline in DSQ total score at week 24) or other EoE disease symptoms (as measured by the absolute change from baseline in EoE-SQ score at week 24).

The proportion of participants who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24 was greater in the dupilumab 300 mg Q2W (60.5%) than in 300 mg QW group (58.8%) and the placebo group (6.3%). However, the improvement in DSQ total score at week 24 was with −14.37 points in the dupilumab 300 mg Q2W group only similar to placebo −13.86 points. Supplemental and post-hoc analyses performed to further evaluate the difference between the dupilumab 300 mg QW and Q2W regimens with respect to the DSQ endpoint supported the primary analysis. The difference between the QW and Q2W regimens could not be explained by an imbalance of responses to the DSQ questions that contributed to the calculation of the DSQ total score. The results from the secondary endpoints were consistent with the results from co-primary endpoints and showed no improvement with the dupilumab 300 mg Q2W dosing regimen in EoE disease symptoms or health-related quality-of-life measures compared with placebo although the magnitude of improvements in all other secondary histologic, endoscopic and molecular endpoints of EoE were similar to the ones observed with the dupilumab 300 mg QW dosing regimen. The reason for the different results for the co-primary endpoint between the dupilumab 300 mg QW and 300 mg Q2W regimens remains unclear. At the CHMP request, the MAH discussed the difference in results. One hypothesis is that in addition to the effect on infiltration of eosinophils in the esophageal mucosa, the drug effect on dysphagia may be modulated by a different effect compartment (e.g., muscularis layer, esophageal nervous plexus). Although dupilumab 300 mg Q2W dosing regimen did improve histologic outcomes, it did not achieve the same level of improvements in dysphagia as dupilumab 300 mg QW at Week 24 and 52. This is indicating that dupilumab 300 mg QW is the appropriate regimen to achieve continuous improvement and thus recommended in section 4.2 of the SmPC.

At the end of **Part A/C** treatment period, more than half (57.8%) of participants achieved a peak esophageal intraepithelial eosinophil count ≤6/hpf. Of participants receiving dupilumab 300 mg QW in

Part A and C, 68.4% had histological remission at the Part C baseline (end of Part A [week 24]) and 55.9% at week 52 (end of Part C). Of participants previously treated with placebo in Part A, 60.0% achieved a peak esophageal intraepithelial eosinophil count ≤6/hpf after 28 weeks of dupilumab treatment in Part C (week 52), which is similar to the proportion of participants treated with dupilumab during Part A.

Dupilumab also reduced dysphagia, as demonstrated by an overall 71.48% reduction from study baseline (start of Part A) to week 52 in DSQ total score. Participants in the dupilumab 300 mg QW group maintained their improvement in DSQ total score observed in Part A with continued dupilumab treatment up to week 52 in Part C. The mean percent reduction from the Part A baseline was 70.06% at week 24 (Part C baseline) and 75.93% at week 52 (after 28 weeks of dupilumab). Participants in the placebo/dupilumab 300 mg QW group showed improvement in the DSQ score, the mean percent reduction from the Part A baseline in DSQ total score was 31.23% at week 24 (Part C baseline) compared with a 65.87% reduction at week 52 (after 28 weeks of dupilumab). The improvement in DSQ total score in this group at week 52 was similar to the improvement noted at the Part C baseline in the dupilumab 300 mg QW/dupilumab 300 mg QW group. Several other secondary endpoints evaluated show consistent results in reduction of disease symptoms.

In **Part B/C**, numerically greater effects in all endpoints were observed in participants treated with dupilumab 300 mg QW for 52 weeks compared with those treated with dupilumab 300 mg Q2W. Furthermore, efficacy continued to improve during Part C. In Part B, 58.8% of participants had achieved peak esophageal intraepithelial eosinophil count ≤6/hpf at Week 24, while 84.6% had achieved this after 52 weeks. Similarly, DSQ scores continued to improve participants treated with dupilumab 300 mg QW/ dupilumab 300 mg QW group from -23.78 at Week 24 to -30.26 at Week 52. Participants who received placebo in Part B achieved improvements after 28 weeks on dupilumab 300 mg QW in Part C similar to those observed for participants who received 24 weeks of dupilumab treatment during Part B.

In summary, Part C efficacy data for up to one year provide further evidence that treatment with dupilumab 300 mg QW shows clinically meaningful efficacy in the treatment of EoE patients. The results of the study have been included in section 5.1 of the SmPC.

Pooling of data for Part A and Part B were performed to ensure an adequate sample size for subgroup analyses of efficacy for the co-primary efficacy endpoints (**Pool 1**). Pool 1 was used for analyses of the additional clinico-pathologic remission endpoint and for efficacy subgroup analyses of the histologic remission and clinical symptoms endpoints. The results in the pooled analyses showed greater proportion of dupilumab-treated participants achieved clinico-pathologic remission compared to placebo-treated participants in Part A, Part B and the Pool 1 population. The results were consistent between Parts A and B and Pool 1, with a significant difference observed ($p<0.0001$) compared to placebo.

Dupilumab 300 mg QW demonstrated a consistent effect on the proportion of participants in both Part A and Part B of R668-EE-1774 who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24 and absolute change in DSQ total score from baseline to week 24 compared to placebo across all subgroups assessed, including in particular age, gender, history of atopic dermatitis, history of asthma, history of food allergy, and previous use of STC for EoE.

Although it can be agreed that the data from B/C indicate that continued use for up to one year was generally well tolerated it remains unclear whether a frequency of weekly dosing is required after a patient achieves remission, or after one year of therapy. The weekly dosing is a considerable disease burden, which might not be tolerated by all patients for long term use. As no data beyond week 52 are

available, at the CHMP request, the MAH included a statement in section 4.2 of the SmPC that 'Dosing beyond 52 weeks has not been studied' to address this concern

The primary endpoint of supportive study **R668-EE-1324** was the absolute change in SDI total score from baseline to week 10. The results show a higher reduction in the SDI total score of -3.0 in the dupilumab group compared to -1.3 in the placebo group, which indicates a clinical meaningful improvement. The results of the high number of secondary endpoints evaluated are consistent with the results of the primary endpoint indicating an improvement in signs and symptoms of patients with EoE.

Assessment of paediatric data on clinical efficacy

In **Part A**, 20 adolescent participants (12 to <18 years of age) were randomized. 11 adolescents received dupilumab 300 mg QW and 9 received placebo. The study was not powered for any of the subgroups. The results show that a higher proportion of adolescent participants achieved a peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24 in the dupilumab 300 mg QW (04/11, 36.4%) group than in the placebo group (0/9, 0%). However, the proportion of patients is lower than in the Dupilumab 300 mg QW group in Part B and in adult participants treated with dupilumab. The improvement from baseline in DSQ total score at week 24 were also greater in the dupilumab 300 mg QW (−23.48) group than in the placebo group (−15.93).

In **Part B**, 79 (32.9%) adolescents (≥12 to <18 years of age) were randomized: 26 participants in the dupilumab 300 mg QW group, 27 participants in the dupilumab 300 mg Q2W group, and 26 participants in the placebo group. The proportion of adolescents who achieved a peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24 was greater in both the dupilumab 300 mg QW (15/26, 57.7%) and 300 mg Q2W (13/27, 48.1%) groups than in the placebo group (2/26, 7.7%). The improvements in the dupilumab groups followed a similar pattern to those in adult participants. In the improvement from baseline in DSQ total score at week 24 the reduction in DSQ score was greater in the dupilumab 300 mg QW (−19.54) group than in the placebo group (−16.42). However, less improvement compared to placebo was seen in the dupilumab 300 mg Q2W (−12.14).

In **Part A/C**, 3 of 9 (33.3%) adolescent participants in the dupilumab 300 mg QW/dupilumab 300 mg QW group and 6 of 8 (75.0%) in the placebo/dupilumab 300 mg QW group achieved a peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 52. Two adolescent participants in the dupilumab 300 mg QW/dupilumab 300 mg QW group achieved a peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at baseline of Part C but were no longer responders at week 52.

Adolescent participants in the dupilumab 300 mg QW/dupilumab 300 mg QW group maintained improvement in DSQ total score with continued treatment during Part C. The mean change from the Part A baseline (36.21) was -24.80 points at the Part C baseline (week 24; N=10) and −25.57 points at week 52 (N=6). Adolescent participants in the placebo/dupilumab 300 mg QW group who started dupilumab treatment in Part C showed progressive improvement. The mean change from the Part A baseline (36.04) was -25.45 points at week 52 (N=5).

The results of Part C show that adolescent participants in the dupilumab/dupilumab group had a decrease in Proportion of Participants Achieving Peak Esophageal Intraepithelial Eosinophil Count ≤6 eos/hpf from 55.6% at the end of Part A to 33.3% at week 52. In contrast the improvement in DSQ score was -3.97 from the end of Part A.

The results from **Part B/C** for adolescent participants entering from Part B, submitted at the CHMP request, showed further improvements especially in the dupilumab 300 mg QW group. Continued improvement was seen from 66.7% at baseline (Week 24) to 81.8% of the adolescent participants in

the dupilumab 300 mg QW/dupilumab 300 mg QW achieving histological remission at Week 52. The dupilumab 300 mg Q2W/dupilumab 300 mg Q2W group also demonstrated improvement from 53.8% at baseline (Week 24) to 60.0% of participants achieving histological remission in all 3 regions at Week 52.

Higher reductions in DSQ were also seen in the dupilumab 300 mg QW groups (-25.02 in the placebo/dupilumab 300 mg QW and -26.86 in dupilumab 300 mg QW/dupilumab 300 mg QW group) compared to the 300 mg Q2W group and to baseline, indicating higher continued improvement for the dupilumab 300 mg QW dosing regimen. Although, improvements were also seen in the 300 mg Q2W groups, the results are of lesser extent.

Overall the 300 mg QW dosing regimen showed higher efficacy in achieving histological remission and the reduction of dysphagia burden in the adolescent participants. Therefore, this is the proposed dosing regimen for adolescents weighting more than 40 kgs. No data are available for paediatric patients weighting less than 40 kgs.

In Pool 1, the Co-Primary endpoints were analysed by age. The results show that in the ≥12 to <18 years of age group, the proportion of participants who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24 was 19/37 (51.4%) in the dupilumab 300 mg QW group versus 2/35 (5.7%) in the placebo group. In the ≥12 to <18 years of age group, the improvement in DSQ total score from baseline to week 24 was -21.07 points in the dupilumab 300 mg QW group (n=37) and -17.23 points in the placebo group (n=35).

When compared to the ≥18 years of age subgroup, the improvement from baseline in DSQ total score at week 24 relative to placebo in the adolescent subgroup was smaller. The MAH claims that this is likely due to higher placebo effect, which is acknowledged. However, at the end of part B, the results for the dupilumab treated adolescents are lower than in adults with −19.54 in DSQ score compared to adults with -26.68. Of note, the results in Part A show a higher improvement from baseline in DSQ total score at week 24 in the dupilumab 300 mg QW of −23.48 than in Part B.

Results from Part C (28-week) for the participants who originally participated in Part B (24-week) of the study support the long-term efficacy of dupilumab 300 mg QW in adolescent participants with EoE.

2.5.4. Conclusions on the clinical efficacy

The study design of the Phase 3 Study R668-EE-1774 with Part A and Part B carried out as 2 separate sequential independent parts was adequate. Therefore, this study is considered acceptable as pivotal study.

In adult and adolescent participants Dupilumab 300 mg QW showed clinical meaningful improvements of signs and symptoms of active EoE and with substantial disease burden in Part A and B of study R668-EE-1774. Results from Part C of this study showed that the improvements in signs and symptoms of EoE were maintained or even further improved with long-term treatment through week 52. In addition, participants who switched from placebo to dupilumab 300 mg QW in Part C showed similar improvement as participant treated with dupilumab in the previous study parts.

In contrast, dupilumab 300 mg Q2W did not show improvements in clinical symptoms or health-related QoL compared with placebo, even though the magnitude of improvements in all histologic, endoscopic, and molecular endpoints of EoE were similar to those observed with the dupilumab 300 mg QW dosing regimen. The dupilumab 300 mg QW dosing regimen is therefore considered to be the appropriate dosing regimen to have meaningful benefit for adult and adolescent patients with EoE weighting more than 40 kgs.

Since no clinical experience was available for patients weighting less than 40kg, initially proposed to be included in the therapeutic indication, the MAH revised their claim during the procedure to exclude patients weighting less than 40kg from the indication.

In conclusion, the CHMP considered that the efficacy data available supports the following indication:

Dupixent is indicated for the treatment of eosinophilic esophagitis in adults and adolescents 12 years and older, weighing at least 40 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy (see section 5.1).

2.6. Clinical safety

Introduction

The assessment of safety was a secondary objective in both the pivotal study R668-EE-1774 and the supportive study R668-EE-1324 and included an evaluation of the safety, tolerability and immunogenicity of dupilumab treatment for up to 52 weeks in adult and adolescent patients with EoE (in study R668-EE-1774) and in adult patients with EoE (in study R668-EE-1324).

Safety was similarly assessed in the individual studies by collecting information on TEAEs, treatment-emergent serious adverse events (SAEs), adverse events (AEs) leading to discontinuation or death and AESIs. Treatment-emergent adverse events were defined as AEs that developed or worsened in severity compared to the baseline during the treatment-emergent period. Treatment-emergent abnormal laboratory values (haematology, chemistry, and urinalysis), vital signs, physical findings, and electrocardiograms (ECGs) were also evaluated.

For all ongoing studies in the dupilumab clinical program, suspected unexpected serious adverse reactions (SUSARs) were reported up to a cut-off date of 28 Sept 2021 in the atopic dermatitis (AD) paediatric 6 months to 5 years old application (EMEA/H/C/004390/II/0060). SUSARs from ongoing studies reported from 28 Sept 2021 to a new cut-off of 20 Dec 2021 were provided in the Prurigo Nodularis application (EMEA/H/C/004390/II/0063).

Table 39 Status of Studies of Dupilumab in the Eosinophilic Esophagitis Program

Study R668-EE-1774 Part A

Study Period	Screening →	Part A Double-blind Treatment Period[a] →	Extended Treatment Period (Part A/C) →	Follow-up Period[b]
Study treatment groups	(N=157)	Placebo (N=39) Dupilumab 300 mg QW (N=42)	Dupilumab 300 mg QW (N=77)	(N=50)
Duration	Up to 12 weeks	24 weeks	28 weeks	12 weeks
Data cutoff date for Primary CSR		08 May 2020	18 Nov 2020	
Database lock date		20 May 2020	17 Dec 2020	
Study status		Completed	Completed	Completed
Reporting status		Part A CSR and Addendum Report[c]	Part A/C CSR and Addendum Report[c]	Reported up to 18 Nov 2020

Study R668-EE-1774 Part B

Study Period	Screening	→	Part B Double-blind Treatment Period[d]	→	Extended Treatment Period (Part B/C)	→	Follow-up Period
Study treatment groups	(N=462)		Placebo (N=79) Dupilumab 300 mg QW (N=80) Dupilumab 300 mg Q2W (N=81)				
Duration	Up to 12 weeks		24 weeks				
Final database lock			30 Sep 2021				
Study status			Completed		Ongoing		Ongoing
Reporting status			Part B CSR		Not yet reported		Not yet reported

Study R668-EE-1324

Study Period	Screening	→	Double-blind Treatment Period	→	Follow-up Period
Study treatment groups	(N=80)		Placebo (N=24) Dupilumab 300 mg QW (N=23)		Off-treatment
Duration	Up to 5 weeks		12 weeks		16 weeks
Final database lock					26 Jul 2017
Study status					Completed
Reporting status					Final CSR

a No participant entered the follow-up period directly from Part A.
b The follow-up period of the A/C study was ongoing at the time the A/C CSR was written. The available data at the time of the data cutoff for the A/C CSR (18 Nov 2020) are included in the A/C CSR. The complete set of follow-up data will be reported in a future report.

The integrated analysis of safety is based on 2 pools (Pool 2a and Pool 2b see ancillary analyses).

Integrated analyses from the phase 3, 24-week treatment periods (Pool 2a), and from the phase 2 (12-week treatment period) and phase 3 (24-week treatment period) studies (Pool 2b), are presented to evaluate the safety of dupilumab in patients with EoE. Supportive long-term safety data (52 weeks' exposure in the participants randomized to dupilumab in Part A) are presented from Part A/C results of study R668-EE-1774.

In addition, Pool 3 was specified to determine the overall extent of treatment exposure of patients with EoE in phase 2 and 3 clinical studies, including the extended active treatment period (Part A/C).

Table 40 Numbers of Participants in the Integrated Databases for Safety and Exposure Pools

Phase	Studies (Study Parts)	Database	Pool 2a Safety	Pool 2b Safety	Pool 3 Exposure Only
Phase 2	R668-EE-1324	12-week treatment	NA	47	47
Phase 3	R668-EE-1774 Part A[a]	24-week treatment	81	81	81
Phase 3	R668-EE-1774 Part B	24-week treatment	239	239	239
Phase 3	R668-EE-1774 Part A/C[b]	28-week treatment	NA	NA	77[c]
	Total number of participants included		320	367	367

a Complete safety and exposure data from Part A are included in the respective pooled databases and consist of: a) all safety and exposure data as reported in Part A CSR (data cutoff date 08 May 2020) and b) safety and exposure data from participants who were ongoing in the study at the time of Part A database lock and had delayed end of treatment visits in Part A due to the COVID-19 pandemic, as reported in the Part A CSR addendum (data up to the last delayed week 24 visit in Part A on 06 Aug 2020).

b Complete exposure data from Part A/C are included in the pooled exposure database and consist of: a) all exposure data as reported in Part A/C CSR (data cutoff date 18 Nov 2020) and b) exposure data from participants who were ongoing in the study at the time of Part A/C database lock and had delayed end of treatment visits in Part C due to the COVID-19 pandemic as reported in the Part A/C CSR addendum (data up to LPLV on 27 May 2021).

c To avoid double-counting, these participants are only counted once for the total number (counted in the Part A population).

Abbreviations: CSR=clinical study report; LPLV=last patient, last visit; NA=not applicable as not included in respective pool.

Patient exposure

The EoE patient safety database contains exposure data from **367 participants** who were exposed to study medication during the 2 placebo-controlled studies (studies **R668-EE-1324 and R668-EE-1774**) and including the extended active treatment period from study R668-EE-1774 Part A/C.

104 participants received only placebo (78 from study R668-EE-1774 Part B, 2 from Part A who did not continue to Part C and 24 from study R668-EE-1324). **263 received dupilumab** (all participants who were originally randomized to dupilumab in study R668-EE-1774 Parts A and B and in study R668-EE-1324 and those participants originally randomized to placebo in Part A who continued to Part C and received dupilumab). Of these 46 participants were adolescents, of which 10 participants received dupilumab 300 mg QW over a period of about 1 year (Part A/C).

Of note, Dupilumab 300 mg QW has not been studied in adolescents outside of study R668-EE-1774 therefore no supportive data for the 300mg QW dose from adolescents is available from other indications as it has never been administered to adolescents outside of the pivotal study. PK data from Parts A and B show that adolescents with EoE had approximately 25% higher functional dupilumab levels than adults with EoE at the proposed dose of dupilumab 300mg QW.

Table 41 Descriptive Statistics of Functional Dupilumab Concentrations in Serum by Time and Age Group in Adult and Adolescent Participants with Eosinophilic Esophagitis Receiving Dupilumab 300mg QW (Study R668-EE-1774 Parts A and B, PKAS)

	Concentration of Functional Dupilumab in Serum (mg/L)										
Sampling Time Post First Dose (Week)	n	Mean	SD	SE	CV%	Min	Q1	Median	Q3	Max	Geometric Mean
Adults											
0	79	0	0	0	--	0	0	0	0	0	--
12	69	156	68.0	8.18	43.5	6.05	111	149	216	283	134
24	71	177	83.3	9.89	47.1	0	105	187	238	415	140
Adolescents											
0	35	0	0	0	--	0	0	0	0	0	--
12	30	207	87.2	15.9	42.1	26.5	157	210	277	324	181
24	29	227	95.3	17.7	42.0	48.7	169	221	264	508	206

Abbreviations: BLQ=below the limit of quantitation; CV=coefficient of variation; LLOQ=lower limit of quantitation; n=number of participants; Q=quartile; QW=once weekly; SD=standard deviation; SE=standard error.
Note: Includes protocol defined schedule visit only. BLQ concentrations were set to 0 except for geometric mean which were set to LLOQ/2. Adult (≥18 years of age) and adolescent (≥12 to <18 years of age) participants.
Mean (SD) body weight in R668-EE-1774 Parts A and B:
Adolescents: 57.6 (12.1) kg (Part A) and 62.4 (17.4) kg (Part B)
Adults: 89.1 (22.9) kg (Part A) and 80.5 (18.3) kg (Part B)
Source: _PC_AGPAP_AB, Module 5.3.5.1 R668-EE-1774 Part A Appendix 16.1.15 Appendix A, Table 10 and Module 5.3.5.1 R668-EE-1774 Part B Appendix 16.1.15 Appendix A, Table 13

Adolescent data from other dupilumab indications was studied with lower doses, 200mg-300mg every 2 weeks. The highest exposures in adolescents were achieved for 3 participants on 4 mg/kg QW in the open-label extension Study R668-AD-1434. However, adult participants with AD (R668-AD-1334, R668-AD-1416, R668-AD-1224, and R668-AD-1117) or asthma (ACT11457) assigned to dupilumab 300 mg QW regimens have included participants with a baseline body weight as low as 42 kg. Previous population PK analyses including adolescents with AD or asthma indicate that weight was a primary factor accounting for variability in dupilumab exposure and that age was not a significant covariate after accounting for weight in adults and adolescents. As dupilumab 300 mg QW has not been studied in lighter body weight patients with EoE, participants with body weight <40 kg were excluded from R668-EE-1774.

With the responses to the Request for Supplementary Information the MAH submitted additional safety data from 75 adolescent participants who entered Part C from Part B up to Week 52.

Table 42 Number of Participants with Eosinophilic Esophagitis Included in the Summary of Clinical Safety by Study (SAF)

Study Number Treatment Duration	Dosage and Regimen	Number of Adult Participants (≥18 years old)	Number of Adolescent Participants (≥12 to <18 years)	Total
R668-EE-1324 12 weeks	Placebo	24	0	24
	Dupilumab 300 mg QW	23	0	23
R668-EE-1774 Part A 24 weeks	Placebo	30	9	39
	Dupilumab 300 mg QW	31	11	42
R668-EE-1774 Part B 24 weeks	Placebo	52	26	78
	Dupilumab 300 mg QW	54	26	80
	Dupilumab 300 mg Q2W	54	27	81
R668-EE-1774 Part C (Participants from Part A)[a] 28 weeks	Placebo/dupilumab 300 mg QW	28	9	37
	Dupilumab 300 mg QW/ dupilumab 300 mg QW	30	10	40
Total	Placebo[b]	106	35	141
	Dupilumab combined (300 mg Q2W and QW)[c]	190	73	263
	Dupilumab 300 mg QW	136	46	182
	Dupilumab 300 mg Q2W	54	27	81

a Treatment groups are shown as "Treatment received during Part A/ Treatment received during Part C"
b Summed from R668-EE-1324 (placebo group) and Part A and Part B (placebo group) portions of R668-EE-1774.
c Summed from R668-EE-1324 (300 mg QW group), and Part A (300 mg QW group), Part B (300 mg QW and 300 mg Q2W), and Part A/C (placebo/dupilumab 300 mg QW group) portions of R668-EE-1774.
Abbreviations: Q2W=every 2 weeks; QW=once weekly; SAF=safety analysis set of respective study

- **Safety Analysis Set**

The safety analysis set (SAF) for the integrated analysis included all participants who received at least 1 dose of study drug. Participants were analysed according to the treatment group determined in the individual studies.

The analysis periods for the pooled analyses were as follows:

- For Pool 2a: the analysis period is the "24-week treatment period" from study R668-EE-1774 Part A and Part B corresponding to that defined in the Part A and Part B SAPs:
  - For participants who entered Part C: from day 1 to the date of first dose of Part C study drug (or week 24 visit if participant entered Part C but never received any Part C study drug)
  - For participants who did not enter Part C but completed the week 24 visit with known visit date: from day 1 to the week 24 visit
  - For participants who did not enter Part C and did not complete the week 24 visit, or had a missing week 24 visit date: from day 1 to study day 169 (i.e., 24 weeks ×7 days/week) or to participant's last study participation date, whichever was earlier. Note: For participants in this category who received extended dosing in the placebo-controlled period due to the COVID-19 pandemic, the 24-week treatment period ended on their last study participation date.
- For Pool 2b: the analysis period is the "24-week treatment period" from R668-EE-1774 Part A and Part B as defined above and the R668-EE-1324 "12-week treatment period" corresponding to that defined in its SAP, i.e., day 1 from start of administration of the first dose of study drug

through week 12 of the double-blind period (85 days starting from the first dose of study drug if the date of the week-12 treatment visit was unavailable).

Adverse events

Study R668-EE-1774

- **Part A**

Table 43 Overall Summary of Number of Participants with TEAEs (Part A SAF)

	Placebo (N=39)	Dupilumab 300 mg QW (N=42)
Any TEAE, n (%)	32 (82.1%)	36 (85.7%)
Any drug related TEAE, n (%)	15 (38.5%)	16 (38.1%)
Any TEAE leading to discontinuation of study drug permanently, n (%)	0	1 (2.4%)
Maximum intensity for any TEAE, n (%)		
Mild	21 (53.8%)	24 (57.1%)
Moderate	11 (28.2%)	10 (23.8%)
Severe	0	2 (4.8%)
Any TEAE death, n (%)	0	0
Any TE SAE, n (%)	0	2 (4.8%)
Any TE SAE leading to discontinuation of study drug permanently, n (%)	0	0

Abbreviations: QW=once weekly; SAE=serious adverse event; SAF=safety analysis set; TE=treatment-emergent; TEAE=treatment-emergent adverse event.

Table 44 Summary of TEAEs Reported by ≥5% of Participants in any Treatment Group During Part A-(Part A SAF)

Primary System Organ Class Preferred Term	Placebo (N=39)	Dupilumab 300 mg QW (N=42)
Number of such events	131	173
Number of patients with at least one such event, n (%)	32 (82.1%)	36 (85.7%)
General disorders and administration site conditions	15 (38.5%)	17 (40.5%)
Injection site reaction	4 (10.3%)	7 (16.7%)
Injection site pain	3 (7.7%)	4 (9.5%)
Injection site erythema	5 (12.8%)	3 (7.1%)
Injection site swelling	1 (2.6%)	3 (7.1%)
Injection site pruritus	2 (5.1%)	1 (2.4%)
Infections and infestations	10 (25.6%)	15 (35.7%)
Nasopharyngitis	4 (10.3%)	5 (11.9%)
Upper respiratory tract infection	0	4 (9.5%)
Sinusitis	2 (5.1%)	1 (2.4%)
Gastrointestinal disorders	12 (30.8%)	8 (19.0%)
Diarrhoea	2 (5.1%)	2 (4.8%)
Abdominal pain	2 (5.1%)	1 (2.4%)
Nausea	3 (7.7%)	1 (2.4%)
Dysphagia	2 (5.1%)	0

Respiratory, thoracic and mediastinal disorders	5 (12.8%)	7 (16.7%)
Rhinorrhoea	0	3 (7.1%)
Oropharyngeal pain	2 (5.1%)	0
Nervous system disorders	8 (20.5%)	6 (14.3%)
Headache	4 (10.3%)	2 (4.8%)
Investigations	3 (7.7%)	3 (7.1%)
Blood creatine phosphokinase increased	2 (5.1%)	0
Skin and subcutaneous tissue disorders	7 (17.9%)	2 (4.8%)
Dermatitis atopic	3 (7.7%)	0
Rash	4 (10.3%)	0

At each level of patient summarization, a patient is counted once if the patient reported one or more events.
MedDRA (Version 23.0) coding dictionary applied.
Sorted by decreasing frequency at all levels in the dupilumab group
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; QW=once weekly; SAF=safety analysis set; TEAE=treatment-emergent adverse event.

The most frequently reported TEAEs in Part A were in the System organ class (SOC) General Disorders and Administration Site Conditions with 15 participants (38.5%) in the placebo group and 17 participants (40.5%) in the dupilumab 300 mg QW group, and were mostly driven by injection site reactions.

The proportion of participants with TEAEs in the SOC Infections and Infestations was higher in the dupilumab 300 mg QW group (15 participants [35.7%]) than the placebo group (10 participants [25.6%]) with the difference being predominantly driven by Upper Respiratory Tract Infections (9.5% in the dupilumab 300 mg QW group and 0% in the placebo group). The Preferred term (PT) Nasopharyngitis showed a similar incidence (11.9% in in the dupilumab 300 mg QW group and 10.3% in the placebo group).

A higher frequency of Gastrointestinal Disorders was reported in the placebo group (30.8%) compared to the dupilumab 300 mg QW group (19.0%) with the most frequent PT being Nausea (7.7% in the placebo group and 2.4% in the dupilumab 300 mg QW group).

Also, a higher proportion of participants in the placebo group (20.5%) reported TEAEs in the SOC Nervous System Disorders than the dupilumab 300 mg QW group (14.3%) with the only frequent PT being Headache (4.8% in the dupilumab 300 mg QW group and 10.3% in the placebo group).

PTs that occurred with a higher frequency in the dupilumab 300 mg QW group (≥5% higher) than the placebo group were: Injection Site Reaction, Upper Respiratory Tract Infection, and Rhinorrhoea. All injection site reactions were assessed as mild or moderate in intensity. There were no severe or serious injection site reactions.

PTs that occurred with a higher frequency in the placebo group (≥5%) than in the dupilumab 300 mg QW group were: Injection Site Erythema, Nausea, Dysphagia, Headache, Blood Creatine Phosphokinase Increased, Dermatitis Atopic, Oropharyngeal Pain, and Rash.

Table 45 Number of Patients With Treatment-Emergent Adverse Events (TEAE) By Primary System Organ Class and Preferred Term During Part A 24-week Treatment Period by Age Group (Part A Safety Analysis Set)

Age Group: >= 12 -< 18 years

Primary System Organ Class Preferred Term	Placebo (N=9)	Dupilumab 300 mg QW (N=11)
Number of such events	24	55
Number of patients with at least one such event, n (%)	9 (100%)	11 (100%)
General disorders and administration site conditions	4 (44.4%)	6 (54.5%)
Injection site reaction	3 (33.3%)	5 (45.5%)
Injection site pain	0	1 (9.1%)
Injection site erythema	1 (11.1%)	0
Injection site induration	1 (11.1%)	0
Injection site pruritus	1 (11.1%)	0
Infections and infestations	3 (33.3%)	3 (27.3%)
Bronchitis	0	1 (9.1%)
Gastroenteritis viral	0	1 (9.1%)
Gastrointestinal viral infection	0	1 (9.1%)
Influenza	0	1 (9.1%)
Nasopharyngitis	1 (11.1%)	1 (9.1%)
Rhinitis	0	1 (9.1%)
Sinusitis	1 (11.1%)	1 (9.1%)
Upper respiratory tract infection	0	1 (9.1%)
Viral upper respiratory tract infection	0	1 (9.1%)
Conjunctivitis	1 (11.1%)	0
Gastrointestinal disorders	2 (22.2%)	2 (18.2%)
Gastrointestinal disorder	0	1 (9.1%)

Age Group: >= 18 years

Primary System Organ Class Preferred Term	Placebo (N=30)	Dupilumab 300 mg QW (N=31)
Number of such events	107	118
Number of patients with at least one such event, n (%)	23 (76.7%)	25 (80.6%)
Infections and infestations	7 (23.3%)	12 (38.7%)
Nasopharyngitis	3 (10.0%)	4 (12.9%)
Upper respiratory tract infection	0	3 (9.7%)
Ear infection	0	1 (3.2%)
Furuncle	0	1 (3.2%)
Pharyngitis	0	1 (3.2%)
Tinea versicolour	0	1 (3.2%)
Urinary tract infection	0	1 (3.2%)
Viral upper respiratory tract infection	1 (3.3%)	1 (3.2%)
Bronchitis	1 (3.3%)	0
Cystitis	1 (3.3%)	0
Influenza	1 (3.3%)	0
Sinusitis	1 (3.3%)	0
Tinea cruris	1 (3.3%)	0
Wound infection	1 (3.3%)	0
General disorders and administration site conditions	11 (36.7%)	11 (35.5%)
Injection site erythema	4 (13.3%)	3 (9.7%)
Injection site pain	3 (10.0%)	3 (9.7%)
Injection site swelling	1 (3.3%)	3 (9.7%)
Injection site oedema	1 (3.3%)	2 (6.5%)

At each level of patient summarization, a patient is counted once if the patient reported one or more events.
MedDRA (Version 23.0) coding dictionary applied.
Sorted by decreasing frequency at all levels in the dupilumab group

The incidence of TEAEs for **adolescents** was similar to that of adults, with numerically higher proportion of adolescents reporting general disorder and administrative site conditions related to injections side reactions in both the placebo (4/9, 44.4%) and dupilumab 300 mg QW groups (6/11, 54.5%) compared to adult participants in both the placebo (11/30, 36.7%) and dupilumab 300 mg QW groups (11/31, 35.5%)

- **Part B**

Table 46 Overall Summary of Number of Participants with TEAEs During the Part B 24-week Treatment Period (Part B SAF)

		Dupilumab		
	Placebo (N=78)	300 mg Q2W (N=81)	300 mg QW (N=80)	Combined (N=161)
Any TEAE, n (%)	55 (70.5%)	63 (77.8%)	67 (83.8%)	130 (80.7%)
Any drug related TEAE, n (%)	28 (35.9%)	39 (48.1%)	27 (33.8%)	66 (41.0%)
Any TEAE leading to discontinuation of study drug permanently, n (%)	2 (2.6%)	2 (2.5%)	2 (2.5%)	4 (2.5%)
Maximum intensity for any TEAE, n (%)				
Mild	40 (51.3%)	42 (51.9%)	44 (55.0%)	86 (53.4%)
Moderate	13 (16.7%)	20 (24.7%)	17 (21.3%)	37 (23.0%)
Severe	2 (2.6%)	1 (1.2%)	6 (7.5%)	7 (4.3%)
Any TEAE leading to death, n (%)	0	0	0	0
Any TE SAE, n (%)	1 (1.3%)	1 (1.2%)	5 (6.3%)	6 (3.7%)
Any TE SAE leading to discontinuation of study drug permanently, n (%)	0	0	1 (1.3%)	1 (0.6%)

Abbreviations: Q2W=every 2 weeks; QW=once weekly; SAE=serious adverse event; SAF=safety analysis set; TE=treatment-emergent; TEAE=treatment-emergent adverse event.

Table 47 Summary of TEAEs Reported by ≥5% of Participants in any Treatment Group During Part B 24-week Treatment Period (Part B SAF)

		Dupilumab		
Primary System Organ Class Preferred Term	Placebo (N=78)	300 mg Q2W (N=81)	300 mg QW (N=80)	Combined (N=161)
Number of such events	405	469	354	823
Number of patients with at least one such event, n (%)	55 (70.5%)	63 (77.8%)	67 (83.8%)	130 (80.7%)
General disorders and administration site conditions	31 (39.7%)	46 (56.8%)	34 (42.5%)	80 (49.7%)
Injection site reaction	16 (20.5%)	18 (22.2%)	16 (20.0%)	34 (21.1%)
Injection site erythema	9 (11.5%)	18 (22.2%)	8 (10.0%)	26 (16.1%)
Injection site pain	4 (5.1%)	10 (12.3%)	7 (8.8%)	17 (10.6%)
Injection site swelling	2 (2.6%)	7 (8.6%)	10 (12.5%)	17 (10.6%)
Pyrexia	1 (1.3%)	3 (3.7%)	5 (6.3%)	8 (5.0%)
Fatigue	4 (5.1%)	2 (2.5%)	4 (5.0%)	6 (3.7%)
Injection site bruising	0	6 (7.4%)	0	6 (3.7%)
Injection site urticaria	2 (2.6%)	6 (7.4%)	0	6 (3.7%)
Injection site pruritus	3 (3.8%)	1 (1.2%)	4 (5.0%)	5 (3.1%)
Infections and infestations	18 (23.1%)	26 (32.1%)	24 (30.0%)	50 (31.1%)
COVID-19	0	5 (6.2%)	4 (5.0%)	9 (5.6%)
Sinusitis	0	0	4 (5.0%)	4 (2.5%)

Gastrointestinal disorders	20 (25.6%)	21 (25.9%)	17 (21.3%)	38 (23.6%)
Nausea	6 (7.7%)	4 (4.9%)	4 (5.0%)	8 (5.0%)
Abdominal pain	4 (5.1%)	2 (2.5%)	4 (5.0%)	6 (3.7%)
Vomiting	4 (5.1%)	3 (3.7%)	2 (2.5%)	5 (3.1%)
Diarrhoea	8 (10.3%)	3 (3.7%)	1 (1.3%)	4 (2.5%)
Dyspepsia	4 (5.1%)	1 (1.2%)	0	1 (0.6%)
Respiratory, thoracic and mediastinal disorders	14 (17.9%)	11 (13.6%)	8 (10.0%)	19 (11.8%)
Oropharyngeal pain	6 (7.7%)	5 (6.2%)	3 (3.8%)	8 (5.0%)
Nervous system disorders	13 (16.7%)	10 (12.3%)	8 (10.0%)	18 (11.2%)
Headache	9 (11.5%)	5 (6.2%)	6 (7.5%)	11 (6.8%)
Vascular disorders	1 (1.3%)	1 (1.2%)	4 (5.0%)	5 (3.1%)
Hypertension	1 (1.3%)	1 (1.2%)	4 (5.0%)	5 (3.1%)

At each level of patient summarization, a patient is counted once if the patient reported one or more events.
MedDRA (Version 24.0) coding dictionary applied.
Sorted by decreasing frequency at all levels in the combined dupilumab group.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; Q2W=every 2 weeks; QW=once weekly; SAF=safety analysis set; TEAE=treatment-emergent adverse event.

The proportion of participants with TEAEs in the SOC General disorders and administration site conditions was higher in the dupilumab 300 mg Q2W (56.8%) group than in the dupilumab 300 mg QW (42.5%) and placebo groups (39.7%), and mostly driven by injection site reactions of erythema, pain, and bruising.

In the Infections and infestations SOC, the incidence of TEAEs was numerically higher in the dupilumab 300 mg QW group (30.0%) and the dupilumab 300 mg Q2W group (32.1%) than in the placebo group (23.1%). The pattern of TEAEs within the Infections and infestations SOC was closely examined to determine if there was an association of TEAEs of infections with dupilumab use.

Table 48 Summary of TEAEs in the Primary System Organ Class Infections and Infestations by High Level Term and Preferred Term Reported in ≥2.0% of Participants in Any Treatment Group During the Part B 24-week Treatment Period (Part B SAF)

		Dupilumab		
Primary System Organ Class High Level Term Preferred Term	Placebo (N=78)	300 mg Q2W (N=81)	300 mg QW (N=80)	Combined (N=161)
Infections and infestations	18 (23.1%)	26 (32.1%)	24 (30.0%)	50 (31.1%)
Upper respiratory tract infections	5 (6.4%)	8 (9.9%)	9 (11.3%)	17 (10.6%)
Nasopharyngitis	3 (3.8%)	4 (4.9%)	2 (2.5%)	6 (3.7%)
Upper respiratory tract infection	2 (2.6%)	2 (2.5%)	3 (3.8%)	5 (3.1%)
Sinusitis	0	0	4 (5.0%)	4 (2.5%)
Acute sinusitis	0	2 (2.5%)	0	2 (1.2%)
Coronavirus infections	0	5 (6.2%)	4 (5.0%)	9 (5.6%)
COVID-19	0	5 (6.2%)	4 (5.0%)	9 (5.6%)
Viral infections NEC	1 (1.3%)	4 (4.9%)	4 (5.0%)	8 (5.0%)
Gastroenteritis viral	0	1 (1.2%)	3 (3.8%)	4 (2.5%)
Herpes viral infections	1 (1.3%)	1 (1.2%)	3 (3.8%)	4 (2.5%)
Herpes simplex	0	0	2 (2.5%)	2 (1.2%)
Urinary tract infections	1 (1.3%)	3 (3.7%)	1 (1.3%)	4 (2.5%)
Urinary tract infection	1 (1.3%)	3 (3.7%)	0	3 (1.9%)
Eye and eyelid infections	1 (1.3%)	3 (3.7%)	0	3 (1.9%)
Conjunctivitis	1 (1.3%)	3 (3.7%)	0	3 (1.9%)

Abdominal and gastrointestinal infections	2 (2.6%)	1 (1.2%)	1 (1.3%)	2 (1.2%)
Gastroenteritis	2 (2.6%)	1 (1.2%)	0	1 (0.6%)
Ear infections	1 (1.3%)	2 (2.5%)	0	2 (1.2%)
Ear infection	1 (1.3%)	2 (2.5%)	0	2 (1.2%)
Streptococcal infections	1 (1.3%)	2 (2.5%)	0	2 (1.2%)
Pharyngitis streptococcal	1 (1.3%)	2 (2.5%)	0	2 (1.2%)
Lower respiratory tract and lung infections	2 (2.6%)	0	0	0

At each level of patient summarization, a patient is counted once if the patient reported one or more events.
MedDRA (Version 24.0) coding dictionary applied.
Sorted by decreasing frequency at all levels in the combined dupilumab group.
All HLTs and PTs included with an incidence of ≥2.0% of participants in any treatment group.
Abbreviations: HLT=high level term; MedDRA=Medical Dictionary for Regulatory Activities; NEC=not elsewhere classified; PT=preferred term; Q2W=every 2 weeks; QW=once weekly; SAF=safety analysis set.

Upon examination of individual PTs, the incidence of Nasopharyngitis and Upper respiratory tract infection was found to be similar across the treatment groups. Sinusitis was only reported in the dupilumab 300 mg QW group, by 5.0% of participants, and Acute sinusitis only in the dupilumab 300 mg Q2W group, in 2.5% of participants. All TEAEs of Sinusitis and Acute sinusitis were non-serious, of mild to moderate intensity and all were assessed by the investigator as not related to study drug and all resolved. It should be noted that one TEAE each of Allergic sinusitis and Sinus congestion in the placebo group was reported in the Respiratory, thoracic and mediastinal disorders SOC (under the HLT Paranasal sinus disorders). The incidence of TEAEs under the SOC Respiratory, thoracic and mediastinal disorders was higher in the placebo group (17.9%) than in the dupilumab combined group (11.8%), with the most frequently reported HLT being Upper respiratory tract signs and symptoms, which also had a higher incidence in the placebo group (7.7%) versus the dupilumab combined group (5.6%).

The study was conducted during the COVID-19 pandemic. Vaccination rates were similar across the treatment groups. 9 participants in the dupilumab 300 mg QW group, 8 in the dupilumab 300 mg Q2W group and 11 in the placebo group received at least 1 dose of COVID-19 vaccination during the study. No participant was vaccinated prior to study baseline. There was a higher incidence of TEAEs with a PT of COVID-19 in the dupilumab groups (5.0% in the dupilumab 300 mg QW group and 6.2% in the dupilumab 300 mg Q2W group) than in the placebo group (0.0%). These TEAEs all occurred between 16 Mar 2020 and 08 Apr 2021. Eight of the participants were in the US and 1 was in Belgium. The majority of COVID-19 infections were in adults (7 of the 9 cases), were mild in intensity, all were assessed as not related to study drug by the investigator and all resolved. One participant had received the first COVID-19 mRNA vaccine dose 4 days before the COVID-19 TEAE started. All other participants were not vaccinated.

The majority of the events of COVID-19 infection in the dupilumab arm were reported as mild to moderate. There was 1 TEAE of COVID-19 reported as severe in intensity in the dupilumab 300 mg QW group in a 12-year-old White female. The TEAE started on study day 1 and resolved on study day 19. None of the events of COVID-19 infection were serious TEAEs or required hospitalization or supplemental oxygen therapy and study drug was continued in all cases.

Review of the reporting rate of COVID-19 infection during dupilumab use, calculated using global post-marketing (PM) pharmacovigilance (PV) data, indicated no increased occurrence of COVID-19 infection when compared to the incidence rate of COVID-19 in the 6 countries (US, Colombia, Brazil, UK, UAE, and Canada) which contributed >1% of all cases to the Sanofi PM PV database. The current review of the FDA Adverse Event Reporting System (FAERS) 2021 Q2 database shows the lower bound of the 90% confidence interval of empirical Bayesian geometric mean (EB05) <2 for COVID-19 MedDRA standardized MedDRA query (SMQ) and COVID-19 related PTs. Thus, no signal of unbalanced reporting has been observed from FAERS.

To date, the data for dupilumab suggest that blockade of the IL-4Rα provides specific targeted suppression of type 2 inflammation with no discernible impact on suppressing immune responses to viral and bacterial pathogens. There is no evidence that dupilumab interferes with the induction of IgG antibodies following vaccination, nor the persistence of IgG isotypes. Dupilumab has not been shown to increase the risk of viral infections in the clinical program except in AD for recurrence of local oral Herpes simplex infections. Dupilumab also did not impact T-cell dependent and independent humoral responses to tetanus and meningococcal vaccines.

The totality of the data from the dupilumab clinical trial program and post-marketing data, as well as the published literature, shows no evidence of an increased incidence of opportunistic or serious infections with dupilumab.

For Gastrointestinal disorders SOC, all of the most common PTs (i.e., ≥5% in any treatment group) had a higher incidence in the placebo group versus the 2 dupilumab groups, with the largest differences seen for Diarrhoea, Dyspepsia, and Nausea. For the SOCs Respiratory, thoracic and mediastinal disorders, Nervous system disorders, and Vascular disorders there were similar proportions of participants with TEAEs in the respective SOC across the treatment groups.

The most frequent TEAE reported in each treatment group was Injection site reaction (approximately 20% across all 3 treatment groups). For the TEAE Injection site erythema, in the dupilumab 300 mg Q2W group, 1 event was of moderate intensity, all others were mild and all resolved. For the TEAEs of Injection site pain, Injection site swelling, and Injection site bruising all events in the dupilumab 300 mg Q2W group were mild and resolved without drug therapy.

Table 49 Overall Summary of Number of Adolescent Participants with TEAEs During the Part B 24-week Treatment Period (Part B SAF)

		Dupilumab		
	Placebo (N=26)	300 mg Q2W (N=27)	300 mg QW (N=26)	Combined (N=53)
Any TEAE, n (%)	19 (73.1%)	23 (85.2%)	24 (92.3%)	47 (88.7%)
Any drug related TEAE, n (%)	15 (57.7%)	16 (59.3%)	9 (34.6%)	25 (47.2%)
Any TEAE leading to discontinuation of study drug permanently, n (%)	0	1 (3.7%)	0	1 (1.9%)
Maximum intensity for any TEAE, n (%)				
Mild	12 (46.2%)	16 (59.3%)	13 (50.0%)	29 (54.7%)
Moderate	7 (26.9%)	7 (25.9%)	7 (26.9%)	14 (26.4%)
Severe	0	0	4 (15.4%)	4 (7.5%)
Any TEAE leading to death, n (%)	0	0	0	0
Any TE SAE, n (%)	0	1 (3.7%)	4 (15.4%)	5 (9.4%)
Any TE SAE leading to discontinuation of study drug permanently, n (%)	0	0	0	0

Abbreviations: Q2W=every 2 weeks; QW=once weekly; SAE=serious adverse event; SAF=safety analysis set; TE=treatment-emergent; TEAE=treatment-emergent adverse event.

The incidence of all TEAEs **in adolescents** was higher in the dupilumab 300 mg groups (QW: 92.3%; Q2W: 85.2%) than in the placebo group (73.1%). The number of drug related TEAEs were lower in the 300 mg QW group (34.6%) compared to the placebo (57.7%) and the 300 mg Q2W (59.3%) groups. Most of the TEAEs were mild or moderate in intensity.

There were 4 adolescent participants in the dupilumab 300 mg QW group (Depression suicidal, Campylobacter colitis, Blood creatine phosphokinase abnormal, and Pneumonia aspiration) and 1 adolescent participant in the dupilumab 300 mg Q2W group (Suicidal ideation) who reported a treatment-emergent SAE. All SAEs were assessed by the investigators as unrelated to study drug. Two TEAEs leading to permanent discontinuation of the study drug were reported by 1 adolescent participant in the dupilumab 300 mg Q2W group (Congenital coronary artery malformation and Dyspnoea).

- **Part C**

➢ Participant from Part A

Table 50 Overall Summary of Number of Participants with TEAEs During Part C 28-Week Treatment Period (Part C SAF – Participants from Part A)

	Placebo / Dupilumab 300 mg QW (N=37)	Dupilumab 300 mg QW / Dupilumab 300 mg QW (N=40)	Total (N=77)
Any TEAE, n (%)	27 (73.0%)	24 (60.0%)	51 (66.2%)
Any drug related TEAE, n (%)	15 (40.5%)	8 (20.0%)	23 (29.9%)
Any TEAE leading to discontinuation of study drug permanently, n (%)	2 (5.4%)	0	2 (2.6%)
Maximum intensity for any TEAE, n (%)			
Mild	19 (51.4%)	17 (42.5%)	36 (46.8%)
Moderate	7 (18.9%)	6 (15.0%)	13 (16.9%)
Severe	1 (2.7%)	1 (2.5%)	2 (2.6%)
Any TEAE death, n (%)	0	0	0
Any TE SAE, n (%)	1 (2.7%)	0	1 (1.3%)
Any TE SAE leading to discontinuation of study drug permanently, n (%)	1 (2.7%)	0	1 (1.3%)

Abbreviations: QW=once weekly; SAE=serious adverse event; SAF=safety analysis set; TE=treatment-emergent; TEAE=treatment-emergent adverse event

Table 51 Overall Summary of Number of Participants with TEAEs During Part A/C Follow-Up Period to Data Cut-off (Part C SAF – Participants From Part A Who Entered Follow-Up After Part C)

	Placebo / Dupilumab 300 mg QW (N=23)	Dupilumab 300 mg QW / Dupilumab 300 mg QW (N=27)	Total (N=50)
Any TEAE, n (%)	4 (17.4%)	5 (18.5%)	9 (18.0%)
Any drug related TEAE, n (%)	0	1 (3.7%)	1 (2.0%)
Any TEAE leading to discontinuation of study drug permanently, n (%)	0	0	0
Maximum intensity for any TEAE, n (%)			
Mild	3 (13.0%)	4 (14.8%)	7 (14.0%)
Moderate	1 (4.3%)	1 (3.7%)	2 (4.0%)
Severe	0	0	0
Any TEAE death, n (%)	0	0	0
Any TE SAE, n (%)	0	0	0
Any TE SAE leading to discontinuation of study drug permanently, n (%)	0	0	0

Note: Table includes data up to data cutoff for Part A/C CSR (18 Nov 2020)
Abbreviations: CSR=clinical study report; QW=once weekly; SAE=serious adverse event; SAF=safety analysis set; TE=treatment-emergent; TEAE=treatment-emergent adverse event.

In the placebo/dupilumab 300 mg QW group, 73.0% of participants experienced a TEAE, and 40.5% experienced a drug-related TEAE. The corresponding proportions in the dupilumab 300 mg QW/dupilumab 300 mg QW group were 60.0% and 20.0%. The difference was largely due to a higher incidence of injection site reactions and related TEAEs in the placebo/dupilumab 300 mg QW group compared to the dupilumab 300 mg QW/dupilumab 300 mg QW group.

The General disorders and administration site conditions SOC had the highest proportion of participants with TEAEs (24 participants, 31.2%). 15 participants (40.5%) were in the placebo/dupilumab 300 mg QW group and 9 participants (22.5%) in the dupilumab 300 mg QW/dupilumab 300 mg QW group. The results were mainly driven by TEAEs of injection site reactions. The proportion of participants with TEAEs in the Infections and infestations SOC was 22.1% (17 participants) with 9 participants (24.3%) in the placebo/dupilumab 300 mg QW group and 8 participants (20.0%) in the dupilumab 300 mg QW/dupilumab 300 mg QW group. In the Skin and subcutaneous tissue disorders SOC the proportion of participants with TEAEs was 14.3% (11 participants).

In the 50 participants who entered the post-treatment follow-up period after participating in Part C of the study, 9 (18.0%) experienced TEAEs. All TEAEs were mild or moderate in intensity.

The most frequently reported PTs (in ≥5% of participants overall) during Part C were: Injection site reaction (15.6%), Injection site erythema (11.7%), Injection site pain (6.5%), Headache (6.5%), Nasopharyngitis (5.2%), Acne (5.2%), and Insomnia (5.2%). The proportion of participants with TEAEs in the Nervous system disorders and Psychiatric disorders SOC were 10.4% (8 participants) and 9.1% (7 participants), respectively.

Table 52 Summary of TEAEs Reported by ≥5% of Participants in any Treatment Group During Part C 28-Week Treatment Period by Primary SOC and PT (Part C SAF – Participants from Part A)

Primary System Organ Class Preferred Term	Placebo / Dupilumab 300 mg QW (N=37)	Dupilumab 300 mg QW / Dupilumab 300 mg QW (N=40)	Total (N=77)
Number of such events	115	126	241
Number of patients with at least one such event, n (%)	27 (73.0%)	24 (60.0%)	51 (66.2%)
General disorders and administration site conditions	15 (40.5%)	9 (22.5%)	24 (31.2%)
Injection site reaction	8 (21.6%)	4 (10.0%)	12 (15.6%)
Injection site erythema	5 (13.5%)	4 (10.0%)	9 (11.7%)
Injection site pain	3 (8.1%)	2 (5.0%)	5 (6.5%)
Injection site bruising	3 (8.1%)	0	3 (3.9%)
Injection site oedema	1 (2.7%)	2 (5.0%)	3 (3.9%)
Injection site swelling	0	2 (5.0%)	2 (2.6%)
Infections and infestations	9 (24.3%)	8 (20.0%)	17 (22.1%)
Nasopharyngitis	3 (8.1%)	1 (2.5%)	4 (5.2%)
Upper respiratory tract infection	1 (2.7%)	2 (5.0%)	3 (3.9%)
Sinusitis	2 (5.4%)	0	2 (2.6%)
Gastrointestinal disorders	7 (18.9%)	6 (15.0%)	13 (16.9%)
Dyspepsia	2 (5.4%)	1 (2.5%)	3 (3.9%)
Vomiting	1 (2.7%)	2 (5.0%)	3 (3.9%)
Abdominal pain	0	2 (5.0%)	2 (2.6%)
Skin and subcutaneous tissue disorders	7 (18.9%)	4 (10.0%)	11 (14.3%)
Acne	4 (10.8%)	0	4 (5.2%)
Urticaria	2 (5.4%)	1 (2.5%)	3 (3.9%)
Injury, poisoning and procedural complications	3 (8.1%)	5 (12.5%)	8 (10.4%)
Foot fracture	1 (2.7%)	2 (5.0%)	3 (3.9%)
Animal bite	0	2 (5.0%)	2 (2.6%)

Nervous system disorders	4 (10.8%)	4 (10.0%)	8 (10.4%)
Headache	2 (5.4%)	3 (7.5%)	5 (6.5%)
Psychiatric disorders	4 (10.8%)	3 (7.5%)	7 (9.1%)
Insomnia	3 (8.1%)	1 (2.5%)	4 (5.2%)
Anxiety	2 (5.4%)	1 (2.5%)	3 (3.9%)
Respiratory, thoracic and mediastinal disorders	1 (2.7%)	4 (10.0%)	5 (6.5%)
Dyspnoea	0	2 (5.0%)	2 (2.6%)
Ear and labyrinth disorders	3 (8.1%)	0	3 (3.9%)
Vertigo	2 (5.4%)	0	2 (2.6%)
Vascular disorders	0	2 (5.0%)	2 (2.6%)
Hypertension	0	2 (5.0%)	2 (2.6%)

At each level of patient summarization, a patient is counted once if the patient reported one or more events.
MedDRA (Version 23.1) coding dictionary applied.
Sorted by decreasing frequency at all levels in treatment total group
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; QW=once weekly; SAF=safety analysis set; SOC=system organ class; TEAE=treatment-emergent adverse event.

In the placebo/dupilumab 300 mg QW group, 7 (77.8%) adolescent participants experienced a TEAE and 2 (22.2%) experienced a drug-related TEAE. The corresponding numbers and proportions in the dupilumab 300 mg QW/dupilumab 300 mg QW group were 8 (80.0%) and 4 (40.0%). The most frequently reported PTs (in ≥2 adolescent participants in either treatment group) during Part C were: Acne (4 participants; 44.4%) and Injection site reaction (2 participants; 22.2%) in the placebo/dupilumab 300 mg QW group and Injection site reaction (3 participants; 30.0%), and Injection site swelling, Foot fracture and Headache (all in 2 participants; 20.0%) in the dupilumab 300 mg QW/dupilumab 300 mg QW group.

- Participants from Part B

The MAH submitted additional safety data from participants who entered Part C from Part B.

Table 53 Overall Summary of Number of Adult Participants with TEAEs During Part B/C 28-week Treatment Period (Part C Safety Analysis Set - Participants from Part B)

	Placebo / Dupilumab 300 mg Q2W (N=22)	Placebo / Dupilumab 300 mg QW (N=27)	Placebo / Dupilumab (N=49)	Dupilumab 300 mg Q2W / Dupilumab 300 mg Q2W (N=53)	Dupilumab 300 mg QW / Dupilumab 300 mg QW (N=50)	Dupilumab Combined (N=103)	Total (N=152)
Any TEAE, n (%)	11 (50.0%)	16 (59.3%)	27 (55.1%)	38 (71.7%)	34 (68.0%)	72 (69.9%)	99 (65.1%)
Any drug related TEAE, n (%)	6 (27.3%)	6 (22.2%)	12 (24.5%)	17 (32.1%)	8 (16.0%)	25 (24.3%)	37 (24.3%)
Any TEAE leading to discontinuation of study drug permanently, n (%)	2 (9.1%)	0	2 (4.1%)	0	0	0	2 (1.3%)
Maximum intensity for any TEAE, n (%)							
Mild	6 (27.3%)	12 (44.4%)	18 (36.7%)	29 (54.7%)	23 (46.0%)	52 (50.5%)	70 (46.1%)
Moderate	5 (22.7%)	2 (7.4%)	7 (14.3%)	9 (17.0%)	11 (22.0%)	20 (19.4%)	27 (17.8%)
Severe	0	2 (7.4%)	2 (4.1%)	0	0	0	2 (1.3%)
Any TEAE death, n (%)	0	0	0	0	0	0	0
Any TE SAE, n (%)	0	2 (7.4%)	2 (4.1%)	0	2 (4.0%)	2 (1.9%)	4 (2.6%)
Any TE SAE leading to discontinuation of study drug permanently, n (%)	0	0	0	0	0	0	0

During the 28-week treatment period in Part C (for participants enrolling from Part B), the majority of TEAEs were mild or moderate in intensity. The proportion of participants who experienced a TEAE across the treatment groups ranged from 59.5% in the placebo/dupilumab 300 mg Q2W group to 70.9% in the dupilumab 300 mg Q2W/dupilumab 300 mg Q2W group. The proportions of participants experiencing a drug-related TEAE were higher in participants who received dupilumab 300 mg Q2W in Part B/C, regardless of the previous Part B treatment (32.4% in the placebo/dupilumab 300 mg Q2W group and 31.6% in the dupilumab 300 mg Q2W/dupilumab 300 mg Q2W group versus 18.9% in both treatment groups for participants receiving dupilumab 300 mg QW in Part B/C [i.e., in the placebo/dupilumab 300 mg QW and in the dupilumab 300 mg QW/dupilumab 300 mg QW groups]).

The most commonly affected system organ class (SOC) was General disorders and administration site conditions. Overall, the proportion of participants with TEAEs in this SOC was 30.3% (46/152 adult participants).

Table 54 Number of Adult Participants With Treatment-emergent Adverse Events (TEAE) by Primary System Organ Class and Preferred Term During Part C 28-week Treatment Period (Shortened)

Primary System Organ Class Preferred Term	Placebo / Dupilumab 300 mg Q2W (N=22)	Placebo / Dupilumab 300 mg QW (N=27)	Placebo / Dupilumab (N=49)	Dupilumab 300 mg Q2W / Dupilumab 300 mg Q2W (N=53)	Dupilumab 300 mg QW / Dupilumab 300 mg QW (N=50)	Dupilumab Combined (N=103)	Total (N=152)
Number of such events	62	68	130	191	171	362	492
Number of patients with at least one such event, n (%)	11 (50.0%)	16 (59.3%)	27 (55.1%)	38 (71.7%)	34 (68.0%)	72 (69.9%)	99 (65.1%)
General disorders and administration site conditions	4 (18.2%)	10 (37.0%)	14 (28.6%)	19 (35.8%)	13 (26.0%)	32 (31.1%)	46 (30.3%)
Injection site reaction	1 (4.5%)	3 (11.1%)	4 (8.2%)	8 (15.1%)	6 (12.0%)	14 (13.6%)	18 (11.8%)
Injection site erythema	1 (4.5%)	1 (3.7%)	2 (4.1%)	5 (9.4%)	4 (8.0%)	9 (8.7%)	11 (7.2%)
Injection site pain	1 (4.5%)	1 (3.7%)	2 (4.1%)	5 (9.4%)	4 (8.0%)	9 (8.7%)	11 (7.2%)
Injection site bruising	1 (4.5%)	1 (3.7%)	2 (4.1%)	1 (1.9%)	2 (4.0%)	3 (2.9%)	5 (3.3%)
Injection site oedema	0	2 (7.4%)	2 (4.1%)	2 (3.8%)	0	2 (1.9%)	4 (2.6%)
Injection site swelling	2 (9.1%)	0	2 (4.1%)	2 (3.8%)	0	2 (1.9%)	4 (2.6%)
Injection site pruritus	0	0	0	3 (5.7%)	0	3 (2.9%)	3 (2.0%)
Chills	0	0	0	2 (3.8%)	0	2 (1.9%)	2 (1.3%)
Fatigue	0	0	0	1 (1.9%)	1 (2.0%)	2 (1.9%)	2 (1.3%)
Injection site haematoma	0	1 (3.7%)	1 (2.0%)	1 (1.9%)	0	1 (1.0%)	2 (1.3%)
Injection site urticaria	0	0	0	2 (3.8%)	0	2 (1.9%)	2 (1.3%)
Malaise	0	1 (3.7%)	1 (2.0%)	0	1 (2.0%)	1 (1.0%)	2 (1.3%)
Pyrexia	0	0	0	1 (1.9%)	1 (2.0%)	2 (1.9%)	2 (1.3%)
Vaccination site pain	0	0	0	0	2 (4.0%)	2 (1.9%)	2 (1.3%)
Chest pain	0	0	0	0	1 (2.0%)	1 (1.0%)	1 (0.7%)
Influenza like illness	0	0	0	1 (1.9%)	0	1 (1.0%)	1 (0.7%)
Injection site haemorrhage	0	0	0	1 (1.9%)	0	1 (1.0%)	1 (0.7%)
General disorders and administration site conditions							
Injection site mass	0	0	0	0	1 (2.0%)	1 (1.0%)	1 (0.7%)
Injection site rash	0	0	0	0	1 (2.0%)	1 (1.0%)	1 (0.7%)
Vaccination site reaction	0	1 (3.7%)	1 (2.0%)	0	0	0	1 (0.7%)
Infections and infestations	2 (9.1%)	9 (33.3%)	11 (22.4%)	11 (20.8%)	15 (30.0%)	26 (25.2%)	37 (24.3%)
COVID-19	0	3 (11.1%)	3 (6.1%)	5 (9.4%)	6 (12.0%)	11 (10.7%)	14 (9.2%)
Nasopharyngitis	0	3 (11.1%)	3 (6.1%)	1 (1.9%)	2 (4.0%)	3 (2.9%)	6 (3.9%)
Urinary tract infection	0	0	0	0	4 (8.0%)	4 (3.9%)	4 (2.6%)
Kidney infection	0	0	0	2 (3.8%)	0	2 (1.9%)	2 (1.3%)
Pneumonia	1 (4.5%)	1 (3.7%)	2 (4.1%)	0	0	0	2 (1.3%)
Acute sinusitis	1 (4.5%)	0	1 (2.0%)	0	0	0	1 (0.7%)
Cellulitis	0	1 (3.7%)	1 (2.0%)	0	0	0	1 (0.7%)
Enterocolitis infectious	0	0	0	0	1 (2.0%)	1 (1.0%)	1 (0.7%)
Folliculitis	0	0	0	1 (1.9%)	0	1 (1.0%)	1 (0.7%)
Gastroenteritis	0	1 (3.7%)	1 (2.0%)	0	0	0	1 (0.7%)
Gastrointestinal viral infection	0	0	0	0	1 (2.0%)	1 (1.0%)	1 (0.7%)
Gingival abscess	0	0	0	0	1 (2.0%)	1 (1.0%)	1 (0.7%)
Helicobacter gastritis	0	0	0	1 (1.9%)	0	1 (1.0%)	1 (0.7%)
Helicobacter infection	0	0	0	0	1 (2.0%)	1 (1.0%)	1 (0.7%)
Hordeolum	0	0	0	0	1 (2.0%)	1 (1.0%)	1 (0.7%)
Influenza	0	0	0	1 (1.9%)	0	1 (1.0%)	1 (0.7%)
Oesophageal candidiasis	0	1 (3.7%)	1 (2.0%)	0	0	0	1 (0.7%)
Infections and infestations							
Pharyngitis streptococcal	0	1 (3.7%)	1 (2.0%)	0	0	0	1 (0.7%)
Sinusitis	0	0	0	1 (1.9%)	0	1 (1.0%)	1 (0.7%)
Tooth infection	0	0	0	0	1 (2.0%)	1 (1.0%)	1 (0.7%)
Upper respiratory tract infection	0	0	0	0	1 (2.0%)	1 (1.0%)	1 (0.7%)
Gastrointestinal disorders	3 (13.6%)	6 (22.2%)	9 (18.4%)	7 (13.2%)	3 (6.0%)	10 (9.7%)	19 (12.5%)
Vomiting	0	2 (7.4%)	2 (4.1%)	2 (3.8%)	1 (2.0%)	3 (2.9%)	5 (3.3%)
Dysphagia	1 (4.5%)	0	1 (2.0%)	2 (3.8%)	1 (2.0%)	3 (2.9%)	4 (2.6%)
Diarrhoea	1 (4.5%)	1 (3.7%)	2 (4.1%)	1 (1.9%)	0	1 (1.0%)	3 (2.0%)
Dyspepsia	0	2 (7.4%)	2 (4.1%)	0	1 (2.0%)	1 (1.0%)	3 (2.0%)
Nausea	1 (4.5%)	1 (3.7%)	2 (4.1%)	1 (1.9%)	0	1 (1.0%)	3 (2.0%)
Abdominal discomfort	0	0	0	1 (1.9%)	0	1 (1.0%)	1 (0.7%)
Abdominal pain upper	0	0	0	1 (1.9%)	0	1 (1.0%)	1 (0.7%)
Flatulence	0	0	0	1 (1.9%)	0	1 (1.0%)	1 (0.7%)
Gastritis erosive	1 (4.5%)	0	1 (2.0%)	0	0	0	1 (0.7%)
Gastrooesophageal reflux disease	0	1 (3.7%)	1 (2.0%)	0	0	0	1 (0.7%)
Large intestine polyp	1 (4.5%)	0	1 (2.0%)	0	0	0	1 (0.7%)
Lip swelling	0	0	0	1 (1.9%)	0	1 (1.0%)	1 (0.7%)
Oesophagitis	0	1 (3.7%)	1 (2.0%)	0	0	0	1 (0.7%)
Injury, poisoning and procedural complications	2 (9.1%)	2 (7.4%)	4 (8.2%)	5 (9.4%)	4 (8.0%)	9 (8.7%)	13 (8.6%)
Vaccination complication	0	1 (3.7%)	1 (2.0%)	2 (3.8%)	2 (4.0%)	4 (3.9%)	5 (3.3%)

Injury, poisoning and procedural complications							
Abdominal injury	0	0	0	0	1 (2.0%)	1 (1.0%)	1 (0.7%)
Arthropod bite	0	0	0	1 (1.9%)	0	1 (1.0%)	1 (0.7%)
Arthropod sting	0	0	0	0	1 (2.0%)	1 (1.0%)	1 (0.7%)
Contusion	1 (4.5%)	0	1 (2.0%)	0	0	0	1 (0.7%)
Joint injury	1 (4.5%)	0	1 (2.0%)	0	0	0	1 (0.7%)
Post procedural complication	0	1 (3.7%)	1 (2.0%)	0	0	0	1 (0.7%)
Procedural pain	0	0	0	1 (1.9%)	0	1 (1.0%)	1 (0.7%)
Tooth fracture	0	0	0	1 (1.9%)	0	1 (1.0%)	1 (0.7%)
Musculoskeletal and connective tissue disorders	2 (9.1%)	2 (7.4%)	4 (8.2%)	4 (7.5%)	4 (8.0%)	8 (7.8%)	12 (7.9%)
Arthralgia	0	1 (3.7%)	1 (2.0%)	0	3 (6.0%)	3 (2.9%)	4 (2.6%)
Back pain	0	0	0	2 (3.8%)	0	2 (1.9%)	2 (1.3%)
Intervertebral disc protrusion	1 (4.5%)	0	1 (2.0%)	0	0	0	1 (0.7%)
Joint noise	1 (4.5%)	0	1 (2.0%)	0	0	0	1 (0.7%)
Myalgia	0	1 (3.7%)	1 (2.0%)	0	0	0	1 (0.7%)
Osteoarthritis	0	0	0	0	1 (2.0%)	1 (1.0%)	1 (0.7%)
Synovial cyst	0	0	0	1 (1.9%)	0	1 (1.0%)	1 (0.7%)
Temporomandibular joint syndrome	0	0	0	1 (1.9%)	0	1 (1.0%)	1 (0.7%)
Skin and subcutaneous tissue disorders	1 (4.5%)	1 (3.7%)	2 (4.1%)	4 (7.5%)	5 (10.0%)	9 (8.7%)	11 (7.2%)
Eczema	0	0	0	2 (3.8%)	1 (2.0%)	3 (2.9%)	3 (2.0%)

No deaths were reported during Part C. The number of participants reporting treatment-emergent SAEs was low (2.2%) and no SAE was reported by more than 1 participant. The number of participants reporting a TEAE leading to permanent dose withdrawal was low (0.9%) with no PT reported by more than 1 participant.

One participant in the placebo/dupilumab 300 mg Q2W group (0.4%) reported 3 events of (PT) "Anaphylactic reaction". This participant had a history of multiple food allergies (seafood, milk, egg, peanuts/tree nuts, wheat, and banana). The events occurred after eating salmon, wheat and tahini and were reported as not related to the study drug by the Investigator, action taken with study drug reported as dose not changed, and outcome reported as recovered/resolved. There were no events reported under (HLT) "Anaphylactic and anaphylactoid responses" for the QW dose groups.

During the Part B/C treatment period, 7.9% of the participants had a TEAE of COVID-19. All were non-serious, and the majority were mild/moderate in intensity. One event of severe intensity was reported. None of the TEAEs of COVID-19 led to discontinuation of study drug and all events resolved. The event of severe intensity, 3 events of moderate intensity and 1 event of mild intensity led to temporary interruption of study drug. All TEAEs of COVID-19 were assessed as not related to study drug by the investigator. The event of severe intensity occurred in a 14-year-old female participant in the dupilumab 300 mg Q2W/dupilumab 300 mg Q2W group. The COVID-19 events were reported from 22 October 2020 to 23 January 2022, an exposure period occurring during a global pandemic involving the highly infectious DELTA and later OMICRON variants of COVID-19.

The most frequently reported TEAEs (in ≥5% of participants overall) were Injection site reaction (ISR), Injection site pain, Injection site erythema and COVID-19. None of the ISRs led to treatment discontinuation. The frequency of ISRs (at HLT level) was either similar or lower for QW dosing as compared to Q2W during the 28-week of Part B/C and was lower than the 24-week treatment period of Part B combined dupilumab arm (46.0%) and dupilumab 300 mg QW (37.5%). This indicates that the incidence of ISRs is not increasing with continued dosing over 52 weeks.

Safety in the Adolescent Participants in Study Part B/C at Week 52:

Overall, treatment-emergent adverse events (TEAEs) were reported in 70.7% of adolescent participants during the treatment period in Part B/C. This was similar to the adult population where TEAEs were reported in 65.1% of adult participants during the treatment period in Part B/C. The proportion of adolescent participants who experienced a TEAE was similar across the treatment groups, ranging from 69.2% (18/26) in the dupilumab 300 mg Q2W/dupilumab 300 mg Q2W group, 70.0% (7/10) in the placebo/dupilumab 300 mg QW group, 70.8% (17/24) in the dupilumab 300 mg QW/dupilumab 300 mg QW group, to 73.3% (11/15) in the placebo/dupilumab 300 mg Q2W group.

Table 55 Overall Summary of Number of Adolescent Participants with TEAEs During Part B/C 28-week Treatment Period (Part C Safety Analysis Set - Participants from Part B)

	Placebo / Dupilumab 300 mg Q2W (N=15)	Placebo / Dupilumab 300 mg QW (N=10)	Placebo / Dupilumab (N=25)	Dupilumab 300 mg Q2W / Dupilumab 300 mg Q2W (N=26)	Dupilumab 300 mg QW / Dupilumab 300 mg QW (N=24)	Dupilumab Combined (N=50)	Total (N=75)
Any TEAE, n (%)	11 (73.3%)	7 (70.0%)	18 (72.0%)	18 (69.2%)	17 (70.8%)	35 (70.0%)	53 (70.7%)
Any drug related TEAE, n (%)	6 (40.0%)	1 (10.0%)	7 (28.0%)	8 (30.8%)	6 (25.0%)	14 (28.0%)	21 (28.0%)
Any TEAE leading to discontinuation of study drug permanently, n (%)	0	0	0	0	0	0	0
Maximum intensity for any TEAE, n (%)							
Mild	2 (13.3%)	5 (50.0%)	7 (28.0%)	13 (50.0%)	9 (37.5%)	22 (44.0%)	29 (38.7%)
Moderate	9 (60.0%)	2 (20.0%)	11 (44.0%)	4 (15.4%)	7 (29.2%)	11 (22.0%)	22 (29.3%)
Severe	0	0	0	1 (3.8%)	1 (4.2%)	2 (4.0%)	2 (2.7%)
Any TEAE death, n (%)	0	0	0	0	0	0	0
Any TE SAE, n (%)	0	0	0	0	1 (4.2%)	1 (2.0%)	1 (1.3%)
Any TE SAE leading to discontinuation of study drug permanently, n (%)	0	0	0	0	0	0	0

The majority of TEAEs in both adolescents and adults were mild in intensity. The most commonly affected system organ class (SOC) in both adolescents and adults was General disorders and administration site conditions. Overall, the proportion of adolescent participants with TEAEs in this SOC was 33.3% (25/75 adolescent participants). The number of adolescent participants with TEAEs in this SOC were similar across the treatment groups, except for the placebo/dupilumab 300 mg QW group which had the lowest incidence (20.0%). This SOC incidence in adolescent participants was mostly driven by various injection site reaction preferred terms (PTs) including injection site reaction (17.3%), injection site pain (10.7%), injection site erythema (5.3%) and injection site swelling (5.3%). Further SOCs were Infections and infestations (29.3%) and Gastrointestinal disorders (26.7%). In both SOCs, no individual PTs were identified driving the incidences. Common TEAEs in the Infections and infestations SOC reported were COVID-19 (5.3%), nasopharyngitis (5.3%) and upper respiratory tract infections (4.0%). The majority of these TEAEs were of mild to moderate severity. All TEAEs in the SOC Infections and infestations were considered not related by the investigator. The most common TEAEs in the Gastrointestinal disorders SOC were abdominal pain (5.3%), nausea (5.3%), and dysphagia (4.0%).

Serious adverse event/deaths/other significant events

Serious adverse event

- **Part A**

Table 56 Summary of Serious TEAEs by SOC and PT – (Part A SAF) Cut-off date 08 May 2020

Primary System Organ Class Preferred Term	Placebo (N=39)	Dupilumab 300 mg QW (N=42)
Number of such events	0	2
Number of patients with at least one such event, n (%)	0	2 (4.8%)
Gastrointestinal disorders	0	1 (2.4%)
Abdominal pain	0	1 (2.4%)
Reproductive system and breast disorders	0	1 (2.4%)
Uterine polyp	0	1 (2.4%)

At each level of patient summarization, a patient is counted once if the patient reported one or more events.
MedDRA (Version 23.0) coding dictionary applied.
Sorted by decreasing frequency at all levels in the dupilumab group.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT= preferred term; QW=once weekly; SAF=safety analysis set; SOC= system organ class; TEAE=treatment-emergent adverse event.

Two participants in the dupilumab 300 mg QW group and one in the placebo group reported an SAE in Part A. (including data through 20 May 2020)

- One participant in the dupilumab 300 mg QW group had one event of Abdominal Pain. This participant had colonic polyps which were removed a few days prior to the pain. The event was assessed as not related to study drug.
- Another participant in the dupilumab 300 mg QW group had one event of Uterine Polyp. Relevant medical history for this participant included uterine polyp. This participant underwent a sub-total abdominal hysterectomy 17 days after the diagnosis of worsening uterine polyp. The event was assessed as not related to study drug.
- One participant in the placebo group, developed an SAE of Suicidal ideation. This event was not included in the Part A CSR as the categorization to serious was only identified by the study monitor at a later date. The event was of moderate intensity and was not considered related to study drug. The participant had concurrent Depression. The event of Suicidal ideation started on study day 109 and resolved on study day 313. The treatment with study drug was not discontinued.

- **Part B**

Table 57 Summary of Serious TEAEs by SOC and PT (Part B SAF)

		Dupilumab		
Primary System Organ Class Preferred Term	Placebo (N=78)	300 mg Q2W (N=81)	300 mg QW (N=80)	Combined (N=161)
Number of such events	1	1	5	6
Number of patients with at least one such event, n (%)	1 (1.3%)	1 (1.2%)	5 (6.3%)	6 (3.7%)
Psychiatric disorders	1 (1.3%)	1 (1.2%)	1 (1.3%)	2 (1.2%)
Depression suicidal	0	0	1 (1.3%)	1 (0.6%)
Suicidal ideation	0	1 (1.2%)	0	1 (0.6%)
Mental status changes	1 (1.3%)	0	0	0
Infections and infestations	0	0	1 (1.3%)	1 (0.6%)
Campylobacter colitis	0	0	1 (1.3%)	1 (0.6%)
Investigations	0	0	1 (1.3%)	1 (0.6%)
Blood creatine phosphokinase abnormal	0	0	1 (1.3%)	1 (0.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (1.3%)	1 (0.6%)
Breast cancer	0	0	1 (1.3%)	1 (0.6%)
Respiratory, thoracic and mediastinal disorders	0	0	1 (1.3%)	1 (0.6%)
Pneumonia aspiration	0	0	1 (1.3%)	1 (0.6%)

At each level of patient summarization, a patient is counted once if the patient reported one or more events.
MedDRA (Version 24.0) coding dictionary applied.
Sorted by decreasing frequency at all levels in the combined dupilumab group.
Abbreviations: PT=preferred term; Q2W=every 2 weeks; QW=once weekly; SAF=safety analysis set; SOC=system organ class; TEAE=treatment-emergent adverse event.

Five participants in the dupilumab 300 mg QW group, one participant in the dupilumab 300 mg Q2W group, and one in the placebo group had a treatment-emergent SAE in the Part B SAE. All were assessed as not related to study drug.

In the dupilumab 300 mg QW group, one participant each had an SAE of Depression suicidal (14 y /severe; resolving), Campylobacter colitis (16 y/ moderate; resolved), Blood creatine phosphokinase abnormal (16-y/ moderate; resolved), Breast cancer (39 y/ severe; not resolved) and Pneumonia aspiration (15 y/ severe; resolved).

In the dupilumab 300 mg Q2W group, one participant (14 y) had a mild SAE of Suicidal ideation following bullying at school.

In the placebo group, one participant had a severe SAE of Mental status changes (19y/ resolved).

The 2 participants in the dupilumab groups both had a history of psychiatric illness.

- **Part C**

Participants from Part A (Part A/C)

One participant in the placebo/dupilumab 300 mg QW group and none in the dupilumab 300 mg QW/dupilumab 300 mg QW group had a treatment-emergent SAE during the Part C treatment period.

This participant was in the placebo/dupilumab 300 mg QW group and had a treatment-emergent SAE of Systemic inflammatory response syndrome that started at study day 237, approximately 10 to 12 hours after the most recent dose of dupilumab. The participant (24 y) had a prior medical history of asthma induced by exercise and food and other allergies and experienced severe shortness of breath and diaphoresis. At the emergency room, the vital signs were within the normal range, oxygen saturation was 100% but laboratory tests showed increased WBC count (30,000 cells/cubic millimeter with 7% of bands). After further exploration no obvious source of infection could be identified. The participant was treated with two different IV antibiotics during the overnight hospitalization and had no further episodes of acute shortness of breath. The participant was discharged the next day with a decreased WBC count of 16,000 cells/cubic milliliter treatment and with the presumptive diagnosis of "shortness of breath due to asthma and seasonal allergies". The event resulted in withdrawal of the study drug and was considered related to the study drug by the investigator due to the temporal relationship to the previous dose. The event was considered severe in intensity and resolved on study day 257.

Participants from Part B (Part B/C)

The proportion of participants with serious adverse events (SAEs) in Part C for participants entering from Part B was low with 1 adolescent participant (1.3%) reporting a SAE in the dupilumab 300 mg QW/dupilumab 300 mg QW group (PTs: diarrhoea and rectal tenesmus, serious criteria for both was hospitalization). Both PTs were assessed as not related to study drug by the Investigator. There were no TEAEs in the adolescent participants that led to permanent discontinuation of study drug.

Other significant events

- **Part A**

Adverse Events of Special Interest

Two participants experienced events of Arthralgia during Part A.

- One participant in the dupilumab 300mg QW group, experienced 2 AESIs of Arthralgia: mild left shoulder pain on study day 68 and moderate right hip pain on study day 72. Both events resolved and were not considered related to study drug. Treatment with study drug continued.

- One participant (17 y) in the dupilumab group, experienced an AESI of Arthralgia (joint[s] not defined) that led to discontinuation of the study drug. The event started on study day 106, was of moderate intensity, and resolved on study day 122. The AESI was considered related to study drug.

Injection site reactions

Table 58 Summary of Injection Site Reaction by PT– (Part A SAF)

Preferred Term	Placebo (N=39)	Dupilumab 300 mg QW (N=42)
Number of such events	45	72
Number of patients with at least one such event, n (%)	12 (30.8%)	15 (35.7%)
Injection site reaction	4 (10.3%)	7 (16.7%)
Injection site pain	3 (7.7%)	4 (9.5%)
Injection site erythema	5 (12.8%)	3 (7.1%)
Injection site swelling	1 (2.6%)	3 (7.1%)
Injection site oedema	1 (2.6%)	2 (4.8%)
Injection site bruising	0	1 (2.4%)
Injection site haemorrhage	0	1 (2.4%)
Injection site pruritus	2 (5.1%)	1 (2.4%)
Injection site rash	0	1 (2.4%)
Injection site induration	1 (2.6%)	0
Injection site nodule	1 (2.6%)	0

At each level of patient summarization, a patient is counted once if the patient reported one or more events.
MedDRA (Version 23.0) coding dictionary applied.
Sorted by decreasing frequency at all levels in the dupilumab group.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT= preferred term; QW=once weekly; SAF=safety analysis set; TEAE=treatment-emergent adverse event.
Source: PTT 7.2.3.2/1A

Injection Site Reaction occurred at a higher frequency in the dupilumab 300 mg QW group (35.7%) than the placebo group (30.8%). None of these injection site reactions were serious or led to permanent discontinuation of study drug. All injection site reactions were assessed as mild or moderate in intensity. There were no severe injection site reactions and all resolved. Injection Site Erythema occurred at a higher frequency in the placebo group (≥5% higher) than the dupilumab 300 mg QW group.

Pregnancy

A pregnancy was reported in one participant in the placebo group, who had requested to withdraw from the study after completing Part A treatment. The pregnancy occurred within the 12-week follow-up period after the last dose and is included in the safety database, however, no data relating to the event were included in the clinical database.

- **Part B**

Adverse Events of Special Interest

The most common type of AESI was herpes simplex infection reported in 3 participants in the dupilumab 300 mg QW group, 1 participant in the dupilumab 300 mg Q2W group, and 1 in the placebo group. Local herpes simplex infections are a known ADR associated with dupilumab use and are described in the product labelling. The other AESI categories reported were arthralgia and systemic hypersensitivity reactions, both reported in 1 participant in the dupilumab 300 mg QW group and 1 in the placebo group.

Table 59 Summary of TEAEs of Special Interest by SOC, HLT, and PT (Part B SAF)

AESI Category High Level Term Preferred Term	Placebo (N=78)	Dupilumab 300 mg Q2W (N=81)	Dupilumab 300 mg QW (N=80)	Dupilumab Combined (N=161)
Number of such events	4	1	6	7
Number of patients with at least one such event, n (%)	3 (3.8%)	1 (1.2%)	5 (6.3%)	6 (3.7%)
Herpes simplex infection	1 (1.3%)	1 (1.2%)	3 (3.8%)	4 (2.5%)
Herpes viral infections	1 (1.3%)	1 (1.2%)	3 (3.8%)	4 (2.5%)
Herpes simplex	0	0	2 (2.5%)	2 (1.2%)
Oral herpes	1 (1.3%)	1 (1.2%)	1 (1.3%)	2 (1.2%)
Arthralgia	1 (1.3%)	0	1 (1.3%)	1 (0.6%)
Joint related signs and symptoms	1 (1.3%)	0	1 (1.3%)	1 (0.6%)
Arthralgia	1 (1.3%)	0	1 (1.3%)	1 (0.6%)
Systemic hypersensitivity reactions	1 (1.3%)	0	1 (1.3%)	1 (0.6%)
Injection site reactions	0	0	1 (1.3%)	1 (0.6%)
Injection site hypersensitivity	0	0	1 (1.3%)	1 (0.6%)
Allergic conditions NEC	1 (1.3%)	0	0	0
Hypersensitivity	1 (1.3%)	0	0	0

MedDRA (Version 24.0) coding dictionary applied.
Sorted by decreasing frequency at all levels in the combined dupilumab group.
Abbreviations: AESI=adverse event of special interest; HLT=high-level term; NEC=not elsewhere classified; PT=preferred term; Q2W=every 2 weeks; QW=once weekly; SAF=safety analysis set; SOC=system organ class; TEAE=treatment-emergent adverse event.

Five participants in the dupilumab 300 mg QW group, 1 participant in the dupilumab 300 mg Q2W group, and 3 in the placebo group had an AESI during Part B of the study.

In the dupilumab 300 mg QW:

- One participant had a moderate event of Herpes simplex, assessed by the investigator as related to study drug, started on study 127 and resolved on study day 135 without treatment. This participant also had an SAE of Campylobacter colitis.
- Another participant, with a history of herpes simplex infections, had an event of Herpes simplex that was mild and assessed as not related. It started on study day 45 and was resolving on treatment with aciclovir.
- One participant had 2 separate AESIs reported as Oral herpes. The first was mild, assessed as related to study drug, started on study day 3 and resolved without treatment on study day 7. The second was moderate, assessed as not related, started on study day 73, and resolved without treatment on study day 76. This participant had no relevant medical history.
- One participant had an AESI of moderate Arthralgia that was assessed as not related. The event started on study day 133 and resolved without treatment on study day 149. The participant had a concurrent TEAE of moderate Pyrexia, accompanied by muscle aches, sore ankles and knees and stiffness and pain in joints. No relevant medical history was reported.
- One participant had an AESI of moderate Injection site hypersensitivity that was assessed as related to study drug. The event started on study day 11 with an erythematous, mildly itchy area at the injection site. On study day 12, a second erythematous area was noted, and the following day the participant had low grade fever, chills, malaise, and fatigue. The

participant was administered oral cefalexin, fexofenadine, and paracetamol and topical hydrocortisone and the event resolved on study day 16. This event led to temporary interruption of the study drug. The next dose was delayed until study day 36. Dosing then continued through to the end of treatment visit at week 24. On study day 8, the participant had a mild Injection site reaction that resolved the same day. The participant had a positive ADA result on study day 84, with a transient low titer of 480 and a negative result at week 24. The participant had multiple mild injection site reactions, all of which resolved within 24 hours. The AESI was classified as a systemic hypersensitivity reaction due to the systemic symptoms.

In the dupilumab 300 mg Q2W group:

- One participant had an AESI of mild Oral herpes starting on study day 2 that resolved on study day 25 following drug therapy and was assessed by the investigator as related to study drug. Study drug was continued. Relevant medical history included recurrent herpes simplex on the lip. The participant received ongoing intermittent treatment for oral herpes simplex with valaciclovir, which started approximately 7 years prior to joining the study. This participant also had a TEAE of Rhabdomyolysis that led to permanent discontinuation of study drug on study day 120.

In the placebo group:

- One participant had a moderate AESI of Oral herpes (outcome: resolved) that was assessed as related to study drug. This event led to permanent discontinuation of study drug.
- One participant had 2 concurrent AESIs of mild Arthralgia starting on study day 210 that were assessed as not related to study drug, and were ongoing at the last assessment. Relevant medical history included mild muscular dystrophy, genu valgum, and pes planus. The participant discontinued from the study on study day 289 for reasons unrelated to the AESIs.
- One participant had a severe AESI of Hypersensitivity on study day 93 (week 13) that was assessed as related to study drug and resolved the same day without drug therapy. The TEAE occurred 90 minutes after the fourteenth dose of study drug, with symptoms of redness around the injection site and vomiting. The participant also had mild TEAEs of Fatigue and Palpitations on the same day as the AESI that were also assessed as related to study drug. Dosing of study drug continued through week 24. The participant was ADA negative. The AESI was classified as a systemic hypersensitivity reaction.

None of the AESIs were considered to be SAEs.

Two of the AESIs were reported in adolescent participants: an AESI of Herpes simplex in the dupilumab 300 mg QW group, and Arthralgia in the placebo group. All other AESIs were reported in adult participants.

Table 60 Summary of Participants with Broad Conjunctivitis by PT During Part B 24-week Treatment Period (Part B SAF)

Preferred Term	Placebo (N=78)	Dupilumab 300 mg Q2W (N=81)	Dupilumab 300 mg QW (N=80)	Dupilumab Combined (N=161)
Number of such events	7	9	5	14
Number of patients with at least one such event, n (%)	6 (7.7%)	6 (7.4%)	5 (6.3%)	11 (6.8%)
Dry eye	2 (2.6%)	2 (2.5%)	2 (2.5%)	4 (2.5%)
Conjunctivitis	1 (1.3%)	3 (3.7%)	0	3 (1.9%)
Eye discharge	0	0	1 (1.3%)	1 (0.6%)
Eye irritation	0	1 (1.2%)	0	1 (0.6%)
Eye pruritus	2 (2.6%)	0	1 (1.3%)	1 (0.6%)
Lacrimation increased	2 (2.6%)	0	1 (1.3%)	1 (0.6%)
Ocular hyperaemia	0	1 (1.2%)	0	1 (0.6%)

At each level of patient summarization, a patient is counted once if the patient reported one or more events.
MedDRA (Version 24.0) coding dictionary applied.
Sorted by decreasing frequency at all levels in the combined dupilumab group
Broad conjunctivitis CMQ search included 16 PTs: Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic Keratoconjunctivitis, Blepharitis, Dry eye, Eye irritation, Eye pruritus, Lacrimation increased, Eye discharge, Foreign body sensation in eyes, Photophobia, Ocular hyperaemia, Conjunctival hyperaemia, Xerophthalmia
Abbreviations: CMQ=customized MedDRA query; MedDRA=Medical Dictionary for Regulatory Activities; Q2W=every 2 weeks; QW=once weekly; SAF=safety analysis set.

Injection Site Reactions

Injection site reactions were reported in a significant higher proportion of participants in the dupilumab 300 mg Q2W (54.3%) group than in the dupilumab 300 mg QW (37.5%) and placebo (33.3%) groups. Of note, the dupilumab 300 mg Q2W group received placebo injections every other week, so all participants in the study received weekly injections. All injection site reactions were assessed as mild or moderate in intensity. None of these injection site reactions were serious and none led to permanent discontinuation of study drug. One injection site reaction in the dupilumab 300 mg QW group was classified as an AESI and led to temporary interruption of the study drug (see above).

Table 61 Summary of Injection Site Reactions by Preferred Term During the Part B 24-week Treatment Period (Part B SAF)

Preferred Term	Placebo (N=78)	Dupilumab 300 mg Q2W (N=81)	Dupilumab 300 mg QW (N=80)	Dupilumab Combined (N=161)
Number of such events	164	259	191	450
Number of patients with at least one such event, n (%)	26 (33.3%)	44 (54.3%)	30 (37.5%)	74 (46.0%)
Injection site reaction	16 (20.5%)	18 (22.2%)	16 (20.0%)	34 (21.1%)
Injection site erythema	9 (11.5%)	18 (22.2%)	8 (10.0%)	26 (16.1%)
Injection site pain	4 (5.1%)	10 (12.3%)	7 (8.8%)	17 (10.6%)
Injection site swelling	2 (2.6%)	7 (8.6%)	10 (12.5%)	17 (10.6%)
Injection site bruising	0	6 (7.4%)	0	6 (3.7%)
Injection site urticaria	2 (2.6%)	6 (7.4%)	0	6 (3.7%)
Injection site pruritus	3 (3.8%)	1 (1.2%)	4 (5.0%)	5 (3.1%)
Injection site oedema	3 (3.8%)	4 (4.9%)	0	4 (2.5%)
Injection site haemorrhage	1 (1.3%)	2 (2.5%)	1 (1.3%)	3 (1.9%)
Injection site mass	1 (1.3%)	0	2 (2.5%)	2 (1.2%)
Injection site discolouration	0	1 (1.2%)	0	1 (0.6%)
Injection site haematoma	0	1 (1.2%)	0	1 (0.6%)
Injection site hypersensitivity	0	0	1 (1.3%)	1 (0.6%)
Injection site inflammation	1 (1.3%)	1 (1.2%)	0	1 (0.6%)
Injection site nodule	0	1 (1.2%)	0	1 (0.6%)
Injection site rash	1 (1.3%)	0	1 (1.3%)	1 (0.6%)
Injection site extravasation	1 (1.3%)	0	0	0

At each level of patient summarization, a patient is counted once if the patient reported one or more events.
MedDRA (Version 24.0) coding dictionary applied.
Sorted by decreasing frequency at all levels in the combined dupilumab group.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; Q2W=every 2 weeks; QW=once weekly; SAF=safety analysis set.

Infections and infestations

In the Infections and infestations SOC, the incidence of TEAEs was numerically higher in the dupilumab groups (30.0% in the dupilumab 300 mg QW group and 32.1% in the dupilumab 300 mg Q2W group) than in the placebo group (23.1%). The pattern of TEAEs within the Infections and infestations SOC was closely examined to determine if there was an association of TEAEs of infections with dupilumab use. (For more details on AEs in the Infections and infestations SOC see Section Adverse Events for Part B)

In the HLT Viral infections Not elsewhere classified (NEC), the incidence of TEAEs was 5.0% in the dupilumab 300 mg QW group, 4.9% in the dupilumab 300 mg Q2W group, and 1.3% in the placebo group. The higher incidence in the dupilumab groups was mainly driven by Gastroenteritis viral (3.8% in the dupilumab 300 mg QW group and 1.2% in the dupilumab 300 mg Q2W group versus 0% in the placebo group). All TEAEs of Gastroenteritis viral resolved, 3 were mild and 1 was moderate in intensity, and all were assessed as not related to study drug by the investigator.

The reported TEAEs were reviewed for any indication of an increased susceptibility to local infections of the esophagus. There was 1 event of Esophageal candidiasis:

One participant (16 years old) in the dupilumab 300 mg QW group, had a non-serious, mild TEAE of Esophageal candidiasis that began on study day 1 and resolved on day 176. The participant initially received a 14-day course of oral fluconazole. The participant had previously received swallowed topical/systemic corticosteroids for approximately 7 years until 2 months before screening for this study and started treatment with a PPI (lansoprazole) approximately 2.5 months before screening. The participant continued study drug, completed Part B, and entered Part C. The event was assessed as not related to study drug.

- **Part C**

Adverse Events of Special Interest

Two participants in the placebo/dupilumab 300 mg QW group and 1 in the dupilumab 300 mg QW/dupilumab 300 mg QW group had treatment-emergent AESIs during Part C of the study.

- One participant in the placebo/dupilumab 300 mg QW group had a treatment-emergent AESI of Arthralgia.
- The second participant in the placebo/dupilumab 300 mg QW group with multiple atopic comorbidities had a treatment-emergent AESI of Vernal keratoconjunctivitis of moderate intensity that started 132 days after starting dupilumab. The participant received treatment with topical eye drops: olopatadine (study day 297 through 319), followed by prednisone acetate (study day 319 through 339). This event was assessed by the investigator as related to study drug. The event resolved on study day 339. Treatment with study drug was continued. This AESI was categorized as a systemic hypersensitivity reaction and as keratitis.
- One participant in the dupilumab 300 mg QW/dupilumab 300 mg QW group with a history of multiple food allergies, other allergies, asthma, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, chronic rhinosinusitis and urticaria, had 2 treatment-emergent AESIs of Anaphylactic reaction and Anaphylactic shock. The event of Anaphylactic reaction started on study day 267, 6 days after the week 37 dose of dupilumab, after eating food that the investigator thought had probably been contaminated with milk products. The participant experienced tongue, lip and face swelling, difficulty breathing, and face redness and was treated in the emergency room with intravenous corticosteroid, intramuscular EpiPen

(epinephrine) and was started on oral treatment with Zyrtec (cetirizine) and famotidine. After 5 hours the participant was sent home and on study day 270, the event was considered resolved and the treatment with famotidine and Zyrtec was discontinued. The event of Anaphylactic shock started on study day 317, 7 days after the week 44 dose of dupilumab, after ingestion of an energy drink. The participant developed nausea and had multiple vomiting episodes but no systemic symptoms. Approximately 6 hours later, the participant developed congestion and shortness of breath, which led to Anaphylactic shock. The participant started treatment with prednisone, Zyrtec (cetirizine) and Pepcid (famotidine) (study days 317 through 322), Benadryl (diphenhydramine) (study days 317 through 323), Sudafed (pseudoephedrine) (study days 318 through 320), Flonase (fluticasone propionate) (study days 322 through 323) and oral Allegra (fexofenadine) (study days 325 through 334). On study day 334, the event Anaphylactic shock was considered resolved. Both events were severe in intensity and assessed by the investigator as not related to study drug and gave cross-contaminated food and the energy drink, respectively, as suspected causes. In both cases, treatment with study drug was not discontinued.

Table 62 Summary of Treatment-Emergent AESIs Reported by Participants in any Treatment Group during Part C 28-Week Treatment Period by AESI Category, High Level Term, and PT (Part C SAF – Participants from Part A)

AESI Category High Level Term Preferred Term	Placebo / Dupilumab 300 mg QW (N=37)	Dupilumab 300 mg QW / Dupilumab 300 mg QW (N=40)	Total (N=77)
Number of patients with at least one such event, n (%)	2 (5.4%)	1 (2.5%)	3 (3.9%)
Systemic hypersensitivity reactions	1 (2.7%)	1 (2.5%)	2 (2.6%)
Anaphylactic and anaphylactoid responses	0	1 (2.5%)	1 (1.3%)
Anaphylactic reaction	0	1 (2.5%)	1 (1.3%)
Anaphylactic shock	0	1 (2.5%)	1 (1.3%)
Corneal infections, oedemas and inflammations	1 (2.7%)	0	1 (1.3%)
Vernal keratoconjunctivitis	1 (2.7%)	0	1 (1.3%)
Anaphylactic reactions	0	1 (2.5%)	1 (1.3%)
Anaphylactic and anaphylactoid responses	0	1 (2.5%)	1 (1.3%)
Anaphylactic reaction	0	1 (2.5%)	1 (1.3%)
Anaphylactic shock	0	1 (2.5%)	1 (1.3%)
Arthralgia	1 (2.7%)	0	1 (1.3%)
Joint related signs and symptoms	1 (2.7%)	0	1 (1.3%)
Arthralgia	1 (2.7%)	0	1 (1.3%)
Keratitis	1 (2.7%)	0	1 (1.3%)
Corneal infections, oedemas and inflammations	1 (2.7%)	0	1 (1.3%)
Vernal keratoconjunctivitis	1 (2.7%)	0	1 (1.3%)

At each level of patient summarization, a patient is counted once if the patient reported one or more events.
MedDRA (Version 23.1) coding dictionary applied.
Sorted by decreasing frequency at all levels in treatment total group
Abbreviations: AESI=adverse event of special interest; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; QW=once weekly; SAF=safety analysis set; TEAE=treatment-emergent adverse event.

Injection site reactions

In total, 27.3% of participants reported TEAEs of injection site reactions. The proportion of participants who experienced injection site reactions during the Part C treatment period was 35.1% in the placebo/dupilumab 300 mg QW group and 20.0% in the dupilumab 300 mg QW/dupilumab 300 mg QW group. None of the injection site reactions were severe in intensity, led to permanent

discontinuation of study drug, or met the criteria for an SAE. By PT, Injection site reaction (15.6% of participants) and Injection site erythema (11.7%) occurred at the highest frequency in both groups.

Table 63 Summary of Injection Site Reactions by PT During Part C 28-Week Treatment Period – (Part C SAF - Participants from Part A)

Preferred Term	Placebo / Dupilumab 300 mg QW (N=37)	Dupilumab 300 mg QW / Dupilumab 300 mg QW (N=40)	Total (N=77)
Number of such events	37	58	95
Number of patients with at least one such event, n (%)	13 (35.1%)	8 (20.0%)	21 (27.3%)
Injection site reaction	8 (21.6%)	4 (10.0%)	12 (15.6%)
Injection site erythema	5 (13.5%)	4 (10.0%)	9 (11.7%)
Injection site pain	3 (8.1%)	2 (5.0%)	5 (6.5%)
Injection site bruising	3 (8.1%)	0	3 (3.9%)
Injection site oedema	1 (2.7%)	2 (5.0%)	3 (3.9%)
Injection site haemorrhage	1 (2.7%)	1 (2.5%)	2 (2.6%)
Injection site swelling	0	2 (5.0%)	2 (2.6%)
Injection site pruritus	1 (2.7%)	0	1 (1.3%)

At each level of patient summarization a patient is counted once if the patient reported one or more events.
MedDRA (Version 23.1) coding dictionary applied.
Sorted by decreasing frequency at all levels in treatment total group.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT= preferred term; QW=once weekly; SAF=safety analysis set; TEAE=treatment-emergent adverse event.

In the adolescents subgroup, there was a high incidence of injection site reactions in the dupilumab 300 mg QW/dupilumab 300 mg QW group.

Table 64 Summary of Injection Site Reactions in Adolescent Participants by PT During Part C 28-Week Treatment Period – (Part C SAF - Participants from Part A)

Preferred Term	Placebo / Dupilumab 300 mg QW (N=9)	Dupilumab 300 mg QW / Dupilumab 300 mg QW (N=10)	Total (N=19)
Number of such events	6	46	52
Number of patients with at least one such event, n (%)	2 (22.2%)	5 (50.0%)	7 (36.8%)
Injection site reaction	2 (22.2%)	3 (30.0%)	5 (26.3%)
Injection site swelling	0	2 (20.0%)	2 (10.5%)
Injection site erythema	0	1 (10.0%)	1 (5.3%)
Injection site haemorrhage	0	1 (10.0%)	1 (5.3%)
Injection site pain	0	1 (10.0%)	1 (5.3%)

At each level of patient summarization a patient is counted once if the patient reported one or more events.
MedDRA (Version 23.1) coding dictionary applied.
Sorted by decreasing frequency at all levels in treatment total group.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT= preferred term; QW=once weekly; SAF=safety analysis set; TEAE=treatment-emergent adverse event.

Deaths

There were no deaths reported during each part (**Part A, Part B, Part C)** of the study.

Laboratory findings

- **Part A**

No consistent trend towards an increase or decrease in mean or median values over time was seen in either treatment group for any haematology parameter. Small and similar median reductions in eosinophils from baseline were observed in both the dupilumab 300 mg QW and placebo treatment groups at week 24. There were no clinically meaningful differences between the 2 treatment groups in the number of participants with treatment-emergent potentially clinically significant value (PCSVs) for any of these haematology parameters.

Similar no consistent trend towards an increase or decrease in mean or median values over time was seen in either treatment group for any chemistry parameter, function parameters, electrolyte parameters, renal function parameters, liver function parameters and lipid parameters.

No participant demonstrated a treatment-emergent or treatment-boosted ADA response in either the placebo or dupilumab 300 mg QW groups during Part A. One participant in the placebo group had pre-existing immune-reactivity with low ADA titer at baseline and ADA negative at all post-treatment visits. The participant with pre-existing immune-reactivity had a negative Nab response in Part A of the study.

- **Part B**

No consistent trend towards an increase or decrease in mean or median values over time was seen in any treatment group for all haematology parameters except eosinophils. Median eosinophil counts were similar at baseline (0.420×109/L in the dupilumab 300 mg QW group, 0.380×109/L in the dupilumab 300 mg Q2W group, and 0.430×109/L in the placebo group) and decreased across the 3 treatment groups, with larger median decreases in the dupilumab 300 mg QW (−0.175×109/L) and dupilumab 300 mg Q2W groups (−0.150×109/L) than in the placebo group (−0.020×109/L) at week 24.

There were no clinically meaningful trends in shifts from baseline in haematology parameters across the treatment groups. Only sporadic cases of normal-to-high and normal-to-low shifts from baseline in some haematology parameters were observed in each treatment group. No clinically meaningful differences were reported between the 3 treatment groups in the number of participants with treatment-emergent PCSVs for any of the haematology parameters with 8/75 (10.7%) in the placebo group, 7/76 (9.2%) in the dupilumab 300 mg Q2W group and 5/72 (6.9%) in the dupilumab 300mg QW group. No consistent trend towards an increase or decrease in mean or median values over time and no clinically meaningful differences in the number of participants with treatment-emergent PCSVs for any of the chemistry parameters was seen in and between any of the treatment groups for any chemistry parameter.

A treatment-emergent ADA response to dupilumab was observed in 2 participants in the dupilumab 300 mg Q2W group and in 1 participant in the dupilumab 300 mg QW group. These participants developed transient, low, or moderate titer responses that had no impact on functional dupilumab exposure. Only one participant receiving dupilumab 300 mg Q2W was NAb positive. ADA titer had no impact on functional dupilumab exposure in the 3 participants for whom a treatment-emergent ADA response was observed.

- **Part C**

No consistent trend towards an increase or decrease or clinically meaningful trends in shifts from the Part A/C baseline in mean or median values over time was seen for any haematology parameter during Part A/C. Mean eosinophil counts were stable over the treatment period and during the follow-up period in the dupilumab 300 mg QW/dupilumab 300 mg QW group. There were small mean reductions in the placebo/dupilumab 300 mg QW group at week 52, which returned to baseline values at the end

of follow-up. There were no clinically meaningful treatment-emergent potentially clinically significant values (PCSVs) for any of the haematology parameters during Part C.

No consistent trend towards an increase or decrease or clinically meaningful trends in shifts from the Part C baseline in mean or median values over time were seen for any chemistry parameter during Part C like metabolic function parameters, electrolyte parameters, renal function parameters, liver function parameters, and lipid parameters.

One treatment-emergent PCSV for chemistry parameters was reported as a TEAE of Blood creatine phosphokinase increased was reported in 1 participant in the dupilumab 300 mg QW/dupilumab 300 mg QW group. The event was initially mild and then worsened to moderate. The event was assessed as not related to study drug.

Treatment-emergent ADA responses to dupilumab were observed in 7% of participants (5 of 71), most of whom exhibited a transient, low-titer response and had received placebo in Part A. All 5 participants with treatment-emergent ADA responses became positive for ADA in Part C. One participant treated with placebo in Part A developed a treatment-emergent, moderate titer ADA response and was also positive for neutralizing antibodies in Part C. No other participants were positive for neutralizing antibodies in Part C.

Treatment-emergent ADA responses to dupilumab were observed in 7% of participants (5 of 71). 4/34 placebo/dupilumab 300 mg QW and 1 of 37 dupilumab 300 mg QW/dupilumab 300 mg QW participants. All 5 participants with treatment-emergent ADA responses became positive for ADA in Part C. Of these 5 participants 3 experienced TEAEs. All 3 participants were in the placebo/dupilumab 300 mg QW group.

In Part B/C 6 ADA-positive participants were reported. A review of their TEAEs did not identify any specific ADA related safety events. None of these 6 participants reported anaphylactic or serum sickness/serum sickness like reactions.

Safety in special populations

The subgroups analysed for safety were:

- Age (≥12 to <18 years, ≥18 years)
- Sex (Male, Female)
- Race (White, Black or African American/Asian/Other/Asian/Not Reported [combined due to small group size])
- Duration of EoE (<5 years, ≥5 years)
- Prior use of swallowed topical steroids (STC) for the treatment of EoE (Yes, No)
- History of food allergy (Yes, No)
- History of AD (Yes, No)
- History of asthma (Yes, No)
- Baseline weight group (<60 kg, ≥60 kg)

Subgroup analyses were performed for all TEAEs by SOC and PT and TEAEs of special interest by AESI category and PT.

Overall, the subgroup analyses did not reveal marked differences in the incidence of TEAEs within subgroups. The largest differences in overall TEAE incidence in the combined dupilumab groups were seen in the age subgroup, with a higher incidence in adolescents (90.6%) than in adults (77.7%) and in the subgroup concerning EoE disease duration. Participants in the dupilumab 300 mg QW group with

an EoE disease duration less than 5 years had a higher incidence in TEAEs compared to participants with a longer duration.

Table 65 Number of Participants with Treatment-Emergent Adverse Events by Subgroup: Overall and by SOC and PT (>20% of Participants in Any Treatment Group) During the 24-Week Treatment Period– Pool 2a – SAF

Primary System Organ Class Preferred Term	Placebo (N=35)	Dupilumab 300 mg Q2W (N=27)	Dupilumab 300 mg QW (N=37)	Dupilumab Combined (N=64)	Placebo (N=82)	Dupilumab 300 mg Q2W (N=54)	Dupilumab 300 mg QW (N=85)	Dupilumab Combined (N=139)
AGE GROUP	Age Group: ≥12 - <18 years				Age Group: ≥18 years			
Number of patients with at least one such event, n (%)	28 (80.0%)	23 (85.2%)	35 (94.6%)	58 (90.6%)	59 (72.0%)	40 (74.1%)	68 (80.0%)	108 (77.7%)
General disorders and administration site conditions	18 (51.4%)	16 (59.3%)	19 (51.4%)	35 (54.7%)	29 (35.4%)	30 (55.6%)	32 (37.6%)	62 (44.6%)
Injection site reaction	14 (40.0%)	9 (33.3%)	12 (32.4%)	21 (32.8%)	7 (8.5%)	9 (16.7%)	12 (14.1%)	21 (15.1%)
Injection site erythema	5 (14.3%)	5 (18.5%)	3 (8.1%)	8 (12.5%)	10 (12.2%)	13 (24.1%)	9 (10.6%)	22 (15.8%)
Infections and infestations	10 (28.6%)	9 (33.3%)	13 (35.1%)	22 (34.4%)	19 (23.2%)	17 (31.5%)	26 (30.6%)	43 (30.9%)
Gastrointestinal disorders	13 (37.1%)	6 (22.2%)	9 (24.3%)	15 (23.4%)	20 (24.4%)	15 (27.8%)	17 (20.0%)	32 (23.0%)
Respiratory, thoracic and mediastinal disorders	6 (17.1%)	7 (25.9%)	6 (16.2%)	13 (20.3%)	13 (15.9%)	4 (7.4%)	10 (11.8%)	14 (10.1%)
Skin and subcutaneous tissue disorders	4 (11.4%)	9 (33.3%)	1 (2.7%)	10 (15.6%)	14 (17.1%)	3 (5.6%)	4 (4.7%)	7 (5.0%)
Nervous system disorders	9 (25.7%)	4 (14.8%)	4 (10.8%)	8 (12.5%)	12 (14.6%)	6 (11.1%)	10 (11.8%)	16 (11.5%)

	Placebo (N=78)	Dupilumab 300 mg Q2W (N=45)	Dupilumab 300 mg QW (N=78)	Dupilumab Combined (N=123)	Placebo (N=39)	Dupilumab 300 mg Q2W (N=36)	Dupilumab 300 mg QW (N=44)	Dupilumab Combined (N=80)
SEX	Male				Female			
Number of patients with at least one such event, n (%)	56 (71.8%)	31 (68.9%)	66 (84.6%)	97 (78.9%)	31 (79.5%)	32 (88.9%)	37 (84.1%)	69 (86.3%)
General disorders and administration site conditions	30 (38.5%)	20 (44.4%)	31 (39.7%)	51 (41.5%)	17 (43.6%)	26 (72.2%)	20 (45.5%)	46 (57.5%)
Injection site reaction	15 (19.2%)	6 (13.3%)	15 (19.2%)	21 (17.1%)	6 (15.4%)	12 (33.3%)	9 (20.5%)	21 (26.3%)
Injection site erythema	7 (9.0%)	7 (15.6%)	5 (6.4%)	12 (9.8%)	8 (20.5%)	11 (30.6%)	7 (15.9%)	18 (22.5%)
Infections and infestations	19 (24.4%)	12 (26.7%)	24 (30.8%)	36 (29.3%)	10 (25.6%)	14 (38.9%)	15 (34.1%)	29 (36.3%)
Gastrointestinal disorders	17 (21.8%)	8 (17.8%)	17 (21.8%)	25 (20.3%)	16 (41.0%)	13 (36.1%)	9 (20.5%)	22 (27.5%)
Nervous system disorders	13 (16.7%)	5 (11.1%)	8 (10.3%)	13 (10.6%)	8 (20.5%)	5 (13.9%)	6 (13.6%)	11 (13.8%)

RACE	White				Other (non-White)			
Number of patients with at least one such event, n (%)	80 (74.1%)	58 (78.4%)	94 (83.9%)	152 (81.7%)	7 (77.8%)	5 (71.4%)	9 (90.0%)	14 (82.4%)
General disorders and administration site conditions	43 (39.8%)	43 (58.1%)	45 (40.2%)	88 (47.3%)	4 (44.4%)	3 (42.9%)	6 (60.0%)	9 (52.9%)
Injection site reaction	18 (16.7%)	17 (23.0%)	22 (19.6%)	39 (21.0%)	3 (33.3%)	1 (14.3%)	2 (20.0%)	3 (17.6%)
Injection site erythema	14 (13.0%)	16 (21.6%)	12 (10.7%)	28 (15.1%)	1 (11.1%)	2 (28.6%)	0	2 (11.8%)
Infections and infestations	27 (25.0%)	24 (32.4%)	36 (32.1%)	60 (32.3%)	2 (22.2%)	2 (28.6%)	3 (30.0%)	5 (29.4%)
Gastrointestinal disorders	29 (26.9%)	21 (28.4%)	23 (20.5%)	44 (23.7%)	4 (44.4%)	0	3 (30.0%)	3 (17.6%)
Investigations	9 (8.3%)	4 (5.4%)	7 (6.3%)	11 (5.9%)	1 (11.1%)	0	3 (30.0%)	3 (17.6%)
Nervous system disorders	18 (16.7%)	10 (13.5%)	12 (10.7%)	22 (11.8%)	3 (33.3%)	0	2 (20.0%)	2 (11.8%)
Respiratory, thoracic and mediastinal disorders	18 (16.7%)	11 (14.9%)	14 (12.5%)	25 (13.4%)	1 (11.1%)	0	2 (20.0%)	2 (11.8%)

	Placebo (N=73)	Dupilumab 300 mg Q2W (N=44)	Dupilumab 300 mg QW (N=66)	Dupilumab Combined (N=110)	Placebo (N=44)	Dupilumab 300 mg Q2W (N=37)	Dupilumab 300 mg QW (N=56)	Dupilumab Combined (N=93)
DURATION OF EoE	Duration of EoE: <5 years				Duration of EoE: ≥5 years			
Number of patients with at least one such event, n (%)	56 (76.7%)	37 (84.1%)	60 (90.9%)	97 (88.2%)	31 (70.5%)	26 (70.3%)	43 (76.8%)	69 (74.2%)
General disorders and administration site conditions	33 (45.2%)	26 (59.1%)	27 (40.9%)	53 (48.2%)	14 (31.8%)	20 (54.1%)	24 (42.9%)	44 (47.3%)
Injection site reaction	17 (23.3%)	11 (25.0%)	14 (21.2%)	25 (22.7%)	4 (9.1%)	7 (18.9%)	10 (17.9%)	17 (18.3%)
Injection site erythema	11 (15.1%)	12 (27.3%)	5 (7.6%)	17 (15.5%)	4 (9.1%)	6 (16.2%)	7 (12.5%)	13 (14.0%)
Infections and infestations	20 (27.4%)	17 (38.6%)	20 (30.3%)	37 (33.6%)	9 (20.5%)	9 (24.3%)	19 (33.9%)	28 (30.1%)
Gastrointestinal disorders	23 (31.5%)	12 (27.3%)	15 (22.7%)	27 (24.5%)	10 (22.7%)	9 (24.3%)	11 (19.6%)	20 (21.5%)
Respiratory, thoracic and mediastinal disorders	10 (13.7%)	4 (9.1%)	7 (10.6%)	11 (10.0%)	9 (20.5%)	7 (18.9%)	9 (16.1%)	16 (17.2%)
Nervous system disorders	11 (15.1%)	5 (11.4%)	8 (12.1%)	13 (11.8%)	10 (22.7%)	5 (13.5%)	6 (10.7%)	11 (11.8%)

PRIOR STC HISTORY	History of Ever swallowed topical steroid for EoE: Yes				History of Ever swallowed topical steroid for EoE: No			
Number of patients with at least one such event, n (%)	66 (76.7%)	48 (73.8%)	71 (84.5%)	119 (79.9%)	21 (67.7%)	15 (93.8%)	32 (84.2%)	47 (87.0%)
General disorders and administration site conditions	33 (38.4%)	34 (52.3%)	37 (44.0%)	71 (47.7%)	14 (45.2%)	12 (75.0%)	14 (36.8%)	26 (48.1%)
Injection site reaction	14 (16.3%)	14 (21.5%)	18 (21.4%)	32 (21.5%)	7 (22.6%)	4 (25.0%)	6 (15.8%)	10 (18.5%)
Injection site erythema	12 (14.0%)	12 (18.5%)	9 (10.7%)	21 (14.1%)	3 (9.7%)	6 (37.5%)	3 (7.9%)	9 (16.7%)
Infections and infestations	16 (18.6%)	18 (27.7%)	29 (34.5%)	47 (31.5%)	13 (41.9%)	8 (50.0%)	10 (26.3%)	18 (33.3%)
Gastrointestinal disorders	23 (26.7%)	17 (26.2%)	20 (23.8%)	37 (24.8%)	10 (32.3%)	4 (25.0%)	6 (15.8%)	10 (18.5%)
Musculoskeletal and connective tissue disorders	7 (8.1%)	5 (7.7%)	9 (10.7%)	14 (9.4%)	3 (9.7%)	4 (25.0%)	3 (7.9%)	7 (13.0%)
Skin and subcutaneous tissue disorders	14 (16.3%)	8 (12.3%)	4 (4.8%)	12 (8.1%)	4 (12.9%)	4 (25.0%)	1 (2.6%)	5 (9.3%)

		Dupilumab				Dupilumab		
	Placebo (N=58)	300 mg Q2W (N=42)	300 mg QW (N=65)	Combined (N=107)	Placebo (N=59)	300 mg Q2W (N=39)	300 mg QW (N=57)	Combined (N=96)
FOOD ALLERGY	History of Food Allergy: Yes				History of Food Allergy: No			
Number of patients with at least one such event, n (%)	42 (72.4%)	34 (81.0%)	57 (87.7%)	91 (85.0%)	45 (76.3%)	29 (74.4%)	46 (80.7%)	75 (78.1%)
General disorders and administration site conditions	24 (41.4%)	29 (69.0%)	26 (40.0%)	55 (51.4%)	23 (39.0%)	17 (43.6%)	25 (43.9%)	42 (43.8%)
Injection site reaction	11 (19.0%)	13 (31.0%)	16 (24.6%)	29 (27.1%)	8 (13.6%)	7 (17.9%)	8 (14.0%)	15 (15.6%)
Injection site erythema	7 (12.1%)	11 (26.2%)	4 (6.2%)	15 (14.0%)	10 (16.9%)	5 (12.8%)	8 (14.0%)	13 (13.5%)
Infections and infestations	14 (24.1%)	10 (23.8%)	23 (35.4%)	33 (30.8%)	15 (25.4%)	16 (41.0%)	16 (28.1%)	32 (33.3%)
Gastrointestinal disorders	16 (27.6%)	13 (31.0%)	17 (26.2%)	30 (28.0%)	17 (28.8%)	8 (20.5%)	9 (15.8%)	17 (17.7%)
Injury, poisoning and procedural complications	3 (4.0%)	3 (7.1%)	1 (1.3%)	4 (3.3%)	1 (1.7%)	8 (20.5%)	8 (14.0%)	16 (16.7%)

ATOPIC DERMATITIS HISTORY	History of Atopic Dermatitis: Yes				History of Atopic Dermatitis: No			
Number of patients with at least one such event, n (%)	25 (80.6%)	16 (76.2%)	22 (84.6%)	38 (80.9%)	62 (72.1%)	47 (78.3%)	81 (84.4%)	128 (82.1%)
General disorders and administration site conditions	14 (45.2%)	13 (61.9%)	14 (53.8%)	27 (57.4%)	33 (38.4%)	33 (55.0%)	37 (38.5%)	70 (44.9%)
Injection site reaction	7 (22.6%)	8 (38.1%)	9 (34.6%)	17 (36.2%)	14 (16.3%)	10 (16.7%)	15 (15.6%)	25 (16.0%)
Injection site erythema	5 (16.1%)	2 (9.5%)	5 (19.2%)	7 (14.9%)	10 (11.6%)	16 (26.7%)	7 (7.3%)	23 (14.7%)
Infections and infestations	7 (22.6%)	6 (28.6%)	7 (26.9%)	13 (27.7%)	22 (25.6%)	20 (33.3%)	32 (33.3%)	52 (33.3%)
Gastrointestinal disorders	12 (38.7%)	6 (28.6%)	6 (23.1%)	12 (25.5%)	21 (24.4%)	15 (25.0%)	20 (20.8%)	35 (22.4%)
Respiratory, thoracic and mediastinal disorders	5 (16.1%)	5 (23.8%)	3 (11.5%)	8 (17.0%)	14 (16.3%)	6 (10.0%)	13 (13.5%)	19 (12.2%)
Skin and subcutaneous tissue disorders	7 (22.6%)	5 (23.8%)	1 (3.8%)	6 (12.8%)	11 (12.8%)	7 (11.7%)	4 (4.2%)	11 (7.1%)

		Dupilumab				Dupilumab		
	Placebo (N=44)	300 mg Q2W (N=41)	300 mg QW (N=51)	Combined (N=92)	Placebo (N=73)	300 mg Q2W (N=40)	300 mg QW (N=71)	Combined (N=111)
ASTHMA HISTORY	History of Asthma: Yes				History of Asthma: No			
Number of patients with at least one such event, n (%)	32 (72.7%)	31 (75.6%)	43 (84.3%)	74 (80.4%)	55 (75.3%)	32 (80.0%)	60 (84.5%)	92 (82.9%)
General disorders and administration site conditions	16 (36.4%)	25 (61.0%)	21 (41.2%)	46 (50.0%)	31 (42.5%)	21 (52.5%)	30 (42.3%)	51 (45.9%)
Injection site reaction	8 (18.2%)	14 (34.1%)	11 (21.6%)	25 (27.2%)	13 (17.8%)	4 (10.0%)	13 (18.3%)	17 (15.3%)
Injection site erythema	5 (11.4%)	8 (19.5%)	3 (5.9%)	11 (12.0%)	10 (13.7%)	10 (25.0%)	9 (12.7%)	19 (17.1%)
Infections and infestations	13 (29.5%)	11 (26.8%)	16 (31.4%)	27 (29.3%)	16 (21.9%)	15 (37.5%)	23 (32.4%)	38 (34.2%)
Gastrointestinal disorders	13 (29.5%)	7 (17.1%)	13 (25.5%)	20 (21.7%)	20 (27.4%)	14 (35.0%)	13 (18.3%)	27 (24.3%)

BASELINE WEIGHT	Baseline Weight Group: <60 kg				Baseline Weight Group: ≥60 kg			
Number of patients with at least one such event, n (%)	16 (76.2%)	19 (86.4%)	26 (86.7%)	45 (86.5%)	71 (74.0%)	44 (74.6%)	77 (83.7%)	121 (80.1%)
General disorders and administration site conditions	8 (38.1%)	13 (59.1%)	18 (60.0%)	31 (59.6%)	39 (40.6%)	33 (55.9%)	33 (35.9%)	66 (43.7%)
Injection site reaction	6 (28.6%)	7 (31.8%)	8 (26.7%)	15 (28.8%)	15 (15.6%)	11 (18.6%)	16 (17.4%)	27 (17.9%)
Injection site erythema	3 (14.3%)	4 (18.2%)	6 (20.0%)	10 (19.2%)	12 (12.5%)	14 (23.7%)	6 (6.5%)	20 (13.2%)
Infections and infestations	7 (33.3%)	7 (31.8%)	5 (16.7%)	12 (23.1%)	22 (22.9%)	19 (32.2%)	34 (37.0%)	53 (35.1%)
Gastrointestinal disorders	7 (33.3%)	5 (22.7%)	7 (23.3%)	12 (23.1%)	26 (27.1%)	16 (27.1%)	19 (20.7%)	35 (23.2%)
Skin and subcutaneous tissue disorders	2 (9.5%)	8 (36.4%)	1 (3.3%)	9 (17.3%)	16 (16.7%)	4 (6.8%)	4 (4.3%)	8 (5.3%)
Nervous system disorders	5 (23.8%)	4 (18.2%)	3 (10.0%)	7 (13.5%)	16 (16.7%)	6 (10.2%)	11 (12.0%)	17 (11.3%)
Respiratory, thoracic and mediastinal disorders	5 (23.8%)	4 (18.2%)	3 (10.0%)	7 (13.5%)	14 (14.6%)	7 (11.9%)	13 (14.1%)	20 (13.2%)

Notes: The incidence of the PT Vomiting was 22.2% (2/9) in the Non-white placebo group, but as the group was N=9, this term was not included in the table.
At each level of patient summarization, a patient is counted once if the patient reported one or more events.
MedDRA (Version 24.0) coding dictionary applied. Table sorted by decreasing frequency at all levels in the dupilumab combined group.
Pool 2a includes Part A (placebo and 300 mg QW) and Part B (placebo, 300 mg Q2W, and 300 mg QW) of study R668-EE-1774.
Abbreviations: EoE=eosinophilic esophagitis; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; Q2W=every 2 weeks; QW=once weekly; SAF=safety analysis set; SOC=system organ class; STC=swallowed topical corticosteroid.

Subgroup Analysis by Age Group

- **Part A**

The incidence of TEAEs for adolescents was similar to that of adults, with numerically higher proportion of adolescents reporting general disorder and administrative site conditions related to injections in both

the placebo (44.4%) and dupilumab 300 mg QW groups (54.5%) compared to adult participants in both the placebo (36.7%) and dupilumab 300 mg QW groups (35.5%).

- **Part B**

In the subgroup analysis by age group, in both dupilumab 300 mg treatment groups the incidence of TEAEs was higher in the adolescent cohort versus the adult cohort (QW: 92.3% of adolescents versus 79.6% of adults; Q2W: 85.2% of adolescents versus 74.1% of adults). In the placebo group, the incidence of TEAEs was similar (73.1% of adolescents and 69.2% of adults).

In both age groups, the SOC with the highest incidence of TEAEs across all treatment groups was General disorders and administration site conditions. Within the adolescent subgroup, the incidence of TEAEs in this SOC was similar across the treatment groups: the lowest incidence was 50.0% in the dupilumab 300 mg QW group and the highest 59.3% in the Q2W group.

The most common PTs across all treatment groups in the adolescent subgroup were Injection site reaction and Injection site swelling in the dupilumab 300 mg QW group. Within the adult subgroup, there was more variability, with the lowest incidence in the placebo group (32.7%) and the highest in the dupilumab 300 mg Q2W group (55.6%). In the adult subgroup, the most common PT was Injection site reaction in the dupilumab 300 mg QW and placebo groups, and Injection site erythema in the dupilumab 300 mg Q2W group.

Infections and infestations was the SOC with the next highest incidence in the dupilumab groups. In both age subgroups the lowest incidence was seen in the placebo group (23.1% in both subgroups). In the dupilumab 300 mg QW group, the incidences were 38.5% in adolescents and 25.9% in adults, and in the dupilumab 300 mg Q2W group 33.3% and 31.5%, respectively. No individual PT driving the differences was identified.

In the SOC Gastrointestinal disorders, the incidence was similar across both age subgroups and across treatment groups (between 17.3% and 27.8%), except for the adolescent placebo group with an incidence of 42.3% that was mainly driven by the PT of Diarrhoea.

In the SOCs Respiratory, thoracic and mediastinal disorders and Skin and subcutaneous tissue disorders, the incidences of TEAEs in the dupilumab 300 mg Q2W group was higher within the adolescent subgroup than in the placebo group (25.9% versus 19.2% in the placebo group for Respiratory, thoracic and mediastinal disorders and 33.3% versus 15.4% for Skin and subcutaneous tissue disorders) and also if the adolescent subgroup is compared to the adult subgroup (incidences of 7.4% and 5.6% in the adult subgroup for the 2 SOCs, respectively). No individual PT driving these differences was identified. In the dupilumab 300 mg QW group, the incidences of TEAEs were lower versus placebo for both SOCs in both age groups.

- **Part C**

  - <u>Adolescent Participants from Part A (Part A/C)</u>

In the placebo/dupilumab 300 mg QW group, 7 (77.8%) adolescent participants experienced a TEAE, and 2 (22.2%) experienced a drug-related TEAE the proportions in the dupilumab 300 mg QW/dupilumab 300 mg QW group were 8 (80.0%) and 4 (40.0%), respectively. The most frequently reported PTs during Part C were Acne (4 participants; 44.4%) and Injection site reaction (2 participants; 22.2%) in the placebo/dupilumab 300 mg QW group compared to Injection site reaction (3 participants; 30.0%), and Injection site swelling, Foot fracture and Headache (all in 2 participants; 20.0%) in the dupilumab 300 mg QW/dupilumab 300 mg QW group.

TEAEs related to study drug were reported in 2 (22.2%) adolescent participants in the placebo/dupilumab 300 mg QW group (Injection site reaction, Conjunctivitis allergic, and Vernal

keratoconjunctivitis) and in 4 (40.0%) adolescent participants in the dupilumab 300 mg QW/dupilumab 300 mg QW group (Injection site reaction, Injection site swelling, Injection site erythema, and Injection site pain).

Table 66 Summary of TEAEs Reported by ≥10% of All Adolescent Participants (≥12 to <18 years) During Part C 28-Week Treatment Period by Primary SOC and PT (Part C SAF - Participants from Part A)

Primary System Organ Class Preferred Term	Placebo / Dupilumab 300 mg QW (N=9)	Dupilumab 300 mg QW / Dupilumab 300 mg QW (N=10)	Total (N=19)
Number of such events	28	68	96
Number of patients with at least one such event, n (%)	7 (77.8%)	8 (80.0%)	15 (78.9%)
General disorders and administration site conditions	2 (22.2%)	5 (50.0%)	7 (36.8%)
Injection site reaction	2 (22.2%)	3 (30.0%)	5 (26.3%)
Injection site swelling	0	2 (20.0%)	2 (10.5%)
Skin and subcutaneous tissue disorders	5 (55.6%)	2 (20.0%)	7 (36.8%)
Acne	4 (44.4%)	0	4 (21.1%)
Urticaria	1 (11.1%)	1 (10.0%)	2 (10.5%)
Gastrointestinal disorders	3 (33.3%)	2 (20.0%)	5 (26.3%)
Vomiting	1 (11.1%)	1 (10.0%)	2 (10.5%)
Injury, poisoning and procedural complications	2 (22.2%)	3 (30.0%)	5 (26.3%)
Foot fracture	1 (11.1%)	2 (20.0%)	3 (15.8%)
Nervous system disorders	1 (11.1%)	2 (20.0%)	3 (15.8%)
Headache	1 (11.1%)	2 (20.0%)	3 (15.8%)
Psychiatric disorders	1 (11.1%)	1 (10.0%)	2 (10.5%)
Insomnia	1 (11.1%)	1 (10.0%)	2 (10.5%)
Respiratory, thoracic and mediastinal disorders	0	2 (20.0%)	2 (10.5%)

At each level of patient summarization, a patient is counted once if the patient reported one or more events.
MedDRA (Version 23.1) coding dictionary applied.
Sorted by decreasing frequency at all levels in treatment total group
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; QW=once weekly; SAF=safety analysis set; SOC=system organ class; TEAE=treatment-emergent adverse event.

- Adolescent Participants from Part B (Part B/C)

With the responses to the Request for Supplementary Information the MAH submitted additional data from 75 adolescent participants up to 1 year (exposure from Part B and Part C combined) in adolescent participants with EoE.

Overall, treatment-emergent adverse events (TEAEs) were reported in 70.7% of adolescent participants during the treatment period in Part B/C. This was similar to the adult population where TEAEs were reported in 65.1% of adult participants during the treatment period in Part B/C. The proportion of adolescent participants who experienced a TEAE was similar across the treatment groups, ranging from 69.2% (18/26) in the dupilumab 300 mg Q2W/dupilumab 300 mg Q2W group, 70.0% (7/10) in the placebo/dupilumab 300 mg QW group, 70.8% (17/24) in the dupilumab 300 mg QW/dupilumab 300 mg QW group, to 73.3% (11/15) in the placebo/dupilumab 300 mg Q2W group. The majority of TEAEs in both adolescents and adults were mild in intensity. The most commonly affected system organ class (SOC) in both adolescents and adults was General disorders and

administration site conditions with 33.3% (25/75 adolescent participants), while the placebo/dupilumab 300 mg QW group had the lowest incidence (20.0%). This SOC incidence was mostly driven by various injection site reaction preferred terms (PTs) including injection site reaction (17.3% of adolescent participants), injection site pain (10.7% of adolescent participants), injection site erythema (5.3% of adolescent participants), and injection site swelling (5.3% of adolescent participants). The proportion of participants with serious adverse events (SAEs) was low with 1 adolescent participant (1.3%) reporting a SAE in the dupilumab 300 mg QW/dupilumab 300 mg QW group.

Table 67 Number of Adolescent Participants With Treatment-emergent Adverse Events (TEAE) by Primary System Organ Class and Preferred Term During Part C 28-week Treatment Period (Shortened)

Primary System Organ Class Preferred Term	Placebo / Dupilumab 300 mg Q2W (N=15)	Placebo / Dupilumab 300 mg QW (N=10)	Placebo / Dupilumab (N=25)	Dupilumab 300 mg Q2W / Dupilumab 300 mg Q2W (N=26)	Dupilumab 300 mg QW / Dupilumab 300 mg QW (N=24)	Dupilumab Combined (N=50)	Total (N=75)
Number of such events	89	33	122	109	109	218	340
Number of patients with at least one such event, n (%)	11 (73.3%)	7 (70.0%)	18 (72.0%)	18 (69.2%)	17 (70.8%)	35 (70.0%)	53 (70.7%)
General disorders and administration site conditions	6 (40.0%)	2 (20.0%)	8 (32.0%)	10 (38.5%)	7 (29.2%)	17 (34.0%)	25 (33.3%)
Injection site reaction	2 (13.3%)	1 (10.0%)	3 (12.0%)	6 (23.1%)	4 (16.7%)	10 (20.0%)	13 (17.3%)
Injection site pain	3 (20.0%)	1 (10.0%)	4 (16.0%)	1 (3.8%)	3 (12.5%)	4 (8.0%)	8 (10.7%)
Injection site erythema	1 (6.7%)	0	1 (4.0%)	1 (3.8%)	2 (8.3%)	3 (6.0%)	4 (5.3%)
Injection site swelling	2 (13.3%)	0	2 (8.0%)	0	2 (8.3%)	2 (4.0%)	4 (5.3%)
Injection site oedema	0	0	0	1 (3.8%)	1 (4.2%)	2 (4.0%)	2 (2.7%)
Catheter site pain	1 (6.7%)	0	1 (4.0%)	0	0	0	1 (1.3%)
Chest discomfort	0	0	0	1 (3.8%)	0	1 (2.0%)	1 (1.3%)
Chest pain	0	0	0	0	1 (4.2%)	1 (2.0%)	1 (1.3%)
Fatigue	1 (6.7%)	0	1 (4.0%)	0	0	0	1 (1.3%)
Influenza like illness	0	0	0	1 (3.8%)	0	1 (2.0%)	1 (1.3%)
Injection site bruising	0	0	0	0	1 (4.2%)	1 (2.0%)	1 (1.3%)
Injection site pruritus	1 (6.7%)	0	1 (4.0%)	0	0	0	1 (1.3%)
Non-cardiac chest pain	0	0	0	0	1 (4.2%)	1 (2.0%)	1 (1.3%)
Infections and infestations	4 (26.7%)	2 (20.0%)	6 (24.0%)	12 (46.2%)	4 (16.7%)	16 (32.0%)	22 (29.3%)
COVID-19	1 (6.7%)	1 (10.0%)	2 (8.0%)	1 (3.8%)	1 (4.2%)	2 (4.0%)	4 (5.3%)
Nasopharyngitis	1 (6.7%)	1 (10.0%)	2 (8.0%)	1 (3.8%)	1 (4.2%)	2 (4.0%)	4 (5.3%)
Infections and infestations							
Upper respiratory tract infection	0	0	0	0	3 (12.5%)	3 (6.0%)	3 (4.0%)
Ear infection	0	0	0	2 (7.7%)	0	2 (4.0%)	2 (2.7%)
Gastroenteritis	1 (6.7%)	0	1 (4.0%)	1 (3.8%)	0	1 (2.0%)	2 (2.7%)
Pharyngitis streptococcal	1 (6.7%)	0	1 (4.0%)	1 (3.8%)	0	1 (2.0%)	2 (2.7%)
Urinary tract infection	0	0	0	2 (7.7%)	0	2 (4.0%)	2 (2.7%)
Bronchitis viral	0	0	0	0	1 (4.2%)	1 (2.0%)	1 (1.3%)
Conjunctivitis	0	0	0	1 (3.8%)	0	1 (2.0%)	1 (1.3%)
Coronavirus infection	0	0	0	1 (3.8%)	0	1 (2.0%)	1 (1.3%)
Oral herpes	0	0	0	1 (3.8%)	0	1 (2.0%)	1 (1.3%)
Pneumonia	0	0	0	1 (3.8%)	0	1 (2.0%)	1 (1.3%)
Rhinitis	0	0	0	1 (3.8%)	0	1 (2.0%)	1 (1.3%)
Sinusitis	0	0	0	1 (3.8%)	0	1 (2.0%)	1 (1.3%)
Viral infection	0	0	0	1 (3.8%)	0	1 (2.0%)	1 (1.3%)
Viral pharyngitis	1 (6.7%)	0	1 (4.0%)	0	0	0	1 (1.3%)
Viral upper respiratory tract infection	0	0	0	1 (3.8%)	0	1 (2.0%)	1 (1.3%)
Gastrointestinal disorders	5 (33.3%)	0	5 (20.0%)	6 (23.1%)	9 (37.5%)	15 (30.0%)	20 (26.7%)
Abdominal pain	0	0	0	2 (7.7%)	2 (8.3%)	4 (8.0%)	4 (5.3%)
Nausea	1 (6.7%)	0	1 (4.0%)	1 (3.8%)	2 (8.3%)	3 (6.0%)	4 (5.3%)
Dysphagia	0	0	0	1 (3.8%)	2 (8.3%)	3 (6.0%)	3 (4.0%)
Diarrhoea	1 (6.7%)	0	1 (4.0%)	0	1 (4.2%)	1 (2.0%)	2 (2.7%)
Dyspepsia	0	0	0	0	2 (8.3%)	2 (4.0%)	2 (2.7%)
Vomiting	1 (6.7%)	0	1 (4.0%)	0	1 (4.2%)	1 (2.0%)	2 (2.7%)

Gastrointestinal disorders							
Abdominal pain upper	0	0	0	0	1 (4.2%)	1 (2.0%)	1 (1.3%)
Cheilitis	0	0	0	1 (3.8%)	0	1 (2.0%)	1 (1.3%)
Constipation	0	0	0	1 (3.8%)	0	1 (2.0%)	1 (1.3%)
Dental caries	1 (6.7%)	0	1 (4.0%)	0	0	0	1 (1.3%)
Enteritis	0	0	0	0	1 (4.2%)	1 (2.0%)	1 (1.3%)
Eosinophilic oesophagitis	1 (6.7%)	0	1 (4.0%)	0	0	0	1 (1.3%)
Gastric ulcer	0	0	0	1 (3.8%)	0	1 (2.0%)	1 (1.3%)
Gastrooesophageal reflux disease	0	0	0	0	1 (4.2%)	1 (2.0%)	1 (1.3%)
Impaired gastric emptying	0	0	0	1 (3.8%)	0	1 (2.0%)	1 (1.3%)
Lip swelling	1 (6.7%)	0	1 (4.0%)	0	0	0	1 (1.3%)
Oesophageal spasm	0	0	0	1 (3.8%)	0	1 (2.0%)	1 (1.3%)
Rectal tenesmus	0	0	0	0	1 (4.2%)	1 (2.0%)	1 (1.3%)
Skin and subcutaneous tissue disorders	2 (13.3%)	1 (10.0%)	3 (12.0%)	5 (19.2%)	4 (16.7%)	9 (18.0%)	12 (16.0%)
Rash	1 (6.7%)	0	1 (4.0%)	2 (7.7%)	0	2 (4.0%)	3 (4.0%)
Dermatitis atopic	0	0	0	1 (3.8%)	1 (4.2%)	2 (4.0%)	2 (2.7%)
Dry skin	0	0	0	1 (3.8%)	1 (4.2%)	2 (4.0%)	2 (2.7%)
Rash papular	0	1 (10.0%)	1 (4.0%)	0	1 (4.2%)	1 (2.0%)	2 (2.7%)
Acne	0	0	0	0	1 (4.2%)	1 (2.0%)	1 (1.3%)
Butterfly rash	0	0	0	0	1 (4.2%)	1 (2.0%)	1 (1.3%)
Erythema	0	0	0	1 (3.8%)	0	1 (2.0%)	1 (1.3%)
Psoriasis	1 (6.7%)	0	1 (4.0%)	0	0	0	1 (1.3%)
Rosacea	0	0	0	1 (3.8%)	0	1 (2.0%)	1 (1.3%)

With the responses to the Request for Supplementary Information the MAH submitted an analysis higher trough concentration at lower body weight and its impact on the safety, especially on the adolescent participants.

The number of participants in weight group ≥40 kg and <50 kg receiving 300 mg QW was very limited in study R668-EE-1774 (3 participants in Part A, 5 participants in Part B, 5 participants in Part A/C, 3 of whom received dupilumab 300 mg QW for 52 weeks, and 7 participants in Part B/C, 5 of whom received dupilumab 300 mg QW for 52 weeks). Although the Ctrough concentrations are higher in the lower weight group, no specific safety concerns were identified for this group of participants. All TEAEs were mild to moderate in intensity, no TEAEs led to permanent dose withdrawal, and no SAEs or AEs of severe intensity were reported for this group.

Table 68 Overall Summary of Number of Patients With Treatment-emergent Adverse Events (TEAE) During 24-week Treatment Period by Weight Group (≥40 to <50 kg versus ≥50 kg) (R668-EE-1774 Part A Safety Analysis Set)

Baseline Weight Group: >= 40 -< 50 kg		
	Placebo (N=2)	Dupilumab 300 mg QW (N=3)
Any TEAE, n (%)	2 (100%)	3 (100%)
Any drug related TEAE, n (%)	0	1 (33.3%)
Any TEAE leading to discontinuation of study drug permanently, n (%)	0	0
Maximum intensity for any TEAE, n (%)		
Mild	1 (50.0%)	3 (100%)
Moderate	1 (50.0%)	0
Severe	0	0
Any TEAE death, n (%)	0	0
Any TE SAE, n (%)	0	0
Any TE SAE leading to discontinuation of study drug permanently, n (%)	0	0

Baseline Weight Group: >= 50 kg

	Placebo (N=37)	Dupilumab 300 mg QW (N=39)
Any TEAE, n (%)	30 (81.1%)	33 (84.6%)
Any drug related TEAE, n (%)	18 (48.6%)	15 (38.5%)
Any TEAE leading to discontinuation of study drug permanently, n (%)	0	1 (2.6%)
Maximum intensity for any TEAE, n (%)		
Mild	19 (51.4%)	21 (53.8%)
Moderate	11 (29.7%)	10 (25.6%)
Severe	0	2 (5.1%)
Any TEAE death, n (%)	0	0
Any TE SAE, n (%)	1 (2.7%)	2 (5.1%)
Any TE SAE leading to discontinuation of study drug permanently, n (%)	0	0

Table 69 Overall Summary of Number of Patients With Treatment-emergent Adverse Events (TEAE) During 24-week Treatment Period by Weight Group (≥40 to <50 kg versus ≥50 kg) (R668-EE-1774 Part B Safety Analysis Set)

Baseline Weight Group: >= 40 -< 50 kg

	Placebo (N=3)	Dupilumab 300 mg QW (N=5)
Any TEAE, n (%)	2 (66.7%)	4 (80.0%)
Any drug related TEAE, n (%)	2 (66.7%)	3 (60.0%)
Any TEAE leading to discontinuation of study drug permanently, n (%)	0	0
Maximum intensity for any TEAE, n (%)		
Mild	1 (33.3%)	2 (40.0%)
Moderate	1 (33.3%)	2 (40.0%)
Severe	0	0
Any TEAE death, n (%)	0	0
Any TE SAE, n (%)	0	0
Any TE SAE leading to discontinuation of study drug permanently, n (%)	0	0

Baseline Weight Group: >= 50 kg

	Placebo (N=75)	Dupilumab 300 mg QW (N=75)
Any TEAE, n (%)	53 (70.7%)	63 (84.0%)
Any drug related TEAE, n (%)	26 (34.7%)	24 (32.0%)
Any TEAE leading to discontinuation of study drug permanently, n (%)	2 (2.7%)	2 (2.7%)
Maximum intensity for any TEAE, n (%)		
Mild	39 (52.0%)	42 (56.0%)
Moderate	12 (16.0%)	15 (20.0%)
Severe	2 (2.7%)	6 (8.0%)
Any TEAE death, n (%)	0	0
Any TE SAE, n (%)	1 (1.3%)	5 (6.7%)
Any TE SAE leading to discontinuation of study drug permanently, n (%)	0	1 (1.3%)

Table 70 Overall Summary of Number of Patients With Treatment-emergent Adverse Events (TEAE) During 28-week Treatment Period by Weight Group (≥40 to <50 kg versus ≥50 kg) (R668-EE-1774 Part C Safety Analysis Set - Patients from Part A)

Baseline Weight Group: >= 40 -< 50 kg

	Placebo / Dupilumab 300 mg QW (N=2)	Dupilumab 300 mg QW / Dupilumab 300 mg QW (N=3)
Any TEAE, n (%)	2 (100%)	2 (66.7%)
Any drug related TEAE, n (%)	0	2 (66.7%)
Any TEAE leading to discontinuation of study drug permanently, n (%)	0	0
Maximum intensity for any TEAE, n (%)		
Mild	2 (100%)	1 (33.3%)
Moderate	0	1 (33.3%)
Severe	0	0
Any TEAE death, n (%)	0	0
Any TE SAE, n (%)	0	0
Any TE SAE leading to discontinuation of study drug permanently, n (%)	0	0

Baseline Weight Group: >= 50 kg

	Placebo / Dupilumab 300 mg QW (N=35)	Dupilumab 300 mg QW / Dupilumab 300 mg QW (N=37)
Any TEAE, n (%)	25 (71.4%)	22 (59.5%)
Any drug related TEAE, n (%)	15 (42.9%)	6 (16.2%)
Any TEAE leading to discontinuation of study drug permanently, n (%)	2 (5.7%)	0
Maximum intensity for any TEAE, n (%)		
Mild	17 (48.6%)	16 (43.2%)
Moderate	7 (20.0%)	5 (13.5%)
Severe	1 (2.9%)	1 (2.7%)
Any TEAE death, n (%)	0	0
Any TE SAE, n (%)	1 (2.9%)	0
Any TE SAE leading to discontinuation of study drug permanently, n (%)	1 (2.9%)	0

Table 71 Overall Summary of Number of Patients with Treatment-emergent Adverse Events (TEAE) During 28-week Treatment Period by Weight Group (≥40 to <50 kg versus ≥50 kg) (R668-EE-1774 Part C Safety Analysis Set - Patients from Part B)

Baseline Weight Group: >= 40 -< 50 kg

	Placebo / Dupilumab 300 mg QW (N=2)	Dupilumab 300 mg QW / Dupilumab 300 mg QW (N=5)
Any TEAE, n (%)	1 (50.0%)	4 (80.0%)
Any drug related TEAE, n (%)	0	2 (40.0%)
Any TEAE leading to discontinuation of study drug permanently, n (%)	0	0
Maximum intensity for any TEAE, n (%)		
Mild	1 (50.0%)	4 (80.0%)
Moderate	0	0
Severe	0	0
Any TEAE death, n (%)	0	0
Any TE SAE, n (%)	0	0
Any TE SAE leading to discontinuation of study drug permanently, n (%)	0	0

Baseline Weight Group: >= 50 kg		
	Placebo / Dupilumab 300 mg QW (N=35)	Dupilumab 300 mg QW / Dupilumab 300 mg QW (N=69)
Any TEAE, n (%)	22 (62.9%)	47 (68.1%)
Any drug related TEAE, n (%)	7 (20.0%)	12 (17.4%)
Any TEAE leading to discontinuation of study drug permanently, n (%)	0	0
Maximum intensity for any TEAE, n (%)		
Mild	16 (45.7%)	28 (40.6%)
Moderate	4 (11.4%)	18 (26.1%)
Severe	2 (5.7%)	1 (1.4%)
Any TEAE death, n (%)	0	0
Any TE SAE, n (%)	2 (5.7%)	3 (4.3%)
Any TE SAE leading to discontinuation of study drug permanently, n (%)	0	0

Due to the small number of participants in the lower weight group treated with dupilumab 300 mg QW in study R668-EE-1774, a similar analysis was conducted with data from participants treated with dupilumab 300 mg QW in the AD clinical trials R668-AD-1224 (including 10 patients within weight group ≥40 kg and <50 kg receiving 300 mg QW (52 week treatment period)), R668-AD-1334 (A Phase 3 study including 7 patients within weight group ≥40 kg and <50 kg receiving 300 mg QW (16 week treatment period)) and R668-AD-1416 (A Phase 3 Study including 14 patients within weight group ≥40 kg and <50 kg receiving 300 mg QW (16 week treatment period)) to determine whether the small numeric differences in the overall safety profile in the EoE studies were consistently observed for participants of lower and higher weights.

The data comparing the safety profile of participants weighing ≥40 kg and <50 kg versus participants weighing >50 kg in these studies showed no clinically meaningful differences between the two weight groups.

Pooled Analyses by age group

In the Pool 2a subgroup analysis by age group show that in both dupilumab 300 mg treatment groups the incidence of TEAEs was higher in the adolescent cohort versus the adult cohort (dupilumab 300 mg QW: 94.6% of adolescents versus 80.0% of adults; dupilumab 300 mg Q2W: 85.2% of adolescents versus 74.1% of adults). In the placebo group, the difference in incidence of TEAEs was less marked (80.0% of adolescents versus 72.0% of adults).

Table 72 Overview of Treatment-Emergent Adverse Events in Adolescents During the 24-Week Treatment Period – Pool 2a – SAF

		Dupilumab		
	Placebo (N=35)	300 mg Q2W (N=27)	300 mg QW (N=37)	Combined (N=64)
Any TEAE, n (%)	28 (80.0%)	23 (85.2%)	35 (94.6%)	58 (90.6%)
Any drug related TEAE, n (%)	22 (62.9%)	16 (59.3%)	14 (37.8%)	30 (46.9%)
Any TEAE leading to discontinuation of study drug permanently, n (%)	0	1 (3.7%)	1 (2.7%)	2 (3.1%)
Maximum intensity for any TEAE, n (%)				
Mild	19 (54.3%)	16 (59.3%)	21 (56.8%)	37 (57.8%)
Moderate	9 (25.7%)	7 (25.9%)	10 (27.0%)	17 (26.6%)
Severe	0	0	4 (10.8%)	4 (6.3%)
Any TEAE death, n (%)	0	0	0	0
Any TE SAE, n (%)	0	1 (3.7%)	4 (10.8%)	5 (7.8%)
Any TE SAE leading to discontinuation of study drug permanently, n (%)	0	0	0	0

Note: Pool 2a includes Part A (placebo and 300 mg QW) and Part B (placebo, 300 mg Q2W, and 300 mg QW) of study R668-EE-1774.
Abbreviations: Q2W=every 2 weeks; QW=once weekly; SAE=serious adverse event; SAF=safety analysis set; TE=treatment-emergent; TEAE=treatment-emergent adverse event.

The SOC with the highest incidence of TEAEs across all treatment groups in both age groups was General disorders and administration site conditions. Within the adolescent subgroup, the incidence of TEAEs in this SOC was similar across the treatment groups. The lowest incidence was 51.4% in the dupilumab 300 mg QW group and placebo group and the highest 59.3% in the Q2W group. Injection site reaction was the most common PT across all treatment groups in the adolescent subgroup, with the highest incidence in the placebo group (40.0% versus 32.4% in the dupilumab 300 mg QW group and 33.3% in the dupilumab 300 mg Q2W group). Within the adult subgroup, the incidence in this SOC was lower versus adolescents and there was more variability, with the lowest incidence in the placebo group (35.4%) and the highest in the dupilumab 300 mg Q2W group (55.6%).

The next highest incidence in the dupilumab groups was seen in the SOC Infections and infestations. The lowest incidence was seen in the placebo group (28.6% in the adolescent subgroup and 23.2% in the adult subgroup). In the dupilumab 300 mg QW group, the incidences were 35.1% in adolescents and 30.6% in adults, and in the dupilumab 300 mg Q2W group 33.3% and 31.5%, respectively. There was no individual PT driving the differences. Furthermore, there was no apparent difference in the pattern of TEAEs between adults and adolescents.

The incidence in the SOC Gastrointestinal disorders was similar across both age subgroups and across treatment groups (between 20.0% and 27.8%), except for the adolescent placebo group with an incidence of 37.1%. There was no individual PT driving this difference.

In the SOCs Respiratory, thoracic and mediastinal disorders and Skin and subcutaneous tissue disorders, within the adolescent subgroup the incidences of TEAEs in the dupilumab 300 mg Q2W group were higher versus placebo (25.9% versus 17.1% in the placebo group for Respiratory, thoracic and mediastinal disorders and 33.3% versus 11.4% for Skin and subcutaneous tissue disorders), but the incidence in the dupilumab 300 mg QW group was lower versus placebo (16.2% and 2.7% for the 2 SOCs, respectively).

Other Subgroup Analyses

There were no clinically meaningful differences in the other subgroup analyses.

Safety related to drug-drug interactions and other interactions

No new drug-drug interactions studies were performed.

Discontinuation due to adverse events

- **Part A**

One participant in dupilumab 300 mg QW group and no participant in the placebo group experienced a TEAE leading to permanent study drug discontinuation during Part A of the study. The participant in the dupilumab 300 mg QW group discontinued the study due to Arthralgia. This event was moderate in intensity and was assessed by the investigator as related to study drug.

- **Part B**

Two participants in each treatment group experienced TEAEs that led to permanent discontinuation of study drug. In the dupilumab 300 mg QW group, 1 participant permanently discontinued study drug due to a serious TEAE of Breast cancer and 1 due to non-serious TEAEs of Hypermobility syndrome and Myalgia. In the dupilumab 300 mg Q2W group, 2 participants permanently discontinued study drug due to non-serious TEAEs, 1 participant due to Rhabdomyolysis and 1 participant due to 2 TEAEs i.e. Congenital coronary artery malformation (first discovered during the study) and Dyspnoea. In the placebo group, 2 participants permanently discontinued study drug due to non-serious TEAEs of Oral herpes and Hepatic enzyme increased, respectively.

Two participants in the dupilumab 300 mg QW group, 2 participants in the dupilumab 300 mg Q2W group, and 2 in the placebo group had at least 1 TEAE leading to permanent withdrawal of study drug during Part B of the study.

In the dupilumab 300 mg QW group:

− 1 participant discontinued study drug due to a serious and severe TEAE of Breast cancer (outcome: not resolved). Study drug was permanently discontinued due to this SAE. No relevant medical history was reported. On study day 55, the participant detected a mass in the left breast. The last dose (the 12th) of study drug was administered on study day 79. On study day 85, following a mammogram, Breast cancer was reported as an SAE and the participant withdrew from the study the same day.

− 1 participant discontinued study drug due to non-serious, moderate TEAEs of Hypermobility syndrome and Myalgia that were both ongoing at the last assessment. Both events were assessed by the investigator as not related to study drug. The participant's medical history included chronic pain from hypermobility, vitamin D deficiency, osteopenia, neuralgia, and myalgia. Both events started on study day 31, after 5 doses of study drug. The physician decided to withdraw the participant from the study on study day 61, after a total of 8 doses of study drug.

In the dupilumab 300 mg Q2W group, all 3 TEAEs leading to permanent withdrawal of study drug were non-serious:

− 1 participant discontinued study drug due to moderate Rhabdomyolysis starting on study day 115. The event was assessed by the investigator as related to study drug and was ongoing at the time of the last assessment. The most recent dose of study drug prior to the event was administered on study day 114 and the last dose in the study on study day 120. The participant had a mild AE of Blood creatine phosphokinase increased that started during screening and resolved on study day 8 (value on study day 1 was 286 IU/L [normal range 24-207 IU/L]). A muscle biopsy was done on study day 135 (results not provided). The participant had a PCSV for creatine kinase on study day 129 of 4795 IU/L,

which decreased to 222 IU/L on study day 142. The participant discontinued from the study on study day 162 due to the TEAE.

− 1 participant discontinued study drug due to 2 TEAEs of moderate Congenital coronary artery malformation and mild Dyspnoea, both of which were assessed as not related and were resolving. The malformation of the right coronary artery was discovered on study day 170, on the same day as the increasing dyspnoea started (and the last day of study drug dosing). Relevant medical history included asthma and Klinefelter's syndrome. The participant discontinued from the study on study day 259 due to the TEAEs.

In the placebo group, both TEAEs leading to permanent withdrawal of study drug were non-serious:

− 1 participant permanently discontinued study drug due to a moderate TEAE of Oral herpes. Relevant medical history included oral herpes. The event started on study day 24, after 3 doses of study drug, and resolved on study day 51 following treatment with aciclovir. The TEAE was assessed as related to study drug by the investigator. The participant discontinued from the study on study day 29 due to the TEAE.

− 1 participant permanently discontinued study drug due to a moderate TEAE of Hepatic enzyme increased. The participant had no relevant medical history. The event started on study day 87, after 13 doses of study drug, and was ongoing at the last assessment. The TEAE was assessed as not related to study drug by the investigator. The participant had an AST of 218 IU/L. Other TEAEs reported were mild Headache (study days 50 through 52) and moderate Dyspepsia (ongoing from study day 73). The participant discontinued from the study on study day 121 due to the TEAE.

- **Part C**

Two participants in the placebo/dupilumab 300 mg QW group and none in the dupilumab 300 mg QW/dupilumab 300 mg QW group had a TEAE leading to permanent study drug discontinuation during Part C of the study

One participant, a 24-year-old female, with a treatment-emergent SAE of severe intensity 69 days after starting dupilumab in Part C that led to permanent discontinuation of study drug (see also section serious adverse events). A second participant in the placebo/dupilumab 300 mg QW group had a TEAE that led to permanent discontinuation of study drug (Arthralgia). The participant, a 36-year-old male, developed moderate bilateral elbow arthralgia 51 days after starting dupilumab in Part C.

Pooled analyses

Pool 2a: Phase 3 Placebo-Controlled 24-Week Treatment Period for Safety

Pool 2a is the randomized, placebo-controlled, phase 3 safety pool intended to assess the safety profile of dupilumab (300 mg QW or 300 mg Q2W) versus placebo in adult and adolescent patients with EoE.

- Two 24-week placebo-controlled parts of phase 3 study R668-EE-1774 are included in this pool: Part A and Part B participants who received any dose of study drug.
- Treatment groups are summarized as follows for Pool 2a:
  - Placebo (from Part A and Part B)
  - Dupilumab 300 mg Q2W (from Part B only)
  - Dupilumab 300 mg QW (from Part A and Part B)
  - Dupilumab combined: combined dupilumab dose regimens

Pool 2b: Phase 2 and Phase 3 Placebo-Controlled 12- to 24-Week Treatment Period for Safety

Pool 2b is the randomized, placebo-controlled, phase 2 and phase 3 safety pool intended to assess the safety profile of dupilumab (300 mg QW or 300 mg Q2W) versus placebo in adult and adolescent patients with EoE. It consists of:

- Phase 2 study R668-EE-1324 with a 12-week placebo-controlled treatment period
- Phase 3 study R668-EE-1774 Part A and Part B with a 24-week treatment period
- Treatment groups are summarized as follows for Pool 2b:
  - Placebo (from study R668-EE-1324 and from Part A and Part B of study R668-EE-1774)
  - Dupilumab 300 mg Q2W (from Part B of study R668-EE-1774 only)
  - Dupilumab 300 mg QW (from study R668-EE-1324 and from Part A and Part B of study R668-EE-1774)
  - Dupilumab combined: combined dupilumab dose regimens

- **Adverse Events**

Pool 2a (Phase 3 Placebo-Controlled Pooled Analysis Set)

Table 73 Overview of Treatment-Emergent Adverse Events During the 24-Week Treatment Period – Pool 2a – SAF

		Dupilumab		
	Placebo (N=117)	300 mg Q2W (N=81)	300 mg QW (N=122)	Combined (N=203)
Any TEAE, n (%)	87 (74.4%)	63 (77.8%)	103 (84.4%)	166 (81.8%)
Any drug related TEAE, n (%)	46 (39.3%)	39 (48.1%)	43 (35.2%)	82 (40.4%)
Any TEAE leading to discontinuation of study drug permanently, n (%)	2 (1.7%)	2 (2.5%)	3 (2.5%)	5 (2.5%)
Maximum intensity for any TEAE, n (%)				
Mild	60 (51.3%)	42 (51.9%)	68 (55.7%)	110 (54.2%)
Moderate	25 (21.4%)	20 (24.7%)	27 (22.1%)	47 (23.2%)
Severe	2 (1.7%)	1 (1.2%)	8 (6.6%)	9 (4.4%)
Any TEAE death, n (%)	0	0	0	0
Any TE SAE, n (%)	2 (1.7%)	1 (1.2%)	7 (5.7%)	8 (3.9%)
Any TE SAE leading to discontinuation of study drug permanently, n (%)	0	0	1 (0.8%)	1 (0.5%)

Note: Pool 2a includes Part A (placebo and 300 mg QW) and Part B (placebo, 300 mg Q2W, and 300 mg QW) of study R668-EE-1774.
Abbreviations: Q2W=every 2 weeks; QW=once weekly; SAE=serious adverse event; SAF=safety analysis set; TE=treatment-emergent; TEAE=treatment-emergent adverse event.

Table 74 Treatment-Emergent Adverse Events Reported During the 24-Week Treatment Period in ≥ 5% of Participants in Any Treatment Group by Primary System Organ Class and Preferred Term - Pool 2a - SAF

Primary System Organ Class Preferred Term	Placebo (N=117)	Dupilumab 300 mg Q2W (N=81)	Dupilumab 300 mg QW (N=122)	Dupilumab Combined (N=203)
Number of such events	555	469	537	1006
Number of patients with at least one such event, n (%)	87 (74.4%)	63 (77.8%)	103 (84.4%)	166 (81.8%)
General disorders and administration site conditions	47 (40.2%)	46 (56.8%)	51 (41.8%)	97 (47.8%)
Injection site reaction	21 (17.9%)	18 (22.2%)	24 (19.7%)	42 (20.7%)
Injection site erythema	15 (12.8%)	18 (22.2%)	12 (9.8%)	30 (14.8%)
Injection site swelling	3 (2.6%)	7 (8.6%)	15 (12.3%)	22 (10.8%)
Injection site pain	7 (6.0%)	10 (12.3%)	11 (9.0%)	21 (10.3%)
Pyrexia	2 (1.7%)	3 (3.7%)	7 (5.7%)	10 (4.9%)
Injection site bruising	1 (0.9%)	6 (7.4%)	1 (0.8%)	7 (3.4%)
Injection site urticaria	2 (1.7%)	6 (7.4%)	0	6 (3.0%)
Infections and infestations	29 (24.8%)	26 (32.1%)	39 (32.0%)	65 (32.0%)
Nasopharyngitis	7 (6.0%)	4 (4.9%)	7 (5.7%)	11 (5.4%)
COVID-19	1 (0.9%)	5 (6.2%)	4 (3.3%)	9 (4.4%)
Upper respiratory tract infection	2 (1.7%)	2 (2.5%)	7 (5.7%)	9 (4.4%)
Gastrointestinal disorders	33 (28.2%)	21 (25.9%)	26 (21.3%)	47 (23.2%)
Nausea	9 (7.7%)	4 (4.9%)	5 (4.1%)	9 (4.4%)
Abdominal pain	6 (5.1%)	2 (2.5%)	6 (4.9%)	8 (3.9%)
Diarrhoea	10 (8.5%)	3 (3.7%)	3 (2.5%)	6 (3.0%)
Respiratory, thoracic and mediastinal disorders	19 (16.2%)	11 (13.6%)	16 (13.1%)	27 (13.3%)
Oropharyngeal pain	8 (6.8%)	5 (6.2%)	3 (2.5%)	8 (3.9%)
Nervous system disorders	21 (17.9%)	10 (12.3%)	14 (11.5%)	24 (11.8%)
Headache	13 (11.1%)	5 (6.2%)	8 (6.6%)	13 (6.4%)

Notes: At each level of patient summarization, a patient is counted once if the patient reported one or more events.
MedDRA (Version 24.0) coding dictionary applied. Table sorted by decreasing frequency at all levels in the dupilumab combined group.
Pool 2a includes Part A (placebo and 300 mg QW) and Part B (placebo, 300 mg Q2W, and 300 mg QW) of study R668-EE-1774.
Abbreviations: Q2W=every 2 weeks; QW=once weekly; SAF=safety analysis set.

Pool 2b (Phase 2 and Phase 3 Placebo-Controlled Pooled Analysis Set)

A similar overall pattern of TEAEs was seen in Pool 2b to that in Pool 2a, with similar incidences in each category.

Table 75 Overall Summary of Number of Patients with Treatment-Emergent Adverse Events (TEAE) During Treatment Period (Pool 2b - Safety Analysis Set)

	Placebo (N=141)	Dupilumab 300 mg Q2W (N=81)	Dupilumab 300 mg QW (N=145)	Dupilumab Combined (N=226)
Any TEAE, n (%)	102 (72.3%)	63 (77.8%)	121 (83.4%)	184 (81.4%)
Any drug related TEAE, n (%)	55 (39.0%)	39 (48.1%)	55 (37.9%)	94 (41.6%)
Any TEAE leading to discontinuation of study drug permanently, n (%)	2 (1.4%)	2 (2.5%)	4 (2.8%)	6 (2.7%)
Maximum intensity for any TEAE, n (%)				
Mild	71 (50.4%)	42 (51.9%)	80 (55.2%)	122 (54.0%)
Moderate	29 (20.6%)	20 (24.7%)	32 (22.1%)	52 (23.0%)
Severe	2 (1.4%)	1 (1.2%)	9 (6.2%)	10 (4.4%)
Any TEAE death, n (%)	0	0	0	0
Any TE SAE, n (%)	2 (1.4%)	1 (1.2%)	7 (4.8%)	8 (3.5%)
Any TE SAE leading to discontinuation of study drug permanently, n (%)	0	0	1 (0.7%)	1 (0.4%)

Pool 2b includes Part A (placebo and 300 mg qw) and Part B (placebo, 300 mg q2w, and 300 mg qw) 24-week treatment period of study EE-1774, and study EE-1324 (12-week treatment period; 24 patients in placebo and 23 patients in 300 mg qw).

- **Severity of Treatment-Emergent Adverse Events**

Pool 2a (Phase 3 Placebo-Controlled Pooled Analysis Set)

Table 76 Number of Patients with Treatment-Emergent Adverse Events During 24-Week Treatment Period by Severity– Pool 2a – SAF

		Dupilumab		
Severity	Placebo (N=117)	300 mg Q2W (N=81)	300 mg QW (N=122)	Combined (N=203)
Number of such events	555	469	537	1006
Mild	515	426	468	894
Moderate	38	42	61	103
Severe	2	1	8	9
Number of patients with at least one such event, n (%)	87 (74.4%)	63 (77.8%)	103 (84.4%)	166 (81.8%)
Mild	60 (51.3%)	42 (51.9%)	68 (55.7%)	110 (54.2%)
Moderate	25 (21.4%)	20 (24.7%)	27 (22.1%)	47 (23.2%)
Severe	2 (1.7%)	1 (1.2%)	8 (6.6%)	9 (4.4%)

Notes: At each level of patient summarization, a patient is counted once if the patient reported one or more events.
MedDRA (Version 24.0) coding dictionary applied. Table sorted by decreasing frequency at all levels in the dupilumab combined group.
Pool 2a includes Part A (placebo and 300 mg QW) and Part B (placebo, 300 mg Q2W, and 300 mg QW) of study R668-EE-1774.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; Q2W=every 2 weeks; QW=once weekly; SAF=safety analysis set.

Table 77 Summary of Severe Treatment-Emergent Adverse Events by Preferred Term During 24-Week Treatment Period – Pool 2a – SAF

		Dupilumab		
Preferred Term	Placebo (N=117)	300 mg Q2W (N=81)	300 mg QW (N=122)	Combined (N=203)
Tooth fracture	0	1 (1.2%)	0	1 (0.5%)
Abdominal pain	0	0	1 (0.8%)	1 (0.5%)
Breast cancer	0	0	1 (0.8%)	1 (0.5%)
COVID-19	0	0	1 (0.8%)	1 (0.5%)
Depression suicidal	0	0	1 (0.8%)	1 (0.5%)
Large intestine infection	0	0	1 (0.8%)	1 (0.5%)
Pneumonia aspiration	0	0	1 (0.8%)	1 (0.5%)
Syncope	0	0	1 (0.8%)	1 (0.5%)
Uterine polyp	0	0	1 (0.8%)	1 (0.5%)
Hypersensitivity	1 (0.9%)	0	0	0
Mental status changes	1 (0.9%)	0	0	0

Notes: At each level of patient summarization, a patient is counted once if the patient reported one or more events.
MedDRA (Version 24.0) coding dictionary applied.
Pool 2a includes Part A (placebo and 300 mg QW) and Part B (placebo, 300 mg Q2W, and 300 mg QW) of study R668-EE-1774.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; Q2W=every 2 weeks; QW=once weekly; SAF=safety analysis set.

The results for Pool 2b were consistent with Pool 2a. One additional participant in the dupilumab 300 mg QW group experienced a severe TEAE of hypoventilation in Pool 2b.

- **Treatment-Emergent Serious Adverse Events**

Pool 2a

Table 78 Number of Patients with Serious Treatment-Emergent Adverse Events During 24-Week Treatment Period by Primary System Organ Class and Preferred Term – Pool 2a – SAF

Primary System Organ Class Preferred Term	Placebo (N=117)	Dupilumab 300 mg Q2W (N=81)	Dupilumab 300 mg QW (N=122)	Dupilumab Combined (N=203)
Number of such events	2	1	7	8
Number of patients with at least one such event, n (%)	2 (1.7%)	1 (1.2%)	7 (5.7%)	8 (3.9%)
Psychiatric disorders	2 (1.7%)	1 (1.2%)	1 (0.8%)	2 (1.0%)
Depression suicidal	0	0	1 (0.8%)	1 (0.5%)
Suicidal ideation	1 (0.9%)	1 (1.2%)	0	1 (0.5%)
Mental status changes	1 (0.9%)	0	0	0
Gastrointestinal disorders	0	0	1 (0.8%)	1 (0.5%)
Abdominal pain	0	0	1 (0.8%)	1 (0.5%)
Infections and infestations	0	0	1 (0.8%)	1 (0.5%)
Campylobacter colitis	0	0	1 (0.8%)	1 (0.5%)
Investigations	0	0	1 (0.8%)	1 (0.5%)
Blood creatine phosphokinase abnormal	0	0	1 (0.8%)	1 (0.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (0.8%)	1 (0.5%)
Breast cancer	0	0	1 (0.8%)	1 (0.5%)
Reproductive system and breast disorders	0	0	1 (0.8%)	1 (0.5%)
Uterine polyp	0	0	1 (0.8%)	1 (0.5%)
Respiratory, thoracic and mediastinal disorders	0	0	1 (0.8%)	1 (0.5%)
Pneumonia aspiration	0	0	1 (0.8%)	1 (0.5%)

Notes: At each level of patient summarization, a patient is counted once if the patient reported one or more events.
MedDRA (Version 24.0) coding dictionary applied. Table sorted by decreasing frequency at all levels in the dupilumab combined group.
Pool 2a includes Part A (placebo and 300 mg QW) and Part B (placebo, 300 mg Q2W, and 300 mg QW) of study R668-EE-1774.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; Q2W=every 2 weeks; QW=once weekly; SAF=safety analysis set.

Pool 2b (Phase 2 and Phase 3 Placebo-Controlled Pooled Analysis Set)

No SAEs were reported during the treatment period of study R668-EE-1324. Therefore, there are no additional SAEs in Pool 2b.

- **Adverse Events Leading to Permanent Study Drug Discontinuation**

Pool 2a (Phase 3 Placebo-Controlled Pooled Analysis Set)

Table 79 Number of Patients with Treatment-Emergent Adverse Events Leading to Permanent Drug Withdrawal During the 24-Week Treatment Period by Primary System Organ Class and Preferred Term – Pool 2a – SAF

Primary System Organ Class Preferred Term	Placebo (N=117)	Dupilumab 300 mg Q2W (N=81)	Dupilumab 300 mg QW (N=122)	Dupilumab Combined (N=203)
Number of such events	2	3	4	7
Number of patients with at least one such event, n (%)	2 (1.7%)	2 (2.5%)	3 (2.5%)	5 (2.5%)
Musculoskeletal and connective tissue disorders	0	1 (1.2%)	2 (1.6%)	3 (1.5%)
Arthralgia	0	0	1 (0.8%)	1 (0.5%)
Hypermobility syndrome	0	0	1 (0.8%)	1 (0.5%)
Myalgia	0	0	1 (0.8%)	1 (0.5%)
Rhabdomyolysis	0	1 (1.2%)	0	1 (0.5%)
Congenital, familial and genetic disorders	0	1 (1.2%)	0	1 (0.5%)
Congenital coronary artery malformation	0	1 (1.2%)	0	1 (0.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (0.8%)	1 (0.5%)
Breast cancer	0	0	1 (0.8%)	1 (0.5%)
Respiratory, thoracic and mediastinal disorders	0	1 (1.2%)	0	1 (0.5%)
Dyspnoea	0	1 (1.2%)	0	1 (0.5%)
Infections and infestations	1 (0.9%)	0	0	0
Oral herpes	1 (0.9%)	0	0	0
Investigations	1 (0.9%)	0	0	0
Hepatic enzyme increased	1 (0.9%)	0	0	0

Notes: At each level of patient summarization, a patient is counted once if the patient reported one or more events.
MedDRA (Version 24.0) coding dictionary applied. Table sorted by decreasing frequency at all levels in the dupilumab combined group.
Pool 2a includes Part A (placebo and 300 mg QW) and Part B (placebo, 300 mg Q2W, and 300 mg QW) of study R668-EE-1774.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; Q2W=every 2 weeks; QW=once weekly; SAF=safety analysis set.

- **Adverse Events of Special Interest**

Table 80 Overall Summary of Number of Patients with Treatment-Emergent Adverse Events of Special Interest by Category and PT During 24-Week Treatment Period – Pool 2a – SAF

AESI Category PT	Placebo (N=117)	Dupilumab 300 mg Q2W (N=81)	Dupilumab 300 mg QW (N=122)	Dupilumab Combined (N=203)
Number of patients with at least one AESI, n (%)	3 (2.6%)	1 (1.2%)	7 (5.7%)	8 (3.9%)
Anaphylactic reactions	0	0	0	0
Systemic hypersensitivity reactions	1 (0.9%)	0	1 (0.8%)	1 (0.5%)
Injection site hypersensitivity	0	0	1 (0.8%)	1 (0.5%)
Hypersensitivity	1 (0.9%)	0	0	0
Helminthic infections	0	0	0	0
Severe Conjunctivitis/Blepharitis	0	0	0	0
Keratitis	0	0	0	0
Clinically symptomatic eosinophilia	0	0	0	0
Severe injection site reactions	0	0	0	0
Herpes simplex infection	1 (0.9%)	1 (1.2%)	3 (2.5%)	4 (2.0%)
Herpes simplex	0	0	2 (1.6%)	2 (1.0%)
Oral herpes	1 (0.9%)	1 (1.2%)	1 (0.8%)	2 (1.0%)
Arthralgia	1 (0.9%)	0	3 (2.5%)	3 (1.5%)
Arthralgia	1 (0.9%)	0	3 (2.5%)	3 (1.5%)

Notes: At each level of patient summarization, a patient is counted once if the patient reported one or more events.
MedDRA (Version 24.0) coding dictionary applied.
Pool 2a includes Part A (placebo and 300 mg QW) and Part B (placebo, 300 mg Q2W, and 300 mg QW) of study R668-EE-1774.
Abbreviations: AESI=adverse event of special interest; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; Q2W=every 2 weeks; QW=once weekly; SAF=safety analysis set.

The results for Pool 2b only captured the Systemic hypersensitivity reactions (which are already summarized in Pool 2a) owing to fewer AESI categories in the R668-EE-1324 study (only Anaphylactic

reactions, Systemic hypersensitivity reactions, Helminthic infections, and Severe injection site reactions), and hence fewer categories in the pooled summary. No additional AESIs were identified.

- **Injection Site Reactions**

Table 81 Number of Patients with Injection Site Reaction During 24-Week Treatment Period by Preferred Term - Pool 2a - SAF

		Dupilumab		
Preferred Term	Placebo (N=117)	300 mg Q2W (N=81)	300 mg QW (N=122)	Combined (N=203)
Number of such events	225	259	278	537
Number of patients with at least one such event, n (%)	39 (33.3%)	44 (54.3%)	46 (37.7%)	90 (44.3%)
Injection site reaction	21 (17.9%)	18 (22.2%)	24 (19.7%)	42 (20.7%)
Injection site erythema	15 (12.8%)	18 (22.2%)	12 (9.8%)	30 (14.8%)
Injection site swelling	3 (2.6%)	7 (8.6%)	15 (12.3%)	22 (10.8%)
Injection site pain	7 (6.0%)	10 (12.3%)	11 (9.0%)	21 (10.3%)
Injection site bruising	1 (0.9%)	6 (7.4%)	1 (0.8%)	7 (3.4%)
Injection site oedema	5 (4.3%)	4 (4.9%)	2 (1.6%)	6 (3.0%)
Injection site pruritus	5 (4.3%)	1 (1.2%)	5 (4.1%)	6 (3.0%)
Injection site urticaria	2 (1.7%)	6 (7.4%)	0	6 (3.0%)
Injection site haemorrhage	1 (0.9%)	2 (2.5%)	2 (1.6%)	4 (2.0%)
Injection site discolouration	0	1 (1.2%)	1 (0.8%)	2 (1.0%)
Injection site inflammation	1 (0.9%)	1 (1.2%)	1 (0.8%)	2 (1.0%)
Injection site mass	1 (0.9%)	0	2 (1.6%)	2 (1.0%)
Injection site rash	1 (0.9%)	0	2 (1.6%)	2 (1.0%)
Injection site haematoma	0	1 (1.2%)	0	1 (0.5%)
Injection site hypersensitivity	0	0	1 (0.8%)	1 (0.5%)
Injection site nodule	1 (0.9%)	1 (1.2%)	0	1 (0.5%)
Injection site extravasation	1 (0.9%)	0	0	0
Injection site induration	1 (0.9%)	0	0	0

Notes: At each level of patient summarization, a patient is counted once if the patient reported one or more events.
MedDRA (Version 24.0) coding dictionary applied. Table sorted by decreasing frequency at all levels in the dupilumab combined group.
Pool 2a includes Part A (placebo and 300 mg QW) and Part B (placebo, 300 mg Q2W, and 300 mg QW) of study R668-EE-1774.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; Q2W=every 2 weeks; QW=once weekly; SAF=safety analysis set.

The results for Pool 2b were consistent with Pool 2a.

In Study R668-EE-1774 Part A/C The proportion of participants who experienced injection site reactions during the Part A/C 28-week treatment period was 35.1% in the placebo/dupilumab 300 mg QW group, similar to that of 37.7% for the dupilumab 300 mg QW in Pool 2a and 20.0% in the dupilumab 300 mg QW/dupilumab 300 mg QW group, suggestive of a reduction in injection site reaction incidence with continued dupilumab treatment.

- **Conjunctivitis and Eye Disorder Events**

Table 82 Summary of Participants with Broad Conjunctivitis CMQ by Preferred Term During 24-Week Treatment Period – Pool 2a – SAF

Preferred Term	Placebo (N=117)	Dupilumab 300 mg Q2W (N=81)	Dupilumab 300 mg QW (N=122)	Dupilumab Combined (N=203)
Number of such events	9	9	7	16
Number of patients with at least one such event, n (%)	7 (6.0%)	6 (7.4%)	7 (5.7%)	13 (6.4%)
Dry eye	2 (1.7%)	2 (2.5%)	2 (1.6%)	4 (2.0%)
Conjunctivitis	2 (1.7%)	3 (3.7%)	0	3 (1.5%)
Eye pruritus	2 (1.7%)	0	3 (2.5%)	3 (1.5%)
Eye discharge	0	0	1 (0.8%)	1 (0.5%)
Eye irritation	1 (0.9%)	1 (1.2%)	0	1 (0.5%)
Lacrimation increased	2 (1.7%)	0	1 (0.8%)	1 (0.5%)
Ocular hyperaemia	0	1 (1.2%)	0	1 (0.5%)

Notes: Broad conjunctivitis CMQ search included 16 PTs: Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis, Blepharitis, Dry eye, Eye irritation, Eye pruritus, Lacrimation increased, Eye discharge, Foreign body sensation in eyes, Photophobia, Ocular hyperaemia, Conjunctival hyperaemia, Xerophthalmia.
At each level of patient summarization, a patient is counted once if the patient reported one or more events. MedDRA (Version 24.0) coding dictionary applied. Sorted by decreasing frequency at all levels in the combined dupilumab group.
Pool 2a includes Part A (placebo and 300 mg QW) and Part B (placebo, 300 mg Q2W, and 300 mg QW) of study R668-EE-1774.
Abbreviations: CMQ=customized MedDRA query; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; Q2W=every 2 weeks; QW=once weekly; SAF=safety analysis set.

No additional conjunctivitis or keratitis events were observed in the Pool 2b

- **Analysis of Adverse Events by Organ System**

In Pool 2a, the SOCs with a TEAE incidence ≥10% in any treatment group and a higher incidence in any dupilumab group versus placebo were General disorders and administration site conditions, Infections and infestations, Musculoskeletal and connective tissue disorders and Injury, poisoning and procedural complications. The results in Pool 2b were consistent with the Pool 2a results.

General Disorders and Administration Site Conditions

In the dupilumab 300 mg Q2W group the proportion of participants with TEAEs in the SOC General disorders and administration site conditions was higher (56.8%) than in the dupilumab 300 mg QW (41.8%) and placebo groups (40.2%) and mostly driven by PTs of Injection site reactions, Injection site erythema, Injection site pain, Injection site swelling, Injection site bruising, and Injection site urticaria.

Infections and Infestations

The proportion of participants with TEAEs in the Infections and infestations SOC was higher in the dupilumab 300 mg QW (32.0%) and dupilumab 300 mg Q2W (32.1%) groups than in the placebo group (24.8%). This was partly driven by TEAEs of COVID-19 and Upper respiratory tract infection. The pattern of TEAEs within the Infections and infestations SOC was closely examined by the MAH to determine if there was an association of TEAEs of infections with dupilumab use (see also AR Section Adverse Events Part B). This approach was also taken with the pooled data.

To investigate this apparent imbalance further, data from study R668-EE-1774 were pooled with data from 6 other double-blind, placebo-controlled dupilumab studies completed during the COVID-19 pandemic. In this pooled safety data from 7 dupilumab studies, the incidence of COVID-19 infections was low in both dupilumab (2.5%) and placebo arms (1.5%). This difference of 1.0% is attributable to Study R668-EE-1774 Part B. Upon excluding data from study R668-EE-1774 Part B, the incidence of

COVID-19 infections was numerically lower in the dupilumab arm (1.7%) as compared to the placebo arm (1.8%).

The majority of the events of COVID-19 infection in the dupilumab arm were reported as mild to moderate with no serious events reported, and all events were reported as resolved.

The totality of the data from the dupilumab clinical trial program and post-marketing data, as well as the published literature, shows no evidence of an increased incidence of opportunistic or serious infections with dupilumab, including COVID-19. The exceptions are: increase in localized, herpes virus infections, which are generally a reactivation of endogenous infection. Furthermore, an increase in helminthic infections in some paediatric studies and a decrease in bacterial skin infections in patients with AD.

There were no additional serious or severe infections, infections leading to study drug discontinuation, or other infections of concern to those reported for the Part B.

Table 83 Number of Participants with Treatment-Emergent Adverse Events (Preferred Term ≥2% in Any Treatment Group) in the System Organ Class of Infections and Infestations During the 24-Week Treatment Period - Pool 2a – SAF

		Dupilumab		
Primary System Organ Class Preferred Term	Placebo (N=117)	300 mg Q2W (N=81)	300 mg QW (N=122)	Combined (N=203)
Infections and infestations	29 (24.8%)	26 (32.1%)	39 (32.0%)	65 (32.0%)
Nasopharyngitis	7 (6.0%)	4 (4.9%)	7 (5.7%)	11 (5.4%)
COVID-19	1 (0.9%)	5 (6.2%)	4 (3.3%)	9 (4.4%)
Upper respiratory tract infection	2 (1.7%)	2 (2.5%)	7 (5.7%)	9 (4.4%)
Gastroenteritis viral	0	1 (1.2%)	4 (3.3%)	5 (2.5%)
Sinusitis	2 (1.7%)	0	5 (4.1%)	5 (2.5%)
Urinary tract infection	1 (0.9%)	3 (3.7%)	1 (0.8%)	4 (2.0%)
Conjunctivitis	2 (1.7%)	3 (3.7%)	0	3 (1.5%)
Ear infection	1 (0.9%)	2 (2.5%)	1 (0.8%)	3 (1.5%)
Acute sinusitis	0	2 (2.5%)	0	2 (1.0%)
Pharyngitis streptococcal	1 (0.9%)	2 (2.5%)	0	2 (1.0%)

Notes: At each level of patient summarization, a patient is counted once if the patient reported one or more events.
MedDRA (Version 24.0) coding dictionary applied. Sorted by decreasing frequency at all levels in the combined dupilumab group.
Pool 2a includes Part A (placebo and 300 mg QW) and Part B (placebo, 300 mg Q2W, and 300 mg QW) of study R668-EE-1774.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; Q2W=every 2 weeks; QW=once weekly; SAF=safety analysis set.

Musculoskeletal and Connective Tissue Disorders

The proportion of participants with TEAEs in the Musculoskeletal and connective tissue disorders SOC was slightly higher in the dupilumab 300 mg QW (9.8%) and dupilumab 300 mg Q2W (11.1%) groups than in the placebo group (8.5%). However, Arthralgia is a known ADR for dupilumab and was defined as an AESI in study R668-EE-1774.

Gastrointestinal Disorders

The proportion of participants with TEAEs in the Gastrointestinal disorders SOC was higher in the placebo group (28.2%) than in the dupilumab 300 mg QW group (21.3%) and the dupilumab 300 mg Q2W group (25.9%), with the most frequent PTs being Diarrhoea, Nausea, and Abdominal pain in the placebo group, all at a higher incidence than both dupilumab groups.

Respiratory, Thoracic and Mediastinal Disorders

A higher incidence of TEAEs in the Respiratory, thoracic and mediastinal disorders SOC was reported for the placebo group (16.2%) compared to the dupilumab 300 mg QW group (13.1%) and dupilumab 300 mg Q2W group (13.6%). The most frequent PT being Oropharyngeal pain in the placebo group, which was at a higher incidence than both dupilumab groups.

Nervous System Disorders

Also, for the Nervous system disorders SOC more TEAEs were reported in the placebo group (17.9%) compared to the dupilumab 300 mg QW group (11.5%) and dupilumab 300 mg Q2W group (12.3%). The only frequent PT was Headache.

- **Adverse Drug Reactions**

Two PTs in Pool 2a were identified meeting the criteria for ADRs: Injection site swelling and Injection site bruising. Injection site reactions have previously been identified as common ADRs in other dupilumab indications (AD, asthma, and CRSwNP) and are listed as ADRs in the SmPC.

Table 84 Cox Hazard Ratio and 95% Confidence Interval for Treatment Emergent Injection Site Swelling or Injection Site Bruising During 24-Week Treatment Period – Pool 2a – SAF

		Dupilumab		
Preferred Term	Placebo (N=117) n(%)	300 mg Q2W (N=81) n(%) [HR (95%CI)]	300 mg QW (N=122) n(%) [HR (95%CI)]	Combined (N=203) n(%) [HR (95%CI)]
Any Event of Injection site swelling or bruising	4 (3.4%)	10 (12.3%) [3.92 (1.22 - 12.55)]	15 (12.3%) [3.72 (1.23 - 11.21)]	25 (12.3%) [3.83 (1.33 - 11.07)]
Injection site swelling	3 (2.6%)	7 (8.6%) [3.42 (0.89 - 13.24)]	15 (12.3%) [4.97 (1.44 - 17.16)]	22 (10.8%) [4.40 (1.31 - 14.77)]
Injection site bruising	1 (0.9%)	6 (7.4%) [9.91 (1.18 - 83.25)]	1 (0.8%) [0.94 (0.06 - 15.03)]	7 (3.4%) [4.45 (0.54 - 36.61)]

Notes: Patient without event is censored at the end of week 24 treatment period
Hazard ratio (HR) and its 95% CI are from Cox regression model, which includes treatment group as a factor. For 300 mg QW vs. placebo comparison and for dupilumab combined vs. placebo comparison the Cox regression is also stratified by study part (Part A versus Part B).
MedDRA (Version 24.0) coding dictionary applied.
Pool 2a includes Part A (placebo and 300 mg QW) and Part B (placebo, 300 mg Q2W, and 300 mg QW) of study R668-EE-1774.
Abbreviations: CI=confidence interval; HR=Hazard ratio; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; Q2W=every 2 weeks; QW=once weekly; SAF=safety analysis set.

- **Clinical Laboratory Evaluations**

In R668-EE-1774 Parts A, B, and A/C, and in the R668-EE-1324 study, there were no consistent trends towards an increase or decrease in mean or median values over time in any treatment group for any haematology parameter except eosinophils. Mean and median baseline blood eosinophil counts were similar across the treatment groups and there were larger mean and median changes from baseline in the dupilumab groups versus placebo. Median decreases to week 24 were 0.17×10^9/L in the dupilumab 300 mg QW group, 0.15×10^9/L in the dupilumab 300 mg Q2W group, and 0.06×10^9/L in the placebo group. Furthermore, there were no clinically meaningful trends in shifts from baseline in haematology parameters in all treatment groups.

There were no trends towards an increase or decrease in mean or median values over time in any treatment group and no clinically meaningful differences between the 3 treatment groups in the

number of participants with treatment-emergent PCSVs for any chemistry parameter. Additionally, no clinically meaningful trends in shifts from baseline in chemistry parameters in all treatment groups were reported. Sporadic cases of normal-to-high and normal-to-low shifts from baseline in some chemistry parameters were observed in all treatment groups.

- **Immunogenicity**

The incidence of treatment-emergent ADA-positive responses was <5% in all treatment groups and therefore the planned statistical analysis into possible associations between immunogenicity and safety were not done. The adverse event profiles of participants with ADA-positive responses were examined at the individual participant level. In general, the available immunogenicity data did not show a clinically significant effect of ADA on safety. There was no clear association between injection site reactions seen across all the treatment groups or other commonly related TEAEs and development of ADA.

In Pool 2a (phase 3 placebo-controlled pooled study parts), a transient, treatment-emergent ADA-positive response was seen in 1.5% (3/195) of participants receiving dupilumab and 0.8% (1/118) in the dupilumab 300 mg QW group. In Pool 2b, a transient, treatment-emergent ADA-positive response was seen in 1.4% (3/218) of participants receiving dupilumab and in 0.7% (1/141) in the dupilumab 300 mg QW Group.

Supportive Study

In Study R668-EE-1324 the safety was evaluated in 23 patients who received at least 1 dose of dupilumab compared to 24 patients who received at least 1 dose of placebo. The mean treatment duration was slightly greater in the dupilumab group than in the placebo group. Similarly, the mean duration of observation was higher in the dupilumab group than in the placebo group.

Overall, dupilumab at 300 mg SC QW for 12 weeks was well tolerated in the study patients with active EoE, and had a safety profile comparable to that of the placebo-treated patients.

During the 12-week treatment period, 15 (62.5%) patients in the placebo group and 18 (78.3%) patients in the dupilumab group experienced at least 1 TEAE. The majority of the TEAEs were of mild or moderate severity for both treatment groups.

Table 85 Summary of Treatment-Emergent Adverse Events Occurring in >1 Patients in Any Preferred Term in Any Treatment Group during the 12-Week Treatment Period – SAF

Primary System Organ Class Preferred Term MedDRA version 19.1	Placebo (N=24)	Dupilumab 300 mg QW (N=23)
Patients with at least 1 TEAE	15 (62.5%)	18 (78.3%)
General disorders and administration site conditions	9 (37.5%)	13 (56.5%)
Injection site erythema	2 (8.3%)	8 (34.8%)
Injection site inflammation	0	3 (13.0%)
Injection site rash	0	3 (13.0%)
Injection site pain	2 (8.3%)	2 (8.7%)
Injection site urticaria	0	2 (8.7%)
Pyrexia	1 (4.2%)	2 (8.7%)
Gastrointestinal disorders	7 (29.2%)	8 (34.8%)
Vomiting	1 (4.2%)	2 (8.7%)
Nausea	3 (12.5%)	1 (4.3%)
Abdominal pain	2 (8.3%)	0
Oesophageal stenosis	2 (8.3%)	0

Infections and infestations	4 (16.7%)	8 (34.8%)
Nasopharyngitis	1 (4.2%)	4 (17.4%)
Upper respiratory tract infection	2 (8.3%)	3 (13.0%)
Musculoskeletal and connective tissue disorders	1 (4.2%)	6 (26.1%)
Pain in extremity	0	2 (8.7%)
Respiratory, thoracic and mediastinal disorders	1 (4.2%)	5 (21.7%)
Oropharyngeal pain	1 (4.2%)	2 (8.7%)
Nervous system disorders	3 (12.5%)	2 (8.7%)
Dizziness	2 (8.3%)	0

Patients who experienced more than 1 TEAE were counted only once in each category.

The most common TEAEs in the dupilumab-treated patients were Injection Site Erythema (34.8% versus 8.3% for placebo), Injection Site Inflammation and Injection Site Rash (13.0% versus 0 for placebo for both PTs), Injection Site Urticarial (8.7% versus 0 for placebo), Nasopharyngitis (17.4% versus 4.2% for placebo), and Pain in Extremity (8.7% versus 0 for placebo).

A higher percentage of patients in the dupilumab group than in placebo group experienced any TEAE that was considered by the investigator to be related to the study drug. The majority of such TEAEs were injection site reaction related.

No death occurred during this study.

No patient in either treatment group experienced an SAE during the 12-week treatment period. Three patients (13.0%) in the dupilumab group experienced 3 SAEs during the follow-up period of 16 weeks (Elevated CPK due to excessive strenuous exercise, spontaneous abortion most likely due to history cervical surgery, Drug hypersensitivity other than dupilumab).

Two patients in the dupilumab group experienced a severe TEAE of experienced a non-serious severe Hypoventilation (verbatim term: Hypoventilation during Upper GI Endoscopy) during the 12-week treatment period on study day 87, during the endoscopy procedure, performed under sedation, which was resolved the same day. Another patient experienced a serious severe Food Allergy during the post-treatment follow-up period on study day 90, which was resolved on day 92. All 3 events were assessed by the investigator as not related to the study drug.

One (4.3%) patient in the dupilumab group and none in the placebo group experienced a TEAE that led to permanent discontinuation of study drug. The participant, a 27-year-old female, experienced a non-serious moderate Nail Disorder (verbatim term: Left Index Fingernail Indentation) on study day 37, after receiving 5 weekly doses of dupilumab. The patient received her sixth dose on study day 38. Afterwards, the event led to permanent discontinuation of study drug. The event was assessed by the investigator to be not related to study drug. The event was ongoing at the time of her last study visit.

No clinically significant changes or differences between the 2 treatment groups were observed in laboratory test results, vital signs, 12-lead ECG findings, and physical examination findings. Anti-dupilumab antibodies were not detected in any patient in the placebo group. Two of the 23 dupilumab-treated patients developed a treatment-emergent ADA response with low titers at week 28 (the last study visit). The ADA status for both cases was classified as indeterminate and both positive ADA results were negative in the NAb assay.

Post marketing experience

Over 10,565 study participants have been exposed to dupilumab (as of 28 September 2021 data lock point). Of these, approximately 3,000 participants have been exposed to dupilumab 300 mg QW in the phase 2 asthma, AD, and CRSwNP studies and the phase 3 AD and EoE studies. In Study R668-AD-1225, an open-label extension AD study, approximately 2,250 participants have been treated with dupilumab 300 mg QW for at least 52 weeks. Adult participants may be treated with dupilumab 300 mg QW for up to 5 years in the open-label extension AD study.

2.6.1. Discussion on clinical safety

Study R668-EE-1774 was the pivotal phase 3 study consisting of 3 parts and a follow up period. Part A and Part B (each consisting of a 24-week double-blind treatment period), Part C (a 28-week extended active treatment period), and a 12-week follow-up period. In Part A of the study dupilumab 300 mg QW or matching placebo were administered. In Part B participants received dupilumab 300 mg QW or dupilumab 300 mg Q2W or matching placebo. In Part A/C all patients received dupilumab 300 mg QW. In Part B/C patients received either dupilumab 300 mg QW or dupilumab 300 mg Q2W.

The assessment of safety was a secondary objective, the aim was to evaluate the safety, tolerability and immunogenicity of dupilumab treatment for up to 52 weeks in adult and adolescent patients with EoE (in study R668-EE-1774) and in adult patients with EoE (in study R668-EE-1324).

In total, 367 participants were enrolled. Of these 263 participants received dupilumab. In total, 73 adolescents received any dose of dupilumab, of which 46 received the proposed dose of dupilumab 300 mg QW. Of these, 10 adolescents received dupilumab 300 mg QW over a period of about 1 year (Part A/C). At the CHMP request, additional data for 75 adolescents participants (Part B/C) were submitted including 24 adolescents who received dupilumab 300 mg QW over a period of about 1 year.

Part A

The incidence of all TEAEs reported during Part A of the study was similar between the 2 treatment groups (dupilumab 85.7% compared to placebo 82.11%). The highest incidence of TEAEs was reported in the SOC General Disorders and Administration Site Conditions with 38.5% in the placebo group and 40.5% in the dupilumab 300 mg QW group and were mostly driven by injection site reactions. All Injection Site Reactions were mild or moderate in intensity and all resolved. No events of systemic hypersensitivity, including anaphylactic reactions, and no deaths were reported with dupilumab 300 mg QW.
Two treatment-emergent SAEs were reported in the dupilumab 300 mg QW group (Abdominal Pain and Uterine Polyp) and one in the placebo group (Suicidal ideation). All were assessed as unrelated to treatment, which is reasonable based on the submitted data. One participant in the dupilumab 300 mg QW group permanently discontinued study drug due to a non-serious TEAE of Arthralgia.
The overall incidence of TEAEs for adolescents was similar to that of adults. However, a numerically higher proportion of adolescents reported general disorder and administrative site conditions related to injections in the placebo (44.4%) and the dupilumab 300 mg QW group (54.5%) compared to adult participants in the placebo (36.7%) and the dupilumab 300 mg QW groups (35.5%).

Part B

The incidence of all TEAEs reported during Part B of the study was higher in the dupilumab 300 mg groups (QW: 83.8%; Q2W: 77.8%) than in the placebo group (70.5%). This difference was mainly driven by injection site reactions (most frequent TEAE reported in each treatment group). All injection site reactions were assessed as mild or moderate in intensity and all resolved.
The majority of the TEAEs of Pyrexia were associated with other symptoms and were mild in intensity. All were assessed as not related to study drug, which is reasonable. No deaths were reported in Part B. Five treatment-emergent SAEs (Depression suicidal, Campylobacter colitis, Blood creatine phosphokinase abnormal, Breast cancer and Pneumonia aspiration) were reported in the dupilumab 300 mg QW group, 1 SAE (Suicidal ideation) in the 300 mg Q2W group and 1 SAE (Mental Status Changes) in the placebo group. All were assessed as unrelated to study treatment, which appears reasonable. However, five out of seven SAEs in Part B were reported in adolescents, of which 4 SAEs

occurred in the dupilumab 300 mg QW treated adolescents. Taking the total number of dupilumab treated adolescent participant into account, this higher incidence of SAEs in this age group was further discussed by the MAH. None of the SAEs was considered related to dupilumab by Investigators as all participants had alternate aetiologies and/or risk factors in past medical history. Furthermore, no pattern could be identified and none led to treatment discontinuation. The clarification presented by the MAH is considered acceptable by the CHMP.

The study was conducted during the COVID-19 pandemic. There was a higher incidence of TEAEs in the Infections and infestations SOC in both dupilumab groups versus the placebo group, mainly driven by a higher incidence of COVID-19 TEAEs in the dupilumab groups. One of the TEAEs in this SOC was an SAE (Campylobacter colitis) in the dupilumab 300 mg QW group that resolved without antibiotic treatment and was assessed as not related to study drug by the investigator, which is reasonable. None of the COVID-19 TEAEs was serious or led to study drug discontinuation. The majority were mild in intensity. One Covid-19 TEAE in the dupilumab 300 mg QW group was of severe intensity and was resolved after 19 days.
All COVID-19 TEAEs were assessed as not related to study drug by the investigator and occurred in participants who were either unvaccinated or not fully vaccinated for COVID-19 at the time of the event. The MAH conducted a review of COVID-19 cases throughout the dupilumab clinical database and the patterns of TEAEs within the Infections and infestations SOC were closely examined to determine if there was an association of TEAEs of infections with dupilumab use. No imbalances in COVID-19 or infection TEAEs were identified. Furthermore, a review of the reporting rate of COVID-19 infection during dupilumab use, calculated using global post-marketing pharmacovigilance data, indicated no increased occurrence of COVID-19 infection when compared to the incidence rate of COVID-19 in 6 countries (US, Colombia, Brazil, UK, UAE, and Canada). Based on the data submitted, the conclusion drawn by the MAH that the imbalance of COVID-19 TEAEs observed in this study was not representative of the larger experience with the drug is reasonable.

There were 2 AESIs classified as systemic hypersensitivity reactions, reported in 1 participant in the dupilumab 300 mg QW group and 1 in the placebo group, respectively. The event in the dupilumab 300 mg QW group of Injection site hypersensitivity resolved after a short delay of study treatment. The participant continued and completed study treatment in Part B and entered Part C.

The safety profile for adolescents showed higher incidences of TEAEs in the dupilumab 300 mg groups (QW: 92.3%; Q2W: 85.2%) than in the placebo group (73.1%) mainly driven by General disorders and administration site conditions, however there was no consistent pattern in the incidence of PTs by treatment group. Most of the TEAEs were mild or moderate in intensity.

Two TEAEs leading to permanent discontinuation of the study drug were reported by one adolescent participant in the dupilumab 300 mg Q2W group (Congenital coronary artery malformation and Dyspnoea).

There were larger median decreases in eosinophils in the dupilumab 300 mg QW and Q2W groups versus the placebo group. Otherwise, there were no clinically meaningful changes or differences between the 3 treatment groups observed for chemistry, haematology, urinalysis laboratory values, vital signs, ECG, or physical examination findings.

Part C

The safety profile of dupilumab 300 mg QW in the 28-week treatment period was consistent with that observed in adolescents and adults in the 24-week placebo-controlled Part A of the study. (Part A/C)

The majority of TEAEs were mild or moderate in intensity. In the placebo/dupilumab 300 mg QW group, 73.0% of participants experienced a TEAE and 40.5% experienced a drug-related TEAE. The

corresponding proportions in the dupilumab 300 mg QW/dupilumab 300 mg QW group were 60.0% and 20.0%, respectively.

There was a higher incidence of drug-related TEAEs in those participants previously treated with placebo and switched to dupilumab in Part C, which was mainly driven by the higher incidence of injection site reactions. This was consistent with other dupilumab clinical studies where injection site reactions tend to occur more commonly in the first few weeks after initiation of dupilumab.

In the placebo/dupilumab 300 mg QW group, one participant had a SAE (Systemic inflammatory response syndrome) of severe intensity that led to permanent discontinuation of study drug. However, due to the rapidity of recovery without specific treatment and the discharge diagnosis of "asthma attack and allergic reaction", the MAH believes that the discharge diagnosis is a better characterization of the patient's TEAE, which can be followed based on data submitted.
Another participant in the placebo/dupilumab group had a TEAE (Arthralgia) that led to permanent discontinuation of study drug. Both events were assessed as related to study drug, which is reasonable. No treatment-emergent SAEs or TEAEs leading to permanent discontinuation of the study drug were reported in the dupilumab 300 mg QW/dupilumab 300 mg QW group.
Other AESIs reported were Vernal keratoconjunctivitis and 1 participant in the dupilumab 300 mg QW/dupilumab 300 mg QW group reported AESIs of Anaphylactic reaction and Anaphylactic shock, which was related to food allergy and not to the study drug.

There were no clinically significant trends observed for haematology, chemistry, or urinalysis laboratory values, vital signs, ECGs, or physical examination findings.

Treatment-emergent ADA responses to dupilumab were observed in 7% of participants (5 of 71), most of whom exhibited a transient, low-titer response. One participant developed a treatment-emergent, moderate titer ADA response and was also positive for neutralizing antibodies in Part C.

During the 28-week treatment period in Part C for participants enrolling from Part B (Part B/C), the majority of TEAEs were mild or moderate in intensity. The proportion of participants who experienced a TEAE across the treatment groups ranged from 59.5% in the placebo/dupilumab 300 mg Q2W group to 70.9% in the dupilumab 300 mg Q2W/dupilumab 300 mg Q2W group. The proportions of participants experiencing a drug-related TEAE were higher in participants who received dupilumab 300 mg Q2W in Part B/C, regardless of the previous Part B treatment (32.4% in the placebo/dupilumab 300 mg Q2W group and 31.6% in the dupilumab 300 mg Q2W/dupilumab 300 mg Q2W group versus 18.9% in the placebo/dupilumab 300 mg QW and in the dupilumab 300 mg QW/dupilumab 300 mg QW groups.

The most commonly affected SOC was General disorders and administration site conditions. Overall, the proportion of participants with TEAEs in this SOC was 30.3% (46/152 adult participants). The majority of TEAEs were mild in intensity. No new safety signals were identified and no deaths or TEAEs leading to discontinuation were reported.

Pooled data (Pool 2a and 2b)

Pool 2a is the randomized, placebo-controlled, phase 3 safety pool intended to assess the safety profile of dupilumab (300 mg QW or 300 mg Q2W) versus placebo in adult and adolescent patients with EoE. Part A and Part B participants who received any dose of study drug were included in Pool 2a.
Pool 2b included participants from the phase 2 study R668-EE-1324 with a 12-week placebo-controlled treatment period and the phase 3 study R668-EE-1774 Part A and Part B with a 24-week treatment period.
The data show that Injection site reactions were the most commonly reported type of TEAE in all treatment groups. None were severe, serious or led to study drug discontinuation. Injection site swelling and Injection site bruising met the criteria for ADRs. Injection site reactions have previously

been identified as common ADRs in other dupilumab indications (AD, asthma, and CRSwNP). However, the incidence of Injection Site Reaction reported in all Parts of Study R668-EE-1774 and in Study R668-EE-1324 is high in the EoE population. Although, the reactions were mild to moderate in intensity, the high incidence could impair the compliance of patients, especially in the younger age group. The MAH was asked to discuss possible reasons for the higher incidences of injection site reactions. In the summary of HLT Injection site reactions in adult and adolescent groups in study R668-EE-1774 parts A, B, A/C and B/C provided by the MAH no clear pattern regarding the incidence for ISRs can be identified. The frequency of ISRs varied considerably, ranging from 25% to 50% for placebo compared to 10.0% to 59.3% for dupilumab. Furthermore, considering the data from Part B/C, no dose-dependent correlation for the ISRs could be identified. This issue was considered resolved.

There was a low proportion of participants with TEAEs leading to permanent study drug discontinuation and there no deaths were reported in pool 2a and 2b. There was no evidence of a pattern among the reported SAEs to suggest any relationship to dupilumab treatment.

Two events of systemic hypersensitivity were reported in Pool 2a. One in the dupilumab 300 mg QW group and one in the placebo group. Both were associated with injection site reactions and concurrent systemic symptoms. In both cases treatment with study drug was continued.

The risk of infections was closely examined in the polled analyses due to a higher incidence of reported TEAEs in the Infections and infestations SOC in the dupilumab treatment groups (32%) compared to the placebo group (24.8%), serious infections were reported in 0.5% of patients treated with dupilumab and 0% of patients treated with placebo. Section 4.8 of the SmPC has been updated with this information. This higher incidence was partly driven by TEAEs of COVID-19 (by PT: 3.3% for the dupilumab 300 mg QW group and 6.2% for the dupilumab 300 mg Q2W group versus 0.9% for placebo group in Pool 2a) and Upper respiratory tract infection (by PT: 5.7% for the dupilumab 300 mg QW group and 2.5% for the dupilumab 300 mg Q2W group versus 1.7% for placebo group in Pool 2a).

Regarding infection in general, on examination of both individual events and incidence in other SOCs no clear pattern or trend was observed related to infections, with most imbalances being stochastic and/or observed bi-directionally. The only exception was noted for COVID-19-related PTs, for which a cumulative analysis of all dupilumab data was performed by the MAH. This analysis did not show evidence of a causal association between Dupilumab and an increased risk of serious, severe or opportunistic infections.

The largest differences in overall TEAE incidence in the dupilumab groups were seen in the age subgroup, with a higher incidence of TEAEs in adolescents than in adults, in particular for injection site reactions. However, there was no consistent pattern in the incidence and type of PTs across the treatment groups.

Injection site swelling and Injection site bruising met the criteria for ADRs based on the safety pool results. Injection site reactions, including injection site swelling, are already identified ADRs for other approved indications for dupilumab. Injection site bruising has been added in section 4.8 of the SmPC. No other ADRs were identified in the population of adolescents and adults with EoE.

Results in Pool 2b showed a similar safety profile to Pool 2a. The clinical laboratory results in Pool 2a were generally without clinically meaningful findings. Results from Pool 2b and the extended active treatment period (Part A/C) were consistent with the Pool 2a results. However, in other dupilumab indications (AD, asthma, CRSwNP), transient increases from baseline in mean blood eosinophil counts have been observed in dupilumab-treated participants, which returned towards baseline levels by the end of the treatment period. In contrast, in EoE participants treated with dupilumab, small decreases from baseline in mean/median blood eosinophil counts were observed, which were further discussed by

the MAH. It was agreed that the differences in mean blood eosinophil levels observed across different indications are clinically not meaningful and mostly transient.

Supportive study R668-EE-1324

In Study R668-EE-1324 safety was evaluated in 23 patients who received at least 1 dose of dupilumab compared to 24 patients who received at least 1 dose of placebo. Overall, the safety profile reported for dupilumab at 300 mg SC QW administered was comparable to that of the placebo-treated patients. The overall incidence of TEAEs in the dupilumab group were 78.3% and 62.5% in the placebo group. The most common TEAEs in the dupilumab-treated patients were Injection Site Erythema (very high compared to placebo: 34.8% versus 8.3% for placebo), Injection Site Inflammation and Injection Site Rash (13.0% versus 0 for placebo for both PTs), Injection Site Urticarial (8.7% versus 0 for placebo), Nasopharyngitis (17.4% versus 4.2% for placebo), and Pain in Extremity (8.7% versus 0 for placebo).

No patient in either treatment group experienced an SAE during the 12-week treatment period. Three patients in the dupilumab group experienced 3 SAEs (Blood Creatine Phosphokinase Increased, Abortion Spontaneous, and Food Allergy) during the follow-up period, which were all assessed by the investigator as not related to the study drug and all events resolved. One patient in the dupilumab group experienced a TEAE (Nail Disorder) that led to permanent discontinuation of study but was not related to the study drug.

Overall, the safety data reported for study R668-EE-1324 are in line with the results seen in Study R668-EE-1774. Injection site reactions were the most frequent reported TEAEs. Severe Adverse Events were not reported during the 12-week treatment period and the 3 SAEs reported during the follow-up period were not related to study drug.

Assessment of paediatric data on clinical safety

Overall, 64 adolescents were included in the Pool 2A analyses (35 in the placebo, 27 in the dupilumab 300 mg Q2W and 37 in the dupilumab 300 mg QW group).

In the Pool 2a subgroup analysis by age group, in both dupilumab 300 mg treatment groups the incidence of TEAEs was higher in the adolescent cohort versus the adult cohort (dupilumab 300 mg QW: 94.6% of adolescents versus 80.0% of adults; dupilumab 300 mg Q2W: 85.2% of adolescents versus 74.1% of adults). In the placebo group, the difference in incidence of TEAEs was less marked (80.0% of adolescents versus 72.0% of adults).

In both age groups, the SOC with the highest incidence of TEAEs across all treatment groups was General disorders and administration site conditions. Within the adolescent subgroup, the incidence of TEAEs in this SOC was similar across the treatment groups with the lowest incidence of 51.4% in the dupilumab 300 mg QW group and placebo group and the highest incidence of 59.3% in the Q2W group. The PT Injection site reaction was by far the most common PT across all treatment groups in the adolescent subgroup, with the highest incidence of 40.0% in the placebo group compared to 32.4% in the dupilumab 300 mg QW group and 33.3% in the dupilumab 300 mg Q2W group. Within the adult subgroup, the incidence in this SOC was lower versus adolescents and there was more variability, with the lowest incidence in the placebo group (35.4%) and the highest in the dupilumab 300 mg Q2W group (55.6%).

The SOC with the next highest incidence in the dupilumab groups was Infections and infestations. In both age subgroups, the lowest incidence was seen in the placebo group (28.6% in the adolescent subgroup and 23.2% in the adult subgroup). In the dupilumab 300 mg QW group, the incidences were 35.1% in adolescents and 30.6% in adults, and in the dupilumab 300 mg Q2W group 33.3% and 31.5%, respectively. There was no individual PT driving the differences. There was no apparent

difference in the pattern of TEAEs between adults and adolescents. In the SOC Gastrointestinal disorders, the incidence was similar across both age subgroups and across treatment groups (between 20.0% and 27.8%), except for the adolescent placebo group with an incidence of 37.1%. There was no individual PT identified driving this difference.

In the SOCs Respiratory, thoracic and mediastinal disorders and Skin and subcutaneous tissue disorders, within the adolescent subgroup the incidences of TEAEs in the dupilumab 300 mg Q2W group were higher versus placebo with 25.9% compared to 17.1% in the placebo group for Respiratory, thoracic and mediastinal disorders and 33.3% compared to 11.4% for Skin and subcutaneous tissue disorders. However, the incidence in the dupilumab 300 mg QW group was lower versus placebo (16.2% and 2.7% for the 2 SOCs, respectively).

In Part A/C data from only 10 adolescent participants through week 52 were available. Of these 80% reported at least one TEAE. The SOC with the highest incidence of TEAEs across all treatment groups was General disorders and administration site conditions with 50%.

At the CHMP request, in addition to the data from 10 EoE adolescent participants who completed 52 weeks on dupilumab 300 mg every week (QW) in Study Part A/C, the MAH submitted the additional data from a further 75 adolescent participants who completed study Parts B and C (Part B/C). These additional data include 24 adolescents who completed 52 weeks on dupilumab 300 mg QW and generally confirm the safety profile seen in adolescents in study parts A, B and A/C.

Overall, TEAEs were reported in 70.7% of adolescent participants, which was slightly higher than in the adult population with 65.1%. The proportion of adolescent participants who experienced a TEAE was similar across the treatment groups, ranging from 69.2% (18/26) in the dupilumab 300 mg Q2W/dupilumab 300 mg Q2W group, 70.0% (7/10) in the placebo/dupilumab 300 mg QW group, 70.8% (17/24) in the dupilumab 300 mg QW/dupilumab 300 mg QW group, to 73.3% (11/15) in the placebo/dupilumab 300 mg Q2W group. The difference is most noticeable in the arms that switched from placebo in Part B to dupilumab (either QW or Q2W) in Part C. In those arms receiving dupilumab for the first time, 55.1% of the adults reported a TEAE versus 72% of the adolescents. By contrast in the arms that continued their dupilumab dose into Part C from Part B (QW or Q2W), there is not such a discernible difference in overall TEAE rates between adolescents and adults (70% in adolescents v 69.9% in adults).

In Part B/C the most commonly affected SOC in adolescents was General disorders and administration site conditions. Overall, the proportion of adolescent participants with TEAEs in this SOC was 33.3%, similar to adults in which the proportion was 30.3%. This SOC incidence was mostly driven by various injection site reaction PTs including injection site reaction (17.3%), injection site pain (10.7%), injection site erythema (5.3%), and injection site swelling (5.3%). The next most common TEAE grouping seen in adolescents was Infections and Infestations- overall 29.3% of adolescents (most commonly COVID19, followed by nasopharyngitis, followed by UTI) which is broadly similar to the overall rate seen in adults, 24.3%.

The majority of TEAEs in adolescents were mild to moderate in intensity with low rates of severe TEAEs overall in adolescents, 2 overall (2.7%), compared to 2 in the adult group overall (1.3%). No TEAE deaths or SAEs leading to study drug discontinuation in adolescents were reported. One SAE was reported in adolescent participants (1.3% versus 2.6% in the adult cohort). The SAE was in an adolescent in the dupilumab 300mg QW/dupilumab 300mg QW group and the adolescent was hospitalised due to diarrhoea/rectal tenesmus and investigator assessed as unrelated to study drug.

Overall, it is agreed that the safety profile in adolescents with EoE is generally similar to that of adults, although a slightly higher occurrence of TEAEs is observed, albeit that the additional TEAEs seem to fall into the mild to moderate category. Furthermore, the MAH reports literature that Injection Site

Reactions (ISR) AEs are reported more frequently in childhood and adolescents than adults. The reporting rates of ISR fall during adult life, possibly due to higher tolerance to pain. This rationale can be followed.

However, even with the B/C data, the numbers of adolescents compared to adults are still relatively low, making it difficult to compare the TEAE rates with certainty. In any case, it is agreed, that even if AEs are reported more frequently in adolescents, they are generally mild or moderate.

The 300 mg QW dose of dupilumab has not been administered to adolescents outside of study R668-EE-1774.

In addition to the data from 10 adolescent eosinophilic esophagitis (EoE) participants who completed 52 weeks on dupilumab 300 mg every week (QW) in Study Part A/C, the MAH submitted the additional data from a further 75 adolescent participants who completed study Parts B and C (Part B/C) with the responses to the Request for Supplementary Information. These participant numbers are considered important especially in the context of a rare disease like EoE. These additional data include 24 adolescents who completed 52 weeks on dupilumab 300 mg QW and generally confirm the safety profile seen in adolescents in study parts A, B and A/C.

The additional data provided a more detailed view of the safety profile in adolescents and particularly of the longer-term use for up to one year.

Additionally, the MAH has provided a high level break down of safety events in the 20 patients in the EoE studies that weighed 40-50kg and received 300mg weekly versus those weighing more than 50kg. The provided comparison of TEAEs rates and top line TEAE results from the AD and EoE studies do not signal any increase in toxicity in the 40-50kg weight band, versus those patients heavier than 50kg.

Overall, it is agreed that the submitted data suggest that adolescents and adults of similar weights have similar exposures. While based on small numbers, and that definite conclusion cannot be drawn, it can be agreed that lighter patients did not display an increased rate of TEAEs.

2.6.2. Conclusions on clinical safety

The safety of the Dupilumab 300 mg QW dosing regimen has already been evaluated in different trials for other indications in the dupilumab development program (AD, asthma, and CRSwNP). Approximately 3,000 participants have been exposed to dupilumab 300 mg QW mainly in the AD indication. No new safety signals associated with the use of dupilumab in participants with EoE were identified in this application. The overall safety profile was consistent with that seen in the other dupilumab indications.

The SOC with the highest incidence of TEAEs across all treatment groups was General disorders and administration site conditions. Injection site swelling and Injection site bruising met the criteria for ADRs based on the safety pool results. Injection site reactions, including injection site swelling, are already identified ADRs for other approved indications for dupilumab. Injection site bruising has been added in section 4.8 of the SmPC as it was not observed for other indications. Although these TEAEs were of mild to moderate intensity, there was a high incidence especially in the adolescent participants.

The rate of Serious Adverse Events and Adverse Events leading to discontinuation was low in all treatment groups and no clear pattern was identified indicating a relationship to the study treatment.

Overall, the safety profile in adult participants is adequately evaluated and consistent with the safety profile of 300 mg QW reported in other indications.

In adolescent participants, the rates of TEAEs are higher in adolescents compared to the adults and most SAEs were reported in this age group. The safety data confirmed a broadly similar safety profile in adolescents with EoE to that seen in adults with EoE, even though slightly higher rates of TEAE are observed.

2.6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Risk management plan

The MAH submitted to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 8.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 8.2 with the following content:

Safety concerns

Important identified risks	Systemic hypersensitivity (including events associated with immunogenicity) Conjunctivitis and keratitis related events in AD patients
Important potential risk	None
Missing information	Use in pregnant and lactating women Long-term safety

AD: Atopic Dermatitis.

Pharmacovigilance plan

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1				
Not applicable				
Category 2				
Not applicable				
Category 3				
Pregnancy registry (R668-AD-1639) Ongoing	To evaluate the effect of exposure to dupilumab on pregnancy and infant.	Use in pregnant and lactating women	Protocol submission	Submitted to PRAC in Jan-2018 (and amendment #1 in Sep-2018)

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
			Amended protocol (asthma cohorts) Final report	Submitted for information with EU-RMP v5.0 Jan-2027
Pregnancy Outcomes Database Study (R668-AD-1760) Ongoing	To measure the prevalence of adverse pregnancy and infant outcomes in a cohort of women with AD exposed to dupilumab during pregnancy compared to a disease-matched cohort exposed to systemic medication or phototherapy (but unexposed to dupilumab) in AD patients and a disease-matched cohort who were not exposed to these treatments during pregnancy.	Use in pregnant and lactating women	Protocol submission (amendment 1)	Submitted for information with EU-RMP v5.0
			Final report	Apr-2027
A single-arm extension study of dupilumab in patients with AD who participated in previous dupilumab clinical trials; including a sub study consisting of standardized ophthalmology assessments (Phase IV) (R668-AD-1225) (LTS14041) Ongoing	To assess the long-term safety, efficacy, PK, and immunogenicity of REGN668 in adult patients with moderate-to-severe AD.	Long-term safety (Ophthalmology sub study: additional information on conjunctivitis and keratitis related events in AD patients)	Final report	Q3 2023
An open-label extension study to assess the long-term safety of dupilumab in patients ≥6 months to <18 years of age with AD (Phase III) (LTS1434) (R668-AD-1434)	To assess the long-term safety of dupilumab in pediatric patients with AD.	Long-term safety of dupilumab in pediatric patients with AD	Final report	Q4 2024

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Ongoing				
An open-label study to evaluate the long-term safety and tolerability of dupilumab in pediatric patients with asthma who participated in a previous dupilumab asthma clinical study (Phase III) (LTS14424) Ongoing	To assess the long-term safety, tolerability and efficacy of dupilumab in pediatric patients with asthma	Long-term safety of dupilumab in pediatric patients with Asthma	Final report	Sep-2024
AD: Atopic Dermatitis; PK: Pharmacokinetic; PRAC: Pharmacovigilance Risk Assessment Committee; Q: Quarter; RMP: Risk Management Plan.				

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Systemic hypersensitivity (including events associated with immunogenicity)	**Routine risk minimization measures:** SmPC sections 4.3, 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Hypersensitivity questionnaire **Additional pharmacovigilance activities:** None
Conjunctivitis and keratitis related events in AD patients	**Routine risk minimization measures:** SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Ophthalmology substudy in LTS14041 (R668-AD-1225)
Use in pregnant and lactating women	**Routine risk minimization measures:** SmPC sections 4.6 and 5.3 PIL section 2 Prescription only medicine A**dditional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Pregnancy questionnaire **Additional pharmacovigilance activities:** • Pregnancy registry study (R668-AD-1639)

Safety concern	Risk minimization measures	Pharmacovigilance activities
		• Pregnancy Outcomes Database Study (R668-AD-1760) in AD patients
Long-term safety	**Routine risk minimization measures:** Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Studies LTS14041 (R668-AD-1225), LTS1434 (R668-AD-1434), and LTS14424

AD: Atopic Dermatitis; EU: European Union; PIL: Patient Information Leaflet; PK: Pharmacokinetic; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics.

2.8. Update of the Product information

As a consequence of this new indication, the sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The changes of the package leaflet are included in section 1 (EoE extension of indication), section 2 (to exclude children under 12 years of age), section 3 (300 mg given every week for patients ≥12 years old and with a bw ≥40 kg) and section 4 (commonly occurred side effect bruising). Neither a full user testing nor a bridging/ focus test are performed by the marketing authorisation holder, which is considered acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Eosinophilic esophagitis (EoE) is a serious, chronic, type 2 inflammatory, immune-mediated disease of the esophagus. The prevalence of EoE is estimated at 22.7 per 100,000 worldwide and has been increasing. Eosinophilic esophagitis has been reported in all ages. However, most cases are in children and adults younger than 50 years.

The disease is characterized by type 2 inflammation with esophageal eosinophilia leading to symptoms of esophageal dysfunction. Growing evidence suggests that a type 2 cytokine-mediated immune response plays an important role in the development of EoE. Patients with EoE have increased levels of

esophageal inflammatory infiltrates, including eosinophils, T-lymphocytes, mast cells, and basophils, as well as type 2-associated chemokines and cytokines, such as eotaxin-3, interleukin (IL)-4, IL-5, and IL-13. Esophageal biopsies and blood samples of patients with active EoE have increased levels of the type 2 prototypical cytokines and chemokines including IL-4, IL-5, and IL-13. Eosinophilic esophagitis is also distinguished by the expression of a unique esophageal transcriptome and the interplay of early life environmental factors with distinct genetic susceptibility elements at 5q22 (thymic and stromal lymphopoietin [TSLP]) and 2p23 (calpain 14 [CAPN14]). CAPN14 is overexpressed by the esophageal epithelia in patients with EoE and may account for the tissue specificity of esophageal disease in EoE because CAPN14 invokes a pathway that alters basic epithelial cell functions, including barrier integrity.

The primary clinical manifestations of EoE in both adults and children over 10 years of age are dysphagia and food impaction. Other clinical manifestations such as heartburn, diarrhea and weight loss have also been reported. The symptoms lead to substantially impaired quality of life (QOL). Food impaction is a traumatic event for patients, and often requires medical intervention, including emergency room visits for manual removal to relieve the impaction. Eosinophilic esophagitis is the underlying cause of approximately 50% of the food impaction cases that present in the emergency department.

Complications of EoE include food impaction, strictures, esophageal dysmotility, increased esophageal infections, aspiration, and spontaneous esophageal rupture. Food impaction can occur at any stage of the disease, either as an initial manifestation of EoE or after many years of EoE disease duration. Dysphagia, food impaction and regurgitation may increase the risk for aspiration, including aspiration pneumonia. Esophageal inflammation in EoE may also result in esophageal perforation.

3.1.2. Available therapies and unmet medical need

Current therapeutic approaches include chronic dietary elimination, conventional medicinal therapies, and esophageal dilation. The combination of diet modification and conventional medicinal therapies (swallowed topical corticosteroid formulations like orodispersible budesonide (Jorveza) is approved in adults in the European Union and off-label proton-pump inhibitors) can be effective in the management of some patients with EoE. About 25% of patients may have significant ongoing symptoms, despite treatment with dietary modification and corticosteroids. Additionally, a significant portion of patients do not respond to corticosteroids, and those who do respond may not have sustained benefit, a critical limitation for this chronic disease. Furthermore, swallowed topical corticosteroids may have adverse reactions associated with systemic glucocorticoid absorption, including increased risk of Cushing's syndrome, adrenal suppression, growth retardation in children, muscle weakness and osteoporosis. Long-term use of PPIs has been associated with an increased risk of chronic kidney disease and may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. Endoscopic dilation can provide immediate relief but carries a risk (albeit low) of serious complications due to esophageal perforation and does not have any affect the underlying inflammatory pathology of EoE.

Overall, the current available medicinal therapies for EoE are limited by variable response rates, variable symptom improvement, relapse after therapy cessation, failure to show sustained benefit, the potential for side effects and adverse effects on QoL. Therefore, an unmet need is seen for safe and effective treatment options that address the underlying inflammation of EoE to prevent the disease progression and improve clinical symptoms in adults and adolescents inadequately controlled by, intolerant to, or who are not candidates for conventional medicinal therapy.

3.1.3. Main clinical studies

Study R668-EE-1774 was a randomized, double-blind, multi-centre, pivotal phase 3 study to evaluate the efficacy of dupilumab treatment compared with placebo in adult and adolescent patients with EoE. This study consisted of 3 parts. Part A and Part B consisted of a 24-week double-blind treatment period each, Part C of a 28-week extended active treatment period. A 12-week post treatment follow-up period followed at the end of Part C or at the end of Parts A or B for participants who did not enter Part C.
Part A and Part B were carried out as 2 separate sequential independent parts and participants could only be enrolled in either Part A or Part B. Part A evaluated efficacy and safety of dupilumab 300 mg QW versus placebo. Part B evaluated efficacy and safety of dupilumab 300 mg QW and 300 mg Q2W versus placebo. Participants were stratified by age (≥18 years versus ≥12 to <18 years of age) and use of PPI at randomization.
Part C of Study R668-EE-1774 extended the treatment period for an additional 28 weeks. All participants who entered Part C from Part A were administered dupilumab 300 mg SC QW for 28 weeks during Part C. Participants who entered Part C from Part B were administered either dupilumab 300 mg SC QW or dupilumab 300 mg SC Q2W for 28 weeks during Part C.

3.2. Favourable effects

The co-primary endpoint in Part A and B were Proportion of Participants Achieving Peak Esophageal Intraepithelial Eosinophil Count ≤6 eos/hpf at week 24 and Absolute Change from Baseline in DSQ Total Score at week 24.

The results of Part A show that the proportion of participants who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24 was significantly greater in the dupilumab 300 mg QW group (59.55%) compared to the placebo group (5.1%). The results from the other co-primary endpoint showed an improvement in DSQ total score compared to placebo at week 24. The reduction from baseline in DSQ total score at week 24 was greater in the dupilumab 300 mg QW group (-21.92 points) versus the placebo group (-9.60 points). The results of the secondary endpoints evaluated show consistent improvement of EoE disease symptoms and health-related quality-of-life measures consistent with results of the primary endpoints.

In Part B, Dupilumab 300 mg QW demonstrated clinically meaningful improvement over placebo in the co-primary and secondary endpoints. The proportion of participants who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24 was greater in the dupilumab 300 mg QW group (58.8%) compared to placebo (6.3%). Higher improvement from baseline in DSQ total score at week 24 was seen in the dupilumab 300 mg QW group (−23.78 points) compared to placebo (−13.86 points). The results of the high number of secondary endpoints also show greater improvement of EoE disease symptoms and health-related quality-of-life measures with Dupilumab 300 mg QW compared to placebo.

At the end of the Part A/C treatment period, more than half (57.8%) of participants achieved a peak esophageal intraepithelial eosinophil count ≤6/hpf. Of participants receiving dupilumab 300 mg QW in Part A and C, 68.4% had histological remission at the Part C baseline (end of Part A) and 55.9% at week 52 (end of Part C). Of participants previously treated with placebo in Part A, 60.0% achieved a peak esophageal intraepithelial eosinophil count ≤6/hpf after 28 weeks of dupilumab treatment in Part C (week 52), which is similar to the proportion of participants treated with dupilumab during Part A.

Furthermore, participants receiving the 300 mg QW dosing regimen continued to improve during Part C. While 58.8% of participants in Part B had achieved peak esophageal intraepithelial eosinophil count

≤6/hpf at Week 24 on dupilumab 300 mg QW, 84.6% had achieved this after 52 weeks. Similarly, DSQ scores continued to improve in Part B participants treated with dupilumab 300 mg QW from -23.78 at 24 weeks to -30.26 at 52 weeks. Participants who received placebo in Part B achieved improvements after 28 weeks on dupilumab 300 mg QW in Part C similar to those observed for participants who received 24 weeks of dupilumab treatment during Part B.

In conclusion, the results reported for the Dupilumab 300 mg QW dosing regimen administered in Study R668-EE-1771 show clinically meaningful improvements of signs and symptoms in patients with EoE measured by the co-primary endpoints `Proportion of participants who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24´ and `Absolute Change from Baseline in DSQ Total Score at week 24´ compared to placebo. Consistent results are seen for the high number of secondary endpoints showing improvements of EoE disease symptoms, health-related quality-of-life measures and histologic, endoscopic and molecular endpoints.

Similar results were seen in the adolescent subgroup. In Pool 1, the Co-Primary endpoints were analysed by age. The results show that in the ≥12 to <18 years of age group, the proportion of participants who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24 was 19/37 (51.4%) in the dupilumab 300 mg QW group versus 2/35 (5.7%) in the placebo group. In the ≥12 to <18 years of age group, the improvement in DSQ total score from baseline to week 24 was -21.07 points in the dupilumab 300 mg QW group (n=37) and -17.23 points in the placebo group (n=35).

3.3. Uncertainties and limitations about favourable effects

No patients weighting less than 40kg were included in the study R668-EE-1774. Therefore as no clinical experience is available for this weight group, the MAH decided to exclude this group from the indication.

In Part B of study R668-EE-1774 the dupilumab 300 mg Q2W showed similar results in the proportion of patient achieving a peak esophageal intraepithelial eosinophil count ≤6/hpf to the 300 mg QW dose but the change in the DSQ score was only similar to placebo in adults and even lower in adolescents. As the dupilumab 300 mg Q2W regimen achieved similar efficacy to the 300 mg QW regimen with respect to reducing eosinophilic infiltration to the esophagus, the cause of failure of the 300 mg Q2W regimen to achieve efficacy on reducing dysphagia is not likely due to insufficient drug distribution to the esophageal mucosa. These results suggest that reducing eosinophilic infiltration to the esophageal mucosa may be necessary but insufficient to achieve improvement in symptoms of EoE such as dysphagia. The reason for the different results for the co-primary endpoint between the dupilumab 300 mg QW and 300 mg Q2W regimens remains unclear. One hypothesis is that in addition to the effect on infiltration of eosinophils in the esophageal mucosa, the drug effect on dysphagia may be modulated by a different effect compartment (e.g., muscularis layer, esophageal nervous plexus). Similarly, the results from 227 out of 240 Part B participants who entered Part C (Part B/C) show that numerically greater effects in all endpoints were observed in participants who had been treated with dupilumab 300 mg QW for 52 weeks compared with those treated with dupilumab 300 mg Q2W.

Although it can be agreed that the data from B/C indicate that continued use for up to one year was generally well tolerated it remains unclear whether a frequency of weekly dosing is required after a patient achieves remission, or after one year of therapy. The weekly dosing is a considerable disease burden, which might not be tolerated by all patients for long term use. Therefore, at the CHMP request, the MAH added in section 4.2 of the SmPC that dosing beyond 52 weeks has not been studied.

3.4. Unfavourable effects

The incidence of Injection Site Reaction reported in all Parts of Study R668-EE-1774 and in Study R668-EE-1324 is high in the EoE population. Pool 2a shows that there is a high difference in the PT of injection site swelling between dupilumab the 300 mg QW and Placebo. In the supportive study R668-EE-1324 the most common TEAEs in the dupilumab-treated patients were Injection Site Erythema. The incidence was very high in the dupilumab treated patients: 34.8% compared to 8.3% for placebo.

Injection site reactions have previously been identified as common ADRs in other dupilumab indications (AD, asthma, and CRSwNP). Injection site bruising has been added in section 4.8 of the SmPC. Although, the reactions were mild to moderate in intensity, the high incidence could impair the compliance of patients, especially in the younger age group.

A higher incidence of TEAEs in the Infections and infestations SOC was reported in the dupilumab treatment groups (32%) compared to the placebo group (24.8%), serious infections were reported in 0.5% of patients treated with dupilumab and 0% of patients treated with placebo. Section 4.8 of the SmPC has been updated with this information.

In the subgroup analysis by age group, in both dupilumab 300 mg treatment groups the incidence of TEAEs was higher in the adolescent cohort versus the adult cohort (QW: 92.3% of adolescents versus 79.6% of adults; Q2W: 85.2% of adolescents versus 74.1% of adults). In the placebo group, the incidence of TEAEs was similar (73.1% of adolescents and 69.2% of adults).

Five out of seven SAEs in Part B were reported in adolescents up to week 24, of which 4 SAEs occurred in dupilumab 300 mg QW treated adolescents. Of note, only 26 of the 161 of the dupilumab treated participants in this study part were adolescents, this higher incidence of SAEs in this age group was further explored. None of the SAEs was considered related to dupilumab by Investigators as all participants had alternate aetiologies and/or risk factors in past medical history. Furthermore, no pattern could be identified and none led to treatment discontinuation.

In Part B/C a slightly higher rate of TEAEs was reported for adolescents (70%) compared to adults (65%), a trend similar to results in Part A, B and A/C. The difference is most noticeable in the arms that switched from placebo in Part B to dupilumab (either QW or Q2W) in Part C. In those arms receiving dupilumab for the first time, 55.1% of the adults reported a TEAE versus 72% of the adolescents. By contrast in the arms that continued their dupilumab dose into Part C from Part B (QW or Q2W), there is not such a discernible difference in overall TEAE rates between adolescents and adults (70% in adolescents vs 69.9% in adults).

In conclusion no new safety signals associated with the use of dupilumab in participants with EoE were identified. The overall safety profile was consistent with that seen in other indications in the dupilumab development program (AD, asthma, and CRSwNP).

3.5. Uncertainties and limitations about unfavourable effects

Most of the TEAEs reported were of mild or moderate intensity. The high incidence of the TEAEs was mainly driven by injection site reactions. No specific pattern of PTs was identified.

The 300 mg dose has not been administered to adolescents outside of the pivotal study. Although additional safety data from 75 adolescents have been submitted during the evaluation, the number of adolescent participants, who received the dupilumab 300 mg QW through week 52 is still relatively limited. These additional data included 24 adolescents who completed 52 weeks on dupilumab 300 mg QW in study part B/C, (in addition to the data from the 10 adolescents who completed 52 weeks on dupilumab 300 mg QW in Study Part A/C). This makes the comparison of the TEAE rates of

adolescents vs adults difficult to conclude for the intended indication. However, it has to be taken into account that Eosinophilic Esophagitis is defined as a rare disease.

As no data are available beyond 52 weeks; this has been adequately mentioned in section 4.2 of the SmPC.

3.6. Effects Table

Table 86 Effects Table for Dupixent for the treatment of EoE (Data base lock Part A: 20 May 2020; Part B: 30 Sep 2021).

Effect	Short description	Unit	Treatment DUP 300mg QW	Control PBO	Uncertainties / Strength of evidence	References
Favourable Effects						
Co-prim EP Eosinophil Count	Proportion of participants who achieved peak esophageal intraepithelial eosinophil count ⩽6 eos/hpf at week 24	N (%)	Part A 25 (59.5) Part B 47 (58.8)	2 (5.1) 5 (6.3)	Statistically significant and clinically meaningful (FAS)	Study R668-EE-1774 Part A and Part B
		N (%)	Part A 4 (36.4) Part B 15 (57.7)	0 (0.0) 2 (7.7)	Subgroup Analyses (Adolescents) Limited in numbers	
Co-prim EP DSQ	Absolute change from baseline in DSQ total score at week 24	LS mean (SE)	Part A -21.92 (2.526) Part B -23.78 (1.861)	-9.60 (2.785) -13.86 (1.909)	Statistically significant and clinically meaningful (FAS)	Study R668-EE-1774 Part A and Part B
		LS mean (SE)	Part A -23.48 (4.767) Part B -19.54 (3.574)	-15.93 (5.250) -16.42 (3.600)	Subgroup Analyses (Adolescents) Limited in numbers	
Reduction Eosinophils	Percent change from baseline in peak esophageal intraepithelial eosinophil count at week 24	LS mean (SE)	Part A -71.24 (6.948) Part B -80.24 (8.340)	-2.98 (7.596) 8.38 (10.089)	Statistically significant and clinically meaningful	Study R668-EE-1774 Part A and Part B
Unfavourable Effects						
						Safety

Effect	Short description	Unit	Treatment DUP 300mg QW	Control PBO	Uncertainties / Strength of evidence	References
TEAE PT	Injection side swelling	%	12.3	2.6	Higher incidence	Analysis Pool 2a (Study R668-EE-1774)
TEAE PT	Injection side reaction	%	19.7	17.9		Safety Analysis Pool 2a
TEAE PT	Injection side pain	%	9.0	6.0		Safety Analysis Pool 2a
TEAE PT	Pyrexia	%	5.7	1.7		Safety Analysis Pool 2a
AESI	Herpes Simplex	%	2.5	0.9		Safety Analysis Pool 2a

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The results from the co-primary endpoints and secondary endpoints of Part A and Part B of Study R668-EE-1774 show clinically meaningful improvements with dupilumab 300 mg QW treatment in signs and symptoms of EoE after 24 weeks of treatment. The proportion of participants who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf, which indicates reduced esophageal inflammation was significantly greater in the dupilumab 300 mg QW group compared to the placebo group. Additionally, the dupilumab 300 mg QW group also showed a reduction (improvement) in the DSQ (Dysphagia Symptom Questionnaire) total score compared to placebo. Furthermore, at the end of Part A/C after 52 weeks of treatment the participants on dupilumab 300 mg QW mostly sustained the improvement seen at week 24 in histological reduction of intraepithelial eosinophilic infiltration as well as reduced clinical symptoms of esophageal dysfunction (dysphagia).

However, in Part B of study R668-EE-1774 the dupilumab 300 mg Q2W showed similar results in the proportion of patient achieving a peak esophageal intraepithelial eosinophil count ≤6/hpf to the 300 mg QW dose but the change in the DSQ score was only similar to placebo in adults and even lower in adolescents.

Both endpoints are relevant in determining the efficacy of dupilumab in EoE. The 300 mg QW dose met its endpoints and showed continued improvement in adult and adolescent participants with EoE in both histologic and clinical efficacy endpoints up to week 52 with acceptable safety profile similar to other approved indications. This is the proposed dose regimen for adult and adolescent patients with EoE.

Injection site reactions have previously been identified as common ADRs in other dupilumab indications (AD, asthma, and CRSwNP). Injection site bruising has been added in section 4.8 of the SmPC. Although, the reactions were mild to moderate in intensity, the high incidence could impair the compliance of patients, especially in the younger age group.

3.7.2. Balance of benefits and risks

The beneficial effects of Dupilumab 300 mg QW has been shown in all parts of study R668-EE-1774 showing meaningful improvements across all histologic, clinical, endoscopic, QoL, and molecular signature of gene expression in EoE endpoints in adult. In adolescent participants similar improvements were reported with the Dupilumab 300 mg QW.

However, the numbers of adolescents compared to adults are still relatively low, making it difficult to fully characterise the safety profile and to compare the TEAE rates with certainty. Although the rate of TEAEs was high, most events were mild or moderate in intensity. The rate of SAEs was low and no new safety risks compared to other indication were identified. Of note the safety profile of Dupilumab 300 mg QW has already been evaluated in adult and adolescent participants in other indications, mainly in Atopic Dermatitis. It will be further characterised in the post authorisation setting, especially for the paediatric population given the limited data available in this relatively rare condition.

The benefit-risk ratio for the treatment of adult and adolescent patients with EoE is considered positive for the dupilumab 300 mg QW dosing regimen.

3.8. Conclusions

The overall B/R of Dupixent is positive in the following indication:

Dupixent is indicated for the treatment of eosinophilic esophagitis in adults and adolescents 12 years and older, weighing at least 40 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy (see section 5.1).

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of eosinophilic esophagitis (EoE) in adults and adolescents 12 years and older, weighing at least 40 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy, based on the pivotal Study R668-EE-1774. This is an ongoing phase 3, randomized, double-blind, placebo-controlled, 3-part (A, B, C) safety and efficacy study with an initial 24-week treatment period in adults (≥18 years of age) and adolescents (≥12 to <18 years of age) with EoE, and which includes an extended treatment period to a total of 52 weeks. As a consequence, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.
Version 8.2 of the RMP has also been approved.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and

to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0361/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Dupixent is not similar to Jorveza within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Dupixent-H-C-004390-II-0062'